Contact
COVID-19 rapid guideline: Managing COVID-19 - The National Institute for Health and Care Excellence (NICE)

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2. Introduction

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4. Communication and shared decision making

   Consensus recommendation

   Communicate with people with COVID-19, and their families and carers, and support their mental wellbeing to help alleviate any anxiety and fear they may have. Signpost to charities and support groups (including NHS Volunteer Responders), to NHS every mind matters and to Royal College of Paediatrics and Child Health resources for parents and carers.

   Remark:
   Give people information in a way that they can use and understand, to help them take part in decisions about their care. Follow relevant national guidance on communication, providing information (including in different formats and languages) and shared decision making, for example, NICE’s guideline on shared decision making and NICE’s guideline on patient experience in adult NHS services.

   The Royal College of Obstetricians and Gynaecologists has produced information on COVID-19 and pregnancy for pregnant women and their families.

   Consensus recommendation

   Explain to people with COVID-19, and their families, carers and close contacts that they should follow the UK Heath Security Agency’s guidance for people with symptoms of a respiratory infection including COVID-19.

   Consensus recommendation

   For carers of people with COVID-19 who should isolate but are unable to (for example, some people with dementia), signpost to relevant support and resources.

   Remark:
   For example, the Alzheimer’s Society has information on staying safe from coronavirus and reducing the risk of infection.

   Consensus recommendation

   When possible, discuss the risks, benefits and possible likely outcomes of the treatment options with people with COVID-19, and their families and carers. Use decision support tools (when available).

5. Assessment

   5.1 In the community
Consensus recommendation

5.1.1 Identifying severe COVID-19 Use the following signs and symptoms to help identify people with COVID-19 with the most severe illness:

- severe shortness of breath at rest or difficulty breathing
- reduced oxygen saturation levels measured by pulse oximetry (see the recommendation on pulse oximetry levels that indicate serious illness)
- coughing up blood
- blue lips or face
- feeling cold and clammy with pale or mottled skin
- collapse or fainting (syncope)
- new confusion
- becoming difficult to rouse
- reduced urine output.

Remark:
For signs and symptoms to help identify paediatric inflammatory multisystem syndrome (PIMS) temporarily associated with COVID-19, see the guidance on PIMS from the Royal College of Paediatrics and Child Health.

Consensus recommendation

When pulse oximetry is available in primary and community care settings, to assess the severity of illness and detect early deterioration, use:

- NHS England’s guide to pulse oximetry in people 18 years and over with COVID-19
- oxygen saturation levels below 91% in room air at rest in children and young people (17 years and under) with COVID-19.

Remark:
Be aware that some pulse oximeters can underestimate or overestimate oxygen saturation levels, especially if the saturation level is borderline. Overestimation has been reported in people with dark skin. For more information about this, see NHS England’s guide on how to look after yourself at home if you have COVID-19 or symptoms of COVID-19.

For information on pulse oximetry at home, see NHS England’s COVID oximetry @home service.

Info Box

Assessing shortness of breath (dyspnoea) is important, but may be difficult via remote consultation. Tools such as the Medical Research Council’s dyspnoea scale or the Centre for Evidence Based Medicine’s review of ways of assessing dyspnoea (breathlessness) by telephone or video can be useful.

The NEWS2 tool may be used in adults in addition to clinical judgement to assess a person’s risk of deterioration. Note that use of NEWS2 is not advised in children or pregnant women. Although the NEWS2 tool is not validated for predicting the risk of clinical deterioration in prehospital settings, it may be a helpful adjunct to clinical judgement in adults. A face-to-face consultation should not be arranged solely to calculate a NEWS2 score.

Locally approved Paediatric Early Warning Scores should be used for children. When using early warning scores, ensure that readings are based on calibrated machines. Be aware that readings may be incomplete when doing remote consultations.

Consensus recommendation

For people with severe respiratory symptoms associated with COVID-19 (for example, suspected pneumonia) being managed in the community, see the recommendation on venous thromboembolism in hospital-led acute care in the community.
5.1.2 Care planning

Discuss with people with COVID-19, and their families and carers, the benefits and risks of hospital admission or other acute care delivery services (for example, virtual wards or hospital at home teams).

Remark: Some benefits and risks may be similar for all patients (for example, improved diagnostic tests and access to treatments, or better contact with families in the community), but others may be personal to the individual (such as loss of access to carers who can anticipate needs well in someone unable to communicate themselves, or risks of spreading COVID-19).

Consensus recommendation

Explain that people with COVID-19 may deteriorate rapidly. Discuss future care preferences at the first assessment to give people who do not have existing advance care plans an opportunity to express their preferences.

5.2 In hospital

Consensus recommendation

When a person is admitted to hospital with COVID-19, ensure a holistic assessment is done, including discussion about their treatment expectations and care goals:

- Document and assess the stability of underlying health conditions, involving relevant specialists as needed.
- Use the Clinical Frailty Scale (CFS) when appropriate, available from the NHS Specialised Clinical Frailty Network, to assess baseline health and inform discussions on treatment expectations.
- Use the CFS within an individualised assessment of frailty.
- Do not use the CFS for younger people, people with stable long-term disabilities (for example, cerebral palsy), learning disabilities or autism. Make an individualised assessment of frailty in these people, using clinical assessment and alternative scoring methods.
- Record the assessment and discussion in the person’s medical records.

Remark:

For assessment of paediatric inflammatory multisystem syndrome (PIMS), follow the guidance on PIMS from the Royal College of Paediatrics and Child Health.

Consensus recommendation

When making decisions about the care of children and young people under 18 years, people with learning disabilities or adults who lack mental capacity for health decision making, for example, people with advanced dementia, see the NICE guideline on decision-making and mental capacity.

Ensure discussions on significant care interventions involve families and carers as appropriate, and local experts or advocates.

6. Management

6.1 In the community

6.1.1 Care planning
Consensus recommendation

In the community, consider the risks and benefits of face-to-face and remote care for each person. Where the risks of face-to-face care outweigh the benefits, remote care can be optimised by:

- offering telephone or video consultations (see BMJ guidance on Covid-19: a remote assessment in primary care for a useful guide, including a visual summary for remote consultation)
- cutting non-essential face-to-face follow up
- using electronic prescriptions rather than paper
- using different methods to deliver medicines to people, for example, pharmacy deliveries, postal services and NHS volunteers, or introducing drive-through pick-up points for medicines.

Consensus recommendation

Put treatment escalation plans in place in the community after sensitively discussing treatment expectations and care goals with people with COVID-19, and their families and carers.

Remark: People with COVID-19 may deteriorate rapidly. If it is agreed that the next step is a move to secondary care, ensure that they and their families understand how to access this with the urgency needed. If the next step is other community-based support (whether virtual wards, hospital at home services or palliative care), ensure that they and their families understand how to access these services, both in and out of hours.

6.1.2 Managing cough

Consensus recommendation

Encourage people with cough to avoid lying on their backs, if possible, because this may make coughing less effective.

Remark: Be aware that older people or those with comorbidities, frailty, impaired immunity or a reduced ability to cough and clear secretions are more likely to develop severe pneumonia. This could lead to respiratory failure and death.

Consensus recommendation New

For guidance on managing acute cough, see the NICE guideline on cough (acute): antimicrobial prescribing.

6.1.3 Managing fever

Consensus recommendation

Advise people with COVID-19 and fever to drink fluids regularly to avoid dehydration. Support their families and carers to help when appropriate. Communicate that fluid intake needs can be higher than usual because of fever.
Consensus recommendation

Advise people to take paracetamol or ibuprofen if they have fever and other symptoms that antipyretics would help treat. Tell them to continue only while both the symptoms of fever and the other symptoms are present.

Remark:
People can take paracetamol or ibuprofen when self-medicating for symptoms of COVID-19, such as fever (see the Central Alerting System: novel coronavirus - anti-inflammatory medications for further details of ibuprofen including dosage).

For people 18 years and over, the paracetamol dosage is 1 g orally every 4 to 6 hours (maximum 4 g per day). See the BNF and Medicines and Healthcare products Regulatory Agency advice for appropriate use and dosage in specific adult populations.

For children and young people over 1 month and under 18 years, see the dosing information on the pack or the BNF for children.

Rectal paracetamol, if available, can be used as an alternative. For rectal dosage information, see the BNF and BNF for children.

6.1.4 Managing breathlessness

Consensus recommendation

Identify and treat reversible causes of breathlessness, for example, pulmonary oedema, pulmonary embolism, chronic obstructive pulmonary disorder and asthma.

Remark:
For further information on identifying and managing pulmonary embolism, see the NICE guideline on venous thromboembolic diseases: diagnosis, management and thrombophilia testing.

Consensus recommendation

When significant medical pathology has been excluded or further investigation is inappropriate, the following may help to manage breathlessness as part of supportive care:

- keeping the room cool
- encouraging relaxation and breathing techniques, and changing body positioning
- encouraging people who are self-isolating alone to improve air circulation by opening a window or door.

If hypoxia is the likely cause of breathlessness:

- consider a trial of oxygen therapy
- discuss with the person, their family or carer possible transfer to and evaluation in secondary care.

Remark: Breathlessness with or without hypoxia often causes anxiety, which can then increase breathlessness further.

6.1.5 Managing anxiety, delirium and agitation

Consensus recommendation

Assess reversible causes of delirium. See the NICE guideline on delirium: prevention, diagnosis and management.
Consensus recommendation
Address reversible causes of anxiety by:

- exploring the person’s concerns and anxieties
- explaining to people providing care how they can help.

6.1.6 Managing medicines

Consensus recommendation

When supporting people with symptoms of COVID-19 who are having care in the community delivered by social care, follow the NICE guideline on managing medicines for adults receiving social care in the community. This includes processes for ordering and supplying medicines, and transporting, storing and disposing of medicines.

Consensus recommendation

When prescribing, handling, administering and disposing of medicines in care homes and hospices, follow the NICE guideline on managing medicines in care homes.

6.2 In hospital

6.2.1 Deciding when to escalate treatment

Consensus recommendation

Base decisions about escalating treatment within the hospital on the likelihood of a person’s recovery. Take into account their treatment expectations, goals of care and the likelihood that they will recover to an outcome that is acceptable to them.

Remark:
For support with decision making, see:

- advice on ethics from the British Medical Association
- ethical guidance from the Royal College of Physicians
- national guidance presented by the Faculty of Intensive Care Medicine, Intensive Care Society, Association of Anaesthetists and Royal College of Anaesthetists
- advice on decision making under pandemic conditions by the Intensive Care Society, and
- advice on decision making and consent from the General Medical Council

Consensus recommendation

Ensure healthcare professionals have access to resources to support discussions about treatment plans (see, for example, decision-making for escalation of treatment and referring for critical care support, and an example decision support form).

Remark:
Tools such as the British Medical Journal emergency care and resuscitation plan may be useful when making decisions about a treatment plan.
Consensus recommendation

Discuss treatment escalation with a multidisciplinary team of medical and allied health professional colleagues (such as from critical care, respiratory medicine, geriatric medicine and palliative care) when there is uncertainty about treatment escalation decisions.

Consensus recommendation

Document referral to and advice from critical care services and respiratory support units in a standard format. When telephone advice from critical care or respiratory support units is appropriate, this should still be documented in a standard format (see an example of a tool for documentation).

6.2.2 Escalating and de-escalating treatment

Consensus recommendation

Before escalating respiratory or other organ support, identify agreed treatment goals with the person (if possible), and their family and carers, or an independent mental capacity advocate (if appropriate). Start all advanced respiratory support or organ support with a clear plan of how it will address the diagnosis and lead to agreed treatment goals (outcomes). Ensure this includes management plans for when there is further deterioration or no response to treatment.

Do not continue respiratory or other organ support if it is considered that it will no longer result in the desired overall goals (outcomes). Record the decision and the discussion with the person (if possible), and their family and carers, or an independent mental capacity advocate (if appropriate).

6.2.3 Delivering services in critical care and respiratory support units

Consensus recommendation

Trusts should review:

- their strategy on management for people who are deteriorating and
- use of the track-and-trigger system (NEWS2 has been endorsed by NHS England and Improvement).

See the NICE guideline on acutely ill adults in hospital for recommendations on identifying patients whose clinical condition is deteriorating or is at risk of deterioration.

Remark:
See the Royal College of Physician’s information on the place of NEWS2 in managing patients with COVID-19.

6.2.4 Non-invasive respiratory support
Definitions

**High-flow nasal oxygen (HFNO):** involves the delivery of warm and humidified oxygen (up to 70 litres per minute) through small nasal cannulae. The delivered gas flow is equal to or higher than the flow of air when the person is breathing in (inspiratory flow). This means that HFNO can deliver a higher and more stable concentration of inspired oxygen than conventional oxygen alone with nasal prongs. The higher flow also increases carbon dioxide washout in the upper airways and improves carbon dioxide clearance. Unlike continuous positive airway pressure (CPAP), any positive pressure provided by HFNO is not measurable or sizeable.

**Continuous positive airway pressure (CPAP):** is a type of non-invasive positive airway pressure that delivers a set pressure of airflow to the airways. This pressure is maintained throughout the respiratory cycle, both when the person is breathing in (inspiration) and breathing out (expiration). A CPAP device consists of a unit that generates airflow, which is delivered to the airway through a tight-fitting mask or other airtight interface.

**Non-invasive ventilation (NIV):** refers to a mode of positive pressure ventilation that delivers airflow to the airways through a tight-fitting mask or other airtight interface. Airflow is delivered at variable pressures that are higher when the person is breathing in (inspiratory pressure) and lower than when the person is breathing out (expiratory pressure). NIV differs from CPAP by providing additional inspiratory pressure assistance. Most devices have an option of adding positive expiratory airway pressure that can fulfil a similar role to CPAP by maintaining a positive pressure in the airways to aid lung recruitment (opening of the airways).

**Non-invasive respiratory support:** is a broad umbrella term for different types of respiratory support given through external interfaces, and includes HFNO, CPAP and NIV. These are more intensive interventions than conventional oxygen therapy alone. The different types of support are not, however, interchangeable because they have differing effects on a person’s respiratory and cardiac physiology. So, they typically have different indications for their use.

**Invasive mechanical ventilation:** any method of controlled ventilation delivered through a tracheostomy tube, or other methods as defined by the Intensive Care National Audit & Research Centre definition of ‘advanced respiratory support’.

For information on deciding when to escalate and de-escalate treatment, see the sections on deciding when to escalate treatment and escalating and de-escalating treatment. Also, consider factors such as:

- how much supplemental oxygen is needed to reach target oxygen saturation
- the person’s overall clinical trajectory
- the person’s effort of breathing (inspiratory effort and respiratory rate)
- whether the person needs relief of the sensation of breathlessness
- how well the person has tolerated treatments so far
- treatment preferences after discussion with the person, and their family and carers (when appropriate).

**Remark:**
The Royal College of Obstetricians and Gynaecologists has produced information on management of coronavirus infection in pregnancy.

The Royal College of Paediatrics and Child Health has produced information on management of coronavirus infection in children.

For information on how to manage COVID-19 in people who are having non-invasive respiratory support, see the sections on management and therapeutics for COVID-19.
Consensus recommendation

Optimise pharmacological and non-pharmacological management strategies in people who need non-invasive respiratory support.

Remark:
The British Thoracic Society and Intensive Care Society have produced information on management of acute respiratory hypoxaemia associated with COVID-19.

The Royal College of Obstetricians and Gynaecologists has produced information on management of coronavirus infection in pregnancy.

Conditional recommendation

Consider awake prone positioning for people in hospital with COVID-19 who are not intubated and have higher oxygen needs. Discuss this with the person to reach a shared decision on whether to try the position.

Remark:
Factors to consider when trying awake prone positioning may include:

• whether the person has any contraindications to prone positioning (for example, communication difficulties that affect their ability to try the position, respiratory distress, potential need for invasive ventilation, untreated pneumothorax, or recent abdominal, thoracic, facial, pelvic or spinal injury)
• availability of support from healthcare professionals with skills and experience in prone positioning
• allowing a suitable duration to measure response to prone positioning (for example, by monitoring oxygen saturation, need for supplemental oxygen, respiratory rate, sensation of breathlessness)
• ensuring regular review and continuous monitoring (for example, oxygen saturation level)
• how well the person can tolerate prone positioning and the importance of breaks
• stopping prone positioning if it causes excessive discomfort (including pressure damage, or pins and needles or numbness in the upper limbs), or there is worsening hypoxia or excessive breathlessness.

The British Thoracic Society and Intensive Care Society have produced information on management of acute respiratory hypoxaemia associated with COVID-19.

The Intensive Care Society has produced information on conscious prone positioning for people with COVID-19.

The Royal College of Obstetricians and Gynaecologists has produced information on management of coronavirus infection in pregnancy, including body positioning.

Follow relevant national guidance on communication, providing information (including in different formats and languages) and shared decision making, for example, NICE’s guideline on shared decision making.

Conditional recommendation against

Do not routinely offer high-flow nasal oxygen as the main form of respiratory support for people with COVID-19 and respiratory failure in whom escalation to invasive mechanical ventilation would be appropriate.

Remark:
See the recommendation on when to consider high-flow nasal oxygen.
Conditional recommendation

Consider continuous positive airway pressure (CPAP) for people with COVID-19 when:

- they have hypoxaemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of 0.4 (40%) or more, and either
  - escalation to invasive mechanical ventilation would be an option but it is not immediately needed, or
  - it is agreed that respiratory support should not be escalated beyond CPAP.

Remark:
In June 2021, the Medicines and Healthcare products Regulatory Agency issued a National Patient Safety Alert for Philips ventilator, CPAP and bilevel positive airway pressure devices because of a potential for harm from inhaled particles and volatile organic compounds. This applies to all devices manufactured before 26 April 2021.

Consensus recommendation

For people with COVID-19 having continuous positive airway pressure (CPAP), ensure:

- there is access to critical care providers for advice, review and prompt escalation of treatment if needed
- regular review by an appropriate senior clinician (such as every 12 hours) and more frequent review if needed, in line with the British Thoracic Society guidance on respiratory support units and the Faculty of Intensive Care Medicine guidelines on the provision of intensive care services
- regular assessment and management of symptoms alongside non-invasive respiratory support.

Remark:
Staff caring for people with COVID-19 having CPAP should have appropriate skills and competencies and provide appropriate monitoring. For further information on standards of care and provision of services see the Faculty of Intensive Care Medicine and Intensive Care Society guidelines on the provision of intensive care services, the British Thoracic Society and Intensive Care Society guidance on development and implementation of respiratory support units and the Paediatric Intensive Care Society guidance on the management of critically ill children.

The British Thoracic Society and Intensive Care Society have produced information on management of acute hypoxaemic respiratory failure associated with COVID-19, which includes the use of CPAP.

Consensus recommendation

Consider using high-flow nasal oxygen for people when:

- they cannot tolerate continuous positive airway pressure (CPAP) but need humidified oxygen at high flow rates
- maximal conventional oxygen is not maintaining their target oxygen saturations and:
  - they do not need immediate invasive mechanical ventilation or escalation to invasive mechanical ventilation is not suitable, and
  - CPAP is not suitable
- they need:
  - a break from CPAP (such as at mealtimes, for skin and pressure area relief, or for mouth care)
  - humidified oxygen or nebulisers (or both)
  - weaning from CPAP.

Remark:
The British Thoracic Society and Intensive Care Society have produced information on management of acute hypoxaemic respiratory failure associated with COVID-19, which includes the use of CPAP.
7. **Therapeutics for COVID-19**

7.1 **Antivirals**

7.1.1 **Nirmatrelvir and ritonavir**

**Recommended**

Nirmatrelvir plus ritonavir is recommended as an option for treating COVID-19 in adults, only if they:

- do not need supplemental oxygen for COVID-19 and
- have an increased risk for progression to severe COVID-19, as defined in section 5 of NICE’s technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.

Remark:
This recommendation is from NICE’s technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.

7.1.2 **Remdesivir**

**Info Box**

Evidence on the clinical and cost effectiveness of remdesivir is currently under review through the NICE multiple technology appraisal process.
**Definitions**

**Invasive mechanical ventilation:** any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the Intensive Care National Audit & Research Centre definition of ‘advanced respiratory support’.

**Low-flow supplemental oxygen:** oxygen delivered by a simple face mask or nasal canula at a flow rate usually up to 15 litres/min.

### Conditional recommendation

Consider a 3-day course of remdesivir for children and young people who weigh at least 40 kg and adults with COVID-19 who:

- do not need supplemental oxygen for COVID-19, and
- are within 7 days of symptom onset, and
- are thought to be at high risk of progression to severe COVID-19. (NHS England’s Interim Clinical Commissioning Policy on remdesivir and molnupiravir provides a list of people prioritised for treatment with antivirals.)

When assessing the person, take into account likely response to any vaccinations against COVID-19 they have already had, any comorbidities or risk factors, and whether their condition is deteriorating.

**Remark:**

This recommendation is informed by the results of the PINETREE trial, which only included people not vaccinated against COVID-19. The trial took place before the emergence of the Delta (B.1.617.2) and Omicron (B.1.1.529) variants.

### Conditional recommendation

Consider a course of remdesivir (up to 5 days) for people who:

- have COVID-19 pneumonia, and
- are in hospital and need low-flow supplemental oxygen.

**Remark:**

The criteria for accessing remdesivir in the UK are outlined in NHS England’s Interim Clinical Commissioning Policy on remdesivir for people in hospital with COVID-19, which includes people who are significantly immunocompromised.

For remdesivir use in pregnancy, follow the Royal College of Obstetrics and Gynaecology guidance on COVID-19 and pregnancy.

This recommendation is informed by the results of clinical trials that included very few people who had been vaccinated against COVID-19. Also, the trials took place before the emergence of the Delta (B.1.617.2) and Omicron (B.1.1.519) variants.

### Only in research settings

Do not use remdesivir for COVID-19 pneumonia in anyone in hospital and on high-flow nasal oxygen, continuous positive airway pressure, non-invasive mechanical ventilation or invasive mechanical ventilation, except as part of an ongoing clinical trial.
7.1.3 Molnupiravir

Evidence on the clinical and cost effectiveness of molnupiravir is currently under review through the NICE multiple technology appraisal process.

**Conditional recommendation In review**

Consider a 5-day course of molnupiravir for adults with COVID-19 who:

- do not need supplemental oxygen for COVID-19, and
- are within 5 days of symptom onset, and
- are thought to be at high risk of progression to severe COVID-19. (NHS England’s Interim Clinical Commissioning Policy on remdesivir and molnupiravir provides a list of people prioritised for treatment with antivirals.)

When assessing the person, take into account their likely response to any vaccinations already given, any comorbidities or risk factors, and whether their condition is deteriorating.

**Remark:**
This recommendation is informed by the results of the MOVe-OUT trial, which included only unvaccinated people. The trial ran before the emergence of the Omicron (B.1.1.529) variant.

We are aware that the results of the PANORAMIC trial have published, and are reviewing this recommendation.

**Not recommended In review**

Do not offer molnupiravir to children and young people aged under 18, or pregnant women.

7.2 Sotrovimab

**Recommended**

Sotrovimab is recommended as an option for treating COVID-19 in adults and young people aged 12 years and over and weighing at least 40 kg, only if:

- they do not need supplemental oxygen for COVID-19 and
- they have an increased risk for progression to severe COVID-19, as defined in section 5 of NICE’s technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab and
- nirmatrelvir plus ritonavir is contraindicated or unsuitable.

Sotrovimab is only recommended if the company provides it according to the commercial arrangement.

**Remark:**
This recommendation is from NICE’s technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.
### 7.3 Corticosteroids

**Recommended**

Offer dexamethasone, or either hydrocortisone or prednisolone when dexamethasone cannot be used or is unavailable, to people with COVID-19 who:

- need supplemental oxygen to meet their prescribed oxygen saturation levels or
- have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it.

Continue corticosteroids for up to 10 days unless there is a clear indication to stop early, which includes discharge from hospital or a hospital-supervised virtual COVID ward.

**Remark:**

Being on a hospital-supervised virtual COVID ward is not classed as being discharged from hospital.

See Practical info for dosage information.

For full details of adverse events and contraindications, see the summaries of product characteristics.

For children with a greater than 44-week corrected gestational age, follow the risk criteria set out in Royal College of Paediatric and Child Health guidance for assessing children admitted to hospital with COVID-19. For preterm babies with a corrected gestational age of less than 44 weeks, seek specialist advice.

**Not recommended**

Do not use corticosteroids to treat COVID-19 in people who do not need supplemental oxygen.

**Remark:**

People who need corticosteroids for another medical reason should still have them.

### 7.4 Casirivimab and imdevimab

**Not recommended**

Casirivimab plus imdevimab is not recommended, within its marketing authorisation, for treating COVID-19.

**Remark:**

This recommendation is from NICE’s technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab. For the full marketing authorisation for casirivimab plus imdevimab, see the summary of product characteristics.

### 7.5 Tocilizumab
**Recommended**

Tocilizumab is recommended, within its marketing authorisation, as an option for treating COVID-19 in adults who:

- are having systemic corticosteroids and
- need supplemental oxygen or mechanical ventilation.

Tocilizumab is only recommended if the company provides it according to the commercial arrangement.

Remark: This recommendation is from NICE’s technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.

The summary of product characteristics for tocilizumab specifies that it should only be offered when there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by tocilizumab. It also states that the efficacy of tocilizumab has not been established in the treatment of COVID-19 in people who do not have elevated C-reactive protein levels.

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**7.6 Baricitinib**

Conditional recommendation

Consider baricitinib for people 2 years and over in hospital with COVID-19 who:

- need supplemental oxygen for COVID-19, and
- are having or have completed a course of corticosteroids such as dexamethasone, unless they cannot have corticosteroids, and
- have no evidence of infection (other than SARS-CoV-2) that might be worsened by baricitinib.

Remark: In March 2023, this was an off-label use of baricitinib. See NICE’s information on prescribing medicines.

Baricitinib may be considered in people who meet the above criteria, and who cannot have tocilizumab. When there is clinical deterioration despite treatment with tocilizumab, it may be appropriate to add baricitinib.

Baricitinib is contraindicated in pregnancy and breastfeeding. The Royal College of Obstetricians and Gynaecologists has produced guidance on managing coronavirus infection in pregnancy.

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**7.7 Low molecular weight heparins**

Info Box

For recommendations on the therapeutic use of low molecular weight heparins, see the section on venous thromboembolism (VTE) prophylaxis.

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**7.8 Antibiotics**
Antibiotics should not be used for preventing or treating COVID-19 unless there is clinical suspicion of additional bacterial co-infection. See the section on suspected or confirmed co-infection.

See also the recommendations on azithromycin and doxycycline in the section on therapeutics for COVID-19.

7.9 Azithromycin

Not recommended

Do not use azithromycin to treat COVID-19.

7.10 Budesonide (inhaled)

Only in research settings

Only use budesonide to treat COVID-19 as part of a clinical trial.

Remark:
People already on budesonide for conditions other than COVID-19 should continue treatment if they test positive for COVID-19.

7.11 Colchicine

Not recommended

Do not use colchicine to treat COVID-19.

7.12 Doxycycline

Not recommended

Do not use doxycycline to treat COVID-19 in the community.

7.13 Ivermectin

Only in research settings

Do not use ivermectin to treat COVID-19 except as part of an ongoing clinical trial.

7.14 Vitamin D
Only in research settings

Do not use vitamin D to treat COVID-19 except as part of a clinical trial.

Remark:
For existing UK guidance on taking vitamin D to maintain muscle and bone health, see NHS advice on vitamin D.

7.15 Ongoing review of therapeutics for COVID-19

We are currently reviewing new and existing therapeutics for treating COVID-19 as part of a living guidelines approach. New and updated recommendations will be published for this guideline as they become available (see Update information | COVID-19 rapid guideline: managing COVID-19 | Guidance | NICE).

8. Preventing and managing acute complications

8.1 Acute kidney injury (AKI)

In people with COVID-19, AKI:

- may be common, but prevalence is uncertain and depends on clinical setting (the Intensive Care National Audit and Research Centre’s report on COVID-19 in critical care provides information on people in critical care who need renal replacement therapy for AKI)
- is associated with an increased risk of dying
- can develop at any time (before, during or after hospital admission)
- may be caused by volume depletion (hypovolaemia), haemodynamic changes, viral infection leading directly to kidney tubular injury, thrombotic vascular processes, glomerular pathology or rhabdomyolysis
- may be associated with haematuria, proteinuria and abnormal serum electrolyte levels (both increased and decreased serum sodium and potassium).

In people with COVID-19:

- maintaining optimal fluid status (euvolaemia) is difficult but critical to reducing the incidence of AKI
- treatments for COVID-19 may increase the risk of AKI
- treatments for pre-existing conditions may increase the risk of AKI
- fever and increased respiratory rate increase insensible fluid loss.

8.1.1 Assessing and managing acute kidney injury (AKI)

The potassium binders patiromer and sodium zirconium cyclosilicate can be used as options alongside standard care for the emergency management of acute life-threatening hyperkalaemia (see NICE’s technology appraisal guidance on patiromer and sodium zirconium cyclosilicate for treating hyperkalaemia).
For information on assessing and managing AKI, see the NICE guideline on acute kidney injury: prevention, detection and management and the NHS England Acute Kidney Injury (AKI) Algorithm.

For information on using intravenous fluids, see the NICE guideline on intravenous fluid therapy in adults in hospital and the NICE guideline on intravenous fluid therapy in children and young people in hospital.

For information on managing renal replacement therapy for adults who are critically unwell with COVID-19, see the Renal Association’s guidelines on renal replacement therapy for critically unwell adults.

8.1.2 Follow up

Consensus recommendation

Monitor people with chronic kidney disease for at least 2 years after AKI, in line with the NICE guideline on chronic kidney disease: assessment and management.

Remark:
See guidance on care after hospital discharge in the Royal College of General Practitioners AKI toolkit.

8.2 Acute myocardial injury

8.2.1 Diagnosing acute myocardial injury

Consensus recommendation

For people in hospital with COVID-19 with signs or symptoms that suggest acute myocardial injury, measure high sensitivity troponin I (hs-cTnI) or T (hs-cTnT) and N-terminal pro B-type natriuretic peptide, and do an ECG.

Use the following test results to help inform a diagnosis:
- evolving ECG changes suggesting myocardial ischaemia
- an NT-proBNP level above 400 ng/litre
- high levels of hs-cTnI or hs-cTnT, particularly levels increasing over time.

Info Box

Elevated troponin levels may reflect cardiac inflammatory response to severe COVID-19 rather than acute coronary syndrome.

8.2.2 Managing myocardial injury

Consensus recommendation

For all people with COVID-19 and suspected or confirmed acute myocardial injury:
- monitor in a setting where cardiac or respiratory deterioration can be rapidly identified
- do continuous ECG monitoring
- monitor blood pressure, heart rate and fluid balance.
Consensus recommendation

For people with a clear diagnosis of myocardial injury:

- seek specialist cardiology advice on treatment, further tests and imaging
- follow local treatment protocols.

Consensus recommendation

For people with a high clinical suspicion of myocardial injury, but without a clear diagnosis:

- repeat high sensitivity troponin (hs-cTnI or hs-cTnT) measurements and ECG monitoring daily, because dynamic change may help to monitor the course of the illness and establish a clear diagnosis
- seek specialist cardiology advice on further investigations such as transthoracic echocardiography and their frequency.

Remark:
See also the management section for recommendations on care planning and recommendations on escalating and de-escalating treatment.

Info Box

See the Medicines and Healthcare products Regulatory Agency's Drug Safety Update on erythromycin: caution required due to cardiac risks (QT interval prolongation); drug interaction with rivaroxaban.

8.3 Venous thromboembolism (VTE) prophylaxis

Info Box

Definitions

**Invasive mechanical ventilation**: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the Intensive Care National Audit & Research Centre definition of ‘advanced respiratory support’.

**Hospital-led acute care in the community**: a setting in which people who would otherwise be admitted to hospital have acute medical care provided by members of the hospital team, often working with the person’s GP team. They include hospital at home services and COVID-19 virtual wards.

**Standard prophylactic dose**: the prophylactic dose of a low molecular weight heparin (LMWH), as listed in the medicine’s summary of product characteristics, for medical patients.

**Intermediate dose**: double the standard prophylactic dose of an LMWH for medical patients.

**A treatment dose**: the licensed dose of anticoagulation used to treat confirmed VTE.

8.3.1 In hospital
Consensus recommendation

For young people and adults with COVID-19 that is being managed in hospital, assess the risk of bleeding as soon as possible after admission or by the time of the first consultant review. Use a risk assessment tool published by a national UK body, professional network or peer-reviewed journal.

Remark:
The Department of Health VTE risk assessment tool is commonly used to develop treatment plans.

Recommended

Offer a standard prophylactic dose of a low molecular weight heparin as soon as possible, and within 14 hours of admission, to young people and adults with COVID-19 who need low-flow or high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation, and who do not have an increased bleeding risk.

Treatment should be continued for a minimum of 7 days, including after discharge.

See the NICE recommendation on low molecular weight heparin self-administration.

Conditional recommendation

Consider a treatment dose of a low molecular weight heparin (LMWH) for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk.

Treatment should be continued for 14 days or until discharge, whichever is sooner. Dose reduction may be needed to respond to any changes in a person’s clinical circumstances.

Remark:
For people with COVID-19 who do not need low-flow oxygen, follow the recommendations in NICE’s guideline on venous thromboembolism in over 16s.

In August 2021, using a treatment dose of a LMWH outside the treatment of confirmed VTE was an off-label use of parenteral anticoagulants. See NICE’s information on prescribing medicines.

Only in research settings

Only offer an intermediate or treatment dose of a low molecular weight heparin to young people and adults with COVID-19 who are receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation as part of a clinical trial.

Consensus recommendation

Do not base prophylactic dosing of heparin on levels of D-dimer.

Consensus recommendation

For people at extremes of body weight or with impaired renal function, consider adjusting the dose of low molecular weight heparins in line with the summary of product characteristics and locally agreed protocols.
Consensus recommendation

For people who cannot have low molecular weight heparins (LMWHs), use fondaparinux sodium or unfractionated heparin (UFH).

Remark:
In August 2021, LMWHs and fondaparinux sodium were off label for people under 18 years. See NICE’s information on prescribing medicines.

Consensus recommendation

For people who are already having anticoagulation treatment for another condition when admitted to hospital:

- continue their current treatment dose of anticoagulant unless contraindicated by a change in clinical circumstances
- consider switching to a low molecular weight heparin (LMWH) if their current anticoagulant is not an LMWH and their clinical condition is deteriorating.

Consensus recommendation

If a person’s clinical condition changes, assess the risk of VTE, reassess bleeding risk and review VTE prophylaxis.

Consensus recommendation

Organisations should collect and regularly review information on bleeding and other adverse events in people with COVID-19 having treatment or intermediate doses of low molecular weight heparins.

Consensus recommendation

Ensure that people who will be completing VTE prophylaxis after discharge from hospital are able to use it correctly or have arrangements made for someone to help them.

8.3.1.1 In hospital-led acute care in the community

Consensus recommendation

For people with COVID-19 managed in hospital-led acute care in the community settings:

- assess the risks of VTE and bleeding
- consider pharmacological prophylaxis if the risk of VTE outweighs the risk of bleeding.

8.3.2 People with COVID-19 and additional risk factors

Consensus recommendation

For women with COVID-19 who are pregnant or have given birth within the past 6 weeks, follow the advice on VTE prevention in the Royal College of Obstetricians and Gynaecologists guidance on coronavirus (COVID-19) in pregnancy.

Consensus recommendation

For children with COVID-19 admitted into hospital, follow the advice on COVID-19 guidance for management of children admitted to hospital in the Royal College of Paediatrics and Child Health guidance.
8.3.3 Information and support

Consensus recommendation

Give people with COVID-19, and their families or carers if appropriate, information about the benefits and risks of VTE prophylaxis.

Remark:
See the recommendations on giving information and planning for discharge in the NICE guideline on venous thromboembolism in over 16s, including information on alternatives to heparin for people who have concerns about using animal products.

Consensus recommendation

Offer people the opportunity to take part in ongoing clinical trials on COVID-19.

9. Identifying and managing co-infections

Consensus recommendation

Do not offer an antibiotic for preventing or treating pneumonia if SARS-CoV-2, another virus, or a fungal infection is likely to be the cause.

Remark:
Antibiotics do not work on viruses, and inappropriate antibiotic use may reduce availability. Also, inappropriate use may lead to Clostridioides difficile infection and antimicrobial resistance, particularly with broad-spectrum antibiotics.

Info Box

Evidence as of March 2021 suggests that bacterial co-infection occurs in less than about 8% of people with COVID-19, and could be as low as 0.1% in people in hospital with COVID-19. Viral and fungal co-infections occur at lower rates than bacterial co-infections.

Secondary infection or co-infection (bacterial, viral or fungal) is more likely the longer a person is in hospital and the more they are immunosuppressed (for example, because of certain types of treatment).

The type and number of secondary infections or co-infections will vary depending on the season and any restrictions in place (for example, lockdowns).

9.1 Other causes of pneumonia

9.1.1 Identifying other causes of pneumonia

Consensus recommendation

To help identify other causes of pneumonia and to inform decision making about using antibiotics, consider the following tests:

- a full blood count
- chest imaging (X-ray, CT or ultrasound)
- respiratory and blood samples (for example, sputum or a tracheal aspirate sample, blood culture)
- urine samples for legionella and pneumococcal antigen testing
- throat, nasopharyngeal or sputum samples for respiratory viral (and atypical pathogen) polymerase chain reaction testing; for more information, see Public Health England’s COVID-19 guidance for sampling and for diagnostic laboratories.
High C-reactive protein levels do not necessarily indicate whether pneumonia is due to bacteria or SARS-COV-2.

Low C-reactive protein level indicates that a secondary bacterial infection is less likely.

**Consensus recommendation**
Do not use C-reactive protein to assess whether a person has a secondary bacterial infection if they have been having immunosuppressant treatment.

**Info Box**
There is insufficient evidence to recommend routine procalcitonin testing to guide decisions about antibiotics. Centres already using procalcitonin tests are encouraged to participate in research and data collection.

Procalcitonin tests could be useful in identifying whether there is a bacterial infection. However, it is not clear whether they add benefit beyond what is suggested in the recommendation on tests to help differentiate between viral and bacterial pneumonia to guide decisions about antibiotics. The most appropriate threshold for procalcitonin is also uncertain.

### 9.1.2 Antibiotic treatment in the community

**Consensus recommendation**
Do not offer an antibiotic for preventing secondary bacterial pneumonia in people with COVID-19.

**Consensus recommendation**
If a person has suspected or confirmed secondary bacterial pneumonia, start antibiotic treatment as soon as possible. Take into account any different methods needed to deliver medicines during the COVID-19 pandemic (see the recommendation on minimising face-to-face contact in communication and shared decision making).

**Info Box**
For antibiotic choices to treat community-acquired pneumonia caused by a secondary bacterial infection, see the recommendations on choice of antibiotic in the NICE antimicrobial prescribing guideline on community-acquired pneumonia.

**Consensus recommendation**
Advise people to seek medical help without delay if their symptoms do not improve as expected, or worsen rapidly or significantly, whether they are taking an antibiotic or not.

**Consensus recommendation**
On reassessment, reconsider whether the person has signs and symptoms of more severe illness (see the recommendation on signs and symptoms to help identify people with COVID-19 with the most severe illness) and whether to refer them to hospital, other acute community support services or palliative care services.

### 9.1.3 Starting antibiotics in hospital
Consensus recommendation

Start empirical antibiotics if there is clinical suspicion of a secondary bacterial infection in people with COVID-19. When a decision to start antibiotics has been made:

- start empirical antibiotic treatment as soon as possible after establishing a diagnosis of secondary bacterial pneumonia, and certainly within 4 hours
- start treatment within 1 hour if the person has suspected sepsis and meets any of the high-risk criteria for this outlined in the NICE guideline on sepsis.

9.1.4 Choice of antibiotics in hospital

Info Box

To guide decision making about antibiotics for secondary bacterial pneumonia in people with COVID-19, see the NICE guideline on pneumonia (hospital acquired): antimicrobial prescribing.

Consensus recommendation

When choosing antibiotics, take account of:

- local antimicrobial resistance data and
- other factors such as their availability.

Consensus recommendation

Give oral antibiotics if the person can take oral medicines and their condition is not severe enough to need intravenous antibiotics.

Consensus recommendation

Consider seeking specialist advice on antibiotic treatment for people who:

- are immunocompromised
- have a history of infection with resistant organisms
- have a history of repeated infective exacerbations of lung disease
- are pregnant
- are receiving advanced respiratory support or organ support.

Consensus recommendation

Seek specialist advice if:

- there is a suspicion that the person has an infection with multidrug-resistant bacteria and may need a different antibiotic or
- there is clinical or microbiological evidence of infection and the person's condition does not improve as expected after 48 to 72 hours of antibiotic treatment.

9.1.5 Reviewing antibiotic treatment in hospital
Review all antibiotics at 24 to 48 hours, or as soon as test results are available. If appropriate, switch to a narrower spectrum antibiotic, based on microbiological results.

For intravenous antibiotics, review within 48 hours and think about switching to oral antibiotics (in line with the NICE guideline on pneumonia (hospital-acquired): antimicrobial prescribing).

Give antibiotics for 5 days, and then stop them unless there is a clear indication to continue (see the recommendation on when to seek specialist advice).

Reassess people if their symptoms do not improve as expected, or worsen rapidly or significantly.

**9.2 COVID-19-associated pulmonary aspergillosis (CAPA)**

**Info Box**

For people who are critically ill and have, or have had, COVID-19 as part of their acute illness:

- CAPA is a recognised cause of someone’s condition not improving despite treatment (for example, antibiotic therapy, ventilatory support)
- there are no specific combinations of signs or symptoms for diagnosing CAPA
- the risk of having CAPA may increase with age and chronic lung disease.

**9.2.1 Diagnosing CAPA**

When deciding whether to suspect CAPA in someone who is critically ill and has, or has had, COVID-19 as part of their acute illness:

- base your decisions on individual risk factors and the person’s clinical condition
- involve a multidisciplinary team, including infection specialists
- refer to local protocols on diagnosing and managing CAPA.

Remark:
Local protocols for diagnosing and managing CAPA should be developed with a multidisciplinary team and based on knowledge of local prevalence.

Do not do diagnostic tests for CAPA if there is low clinical suspicion of the condition.
When investigating suspected CAPA:

- use a range of tests to increase the likelihood of making a confident diagnosis
- if possible, include bronchoalveolar lavage (BAL) as part of diagnostic testing, taking into account the risks of BAL in relation to the person’s clinical condition
- discuss the diagnostic testing strategy and final diagnosis with a multidisciplinary team that includes infection specialists.

**Consensus recommendation**

Test for antifungal resistance if an Aspergillus isolate is cultured from a CAPA test sample.

**Consensus recommendation**

Commissioners and local trusts should ensure that results of diagnostic tests for CAPA are available in a timeframe that informs and supports clinical decision making.

**Consensus recommendation**

Monitor and report testing for, and diagnosis and management of, CAPA in line with local protocols.

Remark:
Local protocols for diagnosing and managing CAPA should be developed with a multidisciplinary team and based on knowledge of local prevalence.

### 9.2.2 Treating CAPA

**Consensus recommendation**

Only use antifungal treatments to treat CAPA if:

- diagnostic investigations support a diagnosis of CAPA or
- the results of diagnostic investigations are not available yet, but CAPA is suspected, and a multidisciplinary team or local protocols support starting treatment.

Remark:
See NICE’s recommendations on diagnosing CAPA.
When considering antifungal treatment for CAPA:

- discuss treatment options with a multidisciplinary team that includes infection specialists
- follow local protocols that include best practice guidance on treating invasive aspergillosis.

Remark:
There is not enough evidence to recommend specific antifungal treatments for CAPA.

The panel noted the importance of national antifungal stewardship guidance, such as NICE's guideline on antimicrobial stewardship.

Consensus recommendation

For people having antifungal treatment for suspected CAPA, stop treatment if the results of investigations do not support a diagnosis of CAPA and a multidisciplinary team agrees.

10. Discharge, follow up and rehabilitation

Info Box

For follow up and rehabilitation for people who have either ongoing symptomatic COVID-19 or post-COVID-19 syndrome, see the NICE guideline on the long-term effects of COVID-19.

Be aware of the UK Government’s information on the COVID-19 vaccination programme.

11. Palliative care

11.1 Principles of care

Info Box

For people who are nearing the end of their life, see:

- The NICE guideline on care of dying adults in the last days of life: this includes recommendations on recognising when a person may be in the last days of life, communication and shared decision making.
- The NICE guideline on end of life care for adults: service delivery: this includes recommendations for service providers on systems to help identify adults who may be at the end of their life, providing information and advanced care planning.
- The NICE guideline on care and support of people growing older with learning disabilities: this includes recommendations on accessing end-of-life care services, person-centred care, and involving families and support networks in end-of-life care planning.
- The NICE guideline on end of life care for infants, children and young people with life-limiting conditions: planning and management: this includes recommendations on planning and managing end of life and palliative care for infants, children and young people (aged 0 to 17 years) with life-limiting conditions.

12. Research recommendations
What is the clinical effectiveness and safety of vitamin D for treating COVID-19 in children, young people and adults?

Remark:
Suggested PICO (Population, Intervention, Comparator, Outcome)

P: people with COVID-19, particularly groups for which current evidence is lacking, for example:
- in pregnancy and breastfeeding
- people 65 years and over
- children and young people under 18
- people from minority ethnic family backgrounds
- people with risk factors for severe COVID-19

I: vitamin D (800 IU/day or less and more than 800 IU/day; single or multiple doses)

C:
- standard care
- placebo

O: effectiveness outcomes:
- all-cause hospitalisation
- all-cause mortality
- need for mechanical ventilation
- need for non-invasive respiratory support
- admission to intensive care
- symptom alleviation
- adherence to therapy
- long-term effects of COVID-19 (at least 4 weeks from acute COVID-19 onset)

Safety outcomes:
- any adverse event
- adverse event leading to trial discontinuation
- serious adverse events
What is the effectiveness of awake body positioning in improving outcomes for people in hospital with COVID-19 who are not intubated and have higher oxygen needs?

Remark:
Suggested PICO (Population, Intervention, Comparator, Outcomes)

P: people in hospital with COVID-19 who are not intubated and have higher oxygen needs
I: awake body positioning
C: standard care or a different specified awake body position
O:
• adherence to and compliance with body position (including total duration of awake body positioning and duration of each body positioning session)
• patient reported outcomes including dyspnoea, anxiety, delirium, pain, discomfort, breathlessness, impact on sleep
• mortality
• time to non-invasive respiratory support
• intubation
• length of hospital stay
• admission to intensive care unit
• complications (for example: pneumothorax, pneumomediastinum, delirium, intolerance of positioning or haemodynamic instability)

Subgroups:
• mean duration of body positioning
• people on general wards, and those with do-not-intubate goals of care
• supplemental oxygen type
• adults aged 50 years and older
• children aged 12 years and younger
• disease severity
• sex
• ethnic background
• religion or belief
• deprivation or socioeconomic status
• frailty
• BMI of 30 or higher
• pregnant women (including gestational age)
• people with learning disability or physical disability (or both)
• people who use aids (for example, spectacles, hearing aids)
• comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity)
What is the efficacy and safety of COVID-specific antiviral drugs in combination with other COVID-specific antiviral drugs or COVID-specific neutralising monoclonal antibodies in people who do not need supplemental oxygen and are within 7 days of symptom onset?

Remark:
Suggested PICO (Population, Intervention, Comparator, Outcomes)

P: people with COVID-19 who do not need supplemental oxygen and are within 7 days of symptom onset

- subgroups of particular interest
  - people with at least 1 risk factor for progression to severe COVID-19 disease, including (but not limited to):
    - aged 60 or over
    - immunosuppression
    - obesity
    - hypertension
    - chronic lung disease
    - cardiovascular disease
    - cerebrovascular disease
    - active cancer
  - ethnic minorities
  - pregnant women
  - children and young people aged under 18
  - people who have had different types of vaccines and/or different numbers of vaccine doses
  - people who are at high risk of not mounting an antibody response when vaccinated against COVID-19

I:

- antiviral-antiviral
- antiviral-monoclonal antibodies

C:

- standard care without the combination treatment

O:

- effectiveness outcomes
  - COVID-19 related hospitalisation
  - duration of COVID-19 related hospitalisation
  - all-cause hospitalisation
  - all-cause mortality
  - need for mechanical ventilation
  - need for non-invasive respiratory support
  - ICU admission
  - symptom alleviation
  - adherence to therapy

- safety outcomes
  - any adverse event
  - adverse event leading to trial discontinuation
What are the clinical and cost effectiveness, and the safety, of specific antifungal treatments for treating suspected or confirmed COVID-19-associated pulmonary aspergillosis (CAPA), and the optimal treatment duration? When should treatment be started, stopped or modified?

Remark:
Suggested PICO (Population, Intervention, Comparator, Outcome)

P: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness and have probable or diagnosed CAPA. Subgroups of particular interest: children and young people, pregnant women, ethnicity, immunosuppression, and subgroups who have higher rates of COVID-19.

I: voriconazole, isavuconazole, liposomal amphotericin B, posaconazole, echinocandins (for example, caspofungin, anidulafungin) and amphotericin B deoxycholate

C: Standard care (usually voriconazole)

O: 
- all-cause mortality (at any time during treatment)
- number of people having 1 or more serious adverse events
- number of days without respiratory or organ support (organ support includes use of vasopressors and renal replacement therapy)
- length of stay in intensive care
- number of people having 1 or more adverse events
- treatment duration
- timing of starting treatment
- need for treatment modification
- length of hospital stays
- need for and duration of invasive mechanical ventilation
- need for switching, starting or restarting antifungal treatment

What are the views, preferences and experiences of people with COVID-19-associated pulmonary aspergillosis (CAPA), and their families or carers, on:

- available tests for diagnosing CAPA
- available treatments for CAPA?

Remark:
Suggested PIC (Population, Interest, Context)

P: people who have been diagnosed with and treated for CAPA, and their families or carers. Subgroups of particular interest include young people and children, and pregnant women.

I: tests for diagnosing CAPA and treatments for CAPA

C: people who have been diagnosed with, and had treatment for, CAPA in hospital
In people with suspected COVID-19-associated pulmonary aspergillosis (CAPA), what are the most accurate tests for diagnosing the infection and when should they be done?

Remark:
Suggested research details

Population: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness, and suspected CAPA. Subgroups of particular interest include young people and children, and pregnant women.

Diagnostic tests:
- any methods used to diagnose pulmonary aspergillosis (for example, CT imaging, testing of bronchoalveolar lavage, non-bronchoscopic lavage, endotracheal aspirate, sputum samples, serum assays)

Reference standard:
- lung biopsy or postmortem diagnosis

Target condition:
- CAPA

Outcomes:
- sensitivity and specificity
- positive and negative likelihood ratios

Analysis:
- optimal time of diagnostic testing

What are the possible outcomes for people who are critically ill and have COVID-19-associated pulmonary aspergillosis (CAPA)?

Remark:
Suggested research details

Population: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness, and who have CAPA. Subgroups of particular interest: young people and children, pregnant women, ethnicity, immunosuppression and subgroups who have higher rates of COVID-19

Outcomes:
- presence of fungal serum biomarkers (for example galactomannan and beta-D-glucan)
- measures of inflammation (for example C-reactive protein)
- need for respiratory support (for example, invasive mechanical ventilation or extracorporeal membrane oxygenation [ECMO])
- hospitalisation metrics (for example, mortality, length of hospital stay, admission to and length of stay in intensive care)
- long-term morbidity outcomes, functional measures and patient outcomes
- results may be stratified (for example, disease severity, use of ECMO)
What risk factors in people who are critically ill and have, or have had, COVID-19 as part of their acute illness are associated with developing COVID-19-associated pulmonary aspergillosis (CAPA)?

Remark:
Suggested research details

Population: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness. Subgroups of particular interest include children and young people, and pregnant women.

Exposure: any

Outcomes:
- association of CAPA with individual factors (for example, age, sex, ethnicity, comorbidities, COVID-19 vaccination status,)
- association of CAPA with COVID-19 treatments (for example, respiratory support for COVID-19, high-dose corticosteroids, interleukin-6 inhibition)
- association of CAPA with length of stay in hospital

What is the clinical and cost effectiveness of budesonide for treating COVID-19 in the community in adults, young people and children?

Remark:
Suggested PICO (Population, Intervention, Comparator, Outcome)

P: Adults, young people and children who have COVID-19 and are not in hospital

Subgroups of particular interest:
- People 18 to 49 years
- Children and young people

I: Inhaled budesonide

C: Inhaled placebo (to accommodate blinding)

O:
- All-cause mortality
- Hospitalisation
- Need for oxygen therapy (including thresholds for this decision)
- Costs of treatment
- Time to recovery
- Health-related quality of life
- Adverse events
Does a multidisciplinary team agreed approach to weaning from continuous positive airway pressure improve weaning times and result in stopping continuous positive airway pressure for people with COVID-19 and acute respiratory failure?

Remark:
Suggested PICO (Population, Intervention, Comparator, Outcome)

P: people with COVID-19 having continuous positive airway pressure for respiratory support

I: multidisciplinary team agreed approach to weaning

C:
- standard care
- different multidisciplinary team approaches

O:
- patient experience
- symptom improvement
- length of time to wean

Is high-flow nasal oxygen effective in reducing breathlessness compared with standard care or conventional oxygen therapy for people in hospital with COVID-19 and respiratory failure when it is agreed that treatment will not be escalated beyond non-invasive respiratory support or palliative care is needed?

Remark:
Suggested PICO (Population, Intervention, Comparator, Outcome)

P: adults over 18 years with COVID-19 having treatment for respiratory failure

I: high-flow nasal oxygen

C:
- standard care
- conventional oxygen therapy

O:
- patient experience
- symptom improvement
- frequency of coughing
- assessment of breathing pattern disorder
- impact of breathlessness on activities of daily living such as eating, drinking and movement
- recovery of sense of smell
- practicalities of maintaining high-flow nasal oxygen at home for patients who wish their end of life care to occur at home.

Subgroups: palliative care
Does early review and referral to specialist palliative care services improve outcomes for adults with COVID-19 thought to be approaching the end of their life?

Remark: Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients with a confirmed diagnosis of COVID-19 in hospital or community approaching the last days of life

I: early referral to specialist palliative care services (for example, in the last days of life)

C: late referral (for example, within the final day of life) or no referral

O:
   • quality of life
   • changes to clinical care
   • patient or carer satisfaction (feeling supported)
   • identification and/or achievement of patient wishes such as preferred place of death

What is the effectiveness and safety of a treatment dose with a low molecular weight heparin (LMWHs) compared with a standard prophylactic dose for venous thromboembolism (VTE) prophylaxis in young people under 18 years with COVID-19?

Remark: Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients 18 years and under who have COVID-19 pneumonia

I: treatment-dose LMWH

C: standard prophylaxis with LMWH

O:
   • incidence of VTE
   • mortality (all-cause, inpatient, COVID-19 related)
   • admission to critical care (including use of advanced organ support)
   • serious adverse events such as major bleeding or admission to hospital

What is the effectiveness and safety of extended pharmacological venous thromboembolism (VTE) prophylaxis for people who have been discharged after treatment for COVID-19?

Remark: Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients 16 years and over who have been discharged after treatment for COVID-19 pneumonia

I: extended (2 to 6 weeks) pharmacological VTE prophylaxis with standard-dose:
   • low molecular weight heparins
   • unfractionated heparins
   • fondaparinux sodium
   • direct-acting anticoagulant
   • vitamin K antagonists

C: No extended pharmacological VTE prophylaxis

O:
   • incidence of VTE
   • mortality (all-cause, inpatient, COVID-19 related)
   • serious adverse events such as major bleeding or admission to hospital
What is the effectiveness and safety of standard-dose compared with intermediate-dose pharmacological venous thromboembolism (VTE) prophylaxis for people with COVID-19, with or without additional risk factors for VTE?

Remark: Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients 16 years and over being treated for COVID-19 pneumonia in hospital or the community who have:

- no additional risk factors for VTE
- additional risk factors for VTE

I: intermediate dose:

- low molecular weight heparins (LMWH)
- unfractionated heparin (UFH)
- fondaparinux sodium
- direct-acting anticoagulant
- vitamin K antagonists

C: Standard-dose:

- LMWH
- UFH
- fondaparinux sodium
- direct-acting anticoagulants
- vitamin K antagonists
- antiplatelets

O:

- incidence of VTE
- mortality (all-cause, inpatient, COVID-19 related)
- admission to critical care (including use of advanced organ support)
- serious adverse events such as major bleeding or admission to hospital

13. Equality considerations

13.1 Equalities impact assessment during scoping - draft scope

13.2 Equalities impact assessment during scoping - final scope

13.3 Equalities impact assessment during guideline development

14. Methods and processes
1. How to use this guideline

In response to the COVID-19 pandemic, NICE produced multiple rapid guidelines to support the health and social care system. We know that having different products can make it difficult for people trying to find guidance, so we have brought together NICE's published recommendations on managing COVID-19 into this single guideline. We hope users will find the content easier to find and use.

Many of the recommendations made early in the pandemic were based on the consensus of the guideline expert panels, so supporting information is limited. We have reviewed all content, using topic expert input and more recent evidence, and updated the recommendations where needed.

We aim to update these recommendations frequently in line with new evidence and will produce new recommendations where gaps are identified. We search and sift the evidence weekly to produce living recommendations that reflect the latest best available evidence.

We have developed this guideline using our methods and processes for guidelines developed during health and social care emergencies. For more details of the methods and processes used for this guideline, including details of the expert advisory panel members, see the methods and processes section.

Using the guideline in MAGICapp
The guideline consists of 2 layers: recommendations and supporting information.

1. Recommendations

Recommendation for (Green)

A strong recommendation is given when there is high-certainty evidence, or lower-certainty evidence paired with consistent panel expertise, 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, or lower-certainty evidence paired with important contextual factors, showing that the overall disadvantages of the intervention are clearly greater than the benefits, or that the intervention is not effective. 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 intervention may not be effective, but certainty is low. This recommendation is also used where the intervention is not likely to be effective, but it may be useful in specific settings or populations. Likewise, it is also used when patient preferences vary.

Only in research settings

A recommendation only for research settings is given where there is significant uncertainty about the effectiveness of an intervention, and it is not clear whether the benefits of the intervention are greater than the disadvantages or
adverse effects.

**Consensus Recommendation (Bluish-Purple)**

A consensus recommendation can be given for or against an intervention, or may outline good practice or steps required to support other recommendations. 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. As stated, supporting information is limited for recommendations created early in the pandemic. Additional information will be added as recommendations are updated in light of new evidence.

Recommendations will have supporting information in some or all of the following areas:

- **Research evidence:** The overall effect estimates and references to the studies.
- **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 statistically significantly different.
  - **Low:** We have limited confidence in the estimated effect. The true effect may be statistically significantly different from the estimated effect.
  - **Very low:** We have very little confidence in the estimated effect. The true effect is likely to be statistically significantly different from the 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 panel reached its decision.
- **Practical information:** Practical information about the treatment and information on any special patient considerations.
- **Adaption:** If a recommendation has been adapted from another guideline, this will provide further details.
- **Feedback:** If you are logged in as a user, you can use the 'Feedback' option to comment on specific recommendations.
- **References:** Reference list for the recommendation.
2. Introduction

Scope and purpose
This guideline is for health and care practitioners, and those involved in planning and delivering services. It provides guidance on managing COVID-19. The guideline makes recommendations about care in all settings for adults, children and young people with clinically diagnosed or laboratory-confirmed COVID-19.

Key questions
This section lists the key questions that the guideline addresses. These are a broad set of overarching review questions. Through our living approach, we will review the scope, and develop more specific review questions to address gaps in content and, where needed, additional review questions.

• What investigations should be carried out, and when, to determine the appropriate management of COVID-19 and any complications?
• What is the clinical effectiveness and safety of pharmacological and non-pharmacological treatments for acute symptoms and complications of COVID-19?
• How should symptoms and complications be managed?
• How, and how often, should people with COVID-19 be followed up?
• What palliative and end-of-life strategies are effective for people with COVID-19?

Areas to be excluded
The following areas are outside of the scope of this guideline and we will not look at evidence in these areas:

• procuring and distributing medicines and technologies, including vaccines
• procuring, distributing and using personal protective equipment
• procuring and distributing COVID-19 tests
• frequency of staff testing for COVID-19.

Acknowledgement
This work was done by NICE. The views expressed in this publication are those of the authors. We collaborated with the Australian National COVID-19 Clinical Evidence Taskforce based at Cochrane Australia, in the School of Population Health and Preventive Medicine at Monash University, to ensure appropriate development of the guideline, and acknowledge their contribution to identifying and reviewing the evidence for therapeutics.
3. Definition of disease severity

COVID-19 disease severity definitions are outlined in the World Health Organization's COVID-19 clinical management living guidance.
4. Communication and shared decision making

Consensus recommendation

Communicate with people with COVID-19, and their families and carers, and support their mental wellbeing to help alleviate any anxiety and fear they may have. Signpost to charities and support groups (including NHS Volunteer Responders), to NHS every mind matters and to Royal College of Paediatrics and Child Health resources for parents and carers.

Give people information in a way that they can use and understand, to help them take part in decisions about their care. Follow relevant national guidance on communication, providing information (including in different formats and languages) and shared decision making, for example, NICE’s guideline on shared decision making and NICE’s guideline on patient experience in adult NHS services.

The Royal College of Obstetricians and Gynaecologists has produced information on COVID-19 and pregnancy for pregnant women and their families.

Consensus recommendation

Explain to people with COVID-19, and their families, carers and close contacts that they should follow the UK Heath Security Agency’s guidance for people with symptoms of a respiratory infection including COVID-19.

Consensus recommendation

For carers of people with COVID-19 who should isolate but are unable to (for example, some people with dementia), signpost to relevant support and resources.

For example, the Alzheimer’s Society has information on staying safe from coronavirus and reducing the risk of infection.

Consensus recommendation

When possible, discuss the risks, benefits and possible likely outcomes of the treatment options with people with COVID-19, and their families and carers. Use decision support tools (when available).
5. Assessment

5.1 In the community
5.1.1 Identifying severe COVID-19

Consensus recommendation

Use the following signs and symptoms to help identify people with COVID-19 with the most severe illness:

- severe shortness of breath at rest or difficulty breathing
- reduced oxygen saturation levels measured by pulse oximetry (see the recommendation on pulse oximetry levels that indicate serious illness)
- coughing up blood
- blue lips or face
- feeling cold and clammy with pale or mottled skin
- collapse or fainting (syncope)
- new confusion
- becoming difficult to rouse
- reduced urine output.

For signs and symptoms to help identify paediatric inflammatory multisystem syndrome (PIMS) temporarily associated with COVID-19, see the guidance on PIMS from the Royal College of Paediatrics and Child Health.

Consensus recommendation

When pulse oximetry is available in primary and community care settings, to assess the severity of illness and detect early deterioration, use:

- NHS England’s guide to pulse oximetry in people 18 years and over with COVID-19
- oxygen saturation levels below 91% in room air at rest in children and young people (17 years and under) with COVID-19.

Be aware that some pulse oximeters can underestimate or overestimate oxygen saturation levels, especially if the saturation level is borderline. Overestimation has been reported in people with dark skin. For more information about this, see NHS England’s guide on how to look after yourself at home if you have COVID-19 or symptoms of COVID-19.

For information on pulse oximetry at home, see NHS England’s COVID oximetry @home service.

Rationale

This recommendation is based on the expert panel’s consensus view. The panel agreed that using pulse oximetry to measure oxygen saturation threshold levels is appropriate for helping to identify people with acute COVID-19 in primary or community care, and to predict outcomes such as hospitalisation. NHS England has guidance on pulse oximetry in assessment in adults in the community. The panel agreed that it is appropriate to cross-refer to this guidance for adults but not for children. The panel’s recommended oxygen saturation level for children and young people was based on their consensus view that oxygen saturation levels below 91% in room air at rest are appropriate to assess the severity of illness and detect early deterioration in this group.
5.1.2 Care planning

Consensus recommendation

Discuss with people with COVID-19, and their families and carers, the benefits and risks of hospital admission or other acute care delivery services (for example, virtual wards or hospital at home teams).

Some benefits and risks may be similar for all patients (for example, improved diagnostic tests and access to treatments, or better contact with families in the community), but others may be personal to the individual (such as loss of access to carers who can anticipate needs well in someone unable to communicate themselves, or risks of spreading COVID-19).

Consensus recommendation

Explain that people with COVID-19 may deteriorate rapidly. Discuss future care preferences at the first assessment to give people who do not have existing advance care plans an opportunity to express their preferences.

5.2 In hospital
Consensus recommendation

When a person is admitted to hospital with COVID-19, ensure a holistic assessment is done, including discussion about their treatment expectations and care goals:

- Document and assess the stability of underlying health conditions, involving relevant specialists as needed.
- Use the Clinical Frailty Scale (CFS) when appropriate, available from the NHS Specialised Clinical Frailty Network, to assess baseline health and inform discussions on treatment expectations.
- Use the CFS within an individualised assessment of frailty.
- Do not use the CFS for younger people, people with stable long-term disabilities (for example, cerebral palsy), learning disabilities or autism. Make an individualised assessment of frailty in these people, using clinical assessment and alternative scoring methods.
- Record the assessment and discussion in the person’s medical records.

For assessment of paediatric inflammatory multisystem syndrome (PIMS), follow the guidance on PIMS from the Royal College of Paediatrics and Child Health.

Consensus recommendation

When making decisions about the care of children and young people under 18 years, people with learning disabilities or adults who lack mental capacity for health decision making, for example, people with advanced dementia, see the NICE guideline on decision-making and mental capacity.

Ensure discussions on significant care interventions involve families and carers as appropriate, and local experts or advocates.
6. Management

6.1 In the community

6.1.1 Care planning

**Consensus recommendation**

In the community, consider the risks and benefits of face-to-face and remote care for each person. Where the risks of face-to-face care outweigh the benefits, remote care can be optimised by:

- offering telephone or video consultations (see BMJ guidance on Covid-19: a remote assessment in primary care for a useful guide, including a visual summary for remote consultation)
- cutting non-essential face-to-face follow up
- using electronic prescriptions rather than paper
- using different methods to deliver medicines to people, for example, pharmacy deliveries, postal services and NHS volunteers, or introducing drive-through pick-up points for medicines.

**Consensus recommendation**

Put treatment escalation plans in place in the community after sensitively discussing treatment expectations and care goals with people with COVID-19, and their families and carers.

*People with COVID-19 may deteriorate rapidly. If it is agreed that the next step is a move to secondary care, ensure that they and their families understand how to access this with the urgency needed. If the next step is other community-based support (whether virtual wards, hospital at home services or palliative care), ensure that they and their families understand how to access these services, both in and out of hours.*

6.1.2 Managing cough

**Consensus recommendation**

Encourage people with cough to avoid lying on their backs, if possible, because this may make coughing less effective.

*Be aware that older people or those with comorbidities, frailty, impaired immunity or a reduced ability to cough and clear secretions are more likely to develop severe pneumonia. This could lead to respiratory failure and death.*

**Consensus recommendation**

For guidance on managing acute cough, see the [NICE guideline on cough (acute): antimicrobial prescribing](https://www.nice.org.uk/guidance/cg211).
6.1.4 Managing breathlessness

Consensus recommendation

Advise people with COVID-19 and fever to drink fluids regularly to avoid dehydration. Support their families and carers to help when appropriate. Communicate that fluid intake needs can be higher than usual because of fever.

Consensus recommendation

Advise people to take paracetamol or ibuprofen if they have fever and other symptoms that antipyretics would help treat. Tell them to continue only while both the symptoms of fever and the other symptoms are present.

People can take paracetamol or ibuprofen when self-medicating for symptoms of COVID-19, such as fever (see the Central Alerting System: novel coronavirus - anti-inflammatory medications for further details of ibuprofen including dosage).

For people 18 years and over, the paracetamol dosage is 1 g orally every 4 to 6 hours (maximum 4 g per day). See the BNF and Medicines and Healthcare products Regulatory Agency advice for appropriate use and dosage in specific adult populations.

For children and young people over 1 month and under 18 years, see the dosing information on the pack or the BNF for children.

Rectal paracetamol, if available, can be used as an alternative. For rectal dosage information, see the BNF and BNF for children.

Consensus recommendation

Identify and treat reversible causes of breathlessness, for example, pulmonary oedema, pulmonary embolism, chronic obstructive pulmonary disorder and asthma.

For further information on identifying and managing pulmonary embolism, see the NICE guideline on venous thromboembolic diseases: diagnosis, management and thrombophilia testing.

Consensus recommendation

When significant medical pathology has been excluded or further investigation is inappropriate, the following may help to manage breathlessness as part of supportive care:

- keeping the room cool
- encouraging relaxation and breathing techniques, and changing body positioning
- encouraging people who are self-isolating alone to improve air circulation by opening a window or door.

If hypoxia is the likely cause of breathlessness:

- consider a trial of oxygen therapy
- discuss with the person, their family or carer possible transfer to and evaluation in secondary care.

Breathlessness with or without hypoxia often causes anxiety, which can then increase breathlessness further.
6.1.5 Managing anxiety, delirium and agitation

Consensus recommendation

Assess reversible causes of delirium. See the NICE guideline on delirium: prevention, diagnosis and management.

Consensus recommendation

Address reversible causes of anxiety by:

- exploring the person’s concerns and anxieties
- explaining to people providing care how they can help.

6.1.6 Managing medicines

Consensus recommendation

When supporting people with symptoms of COVID-19 who are having care in the community delivered by social care, follow the NICE guideline on managing medicines for adults receiving social care in the community. This includes processes for ordering and supplying medicines, and transporting, storing and disposing of medicines.

Consensus recommendation

When prescribing, handling, administering and disposing of medicines in care homes and hospices, follow the NICE guideline on managing medicines in care homes.

6.2 In hospital

6.2.1 Deciding when to escalate treatment

Consensus recommendation

Base decisions about escalating treatment within the hospital on the likelihood of a person’s recovery. Take into account their treatment expectations, goals of care and the likelihood that they will recover to an outcome that is acceptable to them.

For support with decision making, see:

- advice on ethics from the British Medical Association
- ethical guidance from the Royal College of Physicians
- national guidance presented by the Faculty of Intensive Care Medicine, Intensive Care Society, Association of Anaesthetists and Royal College of Anaesthetists
- advice on decision making under pandemic conditions by the Intensive Care Society, and
- advice on decision making and consent from the General Medical Council
Consensus recommendation

Ensure healthcare professionals have access to resources to support discussions about treatment plans (see, for example, decision-making for escalation of treatment and referring for critical care support, and an example decision support form).

Tools such as the British Medical Journal emergency care and resuscitation plan may be useful when making decisions about a treatment plan.

Consensus recommendation

Discuss treatment escalation with a multidisciplinary team of medical and allied health professional colleagues (such as from critical care, respiratory medicine, geriatric medicine and palliative care) when there is uncertainty about treatment escalation decisions.

Consensus recommendation

Document referral to and advice from critical care services and respiratory support units in a standard format. When telephone advice from critical care or respiratory support units is appropriate, this should still be documented in a standard format (see an example of a tool for documentation).

6.2.2 Escalating and de-escalating treatment

Consensus recommendation

Before escalating respiratory or other organ support, identify agreed treatment goals with the person (if possible), and their family and carers, or an independent mental capacity advocate (if appropriate). Start all advanced respiratory support or organ support with a clear plan of how it will address the diagnosis and lead to agreed treatment goals (outcomes). Ensure this includes management plans for when there is further deterioration or no response to treatment.

Do not continue respiratory or other organ support if it is considered that it will no longer result in the desired overall goals (outcomes). Record the decision and the discussion with the person (if possible), and their family and carers, or an independent mental capacity advocate (if appropriate).

6.2.3 Delivering services in critical care and respiratory support units
Consensus recommendation

Trusts should review:

- their strategy on management for people who are deteriorating and
- use of the track-and-trigger system (NEWS2 has been endorsed by NHS England and Improvement).

See the NICE guideline on acutely ill adults in hospital for recommendations on identifying patients whose clinical condition is deteriorating or is at risk of deterioration.

See the *Royal College of Physician's information on the place of NEWS2 in managing patients with COVID-19*.

### 6.2.4 Non-invasive respiratory support

**Info Box**

**Definitions**

**High-flow nasal oxygen (HFNO):** involves the delivery of warm and humidified oxygen (up to 70 litres per minute) through small nasal cannulae. The delivered gas flow is equal to or higher than the flow of air when the person is breathing in (inspiratory flow). This means that HFNO can deliver a higher and more stable concentration of inspired oxygen than conventional oxygen alone with nasal prongs. The higher flow also increases carbon dioxide washout in the upper airways and improves carbon dioxide clearance. Unlike continuous positive airway pressure (CPAP), any positive pressure provided by HFNO is not measurable or sizeable.

**Continuous positive airway pressure (CPAP):** is a type of non-invasive positive airway pressure that delivers a set pressure of airflow to the airways. This pressure is maintained throughout the respiratory cycle, both when the person is breathing in (inspiration) and breathing out (expiration). A CPAP device consists of a unit that generates airflow, which is delivered to the airway through a tight-fitting mask or other airtight interface.

**Non-invasive ventilation (NIV):** refers to a mode of positive pressure ventilation that delivers airflow to the airways through a tight-fitting mask or other airtight interface. Airflow is delivered at variable pressures that are higher when the person is breathing in (inspiratory pressure) and lower than when the person is breathing out (expiratory pressure). NIV differs from CPAP by providing additional inspiratory pressure assistance. Most devices have an option of adding positive expiratory airway pressure that can fulfil a similar role to CPAP by maintaining a positive pressure in the airways to aid lung recruitment (opening of the airways).

**Non-invasive respiratory support:** is a broad umbrella term for different types of respiratory support given through external interfaces, and includes HFNO, CPAP and NIV. These are more intensive interventions than conventional oxygen therapy alone. The different types of support are not, however, interchangeable because they have differing effects on a person’s respiratory and cardiac physiology. So, they typically have different indications for their use.

**Invasive mechanical ventilation:** any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the Intensive Care National Audit & Research Centre definition of ‘advanced respiratory support’.
Evidence to decision

Info Box

For information on deciding when to escalate and de-escalate treatment, see the sections on deciding when to escalate treatment and escalating and de-escalating treatment. Also, consider factors such as:

- how much supplemental oxygen is needed to reach target oxygen saturation
- the person’s overall clinical trajectory
- the person’s effort of breathing (inspiratory effort and respiratory rate)
- whether the person needs relief of the sensation of breathlessness
- how well the person has tolerated treatments so far
- treatment preferences after discussion with the person, and their family and carers (when appropriate).

The Royal College of Obstetricians and Gynaecologists has produced information on management of coronavirus infection in pregnancy.

The Royal College of Paediatrics and Child Health has produced information on management of coronavirus infection in children.

Info Box

For information on how to manage COVID-19 in people who are having non-invasive respiratory support, see the sections on management and therapeutics for COVID-19.

Consensus recommendation

Optimise pharmacological and non-pharmacological management strategies in people who need non-invasive respiratory support.

The British Thoracic Society and Intensive Care Society have produced information on management of acute respiratory hypoxaemia associated with COVID-19.

The Royal College of Obstetricians and Gynaecologists has produced information on management of coronavirus infection in pregnancy.

Evidence to decision

Benefits and harms

No evidence on optimising medical management in people who need non-invasive respiratory support was identified in the evidence review. Based on clinical experience, the panel made a consensus recommendation to ensure that medical management (including pharmacological and non-pharmacological treatment) is optimised in people who need non-invasive respiratory support.

Certainty of the Evidence

No evidence on optimising medical management was identified in the evidence review, but the panel still regarded it as important to give a recommendation by consensus because of the need to optimise
Rationale

Based on their experience, the panel concluded that to improve outcomes for patients it was important to ensure that existing management is optimised for people who need escalation of respiratory support.

Evidence to decision

management to improve outcomes of people with COVID-19 who need non-invasive respiratory support.

Values and preferences

The panel agreed that pharmacological and non-pharmacological management strategies need to be optimised for people who need non-invasive respiratory support. It is likely that this would be of similar importance to patients.

Resources

Resource use was not assessed as part of the evidence review.

Rationale

Consider awake prone positioning for people in hospital with COVID-19 who are not intubated and have higher oxygen needs. Discuss this with the person to reach a shared decision on whether to try the position.

Factors to consider when trying awake prone positioning may include:

- whether the person has any contraindications to prone positioning (for example, communication difficulties that affect their ability to try the position, respiratory distress, potential need for invasive ventilation, untreated pneumothorax, or recent abdominal, thoracic, facial, pelvic or spinal injury)
- availability of support from healthcare professionals with skills and experience in prone positioning
- allowing a suitable duration to measure response to prone positioning (for example, by monitoring oxygen saturation, need for supplemental oxygen, respiratory rate, sensation of breathlessness)
- ensuring regular review and continuous monitoring (for example, oxygen saturation level)
- how well the person can tolerate prone positioning and the importance of breaks
- stopping prone positioning if it causes excessive discomfort (including pressure damage, or pins and needles or numbness in the upper limbs), or there is worsening hypoxia or excessive breathlessness.

The British Thoracic Society and Intensive Care Society have produced information on management of acute respiratory hypoxaemia associated with COVID-19.

The Intensive Care Society has produced information on conscious prone positioning for people with COVID-19.

The Royal College of Obstetricians and Gynaecologists has produced information on management of coronavirus infection in pregnancy, including body positioning.

Follow relevant national guidance on communication, providing information (including in different formats and languages) and shared decision making, for example, NICE’s guideline on shared decision making.

Evidence to decision

Benefits and harms

The panel discussed the evidence from the 7 included studies on awake prone positioning in non-
intubated people in hospital with COVID-19 and higher oxygen requirements.

They agreed that the available studies showed that awake prone positioning reduced intubation rates and increased the median time to intubation compared with standard care but that there were no benefits in the other outcomes studied.

The evidence did not show increased harms overall from awake prone positioning compared with standard care. However, the panel noted that there was a lack of patient-reported outcome measures in the trials.

The panel were aware that longer duration of prone positioning sessions may result in clinical benefits.

The panel noted that no studies were from the UK and that available details on ethnicity were limited in the trials. The low adherence and variability in the duration of proning sessions within and between trials were also commented upon. The reported details available in the trials for standard care, for example body positioning, and on patient preferences were limited. The panel were aware that the largest available trial (Ehrmann et al. 2021) was in people mostly in intensive care, intermediate care, or the emergency department who were receiving high-flow nasal oxygen. The panel considered it uncertain whether the findings from the evidence would be generalisable to a general ward setting.

The panel agreed that more research is needed to guide treatment and made a research recommendation for trials done in the UK with a focus on patient-reported outcomes.

**Certainty of the Evidence**

The panel noted that the certainty of evidence was low to very low for all outcomes. Reasons for downgrading evidence included risk of bias (with all studies rated at high risk of bias for reasons that included a lack of blinding and issues with protocol adherence) and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome).

The study by Fralick et al (2021) was only available as a preprint and so had not been peer reviewed.

**Values and preferences**

The panel noted that the available evidence showed benefits from awake prone positioning in reducing intubation rates. It is likely that this outcome would be of similar importance to patients.

**Resources and other considerations**

**Resources**

Some people may need support from healthcare professionals to move in and out of a prone position. It was noted that early prone positioning and longer duration of prone positioning sessions may be beneficial but that there should be appropriate observation and monitoring for safety during prone positioning. The panel commented that the need for healthcare professionals to provide additional support for prone positioning could divert them away from other clinical activities. It was also noted that some people who self prone may not respond and others may deteriorate and so usual resources,
including access to escalation (for example, to higher levels of respiratory support including urgent intubation) should be available for people who are considered for escalation.

The panel also noted that some people may find it physically uncomfortable to be in a prone position (for example, people with recent abdominal wounds) and may require additional pillows to be available to provide support. Some people may prefer an alternative position such as lateral (side) lying or sitting out in a chair.

Cost effectiveness was not assessed as part of this evidence review.

**Equity**

All trials were in adults (except for the trial by Fralick et al. 2021 that did not state whether children were eligible). Although there are no sufficient data on awake prone positioning in children with COVID-19, it was noted that there is evidence of benefit in other causes of acute respiratory distress syndrome.

Pregnant women were excluded in the trials (except for 2 trials [Fralick et al. 2021 and Taylor et al. 2021] where it was not reported whether pregnant women were excluded). The recommendation includes a link to information on body positioning provided by the Royal College of Obstetricians and Gynaecologists.

Some people may not be able to physically move into and out of a prone position by themselves especially when ill. This could include people with mobility issues, chronic disabilities, learning disabilities, attention deficit disorder, people who are very underweight or morbidly obese (BMI > 40), or people with cognitive impairment. If proning was considered suitable, these people would require the availability of healthcare professionals to support them in moving in and out of a prone position.

The panel did not raise any additional concerns.

**Acceptability**

The panel commented that the ability of people with COVID-19 to move into and out of a prone position is likely to vary. They discussed that prone positioning may not be suitable for some people and some may prefer alternative body positioning, for example right and left side lying or being seated in a chair. The panel noted the issues with adherence to prone positioning in the trials and that there was some evidence of mild position-related discomfort from awake prone positioning.

The panel also commented on the need for published trials to include patient-reported outcomes (such as anxiety and breathlessness) and included this in a research recommendation.

**Feasibility**

The panel noted that how well people can tolerate prone positioning and how long they can be in a prone position can vary. Some people may require the availability of additional support from healthcare professionals to move into and out of a prone position. Some may find it uncomfortable to remain in a prone position for an extended length of time. Different physical modalities of non-invasive respiratory support and the position of intravenous cannulae or other lines may also affect comfort, adverse events, and the ability to be in a prone position.

**Rationale**

Evidence shows that, for people in hospital with COVID-19 who are not intubated and have higher oxygen needs, awake prone positioning reduces the need for intubation compared with standard care. There is no evidence showing that awake prone positioning improves other outcomes compared with standard
care. Although evidence is limited and of low to very low certainty, the panel agreed that awake prone positioning may be beneficial for this population.

The panel noted that awake prone positioning may not be suitable for everyone and some people may find it difficult or uncomfortable to be in a prone position. They emphasised the importance of involving the person in decisions to try awake prone positioning.

**Clinical question/ PICO**

**Population:** Hospitalised adults with COVID-19 (non-intubated with higher oxygen requirements)

**Intervention:** Awake prone positioning

**Comparator:** Standard care

**Summary**

Awake prone positioning reduced the need for intubation and increased time to intubation in people in hospital with COVID-19 compared with standard care. No other benefits in outcomes from awake prone positioning were observed compared with standard care.

**What is the evidence informing this conclusion?**

Evidence comes from 1 meta-trial of 6 RCTs (Ehrmann et al. 2021), 2 cluster RCTs (Kharat et al., 2021; Taylor et al. 2021), 3 individually randomised RCTs (Fralick et al. 2021; Jayakumar et al. 2021; Rosen et al. 2021) and 1 post hoc analysis of an RCT included in the meta-trial (Kaur et al. 2021).

The numbers of people included in the trials ranged from 27 (Kharat et al. 2021) to 1,121 (Ehrmann et al. 2021).

The trials were conducted in hospitals, with 1 study based in intensive care (Jayakumar et al. 2021). In the Ehrmann et al. trial only 5% of people were in general wards at enrolment (with 95% in ICU/intermediate care/emergency department). Just under half (47%) of people were based in ICU in the study by Rosen et al. (2021).

No studies were UK-based. Studies were based in Canada, France, Ireland, Mexico, USA, Spain (Ehrmann et al. 2021), Canada and USA (Fralick et al. 2021), India (Jayakumar et al. 2021), Switzerland (Kharat et al. 2021), Sweden (Rosen et al. 2021), and the USA (Taylor et al. 2021).

All studies compared prone positioning with standard care.

**Publication status**

One study was only available as a preprint (Fralick et al., 2021 (COVID-PRONE), posted to medRxiv on November 8 2021) and therefore has not been peer-reviewed.

**Study characteristics**

The average age of people included in the trials ranged from 54 years (Kharat et al. 2021, intervention group) to 66 years (Rosen et al. 2021, intervention group). People included in the trials were mostly males. Children and pregnant women were excluded (with the exception of Fralick et al. 2021 that did not explicitly state that children were excluded and Fralick et al. 2021 and Taylor et al. 2021, where it was not reported whether pregnant women were excluded).

The amount of time people were able to be in the awake prone position varied between and within the included studies.

The types of oxygen support used also varied between the included studies.
For further details see the evidence review.

**What are the main results?**

There was a significant reduction in the number of people requiring intubation and increase in the time to intubation for people who were in the awake prone positioning group compared with standard care.

No significant differences were seen in people who were in the awake prone position compared with standard care in mortality, time to death, intubation within 30 days after enrolment, time from enrolment to invasive mechanical ventilation, ventilator-free days, mechanical ventilation (intubation or bilevel positive airway pressure), use of non-invasive ventilation, time from enrolment to non-invasive ventilation, hospital length of stay, ICU admission, ICU length of stay, or all types of adverse events combined.

A post hoc analysis (Kaur et al. 2021) of 1 of the RCTs included in the meta-trial by Ehrmann et al. 2021 indicated that early awake prone positioning (within 24 hours of high flow nasal cannula initiation) reduced mortality but not intubation or other outcomes compared with later awake prone positioning.

**Our confidence in the results**

All studies were rated at high risk of bias. The certainty of evidence ranged from low to very low. All outcomes were downgraded for risk of bias. Most studies were downgraded at least once for imprecision.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of Evidence</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td>Relative risk 0.9 (CI 95% 0.73 — 1.12)</td>
<td>Standard care</td>
<td>Awake prone positioning</td>
<td>Very low</td>
<td>4 studies showed no significant difference in mortality for awake prone positioning compared with control.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Based on data from 1,504 participants in 4 studies.</td>
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<td>Due to serious imprecision, Due to very serious risk of bias ²</td>
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<td>Difference:</td>
<td>166 per 1000</td>
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<td>18 fewer per 1000</td>
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<td>(CI 95% 50 fewer — 22 more)</td>
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<td>18 fewer per 1000</td>
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<tr>
<td><strong>Intubation</strong></td>
<td></td>
<td>Relative risk 0.83 (CI 95% 0.71 — 0.97)</td>
<td>Standard care</td>
<td>Awake prone positioning</td>
<td>Low</td>
<td>3 studies showed a statistically significant reduction in intubation for awake prone positioning compared with control.</td>
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<td></td>
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<td>Based on data from 1,256 participants in 3 studies.</td>
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<td>Due to very serious risk of bias ⁴</td>
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<td>383 per 1000</td>
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<td>Difference:</td>
<td>318 per 1000</td>
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<td>65 fewer per 1000</td>
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<td>(CI 95% 111 fewer — 11 fewer )</td>
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<tr>
<td><strong>Mechanical ventilation</strong> (intubation or)</td>
<td></td>
<td>Relative risk 1.16 (CI 95% 0.36 — 3.71)</td>
<td>Standard care</td>
<td>Awake prone positioning</td>
<td>Very low</td>
<td>1 study showed no significant difference in mechanical ventilation (intubation or bilevel</td>
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<tr>
<td></td>
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<td>Based on data from 248 participants in 1 studies.</td>
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<td>Due to very serious imprecision, Due</td>
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<td>41 per 1000</td>
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<td>48 per 1000</td>
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<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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<tr>
<td>Bilevel positive airway pressure</td>
<td>5 (Randomized controlled)</td>
<td>Difference: 7 more per 1000 (CI 95% 26 fewer — 111 more)</td>
<td>Standard care</td>
<td>Awake prone positioning</td>
<td>Very low due to serious risk of bias</td>
<td>Positive airway pressure) for awake prone positioning compared with control.</td>
</tr>
<tr>
<td>Use of non-invasive ventilation</td>
<td>Relative risk 0.87 (CI 95% 0.66 — 1.15) 3 studies. 1 (Randomized controlled)</td>
<td>Relative risk 0.87 per 1000 220 (CI 95% 29 fewer — 33 more)</td>
<td>Standard care</td>
<td>191 per 1000</td>
<td>Very low due to serious imprecision, Due to very serious risk of bias 8</td>
<td>3 studies showed no significant difference in use of NIV for awake prone positioning compared with control.</td>
</tr>
<tr>
<td>ICU admission required within 48 hours</td>
<td>Relative risk 0.88 (CI 95% 0.21 — 3.72) 23 participants in 1 studies. 9 (Randomized controlled)</td>
<td>Relative risk 1.04 per 1000 286 (CI 95% 34 fewer — 33 more)</td>
<td>Standard care</td>
<td>252 per 1000</td>
<td>Very low due to very serious risk of bias</td>
<td>1 study showed no significant difference in ICU admission required within 48 hours for awake prone positioning compared with control.</td>
</tr>
<tr>
<td>ICU admission during hospitalisation</td>
<td>Relative risk 1.04 (CI 95% 0.77 — 1.41) 98 participants in 2 studies. 11 (Randomized controlled)</td>
<td>Relative risk 1.04 per 1000 652 (CI 95% 26 more — 267 more)</td>
<td>Standard care</td>
<td>678 per 1000</td>
<td>Very low due to very serious imprecision, Due to very serious risk of bias 10</td>
<td>2 studies showed no significant difference in ICU admission during hospitalisation for awake prone positioning compared with control.</td>
</tr>
<tr>
<td>Adverse events (all)</td>
<td>Relative risk 1.12 (CI 95% 0.6 — 2.11) 1,487 participants in 5 studies. 13 (Randomized controlled)</td>
<td>Relative risk 1.12 per 1000 80 (CI 95% 10 more — 89 more)</td>
<td>Standard care</td>
<td>90 per 1000</td>
<td>Very low due to serious imprecision, Due to very serious risk of bias 14</td>
<td>5 studies showed no significant difference in adverse events for awake prone positioning compared with control.</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>Based on data from 1,121 participants in 1 studies. 15 (Randomized controlled)</td>
<td>Based on data from 1,121 participants in 1 studies. 15 (Randomized controlled)</td>
<td>Standard care</td>
<td>Difference: MD 0.1 lower (CI 95% 1.28 lower — 1.08 higher)</td>
<td>Very low due to serious imprecision, Due to very serious risk of bias 16</td>
<td>1 study showed no significant difference in hospital length of stay for awake prone positioning compared with control.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
<td>Summary</td>
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<tr>
<td>Hospital length of stay (days)</td>
<td>Based on data from 75 participants in 1 studies. (Randomized controlled)</td>
<td>18 (Median)</td>
<td>16 (Median)</td>
<td>Very low</td>
<td>Due to very serious imprecision, Due to very serious risk of bias 17</td>
<td>1 study (Rosen et al. 2021) showed no significant difference in hospital length of stay for awake prone positioning compared with control.</td>
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<tr>
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<td>CI 95%</td>
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<td>1 study (Taylor et al. 2021) showed no significant difference in hospital length of stay for awake prone positioning compared with control.</td>
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<td>1 study (Fralick et al. 2021) showed no significant difference in hospital length of stay for awake prone positioning compared with control.</td>
</tr>
<tr>
<td>ICU length of stay units not reported</td>
<td>Based on data from 60 participants in 1 studies. 20 (Randomized controlled)</td>
<td>Difference: MD 1.56 higher ( CI 95% 1.65 lower — 4.77 higher )</td>
<td></td>
<td>Very low</td>
<td>Due to very serious imprecision, Due to very serious risk of bias 21</td>
<td>1 study showed no significant difference in ICU length of stay for awake prone positioning compared with control.</td>
</tr>
<tr>
<td>ICU length of stay (days)</td>
<td>Based on data from 75 participants in 1 studies. (Randomized controlled)</td>
<td>11 (Median)</td>
<td>5 (Median)</td>
<td>Very low</td>
<td>Due to very serious imprecision, Due to very serious risk of bias 22</td>
<td>1 study showed no significant difference in ICU length of stay for awake prone positioning compared with control.</td>
</tr>
<tr>
<td>Time from enrolment to non-invasive ventilation (days)</td>
<td>Based on data from 75 participants in 1 studies. (Randomized controlled)</td>
<td>0.25 (Median)</td>
<td>0.23 (Median)</td>
<td>Very low</td>
<td>Due to very serious imprecision, Due to very serious risk of bias 23</td>
<td>1 study showed no significant difference in time from enrolment to non-invasive ventilation for awake prone positioning compared with control.</td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>Based on data from 75 participants in 1 studies.</td>
<td>30 (Median)</td>
<td>30 (Median)</td>
<td>Very low</td>
<td>Due to very serious imprecision, Due to very serious risk of bias 24</td>
<td>1 study showed no significant difference in ventilator-free days for awake prone positioning compared with control.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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<tr>
<td>Time from enrolment to invasive mechanical ventilation (days)</td>
<td>Based on data from 75 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Awake prone positioning</td>
<td>CI 95% to very serious risk of bias 24</td>
<td>positioning compared with control.</td>
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<tr>
<td>Time to death (days)</td>
<td>Based on data from 249 participants in 1 studies. (Randomized controlled)</td>
<td></td>
<td>2 (Median) 2 (Median) CI 95%</td>
<td>Very low Due to very serious imprecision, Due to very serious risk of bias 25</td>
<td>1 study showed no significant difference in time from enrolment to invasive mechanical ventilation for awake prone positioning compared with control.</td>
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<tr>
<td>Hospital length of stay (days)</td>
<td>Based on data from 248 participants in 1 studies. (Randomized controlled)</td>
<td>Hazard ratio (95% CI) 0.91 (0.69 to 1.2)</td>
<td>Very low Due to very serious imprecision, Due to very serious risk of bias 26</td>
<td>1 study showed no significant difference in time to death for awake prone positioning compared with control.</td>
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<tr>
<td>Intubation within 30 days after enrolment</td>
<td>Based on data from 75 participants in 1 studies. (Randomized controlled)</td>
<td>Hazard ratio (95% CI) 1.01 (0.46 to 2.21), P=0.99</td>
<td>Very low Due to very serious imprecision, Due to very serious risk of bias 27</td>
<td>1 study showed no significant difference in intubation within 30 days after enrolment for awake prone positioning compared with control.</td>
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<tr>
<td>Intubation within 30 days after enrolment (patients with PaO2/FiO2 ratio 15 kPa or less) (unadjusted analysis)</td>
<td>Based on data from 75 participants in 1 studies. (Randomized controlled)</td>
<td>Hazard ratio (95% CI) 0.94 (0.35 to 2.50), P=0.90</td>
<td>Very low Due to very serious imprecision, Due to very serious risk of bias 28</td>
<td>1 study showed no significant difference in intubation within 30 days after enrolment for awake prone positioning compared with control.</td>
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<tr>
<td>Intubation within 30 days</td>
<td>Based on data from 75 participants in 1 studies.</td>
<td>Hazard ratio (95% CI) 0.51 (0.25 to 1.89), P=0.49</td>
<td>Very low Due to very</td>
<td>1 study showed no significant difference in intubation within 30 days after enrolment for awake prone positioning compared with control.</td>
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<tr>
<td>Outcome</td>
<td>Timeframe</td>
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<td>Standard care</td>
<td>Awake prone positioning</td>
<td>Serious imprecision, Due to very serious risk of bias</td>
<td>intubation within 30 days after enrolment for awake prone positioning compared with control.</td>
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<td>after enrolment (patients with PaO2/FiO2 ratio 15 kPa or less) (adjusted for age)</td>
<td>(Randomized controlled)</td>
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<tr>
<td>Time to intubation (days)</td>
<td>Based on data from 408 participants in 1 studies. (Randomized controlled)</td>
<td>Hazard ratio (95% CI) 0.75 (0.62 to 0.91)</td>
<td>Low Due to very serious risk of bias</td>
<td>1 study showed a significant increase in the median time to intubation for awake prone positioning compared with control.</td>
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<tr>
<td>Time to death (days)</td>
<td>Based on data from 249 participants in 1 studies. (Randomized controlled)</td>
<td>Hazard ratio (95% CI) 0.87 (0.68 to 1.11)</td>
<td>Very low Due to very serious imprecision, Due to very serious risk of bias</td>
<td>1 study showed no significant difference in time to death for awake prone positioning compared with control.</td>
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</tbody>
</table>

2. Risk of Bias: very serious. greater than 33.3% of weight comes from outcomes assessed as high risk of bias. Inconsistency: no serious. I-squared value less than 50%. Indirectness: no serious. Imprecision: serious. Confidence interval crosses line of no effect. Publication bias: no serious.
4. Risk of Bias: very serious. greater than 33.3% of weight comes from outcomes assessed as high risk of bias. Inconsistency: no serious. I-squared value below 50%. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.
6. Risk of Bias: very serious. greater than 33.3% of weight comes from outcomes assessed as high risk of bias. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Confidence interval crosses line of no effect, fewer than 300 people contribute to outcome. Publication bias: no serious.
10. Risk of Bias: very serious. greater than 33.3% of weight comes from outcomes assessed as high risk of bias. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Confidence interval crosses line of no effect, fewer than 300 people contribute to outcome, low.
number of events. **Publication bias: no serious.**

11. Systematic review [116]. **Baseline/comparator:** Control arm of reference used for intervention.

12. **Risk of Bias: very serious.** greater than 33.3% of weight comes from outcomes assessed as high risk of bias. **Inconsistency: no serious.** I-squared value below 50%. **Indirectness: no serious.**

**Imprecision: very serious.** confidence interval crosses line of no effect, fewer than 300 people contribute to outcome. **Publication bias: no serious.**

13. Systematic review [116]. **Baseline/comparator:** Control arm of reference used for intervention.

14. **Risk of Bias: very serious.** greater than 33.3% of weight comes from outcomes assessed as high risk of bias. **Inconsistency: no serious.** I-squared value below 50%. **Indirectness: no serious.**

**Imprecision: very serious.** confidence interval crosses line of no effect. **Publication bias: no serious.**

15. Systematic review [116]. **Baseline/comparator:** Control arm of reference used for intervention.

16. **Risk of Bias: very serious.** greater than 33.3% of weight comes from outcomes assessed as high risk of bias. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: very serious.** IQR overlap, fewer than 300 people contribute to outcome. **Publication bias: no serious.**

17. **Risk of Bias: very serious.** greater than 33.3% of weight comes from outcomes assessed as high risk of bias. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: very serious.** IQR overlap, fewer than 300 people contribute to outcome. **Publication bias: no serious.**

18. **Risk of Bias: very serious.** greater than 33.3% of weight comes from outcomes assessed as high risk of bias. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: very serious.** IQR overlap, fewer than 300 people contribute to outcome. **Publication bias: no serious.**

19. **Risk of Bias: very serious.** greater than 33.3% of weight comes from outcomes assessed as high risk of bias. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: very serious.** IQR overlap, fewer than 300 people contribute to outcome. **Publication bias: no serious.**

20. Systematic review [116]. **Baseline/comparator:** Control arm of reference used for intervention.

21. **Risk of Bias: very serious.** greater than 33.3% of weight comes from outcomes assessed as high risk of bias. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: very serious.** IQR overlap, fewer than 300 people contribute to outcome. **Publication bias: no serious.**

22. **Risk of Bias: very serious.** greater than 33.3% of weight comes from outcomes assessed as high risk of bias. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: very serious.** IQR overlap, fewer than 300 people contribute to outcome. **Publication bias: no serious.**

23. **Risk of Bias: very serious.** greater than 33.3% of weight comes from outcomes assessed as high risk of bias. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: very serious.** IQR overlap, fewer than 300 people contribute to outcome. **Publication bias: no serious.**

24. **Risk of Bias: very serious.** greater than 33.3% of weight comes from outcomes assessed as high risk of bias. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: very serious.** IQR overlap, fewer than 300 people contribute to outcome. **Publication bias: no serious.**

25. **Risk of Bias: very serious.** greater than 33.3% of weight comes from outcomes assessed as high risk of bias. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: very serious.** IQR overlap, fewer than 300 people contribute to outcome. **Publication bias: no serious.**
Confidence interval crosses line of no effect, fewer than 300 people contribute to outcome. 

**Publication bias: no serious.**

29. **Risk of Bias: very serious.** greater than 33.3% of weight comes from outcomes assessed as high risk of bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.**

Confidence interval crosses line of no effect, fewer than 300 people contribute to outcome. 

**Publication bias: no serious.**

30. **Risk of Bias: very serious.** greater than 33.3% of weight comes from outcomes assessed as high risk of bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.**

Confidence interval crosses line of no effect, fewer than 300 people contribute to outcome. 

**Publication bias: no serious.**

31. **Risk of Bias: very serious.** greater than 33.3% of weight comes from outcomes assessed as high risk of bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.**

32. **Risk of Bias: very serious.** greater than 33.3% of weight comes from outcomes assessed as high risk of bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.**

Confidence interval crosses line of no effect, fewer than 300 people contribute to outcome. 

**Publication bias: no serious.**

### References

116. Prone positioning for COVID-19..


Conditional recommendation against

Do not routinely offer high-flow nasal oxygen as the main form of respiratory support for people with COVID-19 and respiratory failure in whom escalation to invasive mechanical ventilation would be appropriate.

See the recommendation on when to consider high-flow nasal oxygen.

Evidence to decision

Benefits and harms

The panel discussed the findings from 4 randomised controlled trials (Perkins 2022, Ospina-Tascon 2021, Grieco 2021 and Nair 2021) included in the evidence review.

They noted that aggregated evidence from Perkins 2022 and Ospina-Tascon 2021 does not show that using high-flow nasal oxygen (HFNO) has any benefits compared with conventional oxygen therapy. They noted that evidence from Nair 2021 shows that HFNO reduces intubation within 30 days and 7 days compared to non-invasive ventilation (NIV). They noted that evidence from Grieco 2021 shows that helmet NIV followed by HFNO reduces intubation within 28 days from enrolment compared to HFNO alone. However, the panel agreed that these comparisons were not directly applicable because NIV and helmet NIV are not standards of care in the UK and there is uncertainty regarding how NIV was delivered in Nair 2021. They also noted that there was a lack of patient-reported outcome measures. The panel noted that the clinical situation has changed since these trials were conducted because there is now a high proportion of vaccinated individuals and a different COVID-19 variant (Omicron) is now prevalent and may have different clinical characteristics to previous strains.

They made a recommendation to not routinely offer HFNO as the main form of respiratory support for people with respiratory failure due to COVID-19 in whom escalation to invasive mechanical ventilation would be appropriate.

Certainty of the Evidence

The panel were aware that the certainty of the evidence for outcomes in the Perkins 2022, Grieco 2021, and Nair 2021 studies ranged from moderate to very low mostly because of risk of bias, and imprecision because of confidence intervals crossing the line of no effect.

Values and preferences

Lay members noted that people with COVID-19 may have different opinions on how acceptable non-invasive respiratory support is. Some people may be apprehensive of its use and others may be willing
to accept it as an available treatment option. Patient preferences should be considered in a shared discussion.

The panel agreed that treatment plans, preferences and wishes should be discussed with patients, families, and carers before starting non-invasive respiratory support. Therefore, the panel concluded that it was important to augment the recommendations in the section ‘Deciding when to escalate treatment’ by adding information boxes that have links to further advice from professional organisations.

The panel noted that outcomes, such as symptom control, would be important to people with COVID-19 and should be reported in future trials provided there are adequate staff and personal protective equipment to facilitate measurement. The panel made a research recommendation to explore the role of high-flow nasal oxygen in reducing breathlessness compared with standard care or conventional oxygen therapy, to help improve the evidence base in this area.

**Resources**

The panel indicated that high-flow nasal oxygen (HFNO), in particular, consumes a large amount of oxygen. Therefore, when oxygen supplies are low, this should be taken into account when deciding whether to use HFNO.

Cost effectiveness was not assessed as part of the evidence review.

**Equity**

The panel noted that for high-flow nasal oxygen compared with conventional oxygen (Perkins 2022), the composite outcome of tracheal intubation or mortality within 30 days was not statistically significant for any particular ethnic group.

The scope of this evidence review was limited to adults and so no evidence in children and young people was included.

The panel noted that some people, including those with cognitive impairment for example, may find it difficult to tolerate non-invasive respiratory support. As such, patient preferences should be considered in a shared discussion with the person and their family or carer.

**Acceptability**

The panel acknowledged that although high-flow nasal oxygen should not be routinely offered as the main form of respiratory support, it may be considered in some situations, which are provided in a consensus recommendation to consider using high-flow nasal oxygen under certain conditions. The panel also proposed a research recommendation to explore which treatment methods are effective for weaning people with COVID-19 from CPAP and the acceptability and safety of these methods.

**Feasibility**

High-flow nasal oxygen is an established treatment in the NHS. It may be considered in certain situations as outlined in this recommendation to consider use of high-flow nasal oxygen.
Rationale
Evidence does not show that high-flow nasal oxygen has treatment benefits over conventional oxygen therapy for people in whom escalation to invasive mechanical ventilation would be appropriate. So, the panel agreed that it should not be used as the preferred treatment option for this population.

The panel acknowledged that although high-flow nasal oxygen should not be routinely offered as the main form of respiratory support, it may be considered in some situations.

Clinical question/ PICO
- **Population:** People with COVID-19
- **Intervention:** HFNO
- **Comparator:** Conventional oxygen

Summary
The evidence does not support the use of HFNO as a main treatment option.

What is the evidence informing this conclusion?
Evidence comes from 2 randomised controlled trials (RCTs) of patients with COVID-19 and respiratory failure (Perkins 2022 and Ospina-Tascon 2021).

The 2 included RCTs allowed 1 comparison of respiratory support modalities to be made:

- HFNO versus conventional oxygen (Perkins 2022 and Ospina-Tascon 2021)

It was possible to meta-analyse Perkins 2022 and Ospina-Tascon 2021 for the HFNO versus conventional oxygen comparison.

Publication status
Perkins 2022 and Ospina-Tascon 2021 are both full publications.

Study characteristics
Two RCTs included adult (≥18-years) hospitalised patients with known or suspected COVID-19 if they had acute respiratory failure. One of these defined respiratory failure as peripheral oxygen saturations (SpO2) of 94% or below despite receiving a fraction of inspired oxygen (FiO2) of at least 0.4, and when tracheal intubation was considered a clinically appropriate treatment option if treatment escalation was required (Perkins 2022). The other RCT defined respiratory failure as participants having a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FiO2) of less than 200, accompanied by clinical signs of respiratory distress (Ospina-Tascon 2021).

The mean age in Perkins 2022 was 57.4 (95% CI, 56.7 to 58.1) years with the proportion of women being 33.6%. The total number of participants was 785. The mean age in Ospina-Tascon 2021 was 59 to 60 years (49-69) with the proportion of women being 28-37%. The total number of participants was 199.

For further details see the evidence review.

What are the main results?
No difference was observed between HFNO and conventional oxygen for any outcome measured. These outcomes were: mortality at 30 days, tracheal intubation or mortality at 30 days, intubation within 30 days, median time to intubation, admission to critical care, mean length of stay in hospital, and mean length of stay in critical care.

**Our confidence in the results**

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for tracheal intubation or mortality (30 days), median time to intubation, admission to critical care, mortality (28-30 days), length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision). The certainty of the evidence was very low for tracheal intubation (28-30 days) (due to serious risk of bias, serious inconsistency, and serious imprecision).

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at 28 or 30 days</td>
<td>Relative risk 0.77 (CI 95% 0.44 — 1.36) Based on data from 984 participants in 2 studies.</td>
<td>Conventional oxygen</td>
<td>191 per 1000</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>Two studies found no statistically significant difference in mortality with HFNO compared with conventional oxygen in people with COVID-19.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HFNO</td>
<td>147 per 1000</td>
<td>44 fewer per 1000 (CI 95% 107 fewer — 69 more)</td>
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<td>Difference:</td>
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<td>44 fewer per 1000</td>
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<td>Low Due to serious risk of bias, Due to serious imprecision</td>
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<tr>
<td>Tracheal intubation or mortality 30 days</td>
<td>Relative risk 0.99 (CI 95% 0.84 — 1.15) Based on data from 782 participants in 1 studies.</td>
<td>Conventional oxygen</td>
<td>451 per 1000</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>One study found no statistically significant difference in the composite outcome of tracheal intubation or mortality with HFNO compared with conventional oxygen in people with COVID-19.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HFNO</td>
<td>446 per 1000</td>
<td>5 fewer per 1000 (CI 95% 72 fewer — 68 more)</td>
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<td></td>
<td>Difference:</td>
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<td>446 per 1000</td>
<td>5 fewer per 1000</td>
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<td></td>
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<td>Low Due to serious risk of bias, Due to serious imprecision</td>
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<tr>
<td>Intubation within 28-30 days of starting treatment</td>
<td>Relative risk 0.84 (CI 95% 0.58 — 1.22) Based on data from 981 participants in 2 studies.</td>
<td>Conventional oxygen</td>
<td>436 per 1000</td>
<td>Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision</td>
<td>Two studies found no statistically significant difference in intubation with HFNO compared with conventional oxygen in people with COVID-19.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HFNO</td>
<td>366 per 1000</td>
<td>70 fewer per 1000 (CI 95% 183 fewer — 96 more)</td>
<td></td>
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<tr>
<td></td>
<td>Difference:</td>
<td></td>
<td>366 per 1000</td>
<td>70 fewer per 1000</td>
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<td></td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision</td>
<td></td>
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<tr>
<td>Median time to intubation</td>
<td>Hazard ratio 0.91 (CI 95% 0.72 — 1.15) Based on data from 784 participants in 1 studies. (Randomized controlled)</td>
<td>Conventional oxygen</td>
<td></td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>One study found no statistically significant difference in intubation with HFNO compared with conventional oxygen in people with COVID-19.</td>
</tr>
<tr>
<td></td>
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<td>HFNO</td>
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<td></td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
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<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Conventional oxygen</th>
<th>Intervention HFNO</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission to critical care</td>
<td>Relative risk 1.05 (CI 95% 0.93 — 1.17) Based on data from 784 participants in 1 studies.</td>
<td>582 per 1000</td>
<td>611 per 1000</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>One study found no statistically significant difference in admission to critical care with HFNO compared with conventional oxygen in people with COVID-19.</td>
</tr>
<tr>
<td>Median length of stay in hospital (days)</td>
<td>Odds ratio 0.77 (CI 95% 0.47 — 1.26) Based on data from 199 participants in 1 studies. (Randomized controlled)</td>
<td>17.1 (Mean)</td>
<td>18.3 (Mean)</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>One study found no statistically significant difference in median length of stay in hospital with HFNO compared with conventional oxygen in people with COVID-19.</td>
</tr>
<tr>
<td>Median length of stay in critical care (days)</td>
<td>Odds ratio 0.74 (CI 95% 0.45 — 1.22) Based on data from 199 participants in 1 studies.</td>
<td>17.1 (Mean)</td>
<td>18.3 (Mean)</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>One study found no statistically significant difference in median length of stay in critical care with HFNO compared with conventional oxygen in people with COVID-19.</td>
</tr>
<tr>
<td>Mean length of stay in hospital (days)</td>
<td>Lower better Based on data from 782 participants in 1 studies.</td>
<td>17.1 (Mean)</td>
<td>18.3 (Mean)</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>One study found no statistically significant difference in length of hospital stay with HFNO compared with conventional oxygen in people with COVID-19.</td>
</tr>
<tr>
<td>Mean length of stay in critical care (days)</td>
<td>Lower better Based on data from 782 participants in 1 studies.</td>
<td>9.5 (Mean)</td>
<td>10.5 (Mean)</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>One study found no statistically significant difference in length of hospital stay with HFNO compared with conventional oxygen in people with COVID-19.</td>
</tr>
</tbody>
</table>

Confidence interval crosses line of no effect. **Publication bias: no serious.**


4. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crossed line of no effect. **Publication bias: no serious.**


6. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with $I^2$: 75%. **Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

7. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study, due to [reason]. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**


10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Confidence interval crosses line of no effect, Low number of patients. **Publication bias: no serious.**

11. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Confidence interval crosses line of no effect, Low number of patients. **Publication bias: no serious.**


15. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**
Clinical question/ PICO

**Population:** People with COVID-19  
**Intervention:** HFNO  
**Comparator:** NIV

Summary

Evidence indicates that high-flow nasal oxygen (HFNO) may have some treatment benefits, including tracheal intubation or mortality at 30 days and intubation within 7 days, in people with COVID-19 who have failed oxygen therapy by face mask, compared with NIV.

What is the evidence informing this conclusion?

Evidence comes from one randomised controlled trial (RCT) of patients with COVID-19 who have failed oxygen therapy by face mask (Nair 2021). This RCT allowed 1 comparison of respiratory support to be made:

- High-flow nasal oxygen (HFNO) versus non-invasive ventilation (NIV) (Nair 2021)

Meta-analysis was not possible because there was only 1 study.

Publication status

Nair et al. (2021) is a full publication.

Study characteristics

One RCT included adult patients (18-75 years) in an intensive care unit (ICU) with known COVID-19 if they had presented with severe COVID-19 pneumonia and had failed oxygen therapy by face mask (Nair 2021).

The mean age in Nair 2021 was 57 years (95% CI 48 to 65) in the HFNO group and 57.5 years (95% CI 47 to 64) in the NIV group with the proportion of women being 20-35%. The total number of participants was 109.

For further details see the evidence review.
**What are the main results?**

Compared with NIV, HFNO significantly reduced tracheal intubation or mortality at 30 days (Hazard Ratio 0.51 (95% CI 0.28 to 0.93)) in people who have failed oxygen therapy by face mask. Intubation within 7 days (RR 0.59 (95% CI 0.35 to 0.99)) was significantly reduced in the group receiving HFNO compared with NIV in people who have failed oxygen therapy by face mask.

No difference was observed between HFNO and NIV for in-hospital mortality at 30 days, intubation within 48 hours, or median length of stay in hospital.

**Our confidence in the results**

In patients with COVID-19 who had failed oxygen therapy by face mask, certainty of the evidence is moderate for tracheal intubation or mortality (30 days), intubation (7 days), and length of stay in hospital (due to serious risk of bias). The certainty of the evidence was low for in-hospital mortality (30 days), and intubation (48 hours) (due to serious risk of bias and serious imprecision).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
</table>
| In-hospital mortality 30 days     |                 | Relative risk 0.63 (CI 95% 0.38 — 1.04) Based on data from 109 participants in 1 studies. |            | 463 per 1000 | Very low Due to serious risk of bias, Due to very serious imprecision | One study found no statistically significant difference in in-hospital mortality with HFNO compared with NIV in people with COVID-19.
<p>|                                  |                 |                                | NIV        | 292 per 1000 |                                                    |                                                                        |
|                                  |                 |                                | HFNO       | 171 fewer per 1000 ( CI 95% 287 fewer — 19 more )     |                                                                        |
| Intubation within 30 days         |                 | Hazard ratio 0.51 (CI 95% 0.27 — 0.97) Based on data from 109 participants in 1 studies. (Randomized controlled) |            |              | Moderate Due to serious risk of bias              | One study found a statistically significant reduction in intubation within 30 days with HFNO compared with NIV in people with COVID-19. |
| Tracheal intubation or mortality 30 days |                 | Hazard ratio 0.51 (CI 95% 0.28 — 0.93) Based on data from 109 participants in 1 studies. (Randomized controlled) |            |              | Moderate Due to serious risk of bias               | One study found a statistically significant reduction in intubation or mortality with HFNO compared with NIV in people with COVID-19. |
| Intubation within 7 days          |                 | Relative risk 0.59 (CI 95% 0.35 — 0.99) Based on data from 109 participants in 1 studies. |            | 463 per 1000 | Moderate Due to serious risk of bias               | One study found no statistically significant difference in intubation within 7 days with HFNO compared with NIV in people with COVID-19. |
|                                  |                 |                                | NIV        | 273 per 1000 |                                                    |                                                                        |
|                                  |                 |                                | HFNO       | 190 fewer per 1000                                    |                                                                        |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>NIV</td>
<td>HFNO</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(CI 95% 301 fewer — 5 fewer)</td>
<td></td>
<td>COVID-19.</td>
</tr>
<tr>
<td>Intubation within 48 hours</td>
<td>Relative risk 0.6 (CI 95% 0.31 — 1.15) Based on data from 109 participants in 1 studies.</td>
<td>333 per 1000 Difference:</td>
<td>200 per 1000 133 fewer per 1000 (CI 95% 230 fewer — 50 more)</td>
<td>Very low Due to serious risk of bias, Due to very serious imprecision</td>
<td>One study found no statistically significant difference in intubation within 48 hours with HFNO compared with NIV in people with COVID-19</td>
<td></td>
</tr>
<tr>
<td>Median (IQR) length of stay in hospital (days)</td>
<td>Based on data from 109 participants in 1 studies. (Randomized controlled)</td>
<td>Hospital length of stay was 9 days (IQR 7, 13) for HFNO compared with 9 days (IQR 6, 12) for NIV</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td></td>
<td>One study found that the median length of stay in hospital was similar for HFNO compared with NIV in people with COVID-19</td>
<td></td>
</tr>
</tbody>
</table>

2. **Risk of Bias:** **serious.** The HFNC arm had awake prone positioning but the NIV arm did not adhere to awake prone positioning because of the practical difficulty with the NIV interface. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Confidence interval crosses line of no effect, Low number of patients. **Publication bias:** no serious.
3. **Risk of Bias:** **serious.** Because the HFNC arm had awake prone positioning but the NIV arm did not adhere to awake prone positioning because of the practical difficulty with the NIV interface., **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** no serious. **Publication bias:** no serious.
4. **Risk of Bias:** **serious.** The HFNC arm had awake prone positioning but the NIV arm did not adhere to awake prone positioning because of the practical difficulty with the NIV interface. **Inconsistency:** serious. **Indirectness:** no serious. **Imprecision:** no serious. **Publication bias:** no serious.
6. **Risk of Bias:** **serious.** The HFNC arm had awake prone positioning but the NIV arm did not adhere to awake prone positioning because of the practical difficulty with the NIV interface. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** no serious. **Publication bias:** no serious.
8. **Risk of Bias:** **serious.** The HFNC arm had awake prone positioning but the NIV arm did not adhere to awake prone positioning because of the practical difficulty with the NIV interface. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Confidence interval crosses line of no effect, Low number of patients. **Publication bias:** no serious.
9. **Risk of Bias:** **serious.** The HFNC arm had awake prone positioning but the NIV arm did not adhere to awake prone positioning because of the practical difficulty with the NIV interface. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. The point estimates and interquartile
ranges were similar. **Publication bias: no serious.**

### References


### Clinical question/ PICO

**Population:** People with COVID-19  
**Intervention:** Helmet non-invasive ventilation followed by HFNO  
**Comparator:** HFNO

### Summary

Evidence indicates that the use of helmet NIV followed by HFNO may have some treatment benefits, including intubation outcomes and invasive ventilation free days, in people with COVID-19 and respiratory failure compared with HFNO alone.

**What is the evidence informing this conclusion?**

Evidence comes from 1 randomised controlled trials (RCT) of patients with COVID-19 and respiratory failure (Grieco 2021).

The 1 included RCT allowed 1 comparison of respiratory support modalities to be made:

- Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

Because there was only 1 RCT, it was not possible to meta-analyse the included data.

### Publication status

Grieco et al. (2021) is a full publication.

### Study characteristics

One RCT included adults with confirmed COVID-19 adults admitted in the ICU due to acute hypoxaemic respiratory failure (Grieco 2021).

The median and interquartile range for age in the Greico 2021 RCT was 66 years (57-72) in the intervention group and 63 years (55-69) in the comparator group and the proportion of women was 19%. The total number of participants was 109.

For further details see the evidence review.

### What are the main results?

Compared with HFNO, helmet NIV followed by HFNO significantly reduces intubation within 28 days from enrolment (RR 0.58 (95% CI 0.36 - 0.95)), intubation within 28 days from enrolment after
adjudication of intubation criteria by external experts (RR 0.55 (95% CI 0.33 - 0.9)) and invasive ventilation free days at 28 days (Mean difference 3 more (95% CI 0 more - 7 more)).

No difference was observed between helmet non-invasive ventilation followed by HFNO and HFNO for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (at 60 days), duration of hospital stay and duration of ICU stay.

Our confidence in the results

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for intubation within 28 days from enrolment, intubation within 28 days from enrolment after adjudication of intubation criteria by external experts and invasive ventilation free days (28 days) (due to serious risk of bias and serious indirectness).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is very low for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (60 days), duration of hospital stay and duration of ICU stay.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at 28 days</td>
<td>Relative risk 0.81 (CI 95% 0.35 — 1.91) Based on data from 109 participants in 1 studies.¹ (Randomized controlled)</td>
<td>182 per 1000 Difference:</td>
<td>147 per 1000 35 fewer per 1000 ( CI 95% 118 fewer — 166 more )</td>
<td>Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision ²</td>
<td>One study found no statistically significant difference in mortality with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.</td>
</tr>
<tr>
<td>Mortality at 60 days</td>
<td>Relative risk 1.1 (CI 95% 0.55 — 2.2) Based on data from 109 participants in 1 studies.³ (Randomized controlled)</td>
<td>218 per 1000 Difference:</td>
<td>240 per 1000 22 more per 1000 ( CI 95% 98 fewer — 262 more )</td>
<td>Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision ⁴</td>
<td>One study found no statistically significant difference in mortality with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>Relative risk 0.95 (CI 95% 0.49 — 1.82) Based on data from 109 participants in 1 studies.⁵ (Randomized controlled)</td>
<td>255 per 1000 Difference:</td>
<td>242 per 1000 13 fewer per 1000 ( CI 95% 130 fewer — 209 more )</td>
<td>Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision ⁶</td>
<td>One study found no statistically significant difference in in-hospital mortality with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
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</tr>
<tr>
<td>In–intensive care unit mortality</td>
<td>Relative risk 0.8 (CI 95% 0.4 — 1.6) Based on data from 109 participants in 1 studies. 7 (Randomized controlled)</td>
<td>Helmet non-invasive ventilation following by HFNO</td>
<td>255 per 1000 Difference: 204 per 1000</td>
<td>Very low: Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision 8</td>
<td>One study found no statistically significant difference in intensive care mortality with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.</td>
</tr>
<tr>
<td>Intubation within 28 days from enrolment</td>
<td>Relative risk 0.58 (CI 95% 0.36 — 0.95) Based on data from 109 participants in 1 studies. 9 (Randomized controlled)</td>
<td>Helmet non-invasive ventilation following by HFNO</td>
<td>509 per 1000 Difference: 295 per 1000</td>
<td>Low: Due to serious risk of bias, Due to serious indirectness 10</td>
<td>One study found a statistically significant reduction in intubation with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.</td>
</tr>
<tr>
<td>Intubation within 28 days from enrolment after adjudication of intubation criteria by external experts</td>
<td>Relative risk 0.55 (CI 95% 0.33 — 0.9) Based on data from 109 participants in 1 studies. 11 (Randomized controlled)</td>
<td>Helmet non-invasive ventilation following by HFNO</td>
<td>509 per 1000 Difference: 280 per 1000</td>
<td>Low: Due to serious risk of bias, Due to serious indirectness 12</td>
<td>One study found a statistically significant reduction in intubation with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.</td>
</tr>
<tr>
<td>Respiratory support free days</td>
<td>Based on data from 109 participants in 1 studies. (Randomized controlled)</td>
<td></td>
<td>18 (Median) Difference: 20 (Median)</td>
<td>Very low: Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision 13</td>
<td>One study found no statistically significant difference in respiratory support free days with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.</td>
</tr>
<tr>
<td>Invasive ventilation free days 28 days</td>
<td>Based on data from 109 participants in 1 studies. (Randomized controlled)</td>
<td></td>
<td>25 (Median) Difference: 28 (Median)</td>
<td>Low: Due to serious risk of bias, Due to serious indirectness 14</td>
<td>One study found a statistically significant increase in invasive ventilation free days with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
<td>Summary</td>
</tr>
<tr>
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</tr>
<tr>
<td>Invasive ventilation free days</td>
<td>Based on data from 109 participants in 1 studies. (Randomized controlled)</td>
<td>57 (Median)</td>
<td>Helmet non-invasive ventilation followed by HFNO</td>
<td>Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision</td>
<td>One study found no statistically significant difference in invasive ventilation free days with helmet non-invasive ventilation followed by HFNO compared with HFNO in people with COVID-19.</td>
</tr>
<tr>
<td>Invasive ventilation free days</td>
<td>Based on data from 109 participants in 1 studies. (Randomized controlled)</td>
<td>60 (Median)</td>
<td>Median</td>
<td>CI 95% 3 fewer — 15 more</td>
<td></td>
</tr>
<tr>
<td>Duration of hospital stay (days)</td>
<td>Based on data from 109 participants in 1 studies. (Randomized controlled)</td>
<td>22 days (Median)</td>
<td>Difference:</td>
<td>MD 6 fewer</td>
<td>Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision</td>
</tr>
<tr>
<td>Duration of hospital stay (days)</td>
<td>Based on data from 109 participants in 1 studies. (Randomized controlled)</td>
<td>21 days (Median)</td>
<td>(CI 95% 14 fewer — 1 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of ICU stay (days)</td>
<td>Based on data from 109 participants in 1 studies. (Randomized controlled)</td>
<td>10 (Median)</td>
<td>Difference:</td>
<td>MD 6 fewer</td>
<td>Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision</td>
</tr>
<tr>
<td>Duration of ICU stay (days)</td>
<td>Based on data from 109 participants in 1 studies. (Randomized controlled)</td>
<td>9 (Median)</td>
<td>(CI 95% 13 fewer — 1 more)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** serious, due to applicability of study design. **Imprecision:** very serious. Confidence interval crosses line of no effect, Wide confidence intervals, Low number of patients. **Publication bias:** no serious.
4. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** serious, due to applicability of study design. **Imprecision:** very serious. Confidence interval crosses line of no effect, Wide confidence intervals, Low number of patients. **Publication bias:** no serious.
5. Systematic review [54] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** serious, due to applicability of
study design. **Imprecision: very serious.** Confidence interval crosses line of no effect, Wide confidence intervals, Low number of patients. **Publication bias: no serious.**

7. Systematic review [54] with included studies: Grieco 2021. **Baseline/comparator:** Control arm of reference used for intervention.

8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: very serious.** Confidence interval crosses line of no effect, Wide confidence intervals, Low number of patients. **Publication bias: no serious.**


10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: no serious. Publication bias: no serious.**


12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: no serious. Publication bias: no serious.**

13. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: very serious.** Confidence interval crosses line of no effect, Wide confidence intervals, Low number of patients. **Publication bias: no serious.**

14. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: no serious. Publication bias: no serious.**

15. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: very serious.** Confidence interval crosses line of no effect, Wide confidence intervals, Low number of patients. **Publication bias: no serious.**

16. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: very serious.** Confidence interval crosses line of no effect, Wide confidence intervals, Low number of patients. **Publication bias: no serious.**

17. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** due to applicability of study design. **Imprecision: very serious.** Confidence interval crosses line of no effect, Low number of patients, Wide confidence intervals. **Publication bias: no serious.**
Consider continuous positive airway pressure (CPAP) for people with COVID-19 when:

- they have hypoxaemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of 0.4 (40%) or more, and either
  - escalation to invasive mechanical ventilation would be an option but it is not immediately needed, or
  - it is agreed that respiratory support should not be escalated beyond CPAP.

In June 2021, the Medicines and Healthcare products Regulatory Agency issued a National Patient Safety Alert for Philips ventilator, CPAP and bilevel positive airway pressure devices because of a potential for harm from inhaled particles and volatile organic compounds. This applies to all devices manufactured before 26 April 2021.

Benefits and harms

The panel discussed the findings from 1 randomised controlled trial (Perkins 2022) included in the evidence review.

The panel agreed that the evidence from Perkins 2022 shows that using continuous positive airway pressure (CPAP) reduces the number of people who need invasive ventilation and admission to critical care. They also noted that evidence from Perkins 2022 suggests there is a small increase in the number of serious adverse events with CPAP compared with conventional oxygen therapy. However, they considered that there are uncertainties with the available evidence, including evidence on standard care, staffing ratios, and where people had CPAP and which staff gave it. The panel agreed that these uncertainties warranted a recommendation to consider offering CPAP to people with COVID-19 when they:

- have hypoxaemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of 40% or more, and
- escalation to invasive mechanical ventilation is appropriate but not immediately needed.

The panel noted that sometimes people who experience an increased effort of breathing have CPAP or high flow nasal oxygen. However, this indication is generally not included in studies because it is difficult to measure this in an objective way. The panel noted that it is important for staff to have skills and competencies in CPAP and that people have CPAP in an appropriate setting. They provided a
The panel discussed the importance of ensuring that CPAP is not used for longer than it is needed. They strongly emphasised the importance of regularly reviewing people having CPAP (for example every 12 hours) to ensure that it is promptly recognised when treatment has failed and that treatment is escalated when needed. They made a consensus recommendation to support this. The panel agreed not to define treatment failure to allow for individual clinical decision making.

The panel also made a consensus recommendation to optimise pharmacological and non-pharmacological management strategies in people who need non-invasive respiratory support.

Certainty of the Evidence

The panel were aware that the certainty of the evidence for outcomes in Perkins 2022 ranged from moderate to low mostly because of risk of bias and imprecision due to the confidence interval crossing the line of no effect.

Values and preferences

Lay members noted that people with COVID-19 may have different opinions on how acceptable non-invasive respiratory support is. Some people may be apprehensive of its use and others may be willing to accept it as an available treatment option. People’s preferences should be considered in a shared discussion. For example, the panel noted that some people tolerate high flow nasal oxygen better than continuous positive airway pressure (CPAP).

The panel agreed that treatment plans, preferences and wishes should be discussed with patients, families and carers before starting non-invasive respiratory support. For this reason, information boxes linking to the existing guideline recommendations on escalation and de-escalation of treatment have been provided. The panel also considered that care of people who will not have treatment escalation should be supported by provision of an information box linking to existing recommendations on pharmacological and non-pharmacological treatment options.

The panel noted that outcomes, such as symptom control, would be important to people with COVID-19 and should be reported in future trials.

Resources

The panel considered that using continuous positive airway pressure (CPAP) for people with COVID-19 in appropriate settings outside of the intensive care unit (ICU) has the potential to increase available ICU capacity. Avoiding the need for invasive mechanical intubation may also result in cost savings and avoid adverse outcomes from intubation. However, the panel were mindful that CPAP must be given by staff who have skills and competencies in CPAP, be accompanied by careful review, prompt recognition of when treatment has failed, and have a management plan should the CPAP fail.

Cost-effectiveness was not assessed as part of the evidence review.
Evidence from a clinical trial suggests that there may be some treatment benefits with continuous positive airway pressure (CPAP) for people who have hypoxaemia and when mechanical ventilation is not immediately needed. These benefits are mostly for intubation outcomes (including likelihood of needing tracheal intubation and invasive mechanical ventilation), but there are uncertainties in the evidence. In this clinical trial, hypoxaemia was defined as less than or equal to 94% using pulse oximetry.

The panel noted that some people, including those with cognitive impairment for example, may find it difficult to tolerate non-invasive respiratory support. As such, patient preferences should be considered in a shared discussion with the person and their family or carer.

In Perkins 2022, hypoxaemia was defined by reference to pulse oximetry. The MHRA has issued advice on the use of pulse oximeters and the factors which may affect their accuracy (which include skin colour).

The panel discussed that some people find continuous positive airway pressure (CPAP) uncomfortable. The panel also commented that some people may find it difficult to tolerate non-invasive respiratory support. They noted that high-flow nasal oxygen would allow people having CPAP to take treatment breaks for mealtimes and when CPAP is being gradually reduced. They made a consensus recommendation to support this. The panel proposed a research recommendation to explore which treatment methods are effective for weaning people with COVID-19 from CPAP and the acceptability and safety of these methods.

The panel also commented on the importance of discussing and reaching a shared decision with the person on the modality of CPAP used (for example, mask or helmet).

Continuous positive airway pressure (CPAP) is an established treatment in the NHS. However, the panel advised that context-specific factors influence when CPAP may be used, for example staff skills and competencies, staffing ratios and the availability of different CPAP interfaces, so CPAP use may vary in practice.

Rationale

Evidence from a clinical trial suggests that there may be some treatment benefits with continuous positive airway pressure for people who have hypoxaemia and when mechanical ventilation is not immediately needed. These benefits are mostly for intubation outcomes (including likelihood of needing tracheal intubation and invasive mechanical ventilation), but there are uncertainties in the evidence. In this clinical trial, hypoxaemia was defined as less than or equal to 94% using pulse oximetry.

Clinical question/ PICO

**Population:** People with COVID-19

**Intervention:** CPAP

**Comparator:** Conventional oxygen
Summary
Evidence indicates that the use of continuous positive airway pressure (CPAP) may have some treatment benefits, including intubation outcomes, in people with COVID-19 and respiratory failure.

What is the evidence informing this conclusion?
Evidence comes from 1 randomised controlled trial (RCT) of patients with COVID-19 and respiratory failure (Perkins et al., 2022).
The RCT allowed 1 comparison of respiratory support modalities to be made:
• Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2022)

Because there was only 1 study, it was not possible to meta-analyse the included data.

Publication status
Perkins 2022 is a full publication.

Study characteristics
One RCT included adult (≥18-years) hospitalised patients with known or suspected COVID-19 if they had acute respiratory failure, defined as peripheral oxygen saturations (SpO2) of 94% or below despite receiving a fraction of inspired oxygen (FiO2) of at least 0.4, and when tracheal intubation was considered a clinically appropriate treatment option if treatment escalation was required (Perkins 2022).

Mean age in Perkins (2022) 57.4 (95% CI, 56.7 to 58.1) years with the proportion of women being 33.6%. The total number of participants was 737.

For further details see the evidence review.

What are the main results?
Compared with conventional oxygen, CPAP significantly reduces tracheal intubation or mortality at 30 days (RR 0.82 95% CI 0.69 – 0.98)) in people with COVID-19 and acute respiratory failure.
Median time to intubation (Hazard Ratio (adjusted): 0.67 (95% CI 0.52 - 0.86)) was significantly delayed and admissions to critical care (RR 0.88 (95% CI 0.78 - 1.00)) was significantly reduced in the group receiving CPAP compared with conventional oxygen in people with COVID-19.

No difference was observed between CPAP and conventional oxygen for mortality, length of hospital stay and length of critical care stay.

Our confidence in the results
In patients with COVID-19 with acute respiratory failure, certainty of the evidence is moderate for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation and admission to critical care (due to serious risk of bias).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecise).
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>30 days</td>
<td>Relative risk 0.87 (CI 95% 0.64 — 1.18) Based on data from 737 participants in 1 studies.</td>
<td>Conventional oxygen</td>
<td>CPAP</td>
<td>Low</td>
<td>One study found no statistically significant difference in mortality with CPAP compared with conventional oxygen in people with COVID-19.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>192 per 1000</td>
<td>167 per 1000</td>
<td>Due to serious risk of bias, Due to serious imprecision</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Difference:</td>
<td></td>
<td>25 fewer per 1000 (CI 95% 69 fewer — 35 more)</td>
<td></td>
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</tr>
<tr>
<td>Tracheal intubation or mortality</td>
<td>30 days</td>
<td>Relative risk 0.82 (CI 95% 0.69 — 0.98) Based on data from 733 participants in 1 studies.</td>
<td>Conventional oxygen</td>
<td>CPAP</td>
<td>Moderate</td>
<td>One study found a statistically significant reduction in the composite outcome of tracheal intubation or mortality with CPAP compared with conventional oxygen in people with COVID-19.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>444 per 1000</td>
<td>364 per 1000</td>
<td>Due to serious risk of bias</td>
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<tr>
<td></td>
<td></td>
<td>Difference:</td>
<td></td>
<td>80 fewer per 1000 (CI 95% 138 fewer — 9 fewer)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intubation</td>
<td>30 days</td>
<td>Relative risk 0.81 (CI 95% 0.67 — 0.98) Based on data from 733 participants in 1 studies.</td>
<td>Conventional oxygen</td>
<td>CPAP</td>
<td>Moderate</td>
<td>One study found a statistically significant reduction in intubation with CPAP compared with conventional oxygen in people with COVID-19.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>413 per 1000</td>
<td>335 per 1000</td>
<td>Due to serious risk of bias</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Difference:</td>
<td></td>
<td>78 fewer per 1000 (CI 95% 136 fewer — 8 fewer)</td>
<td></td>
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<tr>
<td>Admission to critical care</td>
<td></td>
<td>Relative risk 0.88 (CI 95% 0.78 — 1) Based on data from 735 participants in 1 studies.</td>
<td>Conventional oxygen</td>
<td>CPAP</td>
<td>Moderate</td>
<td>One study found a statistically significant reduction in admission to critical care with CPAP compared with conventional oxygen in people with COVID-19.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>615 per 1000</td>
<td>541 per 1000</td>
<td>Due to serious risk of bias</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Difference:</td>
<td></td>
<td>74 fewer per 1000 (CI 95% 135 fewer — 0 fewer)</td>
<td></td>
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<tr>
<td>Median time to intubation</td>
<td></td>
<td>Hazard ratio 0.67 (CI 95% 0.52 — 0.86) Based on data from 737 participants in 1 studies. (Randomized controlled)</td>
<td>Conventional oxygen</td>
<td>CPAP</td>
<td>Moderate</td>
<td>One study found a statistically significant difference in median time to intubation with CPAP compared with conventional oxygen in people with COVID-19.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17.2 (Mean)</td>
<td>16.4 (Mean)</td>
<td>Due to serious risk of bias, Due to serious imprecision</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference:</td>
<td></td>
<td>MD 0.9 lower (CI 95% 3.48 lower — 1.68 higher)</td>
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</tr>
<tr>
<td>Mean length of stay in hospital</td>
<td></td>
<td>Based on data from 733 participants in 1 studies. (Randomized controlled)</td>
<td>Conventional oxygen</td>
<td>CPAP</td>
<td>Low</td>
<td>One study found no statistically significant difference in length of hospital stay with CPAP compared with conventional oxygen in people with COVID-19.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17.2 (Mean)</td>
<td>16.4 (Mean)</td>
<td>Due to serious risk of bias, Due to serious imprecision</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference:</td>
<td></td>
<td>MD 0.9 lower (CI 95% 3.48 lower — 1.68 higher)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Conventional oxygen</td>
<td>Intervention CPAP</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
<td></td>
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</tr>
<tr>
<td>Mean length of stay in critical care</td>
<td>Based on data from 733 participants in 1 studies.</td>
<td>9.6 (Mean)</td>
<td>9.5 (Mean)</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>One study found no statistically significant difference in length of critical care stay with CPAP compared with conventional oxygen in people with COVID-19.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Difference:</td>
<td>MD 0.1 lower ( CI 95% 2.22 lower — 2.02 higher )</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Risk of Bias:** **serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Confidence interval crosses line of no effect. **Publication bias:** no serious.
4. **Risk of Bias:** **serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** no serious. **Publication bias:** no serious.
6. **Risk of Bias:** **serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** no serious. **Publication bias:** no serious.
8. **Risk of Bias:** **serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** no serious. **Publication bias:** no serious.
9. **Risk of Bias:** **serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** no serious. **Publication bias:** no serious.
11. **Risk of Bias:** **serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** no serious. **Publication bias:** no serious.
13. **Risk of Bias:** **serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for...
detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval crosses line of no effect. **Publication bias: no serious.**

**References**

117. Respiratory support for COVID-19.


**Consensus recommendation**

For people with COVID-19 having continuous positive airway pressure (CPAP), ensure:

- there is access to critical care providers for advice, review and prompt escalation of treatment if needed
- regular review by an appropriate senior clinician (such as every 12 hours) and more frequent review if needed, in line with the British Thoracic Society guidance on respiratory support units and the Faculty of Intensive Care Medicine guidelines on the provision of intensive care services
- regular assessment and management of symptoms alongside non-invasive respiratory support.

*Staff caring for people with COVID-19 having CPAP should have appropriate skills and competencies and provide appropriate monitoring. For further information on standards of care and provision of services see the Faculty of Intensive Care Medicine and Intensive Care Society guidelines on the provision of intensive care services, the British Thoracic Society and Intensive Care Society guidance on development and implementation of respiratory support units and the Paediatric Intensive Care Society guidance on the management of critically ill children.*

*The British Thoracic Society and Intensive Care Society have produced information on management of acute hypoxaemic respiratory failure associated with COVID-19, which includes the use of CPAP.*

**Evidence to decision**

**Benefits and harms**

No evidence was found on reviewing and monitoring people having continuous positive airway pressure (CPAP). However, the panel noted that it is important that staff have skills and competencies in CPAP and that people have CPAP in an appropriate setting. They provided a consensus recommendation to support this.

The panel also discussed the importance of ensuring that CPAP is not used for longer than it is needed. They strongly emphasised the importance of regularly reviewing people having CPAP (for example every 12 hours) to ensure that it is promptly recognised when treatment has failed and that treatment is escalated when needed. They made a consensus recommendation to support this.
Certainty of the Evidence

No evidence was identified in the evidence review, but the panel still regards it as important to give a recommendation by consensus because it is important that staff have skills and competencies in CPAP and that people having CPAP are regularly reviewed.

Values and preferences

The panel discussed the importance of ensuring that CPAP is not used for longer than is required and the importance of recognising when treatment has failed so that treatment is escalated when needed.

Resources

Resource use was not assessed as part of the evidence review. However, the panel noted that review and monitoring may result in additional use of staff resources.

Rationale

Based on their experience, the panel agreed that it is important to closely review people with COVID-19 having continuous positive airway pressure (CPAP). This is to ensure that CPAP is not used for longer than necessary and that treatment is escalated when needed.

Consensus recommendation

Consider using high-flow nasal oxygen for people when:

- they cannot tolerate continuous positive airway pressure (CPAP) but need humidified oxygen at high flow rates
- maximal conventional oxygen is not maintaining their target oxygen saturations and:
  - they do not need immediate invasive mechanical ventilation or escalation to invasive mechanical ventilation is not suitable, and
  - CPAP is not suitable
- they need:
  - a break from CPAP (such as at mealtimes, for skin and pressure area relief, or for mouth care)
  - humidified oxygen or nebulisers (or both)
  - weaning from CPAP.

The British Thoracic Society and Intensive Care Society have produced information on management of acute hypoxaemic respiratory failure associated with COVID-19, which includes the use of CPAP.

Evidence to decision

Benefits and harms

Although there is no evidence on treatment breaks from continuous positive airway pressure (CPAP), the panel noted this was an important consideration. The panel acknowledged that although high-flow nasal oxygen should not be routinely offered as the main form of respiratory support, it may be considered in some situations. This includes when maximal conventional oxygen is not maintaining the person’s target oxygen saturations and they do not need
immediate intubation. It also includes people having CPAP who cannot tolerate CPAP, or who need a break from CPAP (such as at mealtimes), humidified oxygen or weaning from CPAP. They made a consensus recommendation to support this.

**Certainty of the Evidence**

No evidence was identified in the evidence review, but the panel still regards it as important to give a recommendation by consensus to consider high-flow nasal oxygen (HFNO) in some situations because HFNO is the only intervention that will deliver high volume oxygen for a hypoxic person which is humidified over a period of days to potentially weeks.

**Values and preferences**

The panel discussed that people can find CPAP uncomfortable. The panel commented that some people may find it difficult to tolerate non-invasive respiratory support. Therefore, the panel made a consensus recommendation to provide situations when HFNO may be considered.

**Resources**

Resource use was not assessed as part of the evidence review.

**Rationale**

Evidence showed no statistically significant benefits between high-flow nasal oxygen (HFNO) compared with conventional oxygen. The panel acknowledged that although HFNO should not be the main form of respiratory support, it may be considered in some situations. The panel used their expertise to inform the recommendation on when to consider HFNO.
7. Therapeutics for COVID-19

Info Box

In March 2023, we updated and replaced recommendations on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab. The evidence on the clinical and cost effectiveness of these therapeutics was reviewed through the NICE multiple technology appraisal process. For evidence and information about the decision making, see NICE’s technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.

We amended the recommendation on baricitinib to provide clarity on when it can be used. We also amended the recommendations on remdesivir to account for an extension to the marketing authorisation to include the paediatric population.

We removed the recommendation on sarilumab. The recommendation was for off-label use of sarilumab because it is not licensed for use in COVID-19. This recommendation has been superseded by NICE’s technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for people with COVID-19, which recommends tocilizumab, an interleukin-6 inhibitor licensed for use in COVID-19.

Evidence on the clinical and cost effectiveness of molnupiravir, remdesivir, and tixagevimab plus cilgavimab is currently under review through the NICE multiple technology appraisal process.

7.1 Antivirals

7.1.1 Nirmatrelvir and ritonavir

Recommended

Nirmatrelvir plus ritonavir is recommended as an option for treating COVID-19 in adults, only if they:

- do not need supplemental oxygen for COVID-19 and
- have an increased risk for progression to severe COVID-19, as defined in section 5 of NICE’s technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.

This recommendation is from NICE’s technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.

Rationale

There is some clinical evidence suggesting that nirmatrelvir plus ritonavir is effective at treating COVID-19. Nirmatrelvir plus ritonavir is recommended because the likely cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources. For evidence and information on how this decision was made, see NICE’s technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.

7.1.2 Remdesivir
Evidence on the clinical and cost effectiveness of remdesivir is currently under review through the NICE multiple technology appraisal process.

**Definitions**

**Invasive mechanical ventilation:** any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the Intensive Care National Audit & Research Centre definition of ‘advanced respiratory support’.

**Low-flow supplemental oxygen:** oxygen delivered by a simple face mask or nasal canula at a flow rate usually up to 15 litres/min.

**Conditional recommendation**

Consider a 3-day course of remdesivir for children and young people who weigh at least 40 kg and adults with COVID-19 who:

- do not need supplemental oxygen for COVID-19, and
- are within 7 days of symptom onset, and
- are thought to be at high risk of progression to severe COVID-19. (NHS England’s Interim Clinical Commissioning Policy on remdesivir and molnupiravir provides a list of people prioritised for treatment with antivirals.)

When assessing the person, take into account likely response to any vaccinations against COVID-19 they have already had, any comorbidities or risk factors, and whether their condition is deteriorating.

*This recommendation is informed by the results of the PINETREE trial, which only included people not vaccinated against COVID-19. The trial took place before the emergence of the Delta (B.1.617.2) and Omicron (B.1.1.529) variants.*

**Evidence to decision**

**Benefits and harms**

Two randomised controlled trials were included as part of the evidence review for remdesivir in people who do not need supplementary oxygen and are within 7 days of symptom onset, Abd-Elsalam (2021) and PINETREE. Because of serious concerns about risk of bias for Abd-Elsalam and concerns about the comparability of the 2 study populations, the panel focused on PINETREE when making recommendations.

The primary outcome of PINETREE was the composite outcome of COVID-19-related hospitalisation or death from any cause within 28 days. A secondary outcome was the composite outcome of COVID-19-related medical visits or death from any cause within 28 days. Both of these composite outcomes included ‘death from any cause within 28 days’. But the panel noted that there were no deaths reported in either arm of the study. So, they considered the frequency of hospitalisations and
medical visits in the study to inform the recommendations.

The panel noted that PINETREE enrolled people who had not been vaccinated against COVID-19 and who had at least 1 risk factor for progression to severe COVID-19 (including being over 60, or having a body mass index of 30 or more, hypertension, diabetes, chronic lung disease or other comorbidities). The panel agreed that the evidence in this population suggests there is a reduction in COVID-19-related hospitalisation and COVID-19-related medical visits within 28 days with remdesivir compared with placebo. They also agreed that the results were consistent across the subgroup analyses presented. However, the panel noted that the difference in the absolute number of events between the remdesivir and placebo groups was modest. There were 2 hospitalisations within 28 days with remdesivir compared with 15 hospitalisations within 28 days with placebo. The panel considered that the absolute benefit of remdesivir would potentially be smaller among people who have been vaccinated against COVID-19.

The panel noted that the eligibility criteria for PINETREE included being 12 years and over. However, of the 562 people in the trial, only 8 were between 12 and 18 years, and outcomes were not presented for this group. The panel also noted that the indication for remdesivir for people with COVID-19 who do not need supplemental oxygen and who are at increased risk of progressing to severe COVID-19 includes children and young people weighing 40kg and over as well as adults.

The panel noted that there were no statistically significant differences in the frequency of adverse events:

- among people having remdesivir compared with those having placebo, or
- leading to treatment being stopped.

They noted that people in PINETREE had normal baseline renal function and blood tests. They also noted that serious adverse events were statistically significantly less frequent with remdesivir. Based on this evidence, the panel concluded that there were no serious safety concerns associated with remdesivir in the study.

The panel also discussed the potential benefits and harms of combination treatment with an antiviral drug and a neutralising monoclonal antibody or another antiviral drug in people who do not need supplemental oxygen for COVID-19 and who are at high risk of progression to severe disease.

**Certainty of the Evidence**

The certainty of all outcomes from the PINETREE study was downgraded because of indirectness. This was because it took place before the emergence of the Delta and Omicron variants of COVID-19 and because no one in the study had been vaccinated against COVID-19. The panel agreed that these factors meant that the evidence from PINETREE was not directly relevant to the COVID-19 situation in the UK in early 2022, when the Omicron variant was dominant and many people had been vaccinated against COVID-19. So, the certainty of the evidence for the key outcome that the panel referenced in their decision making (COVID-19-related hospitalisation or death from any cause within 28 days) was rated as moderate.

Some outcomes from PINETREE were downgraded further because of imprecision. This applied to the outcomes for ‘any adverse event’ and ‘adverse event leading to trial discontinuation’, which were
graded as low certainty because of imprecision. This was because the confidence interval crossed the line of no effect.

One outcome from PINETREE was downgraded further because of risk of bias. The study authors did not provide data for everyone in the study for ‘COVID-19-related medical visit or death from any cause within 28 days’. Also, they did not specify the reasons for the exclusion of people from this outcome, so the certainty in this outcome was rated as low.

The panel noted that the evidence was from people with COVID-19 who were not in hospital. But, they agreed that the results could be generalised to people in hospital for reasons other than COVID-19 who meet the criteria set out in the recommendation.

Values and preferences

The panel were not aware of any systematically collected data on peoples’ preferences and values. But, they noted that remdesivir’s intravenous mode of delivery is likely to influence patient preference, particularly because it would mean people would need to travel to an infusion site on 3 consecutive days for treatment. The panel discussed that the time involved in the infusion process may affect people's preferences because they would need to set aside time to travel to and from the infusion site. It could also mean they may need to take time away from caring responsibilities or work to have remdesivir. The panel were also aware that some people have a fear of needles or injections.

Resources

The recommendations were not informed by a cost-effectiveness analysis. The panel had concerns about the opportunity costs associated with using remdesivir, including drug costs, costs associated with running outpatient infusion facilities and NHS staff time, and the importance of not diverting resources away from hospital care.

Equity

The panel raised several concerns about potential inequities that may result from this recommendation. Primarily, the panel were concerned that the intravenous mode of delivery for remdesivir could make it inaccessible to subgroups with lower socioeconomic status. This was because they may not be able to access transport to an infusion facility or take time away from work on consecutive days to complete their treatment. The panel noted that people who use public transport to access their remdesivir infusion might also risk exposing others to COVID-19 throughout their transit. The panel were aware that some trusts provide transport to help people with COVID-19 safely attend infusion appointments, but noted that this may be difficult to access. The panel also noted that people with mobility issues, people with caring responsibilities who need to arrange care cover over consecutive days and people who are homeless or from Traveller communities could face additional barriers in accessing remdesivir treatment.

When discussing the evidence, the panel noted that underrepresentation of several groups in PINETREE could result in inequities. The panel noted that only 8 young people aged 12 to 17, and no one younger than this, were included. It also noted that only 4% of the study population were immunocompromised. Also, the study authors did not specify whether anyone in the study was pregnant.
The panel also noted that people from a minority ethnic family background were underrepresented in the study, including people from a Black or Asian family background. This underrepresentation presented an important inequity issue because COVID-19 incidence and severity in the UK are higher in these groups. The panel were concerned that inequitable access to treatment could exacerbate existing health inequalities. They emphasised that the underrepresentation of these groups in PINETREE, and the subsequent lack of evidence, should not prevent people from these groups, who are otherwise eligible for treatment, from being offered remdesivir.

The panel acknowledged that additional information is needed to understand how potential inequities may arise from this recommendation and how those inequities might be minimised. So, they proposed a research recommendation on remdesivir that includes pregnant women, people from minority ethnic family backgrounds, and children and young people as subgroups of particular interest.

**Acceptability**

The panel were not aware of any systematically collected evidence about acceptability. However, they noted that an intravenous treatment needing 3 consecutive days of infusion may not be acceptable to all people who are eligible for treatment. They noted that alternative treatments may be preferred. The panel thought that it was likely that some people who would qualify for and benefit from treatment with remdesivir to prevent progression to severe COVID-19 may elect not to have treatment. They might instead see if their symptoms resolve without remdesivir treatment.

**Feasibility**

The panel discussed the availability and feasibility of administering remdesivir in different areas in the UK. They were concerned that some NHS trusts may struggle to accommodate people wanting remdesivir infusions. They noted that COVID-19 Medicine Delivery Units (CMDUs) or similar units in the devolved administrations will be the main hub for people to have these treatments. But they were aware that travel to a CMDU for 3 consecutive days of remdesivir infusions may not be feasible for some people. The panel concluded that there are significant barriers to using remdesivir for people with COVID-19 in the community.

**Rationale**

Evidence from 1 randomised controlled trial (PINETREE) in adults who do not need supplemental oxygen and have at least 1 risk factor for developing severe COVID-19 suggests that treatment with remdesivir within 7 days of symptom onset reduces the risk of hospitalisation compared with placebo.

The evidence from this trial in young people aged 12 to 17 is limited because only 1% of people in the study were in this age range. However, the panel were aware that the marketing authorisation for remdesivir for people with COVID-19 who do not need supplemental oxygen includes children and young people who weigh 40 kg or more.

Overall, there is uncertainty about the generalisability of the clinical trial evidence to current clinical practice. This is because the trial only included people not vaccinated against COVID-19, and took place before the emergence of the Delta and Omicron variants.
Clinicians should refer to the NHS England Interim Clinical Commissioning Policy for the most up-to-date information about people prioritised for treatment with antivirals.

**Clinical question/ PICO**

- **Population:** People with COVID-19 and symptom onset in the last 7 days
- **Intervention:** Remdesivir
- **Comparator:** Standard care, standard care plus placebo, or placebo

**Summary**

*What is the effectiveness and safety of early remdesivir for adults, young people and children with COVID-19?*

**Key results**

Among people with COVID-19, the evidence suggests that early use of remdesivir (7 days or less from symptom onset) may reduce the need for further medical care and hospitalisation in people who are unvaccinated and have at least one risk factor for developing severe COVID-19 disease, compared to placebo.

**What is the evidence informing this conclusion?**

Evidence comes from 2 randomised controlled trials in unvaccinated people that compared remdesivir with placebo or standard care in 762 participants with confirmed SARS-COV-2 infection (Abd-Elsalam 2021; Gottlieb 2021). Most data are from the PINETREE trial [Gottleib 2021] which included 562 people with COVID-19. In this study, participants were randomised to remdesivir or placebo within 7 days of symptom onset. Participants in the PINETREE study had at least one ongoing COVID-19 symptom and had at least one risk factor for progression (age 60 and over or a comorbidity). In the Abd-Elsalam study, participants were randomised to remdesivir or standard care within 3 days of symptom onset, and severe COVID-19 patients were excluded. The PINETREE trial took place in outpatient settings while participants in the Abd-Elsalam 2021 study were treated in hospital.

**Publication status**

Both studies included in this review have been peer-reviewed.

**Study characteristics**

The severity of COVID across both studies was mild-to-moderate: severe COVID patients did not meet eligibility criteria in either study. The PINETREE study excluded patients requiring supplemental oxygen; the Abd-Elsalam study did not specify whether people requiring supplemental oxygen were excluded. Both studies took place prior to the emergence of the Delta and Omicron variants of COVID-19 and before the availability of vaccination against COVID-19.

Broadly speaking, the remdesivir and control arms in the PINETREE study are similar to one another while in the Abd-Elsalam study, there are meaningful differences in key patient characteristics across the different study arms. Those differences are noted below.

Eligibility criteria for age were similar in both studies: the PINETREE study was open to participants aged 12 and over, the Abd-Elsalam was open to participants aged 18-80. The mean age in the PINETREE study was 50 years, and the mean ages in the Abd-Elsalam study were 55 (remdesivir arm) and 52 (standard care arm). Note that the PINETREE study only enrolled 8 adolescent patients.

The proportion of males in the PINETREE trial was 53%, whereas in the Abd-Elsalam study, men...
comprised 66% of those in the remdesivir arm and 53% of those in the control arm.

The PINETREE study enrolled participants who were at elevated risk of disease progression due to at least one of the following factors: age 60 and over, obesity, or another comorbidity [incl. diabetes mellitus, hypertension, chronic lung disease among others]. The presence of these comorbidities was balanced across the treatment arms. Participants in the PINETREE study had normal blood tests at baseline. In the Abd-Elsalam study, the presence of diabetes mellitus was significantly higher in the remdesivir arm (39%) than in the placebo arm (27%). Aside from diabetes and hypertension, other comorbid conditions are not specified in the Abd-Elsalam study.

The starting dose and maintenance of intravenous (IV) remdesivir was the same in both studies (200 mg starting dose) followed by 100 mg on subsequent days, but the duration of treatment differed between the studies: 3 days in the PINETREE and 10 days in the Abd-Elsalam study. The cumulative dosage of remdesivir was higher in the Abd-Elsalam study.

Outcomes presented in both studies aimed to measure the differences in risk of disease progression between those treated with remdesivir vs. standard care. The PINETREE study also provided adverse event frequency as a measure of safety.

The PINETREE study was funded by Gilead Sciences; funding source is not disclosed for the Abd-Elsalam study.

For further details see the evidence review.

**What are the main results?**

Overall, COVID-19-related medical visits and hospitalisation, as well as serious adverse events, were significantly lower with remdesivir than standard care. See MAGICapp for full GRADE profiles. Forest plots were not conducted for this evidence review. This is because the study populations were too heterogeneous to combine in a meta-analysis, and because there were serious concerns about the risk of bias from the Abd-Elsalam study.

**COVID-19-related hospitalisation or death (at day 14 and 28)**

The PINETREE trial found a statistically significant reduction in the composite outcome of hospitalisation or death in people with at least one risk factor for COVID-19 who were treated with remdesivir compared to placebo.

Subgroup analyses presented based on several patient risk factors [age 60 and over, male sex, obesity, hypertension, and diabetes] were consistent with the overall finding. For the subgroups of patients with chronic lung disease, cardiovascular or cerebrovascular disease, and cancer, the differences between remdesivir and placebo were not statistically significant. Differences between remdesivir and placebo were also not statistically significant for ethnic subgroups represented in the PINETREE study.

**COVID-19-related medical visit or death (at day 14 and 28)**

The PINETREE trial found a statistically significant reduction in the composite outcome of medically attended visit or death in people with at least one risk factor for COVID-19 who were treated with remdesivir compared to placebo. Note that this outcome was only reported for 88% of patients in the PINETREE study.

**Death**

No patients in either arm of the PINETREE study had died at day 28.

The Abd-Elsalam study found no statistically significant difference in mortality in people
hospitalised with mild-to-moderate COVID-19 3 days after symptom onset who were treated with remdesivir compared to standard care.

Due to differences in study populations, these outcomes were not combined into meta-analysis.

**Hospitalisation (all causes, at day 28)**

The PINETREE trial found a statistically significant reduction in all-cause hospitalisation in people with at least one risk factor for COVID-19 who were treated with remdesivir compared to placebo.

**Duration of hospital stay**

The Abd-Elsalam study found a statistically significant reduction in the duration of hospital stay in people hospitalised with mild-to-moderate COVID-19 3 days after symptom onset who were treated with remdesivir compared to standard care.

**Need for mechanical ventilation**

The Abd-Elsalam study found no statistically significant difference in need for mechanical ventilation in people hospitalised with mild-to-moderate COVID-19 3 days after symptom onset who were treated with remdesivir compared to standard care.

**Adverse events (any)**

The PINETREE trial found no statistically significant difference in the frequency of any adverse event in people with at least one risk factor for COVID-19 who were treated with remdesivir compared to placebo. Adverse events that were determined by the investigators to be related to the trial regimen occurred in 34 of 279 patients (12.2%) in the remdesivir group and in 25 of 283 (8.8%) in the placebo group.

Adverse events measured in the study included (from most to least frequent): nausea, headache, cough, diarrhea, dyspnea, fatigue, ageusia, anosmia, dizziness, chills, pyrexia, and COVID-19 pneumonia.

**Serious adverse events**

The PINETREE trial found a statistically significant reduction in the frequency of serious adverse events in people with at least one risk factor for COVID-19 who were treated with remdesivir compared to placebo.

Note that severity grades were defined according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1.

**Discontinuation of trial regimen due to adverse events**

The PINETREE trial found no statistically significant difference in the frequency of discontinuation due to adverse events in people with at least one risk factor for COVID-19 who were treated with remdesivir compared to placebo.

**Symptom resolution**

The PINETREE trial found no statistically significant difference in the reduction of baseline COVID-19 symptoms among those treated with remdesivir compared to placebo. Note that this outcome is based on patient-reported symptoms in the FLU-PRO plus questionnaire and that data was not available for all patients in the PINETREE study.

**Viral load**
The PINETREE trial found no statistically significant change in nasopharyngeal SARS-CoV-2 viral load from baseline to day 7 in people with at least one risk factor for COVID-19 who were treated with remdesivir compared to placebo.

**Our confidence in the results**

Since both studies cited in this review took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the populations measured in the study may not be directly relevant or comparable to current populations in the UK, where the Delta and Omicron variants are dominant and many people have been vaccinated against COVID-19. As a result, the certainty in all outcomes presented was downgraded due to indirectness.

Altogether, we have moderate confidence in results from the PINETREE study but very low confidence in results from the Abd-Elsalam study.

Most outcomes from the PINETREE study were assessed as being at low risk of bias, and the certainty of the evidence was moderate to high due to large n-size (n>300), appropriate analysis methods used and sufficient information provided to assess the methods. There were some notable exceptions: certainty of evidence presented for two outcomes (COVID-19-related medical visits and patient-reported symptom alleviation) were downgraded due to risk of bias, since this data were only available for an unspecified subgroup of the study population.

All outcomes from the Abd-Elsalam study were assessed as being at high risk of bias, due to significant differences in baseline patient characteristics of those allocated to remdesivir vs. standard care. Evidence from the Abd-Elsalam study was imprecise as the total study n-size was 200 patients (n<300).

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care, standard care plus placebo, or placebo</th>
<th>Intervention Remdesivir</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
</table>
| COVID-19–related hospitalisation or death from any cause by day 28 | Relative risk 0.14 (CI 95% 0.03 — 0.59) Based on data from 562 participants in 1 studies.  
1 (Randomized controlled) | 53 per 1000 Difference: 7 per 1000  
46 fewer per 1000 (CI 95% 51 fewer — 22 fewer) | Moderate Due to serious indirectness 2 | One study found a statistically significant reduction in COVID-19 related hospitalisation or death from any cause within 28 days among unvaccinated people treated with remdesivir compared to placebo. |
| COVID-19–related hospitalisation or death from any cause by day 14 | Relative risk 0.14 (CI 95% 0.03 — 0.59) Based on data from 562 participants in 1 studies.  
3 (Randomized controlled) | 53 per 1000 Difference: 7 per 1000  
46 fewer per 1000 (CI 95% 51 fewer — 22 fewer) | Moderate Due to serious indirectness 4 | One study found a statistically significant reduction in COVID-19 related hospitalisation or death from any cause within 14 days among unvaccinated people treated with remdesivir compared to placebo. |
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COVID-19–related medically attended visit or death from any cause by day 28</strong>&lt;br&gt;Relative risk 0.2 (CI 95% 0.07 — 0.56) Based on data from 498 participants in 1 studies.</td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>Remdesivir</td>
<td>83 per 1000&lt;br&gt;66 fewer per 1000 (CI 95% 77 fewer — 37 fewer)</td>
<td>Low Due to serious risk of bias and serious indirectness</td>
<td>One study found a statistically significant reduction in COVID-19 related medical visit or death from any cause within 28 days among unvaccinated people treated with remdesivir compared to placebo.</td>
</tr>
<tr>
<td><strong>COVID-19–related medically attended visit or death from any cause by day 14</strong>&lt;br&gt;Relative risk 0.1 (CI 95% 0.02 — 0.43) Based on data from 498 participants in 1 studies.</td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>Remdesivir</td>
<td>79 per 1000&lt;br&gt;71 fewer per 1000 (CI 95% 77 fewer — 45 fewer)</td>
<td>Low Due to serious risk of bias and serious indirectness</td>
<td>One study found a statistically significant reduction in COVID-19 related medical visit or death from any cause within 14 days among unvaccinated people treated with remdesivir compared to placebo.</td>
</tr>
<tr>
<td><strong>Death from all causes by day 28</strong>&lt;br&gt;Relative risk</td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>Remdesivir</td>
<td>0 per 1000&lt;br&gt;0 fewer per 1000 (CI 95% 0 fewer — 0 fewer)</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
<td>One study found no deaths among unvaccinated people treated with remdesivir or placebo.</td>
</tr>
<tr>
<td><strong>Death</strong>&lt;br&gt;Relative risk 1.29 (CI 95% 0.5 — 3.32) Based on data from 200 participants in 1 studies.</td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>Remdesivir</td>
<td>70 per 1000&lt;br&gt;20 more per 1000 (CI 95% 35 fewer — 162 more)</td>
<td>Very low Due to serious risk of bias, very serious imprecision and serious indirectness</td>
<td>One study found no statistically significant difference in mortality among unvaccinated people treated with remdesivir compared to placebo.</td>
</tr>
<tr>
<td><strong>Hospitalisation from all causes by day 28</strong>&lt;br&gt;Relative risk 0.28 (CI 95% 0.11 — 0.75) Based on data from 562 participants in 1 studies.</td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>Remdesivir</td>
<td>64 per 1000&lt;br&gt;46 fewer per 1000 (CI 95% 57 fewer — 16 fewer)</td>
<td>Moderate Due to serious indirectness</td>
<td>One study found a statistically significant reduction in hospitalisation from any cause within 28 days among unvaccinated people treated with remdesivir compared to placebo.</td>
</tr>
<tr>
<td><strong>Need for mechanical ventilation</strong>&lt;br&gt;Relative risk 1.38 (CI 95% 0.58 — 3.27) Based on data from 200 participants in 1 studies.</td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>Remdesivir</td>
<td>80 per 1000&lt;br&gt;30 more per 1000</td>
<td>Very low Due to very serious imprecision, serious risk of bias, and serious</td>
<td>One study found no statistically significant difference in the need for mechanical ventilation among unvaccinated people</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
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<tr>
<td>Any adverse event</td>
<td>Relative risk 0.91 (CI 95% 0.76 — 1.1) Based on data from 562 participants in 1 studies.</td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>Remdesivir</td>
<td>Low Due to serious imprecision and serious indirectness</td>
<td>One study found no statistically significant difference in the frequency of adverse events among unvaccinated people treated with remdesivir compared to placebo.</td>
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<tr>
<td>Serious adverse event</td>
<td>Relative risk 0.27 (CI 95% 0.1 — 0.7) Based on data from 562 participants in 1 studies.</td>
<td></td>
<td>Remdesivir</td>
<td>Moderate Due to serious indirectness</td>
<td>One study found a statistically significant reduction in the frequency of serious adverse events among unvaccinated people treated with remdesivir compared to placebo.</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation of trial regimen</td>
<td>Relative risk 0.41 (CI 95% 0.08 — 2.07) Based on data from 562 participants in 1 studies.</td>
<td></td>
<td>Remdesivir</td>
<td>Low Due to serious imprecision and serious indirectness</td>
<td>One study found no statistically significant difference in the frequency of adverse events leading to trial discontinuation among unvaccinated people treated with remdesivir compared to placebo.</td>
</tr>
<tr>
<td>Alleviated baseline COVID-19 symptoms [based on FLU-PRO Plus questionnaire]</td>
<td>Relative risk 1.39 (CI 95% 0.81 — 2.41) Based on data from 126 participants in 1 studies.</td>
<td></td>
<td>Remdesivir</td>
<td>Very low Due to very serious imprecision and serious indirectness</td>
<td>One study found no statistically significant difference in the alleviation of self-reported symptoms among unvaccinated people treated with remdesivir compared to placebo.</td>
</tr>
<tr>
<td>Duration of hospital stay</td>
<td>Based on data from 200 participants in 1 studies.</td>
<td></td>
<td>Remdesivir</td>
<td>Low Due to serious risk of bias and serious indirectness</td>
<td>One study found a statistically significant reduction in duration of hospital stay among unvaccinated people treated with remdesivir compared to placebo.</td>
</tr>
</tbody>
</table>
1. Systematic review [120]. Baseline/comparator: Control arm of reference used for intervention.
2. Inconsistency: no serious. Indirectness: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
   Imprecision: no serious. Publication bias: no serious.
4. Inconsistency: no serious. Indirectness: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
   Imprecision: no serious. Publication bias: no serious.
5. Systematic review [120]. Baseline/comparator: Control arm of reference used for intervention.
6. Risk of Bias: serious. Certainty of this outcome was downgraded because data were only available for a subset (88%) of the full study population, study authors did not provide a clear explanation as to why some patients were excluded from this analysis. Inconsistency: no serious. Indirectness: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations. Imprecision: no serious. Publication bias: no serious.
7. Systematic review [120]. Baseline/comparator: Control arm of reference used for intervention.
8. Risk of Bias: serious. Certainty of this outcome was downgraded because data were only available for a subset (88%) of the full study population, study authors did not provide a clear explanation as to why some patients were excluded from this analysis. Inconsistency: no serious. Indirectness: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations. Imprecision: no serious. Publication bias: no serious.
10. Inconsistency: no serious. Indirectness: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
   Imprecision: very serious. Publication bias: no serious.
12. Risk of Bias: serious. Certainty of this outcome was downgraded because of serious concerns about the randomisation approach used in the study. There were significant baseline differences between the remdesivir and placebo groups that could have biased the outcome: specifically, a higher proportion of males and greater incidence of diabetes mellitus among patients in the remdesivir arm compared to patients in the placebo arm. Inconsistency: no serious. Indirectness: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations. Imprecision: very serious. Certainty in this outcome is further downgraded due to small n-size and because the confidence interval includes no effect. Publication bias: no serious.
14. Inconsistency: no serious. Indirectness: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
   Imprecision: no serious. Publication bias: no serious.
15. Systematic review [120]. Baseline/comparator: Control arm of reference used for intervention.
16. Risk of Bias: serious. Certainty of this outcome was downgraded because of serious concerns about the randomisation approach used in the study. There were significant baseline differences between the remdesivir and placebo groups that could have biased the outcome: specifically, a higher proportion of males and greater incidence of diabetes mellitus among patients in the remdesivir arm
compared to patients in the placebo arm. **Inconsistency:** no serious. **Indirectness:** serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations. **Imprecision:** very serious. Certainty in this outcome is further downgraded due to small n-size and because the confidence interval includes no effect. **Publication bias:** no serious.

17. Systematic review [120]. **Baseline/comparator:** Control arm of reference used for intervention.

18. **Inconsistency:** no serious. **Indirectness:** serious. **Imprecision:** serious. Certainty of this outcome was downgraded because the confidence interval includes no effect. **Publication bias:** no serious.

19. Systematic review [120]. **Baseline/comparator:** Control arm of reference used for intervention.

20. **Inconsistency:** no serious. **Indirectness:** serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations. **Imprecision:** no serious. **Publication bias:** no serious.

21. Systematic review [120]. **Baseline/comparator:** Control arm of reference used for intervention.

22. **Inconsistency:** no serious. **Indirectness:** serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations. **Imprecision:** very serious. Certainty of this outcome was downgraded because the confidence interval includes no effect and the n-size for this outcome was <300. **Publication bias:** no serious.

23. Systematic review [120]. **Baseline/comparator:** Control arm of reference used for intervention.

24. **Inconsistency:** no serious. **Indirectness:** serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations. **Imprecision:** very serious. Certainty of this outcome was downgraded because of serious concerns about the randomisation approach used in the study. There were significant baseline differences between the remdesivir and placebo groups that could have biased the outcome: specifically, a higher proportion of males and greater incidence of diabetes mellitus among patients in the remdesivir arm compared to patients in the placebo arm. **Inconsistency:** no serious. **Indirectness:** serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations. **Imprecision:** no serious. **Publication bias:** no serious.

**References**


Evidence to decision

**Conditional recommendation**

Consider a course of remdesivir (up to 5 days) for people who:

- have COVID-19 pneumonia, and
- are in hospital and need low-flow supplemental oxygen.

**The criteria for accessing remdesivir in the UK are outlined in NHS England's Interim Clinical Commissioning Policy on remdesivir for people in hospital with COVID-19, which includes people who are significantly immunocompromised.**

**For remdesivir use in pregnancy, follow the Royal College of Obstetrics and Gynaecology guidance on COVID-19 and pregnancy.**

**This recommendation is informed by the results of clinical trials that included very few people who had been vaccinated against COVID-19. Also, the trials took place before the emergence of the Delta (B.1.617.2) and Omicron (B.1.1.519) variants.**

**Evidence to decision**

**Benefits and harms**

Ten randomised controlled trials and 1 systematic review were included as part of the evidence review for remdesivir for people in hospital and needing supplementary oxygen. These studies compared the outcomes between people having remdesivir and people having placebo or standard care. The outcome of all-cause mortality was evaluated based on the level of respiratory support that people needed at baseline. For all other outcomes, including invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO), adverse events, serious adverse events, stopping treatment because of adverse events, clinical recovery, oxygen-free days, ventilator-free days, duration of hospital stay and hospital discharge, it was not possible to split the data by level of respiratory support.

When considering the benefits and harms of remdesivir treatment, the panel focused on the outcome of all-cause mortality. This was evaluated separately for people not having oxygen support or having low-flow supplemental oxygen at baseline and for people having high-flow supplemental oxygen, non-invasive ventilation (NIV) or IMV at baseline. Although not always described in the evidence, the panel considered that continuous positive airway pressure (CPAP) was included as a type of NIV.

The panel noted difficulties in disaggregating data on different modalities of respiratory support to inform subgroup analysis. Notably, the WHO-SOLIDARITY trial did not report high-flow and low-flow oxygen separately. Also, it did not distinguish between NIV and IMV. The subgroups presented in this trial were people not having supplemental oxygen at baseline, people having supplemental oxygen at baseline and people having ventilation at baseline. However, the panel agreed that subgroup data should be distinguished between high-flow oxygen, NIV or IMV and low-flow oxygen modalities in the pooled meta-analysis of included studies. For the WHO-SOLIDARITY trial, the panel agreed to include people having supplemental oxygen in the meta-analyses for people having low-flow or no oxygen at baseline. Also, people having ventilation were included in the meta-analyses for people having high-flow oxygen, NIV or IMV at baseline.

The panel noted that there was a statistically significant reduction in all-cause mortality among people having no or low-flow oxygen. There was no difference in mortality between remdesivir and control among people having high-flow oxygen, NIV or IMV at baseline.

The panel discussed a clinical rationale for this trend, based on the mechanism of action of antiviral...
treatments. This hypothesis states that antivirals are expected to be:

- most effective early in the disease course, when viral replication is a driver of disease
- less likely to be effective in the later stages in the disease course, when it enters the hyperinflammatory phase when people are more likely to need more extensive respiratory support.

Note that the studies included in this evidence review did not provide data on viral load.

Evidence from randomised controlled trials of remdesivir compared with standard care shows that remdesivir has an acceptable safety profile. There was no statistically significant difference in adverse events, serious adverse events, stopping because of adverse events, respiratory failure or acute respiratory distress syndrome, or septic shock among people having remdesivir compared with standard care.

The panel noted that the direction of effect was consistently in favour of remdesivir across studies for people having low-flow oxygen or no oxygen. They agreed that a ‘consider’ recommendation for people on low-flow oxygen and not on high-flow oxygen, NIV or IMV would allow for clinical discretion in making individualised treatment decisions. They also agreed that it would reflect the level of uncertainty in the evidence.

Based on the results of 2 studies that compared 10-day with 5-day courses of remdesivir, the current evidence does not suggest any greater benefit for a 10-day duration but suggests an increased risk of harm. The panel also acknowledged that, if disease progression results in the need for more respiratory support while using remdesivir, there may be no benefit in completing the full course. For these reasons, along with resource impact considerations (see also Resources), the panel agreed to recommend remdesivir for up to 5 days.

The panel noted the unclear additive benefit of remdesivir when used with dexamethasone, particularly because the 2 main trials, SOLIDARITY and ACTT-1, were done before the routine use of dexamethasone.

The panel also reviewed data from an observational study but did not consider this to have any effect on the recommendations.

**Certainty of the Evidence**

For outcomes relevant to the benefit of remdesivir treatment (including all-cause mortality, need for mechanical ventilation, need for oxygen supplementation, clinical recovery, duration of hospital stay, discharge from hospital, oxygen-free days, ventilator-free days, time to improvement and time to recovery), the certainty of evidence was very low to moderate.

Certainty of the evidence was moderate for all-cause mortality in people who need low-flow supplemental oxygen or no oxygen because of serious risk of bias. This is because there is a risk that people enrolled in the WHO-SOLIDARITY were also included in published results of add-on trials, including CATCO (Ali 2022) in Canada and DisCoVeRy (Ader 2022) in France. The certainty of the evidence for all-cause mortality in people who need high-flow oxygen, NIV or IMV was downgraded...
further for imprecision because the confidence interval crossed the line of no effect.

For outcomes relevant to the safety of remdesivir (including adverse events, serious adverse events, stopping because of adverse events, respiratory failure or ARDS, and septic shock), the certainty of the evidence was low to very low. This is because of inconsistency in outcomes resulting from statistical heterogeneity in the meta-analysis, imprecision when the confidence interval crossed the line of no effect and serious risk of bias because 2 of the included studies were unblinded.

Values and preferences

The panel were not aware of any systematically collected data on peoples’ preferences and values. They identified critical outcomes that would be important for decision making. These included all-cause mortality, the need for IMV and serious adverse events. It is likely that these outcomes would also be of similar importance to people with COVID-19. In addition, other outcomes including less serious adverse events, discharge from hospital, duration of hospital stay and longer-term outcomes such as functional independence are likely to be of particular importance to people with COVID-19. These outcomes were not as commonly reported in studies. The outcome of functional independence was not reported at all in studies included in this review.

The panel inferred that, in view of the probable mortality benefits for people with COVID-19 who need low-flow supplemental oxygen, most would choose remdesivir.

Resources

Cost effectiveness was not assessed as part of the evidence review.

The panel raised concerns about opportunity costs where remdesivir is being used in critical care, and the importance of not diverting resources away from best supportive care. The panel noted the value of targeting treatment to optimise use of resources. The panel also noted the lack of evidence showing any benefit of a 10-day over a 5-day regimen, a direction of effect indicating potential harms of the 10-day duration and the resource impact for a longer treatment duration. See also the benefits and harms section.

Equity

The panel noted an absence of evidence from randomised controlled trials on remdesivir use in children. However, it was considered unlikely that most children would benefit from this intervention because most children will recover without the need for it.

The panel also noted a lack of evidence from randomised controlled trials on remdesivir use in people who were immunocompromised. The studies included in this review did not exclude people in this subgroup, but it was not possible to analyse the effect of remdesivir in them. The panel decided to refer to NHS England’s Interim Clinical Commissioning Policy on remdesivir for people in hospital with COVID-19, which includes people who are significantly immunocompromised. This policy states that ‘for significantly immunocompromised patients hospitalised for COVID-19 symptoms, a course of remdesivir can be extended to a maximum of 10 days’.
Evidence suggests that remdesivir reduces the risk of death in people in hospital with COVID-19 pneumonia needing low-flow supplemental oxygen. This is likely because it is being used early in the disease course (that is, before the need for high-flow supplemental oxygen, non-invasive ventilation or invasive mechanical ventilation) when viral replication is a driver of the condition.

The evidence for remdesivir in babies, children and young people is limited. However, the panel were aware that the marketing authorisation for remdesivir for people with COVID-19 pneumonia and who need supplemental oxygen includes babies, children and young people aged 4 weeks and weighing 3 kg or more.

The evidence does not suggest any greater benefit with a 10-day course of remdesivir compared with a 5-day course, but suggests an increased risk of harm. There may also be no benefit in completing the full course of remdesivir if there is progression to high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation during treatment. The panel also acknowledged that using remdesivir for longer would have greater resource implications.

No evidence for using remdesivir in pregnancy was identified. The marketing authorisation confirms the lack of evidence, and notes that remdesivir should be avoided in pregnancy unless 'the clinical condition of the women requires treatment with it'. Any decisions to use remdesivir in someone who is pregnant should involve them and a multidisciplinary team, if possible.

Some people with COVID-19 may have treatment through virtual wards. However, supporting information published by NHS England about virtual wards does not include criteria for specific treatments, including remdesivir, in this acute setting. No evidence was identified on remdesivir use in hospital-led acute care in the community, including hospital at home and virtual wards. But new evidence and intelligence on policy changes to services will be monitored through surveillance.

No other equity issues were identified.

**Acceptability**

The panel were not aware of any systematically collected evidence about acceptability. A potential deterring factor to acceptability could be that the certainty of current evidence is very low to moderate. However, the panel noted the consistent direction of effect in favour of remdesivir for those on lower levels of respiratory support.

It is anticipated that, when considering the risks and benefits of treatment, most people who are admitted to hospital with COVID-19 pneumonia and need low-flow supplemental oxygen would choose to have remdesivir.

**Feasibility**

Although there is no systematically collected evidence about feasibility, the panel noted that current widespread use of remdesivir in clinical practice is an indicator of feasibility.

**Rationale**

Evidence suggests that remdesivir reduces the risk of death in people in hospital with COVID-19 pneumonia needing low-flow supplemental oxygen. This is likely because it is being used early in the disease course (that is, before the need for high-flow supplemental oxygen, non-invasive ventilation or invasive mechanical ventilation) when viral replication is a driver of the condition.

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The evidence does not suggest any greater benefit with a 10-day course of remdesivir compared with a 5-day course, but suggests an increased risk of harm. There may also be no benefit in completing the full course of remdesivir if there is progression to high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation during treatment. The panel also acknowledged that using remdesivir for longer would have greater resource implications.
Clinical question/ PICO

Population: People with COVID-19
Intervention: Remdesivir 5 days
Comparator: Remdesivir 10 days

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 moderate to critical COVID-19 (Goldman 2020; Spinner 2020).

Study characteristics
Mean or median age ranged between 56 to 62 years and women comprised 32 to 40% of patients across both studies. Pregnant people and children were ineligible, with the exception of 1 trial (Spinner 2020) which included children over 12 years weighing 40kg or more.

The majority of people (84%) in 1 trial (Spinner 2020) were not receiving oxygen supplementation at baseline. In the second trial 55% were receiving oxygen supplementation at baseline and 30.5% were ventilated (Goldman 2020).

What are the main results?

Critical outcomes

All-cause mortality
Moderate quality evidence from 2 studies found no statistically significant difference in all-cause mortality at 14 days with remdesivir 5-day treatment compared to 10-day treatment (16 fewer deaths per 1000 people [RR 0.73 95% CI 0.40 to 1.33; 781 people in 2 studies]).

Low quality evidence from 1 study found no statistically significant difference in all-cause mortality at 28 days with remdesivir 5-day treatment compared to 10-day treatment (5 fewer deaths per 1000 people [RR 0.67 95% CI 0.11 to 3.99; 384 people in 1 study]).

Serious adverse events
Moderate quality evidence from 2 studies found a statistically significant reduction in serious adverse events with remdesivir 5-day treatment compared to 10-day treatment (72 fewer events per 1000 people [RR 0.64 95% CI 0.47 to 0.87; 781 people in 2 studies]).

Important outcomes

Acute respiratory failure or ARDS
Low quality evidence from 1 study found a statistically significant reduction in acute respiratory failure or ARDS at 30 days with remdesivir 5-day treatment compared to 10-day treatment (62 fewer events per 1000 people [RR 0.47 95% CI 0.24 to 0.94; 397 people in 1 study]).

Septic shock
Very low-quality evidence from 1 study found no statistically significant difference in septic shock....
at 30 days with remdesivir 5-day treatment compared to 10-day treatment (15 fewer events per 1000 people [RR 0.39 95% CI 0.08 to 2.01; 397 people in 1 study]).

Clinical recovery
Low quality evidence from 1 study found a statistically significant increase in clinical recovery at 14 days with remdesivir 5-day treatment compared to 10-day treatment (108 more events per 1000 people [RR 1.20 95% CI 1.02 to 1.14; 397 people in 1 study]).

Adverse events
Moderate quality evidence from 2 studies found no statistically significant difference in adverse events with remdesivir 5-day treatment compared to 10-day treatment (46 fewer events per 1000 people [RR 0.93 95% CI 0.84 to 1.03; 781 people in 2 studies]).

Discontinuation due to adverse events
Low quality evidence from 2 studies found no statistically significant difference in discontinuation due to adverse events at 14 days with remdesivir 5-day treatment compared to 10-day treatment (23 fewer events per 1000 people [RR 0.59 95% CI 0.30 to 1.15; 781 people in 2 studies]).

Discharge from hospital
Moderate quality evidence from 2 studies found no statistically significant difference in discharge from hospital at 14 days with remdesivir 5-day treatment compared to 10-day treatment (38 more events per 1000 people [RR 1.06 95% CI 0.93 to 1.20; 781 people in 2 studies]).

Low quality evidence from 1 study found no statistically significant difference in discharge from hospital at 28 days with remdesivir 5-day treatment compared to 10-day treatment (9 fewer events per 1000 people [RR 0.99 95% CI 0.92 to 1.06; 384 people in 1 study]).

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 or discontinuation due to adverse event within 14 days and discharge from hospital within 28 days. This judgement is based on serious risk of bias (problems with randomisation, lack of blinding), serious imprecision (low event rate for the outcome of death within 14 days) and very serious imprecision (reliance on a single study with few patients and/or few events). Certainty of the evidence is very low for septic shock due to lack of blinding and reliance on a single study with few patients and few events.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Remdesivir 10 days</th>
<th>Intervention Remdesivir 5 days</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality Within 14 days of commencing treatment</td>
<td>Relative risk 0.73 (CI 95% 0.4 — 1.33) Based on data from 781 participants in 2 studies. 1 (Randomized controlled)</td>
<td>59 per 1000 Difference:</td>
<td>43 per 1000 16 fewer per 1000 ( CI 95% 35 fewer</td>
<td>Moderate Due to serious imprecision 2</td>
<td>A pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 14 days with remdesivir 5-day treatment compared to</td>
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<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
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<tr>
<td></td>
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<td>Relative risk 0.67 (CI 95% 0.11 — 3.99) Based on data from 384 participants in 1 studies.</td>
<td>Remdesivir 10</td>
<td>— 19 more )</td>
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<td>(Randomized controlled)</td>
<td>days</td>
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<td></td>
<td>Relative risk 0.64 (CI 95% 0.47 — 0.87) Based on data from 781 participants in 2 studies.</td>
<td>Remdesivir 5</td>
<td>11 per 1000</td>
<td>Moderate</td>
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<td>5 fewer per</td>
<td>Due to serious risk of bias</td>
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<td>(CI 95% 14 fewer — 48 more)</td>
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<td>Relative risk 0.47 (CI 95% 0.24 — 0.94) Based on data from 397 participants in 1 studies.</td>
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<td>128 per 1000</td>
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<td>(Randomized controlled)</td>
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<td>72 fewer per</td>
<td>Due to very serious imprecision</td>
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<td>1000</td>
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<td>(CI 95% 89 fewer — 7 fewer)</td>
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<td></td>
<td>Relative risk 0.39 (CI 95% 0.08 — 2.01) Based on data from 397 participants in 1 studies.</td>
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<td>25 per 1000</td>
<td>Very low</td>
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<td>(Randomized controlled)</td>
<td></td>
<td>15 fewer per</td>
<td>Due to very serious imprecision and serious risk of bias</td>
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<td>(CI 95% 23 fewer — 25 more)</td>
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<td>Relative risk 1.2 (CI 95% 1.02 — 1.41) Based on data from 397 participants in 2 studies.</td>
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<td>538 per 1000</td>
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<td>(Randomized controlled)</td>
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<td>646 per 1000</td>
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<td>(CI 95% 11 more — 221 more)</td>
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<tr>
<td></td>
<td></td>
<td>Relative risk 0.93</td>
<td></td>
<td>662</td>
<td>Moderate</td>
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</tbody>
</table>

Adverse events

Relative risk 0.93

662

616

Moderate
<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
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<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of follow-up 6 Important</td>
<td>Mean (CI) 0.84 — 1.03 Based on data from 781 participants in 2 studies. 13 (Randomized controlled)</td>
<td>46 fewer per 1000 (CI 95% 106 fewer — 20 more)</td>
<td>Due to serious risk of bias 14</td>
<td>studies found no statistically significant difference in adverse events with remdesivir 5-day treatment compared to 10-day treatment.</td>
<td></td>
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<tr>
<td>Discontinued due to adverse event Within 14 days of commencing treatment 6 Important</td>
<td>Relative risk 0.59 (CI 95% 0.3 — 1.15) Based on data from 781 participants in 2 studies. 15 (Randomized controlled)</td>
<td>23 fewer per 1000 (CI 95% 39 fewer — 8 more)</td>
<td>Low Due to serious risk of bias and serious imprecision 16</td>
<td>A pooled analysis of 2 studies found no statistically significant difference in discontinuation due to adverse events at 14 days with remdesivir 5-day treatment compared to 10-day treatment.</td>
<td></td>
</tr>
<tr>
<td>Discharged from hospital Within 14 days of commencing treatment 6 Important</td>
<td>Relative risk 1.06 (CI 95% 0.93 — 1.2) Based on data from 781 participants in 2 studies. 17 (Randomized controlled)</td>
<td>38 more per 1000 (CI 95% 45 fewer — 128 more)</td>
<td>Moderate Due to serious risk of bias 18</td>
<td>A pooled analysis of 2 studies found no statistically significant difference in discharge from hospital at 14 days with remdesivir 5-day treatment compared to 10-day treatment.</td>
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<tr>
<td>Discharged from hospital Within 28 days of commencing treatment 6 Important</td>
<td>Relative risk 0.99 (CI 95% 0.92 — 1.06) Based on data from 384 participants in 1 study. 19 (Randomized controlled)</td>
<td>9 fewer per 1000 (CI 95% 72 fewer — 54 more)</td>
<td>Low Due to very serious imprecision 20</td>
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</tbody>
</table>

2. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. due to few events.
4. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Low number of patients, Only data from one study, due to few events.
6. **Risk of Bias:** serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** no serious. **Publication bias:** no serious.

References
22. Remdesivir for COVID-19 internal meta-analyses..
Clinical question/ PICO

Population: People with COVID-19 (Hospitalised)
Intervention: Remdesivir
Comparator: Placebo or standard care

Summary

What is the effectiveness and safety of remdesivir for adults, young people and children hospitalised with COVID-19?

Key results

Compared with standard care, remdesivir reduces death at day 28 in hospitalised people who require no or low-flow oxygen.

There is no evidence that remdesivir is more effective than placebo or standard care in treating hospitalised patients with COVID-19 who require high-flow oxygen supplementation, non-invasive ventilation or invasive ventilation compared to standard care.

What is the evidence informing this conclusion?

Evidence comes from 10 randomised controlled trials and 1 systematic review that compared remdesivir to standard care or placebo in nearly 10,000 adults hospitalised with COVID-19 (Abd-Elsalam 2021, Ader 2022 [DisCoVeRy], Ali 2022 [CATCO], Barratt-Due 2021 [NOR-SOLIDARITY], Beigel 2020 [ACTT-1], Goldman 2020, Mahajan 2021, WHO-SOLIDARITY 2022, Spinner 2020, Wang 2020, Lee 2022). The majority of evidence is from the WHO SOLIDARITY and ACTT-1 trials, which randomised 8275 and 1062 patients, respectively, hospitalised with COVID-19 and requiring varying levels of oxygen support at baseline (see Table 1). Of the 10 RCTs included in this review, 9 compared remdesivir to standard care while 1 study (Beigel 2020) compared remdesivir to placebo.

For patients who require supplemental oxygen, corticosteroids are currently part of standard care for COVID-19 in hospital in the UK. Beigel 2020 and Abd-Elsalam 2021 did not report use of corticosteroids as part of the standard care.

Eight RCTs included in this comparison evaluated mortality at 28 days after starting treatment. The WHO-SOLIDARITY study evaluated in-hospital mortality, regardless of whether before or after day 28. The majority of studies also reported the need for invasive mechanical ventilation or oxygen supplementation during the trial. Other outcomes evaluated included clinical recovery, discharge from hospital, duration of hospital stay, respiratory failure or acute respiratory distress syndrome (ARDS), time to recovery, time to improvement, oxygen or ventilator-free days by day 28, serious adverse events and adverse events including septic shock.

Ader 2022 [DISCOVERY], Barrat-Due 2021 [NOR-SOLIDARITY] and Ali 2022 [CATCO] trials were
previously partially reported as part of the WHO-SOLIDARITY trial. The DisCoVeRy and CATCO trials reported on the same outcomes as WHO-SOLIDARITY [mortality, progression to ventilation and discharge from hospital] while NOR-SOLIDARITY reported on other outcomes.

Therefore, to avoid duplication for the outcome of mortality, we obtained mortality data for Ader 2022 [DisCoVeRy] and Ali 2022 [CATCO] from Lee 2022 which performed a meta-analyses of mortality in people treated with remdesivir vs. standard care. The authors of the Lee 2022 systematic review obtained data directly from the researchers on the subset of patients who were not already included in the WHO-SOLIDARITY 2022 report. See Appendix H of the evidence review document for differences between published data in the DisCoVeRy and CATCO trials vs. data extracted from the Lee 2022 systematic review.

Since data was not available to distinguish between patients included in WHO-SOLIDARITY vs those not included in WHO-SOLIDARITY for the outcomes progression to ventilation and discharge from hospital, Ader 2022 [DisCoVeRy] and Ali 2022 [CATCO] were excluded from the meta-analyses for these outcomes to prevent double counting of data.

The evidence for mortality was divided into 2 analyses based on the level of respiratory support required. This is because it is expected that antivirals will most likely be more effective in the early stages of disease progression. The levels of respiratory support have been used as a proxy to measure disease progression in the trials. Low levels of respiratory support were considered to be no oxygen supplementation or low-flow oxygen supplementation. Higher levels of respiratory support included high-flow oxygen supplementation, non-invasive ventilation (NIV) [such as Bilevel Positive Airway Pressure (BiPAP) and Continuous Positive Airway Pressure (CPAP)] and invasive ventilation.

The WHO-SOLIDARITY trial did not report data separately for patients on low-flow vs. high-flow oxygen. Subgroups presented in this study were: patients on no oxygen supplementation, patients on oxygen supplementation (any), and patients on ventilation (any). In a previous panel discussion, it was agreed that subgroups of patients on no oxygen supplementation and those on oxygen supplementation would be included in meta-analyses of “low levels of respiratory support” as it was likely that the majority of those patients on oxygen supplementation were on low-flow oxygen supplementation.

For further details, please see the evidence review.

**Publication status**

All studies were full publications.

**Study characteristics**
Mean or median age in the studies ranged between 53 and 69 years and the proportion of men ranged between 56% and 70%.

The severity of COVID-19 across the studies were generally defined as moderate-to-severe. Moderate was mostly defined as people who either did not require oxygen at baseline or required low-flow oxygen supplementation. Severe was defined as people who required high-flow oxygen supplementation or non-invasive mechanical ventilation (NIV) at baseline or invasive mechanical ventilation (IMV). There was variability in disease severity and the corresponding levels of oxygen support and ventilation required among patients at baseline (see Table 1).

The dosage of remdesivir was consistent across all studies (200mg loading dose followed by 100mg daily) but the duration of the course ranged between 5 and 10 days.

All studies used the intravenous (IV) route of administration for remdesivir.

Children and pregnant women were excluded from almost all the trials. Ali 2021 included one pregnant woman. Spinner 2020 included children aged 12-17 but didn’t report data for this group separately. Most studies also excluded patients with organ failure or severe comorbid conditions.

### Table 1: Levels of respiratory support at baseline

<table>
<thead>
<tr>
<th>Level of respiratory support at baseline</th>
<th>Beigel 2020 (n=1062)</th>
<th>Wang 2020 (n=236)</th>
<th>Spinner 2020 (n=384)</th>
<th>WHO-SOLIDARITY 2022 (n=8275)</th>
<th>Abd-Elsalam 2021 (n=100)</th>
<th>Ader 2022 (n=857)**</th>
<th>Ali 2022 (n=1267)**</th>
<th>Barratt-Due 2021 (n=99)</th>
<th>Mahajan 2021 (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No oxygen or low-flow oxygen supplementation</td>
<td>573 (54%)</td>
<td>197 (83%)</td>
<td>584 (100%)</td>
<td>7569 (91.5%)*</td>
<td>200** (100%)</td>
<td>493 (60%)</td>
<td>822 (65%)</td>
<td>Not specified</td>
<td>53 (76%)</td>
</tr>
<tr>
<td>High-flow oxygen supplementation or NIV</td>
<td>193 (18%)</td>
<td>39 (17%)</td>
<td>0 (0%)</td>
<td>N/A</td>
<td>N/A</td>
<td>179 (22%)</td>
<td>347 (27%)</td>
<td>Not specified</td>
<td>17 (24%)</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>285 (27%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>487 (8.5%)</td>
<td>0 (0%)</td>
<td>149 (18%)</td>
<td>112 (8%)</td>
<td>Not specified</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*Note that in the WHO-SOLIDARITY trial, subgroups provided were “No oxygen at baseline” [21%], “Low-flow or high-flow oxygen at baseline” [70.5%], and “Ventilation (any type) at baseline” [8.5%]*

**Note that in the Abd-Elsalam study, levels of respiratory support at baseline were not specified. Study authors clarified that none of the patients in the trial required ventilation at baseline.

*** Note that, due to overlap with WHO-SOLIDARITY 2022, data from the Lee 2022 systematic review was used in place of data from Ali and Ader in meta-analyses of mortality by level of respiratory support.

### What are the main results?
All-cause mortality at day 28 (Updated)

People not receiving oxygen or receiving low-flow oxygen supplementation at baseline (Updated)

Data for mortality from 8 studies (n=10,483) reporting no or low-flow oxygen support at baseline (Ali 2022, Ader 2022 [DisCoVeRy], Beigel 2020, WHO-SOLIDARITY 2022, Spinner 2020, Abd-Elsalam 2021, Mahajan 2021 and Wang 2020) were included in the meta-analysis. Barratt-Due 2021 [NOR-SOLIDARITY] did not specify baseline level of oxygen support so was excluded from this analysis. Data from a systematic review by Lee 2022 was used in place of published data from Ali 2022 [CATCO] and Ader 2022 [DisCoVeRy] trials to avoid double-counting patients included in the WHO-SOLIDARITY trial.

The analysis found a statistically significant reduction in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving low-flow or no oxygen supplementation (RR 0.81 95% CI 0.68 to 0.96).

Two studies (Beigel 2020 and Abd-Elsalam 2021) did not report use of corticosteroids as part of standard care in the trials. A sensitivity analysis removing these two studies from the analysis did not differ from the overall results (RR 0.87 95% CI 0.78 to 0.97).

People receiving high-flow oxygen supplementation, NIV or IMV at baseline (Updated)

Data for mortality from 5 studies (n= 1,486) reporting high-flow oxygen support, NIV or IMV at baseline (Ader 2022, Ali 2022, Beigel 2020, WHO-SOLIDARITY 2022, and Wang 2020) were included in the meta-analysis. Barratt-Due 2021 [NOR-SOLIDARITY] did not specify baseline level of oxygen support so was excluded from this analysis. Data from Lee 2022 was used in place of published data from Ali 2022 [CATCO] and Ader 2022 [DisCoVeRy] trials to avoid double-counting patients included in the WHO-SOLIDARITY trial.

The analysis found no significant difference in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving high-flow oxygen supplementation, NIV or IMV (RR 1.08 95% CI 0.93 to 1.25).

One study (Beigel 2020) did not report use of corticosteroids as part of standard care in the trials. A sensitivity analysis removing this study from the analysis did not differ from the overall results (RR 1.10 95% CI 0.92 to 1.30).

For the following outcomes it was not possible to split the data by level of respiratory support:
Invasive mechanical ventilation or ECMO (Updated)

Data for the need for invasive mechanical ventilation or ECMO from 4 studies (Abd-Elsalam 2021, Beigel 2020, Mahajan 2021, WHO-SOLIDARITY 2022) were included in the meta-analysis (n=8,605). The analysis found no significant difference in need for invasive mechanical ventilation or ECMO at day 28 with remdesivir compared with standard care, in hospitalised patients not on invasive ventilation at baseline (RR 0.85 95% CI 0.65 to 1.13).

Data from Ali 2022 [CATCO] and Ader 2022 [DisCoVeRy] were excluded from this analysis as it was not possible to avoid double-counting with WHO-SOLIDARITY 2022.

Most studies in this analysis did not report this outcome by baseline level of support so it was not possible to do separate analyses for those on no/low-flow oxygen and those on high-flow oxygen or NIV. Only WHO-SOLIDARITY 2022 reported separately on need for IMV or ECMO among patients not receiving oxygen at baseline. Data for this subgroup did not differ from the overall results (RR 0.97 95% CI 0.63 to 1.49).

Need for oxygen supplementation [high-flow oxygen or NIV] (Updated)

Data for this outcome from 3 studies (Ali 2022, Beigel 2020 and Mahajan 2021) were included in this meta-analysis (n=906). The analysis found a statistically significant reduction in the need for high-flow oxygen or NIV for those treated with remdesivir compared to standard care.

Clinical recovery (No change)

Data for this outcome from 3 studies (Beigel 2020, Wang 2020, Spinner 2020) were included in this meta-analysis (n=1,876). It found no statistically significant difference in clinical recovery at day 28 between remdesivir and standard care. 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 (Beigel 2020) or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale (Spinner 2020).

Respiratory failure or ARDS (No change)

Data for this outcome from 2 studies (Beigel 2020, Wang 2020) were included in this meta-analysis (n=1,296). It found no statistically significant difference in respiratory failure or ARDS at day 28 with remdesivir compared with standard care in hospitalised patients not on invasive ventilation at baseline.
Septic Shock (No change)

Data for this outcome from 2 studies (Beigel 2020, Wang 2020) were included in the meta-analysis (n=1,296). It found no statistically significant difference in septic shock at day 28 between remdesivir and standard care.

Adverse events (Updated)

Data for this outcome from 6 studies (Ader 2022, Ali 2022, Barratt-Due 2021, Beigel 2020, Spinner 2020, Wang 2020) were included in the meta-analysis (n= 4,123). It found no statistically significant difference in adverse events at the end of follow up between remdesivir and standard care.

Serious adverse events (Updated)

Data for this outcome from 5 studies (Ader 2022, Barratt-Due 2021, Beigel 2020, Spinner 2020, Wang 2020) were included in the meta-analysis (n= 2,536). It found no statistically significant difference in serious adverse events at the end of follow up between remdesivir and standard care.

Discontinuation due to adverse events (No change)

Data for this outcome from 3 studies (Beigel 2020, Spinner 2020, Wang 2020) were included in the meta-analysis (n= 1,880). It found no statistically significant difference in discontinuation due to adverse events during treatment with remdesivir compared with standard care.

Discharge from hospital (Updated)

Data from WHO-SOLIDARITY 2022 was used for this outcome (n= 8,275). This analysis found no statistically significant difference in discharge from hospital with remdesivir compared with standard care. Data from Ader 2022 [DisCoVeRy] was excluded from this analysis as it was not possible to avoid double-counting with WHO-SOLIDARITY 2022.

Time to recovery (No change)

Data for this outcome from 2 studies (Beigel 2020, Spinner 2020) were included in the meta-analysis (n=1643). It found a statistically significant decrease in time to improvement between remdesivir and standard care.
**Time to improvement (Updated)**

Data for this outcome from 3 studies (Ader 2022, Spinner 2020, Wang 2020) were included in the meta-analysis (n=1642). It found no statistically significant difference in time to improvement between remdesivir and standard care.

**Duration of hospital stay (New at this update)**

One study (Ali 2022) reported on duration of hospital stay for those treated with remdesivir compared to standard care (n= 200). The study found a statistically significant decrease in days in hospital for those treated with remdesivir compared with standard care.

**Oxygen-free days (New at this update)**

One study (Ali 2022) reported on the number of oxygen-free days at day 28 for those treated with remdesivir compared to standard care (n= 1,168). The study found a statistically significant increase in oxygen-free days among those treated with remdesivir compared with standard care.

**Ventilator-free days (New at this update)**

One study (Ali 2022) reported on the number of ventilator-free days at day 28 for those treated with remdesivir compared to standard care (n= 1,168). The study found a statistically significant increase in ventilator-free days among those treated with remdesivir compared with standard care.

**Our confidence in the results**

All but one outcome (Respiratory failure or ARDS) were downgraded for risk of bias. In the case of the mortality outcomes, there was a risk of double-counting patients from the WHO-SOLIDARITY trial in the add-on trials [DisCoVeRy and CATCO]. For these outcomes, we noted a serious risk of bias due to uncertainty over how the trialists managed data across the studies, but we also used data from the Lee 2022 systematic review to minimise the risk of double-counting.

All studies were open-label. For outcomes that were considered subjective and where clinical judgement could be influenced by knowledge of treatment allocation, a rating of moderate risk of bias was given for the domain of outcome assessment.
Outcomes were downgraded for inconsistency where there was evidence of statistical heterogeneity ($I^2 > 50\%$). These included invasive mechanical ventilation or ECMO, serious adverse events, respiratory failure or ARDS, clinical recovery, adverse events, and discontinuation due to adverse events. Analyses which were not split by level of respiratory support may also be considered as clinically heterogenous.

All included studies met the PICO eligibility criteria so outcomes were not downgraded for indirectness. However, it is noted that all studies were carried out before the rollout of COVID-19 vaccination. Two studies (Abd-Elsalam 2021 and Beigel 2020) did not use corticosteroids as standard of care which is routinely used in the UK for people hospitalised for COVID-19. However, a sensitivity analysis without these studies showed no difference to the overall results.

Outcomes were downgraded for imprecision where the 95% confidence interval crossed the line of no effect.

Outcomes rated as moderate certainty included: all-cause mortality (no oxygen or low flow oxygen), need for oxygen supplementation, time to recovery).

Outcomes rated as low certainty included: all-cause mortality (High flow O2, NIV or IMV), invasive mechanical ventilation or ECMO, respiratory failure or ARDS, time to improvement, duration of hospital stay, oxygen-free days and ventilator-free days.

All the remaining outcomes were rated as very low certainty.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Placement or standard care</th>
<th>Intervention Remdesivir</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (day 28; No oxygen or low flow oxygen) Within 28 days of commencing treatment</td>
<td>Relative risk 0.81 (CI 95% 0.68 — 0.96) Based on data from 10,483 participants in 8 studies. ¹ (Randomized controlled)</td>
<td>95 per 1000 Difference: 77 per 1000 18 fewer per 1000 (CI 95% 30 fewer — 4 fewer)</td>
<td>Moderate Due to serious risk of bias ²</td>
<td>A pooled analysis of 8 studies found a statistically significant reduction in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving low-flow or no oxygen supplementation</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality (day 28; High flow)</td>
<td>Relative risk 1.08 (CI 95% 0.93 — 1.25) Based on data from 253 participants in 6 studies.</td>
<td>253 per 1000</td>
<td>273 per 1000</td>
<td>Low Due to serious imprecision, Due</td>
<td>A pooled analysis of 6 studies found no statistically significant</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator Placebo or standard care</td>
<td>Intervention Remdesivir</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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</tr>
<tr>
<td>O2, NIV or IMV)</td>
<td>1,486 participants in 6 studies. 3 (Randomized controlled)</td>
<td>Difference: 20 more per 1000 (CI 95% 18 fewer — 63 more)</td>
<td>Low</td>
<td>Difference in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving high-flow oxygen supplementation, NIV or IMV.</td>
<td></td>
</tr>
<tr>
<td>Invasive mechanical ventilation or ECMO</td>
<td>Relative risk 0.85 (CI 95% 0.65 — 1.13) Based on data from 8,605 participants in 4 studies. 3 (Randomized controlled)</td>
<td>141 per 1000 Difference: 21 fewer per 1000 (CI 95% 49 fewer — 18 more)</td>
<td>Low</td>
<td>A pooled analysis of 4 studies found no statistically significant difference in need for invasive mechanical ventilation or ECMO at day 28 with remdesivir compared to standard care, in hospitalised patients not on invasive ventilation at baseline.</td>
<td></td>
</tr>
<tr>
<td>Need for oxygen supplementation (low-flow, high-flow or NIV)</td>
<td>Relative risk 0.79 (CI 95% 0.64 — 0.96) Based on data from 906 participants in 3 studies. 3 (Randomized controlled)</td>
<td>310 per 1000 Difference: 65 fewer per 1000 (CI 95% 112 fewer — 12 fewer)</td>
<td>Moderate</td>
<td>A pooled analysis of 3 studies found a statistically significant decrease in need for oxygen supplementation with remdesivir compared to standard care, in hospitalised patients not on oxygen at baseline.</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events End of follow-up</td>
<td>Relative risk 0.87 (CI 95% 0.68 — 1.11) Based on data from 2,827 participants in 5 studies. 3 (Randomized controlled)</td>
<td>270 per 1000 Difference: 35 fewer per 1000 (CI 95% 86 fewer — 30 more)</td>
<td>Very low</td>
<td>A pooled analysis of 5 studies found no statistically significant difference in serious adverse events at the end of follow up between remdesivir and standard care.</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure or ARDS Within 28 days of commencing treatment</td>
<td>Relative risk 0.79 (CI 95% 0.35 — 1.78) Based on data from 1,296 participants in 2 studies. 3 (Randomized controlled)</td>
<td>143 per 1000 Difference: 30 fewer per 1000 (CI 95% 93 fewer — 112 more)</td>
<td>Low</td>
<td>Two studies found no statistically significant difference in respiratory failure or ARDS at day 28 with remdesivir compared to standard care.</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator: Placebo or standard care</td>
<td>Intervention: Remdesivir</td>
<td>Certainty of the Evidence: (Quality of evidence)</td>
</tr>
<tr>
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</tr>
<tr>
<td>Septic shock</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.02 (CI 95%: 0.34 — 3.01) Based on data from 1,296 participants in 2 studies.</td>
<td>10 per 1000</td>
<td>10 per 1000</td>
<td>Very low Due to serious risk of bias, serious inconsistency and serious imprecision</td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.99 (CI 95%: 0.86 — 1.14) Based on data from 1,876 participants in 3 studies.</td>
<td>711 per 1000</td>
<td>704 per 1000</td>
<td>Very low Due to serious risk of bias, serious inconsistency and serious imprecision</td>
</tr>
<tr>
<td>Adverse events</td>
<td>End of follow up</td>
<td>Relative risk 1.13 (CI 95%: 0.96 — 1.33) Based on data from 4,123 participants in 6 studies.</td>
<td>415 per 1000</td>
<td>469 per 1000</td>
<td>Very low Due to serious risk of bias, serious inconsistency, and serious imprecision</td>
</tr>
<tr>
<td>Time to improvement</td>
<td>Days</td>
<td>Hazard ratio 1.08 (CI 95%: 0.97 — 1.19) Based on data from 1,642 participants in 3 studies.</td>
<td>93 per 1000</td>
<td>161 per 1000</td>
<td>Low Due to serious risk of bias and serious imprecision</td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>During treatment</td>
<td>Relative risk 1.73 (CI 95%: 0.57 — 5.28) Based on data from 1,880 participants in 3 studies.</td>
<td>701 per 1000</td>
<td>708 per 1000</td>
<td>Very low Due to serious risk of bias, serious inconsistency and serious imprecision</td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td></td>
<td>Relative risk 1.01 (CI 95%: 0.99 — 1.03) Based on data from 8,275 participants in 1 studies.</td>
<td>701 per 1000</td>
<td>708 per 1000</td>
<td>Low Due to serious risk of bias and serious imprecision</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Placebo or standard care</td>
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<tr>
<td><strong>Time to recovery</strong>&lt;br&gt;Days&lt;br&gt;6 Important</td>
<td>Hazard ratio 1.24 (CI 95% 1.08 — 1.42)&lt;br&gt;Based on data from 1,643 participants in 2 studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td>Moderate Due to serious risk of bias 24</td>
<td>Two studies found a statistically significant decrease in time to recovery with remdesivir compared with standard care.</td>
</tr>
<tr>
<td><strong>Duration of hospital stay</strong>&lt;br&gt;End of follow-up&lt;br&gt;6 Important</td>
<td>Lower better&lt;br&gt;Based on data from 200 participants in 1 studies. 25 (Randomized controlled)</td>
<td>16.72 days (Mean) Difference:</td>
<td>12.37 days (Mean) MD 4.35 lower (CI 95% 6.44 lower — 2.26 lower)</td>
<td>Very low Due to serious risk of bias, serious indirectness, and serious imprecision 26</td>
<td>One study found a statistically significant decrease in duration of hospital stay for treatment with remdesivir compared with standard care.</td>
</tr>
<tr>
<td><strong>Oxygen free days at day 28</strong>&lt;br&gt;Within 28 days of starting treatment&lt;br&gt;6 Important</td>
<td>Scale: 0 — 28 High better&lt;br&gt;Based on data from 1,168 participants in 1 studies. 27 (Randomized controlled)</td>
<td>14.2 Days (Mean) Difference:</td>
<td>15.9 Days (Mean) MD 1.7 higher (CI 95% 0.46 higher — 2.94 higher)</td>
<td>Low Due to very serious risk of bias 28</td>
<td>One study found a statistically significant increase in number of oxygen-free days for treatment with remdesivir compared with standard care.</td>
</tr>
<tr>
<td><strong>Ventilator free days at day 28</strong>&lt;br&gt;Within 28 days of starting treatment&lt;br&gt;6 Important</td>
<td>Scale: 0 — 28 High better&lt;br&gt;Based on data from 1,168 participants in 1 studies. 29 (Randomized controlled)</td>
<td>19.5 Days (Mean) Difference:</td>
<td>21.4 Days (Mean) MD 1.9 higher (CI 95% 0.55 higher — 3.25 higher)</td>
<td>Low Due to very serious risk of bias 30</td>
<td>One study found a statistically significant increase in number of ventilator-free days for treatment with remdesivir compared with standard care.</td>
</tr>
</tbody>
</table>

2. **Risk of Bias: serious.** Incomplete information to understand the overlap between studies. **Inconsistency: no serious. Indirectness: no serious.** To note that these studies were conducted before vaccination for COVID-19 was rolled out. **Imprecision: no serious. Publication bias: no serious.**
3. Systematic review [165]. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Incomplete information to understand the overlap between studies. **Inconsistency: no serious. Indirectness: no serious.** To note that these studies were conducted before vaccination for COVID-19 was rolled out. **Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**
of reference used for intervention.

6. **Risk of Bias: serious.** Incomplete information to understand the overlap between studies. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with $I^2: 77\%$. May also be considered clinically heterogenous due to baseline severity differences. **Indirectness: no serious.** To note that these studies were conducted before vaccination for COVID-19 was rolled out. **Imprecision: no serious. Publication bias: no serious.**

7. Systematic review [165] with included studies: Ali 2022, Beigel 2020 hi flow or NIV, Mahajan 2021, Beigel 2020 low-flow. **Baseline/comparator:** Control arm of reference used for intervention. **Risk of Bias: serious.** Missing data in two studies. One study has a deviation from intended intervention for one participant. **Inconsistency: no serious. Indirectness: no serious.** To note that these studies were conducted before vaccination for COVID-19 was rolled out. **Imprecision: no serious. Publication bias: no serious.**

8. Systematic review [165] with included studies: Spinner 2020, NOR-SOLIDARITY 2021, Beigel 2020, Wang 2020, Ader 2022 DISCOVERY, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with $I^2: 50\%$. May also be considered clinically heterogenous due to baseline severity differences. **Indirectness: no serious.** To note that these studies were conducted before vaccination for COVID-19 was rolled out. **Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**


10. Systematic review [165] with included studies: Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Indirectness: no serious. Imprecision: serious.** 95% CI crosses line of no effect. **Publication bias: no serious.**

11. Systematic review [165] with included studies: Beigel 2020, Wang 2020. **Baseline/comparator:** Control arm of reference used for intervention. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies. **Indirectness: no serious. Imprecision: serious.** 95% CI crosses line of no effect. **Publication bias: no serious.**

12. Systematic review [165] with included studies: Beigel 2020, Wang 2020, Beigel 2020, Spinner 2020, NOR-SOLIDARITY 2021, Ali 2022, Ader 2022 DISCOVERY, Spinner 2020, NOR-SOLIDARITY 2021. **Baseline/comparator:** Control arm of reference used for intervention. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with $I^2: 81\%$. **Indirectness: no serious.** To note that these studies were conducted before vaccination for COVID-19 was rolled out. **Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**
vaccination for COVID-19 was rolled out. **Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**

19. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses line of no effect. **Publication bias: no serious.**


21. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Indirectness: no serious. Imprecision: serious.** 95% CI crosses line of no effect. **Publication bias: no serious.**


23. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious.** To note that these studies were conducted before vaccination for COVID-19 was rolled out. **Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**

24. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious.** **Imprecision: no serious. Publication bias: no serious.**


26. **Risk of Bias: serious.** Potential selective reporting. **Inconsistency: no serious. Indirectness: serious.** Corticosteroids were not included in standard care. **Imprecision: serious.** n<300. **Publication bias: no serious.**


28. **Risk of Bias: very serious.** Missing data unaccounted for; open label study and subjective outcome. **Inconsistency: no serious. Indirectness: no serious.** To note that this study was conducted before vaccination for COVID-19 was rolled out. **Imprecision: no serious. Publication bias: no serious.**


30. **Risk of Bias: very serious.** Missing data unaccounted for; open label study and subjective outcome. **Inconsistency: no serious. Indirectness: no serious.** To note that this study was conducted before vaccination for COVID-19 was rolled out. **Imprecision: no serious. Publication bias: no serious.**

**References**


165. Remdesivir for COVID-19 [June 2022].

Only in research settings

Do not use remdesivir for COVID-19 pneumonia in anyone in hospital and on high-flow nasal oxygen, continuous positive airway pressure, non-invasive mechanical ventilation or invasive mechanical ventilation, except as part of an ongoing clinical trial.
Evidence to decision

Benefits and harms

Ten randomised controlled trials and 1 systematic review were included as part of the evidence review for remdesivir for people in hospital and needing supplemental oxygen. These studies compared the outcomes between people on remdesivir, and people on placebo or standard care. The outcome of all-cause mortality was evaluated based on the level of respiratory support that people needed at baseline. For all other outcomes, it was not possible to split the data by level of respiratory support.

When considering the benefits and harms of remdesivir treatment, the panel focused on the outcome of all-cause mortality. This was evaluated separately for people not having oxygen support or having low-flow oxygen at baseline, and for those having high-flow oxygen, non-invasive ventilation (NIV) or invasive mechanical ventilation (IMV) at baseline for COVID-19 management. Although not always described in the evidence, the panel considered that continuous positive airway pressure (CPAP) was included as a type of NIV.

The panel noted that, for high-flow oxygen, NIV or IMV, there was no statistically significant difference in all-cause mortality within 28 days of starting treatment between remdesivir and standard care. The panel also noted that there was a statistically significant reduction in all-cause mortality with remdesivir compared with control in people having no or low-flow oxygen.

The panel discussed a clinical rationale for this trend, based on the mechanism of action of antiviral treatments. This hypothesis states that antivirals are:

- expected to be more effective early in the disease course, when viral replication is a driver of disease
- less likely to be effective in the later stages in the disease course when it enters the hyperinflammatory phase, when people are more likely to need more extensive respiratory support.

Note that the studies included in this evidence review did not provide data on viral load.

Because of the uncertainty of the evidence, the panel advised that people in hospital with COVID-19 and having high-flow oxygen, NIV or IMV should not have remdesivir except in the context of an ongoing clinical trial. The panel discussed that additional clinical research would be helpful to understand with certainty the benefits or potential harms of remdesivir for people having high-flow oxygen, NIV or IMV.

Certainty of the Evidence

The certainty of the evidence was low for all-cause mortality in people who need high-flow oxygen, NIV or IMV for COVID-19 management. The certainty of this outcome was downgraded because of risk of bias. This is because there is a risk that people who were enrolled in the WHO-SOLIDARITY were also included in published results of add-on trials, including CATCO (Ali 2022) in Canada and DisCoVeRy (Ader 2022) in France. The possibility of double-counting introduces a risk of bias into this outcome. The certainty of this outcome was downgraded further because of imprecision because the confidence interval crossed the line of no effect.

For outcomes relevant to the safety of remdesivir (including adverse events, serious adverse events, stopping because of adverse events, respiratory failure or ARDS, and septic shock), the certainty of the evidence was low to very low. This is because of inconsistency in outcomes resulting from statistical heterogeneity in the meta-analysis, imprecision when the confidence interval crossed the line of no effect.
effect and serious risk of bias because of 2 of the included studies being unblinded.

Values and preferences

The panel were not aware of any systematically collected data on peoples' preferences and values. They identified critical outcomes that would be important for decision making. These included all-cause mortality, IMV or extracorporeal membrane oxygenation (ECMO) and serious adverse events. In addition, other outcomes including less serious adverse events, discharge from hospital, duration of hospital stay and longer-term outcomes such as functional independence are likely to be of particular importance to people with COVID-19. These outcomes were not as commonly reported in studies. The outcome of functional independence was not reported in any of the studies included in this review.

Overall, the panel inferred that, in view of the lack of evidence of benefit for people with COVID-19 having high-flow oxygen, NIV or IMV, most would not choose remdesivir.

Resources

Cost effectiveness was not assessed as part of the evidence review.

Equity

The panel noted an absence of evidence on remdesivir use for children. However, they considered it unlikely that most children would benefit from this intervention because most children will recover without the need for it.

Children are often excluded from clinical trials. It was suggested that the recommendation could lead to inequity if adults could have remdesivir as part of a trial, but children could not. However, the proposed inequity is outweighed by the possibility of harm from remdesivir use in people who need high-flow or more intensive oxygen therapy.

No evidence for using remdesivir in pregnancy was identified. The marketing authorisation confirms the lack of evidence and notes that remdesivir should be avoided in pregnancy unless 'the clinical condition of the women requires treatment with it'. People who are pregnant are often excluded from clinical trials, which could lead to inequity if some people could have remdesivir as part of a clinical trial but not if they are pregnant. However, the proposed inequity is outweighed by the possibility of harm from remdesivir use in people who need high-flow or more intensive oxygen therapy.

No other equity issues were identified.

Acceptability

The panel were not aware of any systematically collected evidence about acceptability. A potential deterring factor to acceptability could be that the certainty of current evidence is low to very low.
However, the panel noted the consistent direction of effect in favour of standard care for people on higher levels of respiratory support.

It is anticipated that, when considering the risks and benefits of treatment, most people who are admitted to hospital with COVID-19 pneumonia and need high-flow oxygen, NIV or IMV would choose not to have remdesivir.

Feasibility

Although there is no systematically collected evidence about feasibility, the panel noted that current widespread use of remdesivir in clinical practice is an indicator of feasibility.

Rationale

Overall, there is a high degree of uncertainty about whether remdesivir is more effective than control (placebo, standard care or both) for reducing the risk of death from COVID-19 in people on high-flow nasal oxygen, continuous positive airway pressure (CPAP), non-invasive ventilation (NIV) or invasive mechanical ventilation (IMV) for managing COVID-19. This is likely because it is being used later in the disease course, when viral replication may not be the primary driver. The panel were aware of ongoing trials of remdesivir that include this group of people. They agreed that remdesivir should only be used for COVID-19 pneumonia in this group as part of ongoing well-conducted trials to:

- support recruitment into these trials, and
- improve the certainty of the evidence on the effectiveness of remdesivir for managing COVID-19 in people on high-flow nasal oxygen, CPAP, NIV or IMV.

Clinical question/ PICO

Population: People with COVID-19
Intervention: Remdesivir 5 days
Comparator: Remdesivir 10 days

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 moderate to critical COVID-19 (Goldman 2020; Spinner 2020).

Study characteristics

Mean or median age ranged between 56 to 62 years and women comprised 32 to 40% of patients across both studies. Pregnant people and children were ineligible, with the exception of 1 trial (Spinner 2020) which included children over 12 years weighing 40kg or more.

The majority of people (84%) in 1 trial (Spinner 2020) were not receiving oxygen supplementation at baseline. In the second trial 55% were receiving oxygen supplementation at baseline and 30.5%
were ventilated (Goldman 2020).

**What are the main results?**

**Critical outcomes**

All-cause mortality
Moderate quality evidence from 2 studies found no statistically significant difference in all-cause mortality at 14 days with remdesivir 5-day treatment compared to 10-day treatment (16 fewer deaths per 1000 people [RR 0.73 95% CI 0.40 to 1.33; 781 people in 2 studies]).

Low quality evidence from 1 study found no statistically significant difference in all-cause mortality at 28 days with remdesivir 5-day treatment compared to 10-day treatment (5 fewer deaths per 1000 people [RR 0.67 95% CI 0.11 to 3.99; 384 people in 1 study]).

Serious adverse events
Moderate quality evidence from 2 studies found a statistically significant reduction in serious adverse events with remdesivir 5-day treatment compared to 10-day treatment (72 fewer events per 1000 people [RR 0.64 95% CI 0.47 to 0.87; 781 people in 2 studies]).

**Important outcomes**

Acute respiratory failure or ARDS
Low quality evidence from 1 study found a statistically significant reduction in acute respiratory failure or ARDS at 30 days with remdesivir 5-day treatment compared to 10-day treatment (62 fewer events per 1000 people [RR 0.47 95% CI 0.24 to 0.94; 397 people in 1 study]).

Septic shock
Very low-quality evidence from 1 study found no statistically significant difference in septic shock at 30 days with remdesivir 5-day treatment compared to 10-day treatment (15 fewer events per 1000 people [RR 0.39 95% CI 0.08 to 2.01; 397 people in 1 study]).

Clinical recovery
Low quality evidence from 1 study found a statistically significant increase in clinical recovery at 14 days with remdesivir 5-day treatment compared to 10-day treatment (108 more events per 1000 people [RR 1.20 95% CI 1.02 to 1.14; 397 people in 1 study]).

Adverse events
Moderate quality evidence from 2 studies found no statistically significant difference in adverse events with remdesivir 5-day treatment compared to 10-day treatment (46 fewer events per 1000 people [RR 0.93 95% CI 0.84 to 1.03; 781 people in 2 studies]).

Discontinuation due to adverse events
Low quality evidence from 2 studies found no statistically significant difference in discontinuation due to adverse events at 14 days with remdesivir 5-day treatment compared to 10-day treatment (23 fewer events per 1000 people [RR 0.59 95% CI 0.30 to 1.15; 781 people in 2 studies]).

Discharge from hospital
Moderate quality evidence from 2 studies found no statistically significant difference in discharge from hospital at 14 days with remdesivir 5-day treatment compared to 10-day treatment (38 more
events per 1000 people (RR 1.06 95% CI 0.93 to 1.20; 781 people in 2 studies)).

Low quality evidence from 1 study found no statistically significant difference in discharge from hospital at 28 days with remdesivir 5-day treatment compared to 10-day treatment (9 fewer events per 1000 people [RR 0.99 95% CI 0.92 to 1.06; 384 people in 1 study]).

**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 or discontinuation due to adverse event within 14 days and discharge from hospital within 28 days. This judgement is based on serious risk of bias (problems with randomisation, lack of blinding), serious imprecision (low event rate for the outcome of death within 14 days) and very serious imprecision (reliance on a single study with few patients and/or few events). Certainty of the evidence is very low for septic shock due to lack of blinding and reliance on a single study with few patients and few events.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Remdesivir 10 days</th>
<th>Intervention Remdesivir 5 days</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality Within 14 days of commencing treatment</td>
<td>Relative risk 0.73 (CI 95% 0.4 — 1.33) Based on data from 781 participants in 2 studies. ¹ (Randomized controlled)</td>
<td>59 per 1000</td>
<td>43 per 1000</td>
<td>Moderate Due to serious imprecision ²</td>
<td>A pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 14 days with remdesivir 5-day treatment compared to 10-day treatment.</td>
</tr>
<tr>
<td>All-cause mortality Within 28 days of commencing treatment</td>
<td>Relative risk 0.67 (CI 95% 0.11 — 3.99) Based on data from 384 participants in 1 studies. ³ (Randomized controlled)</td>
<td>16 per 1000</td>
<td>11 per 1000</td>
<td>Low Due to very serious imprecision ⁴</td>
<td>Evidence from 1 study found no statistically significant difference in all-cause mortality at 28 days with remdesivir 5-day treatment compared to 10-day treatment.</td>
</tr>
<tr>
<td>Serious adverse events End of follow-up</td>
<td>Relative risk 0.64 (CI 95% 0.47 — 0.87) Based on data from 781 participants in 2 studies. ⁵ (Randomized controlled)</td>
<td>200 per 1000</td>
<td>128 per 1000</td>
<td>Moderate Due to serious risk of bias ⁶</td>
<td>A pooled analysis of 2 studies found a statistically significant reduction in serious adverse events with remdesivir 5-day treatment compared to 10-day treatment.</td>
</tr>
<tr>
<td>Acute respiratory</td>
<td>Relative risk 0.47 (CI 95% 0.24 — 0.94)</td>
<td>117</td>
<td>55</td>
<td>Low Due to very</td>
<td>Evidence from 1 study found a statistically</td>
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<tr>
<td>Outcome</td>
<td>Timeframe</td>
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<td>Intervention</td>
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</tr>
<tr>
<td>failure or ARDS</td>
<td>Within 30 days of commencing</td>
<td>Based on data from 397 participants in 1 studies.</td>
<td>Remdesivir 10 days</td>
<td>Remdesivir 5 days</td>
<td>per 1000</td>
</tr>
<tr>
<td></td>
<td>treatment</td>
<td>6 Important</td>
<td>per 1000</td>
<td>Difference:</td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>Within 30 days of commencing</td>
<td>Relative risk 0.39 (CI 95% 0.08 — 2.01)</td>
<td>Remdesivir 10 days</td>
<td>Remdesivir 5 days</td>
<td>25 per 1000</td>
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<tr>
<td></td>
<td>treatment</td>
<td>6 Important</td>
<td>per 1000</td>
<td>Difference:</td>
<td></td>
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<tr>
<td>Clinical recovery</td>
<td>Within 14 days of commencing</td>
<td>Relative risk 1.2 (CI 95% 1.02 — 1.41)</td>
<td>Remdesivir 10 days</td>
<td>Remdesivir 5 days</td>
<td>538 per 1000</td>
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<td></td>
<td>treatment</td>
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<tr>
<td>Adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 0.93 (CI 95% 0.84 — 1.03)</td>
<td>Remdesivir 10 days</td>
<td>Remdesivir 5 days</td>
<td>662 per 1000</td>
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<td>6 Important</td>
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<td>per 1000</td>
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<td>Discontinued due to</td>
<td>Within 14 days of commencing</td>
<td>Relative risk 0.59 (CI 95% 0.3 — 1.15)</td>
<td>Remdesivir 10 days</td>
<td>Remdesivir 5 days</td>
<td>56 per 1000</td>
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<td>adverse event</td>
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<td>per 1000</td>
<td>Difference:</td>
<td></td>
</tr>
<tr>
<td>Discharged from hospital</td>
<td>Within 14 days of commencing</td>
<td>Relative risk 1.06 (CI 95% 0.93 — 1.2)</td>
<td>Remdesivir 10 days</td>
<td>Remdesivir 5 days</td>
<td>638 per 1000</td>
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<td>treatment</td>
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<td>Difference:</td>
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</tr>
</tbody>
</table>

2. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. due to few events.


4. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Low number of patients, Only data from one study.


6. **Risk of Bias:** serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** no serious. **Publication bias:** no serious.


8. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Low number of patients, Only data from one study. **Publication bias:** no serious.


10. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Low number of patients, Only data from one study. **Publication bias:** no serious.


12. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Only data from one study. **Publication bias:** no serious.


14. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in
potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**


16. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** due to few events. **Publication bias: no serious.**


20. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Only data from one study. **Publication bias: no serious.**

**References**

22. Remdesivir for COVID-19 internal meta-analyses..


**Clinical question/ PICO**

**Population:** People with COVID-19 (Hospitalised)

**Intervention:** Remdesivir

**Comparator:** Placebo or standard care

**Summary**

**What is the effectiveness and safety of remdesivir for adults, young people and children hospitalised with COVID-19?**

**Key results**

Compared with standard care, remdesivir reduces death at day 28 in hospitalised people who
require no or low-flow oxygen.

There is no evidence that remdesivir is more effective than placebo or standard care in treating hospitalised patients with COVID-19 who require high-flow oxygen supplementation, non-invasive ventilation or invasive ventilation compared to standard care.

**What is the evidence informing this conclusion?**

Evidence comes from 10 randomised controlled trials and 1 systematic review that compared remdesivir to standard care or placebo in nearly 10,000 adults hospitalised with COVID-19 (Abd-Elsalam 2021, Ader 2022 [DisCoVeRy], Ali 2022 [CATCO], Barratt-Due 2021 [NOR-SOLIDARITY], Beigel 2020 [ACTT-1], Goldman 2020, Mahajan 2021, WHO-SOLIDARITY 2022, Spinner 2020, Wang 2020, Lee 2022). The majority of evidence is from the WHO SOLIDARITY and ACTT-1 trials, which randomised 8275 and 1062 patients, respectively, hospitalised with COVID-19 and requiring varying levels of oxygen support at baseline (see Table 1). Of the 10 RCTs included in this review, 9 compared remdesivir to standard care while 1 study (Beigel 2020) compared remdesivir to placebo. For patients who require supplemental oxygen, corticosteroids are currently part of standard care for COVID-19 in hospital in the UK. Beigel 2020 and Abd-Elsalam 2021 did not report use of corticosteroids as part of the standard care.

Eight RCTs included in this comparison evaluated mortality at 28 days after starting treatment. The WHO-SOLIDARITY study evaluated in-hospital mortality, regardless of whether before or after day 28. The majority of studies also reported the need for invasive mechanical ventilation or oxygen supplementation during the trial. Other outcomes evaluated included clinical recovery, discharge from hospital, duration of hospital stay, respiratory failure or acute respiratory distress syndrome (ARDS), time to recovery, time to improvement, oxygen or ventilator-free days by day 28, serious adverse events and adverse events including septic shock.

Ader 2022 [DISCOVERY], Barrat-Due 2021 [NOR-SOLIDARITY] and Ali 2022 [CATCO] trials were previously partially reported as part of the WHO-SOLIDARITY trial. The DisCoVeRy and CATCO trials reported on the same outcomes as WHO-SOLIDARITY [mortality, progression to ventilation and discharge from hospital] while NOR-SOLIDARITY reported on other outcomes.

Therefore, to avoid duplication for the outcome of mortality, we obtained mortality data for Ader 2022 [DisCoVeRy] and Ali 2022 [CATCO] from Lee 2022 which performed a meta-analyses of mortality in people treated with remdesivir vs. standard care. The authors of the Lee 2022 systematic review obtained data directly from the researchers on the subset of patients who were not already included in the WHO-SOLIDARITY 2022 report. See Appendix H of the evidence review document for differences between published data in the DisCoVeRy and CATCO trials vs. data extracted from the Lee 2022 systematic review.

Since data was not available to distinguish between patients included in WHO-SOLIDARITY vs
those not included in WHO-SOLIDARITY for the outcomes progression to ventilation and discharge from hospital, Ader 2022 [DisCoVeRy] and Ali 2022 [CATCO] were excluded from the meta-analyses for these outcomes to prevent double counting of data.

The evidence for mortality was divided into 2 analyses based on the level of respiratory support required. This is because it is expected that antivirals will most likely be more effective in the early stages of disease progression. The levels of respiratory support have been used as a proxy to measure disease progression in the trials. Low levels of respiratory support were considered to be no oxygen supplementation or low-flow oxygen supplementation. Higher levels of respiratory support included high-flow oxygen supplementation, non-invasive ventilation (NIV) [such as Bilevel Positive Airway Pressure (BiPAP) and Continuous Positive Airway Pressure (CPAP)] and invasive ventilation.

The WHO-SOLIDARITY trial did not report data separately for patients on low-flow vs. high-flow oxygen. Subgroups presented in this study were: patients on no oxygen supplementation, patients on oxygen supplementation (any), and patients on ventilation (any). In a previous panel discussion, it was agreed that subgroups of patients on no oxygen supplementation and those on oxygen supplementation would be included in meta-analyses of “low levels of respiratory support” as it was likely that the majority of those patients on oxygen supplementation were on low-flow oxygen supplementation.

For further details, please see the evidence review.

Publication status

All studies were full publications.

Study characteristics

Mean or median age in the studies ranged between 53 and 69 years and the proportion of men ranged between 56% and 70%.

The severity of COVID-19 across the studies were generally defined as moderate-to-severe. Moderate was mostly defined as people who either did not require oxygen at baseline or required low-flow oxygen supplementation. Severe was defined as people who required high-flow oxygen supplementation or non-invasive mechanical ventilation (NIV) at baseline or invasive mechanical ventilation (IMV). There was variability in disease severity and the corresponding levels of oxygen support and ventilation required among patients at baseline (see Table 1).

The dosage of remdesivir was consistent across all studies (200mg loading dose followed by
100mg daily) but the duration of the course ranged between 5 and 10 days.

All studies used the intravenous (IV) route of administration for remdesivir.

Children and pregnant women were excluded from almost all the trials. Ali 2021 included one pregnant woman. Spinner 2020 included children aged 12-17 but didn’t report data for this group separately. Most studies also excluded patients with organ failure or severe comorbid conditions.

Table 1: Levels of respiratory support at baseline

<table>
<thead>
<tr>
<th>Level of respiratory support at baseline</th>
<th>Beigel 2020 (n=1062)</th>
<th>Wang 2020 (n=236)</th>
<th>Spinner 2020 (n=584)</th>
<th>WHO-SOLIDARITY 2022 (n=8275)</th>
<th>Abd-Elsalam 2021 (n=100)</th>
<th>Ader 2022 (n=857)**</th>
<th>Ali 2022 (n=1267)**</th>
<th>Barratt-Due 2021 (n=99)</th>
<th>Mahajan 2021 (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No oxygen or low-flow oxygen supplementation</td>
<td>573 (54%)</td>
<td>197 (83%)</td>
<td>584 (100%)</td>
<td>7569 (91.5%)*</td>
<td>200** (100%)</td>
<td>493 (60%)</td>
<td>822 (65%)</td>
<td>Not specified</td>
<td>53 (76%)</td>
</tr>
<tr>
<td>High-flow oxygen supplementation or NIV</td>
<td>193 (18%)</td>
<td>39 (17%)</td>
<td>0 (0%)</td>
<td>N/A</td>
<td>N/A</td>
<td>179 (22%)</td>
<td>347 (27%)</td>
<td>Not specified</td>
<td>17 (24%)</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>285 (27%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>487 (8.5%)</td>
<td>0 (0%)</td>
<td>149 (18%)</td>
<td>112 (8%)</td>
<td>Not specified</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*Note that in the WHO-SOLIDARITY trial, subgroups provided were “No oxygen at baseline” [21%], “Low-flow or high-flow oxygen at baseline” [70.5%], and “Ventilation (any type) at baseline” [8.5%]

**Note that in the Abd-Elsalam study, levels of respiratory support at baseline were not specified. Study authors clarified that none of the patients in the trial required ventilation at baseline.

*** Note that, due to overlap with WHO-SOLIDARITY 2022, data from the Lee 2022 systematic review was used in place of data from Ali and Ader in meta-analyses of mortality by level of respiratory support.

What are the main results?

All-cause mortality at day 28 (Updated)

People not receiving oxygen or receiving low-flow oxygen supplementation at baseline (Updated)

Data for mortality from 8 studies (n=10,483) reporting no or low-flow oxygen support at baseline (Ali 2022, Ader 2022 [DisCoVeRy], Beigel 2020, WHO-SOLIDARITY 2022, Spinner 2020, Abd-Elsalam 2021, Mahajan 2021 and Wang 2020) were included in the meta-analysis. Barratt-Due 2021 [NOR-SOLIDARITY] did not specify baseline level of oxygen support so was excluded from this analysis. Data from a systematic review by Lee 2022 was used in place of published data from Ali 2022 [CATCO] and Ader 2022 [DisCoVeRy] trials to avoid double-counting patients included in the WHO-SOLIDARITY trial.
The analysis found a statistically significant reduction in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving low-flow or no oxygen supplementation (RR 0.81 95% CI 0.68 to 0.96).

Two studies (Beigel 2020 and Abd-Elsalam 2021) did not report use of corticosteroids as part of standard care in the trials. A sensitivity analysis removing these two studies from the analysis did not differ from the overall results (RR 0.87 95% CI 0.78 to 0.97).

**People receiving high-flow oxygen supplementation, NIV or IMV at baseline (Updated)**

Data for mortality from 5 studies (n= 1,486) reporting high-flow oxygen support, NIV or IMV at baseline (Ader 2022, Ali 2022, Beigel 2020, WHO-SOLIDARITY 2022, and Wang 2020) were included in the meta-analysis. Barratt-Due 2021 [NOR-SOLIDARITY] did not specify baseline level of oxygen support so was excluded from this analysis. Data from Lee 2022 was used in place of published data from Ali 2022 [CATCO] and Ader 2022 [DisCoVeRy] trials to avoid double-counting patients included in the WHO-SOLIDARITY trial.

The analysis found no significant difference in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving high-flow oxygen supplementation, NIV or IMV (RR 1.08 95% CI 0.93 to 1.25).

One study (Beigel 2020) did not report use of corticosteroids as part of standard care in the trials. A sensitivity analysis removing this study from the analysis did not differ from the overall results (RR 1.10 95% CI 0.92 to 1.30).

For the following outcomes it was not possible to split the data by level of respiratory support:

**Invasive mechanical ventilation or ECMO (Updated)**

Data for the need for invasive mechanical ventilation or ECMO from 4 studies (Abd-Elsalam 2021, Beigel 2020, Mahajan 2021, WHO-SOLIDARITY 2022) were included in the meta-analysis (n= 8,605). The analysis found no significant difference in need for invasive mechanical ventilation or ECMO at day 28 with remdesivir compared with standard care, in hospitalised patients not on invasive ventilation at baseline (RR 0.85 95% CI 0.65 to 1.13).

Data from Ali 2022 [CATCO] and Ader 2022 [DisCoVeRy] were excluded from this analysis as it was not possible to avoid double-counting with WHO-SOLIDARITY 2022.
Most studies in this analysis did not report this outcome by baseline level of support so it was not possible to do separate analyses for those on no/low-flow oxygen and those on high-flow oxygen or NIV. Only WHO-SOLIDARITY 2022 reported separately on need for IMV or ECMO among patients not receiving oxygen at baseline. Data for this subgroup did not differ from the overall results (RR 0.97 95% CI 0.63 to 1.49).

**Need for oxygen supplementation [high-flow oxygen or NIV] (Updated)**

Data for this outcome from 3 studies (Ali 2022, Beigel 2020 and Mahajan 2021) were included in this meta-analysis (n= 906). The analysis found a statistically significant reduction in the need for high-flow oxygen or NIV for those treated with remdesivir compared to standard care.

**Clinical recovery (No change)**

Data for this outcome from 3 studies (Beigel 2020, Wang 2020, Spinner 2020) were included in this meta-analysis (n= 1,876). It found no statistically significant difference in clinical recovery at day 28 between remdesivir and standard care. 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 (Beigel 2020) or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale (Spinner 2020).

**Respiratory failure or ARDS (No change)**

Data for this outcome from 2 studies (Beigel 2020, Wang 2020) were included in this meta-analysis (n= 1,296). It found no statistically significant difference in respiratory failure or ARDS at day 28 with remdesivir compared with standard care in hospitalised patients not on invasive ventilation at baseline.

**Septic Shock (No change)**

Data for this outcome from 2 studies (Beigel 2020, Wang 2020) were included in the meta-analysis (n=1,296). It found no statistically significant difference in septic shock at day 28 between remdesivir and standard care.

**Adverse events (Updated)**

Data for this outcome from 6 studies (Ader 2022, Ali 2022, Barratt-Due 2021, Beigel 2020, Spinner 2020, Wang 2020) were included in the meta-analysis (n= 4,123). It found no statistically significant difference in adverse events at the end of follow up between remdesivir and standard care.
### Serious adverse events (Updated)

Data for this outcome from 5 studies (Ader 2022, Barratt-Due 2021, Beigel 2020, Spinner 2020, Wang 2020) were included in the meta-analysis (n= 2,536). It found no statistically significant difference in serious adverse events at the end of follow up between remdesivir and standard care.

### Discontinuation due to adverse events (No change)

Data for this outcome from 3 studies (Beigel 2020, Spinner 2020, Wang 2020) were included in the meta-analysis (n= 1,880). It found no statistically significant difference in discontinuation due to adverse events during treatment with remdesivir compared with standard care.

### Discharge from hospital (Updated)

Data from WHO-SOLIDARITY 2022 was used for this outcome (n= 8,275). This analysis found no statistically significant difference in discharge from hospital with remdesivir compared with standard care. Data from Ader 2022 [DisCoVeRy] was excluded from this analysis as it was not possible to avoid double-counting with WHO-SOLIDARITY 2022.

### Time to recovery (No change)

Data for this outcome from 2 studies (Beigel 2020, Spinner 2020) were included in the meta-analysis (n=1643). It found a statistically significant decrease in time to improvement between remdesivir and standard care.

### Time to improvement (Updated)

Data for this outcome from 3 studies (Ader 2022, Spinner 2020, Wang 2020) were included in the meta-analysis (n=1642). It found no statistically significant difference in time to improvement between remdesivir and standard care.

### Duration of hospital stay (New at this update)

One study (Ali 2022) reported on duration of hospital stay for those treated with remdesivir compared to standard care (n= 200). The study found a statistically significant decrease in days in hospital for those treated with remdesivir compared with standard care.
Oxygen-free days (New at this update)

One study (Ali 2022) reported on the number of oxygen-free days at day 28 for those treated with remdesivir compared to standard care (n=1,168). The study found a statistically significant increase in oxygen-free days among those treated with remdesivir compared with standard care.

Ventilator-free days (New at this update)

One study (Ali 2022) reported on the number of ventilator-free days at day 28 for those treated with remdesivir compared to standard care (n=1,168). The study found a statistically significant increase in ventilator-free days among those treated with remdesivir compared with standard care.

Our confidence in the results

All but one outcome (Respiratory failure or ARDS) were downgraded for risk of bias. In the case of the mortality outcomes, there was a risk of double-counting patients from the WHO-SOLIDARITY trial in the add-on trials [DisCoVeRy and CATCO]. For these outcomes, we noted a serious risk of bias due to uncertainty over how the trialists managed data across the studies, but we also used data from the Lee 2022 systematic review to minimise the risk of double-counting.

All studies were open-label. For outcomes that were considered subjective and where clinical judgement could be influenced by knowledge of treatment allocation, a rating of moderate risk of bias was given for the domain of outcome assessment.

Outcomes were downgraded for inconsistency where there was evidence of statistical heterogeneity ($I^2 > 50\%$). These included invasive mechanical ventilation or ECMO, serious adverse events, respiratory failure or ARDS, clinical recovery, adverse events, and discontinuation due to adverse events. Analyses which were not split by level of respiratory support may also be considered as clinically heterogenous.

All included studies met the PICO eligibility criteria so outcomes were not downgraded for indirectness. However, it is noted that all studies were carried out before the rollout of COVID-19 vaccination. Two studies (Abd-Elsalam 2021 and Beigel 2020) did not use corticosteroids as standard of care which is routinely used in the UK for people hospitalised for COVID-19. However, a sensitivity analysis without these studies showed no difference to the overall results.

Outcomes were downgraded for imprecision where the 95% confidence interval crossed the line of
Outcomes rated as moderate certainty included: all-cause mortality (no oxygen or low flow oxygen), need for oxygen supplementation, time to recovery.

Outcomes rated as low certainty included: all-cause mortality (High flow O2, NIV or IMV), invasive mechanical ventilation or ECMO, respiratory failure or ARDS, time to improvement, duration of hospital stay, oxygen-free days and ventilator-free days.

All the remaining outcomes were rated as very low certainty.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Placebo or standard care</th>
<th>Intervention Remdesivir</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (day 28; No oxygen or low flow oxygen)</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.81 (CI 95% 0.68 — 0.96) Based on data from 10,483 participants in 8 studies.</td>
<td>95 per 1000</td>
<td>77 per 1000</td>
<td>Moderate Due to serious risk of bias</td>
<td>A pooled analysis of 8 studies found a statistically significant reduction in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving low-flow or no oxygen supplementation</td>
</tr>
<tr>
<td>All-cause mortality (day 28; High flow O2, NIV or IMV)</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.08 (CI 95% 0.93 — 1.25) Based on data from 1,486 participants in 6 studies.</td>
<td>253 per 1000</td>
<td>273 per 1000</td>
<td>Low Due to serious imprecision, Due to serious risk of bias</td>
<td>A pooled analysis of 6 studies found no statistically significant difference in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving high-flow oxygen supplementation, NIV or IMV.</td>
</tr>
<tr>
<td>Invasive mechanical ventilation or ECMO</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.85 (CI 95% 0.65 — 1.13) Based on data from 8,605 participants in 4 studies.</td>
<td>141 per 1000</td>
<td>120 per 1000</td>
<td>Low Due to serious inconsistency, Due to serious risk of bias</td>
<td>A pooled analysis of 4 studies found no statistically significant difference in need for invasive mechanical ventilation or ECMO at day 28 with remdesivir compared with standard care, in hospitalised</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
</tr>
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<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Critical patients not on invasive ventilation at baseline.</td>
<td>9 Critical</td>
<td>Relative risk 0.79 (CI 95% 0.64 — 0.96) Based on data from 906 participants in 3 studies. 7 (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Remdesivir</td>
<td>Moderate Due to serious risk of bias 8</td>
<td>A pooled analysis of 3 studies found a statistically significant decrease in need for oxygen supplementation with remdesivir compared with standard care, in hospitalised patients not on oxygen at baseline.</td>
</tr>
<tr>
<td>Need for oxygen supplementation (low-flow, high-flow or NIV)</td>
<td>Within 28 days of commencing treatment</td>
<td>310 per 1000 Difference: 245 per 1000 65 fewer per 1000 (CI 95% 112 fewer — 12 fewer)</td>
<td>9 Critical</td>
<td>9 Critical</td>
<td>Very low Due to serious risk of bias, serious inconsistency, and serious imprecision 10</td>
<td>A pooled analysis of 5 studies found no statistically significant difference in need for oxygen supplementation compared with standard care.</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>End of follow-up</td>
<td>Relative risk 0.87 (CI 95% 0.68 — 1.11) Based on data from 2,827 participants in 5 studies. 9 (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Remdesivir</td>
<td>Low Due to serious inconsistency and serious imprecision 12</td>
<td>A pooled analysis of 5 studies found no statistically significant difference in serious adverse events at the end of follow up between remdesivir and standard care.</td>
</tr>
<tr>
<td>Respiratory failure or ARDS</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.79 (CI 95% 0.35 — 1.78) Based on data from 1,296 participants in 2 studies. 11 (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Remdesivir</td>
<td>Two studies found no statistically significant difference in respiratory failure or ARDS at day 28 with remdesivir compared with standard care.</td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.02 (CI 95% 0.34 — 3.01) Based on data from 1,296 participants in 2 studies. 13 (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Remdesivir</td>
<td>Very low Due to serious risk of bias, serious inconsistency and serious imprecision 14</td>
<td>Two studies found no statistically significant difference in septic shock at day 28 between remdesivir and standard care.</td>
</tr>
<tr>
<td>Clinical recovery</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.99 (CI 95% 0.86 — 1.14) Based on data from 1,876 participants in 3 studies. 15 (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Remdesivir</td>
<td>Very low Due to serious risk of bias, serious inconsistency and serious imprecision 16</td>
<td>Three studies found no statistically significant difference in clinical recovery at day 28 between remdesivir and standard care.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>Relative risk 1.13 (CI 95% 0.96 — 1.33) Based on data from 4,123 participants in 6 studies. 17 (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Remdesivir</td>
<td>Very low Due to serious risk of bias, serious inconsistency, and serious imprecision 18</td>
<td>A pooled analysis of 6 studies found no statistically significant difference in adverse events at the end of follow up between remdesivir and standard care.</td>
<td></td>
</tr>
<tr>
<td>Time to improvement</td>
<td>Hazard ratio 1.08 (CI 95% 0.97 — 1.19) Based on data from 1,642 participants in 3 studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low Due to serious risk of bias and serious imprecision 19</td>
<td>Three studies found no statistically significant difference in time to improvement between remdesivir and standard care.</td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to adverse events</td>
<td>Relative risk 1.73 (CI 95% 0.57 — 5.28) Based on data from 1,880 participants in 3 studies. 20 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias, serious inconsistency and serious imprecision 21</td>
<td>Three studies found no statistically significant difference in discontinuation due to adverse events during treatment with remdesivir compared with standard care.</td>
<td></td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>Relative risk 1.01 (CI 95% 0.99 — 1.03) Based on data from 8,275 participants in 1 studies. 22 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low Due to serious risk of bias and serious imprecision 23</td>
<td>One study found no significant difference in discharge from hospital at day 28 between remdesivir and standard care.</td>
<td></td>
</tr>
<tr>
<td>Time to recovery</td>
<td>Hazard ratio 1.24 (CI 95% 1.08 — 1.42) Based on data from 1,643 participants in 2 studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td>Moderate Due to serious risk of bias 24</td>
<td>Two studies found a statistically significant decrease in time to recovery with remdesivir compared with standard care.</td>
<td></td>
</tr>
<tr>
<td>Duration of hospital stay</td>
<td>Lower better Based on data from 200 participants in 1 studies. 25 (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias, serious indirectness, and serious imprecision 26</td>
<td>One study found a statistically significant decrease in duration of hospital stay for treatment with remdesivir compared with standard care.</td>
<td></td>
</tr>
<tr>
<td>Oxygen free days at day 28</td>
<td>Scale: 0 — 28 High better</td>
<td></td>
<td></td>
<td>Low Due to very serious risk of</td>
<td>One study found a statistically significant increase in number of</td>
<td></td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Placebo or standard care</td>
<td>Intervention Remdesivir</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
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<td></td>
</tr>
<tr>
<td>starting treatment</td>
<td>Based on data from 1,168 participants in 1 studies. (Randomized controlled)</td>
<td>Difference: MD 1.7 higher (CI 95% 0.46 higher — 2.94 higher)</td>
<td></td>
<td>Low Due to very serious risk of bias</td>
<td>oxygen-free days for treatment with remdesivir compared with standard care.</td>
<td></td>
</tr>
<tr>
<td>Ventilator free days at day 28</td>
<td>Scale: 0 — 28 High better Based on data from 1,168 participants in 1 studies. (Randomized controlled)</td>
<td>19.5 Days (Mean)</td>
<td>21.4 Days (Mean)</td>
<td>MD 1.9 higher (CI 95% 0.55 higher — 3.25 higher)</td>
<td>One study found a statistically significant increase in number of ventilator-free days for treatment with remdesivir compared with standard care.</td>
<td></td>
</tr>
</tbody>
</table>


2. **Risk of Bias: serious.** Incomplete information to understand the overlap between studies. **Inconsistency: no serious.** **Indirectness: no serious.** To note that these studies were conducted before vaccination for COVID-19 was rolled out. **Imprecision: no serious.** **Publication bias: no serious.**

3. Systematic review [165]. **Baseline/comparator:** Control arm of reference used for intervention. **Risk of Bias: serious.** Incomplete information to understand the overlap between studies. **Inconsistency: no serious.** **Indirectness: no serious.** To note that these studies were conducted before vaccination for COVID-19 was rolled out. **Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**

4. Systematic review [165] with included studies: Abd-Elsalam 2021, WHO-SOLIDARITY 2022 Low/Hi Flow, Mahajan 2021, Beigel 2020, WHO-SOLIDARITY 2022 No O2. **Baseline/comparator:** Control arm of reference used for intervention. **Risk of Bias: serious.** Incomplete information to understand the overlap between studies. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 77%. May also be considered clinically heterogenous due to baseline severity differences. **Indirectness: no serious.** To note that these studies were conducted before vaccination for COVID-19 was rolled out. **Imprecision: no serious.** **Publication bias: no serious.**

5. Systematic review [165] with included studies: Ali 2022, Beigel 2020 hi flow or NIV, Mahajan 2021, Beigel 2020 low-flow. **Baseline/comparator:** Control arm of reference used for intervention. **Risk of Bias: serious.** Missing data in two studies. One study has a deviation from intended intervention for one participant. **Inconsistency: no serious.** **Indirectness: no serious.** To note that these studies were conducted before vaccination for COVID-19 was rolled out. **Imprecision: no serious.** **Publication bias: no serious.**

6. **Risk of Bias: serious.** Incomplete information to understand the overlap between studies. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 77%. May also be considered clinically heterogenous due to baseline severity differences. **Indirectness: no serious.** To note that these studies were conducted before vaccination for COVID-19 was rolled out. **Imprecision: no serious.** **Publication bias: no serious.**

7. Systematic review [165] with included studies: Spinner 2020, NOR-SOLIDARITY 2021, Beigel 2020, Wang 2020, Ader 2022 DISCOVERY, Spinner 2020. **Baseline/comparator:** Control arm of reference used for intervention. **Risk of Bias: serious.** Missing data in two studies. One study has a deviation from intended intervention for one participant. **Inconsistency: no serious.** **Indirectness: no serious.** To note that these studies were conducted before vaccination for COVID-19 was rolled out. **Imprecision: no serious.** **Publication bias: no serious.**

8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in
potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with $I^2$: 50%. May also be considered clinically heterogenous due to baseline severity differences. **Indirectness: no serious.** To note that these studies were conducted before vaccination for COVID-19 was rolled out. **Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**


12. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Indirectness: no serious.** Imprecision: serious. 95% CI crosses line of no effect. **Publication bias: no serious.**


14. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Indirectness: no serious.** Imprecision: serious. 95% CI crosses line of no effect. **Publication bias: no serious.**


16. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies. **Indirectness: no serious.** Imprecision: serious. 95% CI crosses line of no effect. **Publication bias: no serious.**


18. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with $I^2$: 81%. **Indirectness: no serious.** To note that these studies were conducted before vaccination for COVID-19 was rolled out. **Imprecision: serious.** 95% CI crosses the line of no effect. **Publication bias: no serious.**

19. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious.** Indirectness: no serious. Imprecision: serious. 95% CI crosses line of no effect. **Publication bias: no serious.**


21. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Indirectness: no serious.** Imprecision: serious. 95% CI crosses line of no effect. **Publication bias: no serious.**


23. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in
potentially for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. To note that these studies were conducted before vaccination for COVID-19 was rolled out. **Imprecision:** serious. 95% CI crosses the line of no effect. **Publication bias:** no serious.

24. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** no serious. **Publication bias:** no serious.


26. **Risk of Bias:** serious. Potential selective reporting. **Inconsistency:** no serious. **Indirectness:** serious. Corticosteroids were not included in standard care. **Imprecision:** serious. n<300. **Publication bias:** no serious.


28. **Risk of Bias:** very serious. Missing data unaccounted for; open label study and subjective outcome. **Inconsistency:** no serious. **Indirectness:** no serious. To note that this study was conducted before vaccination for COVID-19 was rolled out. **Imprecision:** no serious. **Publication bias:** no serious.


30. **Risk of Bias:** very serious. Missing data unaccounted for; open label study and subjective outcome. **Inconsistency:** no serious. **Indirectness:** no serious. To note that this study was conducted before vaccination for COVID-19 was rolled out. **Imprecision:** no serious. **Publication bias:** no serious.

**References**


7.1.3 Molnupiravir

Info Box

Evidence on the clinical and cost effectiveness of molnupiravir is currently under review through the NICE multiple technology appraisal process.

Conditional recommendation

Consider a 5-day course of molnupiravir for adults with COVID-19 who:

- do not need supplemental oxygen for COVID-19, and
- are within 5 days of symptom onset, and
- are thought to be at high risk of progression to severe COVID-19. (NHS England's Interim Clinical Commissioning Policy on remdesivir and molnupiravir provides a list of people prioritised for treatment with antivirals.)

When assessing the person, take into account their likely response to any vaccinations already given, any comorbidities or risk factors, and whether their condition is deteriorating.

This recommendation is informed by the results of the MOVE-OUT trial, which included only unvaccinated people. The trial ran before the emergence of the Omicron (B.1.1.529) variant.

We are aware that the results of the PANORAMIC trial have published, and are reviewing this recommendation.
Evidence to decision

Benefits and harms

This recommendation is based on evidence presented in two randomised controlled trials: the MOVe-OUT trial and Fischer 2021. Both studies administered 800mg of molnupiravir for 5 days. Participants recruited to the MOVe-OUT trial had at least one risk factor for developing severe disease (including age over 60, obesity [BMI ≥30], diabetes, active cancer, chronic kidney disease, chronic obstructive pulmonary disease and serious heart conditions). In Fischer 2021, around 60% of the participants had at least one risk factor for developing severe disease. Both studies recruited people who did not require supplementary oxygen.

The MOVe-OUT study suggested that molnupiravir statistically significantly reduced the risk of hospitalisation or death (all-cause) compared to placebo. Evidence from both studies suggested a larger reduction in viral load at day 3 and day 5 since baseline in people who received molnupiravir than those who received placebo. The panel noted that although reduction in viral load may not mean a reduction in time to recovery, it may shorten the time that the person is infectious. This may be an important factor for people living with vulnerable or at risk people. Overall, the panel noted that molnupiravir may have benefits in people at risk of progression to severe disease. In the MOVe-OUT study, the published results were for people who had treatment within 5 days of symptom onset, and the panel agreed that this was when treatment was likely to be most effective.

Evidence on adverse events was pooled from both studies. There was no significant difference in adverse events or serious adverse events between the molnupiravir and placebo groups. In the MOVe-OUT trial, the risk of COVID-19 related death was statistically lower in the molnupiravir group compared with placebo (1 COVID-19 related death was reported in the molnupiravir group compared with 9 in the placebo group). In the 14 days beyond the treatment period, there were 2 additional deaths in the placebo group and 1 in the molnupiravir group. The panel agreed that molnupiravir could potentially benefit people with high risk of developing severe disease compared with placebo. The panel considered that the absolute benefit would potentially be smaller among vaccinated people.

The panel also discussed the potential benefits and harms of combination treatment with an antiviral drug and a neutralising monoclonal antibody or another antiviral drug in people who do not need supplemental oxygen for COVID-19 and who are at high risk of progression to severe disease. The panel were not aware of any clinical trial evidence on combination treatment in this population.

Certainty of the Evidence

The certainty of all outcomes from the included studies was downgraded due to indirectness, as the studies took place before the emergence of the Omicron variant of COVID-19 and because no patients in the studies had been vaccinated for COVID-19. The panel agreed that these factors meant evidence from the included studies was not directly relevant to the current situation of COVID-19 in the UK, where the Omicron variant is dominant and many people are vaccinated for COVID-19. The panel were aware that the ongoing UK-wide PANORAMIC study would provide more direct evidence on the effectiveness of molnupiravir in people with COVID-19 in the UK.

In the MOVe-OUT trial, the incidence of all-cause hospitalisation or death and COVID-19 related hospitalisation or death were graded as ‘moderate’ certainty due to indirectness of the study population. Change in viral load at days 3 and 5 were of ‘moderate’ certainty due to the same concern. Other outcomes such as adverse events and serious adverse events were of ‘low’ certainty, because the confidence intervals crossed the line of no effect in addition to indirectness. Imprecision resulted
in downgrading of other outcomes to ‘low’ certainty such as risk of COVID-19 related hospitalisation and change in viral load at days 7-10 and days 14-15.

The panel noted that there were subgroup differences for the outcome of hospitalisation or death, according to serostatus. There was a statistically significant difference in all-cause hospitalisation or death in the seronegative subgroup, but not in the seropositive subgroup. The panel discussed this and agreed that as the result for the overall population showed a significant reduction, and the absolute numbers for the subgroup results were small, they would not differentiate between seronegative and seropositive groups in the recommendation. They also pointed out that it was unlikely to be possible to test for serostatus within the timeframes of these treatments, and that delaying for testing would reduce the benefit of treatment.

The panel noted that the evidence was from non-hospitalised people with COVID-19, however the results could also be generalised to people in hospital for reasons other than COVID-19 who meet the criteria set out in the recommendation.

Values and preferences

The panel were not aware of any systematically collected data on peoples’ preferences and values. Molnupiravir can be administered orally and the current formulation is in 200mg capsules, meaning four capsules must be taken twice a day to achieve the dose recommended in the Summary of Product Characteristics (SmPC). The panel noted that the capsules are large and that some people might find them difficult to take. Therefore adherence and patient preferences might vary.

The panel noted that there is no evidence on the efficacy and safety of molnupiravir in children and young people, or pregnant women, and therefore it cannot be recommended in these groups. The panel believed that, if fully informed, most pregnant women and people under 18 would not choose molnupiravir because of the lack of evidence and the potential harms. Please refer to the following recommendation ’Do not offer molnupiravir to children and young people aged under 18, or pregnant women’ for further information.

Resources

The recommendations were not informed by a cost effectiveness analysis, however use of molnupiravir on a large scale is likely to incur costs to the healthcare system. These costs may be offset by a reduction in hospitalisation of people with COVID-19 who are at risk of progressing to severe disease.

Equity

The panel noted that the ability to access molnupiravir in the community may benefit people who have limited access to healthcare facilities as it can be delivered to their home. This may be especially relevant for those who find it difficult to travel, for example due to poor access to transport, disability or mobility issues, or childcare or caring responsibilities. In addition, having treatment whilst self-isolating at home may also minimise spread of the virus. However, there may be challenges for some patient groups if travel is needed to access treatment.

The panel noted that the use of molnupiravir to prevent progression to severe COVID-19 disease may not be safe for children and young people under 18, or for pregnant women. The panel noted the inequity of
There is evidence from 2 randomised controlled trials that treatment with molnupiravir within 5 days of symptom onset reduces the risk of hospitalisation or death compared with placebo in adults who do not need supplemental oxygen and have at least 1 risk factor for development of severe COVID-19 disease. However, there is uncertainty about the generalisability of the evidence to current clinical practice because the trials only included people who were not vaccinated against COVID-19, and took place before the emergence of the Omicron variant. Clinicians should refer to the NHS England Interim Clinical Commissioning Policy for the most up-to-date information about people prioritised for treatment with antivirals.

Acceptability
The panel were not aware of any systematically collected evidence about acceptability. However, they noted that receiving a treatment outside of hospital may be more acceptable for many people. The panel noted that although the risks of long-term effects of molnupiravir were assessed as low in the Summary of Product Characteristics (SmPC), these concerns may cause some people to choose not to take molnupiravir.

Feasibility
The dosage administration of molnupiravir might cause adherence issues for some patients. The panel noted that four capsules of 200mg twice a day may be difficult for patients to adhere to for five days.

Rationale
There is evidence from 2 randomised controlled trials that treatment with molnupiravir within 5 days of symptom onset reduces the risk of hospitalisation or death compared with placebo in adults who do not need supplemental oxygen and have at least 1 risk factor for development of severe COVID-19 disease. However, there is uncertainty about the generalisability of the evidence to current clinical practice because the trials only included people who were not vaccinated against COVID-19, and took place before the emergence of the Omicron variant. Clinicians should refer to the NHS England Interim Clinical Commissioning Policy for the most up-to-date information about people prioritised for treatment with antivirals.

Clinical question/ PICO

| Population | People with COVID-19 and symptom onset in the last 7 days |
| Intervention | Molnupiravir |
| Comparator | Placebo |

Summary

Key results
The evidence suggests that molnupiravir reduces the risk of hospitalisation or death and COVID-19-related death in unvaccinated, non-hospitalised people with mild or moderate COVID-19 who are at increased risk of developing severe COVID-19 disease, and may also reduce time to viral RNA clearance, compared to placebo.

What is the evidence informing this conclusion?
The evidence comes from two randomised controlled trials comparing 800 mg molnupiravir twice a day for five days with placebo in non-hospitalised adults with mild or moderate COVID-19 (Jayk Bernal 2021; Fischer 2021). Jayk Bernal 2021 is a phase III trial (known as MOVe-OUT) that included 1433 patients to either molnupiravir or placebo. Recruitment of participants was carried out in 20 countries.

Fischer 2021 is a phase IIa trial in which 55 patients received 800mg molnupiravir and 62 received
placebo. This trial was conducted in the USA.

The published results were for people who had treatment within 5 days of symptom onset in MOVe-OUT and within 7 days in the Fischer 2021 study. In MOVe-OUT, standard-of-care treatment was allowed with antipyretic agents, anti-inflammatory agents, glucocorticoids, or a combination. Use of therapies for COVID-19 treatments, such as monoclonal antibodies and remdesivir, was prohibited until day 29. The study by Fischer 2021 did not report details about standard of care, however use of therapeutic interventions for COVID-19 prior to study entry was one of the exclusion criteria.

Publication status
Both studies are full publications.

Study characteristics
The MOVe-OUT study enrolled participants who were at increased risk of disease progression due to at least one of the following factors: age over 60, obesity, or another comorbidity including active cancer; chronic kidney disease; COPD; serious heart conditions, or diabetes mellitus. In the Fisher 2021 study, 60% of participants had at least one risk factor for developing severe COVID-19 disease (risk factors not reported). The MOVe-OUT trial followed up participants through to 29 days after randomisation while Fischer 2021 assessed outcomes for up to 28 days following treatment initiation. Pregnant women were excluded from both studies. Both studies excluded SARS-CoV-2 vaccinated participants. Both studies excluded patients who need supplemental oxygen or have an anticipated need for hospitalisation.

In the MOVe-OUT study, the median age of the participants was 43 (range 18-90). In Fischer 2021, the age range was 18 to 71 years. In MOVe-OUT, the proportion of females was 51.3% overall, and was higher in the molnupiravir group (53.6%) than the placebo group (49.0%). In Fischer 2021, 54.8% of the study population in placebo and 49.1% in molnupiravir were female.

For further details see the evidence review.

What are the main results?

Hospitalisation or death
The MOVe-OUT study reported a statistically significant reduction in the composite outcome of all-cause hospitalisation or death, and in COVID-19-related death to day 29 in people treated with molnupiravir compared to placebo.

The composite outcome of hospitalisation or death did not differ by subgroups for people treated within 3 days of symptom onset, or within 3-5 days of symptom onset. There was a potential subgroup effect of serostatus at baseline (subgroup effect $I^2$ was 68.8%, P-value was 0.07)

Viral load
There was a statistically larger reduction in viral load from baseline to day 3 and day 5 in molnupiravir compared to placebo. Results for day 7-10, day 14-15 and day 29 showed no difference in change in viral RNA load from baseline between the groups.

Adverse Events
The frequency of adverse events and discontinuation of treatment due to adverse events was not significantly different between the molnupiravir and placebo groups in either study.

Our confidence in the results
Outcomes from both studies were rated as having a low risk of bias due to there being very few concerns around study design and results. In the MOVe-OUT trial, there was a greater proportion of females in the molnupiravir group (53.6%) compared with the placebo group (49%), however an analysis for the primary outcome of hospitalisation or death was adjusted for participant sex, and the results were consistent with the primary analysis.

In Fischer 2021, sample collection was carried out for antiviral efficacy and safety at day 1, 3, 5, 7, 14 and 28. However, no outcomes were reported at 28 days and only data at day 14 was available as an endpoint. Time to viral clearance was not reported in sufficient detail to be extracted and included in this review. Fischer 2021 did not report outcomes on hospitalisation or death.

Since both studies cited in this review took place before the emergence of the Omicron variant, and before the availability of vaccination against COVID-19, the populations measured in the study may not be directly relevant or comparable to current populations in the UK, where the Delta and Omicron variants are dominant and many people have been vaccinated against COVID-19. As a result, the certainty in all outcomes presented was downgraded due to indirectness.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause hospitalisation or death Day 29</td>
<td>Relative risk 0.7 (CI 95% 0.49 — 0.99) Based on data from 1,408 participants in 1 studies.</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Moderate Due to serious indirectness ²</td>
<td>One study found a statistically significant reduction in all-cause hospitalisation or death in unvaccinated people who received molnupiravir compared to those who received placebo</td>
</tr>
<tr>
<td>COVID-19 related hospitalisation or death Day 29</td>
<td>Relative risk 0.69 (CI 95% 0.48 — 1) Based on data from 1,408 participants in 1 studies.</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Low Due to serious imprecision and serious indirectness ⁴</td>
<td>One study found a non-statistically significant reduction in COVID-19 related hospitalisation in unvaccinated people who received molnupiravir compared to those who received placebo.</td>
</tr>
<tr>
<td>COVID-19 related death Day 29</td>
<td>Relative risk 0.11 (CI 95% 0.01 — 0.86) Based on data from 1,408 participants in 1 studies.</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Moderate Due to serious indirectness ⁶</td>
<td>One study found a statistically significant reduction in COVID-19 related death in unvaccinated people who received molnupiravir compared to those who received placebo.</td>
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<tr>
<td>COVID-19 related hospitalisation</td>
<td>Day 29</td>
<td>Relative risk 0.79 (CI 95% 0.54 — 1.16) Based on data from 1,408 participants in 1 studies.</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Low Due to serious imprecision and serious indirectness</td>
</tr>
<tr>
<td>Hospitalisation or Death - ≤ 3 days since symptom onset</td>
<td>Day 29</td>
<td>Relative risk 0.88 (CI 95% 0.53 — 1.48) Based on data from 674 participants in 1 studies.</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Low Due to serious imprecision and serious indirectness</td>
</tr>
<tr>
<td>Hospitalisation or Death -&gt; 3 days since symptom onset</td>
<td>Day 29</td>
<td>Relative risk 0.57 (CI 95% 0.35 — 0.93) Based on data from 734 participants in 1 studies.</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Moderate Due to serious indirectness</td>
</tr>
<tr>
<td>People who discontinued treatment because of an adverse event</td>
<td>Day 29</td>
<td>Relative risk 0.49 (CI 95% 0.23 — 1.05) Based on data from 1,411 participants in 1 studies.</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Low Due to serious imprecision and serious indirectness</td>
</tr>
<tr>
<td>Participants with adverse events - ≥1</td>
<td>Adverse event Day 28-29</td>
<td>Relative risk 0.91 (CI 95% 0.78 — 1.05) Based on data from 1,528 participants in 2 studies.</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Low Due to serious imprecision and serious indirectness</td>
</tr>
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<tr>
<td><strong>Participants with adverse events - ≥1</strong>&lt;br&gt;<strong>Serious adverse event</strong>&lt;br&gt;<strong>Day 28-29</strong></td>
<td>Relative risk 0.73 (CI 95% 0.51 — 1.03)&lt;br&gt;Based on data from 1,528 participants in 2 studies. 17 (Randomized controlled)</td>
<td>89 per 1000</td>
<td>65 per 1000</td>
<td>24 fewer per 1000 (CI 95% 44 fewer — 3 more)</td>
<td>Low Due to serious imprecision and serious indirectness</td>
</tr>
<tr>
<td><strong>Hospitalisation or death - Seropositive nucleocapsid antibody status at baseline</strong>&lt;br&gt;<strong>Day 29</strong></td>
<td>Relative risk 2.68 (CI 95% 0.53 — 13.6)&lt;br&gt;Based on data from 282 participants in 1 studies. 19 (Randomized controlled)</td>
<td>14 per 1000</td>
<td>38 per 1000</td>
<td>24 more per 1000 (CI 95% 7 fewer — 176 more)</td>
<td>Low Due to serious indirectness and serious imprecision</td>
</tr>
<tr>
<td><strong>Hospitalisation or death - Seronegative nucleocapsid antibody status at baseline</strong>&lt;br&gt;<strong>Day 29</strong></td>
<td>Relative risk 0.59 (CI 95% 0.4 — 0.86)&lt;br&gt;Based on data from 1,061 participants in 1 studies. 21 (Randomized controlled)</td>
<td>123 per 1000</td>
<td>73 per 1000</td>
<td>50 fewer per 1000 (CI 95% 74 fewer — 17 fewer)</td>
<td>Moderate Due to serious indirectness</td>
</tr>
<tr>
<td><strong>Change in Viral Load - Day 3</strong>&lt;br&gt;<strong>Day 3</strong></td>
<td>Based on data from 1,113 participants in 2 studies. 23 (Randomized controlled)</td>
<td></td>
<td></td>
<td>MD 0.23 lower (CI 95% 0.38 lower — 0.09 lower)</td>
<td>Moderate Due to serious indirectness</td>
</tr>
<tr>
<td><strong>Change in Viral Load - Day 5</strong></td>
<td>Based on data from 1,073 participants in 2 studies. 25 (Randomized controlled)</td>
<td></td>
<td></td>
<td>MD 0.41 lower (CI 95% 0.65 lower — 0.17 lower)</td>
<td>Moderate Due to serious indirectness</td>
</tr>
</tbody>
</table>

1. **Participants with adverse events - ≥1**<br>**Serious adverse event**<br>Day 28-29: Relative risk 0.73 (CI 95% 0.51 — 1.03). Based on data from 1,528 participants in 2 studies. 17 (Randomized controlled).<br>Summary: Two studies found a non-statistically significant reduction in participants with ≥1 serious adverse events in unvaccinated people who received molnupiravir compared to those who received placebo.<br>

2. **Hospitalisation or death - Seropositive nucleocapsid antibody status at baseline**<br>Day 29: Relative risk 2.68 (CI 95% 0.53 — 13.6). Based on data from 282 participants in 1 studies. 19 (Randomized controlled).<br>Summary: One study found no statistically significant difference in hospitalisation or death in unvaccinated people who were seropositive for nucleocapsid antibody treated with molnupiravir compared to those who received placebo.<br>

3. **Hospitalisation or death - Seronegative nucleocapsid antibody status at baseline**<br>Day 29: Relative risk 0.59 (CI 95% 0.4 — 0.86). Based on data from 1,061 participants in 1 studies. 21 (Randomized controlled).<br>Summary: One study found a statistically significant reduction in hospitalisation or death in unvaccinated people who were seronegative for nucleocapsid antibody and received molnupiravir compared to those who received placebo.<br>

4. **Change in Viral Load - Day 3**<br>Day 3: Based on data from 1,113 participants in 2 studies. 23 (Randomized controlled).<br>Summary: Two studies found a statistically larger reduction in viral load at day 3 in unvaccinated people who received molnupiravir compared to those who received placebo.<br>

5. **Change in Viral Load - Day 5**<br>Day 5: Based on data from 1,073 participants in 2 studies. 25 (Randomized controlled).<br>Summary: Two studies found a statistically larger reduction in viral load at day 5 in unvaccinated people who received molnupiravir compared to those who received placebo.
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<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in Viral Load - Day 7-10</td>
<td>Day 7-10</td>
<td>Based on data from 990 participants in 2 studies.</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>MD 0.33 lower (CI 95% 0.66 lower — 0 higher)</td>
<td>Low Due to serious imprecision and serious indirectness</td>
</tr>
<tr>
<td>Change in Viral Load - Day 14-15</td>
<td>Day 14 or 15</td>
<td>Based on data from 939 participants in 2 studies.</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>MD 0.15 lower (CI 95% 0.32 lower — 0.01 higher)</td>
<td>Low Due to serious imprecision and serious indirectness</td>
</tr>
<tr>
<td>Change in RNA titre - Overall</td>
<td>Day 29</td>
<td>Based on data from 735 participants in 1 studies.</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>MD 0.08 higher (CI 95% 0.16 lower — 0.32 higher)</td>
<td>Low Due to serious imprecision and serious indirectness</td>
</tr>
</tbody>
</table>

1. Systematic review [121]. **Baseline/comparator**: Control arm of reference used for intervention.
2. **Inconsistency: no serious. Indirectness: serious.** Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
   **Imprecision: no serious. Publication bias: no serious.**
3. Systematic review [121]. **Baseline/comparator**: Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: serious.** Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
   **Imprecision: serious.** CI includes line of no effect. **Publication bias: no serious.**
5. Systematic review [121]. **Baseline/comparator**: Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: serious.** Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
   **Imprecision: no serious. Publication bias: no serious.**
7. Systematic review [121]. **Baseline/comparator**: Control arm of reference used for intervention.
8. **Inconsistency: no serious. Indirectness: serious.** Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.

**Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**

9. Systematic review [121]. **Baseline/comparator:** Control arm of reference used for intervention.

10. **Inconsistency: no serious. Indirectness: serious.** Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.

**Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**

11. Systematic review [121]. **Baseline/comparator:** Control arm of reference used for intervention.

12. **Inconsistency: no serious. Indirectness: serious.** Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.

**Imprecision: no serious.** CIs do not cross line of no effect. **Publication bias: no serious.**

13. Systematic review [121]. **Baseline/comparator:** Control arm of reference used for intervention.

14. **Inconsistency: no serious. Indirectness: serious.** Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.

**Imprecision: serious.** CIs include line of no effect. **Publication bias: no serious.**

15. Systematic review [121]. **Baseline/comparator:** Control arm of reference used for intervention.

16. **Inconsistency: no serious. Indirectness: serious.** Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.

**Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**

17. Systematic review [121]. **Baseline/comparator:** Control arm of reference used for intervention.

18. **Inconsistency: no serious. Indirectness: serious.** Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.

**Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**

19. Systematic review [121]. **Baseline/comparator:** Control arm of reference used for intervention.

20. **Inconsistency: no serious. Indirectness: serious.** Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.

**Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**

21. Systematic review [121]. **Baseline/comparator:** Control arm of reference used for intervention.

22. **Inconsistency: no serious. Indirectness: serious.** Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.

**Imprecision: no serious.** **Publication bias: no serious.**

23. Systematic review [121]. **Baseline/comparator:** Control arm of reference used for intervention.

24. **Inconsistency: no serious. Indirectness: serious.** Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.

**Imprecision: no serious.** **Publication bias: no serious.**

25. Systematic review [121]. **Baseline/comparator:** Control arm of reference used for intervention.

26. **Inconsistency: no serious. Indirectness: serious.** Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.

**Imprecision: no serious.** **Publication bias: no serious.**
Do not offer molnupiravir to children and young people aged under 18, or pregnant women.

Evidence to decision

Benefits and harms

This recommendation has been drafted based on evidence presented in two randomised controlled trials: the MOVe-OUT trial and Fischer 2021. Both trials included patients aged 18 and above, with at least one risk factor for progressing to severe disease. The panel noted that molnupiravir should not be offered in people below 18 years of age. There is no evidence for safety and efficacy in this age group in both trials. Both studies excluded people under 18 and pregnant women.

The panel noted that safety data in the summary of product characteristics raised concerns about the long-term safety of molnupiravir in children and young people, and that studies in animals have shown reproductive toxicity. They also acknowledged that there is no evidence on efficacy and safety of molnupiravir in people under 18 or...
pregnant women in either trial. Based on this information, the panel agreed that molnupiravir should not be offered to children and young people under 18, or pregnant women. For further information, see the summary of product characteristics.

**Certainty of the Evidence**

There is no evidence on the safety and efficacy of molnupiravir in children and young people or pregnant women. The panel were not presented with risk of hospitalisation or risk of COVID-19 related death in these groups.

**Values and preferences**

The panel took into account patient preferences and values while making this recommendation. The panel inferred that, if fully informed, most pregnant women and people under 18 would not choose molnupiravir because of the lack of evidence and the potential harms.

**Equity**

The panel were not aware of any systematically collected evidence on equity in children and young people.

Molnupiravir should not be used in pregnancy and no evidence in children or young people was identified. The recommendation not to offer molnupiravir to these groups means differential access, however the panel agreed that this was justified based on safety concerns.

No other issues related to equity were identified.

**Acceptability**

The panel were not aware of any systematically collected evidence about acceptability. However, the panel discussed the potential harms of molnupiravir and concluded that there is not enough evidence in children and young people or pregnant women to recommend it. They agreed that its use in these groups is not likely to be acceptable.

**Feasibility**

The panel were not aware of any systematically collected evidence on feasibility of the recommendation.

**Rationale**

Two trials were included in the evidence, and both trials only included people aged 18 and above.
Pregnant women were also excluded from the study population.

The summary of product characteristics states that molnupiravir is of low risk for mutagenicity or genotoxicity in adults. However, the safety and efficacy of molnupiravir has not been established in children and young people or pregnant women. Based on this, and the absence of these groups from the study populations, the panel concluded that there is no evidence on the efficacy and safety of molnupiravir for children and young people, or pregnant women, and so it cannot be recommended for them.

**Clinical question/ PICO**

**Population:** People with COVID-19 and symptom onset in the last 7 days  
**Intervention:** Molnupiravir  
**Comparator:** Placebo

**Summary**

**Key results**

The evidence suggests that molnupiravir reduces the risk of hospitalisation or death and COVID-19-related death in unvaccinated, non-hospitalised people with mild or moderate COVID-19 who are at increased risk of developing severe COVID-19 disease, and may also reduce time to viral RNA clearance, compared to placebo.

**What is the evidence informing this conclusion?**

The evidence comes from two randomised controlled trials comparing 800 mg molnupiravir twice a day for five days with placebo in non-hospitalised adults with mild or moderate COVID-19 (Jayk Bernal 2021; Fischer 2021). Jayk Bernal 2021 is a phase III trial (known as MOVe-OUT) that included 1433 patients to either molnupiravir or placebo. Recruitment of participants was carried out in 20 countries.

Fischer 2021 is a phase IIa trial in which 55 patients received 800mg molnupiravir and 62 received placebo. This trial was conducted in the USA.

The published results were for people who had treatment within 5 days of symptom onset in MOVe-OUT and within 7 days in the Fischer 2021 study. In MOVe-OUT, standard-of-care treatment was allowed with antipyretic agents, anti-inflammatory agents, glucocorticoids, or a combination. Use of therapies for COVID-19 treatments, such as monoclonal antibodies and remdesivir, was prohibited until day 29. The study by Fischer 2021 did not report details about standard of care, however use of therapeutic interventions for COVID-19 prior to study entry was one of the exclusion criteria.

**Publication status**

Both studies are full publications.

**Study characteristics**

The MOVe-OUT study enrolled participants who were at increased risk of disease progression due to at least one of the following factors: age over 60, obesity, or another comorbidity including active cancer; chronic kidney disease; COPD; serious heart conditions, or diabetes mellitus. In the Fisher 2021 study, 60% of participants had at least one risk factor for developing severe COVID-19 disease (risk factors not reported). The MOVe-OUT trial followed up participants through to 29 days after randomisation while Fischer 2021 assessed outcomes for up to 28 days following treatment initiation. Pregnant women were excluded from both studies. Both studies excluded SARS-CoV-2 vaccinated participants. Both studies excluded patients who need supplemental
oxygen or have an anticipated need for hospitalisation.

In the MOVe-OUT study, the median age of the participants was 43 (range 18-90). In Fischer 2021, the age range was 18 to 71 years. In MOVe-OUT, the proportion of females was 51.3% overall, and was higher in the molnupiravir group (53.6%) than the placebo group (49.0%). In Fischer 2021, 54.8% of the study population in placebo and 49.1% in molnupiravir were female.

For further details see the evidence review.

What are the main results?

Hospitalisation or death

The MOVe-OUT study reported a statistically significant reduction in the composite outcome of all-cause hospitalisation or death, and in COVID-19-related death to day 29 in people treated with molnupiravir compared to placebo.

The composite outcome of hospitalisation or death did not differ by subgroups for people treated within 3 days of symptom onset, or within 3-5 days of symptom onset. There was a potential subgroup effect of serostatus at baseline (subgroup effect I² was 68.8%, P-value was 0.07).

Viral load

There was a statistically larger reduction in viral load from baseline to day 3 and day 5 in molnupiravir compared to placebo. Results for day 7-10, day 14-15 and day 29 showed no difference in change in viral RNA load from baseline between the groups.

Adverse Events

The frequency of adverse events and discontinuation of treatment due to adverse events was not significantly different between the molnupiravir and placebo groups in either study.

Our confidence in the results

Outcomes from both studies were rated as having a low risk of bias due to there being very few concerns around study design and results. In the MOVe-OUT trial, there was a greater proportion of females in the molnupiravir group (53.6%) compared with the placebo group (49%), however an analysis for the primary outcome of hospitalisation or death was adjusted for participant sex, and the results were consistent with the primary analysis.

In Fischer 2021, sample collection was carried out for antiviral efficacy and safety at day 1, 3, 5, 7, 14 and 28. However, no outcomes were reported at 28 days and only data at day 14 was available as an endpoint. Time to viral clearance was not reported in sufficient detail to be extracted and included in this review. Fischer 2021 did not report outcomes on hospitalisation or death.

Since both studies cited in this review took place before the emergence of the Omicron variant, and before the availability of vaccination against COVID-19, the populations measured in the study may not be directly relevant or comparable to current populations in the UK, where the Delta and Omicron variants are dominant and many people have been vaccinated against COVID-19. As a result, the certainty in all outcomes presented was downgraded due to indirectness.
<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause hospitalisation or death Day 29</td>
<td>Relative risk 0.7 (CI 95% 0.49 — 0.99) Based on data from 1,408 participants in 1 studies. ¹ (Randomized controlled)</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Moderate Due to serious indirectness ²</td>
<td>One study found a statistically significant reduction in all-cause hospitalisation or death in unvaccinated people who received molnupiravir compared to those who received placebo.</td>
</tr>
<tr>
<td>COVID-19 related hospitalisation or death Day 29</td>
<td>Relative risk 0.69 (CI 95% 0.48 — 1) Based on data from 1,408 participants in 1 studies. ³ (Randomized controlled)</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Low Due to serious imprecision and serious indirectness ⁴</td>
<td>One study found a non-statistically significant reduction in COVID-19 related hospitalisation in unvaccinated people who received molnupiravir compared to those who received placebo.</td>
</tr>
<tr>
<td>COVID-19 related death Day 29</td>
<td>Relative risk 0.11 (CI 95% 0.01 — 0.86) Based on data from 1,408 participants in 1 studies. ⁵ (Randomized controlled)</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Moderate Due to serious indirectness ⁶</td>
<td>One study found a statistically significant reduction in COVID-19 related death in unvaccinated people who received molnupiravir compared to those who received placebo.</td>
</tr>
<tr>
<td>COVID-19 related hospitalisation Day 29</td>
<td>Relative risk 0.79 (CI 95% 0.54 — 1.16) Based on data from 1,408 participants in 1 studies. ⁶ (Randomized controlled)</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Low Due to serious imprecision and serious indirectness ⁸</td>
<td>One study found no statistically significant difference in COVID-19 related hospitalisation in unvaccinated people who received molnupiravir compared to those who received placebo.</td>
</tr>
<tr>
<td>Hospitalisation or Death ≤ 3 days since symptom onset Day 29</td>
<td>Relative risk 0.88 (CI 95% 0.53 — 1.48) Based on data from 674 participants in 1 studies. ⁹ (Randomized controlled)</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Low Due to serious imprecision and serious indirectness ¹⁰</td>
<td>One study found no statistically significant difference in hospitalisation or death in unvaccinated people who received molnupiravir within 3 days of onset of symptoms compared to those who received placebo.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
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<tr>
<td>Hospitalisation or Death -&gt; 3 days since symptom onset</td>
<td>Day 29</td>
<td>Relative risk 0.57 (CI 95% 0.35 — 0.93) Based on data from 734 participants in 1 studies. (^{11}) (Randomized controlled)</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Moderate Due to serious indirectness (^{12})</td>
</tr>
<tr>
<td>People who discontinued treatment because of an adverse event</td>
<td>Day 29</td>
<td>Relative risk 0.49 (CI 95% 0.23 — 1.05) Based on data from 1,411 participants in 1 studies. (^{13}) (Randomized controlled)</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Low Due to serious imprecision and serious indirectness (^{14})</td>
</tr>
<tr>
<td>Participants with adverse events - ≥1 Adverse event</td>
<td>Day 28-29</td>
<td>Relative risk 0.91 (CI 95% 0.78 — 1.05) Based on data from 1,528 participants in 2 studies. (^{15}) (Randomized controlled)</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Low Due to serious imprecision and serious indirectness (^{16})</td>
</tr>
<tr>
<td>Participants with adverse events - ≥1 Serious adverse event</td>
<td>Day 28-29</td>
<td>Relative risk 0.73 (CI 95% 0.51 — 1.03) Based on data from 1,528 participants in 2 studies. (^{17}) (Randomized controlled)</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Low Due to serious imprecision and serious indirectness (^{18})</td>
</tr>
<tr>
<td>Hospitalisation or death - Seropositive nucleocapsid antibody status at baseline</td>
<td>Day 29</td>
<td>Relative risk 2.68 (CI 95% 0.33 — 13.6) Based on data from 282 participants in 1 studies. (^{19}) (Randomized controlled)</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Low Due to serious indirectness and serious imprecision (^{20})</td>
</tr>
<tr>
<td>Outcome</td>
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<tr>
<td>Hospitalisation or death - Seronegative nucleocapsid antibody status at baseline Day 29</td>
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<tr>
<td>Timeframe</td>
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<tr>
<td>Study results and measurements</td>
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<tr>
<td>Comparator Placebo</td>
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<tr>
<td>Intervention Molnupiravir</td>
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<tr>
<td>Certainty of the Evidence (Quality of evidence)</td>
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<tr>
<td>Summary</td>
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</tr>
<tr>
<td>Relative risk 0.59 (CI 95% 0.4 — 0.86) Based on data from 1,061 participants in 1 studies. (Randomized controlled)</td>
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<tr>
<td>123 per 1000 Difference: 73 per 1000 50 fewer per 1000 (CI 95% 74 fewer — 17 fewer)</td>
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<tr>
<td>Moderate Due to serious indirectness</td>
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<tr>
<td>molnupiravir compared to those who received placebo.</td>
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</tbody>
</table>

One study found a statistically significant reduction in hospitalisation or death in unvaccinated people who were seronegative for nucleocapsid antibody and received molnupiravir compared to those who received placebo.

| Change in Viral Load - Day 3 Day 3 |
| Comparator Placebo |
| Intervention Molnupiravir |
| Certainty of Evidence (Quality of Evidence) |
| Summary |
| Based on data from 1,113 participants in 2 studies. (Randomized controlled) |
| Difference: MD 0.23 lower (CI 95% 0.38 lower — 0.09 lower) |
| Moderate Due to serious indirectness |
| Two studies found a statistically larger reduction in viral load at day 3 in unvaccinated people who received molnupiravir compared to those who received placebo |

| Change in Viral Load - Day 5 |
| Comparator Placebo |
| Intervention Molnupiravir |
| Certainty of Evidence (Quality of Evidence) |
| Summary |
| Based on data from 1,073 participants in 2 studies. (Randomized controlled) |
| Difference: MD 0.41 lower (CI 95% 0.65 lower — 0.17 lower) |
| Moderate Due to serious indirectness |
| Two studies found a statistically larger reduction in viral load at day 5 in unvaccinated people who received molnupiravir compared to those who received placebo |

| Change in Viral Load - Day 7-10 Day 7-10 |
| Comparator Placebo |
| Intervention Molnupiravir |
| Certainty of Evidence (Quality of Evidence) |
| Summary |
| Based on data from 990 participants in 2 studies. (Randomized controlled) |
| Difference: MD 0.33 lower (CI 95% 0.66 lower — 0 higher) |
| Low Due to serious imprecision and serious indirectness |
| Two studies found a non-statistically significantly larger reduction in viral load from baseline to day 7 to 10 in unvaccinated people who received molnupiravir compared to those who received placebo |

| Change in Viral Load - Day 14-15 Day 14 or 15 |
| Comparator Placebo |
| Intervention Molnupiravir |
| Certainty of Evidence (Quality of Evidence) |
| Summary |
| Based on data from 939 participants in 2 studies. (Randomized controlled) |
| Difference: MD 0.15 lower (CI 95% 0.32 lower — 0.01 higher) |
| Low Due to serious imprecision and serious indirectness |
| Two studies found no statistically significant difference in viral load at day 14 to 15 in unvaccinated people who received molnupiravir compared to those who received
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in RNA titre - Overall Day 29</td>
<td>Based on data from 735 participants in 1 studies. (^{31}) (Randomized controlled)</td>
<td>Placebo</td>
<td>Molnupiravir</td>
<td>Low Due to serious imprecision and serious indirectness (^{32})</td>
<td>One study found no statistically significant difference in viral load at day 29 in unvaccinated people who received molnupiravir compared to those who received placebo</td>
</tr>
</tbody>
</table>

1. Systematic review [121]. **Baseline/comparator**: Control arm of reference used for intervention.  
2. **Inconsistency**: no serious. **Indirectness**: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.  
   **Imprecision**: no serious. **Publication bias**: no serious.  
3. Systematic review [121]. **Baseline/comparator**: Control arm of reference used for intervention.  
4. **Inconsistency**: no serious. **Indirectness**: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.  
   **Imprecision**: serious. CI includes line of no effect. **Publication bias**: no serious.  
5. Systematic review [121]. **Baseline/comparator**: Control arm of reference used for intervention.  
6. **Inconsistency**: no serious. **Indirectness**: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.  
   **Imprecision**: no serious. **Publication bias**: no serious.  
7. Systematic review [121]. **Baseline/comparator**: Control arm of reference used for intervention.  
8. **Inconsistency**: no serious. **Indirectness**: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.  
   **Imprecision**: serious. CIs cross line of no effect. **Publication bias**: no serious.  
9. Systematic review [121]. **Baseline/comparator**: Control arm of reference used for intervention.  
10. **Inconsistency**: no serious. **Indirectness**: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.  
   **Imprecision**: serious. CIs include the line of effect. **Publication bias**: no serious.  
11. Systematic review [121]. **Baseline/comparator**: Control arm of reference used for intervention.  
12. **Inconsistency**: no serious. **Indirectness**: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.  
   **Imprecision**: no serious. CIs do not cross line of no effect. **Publication bias**: no serious.  
13. Systematic review [121]. **Baseline/comparator**: Control arm of reference used for intervention.  
14. **Inconsistency**: no serious. **Indirectness**: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
Imprecision: serious. CI includes line of no effect. Publication bias: no serious.
15. Systematic review [121]. Baseline/comparator: Control arm of reference used for intervention.
16. Inconsistency: no serious. Indirectness: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
Imprecision: serious. CIs cross line of no effect. Publication bias: no serious.
17. Systematic review [121]. Baseline/comparator: Control arm of reference used for intervention.
18. Inconsistency: no serious. Indirectness: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
Imprecision: serious. CIs cross line of no effect. Publication bias: no serious.
20. Inconsistency: no serious. Indirectness: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
Imprecision: no serious. Publication bias: no serious.
22. Inconsistency: no serious. Indirectness: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
Imprecision: no serious. Publication bias: no serious.
24. Inconsistency: no serious. Indirectness: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
Imprecision: no serious. Publication bias: no serious.
26. Inconsistency: no serious. Indirectness: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
Imprecision: no serious. Publication bias: no serious.
27. Systematic review [121]. Baseline/comparator: Control arm of reference used for intervention.
28. Inconsistency: no serious. Indirectness: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
Imprecision: serious. CIs cross line of effect. Publication bias: no serious.
29. Systematic review [121]. Baseline/comparator: Control arm of reference used for intervention.
30. Inconsistency: no serious. Indirectness: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
Imprecision: serious. CIs cross line of effect. Publication bias: no serious.
31. Systematic review [121]. Baseline/comparator: Control arm of reference used for intervention.
32. Inconsistency: no serious. Indirectness: serious. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
Imprecision: serious. CIs cross line of no effect. Publication bias: no serious.
There is some evidence suggesting that sotrovimab is likely to be effective at treating COVID-19. Its likely cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources for people in whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. So, sotrovimab is recommended for this group. For evidence and information on how this decision was made, see NICE's technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.

Sotrovimab is only recommended if the company provides it according to the commercial arrangement.

This recommendation is from NICE's technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.

There is some evidence suggesting that sotrovimab is likely to be effective at treating COVID-19. Its likely cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources for people in whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. So, sotrovimab is recommended for this group. For evidence and information on how this decision was made, see NICE's technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.

Sotrovimab is recommended as an option for treating COVID-19 in adults and young people aged 12 years and over and weighing at least 40 kg, only if:

- they do not need supplemental oxygen for COVID-19 and
- they have an increased risk for progression to severe COVID-19, as defined in section 5 of NICE's technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab and
- nirmatrelvir plus ritonavir is contraindicated or unsuitable.

Sotrovimab is only recommended if the company provides it according to the commercial arrangement.

References

121. Molnupiravir for Covid-19..


7.3 Corticosteroids
Practical info

Adult dosage

Dexamethasone:

• 6 mg orally once a day for 10 days (three 2 mg tablets or 15 ml of 2 mg/5 ml oral solution) or
• 6 mg intravenously once a day for 10 days (1.8 ml of 3.3 mg/ml ampoules [5.94 mg])

For people able to swallow and in whom there are no significant concerns about enteral absorption, prescribe tablets. Only use intravenous administration when tablets or oral solutions are inappropriate or unavailable.

Suitable alternatives:

• Prednisolone: 40 mg orally once a day for 10 days
• Hydrocortisone: 50 mg intravenously every 8 hours for 10 days (0.5 ml of 100 mg/ml solution; powder for solution for injection or infusion is also available); this may be continued for up to 28 days for people with septic shock

Dosage in pregnancy

Follow Royal College of Obstetrics and Gynaecology guidance.

Dosage for children with a greater than 44-week corrected gestational age

• Dexamethasone: 150 micrograms/kg (as a base) orally, nasogastrically or intravenously once a day for 10 days (max 6 mg)
• Prednisolone: 1 mg/kg orally, nasogastrically or intravenously once a day for 10 days (max 40 mg; doses can be rounded as per routine clinical practice)

For people able to swallow and in whom there are no significant concerns about enteral absorption,
prescribe tablets. Only use intravenous administration when tablets or oral solutions are inappropriate or unavailable.

**Dosage for preterm babies with a corrected gestational age of less than 44 weeks**
Seek specialist advice.

**Evidence to decision**

<table>
<thead>
<tr>
<th>Benefits and harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>For adults with COVID-19 needing supplemental oxygen, corticosteroids compared with usual care or placebo lower all-cause mortality, improve discharge from hospital, and may decrease the need for invasive mechanical ventilation (IMV) and death within 28 days of starting treatment.</td>
</tr>
<tr>
<td>For adults with COVID-19 not needing supplemental oxygen, corticosteroids may increase the need for IMV and death within 28 days of starting treatment.</td>
</tr>
<tr>
<td>Based on indirect evidence from non-COVID-19 populations, hyperglycaemia is the only statistically significant adverse event associated with corticosteroids.</td>
</tr>
</tbody>
</table>

**Discussion**
The panel noted the evidence to support using corticosteroids for adults with COVID-19 on supplemental oxygen, or adults with a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it. They noted that it is now established standard practice to offer dexamethasone. This is based on the most robust evidence on corticosteroids covering this treatment, and its widespread availability, ease of administration and acceptable safety profile. The panel indicated that, if dexamethasone cannot be used or is unavailable, suitable alternatives are hydrocortisone or prednisolone. Because of the risk of harm, the panel cautioned against using corticosteroids for other people with COVID-19.

The panel noted the need for clear and unambiguous terminology. Therefore, they agreed that reference to COVID-19 severity would not be used. Instead, they agreed that a person’s oxygen saturation should be used to determine whether corticosteroid treatment was appropriate. The panel highlighted the need to allow for varying prescribed oxygen saturation levels in different population groups. Because of this, they agreed that the recommendation should not detail specific oxygen saturation levels.

The course duration recommended, for up to 10 days unless there is a clear indication to stop early (including discharge from hospital or a hospital-supervised virtual COVID ward), is based on that used in the RECOVERY trial. The panel recognised the importance of minimising risk of harm caused by continuing treatment for people whose condition is improving and who are discharged. They agreed that the long pharmacodynamic half-life of dexamethasone would reduce the risk of any rebound effect caused by stopping the course before 10 days in the event of discharge. The panel agreed that, where patients are transferred to a virtual ward environment, the course could be completed safely under clinical supervision.

The panel acknowledged the lack of evidence outside the hospital setting. They also acknowledged that the supply and use of corticosteroids in other settings is based on clinical experience and knowledge of service delivery. It was the panel’s opinion that, when corticosteroids are first started in community settings, GPs are suitably qualified to assess oxygen levels with pulse oximetry and the need for corticosteroids. They agreed that it is realistic that treatment with dexamethasone could be started in the community setting. They also agreed that the class effect of corticosteroids would allow for
hydrocortisone or prednisolone as suitable alternatives if dexamethasone cannot be used or is unavailable.

Use of corticosteroids in children was considered. The panel decided that the recommendation should not be limited to adults because the evidence included both adults and children. The panel therefore agreed to avoid age-specific wording in the recommendation. Instead, they agreed that the dosing for adults and children should be provided as supplementary advice. Paediatric experts highlighted that the risk of progression for a child with a stable minimal oxygen requirement is not as high as for adults. Therefore, they suggested cross reference to Royal College of Child and Paediatric Health risk criteria markers for assessing corticosteroid use. For preterm babies with a corrected gestational age of less than 44 weeks, specialist advice is considered necessary because evidence is lacking for corticosteroid use in this age group.

The panel noted the indirect evidence about the risk of hyperglycaemia in other non-COVID-19 populations. They agreed that whether to monitor for hyperglycaemia and other adverse effects should be determined by their healthcare professionals, without the need for specific advice in the guideline. They added that potential adverse effects and contraindications would need to be balanced against the risks of depriving a person of a potentially life-saving treatment.

The panel considered that clinical judgement should guide management for people who do not need supplemental oxygen and who are already having corticosteroids for pre-existing or new comorbid conditions, without the need for specific advice in the guideline.

**Certainty of the Evidence**

Certainty of the evidence is moderate for all-cause mortality within 28 days in both subgroups (adults needing oxygen, and adults not needing oxygen) because of serious imprecision (inconsistent direction of effects for studies of adults needing oxygen and only a single study for adults not needing oxygen). The panel noted that, despite serious imprecision, the pooled effect was statistically significantly in favour of corticosteroids for adults needing oxygen, and showed a direction of effect in favour of control for adults not needing oxygen that was only marginally non-significant.

Certainty of the evidence is moderate for invasive mechanical ventilation or death at 28 days in both subgroups because of serious imprecision (only a single study for both subgroups). The panel noted that, despite serious imprecision, the effect was statistically significantly in favour of dexamethasone for adults needing oxygen, and showed a direction of effect in favour of control for adults not needing oxygen that was only marginally non-significant.

Certainty of evidence is moderate for discharge from hospital in both subgroups because of serious imprecision (inconsistent confidence intervals for studies of adults needing oxygen and only a single study for adults not needing oxygen). However, the panel noted that, for adults with COVID-19 needing oxygen, there was a statistically significant effect in favour of corticosteroids for improving discharge from hospital at 28 days.

Certainty of evidence was moderate for serious adverse events of corticosteroids in adults with COVID-19 needing oxygen. The panel noted that corticosteroids probably have little effect on serious adverse events in this group of people, but were aware of indirect systematic review evidence showing a
statistically significant risk of hyperglycaemia among people without COVID-19.

Certainty of evidence was low to moderate for other individual adverse effects, none of which showed statistically significant effects estimates.

**Values and preferences**

The panel were not aware of any systematically collected data on peoples' preferences and values. The panel inferred that, in view of the probable mortality benefits for people with COVID-19 who need oxygen, most would choose corticosteroids after shared decision making with healthcare professionals. Dexamethasone was considered to be the preferred corticosteroid treatment because of the larger amount of data supporting its use. The panel agreed that the class effect of corticosteroids would allow for hydrocortisone or prednisolone as suitable alternatives if dexamethasone cannot be used or is unavailable.

**Resources**

Use of corticosteroids in adults with COVID-19 who are on supplemental oxygen is unlikely to affect the availability of these medicines for other indications.

The panel expressed concern over specifying oxygen therapy as a requirement for corticosteroid treatment in a recommendation. They agreed that this might result in inequalities in access to treatments because of certain groups of people not being able to have oxygen therapy, even though their oxygen saturations may indicate that they should. This may also result in supply issues in the event of oxygen shortages. The panel agreed that the emphasis should be on oxygen saturation targets for people who need oxygen supplementation.

The panel noted possible supply issues with corticosteroids in community pharmacies where people have treatment outside the hospital setting, such as in residential care. However, they agreed that GP assessment with pulse oximetry and treatment with dexamethasone is realistic in the community setting. The class effect of corticosteroids would allow for suitable alternatives. The panel acknowledged the lack of evidence outside the hospital setting. They also noted that the use and supply of corticosteroids in other settings is based on clinical experience and knowledge of service delivery.

**Equity**

The panel noted limited evidence on the use of corticosteroids in children with COVID-19 but that children should not be excluded from the recommendations. The panel agreed that all age groups should be encompassed with appropriate age-specific advice on dosage.

The panel also noted the lack of evidence on the use of corticosteroids in community settings and the risk of inequitable treatment if limited to people in hospital. The panel were aware of people with COVID-19 needing supplemental oxygen who are having treatment outside the hospital setting and would benefit from corticosteroids. For this reason, the panel agreed that the recommendation should not specify any treatment setting.
There is evidence to support using corticosteroids for people with COVID-19 who need supplemental oxygen, or who have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it. It is now established standard practice to offer dexamethasone. The growing evidence base, combined with its widespread availability, ease of administration and acceptable safety profile, supports its continued use. Hydrocortisone and prednisolone are suitable alternatives if dexamethasone cannot be used or is unavailable. The course duration recommended, for up to 10 days unless there is a clear indication to stop early (including discharge from hospital or a hospital-supervised virtual COVID ward), is based on that used in clinical trials.

See the Resources section for the panel's concern over potential inequality of access to corticosteroids if oxygen therapy is stated as a requirement for corticosteroid treatment, and the need for this to be reflected in the wording of the recommendation.

**Acceptability**

The panel considered that acceptability of corticosteroids would be high given the widespread availability, ease of oral ingestion in any setting and established safety profile. They anticipated that, when considering the risks and benefits of treatment through shared decision making, most people with COVID-19 who:

- need supplemental oxygen would choose to have corticosteroids
- do not need supplemental oxygen would choose not to have corticosteroids.

**Feasibility**

Although there is no systematically collected evidence about feasibility, the panel noted that the established distribution, supply and use of corticosteroids in clinical practice is an indicator of feasibility.

**Rationale**

There is evidence to support using corticosteroids for people with COVID-19 who need supplemental oxygen, or who have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it. It is now established standard practice to offer dexamethasone. The growing evidence base, combined with its widespread availability, ease of administration and acceptable safety profile, supports its continued use. Hydrocortisone and prednisolone are suitable alternatives if dexamethasone cannot be used or is unavailable. The course duration recommended, for up to 10 days unless there is a clear indication to stop early (including discharge from hospital or a hospital-supervised virtual COVID ward), is based on that used in clinical trials.

**Clinical question/ PICO**

- **Population:** People with COVID-19
- **Intervention:** Corticosteroids
- **Comparator:** Control

**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 recent meta-analysis and associated living guidance [9] of seven randomised controlled trials (RCTs) of patients with critical COVID-19 [10][20][11][17][16][10][15], one study of patients with moderate, severe and critical COVID-19 [14], and one study of patients with severe COVID-19 [13]. Over 5,700 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 [18] and sepsis [21] – provided indirect evidence for serious adverse events.

**Study characteristics**
Three RCTs compared dexamethasone with standard care [10][17][14], three compared hydrocortisone with standard care [16][11][12] and three compared methylprednisolone with standard care [20][15][13].

Disease severity was reported independently for each trial. Definitions included patients who required mechanical ventilation or non-invasive ventilation, PaO\textsubscript{2}/FiO\textsubscript{2} < 200, positive end-expiratory pressure (PEEP) ≥ 5 cm H\textsubscript{2}O, 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 RCTs). Corticosteroids in patients requiring oxygen also probably reduce the composite outcome of requirement for invasive mechanical ventilation or death, and discharge from hospital within 28 days.

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 showed no difference in the incidence of gastrointestinal bleeding, bacterial co-infections, 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 24 studies).

**Our confidence in the results**
In patients with COVID-19 requiring oxygen, 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 (due to only one study), and discharge from hospital (due to serious inconsistency).

In patients with COVID-19 who do not require oxygen, certainty is moderate for all outcomes (all-cause mortality, invasive mechanical ventilation or death and discharge from hospital) due to serious imprecision (reliance on a single study and wide confidence intervals).

For the adverse events (gastrointestinal bleeding, super infections, neuromuscular weakness and neuropsychiatric effects), certainty is low due to serious indirectness (evidence from non-COVID-19 patients) and serious imprecision. For hyperglycaemia, certainty is moderate due to serious indirectness (evidence from non-COVID-19 patients).
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.84 (CI 95% 0.73 — 0.98) Based on data from 5,789 participants in 9 studies.² (Randomized controlled)</td>
<td>316 per 1000 Difference:</td>
<td>265 per 1000 51 fewer per 1000 (CI 95% 85 fewer — 6 fewer )</td>
<td>Moderate Due to some inconsistency ²</td>
<td>Nine studies found a statistically significantly lower incidence of all-cause mortality at day 28 with corticosteroids compared with standard care in adults who require oxygen.</td>
</tr>
<tr>
<td>All-cause mortality [adults not requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.27 (CI 95% 1 — 1.61) Based on data from 1,535 participants in 1 studies.³ (Randomized controlled)</td>
<td>140 per 1000 Difference:</td>
<td>178 per 1000 38 more per 1000 (CI 95% 85 fewer — 85 more )</td>
<td>Moderate Only data from one study</td>
<td>One study found no statistically significant difference in all-cause mortality at day 28 with corticosteroids compared with placebo.</td>
</tr>
<tr>
<td>Invasive mechanical ventilation or death [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 0.88 (CI 95% 0.79 — 0.97) Based on data from 3,883 participants in 1 studies.⁴ (Randomized controlled)</td>
<td>320 per 1000 Difference:</td>
<td>282 per 1000 38 fewer per 1000 (CI 95% 67 fewer — 10 fewer )</td>
<td>Moderate Due to only one study</td>
<td>One study found a statistically significant reduction in death or the need for invasive mechanical ventilation at day 28 with corticosteroids compared with standard care in adults who require oxygen.</td>
</tr>
<tr>
<td>Invasive mechanical ventilation or death [adults not requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.25 (CI 95% 1 — 1.57) Based on data from 1,535 participants in 1 studies.⁵ (Randomized controlled)</td>
<td>155 per 1000 Difference:</td>
<td>194 per 1000 39 more per 1000 (CI 95% 0 fewer — 88 more )</td>
<td>Moderate Due to only one study ⁷</td>
<td>One study found no statistically significant reduction in death or the need for invasive mechanical ventilation at day 28 with corticosteroids compared with standard care in adults who do not require oxygen.</td>
</tr>
<tr>
<td>Discharge from hospital [adults not requiring oxygen]</td>
<td></td>
<td>Relative risk 0.96 (CI 95% 0.9 — 1.01) Based on data from 1,535 participants in 1</td>
<td>804 per 1000</td>
<td>772 per 1000</td>
<td>Moderate Due to only one study ⁹</td>
<td>One study found no statistically significant difference in discharge from hospital at day 28</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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</tr>
<tr>
<td>Discharge from hospital [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>9 Critical studies. 8 (Randomized controlled)</td>
<td>Difference:</td>
<td>32 fewer per 1000 (CI 95% 80 fewer — 8 more)</td>
<td>Moderate Due to serious inconsistency 11</td>
<td>with corticosteroids compared with standard care in adults who do not require oxygen.</td>
</tr>
<tr>
<td>Serious adverse events [adults requiring oxygen]</td>
<td>Within 28 days of commencing treatment</td>
<td>Relative risk 1.1 (CI 95% 1.06 — 1.15) Based on data from 4,952 participants in 2 studies. 10 (Randomized controlled)</td>
<td>Difference:</td>
<td>582 per 1000</td>
<td>Moderate Due to serious inconsistency 11</td>
<td>Two studies found a statistically significant increase in discharge from hospital at day 28 with corticosteroids compared with standard care in adults who require oxygen.</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>End of treatment</td>
<td>Relative risk 1.06 (CI 95% 0.82 — 1.33) Based on data from 5,403 participants in 30 studies.</td>
<td>Difference:</td>
<td>234 per 1000</td>
<td>Moderate Due to serious indirectness and imprecision</td>
<td>Six studies found no statistically significant difference in serious adverse events at day 28 with corticosteroids compared with standard care.</td>
</tr>
<tr>
<td>Bacterial co-infections</td>
<td>End of treatment</td>
<td>Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 participants in 32 studies.</td>
<td>Difference:</td>
<td>186 per 1000</td>
<td>Low Due to serious indirectness and imprecision</td>
<td>Thirty two studies found no statistically significant difference in the incidence of bacterial coinfections with corticosteroids compared with standard care.</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>End of treatment</td>
<td>Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 participants in 24 studies.</td>
<td>Difference:</td>
<td>286 per 1000</td>
<td>Moderate Due to serious indirectness</td>
<td>Twenty four studies found a statistically significant increase in the incidence of hyperglycaemia with corticosteroids compared with standard care.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
<td>Summary</td>
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<tr>
<td>Neuromuscular weakness</td>
<td>Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 participants in 8 studies.</td>
<td>Control</td>
<td>Corticosteroids</td>
<td>Low</td>
<td>Eight studies found no statistically significant difference in the incidence of neuromuscular weakness with corticosteroids compared with standard care.</td>
<td></td>
</tr>
<tr>
<td>End of treatment</td>
<td>69 per 1000 Difference:</td>
<td>— 72 more</td>
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<tr>
<td>6 Important</td>
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<tr>
<td>Neuropsychiatric effects</td>
<td>Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 participants in 7 studies.</td>
<td>Control</td>
<td>Corticosteroids</td>
<td>Low</td>
<td>Seven studies found no statistically significant difference in the incidence of neuropsychiatric effects with corticosteroids compared with standard care.</td>
<td></td>
</tr>
<tr>
<td>End of treatment</td>
<td>35 per 1000 Difference:</td>
<td>— 10 fewer</td>
<td>28 per 1000 7 fewer per 1000 (CI 95% 21 fewer — 22 more )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Important</td>
<td></td>
<td>— 27 more</td>
<td></td>
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</tbody>
</table>

2. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies.
4. Detailed description The number of patients with severe illness (i.e. who do not require mechanical ventilation at enrolment) that progress to requiring invasive mechanical ventilation or death within 28 days
7. **Imprecision: serious.** Only data from one study.
9. **Imprecision: serious.** Only data from one study.
11. **Inconsistency: serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.
13. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies.
References


Evidence to decision

**Benefits and harms**

For adults with COVID-19 needing supplemental oxygen, at 28 days, corticosteroids compared with usual care or placebo lower mortality, improve discharge from hospital, and may decrease the risk of needing invasive mechanical ventilation (IMV) and death.

For adults with COVID-19 not needing oxygen, corticosteroids may increase the risk of needing IMV and death within 28 days of starting treatment.

Based on indirect evidence from non-COVID-19 populations, hyperglycaemia is the only statistically significant adverse event associated with corticosteroids.

**Discussion**

The panel noted the evidence that corticosteroids may be harmful for people with COVID-19 not needing supplemental oxygen. Because of the risk of harm, the panel cautioned against using corticosteroids for people with COVID-19 not on oxygen unless there is another medical indication to do so.

The panel noted the need for clear and unambiguous terminology. Therefore, they agreed that reference to COVID-19 severity would not be used. Instead, they agreed that a person’s oxygen saturation should be used to determine whether corticosteroid treatment was appropriate. The panel highlighted the need to allow for varying prescribed oxygen saturation levels in different population groups. Because of this, they agreed that the recommendation should not detail specific oxygen saturation levels.

The panel noted the indirect evidence about the risk of hyperglycaemia in other non-COVID-19 populations. They agreed that whether to monitor for hyperglycaemia and other adverse effects in individuals should be determined by their healthcare professionals, without the need for specific advice in the guideline. They added that potential adverse effects and contraindications would need to be balanced against the risks of depriving a person of a potentially life-saving treatment.

The panel considered that clinical judgement should guide management for people who do not need supplemental oxygen and who are already having corticosteroids for pre-existing or new comorbid conditions, without the need for specific advice in the guideline.

**Certainty of the Evidence**

Certainty of the evidence is moderate for all-cause mortality within 28 days in both subgroups (adults needing oxygen, and adults not needing oxygen) because of serious imprecision (inconsistent direction of effects for studies of adults needing oxygen and only a single study for adults not needing oxygen). The panel noted that, despite serious imprecision, the pooled effect was statistically significantly in favour of corticosteroids for adults needing oxygen, and showed a direction of effect in favour of control for
adults not needing oxygen that was only marginally non-significant.

Certainty of the evidence is moderate for invasive mechanical ventilation or death at 28 days in both subgroups because of serious imprecision (only a single study for both subgroups). The panel noted that, despite serious imprecision, the effect was statistically significantly in favour of dexamethasone for adults needing oxygen, and showed a direction of effect in favour of control for adults not needing oxygen that was only marginally non-significant.

Certainty of evidence is moderate for discharge from hospital in both subgroups because of serious imprecision (inconsistent confidence intervals for studies of adults needing oxygen and only a single study for adults not needing oxygen). However, the panel noted that, for adults with COVID-19 needing oxygen, there was a statistically significant effect in favour of corticosteroids for improving discharge from hospital at 28 days.

Certainty of evidence was moderate for serious adverse events of corticosteroids in adults with COVID-19 needing oxygen. The panel noted that corticosteroids probably have little effect on serious adverse events in this group of people, but were aware of indirect systematic review evidence showing a statistically significant risk of hyperglycaemia among people without COVID-19.

Certainty of evidence was low to moderate for other individual adverse effects, none of which showed statistically significant effects estimates.

Values and preferences

The panel were not aware of any systematically collected data on peoples’ preferences and values. The panel inferred that, in view of the probable mortality benefits for people with COVID-19 who need oxygen, most would choose corticosteroids after shared decision making with healthcare professionals. Dexamethasone was considered to be the preferred corticosteroid treatment because of the larger amount of data supporting its use. The panel agreed that the class effect of corticosteroids would allow for hydrocortisone or prednisolone as suitable alternatives if dexamethasone cannot be used or is unavailable.

The panel also inferred that, because of the risk of harm, most fully informed people with COVID-19 who do not need supplemental oxygen would not want to have systemic corticosteroids. However, some people may want to consider having this intervention through shared decision making with their healthcare professional.

Resources

The panel expressed concern over specifying oxygen therapy as a requirement for corticosteroid treatment in a recommendation. They agreed that this may result in inequalities in access to treatments because of certain groups of people not being able to have oxygen therapy, even though their oxygen saturations may indicate that they should. This may also result in supply issues in the event of oxygen shortages. The panel agreed that the emphasis should be on oxygen saturation targets for people who need oxygen supplementation.

The panel noted possible supply issues with corticosteroids in community pharmacies where people are
having treatment outside the hospital setting, such as in residential care. However, they agreed that GP assessment with pulse oximetry and treatment with dexamethasone is realistic in the community setting. The class effect of corticosteroids would allow for suitable alternatives.

### Equity
The panel noted limited evidence on the use of corticosteroids in children with COVID-19 but that children should not be excluded from the recommendations. The panel agreed that all age groups should be encompassed with appropriate age-specific advice on dosage.

The panel also noted the lack of evidence on the use of corticosteroids in community settings and the risk of inequitable treatment if limited to people in hospital. The panel were aware of people with COVID-19 needing supplemental oxygen who are having treatment outside the hospital setting and would benefit from corticosteroids. For this reason, the panel agreed that the recommendation should not specify any treatment setting.

See the Resources section for the panel’s concern over potential inequality of access to corticosteroids if oxygen therapy is stated as a requirement for corticosteroid treatment, and the need for this to be reflected in the wording of the recommendation.

### Acceptability
The panel considered that acceptability of corticosteroids would be high given the widespread availability, ease of oral ingestion in any setting and established safety profile. They anticipated that, when considering the risks and benefits of treatment through shared decision making, most people with COVID-19 who:

- need supplemental oxygen would choose to have corticosteroids
- do not need supplemental oxygen would choose not to have corticosteroids.

### Feasibility
Although there is no systematically collected evidence about feasibility, the panel noted that the established distribution, supply and use of corticosteroids in clinical practice is an indicator of feasibility.

### Rationale
Evidence suggests that, in people with COVID-19 who do not need supplemental oxygen, corticosteroids may increase the risk of needing invasive mechanical ventilation and death at 28 days. The recommendation therefore cautions against using corticosteroids for people not on supplemental oxygen, unless there is another medical indication to do so.

### 7.4 Casirivimab and imdevimab
Casirivimab plus imdevimab is unlikely to be effective against the dominant Omicron variants, and it is not possible to reliably estimate its cost effectiveness. So, it is not recommended. For evidence and information on how this decision was made, see NICE’s technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.

### 7.5 Tocilizumab

Tocilizumab is recommended, within its marketing authorisation, as an option for treating COVID-19 in adults who:

- are having systemic corticosteroids and
- need supplemental oxygen or mechanical ventilation.

Tocilizumab is only recommended if the company provides it according to the commercial arrangement.

This recommendation is from NICE’s technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.

The summary of product characteristics for tocilizumab specifies that it should only be offered when there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by tocilizumab. It also states that the efficacy of tocilizumab has not been established in the treatment of COVID-19 in people who do not have elevated C-reactive protein levels.

### Rationale

There is some clinical evidence suggesting that tocilizumab is effective at treating COVID-19. Tocilizumab is recommended because the likely cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources. For evidence and information on how this decision was made, see NICE’s technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.

### 7.6 Baricitinib

Casirivimab plus imdevimab is not recommended, within its marketing authorisation, for treating COVID-19. This recommendation is from NICE’s technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab. For the full marketing authorisation for casirivimab plus imdevimab, see the summary of product characteristics.
Conditional recommendation

Consider baricitinib for people 2 years and over in hospital with COVID-19 who:

- need supplemental oxygen for COVID-19, and
- are having or have completed a course of corticosteroids such as dexamethasone, unless they cannot have corticosteroids, and
- have no evidence of infection (other than SARS-CoV-2) that might be worsened by baricitinib.

In March 2023, this was an off-label use of baricitinib. See NICE’s information on prescribing medicines.

Baricitinib may be considered in people who meet the above criteria, and who cannot have tocilizumab. When there is clinical deterioration despite treatment with tocilizumab, it may be appropriate to add baricitinib.

Baricitinib is contraindicated in pregnancy and breastfeeding. The Royal College of Obstetricians and Gynaecologists has produced guidance on managing coronavirus infection in pregnancy.

Evidence to decision

Benefits and harms

The panel considered evidence from 4 randomised controlled trials on the efficacy and safety of baricitinib plus standard care compared to standard care alone (Ely 2022, Horby 2022, Kalil 2021, Marconi 2021).

All the trials compared the effects of treatment with baricitinib on people with COVID-19 who required supplemental oxygen at randomisation. Most people were already in receipt of co-interventions such as corticosteroids and remdesivir but only 1 trial included people receiving tocilizumab (23% of the trial population in Horby 2022). Most people had a pre-existing co-morbidity at the time of study enrolment.

The evidence showed that baricitinib plus standard care significantly reduced mortality, duration of hospitalisation and disease severity. The panel recognised that the trials did not report any significant safety concerns with baricitinib. However, the BNF highlights that clinical trial data report an increased risk of venous thromboembolism and increased risk of diverticulitis in people treated with baricitinib, which the panel acknowledged. To identify serious adverse reactions to baricitinib, there is a Yellow Card reporting system for the Medicines and Healthcare products Regulatory Agency in place.

The panel emphasised the importance of directing baricitinib treatment appropriately to people who need supplementary oxygen specifically for COVID-19, in line with the evidence. This is because there may be people in hospital needing oxygen supplementation for other conditions, but who also have less severe COVID-19 where baricitinib is not needed. The recommendation therefore included the eligibility criterion of needing supplementary oxygen for COVID-19 to make this distinction.

This distinction is also made in the RECOVERY trial eligibility criteria, which stipulate confirmed SARS-CoV-2 infection and the presence of viral pneumonia syndrome, which would need supplemental oxygen. Although the RECOVERY trial criteria have evolved over time, this new wording is reflected in the NHS England clinical commissioning policy, and the panel’s agreed criteria remain consistent with this.

The panel discussed the effects of combining other interventions with baricitinib such as corticosteroids, tocilizumab and remdesivir. At present, corticosteroids are administered to most people hospitalised with COVID-19 in the United Kingdom. From the studies, the evidence of effectiveness for baricitinib appears to be consistent regardless of treatment with systemic corticosteroids, remdesivir or an IL-6 receptor blocker such as tocilizumab. However, in the case of combination therapy of baricitinib with tocilizumab...
the panel agreed it could not be concluded from the evidence whether there was any added value or added harm in co-administration. As such, the panel agreed that clinicians should consider the clinical and contextual factors when deciding whether to use baricitinib or an interleukin-6 inhibitor, or both. These include availability, people’s preference, severity of illness and deterioration, local policies and route of administration.

Baricitinib is contraindicated in pregnant and breastfeeding women. Women of childbearing potential should use effective contraception during treatment and after treatment, for at least 1 week. However, there is uncertainty regarding the benefit to harm ratio for women and their babies. The panel highlighted that the decision regarding the use of baricitinib should be made between the pregnant woman and their healthcare professional while discussing whether the potential benefit justifies the potential risk to the mother and baby.

**Certainty of the Evidence**

The evidence comes from 4 randomised trials (Ely 2022, Horby 2022, Kalil 2021, Marconi 2021). The evidence shows that the combination of baricitinib with standard care alone statistically significantly reduced mortality and duration of hospitalisation in people with moderate to severe COVID-19.

The certainty of the outcomes from these studies was high to moderate. The risk of bias associated with all the trials was rated as low. However, there are some concerns about indirectness with Ely 2022, Kalil 2021 and Marconi 2021 as these trials did not report on vaccination status and the prevalent COVID-19 variant at the time of study. Furthermore, these trials were not based in the United Kingdom there was heterogeneity between standard treatment regimens in the study centres which would affect applicability in the UK context. Lastly, these 3 studies were also conducted before the predominance of the Omicron variant and as such this evidence may not be directly applicable to the UK context. The panel discussed that these variations may contribute to the additive effect sizes and some subgroup analyses may not have reached significance due to this variation. However, the panel also noted that there is likely to be no difference in the effectiveness of treatment with baricitinib in Omicron and non-Omicron variants as baricitinib is a host-directed treatment rather than antiviral treatment.

The panel noted that the Horby 2022 (RECOVERY) trial was the largest trial contributing to the evidence base with 8156 participants. The trial is also based in the United Kingdom and reported on vaccination status and prevalent variant at the time of study recruitment. There were no concerns raised about outcomes that were reported in this study.

**Values and preferences**

The panel were not aware of any systematically collected data on peoples’ preferences and values. The evidence shows significant benefits from baricitinib use on mortality and duration of hospitalisation, which is likely to influence people’s preferences for this drug. The panel acknowledged that there may be potential harms from treatment with baricitinib, however, they agreed that individual factors may influence people’s preferences to receive treatment.

The panel noted that the effects of treatment with tocilizumab either prior to, or following, baricitinib administration remain uncertain. The panel concluded that, in people who are clinically deteriorating, there may be a need to administer further interventions and in these cases co-administration of tocilizumab may be preferred by patients or their families or carers.
The panel noted the uncertain benefits and harms of baricitinib for pregnant and breastfeeding women, which may influence their preference for having this drug.

**Resources**

Baricitinib is currently licensed for use in the United Kingdom for rheumatoid arthritis and atopic dermatitis.

The panel discussed that due to recent reforms to virtual wards and hospital at home schemes, the availability of baricitinib should be considered. However, the panel agreed that, regardless of these changes, appropriate treatment plans can be devised for people to ensure equal access to treatment. Cost-effectiveness was not assessed as part of the evidence review.

**Equity**

Baricitinib is contraindicated in pregnant and breastfeeding women. The panel noted the inequity of access that this may present and the need for suitable alternatives such as an interleukin-6 inhibitor.

The panel noted that baricitinib is not licensed in children and young people under 18 years and the safety profile is unknown for this age group, with only limited data included in the Horby 2022 trial.

**Acceptability**

The panel agreed that, based on the evidence and their clinical judgement, baricitinib is an effective intervention to administer to people with COVID-19, especially in the context of their condition deteriorating. As baricitinib is administered orally once daily, people with COVID-19 should find this treatment acceptable. Clinicians should consider the individual circumstances of the person and any clinical or contextual factors which may affect treatment options, such as safety concerns, patient preference and operational considerations.

**Feasibility**

As of April 2022, baricitinib had not been granted marketing authorisation for use in the treatment of COVID-19.

The panel explored when baricitinib should be administered and agreed that it can be administered early in the treatment pathway for people in hospital with COVID-19 who meet the criteria set out in the recommendation.

**Rationale**

There is evidence to support the use of baricitinib for moderate to severe COVID-19 in adults in hospital. It shows that baricitinib reduces mortality, duration of hospital stay and disease severity. Corticosteroids are part of standard treatment for COVID-19 in the UK, and there is evidence of an additional benefit when baricitinib is also used.

Baricitinib is not licensed for treating COVID-19. Off-label use of baricitinib for COVID-19 may be an option for adults who cannot have tocilizumab (for example, when tocilizumab is not available, the person cannot tolerate intravenous administration, or there are other important patient preferences or circumstances). The
panel noted that, when there is clinical deterioration despite treatment with tocilizumab, it may be appropriate to also add baricitinib.

Based on the evidence supporting the use of baricitinib for moderate to severe COVID-19 in adults, the panel agreed that, in the event of severe or deteriorating illness, it could also be considered for children and young people 2 years and over. This is after careful clinical risk assessment and shared decision making that includes expert input from paediatricians and paediatric infectious disease specialists.

**Clinical question/ PICO**

<table>
<thead>
<tr>
<th>Population:</th>
<th>People with COVID-19 in hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Baricitinib</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Standard Care</td>
</tr>
</tbody>
</table>

**Summary**

**Key results**

Compared to standard care alone, the combination of baricitinib and standard care reduces the risk of death for people in hospital with COVID-19.

**What is the evidence informing this conclusion?**

Evidence comes from 4 randomised controlled trials that compared the use of baricitinib alongside standard care with standard care alone in 10,816 patients hospitalised with COVID-19 (Ely 2022; Horby 2022; Kalil 2021; Marconi 2021). Most data are from the RECOVERY trial (Horby 2022) which included 8156 patients hospitalised with moderate to severe COVID-19.

Standard care within the trials varied but all the trials included a majority of patients in receipt of corticosteroids. Three trials included remdesivir as part of standard care (Ely 2022; Kalil 2021; Marconi 2021). One trial included a minority of patients in receipt of tocilizumab in addition to standard care (Horby 2022).

Due to variability in standard care, subgroup analyses were carried out to measure the effects of co-administered interventions on mortality, hospitalisation and recovery.

**Publication status**

One study is available as a pre-print (Horby 2022 (RECOVERY) posted to medRXiv on 3 March 2022 and has therefore not been peer reviewed.

Three studies are peer reviewed manuscripts (Ely 2022; Kalil 2021 and Marconi (COV-BARRIER) 2021).

**Study characteristics**

The mean age in the studies ranged between 56 and 58 years and the proportion of men ranged between 55% and 66%. The severity of COVID-19 across the studies was moderate to critical and one study included patients who were in critical stage with COVID-19 (Ely 2022) and receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). In all studies, the majority of participants had at least one comorbidity at randomisation. All the trials were open label.

The largest study was the RECOVERY trial (Horby 2022), which included 8156 participants and contributed 75% of the number of participants included in this evidence review. This trial was based in the United Kingdom and 95% of participants received corticosteroids upon admission. Participants were randomised to receive 4mg baricitinib once daily for up to 10 days. 23% of patients in this trial also received tocilizumab in combination with baricitinib and 10% of patients were also randomised to other study drugs such as colchicine and aspirin. This trial included children aged 2 and older and
patients with renal impairment and reduced dosing for these participants. This study also reported on
the proportion of people who had received at least one dose of a COVID-19 vaccine (n= 3420/8156; 42%).

The other 3 studies (Ely 2022; Kalil 2021; Marconi 2021) were based in centres around the world and
were conducted earlier in the pandemic before the Omicron variant became prevalent and did not
report vaccination status. As such the populations may not be directly relevant or comparable to the
UK, where the Omicron variant is dominant, and many people have been vaccinated. These studies
also excluded people who received immunomodulatory agents such as tocilizumab and sarilumab.
The studies randomised participants to receive baricitinib 4mg daily for up to 14 days, as per the
United States Food and Drug Authority recommendations (FDA, 2021), and included corticosteroids
and remdesivir in standard care regimens.

What are the main results?

Mortality and progression to invasive mechanical ventilation were significantly reduced in people who
received baricitinib plus standard care compared to standard care alone.

There was no subgroup effect of co-administered interventions (corticosteroids, remdesivir,
tocilizumab) for the outcome of mortality.

There was a statistically significant increase in the number of patients who were discharged alive and
the number of ventilator-free days in people who received baricitinib plus standard care compared
with standard care alone.

No statistically significant differences were seen in the median time to recovery, days receiving
ventilation or in the cessation of invasive mechanical ventilation.

Moderate quality evidence suggests that there is a lower incidence of serious adverse events in people
who received baricitinib plus standard care compared with standard care alone.

For further details see the evidence review.

Our confidence in the results

Studies are heterogeneous with both clinical and methodological diversity. However, sufficient
information was provided by trial authors to assess the validity of the methods used and as such the
risk of bias for most outcomes was assessed as low. For outcomes from the Ely 2022, Kalil 2021 and
Marconi 2021 studies, there were some concerns surrounding the directness of the outcomes due to
variation in standard care treatment regimens across trial centres as well as a lack of reporting on
vaccination status and prevalent COVID-19 variant. As such, some outcomes from Ely 2022, Kalil 2021
and Marconi 2021 were downgraded for indirectness. Where the RECOVERY (Horby 2022) trial
contributed to an outcome alongside the other three studies, the outcome was not downgraded for
indirectness as RECOVERY was the greatest contributing trial for the outcome. Outcomes were
downgraded for imprecision where confidence intervals included the line of no effect and
downgraded again if fewer than 300 people contributed to the outcome.
<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality - All patients at 28 days</td>
<td>Relative risk 0.84 (CI 95% 0.76 — 0.93) Based on data from 10,816 participants in 4 studies.</td>
<td>Standard Care 133 per 1000</td>
<td>Baricitinib 112 per 1000</td>
<td>High</td>
<td>Four studies found a statistically significant reduction in mortality in people who were treated with baricitinib plus standard care compared with standard care alone.</td>
</tr>
<tr>
<td>All cause mortality - Baseline corticosteroid use at 28 days</td>
<td>Relative risk 0.68 (CI 95% 0.52 — 0.88) Based on data from 1,291 participants in 2 studies.</td>
<td>Standard Care 173 per 1000</td>
<td>Baricitinib 118 per 1000</td>
<td>Moderate Due to serious indirectness</td>
<td>Two studies found a statistically significant reduction in mortality in people who received corticosteroids and who were treated with baricitinib plus standard care compared with standard care alone.</td>
</tr>
<tr>
<td>All-cause mortality - No baseline corticosteroid use at 28 days</td>
<td>Relative risk 0.42 (CI 95% 0.2 — 0.88) Based on data from 328 participants in 2 studies.</td>
<td>Standard Care 124 per 1000</td>
<td>Baricitinib 52 per 1000</td>
<td>Moderate Due to serious indirectness</td>
<td>Two studies found a statistically significant reduction in mortality in people who did not receive corticosteroids and who were treated with baricitinib plus standard care compared with standard care alone.</td>
</tr>
<tr>
<td>All-cause mortality - Baseline remdesivir use at 28 days</td>
<td>Relative risk 0.76 (CI 95% 0.59 — 0.98) Based on data from 1,956 participants in 3 studies.</td>
<td>Standard Care 124 per 1000</td>
<td>Baricitinib 94 per 1000</td>
<td>High</td>
<td>Three studies found a statistically significant reduction in mortality in people who received remdesivir and who were treated with baricitinib plus standard care compared with standard care alone.</td>
</tr>
<tr>
<td>All-cause mortality - No baseline remdesivir use at 28 days</td>
<td>Relative risk 0.88 (CI 95% 0.78 — 0.98) Based on data from 7,819 participants in 3 studies.</td>
<td>Standard Care 144 per 1000</td>
<td>Baricitinib 127 per 1000</td>
<td>High</td>
<td>Three studies found a statistically significant reduction in mortality in people who did not receive remdesivir and who were treated with baricitinib plus standard care compared with standard care alone.</td>
</tr>
<tr>
<td>All cause mortality - Use of tocilizumab</td>
<td>Relative risk 0.83 (CI 95% 0.67 — 1.03) Based on data from</td>
<td>Standard Care 166 per 1000</td>
<td>Baricitinib 138 per 1000</td>
<td>Moderate Due to serious imprecision</td>
<td>One study found no statistically significant difference in mortality in</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard Care</td>
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<tr>
<td>at 28 days</td>
<td>1,872 participants in 1 studies. (Randomized controlled)</td>
<td>Difference:</td>
<td>28 fewer per 1000 ( CI 95% 55 fewer — 5 more )</td>
<td>people who received tocilizumab and who were treated with baricitinib plus standard care compared with standard care alone.</td>
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<tr>
<td></td>
<td>Relative risk 0.78 (CI 95% 0.55 — 1.11)</td>
<td>167 per 1000</td>
<td>130 per 1000</td>
<td>Moderate Due to serious imprecision 11</td>
<td>One study found no statistically significant difference in mortality in people who received tocilizumab within 24 hours of hospitalisation and who were treated with baricitinib plus standard care compared with standard care alone.</td>
</tr>
<tr>
<td></td>
<td>Based on data from 756 participants in 1 studies. (Randomized controlled)</td>
<td>Difference:</td>
<td>37 fewer per 1000 ( CI 95% 75 fewer — 17 more )</td>
<td></td>
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<tr>
<td></td>
<td>All cause mortality - Use of tocilizumab within 24 hours at 28 days</td>
<td></td>
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<tr>
<td></td>
<td>Relative risk 0.97 (CI 95% 0.84 — 1.12)</td>
<td>122 per 1000</td>
<td>118 per 1000</td>
<td>Moderate Due to serious imprecision 13</td>
<td>One study found no statistically significant difference in mortality in people who did not receive tocilizumab and who were treated with baricitinib plus standard care compared with standard care alone.</td>
</tr>
<tr>
<td></td>
<td>Based on data from 5,528 participants in 1 studies. (Randomized controlled)</td>
<td>Difference:</td>
<td>4 fewer per 1000 ( CI 95% 20 fewer — 15 more )</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All cause mortality - No use of tocilizumab at 28 days</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Relative risk 1.08 (CI 95% 1.02 — 1.15)</td>
<td>738 per 1000</td>
<td>797 per 1000</td>
<td>Moderate Due to serious indirectness 15</td>
<td>Two studies found a statistically significant increase in the number of people who recovered and were treated with baricitinib plus standard care compared with standard care alone.</td>
</tr>
<tr>
<td></td>
<td>Based on data from 1,134 participants in 2 studies. (Randomized controlled)</td>
<td>Difference:</td>
<td>59 more per 1000 ( CI 95% 15 more — 111 more )</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Number of patients who recovered - Overall</td>
<td></td>
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<tr>
<td></td>
<td>Relative risk 1.03 (CI 95% 1.01 — 1.05)</td>
<td>783 per 1000</td>
<td>806 per 1000</td>
<td>High</td>
<td>One study found a statistically significant increase in the number of people who were discharged alive and who were treated with baricitinib plus standard care compared with standard care alone.</td>
</tr>
<tr>
<td></td>
<td>Based on data from 8,156 participants in 1 studies. (Randomized controlled)</td>
<td>Difference:</td>
<td>23 more per 1000 ( CI 95% 8 more — 39 more )</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Proportion of patients who were discharged alive</td>
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<tr>
<td></td>
<td>Relative risk 0.9 (CI 95% 0.55 — 1.48)</td>
<td>41 per 1000</td>
<td>37 per 1000</td>
<td>Low Due to serious indirectness, Due to serious imprecision 18</td>
<td>One study found no statistically significant difference in the composite outcome of progression to high flow oxygen, non-invasive ventilation or invasive</td>
</tr>
<tr>
<td></td>
<td>Based on data from 1,525 participants in 1 studies. (Randomized controlled)</td>
<td>Difference:</td>
<td>4 fewer per 1000 ( CI 95% 18 fewer — 20 more )</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Progression to high-flow oxygen, non-invasive ventilation, invasive</td>
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<tr>
<td>Outcome Timeframe</td>
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<td>Comparator Standard Care</td>
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<tr>
<td>mechanical ventilation</td>
<td></td>
<td></td>
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<td></td>
<td>mechanical ventilation or death in people who received baricitinib plus standard care compared with standard care alone.</td>
</tr>
<tr>
<td>Progression to invasive mechanical ventilation or death</td>
<td>Relative risk 0.91 (CI 95% 0.83 — 1.01) Based on data from 7,905 participants in 1 studies. 19 (Randomized controlled)</td>
<td>172 per 1000 Difference: 157 per 1000 15 fewer per 1000 ( CI 95% 29 fewer — 2 more )</td>
<td>Moderate Due to serious imprecision 20</td>
<td>One study found a non-statistically significant reduction in progression to mechanical ventilation or death in people who were treated with baricitinib plus standard care compared with standard care alone.</td>
<td></td>
</tr>
<tr>
<td>Progression to use of oxygen</td>
<td>Relative risk 0.57 (CI 95% 0.34 — 0.95) Based on data from 142 participants in 1 studies. 21 (Randomized controlled)</td>
<td>403 per 1000 Difference: 230 per 1000 173 fewer per 1000 ( CI 95% 266 fewer — 20 fewer )</td>
<td>Moderate Due to serious indirectness 22</td>
<td>One study found a statistically significant reduction in the number of people who progressed to oxygen use and were treated with baricitinib plus standard care compared with standard care alone.</td>
<td></td>
</tr>
<tr>
<td>Progression to non-invasive ventilation</td>
<td>Relative risk 0.82 (CI 95% 0.84 — 1.01) Based on data from 6,684 participants in 2 studies. (Randomized controlled)</td>
<td>212 per 1000 Difference: 174 per 1000 38 fewer per 1000 ( CI 95% 34 fewer — 2 more )</td>
<td>Moderate Due to serious imprecision 23</td>
<td>Two studies found a non-statistically significant reduction in progression to non-invasive ventilation in people who were treated with baricitinib plus standard care compared with standard care alone.</td>
<td></td>
</tr>
<tr>
<td>Progression to invasive mechanical ventilation</td>
<td>Relative risk 0.81 (CI 95% 0.67 — 0.98) Based on data from 6,900 participants in 2 studies. (Randomized controlled)</td>
<td>63 per 1000 Difference: 51 per 1000 12 fewer per 1000 ( CI 95% 21 fewer — 1 fewer )</td>
<td>High</td>
<td>Two studies found a statistically significant reduction in progression to invasive mechanical ventilation in people who were treated with baricitinib plus standard care compared with standard care alone.</td>
<td></td>
</tr>
<tr>
<td>Successful cessation of invasive mechanical ventilation</td>
<td>Relative risk 1.24 (CI 95% 0.92 — 1.67) Based on data from 355 participants in 1 studies. 24 (Randomized controlled)</td>
<td>368 per 1000 Difference: 456 per 1000 88 more per 1000 ( CI 95% 29 fewer — 247 more )</td>
<td>Moderate Due to serious imprecision 25</td>
<td>One study found no statistically significant difference in successful cessation of invasive mechanical ventilation in people who were treated with baricitinib plus standard care compared with standard care alone.</td>
<td></td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard Care</td>
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<tr>
<td>Use of haemodialysis or haemofiltration</td>
<td>Relative risk 0.75 (CI 95% 0.57 — 1) Based on data from 8,143 participants in 1 studies. 26 (Randomized controlled)</td>
<td>27 per 1000 Difference: 7 fewer per 1000 (CI 95% 12 fewer — 0 fewer )</td>
<td>Moderate Due to serious imprecision 27</td>
<td>One study found a non-statistically significant reduction in the use of haemodialysis or haemofiltration in people who were treated with baricitinib plus standard care compared with standard care alone.</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>Relative risk 0.9 (CI 95% 0.78 — 1.05) Based on data from 8,156 participants in 1 studies. 28 (Randomized controlled)</td>
<td>86 per 1000 Difference: 9 fewer per 1000 (CI 95% 19 fewer — 4 more )</td>
<td>Moderate Due to serious imprecision 29</td>
<td>One study found no statistically significant difference in adverse events in people who were treated with baricitinib plus standard care compared with standard care alone.</td>
<td></td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>Relative risk 0.78 (CI 95% 0.67 — 0.91) Based on data from 2,617 participants in 3 studies. 30 (Randomized controlled)</td>
<td>211 per 1000 Difference: 46 fewer per 1000 (CI 95% 70 fewer — 19 fewer )</td>
<td>Moderate Due to serious indirectness 31</td>
<td>Three studies found a statistically significant reduction in serious adverse events in people who received baricitinib plus standard care compared with standard care alone.</td>
<td></td>
</tr>
<tr>
<td>Treatment emergent adverse event</td>
<td>Relative risk 1.01 (CI 95% 0.91 — 1.12) Based on data from 2,618 participants in 3 studies. 32 (Randomized controlled)</td>
<td>312 per 1000 Difference: 3 more per 1000 (CI 95% 28 fewer — 37 more )</td>
<td>Low Due to serious indirectness, Due to serious imprecision 33</td>
<td>Three studies found no statistically significant difference in treatment-emergent adverse events in people who were treated with baricitinib plus standard care compared with standard care alone.</td>
<td></td>
</tr>
<tr>
<td>Ventilator free days - Overall in days</td>
<td>High better Based on data from 1,626 participants in 2 studies. 34 (Randomized controlled)</td>
<td>22.6 (Mean) Difference: MD 0.8 more (CI 95% 0.76 more — 0.84 more )</td>
<td>Moderate Due to serious indirectness 35</td>
<td>Two studies found a statistically significant increase in the number of ventilator-free days in people who were treated with baricitinib plus standard care compared with standard care alone.</td>
<td></td>
</tr>
<tr>
<td>Median duration of initial</td>
<td>Lower better</td>
<td>8</td>
<td>8</td>
<td>Low Due to serious</td>
<td>One study found no statistically significant</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard Care</td>
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<tr>
<td>hospitalisation in days</td>
<td>Based on data from 1,033 participants in 1 studies. (Randomized controlled)</td>
<td>(Median)</td>
<td>(Median)</td>
<td>indirectness, Due to serious imprecision</td>
<td>difference in the median duration of initial hospitalisation in people who were treated with baricitinib plus standard care compared with standard care alone.</td>
</tr>
<tr>
<td>Median time to recovery in days</td>
<td>Lower better Based on data from 2,558 participants in 2 studies. (Randomized controlled)</td>
<td>8.5 (Median)</td>
<td>9.5 (Median)</td>
<td>Moderate Due to serious indirectness</td>
<td>Two studies found no statistically significant difference in the median time to recovery in people who were treated with baricitinib plus standard care compared with standard care alone.</td>
</tr>
<tr>
<td>Median days receiving oxygen in days</td>
<td>Lower better Based on data from 1,033 participants in 1 studies. (Randomized controlled)</td>
<td>12 (Median)</td>
<td>10 (Median)</td>
<td>Low Due to serious indirectness, Due to serious imprecision</td>
<td>One study found no statistically significant difference in the median days of receiving oxygen in people who were treated with baricitinib plus standard care compared with standard care alone.</td>
</tr>
<tr>
<td>Median days of non-invasive ventilation or high flow oxygen in days</td>
<td>Lower better Based on data from 1,033 participants in 1 studies. (Randomized controlled)</td>
<td>5 (Median)</td>
<td>4 (Median)</td>
<td>Low Due to serious indirectness, Due to serious imprecision</td>
<td>One study found no statistically significant difference in the median days of receiving non-invasive ventilation or high-flow oxygen in people who were treated with baricitinib plus standard care compared with standard care alone.</td>
</tr>
<tr>
<td>Median days of mechanical ventilation or ECMO in days</td>
<td>Lower better Based on data from 1,033 participants in 1 studies. (Randomized controlled)</td>
<td>25 (Median)</td>
<td>20 (Median)</td>
<td>Low Due to serious indirectness, Due to serious imprecision</td>
<td>One study found no statistically significant difference in the days of receiving mechanical ventilation or ECMO in people who were treated with baricitinib plus standard care compared with standard care alone.</td>
</tr>
<tr>
<td>Mean duration of hospitalisation - Overall in days</td>
<td>Lower better Based on data from 1,626 participants in 2 studies. (Randomized controlled)</td>
<td>14.4 (Mean)</td>
<td>13.6 (Mean)</td>
<td>Moderate Due to serious indirectness</td>
<td>Two studies found a statistically significant reduction in the mean duration of hospitalisation in people who were treated with</td>
</tr>
</tbody>
</table>


3. **Inconsistency: no serious. Indirectness: serious.** Variation in standard care protocols between participating centres which could affect outcomes with treatment. Lack of reporting on vaccination status of participants. **Imprecision: no serious. Publication bias: no serious.**


5. **Inconsistency: no serious. Indirectness: serious.** Variation in standard care protocols between participating centres which could affect outcomes with treatment. Lack of reporting on vaccination status of participants. **Imprecision: no serious. Publication bias: no serious.**


9. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**


11. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**


13. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**


15. **Inconsistency: no serious. Indirectness: serious.** Variation in standard care protocols between participating centres which could affect outcomes with treatment. Lack of reporting on vaccination status of participants. **Imprecision: no serious. Publication bias: no serious.**


18. **Indirectness: serious.** Variation in standard care protocols between participating centres which could affect outcomes with treatment. Lack of reporting on vaccination status of participants. **Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**

19. Systematic review [139] with included studies: Horby 2022. **Baseline/comparator:** Control arm of...
reference used for intervention.

20. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**


22. **Inconsistency: no serious. Indirectness: serious.** Variation in standard care protocols between participating centres which could affect outcomes with treatment. Lack of reporting on vaccination status of participants. **Imprecision: no serious. Publication bias: no serious.**

23. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**


25. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**


27. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**


29. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**


31. **Inconsistency: no serious. Indirectness: serious.** Variation in standard care protocols between participating centres which could affect outcomes with treatment. Lack of reporting on vaccination status of participants. **Imprecision: no serious. Publication bias: no serious.**


33. **Inconsistency: no serious. Indirectness: serious.** Variation in standard care protocols between participating centres which could affect outcomes with treatment. Lack of reporting on vaccination status of participants. **Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**


35. **Inconsistency: no serious. Indirectness: serious.** Variation in standard care protocols between participating centres which could affect outcomes with treatment. Lack of reporting on vaccination status of participants. **Imprecision: no serious. Publication bias: no serious.**

36. **Inconsistency: no serious. Indirectness: serious.** Variation in standard care protocols between participating centres which could affect outcomes with treatment. Lack of reporting on vaccination status of participants. **Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**

37. **Inconsistency: no serious. Indirectness: serious.** Variation in standard care protocols between participating centres which could affect outcomes with treatment. Lack of reporting on vaccination status of participants. **Imprecision: no serious. Publication bias: no serious.**

38. **Inconsistency: no serious. Indirectness: serious.** Variation in standard care protocols between participating centres which could affect outcomes with treatment. Lack of reporting on vaccination status of participants. **Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**
39. **Inconsistency: no serious. Indirectness: serious.** Variation in standard care protocols between participating centres which could affect outcomes with treatment. Lack of reporting on vaccination status of participants. **Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**

40. **Inconsistency: no serious. Indirectness: serious.** Variation in standard care protocols between participating centres which could affect outcomes with treatment. Lack of reporting on vaccination status of participants. **Imprecision: serious.** Confidence interval includes line of no effect. **Publication bias: no serious.**


42. **Inconsistency: no serious. Indirectness: serious.** Variation in standard care protocols between participating centres which could affect outcomes with treatment. Lack of reporting on vaccination status of participants. **Imprecision: no serious. Publication bias: no serious.**

### References


### 7.7 Low molecular weight heparins

**Info Box**

For recommendations on the therapeutic use of low molecular weight heparins, see the section on venous thromboembolism (VTE) prophylaxis.

### 7.8 Antibiotics

**Info Box**

Antibiotics should not be used for preventing or treating COVID-19 unless there is clinical suspicion of additional bacterial co-infection. See the section on suspected or confirmed co-infection.

See also the recommendations on azithromycin and doxycycline in the section on therapeutics for COVID-19.

### 7.9 Azithromycin
Evidence to decision

Benefits and harms
The panel considered that the results from studies of azithromycin for moderate to critical COVID-19 in the hospital setting and mild to moderate COVID-19 in the community setting showed no meaningful benefit in any of the critical outcomes. They were also aware of the known cardiotoxicity risks associated with macrolide antibiotics. Considering this, the panel decided that the findings could not justify the use of azithromycin to treat COVID-19. They were also concerned that using azithromycin in this way may increase antimicrobial resistance and could have important antibiotic stewardship implications.

Certainty of the Evidence
For people in hospital, the certainty of the evidence for azithromycin for COVID-19 on all-cause mortality and invasive mechanical ventilation is moderate. This is because of serious imprecision with the confidence interval crossing the line of no effect. The certainty of the evidence for serious adverse events is low. This is because of serious risk of bias for some concerns around deviation from treatment protocols and serious imprecision for very few events.

The certainty of the evidence for other important outcomes for azithromycin for COVID-19 in people in hospital ranges from low to very low. This is because of serious risk of bias (for some concerns around deviation from treatment protocols) and serious imprecision (for very few events; only 1 study contributing to an outcome or the confidence interval crossing the line of no effect). The panel also considered that using hydroxychloroquine as standard care does not reflect current standard practice. Outcomes that were informed by evidence mainly from studies using hydroxychloroquine as standard care have therefore been downgraded for indirectness.

The certainty of the evidence ranges from moderate to low for the critical outcomes and very low for important outcomes for azithromycin for COVID-19 in the community setting. This is generally because of serious risk of bias (for concerns about missing data and incomplete reporting in 1 study, and lack of blinding for more subjective outcomes) and serious imprecision (for few events or only 1 study contributing to the outcome).

Values and preferences
The panel were not aware of any systematically collected data on peoples’ preferences and values, but they identified critical outcomes that would be important for decision making. These included all-cause mortality, the need for invasive mechanical ventilation and serious adverse events. It is likely that these outcomes would also be of similar importance to patients. In addition, other outcomes including less serious adverse events, discharge from hospital, duration of hospital stay and longer-term outcomes such as functional independence are likely to be of particular importance to patients. These outcomes were not as commonly reported in studies.

The panel inferred that, in view of the lack of meaningful benefit for people with COVID-19, the potential
for harm and the risk of causing antimicrobial resistance, most would not choose azithromycin.

**Resources**

Cost effectiveness was not assessed as part of the evidence review.

**Equity**

The panel were not aware of any evidence for azithromycin use in children or pregnancy. However, because the overall recommendation is not to offer azithromycin to anyone, it is not expected to cause inequity among any subgroups.

**Acceptability**

The panel were not aware of any systematically collected evidence about acceptability. However, considering the important antibiotic stewardship implications and no evidence of effectiveness to treat COVID-19, use of azithromycin would not be acceptable unless there are other licensed indications for which its use remains appropriate.

**Feasibility**

The panel were not aware of any systematically collected evidence about feasibility.

Azithromycin is not used for treating COVID-19 in the UK, so the recommendation supports current practice.

**Rationale**

The evidence suggests that azithromycin is no better than standard care at reducing risk of death in people in hospital with COVID-19. Limited evidence also suggests that azithromycin does not reduce the risk of hospitalisation or death in people with COVID-19 in the community. There is no evidence for azithromycin use for COVID-19 in children. The panel did not think there were reasons to expect different results in this group, so agreed that the recommendation applies to all age groups. They also noted the risk of antimicrobial resistance with azithromycin.

**Clinical question/ PICO**

- **Population:** People with COVID-19 (Hospitalised)
- **Intervention:** Azithromycin
- **Comparator:** Standard care

**Summary**

Compared to standard care, azithromycin is no better at reducing risk of death in people in hospital with COVID-19.
What is the evidence informing this conclusion?
Evidence comes from 4 randomised controlled trials that compared azithromycin with standard care in almost 10,000 adults hospitalised with COVID-19. (Furtado 2020; Sekhavati 2020; Cavalcanti 2020; Horby 2020). Most data are from the RECOVERY trial (Horby 2020) which included 7763 adults hospitalised with moderate-to-critical COVID-19.

Standard care within the trials varied. There were 3 trials that included hydroxychloroquine as part of standard care (Furtado 2020; Cavalcanti 2020; Sekhavati 2020). One trial also included lopinavir/ritonavir as part of standard care as well as hydroxychloroquine (Sekhavati 2020). The largest trial, which was conducted in the UK, did not include hydroxychloroquine as part of standard care (Horby 2020). The use of corticosteroids were permitted in 3 of the trials (Horby 2020; Furtado 2020; Cavalcanti 2020).

Due to the variability in standard care, subgroup analyses were conducted for key outcomes. These subgroup analyses were for hydroxychloroquine as standard care versus no hydroxychloroquine.

Publication status
All studies have been peer-reviewed.

Study characteristics
The mean age in the studies ranges between 50 and 67 years and the proportion of women ranged between 33 and 58%. The severity of COVID-19 across the studies was moderate-to-critical. One study only included people who required no oxygen or supplemental oxygen at baseline (Cavalcanti 2020). In the largest study, 76% of people were receiving supplemental oxygen at baseline. One study had 42% of people receiving oxygen at baseline and 49% people receiving mechanical ventilation at baseline.

The dosage of azithromycin was consistent across all studies (500mg daily) but the duration of the course ranged between 5 and 10 days. All studies used the oral route of administration for azithromycin. Two studies also used the IV route of administration (Furtado 2020 and Horby 2020) and 1 study used a nasogastric route as an option (Furtado 2020).

Children and pregnant women were excluded from the trials.

What are the main results?

Critical outcomes
All-cause mortality
Moderate quality evidence from 3 studies found no significant difference for all-cause mortality at 28-30 days with azithromycin compared with standard care for people who were hospitalised (5 fewer deaths per 1000 people [RR 0.98 95% CI 0.90 to 1.06; 8271 people in 3 studies]). Subgroup analysis for hydroxychloroquine as standard care versus no hydroxychloroquine was no different from the overall results.

Low quality evidence from 2 studies found no significant difference for all-cause mortality at 15 days with azithromycin compared with standard care for people who were hospitalised (0 fewer deaths per 1000 people [RR 1.00 95% CI 0.75 to 1.34; 728 people in 2 studies]).

Invasive mechanical ventilation
Moderate quality evidence from 1 study found no significant difference for requirement of IMV at 28–30 days with azithromycin compared with standard care for people who were hospitalised (8 fewer events per 1000 people [RR 0.92 95% CI 0.79 to 1.07; 7311 people in 1 study]).

Very low-quality evidence from 1 study found no significant difference for requirement of IMV at 15 days with azithromycin compared with standard care for people who were hospitalised (35 more events per 1000 people [RR 1.46 95% CI 0.73 to 2.92; 331 people in 1 study]).

Serious adverse events
Low quality evidence from 3 studies found no significant difference for serious adverse events with azithromycin compared with standard care for people who were hospitalised (2 more events per 1000 people [RR 1.14 95% CI 0.91 – 1.43; 8640 people in 3 studies]). Subgroup analysis for hydroxychloroquine as standard care versus no hydroxychloroquine were no different from the overall results.

Important outcomes
Discharge from hospital
Low quality evidence from 2 studies found no significant difference for discharge from hospital at 29 days with azithromycin compared with standard care for people who were hospitalised (54 fewer events per 1000 people [RR 0.92 95% CI 0.71 to 1.19; 8161 people in 2 studies]). Subgroup analysis for hydroxychloroquine as standard care versus no hydroxychloroquine remained non-significant. However, there were differences in direction of effect (with hydroxychloroquine RR 0.78 95% CI 0.6 to 1.01; 397 people in 1 study; without hydroxychloroquine RR 1.02 95% CI 0.99 to 1.05; 7764 people in 1 study).

Very low-quality evidence from 2 studies found no significant difference for discharge from hospital at 15 days with azithromycin compared with standard care for people who were hospitalised (42 fewer events per 1000 people [RR 0.92 95% CI 0.82 to 1.02; 728 people in 2 studies]).

ICU admission
Low quality evidence from 1 study found no significant difference for ICU admission with azithromycin compared with standard care for people who were hospitalised (91 fewer events per 1000 people [RR 0.28 95% CI 0.06 to 1.29; 111 people in 1 study]).

Duration of hospital stay
Very low-quality evidence from 2 studies found no significant difference for duration of hospital stay with azithromycin compared with standard care for people who were hospitalised (MD -0.41 days 95% CI -2.42 to 1.59; 442 people in 2 studies).

Adverse events
Very low-quality evidence from 1 study found no significant difference for adverse events with azithromycin compared with standard care for people who were hospitalised (57 more events per 1000 people [RR 1.17 95% CI 0.91 to 1.50; 438 people in 1 study]).

Our confidence in the results
There were few concerns around risk of bias of studies. Although all studies were open label, it was not considered high risk of bias for the outcomes reported. This is because the objective outcomes such as all-cause mortality will not likely be affected by knowledge of intervention allocation. Other outcomes such as discharge from hospital could be affected by knowledge of intervention, but is probably unlikely in the pandemic situation. One study reported minor deviation from intervention...
protocols where some patients in the standard care arms also received azithromycin (Cavalcanti 2020). Outcomes that included this study were downgraded for risk of bias (serious adverse events, adverse events, duration of hospital stay and discharge from hospital).

The outcome discharge from hospital was downgraded for serious inconsistency due to statistical heterogeneity of $I^2$ of more than 50%.

Where an outcome was informed only by studies that had hydroxychloroquine as standard care, the outcome was downgraded due to serious indirectness. This is because hydroxychloroquine is not the current standard of care in the UK. This included 15-day all-cause mortality, 15-day invasive mechanical ventilation, 15-day discharge from hospital, ICU admission, duration of hospital stay and adverse events outcomes.

All outcomes were downgraded for imprecision due to the 95% CI crossing the line of no effect or if only 1 study informed the outcome.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Azithromycin</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Within 28-30 days of starting treatment</td>
<td>Relative risk 0.98 (CI 95% 0.9 — 1.06) Based on data from 8,271 participants in 3 studies. 1  (Randomized controlled)</td>
<td>228 per 1000 Difference: 223 per 1000</td>
<td>5 fewer per 1000 (CI 95% 23 fewer — 14 more)</td>
<td>Moderate Due to serious imprecision 2</td>
<td>A pooled analysis of 3 studies found no significant difference for all-cause mortality at 28-30 days with azithromycin compared with standard care for people who were hospitalised.</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Within 15 days of starting treatment</td>
<td>Relative risk 1 (CI 95% 0.75 — 1.34) Based on data from 728 participants in 2 studies. 3  (Randomized controlled)</td>
<td>175 per 1000 Difference: 175 per 1000</td>
<td>0 fewer per 1000 (CI 95% 44 fewer — 60 more)</td>
<td>Low Due to serious indirectness and due to serious imprecision 4</td>
<td>A pooled analysis of 2 studies found no significant difference for all-cause mortality at 15 days with azithromycin compared with standard care for people who were hospitalised.</td>
</tr>
<tr>
<td>Invasive mechanical</td>
<td>Within 28-30 days of starting treatment</td>
<td>Relative risk 0.92 (CI 95% 0.79 — 1.07) Based on data from 7,311 participants in 1 studies. 5  (Randomized controlled)</td>
<td>94 per 1000 Difference: 86 per 1000</td>
<td>8 fewer per 1000 (CI 95% 20 fewer — 7 more)</td>
<td>Moderate Due to serious imprecision 6</td>
<td>Evidence from 1 study found no significant difference for requirement of IMV at 28-30 days with azithromycin compared with standard care for people who were hospitalised.</td>
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</tr>
</tbody>
</table>
| Invasive mechanical ventilation     | Within 15 days of starting treatment    | Relative risk 1.46 (CI 95% 0.73 — 2.92) Based on data from 331 participants in 1 studies.  
7 (Randomized controlled) | 75 per 1000                                                                                   | 110 per 1000             | Very low Due to serious  
risk of bias, Due to serious  
indirectness, Due to serious  
imprecision  
8                                                                 | Evidence from 1 study found no significant difference for requirement of IMV at 15 days with  
azithromycin compared with standard care for people who were hospitalised |
| Serious adverse events              | During treatment                        | Relative risk 1.14 (CI 95% 0.91 — 1.43) Based on data from 8,640 participants in 3 studies.  
9 (Randomized controlled) | 14 per 1000                                                                                    | 16 per 1000              | Low Due to serious risk of bias and  
serious imprecision  
10                                                                 | A pooled analysis of 3 studies found no significant difference for serious adverse events  
with azithromycin compared with standard care for people who were hospitalised |
| Discharge from hospital             | Within 29 days of starting treatment    | Relative risk 0.92 (CI 95% 0.71 — 1.19) Based on data from 8,161 participants in 2 studies.  
11 (Randomized controlled) | 671 per 1000                                                                                  | 617 per 1000             | Low Due to serious  
inconsistency, Due to serious  
imprecision  
12                                                                 | A pooled analysis of 2 studies found no significant difference for discharge from hospital  
at 29 days with azithromycin compared with standard care for people who were hospitalised |
| Discharge from hospital             | Within 15 days of starting treatment    | Relative risk 0.92 (CI 95% 0.82 — 1.02) Based on data from 728 participants in 2 studies.  
13 (Randomized controlled) | 520 per 1000                                                                                  | 478 per 1000             | Very low Due to serious  
inconsistency, serious  
risk of bias, serious  
indirectness and to serious  
imprecision  
14                                                                 | A pooled analysis of 2 studies found no significant difference for discharge from hospital  
at 15 days with azithromycin compared with standard care for people who were hospitalised |
| ICU admission                        | During treatment                        | Relative risk 0.28 (CI 95% 0.06 — 1.29) Based on data from 111 participants in 2 studies.  
15 (Randomized controlled) | 127 per 1000                                                                                  | 36 per 1000              | Low Due to serious  
imprecision and serious  
indirectness  
16                                                                 | Evidence from 1 study found no significant difference for ICU admission with  
azithromycin compared with standard care for people who were hospitalised |
| Adverse events                      | During treatment                        | Relative risk 1.17 (CI 95% 0.91 — 1.5) Based on data from 438 participants in 1 studies.  
17 (Randomized controlled) | 337 per 1000                                                                                  | 394 per 1000             | Very low Due to serious risk of bias,  
serious indirectness and  
Evidence from 1 study found no significant difference for adverse events with azithromycin compared with standard care for people who were hospitalised |
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<tr>
<td></td>
<td></td>
<td></td>
<td>1000 ( CI 95% 30 fewer — 169 more )</td>
<td>serious imprecision 18</td>
<td>care for people who were hospitalised</td>
</tr>
<tr>
<td>Duration of hospital stay</td>
<td>Measured by: Number of days</td>
<td>Based on data from 442 participants in 2 studies. (Randomized controlled)</td>
<td>Difference: MD 0.41 lower ( CI 95% 2.42 lower — 1.59 higher )</td>
<td>Very low Due to serious risk of bias, serious indirectness and serious imprecision 20</td>
<td>A pooled analysis of 2 studies found no significant difference for duration of hospital stay with azithromycin compared with standard care for people who were hospitalised</td>
</tr>
</tbody>
</table>

2. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. 95% CI crosses the line of no effect. **Publication bias:** no serious.
4. **Inconsistency:** no serious. **Indirectness:** serious. due to use of hydroxychloroquine as standard care. **Imprecision:** serious. due to 95% CI crosses the line of no effect, Only data from one study. **Publication bias:** no serious.
6. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Only data from one study. **Publication bias:** no serious.
8. **Risk of Bias:** serious. due to minor deviation from intervention. **Inconsistency:** no serious. **Indirectness:** serious. due to use of hydroxychloroquine as standard care. **Imprecision:** serious. Only data from one study. **Publication bias:** no serious.
10. **Risk of Bias:** serious. due to minor deviations from intervention. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. due to few events. **Publication bias:** no serious.
12. **Inconsistency:** serious. The magnitude of statistical heterogeneity was high, with I^2: 77 %. **Indirectness:** no serious. **Imprecision:** serious. 95% CI crosses the line of no effect. **Publication bias:** no serious.
14. **Risk of Bias:** serious. due to minor deviations from intervention. **Inconsistency:** no serious. **Indirectness:** serious. due to use of hydroxychloroquine as standard care. **Imprecision:** serious. 95% CI crosses line of no effect, due to [reason]. **Publication bias:** no serious.
15. Systematic review [1] with included studies: Sekhavati 2020. **Baseline/comparator:** Control arm of
reference used for intervention.

16. **Inconsistency: no serious. Indirectness: serious.** due to use of hydroxychloroquine as standard care. **Imprecision: serious.** Only data from one study. **Publication bias: no serious.**


18. **Risk of Bias: serious.** due to minor deviation from intervention. **Inconsistency: no serious. Indirectness: serious.** due to use of hydroxychloroquine as standard care. **Imprecision: serious.** Only data from one study. **Publication bias: no serious.**


20. **Risk of Bias: serious.** due to minor deviation from intervention. **Inconsistency: no serious.** The magnitude of statistical heterogeneity was high, with $I^2$ 77%. **Indirectness: serious.** due to use of hydroxychloroquine as standard care. **Imprecision: serious.** 95%CI crosses line of no effect. **Publication bias: no serious.**

### References

1. Azithromycin for COVID-19 internal meta-analysis..


### Clinical question/ PICO

- **Population:** People with COVID-19 (Outpatients)
- **Intervention:** Azithromycin
- **Comparator:** Standard care

### Summary

Compared to standard care, azithromycin probably does not reduce the risk of hospitalisation or death in people with COVID-19 managed in the community.

**What is the evidence informing this conclusion?**

Evidence comes from 3 randomised controlled trials that compared azithromycin with standard care in over 2000 adults with COVID-19 managed as outpatients or in the community (Omran 2020; Butler 2020; Furtado 2020).
Of these trials, 2 were conducted in the UK (Butler 2021; Hinks 2021). Standard care within the trials varied. There was 1 trial that included hydroxychloroquine as part of standard care (Omrani 2020). The 2 trials conducted in the UK did not include hydroxychloroquine as part of standard care (Butler 2021; Hinks 2021). Concomitant corticosteroids use was reported in 1 trial (Hinks 2021).

Due to the variability in standard care, subgroup analyses were conducted for key outcomes. These subgroup analyses were for hydroxychloroquine as standard care versus no hydroxychloroquine.

The dosage of azithromycin was consistent across all studies (500mg daily) but the duration of the course ranged between 3 and 14 days. All studies used the oral route of administration for azithromycin.

There was 1 trial that was stopped early due to meeting its prespecified futility criterion (Butler 2021).

**Publication status**

There was 1 study which is currently only available as a pre-print which means it has not yet been peer-reviewed (Hinks 2021).

**Study characteristics**

The mean age in the studies ranges between 40 and 60 years and the proportion of women ranged between 48 and 57%. The PRINCIPLE trial recruited people who were 65 years or older or 50 years older with at least 1 comorbidity (Butler 2021). Whilst the Q-PROTECT trial planned to recruit women, over 98% were males (Omrani 2020). This was due female quarantine areas in Qatar often being inaccessible to male study physicians.

The severity of COVID-19 across the studies was mild to moderate but without the need for hospital admission.

The dosage of azithromycin was consistent across all studies (500mg daily) but the duration of the course ranged between 3 and 14 days.

Children and pregnant women were excluded from the trials.

**What are the main results?**

**Critical outcomes**

**All-cause mortality**

Low quality evidence from 3 studies found no significant difference for all-cause mortality with azithromycin compared with standard care for people who were managed as outpatients (0 fewer deaths per 1000 people [RR 1.01 95% CI 0.06 to 16.05; 1919 people in 3 studies]). There were no deaths reported in 2 of these studies (Omrani 2020 and Butler 2020). This meant that subgroup analysis for hydroxychloroquine as standard care versus no hydroxychloroquine was not possible.

**Hospitalisation or death (composite)**

Low quality evidence from 2 studies found no significant difference for hospitalisation or death with azithromycin compared with standard care for people who were managed as outpatients (4 fewer events per 1000 people [RR 0.92 95% CI 0.59 to 1.43; 1615 people in 2 studies]).
Low quality evidence from 1 study found no significant difference for hospitalisation or death with azithromycin compared with standard care for people who tested positive for SARS-CoV-2 and were managed as outpatients (13 fewer events per 1000 people [RR 0.82 95% CI 0.39 to 1.71; 422 people in 1 study]).

NIV/IMV or death (composite)
Moderate quality evidence from 1 study found no significant difference for NIV/IMV or death for azithromycin compared with standard care for people who were managed as outpatients (0 fewer events per 1000 [RR 1.01 95% CI 0.14 to 7.10; 292 people in 1 study]).

Invasive mechanical ventilation or ECMO
Low quality evidence from 1 study found no significant difference for IMV or ECMO for azithromycin compared with standard care for people who were managed as outpatients (4 fewer events per 1000 [RR 0.50 95% CI 0.10 to 2.59; 1121 people in 1 study]).

**Important outcomes**

Virologic clearance
Low quality evidence from 1 study found no significant difference for virologic clearance at day 6 for azithromycin compared with standard care for people who were managed as outpatients (22 fewer events per 1000 [RR 0.83 95% CI 0.44 to 1.54; 301 people in 1 study]).

Low quality evidence from 1 study found no significant difference for virologic clearance at day 14 for azithromycin compared with standard care for people who were managed as outpatients (86 fewer per 1000 [RR 0.70 95% CI 0.46 to 1.05; 295 people in 1 study]).

Patient-reported clinical recovery
Patient reported recovery was defined as the first instance that a participant reported feeling recovered (Butler 2021).

Very low-quality evidence from 1 study found no significant difference for patient reported clinical recovery at 28 days for azithromycin compared with standard care for people who were managed as outpatients (38 more events per 1000 [RR 1.05 95% CI 0.99 to 1.11; 1323 people in 1 study]).

Very low-quality evidence from 1 study found no significant difference for patient reported clinical recovery at 28 days for azithromycin compared with standard care for people who tested positive for SARS-CoV-2 and were managed as outpatients (41 more events per 1000 people [RR 1.06 95% CI 0.94 to 1.20; 422 people in 1 study]).

Sustained clinical recovery
Sustained clinical recovery was defined as a participant who reported feeling recovered and subsequently remained well until 28 days after random assignment (Butler 2021).

Very low-quality evidence from 1 study found no significant difference for sustained clinical recovery at 28 days for azithromycin compared with standard care for people who were managed as outpatients (26 fewer events per 1000 people [RR 0.96 95% CI 0.88 to 1.05; 1129 people in 1 study]).

ICU admission
Very low-quality evidence from 1 study found no significant difference for ICU admission at 28 days for azithromycin compared with standard care for people who were managed as outpatients (2 fewer ICU admissions per 1000 people [RR 0.76 95% CI 0.18 to 3.15; 1120 people in 1 study]).
Supplemental oxygen
Very low-quality evidence from 1 study found no significant difference for need for supplemental oxygen at 28 days for azithromycin compared with standard care for people who were managed as outpatients (4 fewer events per 1000 people [RR 0.84 95% CI 0.38 to 1.85; 1122 people from 1 study]).

Our confidence in the results
Although all studies were open label, it was not considered high risk of bias for the mortality and invasive mechanical ventilation outcomes reported. However, outcomes which were considered more subjective were downgraded for risk of bias due to lack of blinding (patient-reported clinical recovery, sustained clinical recovery, ICU admission and supplemental oxygen). 1 study was unclear in how it accounted for missing data. Outcomes that included this study were downgraded for risk of bias (all-cause mortality, hospitalisation or death, invasive mechanical ventilation, patient-reported recovery, sustained clinical recovery, ICU admission and supplemental oxygen).

All outcomes were downgraded for imprecision due to the 95% CI crossing the line of no effect or if only 1 study informed the outcome.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care</th>
<th>Intervention Azithromycin</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Relative risk 1.01 (CI 95% 0.06 — 16.05) Based on data from 1,919 participants in 3 studies. ¹ (Randomized controlled)</td>
<td>1 per 1000 Difference: 0 fewer per 1000 (CI 95% 1 fewer — 15 more )</td>
<td>Low Due to serious risk of bias and serious imprecision ²</td>
<td>A pooled analysis of 3 studies found no significant difference for all-cause mortality with azithromycin compared with standard care for people who were managed as outpatients.</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation or death (composite) - All patients</td>
<td>Relative risk 0.92 (CI 95% 0.59 — 1.43) Based on data from 1,615 participants in 2 studies. ⁴ (Randomized controlled)</td>
<td>46 per 1000 Difference: 42 per 1000 4 fewer per 1000 (CI 95% 19 fewer — 20 more )</td>
<td>Low Due to serious risk of bias and serious imprecision ⁵</td>
<td>A pooled analysis of 2 studies found no significant difference for hospitalisation or death with azithromycin compared with standard care for people who were managed as outpatients.</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation or death (composite) - SARS-CoV-2 positive population</td>
<td>Relative risk 0.82 (CI 95% 0.39 — 1.71) Based on data from 422 participants in 1 studies. ⁷ (Randomized controlled)</td>
<td>72 per 1000 Difference: 59 per 1000 13 fewer per 1000 (CI 95% 44 fewer — 51 more )</td>
<td>Low Due to serious risk of bias and serious imprecision ⁸</td>
<td>Evidence from 1 study found no significant difference for hospitalisation or death with azithromycin compared with standard care for people who tested positive for SARS-CoV-2 and were managed as outpatients.</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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</tr>
<tr>
<td>Critical NIV/IMV or death (composite)</td>
<td>Relative risk 1.01 (CI 95% 0.14 — 7.1) Based on data from 292 participants in 1 studies.</td>
<td>14 per 1000</td>
<td>14 per 1000</td>
<td>Moderate Due to serious imprecision</td>
<td>Evidence from 1 study found no significant difference for NIV/IMV or death for azithromycin compared with standard care for people who were managed as outpatients.</td>
</tr>
<tr>
<td>Within 28 days of starting treatment</td>
<td>(Randomized controlled)</td>
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</tr>
<tr>
<td>Critical Invasive mechanical ventilation or</td>
<td>Relative risk 0.5 (CI 95% 0.1 — 2.59) Based on data from 1,121 participants in 1 studies.</td>
<td>8 per 1000</td>
<td>4 per 1000</td>
<td>Low Due to serious risk of bias and serious imprecision</td>
<td>Evidence from 1 study found no significant difference for IMV or ECMO for azithromycin compared with standard care for people who were managed as outpatients.</td>
</tr>
<tr>
<td>ECMO</td>
<td>(Randomized controlled)</td>
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<tr>
<td>Within 28 days of starting treatment</td>
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<tr>
<td>Critical Virologic clearance 6 days</td>
<td>Relative risk 0.83 (CI 95% 0.44 — 1.54) Based on data from 301 participants in 1 studies.</td>
<td>128 per 1000</td>
<td>106 per 1000</td>
<td>Low Due to serious indirectness and serious imprecision</td>
<td>Evidence from 1 study found no significant difference for virologic clearance at day 6 for azithromycin compared with standard care for people who were managed as outpatients.</td>
</tr>
<tr>
<td>6 Important</td>
<td>(Randomized controlled)</td>
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<tr>
<td>Virologic clearance 14 days</td>
<td>Relative risk 0.7 (CI 95% 0.46 — 1.05) Based on data from 295 participants in 1 studies.</td>
<td>288 per 1000</td>
<td>202 per 1000</td>
<td>Low Due to serious indirectness and serious imprecision</td>
<td>Evidence from 1 study found no significant difference for virologic clearance at day 14 for azithromycin compared with standard care for people who were managed as outpatients.</td>
</tr>
<tr>
<td>6 Important</td>
<td>(Randomized controlled)</td>
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</tr>
<tr>
<td>Patient reported clinical recovery - All</td>
<td>Relative risk 1.05 (CI 95% 0.99 — 1.11) Based on data from 1,323 participants in 1 studies.</td>
<td>767 per 1000</td>
<td>805 per 1000</td>
<td>Very low Due to very serious risk of bias and serious imprecision</td>
<td>Evidence from 1 study found no significant difference for patient reported clinical recovery at 28 days for azithromycin compared with standard care for people who were managed as outpatients.</td>
</tr>
<tr>
<td>patients</td>
<td>(Randomized controlled)</td>
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<tr>
<td>Within 28 days of starting treatment</td>
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<tr>
<td>6 Important</td>
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</tr>
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<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
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<tr>
<td>Patient reported clinical recovery - SARS-CoV-2 positive population</td>
<td>Relative risk 1.06 (CI 95% 0.94 — 1.2) Based on data from 422 participants in 1 studies. 19 (Randomized controlled)</td>
<td>691 per 1000</td>
<td>732 per 1000</td>
<td>Very low Due to very serious risk of bias and serious imprecision 20</td>
<td>Evidence from 1 study found no significant difference for patient reported clinical recovery at 28 days for azithromycin compared with standard care for people who tested positive for SARS-CoV-2 and were managed as outpatients.</td>
</tr>
<tr>
<td>Sustained clinical recovery</td>
<td>Relative risk 0.96 (CI 95% 0.88 — 1.05) Based on data from 1,129 participants in 1 studies. 21 (Randomized controlled)</td>
<td>658 per 1000</td>
<td>632 per 1000</td>
<td>Very low Due to very serious risk of bias and serious imprecision 22</td>
<td>Evidence from 1 study found no significant difference for sustained clinical recovery at 28 days for azithromycin compared with standard care for people who were managed as outpatients.</td>
</tr>
<tr>
<td>ICU admission</td>
<td>Relative risk 0.76 (CI 95% 0.18 — 3.15) Based on data from 1,120 participants in 1 studies. 23 (Randomized controlled)</td>
<td>8 per 1000</td>
<td>6 per 1000</td>
<td>Very low Due to very serious risk of bias and serious imprecision 24</td>
<td>Evidence from 1 study found no significant difference for ICU admission at 28 days for azithromycin compared with standard care for people who were managed as outpatients.</td>
</tr>
<tr>
<td>Supplemental oxygen</td>
<td>Relative risk 0.84 (CI 95% 0.38 — 1.85) Based on data from 1,122 participants in 1 studies. 25 (Randomized controlled)</td>
<td>24 per 1000</td>
<td>20 per 1000</td>
<td>Very low Due to very serious risk of bias and serious imprecision 26</td>
<td>Evidence from 1 study found no significant difference for need for supplemental oxygen at 28 days for azithromycin compared with standard care for people who were managed as outpatients.</td>
</tr>
</tbody>
</table>

3. Population includes people who tested negative for SARS-CoV-19 during treatment
5. Risk of Bias: serious. Incomplete data and/or large loss to follow up. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. 95% CI crosses the line of no effect. Publication bias: no serious.
6. Subpopulation who testing positive for SARS-CoV-19


26. Risk of Bias: very serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. Inconsistency: no serious.
**References**

1. Azithromycin for COVID-19 internal meta-analysis.


**7.10 Budesonide (inhaled)**

*Only in research settings*

Only use budesonide to treat COVID-19 as part of a clinical trial.

*People already on budesonide for conditions other than COVID-19 should continue treatment if they test positive for COVID-19.*

**Evidence to decision**

**Benefits and harms**

Small net benefit, or little difference between alternatives

The panel considered that the clinical evidence suggests there is no statistically significant difference for the outcomes of hospitalisation and death, or need for mechanical ventilation in people having inhaled budesonide and usual care compared with usual care alone. They considered that inhaled budesonide statistically significantly reduces the need for oxygen administration compared with usual care. The panel acknowledged that the event rates for these outcomes were low. This may be explained in part by the fact that the population had mild COVID-19 that was managed in the community. The panel noted that the thresholds for starting oxygen therapy were not reported in the trials.

Time to first reported recovery (patient reported) and time to sustained recovery was statistically significantly reduced with inhaled budesonide compared with usual care. However, the panel acknowledged that corticosteroids can potentially affect wellbeing without affecting the COVID-19 disease process. There was a statistically significant reduction in the number of people who had COVID-19-related urgent care visits. There was no statistically significant difference in serious adverse events for budesonide compared with usual care. The panel also discussed that non-serious adverse events were not reported in the studies. However, they acknowledged that the side-effect profile of
budesonide is well known.

**Certainty of the Evidence**

Most of the evidence was rated as low to moderate in quality. Outcomes that were self-reported were downgraded because of high risk of bias. When 95% confidence intervals crossed the line of no effect, the outcome was downgraded for imprecision. The outcome for COVID-19-related urgent-care visits was downgraded because of indirectness. It was not possible to determine from the data what the nature of the visits were because it included hospitalisations as well as emergency department attendance. These can lead to different outcomes for people with COVID-19.

The panel discussed the limitations of the trials and noted that the STOIC trial was a small study with very few events. They also noted the trial was stopped early as a result of an independent statistical review.

Risk of bias was rated as ‘low’ or ‘some concerns’ for all outcomes in the studies. Both trials included were open-label studies. So, the lack of blinding could have introduced bias to the more subjective outcomes such as self-reported recovery, resolution of symptoms or sustained recovery. This is because people in the trials would have been aware of the treatment they were having.

The panel discussed that the PRINCIPLE trial had a restricted population of mainly older adults and had concerns about the applicability of the trial to younger people with COVID-19. The panel noted that inhalers can be difficult to use for people unfamiliar with the devices, and so the amount of budesonide inhaled may be variable, potentially affecting the results.

**Values and preferences**

The panel were not aware of any systematically collected data on peoples’ preferences and values, but they identified critical outcomes that would be important for decision making. These included all-cause mortality, the need for invasive mechanical ventilation, time to recovery and serious adverse events. It is likely that these outcomes would also be of similar importance to patients. In addition, other outcomes, including less serious adverse events and longer-term outcomes such as functional independence, are likely to be of particular importance to patients. These outcomes were not reported in studies.

**Resources**

Cost effectiveness was not assessed as part of the evidence review.

**Equity**

The panel discussed that not everyone will be able to use an inhaler, which could cause equity issues should inhaled budesonide be recommended for treating COVID-19 in the future.

**Acceptability**

The panel were not aware of any systematically collected evidence about acceptability.
**Feasibility**

The panel were not aware of any systematically collected evidence about feasibility.

Inhaled budesonide is not routinely used for treating COVID-19 in the UK, so the recommendation supports current practice.

**Rationale**

Trial evidence suggests some benefit with inhaled budesonide in reducing how long it takes to recover from COVID-19. However, this evidence is limited because it comes from only 2 trials, 1 of which was very small and stopped early. Also, the population in the trials was mainly older people, which limits its generalisability to other age groups. The panel concluded that more research is needed to address these issues, and that inhaled budesonide should therefore only be used as part of a clinical trial.

**Clinical question/ PICO**

- **Population:** Non-hospitalised adults with COVID-19
- **Intervention:** Inhaled budesonide
- **Comparator:** Standard care, standard care plus placebo, or placebo

**Summary**

**What is the evidence informing this recommendation?**

The evidence review has been developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

Two studies identified from the search are included in this evidence review. The 2 randomised trials compared inhaled budesonide with usual care in 3217 non-hospitalised people with mild COVID-19 (Ramakrishnan 2021 [STOIC trial] and Yu 2021 [PRINCIPLE trial]).

**Study characteristics**

Both studies used a dosage of 800 micrograms twice daily (1600 micrograms total daily dose) of inhaled budesonide. The included studies compared inhaled budesonide to usual care which was based on advice from the UK National Health Service (NHS). The mean ages in the STOIC trial were 44 (range 19-71) years in the budesonide group and 46 (19-79) years in the usual care group. The PRINCIPLE trial restricted enrolment to a higher risk population with 39% of the participants aged between 50 and 64 years and 61% were aged over 64 years. The proportion of women ranged from 52% to 58%. Both studies were conducted in a non-hospital setting.

**What are the main results?**

**Efficacy**

In non-hospitalised adults with COVID-19, there were no statistically significant differences for reduction of hospitalisation or death, need for mechanical ventilation, ICU admission, symptom-related outcomes or hospital assessment without admission (Yu 2021) but there was a statistically significant difference favouring inhaled budesonide for reducing need for oxygen administration, time to first reported recovery, sustained recovery (Yu 2021) and the number of COVID-19-related urgent care visits, including emergency department assessment or hospitalisation (Ramakrishnan 2021).

**Safety**
There was no statistically significant difference in serious adverse events (Yu 2021).

Subgroup analysis
There was insufficient detail to accurately assess subgroups of interest.

Limitations of the evidence
There were some differences in how the included studies were designed which meant that meta-analysis was not appropriate. The population inclusion criteria of the STOIC trial (Ramakrishnan 2021) was broad (symptomatic adults aged ≥ 18 years) whereas the PRINCIPLE trial (Yu 2021 Academic in confidence) was restricted to adults that were at higher risk of complications with COVID-19 (≥65 years or ≥50 years with comorbidities). This restricted population in the PRINCIPLE trial will mean that the data may not be generalisable to younger adults with or without comorbidities.

The STOIC trial was terminated early after independent statistical review. This was because recruitment was reduced after a second national lockdown came into effect in England and implementation of the COVID-19 vaccine had started. Although the STOIC trial was terminated early and did not reach its target sample size, independent statistical review concluded that the addition of more participants would not have changed the result. However, this means that it was a very small trial with few events which may limit impact on decision-making.

Risk of bias for all outcomes was rated as ‘low’ or ‘some concerns’. Both studies were open-label studies whereby lack of blinding could introduce bias to the more subjective outcomes. Lack of blinding is less likely to introduce bias to objective outcomes such as hospitalisation or death.

All included studies were in adults, so it is not possible to say what the efficacy or safety of inhaled budesonide for treating COVID-19 is in children or young people.

Our confidence in the results
The majority of the evidence was rated as low to moderate quality. Outcomes that were self-reported were downgraded due to high risk of bias. Where 95% confidence intervals crossed the line of no effect, the outcome was downgraded for imprecision. The outcome for COVID-19 related urgent-care visits was downgraded due to indirectness as it was not possible to determine from the data what the nature of the visits were as it included hospitalisations as well as emergency department attendance which can lead to different outcomes for patients.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care, standard care plus placebo, or placebo</th>
<th>Intervention Inhaled budesonide</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisation or death related to COVID-19 [SARS-CoV-2 positive only] Within 28 days of starting treatment</td>
<td>Odds ratio 0.75 (CI 95% 0.55 — 1.03) Based on data from 1,856 participants in 1 studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td>Moderate Due to serious imprecision</td>
<td>1 study found a non-statistically significant reduction in hospitalisation or death with inhaled budesonide compared with usual care.</td>
</tr>
<tr>
<td>Outcome</td>
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<tr>
<td>Hospitalisation or death related to COVID-19 [whole study population] Within 28 days of starting treatment</td>
<td>Odds ratio 0.78 (CI 95% 0.57 — 1.04) Based on data from 2,848 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>Inhaled budesonide</td>
<td>Moderate Due to serious imprecision</td>
<td>1 study found a non-statistically significant reduction in hospitalisation or death with inhaled budesonide compared with usual care.</td>
</tr>
<tr>
<td>Mechanical ventilation [SARS-CoV-2 positive only] Within 28 days of starting treatment</td>
<td>Relative risk 0.94 (CI 95% 0.44 — 1.98) Based on data from 1,560 participants in 1 studies.</td>
<td>18 per 1000 Difference:</td>
<td>17 per 1000</td>
<td>Moderate Due to serious imprecision</td>
<td>1 study found no statistically significant difference in mechanical ventilation with inhaled budesonide compared with usual care</td>
</tr>
<tr>
<td>Serious adverse events Within 28 days of starting treatment</td>
<td>Relative risk 1.36 (CI 95% 0.27 — 6.71) Based on data from 1,856 participants in 1 studies. (Randomized controlled)</td>
<td>3 per 1000 Difference:</td>
<td>4 per 1000</td>
<td>Low Due to very serious imprecision</td>
<td>1 study found no statistically significant difference in serious adverse events with inhaled budesonide compared with usual care</td>
</tr>
<tr>
<td>Time to first reported recovery [SARS-CoV-2 positive only]</td>
<td>Hazard ratio 1.21 (CI 95% 1.08 — 1.36) Based on data from 1,856 participants in 1 studies. (Randomized controlled)</td>
<td>Moderate Due to serious risk of bias</td>
<td></td>
<td>1 study found a statistically significant decrease in time to first reported recovery with inhaled budesonide compared with usual care.</td>
<td></td>
</tr>
<tr>
<td>Time to first reported recovery [whole study population]</td>
<td>Hazard ratio 1.18 (CI 95% 1.07 — 1.3) Based on data from 2,848 participants in 1 studies. (Randomized controlled)</td>
<td>Moderate Due to serious risk of bias</td>
<td></td>
<td>1 study found a statistically significant decrease in time to first reported recovery with inhaled budesonide compared with usual care.</td>
<td></td>
</tr>
<tr>
<td>COVID-19-related urgent care visits, including emergency</td>
<td>Relative risk 0.18 (CI 95% 0.04 — 0.79) Based on data from 146 participants in 1 studies.</td>
<td>151 per 1000</td>
<td>27 per 1000</td>
<td>Moderate Due to serious indirectness</td>
<td>1 study found a statistically significant reduction in people who require urgent care</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
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<tr>
<td>department assessment or hospitalisation [whole study population]</td>
<td>Within 14 days of starting treatment</td>
<td>Difference: 9 (Randomized controlled)</td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>124 fewer per 1000 (CI 95% 145 fewer — 32 fewer)</td>
<td>9 Critical</td>
</tr>
<tr>
<td>COVID-19-related urgent care visits, including emergency department assessment or hospitalisation [SARS-CoV-2 positive only]</td>
<td>Within 14 days of starting treatment</td>
<td>Relative risk 0.12 (CI 95% 0.02 — 0.96) Based on data from 131 participants in 1 studies. (Randomized controlled)</td>
<td>123 per 1000</td>
<td>15 per 1000</td>
<td>Moderate Due to serious indirectness 12</td>
</tr>
<tr>
<td>Hospital assessment without admission [SARS-CoV-2 positive only]</td>
<td>Within 28 days of starting treatment</td>
<td>Relative risk 1.01 (CI 95% 0.57 — 1.82) Based on data from 1,583 participants in 1 studies. (Randomized controlled)</td>
<td>28 per 1000</td>
<td>28 per 1000</td>
<td>Low Due to serious imprecision, Due to serious risk of bias 14</td>
</tr>
<tr>
<td>ICU admission [SARS-CoV-2 positive only]</td>
<td>Within 28 days of starting treatment</td>
<td>Relative risk 0.48 (CI 95% 0.23 — 1.01) Based on data from 1,550 participants in 1 studies. (Randomized controlled)</td>
<td>27 per 1000</td>
<td>13 per 1000</td>
<td>Moderate Due to serious imprecision 16</td>
</tr>
<tr>
<td>Oxygen administration [SARS-CoV-2 positive only]</td>
<td>Within 28 days of starting treatment</td>
<td>Relative risk 0.69 (CI 95% 0.49 — 0.98) Based on data from 1,559 participants in 1 studies. (Randomized controlled)</td>
<td>93 per 1000</td>
<td>64 per 1000</td>
<td>High</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator Standard care, standard care plus placebo, or placebo</td>
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<tr>
<td>Starting treatment</td>
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<td>1000 (CI 95% 47 fewer — 2 fewer)</td>
<td></td>
<td></td>
<td>compared with usual care</td>
</tr>
<tr>
<td>Sustained recovery (SARS-CoV-2 positive only)</td>
<td>Relative risk 1.2 (CI 95% 1.1 — 1.32) Based on data from 1,586 participants in 1 studies.</td>
<td>Moderate Due to serious risk of bias</td>
<td>488 per 1000 Difference: 586 per 1000 98 more per 1000 (CI 95% 49 more — 156 more)</td>
<td>1 study found a statistically significant improvement in sustained recovery with inhaled budesonide compared with usual care.</td>
<td></td>
</tr>
<tr>
<td>Time to sustained recovery (SARS-CoV-2 positive only)</td>
<td>Hazard ratio 1.39 (CI 95% 1.21 — 1.59) Based on data from 1,586 participants in 1 studies. (Randomized controlled)</td>
<td>Moderate Due to serious risk of bias</td>
<td>816 per 1000 Difference: 840 per 1000 24 more per 1000 (CI 95% 8 fewer — 65 more)</td>
<td>1 study found a statistically significant decrease in time to sustained recovery with inhaled budesonide compared with usual care.</td>
<td></td>
</tr>
<tr>
<td>Initial reduction of severity of symptoms (SARS-CoV-2 positive only)</td>
<td>Relative risk 1.03 (CI 95% 0.99 — 1.08) Based on data from 1,583 participants in 1 studies. (Randomized controlled)</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>681 per 1000 Difference: 783 per 1000 102 more per 1000 (CI 95% 34 fewer)</td>
<td>1 study found no statistically significant difference in initial severity of symptoms with inhaled budesonide compared with usual care.</td>
<td></td>
</tr>
<tr>
<td>Time to initial reduction of severity of symptoms (SARS-CoV-2 positive only)</td>
<td>Hazard ratio 1.19 (CI 95% 1.07 — 1.32) Based on data from 1,583 participants in 1 studies. (Randomized controlled)</td>
<td>Moderate Due to serious risk of bias</td>
<td>681 per 1000 Difference: 783 per 1000 102 more per 1000 (CI 95% 34 fewer)</td>
<td>1 study found a statistically significant decrease in time to initial reduction of severity of symptoms with inhaled budesonide compared with usual care.</td>
<td></td>
</tr>
<tr>
<td>Symptom resolution (All patients)</td>
<td>Relative risk 1.15 (CI 95% 0.95 — 1.41) Based on data from 142 participants in 1 studies. (Randomized controlled)</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>681 per 1000 Difference: 783 per 1000 102 more per 1000 (CI 95% 34 fewer)</td>
<td>1 study found no statistically significant difference in symptom resolution with inhaled budesonide compared with usual care.</td>
<td></td>
</tr>
<tr>
<td>Outcome Timeframe</td>
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<tr>
<td>6 Important</td>
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<td>— 279 more )</td>
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<tr>
<td>Alleviation of all of symptoms [SARS-CoV-2 positive only] Within 28 days of starting treatment</td>
<td>Relative risk 0.99 (CI 95%: 0.96 — 1.02) Based on data from 1,433 participants in 1 studies. 26 (Randomized controlled)</td>
<td>910 per 1000 Difference: 901 per 1000 9 fewer per 1000 (CI 95%: fewer — 18 more )</td>
<td>Low Due to serious risk of bias, Due to serious imprecision 27</td>
<td>1 study found no statistically significant difference in alleviation of all symptoms with inhaled budesonide compared with usual care.</td>
<td></td>
</tr>
<tr>
<td>Time to alleviation of all symptoms [SARS-CoV-2 positive only]</td>
<td>Hazard ratio 1.07 (CI 95%: 0.96 — 1.19) Based on data from 1,433 participants in 1 studies. (Randomized controlled)</td>
<td></td>
<td>Low Due to serious risk of bias, Due to serious imprecision 28</td>
<td>1 study found no statistically significant difference in time to alleviation of all symptoms with inhaled budesonide compared with usual care.</td>
<td></td>
</tr>
<tr>
<td>Time to recovery</td>
<td>Measured by: Days Lower better Based on data from 139 participants in 1 studies. 28 (Randomized controlled)</td>
<td></td>
<td>Moderate Due to serious risk of bias 29</td>
<td>1 study found a statistically significant reduction in time to recovery with inhaled budesonide compared with usual care.</td>
<td></td>
</tr>
</tbody>
</table>

1. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. 95% CI crosses the line of no effect. **Publication bias:** no serious.
2. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. 95% CI crosses the line of no effect. **Publication bias:** no serious.
3. Systematic review [56] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. 95% CI crosses the line of no effect. **Publication bias:** no serious.
5. Systematic review [56] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. 95% CI crosses the line of no effect and very few events. **Publication bias:** no serious.
7. **Risk of Bias:** serious. Open label study which may have influenced a subjective outcome..
8. **Risk of Bias:** serious. Open label study which may have influenced a subjective outcome.
10. **Inconsistency:** no serious. **Indirectness:** serious. Differences between the outcomes of interest and those reported (e.g. short-term/surrogate, not patient-important). **Imprecision:** no serious. **Publication bias:** no serious.
12. **Inconsistency:** no serious. **Indirectness:** serious. Differences between the outcomes of interest and those reported (e.g. short-term/surrogate, not patient-important). **Imprecision:** no serious. **Publication bias:** no serious.
13. Systematic review [56] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias:** serious. Open label study which may have influenced a subjective outcome.
   **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. 95% CI crosses the line of no effect. **Publication bias:** no serious.
15. Systematic review [56] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. 95% CI crosses the line of no effect. **Publication bias:** no serious.
17. Systematic review [56] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
18. Systematic review [56] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
19. **Risk of Bias:** serious. Open label study which may have influenced a subjective outcome.
   **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. 95% CI crosses the line of no effect. **Publication bias:** no serious.
20. **Risk of Bias:** serious. Open label study which may have influenced a subjective outcome.
   **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** no serious. **Publication bias:** no serious.
21. Systematic review [56] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
22. **Risk of Bias:** serious. Open label study which may have influenced a subjective outcome.
   **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. 95% CI crosses the line of no effect. **Publication bias:** no serious.
23. **Risk of Bias:** serious. Open label study which may have influenced a subjective outcome.
   **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** no serious. **Publication bias:** no serious.
25. **Risk of Bias:** serious. Open label study which may have influenced a subjective outcome.
   **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. 95% CI crosses the line of no effect. **Publication bias:** no serious.
26. Systematic review [56] with included studies: PRINCIPLE. **Baseline/comparator:** Control arm of reference used for intervention.
27. **Risk of Bias:** serious. Open label study which may have influenced a subjective outcome.
   **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. 95% CI crosses the line of no effect. **Publication bias:** no serious.
28. **Risk of Bias:** serious. Open label study which may have influenced a subjective outcome.
   **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. 95% CI crosses the line of no effect.
7.11 Colchicine

Not recommended

Do not use colchicine to treat COVID-19.

Evidence to decision

Benefits and harms

Hospital settings

The panel considered that the results from studies of colchicine for COVID-19 in hospitals showed no benefit of effect on all-cause mortality, mechanical ventilation, discontinuation due to adverse events, clinical progression, ICU admission, or discharge from hospital within 28 days.

The evidence shows that people having colchicine plus standard care have statistically significantly more adverse events compared with people having standard care alone. Known adverse effects such as diarrhoea appear to have been under-reported in the identified evidence in hospital settings. The panel noted that colchicine commonly causes diarrhoea, which can lead to potassium deficiency (hypokalaemia). They advised that, because of the adverse events, colchicine tends to be used (for the treatment of gout) only for 3 to 4 days.

Although one study suggests that colchicine plus standard care reduces duration of hospital stay at a mean follow-up of 21 days compared with placebo plus standard care, this reduction of hospital stay is not statistically significant (a mean difference of 1.84 days (95% CI 0.78 to 2.90)).
Community settings

The panel considered that the results from studies of colchicine for COVID-19 in the community showed no benefit on hospitalisation for COVID-19, all-cause mortality, all-cause mortality or hospitalisation, mechanical ventilation, number of participants who experienced alleviation of all symptoms, or reported recovery time.

The evidence shows that people having colchicine plus standard care have a statistically significant reduction in serious adverse events compared with standard care alone or with placebo. This is possibly because pneumonia was reported less frequently in patients of the colchicine group compared with those in the placebo group. However, people having colchicine plus standard care have a statistically significant increase in adverse events compared with standard care plus placebo. The adverse event diarrhoea was higher with colchicine than with placebo in Tardif 2021.

Certainty of the Evidence

The panel agreed that the certainty of evidence on colchicine for people with COVID-19 in hospital and in the community ranges from high to very low for all outcomes. Reasons for downgrading evidence included: risk of bias (with most studies having some degree of bias); inconsistency (for example, when point estimates varied widely between studies); indirectness (with, for example, standard care in hospitals not including corticosteroids); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). Two studies were only available as preprints.

Values and preferences

The panel were not aware of any systematically collected data on peoples’ preferences and values.

The panel thought that people would not want to take a treatment with no known benefits but well-established side effects such as diarrhoea.

Resources

Cost effectiveness was not assessed as part of the evidence review.

Colchicine costs from £2.54 for 28 tablets (BNF, November 2021). The panel therefore expected a negligible effect on resources.

Equity

Colchicine should not be used in pregnancy and no studies in children were identified. However, because the overall recommendation is not to offer colchicine to anyone, it is not expected to cause inequity among any subgroups.
Acceptability

The panel were not aware of any systematically collected evidence about acceptability.

Colchicine is not licensed in the UK for treating COVID-19. The panel noted that its side effects are unlikely to be acceptable to patients or prescribers, especially diarrhoea and hypokalaemia. The panel noted that diarrhoea is particularly concerning in older people because frequent toilet visits and dehydration could be a risk factor for falls. They also noted that avoidable diarrhoea would not be acceptable in the intensive care setting.

Feasibility

The panel were not aware of any systematically collected evidence about feasibility.

Colchicine is not used for treating COVID-19 in the UK, so the recommendation supports current practice.

Rationale

The evidence from trials of colchicine to treat COVID-19 in adults, both in hospital and community settings, shows no beneficial effect on all-cause mortality or need for mechanical ventilation compared with standard care. It also shows no effect on duration of hospital stay or hospitalisation. The evidence also shows that colchicine causes statistically significantly more adverse events than standard care within 21 days of starting treatment in hospital or 30 days in the community. There is no evidence for children or young people. Therefore, colchicine should not be used to treat COVID-19 in people of any age.

Clinical question/ PICO

Population: People with COVID-19 in hospital
Intervention: Colchicine
Comparator: Placebo or standard care

Summary

There is no evidence that colchicine is more effective than placebo or standard care in treating hospitalised patients with COVID-19.

What is the evidence informing this conclusion?

This is a November 2021 update of the evidence review from May 2021 and includes 1 new study (RECOVERY 2021). Evidence comes from 4 randomised trials that compared colchicine with placebo or standard care in 11620 adults admitted to hospital with COVID-19 (Deftereos 2020, Lopes 2021, Salehzadeh 2020, RECOVERY 2021).

The colchicine arm of the RECOVERY trial stopped recruitment because of futility of the intervention – that is, no effect on mortality was seen for existing participants and recruitment of further participants was not expected to change this finding.

Publication status

Salehzadeh 2020 was only available as a preprint and has therefore not been peer reviewed.

Study characteristics

The median age ranged from 55 to 64 years and the proportion of women ranged from 42% to
The severity of COVID-19 was not clearly reported across studies. In Deftereos 2020, an arterial oxygen partial pressure of lower than 95 mmHg on room air was a key inclusion criterion. Lopes 2021 specified moderate to severe COVID-19 as an inclusion criterion but did not report how many patients of each category of severity were recruited. Salehzadeh 2020 did not define disease severity other than specifying COVID-19 with confirmed lung involvement. In RECOVERY 2021, 15% of participants had no oxygen support or simple oxygen, 31-33% had non-invasive ventilation, and 45-46% had invasive mechanical ventilation.

The dosage of colchicine differed across the studies. Deftereos 2020, RECOVERY 2021, and Lopes 2021 used a higher initial dose (from 1,000 micrograms daily to 2,000 micrograms daily) for between 1 and 5 days before switching to a lower maintenance dose. The daily dose in the maintenance phase was 1,000 micrograms (Deftereos 2020, RECOVERY 2021, Lopes 2021, Salehzadeh 2020). Duration of treatment ranged from 6 days to 3 weeks across the studies.

Participants in 3 studies received hydroxychloroquine (or chloroquine) and azithromycin as part of standard care (Deftereos 2020, Lopes 2021, Salehzadeh 2020). Deftereos 2020 compared colchicine with standard care which included using hydroxychloroquine (or chloroquine) in 98% of participants and azithromycin in 92% of participants. RECOVERY 2021 compared colchicine with standard care which included using corticosteroids in 93% of participants and remdesivir in 22% of participants.

Follow-up ranged from 2 to 3 weeks; however Lopes 2021 did not clearly report the duration of follow-up.

Pregnant and breastfeeding women were excluded from all studies. No children were included.

For further details see the evidence review.

**What are the main results?**

**Critical outcomes**

There was no statistically significant effect on mortality or need for mechanical ventilation within 21 to 28 days of starting colchicine treatment compared with placebo or standard care.

**Important outcomes**

There was a statistically significant increase in adverse events with colchicine compared with standard care.

No statistically significant differences were seen with colchicine compared with control for the other important outcomes reviewed. This includes duration of hospital stay.

**Our confidence in the results**

The certainty of evidence is moderate to very low for all outcomes. Reasons for downgrading evidence included: risk of bias (with all studies having some degree of risk of bias); inconsistency (for example, when point estimates varied widely between studies); indirectness (with, for example, standard care not including corticosteroids); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). One study was only available as a preprint.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality within 21-28 days of starting treatment</td>
<td>Relative risk 0.66 (CI 95% 0.24 — 1.85) Based on data from 11,517 participants in 3 studies.</td>
<td>Placebo or standard care</td>
<td>206 per 1000 Difference: 136 per 1000 70 fewer per 1000 (CI 95% 157 fewer — 175 more)</td>
<td>Moderate Due to serious imprecision</td>
<td>The pooled estimate of three studies found no statistically significant difference in all-cause mortality at 21 to 28 days, and at an unspecified timepoint with colchicine compared with control</td>
</tr>
<tr>
<td>Mechanical ventilation within 21-28 days of starting treatment</td>
<td>Relative risk 0.53 (CI 95% 0.09 — 3.15) Based on data from 10,916 participants in 2 studies.</td>
<td>Placebo or standard care</td>
<td>244 per 1000 Difference: 129 per 1000 115 fewer per 1000 (CI 95% 222 fewer — 525 more)</td>
<td>Very low Because of serious risk of bias due to lack of blinding, and due to serious imprecision, serious inconsistency, and due to indirectness because standard care did not include dexamethasone for hospitalised patients on oxygen</td>
<td>The pooled estimate of two studies found no statistically significant difference in mechanical ventilation at 21 to 28 days with colchicine compared with control</td>
</tr>
<tr>
<td>Serious adverse events within 21 days of starting treatment</td>
<td>Relative risk</td>
<td>Placebo or standard care</td>
<td>0 per 1000</td>
<td>CI 95%</td>
<td>Moderate Because of serious risk of bias due to lack of blinding, and due to indirectness because standard care did not include dexamethasone for hospitalised patients on oxygen</td>
</tr>
<tr>
<td>Adverse events within 21 days of starting treatment</td>
<td>Relative risk 2.61 (CI 95% 1.67 — 4.07) Based on data from 105 participants in 1 studies.</td>
<td>Placebo or standard care</td>
<td>300 per 1000 Difference: 783 per 1000 483 more per 1000 (CI 95% 201 more — 921 more)</td>
<td>Low Because of serious risk of bias due to lack of blinding, and due to indirectness because standard care did not include</td>
<td>One study found that there was a statistically significant increase in adverse events with colchicine compared with standard care within 21 days of starting treatment</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
<td>Summary</td>
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<tr>
<td>Timeframe</td>
<td>Comparantor Placebo or standard care</td>
<td>Intervention Colchicine</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to adverse events within 21 days of starting treatment</td>
<td>Relative risk 4.55 (CI 95% 0.22 — 92.62) Based on data from 177 participants in 2 studies.</td>
<td>0 per 100 Difference: 0 fewer per 1000 (CI 95% 0 fewer — 0 fewer)</td>
<td>Very low Because of serious bias due to lack of blinding, and due to very serious imprecision with fewer than 300 participants, and due to indirectness because standard care did not include dexamethasone for hospitalised patients on oxygen.</td>
<td>The pooled estimate of two studies found no statistically significant difference in discontinuation due to adverse events with colchicine compared with standard care.</td>
<td></td>
</tr>
<tr>
<td>Clinical progression (scale) within 21 days of starting treatment. Increase of 2 grades on 7-grade scale</td>
<td>Relative risk 0.13 (CI 95% 0.02 — 1.02) Based on data from 105 participants in 1 studies.</td>
<td>140 per 1000 Difference: 122 fewer per 1000 (CI 95% 137 fewer — 3 more)</td>
<td>Very low Because of serious bias due to lack of blinding, and due to very serious imprecision with fewer than 300 participants, and due to indirectness because standard care did not include dexamethasone for hospitalised patients on oxygen.</td>
<td>One study found a non-statistically significant reduction in clinical progression with colchicine compared with standard care.</td>
<td></td>
</tr>
<tr>
<td>ICU admission follow-up timepoint was not provided</td>
<td>Relative risk 0.33 (CI 95% 0.04 — 3.06) Based on data from 72 participants in 1 studies.</td>
<td>83 per 1000 Difference: 56 fewer per 1000 (CI 95% 80 fewer — 171 more)</td>
<td>Very low Because of serious bias due to lack of specified follow-up timepoints, and due to very serious imprecision with fewer than 300 participants.</td>
<td>One study found no statistically significant difference in ICU admission with colchicine compared with placebo.</td>
<td></td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
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<tr>
<td>Discharge from hospital by day 10</td>
<td>Relative risk 1.5 (CI 95% 1.14 — 1.98) Based on data from 72 participants in 1 studies.</td>
<td>Placebo or standard care</td>
<td>Colchicine</td>
<td>Moderate Because of serious bias due to lack of specified follow-up timepoints</td>
<td>One study found that more people were discharged from hospital by day 10 in the colchicine arm compared with placebo</td>
</tr>
<tr>
<td>Discharge from hospital within 28 days</td>
<td>Relative risk 0.99 (CI 95% 0.96 — 1.01) Based on data from 11,340 participants in 1 studies. (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Colchicine</td>
<td>Low Because of serious bias due to lack of blinding, and due to serious imprecision</td>
<td>One study found no statistically significant difference in discharge from hospital within 28 days with colchicine compared with standard care</td>
</tr>
<tr>
<td>Duration of hospital stay at a mean follow-up of 21 days (mean difference)</td>
<td>Based on data from 100 participants in 1 studies.</td>
<td>Placebo or standard care</td>
<td>Colchicine</td>
<td>Very low Because of very serious bias due to randomisation method not being provided, lack of blinding, and due to selective reporting of outcomes, and due to indirectness because standard care did not include corticosteroids for hospitalised patients on oxygen</td>
<td>One study found that the duration of hospital stay was less with colchicine compared with standard care at a mean follow-up of 21 days</td>
</tr>
</tbody>
</table>

1. Systematic review [91] with included studies: Lopes 2021, RECOVERY 2021, GRECCO-19 2020. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [40], [95], [39].
2. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Wide confidence intervals. **Publication bias:** no serious.
4. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency:** serious. The magnitude of statistical heterogeneity was high, with I^2: 70%.
5. **Indirectness:** serious. Standard care did not include dexamethasone for hospitalised patients on oxygen. **Imprecision:** serious. Wide confidence intervals. **Publication bias:** no serious.
6. **Risk of Bias:** serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for
Detection bias. **Inconsistency: no serious. Indirectness: serious.** Standard care did not include dexamethasone for hospitalised patients on oxygen. **Imprecision: no serious. Publication bias: no serious.**


7. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** Standard care did not include dexamethasone for hospitalised patients on oxygen. **Imprecision: no serious. Publication bias: no serious.**


9. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** Standard care did not include dexamethasone for hospitalised patients on oxygen. **Imprecision: very serious.** Wide confidence intervals, Low number of patients. **Publication bias: no serious.**


11. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals, Low number of patients. **Publication bias: no serious.**


13. **Risk of Bias: serious.** Because of serious bias due to lack of specified follow-up timepoints. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals, Low number of patients. **Publication bias: no serious.**


18. Systematic review [91] with included studies: Salehzadeh 2020. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [41].

19. **Risk of Bias: very serious.** Due to randomisation method not being provided, lack of blinding, and due to selective reporting of outcomes. **Inconsistency: no serious. Indirectness: serious.** Because standard care did not include corticosteroids for hospitalised patients on oxygen. **Imprecision: no serious. Publication bias: no serious.**

References

Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial. JAMA network open 2020;3(6):e2013136. Pubmed Journal


41. Salehzadeh F, Pourfarzi F, Ataei S. The Impact of Colchicine on The COVID-19 Patients; A Clinical Trial Study. Research Square 2020.. Journal Website

91. Colchicine for COVID-19 in hospitals - November 2021..


**Clinical question/ PICO**

<table>
<thead>
<tr>
<th><strong>Population:</strong></th>
<th>People with COVID-19 in the community</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention:</strong></td>
<td>Colchicine</td>
</tr>
<tr>
<td><strong>Comparator:</strong></td>
<td>Placebo</td>
</tr>
</tbody>
</table>

**Summary**
There is no evidence that colchicine is more effective than placebo or standard care in treating patients in the community with COVID-19.

**What is the evidence informing this conclusion?**
This is a November 2021 update of an evidence review from May 2021 and includes 1 new study (PRINCIPLE 2021). Evidence comes from 2 randomised trials that compared colchicine with placebo or standard care in 4764 adults in the community with COVID-19 (Tardiff 2021 (COLCORONA trial), PRINCIPLE 2021).

**Publication status**
PRINCIPLE 2021 was only available as a preprint and has therefore not been peer reviewed.

**Study characteristics**
The age of participants ranged from 18 to over 65 years and the proportion of women ranged from 49 to 59%. The studies did not clearly define the severity of COVID-19.

For Tardif 2021, the dosage of colchicine was 500 micrograms twice daily for the first 3 days then once daily for 27 days. For PRINCIPLE 2021, participants received colchicine 500 micrograms daily for 14 days.

As standard care in PRINCIPLE 2021, participants received medications focused on managing symptoms with antipyretics. In Tardif 2021, small percentages of participants were given hydroxychloroquine, oral anticoagulants, aspirin, and/or other platelet agents.

Follow-up after starting treatment was 28 days for PRINCIPLE 2021 and 30 days for Tardif 2021.
Pregnant and breastfeeding women were excluded from all studies. No children were included. For further details see the evidence review.

What are the main results?

Critical outcomes

For the critical outcomes of hospitalisation for COVID-19, all-cause mortality, and need for mechanical ventilation, there was no statistically significant effect 28-30 days after starting colchicine treatment compared with control.

Important outcomes

There was a statistically significant increase in adverse events with colchicine compared with standard care. There was a statistically significant increase in serious adverse events with standard care compared with colchicine. This was potentially due to a greater number of cases of pneumonia in the standard care arm.

No statistically significant differences were seen with colchicine compared with control for the other important outcomes reviewed. This includes time to reported recovery.

Our confidence in the results

The certainty of evidence is high to very low for all outcomes. Reasons for downgrading evidence included: risk of bias (with one study having some degree of risk of bias); inconsistency (for example, when point estimates varied widely between studies); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect). One study was only available as a preprint.

<table>
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<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisation for COVID-19 within 30 days of starting treatment</td>
<td>9 Critical</td>
<td>Relative risk 0.8 (CI 95% 0.62 — 1.03) Based on data from 4,488 participants in 1 studies. 1 (Randomized controlled)</td>
<td>57 per 1000 Difference:</td>
<td>46 per 1000 11 fewer per 1000 ( CI 95% 22 fewer — 2 more )</td>
<td>Moderate Due to serious imprecision 2</td>
<td>One study found no statistically significant difference in hospitalisation for COVID-19 at 30 days with colchicine compared with placebo</td>
</tr>
<tr>
<td>All-cause mortality within 30 days of starting treatment</td>
<td>9 Critical</td>
<td>Relative risk 0.56 (CI 95% 0.19 — 1.67) Based on data from 4,488 participants in 1 studies. 3</td>
<td>4 per 1000 Difference:</td>
<td>2 per 1000 2 fewer per 1000 ( CI 95% 3 fewer — 3 more )</td>
<td>Moderate Due to serious imprecision 4</td>
<td>One study found no statistically significant difference in mortality at 30 days with colchicine compared with placebo</td>
</tr>
<tr>
<td>All-cause mortality or hospitalisation (28 or 30 days)</td>
<td>56 per 1000 Difference:</td>
<td>46 per 1000 10 fewer per</td>
<td>Moderate Due to serious imprecision 6</td>
<td>Two studies found a non-significant reduction in all-cause mortality or hospitalisation at 28 to 30 days with colchicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
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<td>Intervention</td>
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<tr>
<td>9 Critical</td>
<td></td>
<td>Placebo</td>
<td>1000 (CI 95% 20 fewer — 3 more)</td>
<td></td>
<td>compared with control</td>
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<tr>
<td></td>
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<td>Colchicine</td>
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<td>Relative risk 0.53</td>
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<td></td>
<td>(CI 95% 0.26 — 1.09)</td>
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<td>Based on data from 4,763</td>
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<td></td>
<td>participants in 2 studies.</td>
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<td></td>
<td>9 per 1000 Difference:</td>
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<td>5 per 1000 Difference:</td>
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<td>4 fewer per 1000 (CI 95% 7 fewer — 1 more)</td>
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<td></td>
<td>Mechanical ventilation within 28-30 days of starting treatment</td>
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<td></td>
<td>The pooled estimate of two studies found a non-statistically significant reduction in mechanical ventilation at 28 to 30 days with colchicine compared with control</td>
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<tr>
<td>6 Important</td>
<td>Relative risk 0.78</td>
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<td>(CI 95% 0.61 — 0.99)</td>
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<td>Based on data from 4,688</td>
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<td>60 per 1000 Difference:</td>
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<td>47 per 1000 Difference:</td>
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<tr>
<td></td>
<td>13 fewer per 1000 (CI 95% 23 fewer — 1 fewer)</td>
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<td>6 Important</td>
<td>Relative risk 1.56</td>
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<td></td>
<td>(CI 95% 1.38 — 1.76)</td>
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<td>Based on data from 4,412</td>
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<td>participants in 1 studies.</td>
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<td>155 per 1000 Difference:</td>
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<td>242 per 1000 Difference:</td>
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<td></td>
<td>87 more per 1000 (CI 95% 59 more — 118 more)</td>
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<tr>
<td>6 Important</td>
<td>Relative risk 1</td>
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<td>(CI 95% 0.92 — 1.1)</td>
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<td>Based on data from 252</td>
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<td>participants in 1 studies.</td>
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<td>883 per 1000 Difference:</td>
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<td>883 per 1000 Difference:</td>
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<td></td>
<td>0 fewer per 1000 (CI 95% 71 fewer — 88 more)</td>
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<td>6 Important</td>
<td>Odds ratio 0.92</td>
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<td>(CI 95% 0.72 — 1.17)</td>
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<td>Based on data from 276</td>
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<td>participants in 1 studies.</td>
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<td>(Randomized controlled)</td>
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<td>883 per 1000 Difference:</td>
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<td>CI 95%</td>
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<td></td>
<td>One study found no statistically significant difference in reported recovery with colchicine plus standard care compared with standard care alone</td>
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</tbody>
</table>

**Note:** The certainty of the evidence is indicated by the following levels: Very low, Low, Moderate, High, Very high. The summary column provides a brief description of the findings based on the evidence provided.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
</table>
| Time to alleviation of all symptoms estimated treatment effect (median days) within 28 days of starting treatment, mean difference | Based on data from 252 participants in 1 studies. 
14 (Randomized controlled) | Difference: | MD 0.94 higher 
( CI 95% 0.68 higher — 1.2 higher ) | Low
Because of serious risk of bias due to a high dropout rate, concerns with randomisation, and lack of blinding | One study found that alleviation of all symptoms happened sooner with colchicine and standard care compared with standard care |
| Time to reported recovery, median difference in days within 28 days of starting treatment, median difference | Based on data from 276 participants in 1 studies. 
(Randomized controlled) | Median difference: 1.14 (95 CI -1.86 to 5.21). A positive value in estimated median difference in time to recovery corresponds to an increase in time to recovery in days in colchicine compared with standard care | Median difference: 1.14 (95 CI -1.86 to 5.21). A positive value in estimated median difference in time to recovery corresponds to an increase in time to recovery in days in colchicine compared with standard care | Very low
Because of serious risk of bias due to a high dropout rate, concerns with randomisation, lack of blinding, and due to serious imprecision | One study found no statistically significant difference in time to reported recovery with colchicine plus standard care compared with standard care alone |

1. Systematic review [92] with included studies: COLCORONA 2021. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [42],
2. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. **Publication bias:** no serious.
4. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. **Publication bias:** no serious.
5. Systematic review [92] with included studies: PRINCIPLE 2021, COLCORONA 2021. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [96], [42],
6. **Risk of Bias:** serious. **Inconsistency:** serious. **Imprecision:** serious. Due to serious imprecision. **Publication bias:** no serious.
8. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. **Publication bias:** no serious.
10. Systematic review [92] with included studies: COLCORONA 2021. **Baseline/comparator:** Control arm
of reference used for intervention.

References


92. Colchicine for COVID-19 in the community - November 2021..


7.12 Doxycycline

Not recommended

Do not use doxycycline to treat COVID-19 in the community.

Evidence to decision

Benefits and harms

The panel discussed evidence from a trial comparing doxycycline plus standard care with standard care alone to treat COVID-19 in the community in people 65 years and over or people 50 and over if they have comorbidities. They agreed that the evidence suggests that, in these groups, doxycycline plus standard care does not reduce the risk of hospitalisation and death, admission into intensive care, the need for mechanical ventilation or oxygen, or significant adverse events. They also agreed that the evidence suggests doxycycline does not improve symptoms or recovery. The panel noted the lack of statistically significant benefits with doxycycline in both the main analysis population and the analysis in
people with laboratory-confirmed positive COVID-19. The panel were aware that randomisation to doxycycline in the trial was stopped because of futility in December 2020. No evidence was identified for other groups or settings.

The panel noted that doxycycline may cause side effects such as gastrointestinal disturbances and photosensitivity. They were also concerned that using doxycycline to treat COVID-19 in the community may increase risk of antimicrobial resistance, which could have important antibiotic stewardship implications.

**Certainty of the Evidence**

The certainty of evidence was rated as moderate because of serious imprecision (apart from 1 outcome that was rated as high). The panel were aware of imprecision issues, including there being only 1 study, the confidence intervals crossing the line of no effect and few events for some outcomes.

The panel were unclear on which symptoms were included in the measures of symptom alleviation and recovery.

The panel also discussed the relatively low proportion of people in the trial with laboratory-confirmed COVID-19. They thought this reflected the pragmatic treatment of COVID-19 in the community in the early stages of the pandemic, which was based on the presence of symptoms and limited testing capacity. However, they noted that testing is now more widely available in the community.

Because there are potential harms from doxycycline use (side effects and risk of antimicrobial resistance), the panel made a strong recommendation against use in the community.

**Values and preferences**

The panel were not aware of any systematically collected data on peoples' preferences and values. They noted the importance to people with COVID-19 in the community of avoiding hospital admission. However, the included trial only reported a composite outcome of hospitalisation and death, and reported hospital assessment without admission but not hospitalisation. Avoiding admission into intensive care was also considered an important outcome by the panel. They inferred that most people would not choose doxycycline because of the lack of meaningful benefit in treating COVID-19, the potential for side effects and the risk of antimicrobial resistance.

**Resources**

Cost effectiveness was not assessed as part of the evidence review.

**Equity**

No evidence was found in people under 65 years, people under 50 years with comorbidities or pregnant women. However, because the overall recommendation is not to offer doxycycline to anyone in the community, it is not expected to cause inequity among any groups.
There is evidence from 1 trial in the community of doxycycline for COVID-19 in people 65 years and over and in people 50 years and over with comorbidities. The results suggest that, compared with standard care alone, doxycycline plus standard care does not reduce the risk of hospitalisation and death, admission to intensive care, the need for mechanical ventilation or oxygen, or significant adverse events in these groups. The results also suggest that it does not improve symptoms or recovery.

There is no evidence for doxycycline use in the community for COVID-19 in people under 65 years or people under 50 years with comorbidities. But, it is unlikely that the results in these groups will differ, so the panel agreed that the recommendation applies to all age groups in the community. They also noted the risks of side effects and antimicrobial resistance with doxycycline. There was no evidence found for doxycycline use in hospital settings.

Acceptability
The panel were not aware of any systematically collected evidence about acceptability. However, the evidence does not suggest benefits with doxycycline and there are potential harms (from side effects and a risk of promoting antimicrobial resistance). So, its use in the community is not likely to be acceptable unless there are other licensed indications for which its use remains appropriate.

Feasibility
The panel were not aware of any systematically collected evidence about feasibility.

Rationale
There is evidence from 1 trial in the community of doxycycline for COVID-19 in people 65 years and over and in people 50 years and over with comorbidities. The results suggest that, compared with standard care alone, doxycycline plus standard care does not reduce the risk of hospitalisation and death, admission to intensive care, the need for mechanical ventilation or oxygen, or significant adverse events in these groups. The results also suggest that it does not improve symptoms or recovery.

There is no evidence for doxycycline use in the community for COVID-19 in people under 65 years or people under 50 years with comorbidities. But, it is unlikely that the results in these groups will differ, so the panel agreed that the recommendation applies to all age groups in the community. They also noted the risks of side effects and antimicrobial resistance with doxycycline. There was no evidence found for doxycycline use in hospital settings.

Clinical question/ PICO
- **Population:** People with COVID-19 (Community)
- **Intervention:** Doxycycline plus standard care
- **Comparator:** Standard care

Summary
The evidence suggests that doxycycline plus standard care does not give statistically significant improvements in hospitalisation/death, mechanical ventilation, oxygen administration, ICU admission, measures of symptom alleviation and recovery, or significant adverse events in people with COVID-19 in the community.

What is the evidence informing this conclusion?
These findings are based on 1 RCT (PRINCIPLE) (Butler 2021). This UK study recruited participants from the community with ongoing symptoms (starting within the last 14 days) from PCR-confirmed or suspected COVID-19. Participants were aged 65 years and above or aged 50 years and above with comorbidities.

The RCT compared doxycycline plus standard care (N=780) with standard care (N=948) in adults with COVID-19. In December 2020 randomisation to doxycycline was stopped as pre-specified futility criteria were met.

Publication status
All studies have been peer-reviewed.
**Study characteristics**

Participants were recruited from the community (from general practices, online, or by telephone). Eligible participants had ongoing symptoms from PCR-confirmed or suspected COVID-19 (that must have started within the last 14 days) (in accordance with the United Kingdom [UK] National Health Service [NHS] definition of high temperature and/or new, continuous cough and/or change in sense of smell/taste). Eligible participants were aged 65 years and older, or 50 years and older if they had comorbidities (weakened immune system; heart disease; hypertension; asthma or lung disease; diabetes; hepatic impairment; stroke or neurological problem; and self-reported obesity or body mass index ≥35 kg/m².) People who were already taking acute antibiotics were excluded.

The intervention was doxycycline 200mg on day one, followed by 100mg daily for six days. Standard care for suspected uncomplicated COVID-19 in the community in the UK NHS is largely supportive (antibiotics only being recommended for suspected COVID-19 pneumonia if bacterial aetiology is suspected or the patient is at high risk, in which instance guidelines recommend doxycycline).

The proportion of people with a positive swab result varied from 35.1% (standard care group) to 55.4% (doxycycline group). Participants had a mean (standard deviation [SD]) age of 61.1 (7.9) years; over half (55.7%) were female and the majority (87.2%) had comorbidities. The median (interquartile range [IQR]) duration of illness prior to randomisation was 6 (4–9) days.

**What are the main results?**

Hospitalisation/death within 28 days (critical outcome)

One RCT (Butler 2021) found no statistically significant difference in hospitalisation/death within 28 days with doxycycline plus standard care compared with standard care (7 more per 1000 patients; RR 1.13 [95% CI 0.73 — 1.74]) in people with COVID-19 in the community.

Mechanical ventilation (critical outcome)

One RCT (Butler 2021) reported no statistically significant difference in mechanical ventilation within 28 days with doxycycline plus standard care compared with standard care (4 fewer per 1000 patients; RR 0.49 [95% CI 0.12 — 2.05]) in people with COVID-19 in the community.

Significant adverse events (critical outcome)

One RCT (Butler 2021) showed no statistically significant difference in significant adverse events with doxycycline plus standard care compared with standard care (5 fewer per 1000; RR 0.11 [95% CI 0.01 — 1.99]) in people with COVID-19 in the community.

Oxygen administration (important outcome)

One RCT (Butler 2021) reported no statistically significant difference in oxygen administration within 28 days with doxycycline plus standard care compared with standard care (1 fewer per 1000 patients; RR 0.98 [95% CI 0.55 — 1.76]) in people with COVID-19 in the community.

ICU admission (important outcome)

One RCT (Butler 2021) found no statistically significant difference in ICU admission within 28 days with doxycycline plus standard care compared with standard care (5 fewer per 1000; RR 0.55 [95% CI 0.16 — 1.93]) in people with COVID-19 in the community.

Alleviation of all symptoms within 28 days (important outcome)

One RCT (Butler 2021) found a non statistically significant improvement in alleviation of symptoms within 28 days with doxycycline plus standard care compared with standard care (28 fewer per 1000; RR 0.97 [95% CI 0.94 — 1.00]) in people with COVID-19 in the community.
people with COVID-19 in the community.

Initial reduction of severity of symptoms within 28 days (important outcome)

One RCT (Butler 2021) found no statistically significant difference of initial reduction of severity of symptoms within 28 days with doxycycline plus standard care compared with standard care (11 more per 1000; RR 1.01 [95% CI 0.98 — 1.05]) in people with COVID-19 in the community.

Sustained alleviation of all symptoms within 28 days (important outcome)

One RCT (Butler 2021) found no statistically significant difference in alleviation of all symptoms within 28 days with doxycycline plus standard care compared with standard care (5 more per 1000; RR 1.01 [95% CI 0.96 — 1.06]) in people with COVID-19 in the community.

Sustained recovery (important outcome)

One RCT (Butler 2021) found no statistically significant difference in sustained recovery within 28 days with doxycycline plus standard care compared with standard care (29 more per 1000; RR 1.05 [95% CI 0.97 — 1.13]) in people with COVID-19 in the community.

Time to initial reduction of severity of symptoms (important outcome)

One RCT (Butler 2021) reported no statistically significant difference in time to initial reduction of severity of symptoms with doxycycline plus standard care (HR 0.99 [95% CI 0.88 — 1.11]) compared with standard care in people with COVID-19 in the community.

Time to alleviation of all symptoms (important outcome)

There was no statistically significant difference in time to alleviation of all symptoms with doxycycline plus standard care compared with standard care (HR 0.96 [95% CI 0.86 — 1.09]) in 1 RCT (Butler 2021) in people with COVID-19 in the community.

Time to sustained alleviation of all symptoms (important outcome)

There was no statistically significant difference in time to sustained alleviation of all symptoms with doxycycline plus standard care compared with standard care (HR 1.03 [95% CI 0.90 — 1.17]) in people with COVID-19 in the community.

Time to first reported recovery (important outcome)

One RCT (Butler 2021) showed no statistically significant difference in time to first reported recovery with doxycycline plus standard care compared with standard care (HR 1.04 [95% CI 0.93 — 1.17]) in people with COVID-19 in the community.

Time to sustained recovery (important outcome)

One RCT (Butler 2021) found no statistically significant difference in time to sustained recovery with doxycycline plus standard care compared with standard care (HR 1.00 [95% CI 0.88 — 1.14]) in people with COVID-19 in the community.

Our confidence in the results

The certainty of evidence for the critical outcomes of hospitalisation/death, mechanical ventilation and significant adverse events was rated as moderate (due to serious imprecision).

The certainty of evidence for the important outcome of alleviation of all symptoms at 28 days was considered to be high. However, the certainty of evidence for all remaining important outcomes was rated as moderate due to serious imprecision.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of Evidence (Quality of Evidence)</th>
<th>Summary</th>
</tr>
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<tbody>
<tr>
<td>Hospitalisation/death</td>
<td>Within 28 days</td>
<td>Relative risk 1.13 (CI 95% 0.73 — 1.74) Based on data from 1,728 participants in 1 studies. ¹ ² ³ ⁴ (Randomized controlled)</td>
<td>Standard care</td>
<td>Doxycycline plus standard care</td>
<td>Moderate Due to serious imprecision ²</td>
<td>One study found no statistically significant difference in hospitalisation/death within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.</td>
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<tr>
<td>Mechanical ventilation</td>
<td>Within 28 days</td>
<td>Relative risk 0.49 (CI 95% 0.12 — 2.05) Based on data from 1,378 participants in 1 studies. ³ (Randomized controlled)</td>
<td>Standard care</td>
<td></td>
<td>Moderate Due to serious imprecision ⁴</td>
<td>One study found no statistically significant difference in mechanical ventilation within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.</td>
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<tr>
<td>Significant adverse events</td>
<td></td>
<td>Relative risk 0.11 (CI 95% 0.01 — 1.99) Based on data from 1,728 participants in 1 studies. ³ (Randomized controlled)</td>
<td>Standard care</td>
<td></td>
<td>Moderate Due to serious imprecision ⁶</td>
<td>One study found no statistically significant difference in significant adverse events with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.</td>
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<tr>
<td>Oxygen administration</td>
<td>Within 28 days</td>
<td>Relative risk 0.98 (CI 95% 0.55 — 1.76) Based on data from 1,378 participants in 1 studies. ⁷ (Randomized controlled)</td>
<td>Standard care</td>
<td></td>
<td>Moderate Due to serious imprecision ⁸</td>
<td>One study found no statistically significant difference in oxygen administration within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.</td>
</tr>
<tr>
<td>ICU admission</td>
<td>Within 28 days</td>
<td>Relative risk 0.55 (CI 95% 0.16 — 1.93) Based on data from 1,375 participants in 1 studies. ⁹ (Randomized controlled)</td>
<td>Standard care</td>
<td></td>
<td>Moderate Due to serious imprecision ¹⁰</td>
<td>One study found no statistically significant difference in ICU admission within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.</td>
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<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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<tr>
<td>Alleviation of all symptoms Within 28 days</td>
<td>Relative risk 0.97 (CI 95% 0.94 — 1) Based on data from 1,222 participants in 1 studies.</td>
<td>Standard care</td>
<td>Doxycycline plus standard care</td>
<td>High 12</td>
<td>One study found a non-statistically significant improvement in alleviation of all symptoms within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.</td>
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<tr>
<td>Initial reduction of severity of symptoms Within 28 days</td>
<td>Relative risk 1.01 (CI 95% 0.98 — 1.05) Based on data from 1,424 participants in 1 studies.</td>
<td>Standard care</td>
<td>Doxycycline plus standard care</td>
<td>Moderate Due to serious imprecision 14</td>
<td>One study found no statistically significant difference in initial reduction of severity of symptoms within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.</td>
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<tr>
<td>Sustained alleviation of all symptoms Within 28 days</td>
<td>Relative risk 1.01 (CI 95% 0.96 — 1.06) Based on data from 1,163 participants in 1 studies.</td>
<td>Standard care</td>
<td>Doxycycline plus standard care</td>
<td>Moderate Due to serious imprecision 16</td>
<td>One study found no statistically significant difference in sustained alleviation of all symptoms within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.</td>
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<tr>
<td>Sustained recovery Within 28 days</td>
<td>Relative risk 1.05 (CI 95% 0.97 — 1.13) Based on data from 1,424 participants in 1 studies.</td>
<td>Standard care</td>
<td>Doxycycline plus standard care</td>
<td>Moderate Due to serious imprecision 18</td>
<td>One study found no statistically significant difference in sustained recovery within 28 days with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.</td>
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<tr>
<td>Time to initial reduction of severity of symptoms</td>
<td>Hazard ratio 0.99 (CI 95% 0.88 — 1.11) Based on data from 1,424 participants in 1 studies.</td>
<td>Standard care</td>
<td>Doxycycline plus standard care</td>
<td>Moderate Due to serious imprecision 19</td>
<td>One study found no statistically significant difference in time to initial reduction of severity of symptoms with doxycycline plus standard care compared with standard care in people with COVID-19 in the community.</td>
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<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
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<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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<tr>
<td>Time to alleviation of all symptoms</td>
<td>Hazard ratio 0.96 (CI 95% 0.86 — 1.09) Based on data from 1,222 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Doxycycline plus standard care</td>
<td>Moderate Due to serious imprecision 20</td>
<td>One study found no statistically significant difference in time to alleviation of all symptoms with doxycycline plus standard care compared with standard care in people with COVID-19 in the community</td>
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<tr>
<td>Time to sustained alleviation of all symptoms</td>
<td>Hazard ratio 1.03 (CI 95% 0.9 — 1.17) Based on data from 1,163 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Doxycycline plus standard care</td>
<td>Moderate Due to serious imprecision 21</td>
<td>One study found no statistically significant difference in time to sustained alleviation of all symptoms with doxycycline plus standard care compared with standard care in people with COVID-19 in the community</td>
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<tr>
<td>Time to first reported recovery</td>
<td>Hazard ratio 1.04 (CI 95% 0.93 — 1.17) Based on data from 1,728 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Doxycycline plus standard care</td>
<td>Moderate Due to serious imprecision 22</td>
<td>One study found no statistically significant difference in time to first reported recovery with doxycycline plus standard care compared with standard care in people with COVID-19 in the community</td>
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<tr>
<td>Time to sustained recovery</td>
<td>Hazard ratio 1 (CI 95% 0.88 — 1.14) Based on data from 1,424 participants in 1 studies. (Randomized controlled)</td>
<td>Standard care</td>
<td>Doxycycline plus standard care</td>
<td>Moderate Due to serious imprecision 23</td>
<td>One study found no statistically significant difference in time to sustained recovery with doxycycline plus standard care compared with standard care in people with COVID-19 in the community</td>
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</tbody>
</table>

2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, due to confidence intervals crossing line of no effect.
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to confidence intervals crossing line of no effect.

6. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Wide confidence intervals, Low number of patients, Only data from one study.


8. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Only data from one study, due to confidence intervals crossing line of no effect.


10. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Wide confidence intervals, Low number of patients, Only data from one study, due to confidence intervals crossing line of no effect.


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14. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Only data from one study, due to confidence intervals crossing line of no effect.


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20. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Only data from one study, due to confidence intervals crossing line of no effect.

21. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Only data from one study, due to confidence intervals crossing line of no effect.

22. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Only data from one study, due to confidence intervals crossing line of no effect.

23. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Only data from one study, due to confidence intervals crossing line of no effect.

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**References**

7.13 Ivermectin

Only in research settings

Do not use ivermectin to treat COVID-19 except as part of an ongoing clinical trial.

Evidence to decision

Benefits and harms

**Hospital settings**

The panel stated that mortality is important for decision making. They noted that the evidence does not show a statistically significant difference in mortality for people in hospital with COVID-19 having a single dose of ivermectin compared with people having control (standard care or placebo or standard care plus placebo). For 2 to 5 doses of ivermectin, the meta-analysis showed a statistically significant reduction in mortality. However, the panel had concerns about 2 studies judged to have high risk of bias because of randomisation issues and people with a negative or inconclusive PCR for SARS-CoV-2 result included in the trials. A sensitivity analysis removing 2 studies with high risk of bias showed no statistically significant difference for mortality with 2 to 5 doses of ivermectin compared with control. The panel discussed that some studies reported all-cause mortality, so it may be possible that deaths reported may not all be due to COVID-19. The panel considered the certainty of evidence for this outcome to be very low for both 2 to 5 doses of ivermectin and single dose ivermectin. They also agreed that there are issues with the applicability of the evidence in the hospital setting. This was because most people in the studies had less severe COVID-19 than people who would be hospitalised in the UK.

The panel noted that a statistically significant increase in adverse events was seen for people who had 2 to 5 doses of ivermectin compared with those who had control, with moderate certainty of evidence. However, there was no statistically significant difference in adverse events between single dose of ivermectin group and control group. Therefore, there is uncertainty around the safety of oral ivermectin used at the doses and frequencies in the multidose trials.

The panel noted that the evidence shows no statistically significant difference between ivermectin and control for the other outcomes of admission to intensive care, need for invasive mechanical ventilation, discharge from hospital, number of people needing oxygen, clinical improvement, clinical worsening, time to recovery, viral clearance (at days 1 to 6 and 7 to 14), duration to viral clearance and duration of symptoms.

**Community setting**

The panel discussed the evidence on ivermectin use for people with COVID-19 in the community. The evidence showed no statistically significant differences for ivermectin compared to control in: mortality; need for invasive mechanical ventilation; adverse events; serious adverse events; need for hospitalisation;
number of people needing oxygen; clinical deterioration; clinical recovery; viral clearance (at days 1 to 6 and 7 to 14) both in 2 to 5 doses and single dose of ivermectin group. The panel noted that the certainty of evidence is moderate, low or very low for all outcomes.

The panel also noted that evidence suggests a statistically significant increase in stopping treatment because of adverse events with 2 to 5 doses of ivermectin but agreed that this evidence is of low certainty. Therefore, there is uncertainty around the safety of oral ivermectin used at the doses and frequencies in the multidose trials.

The panel saw no statistically significant findings on viral clearance and adverse events in people who had a single dose of ivermectin compared with control group. The certainty of evidence is low for both of these outcomes.

**Other panel considerations**

The panel discussed the potential for the occurrence of rare serious adverse events (such as myocardial infarction which was the most common serious adverse event reported in Lim 2022) with ivermectin. They considered that the available studies were too small to identify such events.

The panel noted that no studies were from the UK. They commented that some of the treatments (such as hydroxychloroquine, doxycycline, azithromycin and lopinavir–ritonavir) used in the control groups are either not used in the UK for COVID-19 or may not be effective against COVID-19. Detail on other treatments was lacking in some studies. The panel considered that this limits the applicability of the evidence to UK practice. Oral ivermectin may be used to treat strongyloidiasis. The panel discussed the possibility that some of the studies contributing to the evidence base may have been conducted in countries with higher prevalence of strongyloidiasis compared with others. Therefore, there is uncertainty around whether results of studies of ivermectin for COVID-19 are generalisable between countries where there is high prevalence of strongyloidiasis and those countries where prevalence is low, with potential confounding effect. The panel also discussed that, because dosage varied widely across the included studies, it is uncertain what a safe dose of ivermectin would be for treating COVID-19.

The panel agreed that the uncertainty around the benefits and safety of ivermectin based on the current evidence means that it cannot be recommended for COVID-19 in people in hospital or community settings. They considered that this was the case for children, young people and adults. The panel were aware of ongoing trials investigating ivermectin, such as the PRINCIPLE trial. They considered that the available evidence for the effectiveness and safety of ivermectin could be improved by evidence from a well-designed randomised controlled trial.

**Certainty of the Evidence**

The panel agreed that the certainty of evidence on ivermectin for people with COVID-19 in hospital and in the community is moderate, low or very low for all outcomes. Reasons for downgrading evidence included: risk of bias (with most studies being at high or unclear risk of bias); inconsistency (for example, when point estimates varied widely between studies); indirectness (with, for example, standard care differing from that in the UK); and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). Some studies were only available as preprints so have not been peer reviewed.
Rationale

Overall, there is a high degree of uncertainty about whether ivermectin is more effective than control (standard care, placebo or both) for managing COVID-19 in hospital or community settings. The panel raised concerns about the quality of the studies on ivermectin. They noted that most of the evidence is of low or very low certainty, with some that is of moderate certainty. The panel also noted the uncertainty about the overall safety and the possibility of rare serious adverse reactions with ivermectin. Because of the uncertainty in the evidence (including small sample sizes and issues with study quality), the panel agreed that ivermectin should only be used to treat COVID-19 in ongoing well-conducted clinical trials. The panel were aware of at least 1 ongoing trial, the results of which may improve the certainty of the evidence on the effectiveness of ivermectin for managing COVID-19.

Clinical question/ PICO

Population: People hospitalised with COVID-19
**Intervention:** Ivermectin (multiple doses)

**Comparator:** Standard care, standard care plus placebo, or placebo

### Summary

**Comparison:** Ivermectin (multiple doses) vs placebo, standard care or placebo plus standard care in hospital setting

**Key result**

Compared to standard care, ivermectin administered for 2-5 days significantly reduced mortality. However, after excluding two studies with high risk of bias, there was no statistically significant reduction in mortality compared to control group. There was statistically significant increase in adverse events in ivermectin group compared to control group.

**What is the evidence informing this conclusion?**

Evidence comes from 8 randomised controlled trials (n=1174) that compared ivermectin (administered daily for 2-5 days) to standard care, placebo or standard care plus placebo in hospitalised for COVID-19 (Mohan 2021, Abd-Elsalam 2021, Mainomaipiboon 2022, Shakhsi Niaee 2020, Ravikirti 2021, Lim 2022, Ahmed 2020, Krolewiecki 2020). Two new trials were added in this update (Mainomaipiboon 2022 and Lim 2022). Studies were conducted in Bangladesh, Malaysia, Thailand, Egypt, Argentina, India, Iran. Two trials were multi-arms studies and compared two different dosage regimens of ivermectin (Mohan 2021 and Niaee 2020); less than 400 micrograms/kg (micrograms/kg) and more than 400 micrograms/kg. 6 other RCTs used either a dose of more than 400 micrograms/kg or less than 400 micrograms/kg (Abd-Elsalam 2021, Mainomaipiboon 2022, Ravikirti 2021, Lim 2022, Ahmed 2020, Krolewiecki 2020).

Subgroup analyses were conducted based on less than 400micrograms/kg and greater than 400 micrograms/kg to highlight the differences in COVID-19 outcomes. For further details, please see the evidence review.

**Publication status**

All trials were full peer-reviewed publications except Mainomaipiboon 2022, which was a preprint and not peer-reviewed.

**Study characteristics**

Severity of COVID across trials was mild to moderate COVID-19. Standard care varied between trials. Lim 2022 included people 50 years or older with at least one comorbidity and had mild to moderate COVID-19. RCT by Abd-Elsalam 2021 had mean age of 42.38 ± 16.02 years in ivermectin and 39.38 ± 16.92 in control group. The mean age of people was 38.33±6.84 in the ivermectin group and 37.33±5.84 in the control group in Abbas 2022. The mean age in trial by Mainomaipiboon 2022 was 48.57± 14.80 years.

The median age varied from 53 to 61 years in different arms of trial by Shakhsi Niaee 2020. A trial by Ravikirti 2021 had mean age of 50.7 ± 12.7 in ivermectin and 54.2 ± 16.3 in comparator group. The mean age was 42.3 ± 12.8 in ivermectin and 38.1 ± 11.7 in control group in Krolewiecki 2020. A study by Mohan 2021 had mean age of 34.3 ± 10.45 in Ivermectin 24mg, 36.3 ± 10.54 in Ivermectin 12mg and 35.3 ± 10.52 in comparator group. Percentage of females varied from 7.5% to 61% across trials. Cumulative ivermectin dose ranged from 12mg to 189mg across trials.

Hydroxychloroquine was part of standard care in two trials (Shakhsi Niaee 2021, Ravikirti 2021) which
is not part of UK standard care. Some trials also used antivirals other than remdesivir which differ from current UK practice.

For further details, see the evidence review.

What are the main results?

**All-cause mortality – [Updated]**

Data on all-cause mortality from 6 trials (n=958) were included in the meta-analysis. The analysis found a statistically significant reduction in all-cause mortality at 28 days for ivermectin compared to standard care in people hospitalised with mild-moderate COVID-19 (RR 0.40 (CI 95% 0.20 — 0.82). However, the certainty of evidence was very low due to different standard of care within studies and risk of bias concerns. Two studies had high risk of bias due to inappropriate randomisation across control group and ivermectin group (Shakhsi Niaee 2020) and inconclusive RT-PCR reports for a high proportion of included participants (Ravikirti 2020). There were participants with negative RT-PCR included in the randomisation process and a relatively larger proportion of negative RT-PCR people were in control group, which resulted in the imbalance in randomisation (Shakhsi Niaee 2020). Due to the high risk of bias concerns, a sensitivity analysis was performed removing these two studies from the analysis. As a result, all-cause mortality was no longer statistically significant in favour of ivermectin compared with control (RR 0.45 (CI 95% 0.17 - 1.19)).

**Viral clearance at day 1-6 and day 7-14 – [Updated]**

Viral clearance has no statistically significant difference between 2-5 doses of ivermectin and control at day 1-6 [RR 0.75 (CI 95% 0.41 — 1.38)] and 7-14 [RR 1.17 (CI 95% 0.43 — 3.13]] in hospital setting.

**Duration of hospitalisation - [Updated]**

The meta-analysis did not show a statistically significant difference in duration of hospitalisation in people who received 2-5 doses of ivermectin in hospital setting (n=699; 3 studies).

**Discharge from hospital**

The meta-analysis did not show a statistically significant difference in discharge from the hospital between 2-5 doses of ivermectin and comparator group.

**Admission to ICU**

There was no statistically significant difference in admission to ICU between 2-5 doses of ivermectin and comparator group.

**Invasive mechanical ventilation**

The meta-analysis did not show a statistically significant difference in invasive mechanical ventilation between 2-5 doses of ivermectin and comparator group.

**Clinical progression**

The meta-analysis did not show a statistically significant difference in clinical progression between 2-5 doses of ivermectin and control group.

**Symptom resolution**

Data from updated meta-analysis showed no statistically significant findings for symptom resolution in people who received 2-5 doses of ivermectin compared to control group.

**Time to progression to severe disease**
No statistically significant difference was observed after the update on the meta-analysis for time to progression to severe disease.

**Serious adverse events**

Serious adverse events were non-statistically higher in 2-5 doses of ivermectin group compared to control group with, RR 3.00 (CI 95% 0.50 - 18.05) in 3 trials n=580.

**Adverse events - Updated**

A statistically significant increase was observed in adverse events in people who received 2-5 doses of ivermectin compared to those who received placebo based on data from 5 studies (n=816), with RR 2.34 (CI 95% 1.05 - 5.22).

**Our confidence in the results**

Studies are heterogeneous with both clinical and methodological diversity. Most studies were assessed as being at unclear risk of bias. Other reasons for downgrading evidence included inconsistency (for example, when point estimates varied widely between studies) and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). The variance in duration of symptoms prior to randomisation across the studies may impact the certainty in outcomes such as viral clearance. Certainty of evidence was moderate, low or very low for all outcomes.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care, standard care plus placebo, or placebo</th>
<th>Intervention Ivermectin (multiple doses)</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
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</thead>
<tbody>
<tr>
<td>All-cause mortality Day 28</td>
<td>Relative risk 0.4 (CI 95% 0.2 — 0.82) Based on data from 958 participants in 6 studies. ¹ (Randomized controlled)</td>
<td>60 per 1000 Difference: 24 per 1000 36 fewer per 1000 (CI 95% 48 fewer — 11 fewer)</td>
<td>Very low Due to very serious risk of bias and serious indirectness ²</td>
<td>Six studies found a statistically significant reduction in all-cause mortality in people who received ivermectin for 2-5 days compared to those who received control</td>
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<tr>
<td>All-cause mortality (Sensitivity analysis) Day 28</td>
<td>Relative risk 0.45 (CI 95% 0.17 — 1.19) Based on data from 726 participants in 3 studies. ³ (Randomized controlled)</td>
<td>38 per 1000 Difference: 17 per 1000 21 fewer per 1000 (CI 95% 32 fewer — 7 more)</td>
<td>Moderate Due to serious imprecision ⁴</td>
<td>Three studies found no statistically significant difference in all-cause mortality in people who received ivermectin for 2-5 days compared to those who received control</td>
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</tr>
<tr>
<td>Adverse Events</td>
<td>Relative risk 2.34 (CI 95% 1.05 — 5.22) Based on data from 816</td>
<td>42 per 1000</td>
<td>98 per 1000</td>
<td>Moderate Due to serious risk of bias ⁵</td>
<td>Five studies found a statistically significant increase in adverse events</td>
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<tr>
<td>Outcome</td>
<td>Comparator Standard care, standard care plus placebo, or placebo</td>
<td>Intervention Ivermectin (multiple doses)</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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<tr>
<td>Timeframe</td>
<td>5 (Randomized controlled)</td>
<td><strong>56 more per 1000</strong> (CI 95% 2 more — 177 more)</td>
<td>Low Due to serious imprecision and serious risk of bias</td>
<td>events in people who received ivermectin for 2-5 days compared to those who received control</td>
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<tr>
<td>Study results and measurements</td>
<td>participants in 5 studies.</td>
<td>Difference:</td>
<td></td>
<td></td>
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<tr>
<td>Serious Adverse Events</td>
<td>3 (Randomized controlled)</td>
<td><strong>9 per 1000</strong></td>
<td>Low Due to very serious risk of bias, serious precision and serious indirectness</td>
<td>Three studies found a non-statistically significant increase in serious adverse events in people who received ivermectin for 2-5 days compared to those who received control</td>
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<tr>
<td>Viral clearance 1-6 days</td>
<td>316 per 1000</td>
<td><strong>237 per 1000</strong></td>
<td>Very low</td>
<td>One study found no statistically significant difference in viral clearance at day 1-6, in people who received ivermectin for 2-5 days compared to those who received control</td>
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<td></td>
<td>Difference: 6 more per 1000 (CI 95% 1 fewer — 51 more)</td>
<td>Difference:</td>
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<td>Viral clearance 7-14 days</td>
<td>167 per 1000</td>
<td><strong>195 per 1000</strong></td>
<td>Low Due to serious risk of bias and serious imprecision</td>
<td>One study found no statistically significant difference in viral clearance at day 7-14 in people who received ivermectin for 2-5 days compared to those who received control</td>
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<td></td>
<td>Difference: 28 more per 1000 (CI 95% 95 fewer — 356 more)</td>
<td>Difference:</td>
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<tr>
<td>Discharge from hospital</td>
<td>737 per 1000</td>
<td><strong>803 per 1000</strong></td>
<td>Very low</td>
<td>One study found no statistically significant difference in proportion of people discharge from hospital who received ivermectin for 2-5 days compared to those who received control</td>
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<tr>
<td></td>
<td>Difference: 66 more per 1000 (CI 95% 81 fewer — 243 more)</td>
<td>Difference:</td>
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<tr>
<td>Invasive mechanical ventilation</td>
<td>45 per 1000</td>
<td><strong>24 per 1000</strong></td>
<td>Low Due to serious imprecision and serious risk of bias</td>
<td>Four studies found no statistically significant difference in invasive mechanical ventilation for people who received ivermectin for 2-5 days compared to those who received control</td>
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<td></td>
<td>Difference: 21 fewer per 1000 (CI 95% 35 fewer — 9 more )</td>
<td>Difference:</td>
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<tr>
<td>Outcome</td>
<td>Timeframe</td>
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<tr>
<td>Admission to ICU</td>
<td></td>
<td>Relative risk 0.81 (CI 95% 0.38 — 1.75) Based on data from 602 participants in 2 studies. (Randomized controlled)</td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>Ivermectin (multiple doses)</td>
<td>Low Due to serious risk of bias and serious imprecision</td>
</tr>
<tr>
<td>Clinical progression</td>
<td></td>
<td>Relative risk 1.25 (CI 95% 0.87 — 1.8) Based on data from 490 participants in 1 studies. (Randomized controlled)</td>
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<td></td>
<td>Low Due to serious imprecision and serious risk of bias</td>
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<tr>
<td>Symptom resolution</td>
<td></td>
<td>Relative risk 0.95 (CI 95% 0.85 — 1.06) Based on data from 597 participants in 2 studies. (Randomized controlled)</td>
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<td></td>
<td>Very low Due to serious risk of bias, imprecision and indirectness</td>
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<tr>
<td>Duration of hospitalisation</td>
<td></td>
<td>Based on data from 699 participants in 3 studies. (Randomized controlled)</td>
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<td></td>
<td>Very low Due to serious inconsistency, imprecision and risk of bias</td>
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<tr>
<td>Time to progression to severe disease</td>
<td></td>
<td>Based on data from 490 participants in 1 studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low Due to serious imprecision and serious risk of bias</td>
</tr>
</tbody>
</table>

2. **Risk of Bias:** very serious. Niaee and Ravikirti have ‘high ROB’ and Abd-Elsalam and Manomaipiboon have unclear ROB. **Inconsistency:** no serious. **Indirectness:** serious. comparator in some studies was
different to the UK standard of care. **Imprecision: no serious. Publication bias: no serious.**


4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**


6. **Risk of Bias: serious.** Lim 2022 has some concerns on ROB due to open label RCT Krolewiecki 2020 has unclear ROB due to single blinding and concerns on reporting of AEs and SAEs (Lim and Krolewiecki contribute more than 33.3% of weight in meta analysis. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** Publication bias: no serious.


8. **Risk of Bias: serious.** all three studies have some concerns on ROB. **Inconsistency: no serious.** **Indirectness: no serious. Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**


10. **Risk of Bias: very serious.** Ravikirti 2021 has moderate risk in ROB. **Inconsistency: no serious. Indirectness: serious.** Hydroxychloroquine in SOC. **Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**


12. **Risk of Bias: serious.** Mainomaipiboon 2022 is a preprint with incomplete information on pre-specified analysis . **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**


14. **Risk of Bias: serious.** Ravikirti 2021 has some concerns in ROB. **Inconsistency: no serious. Indirectness: serious.** Hydroxychloroquine in comparator. **Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**


16. **Risk of Bias: serious.** Lim contributing more than 33.3% with some concerns on ROB. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**


18. **Risk of Bias: serious.** Ravikirti 2021 contributing more than 33.3% and Lim has moderate ROB. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**


20. **Risk of Bias: serious.** Lim was an open label trial with some concerns on ROB. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**


22. **Risk of Bias: serious.** Ravikirti 2021 contributing to the meta-analysis for more than 33.3% and same
applies for Lim trial. **Inconsistency: no serious. Indirectness: serious.** Hydroxychloroquine. **Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**


24. **Risk of Bias: serious.** Lim has blinding concerns and so moderate ROB. **Inconsistency: serious.** I square greater than 50% and point estimates are not in one direction. **Indirectness: no serious. Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**


26. **Risk of Bias: serious.** Lim has some concerns on ROB, due to unblinding. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**

### References


153. Ivermectin versus standard care for COVID-19..


161. Ivermectin versus standard care for COVID-19..
Clinical question/ PICO

Population: People with hospitalised with COVID-19
Intervention: Ivermectin (Single dose)
Comparator: Standard care, standard care plus placebo, or placebo

Summary

Comparison: Ivermectin (single) vs placebo, standard care or placebo plus standard care in hospital setting

Key result

Compared to standard care, single dose of ivermectin did not reduce all-cause mortality, viral clearance, need for invasive mechanical ventilation, admission to ICU, duration of hospitalisation and symptoms of COVID-19 in people hospitalised for COVID-19.

What is the evidence informing this conclusion?

Data from 6 trials (n=598) were included in this comparison, where single dose of ivermectin was given to people hospitalised for COVID-19 (Gonzalez 2022, Mohan 2021, Niaee 2020, Shah Bukhari 2021, Shahbaznejad 2021). One new trial was included in this update (Gonzalez 2022). Studies were conducted in Iran, India, Mexico and Pakistan. There were different dosage regimen within two trials by Mohan 2021 and Niaee 2020; less than 400 micrograms/kg (micrograms/kg) and more than 400 micrograms/kg. Other trials administered one or the other dose regimen.

Subgroup analyses were conducted based on less than 400micrograms/kg and greater than 400 micrograms/kg to highlight the differences in COVID-19 outcomes. For further details, please see evidence review.

Publication status

All trials were full peer-reviewed publications.

Study characteristics

The mean age varied from 34.3 to 48.0 in 6 trials in this comparison except for Shakhsi Niaee 2021, where median age varied from 42 to 70 across multiple arms of the trial. The proportion of females varied from 7.5% to 61% in the trials. People with mild to moderate COVID-19 were included in Kishoria 2020, Mohan 2021, Shahbaznejad 2021, Shakhsi Niaee 2020. A study by Gonzalez 2022 recruited patients with severe COVID-19. Standard care varied between trials. Hydroxychloroquine was administered in comparator group in Kishoria 2020, Shakhsi Niaee 2020 and Shahbaznejad 2021. Placebo was given to control group in Mohan 2021 and calcium citrate as placebo in Gonzalez 2022.

The mean age was 39.5 in ivermectin group and 37.0 in control group in trial by Kishoria 2020. Mohan 2021 had mean age of 34.3 in >400ug/kg ivermectin and 36.3 in <400ug/kg ivermectin, and control group 35.3, while average age was above 50 years in Gonzalez 2022. Cumulative ivermectin dose ranged from 12mg to 25mg across trials.

For further details, see the evidence review.

What are the main results?

All-cause mortality
A meta-analysis of five studies showed no statistically significant difference in all-cause mortality in people who received single dose of ivermectin compared to control group in hospital setting, RR 0.26 (CI 95% 0.04 - 1.79). Data from 3 studies were included (n=345).

**Viral clearance day 1-6 and day 7-14 - [Updated]**

No statistically significant difference was observed between single dose ivermectin and control group in viral clearance at day 1-6, viral clearance day 7-14 based on data from 4 trials.

**Discharge from hospital**

No statistically significant difference was observed in discharge from hospital between single dose ivermectin group and control group.

**Need for supplemental oxygen**

No statistically significant difference was observed in need for supplemental oxygen between single dose ivermectin and comparator group.

**Invasive mechanical ventilation**

No statistically significant difference was observed for invasive mechanical ventilation between single dose of ivermectin and control group.

**Clinical progression of COVID-19 severity**

No statistically significant difference was observed for clinical progression of COVID-19 between single dose of ivermectin and control group.

**Clinical improvement**

No statistically significant difference was observed in clinical improvement between single dose of ivermectin and control group.

**Duration of hospitalisation**

No difference was observed for duration of hospitalisation between single dose ivermectin group and control group.

**Time to resolution of symptoms**

No statistically significant difference was observed in time to resolution of symptoms of COVID-19 between single dose ivermectin group and control group.

**Duration of symptoms**

A statistically significant reduction was observed in duration of symptoms in single dose ivermectin group compared to control group (RR -1.00(CI 95% -1.14 to -0.86)). However, it is worth noting that only one study reported duration of symptoms n=69 (Shahbaznejad 2021) which had unclear risk of bias, with incomplete information on randomisation and allocation procedure.

**Adverse events**

Adverse events had no statistically significant difference between single dose ivermectin and control group, RR 1.21 (CI 95% 0.49 - 2.97). Data from 4 trials were included (n=307)

**Our confidence in the results**

Studies are heterogenous with both clinical and methodological diversity. Most studies were assessed as being at unclear risk of bias. Other reasons for downgrading evidence included inconsistency (for
example, when point estimates varied widely between studies) and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). The variance in duration of symptoms prior to randomisation across the studies may impact the certainty in outcomes such as viral clearance. Certainty of evidence was low and very low for majority of outcomes and moderate for one outcome.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality Day 28</td>
<td>Relative risk 0.26 (CI 95% 0.04 — 1.79) Based on data from 345 participants in 3 studies.</td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>Ivermectin (Single dose)</td>
<td>Low Due to serious imprecision and serious indirectness</td>
<td>Five studies found no statistically significant difference in all-cause mortality in people who received single dose of ivermectin compared to those who received control</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Relative risk 1.21 (CI 95% 0.49 — 2.97) Based on data from 307 participants in 4 studies.</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias, imprecision and indirectness</td>
<td>Four studies found no statistically significant difference in adverse events in people who received single dose of ivermectin compared to those who received control</td>
</tr>
<tr>
<td>Viral clearance 1-6 days</td>
<td>Relative risk 0.91 (CI 95% 0.41 — 2.01) Based on data from 32 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias, imprecision and indirectness</td>
<td>One study found no statistically significant difference in viral clearance at day 1-6 in people who received single dose of ivermectin compared to those who received control</td>
</tr>
<tr>
<td>Viral clearance 7-14 days</td>
<td>Relative risk 1.41 (CI 95% 0.84 — 2.35) Based on data from 200 participants in 3 studies.</td>
<td></td>
<td></td>
<td>Low Due to serious risk of bias and serious imprecision</td>
<td>Three studies found no statistically significant difference in viral clearance at day 7-14 in people who received single dose of ivermectin compared to those who received control</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator Standard care, standard care plus placebo, or placebo</td>
<td>Intervention Ivermectin (Single dose)</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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</tr>
<tr>
<td>Discharge from hospital</td>
<td>Relative risk 1.04 (CI 95% 0.94 — 1.14) Based on data from 236 participants in 4 studies. 9 (Randomized controlled)</td>
<td>782 per 1000 Difference: 813 per 1000 31 more per 1000 (CI 95% 47 fewer — 109 more)</td>
<td>Moderate Due to serious imprecision 10</td>
<td>Four studies found no statistically significant difference in hospital discharge in people who received single dose of ivermectin compared to those who received control</td>
<td></td>
</tr>
<tr>
<td>Supplemental oxygen</td>
<td>Relative risk 1.08 (CI 95% 0.5 — 2.32) Based on data from 69 participants in 1 studies. 11 (Randomized controlled)</td>
<td>265 per 1000 Difference: 286 per 1000 21 more per 1000 (CI 95% 132 fewer — 350 more)</td>
<td>Very low Due to serious risk of bias, imprecision and indirectness 12</td>
<td>One study found no statistically significant difference in supplemental oxygen in people who received single dose of ivermectin compared to those who received control</td>
<td></td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>Relative risk 0.97 (CI 95% 0.09 — 9.98) Based on data from 169 participants in 3 studies. 13 (Randomized controlled)</td>
<td>29 per 1000 Difference: 28 per 1000 1 fewer per 1000 (CI 95% 26 fewer — 260 more)</td>
<td>Very low Due to serious risk of bias, imprecision and indirectness 14</td>
<td>Three studies found no statistically significant difference in invasive mechanical ventilation in people who received single dose of ivermectin compared to those who received control</td>
<td></td>
</tr>
<tr>
<td>Clinical progression</td>
<td>Relative risk 0.56 (CI 95% 0.17 — 1.88) Based on data from 125 participants in 2 studies. 15 (Randomized controlled)</td>
<td>111 per 1000 Difference: 62 per 1000 49 fewer per 1000 (CI 95% 92 fewer — 98 more)</td>
<td>Low Due to serious risk of bias and serious imprecision 16</td>
<td>Two studies found no statistically significant difference in clinical progression of COVID-19 in people who received single dose of ivermectin compared to those who received control</td>
<td></td>
</tr>
<tr>
<td>Clinical Improvement (2 or more decrease WHO)</td>
<td>Relative risk 1.07 (CI 95% 0.94 — 1.22) Based on data from 125 participants in 2 studies. 17 (Randomized controlled)</td>
<td>867 per 1000 Difference: 928 per 1000 61 more per 1000 (CI 95% 52 fewer — 191 more)</td>
<td>Low Due to serious risk of bias and serious imprecision 18</td>
<td>Two studies found no statistically significant difference in clinical improvement of COVID-19 with 2 or more point decrease in WHO scale in people who received single dose of ivermectin compared to those who received control</td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>Based on data from 69 participants in 1 studies.</td>
<td>Difference: MD 1 lower (CI 95% 1.14 lower — 0.86 lower)</td>
<td>Low Due to serious risk of bias and indirectness 20</td>
<td>One study found statistically significant decrease in duration of symptoms in people</td>
<td></td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard care, standard care plus placebo, or placebo</td>
<td>Intervention Ivermectin (Single dose)</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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<tr>
<td>Duration of hospitalisation</td>
<td>Based on data from 69 participants in 1 studies.</td>
<td>(Randomized controlled)</td>
<td>Difference:</td>
<td>MD 1.3 lower ( CI 95% 2.81 lower — 0.21 higher )</td>
<td>Very low Due to serious risk of bias, imprecision and indirectness</td>
</tr>
<tr>
<td>One study found no statistically significant difference in duration of hospital stay in people who received single dose of ivermectin compared to those who received control</td>
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<tr>
<td>Time to recovery (resolution of symptoms)</td>
<td>Based on data from 125 participants in 2 studies.</td>
<td>(Randomized controlled)</td>
<td>Difference:</td>
<td>MD 0.06 lower ( CI 95% 1.08 lower — 0.96 higher )</td>
<td>Low Due to serious risk of bias and serious imprecision</td>
</tr>
<tr>
<td>Two studies found no statistically significant difference in time to resolution of COVID-19 symptoms in people who received single dose of ivermectin compared to those who received control</td>
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</tbody>
</table>

2. **Inconsistency: no serious.** I square greater than 50% but point estimates are in same direction. **Indirectness: serious.** hydroxychloroquine. **Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**  
4. **Risk of Bias: serious.** Mohan study had ROB rating as uncertain. **Inconsistency: no serious.** **Indirectness: serious.** Differences between the intervention/comparator of interest and those studied. **Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**  
5. Systematic review [153]. **Baseline/comparator**: Control arm of reference used for intervention.  
6. **Risk of Bias: serious.** Kishoria 2020 - uncertain ROB. **Inconsistency: no serious.** **Indirectness: serious.** SOC. **Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**  
7. Systematic review [153]. **Baseline/comparator**: Control arm of reference used for intervention.  
8. **Risk of Bias: serious.** Mohan contributing more than 33.3% with 'uncertain ROB'. **Inconsistency: no serious.** I square greater than 50% but all point estimates are in same direction. **Indirectness: no serious.** **Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**  
10. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: serious.** CIs cross line of no
effect. **Publication bias:** no serious.


12. **Risk of Bias:** serious. Shahbaznejad 2021 - ROB unclear. **Inconsistency:** no serious. **Indirectness:** serious. **SOC.** **Imprecision:** serious. CIs cross line of no effect. **Publication bias:** no serious.


14. **Risk of Bias:** serious. Shahbaznejad contributing more than 33.3% and has uncertain ROB. **Inconsistency:** no serious. **Indirectness:** serious. **SOC.** **Imprecision:** serious. CIs cross line of no effect. **Publication bias:** no serious.


16. **Risk of Bias:** serious. Mohan - ROB Uncertain - contributing more 33.3%. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. CIs cross line of no effect. **Publication bias:** no serious.

17. Systematic review [153] . **Baseline/comparator:** Control arm of reference used for intervention.

18. **Risk of Bias:** serious. Mohan - Unclear ROB - contributing more than 33.3%. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. CIs cross line of no effect. **Publication bias:** no serious.


20. **Risk of Bias:** serious. Shahbaznejad - Uncertain ROB. **Inconsistency:** no serious. **Indirectness:** serious. **SOC.** **Imprecision:** no serious. **Publication bias:** no serious.


22. **Risk of Bias:** serious. Shehbaznejad - Unclear ROB. **Inconsistency:** no serious. **Indirectness:** serious. **SOC.** **Imprecision:** serious. CIs cross line of no effect. **Publication bias:** no serious.


24. **Risk of Bias:** serious. Mohan - Uncertain ROB. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. CIs cross line of no effect. **Publication bias:** no serious.

References


Clinical question/ PICO

- **Population:** People with COVID-19 (Community)
- **Intervention:** Ivermectin (multiple doses)
- **Comparator:** Standard care, standard care plus placebo, or placebo

Summary

**Comparison:** Ivermectin (multiple doses) vs placebo, standard care or placebo plus standard care in community setting

**Key results**

There remains a high degree of uncertainty over whether multiple doses of ivermectin is more effective than placebo, placebo plus standard care or standard care for management of COVID-19 in the community.

**What is the evidence informing this conclusion?**

Evidence comes from 7 randomised controlled trials that compared ivermectin with standard care, placebo or standard care plus placebo in 4769 people with COVID-19 managed in the community (Abbas 2022, Biber 2021, Buonfrate 2022, Chachar 2020, Lopez-Medina 2021, Reis 2022 and Vallejos 2021). Three new trials were added in this update (Reis 2022, Buonfrate 2022 and Abbas 2022). Studies were conducted in Argentina, Brazil, China, Colombia, Italy and Israel.

**Publication status**

One study was only available as a preprint (Biber 2021) posted to medRxiv on May 31, 2021, has therefore not been peer reviewed.

**Study characteristics**

The mean or median age in the studies ranges between 37 and 49 years and the proportion of women ranged between 16 and 58%. The severity of COVID-19 across the studies was mild to moderate. All studies included people with mild to moderate or asymptomatic COVID-19, generally not requiring supplemental oxygen. The majority of the data are from the TOGETHER trial (Reis 2022) which included 3515 people who had at least one risk factor for COVID-19 disease progression. The remaining studies were either low risk for COVID-19 disease progression or did not report this data.

Duration of symptoms prior to randomisation varied across the studies ranging between 1 and 7 days. Standard care within the trials varied slightly across the studies but were not too dissimilar from UK
standard care. Dose and duration of ivermectin varied across the studies. Some studies used 200 – 300 micrograms per kg or 12mg as the dosage whereas other studies used higher doses of 400-1200 micrograms per kg. The cumulative ivermectin dose ranged from 24mg to 378mg among trials. The duration of treatment ranged between 2 and 5 days.

Due to the variability in dosage, subgroup analyses were conducted where the data allowed. For further details, please see evidence review.

Children and pregnant women were excluded from the trials.

For further details, see the evidence review.

What are the main results?

Discontinuation of treatment due to adverse events

Discontinuation of treatment due to adverse events was significantly higher with 2-5 doses of ivermectin compared with control. The relative risk is 2.97 (CI 95% 1.10 — 8.02) based on data from 2 trials (n=899).

All-cause mortality

The evidence suggests that, compared with control groups in people with COVID-19 in the community, ivermectin administered for 2 to 5 days does not result in statistically significant differences in all-cause mortality. The relative risk is 1.46 (CI 95% 0.87 — 2.44) based on data from 4 trials (n=2159).

Hospitalisation

There was no statistically significant difference between 2-5 doses of ivermectin and control group in community setting for hospitalisation outcome.

Clinical recovery

No statistically significant findings were observed for clinical recovery between 2-5 doses of ivermectin and control group.

Viral clearance

Viral clearance did not statistically significant difference between 2-5 doses of ivermectin and control group.

Adverse events

There was no statistically significant difference between adverse events in people who received 2-5 doses of ivermectin compared to those who received control in community setting.

Our confidence in the results

Studies are heterogenous with both clinical and methodological diversity. Most studies were assessed as being at unclear risk of bias. Other reasons for downgrading evidence included inconsistency (for example, when point estimates varied widely between studies) and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). The variance in duration of symptoms prior to randomisation across the studies may impact the certainty in outcomes such as viral clearance. Certainty of evidence was moderate, low or very low for all outcomes.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality (day 28) Day 28</td>
<td></td>
<td>Relative risk 1.46 (CI 95% 0.87 — 2.44) Based on data from 2,159 participants in 4 studies.</td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>24 per 1000</td>
<td>Moderate Due to serious imprecision 2</td>
<td>Four studies found no statistically significant difference in all-cause mortality in people who received ivermectin for 2-5 days compared to those who received control</td>
</tr>
<tr>
<td>Serious adverse events End of follow-up</td>
<td></td>
<td>Relative risk 0.88 (CI 95% 0.64 — 1.2) Based on data from 2,546 participants in 6 studies.</td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>60 per 1000</td>
<td>Moderate Due to serious imprecision 4</td>
<td>Six studies found no statistically significant difference in serious adverse events in people who received ivermectin for 2-5 days compared to those who received control</td>
</tr>
<tr>
<td>Viral clearance (1-6 days)</td>
<td></td>
<td>Relative risk 0.74 (CI 95% 0.36 — 1.54) Based on data from 318 participants in 1 studies.</td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>100 per 1000</td>
<td>Moderate Due to serious imprecision 6</td>
<td>One study found no statistically significant difference in viral clearance at day 1-6 in people who received ivermectin for 2-5 days compared to those who received control</td>
</tr>
<tr>
<td>Viral clearance (7-14 days)</td>
<td></td>
<td>Relative risk 1 (CI 95% 0.91 — 1.08) Based on data from 984 participants in 5 studies.</td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>632 per 1000</td>
<td>Low Due to serious inconsistency and serious imprecision 8</td>
<td>Five studies found no statistically significant difference in viral clearance at day 7-14 in people who received ivermectin for 2-5 days compared to those who received control</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td></td>
<td>Relative risk 0.82 (CI 95% 0.48 — 1.42) Based on data from 1,859 participants in 2 studies.</td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>30 per 1000</td>
<td>Moderate Due to serious imprecision 10</td>
<td>Two studies found no statistically significant difference in invasive mechanical ventilation in people who received ivermectin for 2-5 days compared to those who received placebo</td>
</tr>
<tr>
<td>Supplemental oxygen</td>
<td></td>
<td>Relative risk 0.3 (CI 95% 0.01 — 7.14) Based on data from 89 participants in 1 studies.</td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>24 per 1000</td>
<td>Very low Due to serious risk of bias and very serious imprecision, 12</td>
<td>One study found no statistically significant difference in need for supplemental oxygen in people who received ivermectin for 2-5 days compared to those who received placebo</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator Standard care, standard care plus placebo, or placebo</td>
<td>Intervention Ivermectin (multiple doses)</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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<tr>
<td>Hospitalisation</td>
<td></td>
<td>Standard care, standard care plus placebo, or placebo</td>
<td>ivermectin for 2-5 days compared to those who received control</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Relative risk 0.81 (CI 95% 0.63 — 1.05) Based on data from 2,035 participants in 5 studies.</td>
<td>117 per 1000 Difference: 95 per 1000 22 fewer per 1000 (CI 95% 43 fewer — 6 more ) Moderate Due to serious imprecision 14</td>
<td>Five studies found no statistically significant difference in hospitalisation in people who received ivermectin for 2-5 days compared to those who received control</td>
<td></td>
<td></td>
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<tr>
<td>Clinical deterioration</td>
<td></td>
<td>Relative risk 0.58 (CI 95% 0.25 — 1.36) Based on data from 600 participants in 2 studies.</td>
<td>47 per 1000 Difference: 27 per 1000 20 fewer per 1000 (CI 95% 35 fewer — 17 more ) Very low Due to serious imprecision and very serious risk of bias 16</td>
<td>Two studies found no statistically significant difference in clinical deterioration of COVID-19 in people who received ivermectin for 2-5 days compared to those who received control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to adverse event</td>
<td></td>
<td>Relative risk 2.97 (CI 95% 1.1 — 8.02) Based on data from 899 participants in 2 studies.</td>
<td>11 per 1000 Difference: 33 per 1000 22 more per 1000 (CI 95% 1 more — 77 more ) Low Due to very serious risk of bias and serious imprecision 18</td>
<td>Two studies found statistically significant increase in discontinuation due to adverse events in people who received ivermectin for 2-5 days compared to those who received control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events End of follow-up</td>
<td></td>
<td>Relative risk 0.88 (CI 95% 0.75 — 1.03) Based on data from 2,373 participants in 4 studies.</td>
<td>257 per 1000 Difference: 226 per 1000 31 fewer per 1000 (CI 95% 64 fewer — 8 more ) Very low Due to very serious risk of bias and serious imprecision 20</td>
<td>Four studies found no statistically significant difference in adverse events in people who received ivermectin for 2-5 days compared to those who received control</td>
<td></td>
<td></td>
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<tr>
<td>Clinical recovery 21 days</td>
<td></td>
<td>Relative risk 1.1 (CI 95% 0.97 — 1.24) Based on data from 650 participants in 3 studies.</td>
<td>712 per 1000 Difference: 783 per 1000 71 more per 1000 (CI 95% 21 fewer — 171 more ) Very low Due to very serious risk of bias and serious imprecision 22</td>
<td>Three studies found no statistically significant difference in clinical recovery of COVID-19 in people who received ivermectin for 2-5 days compared to those who received control</td>
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</tbody>
</table>

2021. **Baseline/comparator:** Control arm of reference used for intervention.

2. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. CIs cross line of no effect. **Publication bias:** no serious.

3. Systematic review [153]. **Baseline/comparator:** Control arm of reference used for intervention.

4. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. CIs cross line of no effect. **Publication bias:** no serious.

5. Systematic review [153] with included studies: Reis 2022 TOGETHER. **Baseline/comparator:** Control arm of reference used for intervention.

6. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. CIs cross line of no effect. **Publication bias:** no serious.


8. **Inconsistency:** serious. I square greater than 75% time since onset of symptoms was different across the trials. **Indirectness:** no serious. **Imprecision:** serious. CIs cross line of no effect. **Publication bias:** no serious.

9. Systematic review [153]. **Baseline/comparator:** Control arm of reference used for intervention.

10. **Inconsistency:** no serious. **Indirectness:** no serious. High risk population in Reis 2022. **Imprecision:** serious. CIs cross line of no effect. **Publication bias:** no serious.


12. **Risk of Bias:** serious. Biber study has unclear risk of bias due to insufficient information on: if analysed as per protocol analyses and involved retrospective data registry. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. CIs cross line of no effect; less than 300 people contributing to the outcome. **Publication bias:** no serious.


14. **Inconsistency:** no serious. time since onset of symptoms was different across the trials. **Indirectness:** no serious. **Imprecision:** serious. CIs cross line of no effect. **Publication bias:** no serious.


16. **Risk of Bias:** very serious. Lopez 2021 has high ROB due to incomplete information on blinding and missing outcome data. Abbas 2022 has moderate ROB due to insufficient information on pre-specified analysis plan. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. CIs cross line of no effect. **Publication bias:** no serious.


18. **Risk of Bias:** very serious. Lopez 2021 has high risk of bias due to insufficient information on blinding and prespecified analysis plan and is contributing 100% to the analysis. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** no serious. **Publication bias:** no serious.


20. **Risk of Bias:** very serious. Lopez 2021 has high ROB due to incomplete information on blinding and missing outcome data. Lopez contributing more than 33.3% to the analysis of this outcome. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. CIs cross line of no effect. **Publication bias:** no serious.

22. **Risk of Bias: very serious.** Lopez 2021 has high ROB due to incomplete information on blinding and missing outcome data. Abbas 2022 has moderate ROB and provides no information on prespecified analyses plan Chachar 2020 Non-blinded study with subjective outcome. Recording of outcomes factors was not specified, potential for selective reporting. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**

### References


### Clinical question/ PICO

- **Population:** People with COVID-19 (Community)
- **Intervention:** Ivermectin (Single dose)
- **Comparator:** Standard care, standard care plus placebo, or placebo

### Summary

**Comparison:** Ivermectin (single dose) vs placebo, standard care or placebo plus standard care in community setting
Key results
There remains a high degree of uncertainty over whether single dose of ivermectin is more effective than placebo, placebo plus standard care or standard care for management of COVID-19 in the community.

What is the evidence informing this conclusion?
Evidence comes from 2 randomised controlled trials that compared ivermectin with standard care, placebo or standard care plus placebo in 64 people with COVID-19 managed in the community (Podder 2020, Chaccour 2020). Studies were conducted in Bangladesh and Spain.

Publication status
Both trials were published.

Study characteristics
Podder 2020 included people with mild to moderate COVID-19 and Chaccour 2020 had people with non-severe COVID-19. Both trials included people with confirmed positive RT-PCR test for SARS-CoV-2. Placebo was used as comparator in Chaccour 2020, while symptomatic treatment including antipyretics, cough suppressants, capsule doxycycline were administered to the comparator group in Podder 2020. Single dose of 400micrograms/kg ivermectin was used in intervention group by Chaccour 2020 and single dose of 200 micrograms/kg ivermectin by Podder 2020. The cumulative ivermectin dose was 12mg to 25mg in both trials.

Median age was 26 in both intervention and control group in Chaccour 2020. Mean age was 38.4 in ivermectin group and 39.9 in control group in Podder 2020. 28.15 were females in ivermectin group and 30.0% females in comparator group in Podder 2020, while Chaccour 2020 had 42% females in ivermectin and 58% in control group.

For further details, see the evidence review.

What are the main results?

Viral clearance at day 7-14
There was no statistically significant difference in viral clearance at day 7-14 between single dose of ivermectin and control group in community setting. It was based on data from 1 study (n=40).

Adverse events
No statistically significant difference was observed for adverse events in people who received single dose of ivermectin compared to standard of care or control in the community. This outcome was based on data from 1 study (n=24).

Our confidence in the results
Podder 2020 was assessed as high risk of bias due to lack of blinding and inappropriate reporting of outcomes. Chaccour 2020 was assessed as unclear risk of bias due to incomplete information on blinding.

Due to serious risk of bias and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect), both outcomes were marked as ‘low certainty’ of evidence.
<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard care, standard care plus placebo, or placebo</th>
<th>Intervention Ivermectin (Single dose)</th>
<th>Certainty of Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral clearance (7-14 days)</td>
<td>Relative risk 0.95 (CI 95% 0.79 — 1.13) Based on data from 40 participants in 1 studies. ^1 (Randomized controlled)</td>
<td>950 per 1000 Difference: 903 per 1000 47 fewer per 1000 (CI 95% 199 fewer — 124 more)</td>
<td>Low Due to serious risk of bias and serious imprecision ^2</td>
<td>One study found no statistically significant difference in viral clearance at day 7-14 in people who received single dose of ivermectin compared to those who received control</td>
<td></td>
</tr>
<tr>
<td>Adverse events (end of follow up)</td>
<td>Relative risk 1 (CI 95% 0.39 — 2.58) Based on data from 24 participants in 1 studies. ^3 (Randomized controlled)</td>
<td>417 per 1000 Difference: 417 per 1000 0 fewer per 1000 (CI 95% 254 fewer — 659 more)</td>
<td>Low Due to serious risk of bias and serious imprecision ^4</td>
<td>One study found no statistically significant difference in adverse events in people who received single dose of ivermectin compared to those who received control</td>
<td></td>
</tr>
</tbody>
</table>

2. **Risk of Bias: serious.** Podder 2020 study has high risk of bias; no information on missing data and per-protocol analysis plan. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**
4. **Risk of Bias: serious.** Chaccour 2020 has unclear ROB, with incomplete information on blinding. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: serious.** CIs cross line of no effect. **Publication bias: no serious.**

**References**


72. Podder CSP, Chowdhury N, Sina MI, UI Haque WMM. Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study. IMC Journal of Medical Science 2021;14(2). **Website**


**7.14 Vitamin D**
Evidence to decision

Benefits and harms

All included trials compared the effects of vitamin D for treating COVID-19 with placebo or standard care. The trials included diverse populations with different COVID-19 severity, and used varying dosages of vitamin D. All trials compared the effects of vitamin D3 and not D2 for treating COVID-19.

The evidence shows no statistically significant difference in mortality, admissions to intensive care, hospitalisation or oxygen therapy in people having vitamin D compared with standard care or placebo. The panel noted that the certainty of the evidence for mortality and oxygen therapy was moderate, although certainty was lower for the other outcomes. The panel noted a non-statistically significant reduction in progression to mechanical ventilation (relative risk 0.55, 95% confidence interval 0.31 to 1.00) (Mariani 2022, Murai 2021 and Maghbooli 2021). While this result was at low risk for bias, the panel did not consider the result to be certain enough to justify recommending vitamin D.

The panel noted no statistically significant difference in presence of symptoms or positive polymerase chain reaction tests at 7 and 14 days. But in 1 study with 40 people there was increased SARS-CoV-2 negativity within 3 weeks (Rastogi 2020). This outcome was downgraded because of very serious risk of bias, and the panel did not think it represented a meaningful benefit, or that it could be attributed to treatment with vitamin D.

The panel were also presented with evidence on subgroup effects of vitamin D. These analyses show no statistically significant effect on admission to intensive care or mechanical ventilation of different numbers of doses (single or multiple), baseline vitamin D levels or COVID-19 severity. A meta-analysis of 5 studies (Cannata-Andia 2022, Mariani 2022, Murai 2021, Entrenas Castillo 2020, Maghbooli 2021) suggested an association between multiple doses of vitamin D and reduced mortality compared with single doses. But the difference was not statistically significant.

The panel had concerns about adverse events with the high doses of vitamin D used in the studies. Only 1 study reported adverse events as an outcome but showed no statistically significant difference between vitamin D and placebo. The panel acknowledged that there are some well-known adverse effects of vitamin D overdose, including raised concentrations of calcium and phosphate in plasma and urine, and nausea and vomiting (for more details, please see the BNF). They agreed that treating COVID-19 with vitamin D at the dosages used in the included studies could have potential harms, and that more research is needed in this area.

The panel noted that the study populations did not include pregnant women or older populations who may be at more risk of severe COVID-19 outcomes. They also did not include children and young people under 18 years. So, they agreed that more research is also needed in the area.

Certainty of the Evidence

Evidence comes from 7 randomised controlled trials (Cannata-Andia 2022, Entrenas Castillo 2020,
All of the outcomes from the trials were rated as moderate to very low certainty, but the panel agreed that there was no clear evidence of benefit.

Outcomes from Maghbooli 2021, Mariani 2022 and Murai 2021 were assessed to be at low risk of bias. Outcomes from Cannata-Andia 2022 and Entrenas Castillo 2020 were downgraded because of insufficient detail on randomisation or the allocation process. Outcomes from Rastogi 2020 and Sanchez-Zuno 2021 were rated as at high risk of bias because neither trial reported details of study design and analysis plans.

The panel decided not to downgrade for indirectness despite reported vitamin D deficiency in the studies. This was because the deficiency threshold for vitamin D reported in the studies differed from the UK threshold. Vitamin D is a negative acute-phase reactant. This means its serum concentration falls during a systemic inflammatory response, which may occur with severe COVID-19. But, the panel noted that the potential mechanism of action of vitamin D in the context of COVID-19 is unknown. The effect of deficiency on COVID-19 outcomes is also unclear.

Overall, the panel noted that the evidence comes from diverse populations with varying care regimens and vitamin D doses. As such, evidence from the trials may not be generalisable to the UK.

The panel discussed the populations in different ongoing trials and noted that more research into specific subgroups of interest (for example, older people, children and pregnant women) could help determine the effects of vitamin D.

Values and preferences

The panel discussed that vitamin D3 (coleciferylol) supplements can be derived from an animal source. They noted that care providers need to consider people’s concerns about using animal products because of a religious or ethical belief when they are discussing vitamin D products and their provision.

Resources

Vitamin D supplements are widely available in the NHS and public stores.

The panel discussed any resource implications that vitamin D provision for treating COVID-19 might have. They recognised that the doses from the trials are substantially higher than those used for daily supplementation in the UK. They agreed that, because vitamin D is not being recommended for this, there would be no resource implications.

Equity

The panel recognised the existing inequalities in vitamin D status, including those relating to location, health and family background. They noted that people who have dark skin and people who have low or no sunlight exposure, including people who spend more time indoors because of frailty or disability, are more likely to have vitamin D deficiency. They also acknowledged that people with dark skin are at greater risk of infection by SARS-CoV-2.

The panel also discussed that there is a lack of evidence on the effectiveness of vitamin D for COVID-19 in children, older people and when pregnant or breastfeeding, so the effect of treatment in these groups cannot be determined.
Rationale

The panel agreed that the clinical-effectiveness evidence for vitamin D for treating COVID-19 is uncertain, but suggests that there is no clear evidence of benefit. The studies included diverse populations with different COVID-19 severity, and used varying dosages of vitamin D and definitions of standard care. This means the evidence may not be generalisable to the UK.

The panel noted that the daily doses used in the studies were far higher than the standard doses used to prevent or treat vitamin D deficiency in the UK. They also noted that there was limited evidence from the studies on the adverse effects of these doses of vitamin D. The panel pointed out the potential adverse effects of a vitamin D overdose, such as raised plasma and urine concentrations of calcium and phosphate, and nausea and vomiting (see the BNF for more details on adverse effects).

The panel highlighted that existing guidance recommends taking vitamin D to maintain muscle and bone health. They agreed that vitamin D is important and well established for this.

The panel agreed that, until there is more evidence on the effects of vitamin D for treating COVID-19, it should only be used for treating COVID-19 as part of a clinical trial.

Acceptability

The acceptability of vitamin D for treating COVID-19 has not formed part of the evidence review. The panel believed that the lack of effect against COVID-19 shown in the studies and the limited information about adverse events may reduce the acceptability of vitamin D for treating COVID-19.

Feasibility

Vitamin D does not have marketing authorisation for the treatment of COVID-19.

Clinical question/ PICO

- **Population:** People with COVID-19
- **Intervention:** Vitamin D
- **Comparator:** Placebo or standard care

Summary

Key results

There remains a high degree of uncertainty over whether vitamin D supplementation is more effective than placebo plus standard care or standard care for treating COVID-19. But, there is currently no clear evidence of benefit.

What is the evidence informing this conclusion?

This is an update to the December 2020 review. During this update, we have added 6 extra studies (Cannata-Andia 2022, Maghbooli 2021, Mariani 2022, Murai 2021, Rastogi 2020, Sanchez-Zuno 2021) and retained the existing study (Entrenas Castillo 2020).

Evidence comes from 7 randomised controlled trials that compared vitamin D supplementation with standard care (Cannata-Andia 2022, Entrenas-Castillo 2020, Maghbooli 2021, Rastogi 2020) or standard care plus placebo (Murai 2021, Mariani 2022 and Sanchez-Zuno 2021) in 1,262 people with COVID-19. Studies were conducted in Argentina, Brazil, Chile, Guatemala, India, Iran Mexico and
Switzerland. All the studies were conducted in a hospital setting, regardless of disease severity.

All the trials included vitamin D doses higher than 800 IU/day. Three studies used a single-dose intervention of vitamin D (Cannata-Andia 2022, Mariani 2022 and Murai 2021). The remaining studies used a multiple-dose regimen (Entrenas-Castillo 2020, Maghbooli 2021, Rastogi 2020 and Sanchez-Zuno 2021). Two studies included only participants with vitamin D deficiency at baseline, defined as <75nmol/L (Maghbooli 2021) and <50nmol/L (Rastogi 2020) in the studies. It should be noted that these levels are not usually considered deficient in the UK.

Due to variability in dosage, disease severity and baseline vitamin D status, subgroup analyses were carried out to measure the effects of vitamin D supplementation.

Publication status

All studies are peer-reviewed manuscripts.

Study characteristics

The mean or median age in the studies ranged between 43 and 58 years and the proportion of men ranged between 50% and 65%. The severity of COVID-19 in 3 of the studies was reported as moderate-severe (Cannata-Andia 2022, Maghbooli 2021 and Murai 2021), mild to moderate in Mariani (2022) and asymptomatic-mildly symptomatic in Rastogi (2020) and Sanchez-Zuno (2021). Disease severity in one study was not clear (Entrenas-Castillo 2020).

The dose and duration of vitamin D supplementation varied across the trials. Three studies included a single dose of vitamin D of 100,000 IU (Cannata-Andia 2022), 200,000 IU (Murai 2021) or 500,000 IU (Mariani 2022). The remaining studies used multiple doses between 1000 IU/day and 60,000 IU/day for a duration ranging from 7 to 60 days.

Due to the variability in dosage, disease severity and baseline vitamin D concentration, subgroup analyses were conducted where the data allowed.

Children under 18 were excluded from the trials.

For further details, see the evidence review.

What are the main results?

Vitamin D supplementation does not result in statistically significant differences in mortality, ICU admission, requirement for oxygen therapy, adverse events, symptoms at day 7 or 14, PCR test results at day 7 or 14, or duration of: ICU stay, hospitalisation or mechanical ventilation.

Data on adverse events (for example cardiovascular or gastrointestinal serious adverse events) was only reported in one study (Mariani 2022).

The evidence suggests that, compared with control groups, there was a non-statistically significant reduction in mechanical ventilation and an increase in negative COVID-19 test results within 3 weeks in the vitamin D group.

Our confidence in the results

Overall, the studies are heterogeneous with both clinical and methodological diversity. Most studies were assessed to have some concerns with risk of bias due to insufficient reporting around randomisation and allocation and a lack of blinding in studies which did not use placebo.

Other reasons for downgrading evidence included inconsistency (for example, when point estimates varied widely between studies) and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). The
variance in the duration of symptoms prior to randomisation across the studies may impact the certainty of outcomes as well as the effect of standard care regimens. The certainty of the evidence was moderate to very low for most outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive PCR test - Day 7</td>
<td>Relative risk 0.91 (CI 95% 0.54 — 1.53) Based on data from 42 participants in 1 studies. ¹ (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Vitamin D supplementation</td>
<td>Very low Due to very serious risk of bias, Due to very serious imprecision ²</td>
<td>1 study found no statistically significant difference in the number of positive PCR tests at day 7 in people who received vitamin D compared with control.</td>
</tr>
<tr>
<td>ICU admission</td>
<td>Relative risk 0.65 (CI 95% 0.37 — 1.15) Based on data from 1,180 participants in 5 studies. ³ (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Vitamin D supplementation</td>
<td>Low Due to serious risk of bias, Due to serious imprecision ⁴</td>
<td>5 studies found no statistically significant difference in ICU admission in people who received vitamin D compared with control.</td>
</tr>
<tr>
<td>Mortality</td>
<td>Relative risk 1.23 (CI 95% 0.78 — 1.94) Based on data from 1,180 participants in 5 studies. ⁵ (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Vitamin D supplementation</td>
<td>Moderate Due to serious imprecision ⁶</td>
<td>5 studies found no statistically significant difference in mortality in people who received vitamin D compared with control.</td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>Relative risk 0.55 (CI 95% 0.31 — 1) Based on data from 561 participants in 3 studies. ⁷ (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Vitamin D supplementation</td>
<td>Moderate Due to serious imprecision ⁸</td>
<td>3 studies found a non-statistically significant reduction in the risk of mechanical ventilation in people who received vitamin D compared with control.</td>
</tr>
<tr>
<td>Presence of symptoms - Day 7</td>
<td>Relative risk 1.31 (CI 95% 0.72 — 2.38) Based on data from 42 participants in 1 studies. ⁹ (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Vitamin D supplementation</td>
<td>Very low Due to very serious risk of bias, Due to very serious imprecision ¹⁰</td>
<td>1 study found no statistically significant difference in the presence of symptoms at day 7 in people who received vitamin D compared with control.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
<td>Summary</td>
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<tr>
<td>Oxygen therapy</td>
<td>Relative risk 0.96 (CI 95% 0.72 — 1.29) Based on data from 324 participants in 2 studies. (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Vitamin D supplementatio n</td>
<td>Moderate Due to serious imprecision 12</td>
<td>2 studies found no statistically significant difference in progression to oxygen therapy in people who received vitamin D compared with control.</td>
</tr>
<tr>
<td>Presence of symptoms - Day 14</td>
<td>Relative risk 1.59 (CI 95% 0.85 — 2.97) Based on data from 42 participants in 1 studies. (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Vitamin D supplementatio n</td>
<td>Very low Due to very serious risk of bias, Due to very serious imprecision 14</td>
<td>1 study found no statistically significant difference in the presence of symptoms at day 14 in people who were treated with vitamin D compared with control.</td>
</tr>
<tr>
<td>SARS-CoV-2 negativity within 3 weeks</td>
<td>Relative risk 3 (CI 95% 1.26 — 7.14) Based on data from 40 participants in 1 studies. (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Vitamin D supplementatio n</td>
<td>Low Due to very serious risk of bias 16</td>
<td>1 study found a statistically significant increase in the number of people who tested negative for SARS-CoV-2 within 3 weeks and received vitamin D compared with control.</td>
</tr>
<tr>
<td>Positive PCR test - Day 14</td>
<td>Relative risk 0.3 (CI 95% 0.01 — 7.07) Based on data from 42 participants in 1 studies. (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Vitamin D supplementatio n</td>
<td>Very low Due to very serious risk of bias, Due to very serious imprecision 18</td>
<td>1 study found no statistically significant difference in the number of positive PCR tests at day 14 in people who received vitamin D compared with control.</td>
</tr>
<tr>
<td>People who experienced at least 1 adverse event</td>
<td>Relative risk 1.27 (CI 95% 0.64 — 2.53) Based on data from 218 participants in 1 studies. (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Vitamin D supplementatio n</td>
<td>Low Due to very serious imprecision 20</td>
<td>1 study found no statistically significant difference the number of people who experienced at least one adverse event and received vitamin D compared with control.</td>
</tr>
<tr>
<td>Mean duration of hospitalisation</td>
<td>Lower better Based on data from 343 participants in 2 studies. (Randomized controlled)</td>
<td>Placebo or standard care</td>
<td>Vitamin D supplementatio n</td>
<td>Low Due to serious imprecision, Due to serious inconsistency 22</td>
<td>2 studies found no statistically significant difference in the duration of hospitalisation in people who received vitamin D compared with control.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
<td>Summary</td>
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</tr>
<tr>
<td>Timeframe</td>
<td>Placebo or standard care</td>
<td>Vitamin D supplementation</td>
<td>Placebo or standard care</td>
<td></td>
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<tr>
<td>Study results and measurements</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Median duration of hospitalisation</td>
<td>Lower better</td>
<td>9.5 (Median)</td>
<td>10 (Median)</td>
<td>Low</td>
<td>1 study found no statistically significant difference in the median duration of hospitalisation in people who received vitamin D compared with control.</td>
</tr>
<tr>
<td></td>
<td>Based on data from 543 participants in 1 studies.</td>
<td>Difference: 0.5 more (CI 95% 9 fewer — 10.5 more)</td>
<td>Due to serious risk of bias, Due to serious imprecision</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(Randomized controlled)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean duration of mechanical ventilation</td>
<td>Lower better</td>
<td>12.8 (Mean)</td>
<td>15 (Mean)</td>
<td>Moderate</td>
<td>1 study found no statistically significant difference in the mean duration of mechanical ventilation in people who received vitamin D compared with control.</td>
</tr>
<tr>
<td></td>
<td>Based on data from 237 participants in 1 studies.</td>
<td>Difference: MD 2.2 more (CI 95% 8.4 fewer — 12.8 more)</td>
<td>Due to serious imprecision</td>
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<td></td>
<td>(Randomized controlled)</td>
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</tr>
<tr>
<td>Mean duration until SARS-CoV-2 negativity</td>
<td>Lower better</td>
<td>17.6 (Mean)</td>
<td>17.6 (Mean)</td>
<td>Very low</td>
<td>1 study found no statistically significant difference in the mean time until SARS-CoV-2 negativity in people who received vitamin D compared with control.</td>
</tr>
<tr>
<td></td>
<td>Based on data from 40 participants in 1 studies.</td>
<td>Difference: MD 0 fewer (SD 6.1 more — 6.4 more)</td>
<td>Due to very serious risk of bias, Due to very serious imprecision</td>
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</tr>
<tr>
<td></td>
<td>(Randomized controlled)</td>
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</tbody>
</table>

1. Systematic review [167]. **Baseline/comparator:** Control arm of reference used for intervention.  
2. **Risk of Bias:** very serious. One study found no statistically significant difference in the presence of symptoms at day 14 in people who were treated with vitamin D compared with control. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Confidence interval includes line of no effect and small sample size. **Publication bias:** no serious.  
3. Systematic review [167]. **Baseline/comparator:** Control arm of reference used for intervention.  
4. **Risk of Bias:** serious. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. **Publication bias:** no serious.  
5. Systematic review [167]. **Baseline/comparator:** Control arm of reference used for intervention.  
6. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Confidence interval includes line of no effect. **Publication bias:** no serious.  
8. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. Confidence interval includes line of no effect. **Publication bias:** no serious.  
9. Systematic review [167]. **Baseline/comparator:** Control arm of reference used for intervention.  
10. **Risk of Bias:** very serious. No information on study design and analysis were available. It is not clear from manuscript whether assessors were blinded or not. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. Confidence interval includes line of no effect, with a small sample size.  
11. Systematic review [167]. **Baseline/comparator:** Control arm of reference used for intervention.  
12. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. **Publication bias:** no serious.
serious.

14. **Risk of Bias**: very serious. No information on study design and analysis were available. It is not clear from manuscript whether assessors were blinded or not. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: very serious. Confidence interval includes line of no effect and small sample size. **Publication bias**: no serious.

15. Systematic review [167]. **Baseline/comparator**: Control arm of reference used for intervention.

17. Systematic review [167]. **Baseline/comparator**: Control arm of reference used for intervention.
18. **Risk of Bias**: very serious. One study found no statistically significant difference in the presence of symptoms at day 14 in people who were treated with vitamin D compared with control. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: very serious. Confidence interval includes line of no effect and small sample size. **Publication bias**: no serious.

20. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: very serious. Confidence interval includes line of no effect and small sample size. **Publication bias**: no serious.

22. **Inconsistency**: serious. **Indirectness**: no serious. **Imprecision**: serious. **Publication bias**: no serious.

24. **Risk of Bias**: serious. Some concerns due to the presence of confounding from the lack of adjustment for co-administered interventions. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: serious. **Publication bias**: no serious.


27. Systematic review [167]. **Baseline/comparator**: Control arm of reference used for intervention.
28. **Risk of Bias**: very serious. Study design and randomisation information not available. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: very serious. Confidence interval includes line of no effect and small sample size. **Publication bias**: no serious.

**References**

166. Vitamin D supplementation for COVID-19.


7.15 Ongoing review of therapeutics for COVID-19

We are currently reviewing new and existing therapeutics for treating COVID-19 as part of a living guidelines approach. New and updated recommendations will be published for this guideline as they become available (see Update information | COVID-19 rapid guideline: managing COVID-19 | Guidance | NICE).
8. Preventing and managing acute complications

8.1 Acute kidney injury (AKI)

Info Box

In people with COVID-19, AKI:

- may be common, but prevalence is uncertain and depends on clinical setting (the Intensive Care National Audit and Research Centre's report on COVID-19 in critical care provides information on people in critical care who need renal replacement therapy for AKI)
- is associated with an increased risk of dying
- can develop at any time (before, during or after hospital admission)
- may be caused by volume depletion (hypovolaemia), haemodynamic changes, viral infection leading directly to kidney tubular injury, thrombotic vascular processes, glomerular pathology or rhabdomyolysis
- may be associated with haematuria, proteinuria and abnormal serum electrolyte levels (both increased and decreased serum sodium and potassium).

Info Box

In people with COVID-19:

- maintaining optimal fluid status (euvolaemia) is difficult but critical to reducing the incidence of AKI
- treatments for COVID-19 may increase the risk of AKI
- treatments for pre-existing conditions may increase the risk of AKI
- fever and increased respiratory rate increase insensible fluid loss.

8.1.1 Assessing and managing acute kidney injury (AKI)

Info Box

The potassium binders patiromer and sodium zirconium cyclosilicate can be used as options alongside standard care for the emergency management of acute life-threatening hyperkalaemia (see NICE's technology appraisal guidance on patiromer and sodium zirconium cyclosilicate for treating hyperkalaemia).

Info Box

For information on assessing and managing AKI, see the NICE guideline on acute kidney injury: prevention, detection and management and the NHS England Acute Kidney Injury (AKI) Algorithm.

For information on using intravenous fluids, see the NICE guideline on intravenous fluid therapy in adults in hospital and the NICE guideline on intravenous fluid therapy in children and young people in hospital.

For information on managing renal replacement therapy for adults who are critically unwell with COVID-19, see the Renal Association's guidelines on renal replacement therapy for critically unwell adults.

8.1.2 Follow up
8.2 Acute myocardial injury

8.2.1 Diagnosing acute myocardial injury

Consensus recommendation

Monitor people with chronic kidney disease for at least 2 years after AKI, in line with the NICE guideline on chronic kidney disease: assessment and management.

See guidance on care after hospital discharge in the Royal College of General Practitioners AKI toolkit.

For people in hospital with COVID-19 with signs or symptoms that suggest acute myocardial injury, measure high sensitivity troponin I (hs-cTnI) or T (hs-cTnT) and N-terminal pro B-type natriuretic peptide, and do an ECG.

Use the following test results to help inform a diagnosis:

- evolving ECG changes suggesting myocardial ischaemia
- an NT-proBNP level above 400 ng/litre
- high levels of hs-cTnI or hs-cTnT, particularly levels increasing over time.

Info Box

Elevated troponin levels may reflect cardiac inflammatory response to severe COVID-19 rather than acute coronary syndrome.

8.2.2 Managing myocardial injury

Consensus recommendation

For all people with COVID-19 and suspected or confirmed acute myocardial injury:

- monitor in a setting where cardiac or respiratory deterioration can be rapidly identified
- do continuous ECG monitoring
- monitor blood pressure, heart rate and fluid balance.

Consensus recommendation

For people with a clear diagnosis of myocardial injury:

- seek specialist cardiology advice on treatment, further tests and imaging
- follow local treatment protocols.
For people with a high clinical suspicion of myocardial injury, but without a clear diagnosis:

- repeat high sensitivity troponin (hs-cTnI or hs-cTnT) measurements and ECG monitoring daily, because dynamic change may help to monitor the course of the illness and establish a clear diagnosis
- seek specialist cardiology advice on further investigations such as transthoracic echocardiography and their frequency.

See also the management section for recommendations on care planning and recommendations on escalating and de-escalating treatment.

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**Info Box**

See the Medicines and Healthcare products Regulatory Agency’s Drug Safety Update on erythromycin: caution required due to cardiac risks (QT interval prolongation); drug interaction with rivaroxaban.

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### 8.3 Venous thromboembolism (VTE) prophylaxis

**Info Box**

**Definitions**

**Invasive mechanical ventilation**: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the Intensive Care National Audit & Research Centre definition of ‘advanced respiratory support’.

**Hospital-led acute care in the community**: a setting in which people who would otherwise be admitted to hospital have acute medical care provided by members of the hospital team, often working with the person’s GP team. They include hospital at home services and COVID-19 virtual wards.

**Standard prophylactic dose**: the prophylactic dose of a low molecular weight heparin (LMWH), as listed in the medicine’s summary of product characteristics, for medical patients.

**Intermediate dose**: double the standard prophylactic dose of an LMWH for medical patients.

**A treatment dose**: the licensed dose of anticoagulation used to treat confirmed VTE.

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### 8.3.1 In hospital
Evidence to decision

**Consensus recommendation**

For young people and adults with COVID-19 that is being managed in hospital, assess the risk of bleeding as soon as possible after admission or by the time of the first consultant review. Use a risk assessment tool published by a national UK body, professional network or peer-reviewed journal.

*The Department of Health VTE risk assessment tool is commonly used to develop treatment plans.*

**Evidence to decision**

**Benefits and harms**

The panel considered evidence from 6 trials evaluating whether higher doses (intermediate or treatment) of anticoagulation improve clinical outcomes in people in hospital with confirmed COVID-19.

Although the evidence did not show a statistically significantly increased risk of bleeding with higher doses of anticoagulation, the panel agreed that the occurrence of major bleeding events is a well-recognised adverse outcome of anticoagulant treatment. They therefore agreed that risk of bleeding should be assessed as soon as possible using a risk assessment tool to uncover any potential harm to people with a high risk.

**Rationale**

The panel agreed that all people with COVID-19 have an increased risk of VTE. Initial risk assessment for these people (as soon as possible after admission or by the time of their first consultant review) should focus on identifying people whose bleeding risk contraindicates pharmacological VTE prophylaxis.

The panel agreed that a risk assessment tool published by a national UK body, professional body or peer reviewed journal should be prioritised for use.

**Recommended**

Offer a standard prophylactic dose of a low molecular weight heparin as soon as possible, and within 14 hours of admission, to young people and adults with COVID-19 who need low-flow or high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation, and who do not have an increased bleeding risk.

Treatment should be continued for a minimum of 7 days, including after discharge.

See the NICE recommendation on low molecular weight heparin self-administration.

**Evidence to decision**

**Benefits and harms**

The panel agreed that a standard prophylactic dose of a low molecular weight heparin (LMWH) should be offered as soon as possible to manage the risk of VTE based on current standard practice.

The occurrence of major bleeding events is a well-recognised adverse outcome of anticoagulant treatment. The panel
noted that the rate of major bleeding events reported in the studies used was relatively low for adults in hospital with moderate COVID-19 (defined in this guideline as people receiving low flow supplementary oxygen) and severe COVID-19 (defined in this guideline as people receiving high-flow oxygen). Thus the benefits of standard-dose prophylactic anticoagulation may outweigh the potential harms in these populations. The panel also noted that people who are discharged early (before 7 days) could be at risk of clots. They emphasised the importance of continuing treatment after discharge until 7 days has passed to ensure people have had a full dose of a LMWH.

The panel noted that the duration of treatment recommended in NICE’s guideline on VTE in over 16s is a minimum of 7 days and thought that it would be acceptable to align treatment duration of a standard prophylactic dose of a LMWH in people with moderate or severe COVID-19 with standard practice.

Certainty of the Evidence

The panel was presented with evidence from 3 trials (ACTION, ACTIVE-4A-ATTACC-REMAP-CAP, RAPID) that compared the effectiveness of standard-dose VTE prophylaxis with treatment-dose VTE prophylaxis. The outcomes of ACTION, ACTIVE-4a-ATTACC-REMAP-CAP and RAPID were of moderate to very low certainty.

The panel noted that the results from RAPID were preprint results. This meant they had not been peer reviewed, so they interpreted the results with the appropriate caution. Some of the group allocated to the standard prophylactic anticoagulant dose had higher doses in the ACTION and ACTIVE-4a-ATTACC-REMAP-CAP trials (between 26% and 29%), which the panel recognised could have affected the results. However, they considered that the evidence was certain enough to make recommendations to consider standard-dose VTE prophylaxis in young people and adults with moderate or severe COVID-19.

Values and preferences

The panel were not aware of any systematically collected data on peoples’ preferences and values. The panel inferred that, in view of the possible mortality benefits and increase in organ support-free days for people with COVID-19 who need low-flow or high-flow oxygen, many would choose a standard dose of an anticoagulant.

Resources

Cost effectiveness was not assessed as part of the evidence review.

The panel did not have concerns about opportunity costs when an LMWH is being used for people who need low-flow or high-flow oxygen. The panel decided to recommend that treatment is continued for up to 7 days, including after discharge. This may be a higher resource use of anticoagulation because people who are discharged before 7 days will need to learn how to self-administer LMWH at home and monitor levels.

Equity

The panel noted an absence of evidence for anticoagulation in children. They recognised that younger children have different haematological physiology, meaning that VTE is less likely. However, their clinical experience suggested that, after puberty, people under 18 years are also at risk of VTE if admitted to hospital with COVID-19. For that reason, the panel included young people in the recommendations as well as adults.
The panel agreed that a standard prophylactic dose of a low molecular weight heparin (LMWH) should be offered as soon as possible to manage the risk of VTE based on current standard practice. Following standard prophylactic dose administration on admission, a more detailed assessment should be done to see whether people should be offered a treatment dose or not.

The panel also noted that people who are discharged early (before 7 days) could be at risk of clots. They emphasised the importance of continuing treatment after discharge until 7 days has passed to ensure people have had a full dose of a LMWH.

The treatment duration comes from NICE’s guideline on VTE in over 16s.

**Acceptability**

It is anticipated that, when considering the risks and benefits of treatment, most young people and adults who are admitted to hospital with COVID-19, who need low-flow or high-flow oxygen and who do not have an increased bleeding risk might favour standard-dose anticoagulation. However, we have no systematically collected evidence about acceptability.

**Feasibility**

Using standard prophylactic doses in young people and adults receiving low-flow or high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation reflects usual treatment in most centres. For others, it is a minor treatment adjustment that should be feasible to implement.

**Rationale**

The panel agreed that a standard prophylactic dose of a low molecular weight heparin (LMWH) should be offered as soon as possible to manage the risk of VTE based on current standard practice. Following standard prophylactic dose administration on admission, a more detailed assessment should be done to see whether people should be offered a treatment dose or not.

The panel also noted that people who are discharged early (before 7 days) could be at risk of clots. They emphasised the importance of continuing treatment after discharge until 7 days has passed to ensure people have had a full dose of a LMWH.

The treatment duration comes from NICE’s guideline on VTE in over 16s.

**Clinical question/ PICO**

- **Population:** People with moderate COVID-19
- **Intervention:** Treatment dose VTE prophylaxis
- **Comparator:** Standard dose VTE prophylaxis

**Summary**

What is the evidence informing this recommendation?

Evidence comes from 3 randomised controlled trials with 3,298 participants included.
One study (ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, reported in Lawler, 2021; n=2,219) compared treatment dose anticoagulant (UFH or LMWH, mainly enoxaparin) with standard dose venous thromboembolism prophylaxis (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) according to local protocols. Treatment dose LMWH or UFH were administered according to local protocols for up to 14 days or until recovery.

In the ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, most of the intervention group (94.7%) received treatment dose anticoagulation, most commonly enoxaparin and in the control group 71.7% received standard prophylactic dose thromboprophylaxis and 26.5% received intermediate-dose thromboprophylaxis.

The second study (ACTION trial, reported in Lopes, 2021, n=614) compared treatment dose anticoagulant (mainly rivaroxaban) for 30 days, with standard prophylactic dose anticoagulant (unfractionated heparin or enoxaparin) given whilst an inpatient and according to local hospital protocols.

Participants in the ACTION trial had a clinical 'stable' condition (93% and 95% in treatment and standard care group respectively), with a small proportion having a clinically 'unstable' condition (7% and 5% in treatment and standard care group respectively).

In the ACTION trial, most of the intervention group (94.8%) received treatment dose anticoagulation (92% rivaroxaban); stable patients were prescribed rivaroxaban 20mg once daily and clinically unstable patients SC enoxaparin 1mg/kg twice daily, or IV UFH.

Mortality and venous thromboembolism outcomes from the ACTION trial were calculated separately due to the usage of rivaroxaban as therapeutic dose anticoagulation not being standard practice in the UK.

The majority of the control group received prophylactic dose anticoagulation during hospitalisation (99.5%); unfractionated heparin/enoxaparin dosed according to local hospital protocols.

The third study (RAPID trial, reported in Sholzberg 2021, n=465) compared treatment dose anticoagulant (LMWH and UFH) with standard dose prophylactic anticoagulant (dose-capped subcutaneous heparin (LMWH or UFH)). Study treatment was continued until the first day of hospital discharge, for 28 days or until study withdrawal/death.

The majority of participants from the RAPID trial intervention group received treatment dose heparin (98.2%) and (93.7%) received prophylactic heparin as allocated in the first 48 hours post-randomisation. Participants were moderately ill hospitalised patients with elevated D-dimer levels.
Study Characteristics

The mean age in the studies ranged from 56 to 60, and between 54% and 76% of participants were male. Data for the ACTIVE-4a-ATTACC-REMAP-CAP and RAPID trials were collected from Brazil, Canada, Ireland, Netherlands, Australia, UK, Saudi Arabia, Mexico and USA. The ACTION trial was conducted in Brazil only (31 centres).

The definition of moderate severity varied between the studies. In the ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, moderate disease severity was defined as hospitalisation for COVID-19 without the requirement for ICU-level of care. ICU-level of care was defined by use of respiratory or cardiovascular organ support (high flow nasal oxygen, non-invasive or invasive mechanical ventilation, vasopressors, or inotropes) in an ICU. The ACTION trial defined moderate severity disease patients as those with an oxygen saturation <94%, pulmonary infiltrates <50%, or a partial pressure of oxygen to fractional concentration of oxygen in inspired air ratio <300. The RAPID trial defined disease severity as hospitalised patients with elevated D-dimer levels, above the upper limit of normal (ULN) of the local hospital in the presence of an oxygen saturation of ≤93% on room air, or ≥2 times the ULN irrespective of oxygen saturation levels.

The ACTION trial reported 14% of the participants were on high-flow oxygen, the rest were either on no oxygen or low-flow oxygen.

Exclusion criteria varied, but all studies excluded patients with a clinical indication for therapeutic anticoagulation and those who were at high risk of bleeding. The RAPID trial further excluded participants who were pregnant, and any participants that met any of the primary outcomes or would imminently meet them.

Duration of treatment ranged from up to 14 days (ACTIVE-4a-ATTACC-REMAP-CAP) to up to 30 days (RAPID and ACTION).

What are the main results?

Mortality at 30 days

Very low quality evidence from 2 studies found a non-statistically significant reduction in mortality at 30 days with treatment dose anticoagulant (mainly LMWH) compared with standard dose anticoagulant (UFH or LMWH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.50, CI 95% 0.13-1.88; 2,684 people in 2 studies].
Mortality at 30 days - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant increase in mortality at 30 days with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 1.49, CI 95% 0.90 - 2.46; 614 people in 1 study].

All cause mortality or need for invasive ventilation or non-invasive ventilation

Moderate quality evidence from 1 study found a non-statistically significant reduction in all cause mortality and need for ventilation with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.63, CI 95% 0.39 - 1.02; 465 people in 1 study].

Death or need for invasive ventilation or non-invasive ventilation or ICU admission

Moderate quality evidence from 1 study found a non-statistically significant reduction in death and need for ventilation and ICU admission with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.75, CI 95% 0.51 – 1.11; 465 people in 1 study].

Survival

Survival to hospital discharge

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant (mainly enoxaparin) compared with standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 1.01, CI 95% 0.99-1.03; 2,219 people in 1 study].

Survival to hospital discharge without major thrombotic events (a composite of freedom from myocardial infarction, pulmonary embolism, ischemic stroke, systemic arterial embolism, and in-hospital death)

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge without major thrombotic events with treatment dose anticoagulant (mainly enoxaparin) compared with standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 1.00, CI 95% 0.97-1.03; 2,174 people in 1 study].
heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.02, CI 95% 1.00-1.05; 2,226 people in 1 study].

Survival to hospital discharge without any macrovascular thrombotic events (the components of major thrombotic events and symptomatic deep venous thrombosis)

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge without any macrovascular thrombotic events with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.02, CI 95% 1.00-1.05; 2,226 people in 1 study].

Survival without organ support 28 days

Moderate quality evidence from 1 study found a statistically significant increase in survival without organ support at 28 days with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.05, CI 95% 1.01-1.10; 2,221 people in 1 study].

Organ support free days at day 21 (defined as survival to hospital discharge and, among survivors, the number of days free of ICU-level organ support through day 21)

Moderate quality evidence from 1 study found a statistically significant increase in organ support-free days at 21 days with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Mean 25.8 in treatment versus 24.1 standard; CI 95% 0.32 - 3.08; 465 people in 1 study].

VTE

Venous thromboembolism at 30 days

Moderate quality evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.30 CI 95% 0.06 - 1.41; 465 people in 1 study].
Venous thromboembolism at 30 days - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.60, CI 95% 0.29-1.24; 614 people in 1 study].

Composite Thrombotic Outcome: Any venous thromboembolism, myocardial infarction, stroke, systemic embolism, and major adverse limb events

Moderate quality evidence from 1 study found a non-statistically significant reduction in the composite thrombotic outcome with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.75, CI 95% 0.45-1.26; 614 people in 1 study].

ICU admission

Moderate quality evidence from 1 study found a non-statistically significant reduction in ICU admission with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.82, CI 95% 0.54-1.24; 465 people in 1 study].

Need for invasive ventilation or non-invasive ventilation

Moderate quality evidence from 1 study found no statistically significant difference in need for invasive ventilation or non-invasive ventilation with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.84, CI 95% 0.49-1.45; 465 people in 1 study].

Adverse events

Major bleeding was defined in both studies according to the International Society on Thrombosis and Haemostasis.

Major bleeding

Low quality evidence from a pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard dose
anticoagulant for people who were hospitalised with moderate COVID-19. [Relative risk 1.30, CI 95% 0.34-4.98; 2,692 people in 2 studies].

Major bleeding - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant increase in major bleeding with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 2.45, CI 95% 0.78-7.73; 614 people in 1 study].

Clinically relevant non-major bleeding - Rivaroxaban

Moderate quality evidence from 1 study found a statistically significant increase in clinically relevant non-major bleeding with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 5.23, CI 95% 1.54-17.77; 614 people in 1 study].

Our confidence in the results

All studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. One study was a pre-print (RAPID) and two were published manuscripts (ACTION and ACTIVE-4a-ATTACC-REMAP-CAP).

Certainty of the evidence is very low for mortality at 30 days due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate-dose thromboprophylaxis), serious indirectness (mortality was calculated by NICE by subtracting survival from total number of events) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for mortality at 30 days with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and serious imprecisions (confidence intervals cross the line of no effect).

Certainty of the evidence is moderate for all cause mortality or need for invasive ventilation and non-invasive ventilation due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for death or need for invasive ventilation or non-invasive ventilation or ICU admission due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence varies for survival outcomes.
Certainty of the evidence is low for survival to hospital discharge, survival to hospital discharge without any major thrombotic events and survival to hospital discharge without any macrovascular thrombotic events, due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for survival without organ support for 28 days due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis).

Certainty of the evidence is moderate for venous thromboembolism at 30 days due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for venous thromboembolism at 30 days with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty if the evidence is moderate for Composite Thrombotic Outcome, due to serious imprecision (confidence interval includes the line of no effect).

Certainty of the evidence is low for major bleeding due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate- dose thromboprophylaxis) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for major bleeding with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for clinically relevant non-major bleeding with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban).
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<tr>
<td>Mortality</td>
<td>Relative risk 0.5 (CI 95% 0.13 — 1.88) Based on data from 2,684 participants in 2 studies. (Randomized controlled)</td>
<td>Standard dose VTE prophylaxis</td>
<td>Treatment dose VTE prophylaxis</td>
<td>Very low Due to serious indirectness, Due to serious imprecision, Due to serious risk of bias</td>
<td>A pooled analysis of 2 studies found a non-statistically significant reduction in mortality after 30 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>Mortality - rivaroxaban</td>
<td>Relative risk 1.49 (CI 95% 0.9 — 2.46) Based on data from 614 participants in 1 studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>Evidence from 1 study found a non-statistically significant increase in mortality at 30 days with treatment dose rivaroxaban compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>All-cause mortality or need for IV or NIV</td>
<td>Relative risk 0.63 (CI 95% 0.39 — 1.02) Based on data from 465 participants in 1 studies. (Randomized controlled)</td>
<td></td>
<td></td>
<td>Moderate Due to serious imprecision</td>
<td>Evidence from 1 study found a non-statistically significant reduction in all cause mortality and need for ventilation with with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>Death / need for IV or NIV / ICU admission</td>
<td>Relative risk 0.75 (CI 95% 0.51 — 1.11) Based on data from 465 participants in 1 studies. (Randomized controlled)</td>
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<td></td>
<td>Moderate Due to serious imprecision</td>
<td>Evidence from 1 study found a non-statistically significant reduction in death and need for ventilation and ICU admission with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
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<td>Outcome</td>
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<tr>
<td>Survival to hospital discharge</td>
<td>Relative risk 1.01 (CI 95% 0.99 — 1.03) Based on data from 2,219 participants in 1 studies. <em>(9)</em> <em>(Randomized controlled)</em></td>
<td>Standard dose VTE prophylaxis</td>
<td>Treatment dose VTE prophylaxis</td>
<td>Low Due to serious risk of bias. Due to serious imprecision, <em>(10)</em></td>
<td>Evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>Survival to hospital discharge without major thrombotic events</td>
<td>Relative risk 1.02 (CI 95% 1 — 1.05) Based on data from 2,226 participants in 1 studies. <em>(11)</em> <em>(Randomized controlled)</em></td>
<td>Standard dose VTE prophylaxis</td>
<td>Treatment dose VTE prophylaxis</td>
<td>Low Due to serious risk of bias. Due to serious imprecision, <em>(12)</em></td>
<td>Evidence from 1 study found no statistically significant difference in survival to hospital discharge without major thrombotic events with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>Survival to hospital discharge without any macrovascular thrombotic events</td>
<td>Relative risk 1.02 (CI 95% 1 — 1.05) Based on data from 2,226 participants in 1 studies. <em>(13)</em> <em>(Randomized controlled)</em></td>
<td>Standard dose VTE prophylaxis</td>
<td>Treatment dose VTE prophylaxis</td>
<td>Low Due to serious risk of bias. Due to serious imprecision <em>(14)</em></td>
<td>Evidence from 1 study found no statistically significant difference in survival to hospital discharge without any macrovascular thrombotic events with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
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<tr>
<td>Venous thromboembolism 30 days</td>
<td>Relative risk 0.3 (CI 95% 0.06 — 1.41) Based on data from 465 participants in 1 studies. <em>(15)</em> <em>(Randomized controlled)</em></td>
<td>Standard dose VTE prophylaxis</td>
<td>Treatment dose VTE prophylaxis</td>
<td>Moderate Due to serious imprecision <em>(16)</em></td>
<td>Evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised. Uncertainty</td>
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*Critical: 9*

<table>
<thead>
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<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival to hospital discharge</td>
<td>9 Critical</td>
<td>Relative risk 1.01 (CI 95% 0.99 — 1.03) Based on data from 2,219 participants in 1 studies. <em>(9)</em> <em>(Randomized controlled)</em></td>
<td>Standard dose VTE prophylaxis</td>
<td>Treatment dose VTE prophylaxis</td>
<td>Low Due to serious risk of bias. Due to serious imprecision, <em>(10)</em></td>
<td>Evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>Survival to hospital discharge without major thrombotic events</td>
<td>9 Critical</td>
<td>Relative risk 1.02 (CI 95% 1 — 1.05) Based on data from 2,226 participants in 1 studies. <em>(11)</em> <em>(Randomized controlled)</em></td>
<td>Standard dose VTE prophylaxis</td>
<td>Treatment dose VTE prophylaxis</td>
<td>Low Due to serious risk of bias. Due to serious imprecision, <em>(12)</em></td>
<td>Evidence from 1 study found no statistically significant difference in survival to hospital discharge without major thrombotic events with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>Survival to hospital discharge without any macrovascular thrombotic events</td>
<td>9 Critical</td>
<td>Relative risk 1.02 (CI 95% 1 — 1.05) Based on data from 2,226 participants in 1 studies. <em>(13)</em> <em>(Randomized controlled)</em></td>
<td>Standard dose VTE prophylaxis</td>
<td>Treatment dose VTE prophylaxis</td>
<td>Low Due to serious risk of bias. Due to serious imprecision <em>(14)</em></td>
<td>Evidence from 1 study found no statistically significant difference in survival to hospital discharge without any macrovascular thrombotic events with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>Venous thromboembolism 30 days</td>
<td>9 Critical</td>
<td>Relative risk 0.3 (CI 95% 0.06 — 1.41) Based on data from 465 participants in 1 studies. <em>(15)</em> <em>(Randomized controlled)</em></td>
<td>Standard dose VTE prophylaxis</td>
<td>Treatment dose VTE prophylaxis</td>
<td>Moderate Due to serious imprecision <em>(16)</em></td>
<td>Evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised. Uncertainty</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
<td>Summary</td>
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<tr>
<td>Venous thromboembolism - rivaroxaban</td>
<td>30 days</td>
<td>Relative risk 0.6 (CI 95% 0.29 — 1.24) Based on data from 615 participants in 1 studies.</td>
<td>Standard dose VTE prophylaxis</td>
<td>Treatment dose VTE prophylaxis</td>
<td>Low</td>
<td>Evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant compared to standard dose anticoagulant for people who were hospitalised</td>
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<td></td>
<td></td>
<td>(Randomized controlled)</td>
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<tr>
<td>Composite Thrombotic Outcome</td>
<td></td>
<td>Relative risk 0.75 (CI 95% 0.45 — 1.26) Based on data from 614 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Moderate</td>
<td>Evidence from 1 study found a non-statistically significant reduction in thrombotic events (defined as any venous thromboembolism, myocardial infarction, stroke, systemic embolism, and major adverse limb events) with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised</td>
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<td>(Randomized controlled)</td>
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<tr>
<td>Major bleeding</td>
<td></td>
<td>Relative risk 1.3 (CI 95% 0.34 — 4.98) Based on data from 2,692 participants in 2 studies.</td>
<td></td>
<td></td>
<td>Low</td>
<td>A pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised</td>
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<tr>
<td></td>
<td></td>
<td>(Randomized controlled)</td>
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<td></td>
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<tr>
<td>Major bleeding - rivaroxaban</td>
<td></td>
<td>Relative risk 2.45 (CI 95% 0.78 — 7.73) Based on data from 614 participants in 1 studies.</td>
<td></td>
<td></td>
<td>Low</td>
<td>Evidence from 1 study found a non-statistically significant increase in major bleeding with treatment dose rivaroxaban compared to standard prophylactic dose anticoagulant for people who were hospitalised</td>
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<tr>
<td></td>
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<td>(Randomized controlled)</td>
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<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard dose VTE prophylaxis</td>
<td>Intervention Treatment dose VTE prophylaxis</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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<tr>
<td>Survival without organ support 28 days</td>
<td>Relative risk 1.3 (CI 95% 1 — 1.61) Based on data from 2,219 participants in 1 studies.</td>
<td>754 per 1000</td>
<td>980 per 1000</td>
<td>Moderate</td>
<td>Evidence from 1 study found a statistically significant increase in survival without organ support at 28 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
<td></td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding - rivaroxaban</td>
<td>Relative risk 5.23 (CI 95% 1.54 — 17.77) Based on data from 614 participants in 1 studies.</td>
<td>10 per 1000</td>
<td>52 per 1000</td>
<td>Moderate</td>
<td>Evidence from 1 study found a statistically significant increase in clinically relevant non-major bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>Relative risk 0.82 (CI 95% 0.54 — 1.24) Based on data from 465 participants in 1 studies.</td>
<td>177 per 1000</td>
<td>145 per 1000</td>
<td>Moderate</td>
<td>Evidence from 1 study found a non-statistically significant reduction in ICU admission with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
<td></td>
</tr>
<tr>
<td>Need for IV or NIV</td>
<td>Relative risk 0.84 (CI 95% 0.49 — 1.45) Based on data from 465 participants in 1 studies.</td>
<td>110 per 1000</td>
<td>92 per 1000</td>
<td>Moderate</td>
<td>Evidence from 1 study found no statistically significant difference in need for invasive ventilation or non-invasive ventilation with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
<td></td>
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<tr>
<td>Organ support-</td>
<td>24.1</td>
<td>25.8</td>
<td>Moderate</td>
<td>Evidence from 1 study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard dose VTE prophylaxis</td>
<td>Intervention Treatment dose VTE prophylaxis</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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<tr>
<td>free days 6 Important</td>
<td>Based on data from 465 participants in 1 studies. (Randomized controlled)</td>
<td>(Mean) Difference: MD 1.7 higher (CI 95% 0.32 higher — 3.08 higher)</td>
<td>Due to serious risk of bias 34</td>
<td>found a statistically significant increase in organ support-free days at 21 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Risk of Bias:** serious. Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency:** no serious. **Indirectness:** serious. Mortality in REMAP-CAP was calculated by NICE (through subtracting no. survival until discharge from total no. of events). **Imprecision:** serious. 95% CI crossed line of no effect. **Publication bias:** no serious.
4. **Risk of Bias:** serious. Small number of participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. CI included line of no effect. **Publication bias:** no serious.
6. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. CI included line of no effect. **Publication bias:** no serious.
8. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. CI included line of no effect. **Publication bias:** no serious.
10. **Risk of Bias:** serious. Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. 95% CI crosses line of no effect. **Publication bias:** no serious.
12. **Risk of Bias:** serious. Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** serious. 95% CI crossed line of no effect. **Publication bias:** no serious.

Based on data from 465 participants in 1 studies. **(Randomized controlled)**

Due to serious risk of bias 34

MD 1.7 higher (CI 95% 0.32 higher — 3.08 higher)

COVID-19 rapid guideline: Managing COVID-19 - The National Institute for Health and Care Excellence (NICE)
14. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect. **Publication bias: no serious.**


16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect. **Publication bias: no serious.**


18. **Risk of Bias: serious.** Due to study design where participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**


20. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% confidence interval crossed the line of no effect. **Publication bias: no serious.**


22. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals. **Publication bias: no serious.**


24. **Risk of Bias: serious.** Participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed line of effect. **Publication bias: no serious.**

25. Systematic review [50] with included studies: [53]. **Baseline/comparator:** Control arm of reference used for intervention.

26. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** Publication bias: no serious.


30. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect. **Publication bias: no serious.**


32. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect. **Publication bias: no serious.**

33. Systematic review [50] with included studies: RAPID 2021. **Baseline/comparator:** Control arm of
reference used for intervention.
34. **Risk of Bias**: serious. participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis.
   **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: no serious. **Publication bias**: no serious.

**References**
52. Heparins for COVID-19..

**Clinical question/ PICO**

**Population:** People with severe COVID-19  
**Intervention:** Treatment dose VTE prophylaxis  
**Comparator:** Standard dose VTE prophylaxis

**Summary**

**What is the evidence informing this recommendation?**

Evidence comes from 2 randomised controlled trials with 1,089 participants included. Both studies (HESACOVID trial, reported in Lemos, 2020, n=20; and ACTIVE-41, ATACC, REMAP-CAP multiplatform trial, reported in Lawler, 2021, n=1,098) compared treatment dose anticoagulant (unfractionated heparin (UFH) or low molecular weight heparin (LMWH)) with either prophylactic or intermediate dose anticoagulant (mainly enoxaparin).

The comparator group varies between studies. In the HESACOVID trial, half of the comparator group received UFH and half received prophylactic dose enoxaparin. The ACTIVE-41, ATACC, REMAP-CAP trial combines data from three sites, each operating under their own protocols. The protocols are very similar but allow for local practice, meaning that just over 40% of the comparator arm received prophylactic dose enoxaparin, just over 50% received intermediate dose enoxaparin, and 7.4% received either subtherapeutic (dose unclear) or therapeutic dose of either UFH or LMWH. This may reduce the validity of the results from the ACTIVE-41, ATACC, REMAP-CAP trial.
Study characteristics

The mean age in the studies ranged from 55 to 61, and between 68% and 90% of participants were male. Both studies included only adult patients receiving intensive care unit-level respiratory or cardiovascular support. Data was collected from Australia, Brazil, Canada, Ireland, Mexico, Netherlands, New Zealand, Saudi Arabia, UK, and USA.

Exclusion criteria varied, but both studies excluded patients with a separate clinical indication for therapeutic anticoagulation. One study excluded patients over 85.

Duration of treatment was 4-14 days in HESACOVID, and up to 14 days or hospital discharge in ACTIVE-41, ATACC, REMAP-CAP.

What are the main results?

All-cause mortality

Very low quality evidence from 1 study found a non-statistically significant reduction in all-cause mortality at 28 days with treatment dose anticoagulant (LMWH or UFH) compared to either prophylactic or intermediate dose anticoagulant (mainly enoxaparin) for people who were hospitalised. [Relative risk 0.33 CI 95% 0.04 - 2.69; 20 people in 1 study].

Death in hospital

Low quality evidence from a pooled analysis of 2 studies found no significant difference for death in hospital with treatment dose anticoagulant (LMWH at varying doses) compared with either UFH, enoxaparin or usual care venous thromboprophylaxis (dose and treatment varies) for people who were hospitalised. [Relative risk 1.03, CI 95% 0.89-1.21; 1,118 people in 2 studies].

Survival to hospital discharge

Low quality evidence from 1 study found no significant difference for survival to hospital discharge with treatment dose anticoagulant compared with usual care venous thromboprophylaxis (dose and treatment varies) for people who were hospitalised. [Relative risk 0.97, CI 95% 0.89-1.06; 1,098 people in 1 study].

Serious Adverse events: Major bleeding

Low quality evidence from a pooled analysis of 2 studies found no significant difference in major bleeding with treatment dose anticoagulant compared with prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised. [Relative risk 1.63, CI 95% 0.82 - 3.25; 1,111 people in 2 studies].
Organ-support free days at 21 days
Low quality evidence from 1 study found no statistically significant difference in organ-support free days with treatment dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Odds Ratio 0.83, CI 95% 0.67 - 1.03; 1,098 people in 1 study].

Ventilator-free days
Low quality evidence from 1 study found a statistically significant increase in ventilator-free days at 28 days with treatment dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Median 15 versus 0; 20 people in 1 study].

Our confidence in the results
All studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. The two studies were published manuscripts (ACTIVE-41, ATACC, REMAP-CAP and HESACOVID). Following the peer reviewed publication of ACTIVE-41,ATACC,REMAP-CAP (26/08/2021), the data for some of the outcomes was updated to reflect the latest figures in the published manuscript.

There were significant deviations from the intended interventions reported in one study (ACTIVE-41, ATACC, REMAP-CAP) whereby a large proportion of the comparator group received intermediate rather than prophylactic dose anticoagulant. In addition, almost 15% of the treatment group received either low or intermediate dose anticoagulant, where the intended intervention was treatment dose anticoagulant. This means the results from this study are unclear.

One study (HESACOVID) contained only 20 participants (10 in each arm). This trial did not have sufficient power to assess a difference in mortality, and results may be due to chance. This should be considered when looking at the increase in ventilator free days in the treatment group reported by this study.

Certainty of the evidence is very low for all-cause mortality due to serious risk of bias (deviation from intended control group treatment) and very serious imprecision (confidence intervals include the line of no effect and low numbers of participants).

Certainty of the evidence is low for death in hospital due to serious risk of bias, serious inconsistency (high statistical heterogeneity) and serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for survival to hospital discharge due to serious risk of bias and serious imprecision.
Certainty of the evidence is low for major bleeding due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for organ support free days due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for ventilator-free days due to very serious imprecision (confidence intervals include the line of no effect and unable to calculate effect size and 95% confidence intervals).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Standard dose VTE prophylaxis</th>
<th>Intervention Treatment dose VTE prophylaxis</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>28 days</td>
<td>9 Critical</td>
<td>Relative risk 0.33 (CI 95% 0.04 — 2.69) Based on data from 20 participants in 1 studies. ¹ (Randomized controlled)</td>
<td>300 per 1000</td>
<td>99 per 1000</td>
<td>Very low Due to serious risk of bias and very serious imprecision ² Evidence from 1 study found a non-statistically significant reduction in all-cause mortality at 28 days with treatment dose anticoagulant (unfractionated heparin or low molecular weight heparin) compared to either standard prophylactic or intermediate dose anticoagulant (mainly enoxaparin) for people who were hospitalised.</td>
</tr>
<tr>
<td>Death in hospital</td>
<td></td>
<td>9 Critical</td>
<td>Relative risk 1.03 (CI 95% 0.89 — 1.21) Based on data from 1,118 participants in 2 studies. ² (Randomized controlled)</td>
<td>357 per 1000</td>
<td>368 per 1000</td>
<td>Low Due to serious risk of bias, Due to serious imprecision ⁴ A pooled analysis of 2 studies found no statistically significant difference in death in hospital with treatment dose anticoagulant (low molecular weight heparin at varying doses) compared to either unfractionated heparin, enoxaparin or standard prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised.</td>
</tr>
<tr>
<td>Survival to hospital discharge</td>
<td></td>
<td></td>
<td>Relative risk 0.97 (CI 95% 0.89 — 1.06) Based on data from 1,098 participants in 1 study</td>
<td>645 per 1000</td>
<td>626 per 1000</td>
<td>Low Due to serious risk of bias, Due to serious Evidence from 1 study found no statistically significant difference in survival to hospital</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard dose VTE prophylaxis</td>
<td>Intervention Treatment dose VTE prophylaxis</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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<tr>
<td>9 Critical</td>
<td>studies. 5 (Randomized controlled)</td>
<td>Difference: 19 fewer per 1000 (CI 95% 71 fewer — 39 more)</td>
<td>imprecision 6</td>
<td>discharge with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised.</td>
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<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>Relative risk 1.63 (CI 95% 0.82 — 3.25) Based on data from 1,111 participants in 2 studies. 7 (Randomized controlled)</td>
<td>Difference: 23 per 1000</td>
<td>37 per 1000</td>
<td>A pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised.</td>
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<tr>
<td>Organ support free days 21 days</td>
<td>Odds ratio 0.83 (CI 95% 0.67 — 1.03) Based on data from 1,098 participants in 1 studies. (Randomized controlled)</td>
<td>Difference: 567 per 1000</td>
<td>536 per 1000</td>
<td>Evidence from 1 study found no statistically significant difference in organ support free days at 21 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
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</tr>
<tr>
<td>Ventilator-free days 28 days</td>
<td>High better Based on data from 20 participants in 1 studies. (Randomized controlled)</td>
<td>Difference: 0 (Median)</td>
<td>15 (Median)</td>
<td>Evidence from 1 study found a statistically significant increase in ventilator-free days at 28 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
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</tbody>
</table>

2. Risk of Bias: serious. Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis), due to [reason]. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. No
statistically significant effect, and low number of patients., due to [reason]. **Publication bias: no serious.**


4. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**


6. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**


8. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**

9. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI includes line of no effect. **Publication bias: no serious.**

10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Unable to calculate effect size and 95% C.I. **Publication bias: no serious.**

### References


### Clinical question/ PICO

**Population:** People with severe COVID-19  
**Intervention:** Intermediate dose VTE prophylaxis
Comparitor: Standard dose VTE prophylaxis

Summary
What is the evidence informing this recommendation?
Evidence comes from 2 randomised controlled trials with 735 participants included. Both studies (INSPIRATION trial, reported in Sadeghipour 2021 [for 30 day outcomes] and Bikdeli, 2021 [for 90 day outcomes], n=562 and Perepu 2021 n=173) compared intermediate dose enoxoparin (1mg/kg daily if the BMI was <30 or 0.5 mg/kg SC twice daily if the BMI was ≥30) with prophylactic dose enoxaparin (40mg daily).

The intervention and comparator groups were consistent between the studies. However, Perepu (2021) allowed for cointerventions, and more patients received azithromycin in the intermediate dose arm (29%) than in the prophylactic dose arm (13%).

Study characteristics
The mean age in the studies ranged from 61 to 65, and between 56% and 58% of participants were male. Both studies investigate the effects of the interventions in severe patients, but approximately 45% of the participants in the INSPIRATION trial were receiving low-flow oxygen and would therefore not be classed as having severe COVID-19 by the definitions used in the study protocol. The proportion of participants in Perepu (2021) receiving low-flow oxygen is unclear: it is reported that 62% were admitted to intensive care and 23% received invasive mechanical ventilation.

Data was collected from IRAN (INSPIRATION trial) and the USA (Perepu 2021). Participants were excluded if they had recent known major bleeding or indications for a therapeutic dose of anticoagulant. Both studies excluded pregnant women. Duration of treatment was until hospital discharge (Perepu 2021) or for 30 and 90 days (INSPIRATION).

What are the main results?

All-cause mortality
Very low quality evidence from a pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 30 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.01, CI 95% 0.84—1.21; 735 people in 2 studies].

Low quality evidence from 1 study found no significant difference for all-cause mortality at 90 days with intermediate dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.07, CI 95% 0.89 - 1.29; 562 people in 1 study]

Serious Adverse events: Major bleeding
Very low quality evidence from a pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with intermediate dose anticoagulant compared to prophylactic dose anticoagulant (dose and treatment varies) for those people who were hospitalised. [Relative risk 1.53, CI 95% 0.54 –4.28; 735 people in 2 studies]

Venous thromboembolism

Very low quality evidence from a pooled analysis of 2 studies found no statistically significant difference in venous thromboembolism at 30 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.02, CI 95% 0.52 — 2.00; 735 people in 2 studies]

Low quality evidence from 1 study found no statistically significant difference in venous thromboembolism at 90 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 0.93, CI 95% 0.38 — 2.26; 562 people in 1 study]

Ventilator-free days

Very low quality evidence from 1 study found no significant difference for ventilator-free days at 30 days with intermediate dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Median 30 days in intermediate dose group versus 30 days in prophylactic dose group; 562 people in 1 study].

Our confidence in the results

Both studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. One study was a pre-print (Perepu, 21). The other study was from published manuscripts that reported 30 day and 90 day outcomes separately (INSPIRATION 2021).

Certainty of the evidence is low or very low for mortality outcomes due to risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is very low for major bleeding due to risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is very low for VTE outcomes at 30 days due to serious risk of bias.
(uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for VTE outcomes at 90 days to serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of evidence is very low for ventilator-free days at 30 days due to very serious imprecision (confidence intervals include the line of no effect and unable to calculate effect size and 95% confidence intervals) and serious indirectness (dissimilarity between population of interest and those studied).

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<th>Outcome</th>
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<tr>
<td>All-cause mortality</td>
<td>30 days</td>
<td>Relative risk 1.01 (CI 95% 0.84 — 1.21) Based on data from 735 participants in 2 studies. (^1) (Randomized controlled)</td>
<td>Standard dose VTE prophylaxis</td>
<td>Intermediate dose VTE prophylaxis</td>
<td>Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision (^2)</td>
<td>A pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 30 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>90 days</td>
<td>Relative risk 1.07 (CI 95% 0.89 — 1.29) Based on data from 562 participants in 1 studies. (^3) (Randomized controlled)</td>
<td></td>
<td></td>
<td>Low Due to serious indirectness and serious imprecision (^4)</td>
<td>Evidence from 1 study found no statistically significant difference in all-cause mortality at 90 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td>Relative risk 1.53 (CI 95% 0.54 — 4.28) Based on data from 735 participants in 2 studies. (^5) (Randomized controlled)</td>
<td></td>
<td></td>
<td>Very low Due to serious risk of bias, serious indirectness and serious</td>
<td>A pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with intermediate dose</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard dose VTE prophylaxis</td>
<td>Intervention Intermediate dose VTE prophylaxis</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
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<tr>
<td>VTE 30 days</td>
<td>Relative risk 1.02 (CI 95% 0.52 — 2) Based on data from 735 participants in 2 studies. 7 (Randomized controlled)</td>
<td>— 52 more )</td>
<td>imprecision 6</td>
<td>anticoagulant compared to standard prophylactic dose anticoagulant (dose and treatment varies) for those people who were hospitalised.</td>
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</tr>
<tr>
<td>VTE 90 days</td>
<td>Relative risk 0.93 (CI 95% 0.38 — 2.26) Based on data from 562 participants in 1 studies. 9 (Randomized controlled)</td>
<td>43 per 1000 Difference: 1 more per 1000 (CI 95% 21 fewer — 43 more)</td>
<td>Very low Due to serious risk of bias, serious indirectness and serious imprecision 8</td>
<td>A pooled analysis of 2 studies found no statistically significant difference in venous thromboembolism at 30 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
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<tr>
<td>Ventilator-free days 30 days</td>
<td>High better Based on data from 562 participants in 1 studies. (Randomized controlled)</td>
<td>30 (Median)</td>
<td>2 fewer per 1000 (CI 95% 22 fewer — 44 more)</td>
<td>Low Due to serious indirectness and serious imprecision 10</td>
<td>Evidence from 1 study found no statistically significant difference in venous thromboembolism at 90 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
<td></td>
</tr>
</tbody>
</table>

2. **Risk of Bias: serious.** Co-interventions (azithromycin) used more in intervention group in one study. **Inconsistency: no serious. Indirectness: serious.** Some patients have moderate in one study have moderate, not severe COVID-19. **Imprecision: serious.** No statistically significant effect. **Publication bias: no serious.**

4. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.** No statistically significant effect. **Publication bias: no serious.**


6. **Risk of Bias: serious.** Co-interventions (azithromycin) used more in intervention group in one study. **Inconsistency: no serious. Indirectness: serious.** Some patients in one study have moderate, not severe COVID-19. **Imprecision: serious.** No statistically significant effect. **Publication bias: no serious.**


8. **Risk of Bias: serious.** Co-interventions (azithromycin) used more in intervention group in one study. **Inconsistency: no serious. Indirectness: serious.** Some patients in one study have moderate, not severe COVID-19. **Imprecision: serious.** No statistically significant effect. **Publication bias: no serious.**


10. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.** No statistically significant effect. **Publication bias: no serious.**

11. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Unable to calculate effect size and 95% C.I. **Publication bias: no serious.**

**References**


Conditional recommendation

Consider a treatment dose of a low molecular weight heparin (LMWH) for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk.

Treatment should be continued for 14 days or until discharge, whichever is sooner. Dose reduction may be needed to respond to any changes in a person’s clinical circumstances.

*For people with COVID-19 who do not need low-flow oxygen, follow the recommendations in NICE’s guideline on venous thromboembolism in over 16s.*

*In August 2021, using a treatment dose of a LMWH outside the treatment of confirmed VTE was an off-label use of parenteral anticoagulants. See NICE’s information on prescribing medicines.*

Evidence to decision

Benefits and harms  
Small net benefit, or little difference between alternatives

The panel were presented with data from 3 randomised controlled trials (ACTION, ACTIVE-4a-ATTACC-REMAP-CAP and RAPID). These trials evaluated whether empiric use of treatment-dose anticoagulation improves clinical outcomes in adults in hospital with confirmed moderate COVID-19 (defined in this guideline as people receiving low-flow supplementary oxygen).

The panel agreed that, for adults with moderate COVID-19, the studies showed a trend towards improved mortality outcomes with a treatment dose of an anticoagulant compared with the standard prophylactic dose. One study reported no difference in survival to hospital discharge and a statistically significant increase in survival without organ support at 28 days. The panel also emphasised a trend towards a positive effect on VTE at 30 and 90 days, and a statistically significant increase in organ-support-free days.

The occurrence of major bleeding events is a well-recognised adverse outcome of anticoagulant treatment. The panel noted that the rate of major bleeding events was relatively low for adults in hospital with moderate COVID-19. Thus the benefits of treatment-dose prophylactic anticoagulation may outweigh the potential harms in this population.

The panel noted that the duration of treatment recommended should match the duration of the largest study included, which was 14 days or until discharge, whichever was sooner.

Certainty of the Evidence

Moderate

The outcomes of ACTION, ACTIVE-4a-ATTACC-REMAP-CAP and RAPID were of moderate to very low certainty.

The panel noted that the results from RAPID were preprint results. This meant they had not been peer reviewed, so they interpreted the results with the appropriate caution. Some of the group allocated to the standard prophylactic anticoagulant dose had higher doses in the ACTION and ACTIVE-4a-ATTACC-REMAP-CAP trials (between 26% and 29%), which the panel recognised could have affected the results. However, they considered that the evidence was certain enough to make recommendations to consider treatment-dose VTE prophylaxis in young people and adults with moderate COVID-19.

Values and preferences

No substantial variability expected

The panel were not aware of any systematically collected data on peoples’ preferences and values. The panel inferred
that, in view of the possible mortality benefits and increase in organ support-free days for people with COVID-19 who need low-flow oxygen, many would choose a treatment dose of an anticoagulant in spite of a potential increased risk of bleeding.

**Resources**

Cost effectiveness was not assessed as part of the evidence review.

The panel did not have concerns about opportunity costs when a low molecular weight heparin is being used for people who need low-flow oxygen. The panel decided to recommend that treatment is continued for up to 14 days. This may be longer than the standard treatment duration for acute illness (at least 7 days), so may be a higher resource use of anticoagulation in this group. This is to reflect the duration used in the trials contributing evidence to this recommendation.

**Equity**

The panel noted an absence of evidence for anticoagulation in children. They recognised that younger children have different haematological physiology, meaning that VTE is less likely. However, their clinical experience suggested that, after puberty, people under 18 years are also at risk of VTE if admitted to hospital with COVID-19. For that reason, the panel included young people in the recommendations as well as adults. Additionally, a research recommendation was made for this population.

For people under 16 years the risk of VTE is uncertain in the context of COVID-19. The risk benefit of VTE and dosing should be discussed by multidisciplinary teams on a case-by-case basis.

Not all heparins are acceptable to people of certain religions because the products are derived from animals. The panel made a recommendation about other treatments that can be used (including fondaparinux sodium, which is not animal derived).

No other equity issues were identified at this update.

**Acceptability**

The panel were not aware of any systematically collected evidence about acceptability. A potential deterring factor to acceptability could be that the certainty of current evidence is only moderate to very low. However, the panel noted that the direction of effect tended to favour treatment-dose anticoagulation for adults with COVID-19 who need low-flow supplemental oxygen.

It is anticipated that, when considering the risks and benefits of treatment, most young people and adults who are admitted to hospital with COVID-19, who need low-flow oxygen and who do not have an increased bleeding risk might favour treatment-dose anticoagulation.

**Feasibility**

Implementing use of treatment-dose VTE prophylaxis in young people and adults in hospital who are receiving low-flow oxygen is expected to be feasible because it represents an increase in the dose and duration of an established
Rationale
The panel agreed that some young people and adults with COVID-19 who need low-flow oxygen supplementation may benefit from a treatment dose of a low molecular weight heparin (LMWH). The evidence suggests that a treatment dose of an LMWH for adults with COVID-19 who are in hospital and needing low-flow oxygen supplementation may reduce the risk of death and need for organ support compared with a standard prophylactic dose. It also suggests an increased risk in major bleeding compared with a standard prophylactic dose. Because of the fine balance of benefits and harms, the panel agreed that this decision should be carefully considered, and that this choice should be guided by bleeding risk, clinical judgement and local protocols.

The treatment duration in the largest included trial was 14 days or until discharge, whichever was sooner. The panel thought that the timeframe for treatment should reflect the trial evidence.

Clinical question/ PICO

**Population:** People with moderate COVID-19  
**Intervention:** Treatment dose VTE prophylaxis  
**Comparator:** Standard dose VTE prophylaxis

Summary
What is the evidence informing this recommendation?

Evidence comes from 3 randomised controlled trials with 3,298 participants included.

One study (ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, reported in Lawler, 2021; n=2,219) compared treatment dose anticoagulant (UFH or LMWH, mainly enoxaparin) with standard dose venous thromboembolism prophylaxis (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) according to local protocols. Treatment dose LMWH or UFH were administered according to local protocols for up to 14 days or until recovery.

In the ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, most of the intervention group (94.7%) received treatment dose anticoagulation, most commonly enoxaparin and in the control group 71.7% received standard prophylactic dose thromboprophylaxis and 26.5% received intermediate-dose thromboprophylaxis.

The second study (ACTION trial, reported in Lopes, 2021, n=614) compared treatment dose anticoagulant (mainly rivaroxaban) for 30 days, with standard prophylactic dose anticoagulant (unfractionated heparin or enoxaparin) given whilst an inpatient and according to local hospital protocols.
Participants in the ACTION trial had a clinical ‘stable’ condition (93% and 95% in treatment and standard care group respectively), with a small proportion having a clinically ‘unstable’ condition (7% and 5% in treatment and standard care group respectively).

In the ACTION trial, most of the intervention group (94.8%) received treatment dose anticoagulation (92% rivaroxaban); stable patients were prescribed rivaroxaban 20mg once daily and clinically unstable patients SC enoxaparin 1mg/kg twice daily, or IV UFH.

Mortality and venous thromboembolism outcomes from the ACTION trial were calculated separately due to the usage of rivaroxaban as therapeutic dose anticoagulation not being standard practice in the UK.

The majority of the control group received prophylactic dose anticoagulation during hospitalisation (99.5%); unfractionated heparin/enoxaparin dosed according to local hospital protocols.

The third study (RAPID trial, reported in Sholzberg 2021, n=465) compared treatment dose anticoagulant (LMWH and UFH) with standard dose prophylactic anticoagulant (dose-capped subcutaneous heparin (LMWH or UFH)). Study treatment was continued until the first day of hospital discharge, for 28 days or until study withdrawal/death.

The majority of participants from the RAPID trial intervention group received treatment dose heparin (98.2%) and (93.7%) received prophylactic heparin as allocated in the first 48 hours post-randomisation. Participants were moderately ill hospitalised patients with elevated D-dimer levels.

Study Characteristics

The mean age in the studies ranged from 56 to 60, and between 54% and 76% of participants were male. Data for the ACTIVE-4a-ATTACC-REMAP-CAP and RAPID trials were collected from Brazil, Canada, Ireland, Netherlands, Australia, UK, Saudi Arabia, Mexico and USA. The ACTION trial was conducted in Brazil only (31 centres).

The definition of moderate severity varied between the studies. In the ACTIVE-4a-ATTACC-REMAP-CAP multi-platform trial, moderate disease severity was defined as hospitalisation for COVID-19 without the requirement for ICU-level of care. ICU-level of care was defined by use of respiratory or cardiovascular organ support (high flow nasal oxygen, non-invasive or invasive mechanical
ventilation, vasopressors, or inotropes) in an ICU. The ACTION trial defined moderate severity disease patients as those with an oxygen saturation <94%, pulmonary infiltrates <50%, or a partial pressure of oxygen to fractional concentration of oxygen in inspired air ratio <300. The RAPID trial defined disease severity as hospitalised patients with elevated D-dimer levels, above the upper limit of normal (ULN) of the local hospital in the presence of an oxygen saturation of ≤93% on room air, or ≥2 times the ULN irrespective of oxygen saturation levels.

The ACTION trial reported 14% of the participants were on high-flow oxygen, the rest were either on no oxygen or low-flow oxygen.

Exclusion criteria varied, but all studies excluded patients with a clinical indication for therapeutic anticoagulation and those who were at high risk of bleeding. The RAPID trial further excluded participants who were pregnant, and any participants that met any of the primary outcomes or would imminently meet them.

Duration of treatment ranged from up to 14 days (ACTIVE-4a-ATTACC-REMAP-CAP) to up to 30 days (RAPID and ACTION).

What are the main results?

Mortality at 30 days

Very low quality evidence from 2 studies found a non-statistically significant reduction in mortality at 30 days with treatment dose anticoagulant (mainly LMWH) compared with standard dose anticoagulant (UFH or LMWH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.50, CI 95% 0.13-1.88; 2,684 people in 2 studies].

Mortality at 30 days - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant increase in mortality at 30 days with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 1.49, CI 95% 0.90 - 2.46; 614 people in 1 study].

All cause mortality or need for invasive ventilation or non-invasive ventilation

Moderate quality evidence from 1 study found a non-statistically significant reduction in all cause mortality and need for ventilation with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.63, CI 95% 0.39 -1.02; 465 people in 1 study].
Death or need for invasive ventilation or non-invasive ventilation or ICU admission

Moderate quality evidence from 1 study found a non-statistically significant reduction in death and need for ventilation and ICU admission with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.75, CI 95% 0.51 – 1.11; 465 people in 1 study].

Survival

Survival to hospital discharge

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant (mainly enoxaparin) compared with standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 1.01, CI 95% 0.99-1.03; 2,219 people in 1 study].

Survival to hospital discharge without major thrombotic events (a composite of freedom from myocardial infarction, pulmonary embolism, ischemic stroke, systemic arterial embolism, and in-hospital death)

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge without major thrombotic events with treatment dose anticoagulant (mainly enoxaparin) compared with standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.02, CI 95% 1.00-1.05; 2,226 people in 1 study].

Survival to hospital discharge without any macrovascular thrombotic events (the components of major thrombotic events and symptomatic deep venous thrombosis)

Low quality evidence from 1 study found no statistically significant difference in survival to hospital discharge without any macrovascular thrombotic events with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.02, CI 95% 1.00-1.05; 2,226 people in 1 study].
Survival without organ support 28 days

Moderate quality evidence from 1 study found a statistically significant increase in survival without organ support at 28 days with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 1.05, CI 95% 1.01-1.10; 2,221 people in 1 study].

Organ support free days at day 21 (defined as survival to hospital discharge and, among survivors, the number of days free of ICU-level organ support through day 21)

Moderate quality evidence from 1 study found a statistically significant increase in organ support-free days at 21 days with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Mean 25.8 in treatment versus 24.1 standard; CI 95% 0.32 - 3.08; 465 people in 1 study].

VTE

Venous thromboembolism at 30 days

Moderate quality evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.30 CI 95% 0.06 - 1.41; 465 people in 1 study].

Venous thromboembolism at 30 days - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.60, CI 95% 0.29-1.24; 614 people in 1 study].

Composite Thrombotic Outcome: Any venous thromboembolism, myocardial infarction, stroke, systemic embolism, and major adverse limb events

Moderate quality evidence from 1 study found a non-statistically significant reduction in the composite thrombotic outcome with treatment dose anticoagulant (mainly rivaroxaban) compared
to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.75, CI 95% 0.45-1.26; 614 people in 1 study].

ICU admission

Moderate quality evidence from 1 study found a non-statistically significant reduction in ICU admission with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19 [Relative risk 0.82, CI 95% 0.54-1.24; 465 people in 1 study].

Need for invasive ventilation or non-invasive ventilation

Moderate quality evidence from 1 study found no statistically significant difference in need for invasive ventilation or non-invasive ventilation with treatment dose anticoagulant (mainly enoxaparin) compared to standard dose anticoagulant (enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin) for people who were hospitalised with moderate COVID-19. [Relative risk 0.84, CI 95% 0.49-1.45; 465 people in 1 study].

Adverse events

Major bleeding was defined in both studies according to the International Society on Thrombosis and Haemostasis.

Major bleeding

Low quality evidence from a pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard dose anticoagulant for people who were hospitalised with moderate COVID-19. [Relative risk 1.30, CI 95% 0.34-4.98; 2,692 people in 2 studies].

Major bleeding - Rivaroxaban

Low quality evidence from 1 study found a non-statistically significant increase in major bleeding with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19. [Relative risk 2.45, CI 95% 0.78-7.73; 614 people in 1 study].

Clinically relevant non-major bleeding - Rivaroxaban

Moderate quality evidence from 1 study found a statistically significant increase in clinically relevant non-major bleeding with treatment dose anticoagulant (mainly rivaroxaban) compared to standard dose anticoagulant (UFH or enoxaparin) for people who were hospitalised with moderate COVID-19 [Relative risk 5.23, CI 95% 1.54-17.77; 614 people in 1 study].
Our confidence in the results

All studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. One study was a pre-print (RAPID) and two were published manuscripts (ACTION and ACTIVE-4a-ATTACC-REMAP-CAP).

Certainty of the evidence is very low for mortality at 30 days due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate-dose thromboprophylaxis), serious indirectness (mortality was calculated by NICE by subtracting survival from total number of events) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for mortality at 30 days with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and serious imprecisions (confidence intervals cross the line of no effect).

Certainty of the evidence is moderate for all cause mortality or need for invasive ventilation and non-invasive ventilation due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for death or need for invasive ventilation or non-invasive ventilation or ICU admission due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence varies for survival outcomes.

Certainty of the evidence is low for survival to hospital discharge, survival to hospital discharge without any major thrombotic events and survival to hospital discharge without any macrovascular thrombotic events, due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate-dose thromboprophylaxis) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for survival without organ support for 28 days due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate-dose thromboprophylaxis).

Certainty of the evidence is moderate for venous thromboembolism at 30 days due to serious imprecision (confidence intervals include the line of no effect).
Certainty of the evidence is low for venous thromboembolism at 30 days with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty if the evidence is moderate for Composite Thrombotic Outcome, due to serious imprecision (confidence interval includes the line of no effect).

Certainty of the evidence is low for major bleeding due to serious risk of bias (26.5% of participants in the standard care arm receiving intermediate-dose thromboprophylaxis) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for major bleeding with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is moderate for clinically relevant non-major bleeding with mainly rivaroxaban treatment due to serious risk of bias (deviations in dosage of participants with rivaroxaban).

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<tr>
<td>Mortality</td>
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<tr>
<td>30 days</td>
<td>Relative risk 0.5 (CI 95% 0.13 — 1.88) Based on data from 2,684 participants in 2 studies. ¹</td>
<td>Standard dose</td>
<td>Treatment dose VTE prophylaxis</td>
<td>Very low due to serious indirectness, Due to serious imprecision, Due to serious risk of bias ²</td>
<td>A pooled analysis of 2 studies found a non-statistically significant reduction in mortality after 30 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
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<td>9 Critical</td>
<td>(Randomized controlled)</td>
<td>VTE prophylaxis</td>
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<td>Mortality - rivaroxaban</td>
<td>Relative risk 1.49 (CI 95% 0.9 — 2.46) Based on data from 614 participants in 1 studies. ³</td>
<td></td>
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<td>Low Due to serious risk of bias, Due to serious</td>
<td>Evidence from 1 study found a non-statistically significant increase in mortality at 30 days with treatment dose</td>
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<tr>
<td>30 days</td>
<td>(Randomized controlled)</td>
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<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
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</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
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<tr>
<td>30 days</td>
<td>Relative risk 0.5 (CI 95% 0.13 — 1.88) Based on data from 2,684 participants in 2 studies. ¹</td>
<td>Standard dose</td>
<td>Treatment dose VTE prophylaxis</td>
<td>Very low due to serious indirectness, Due to serious imprecision, Due to serious risk of bias ²</td>
<td>A pooled analysis of 2 studies found a non-statistically significant reduction in mortality after 30 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>9 Critical</td>
<td>(Randomized controlled)</td>
<td>VTE prophylaxis</td>
<td></td>
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<tr>
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<tr>
<td>Mortality - rivaroxaban</td>
<td>Relative risk 1.49 (CI 95% 0.9 — 2.46) Based on data from 614 participants in 1 studies. ³</td>
<td></td>
<td></td>
<td>Low Due to serious risk of bias, Due to serious</td>
<td>Evidence from 1 study found a non-statistically significant increase in mortality at 30 days with treatment dose</td>
</tr>
<tr>
<td>30 days</td>
<td>(Randomized controlled)</td>
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<td></td>
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<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence</td>
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<tr>
<td>9 Critical</td>
<td>controlled)</td>
<td>Standard dose VTE prophylaxis</td>
<td>rivaroxaban compared to standard prophylactic dose anticoagulant for people who were hospitalised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality or need for IV or NIV</td>
<td>(Randomized controlled)</td>
<td>Treatment dose VTE prophylaxis</td>
<td>imprecision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Critical</td>
<td>Relative risk 0.63 (CI 0.39 — 1.02) Based on data from 465 participants in 1 studies.</td>
<td>(CI 95% 8 fewer — 111 more )</td>
<td>1000</td>
<td>Moderate Due to serious imprecision</td>
<td></td>
</tr>
<tr>
<td>Death / need for IV or NIV / ICU admission</td>
<td>(Randomized controlled)</td>
<td>Difference: 160 per 1000</td>
<td>Evidence from 1 study found a non-statistically significant reduction in all cause mortality and need for ventilation with with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
<td></td>
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</tr>
<tr>
<td>9 Critical</td>
<td>Relative risk 0.75 (CI 0.51 — 1.11) Based on data from 465 participants in 1 studies.</td>
<td>(CI 95% 59 fewer — 3 more )</td>
<td>101</td>
<td>Moderate Due to serious imprecision</td>
<td></td>
</tr>
<tr>
<td>Survival to hospital discharge</td>
<td>(Randomized controlled)</td>
<td>Difference: 215 per 1000</td>
<td>Evidence from 1 study found a non-statistically significant reduction in death and need for ventilation and ICU admission with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
<td></td>
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</tr>
<tr>
<td>9 Critical</td>
<td>Relative risk 1.01 (CI 0.99 — 1.03) Based on data from 2,219 participants in 1 studies.</td>
<td>(CI 95% 54 fewer — 24 more )</td>
<td>161</td>
<td>Moderate Due to serious imprecision</td>
<td></td>
</tr>
<tr>
<td>Survival to hospital discharge without major thrombotic events</td>
<td>(Randomized controlled)</td>
<td>Difference: 918 per 1000</td>
<td>Evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
<td></td>
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</tr>
<tr>
<td>9 Critical</td>
<td>Relative risk 1.02 (CI 0.99 — 1.05) Based on data from 2,226 participants in 1 studies.</td>
<td>(CI 95% 9 more — 28 more )</td>
<td>927</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td></td>
</tr>
<tr>
<td>Survival to hospital discharge without major thrombotic events</td>
<td>(Randomized controlled)</td>
<td>Difference: 901 per 1000</td>
<td>Evidence from 1 study found no statistically significant difference in survival to hospital discharge without major thrombotic events with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard dose VTE prophylaxis</td>
<td>Intervention Treatment dose VTE prophylaxis</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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<tr>
<td>9 Critical</td>
<td></td>
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<td>treatment dose anticoagulant compared with standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>Survival to hospital discharge without any macrovascular thrombotic events</td>
<td>Relative risk 1.02 (CI 95% 1 — 1.05) Based on data from 2,226 participants in 1 studies. (Randomized controlled)</td>
<td>897 per 1000</td>
<td>915 per 1000</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>Evidence from 1 study found no statistically significant difference in survival to hospital discharge without any macrovascular thrombotic events with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>Venous thromboemboli sm 30 days</td>
<td>Relative risk 0.3 (CI 95% 0.06 — 1.41) Based on data from 465 participants in 1 studies. (Randomized controlled)</td>
<td>30 per 1000</td>
<td>9 per 1000</td>
<td>Moderate Due to serious imprecision</td>
<td>Evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>Venous thromboemboli sm - rivaroxaban 30 days</td>
<td>Relative risk 0.6 (CI 95% 0.29 — 1.24) Based on data from 615 participants in 1 studies. (Randomized controlled)</td>
<td>59 per 1000</td>
<td>35 per 1000</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>Evidence from 1 study found a non-statistically significant reduction in venous thromboembolism at 30 days with treatment dose anticoagulant compared to standard dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>Composite Thrombotic Outcome</td>
<td>Relative risk 0.75 (CI 95% 0.45 — 1.26) Based on data from 614 participants in 1 studies. (Randomized controlled)</td>
<td>99 per 1000</td>
<td>74 per 1000</td>
<td>Moderate Due to serious imprecision</td>
<td>Evidence from 1 study found a non-statistically significant reduction in thrombotic events (defined as any venous</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator Standard dose VTE prophylaxis</td>
<td>Intervention Treatment dose VTE prophylaxis</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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<tr>
<td>9 Critical</td>
<td></td>
<td></td>
<td>(CI 95% 54 fewer — 26 more)</td>
<td>thromboembolism, myocardial infarction, stroke, systemic embolism, and major adverse limb events</td>
<td>A pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
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<tr>
<td>Major bleeding</td>
<td>Relative risk 1.3 (CI 95% 0.34 — 4.98) Based on data from 2,692 participants in 2 studies. (Randomised controlled)</td>
<td>10 per 1000</td>
<td>13 per 1000</td>
<td>Low</td>
<td>Due to serious risk of bias, Due to serious imprecision</td>
</tr>
<tr>
<td>9 Critical</td>
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<tr>
<td>Major bleeding - rivaroxaban</td>
<td>Relative risk 2.45 (CI 95% 0.78 — 7.73) Based on data from 614 participants in 1 studies. (Randomised controlled)</td>
<td>13 per 1000</td>
<td>32 per 1000</td>
<td>Low</td>
<td>Due to serious risk of bias, Due to serious imprecision</td>
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<tr>
<td>9 Critical</td>
<td></td>
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<tr>
<td>Survival without organ support 28 days</td>
<td>Relative risk 1.3 (CI 95% 1 — 1.61) Based on data from 2,219 participants in 1 studies. (Randomised controlled)</td>
<td>754 per 1000</td>
<td>980 per 1000</td>
<td>Moderate</td>
<td>Due to serious risk of bias,</td>
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<tr>
<td>6 Important</td>
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<td></td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding - rivaroxaban</td>
<td>Relative risk 5.23 (CI 95% 1.54 — 17.77) Based on data from 614 participants in 1 studies.</td>
<td>10 per 1000</td>
<td>52 per 1000</td>
<td>Moderate</td>
<td>Due to serious risk of bias,</td>
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COVID-19 rapid guideline: Managing COVID-19 - The National Institute for Health and Care Excellence (NICE)
<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>6 Important</td>
<td>27 (Randomized controlled)</td>
<td>Standard dose VTE prophylaxis</td>
<td>1000 (CI 95% 5 more — 168 more)</td>
<td>Major bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>6 Important</td>
<td>Relative risk 0.82 (CI 95% 0.54 — 1.24) Based on data from 465 participants in 1 studies. 29 (Randomized controlled)</td>
<td>177 per 1000</td>
<td>145 per 1000</td>
<td>Moderate Due to serious imprecision 30</td>
<td>Evidence from 1 study found a non-statistically significant reduction in ICU admission with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>Need for IV or NIV</td>
<td>6 Important</td>
<td>Relative risk 0.84 (CI 95% 0.49 — 1.45) Based on data from 465 participants in 1 studies. 31 (Randomized controlled)</td>
<td>110 per 1000</td>
<td>92 per 1000</td>
<td>Moderate Due to serious imprecision 32</td>
<td>Evidence from 1 study found no statistically significant difference in need for invasive ventilation or non-invasive ventilation with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>Organ support-free days</td>
<td>6 Important</td>
<td>Based on data from 465 participants in 1 studies. 33 (Randomized controlled)</td>
<td>24.1 (Mean)</td>
<td>25.8 (Mean)</td>
<td>Moderate Due to serious risk of bias 34</td>
<td>Evidence from 1 study found a statistically significant increase in organ support-free days at 21 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
</tbody>
</table>

2. **Risk of Bias:** serious. Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-
dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: serious.** Mortality in REMAP-CAP was calculated by NICE (through subtracting no. survival until discharge from total no. of events). **Imprecision: serious.** 95% CI crossed line of no effect. **Publication bias: no serious.**


4. **Risk of Bias: serious.** Small number of participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**


6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**


8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**


10. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crosses line of no effect. **Publication bias: no serious.**


12. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed line of no effect. **Publication bias: no serious.**


14. **Risk of Bias: serious.** Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect. **Publication bias: no serious.**


16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% CI crossed the line of no effect. **Publication bias: no serious.**


18. **Risk of Bias: serious.** Due to study design where participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**


20. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 95% confidence interval crossed the line of no effect. **Publication bias: no serious.**

22. **Risk of Bias**: serious. Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: serious. Wide confidence intervals. **Publication bias**: no serious.


24. **Risk of Bias**: serious. Participants who were dosed with either 20mg rivaroxaban/15mg rivaroxaban and azithromycin or enoxaparin in severe patients. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: serious. 95% CI crossed line of effect. **Publication bias**: no serious.


26. **Risk of Bias**: serious. Deviation from intervention: of participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: no serious. **Publication bias**: no serious.


28. **Risk of Bias**: serious. 13% were prescribed treatment beyond hospital discharge. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: no serious. **Publication bias**: no serious.


30. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: serious. 95% CI crossed the line of no effect. **Publication bias**: no serious.


32. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: serious. 95% CI crossed the line of no effect. **Publication bias**: no serious.


34. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: no serious. **Publication bias**: no serious.

**References**

52. Heparins for COVID-19.


Only in research settings

Only offer an intermediate or treatment dose of a low molecular weight heparin to young people and adults with COVID-19 who are receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation as part of a clinical trial.

**Evidence to decision**

**Benefits and harms**

The panel were presented with data from 4 open-label randomised controlled trials (INSPIRATION, ATTACC, ACTIV-4a, REMAP-CAP, HESACOVID and Perepu [2021]). These trials evaluated the effectiveness and safety of pharmacological prophylaxis to reduce the risk of VTE in adults having care for severe COVID-19 (that is, receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation).

**Intermediate-dose anticoagulant**

Two studies compared intermediate-dose anticoagulation with the standard prophylactic dose (INSPIRATION and Perepu [2021]). The panel agreed that, for adults with severe COVID-19, the studies showed no statistically significant benefit for mortality, VTE prophylaxis or ventilator-free days with an intermediate dose of an anticoagulant compared with the standard prophylactic dose. There was, however, no indication of increased bleeding with an intermediate dose compared with the standard prophylactic dose.

**Treatment-dose anticoagulant**

Two studies compared a treatment dose of an anticoagulant with the standard prophylactic dose (HESACOVID and ATTACC-ACTIV-4a-REMAP-CAP). The panel agreed that, for adults with severe COVID-19, the studies showed no statistically significant benefit for mortality or organ support-free days with a treatment dose of an anticoagulant compared with the standard prophylactic dose. There was no sign of increased bleeding with a treatment dose compared with the standard prophylactic dose.

**Other considerations**

The panel noted that 1 study showed an increase in ventilator-free days with treatment-dose anticoagulation. However, they agreed that the results were not certain enough to base a recommendation on because the study was very small.

The panel recommended not to base prophylactic dosing of heparin on levels of D-dimer because 1 trial presented evidence showing that a person’s D-dimer measurements did not influence the effects of VTE prophylaxis.
Based on the lack of clear benefit with intermediate- or treatment-dose anticoagulation, the panel concluded that young people and adults with severe COVID-19 should be offered standard prophylactic-dose anticoagulation, and that intermediate- or treatment-dose VTE prophylaxis should not be used apart from as part of a clinical trial.

The panel discussed what to do if someone is already on treatment-dose anticoagulation at admission. They noted that people would normally remain on their prescribed anticoagulation if they can take oral medicines. However, they would switch to a low molecular weight heparin when they could no longer take oral medicines, such as when admitted to an intensive care unit.

**Certainty of the Evidence**

INSPIRATION, REMAP-CAP, HESACOVID and Perepu et al. (2021) evaluated the effectiveness and safety of pharmacological prophylaxis to reduce the risk of VTE in adults having care for severe COVID-19.

The panel noted that the interventions that people had were mixed because of the local practices of the sites taking part in the trial. The panel recognised that the HESACOVID trial was very small and likely to be underpowered for the results it presented. Around 45% of people in INSPIRATION did not match the definition of ‘severe COVID-19’ used here. This was reflected in the lower rates of VTE than the committee expected to see in a population with severe COVID-19. The panel took these factors into account when considering the evidence.

**Values and preferences**

The panel were not aware of any systematically collected data on peoples’ preferences and values. The panel inferred that, in view of the lack of clear benefit of intermediate- or treatment-dose anticoagulation, most would choose a standard prophylactic dose of an anticoagulant.

**Resources**

Cost effectiveness was not assessed as part of the evidence review.

The panel recommended that standard prophylactic-dose anticoagulation is used, rather than higher doses. This means there is expected to be no increase in cost related to the treatment.

**Equity**

The panel noted an absence of evidence for anticoagulation in children. They recognised that younger children have different haematological physiology, meaning that VTE is less likely. However, their clinical experience suggested that, after puberty, people under 18 years are also at risk of VTE if admitted to hospital with COVID-19. For that reason, the panel included young people in the recommendations as well as adults. Additionally, a research recommendation was made for this population.

For people under 16 years, the risk of VTE is uncertain in the context of COVID-19. The risk benefit of VTE and dosing should preferably be discussed in multidisciplinary teams on a case-by-case basis considering all risk factors.
Rationale

Based on the lack of clear benefit with intermediate- or treatment-dose anticoagulation, the panel concluded that young people and adults with severe COVID-19 should be offered standard prophylactic-dose anticoagulation. They also concluded that intermediate- or treatment-dose VTE prophylaxis should only be used as part of a clinical trial.

The panel were aware of ongoing trials of low molecular weight heparins (LMWHs) that use intermediate or treatment doses in this group of people, including REMAP-CAP. They agreed that intermediate- or treatment- dose LMWHs should only be used for VTE prophylaxis in this group as part of a clinical trial to support recruitment into these trials.

Acceptability

It is anticipated that, after considering the risks and benefits of treatment, most young people and adults who are admitted to hospital with severe COVID-19 would choose to have standard prophylactic-dose anticoagulation. However, we have no systematically collected evidence about acceptability.

Feasibility

Using standard prophylactic doses in young people and adults receiving high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation reflects usual treatment in some centres. For others, it is a minor treatment adjustment that should be feasible to implement.

Clinical question/ PICO

Population: People with severe COVID-19

Intervention: Treatment dose VTE prophylaxis

Comparator: Standard dose VTE prophylaxis

Summary

What is the evidence informing this recommendation?

Evidence comes from 2 randomised controlled trials with 1,089 participants included. Both studies (HESACOVID trial, reported in Lemos, 2020, n=20; and ACTIVE-41, ATACC, REMAP-CAP multiplatform trial, reported in Lawler, 2021, n=1,098) compared treatment dose anticoagulant (unfractionated heparin (UFH) or low molecular weight heparin (LMWH)) with either prophylactic or intermediate dose anticoagulant (mainly enoxaparin).

The comparator group varies between studies. In the HESACOVID trial, half of the comparator...
The group received UFH and half received prophylactic dose enoxaparin. The ACTIVE-41, ATACC, REMAP-CAP trial combines data from three sites, each operating under their own protocols. The protocols are very similar but allow for local practice, meaning that just over 40% of the comparator arm received prophylactic dose enoxaparin, just over 50% received intermediate dose enoxaparin, and 7.4% received either subtherapeutic (dose unclear) or therapeutic dose of either UFH or LMWH. This may reduce the validity of the results from the ACTIVE-41, ATACC, REMAP-CAP trial.

**Study characteristics**

The mean age in the studies ranged from 55 to 61, and between 68% and 90% of participants were male. Both studies included only adult patients receiving intensive care unit-level respiratory or cardiovascular support. Data was collected from Australia, Brazil, Canada, Ireland, Mexico, Netherlands, New Zealand, Saudi Arabia, UK, and USA.

Exclusion criteria varied, but both studies excluded patients with a separate clinical indication for therapeutic anticoagulation. One study excluded patients over 85.

Duration of treatment was 4-14 days in HESACOVID, and up to 14 days or hospital discharge in ACTIVE-41, ATACC, REMAP-CAP.

**What are the main results?**

**All-cause mortality**

Very low quality evidence from 1 study found a non-statistically significant reduction in all-cause mortality at 28 days with treatment dose anticoagulant (LMWH or UFH) compared to either prophylactic or intermediate dose anticoagulant (mainly enoxaparin) for people who were hospitalised. [Relative risk 0.33 CI 95% 0.04 - 2.69; 20 people in 1 study].

**Death in hospital**

Low quality evidence from a pooled analysis of 2 studies found no significant difference for death in hospital with treatment dose anticoagulant (LMWH at varying doses) compared with either UFH, enoxaparin or usual care venous thromboprophylaxis (dose and treatment varies) for people who were hospitalised. [Relative risk 1.03, CI 95% 0.89-1.21; 1,118 people in 2 studies].

**Survival to hospital discharge**

Low quality evidence from 1 study found no significant difference for survival to hospital discharge with treatment dose anticoagulant compared with usual care venous thromboprophylaxis (dose and treatment varies) for people who were hospitalised. [Relative risk 0.97, CI 95% 0.89-1.06; 1,098 people in 1 study].
Serious Adverse events: Major bleeding

Low quality evidence from a pooled analysis of 2 studies found no significant difference in major bleeding with treatment dose anticoagulant compared with prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised. [Relative risk 1.63, CI 95% 0.82 - 3.25; 1,111 people in 2 studies].

Organ-support free days at 21 days

Low quality evidence from 1 study found no statistically significant difference in organ-support free days with treatment dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Odds Ratio 0.83, CI 95% 0.67 - 1.03; 1,098 people in 1 study].

Ventilator-free days

Low quality evidence from 1 study found a statistically significant increase in ventilator-free days at 28 days with treatment dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Median 15 versus 0; 20 people in 1 study].

Our confidence in the results

All studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. The two studies were published manuscripts (ACTIVE-41, ATACC, REMAP-CAP and HESACOVID). Following the peer reviewed publication of ACTIVE-41, ATACC, REMAP-CAP (26/08/2021), the data for some of the outcomes was updated to reflect the latest figures in the published manuscript.

There were significant deviations from the intended interventions reported in one study (ACTIVE-41, ATACC, REMAP-CAP) whereby a large proportion of the comparator group received intermediate rather than prophylactic dose anticoagulant. In addition, almost 15% of the treatment group received either low or intermediate dose anticoagulant, where the intended intervention was treatment dose anticoagulant. This means the results from this study are unclear.

One study (HESACOVID) contained only 20 participants (10 in each arm). This trial did not have sufficient power to assess a difference in mortality, and results may be due to chance. This should be considered when looking at the increase in ventilator free days in the treatment group reported by this study.

Certainty of the evidence is very low for all-cause mortality due to serious risk of bias (deviation from intended control group treatment) and very serious imprecision (confidence intervals include the line of no effect and low numbers of participants).
Certainty of the evidence is low for death in hospital due to serious risk of bias, serious inconsistency (high statistical heterogeneity) and serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for survival to hospital discharge due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for major bleeding due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for organ support free days due to serious risk of bias and serious imprecision.

Certainty of the evidence is low for ventilator-free days due to very serious imprecision (confidence intervals include the line of no effect and unable to calculate effect size and 95% confidence intervals).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
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<th>Certainty of the Evidence (Quality of evidence)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>28 days</td>
<td>Relative risk 0.33 (CI 95% 0.04 — 2.69) Based on data from 20 participants in 1 studies. 1 (Randomized controlled)</td>
<td>Standard dose VTE prophylaxis</td>
<td>Treatment dose VTE prophylaxis</td>
<td>Very low Due to serious risk of bias and very serious imprecision 2</td>
<td>Evidence from 1 study found a non-statistically significant reduction in all-cause mortality at 28 days with treatment dose anticoagulant (unfractionated heparin or low molecular weight heparin) compared to either standard prophylactic or intermediate dose anticoagulant (mainly enoxaparin) for people who were hospitalised.</td>
</tr>
<tr>
<td>9 Critical</td>
<td></td>
<td></td>
<td>300 per 1000</td>
<td>99 per 1000</td>
<td>201 fewer per 1000 ( CI 95% 288 fewer — 507 more )</td>
<td></td>
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<tr>
<td>Death in hospital</td>
<td></td>
<td>Relative risk 1.03 (CI 95% 0.89 — 1.21) Based on data from 1,118 participants in 2 studies. 3 (Randomized controlled)</td>
<td>357 per 1000</td>
<td>368 per 1000</td>
<td>Low Due to serious risk of bias, Due to serious imprecision 4</td>
<td>A pooled analysis of 2 studies found no statistically significant difference in death in hospital with treatment dose anticoagulant (low molecular weight heparin at varying doses) compared to either unfractionated</td>
</tr>
<tr>
<td>9 Critical</td>
<td></td>
<td></td>
<td>Difference:</td>
<td>Difference:</td>
<td>11 more per 1000 ( CI 95% 39 fewer — 75 more )</td>
<td></td>
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<tr>
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</tr>
<tr>
<td>Survival to hospital discharge</td>
<td>9 Critical</td>
<td>Relative risk 0.97 (CI 95% 0.89 — 1.06) Based on data from 1,098 participants in 1 studies.</td>
<td>Standard dose VTE prophylaxis</td>
<td>Treatment dose VTE prophylaxis</td>
<td>Low (Due to serious risk of bias, Due to serious imprecision)</td>
<td>Evidence from 1 study found no statistically significant difference in survival to hospital discharge with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised.</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>9 Critical</td>
<td>Relative risk 1.63 (CI 95% 0.82 — 3.25) Based on data from 1,111 participants in 2 studies.</td>
<td>Standard dose VTE prophylaxis</td>
<td>Treatment dose VTE prophylaxis</td>
<td>Low (Due to serious risk of bias, Due to serious imprecision)</td>
<td>A pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant (dose and treatment varies) for people who were hospitalised.</td>
</tr>
<tr>
<td>Organ support free days</td>
<td>6 Important</td>
<td>Odds ratio 0.83 (CI 95% 0.67 — 1.03) Based on data from 1,098 participants in 1 studies.</td>
<td>Standard dose VTE prophylaxis</td>
<td>Treatment dose VTE prophylaxis</td>
<td>Low (Due to serious risk of bias, Due to serious imprecision)</td>
<td>Evidence from 1 study found no statistically significant difference in organ support free days at 21 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>6 Important</td>
<td>High better Based on data from 20 participants in 1 studies.</td>
<td>Standard dose VTE prophylaxis</td>
<td>Treatment dose VTE prophylaxis</td>
<td>Low (Due to very serious imprecision)</td>
<td>Evidence from 1 study found a statistically significant increase in ventilator-free days at 28 days with treatment dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
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<td>Outcome Timeframe</td>
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<tr>
<td></td>
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<td>prophylactic dose anticoagulant for people who were hospitalised.</td>
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</tbody>
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2. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis), due to [reason]. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** No statistically significant effect, and low number of patients., due to [reason]. **Publication bias: no serious.**


4. **Risk of Bias: serious.** Among participants allocated to usual care thromboprophylaxis, 71.7% (613/855) received low-dose and 26.5% (227/855) received intermediate-dose thromboprophylaxis). **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI included line of no effect. **Publication bias: no serious.**


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10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Unable to calculate effect size and 95% C.I. **Publication bias: no serious.**

References


Clinical question/ PICO

**Population:** People with severe COVID-19  
**Intervention:** Intermediate dose VTE prophylaxis  
**Comparator:** Standard dose VTE prophylaxis

Summary
What is the evidence informing this recommendation?

Evidence comes from 2 randomised controlled trials with 735 participants included. Both studies (INSPIRATION trial, reported in Sadeghipour 2021 [for 30 day outcomes] and Bikdeli, 2021 [for 90 day outcomes], n=562 and Perepu 2021 n=173) compared intermediate dose enoxoparin (1mg/kg daily if the BMI was <30 or 0.5 mg/kg SC twice daily if the BMI was ≥30) with prophylactic dose enoxaparin (40mg daily).

The intervention and comparator groups were consistent between the studies. However, Perepu (2021) allowed for cointerventions, and more patients received azithromycin in the intermediate dose arm (29%) than in the prophylactic dose arm (13%).

Study characteristics

The mean age in the studies ranged from 61 to 65, and between 56% and 58% of participants were male. Both studies investigate the effects of the interventions in severe patients, but approximately 45% of the participants in the INSPIRATION trial were receiving low-flow oxygen and would therefore not be classed as having severe COVID-19 by the definitions used in the study protocol. The proportion of participants in Perepu (2021) receiving low-flow oxygen is unclear: it is reported that 62% were admitted to intensive care and 23% received invasive mechanical ventilation.

Data was collected from IRAN (INSPIRATION trial) and the USA (Perepu 2021). Participants were excluded if they had recent known major bleeding or indications for a therapeutic dose of anticoagulant. Both studies excluded pregnant women. Duration of treatment was until hospital discharge (Perepu 2021) or for 30 and 90 days (INSPIRATION).

What are the main results?
All-cause mortality

Very low quality evidence from a pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 30 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.01, CI 95% 0.84—1.21; 735 people in 2 studies].

Low quality evidence from 1 study found no significant difference for all-cause mortality at 90 days with intermediate dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.07, CI 95% 0.89 - 1.29; 562 people in 1 study]

Serious Adverse events: Major bleeding

Very low quality evidence from a pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with intermediate dose anticoagulant compared to prophylactic dose anticoagulant (dose and treatment varies) for those people who were hospitalised. [Relative risk 1.53, CI 95% 0.54 -4.28; 735 people in 2 studies]

Venous thromboembolism

Very low quality evidence from a pooled analysis of 2 studies found no statistically significant difference in venous thromboembolism at 30 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 1.02, CI 95% 0.52 — 2.00; 735 people in 2 studies]

Low quality evidence from 1 study found no statistically significant difference in venous thromboembolism at 90 days with intermediate dose anticoagulant compared to prophylactic dose anticoagulant for people who were hospitalised. [Relative risk 0.93, CI 95% 0.38 — 2.26; 562 people in 1 study]

Ventilator-free days

Very low quality evidence from 1 study found no significant difference for ventilator-free days at 30 days with intermediate dose anticoagulant compared with prophylactic dose anticoagulant for people who were hospitalised. [Median 30 days in intermediate dose group versus 30 days in prophylactic dose group; 562 people in 1 study].

Our confidence in the results

Both studies were open-label. While there are clear reasons for this, and it is unlikely to affect the incidence of objective outcomes, it is possible that measurement bias occurred. One study was a pre-print (Perepu, 21). The other study was from published manuscripts that reported 30 day and
90 day outcomes separately (INSPIRATION 2021).

Certainty of the evidence is low or very low for mortality outcomes due to risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is very low for major bleeding due to risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is very low for VTE outcomes at 30 days due to serious risk of bias (uneven distribution of co-interventions), serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of the evidence is low for VTE outcomes at 90 days to serious indirectness (approximately 45% of participants in INSPIRATION trial did not meet criteria for severe COVID-19) and due to serious imprecision (confidence intervals include the line of no effect).

Certainty of evidence is very low for ventilator-free days at 30 days due to very serious imprecision (confidence intervals include the line of no effect and unable to calculate effect size and 95% confidence intervals) and serious indirectness (dissimilarity between population of interest and those studied).

<table>
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<tr>
<td>All-cause mortality 30 days 9 Critical</td>
<td></td>
<td>Standard dose VTE prophylaxis</td>
<td>Intermediate dose VTE prophylaxis</td>
<td>Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision</td>
<td>A pooled analysis of 2 studies found no statistically significant difference in all-cause mortality at 30 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
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<td>Outcome Timeframe</td>
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</tr>
<tr>
<td>All-cause mortality 90 days</td>
<td>Relative risk 1.07 (CI 95% 0.89 — 1.29) Based on data from 562 participants in 1 studies.</td>
<td>430 per 1000</td>
<td>460 per 1000</td>
<td>Low</td>
<td>Evidence from 1 study found no statistically significant difference in all-cause mortality at 90 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>Relative risk 1.53 (CI 95% 0.54 — 4.28) Based on data from 735 participants in 2 studies.</td>
<td>16 per 1000</td>
<td>24 per 1000</td>
<td>Very low</td>
<td>A pooled analysis of 2 studies found a non-statistically significant increase in major bleeding with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant (dose and treatment varies) for those people who were hospitalised.</td>
</tr>
<tr>
<td>VTE 30 days</td>
<td>Relative risk 1.02 (CI 95% 0.52 — 2) Based on data from 735 participants in 2 studies.</td>
<td>43 per 1000</td>
<td>44 per 1000</td>
<td>Very low</td>
<td>A pooled analysis of 2 studies found no statistically significant difference in venous thromboembolism at 30 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>VTE 90 days</td>
<td>Relative risk 0.93 (CI 95% 0.38 — 2.26) Based on data from 562 participants in 1 studies.</td>
<td>35 per 1000</td>
<td>33 per 1000</td>
<td>Low</td>
<td>Evidence from 1 study found no statistically significant difference in venous thromboembolism at 90 days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>High better</td>
<td>30 (Median)</td>
<td>30 (Median)</td>
<td>Very low</td>
<td>Evidence from 1 study found no statistically significant difference in ventilator-free days with intermediate dose anticoagulant compared to standard prophylactic dose anticoagulant for people who were hospitalised.</td>
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</table>

|通风机自由天数 | 30 (中位数) | 30 (中位数) | 非常低 | 证据来自1个研究，未达到统计学显著差异 | 通风机自由天数与标准抗凝剂量相比无统计学显著差异 |

2. **Risk of Bias:** **serious.** Co-interventions (azithromycin) used more in intervention group in one study. **Inconsistency:** **no serious.** **Indirectness:** **serious.** Some patients have moderate in one study have moderate, not severe COVID-19. **Imprecision:** **serious.** No statistically significant effect. **Publication bias:** **no serious.**


4. **Inconsistency:** **no serious.** **Indirectness:** **serious.** Differences between the population of interest and those studied. **Imprecision:** **serious.** No statistically significant effect. **Publication bias:** **no serious.**


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11. **Inconsistency:** **no serious.** **Indirectness:** **serious.** Differences between the population of interest and those studied. **Imprecision:** **very serious.** Unable to calculate effect size and 95% C.I.. **Publication bias:** **no serious.**

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**References**

Evidence to decision

Benefits and harms
See the evidence to decision sections for the recommendation for treatment-dose VTE prophylaxis for young people and adults with COVID-19 who are receiving low-flow supplementary oxygen and the recommendation for treatment- and intermediate-dose VTE prophylaxis for young people and adults who are receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation.

Rationale
The panel agreed that D-dimer levels do not influence peoples’ response to anticoagulation.

Consensus recommendation
Do not base prophylactic dosing of heparin on levels of D-dimer.

Rationale
This recommendation was adapted from the original NICE rapid guideline on reducing the risk of venous thromboembolism in over 16s with COVID-19 (now withdrawn) that considered intermediate doses in this population. In its development, the panel indicated that dose adjustments may be needed for people at extremes of body weight and those with renal impairment. To ensure that everyone gets an appropriate dose, the panel included dose adjustment in their recommendation. They added that summary of product characteristics and local protocols should be used to guide decisions on dose adjustment.
In hospital-led acute care in the community

Rationale

There was no evidence to inform recommendations on reducing the risk of VTE in people with COVID-19 pneumonia managed in hospital-led acute care in the community settings with input from hospital clinicians, such as ‘hospital at home’ services or COVID-19 ‘virtual wards’. People whose condition is managed in these settings have an increased risk of VTE that is similar to that of people...
having management in hospital. The panel therefore included a recommendation to consider pharmacological VTE prophylaxis for these people to ensure that they have the same care as those admitted to hospital.

The panel also made a recommendation for research on extending pharmacological VTE prophylaxis after discharge in people who have had treatment for COVID-19 pneumonia.

### 8.3.2 People with COVID-19 and additional risk factors

**Rationale**

The panel noted the lack of evidence on pharmacological VTE prophylaxis for people with COVID-19 and additional risk factors. They agreed that VTE risk in women with COVID-19 who are pregnant or have given birth in the past 6 weeks should be managed in line with advice on COVID-19 in pregnancy published by the Royal College of Obstetricians and Gynaecologists.

There was no evidence on pharmacological VTE prophylaxis for specific groups with additional risk factors for VTE, including people who are having treatment with sex hormones, have or have previously had cancer, are having renal replacement therapy or extracorporeal membrane oxygenation, have a clotting condition or history of VTE, or have obesity (body mass index 30 kg/m² or higher). The panel made a recommendation for research on standard-dose compared with intermediate-dose pharmacological VTE prophylaxis in people with COVID-19 who have additional risk factors for VTE.

**Consensus recommendation**

For women with COVID-19 who are pregnant or have given birth within the past 6 weeks, follow the advice on VTE prevention in the Royal College of Obstetricians and Gynaecologists guidance on coronavirus (COVID-19) in pregnancy.

**Rationale**

For children with COVID-19 admitted into hospital, follow the advice on COVID-19 guidance for management of children admitted to hospital in the Royal College of Paediatrics and Child Health guidance.

### 8.3.3 Information and support

**Consensus recommendation**

Give people with COVID-19, and their families or carers if appropriate, information about the benefits and risks of VTE prophylaxis.

See the recommendations on giving information and planning for discharge in the NICE guideline on venous thromboembolism in over 16s, including information on alternatives to heparin for people who have concerns about using animal products.
Consensus recommendation

Offer people the opportunity to take part in ongoing clinical trials on COVID-19.
9. Identifying and managing co-infections

Consensus recommendation
Do not offer an antibiotic for preventing or treating pneumonia if SARS-CoV-2, another virus, or a fungal infection is likely to be the cause.

Antibiotics do not work on viruses, and inappropriate antibiotic use may reduce availability. Also, inappropriate use may lead to Clostridioides difficile infection and antimicrobial resistance, particularly with broad-spectrum antibiotics.

Info Box
Evidence as of March 2021 suggests that bacterial co-infection occurs in less than about 8% of people with COVID-19, and could be as low as 0.1% in people in hospital with COVID-19. Viral and fungal co-infections occur at lower rates than bacterial co-infections.

Secondary infection or co-infection (bacterial, viral or fungal) is more likely the longer a person is in hospital and the more they are immunosuppressed (for example, because of certain types of treatment).

The type and number of secondary infections or co-infections will vary depending on the season and any restrictions in place (for example, lockdowns).

9.1 Other causes of pneumonia

9.1.1 Identifying other causes of pneumonia

Consensus recommendation
To help identify other causes of pneumonia and to inform decision making about using antibiotics, consider the following tests:

- a full blood count
- chest imaging (X-ray, CT or ultrasound)
- respiratory and blood samples (for example, sputum or a tracheal aspirate sample, blood culture)
- urine samples for legionella and pneumococcal antigen testing
- throat, nasopharyngeal or sputum samples for respiratory viral (and atypical pathogen) polymerase chain reaction testing; for more information, see Public Health England’s COVID-19 guidance for sampling and for diagnostic laboratories.

Info Box
High C-reactive protein levels do not necessarily indicate whether pneumonia is due to bacteria or SARS-COV-2.

Low C-reactive protein level indicates that a secondary bacterial infection is less likely.
9.1.2 Antibiotic treatment in the community

Consensus recommendation

Do not use C-reactive protein to assess whether a person has a secondary bacterial infection if they have been having immunosuppressant treatment.

Info Box

There is insufficient evidence to recommend routine procalcitonin testing to guide decisions about antibiotics. Centres already using procalcitonin tests are encouraged to participate in research and data collection.

Procalcitonin tests could be useful in identifying whether there is a bacterial infection. However, it is not clear whether they add benefit beyond what is suggested in the recommendation on tests to help differentiate between viral and bacterial pneumonia to guide decisions about antibiotics. The most appropriate threshold for procalcitonin is also uncertain.

Consensus recommendation

Do not offer an antibiotic for preventing secondary bacterial pneumonia in people with COVID-19.

Consensus recommendation

If a person has suspected or confirmed secondary bacterial pneumonia, start antibiotic treatment as soon as possible. Take into account any different methods needed to deliver medicines during the COVID-19 pandemic (see the recommendation on minimising face-to-face contact in communication and shared decision making).

Info Box

For antibiotic choices to treat community-acquired pneumonia caused by a secondary bacterial infection, see the recommendations on choice of antibiotic in the NICE antimicrobial prescribing guideline on community-acquired pneumonia.

Consensus recommendation

Advise people to seek medical help without delay if their symptoms do not improve as expected, or worsen rapidly or significantly, whether they are taking an antibiotic or not.

Consensus recommendation

On reassessment, reconsider whether the person has signs and symptoms of more severe illness (see the recommendation on signs and symptoms to help identify people with COVID-19 with the most severe illness) and whether to refer them to hospital, other acute community support services or palliative care services.
9.1.3 Starting antibiotics in hospital

**Consensus recommendation**

Start empirical antibiotics if there is clinical suspicion of a secondary bacterial infection in people with COVID-19. When a decision to start antibiotics has been made:

- Start empirical antibiotic treatment as soon as possible after establishing a diagnosis of secondary bacterial pneumonia, and certainly within 4 hours.
- Start treatment within 1 hour if the person has suspected sepsis and meets any of the high-risk criteria for this outlined in the NICE guideline on sepsis.

9.1.4 Choice of antibiotics in hospital

**Info Box**

To guide decision making about antibiotics for secondary bacterial pneumonia in people with COVID-19, see the NICE guideline on pneumonia (hospital acquired): antimicrobial prescribing.

**Consensus recommendation**

When choosing antibiotics, take account of:

- local antimicrobial resistance data and
- other factors such as their availability.

**Consensus recommendation**

Give oral antibiotics if the person can take oral medicines and their condition is not severe enough to need intravenous antibiotics.

**Consensus recommendation**

Consider seeking specialist advice on antibiotic treatment for people who:

- are immunocompromised
- have a history of infection with resistant organisms
- have a history of repeated infective exacerbations of lung disease
- are pregnant
- are receiving advanced respiratory support or organ support.
9.1.5 Reviewing antibiotic treatment in hospital

**Consensus recommendation**

Seek specialist advice if:

- there is a suspicion that the person has an infection with multidrug-resistant bacteria and may need a different antibiotic or
- there is clinical or microbiological evidence of infection and the person's condition does not improve as expected after 48 to 72 hours of antibiotic treatment.

**Consensus recommendation**

Review all antibiotics at 24 to 48 hours, or as soon as test results are available. If appropriate, switch to a narrower spectrum antibiotic, based on microbiological results.

For intravenous antibiotics, review within 48 hours and think about switching to oral antibiotics (in line with the NICE guideline on pneumonia (hospital-acquired): antimicrobial prescribing).

Give antibiotics for 5 days, and then stop them unless there is a clear indication to continue (see the recommendation on when to seek specialist advice).

**Consensus recommendation**

Reassess people if their symptoms do not improve as expected, or worsen rapidly or significantly.

9.2 COVID-19-associated pulmonary aspergillosis (CAPA)

**Info Box**

For people who are critically ill and have, or have had, COVID-19 as part of their acute illness:

- CAPA is a recognised cause of someone's condition not improving despite treatment (for example, antibiotic therapy, ventilatory support)
- there are no specific combinations of signs or symptoms for diagnosing CAPA
- the risk of having CAPA may increase with age and chronic lung disease.

9.2.1 Diagnosing CAPA
**Consensus recommendation**

When deciding whether to suspect CAPA in someone who is critically ill and has, or has had, COVID-19 as part of their acute illness:

- base your decisions on individual risk factors and the person's clinical condition
- involve a multidisciplinary team, including infection specialists
- refer to local protocols on diagnosing and managing CAPA.

*Local protocols for diagnosing and managing CAPA should be developed with a multidisciplinary team and based on knowledge of local prevalence.*

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**Evidence to decision**

**Benefits and harms**

The panel were presented with evidence from one systematic review (Chong 2021) and two primary studies (Prattes 2021 and Segrelles-Calvo 2021). The studies presented evidence on the risk factors and signs and symptoms associated with people developing CAPA.

The panel agreed that there was insufficient evidence to define specific risk factors or signs and symptoms of CAPA. Although the studies suggest that increasing age and chronic lung disease may increase the risk of developing CAPA, the panel considered that the evidence was not strong enough to include these specific risk factors in a diagnostic recommendation. They also agreed that, while studies suggest that people who receive invasive mechanical ventilation are at increased risk of CAPA, the thresholds for mechanical ventilation vary across centres and invasive mechanical ventilation may not be considered an independent risk factor for CAPA. The panel also considered the evidence around whether taking long-term immunosuppressants can increase the risk of CAPA, but concluded that the evidence was not strong enough to list 'long-term immunosuppressants' as an independent risk factor for CAPA.

The panel highlighted the need to use clinical judgement and assess the individual needs of people who are suspected to have CAPA, before progressing further with their diagnosis and management.

The panel considered whether existing clinical algorithms for the diagnosis of invasive pulmonary aspergillosis could be applied to CAPA. In particular, the panel discussed the AspICU algorithm, which is a clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. However, the panel agreed not to recommend use of the AspICU algorithm for CAPA because of a lack of evidence of its use in this condition and meaningful differences between the people for which the AspICU algorithm is typically used and the people who are at risk of developing CAPA.

The panel discussed that from their experience, a diagnosis of CAPA should usually be made as part of a multidisciplinary team, with input from infection specialists (for example, medical microbiologists or infectious disease specialists).

**Certainty of the Evidence**

The certainty of the evidence was rated as low to very low for all outcomes. This was due to serious risk of bias, serious indirectness, and serious inconsistency. The panel discussed that heterogeneity of the study participants, and the variations in local practice in reporting and case definitions of CAPA also reduced their certainty in the results.
In particular, the panel discussed that the association shown between invasive mechanical ventilation and CAPA is likely to be at risk of bias from confounding due to the difference in diagnostic approach between those who are invasively mechanically ventilated and those who are not.

**Values and preferences**

The panel were not aware of any systematically collected data about the preferences and values in people who are suspected to have CAPA.

**Resources**

No formal analysis of resource impact has been carried out. The panel recommended that decisions about whether to suspect CAPA should be made as part of a multidisciplinary team which includes infection specialists, which may not currently be in place in all settings where people who are critically ill are cared for.

**Equity**

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but that assessments should take place in the same way for all people who are critically ill and have, or have had, COVID-19 as part of their acute illness.

No other equity issues were identified.

**Acceptability**

The panel were not aware of any systematically collected evidence about the acceptability of assessing for suspicion of CAPA.

**Feasibility**

The panel were not aware of any systematically collected evidence about feasibility, but agreed that this approach should be feasible, particularly where a multidisciplinary team which includes infection specialists is already in place.

**Rationale**

The panel agreed that the evidence was not strong enough to recommend specific factors that increase the risk of CAPA. They noted the importance of multidisciplinary decision making and using local protocols when deciding whether to suspect CAPA.

**Clinical question/ PICO**

- **Population:** Risk factors for People hospitalised with confirmed COVID-19 and CAPA
- **Intervention:** People with CAPA
- **Comparator:** People without CAPA
Summary
There remains a high degree of uncertainty over possible risk factors that are associated with people developing COVID-19-associated pulmonary aspergillosis.

What is the evidence informing this conclusion?
Evidence comes from 2 studies. The first (Chong 2021) was a systematic review and meta-analysis of cohort studies comparing the clinical characteristics of people with CAPA to people without CAPA. The systematic review included cohort studies that investigated the clinical characteristics and outcomes of people who are hospitalised with proven or probable CAPA and confirmed COVID-19 (Bartoletti 2020; Deliere 2021; Gangneux 2020; Lahmer 2021; Segrelles-Calvo 2021; Van Biesen 2021; Velez Pintado 2021; Wang 2020).

The second study identified in this review (Prattes 2021) was a multinational cohort study that evaluated the risk factors associated with developing CAPA in people hospitalised and admitted to the intensive care for COVID-19 acute respiratory failure.

Publication status
The two studies included in this review were full publications (Chong 2021 and Prattes 2021). All 8 of the studies included in the systematic review (Chong 2021) were full publications as well.

Study characteristics
The Chong 2021 systematic review included 8 cohort studies, with 729 participants and ages ranging from 59-71 years. It included people who developed COVID-19 and were admitted to hospitals and later diagnosed with CAPA. The included studies collected data from participants during the early surges of COVID-19 in March-August 2020.

Prattes 2021 evaluated 592 participants, with 109/592 with proven, probable or possible CAPA who were admitted to ICU for COVID-19 acute respiratory failure. Participants in Prattes 2021 were aged between 54-75 years and were admitted between March 2020 – April 2021.

Both studies compared the clinical characteristics, or risk factors, of people with COVID-19 and confirmed CAPA with those without CAPA. The majority of participants in both studies were male (Chong 2021- 71.5% male and Prattes 2021 - 70.8% male), and were adults who were hospitalised with confirmed COVID-19. Participants were diagnosed with CAPA as defined by the ECMM criteria and the AspICU algorithm criteria.

For further details see the evidence review for risk factors of CAPA.

What are the main results?
The results from the studies indicated that there is a possible association between CAPA incidence and increasing age, long-term corticosteroid treatment, higher sequential organ failure assessment (SOFA) score, progression to invasive mechanical ventilation and COVID-19 treatment with tocilizumab. There is an association of borderline significance between the presence of underlying chronic obstructive pulmonary disease (COPD) and CAPA.

Our confidence in the results
The certainty of the evidence for these risk factors was rated as low to very low, due to serious risk of bias with the studies controlling variables, due to serious indirectness (Prattes 2021) from the inclusion of people with possible CAPA (not proven or probable) and due to serious inconsistency as Chong 2021 analysed studies that varied methodologically.

The risk factors in the systematic review and the single cohort study are reported in general terms and not in detail. Details on confounding variables, such as diagnostic criteria and treatment regimens were not clearly defined. It was also unclear how these different variables were controlled in both the CAPA and non-CAPA groups, and how they were accounted for throughout data collection and analysis.
As both studies evaluated people from different waves of the COVID-19 pandemic, it is possible that changes in practice (e.g. treatments for COVID-19 in different centres, different diagnostic criteria for CAPA) throughout the COVID-19 pandemic context (e.g. surges and recovery periods in COVID-19 waves, take-up of vaccinations), may affect the number of people who contracted COVID-19 and CAPA.

Currently, there is limited evidence that identifies the associations between patient characteristics and CAPA development in COVID-19 disease and the current evidence base is small.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator No CAPA</th>
<th>Intervention CAPA</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factor - Age per 5 years</td>
<td>Hazard ratio 1.18 (CI 95% 1.08 — 1.28) Based on data from 592 participants in 1 studies. (Observational (non-randomized))</td>
<td></td>
<td>CI 95%</td>
<td>Low Due to serious risk of bias, Due to serious indirectness</td>
<td>Increasing age is associated with developing CAPA in people hospitalised with COVID-19</td>
</tr>
<tr>
<td>Risk factor - Sex (Female)</td>
<td>Hazard ratio 0.68 (CI 95% 0.42 — 1.09) Based on data from 592 participants in 1 studies.</td>
<td></td>
<td>CI 95%</td>
<td>Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness</td>
<td>Sex is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19</td>
</tr>
<tr>
<td>Risk factor - Sex (Male)</td>
<td>Odds ratio 0.82 (CI 95% 0.43 — 1.55) Based on data from 514 participants in 1 studies. (Observational (non-randomized))</td>
<td></td>
<td>CI 95%</td>
<td>Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision</td>
<td>Sex is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19</td>
</tr>
<tr>
<td>Risk factor - Number of coexisting conditions</td>
<td>Hazard ratio 0.92 (CI 95% 0.76 — 1.1) Based on data from 592 participants in 1 studies.</td>
<td></td>
<td>CI 95%</td>
<td>Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness</td>
<td>Increasing numbers of coexisting conditions are not associated with an increased risk of developing CAPA in people hospitalised with COVID-19</td>
</tr>
<tr>
<td>Risk factor - History of smoking</td>
<td>Hazard ratio 1.36 (CI 95% 0.76 — 2.44) Based on data from 529 participants in 1 studies.</td>
<td></td>
<td>CI 95%</td>
<td>Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness</td>
<td>Smoking is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19</td>
</tr>
<tr>
<td>Risk factor</td>
<td>Outcome</td>
<td>Comparator</td>
<td>Intervention</td>
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<tr>
<td>Obesity</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td>Hazard ratio 0.89 (CI 95% 0.54 — 1.44) Based on data from 592 participants in 1 studies.</td>
<td>No CAPA</td>
<td>CAPA</td>
<td>Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td>Odds ratio 1.2 (CI 95% 0.71 — 2.01) Based on data from 506 participants in 1 studies. (Observational (non-randomized))</td>
<td>No CAPA</td>
<td>CAPA</td>
<td>Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td></td>
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<tr>
<td></td>
<td>9 Critical</td>
<td>Hazard ratio 1.12 (CI 95% 0.73 — 1.73) Based on data from 529 participants in 1 studies.</td>
<td>No CAPA</td>
<td>CAPA</td>
<td>Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness</td>
</tr>
<tr>
<td>Cancer</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td></td>
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<tr>
<td></td>
<td>9 Critical</td>
<td>Odds ratio 2.25 (CI 95% 0.68 — 5.07) Based on data from 332 participants in 1 studies. (Observational (non-randomized))</td>
<td>No CAPA</td>
<td>CAPA</td>
<td>Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision</td>
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<tr>
<td>COPD</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td>Odds ratio 2.75 (CI 95% 1 — 7.52) Based on data from 514 participants in 1 studies. (Observational (non-randomized))</td>
<td>No CAPA</td>
<td>CAPA</td>
<td>Low Due to serious risk of bias, Due to serious inconsistency</td>
</tr>
<tr>
<td>Active malignant disease</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td>Hazard ratio 1.56 (CI 95% 0.81 — 3) Based on data from 529 participants in 1 studies.</td>
<td>No CAPA</td>
<td>CAPA</td>
<td>Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 Critical</td>
<td>Hazard ratio 1.2 (CI 95% 0.81 — 1.78) Based on data from 529 participants in 1 studies.</td>
<td>No CAPA</td>
<td>CAPA</td>
<td>Very low Due to serious risk of bias, Due to serious indirectness</td>
</tr>
</tbody>
</table>

- Obesity is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
- Diabetes is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
- Diabetes is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
- Cancer is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
- COPD is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
- Active malignant disease is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.
- Cardiovascular disease is not associated with an increased risk of developing CAPA in...
<table>
<thead>
<tr>
<th>Outcome / Timeframe</th>
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<tbody>
<tr>
<td>9 Critical</td>
<td></td>
<td>No CAPA</td>
<td>CAPA</td>
<td>Imprecision, Due to serious indirectness 12</td>
<td>People hospitalised with COVID-19.</td>
</tr>
<tr>
<td>9 Critical</td>
<td>Hazard ratio 1.42 (CI 95% 0.89 — 2.24) Based on data from 529 participants in 1 studies.</td>
<td>CI 95%</td>
<td></td>
<td>Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness 13</td>
<td>Pulmonary disease is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.</td>
</tr>
<tr>
<td>9 Critical</td>
<td>Hazard ratio 2.2 (CI 95% 0.9 — 5.42) Based on data from 529 participants in 1 studies.</td>
<td>CI 95%</td>
<td></td>
<td>Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness 14</td>
<td>Solid organ transplantation is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.</td>
</tr>
<tr>
<td>9 Critical</td>
<td>Odds ratio 3.53 (CI 95% 1.16 — 10.69) Based on data from 250 participants in 1 studies. (Observational (non-randomized))</td>
<td>CI 95%</td>
<td></td>
<td>Low Due to serious risk of bias, Due to serious inconsistency 15</td>
<td>Long-term corticosteroid is associated with an increased risk of developing CAPA in people hospitalised with COVID-19.</td>
</tr>
<tr>
<td>9 Critical</td>
<td>Odds ratio 1.87 (CI 95% 0.28 — 12.29) Based on data from 142 participants in 1 studies. (Observational (non-randomized))</td>
<td>CI 95%</td>
<td></td>
<td>Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision 16</td>
<td>Long-term immunosuppressant use is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.</td>
</tr>
<tr>
<td>9 Critical</td>
<td>Hazard ratio 0.08 (CI 95% 0.02 — 0.33) Based on data from 529 participants in 1 studies.</td>
<td>CI 95%</td>
<td></td>
<td>Low Due to serious risk of bias, Due to serious indirectness 17</td>
<td>Non-invasive ventilation is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.</td>
</tr>
<tr>
<td>9 Critical</td>
<td>Hazard ratio 0.8 (CI 95% 0.37 — 1.7) Based on data from 529 participants in 1 studies.</td>
<td>CI 95%</td>
<td></td>
<td>Low Due to serious risk of bias, Due to serious indirectness 18</td>
<td>Extracorporeal Membrane Oxygenation (ECMO) is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator No CAPA</td>
<td>Intervention CAPA</td>
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<tr>
<td>Critical</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Risk factor - Invasive mechanical ventilation</td>
<td>Critical</td>
<td>Hazard ratio 2.53 (CI 95% 1.53 — 4.17) Based on data from 529 participants in 1 studies.</td>
<td></td>
<td>CI 95%</td>
<td>Low Due to serious risk of bias, Due to serious indirectness 19</td>
</tr>
<tr>
<td>Risk factor - Any invasive ventilation</td>
<td>Critical</td>
<td>Hazard ratio 2.93 (CI 95% 1.6 — 5.35) Based on data from 529 participants in 1 studies.</td>
<td></td>
<td>CI 95%</td>
<td>Low Due to serious risk of bias, Due to serious indirectness 20</td>
</tr>
<tr>
<td>Risk factor - COVID-19 treatment with tocilizumab</td>
<td>Critical</td>
<td>Odds ratio 1.85 (CI 95% 0.88 — 3.89) Based on data from 514 participants in 1 studies. (Observational (non-randomized))</td>
<td></td>
<td>CI 95%</td>
<td>Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision 21</td>
</tr>
<tr>
<td>Risk factor - COVID-19 treatment tocilizumab</td>
<td>Critical</td>
<td>Hazard ratio 2.34 (CI 95% 1.03 — 4.06) Based on data from 529 participants in 1 studies.</td>
<td></td>
<td>CI 95%</td>
<td>Low Due to serious risk of bias, Due to serious indirectness 22</td>
</tr>
<tr>
<td>Risk factor - COVID-19 treatment with corticosteroid</td>
<td>Critical</td>
<td>Odds ratio 0.69 (CI 95% 0.19 — 2.58) Based on data from 510 participants in 1 studies.</td>
<td></td>
<td>CI 95%</td>
<td>Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision 23</td>
</tr>
<tr>
<td>Risk factor - COVID-19 treatment with glucocorticoids</td>
<td>Critical</td>
<td>Hazard ratio 1.01 (CI 95% 0.68 — 1.5) Based on data from 529 participants in 1 studies.</td>
<td></td>
<td>CI 95%</td>
<td>Low Due to serious risk of bias, Due to serious imprecision 24</td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
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<td>Intervention</td>
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</tr>
<tr>
<td><strong>Risk factor - COVID-19 treatment with antibiotic</strong> 9 Critical</td>
<td>Odds ratio 0.88 (CI 95% 0.39 — 1.97) Based on data from 542 participants in 1 studies. (Observational (non-randomized))</td>
<td>No CAPA</td>
<td>CAPA</td>
<td>Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision</td>
<td>Treatment of COVID-19 with antibiotics is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.</td>
</tr>
<tr>
<td><strong>Risk factor - COVID-19 treatment with hydroxychloroquine</strong> 9 Critical</td>
<td>Odds ratio 0.43 (CI 95% 0.07 — 2.68) Based on data from 514 participants in 1 studies.</td>
<td>No CAPA</td>
<td>CAPA</td>
<td>Very low Due to serious inconsistency, Due to serious risk of bias, Due to serious imprecision</td>
<td>Treatment of COVID-19 with hydroxychloroquine is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.</td>
</tr>
<tr>
<td><strong>Risk factor - COVID-19 treatment with azithromycin</strong> 9 Critical</td>
<td>Hazard ratio 0.63 (CI 95% 0.33 — 1.21) Based on data from 529 participants in 1 studies.</td>
<td>No CAPA</td>
<td>CAPA</td>
<td>Low Due to serious risk of bias, Due to serious imprecision</td>
<td>Treatment of COVID-19 with azithromycin is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.</td>
</tr>
<tr>
<td><strong>Risk factor - Age</strong> 9 Critical</td>
<td>Based on data from 729 participants in 1 studies.</td>
<td>No CAPA</td>
<td>CAPA</td>
<td>Low Due to serious risk of bias, Due to serious inconsistency</td>
<td>Increasing age is associated with developing CAPA in people hospitalised with COVID-19.</td>
</tr>
<tr>
<td><strong>Risk factor - BMI</strong> 9 Critical</td>
<td>Based on data from 729 participants in 1 studies.</td>
<td>No CAPA</td>
<td>CAPA</td>
<td>Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision</td>
<td>Increasing BMI is not associated with an increased risk of developing CAPA in people hospitalised with COVID-19.</td>
</tr>
<tr>
<td><strong>Sequential Organ Failure Assessment (SOFA) score</strong></td>
<td>7.27 (Mean) Difference:</td>
<td>No CAPA</td>
<td>CAPA</td>
<td>Low Due to serious risk of bias, Due to serious inconsistency</td>
<td>Increasing SOFA score is associated with an increased risk of developing CAPA in people hospitalised with COVID-19.</td>
</tr>
</tbody>
</table>
1. **Risk of Bias**: serious. Unclear how variables in the study were controlled. **Inconsistency**: no serious. **Indirectness**: serious. Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision**: no serious. **Publication bias**: no serious.

2. **Risk of Bias**: serious. Unclear how variables were controlled throughout study. **Inconsistency**: no serious. **Indirectness**: serious. Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision**: serious. CI crosses line of no effect. **Publication bias**: no serious.

3. **Risk of Bias**: serious. Unclear how variables were controlled throughout the study. **Inconsistency**: serious. Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. **Indirectness**: no serious. **Imprecision**: serious. CI crosses line of no effect. **Publication bias**: no serious.

4. **Risk of Bias**: serious. Unclear how variables were controlled. **Indirectness**: serious. Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision**: serious. CI crosses line of no effect.

5. **Risk of Bias**: serious. Unclear how variables were controlled throughout study. **Inconsistency**: no serious. **Indirectness**: serious. Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision**: serious. CI crosses line of no effect. **Publication bias**: no serious.

6. **Risk of Bias**: serious. Unclear how variables were controlled throughout study. **Inconsistency**: no serious. **Indirectness**: serious. Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision**: serious. CI crosses line of no effect. **Publication bias**: no serious.

7. **Risk of Bias**: serious. Unclear how variables were controlled throughout the study. **Inconsistency**: serious. Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. **Indirectness**: no serious. **Imprecision**: serious. CI crosses line of no effect. **Publication bias**: no serious.

8. **Risk of Bias**: serious. Unclear how variables were controlled throughout study. **Inconsistency**: no serious. **Indirectness**: serious. Study analysed patients with possible CAPA with those with proven and probable CAPA. **Imprecision**: serious. CI crosses line of no effect. **Publication bias**: no serious.

9. **Risk of Bias**: serious. Unclear how variables were controlled throughout the study. **Inconsistency**: serious. Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. **Indirectness**: no serious. **Imprecision**: no serious. **Publication bias**: no serious.

10. **Risk of Bias**: serious. Unclear how variables were controlled throughout the study. **Inconsistency**: no serious. **Indirectness**: no serious. **Imprecision**: no serious. **Publication bias**: no serious.
12. Risk of Bias: serious. Unclear how variables were controlled throughout study. Inconsistency: no serious. Indirectness: serious. Study analysed patients with possible CAPA with those with proven and probable CAPA. Imprecision: serious. CI crosses line of no effect. Publication bias: no serious.

13. Risk of Bias: serious. Unclear how variables were controlled throughout study. Inconsistency: no serious. Indirectness: serious. Study analysed patients with possible CAPA with those with proven and probable CAPA. Imprecision: serious. CI crosses line of no effect. Publication bias: no serious.


15. Risk of Bias: serious. Unclear how variables were controlled throughout the study. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.

16. Risk of Bias: serious. Unclear how variables were controlled throughout the study. Inconsistency: serious. Differences in the studies between clinical and mycological evidence in clinical centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA. Indirectness: no serious. Imprecision: no serious. CI crosses line of no effect. Publication bias: no serious.

17. Risk of Bias: serious. Unclear how variables were controlled throughout study. Inconsistency: no serious. Indirectness: serious. Study analysed patients with possible CAPA with those with proven and probable CAPA. Imprecision: no serious. Publication bias: no serious.

18. Risk of Bias: serious. Unclear how variables were controlled throughout study. Inconsistency: no serious. Indirectness: serious. Study analysed patients with possible CAPA with those with proven and probable CAPA. Imprecision: no serious. Publication bias: no serious.

19. Risk of Bias: serious. Unclear how variables were controlled throughout the study. Indirectness: no serious. Imprecision: no serious. CI crosses line of no effect. Publication bias: no serious.

20. Risk of Bias: serious. Unclear how variables were controlled throughout study. Inconsistency: no serious. Indirectness: serious. Study analysed patients with possible CAPA with those with proven and probable CAPA. Imprecision: no serious. Publication bias: no serious.

21. Risk of Bias: serious. Unclear how variables were controlled throughout the study. Indirectness: no serious. Imprecision: no serious. CI crosses line of no effect. Publication bias: no serious.

22. Risk of Bias: serious. Unclear how variables were controlled throughout study. Inconsistency: no serious. Indirectness: serious. Study analysed patients with possible CAPA with those with proven and probable CAPA. Imprecision: no serious. Publication bias: no serious.

23. Risk of Bias: serious. Unclear how variables were controlled throughout the study. Indirectness: no serious. Imprecision: no serious. CI crosses line of no effect. Publication bias: no serious.


25. Risk of Bias: serious. Unclear how variables were controlled throughout the study. Indirectness: no serious. Imprecision: no serious. CI crosses line of no effect. Publication bias: no serious.
centres from different parts of the world, lack of clinical awareness and standard diagnostic approach for evaluating CAPA.  

**Indirectness: serious.** Differences amongst the populations included within the study. **Imprecision: serious.** CI crosses line of no effect. **Publication bias: no serious.**

26. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. 

**Indirectness: no serious.** 

27. **Risk of Bias: serious.** Unclear how variables were controlled throughout study. **Indirectness: no serious.** CI crosses line of no effect. **Publication bias: no serious.**

28. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. 

**Indirectness: no serious.** 

29. **Risk of Bias: serious.** Unclear how variables were controlled throughout the study. 

**Indirectness: no serious.** 

30. **Risk of Bias: serious.** Unclear how variables are controlled throughout the study. **Inconsistency: serious.** 

**Indirectness: no serious.** 

**References**


**Clinical question/ PICO**

**Population:** Signs and symptoms of people hospitalised with COVID-19 and with CAPA 

**Intervention:** NA

**Comparator:** NA

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Summary

There is very limited evidence on symptoms of invasive pulmonary aspergillosis (IPA) in people who have or, as part of their acute illness, have had confirmed COVID-19.

What is the evidence informing this conclusion?

Evidence comes from one small, retrospective cohort study aiming to determine the prevalence of IPA and risk factors for IPA in people admitted to ICU due to severe SARS-CoV-2 infection (Segrellos-Calvo 2021).

Publication status

The included study has been published and peer-reviewed.

Study characteristics

The included study had seven participants. Their ages ranged from 42 to 75. Two participants (29%) were female. All had PCR-confirmed COVID-19. They were diagnosed with IPA using bronchoalveolar lavage using an Aspergillus EIA assay. All participants had been admitted to respiratory ICU.

For further details see the evidence review for signs and symptoms of CAPA.

What are the main results?

Critical outcomes

Fever, dyspnoea and cough were the most common symptoms among the participants (affecting 100%, 86% and 86% respectively).

Important outcomes

All outcomes for this review were classified as critical outcomes

Our confidence in the results

The evidence is extremely sparse and the results could be due to chance. The study was at high risk of bias due to a lack of detail about how outcomes were measured. There could also be variation over time or between people assessing symptoms, potentially introducing bias.

Outcomes were also downgraded twice for imprecision, as the precision of the result was not reported and could not be calculated.

The symptoms reported are also associated with COVID-19, and therefore it is not possible to attribute the symptoms to COVID-19 associated pulmonary aspergillosis (CAPA) alone.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom: Fever</td>
<td>During ICU admission</td>
<td>Based on data from 7 participants in 1 studies. ¹ (Observational (non-randomized))</td>
<td>NA</td>
<td>NA</td>
<td>Very low Due to serious risk of bias, Due to very serious imprecision ²</td>
<td>The prevalence of fever in people diagnosed with CAPA is uncertain.</td>
</tr>
</tbody>
</table>

¹ Observational (non-randomized)
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea During ICU admission</td>
<td>9 Critical</td>
<td>Based on data from 7 participants in 1 studies. (Observational (non-randomized))</td>
<td>6/7 (86%) of participants with CAPA had dyspnoea. No comparator group.</td>
<td>NA</td>
<td>Very low Due to serious risk of bias, Due to very serious imprecision</td>
<td>The prevalence of dyspnoea in people diagnosed with CAPA is uncertain.</td>
</tr>
<tr>
<td>Cough During ICU admission</td>
<td>9 Critical</td>
<td>Based on data from 7 participants in 1 studies. (Observational (non-randomized))</td>
<td>6/7 (86%) of participants with CAPA had cough. No comparator group.</td>
<td>NA</td>
<td>Very low Due to serious risk of bias, Due to very serious imprecision</td>
<td>The prevalence of cough in people diagnosed with CAPA is uncertain.</td>
</tr>
<tr>
<td>Malaise During ICU admission</td>
<td>9 Critical</td>
<td>Based on data from 7 participants in 1 studies. (Observational (non-randomized))</td>
<td>3/7 (43%) of participants with CAPA had malaise. No comparator group.</td>
<td>NA</td>
<td>Very low Due to serious risk of bias, Due to very serious imprecision</td>
<td>The prevalence of malaise in people diagnosed with CAPA is uncertain.</td>
</tr>
<tr>
<td>Sputum During ICU admission</td>
<td>9 Critical</td>
<td>Based on data from 7 participants in 1 studies. (Observational (non-randomized))</td>
<td>1/7 (14%) of participants with CAPA had sputum. No comparator group.</td>
<td>NA</td>
<td>Very low Due to serious risk of bias, Due to very serious imprecision</td>
<td>The prevalence of sputum in people diagnosed with CAPA is uncertain.</td>
</tr>
<tr>
<td>Diarrhoea During ICU admission</td>
<td>9 Critical</td>
<td>Based on data from 7 participants in 1 studies. (Observational (non-randomized))</td>
<td>1/7 (14%) of participants with CAPA had diarrhoea. No comparator group.</td>
<td>NA</td>
<td>Very low Due to serious risk of bias, Due to very serious imprecision</td>
<td>The prevalence of diarrhoea in people diagnosed with CAPA is uncertain.</td>
</tr>
<tr>
<td>Headache During ICU admission</td>
<td>9 Critical</td>
<td>Based on data from 7 participants in 1 studies. (Observational (non-randomized))</td>
<td>1/7 (14%) of participants with CAPA had headache. No comparator group.</td>
<td>NA</td>
<td>Very low Due to serious risk of bias, Due to very serious imprecision</td>
<td>The prevalence of headache in people diagnosed with CAPA is uncertain.</td>
</tr>
</tbody>
</table>

1. Primary study Supporting references: [82],
2. Risk of Bias: serious. The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19. Inconsistency: no serious.
**Evidence to decision**

**Benefits and harms**

The panel were presented with information from a taskforce report by Verweij et al. on diagnosing and managing CAPA that prevalence of CAPA in people being treated in ICU was between 0% and 33% (the average across included studies was 9.3%). They discussed that this prevalence included possible as well as probable and proven CAPA, and was therefore likely to be an overestimation. The

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**Indirectness:** no serious. **Imprecision:** very serious. No CIs could be reported. **Publication bias:** no serious.

3. **Risk of Bias:** serious. The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. No CIs could be reported. **Publication bias:** no serious.

4. **Risk of Bias:** serious. The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. No CIs could be reported. **Publication bias:** no serious.

5. **Risk of Bias:** serious. The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. No CIs could be reported. **Publication bias:** no serious.

6. **Risk of Bias:** serious. The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. No CIs could be reported. **Publication bias:** no serious.

7. **Risk of Bias:** serious. The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. No CIs could be reported. **Publication bias:** no serious.

8. **Risk of Bias:** serious. The study did not give detail about how outcomes were measured. It is not possible to attribute the outcome to CAPA rather than to COVID-19. **Inconsistency:** no serious. **Indirectness:** no serious. **Imprecision:** very serious. No CIs could be reported. **Publication bias:** no serious.

**References**


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Not recommended

Do not do diagnostic tests for CAPA if there is low clinical suspicion of the condition.
panel agreed that in their experience, prevalence of CAPA is low, and so testing for CAPA should only take place if there is clinical suspicion of the condition.

The panel were also presented with evidence from 2 systematic reviews (Chong 2021 and Dimopoulos 2021) and 2 primary studies (Meawed 2021 and van Grootveld 2021). The panel discussed the most common types of diagnostic tests and also referred to the taskforce report by Verweij et al.

The evidence showed that a range of different diagnostic test types are conducted to confirm CAPA diagnosis. The panel agreed that some of the common tests for diagnosing CAPA, for example bronchoalveolar lavage (BAL), are invasive and so the risks of carrying out the test should be considered against the benefit of a potential diagnosis.

**Certainty of the Evidence**

It was not possible to apply GRADE to the outcomes in this review, because the outcomes were descriptive rather than analytical.

The panel agreed that the studies were at moderate to high risk of bias due to high heterogeneity between study participants and variations in practice between study centres. The panel also agreed that the taskforce document was an up to date and relevant source of information on the diagnosis and treatment of CAPA. However, the panel also acknowledged that the evidence identified by the taskforce was sparse.

Based on this evidence the panel agreed that it would not be possible to determine the best diagnostic tests to request when CAPA was suspected. The panel agreed that unless CAPA was suspected clinically, further investigations for CAPA should not be carried out.

**Values and preferences**

The panel considered that some of the diagnostic tests for CAPA, for example a bronchoscopy or BAL, may involve clinical risk or patient discomfort and some people may be apprehensive about having it done. Therefore these tests should be carried out following an appropriate multidisciplinary discussion and decision on the clinical suspicion of CAPA.

The panel were not aware of any systematically collected data on preferences and values of people in relation to bronchoalveolar lavage sampling.

**Resources**

This recommendation advises against investigation when suspicion is low, so has potential for savings in resource use from unnecessary procedures. Cost-effectiveness was not assessed as part of this evidence review.

**Equity**

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but that investigations should take place in the same way for all people who are critically ill because of current or previous COVID-19.
Rationale
Because the incidence of CAPA is low, there is a lack of evidence on how to diagnose the condition. Also, there are no specific combinations of signs and symptoms for diagnosing it. The panel concluded that the likelihood of CAPA should be considered when deciding whether to do diagnostic tests.

Acceptability
The panel were not aware of any systematically collected evidence about the acceptability of assessing for suspicion of CAPA.

Feasibility
The panel were not aware of any systematically collected evidence about feasibility. They agreed that testing for CAPA only in cases where there is a clinical suspicion of CAPA should be feasible, especially where it results in a reduction in testing.

Clinical question/ PICO

<table>
<thead>
<tr>
<th>Population</th>
<th>Diagnostics for CAPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>NA</td>
</tr>
<tr>
<td>Comparator</td>
<td>NA</td>
</tr>
</tbody>
</table>

Summary
This review aimed to determine the diagnostic tests that should be used to diagnose CAPA in people with COVID-19. The evidence highlighted the range of tests that are used in clinical practice.

What is the evidence informing this conclusion?
Evidence comes from 2 systematic reviews that evaluate different diagnostic investigations for people with COVID-19 and suspected CAPA (Chong 2021 and Dimopoulos 2021). A further 2 studies were included in this evidence review to supplement the findings of the included systematic reviews: a cross-sectional study (Meawed 2021) and a cohort study (van Grootveld 2021).

Publication status
All included studies were full publications (Chong 2021, Dimopoulos 2021, Meawed 2021 and van Grootveld 2021).

Study characteristics
Study participant numbers ranged from 63 people (van Grootveld 2021) to 1494 people (Chong 2021b). The average age of participants ranged from 62 to 63 years. The proportion of male participants ranged from 34% to 80% of the study population. All participants had a wide range of underlying comorbidities (for example, hypertension, diabetes, chronic pulmonary disease,
cardiovascular disease, and active malignancies).

Most participants (94%; n= 2829/3026) were hospitalised and admitted to ICU with severe COVID-19 and only 6% had moderate COVID-19 (197/3026). Disease severity was mostly scored against the WHO Clinical Progression Scale.

For further details see the evidence review for diagnostics for CAPA.

What are the main results?

The evidence described the use of bronchoalveolar lavage (BAL), endotracheal aspirates (ETA), serum, non-directed bronchial lavage (NBL) and sputum to diagnose CAPA. The different microbiological investigations performed on each sample (such as tissue culture, galactomannan and beta-d-glucan biomarker levels, PCR) were also described in the literature.

CT imaging, serum assays (galactomannan (GM) and beta-d-glucan (BDG)), ETA culture and BAL are commonly used to support CAPA diagnosis. Further BAL sample investigations such as microscopy, culture, GM, BDG and PCR are also commonly used to support CAPA diagnosis.

The evidence shows that sputum sampling, NBL and ETA investigations like GM, BDG and PCR are not as commonly used to diagnose CAPA, as their prevalence was relatively low when compared to that of CT imaging, BAL, and serum assays.

The findings of this review are consistent with existing recommendations on diagnosing CAPA (Verweij et al. 2021). The Verweij et al. 2021 report states that bronchoscopy alongside BAL is recommended to diagnose CAPA and states that ETA and sputum should not be relied on solely to diagnose CAPA.

Our confidence in the results

GRADE could not be conducted on the results of this review because the results were descriptive rather than analytical.

There were some concerns about risk of bias due to unclear reporting of participant eligibility criteria in all studies (Chong 2021b, Dimopoulous 2021, Meawed 2021 and van Grootveld 2021). There was also insufficient information to assess the data collection and data analysis methods used in Chong 2021b and Dimopoulous 2021 and as such, risk of bias was rated as high for both studies.

The two systematic reviews contained studies from international centres and as such, there may have been differences in standard of care as well as diagnostic investigations and assessment criteria. As such, there is risk of the evidence being indirect to the UK context.

Although Chong 2021b defined clear eligibility criteria to limit the heterogeneity, studies are heterogeneous with epidemiological, clinical, and methodological diversity, meaning that it may not be possible to generalise the prevalence results.

Conclusion

The review has found that CT imaging, serum assays of biomarkers, ETA culture and BAL are the most common investigations for diagnosing CAPA.

The findings of this review are consistent with current recommendations on diagnosing CAPA.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Timeframe</th>
<th>Study results and measurements</th>
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<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT Imaging</td>
<td>Based on data from 1,792 participants in 3 studies.</td>
<td>Three studies (n=1792) found that 10%-43% of participants had undergone a CT imaging investigation to support CAPA diagnosis.</td>
<td></td>
<td></td>
<td>Evidence from four studies found that CT imaging is a common investigation used to support CAPA diagnosis.</td>
<td></td>
</tr>
<tr>
<td>Serum Galactomannan</td>
<td>Based on data from 957 participants in 2 studies.</td>
<td>Two studies (n=957) found that 25%-47% of participants had undergone a serum galactomannan investigation to support CAPA diagnosis.</td>
<td></td>
<td></td>
<td>Evidence from two studies found that serum galactomannan is a common investigation used to support CAPA diagnosis.</td>
<td></td>
</tr>
<tr>
<td>Serum beta-D-glucan</td>
<td>Based on data from 636 participants in 2 studies.</td>
<td>Two studies (n=636) found that 3%-47% of participants had undergone a serum beta-d-glucan investigation to support CAPA diagnosis.</td>
<td></td>
<td></td>
<td>Evidence from two studies found that serum beta-d-glucan is a common investigation used to support CAPA diagnosis.</td>
<td></td>
</tr>
<tr>
<td>Endotracheal Aspirate Culture</td>
<td>Based on data from 370 participants in 3 studies.</td>
<td>Three studies (n = 370) found that 8% - 100% of patients had undergone a endotracheal aspirate microscopy investigation to support CAPA diagnosis.</td>
<td></td>
<td></td>
<td>Evidence from three studies found that endotracheal aspirate culture is a common investigation used to support CAPA diagnosis</td>
<td></td>
</tr>
<tr>
<td>Endotracheal Aspirate Beta-d-glucan</td>
<td>Based on data from 52 participants in 2 studies.</td>
<td>Two studies (n= 52) found that 4%-5% of participants had undergone a endotracheal aspirate beta-d-glucan investigation to support CAPA diagnosis.</td>
<td></td>
<td></td>
<td>Evidence from two studies found that endotracheal aspirate culture is not commonly used to support CAPA diagnosis.</td>
<td></td>
</tr>
<tr>
<td>Endotracheal Aspirate PCR</td>
<td>Based on data from 63 participants in 1 studies.</td>
<td>One study (n = 63) found that 100% of patients had undergone a endotracheal aspirate PCR investigation to support CAPA diagnosis.</td>
<td></td>
<td></td>
<td>Evidence from one study found that endotracheal aspirate PCR is not commonly used to support CAPA diagnosis</td>
<td></td>
</tr>
<tr>
<td>Non-directed Bronchial Lavage Culture</td>
<td>Based on data from 217 participants in 2 studies.</td>
<td>Two studies (n = 217) found that 5% -10% of participants had undergone a non-directed bronchial lavage culture investigation to support CAPA diagnosis.</td>
<td></td>
<td></td>
<td>Evidence from two studies found that non-directed bronchial lavage culture is not commonly used to support CAPA diagnosis.</td>
<td></td>
</tr>
<tr>
<td>Outcome Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
<td>Summary</td>
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<tr>
<td>Non-directed Bronchial Lavage Galactomannan</td>
<td>Based on data from 78 participants in 2 studies.</td>
<td>Two studies (n=78) found that 1%-4% of participants had undergone a non-directed bronchial lavage galactomannan investigation to support CAPA diagnosis.</td>
<td></td>
<td>Evidence from two studies found that non-directed bronchial lavage galactomannan is not commonly used to support CAPA diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-directed Bronchial Lavage PCR</td>
<td>Based on data from 66 participants in 2 studies.</td>
<td>Two studies (n=66) found that 1%-4% of participants had undergone a non-directed bronchial lavage PCR investigation to support CAPA diagnosis.</td>
<td></td>
<td>Evidence from two studies found that non-directed bronchial lavage PCR is not commonly used to support CAPA diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchoalveolar Lavage Microscopy</td>
<td>Based on data from 16 participants in 1 studies.</td>
<td>One study (n=16) found that 1% of participants had undergone a bronchoalveolar lavage microscopy investigation to support CAPA diagnosis.</td>
<td></td>
<td>Evidence from one study found that bronchoalveolar lavage microscopy is not commonly used to support CAPA diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchoalveolar Lavage Culture</td>
<td>Based on data from 572 participants in 3 studies.</td>
<td>Three studies (n = 572) found that 17% -22% of participants had undergone a bronchoalveolar lavage culture investigation to support CAPA diagnosis.</td>
<td></td>
<td>Evidence from three studies found that bronchoalveolar lavage culture is a common investigation to support CAPA diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchoalveolar Lavage Galactomannan</td>
<td>Based on data from 518 participants in 3 studies.</td>
<td>Three studies (n=518) found that 17%-30% of participants had undergone a bronchoalveolar lavage galactomannan investigation to support CAPA diagnosis.</td>
<td></td>
<td>Evidence from one study found that bronchoalveolar lavage galactomannan is a common investigation used to support CAPA diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchoalveolar Lavage PCR</td>
<td>Based on data from 540 participants in 4 studies.</td>
<td>Four studies (n=540) found that 4%-24% of participants had undergone a bronchoalveolar lavage PCR investigation to support CAPA diagnosis.</td>
<td></td>
<td>Evidence from four studies found that bronchoalveolar lavage PCR is a common investigation to support CAPA diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum</td>
<td>Based on data from 241 participants in 3 studies.</td>
<td>Three studies (n=241) found that 1%-100% of participants had undergone a sputum investigation to support CAPA diagnosis.</td>
<td></td>
<td>Evidence from three studies found that sputum sampling is not commonly used to support CAPA diagnosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
References


Recommended

When investigating suspected CAPA:

- use a range of tests to increase the likelihood of making a confident diagnosis
- if possible, include bronchoalveolar lavage (BAL) as part of diagnostic testing, taking into account the risks of BAL in relation to the person’s clinical condition
- discuss the diagnostic testing strategy and final diagnosis with a multidisciplinary team that includes infection specialists.

Evidence to decision

Benefits and harms

The panel were presented with evidence from 2 systematic reviews (Chong 2021 and Dimopoulos 2021), and 2 primary studies (Meawed 2021 and van Grootveld 2021). The panel also considered a taskforce report by Verweij et al. on diagnosing and managing CAPA.

The evidence described the frequency of diagnostic tests that are used to investigate CAPA. It showed that bronchoalveolar lavage (BAL) is one of the most commonly used diagnostic tests for diagnosing CAPA. Of the studies included, 55% of people had a BAL carried out, with further investigations on the sample (for example culture, galactomannan and PCR). The panel noted that BAL is carried out in intensive care units in people who are critically ill and invasively mechanically ventilated to investigate infectious lung disease.

The taskforce report discussed by the panel, recommends bronchoscopy with BAL, stating that it is the most important tool to diagnose invasive pulmonary aspergillosis, including in people who are critically ill and have, or have had, COVID-19 as part of their acute illness. The panel acknowledged that BAL is an invasive procedure that is not risk-free and may not be feasible to carry out in all patients, particularly in patients who remain on non-invasive ventilation.

The reviewed studies and the taskforce report also reported that other tests such as endotracheal
aspirates, serological assays for beta-D-glucan and galactomannan (fungal biomarkers) are used to diagnose CAPA. Overall, the panel agreed that there are variations in the sensitivity and specificity of diagnostic tests, but that BAL may perform most favourably for the diagnosis of CAPA.

The panel concluded that BAL is the preferred diagnostic approach for investigating a CAPA diagnosis, but the risks and harms from carrying out the procedure need to be carefully assessed and other tests should be used alongside BAL or if BAL is not possible.

The panel discussed that, in their experience, a diagnosis of CAPA should usually be made as part of a multidisciplinary team with input from infection specialists, for example medical microbiologists or infectious disease specialists.

The panel agreed that the approach for diagnosing CAPA in children and young people should be the same as the approach for adults, however the levels of serum biomarkers may be different.

Certainty of the Evidence

It was not possible to apply GRADE to the outcomes in this review, because the outcomes were descriptive rather than analytical.

The panel agreed that the studies were at moderate to high risk of bias due to high heterogeneity between study participants and variations in local practice in study centres. The panel agreed that the evidence informing the taskforce report by Verweij et al. on diagnosing and managing CAPA was sparse.

Based on the evidence, the panel agreed that it was not possible to identify with certainty which tests, and in which order, should be used to diagnose CAPA. They agreed with the taskforce report that a BAL is likely to be the most accurate test for diagnosing CAPA based on the evidence of comparisons of diagnostic tests in IPA more broadly.

Values and preferences

The panel agreed that people may experience discomfort during a bronchoalveolar lavage (BAL), and some people may be apprehensive about having it done. They suggested that the risks and patient experience may be different if the person is already on invasive mechanical ventilation. The panel suggested that people's preferences and values should be considered as part of the shared-decision making process with the patients and their families.

The panel were not aware of any systematically collected data on preferences and values of people in relation to the different investigations that are used to diagnose CAPA.

Resources

The panel discussed the need for timely testing and diagnostics to investigate CAPA. Since BAL is a commonly used diagnostic test for the assessment of pulmonary aspergillosis, it is not expected that this recommendation will lead to significant changes in resource utilisation.

Cost-effectiveness was not assessed as part of the evidence review.
Rationale

There is a lack of evidence on diagnosing CAPA, including on what diagnostic tests to use, how frequently to test and the diagnostic value of the different investigations. The panel noted that using a range of tests, including bronchoalveolar lavage (BAL), follows current best practice recommended in a taskforce report by Verweij et al., (2021) on diagnosing and managing CAPA.

Because BAL is an invasive procedure, it is important that any benefits or harms are considered before using it to investigate CAPA. The panel noted that BAL may not always be suitable or feasible. They agreed that other tests could be used instead of BAL, such as serological assays, non-bronchoscopic lavage or endotracheal aspirates.

Equity

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but that assessments should take place in the same way for all people who are critically ill because of current or previous COVID-19.

No other equity issues were identified.

Acceptability

The panel discussed that, in their experience, there are few issues with acceptance of BAL as a diagnostic tool for CAPA among people who are critically ill and have, or have had, COVID-19 as part of their acute illness. However, the panel noted that in some cases, people may reject BAL or bronchoscopy as it may cause some discomfort.

Feasibility

The panel identified several potential barriers to feasibility for this recommendation. They noted that while BAL is recommended to diagnose CAPA, a wait is required for the results of BAL to become available. The panel noted that bronchoscopy may not always be feasible to carry out in patients with suspected CAPA. The panel addressed these feasibility concerns by ensuring that other diagnostic tests for CAPA were also included in the recommendation.

Important issues, or potential issues not investigated

Important issues, or potential issues not investigated

Acceptability

Important issues, or potential issues not investigated

Important issues, or potential issues not investigated

Rationale

There is a lack of evidence on diagnosing CAPA, including on what diagnostic tests to use, how frequently to test and the diagnostic value of the different investigations. The panel noted that using a range of tests, including bronchoalveolar lavage (BAL), follows current best practice recommended in a taskforce report by Verweij et al., (2021) on diagnosing and managing CAPA.

Because BAL is an invasive procedure, it is important that any benefits or harms are considered before using it to investigate CAPA. The panel noted that BAL may not always be suitable or feasible. They agreed that other tests could be used instead of BAL, such as serological assays, non-bronchoscopic lavage or endotracheal aspirates.

Important issues, or potential issues not investigated

Clinical question/ PICO

| Population: | Diagnostics for CAPA |
| Intervention: | NA |
| Comparator: | NA |

Summary

This review aimed to determine the diagnostic tests that should be used to diagnose CAPA in people with COVID-19. The evidence highlighted the range of tests that are used in clinical practice.

What is the evidence informing this conclusion?

Evidence comes from 2 systematic reviews that evaluate different diagnostic investigations for people with COVID-19 and suspected CAPA (Chong 2021 and Dimopoulos 2021). A further 2
studies were included in this evidence review to supplement the findings of the included systematic reviews: a cross-sectional study (Meawed 2021) and a cohort study (van Grootveld 2021).

**Publication status**

All included studies were full publications (Chong 2021, Dimopoulos 2021, Meawed 2021 and van Grootveld 2021).

**Study characteristics**

Study participant numbers ranged from 63 people (van Grootveld 2021) to 1494 people (Chong 2021b). The average age of participants ranged from 62 to 63 years. The proportion of male participants ranged from 34% to 80% of the study population. All participants had a wide range of underlying comorbidities (for example, hypertension, diabetes, chronic pulmonary disease, cardiovascular disease, and active malignancies).

Most participants (94%; n= 2829/3026) were hospitalised and admitted to ICU with severe COVID-19 and only 6% had moderate COVID-19 (197/3026). Disease severity was mostly scored against the WHO Clinical Progression Scale.

For further details see the evidence review for diagnostics for CAPA.

**What are the main results?**

The evidence described the use of bronchoalveolar lavage (BAL), endotracheal aspirates (ETA), serum, non-directed bronchial lavage (NBL) and sputum to diagnose CAPA. The different microbiological investigations performed on each sample (such as tissue culture, galactomannan and beta-d-glucan biomarker levels, PCR) were also described in the literature.

CT imaging, serum assays (galactomannan (GM) and beta-d-glucan (BDG)), ETA culture and BAL are commonly used to support CAPA diagnosis. Further BAL sample investigations such as microscopy, culture, GM, BDG and PCR are also commonly used to support CAPA diagnosis.

The evidence shows that sputum sampling, NBL and ETA investigations like GM, BDG and PCR are not as commonly used to diagnose CAPA, as their prevalence was relatively low when compared to that of CT imaging, BAL, and serum assays.

The findings of this review are consistent with existing recommendations on diagnosing CAPA (Verweij et al. 2021). The Verweij et al. 2021 report states that bronchoscopy alongside BAL is recommended to diagnose CAPA and states that ETA and sputum should not be relied on solely to diagnose CAPA.

**Our confidence in the results**

GRADE could not be conducted on the results of this review because the results were descriptive rather than analytical.

There were some concerns about risk of bias due to unclear reporting of participant eligibility criteria in all studies (Chong 2021b, Dimopoulos 2021, Meawed 2021 and van Grootveld 2021). There was also insufficient information to assess the data collection and data analysis methods used in Chong 2021b and Dimopoulos 2021 and as such, risk of bias was rated as high for both studies.

The two systematic reviews contained studies from international centres and as such, there may have been differences in standard of care as well as diagnostic investigations and assessment criteria. As such, there is risk of the evidence being indirect to the UK context.
Although Chong 2021b defined clear eligibility criteria to limit the heterogeneity, studies are heterogeneous with epidemiological, clinical, and methodological diversity, meaning that it may not be possible to generalise the prevalence results.

**Conclusion**

The review has found that CT imaging, serum assays of biomarkers, ETA culture and BAL are the most common investigations for diagnosing CAPA.

The findings of this review are consistent with current recommendations on diagnosing CAPA.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study results and measurements</th>
<th>Comparator</th>
<th>Intervention</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT Imaging</td>
<td>Based on data from 1,792 participants in 3 studies.</td>
<td>Three studies (n=1792) found that 10%- 43% of participants had undergone a CT imaging investigation to support CAPA diagnosis.</td>
<td>Evidence from four studies found that CT imaging is a common investigation used to support CAPA diagnosis.</td>
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</tr>
<tr>
<td>Serum Galactomannan</td>
<td>Based on data from 957 participants in 2 studies.</td>
<td>Two studies (n=957) found that 25%-47% of participants had undergone a serum galactomannan investigation to support CAPA diagnosis.</td>
<td>Evidence from two studies found that serum galactomannan is a common investigation used to support CAPA diagnosis.</td>
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<tr>
<td>Serum beta-D-glucan</td>
<td>Based on data from 636 participants in 2 studies.</td>
<td>Two studies (n= 636) found that 3%- 47% of participants had undergone a serum beta-d-glucan investigation to support CAPA diagnosis.</td>
<td>Evidence from two studies found that serum beta-d-glucan is a common investigation used to support CAPA diagnosis.</td>
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</tr>
<tr>
<td>Endotracheal Aspirate Culture</td>
<td>Based on data from 370 participants in 3 studies.</td>
<td>Three studies (n = 370) found that 8% - 100% of a participants had undergone a endotracheal aspirate microscopy investigation to support CAPA diagnosis.</td>
<td>Evidence from three studies found that endotracheal aspirate culture is a common investigation used to support CAPA diagnosis.</td>
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</tr>
<tr>
<td>Endotracheal Aspirate Beta-d-glucan</td>
<td>Based on data from 52 participants in 2 studies.</td>
<td>Two studies (n = 52) found that 4%-5% of participants had undergone a endotracheal aspirate beta-d-glucan investigation to support CAPA diagnosis.</td>
<td>Evidence from two studies found that endotracheal aspirate culture is not commonly used to support CAPA diagnosis.</td>
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</tr>
<tr>
<td>Endotracheal</td>
<td>Based on data from 63</td>
<td>One study (n = 63) found that 100%</td>
<td>Evidence from one</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Timeframe</td>
<td>Study results and measurements</td>
<td>Comparator</td>
<td>Intervention</td>
<td>Certainty of the Evidence (Quality of evidence)</td>
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<tr>
<td>Aspirate PCR</td>
<td>participants in 1 studies.</td>
<td>of patients had undergone a endotracheal aspirate PCR investigation to support CAPA diagnosis.</td>
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</tr>
<tr>
<td>Non-directed Bronchial Lavage Culture</td>
<td>Based on data from 217 participants in 2 studies.</td>
<td>Two studies (n = 217) found that 5% - 10% of participants had undergone a non-directed bronchial lavage culture investigation to support CAPA diagnosis.</td>
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<tr>
<td>Non-directed Bronchial Lavage Galactomannan</td>
<td>Based on data from 78 participants in 2 studies.</td>
<td>Two studies (n = 78) found that 1%-4% of participants had undergone a non-directed bronchial lavage galactomannan investigation to support CAPA diagnosis.</td>
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<tr>
<td>Non-directed Bronchial Lavage PCR</td>
<td>Based on data from 66 participants in 2 studies.</td>
<td>Two studies (n = 66) found that 1%-4% of participants had undergone a non-directed bronchial lavage PCR investigation to support CAPA diagnosis.</td>
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<tr>
<td>Bronchoalveolar Lavage Microscopy</td>
<td>Based on data from 16 participants in 1 studies.</td>
<td>One study (n = 16) found that 1% of participants had undergone a bronchoalveolar lavage microscopy investigation to support CAPA diagnosis.</td>
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<tr>
<td>Bronchoalveolar Lavage Culture</td>
<td>Based on data from 572 participants in 3 studies.</td>
<td>Three studies (n = 572) found that 17% -22% of participants had undergone a bronchoalveolar lavage culture investigation to support CAPA diagnosis.</td>
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<tr>
<td>Bronchoalveolar Lavage Galactomannan</td>
<td>Based on data from 518 participants in 3 studies.</td>
<td>Three studies (n = 518) found that 17%-30% of participants had undergone a bronchoalveolar lavage galactomannan investigation to support CAPA diagnosis.</td>
<td></td>
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</tr>
</tbody>
</table>
References


Consensus recommendation

Test for antifungal resistance if an Aspergillus isolate is cultured from a CAPA test sample.

Evidence to decision

Benefits and harms

The panel discussed the risks of antifungal resistance and agreed on the importance of testing for antifungal resistance to guide treatment decisions for CAPA. Resistance to azoles, a type of antifungal treatment, would affect the treatment options available and the panel therefore agreed that resistance should be tested for as soon as possible.
The panel understood that waiting for the results of antifungal resistance tests could lead to a delay in effective treatment. Therefore, the panel advised that CAPA treatment could be started based on clinical judgement while waiting for test results. However, the panel emphasised the importance of using the results of antifungal resistance testing to guide definitive treatment.

The panel was not aware of any harms posed to patients from testing for antifungal resistance, but agreed that there were strong benefits from carrying out antifungal resistance testing as it could aid in identifying the optimal treatment for a CAPA patient.

### Certainty of the Evidence

No evidence was identified on antifungal resistance testing and diagnostic investigations for CAPA. However, the panel highlighted the need for a recommendation and stated that despite the lack of evidence on antifungal resistance in CAPA, based on their experience and expertise, this recommendation should be made to guide clinical management and decision making.

### Values and preferences

The panel were not aware of any systematically collected data on preferences and values of people in relation to testing for antifungal resistance.

### Resources

The panel discussed the need for timely testing and diagnostics to investigate CAPA and agreed that testing was important to guide the need for further intervention, and any resource implications may be offset by savings from prompt treatment.

Cost-effectiveness was not assessed as part of the evidence review.

### Equity

The panel noted that there was no information reported on pregnant women or children aged 17 and under, but that assessments should take place in the same way for all people who are critically ill because of current or previous COVID-19.

No other equity issues were identified.

### Acceptability

The panel were not aware of any systematically collected evidence about the acceptability of testing for antifungal resistance.

### Feasibility

The panel discussed that testing for antifungal resistance may not be routine in all centres, and that feasibility will require access to laboratory expertise.
Rationale
In clinical practice, microbiological investigations can be used to assess antifungal resistance of isolates cultured from test samples. The panel noted the importance of testing for azole resistance to support clinical management decisions and ensure that suitable antifungal treatments are used. They agreed that treatment can be started before test results are confirmed, but should be reviewed when test results are available.

See the British Society for Medical Mycology’s guidance on therapeutic drug monitoring of antifungal agents.

Evidence to decision

Consensus recommendation
Commissioners and local trusts should ensure that results of diagnostic tests for CAPA are available in a timeframe that informs and supports clinical decision making.

Benefits and harms
The panel highlighted the benefits of tests results being available quickly. They agreed that this would more often allow treatment to be started only after a confirmed diagnosis, rather than either starting treatment before diagnosis or accepting delays to treatment. Timely test results would reduce the frequency of treatment being used where diagnosis of CAPA is later determined to be negative, supporting antifungal stewardship aims.

Certainty of the Evidence
The panel did not review any evidence related to the time to availability of diagnostic tests for CAPA but advised that a recommendation was needed on this topic to ensure improved standardisation across centres. The panel’s recommendation was based on their experience observing the variability in arrangements for processing diagnostic tests for CAPA.

Values and preferences
The panel were not aware of any systematically collected data on preferences and values of people in relation to testing for CAPA.

Resources
The panel discussed the need for timely testing and diagnostics to investigate CAPA. They were aware that this might require additional resources, or changes to current processes in some areas, but concluded that the impact would be offset by the savings from appropriate diagnosis and treatment for people with CAPA, which could result in fewer days in hospital and reduced mortality among people with CAPA.

Cost-effectiveness was not assessed as part of the evidence review.
Equity
The panel noted that there was no information reported on pregnant women or children aged 17 and under, but agreed testing should take place in the same way for all people who are critically ill because of current or previous COVID-19.

No other equity issues were identified.

Acceptability
The panel were not aware of any barriers to acceptability in ensuring test results for CAPA are available in a timeframe that supports clinical decision-making.

Feasibility
The panel acknowledged that while some centres can already provide rapid turnaround of tests for CAPA, other centres may be required to make changes to practice to adhere to this recommendation, which may be challenging to implement. However, these changes will support improved care for people who are critically ill and have suspected CAPA.

Rationale
The panel noted that results of laboratory tests, in particular fungal antigen tests, are needed to diagnose CAPA. They also noted that if test results are not timely, there could be a delay in treatment or people could have treatments that they do not need. They highlighted the importance of having test results available in an appropriate timeframe to support clinical decision making and to improve people’s outcomes.

Consensus recommendation
Monitor and report testing for, and diagnosis and management of, CAPA in line with local protocols.

Local protocols for diagnosing and managing CAPA should be developed with a multidisciplinary team and based on knowledge of local prevalence.

Evidence to decision
Benefits and harms
The panel discussed the fact that there is insufficient evidence around the prevalence and management of CAPA. The panel agreed that monitoring and reporting on CAPA in line with local protocols would therefore provide useful information which could be used to improve identification and management of people with CAPA in the future.

Certainty of the Evidence
There was no evidence on the monitoring and reporting of diagnostics used for CAPA. As such, the panel highlighted the importance of monitoring and reporting the prevalence and management of
Rationale
There is a lack of evidence on the tests used to diagnose CAPA and on treatments for CAPA in people who are critically ill and have, or have had, COVID-19 as part of their acute illness. So, the panel agreed that local protocols should be developed to collect more information on the current prevalence of CAPA and practices for diagnosing and managing the condition.

9.2.2 Treating CAPA
**Consensus recommendation**

Only use antifungal treatments to treat CAPA if:

- diagnostic investigations support a diagnosis of CAPA or
- the results of diagnostic investigations are not available yet, but CAPA is suspected, and a multidisciplinary team or local protocols support starting treatment.

*See NICE’s recommendations on diagnosing CAPA.*

**Evidence to decision**

**Benefits and harms**

The panel considered that there are risks from inappropriate use of antifungal agents, including antifungal resistance and adverse drug effects. The panel concluded that the harms of antifungal therapies used for CAPA outweigh the benefits in people who do not have evidence of invasive pulmonary aspergillosis. The panel agreed that antifungal treatments for CAPA should not be offered unless CAPA has been diagnosed or there is clinical suspicion of CAPA and a local multidisciplinary team including infection specialists (for example, medical microbiologists or infectious disease specialists) support starting treatment.

**Certainty of the Evidence**

The panel reviewed evidence on the effectiveness of treatments for people with CAPA. A review of the evidence only found one study available that directly investigates the effect of a specific treatment for patients with CAPA, and the panel agreed that the certainty of the evidence was very low. The study did not present evidence on when antifungal treatments for CAPA should be started.

The panel decision was based on their experience and prior knowledge of the clinical use of antifungal agents and when treatment with these agents should be started. They also drew on expertise about antifungal resistance when making this recommendation.

**Values and preferences**

The panel were not aware of any systematically collected data on people’s preferences and values.

The panel agreed that it was likely that people would not want to take a treatment with no known benefits but well-established side effects in situations when there is a low suspicion of CAPA.

**Resources**

No formal analysis of resource impact has been carried out. However, it is possible that this recommendation will result in a reduction in the use of antifungals when there is low clinical suspicion or before investigations take place.

Cost effectiveness was not assessed as part of the evidence review.
Equity
This recommendation is not expected to cause inequity in any subgroups. Since CAPA is most likely to affect those with the most severe COVID-19 infections, the panel noted that subgroups with disproportionately high incidence of severe COVID-19 infection may be most affected by CAPA.

The panel recognised that the effectiveness and safety of antifungals may differ in pregnant women and children but that there was no evidence in this area.

No other equity issues were identified.

Acceptability
While there was no systematically collected evidence about acceptability, the panel acknowledged that not giving antifungal treatment until CAPA is diagnosed or testing is underway may mean treatment is started later, or not at all, for some people. They acknowledged that clinicians treating people who are hospitalised with COVID-19 will seek to improve people’s health outcomes as much as possible, and that families and carers of people who are hospitalised with COVID-19 would be likely to want to ensure that appropriate measures are taken to support people.

Feasibility
This recommendation may reflect usual practice in some centres. For others it may require adjustments to practice which should be feasible to implement, as this recommendation seeks to ensure appropriate practice and potentially reduce over prescribing.

Rationale
The panel noted that there are risks with antifungal treatments for CAPA, including antifungal resistance and adverse effects. They agreed that treatment should only be started if investigations support a diagnosis of CAPA, or a multidisciplinary team agrees to start treatment.

Clinical question/ PICO
Population: People hospitalised with COVID-19 and with CAPA
Intervention: Voriconazole
Comparator: Other

Summary
What is the evidence informing this conclusion?
Evidence comes from one cohort study (Bartoletti 2020) that compared the survival outcomes of people hospitalised with COVID-19 and CAPA, who had, or did not have, treatment with voriconazole.

Publication status
The study referenced in this review was a full publication that had been peer-reviewed.

Study characteristics
Bartoletti 2020 was a prospective, multicentre cohort study that aimed to describe the incidence...
and outcomes of CAPA in a larger cohort of people hospitalised with COVID-19 and receiving mechanical ventilation. A total of 108 people with COVID-19 that were treated in hospitals in Bologna, Italy, between February and March 2020 were screened for CAPA using bronchoalveolar lavage (BAL). Of these, 30 people were identified as having COVID-19 and CAPA.

For further details see the evidence review for treatments for CAPA.

**What are the main results?**

Of the 30 people who were identified as having COVID-19 and CAPA, 13 were treated with voriconazole, an antifungal therapy. Another 3 patients were treated with a different antifungal therapy, and the study authors do not state what treatment the remaining 14 patients received. Survival at 10, 20, and 30 days after ICU admission was captured for the 30 people with COVID-19 and CAPA, and differences were noted between the group of patients that were treated with voriconazole (n=13) vs. those not treated with voriconazole (n=17). At the end of the 30 days, 7 patients were still alive in each group.

**Our confidence in the results**

The certainty of the evidence for differences in survival between voriconazole treated CAPA patients vs. CAPA patients not treated with voriconazole was rated as very low, due to the small sample size, serious risk of confounding and imprecision.

The study found that there was no statistically significant difference in survival between CAPA patients treated with voriconazole compared with those not treated with voriconazole at 10, 20, and 30 days after ICU admission. However, the study was not powered to detect a difference for this outcome.

Study authors do not provide baseline characteristics for patients by treatment group, nor do they explain the methods used to assign patients to treatment groups. Since it is unclear if the patients treated with voriconazole are different from patients not treated with voriconazole with regards to characteristics that might impact their survival, there is a serious risk of confounding.

**Conclusion**

There was low quality evidence from one cohort study (Bartoletti 2020) reporting on possible treatments for CAPA.

The study showed that, in people with COVID-19 and CAPA, there were no statistically significant differences in survival for those treated with voriconazole compared with those not treated with voriconazole, at 10, 20, and 30 days from ICU admission.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Other</th>
<th>Intervention Voriconazole</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-Day Survival</td>
<td>Relative risk 1.43 (CI 95% 0.97 — 2.1) Based on data from 30 participants in 1 studies.</td>
<td>647 per 1000 Difference:</td>
<td>925 per 1000</td>
<td>Very low Due to very serious risk of bias and very serious imprecision</td>
<td>One study found no statistically significant difference in 10- day survival in people having voriconazole compared with people not having voriconazole</td>
</tr>
<tr>
<td>9 Critical</td>
<td>(Observational (non-randomized))</td>
<td>278 more per 1000 ( CI 95% 19 fewer)</td>
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</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
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</tr>
</thead>
<tbody>
<tr>
<td>20-Day Survival</td>
<td>Relative risk 1.05 (CI 0.95% 0.58 — 1.88) Based on data from 30 participants in 1 studies. (Observational (non-randomized))</td>
<td>588 per 1000</td>
<td>617 per 1000</td>
<td>Very low Due to very serious risk of bias and very serious imprecision</td>
<td>One study found no statistically significant difference in 20-day survival in people having voriconazole compared with people not having voriconazole</td>
</tr>
<tr>
<td>30-Day Survival</td>
<td>Relative risk 1.31 (CI 0.61 — 2.79) Based on data from 30 participants in 1 studies.</td>
<td>412 per 1000</td>
<td>540 per 1000</td>
<td>Very low Due to very serious risk of bias and very serious imprecision</td>
<td>One study found no statistically significant difference in 30-day survival in people having voriconazole compared with people not having voriconazole</td>
</tr>
</tbody>
</table>

2. **Risk of Bias: very serious.** The study was not originally designed to measure the effectiveness of voriconazole in people hospitalized with COVID-19 and CAPA. As such, the study authors did not provide details on the characteristics of the subset of patients treated with voriconazole, compared to the subset of patients not treated with voriconazole. It is also not made clear what the ‘other’ therapies were. Therefore, there is a strong likelihood that other factors (aside from the treatment with voriconazole) may have influenced the difference in 10-day survival between patients treated with voriconazole vs. other therapies. **Inconsistency: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA. **Indirectness: no serious.** The study focused on people hospitalized with COVID-19 and CAPA, so the evidence is relevant. **Imprecision: very serious.** The confidence interval for this outcome includes the possibility that there is no difference in survival between people with CAPA treated with voriconazole vs people with CAPA not treated with voriconazole. Furthermore, this outcome is based on a single study with a total of only 30 patients. Therefore, there are very serious issues with imprecision in this outcome. **Publication bias: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA.  
4. **Risk of Bias: very serious.** The study was not originally designed to measure the effectiveness of voriconazole in people hospitalized with COVID-19 and CAPA. As such, the study authors did not provide details on the characteristics of the subset of patients treated with voriconazole, compared to the subset of patients not treated with voriconazole. It is also not made clear what the ‘other’ therapies were. Therefore, there is a strong likelihood that other factors (aside from the treatment with voriconazole) may have influenced the difference in 20-day survival between patients treated with voriconazole vs. other therapies. **Inadequate sequence generation/ generation of comparable groups,**
resulting in potential for selection bias. **Inconsistency: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA. **Indirectness: no serious.** The study focused on people hospitalized with COVID-19 and CAPA, so the evidence is relevant. **Imprecision: very serious.** The confidence interval for this outcome includes the possibility that there is no difference in survival between people with CAPA treated with voriconazole vs people with CAPA not treated with voriconazole. Furthermore, this outcome is based on a single study with a total of only 30 patients. Therefore, there are very serious issues with imprecision in this outcome.. **Publication bias: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA.


6. **Risk of Bias: very serious.** The study was not originally designed to measure the effectiveness of voriconazole in people hospitalized with COVID-19 and CAPA. As such, the study authors did not provide details on the characteristics of the subset of patients treated with voriconazole, compared to the subset of patients not treated with voriconazole. It is also not made clear what the 'other' therapies were. Therefore, there is a strong likelihood that other factors (aside from the treatment with voriconazole) may have influenced the difference in 30-day survival between patients treated with voriconazole vs. other therapies., **Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias.** **Inconsistency: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA. **Indirectness: no serious.** The study focused on people hospitalized with COVID-19 and CAPA, so the evidence is relevant. **Imprecision: very serious.** The confidence interval for this outcome includes the possibility that there is no difference in survival between people with CAPA treated with voriconazole vs people with CAPA not treated with voriconazole. Furthermore, this outcome is based on a single study with a total of only 30 patients. Therefore, there are very serious issues with imprecision in this outcome.. **Publication bias: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA.

**References**


94. Voriconazole versus [not] for CAPA..
When considering antifungal treatment for CAPA:

- discuss treatment options with a multidisciplinary team that includes infection specialists
- follow local protocols that include best practice guidance on treating invasive aspergillosis.

There is not enough evidence to recommend specific antifungal treatments for CAPA.

The panel noted the importance of national antifungal stewardship guidance, such as NICE's guideline on antimicrobial stewardship.

**Evidence to decision**

**Benefits and harms**

The panel agreed that there is not enough evidence to recommend specific treatments for people with CAPA. Currently there is only one study available that directly investigates the effect of a specific treatment for patients with CAPA. This study (Bartoletti 2021) shows no statistically significant effect of voriconazole on the survival of people with CAPA. The panel noted that this was a small study with 30 participants, and that it provided limited insights on the benefits or harms of voriconazole. No safety outcomes are explored in this study. Based on this information, the panel recommended that decisions around treatments for people with CAPA be discussed with a multidisciplinary team that includes infection specialists, for example medical microbiologists or infectious disease specialists. Decisions around treatments for CAPA should also align with local protocols that include guidance on treating invasive aspergillosis.

The panel acknowledged that in many cases, antifungal therapies may be considered for the management of CAPA. They discussed the risks of antifungal resistance and agreed that the national antifungal stewardship strategy should be consulted if antifungal therapies are being considered for CAPA.

See the NICE's guideline on antimicrobial stewardship for more on the risks from antifungal resistance and recommendations for best practice.

**Certainty of the Evidence**

The overall certainty of the evidence for treatments for CAPA is very low.

Currently there is only one study available that directly investigates the effect of a specific treatment for patients with CAPA. In this non-randomised study (Bartoletti 2021), 30 people hospitalised with CAPA were treated either with voriconazole or another treatment, based on clinician discretion. The control group had either no treatment, or another unspecified antifungal.

The panel reviewed this study and found that there is significant risk of bias in the results due to lack of randomisation, and significant imprecision due to the small study size. Additionally, there is a lack of clarity around the comparators used in this study. Evidence did not include young people and children, therefore it was not possible for the panel to discuss differences that might be required between adults and young people.

Ultimately, the panel agreed that there is not enough evidence to recommend voriconazole or any
other specific antifungal treatment for managing CAPA.

**Values and preferences**

The panel were not aware of any systematically collected data on peoples’ preferences about treatments for CAPA. They discussed that, in view of the lack of clear evidence about the treatments, most people would prefer for treatment decisions to be made based on best practice and relevant expertise.

**Resources**

Cost effectiveness was not assessed as part of the evidence review and no formal analysis of resource impact has been carried out. The panel recommended further research on cost-effectiveness of CAPA treatment as part of the research recommendations.

**Equity**

This recommendation is not expected to cause inequity among any subgroups. Since CAPA is most likely to affect those with the most severe COVID-19 infections, the panel noted that subgroups with disproportionately high incidence of severe COVID-19 infection may be most affected by CAPA.

The panel recognised that the effectiveness and safety of antifungals may differ in pregnant women and children, but that there was no evidence in this area.

No other equity issues were identified.

**Acceptability**

The panel were not aware of any systematically collected evidence about acceptability. Since this recommendation does not recommend a specific treatment and instead defers to best practice and relevant expertise, it is not expected that there are significant barriers to acceptability. There may be variation in existing practice that the development of local protocols will need to resolve.

The panel acknowledged that some clinicians may feel that voriconazole should be recommended for treatment of CAPA. However, the panel agreed that there is not enough evidence to support the use of voriconazole, and decisions should be taken after discussing with multidisciplinary team.

**Feasibility**

This recommendation refers to local protocols and decision-making as part of a multidisciplinary team, and therefore should be feasible to implement.

**Rationale**

The panel noted the lack of evidence on treatments for CAPA. They agreed that treatment decisions, including on when to start treatment, should be guided by advice from infection specialists, and in line with local protocols and best practice guidelines.

For information on monitoring antifungal treatments, see the British Society for Medical Mycology's
guidance on therapeutic drug monitoring of antifungal agents.

Clinical question/ PICO

**Population:** People hospitalised with COVID-19 and with CAPA  
**Intervention:** Voriconazole  
**Comparator:** Other

Summary

What is the evidence informing this conclusion?

Evidence comes from one cohort study (Bartoletti 2020) that compared the survival outcomes of people hospitalised with COVID-19 and CAPA, who had, or did not have, treatment with voriconazole.

Publication status

The study referenced in this review was a full publication that had been peer-reviewed.

Study characteristics

Bartoletti 2020 was a prospective, multicentre cohort study that aimed to describe the incidence and outcomes of CAPA in a larger cohort of people hospitalised with COVID-19 and receiving mechanical ventilation. A total of 108 people with COVID-19 that were treated in hospitals in Bologna, Italy, between February and March 2020 were screened for CAPA using bronchoalveolar lavage (BAL). Of these, 30 people were identified as having COVID-19 and CAPA.

For further details see the evidence review for treatments for CAPA.

What are the main results?

Of the 30 people who were identified as having COVID-19 and CAPA, 13 were treated with voriconazole, an antifungal therapy. Another 3 patients were treated with a different antifungal therapy, and the study authors do not state what treatment the remaining 14 patients received.

Survival at 10, 20, and 30 days after ICU admission was captured for the 30 people with COVID-19 and CAPA, and differences were noted between the group of patients that were treated with voriconazole (n=13) vs. those not treated with voriconazole (n=17). At the end of the 30 days, 7 patients were still alive in each group.

Our confidence in the results

The certainty of the evidence for differences in survival between voriconazole treated CAPA patients vs. CAPA patients not treated with voriconazole was rated as very low, due to the small sample size, serious risk of confounding and imprecision.

The study found that there was no statistically significant difference in survival between CAPA patients treated with voriconazole compared with those not treated with voriconazole at 10, 20, and 30 days after ICU admission. However, the study was not powered to detect a difference for this outcome.

Study authors do not provide baseline characteristics for patients by treatment group, nor do they explain the methods used to assign patients to treatment groups. Since it is unclear if the patients treated with voriconazole are different from patients not treated with voriconazole with regards to characteristics that might impact their survival, there is a serious risk of confounding.

Conclusion
There was low quality evidence from one cohort study (Bartoletti 2020) reporting on possible treatments for CAPA. The study showed that, in people with COVID-19 and CAPA, there were no statistically significant differences in survival for those treated with voriconazole compared with those not treated with voriconazole, at 10, 20, and 30 days from ICU admission.

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Comparator Other</th>
<th>Intervention Voriconazole</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-Day Survival</td>
<td>Relative risk 1.43 (CI 95% 0.97 — 2.1) Based on data from 30 participants in 1 studies.</td>
<td>647 per 1000</td>
<td>925 per 1000</td>
<td>Very low Due to very serious risk of bias and very serious imprecision</td>
<td>One study found no statistically significant difference in 10- day survival in people having voriconazole compared with people not having voriconazole</td>
</tr>
<tr>
<td></td>
<td>(Observational (non-randomized))</td>
<td>Difference: 278 more per 1000 (CI 95% 19 fewer — 712 more)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>20-Day Survival</td>
<td>Relative risk 1.05 (CI 95% 0.58 — 1.88) Based on data from 30 participants in 1 studies.</td>
<td>588 per 1000</td>
<td>617 per 1000</td>
<td>Very low Due to very serious risk of bias and very serious imprecision</td>
<td>One study found no statistically significant difference in 20- day survival in people having voriconazole compared with people not having voriconazole</td>
</tr>
<tr>
<td></td>
<td>(Observational (non-randomized))</td>
<td>Difference: 29 more per 1000 (CI 95% 247 fewer — 517 more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-Day Survival</td>
<td>Relative risk 1.31 (CI 95% 0.61 — 2.79) Based on data from 30 participants in 1 studies.</td>
<td>412 per 1000</td>
<td>540 per 1000</td>
<td>Very low Due to very serious risk of bias and very serious imprecision</td>
<td>One study found no statistically significant difference in 30- day survival in people having voriconazole compared with people not having voriconazole</td>
</tr>
<tr>
<td></td>
<td>(Observational (non-randomized))</td>
<td>Difference: 128 more per 1000 (CI 95% 161 fewer — 737 more)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

2. **Risk of Bias:** very serious. The study was not originally designed to measure the effectiveness of voriconazole in people hospitalized with COVID-19 and CAPA. As such, the study authors did not provide details on the characteristics of the subset of patients treated with voriconazole, compared to the subset of patients not treated with voriconazole. It is also not made clear what the ‘other’ therapies were. Therefore, there is a strong likelihood that other factors (aside from the treatment with voriconazole) may have influenced the difference in 10-day survival between patients treated with voriconazole vs. other therapies. **Indirectness:** no serious. The study focused on people hospitalized with COVID-19 and CAPA, so the
evidence is relevant. **Imprecision: very serious.** The confidence interval for this outcome includes the possibility that there is no difference in survival between people with CAPA treated with voriconazole vs people with CAPA not treated with voriconazole. Furthermore, this outcome is based on a single study with a total of only 30 patients. Therefore, there are very serious issues with imprecision in this outcome. **Publication bias: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA.


4. **Risk of Bias: very serious.** The study was not originally designed to measure the effectiveness of voriconazole in people hospitalized with COVID-19 and CAPA. As such, the study authors did not provide details on the characteristics of the subset of patients treated with voriconazole, compared to the subset of patients not treated with voriconazole. It is also not made clear what the ‘other’ therapies were. Therefore, there is a strong likelihood that other factors (aside from the treatment with voriconazole) may have influenced the difference in 20-day survival between patients treated with voriconazole vs. other therapies. **Inconsistency: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA. **Indirectness: no serious.** The study focused on people hospitalized with COVID-19 and CAPA, so the evidence is relevant. **Imprecision: very serious.** The confidence interval for this outcome includes the possibility that there is no difference in survival between people with CAPA treated with voriconazole vs people with CAPA not treated with voriconazole. Furthermore, this outcome is based on a single study with a total of only 30 patients. Therefore, there are very serious issues with imprecision in this outcome. **Publication bias: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA.


6. **Risk of Bias: very serious.** The study was not originally designed to measure the effectiveness of voriconazole in people hospitalized with COVID-19 and CAPA. As such, the study authors did not provide details on the characteristics of the subset of patients treated with voriconazole, compared to the subset of patients not treated with voriconazole. It is also not made clear what the ‘other’ therapies were. Therefore, there is a strong likelihood that other factors (aside from the treatment with voriconazole) may have influenced the difference in 30-day survival between patients treated with voriconazole vs. other therapies. **Inconsistency: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA. **Indirectness: no serious.** The study focused on people hospitalized with COVID-19 and CAPA, so the evidence is relevant. **Imprecision: very serious.** The confidence interval for this outcome includes the possibility that there is no difference in survival between people with CAPA treated with voriconazole vs people with CAPA not treated with voriconazole. Furthermore, this outcome is based on a single study with a total of only 30 patients. Therefore, there are very serious issues with imprecision in this outcome. **Publication bias: no serious.** There was only one study available that measured the effectiveness of a treatment for people hospitalized with COVID-19 and CAPA.

**References**

For people having antifungal treatment for suspected CAPA, stop treatment if the results of investigations do not support a diagnosis of CAPA and a multidisciplinary team agrees.

**Evidence to decision**

**Benefits and harms**

The panel noted that, on occasion, people will start antifungal treatments for CAPA while a diagnosis of CAPA is being confirmed. The panel agreed that antifungal treatments should usually be stopped if subsequent test results do not support a diagnosis of CAPA.

However, the panel also acknowledged that the performance of diagnostic tests for CAPA is variable and may be influenced by the clinical context. Therefore, the panel recommended that, in cases where treatment has been started before a diagnosis of CAPA is confirmed, a multidisciplinary team including infection specialists (for example, medical microbiologists or infectious disease specialists) should review test results. Where tests do not support a diagnosis of CAPA, consider stopping antifungal treatment.

**Certainty of the Evidence**

The panel decision was based on their experience and prior knowledge of the patient harms of antifungal treatments and national antimicrobial resistance strategies. The panel were not aware of any studies directly investigating the patient harms and risks of antifungal resistance from the use of antifungals for the treatment of CAPA.

**Values and preferences**

The panel were not aware of any systematically collected data on people’s preferences and values.

The panel agreed that it was likely that people would not want to continue taking a treatment with no known benefits but well-established side effects where diagnostic testing does not support a diagnosis of CAPA.

**Resources**

No formal analysis of resource impact has been carried out. However, it is possible that this recommendation will result in a shorter course of antifungals for some people.

Cost effectiveness was not assessed as part of the evidence review, but the panel recommended further research on this topic.
Rationale
The panel noted the importance of good antifungal stewardship for reducing the risk of adverse effects and antifungal resistance, particularly when treatment is started before diagnosis is confirmed. They wanted to ensure that antifungal treatment would be stopped when investigations do not support a diagnosis of CAPA. However, the panel were aware that interpreting diagnostic test results and confirming a diagnosis of CAPA can be challenging. So, they recommended a multidisciplinary approach when deciding whether to stop treatment.

Equity
This recommendation is not expected to cause inequity in any subgroups. Since CAPA is most likely to affect those with the most severe COVID-19 infections, the panel noted that subgroups with disproportionately high incidence of severe COVID-19 infection may be most affected by CAPA.

Acceptability
The panel were not aware of any systematically collected evidence about acceptability of stopping treatment for CAPA. It is likely that stopping treatment where results of investigations do not support a diagnosis of CAPA will be acceptable to most people when considering the recognised risk of adverse drug effects and the important antifungal stewardship implications.

Feasibility
The panel were not aware of any systematically collected evidence about feasibility. This recommendation aims to reduce variation, so there may be a need for a change in practice in some centres.
10. Discharge, follow up and rehabilitation

Info Box

For follow up and rehabilitation for people who have either ongoing symptomatic COVID-19 or post-COVID-19 syndrome, see the NICE guideline on the long-term effects of COVID-19.

Be aware of the UK Government's information on the COVID-19 vaccination programme.
11. Palliative care

11.1 Principles of care

Info Box

For people who are nearing the end of their life, see:

- The NICE guideline on care of dying adults in the last days of life: this includes recommendations on recognising when a person may be in the last days of life, communication and shared decision making.
- The NICE guideline on end of life care for adults: service delivery: this includes recommendations for service providers on systems to help identify adults who may be at the end of their life, providing information and advanced care planning.
- The NICE guideline on care and support of people growing older with learning disabilities: this includes recommendations on accessing end-of-life care services, person-centred care, and involving families and support networks in end-of-life care planning.
- The NICE guideline on end of life care for infants, children and young people with life-limiting conditions: planning and management: this includes recommendations on planning and managing end of life and palliative care for infants, children and young people (aged 0 to 17 years) with life-limiting conditions.
12. Research recommendations

What is the clinical effectiveness and safety of vitamin D for treating COVID-19 in children, young people and adults?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: people with COVID-19, particularly groups for which current evidence is lacking, for example:
- in pregnancy and breastfeeding
- people 65 years and over
- children and young people under 18
- people from minority ethnic family backgrounds
- people with risk factors for severe COVID-19

I: vitamin D (800 IU/day or less and more than 800 IU/day; single or multiple doses)

C:
- standard care
- placebo

O: effectiveness outcomes:
- all-cause hospitalisation
- all-cause mortality
- need for mechanical ventilation
- need for non-invasive respiratory support
- admission to intensive care
- symptom alleviation
- adherence to therapy
- long-term effects of COVID-19 (at least 4 weeks from acute COVID-19 onset)

Safety outcomes:
- any adverse event
- adverse event leading to trial discontinuation
- serious adverse events
What is the effectiveness of awake body positioning in improving outcomes for people in hospital with COVID-19 who are not intubated and have higher oxygen needs?

Suggested PICO (Population, Intervention, Comparator, Outcomes)

P: people in hospital with COVID-19 who are not intubated and have higher oxygen needs

I: awake body positioning

C: standard care or a different specified awake body position

O:
- adherence to and compliance with body position (including total duration of awake body positioning and duration of each body positioning session)
- patient reported outcomes including dyspnoea, anxiety, delirium, pain, discomfort, breathlessness, impact on sleep
- mortality
- time to non-invasive respiratory support
- intubation
- length of hospital stay
- admission to intensive care unit
- complications (for example: pneumothorax, pneumomediastinum, delirium, intolerance of positioning or haemodynamic instability)

Subgroups:
- mean duration of body positioning
- people on general wards, and those with do-not-intubate goals of care
- supplemental oxygen type
- adults aged 50 years and older
- children aged 12 years and younger
- disease severity
- sex
- ethnic background
- religion or belief
- deprivation or socioeconomic status
- frailty
- BMI of 30 or higher
- pregnant women (including gestational age)
- people with learning disability or physical disability (or both)
- people who use aids (for example, spectacles, hearing aids)
- comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity)
What is the efficacy and safety of COVID-specific antiviral drugs in combination with other COVID-specific antiviral drugs or COVID-specific neutralising monoclonal antibodies in people who do not need supplemental oxygen and are within 7 days of symptom onset?

Suggested PICO (Population, Intervention, Comparator, Outcomes)

**P:** people with COVID-19 who do not need supplemental oxygen and are within 7 days of symptom onset

- subgroups of particular interest
  - people with at least 1 risk factor for progression to severe COVID-19 disease, including (but not limited to):
    - aged 60 or over
    - immunosuppression
    - obesity
    - hypertension
    - chronic lung disease
    - cardiovascular disease
    - cerebrovascular disease
    - active cancer
  - ethnic minorities
  - pregnant women
  - children and young people aged under 18
  - people who have had different types of vaccines and/or different numbers of vaccine doses
  - people who are at high risk of not mounting an antibody response when vaccinated against COVID-19

**I:**

- antiviral-antiviral
- antiviral-monoclonal antibodies

**C:**

- standard care without the combination treatment

**O:**

- effectiveness outcomes
  - COVID-19 related hospitalisation
  - duration of COVID-19 related hospitalisation
  - all-cause hospitalisation
  - all-cause mortality
  - need for mechanical ventilation
  - need for non-invasive respiratory support
  - ICU admission
  - symptom alleviation
  - adherence to therapy
- safety outcomes
  - any adverse event
  - adverse event leading to trial discontinuation
What are the clinical and cost effectiveness, and the safety, of specific antifungal treatments for treating suspected or confirmed COVID-19-associated pulmonary aspergillosis (CAPA), and the optimal treatment duration? When should treatment be started, stopped or modified?

Suggested PICO (Population, Intervention, Comparator, Outcome)

**P:** adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness and have probable or diagnosed CAPA. Subgroups of particular interest: children and young people, pregnant women, ethnicity, immunosuppression, and subgroups who have higher rates of COVID-19.

**I:** voriconazole, isavuconazole, liposomal amphotericin B, posaconazole, echinocandins (for example, caspofungin, anidulafungin) and amphotericin B deoxycholate

**C:** Standard care (usually voriconazole)

**O:**
- all-cause mortality (at any time during treatment)
- number of people having 1 or more serious adverse events
- number of days without respiratory or organ support (organ support includes use of vasopressors and renal replacement therapy)
- length of stay in intensive care
- number of people having 1 or more adverse events
- treatment duration
- timing of starting treatment
- need for treatment modification
- length of hospital stays
- need for and duration of invasive mechanical ventilation
- need for switching, starting or restarting antifungal treatment

What are the views, preferences and experiences of people with COVID-19-associated pulmonary aspergillosis (CAPA), and their families or carers, on:

- available tests for diagnosing CAPA
- available treatments for CAPA?

Suggested PIC (Population, Interest, Context)

**P:** people who have been diagnosed with and treated for CAPA, and their families or carers. Subgroups of particular interest include young people and children, and pregnant women.

**I:** tests for diagnosing CAPA and treatments for CAPA

**C:** people who have been diagnosed with, and had treatment for, CAPA in hospital
In people with suspected COVID-19-associated pulmonary aspergillosis (CAPA), what are the most accurate tests for diagnosing the infection and when should they be done?

**Suggested research details**

**Population:** adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness, and suspected CAPA. Subgroups of particular interest include young people and children, and pregnant women.

**Diagnostic tests:**
- any methods used to diagnose pulmonary aspergillosis (for example, CT imaging, testing of bronchoalveolar lavage, non-bronchoscopic lavage, endotracheal aspirate, sputum samples, serum assays)

**Reference standard:**
- lung biopsy or postmortem diagnosis

**Target condition:**
- CAPA

**Outcomes:**
- sensitivity and specificity
- positive and negative likelihood ratios

**Analysis:**
- optimal time of diagnostic testing

What are the possible outcomes for people who are critically ill and have COVID-19-associated pulmonary aspergillosis (CAPA)?

**Suggested research details**

**Population:** adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness, and who have CAPA. Subgroups of particular interest: young people and children, pregnant women, ethnicity, immunosuppression and subgroups who have higher rates of COVID-19

**Outcomes:**
- presence of fungal serum biomarkers (for example galactomannan and beta-D-glucan)
- measures of inflammation (for example C-reactive protein)
- need for respiratory support (for example, invasive mechanical ventilation or extracorporeal membrane oxygenation [ECMO])
- hospitalisation metrics (for example, mortality, length of hospital stay, admission to and length of stay in intensive care)
- long-term morbidity outcomes, functional measures and patient outcomes
- results may be stratified (for example, disease severity, use of ECMO)
What risk factors in people who are critically ill and have, or have had, COVID-19 as part of their acute illness are associated with developing COVID-19-associated pulmonary aspergillosis (CAPA)?

Suggested research details

Population: adults, young people and children who are critically ill and have, or have had, COVID-19 as part of their acute illness. Subgroups of particular interest include children and young people, and pregnant women.

Exposure: any

Outcomes:

• association of CAPA with individual factors (for example, age, sex, ethnicity, comorbidities, COVID-19 vaccination status.)
• association of CAPA with COVID-19 treatments (for example, respiratory support for COVID-19, high-dose corticosteroids, interleukin-6 inhibition)
• association of CAPA with length of stay in hospital

What is the clinical and cost effectiveness of budesonide for treating COVID-19 in the community in adults, young people and children?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: Adults, young people and children who have COVID-19 and are not in hospital

Subgroups of particular interest:

• People 18 to 49 years
• Children and young people

I: Inhaled budesonide

C: Inhaled placebo (to accommodate blinding)

O:

• All-cause mortality
• Hospitalisation
• Need for oxygen therapy (including thresholds for this decision)
• Costs of treatment
• Time to recovery
• Health-related quality of life
• Adverse events
Does a multidisciplinary team agreed approach to weaning from continuous positive airway pressure improve weaning times and result in stopping continuous positive airway pressure for people with COVID-19 and acute respiratory failure?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: people with COVID-19 having continuous positive airway pressure for respiratory support

I: multidisciplinary team agreed approach to weaning

C:
- standard care
- different multidisciplinary team approaches

O:
- patient experience
- symptom improvement
- length of time to wean

Is high-flow nasal oxygen effective in reducing breathlessness compared with standard care or conventional oxygen therapy for people in hospital with COVID-19 and respiratory failure when it is agreed that treatment will not be escalated beyond non-invasive respiratory support or palliative care is needed?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: adults over 18 years with COVID-19 having treatment for respiratory failure

I: high-flow nasal oxygen

C:
- standard care
- conventional oxygen therapy

O:
- patient experience
- symptom improvement
- frequency of coughing
- assessment of breathing pattern disorder
- impact of breathlessness on activities of daily living such as eating, drinking and movement
- recovery of sense of smell
- practicalities of maintaining high-flow nasal oxygen at home for patients who wish their end of life care to occur at home.

Subgroups: palliative care
Does early review and referral to specialist palliative care services improve outcomes for adults with COVID-19 thought to be approaching the end of their life?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients with a confirmed diagnosis of COVID-19 in hospital or community approaching the last days of life

I: early referral to specialist palliative care services (for example, in the last days of life)

C: late referral (for example, within the final day of life) or no referral

O:
- quality of life
- changes to clinical care
- patient or carer satisfaction (feeling supported)
- identification and/or achievement of patient wishes such as preferred place of death

What is the effectiveness and safety of a treatment dose with a low molecular weight heparin (LMWHs) compared with a standard prophylactic dose for venous thromboembolism (VTE) prophylaxis in young people under 18 years with COVID-19?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients 18 years and under who have COVID-19 pneumonia

I: treatment-dose LMWH

C: standard prophylaxis with LMWH

O:
- incidence of VTE
- mortality (all-cause, inpatient, COVID-19 related)
- admission to critical care (including use of advanced organ support)
- serious adverse events such as major bleeding or admission to hospital

What is the effectiveness and safety of extended pharmacological venous thromboembolism (VTE) prophylaxis for people who have been discharged after treatment for COVID-19?

Suggested PICO (Population, Intervention, Comparator, Outcome)

P: patients 16 years and over who have been discharged after treatment for COVID-19 pneumonia

I: extended (2 to 6 weeks) pharmacological VTE prophylaxis with standard-dose:
- low molecular weight heparins
- unfractionated heparins
- fondaparinux sodium
- direct-acting anticoagulant
- vitamin K antagonists

C: No extended pharmacological VTE prophylaxis

O:
- incidence of VTE
- mortality (all-cause, inpatient, COVID-19 related)
- serious adverse events such as major bleeding or admission to hospital
What is the effectiveness and safety of standard-dose compared with intermediate-dose pharmacological venous thromboembolism (VTE) prophylaxis for people with COVID-19, with or without additional risk factors for VTE?

**Suggested PICO (Population, Intervention, Comparator, Outcome)**

**P:** patients 16 years and over being treated for COVID-19 pneumonia in hospital or the community who have:
- no additional risk factors for VTE
- additional risk factors for VTE

**I:** intermediate dose:
- low molecular weight heparins (LMWH)
- unfractionated heparin (UFH)
- fondaparinux sodium
- direct-acting anticoagulant
- vitamin K antagonists

**C:** Standard-dose:
- LMWH
- UFH
- fondaparinux sodium
- direct-acting anticoagulants
- vitamin K antagonists
- antiplatelets

**O:**
- incidence of VTE
- mortality (all-cause, inpatient, COVID-19 related)
- admission to critical care (including use of advanced organ support)
- serious adverse events such as major bleeding or admission to hospital
13. Equality considerations

13.1 Equalities impact assessment during scoping - draft scope

Is the proposed primary focus of the guideline a population with a specific communication or engagement need, related to disability, age or other equality consideration?

No

Have any potential equality issues been identified during the check for an update or during development of the draft scope and, if so, what are they?

Exacerbating inequalities

There is potential for recommendations to exacerbate inequalities, if individual circumstances are not acknowledged. Protected characteristics and assumptions about individual circumstances need to be considered:

Sex

Public Health England’s report on disparities in the risk and outcomes of COVID-19 indicated that diagnosis rates of COVID-19 are higher in women under 40 years and men over 60 years. There are higher death rates from COVID-19 in men (nearly 60%) than women, and men make up a higher proportion of intensive care unit admissions (70% of admissions). This could mean that people in these groups may be at higher risk of poorer outcomes.

Age

Public Health England’s report on disparities in the risk and outcomes of COVID-19 highlighted that both diagnosis of COVID-19 and mortality are more likely as age increases (people 80 years or over are 70 times more likely to die than those under 40 years). Older people are more likely to be frail, and have comorbidities and underlying health conditions. These factors mean that people in these groups are at higher risk of poorer outcomes.

Older people may find it more difficult to access many services, including using digital technology to access remote consultations. This may increase the risk of them not being able to access appropriate services and care. Older people may need support from carers (both paid and unpaid) for both remote and face-to-face consultations, again this may increase the risk of them not being able to access the appropriate care. For some medications, different doses may be needed for older people. Whenever medication dosing is referred to, this should be used with information in the BNF.

Ethnicity

Public Health England’s report on disparities in the risk and outcomes of COVID-19 identified that people from black, Asian and minority ethnic groups are at higher risk of getting COVID-19, more likely to have severe symptoms because of the infection and at higher risk of poorer outcomes. The highest age-standardised diagnosis rates of COVID-19 per 100,000 population are in people from black ethnic groups.

Survival analysis in people with confirmed COVID-19 (after accounting for sex, age, deprivation and region) indicated that people with a Bangladeshi family background have twice the risk of death compared with white British people. It also found that people with a Chinese, Indian, Pakistani, other Asian, Caribbean or other black family background had 10% to 50% higher risk of death compared with white British people. Emerging evidence suggests that excess mortality from COVID-19 is higher in black, Asian and minority ethnic groups. Individuals from black African or black Caribbean family backgrounds may have the highest risk.
Poorer outcomes in black, Asian and minority ethnic groups have been linked to several potential factors. These include higher rates of comorbidities that have been associated with COVID-19 mortality (such as cardiovascular disease, obesity and diabetes) in some black, Asian and minority ethnic populations. They also include a person’s occupation (for example, over-representation in key worker roles in health and social care), and pre-existing socioeconomic factors such as housing conditions that could affect a person’s ability to maintain infection control and prevention measures.

People from black, Asian and minority ethnic groups may feel marginalised, have experienced racism or have had previous experiences with a culturally insensitive health service that could create barriers to engagement with those services. This could mean that people in these groups may be at higher risk of poorer outcomes.

**Disability**
The scope of the guideline includes consideration of communication and shared decision making. For effective communication and shared decision making, specific consideration may need to be given to:

- people with a learning disability (including autism)
- people with a physical impairment (for example, a visual impairment or disability affecting communication)
- people with cognitive impairment (for example, mild or fluctuating dementia)
- people with a mental health issue.

The section on how to use this guideline states that it should be used alongside usual professional guidelines, standards and laws (including equalities, safeguarding, communication and mental capacity).

**Socioeconomic factors**
People who live in more socially deprived areas may be more likely to live in overcrowded housing and have occupations that might make them more at risk of being exposed to COVID-19.

Some people may not have access to the equipment needed to take part in digital consultations. Depending on where a person lives, they may not have access to home delivery services (for example, if they live in a rural area).

**Gender reassignment**
None identified.

**Pregnancy and maternity**
Not all medications are appropriate for people who are pregnant or breastfeeding. Whenever medication dosing is referred to, this should be used with information in the **BNF**.

**Religion or belief**
Not all medications are acceptable to people of certain religions because of the products being animal derived. Whenever medication dosing is referred to, this should be used with information in the **BNF**.

**Sexual orientation**
None identified.

**Other definable characteristics**
Examples are:

- refugees
- asylum seekers
- migrant workers
• people who are homeless.

For people whose first language is not English, there may be communication difficulties, especially for effective shared decision making and minimising risk of infection.

It is recognised that people who are homeless, refugees, asylum seekers and migrant workers may be living in deprived areas (including overcrowded accommodation), which may mean they are more likely to be exposed to COVID-19.

People from these groups may also be less likely to be able to access services.

What is the preliminary view on the extent to which these potential equality issues need addressing by the panel?

The guideline will need to address the potential equality issues by looking at data from studies either focused on the groups identified or looking at subgroup data. No groups will be excluded from the population.

The scope of this guideline does not include specific review of situations in which people lack mental capacity to make their own decisions about healthcare at that point in time. NICE has produced guidance on decision making and mental capacity to help health and social care practitioners:

• support people to make their own decisions as far as possible
• assess people’s capacity to make specific health and social care decisions
• make specific best-interest decisions when people lack capacity, and maximise the person’s involvement in those decisions.

13.2 Equalities impact assessment during scoping - final scope

Have any potential equality issues been identified during review of the draft scope, and, if so, what are they?

Yes. In addition to those outlined in section 12.1 on the equalities impact assessment on the draft scope, the following issues were identified. No changes were made to the scope on the basis of these issues.

Age
Some older people or people who are very frail may receive ‘over-treatment’ and this could remove them from familiar carers and surroundings.

Disability
A person’s mental health can influence their health-seeking behaviours and how they manage their physical health conditions.

Gender reassignment
There may be an interplay between sex hormones in trans people. It is unknown whether sex differences in COVID-19 outcomes are due to genetics, hormonal issues or social factors.

Pregnancy and maternity
There has been an increased rate of maternal death since the start of the COVID-19 pandemic. It has also been reported that COVID-19 infection during pregnancy increases the risk of preterm birth, which is in turn linked to increased elective delivery and ventilation.
Race
There have been reports of vaccine hesitancy in people from black, Asian and minority ethnic groups. Given people in these groups are at risk of worse outcomes with COVID-19, vaccine hesitancy may further increase inequalities in outcomes.

Religion or belief
No further issues identified.

Sex
During the COVID-19 pandemic, women have had barriers to accessing in vitro fertilisation services, contraception and abortion care. Also, there have been increasing inequalities because of the lack of information being provided about alternative options.

Sexual orientation
Some people may feel marginalised because of their sexual orientation, so may have barriers to care because of their differing family or community structures.

Socio-economic factors
No further issues identified.

Were any changes to the scope made as a result of consultation to highlight potential equality issues?
No.

Have any of the changes made led to a change in the primary focus of the guideline which would require consideration of a specific communication or engagement need, related to disability, age, or other equality consideration?
If so, what is it and what action might be taken by NICE or the developer to meet this need? (For example, adjustments to panel processes, additional forms of consultation)

No. The equalities issues identified have not led to a change in the primary focus of the guideline.

13.3 Equalities impact assessment during guideline development

Have the potential equality issues identified during the scoping process been addressed by the panel, and, if so, how?

In the scoping process, a range of potential equality issues were identified. These have been addressed as follows:

Age
At scoping it was highlighted that older people with COVID-19 are at higher risk of poorer outcomes.

It was also noted that older people may have difficulties in accessing services, including using digital technology to access remote consultations, and that they may need carer support to access remote and face-to-face consultations. It is recommended in the communication and shared decision making section that, in the community, the risks and benefits of face-to-face and remote care should be considered for each person. This should allow issues such as an individual's ability to access remote care to be taken into account.

The panel also noted that some older people or people who are very frail could potentially receive ‘over-
treatment’, which could remove them from familiar carers and surroundings. In the section on care planning in the community, it is recommended to discuss with people with COVID-19, and their families and carers, the benefits and risks of hospital admission or other acute care delivery services (such as virtual wards, hospital at home teams). This should allow individualised decisions to be made that can take account of personal preferences to be cared for with familiar people in their usual surroundings.

It is noted that NEWS2 should not be used in children. This has been noted in the section on identifying severe COVID-19 in the community. The panel recommended the use of locally approved paediatric early warning scores in children.

Sex
It has been reported that there are higher death rates from COVID-19 in men than women and that men comprise a higher proportion of intensive care unit admissions. While this guideline does not make specific recommendations based on sex, the guideline allows for consideration of individual characteristics and risk factors in planning care. For example, in the section on assessment in hospital the guideline recommends that, on admission to hospital, a holistic assessment should be completed.

It was also noted that, during the COVID-19 pandemic, women have experienced barriers to accessing in vitro fertilisation services, contraception and abortion care. The provision of these services are outside the scope of this guideline.

Gender reassignment
It was noted during scoping that there may be an interplay between sex hormones in trans people and it is not known if sex differences in COVID-19 outcomes are due to genetic, hormonal or social factors. The panel did not make specific recommendations based on gender reassignment.

Sexual orientation
Some people may feel marginalised due to their sexual orientation and therefore may have barriers to care due to their differing family or community structures. No recommendations were made specific to sexual orientation.

Ethnicity
Emerging evidence suggests that excess mortality due to COVID-19 is higher in black, Asian and minority ethnic groups. The guideline does not make specific recommendations according to ethnicity. However, alongside the recommendation relating to the use of pulse oximetry it is noted that overestimation has been reported in people with dark skin.

There have been reports of vaccine hesitancy in people of from black, Asian and minority ethnic groups. Given that these groups are at risk of worse outcomes with COVID-19, vaccine hesitancy may further increase inequalities in outcomes. Vaccine uptake is outside the scope of this guideline.

Disability
Regarding communication and shared decision making, specific consideration may need to be given to people with a learning disability, people with physical impairments, people with cognitive impairment, and people with mental health issues. The section on communication and shared decision making recommends communicating with people with COVID-19, their families and carers to alleviate any fear or anxiety. This recommendation also advises to provide people with information in a way that they can use and understand, and to follow national guidance on communication, providing information (including in different formats and languages) and shared decision making. The guideline also recommends involving families and carers where appropriate to support discussions relating to care and shared decision making.

We state that this guideline should be used alongside usual professional guidelines, standards and laws.
It has also been noted that a person’s mental health can influence their health-seeking behaviours and how they manage their physical health conditions. As above, the guideline recommends involving families and carers in discussions relating to care where appropriate.

**Socioeconomic factors**
People who live in more socially deprived areas may be more likely to live in conditions and have occupations that may increase the risk of being exposed to COVID-19. No recommendations were made based on levels of social deprivation, living conditions or occupation.

Some people may not have access to equipment needed for remote consultations. It is recommended in the section on communication and shared decision making that, in the community, the risks and benefits of face-to-face and remote care should be considered for each person. This should allow issues such as an individual’s ability to access remote care to be considered.

Depending on where a person lives (for example in rural areas), they may have difficulty accessing home delivery services. The guideline recommends optimising remote care where appropriate, such as pharmacy deliveries, postal services, NHS volunteers and introducing drive-through pick up points for medicines. Providing a range of potential options may support access in different geographical areas. The guideline also covers use of anticipatory medicines at end of life. It is noted that, if there are fewer health and care staff, differing formulations may be prescribed and family members may be able to support administration of medications if they wish and have been provided with appropriate training.

**Pregnancy and maternity**
At scoping, increased rates of maternal death and an increased risk of preterm birth during the COVID-19 pandemic were highlighted. No recommendations were made specifically on pregnancy.

It is noted that NEWS2 should not be used when pregnant. This has been noted in the relevant recommendation under identifying severe COVID-19.

As not all medications are appropriate for people who are pregnant or breastfeeding, whenever medication dosing is referred to, this should be used with information in the BNF.

**Religion or belief**
Not all medications are acceptable to people of certain religions due to the products being animal derived.

**Other definable characteristics**
For people whose first language is not English, there may be communication difficulties, especially relating to shared decision making and minimising risk of infection. The section on communication and shared decision making recommends communicating with people with COVID-19, their families and carers to alleviate any fear or anxiety. This recommendation also advises to provide people with information in a way that they can use and understand, and to follow national guidance on communication, providing information (including in different formats and languages) and shared decision making.

People who are homeless, refugees, asylum seekers and migrant workers may be living in deprived areas (including overcrowded accommodation) and so may be more likely to be exposed to COVID-19 and may also experience difficulties in accessing services. No recommendations were made specific to people who are homeless, refugees, asylum seekers and migrant workers.
Have any other potential equality issues (in addition to those identified during the scoping process) been identified, and, if so, how has the panel addressed them?

**Disability**
The panel identified that children and young people under 18 years, or people with learning disabilities, may need additional consideration around capacity and decision making because of the isolated nature of treatment. The panel agreed that a recommendation should be added stating that, when making decisions about care of children and young people under 18 years, people with learning disabilities or adults who lack mental capacity for health decision making, the NICE guideline on decision making and mental capacity should be referred to. It was also recommended to ensure that discussions on significant care interventions involve family and carers, as appropriate, and local experts or advocates. The panel noted that infection prevention and control, including self-isolation, may be more challenging for some groups of people, including those with dementia or learning disabilities. A recommendation has been added to advise that, for carers of people with COVID-19 who should isolate but are unable to, relevant support and resources should be signposted to (for example, Alzheimer’s society has information on staying safe from coronavirus and reducing the risk of infection).

**Ethnicity**
It was noted that pulse oximeters can be less accurate in people with dark skin, especially at the borderline range of 90% to 92%. Information about this has been added to the recommendation to alert healthcare practitioners to this.

**Religion or belief**
The panel identified that, for people who do not use animal products, honey would not be appropriate for cough. No change was made to this recommendation.

Do the preliminary recommendations make it more difficult in practice for a specific group to access services compared with other groups? If so, what are the barriers to, or difficulties with, access for the specific group?
No. None identified.

Is there potential for the preliminary recommendations to have an adverse impact on people with disabilities because of something that is a consequence of the disability?
No.

Are there any recommendations or explanations that the panel could make to remove or alleviate barriers to, or difficulties with, access to services identified, or otherwise fulfil NICE’s obligation to advance equality?
Not applicable.
14. Methods and processes

Development
This guideline uses the methods and process in NICE’s interim process and methods for guidelines developed in response to health and social care emergencies.

Advisory panel
NICE has set up an expert advisory panel that includes representatives from relevant medical specialties with direct experience in managing and treating COVID-19, and people with lived experience of COVID-19. The panel develop new content, provide ongoing advice for surveillance and assist with updates to recommendations.

Declarations of interest
The expert advisory panel’s declarations of interest (DOI) are recorded according to NICE’s policy on declaring and managing interests for advisory committees. DOIs are reviewed on an ongoing basis and the DOI registry updated as needed. For a list of panel members and corresponding DOI registry for this guideline, see NICE’s guideline page on managing COVID-19.

All NICE staff are asked to declare all interests in line with NICE’s policy on declaring and managing interests for board members and employees. If a member of the NICE internal development team is conflicted, they are not permitted to help in developing that particular topic.

Scope development
The World Health Organization (WHO) guidance on clinical management of COVID-19 was used to develop the scope. The WHO guidance includes recommendations on diagnosing, assessing and managing COVID-19. It was used to inform the key themes in the scope of the NICE guideline.

There was no external stakeholder consultation on the scope to ensure the guideline could be produced as fast as possible, but the scope was reviewed and approved by the expert advisory panel. The scope is reviewed as part of ongoing surveillance and updating of the guideline, which is known as a ‘living’ approach.

See the introduction for details about the scope of this guideline.

Equality impact assessment
The impact on equality was assessed during guidance development according to NICE’s manual on developing guidelines. Potential equality issues identified were discussed with the expert advisory panel to ensure they were addressed, if appropriate. Equality issues are reassessed with the expert advisory panel during updates, and new issues are added to the equality impact assessment when identified.

See equalities considerations for details about the equality impact assessment.

Developing review questions
The review questions developed for this guideline were based on the key areas identified in the guideline scope. They were drafted by the NICE team, and refined and validated by the guideline panel. For full details of the review protocols, see the individual evidence reviews. Evidence reviews can be found under the summary section of the research evidence tab for each relevant recommendation.

Literature searches, critical appraisals and evidence reviews were completed for all review questions.

Structure
The guideline structure follows the main themes and overarching questions set out in the scope. Existing NICE COVID-19 rapid guidelines were reviewed to inform further subsections. The structure was designed to allow for flexibility to refine, remove or add sections in future iterations in a living approach.
Mapping of existing content

NICE compiled a list of all recommendations in the COVID-19 rapid guidelines that were relevant to the scope of this guideline. These recommendations were added to the appropriate section in the draft structure of the new NICE guideline. After NICE technical and clinical quality assurance of this mapping work, the recommendations were transferred to the relevant part of the structure on the publishing platform MAGICapp.

After the initial mapping, the structure was refined. The NICE expert advisory panel identified gaps in guideline and any recommendations that should be changed. The panel were also asked whether any recommendations from the rapid guidelines could be removed because they were:

- no longer relevant
- context specific, so bound to a particular time in the pandemic.

Any changes to recommendation content were based on the consensus view of the expert advisory panel.

Reviewing the evidence

Because there is a need for prompt guidance on managing COVID-19, NICE is collaborating with other guideline development teams to produce evidence reviews. NICE has reused data from the National Australian COVID-19 clinical evidence taskforce for some recommendations. Data provided by other guideline developers may be supplemented with additional trial results that the NICE COVID-19 team have access to through evidence searches.

Evidence provided by the National Australian COVID-19 clinical evidence taskforce is used through the sharing of RevMan files, which the NICE team uses to populate the evidence summary section and GRADE profiles for a review. Data extraction and risk of bias is done in line with NICE’s interim process and methods for guidelines developed in response to health and social care emergencies. Evidence reviews for each review question can be found in the relevant PICO summary sections.

All evidence reviews are quality assured before they are presented to the expert advisory panel.

Cost effectiveness

Because of the urgency for publishing guidance on managing COVID-19, no health economic analyses have been done.

Developing recommendations

Recommendations are developed or updated based on the expert advisory panel’s discussions of:

- the overall quality of the evidence or confidence in the expert opinion
- the trade-off between benefits and harms
- the impact on equity and equality
- the feasibility of implementation (for example, resources, capacity, settings and acceptability).

The guideline includes disease severity definitions that are in line with WHO definitions and approved by the NICE expert advisory panel. These are used to inform severity-specific recommendations when applicable.

Research recommendations

Research recommendations are developed by the expert advisory panel when:

- there is a lack of evidence
- the evidence is uncertain.

Quality assurance

Pragmatic checks and reviews are done iteratively throughout guideline development and during updates by NICE staff with
Consultation
Final recommendations are ratified by the expert advisory panel and external stakeholders through a targeted peer-review process. A range of stakeholders are invited to take part, including relevant national professional, and patient or carer groups. The length of the consultation depends on the urgency and complexity of the recommendations, and may range from 1 day to 2 weeks.

NICE staff collate all comments from stakeholders, so the independent advisory expert panel can consider them. The panel then advises on changes to the recommendation(s) and responses to stakeholder comments. Comments from stakeholders are grouped into themes. Thematic responses are provided to address these themes, instead of responding to individual comments.

All stakeholder comments and thematic responses are available on the NICE guideline page on managing COVID-19.

Sign off
NICE’s guidance executive sign off the guideline, either when new recommendations are published or when recommendations are updated.

Surveillance and future updates
Guideline recommendations are maintained using a continuous ‘living’ surveillance approach. This ensures that recommendations are updated continuously to reflect changes in:

- the evidence base
- clinical or healthcare practice
- the health and social care system, and government policy.

Living surveillance uses a multifactorial approach to identify ‘triggers’ for update. This approach includes:

- identifying studies relevant to the scope through continuous evidence searches
- looking at relevant professional guidance in the area
- intelligence gathering, including feedback from the broader health and social care system
- monitoring ongoing research and checking for publication of these ongoing studies regularly.

Surveillance decisions and outcomes are based on continual assessment of the impact of all the new evidence and intelligence that has been identified. There are 4 possible surveillance outcomes:

**No update:** recommendations will not be updated if new evidence or intelligence does not suggest that any changes are needed.

**Refresh of the recommendations:** this involves simple editorial changes that improve the usability of the recommendations without changing the intent, or correction of factual errors.

**Rapid update of the recommendations:** the recommendations could be updated if changes are needed (for example, new evidence emerges). Examples of updates include:

- covering additional populations or settings
- addressing new review questions
- changes to the original review questions, which mean a new search of the evidence is needed
- when new evidence contradicts existing recommendations.

**Withdrawal of recommendations:** recommendations may be withdrawn if:

- they are no longer needed, for example, because service delivery has changed (such as normal services resuming) or the
recommendations are likely to have limited relevance because of changes in context
• there are safety issues (for example, there is evidence of harm to people using the service)
• the recommendations are duplicated somewhere else (for example, if the recommendations are merged with another guideline).

Funding
NICE is an executive non-departmental public body sponsored by the Department of Health and Social Care.

A range of organisations, including the Department of Health and Social Care, arms-length bodies, professional associations, and voluntary and community sector groups are invited to become stakeholders. Stakeholders review and comment on draft recommendations as part of a targeted peer review. Stakeholders do not contribute to the systematic review and evidence appraisal process, or determine the final wording of recommendations.
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