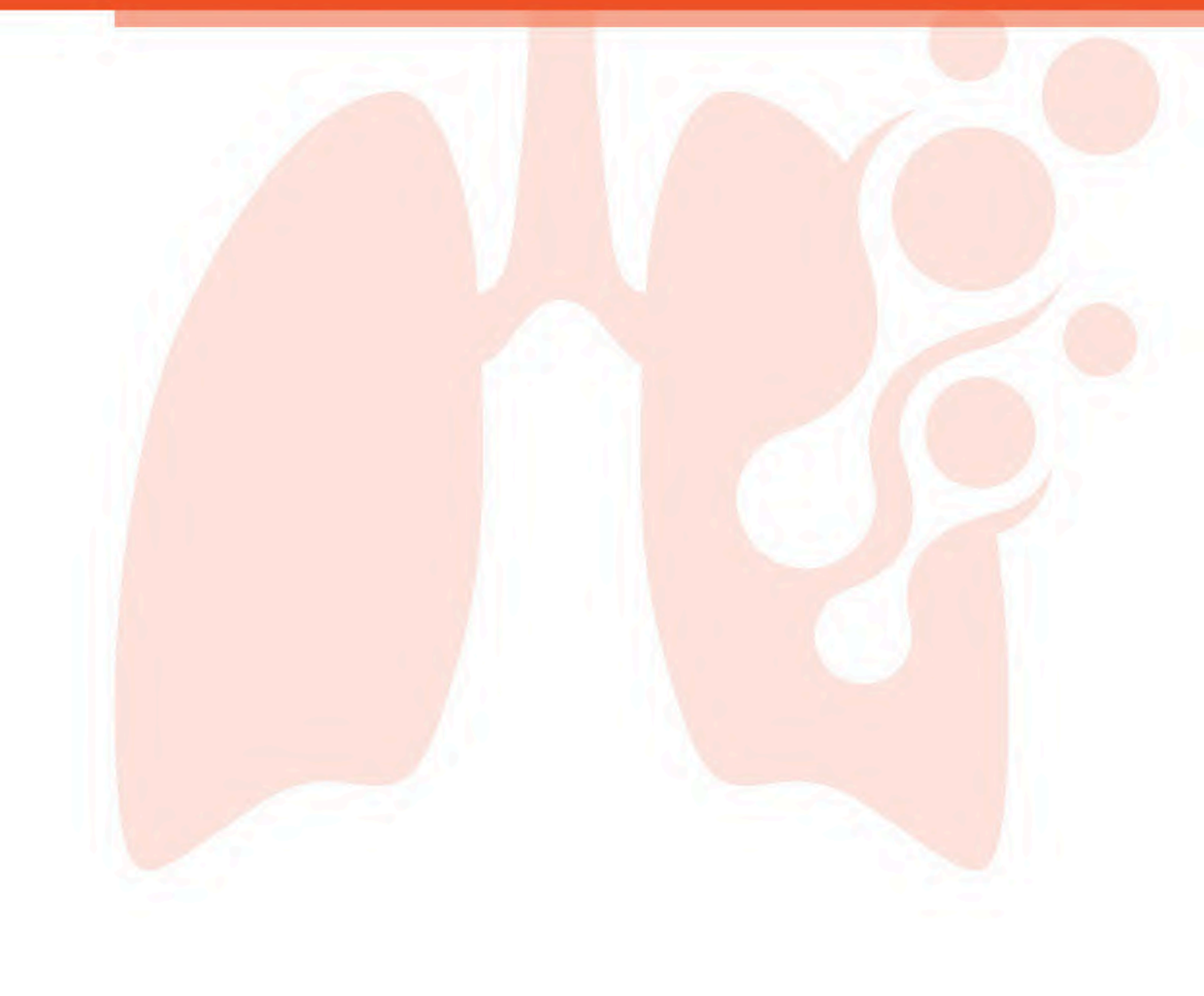
Therapeutics and COVID-19

Living guideline
August 2025

World Health Organization



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Contents

1. Summary of the guideline

Clinical question: What is the role of medicines in the treatment of patients with COVID-19?

New recommendations in this update:

- We suggest administering prophylactic dose heparin instead of therapeutic or intermediate dose heparin for severe or critical COVID-19 (heparin includes unfractionated or low-molecular-weight heparin) (*conditional recommendation).*
- We recommend not to use statins for severe or critical COVID-19 *(strong recommendation against).*
- We recommend not to use SGLT-2 inhibitors for severe or critical COVID-19 *(strong recommendation against).*
- We suggest not to use metformin in the acute management of COVID-19 *(conditional recommendation against).*

Understanding the new recommendations:

The GDGs background considerations remain unchanged in this version, including estimated rates of mortality (0.05% [low risk patients], 0.3% [moderate risk] and 0.6% [high risk]) and hospitalization (0.5% [low risk patients], 3% [moderate risk] and 6% high risk]). For this version, the GDG inferred that the majority of patients with non-severe COVID-19 would consider a 6% reduction in the incidence of post-COVID syndrome as important.

- **For heparins in patients with severe or critical COVID-19**, the GDG reviewed evidence comparing therapeutic dosing compared to intermediate or prophylactic dosing, and intermediate compared to prophylactic dosing. Given the low or very low certainty of evidence for beneficial effects on the main outcomes of mortality and progression to invasive mechanical ventilation or death, the panel made a conditional recommendation favouring prophylactic dosing of heparin (or low-molecular weight heparin).
- **For statins and SGLT-2 inhibitors,** there was low certainty evidence of mortality reduction, and lack of convincing benefit on other outcomes. The GDG made strong recommendations against these after considering the larger and more certain benefits of other therapies for severe and critical COVID-19 (for instance, systemic corticosteroids, IL-6 receptor blockers and baricitinib).
- **For metformin,** collated evidence suggested little or no effect on mortality and need for invasive mechanical ventilation (low certainty), and probably little or no effect on developing post-COVID syndrome (moderate certainty). The GDG inferred that a reasonable proportion of patients may be inclined to value the residual possibility of an important reduction in post-COVID syndrome, particularly given high certainty of little or no increased risk of serious adverse events. However, with no clear important benefit across patient-important outcomes, the existence of other therapeutics for individuals at moderate or high risk of hospitalization, and possible increased pill burden, the panel made a conditional recommendation against therapy.
- **For VV116,** new evidence from one randomized controlled trial was considered. The GDG maintained the previous recommendation for "*only in research settings*".

About this guideline: This living guideline from the World Health Organization (WHO) dynamically incorporates new evidence and updates recommendations for COVID-19 therapeutics. The GDG typically evaluates a medicine when the WHO judges sufficient evidence is available to make a recommendation. While the GDG takes an individual patient perspective in making recommendations, it also considers resource implications, acceptability, feasibility, equity and human rights. This guideline was developed according to standards and methods for trustworthy guidelines. It is supported by living network meta-analyses (LNMAs) *[1][2][3]*, and a recent meta-analysis on heparin.*[206]*

Updates and access: This is the 15th version (14th update), and replaces all earlier versions. The living guideline is written, disseminated, and updated on an easily navigable online platform (MAGICapp). This and previous versions are available through the WHO website *[4]*, the BMJ *[5]*, and MAGICapp (online and PDF).

This living WHO guideline is complemented by the WHO guideline on COVID-19 clinical management which provides additional recommendations on supportive care *[6]*. Guidelines for the use of medicines to prevent (rather than treat) COVID-19 are published separately on the WHO website *[7]* and by the BMJ *[8]*, supported by a LNMA *[9]*. The most recent iteration of the LNMA is under peer review at time of publication of this guideline; most up-to-date evidence is available via https://www.covid19lnma.com/.

2. Abbreviations

Ag-RDT	antigen-based rapid diagnostic test
AI	artificial intelligence
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
CAP	community-acquired pneumonia
CI	confidence interval
COVID-19	coronavirus disease 2019
DOI	declaration of interests
eGFR	estimated glomerular filtration rate
EUA	emergency use authorization
FDA	United States Food and Drug Administration
GDG	Guideline Development Group
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	guideline review committee
ICSR	individual case study report
IL-6	interleukin-6
IM	intramuscular
NAAT	nucleic acid amplification test
NHC	β-D-N4-hydroxycytidine
IV	intravenous
JAK	Janus kinase
LMICs	low- and middle-income countries
LNMA	living network meta-analysis
MAGIC	Magic Evidence Ecosystem Foundation
MD	mean difference
OIS	optimal information size
OR	odds ratio
PCC	Post COVID-19 condition ("Long COVID")
PICO	population, intervention, comparator, outcome
PMA	prospective meta-analysis
RCT	randomized controlled trial
RR	relative risk/risk ratio
SAE	serious adverse event
SSRI	selective serotonin reuptake inhibitor

TACO	transfusion-associated circulatory overload
TRALI	transfusion-related acute lung injury
UN	United Nations
WHO	World Health Organization

3. Introduction

As of March 2025, precise estimates of COVID-19 burden and mortality are limited as many countries discontinue disease-specific reporting and integrate this into respiratory disease surveillance. Cumulatively, over 777 million cases and over 7 million deaths have been confirmed *[10]*.

Vaccination and acquired immunity has had a substantial impact on hospitalizations and death, though patchy global access to vaccine leaves many populations vulnerable *[10][11]*, and uncertainties remain about the duration of protection and effectiveness of current vaccines.

Post-COVID-19 condition (PCC) continues to pose a substantial burden on health systems *[10]*. It is challenging to estimate the incidence of PCC with high precision, with early estimates of global burden suggesting that approximately 6% of symptomatic SARS-CoV-2 infections resulted in PCC symptoms *[204]*. While severe COVID-19 is a significant risk factor for PCC, over 90% of PCC cases arise following mild COVID-19 due to the sheer number of infections *[205]*.

There remains a need for more effective treatments for COVID-19. This living guideline is frequently updated in response to emerging evidence from randomized controlled trials (RCT) on existing and new medicines for COVID-19. Living network meta-analyses (LNMA) are used to incorporate emerging trial data which provides direct and indirect estimates of treatment efficacy. To contextualize and inform the recommendations, the guideline also uses additional relevant evidence on safety, prognosis, and patient values and preferences related to COVID-19 treatments *[18]*.

4. What triggered this update

In deciding which therapeutics to cover, the WHO considers multiple factors, including the extent of available evidence to inform recommendations, and makes a judgment on whether and when additional evidence might be anticipated. The guideline steering committee (see Section 13) evaluates possibilities for new medicine recommendations and updates to existing recommendations.

This update was triggered by:

- Prospective meta-analysis results combining multiple RCTs of unfractionated and low molecular weight heparin
- New RCT evidence on statins, SGLT-2 and metformin which have resulted in new recommendations.
- New RCT evidence concerning VV116, an oral antiviral agent which has affirmed an existing recommendation.

5. Understanding and applying the WHO severity definitions

This guideline applies to all patients with COVID-19. Recommendations may differ based on the severity of COVID-19, according to WHO severity definitions (see below) *[6]*. These definitions avoid reliance on access to health care to define patient subgroups.

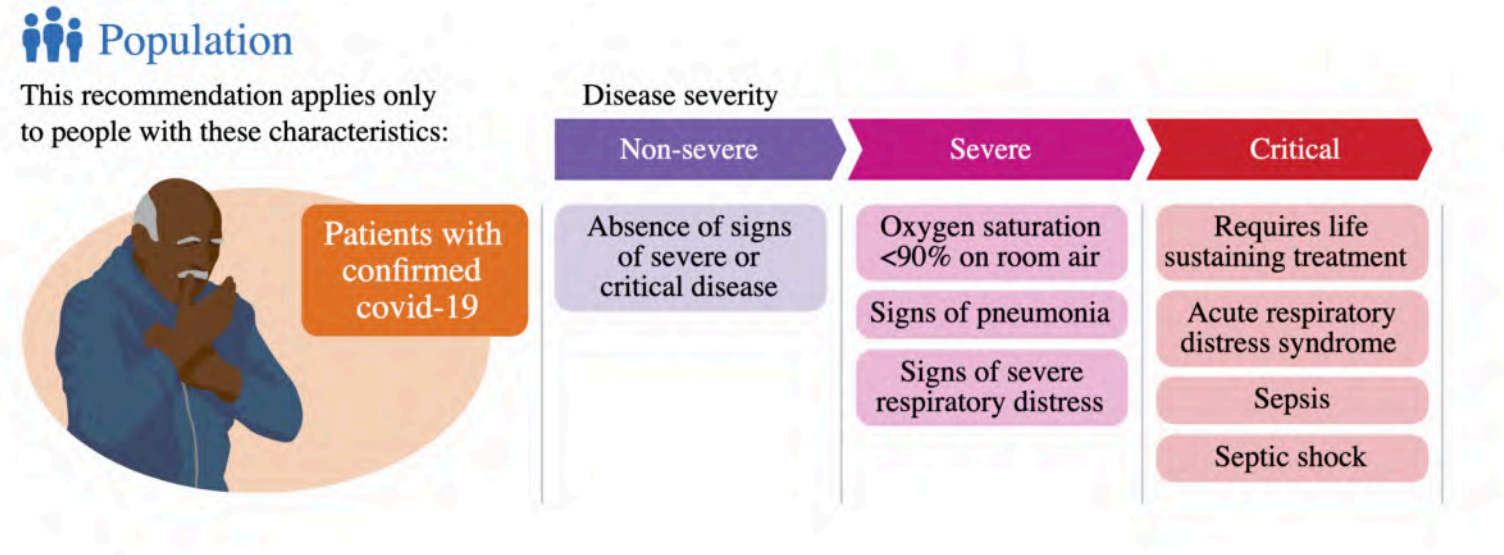
WHO definitions of disease severity for COVID-19

- **Critical COVID-19** – Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.

- **Severe COVID-19** – Defined by any of:
  - oxygen saturation < 90% on room air;
  - signs of pneumonia;
  - signs of severe respiratory distress (in adults, accessory muscle use, inability to complete full sentences, respiratory rate > 30 breaths per minute; and, in children, very severe chest wall in-drawing, grunting, central cyanosis, or presence of any other general danger signs including inability to breastfeed or drink, lethargy, convulsions or reduced level of consciousness).
- **Non-severe COVID-19** – Defined as the absence of any criteria for severe or critical COVID-19.

Caution: The GDG noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary, and should be interpreted cautiously when defining disease severity. For example, clinicians must use their judgment to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, clinicians may interpret a saturation of 90–94% on room air as abnormal in the patient with normal lungs, and as an early sign of severe disease in patients with a downward clinical trajectory. Generally, in cases where there is doubt, the GDG suggested erring on the side of considering disease as severe.

The **infographic** illustrates these three disease severity groups and key characteristics to apply in practice.



Infographic co-produced by the BMJ and MAGIC; designer Will Stahl-Timmins (see BMJ Rapid Recommendations).

6. Overview of medicines, recommendations and key issues to consider when applying them

The infographic summarizes WHO recommendations, mapped against the WHO severity criteria. When applying the recommendations, clinicians should also consider the following key issues:

How to identify patients with non-severe COVID-19 at high, moderate and low risk of hospitalization

Several recommendations to use drugs apply only for those at high risk for hospitalization, because the absolute benefit would be trivial if everyone with non-severe COVID-19 were to receive treatment. The baseline risk estimates for hospital admission and mortality were updated in v14 (see Section 10) where the GDG defined three risk categories for which the recommendations apply; low, moderate and high risk. These were developed based on observational data and updated to consider the evolving pandemic incorporating considerations around patient factors, immunity status, virulence and resistance, and noting the absence of credible risk prediction tools.

- **Patients at high risk (6%) of hospitalization** includes those with diagnosed immunodeficiency syndromes, those who have undergone solid organ transplant and are receiving immunosuppressants, and those with autoimmune illness receiving immunosuppressants.
- **Patients at moderate risk (3%) of hospitalization** are those over 65 years, those with obesity, diabetes and/or chronic cardiopulmonary disease, chronic kidney or liver disease, active cancer, those with disabilities, and those with comorbidities of chronic disease.
- **Patients at low risk (0.5%) of hospitalization** includes those who are neither moderate nor high risk. Most patients are low risk.

Defining a threshold for an important reduction in risk of hospitalization for patients with non-severe COVID-19

No evidence was identified to inform the guideline development group (GDG) regarding what patients with non-severe covid-19 perceive as an important reduction in risk of hospitalization. The GDG initially inferred an absolute reduction of 6% as being the threshold for a patient-important effect. For the fourteenth iteration, the GDG defined 1.5% as a new threshold for an important reduction in risk of hospitalization in patients with non-severe COVID-19. The GDG acknowledged the residual uncertainties regarding anticipated baseline risks in the three defined risk groups - with the living prognosis review unable to provide evidence to inform these judgments - as well as the defined threshold for an important reduction in hospitalization.

The GDG acknowledged that inherent uncertainties remain regarding baseline risks defined for individuals with non-severe COVID-19 at low, moderate and high risk of hospitalization; these baseline risks have natural implications on the absolute risk reduction that is considered patient-important. Reliable risk prognostication models for hospitalization and other patient-important outcomes for patients with non-severe illness remain limited. Similarly, regional data and event rates from the control arms of included trials may both help inform baseline risk estimates, but carry their own respective limitations (i.e. access to reliable data for the former, and issues with generalizability for the latter).

How to choose between therapeutics

Several therapeutic options are available for patients with non-severe COVID-19, and for those with severe or critical COVID-19. Choices will depend on availability of the drugs, routes of administration (e.g. parenteral route only for remdesivir), co-administered medication, duration of treatment, and time from onset of symptoms to treatment initiation. Some can be used in combination, while others are to be used as alternatives. Recommended combinations of treatments are based on direct comparisons from trials demonstrating additional benefit, such as adding the JAK inhibitor baricitinib to IL-6 receptor blockers and to systemic corticosteroids in patients with severe or critical COVID-19.

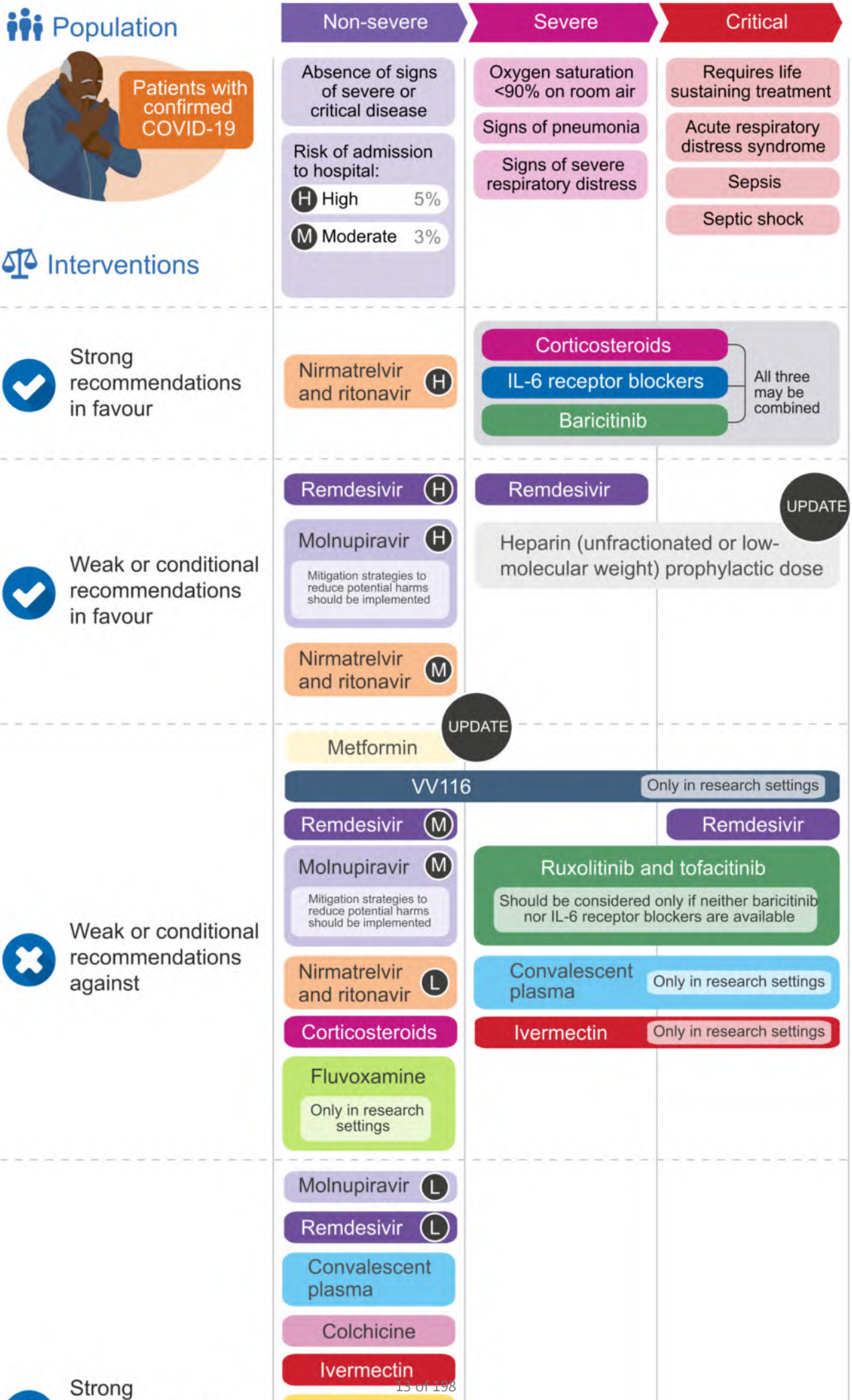
In the absence of direct comparisons of therapeutics in trials, indirect comparisons from the LNMA have been used to inform on the relative merits of one drug over another (see Section 10). To display the benefits and harms for the alternative therapeutics, we provide an interactive decision support tool that can also be used in shared decision-making, for patients with non-severe COVID-19 at high risk of hospitalization.

COVID-19 therapeutics as essential medicines

WHO recommends that effective and safe therapeutics for prevention and treatment of COVID-19 should be considered as essential medicines in the context of the public health emergency *[19]*. The WHO Model List of Essential Medicines notes that selection of essential therapeutics for COVID-19 at the national level should be informed by recommendations in these guidelines, with consideration of the latest evidence, epidemiology and national priorities.

Other supportive care

Therapeutics must be provided in the context of high-quality clinical care. This therapeutic guideline is complemented by the WHO guideline on COVID-19 clinical management which provides additional recommendations on supportive patient management *[6]*.


Population
Non-severe
Severe
Critical
Patients with confirmed COVID-19
Absence of signs of severe or critical disease
Risk of admission to hospital:
H High 5%
M Moderate 3%
Oxygen saturation <90% on room air
Signs of pneumonia
Signs of severe respiratory distress
Requires life sustaining treatment
Acute respiratory distress syndrome
Sepsis
Septic shock
Interventions
Strong recommendations in favour
Nirmatrelvir and ritonavir H
Corticosteroids
IL-6 receptor blockers
Baricitinib
All three may be combined
Weak or conditional recommendations in favour
Remdesivir H
Remdesivir
UPDATE
Molnupiravir H
Mitigation strategies to reduce potential harms should be implemented
Heparin (unfractionated or low-molecular weight) prophylactic dose
Nirmatrelvir and ritonavir M
UPDATE
Metformin
VV116
Only in research settings
Weak or conditional recommendations against
Remdesivir M
Remdesivir
Molnupiravir M
Mitigation strategies to reduce potential harms should be implemented
Ruxolitinib and tofacitinib
Should be considered only if neither baricitinib nor IL-6 receptor blockers are available
Nirmatrelvir and ritonavir L
Convalescent plasma
Only in research settings
Corticosteroids
Ivermectin
Only in research settings
Fluvoxamine
Only in research settings
Molnupiravir L
Remdesivir L
Convalescent plasma
Colchicine
Ivermectin
Strong
Sotrovimab

7. Recommendations for patients with non-severe COVID-19

Metformin (published August 2025)

For patients with non-severe COVID-19 (regardless of risk of hospitalization)

New

Conditional recommendation against

We suggest not to use metformin in the acute management of COVID-19 *(conditional recommendation against)*.

- *This recommendation does not apply to individuals already receiving metformin for an alternate indication.*

Evidence to decision

Benefits and harms

In patients with non-severe COVID-19, metformin may have little or no effect on mortality and need for invasive mechanical ventilation (low certainty), and probably has little or no effect on developing post-COVID syndrome (moderate certainty). Effects on admission to hospital and duration of hospitalization are very uncertain (very low certainty).

Metformin does not increase likelihood of adverse effects leading to discontinuation (high certainty). Effects on severe hypoglycaemia and severe gastrointestinal events, informed by a living network meta-analysis on medicines for adults with type 2 diabetes, are very uncertain (very low certainty).

Certainty of the evidence

The evidence summary on metformin in patients with non-severe COVID-19 was informed by three trials with 1,869 participants included in the LNMA study *[195][196][197]*.

Certainty of evidence was rated as moderate for post-COVID syndrome (rated down for serious imprecision), low for mortality and need for mechanical ventilation (both rated down for very serious imprecision), very low for admission to hospital (rated down for very serious imprecision and serious inconsistency) and duration of hospitalization (rated down for extremely serious imprecision), and high for adverse effects leading to discontinuation. Only one trial informed effect estimates for cases of post-COVID syndrome *[197]*. A living systematic review and network meta-analysis provided very low certainty evidence regarding severe hypoglycaemia and severe gastrointestinal events [cite].

Values and preferences

The GDG judged that the majority of patients would consider a 6% reduction in the incidence of post-COVID syndrome as important. They therefore inferred that while some patients would place a high value on the unlikely possibility of an important reduction in post-COVID syndrome, the majority of patients would place a low value on this possibility. Applying the agreed upon values and preferences (see Section 10), the GDG therefore agreed that the majority of patients would be disinclined from using metformin, though a minority may still be inclined to do so. The panel recognized that patients are likely to vary in their threshold for what they consider an important reduction in developing post-COVID syndrome and their threshold is likely to influence how they perceive results, and thus decisions they would make regarding use of metformin.

Resources and other considerations

Metformin is orally administered, widely available internationally, and is affordable relative to the majority of other candidate therapies, particularly for a short course of treatment during acute COVID-19 infection. The panel did not infer significant concerns regarding acceptability of therapy among the minority of patients who may be inclined to take the medication.

Justification

The GDG emphasized that the majority of patients are unlikely to place a high value on moderate certainty evidence of little or no effect on development of post-COVID syndrome, and low certainty evidence of little or no effect on mortality and need for invasive mechanical ventilation. The panel inferred that the majority of patients with non-severe COVID-19 would consider a 6% reduction (60 fewer cases per 1,000 patients) in the incidence of post-COVID syndrome as important; and interpreted treatment effects for this outcome accordingly. However, the panel recognized that patients are likely to vary in their threshold for what they consider an important reduction in developing post-COVID syndrome. Therefore, they inferred that a reasonable proportion may be inclined to value the residual possibility of an important reduction in post-COVID syndrome, particularly given high certainty of little or no increased risk of serious adverse events leading to discontinuation. Nonetheless, in the face of no clear important benefit across patient-important outcomes, the existence of other therapeutics for individuals at moderate or high risk of hospitalization (including nirmatrelvir-ritonavir, remdesivir and molnupiravir) and possible increased pill burden, the panel judged that a majority of patients would be disinclined from receiving therapy, and accordingly made a conditional recommendation against therapy.

Alternative or combination therapy

The GDG has previously made a strong recommendation for nirmatrelvir-ritonavir and conditional recommendations for molnupiravir and remdesivir in patients at high risk of hospital admission; and has made a conditional recommendation for nirmatrelvir-ritonavir in patients at moderate risk of admission. Given superior effects for other critical outcomes, the GDG concluded that when available and in patients in whom drug interactions are not an issue, nirmatrelvir-ritonavir likely represents a superior choice to other drugs including metformin.

The panel did not perceive significant issues with combining metformin with other recommended candidate therapies for non-severe COVID-19.

Applicability

In one of the three included trials, 6% of included participants were pregnant women *[197]*. Given prior experience with metformin and data from the single trial, the GDG did not identify any applicability concerns for children, breastfeeding or pregnant individuals with COVID-19.

Given the conditional recommendation against using metformin for patients with non-severe COVID-19, practical considerations were felt to be less relevant here. The panel emphasized that the recommendation does not apply to adults already receiving metformin for an alternate indication such as type 2 diabetes.

The GDG emphasized that the recommendation for metformin does not apply to individuals already diagnosed with post-COVID syndrome; rather, it applies to individuals with non-severe COVID-19 at risk of post-COVID syndrome. The GDG agreed that further research is needed to address whether metformin should be used for the treatment of post-COVID syndrome.

Clinical question/ PICO

Population: COVID-19 patients
Intervention: Metformin
Comparator: Placebo

Summary

Data are taken from a published systematic review and meta-analysis *[207]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Metformin	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality	Relative risk 0.76 (CI 95% 0.3 — 1.9) Based on data from 1,615 participants in 2 studies. (Randomized controlled) Follow up: 28 days.	**12** per 1000 Difference:	**9** per 1000 **3 fewer per 1000** (CI 95% 8 fewer — 11 more)	**Low** Due to very serious imprecision [1]	Metformin may have little or no impact on mortality

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Metformin	Certainty of the evidence (Quality of evidence)	Summary
Mechanical ventilation	Risk difference 0.33 (CI 95% 0.9 — 0.23) Based on data from 1,197 participants in 1 studies. (Randomized controlled) Follow up: 28 days.	Difference:	**3 fewer per 1000** (CI 95% 9 fewer — 2 more)	**High** 2	Metformin has little or no important impact on mechanical ventilation
Admission to hospital	Relative risk 0.74 (CI 95% 0.28 — 1.95) Based on data from 1,615 participants in 2 studies. (Randomized controlled) Follow up: 28 days.	**58** per 1000 Difference:	**43** per 1000 **15 fewer per 1000** (CI 95% 42 fewer — 55 more)	**Very low** Due to serious inconsistency, Due to very serious imprecision [3]	We are uncertain whether metformin increases or decreases admission to hospital
Cases of long covid-19	Relative risk 0.6 (CI 95% 0.4 — 0.9) Based on data from 1,126 participants in 1 studies. (Randomized controlled) Follow up: 300 days.	**103** per 1000 Difference:	**62** per 1000 **41 fewer per 1000** (CI 95% 62 fewer — 10 fewer)	**Low** Due to very serious imprecision [4]	Metformin may decrease cases of long covid-19
Adverse effects leading to discontinuation	Risk difference 0.02 (CI 95% 0.27 — 0.31) Based on data from 1,761 participants in 3 studies. (Randomized controlled) Follow up: 14 days.	Difference:	**0 fewer per 1000** (CI 95% 3 fewer — 3 more)	**High**	Metformin has little or no impact on adverse effects leading to discontinuation
Duration of hospitalization	Lower better Based on data from 20 participants in 1 studies. (Randomized controlled) Follow up: 14 days.	**9.8** days (Mean) Difference:	**8.8** days (Mean) **MD 1 fewer** (CI 95% 6.05 fewer — 4.05 more)	**Very low** Due to extremely serious imprecision [5]	We are uncertain whether metformin increases or decreases duration of hospitalization

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals include benefit and harm. **Publication bias: no serious.**
2, 4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Only data from one study. **Publication bias: no serious.**
3. **Inconsistency: serious.** Point estimates vary widely, The magnitude of statistical heterogeneity was high, with I^2: 76.7%, 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: very serious.** Wide confidence intervals include important benefits and harms. **Publication bias: no serious.**
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** Wide confidence intervals include important benefits and harms, Only data from one study, Low number of patients. **Publication bias: no serious.**

Metformin: mechanism of action

Metformin was first synthesized in 1922 and was introduced for glucose lowering in the 1950s. It is a first-line medicine for type 2 diabetes mellitus (T2DM) and is given at daily doses between 0.5–2.5 g to over 200 million people globally. Metformin is excreted 70% unchanged and ecotoxicological studies have demonstrated detrimental effects that have raised environmental concerns.*[189]* In COVID-19, metformin has been proposed as both an antiviral and a disease-modifying drug. For several

reasons, the antiviral mechanism may not be plausible based upon current data. First, antiviral concentrations *in vitro* have been high (>10 mM) in some cases,*[190]* and these concentrations are unlikely to be achieved clinically at doses given to humans. Second, in lung cultures from human donors, antiviral effects of metformin were not consistent and no antiviral effect was observed in 3 of 5 donors.*[191]* Finally and as noted by FDA, *in vitro* Emax values are very close to the minimal inhibition effect despite low EC_{50} / EC_{90} values in some cases.*[192]*

Numerous disease-modifying mechanisms of action have also been suggested with various degrees of plausibility.*[193][189][194]* Understanding the putative disease-modifying mechanism is difficult because the mechanisms underpinning long covid-19 are poorly understood. Furthermore, metformin is a highly pleiotropic drug which has multiple physiological effects, and no direct *in vitro* or *in vivo* preclinical evidence for a mechanism of action for long covd-19 is currently available. Indirect evidence for different mechanisms is of varying quality in terms of the concentrations used (physiological versus supra-physiological) and the sophistication of the conducted methodology.

Nirmatrelvir-ritonavir (updated 10 November 2023)

The recommendations for nirmatrelvir-ritonavir were initially published on 22 April 2022. In this 14th version of the guideline, the GDG maintained a strong recommendation for the use of nirmatrelvir-ritonavir in patients with non-severe COVID-19 at high risk of hospitalization. This recommendation is consistent with the demonstrated preservation of the effects of nirmatrelvir-ritonavir across circulating variants, and contrasts with the loss of effectiveness of monoclonal antibodies that target the spike protein. Considering the newly defined risk estimates, the GDG added a recommendation for patients with non-severe COVID-19 at moderate risk for hospitalization.

For patients with non-severe COVID-19 at high risk of hospitalization

Strong recommendation for

We recommend treatment with nirmatrelvir-ritonavir *(strong recommendation for)*.

- *See Section 6 for help to identify patients at high risk.*
- *Several therapeutic options are available: see decision support tool that displays benefits and harms of nirmatrelvir-ritonavir, molnupiravir and remdesivir for patients at high risk of hospitalization.*
- *The GDG concluded that nirmatrelvir-ritonavir in general represents a superior choice to molnupiravir because it probably has a greater reduction in hospitalization and because of concerns about potential harms of molnupiravir.*
- *The GDG concluded that nirmatrelvir-ritonavir in general represents a superior choice to remdesivir because of the practical difficulty that arises from the intravenous administration of remdesivir.*
- *Clinicians should review all medications and not consider nirmatrelvir-ritonavir in patients with possible dangerous drug interactions (note: many drugs interact with nirmatrelvir-ritonavir).*
- *Given possible benefit and residual uncertainty regarding potential undesirable effects, clinicians should engage pregnant or breastfeeding individuals fully informed shared decision-making regarding the use of nirmatrelvir-ritonavir.*
- *Patients should receive nirmatrelvir-ritonavir as soon as possible after onset of symptoms, ideally within 5 days from symptom onset.*

Practical info

The GDG recognized that there are circumstances in which nirmatrelvir should not be used due to drug interactions that result from its combination with ritonavir. Ritonavir may increase the concentrations of drugs highly dependent on hepatic cytochrome P450 3A (CYP3A) metabolism, which include macrolide antibiotics, immune modulators, warfarin and others. These drugs may also reduce nirmatrelvir concentrations, potentially leading to a loss of virologic response. Trials excluded patients with severe kidney impairment and severe liver impairment; and clinicians should use nirmatrelvir-ritonavir with caution in such patients.

Route, dosage and duration: Additional considerations are available in three summaries of practical issues (nirmatrelvir-ritonavir for COVID-19, administration of nirmatrelvir-ritonavir for COVID-19, safety and monitoring for patients receiving nirmatrelvir-ritonavir for COVID-19). Here follows a brief summary of key points:

- The recommended dose for nirmatrelvir-ritonavir is 300 mg (two 150 mg tablets) of nirmatrelvir and 100 mg of ritonavir every 12 hours daily for 5 days, as per the regimen evaluated in large trials informing the recommendation.
- In renal insufficiency (GFR 30–59 mL/min) the dose should be reduced to150 mg of nirmatrelvir and 100 mg of ritonavir every 12 hours daily for 5 days.

- Administration should be as early as possible in the time course of the disease. In the included studies, nirmatrelvir-ritonavir was administered within 5 days of symptom onset.

In any patient being considered for nirmatrelvir-ritonavir use, clinicians need to give serious consideration to drug interactions. The Liverpool COVID-19 drug interaction checker may be useful in this regard *[20]*.

Evidence to decision

Benefits and harms

In patients with non-severe COVID-19 at high risk of hospitalization, nirmatrelvir-ritonavir reduces admission to hospital and probably reduces mortality. There are no data reported for mechanical ventilation (uncertain effect). Nirmatrelvir-ritonavir may not have an important impact on time to symptom resolution. Treatment does not increase the likelihood of adverse effects leading to drug discontinuation, though diarrhoea and dysgeusia (loss of taste) have occurred more frequently with nirmatrelvir-ritonavir than with placebo.

Nirmatrelvir-ritonavir probably reduces hospitalization to a greater extent than molnupiravir and is not associated with the possible serious toxicity that may occur with molnupiravir.

There may be little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.

There may be little or no difference in impact on mortality and hospitalization between remdesivir and nirmatrelvir-ritonavir.

Certainty of the evidence

The evidence summary on nirmatrelvir-ritonavir in non-severe COVID-19 at high risk of hospitalization was informed by two trials (EPIC-SR and EPIC-HR) with 3100 participants included in the LNMA study *[1][21][22]*.

Certainty of evidence was rated as: high for decreased hospitalization, moderate for mortality (rated down due to serious imprecision), high for adverse effects leading to drug discontinuation and low for time to symptom resolution (rated down due to very serious imprecision).

Because of the very low baseline risk, there is high certainty evidence of little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir. There is, however, moderate certainty evidence of a reduction in hospitalization with nirmatrelvir-ritonavir versus molnupiravir.

Because of the very low baseline risk, there is high certainty evidence of little or no difference in mortality between nirmatrelvir-ritonavir and remdesivir. Due to very serious imprecision, there is low certainty evidence of little or no difference in hospitalization between the two drugs.

Values and preferences

Applying the agreed upon values and preferences (see Section 10), the GDG inferred that almost all well-informed patients with a high risk of hospitalization would choose to use nirmatrelvir-ritonavir.

Resources and other considerations

Acceptability and feasibility

Nirmatrelvir-ritonavir is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. This reinforces that the use of nirmatrelvir-ritonavir should, in many or perhaps most settings, be reserved for those at high risk of hospital admission.

Due to cost and availability, barriers to access in low- and middle-income countries (LMICs) may prove formidable. Those with socioeconomic disadvantages tend to have less access to services, including diagnostic testing and treatments, and thus less access to the interventions. If advantaged patients in these settings receive the intervention, this may exacerbate health inequity. It is important that countries integrate the COVID-19 clinical care pathway in the parts of the health system that provide care for patients with non-severe COVID-19 (i.e. primary care, community care settings).

The necessity for 3 days of intravenous administration represents major feasibility and acceptability obstacles for the administration of remdesivir.

The recommendations should provide a stimulus to engage all possible mechanisms to improve global access to the intervention. In promoting access, WHO has prequalified generic versions of molnupiravir and one generic version of nirmatrelvir-ritonavir. In addition, additional applications are under review. United

Nations (UN) partners procure these products and are making them available to LMICs. WHO and UN partners support allocation and procurement mechanisms for countries to ensure that these medicines are available and integrated into national supply chains. Individual countries may formulate their guidelines considering available resources and prioritize treatment options accordingly.

Access to SARS-CoV-2 diagnostics: Since this recommendation involves ideally administering treatment with nirmatrelvir-ritonavir within 5 days of symptom onset, increasing access and ensuring appropriate use of diagnostic tests is essential for implementation. Thus, availability and use of appropriate SARS-CoV-2 diagnostic tests is needed to improve access to drugs, especially those targeting the early phase of disease. The appropriate use of rapid diagnostic tests such as antigen-detection assays can improve early diagnosis in the community and in primary health care settings. Health care systems must, however, gain expertise in choosing and implementing rapid tests, choosing those most applicable to their settings.

Justification

When moving from evidence to a strong recommendation for nirmatrelvir-rironavir in patients with non-severe COVID-19 at high risk of hospitalization, the GDG emphasized the high certainty evidence demonstrating a reduction in absolute risk for hospitalization and death without an increase in adverse effects. Although the COVID-19 immunity landscape has evolved, in contrast to monoclonal antibodies that target the spike protein, nirmatrelvir-ritonavir has demonstrated consistency in effect across variants.

Alternative or combination therapy

The GDG has previously made a conditional recommendation for molnupiravir and remdesivir in high-risk non-severe populations. Indirect comparisons in high-risk patients demonstrated nirmatrelvir-ritonavir may reduce hospitalization when compared with molnupiravir (low certainty evidence); however, low certainty evidence suggested little or no difference when compared with remdesivir. This evidence regarding benefits, along with concerns regarding possible harms of molnupiravir and acceptability and feasibility concerns given the necessity for parenteral administration of remdesivir, led the GDG to conclude that when available and in patients in whom drug interaction is not an issue, nirmatrelvir-ritonavir represents a superior choice to the other drugs. There is no evidence for combining antiviral therapies; the GDG therefore advised against this.

Applicability

Because pregnancy represents a risk factor for severe or critical illness in those with non-severe COVID-19, pregnant individuals might consider using medication that reduces the risk of disease progression *[6]*. Nirmatrelvir-ritonavir, the drug combination the WHO recommends most highly in the context of non-severe illness for patients at high risk of hospitalization, represents a possible option.

Nevertheless, as with any medication not formally tested in pregnancy, in considering nirmatrelvir-ritonavir, concerns regarding undesirable effects in both pregnant individual and fetus immediately arise. Data from the WHO VigiBase, a comprehensive collection of worldwide unpublished reports of possible adverse reactions to drugs – in this case, nirmatrelvir-ritonavir in pregnant individuals – can inform the issue of undesirable effects.

Up to now, there have been no reports linking nirmatrelvir-ritonavir to serious adverse reactions in pregnant or breastfeeding individuals, either in parent or child. This is reassuring, but only to an extent: we are uncertain of the denominator to which this estimate of no undesirable effects applies. If a large number of inidividuals have been exposed, the absence of reported undesirable effects provides considerable reassurance; if only a small number, not so. We are uncertain which is the case.

In providing guidance on nirmatrelvir-ritonavir use in pregnancy, the GDG considered the likely benefits (there is no reason to think the drug will be less effective in pregnant individuals than in other people) and the uncertainty regarding undesirable effects. The GDG believes that shared, fully informed decision-making between the pregnant patient and health care provider should determine the use or non-use of nirmatrelvir-ritonavir in pregnant or breastfeeding individuals with non-severe COVID-19 at high risk of hospitalization.

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Nirmatrelvir-ritonavir
Comparator: Standard care

Summary

Evidence summary

The LNMA for nirmatrelvir-ritonavir was informed by two RCTs which enrolled 3100 patients with non-severe illness in outpatient settings. One RCT was published with 2246 patients (72.5%); data for the second RCT was provided by authors prior to publication. Neither of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings, effect estimates by outcome and associated forest plots for nirmatrelvir-ritonavir versus standard care.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of nirmatrelvir-ritonavir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

Subgroup analysis

Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

Sufficient data were unavailable to inform any of the pre-specified subgroup analyses. Studies did not enrol children. Data for patients aged 65 years or older or less than 65 years were reported only for the composite outcome of COVID-19 related hospital admission and mortality due to any cause. Studies did not enrol patients with severe or critical illness. All studies enrolled unvaccinated individuals with time from symptom onset within 5 days. Data regarding serological status were reported only for the composite outcome of COVID-19 related hospital admission and mortality due to any cause.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.04 (CI 95% 0 — 0.67) Based on data from 2,224 participants in 1 studies. (Randomized controlled)	**0.5** per 1000 Difference:	**0.02** per 1000 **0.48 fewer per 1000** (CI 95% 0.5 fewer — 0.16 more)	**High** 1	Nirmatrelvir-ritonavir does not result in an important reduction on mortality
Admission to hospital Low risk	Odds ratio 0.15 (CI 95% 0.06 — 0.36) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	**5** per 1000 Difference:	**0.7** per 1000 **4.3 fewer per 1000** (CI 95% 4.7 fewer — 3.2 fewer)	**High** 2	Nirmatrelvir-ritonavir does not result in an important reduction in hospital admission
Mortality Moderate risk	Odds ratio 0.04 (CI 95% 0 — 0.67) Based on data from 2,224 participants in 1 studies. (Randomized controlled)	**3** per 1000 Difference:	**0.1** per 1000 **2.9 fewer per 1000** (CI 95% 3 fewer — 1 fewer)	**High** 3	Nirmatrelvir-ritonavir does not result in an important reduction on mortality
Admission to hospital Moderate risk	Odds ratio 0.15 (CI 95% 0.06 — 0.36) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	**30** per 1000 Difference:	**5** per 1000 **25 fewer per 1000** (CI 95% 28 fewer — 19 fewer)	**High**	Nirmatrelvir-ritonavir reduces hospital admission
Mortality	Odds ratio 0.04 (CI 95% 0 — 0.67)	**6**	**0**	**Moderate** Due to serious	Nirmatrelvir-ritonavir probably reduces mortality.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the evidence** (Quality of evidence)	**Summary**
High risk	Based on data from 2,224 participants in 1 studies. (Randomized controlled)	per 1000 Difference:	per 1000 **6 fewer per 1000** (CI 95% 6 fewer — 2 fewer)	imprecision [4]	
Admission to hospital High risk	Odds ratio 0.15 (CI 95% 0.06 — 0.36) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	**60** per 1000 Difference:	**9** per 1000 **51 fewer per 1000** (CI 95% 56 fewer — 38 fewer)	**High**	Nirmatrelvir-ritonavir reduces hospital admission
Mechanical ventilation				No data [5]	The effect of nirmatrelvir-ritonavir is very uncertain
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.29 — 0.8) Based on data from 2,224 participants in 1 studies. (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**High**	Nirmatrelvir-ritonavir does not result in an important increase in adverse effects leading to drug discontinuation
Time to symptom resolution	Lower better Based on data from 662 participants in 1 studies. (Randomized controlled)	**9** (Median) Difference:	**9** (Median) **MD 0 fewer** (CI 95% 3 fewer — 4.4 more)	**Low** Due to very serious imprecision [6]	Nirmatrelvir-ritonavir may not reduce time to symptom resolution

1, 3. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 12 events total, all in one study. All 12 deaths occurred in the placebo group. **Publication bias: no serious.**
2. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
4. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: serious.** There were only 12 events total, all in one study. All 12 deaths occurred in the placebo group. **Publication bias: no serious.**
5. **Risk of Bias: no serious.** The single trial reporting mechanical ventilation was not blinded. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Very few events (24 total), resulted in wide credible intervals that include important and unimportant effects. **Publication bias: no serious.**
6. **Imprecision: very serious.** Credible interval includes both important benefit and important harm.

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Molnupiravir
Comparator: Nirmatrelvir-ritonavir

Summary

Evidence summary

The LNMA for molnupiravir was informed by 12 RCTs which enrolled 31 512 patients to molnupiravir or a control with non-severe COVID-19. All RCTs were registered; nine RCTs with 29 556 patients (93.8% of total) were published in peer-reviewed journals; the rest were data shared from authors from unpublished trials. None of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of molnupiravir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

Subgroup analyses

Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

Studies did not enrol children. All studies enrolled individuals with time from symptom onset < 5 days. Data regarding serological status were not reported. There was no credible relative effect modification by vaccination status (although the absolute benefit is much lower in patients who have been vaccinated).

Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84) (Randomized controlled)	**0.02** per 1000 Difference:	**0.02** per 1000 **0 fewer per 1000** (CI 95% 0.02 fewer — 0.08 more)	**High** 1	There is little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir.
Admission to hospital Low risk	Odds ratio 4.37 (CI 95% 1.82 — 10.28) (Randomized controlled)	**0.7** per 1000 Difference:	**3.05** per 1000 **2.35 more per 1000** (CI 95% 0.57 more — 6.45 more)	**High** 2	There is little or no difference in admission to hospital between nirmatrelvir-ritonavir and molnupiravir.
Mortality Moderate risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84) (Randomized controlled)	**0.1** per 1000 Difference:	**0.1** per 1000 **0 fewer per 1000** (CI 95% 0.08 fewer — 0.38 more)	**High** 3	There is little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir.
Admission to hospital Moderate risk	Odds ratio 4.37 (CI 95% 1.82 — 10.28) (Randomized controlled)	**5** per 1000 Difference:	**21** per 1000 **16 more per 1000** (CI 95% 4 more — 44 more)	**Moderate** Due to serious imprecision [4]	Nirmatrelvir-ritonavir probably reduces admission to hospital more than molnupiravir.

Outcome Timeframe	Study results and measurements	Comparator Nirmatrelvir-ritonavir	Intervention Molnupiravir	Certainty of the evidence (Quality of evidence)	Summary
Mortality High risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84) (Randomized controlled)	**0.23** per 1000 Difference:	**0.22** per 1000 **0.01 fewer per 1000** (CI 95% 0.18 fewer — 0.88 more)	**High**	There is little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir.
Admission to hospital High risk	Odds ratio 4.37 (CI 95% 1.82 — 10.28) (Randomized controlled)	**9** per 1000 Difference:	**38** per 1000 **29 more per 1000** (CI 95% 7 more — 76 more)	**Moderate** Due to serious imprecision [5]	Nirmatrelvir-ritonavir probably reduces admission to hospital more than molnupiravir.
Adverse effects leading to drug discontinuation	Odds ratio 0.81 (CI 95% 0.05 — 10.07) (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **2 fewer per 1000** (CI 95% 16 fewer — 4 more)	**Moderate** Due to serious risk of bias [6]	There is probably little or no difference in adverse effects leading to drug discontinuation between nirmatrelvir-ritonavir and molnupiravir.
Time to symptom resolution	Lower better (Randomized controlled)	**9** (Median) Difference:	**6.5** (Median) **MD 2.5 fewer** (CI 95% 6.8 fewer — 0.9 more)	**Low** Due to serious risk of bias and imprecision [7]	Molnupiravir may reduce duration of symptoms more than nirmatrelvir-ritonavir.

1, 3. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**
2. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
4. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (2 fewer per 1000).
5. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
6. **Risk of Bias: serious.** The molnupiravir studies were not blinded.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
7. **Risk of Bias: serious.** All three molnupiravir trials were at high risk of bias for deviations from intended intervention (lack of blinding). One trial was at high risk of bias for possible inadequate randomization concealment. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Nirmatrelvir-ritonavir
Comparator: Remdesivir

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**0.33** per 1000 Difference:	**0.1** per 1000 **0.23 fewer per 1000** (CI 95% 0.3 fewer — 0.02 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.
Admission to hospital Low risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**1** per 1000 Difference:	**0.6** per 1000 **0.4 fewer per 1000** (CI 95% 0.94 fewer — 3.82 more)	**High** [1]	There is little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.
Mortality Moderate risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**2** per 1000 Difference:	**0.6** per 1000 **1.4 fewer per 1000** (CI 95% 1.84 fewer — 0.1 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.
Admission to hospital Moderate risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**8** per 1000 Difference:	**5** per 1000 **3 fewer per 1000** (CI 95% 8 fewer — 30 more)	**Moderate** Due to serious imprecision [2]	There is probably little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.
Mortality High risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**4** per 1000 Difference:	**1.2** per 1000 **2.8 fewer per 1000** (CI 95% 3.68 fewer — 0.2 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.
Admission to hospital High risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**16** per 1000 Difference:	**10** per 1000 **6 fewer per 1000** (CI 95% 15 fewer — 57 more)	**Low** Due to very serious imprecision [3]	There may be little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.04 — 5.67) (Randomized controlled)	**4** per 1000 Difference:	**0** per 1000 **3 fewer per 1000** (CI 95% 19 fewer — 4 more)	**High**	There is no little or no difference in adverse effects leading to drug discontinuation between remdesivir and nirmatrelvir-ritonavir.
Time to symptom resolution	Lower better (Randomized controlled)	**8.6** (Median)	**7.8** (Median)	**Very low** Due to very serious imprecision and	The relative impact of nirmatrelvir-ritonavir compared to remdesivir on

Outcome Timeframe	Study results and measurements	Comparator Remdesivir	Intervention Nirmatrelvir-ritonavir	Certainty of the evidence (Quality of evidence)	Summary
		Difference:	**MD 0.8 more** (CI 95% 3.5 fewer — 5.5 more)	serious intransitivity [4]	duration of symptoms is uncertain.

1. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
2. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (2 fewer per 1000).
3, 4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**

For patients with non-severe COVID-19 at moderate risk of hospitalization

Conditional recommendation for

We suggest to use treatment with nirmatrelvir-ritonavir *(conditional recommendation for)*.

- *See Section 6 regarding identifying patients at moderate risk.*
- *Because their risk of hospitalization is sufficiently high such that they will receive an appreciable reduction in hospitalization with the drug, the GDG concluded that a majority of well-informed moderate-risk patients would choose to use nirmatrelvir-ritonavir.*
- *Clinicians should not consider nirmatrelvir-ritonavir in patients with possible dangerous drug interactions (note: many commonly used drugs interact with nirmatrelvir-ritonavir).*
- *The GDG concluded that nirmatrelvir-ritonavir in general represents a superior choice to molnupiravir (due to greater reduction in hospitalization, and safety concerns with molnupiravir) and also a superior choice to remdesivir (due to practical issues with intravenous administration) provided that the intended recipient is not using other drugs that interact with nirmatrelvir-ritonavir.*
- *Given possible benefit and residual uncertainty regarding potential undesirable effects, clinicians should engage pregnant or breastfeeding individuals in fully informed shared decision-making regarding the use of nirmatrelvir-ritonavir.*

Practical info

Route, dosage and duration: Additional considerations are available in three summaries of practical issues (nirmatrelvir-ritonavir for COVID-19, administration of nirmatrelvir-ritonavir for COVID-19, safety and monitoring for patients receiving nirmatrelvir-ritonavir for COVID-19), briefly summarized here:

- The recommended dose for nirmatrelvir-ritonavir is 300 mg (two 150 mg tablets) of nirmatrelvir and 100 mg of ritonavir every 12 hours daily for 5 days, as per the regimen evaluated in large trials informing the recommendation.
- In renal insufficiency (glomerular filtration rate [GFR] 30–59 mL/min) the dose should be reduced to 150 mg of nirmatrelvir and 100 mg of ritonavir every 12 hours daily for 5 days.
- Administration should be as early as possible in the course of disease. In the included studies, nirmatrelvir-ritonavir was administered within 5 days of symptom disease onset.

In any patient being considered for nirmatrelvir-ritonavir use, clinicians need to give serious consideration to drug interactions. The Liverpool COVID-19 drug interaction checker may be useful in this regard *[20]*.

Evidence to decision

Benefits and harms	In patients with non-severe disease and moderate risk for hospitalization, although nirmatrelvir-ritonavir has a similar relative effect on patient-important outcomes of interest as high risk patients, absolute effects are smaller because of substantially lower baseline risks. In particular, the best estimate of reduction in hospitalization is 25 per 1000 patients (2.5%), a magnitude that the GDG considered would be important to the majority of patients, but likely to be unimportant to an appreciable minority.

Across risk strata with non-severe COVID-19, there were no data evaluating need for mechanical ventilation (very low certainty of evidence), and nirmatrelvir-ritonavir may not impact time to symptom resolution (low certainty of evidence). Nirmatrelvir-ritonavir had no effect on adverse effects leading to drug discontinuation (high certainty of evidence).

Nirmatrelvir-ritonavir probably reduces hospitalization to a greater extent than molnupiravir and is not associated with the concerns for potential for toxicity with molnupiravir.

There may be little or no difference in admission to hospital and mortality between remdesivir and nirmatrelvir-ritonavir.

Certainty of the evidence

The evidence summary on nirmatrelvir-ritonavir in patients at moderate risk for hospitalization was informed by two trials (EPIC-SR and EPIC HR) with 3100 participants included in the LNMA study *[1][21][22]*.

Certainty of evidence was rated as: high for hospitalization, mortality and adverse effects leading to drug discontinuation. Certainty was rated as low for time to symptom resolution (due to very serious imprecision) and there were no data evaluating use of mechanical ventilation (very low certainty evidence).

Values and preferences

The GDG believes that many patients at moderate risk would place a high value on the reduction in hospitalization they might achieve with nirmatrelvir-ritonavir but a minority would not.

Resources and other considerations

Nirmatrelvir-ritonavir is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. This reinforces that nirmatrelvir-ritonavir should, in many or perhaps most settings, be reserved for those at high risk of hospital admission.

Due to cost and availability, obstacles to access in LMICs may prove formidable due to cost and availability. Those with socioeconomic disadvantages tend to have less access to services, including diagnostic testing and treatments, in the first 5 days of symptoms, and thus less access to the interventions. Therefore, if advantaged patients in these settings at moderate risk receive the intervention, this may exacerbate health inequity. It is important that countries integrate the COVID-19 clinical care pathway in the parts of the health system that may provide care for patients with non-severe COVID-19 (i.e. primary care, community care settings).

The recommendations should provide a stimulus to engage all possible mechanisms to improve global access to the intervention. In promoting access, WHO has prequalified generic versions of molnupiravir and one generic version of nirmatrelvir-ritonavir. In addition, there are additional applications under review for both products. UN partners procure these products and are making them available to LMICs. WHO and UN partners support allocation and procurement mechanisms for countries to ensure that these medicines are available and integrated into national supply chains. Individual countries may formulate their guidelines considering available resources and prioritize treatment options accordingly.

Justification

The GDG inferred that, for typical patients, the threshold for use of nirmatrelvir-ritonavir, would be a reduction in hospitalizations of 1.5%. The estimated impact of the drugs on hospitalization is 2.5% with a lower boundary of the confidence interval (CI) of 1.9%, and evidence was judged high certainty. If GDG inferences regarding patient values and preferences are accurate, this clearly establishes that a majority of fully informed moderate risk patients would choose the drugs. A conditional recommendation was made due to the uncertainty regarding baseline risk estimates, uncertainty around GDG inferences regarding values and preferences, and likely considerable variability in values and preferences.

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Nirmatrelvir-ritonavir
Comparator: Standard care

Summary

Evidence summary

The LNMA for nirmatrelvir-ritonavir was informed by two RCTs which enrolled 3100 patients with non-severe illness in outpatient settings. One RCT was published with 2246 patients (72.5%); data for the second RCT was provided by authors prior to publication. Neither of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings, effect estimates by outcome and associated forest plots for nirmatrelvir-ritonavir versus standard care.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of nirmatrelvir-ritonavir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

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Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
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3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

Sufficient data were unavailable to inform any of the pre-specified subgroup analyses. Studies did not enrol children. Data for patients aged 65 years or older or less than 65 years were reported only for the composite outcome of COVID-19 related hospital admission and mortality due to any cause. Studies did not enrol patients with severe or critical illness. All studies enrolled unvaccinated individuals with time from symptom onset within 5 days. Data regarding serological status were reported only for the composite outcome of COVID-19 related hospital admission and mortality due to any cause.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.04 (CI 95% 0 — 0.67) Based on data from 2,224 participants in 1 studies. (Randomized controlled)	**0.5** per 1000 Difference:	**0.02** per 1000 **0.48 fewer per 1000** (CI 95% 0.5 fewer — 0.16 more)	**High** 1	Nirmatrelvir-ritonavir does not result in an important reduction on mortality
Admission to hospital Low risk	Odds ratio 0.15 (CI 95% 0.06 — 0.36) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	**5** per 1000 Difference:	**0.7** per 1000 **4.3 fewer per 1000** (CI 95% 4.7 fewer — 3.2 fewer)	**High** 2	Nirmatrelvir-ritonavir does not result in an important reduction in hospital admission
Mortality Moderate risk	Odds ratio 0.04 (CI 95% 0 — 0.67) Based on data from 2,224 participants in 1 studies. (Randomized controlled)	**3** per 1000 Difference:	**0.1** per 1000 **2.9 fewer per 1000** (CI 95% 3 fewer — 1 fewer)	**High** 3	Nirmatrelvir-ritonavir does not result in an important reduction on mortality
Admission to hospital Moderate risk	Odds ratio 0.15 (CI 95% 0.06 — 0.36) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	**30** per 1000 Difference:	**5** per 1000 **25 fewer per 1000** (CI 95% 28 fewer — 19 fewer)	**High**	Nirmatrelvir-ritonavir reduces hospital admission

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality High risk	Odds ratio 0.04 (CI 95% 0 — 0.67) Based on data from 2,224 participants in 1 studies. (Randomized controlled)	**6** per 1000 Difference:	**0** per 1000 **6 fewer per 1000** (CI 95% 6 fewer — 2 fewer)	**Moderate** Due to serious imprecision [4]	Nirmatrelvir-ritonavir probably reduces mortality.
Admission to hospital High risk	Odds ratio 0.15 (CI 95% 0.06 — 0.36) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	**60** per 1000 Difference:	**9** per 1000 **51 fewer per 1000** (CI 95% 56 fewer — 38 fewer)	**High**	Nirmatrelvir-ritonavir reduces hospital admission
Mechanical ventilation				No data [5]	The effect of nirmatrelvir-ritonavir is very uncertain
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.29 — 0.8) Based on data from 2,224 participants in 1 studies. (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**High**	Nirmatrelvir-ritonavir does not result in an important increase in adverse effects leading to drug discontinuation
Time to symptom resolution	Lower better Based on data from 662 participants in 1 studies. (Randomized controlled)	**9** (Median) Difference:	**9** (Median) **MD 0 fewer** (CI 95% 3 fewer — 4.4 more)	**Low** Due to very serious imprecision [6]	Nirmatrelvir-ritonavir may not reduce time to symptom resolution

1, 3. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 12 events total, all in one study. All 12 deaths occurred in the placebo group. **Publication bias: no serious.**
2. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
4. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: serious.** There were only 12 events total, all in one study. All 12 deaths occurred in the placebo group. **Publication bias: no serious.**
5. **Risk of Bias: no serious.** The single trial reporting mechanical ventilation was not blinded. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Very few events (24 total), resulted in wide credible intervals that include important and unimportant effects. **Publication bias: no serious.**
6. **Imprecision: very serious.** Credible interval includes both important benefit and important harm.

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Molnupiravir

Comparator: Nirmatrelvir-ritonavir

Summary

Evidence summary

The LNMA for molnupiravir was informed by 12 RCTs which enrolled 31 512 patients to molnupiravir or a control with non-severe COVID-19. All RCTs were registered; nine RCTs with 29 556 patients (93.8% of total) were published in peer-reviewed journals; the rest were data shared from authors from unpublished trials. None of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of molnupiravir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

Subgroup analyses

Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

Studies did not enrol children. All studies enrolled individuals with time from symptom onset < 5 days. Data regarding serological status were not reported. There was no credible relative effect modification by vaccination status (although the absolute benefit is much lower in patients who have been vaccinated).

Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84) (Randomized controlled)	**0.02** per 1000 Difference:	**0.02** per 1000 **0 fewer per 1000** (CI 95% 0.02 fewer — 0.08 more)	**High** 1	There is little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir.
Admission to hospital Low risk	Odds ratio 4.37 (CI 95% 1.82 — 10.28) (Randomized controlled)	**0.7** per 1000 Difference:	**3.05** per 1000 **2.35 more per 1000** (CI 95% 0.57 more — 6.45 more)	**High** 2	There is little or no difference in admission to hospital between nirmatrelvir-ritonavir and molnupiravir.
Mortality Moderate risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84) (Randomized controlled)	**0.1** per 1000 Difference:	**0.1** per 1000 **0 fewer per 1000** (CI 95% 0.08 fewer — 0.38 more)	**High** 3	There is little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir.
Admission to hospital Moderate risk	Odds ratio 4.37 (CI 95% 1.82 — 10.28) (Randomized controlled)	**5** per 1000 Difference:	**21** per 1000 **16 more per 1000** (CI 95% 4 more — 44 more)	**Moderate** Due to serious imprecision [4]	Nirmatrelvir-ritonavir probably reduces admission to hospital more than molnupiravir.

Outcome Timeframe	Study results and measurements	Comparator Nirmatrelvir-ritonavir	Intervention Molnupiravir	Certainty of the evidence (Quality of evidence)	Summary
Mortality High risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84) (Randomized controlled)	**0.23** per 1000 Difference:	**0.22** per 1000 **0.01 fewer per 1000** (CI 95% 0.18 fewer — 0.88 more)	**High**	There is little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir.
Admission to hospital High risk	Odds ratio 4.37 (CI 95% 1.82 — 10.28) (Randomized controlled)	**9** per 1000 Difference:	**38** per 1000 **29 more per 1000** (CI 95% 7 more — 76 more)	**Moderate** Due to serious imprecision [5]	Nirmatrelvir-ritonavir probably reduces admission to hospital more than molnupiravir.
Adverse effects leading to drug discontinuation	Odds ratio 0.81 (CI 95% 0.05 — 10.07) (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **2 fewer per 1000** (CI 95% 16 fewer — 4 more)	**Moderate** Due to serious risk of bias [6]	There is probably little or no difference in adverse effects leading to drug discontinuation between nirmatrelvir-ritonavir and molnupiravir.
Time to symptom resolution	Lower better (Randomized controlled)	**9** (Median) Difference:	**6.5** (Median) **MD 2.5 fewer** (CI 95% 6.8 fewer — 0.9 more)	**Low** Due to serious risk of bias and imprecision [7]	Molnupiravir may reduce duration of symptoms more than nirmatrelvir-ritonavir.

1, 3. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**
2. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
4. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (2 fewer per 1000).
5. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
6. **Risk of Bias: serious.** The molnupiravir studies were not blinded.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
7. **Risk of Bias: serious.** All three molnupiravir trials were at high risk of bias for deviations from intended intervention (lack of blinding). One trial was at high risk of bias for possible inadequate randomization concealment. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Nirmatrelvir-ritonavir
Comparator: Remdesivir

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**0.33** per 1000 Difference:	**0.1** per 1000 **0.23 fewer per 1000** (CI 95% 0.3 fewer — 0.02 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.
Admission to hospital Low risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**1** per 1000 Difference:	**0.6** per 1000 **0.4 fewer per 1000** (CI 95% 0.94 fewer — 3.82 more)	**High** [1]	There is little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.
Mortality Moderate risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**2** per 1000 Difference:	**0.6** per 1000 **1.4 fewer per 1000** (CI 95% 1.84 fewer — 0.1 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.
Admission to hospital Moderate risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**8** per 1000 Difference:	**5** per 1000 **3 fewer per 1000** (CI 95% 8 fewer — 30 more)	**Moderate** Due to serious imprecision [2]	There is probably little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.
Mortality High risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**4** per 1000 Difference:	**1.2** per 1000 **2.8 fewer per 1000** (CI 95% 3.68 fewer — 0.2 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.
Admission to hospital High risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**16** per 1000 Difference:	**10** per 1000 **6 fewer per 1000** (CI 95% 15 fewer — 57 more)	**Low** Due to very serious imprecision [3]	There may be little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.04 — 5.67) (Randomized controlled)	**4** per 1000 Difference:	**0** per 1000 **3 fewer per 1000** (CI 95% 19 fewer — 4 more)	**High**	There is no little or no difference in adverse effects leading to drug discontinuation between remdesivir and nirmatrelvir-ritonavir.
Time to symptom resolution	Lower better (Randomized controlled)	**8.6** (Median)	**7.8** (Median)	**Very low** Due to very serious imprecision and	The relative impact of nirmatrelvir-ritonavir compared to remdesivir on

Outcome Timeframe	Study results and measurements	Comparator Remdesivir	Intervention Nirmatrelvir-ritonavir	Certainty of the evidence (Quality of evidence)	Summary
		Difference:	**MD 0.8 more** (CI 95% 3.5 fewer — 5.5 more)	serious intransitivity [4]	duration of symptoms is uncertain.

1. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
2. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (2 fewer per 1000).
3, 4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**

For patients with non-severe COVID-19 at low risk of hospitalization

Conditional recommendation against

We suggest not to use nirmatrelvir-ritonavir *(conditional recommendation against)*.

- *See Section 6 regarding identifying patients at low risk.*
- *The marginal benefits of nirmatrelvir-ritonavir for patients at low risk of hospitalization (those expected to have a 0.5% risk of hospital admission) suggest most patients would not want to use this treatment, but a minority may still be inclined to do so.*
- *The GDG noted the uncertainty in baseline risk estimates and uncertainty and variability in patient values and preferences when deciding on a conditional recommendation, rather than a strong recommendation, against nirmatrelvir-ritonavir.*
- *Given considerations regarding resources and equity, the GDG concluded that health care systems may reasonably not offer this drug to patients at low risk of hospitalization.*

Practical info

Given the conditional recommendation against using nirmatrelvir-ritonavir for patients with non-severe COVID-19 at low risk of hospitalization, practical considerations were felt to be less relevant here. See practical info for use of nirmatrelvir-ritonavir in patients with COVID-19 at high and moderate risks of hospitalization if needed.

Evidence to decision

Benefits and harms	For low-risk individuals, benefits of nirmatrelvir-ritonavir are negligible for mortality and very small for hospitalization (best estimate 4 fewer per 1000 patients).
Certainty of the evidence	Because of the very low baseline risk, we have high certainty of little or no benefit for nirmatrelvir-ritonavir for both mortality and hospitalization.
Values and preferences	Despite high certainty evidence of little or no benefit for nirmatrelvir-ritonavir on death and hospitalization in this patient group, the GDG made a conditional recommendation because of residual uncertainty in baseline risk, and because of the possibility that an appreciable minority of patients may place a high value on a very small reduction in hospitalization.
Resources and other considerations	Nirmatrelvir-ritonavir is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. This reinforces that nirmatrelvir-ritonavir should, in many or perhaps most settings, be reserved for those at high risk of hospital admission.

Justification

The best estimates suggest that any benefit of nirmatrelvir-ritonavir in low-risk patients with non-severe COVID-19 are trivial. Nevertheless, the GDG noted the uncertainty in risk estimates and uncertainty and variability of patient values and preferences when deciding for a conditional rather than a strong recommendation against nirmatrelvir-ritonavir.

Clinical question/ PICO

Population: Patients with non-severe COVID-19

Intervention: Nirmatrelvir-ritonavir

Comparator: Standard care

Summary

Evidence summary

The LNMA for nirmatrelvir-ritonavir was informed by two RCTs which enrolled 3100 patients with non-severe illness in outpatient settings. One RCT was published with 2246 patients (72.5%); data for the second RCT was provided by authors prior to publication. Neither of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings, effect estimates by outcome and associated forest plots for nirmatrelvir-ritonavir versus standard care.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of nirmatrelvir-ritonavir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

Subgroup analysis

Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

Sufficient data were unavailable to inform any of the pre-specified subgroup analyses. Studies did not enrol children. Data for patients aged 65 years or older or less than 65 years were reported only for the composite outcome of COVID-19 related hospital admission and mortality due to any cause. Studies did not enrol patients with severe or critical illness. All studies enrolled unvaccinated individuals with time from symptom onset within 5 days. Data regarding serological status were reported only for the composite outcome of COVID-19 related hospital admission and mortality due to any cause.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.04 (CI 95% 0 — 0.67) Based on data from 2,224 participants in 1 studies. (Randomized controlled)	**0.5** per 1000 Difference:	**0.02** per 1000 **0.48 fewer per 1000** (CI 95% 0.5 fewer — 0.16 more)	**High** 1	Nirmatrelvir-ritonavir does not result in an important reduction on mortality
Admission to hospital Low risk	Odds ratio 0.15 (CI 95% 0.06 — 0.36) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	**5** per 1000 Difference:	**0.7** per 1000 **4.3 fewer per 1000** (CI 95% 4.7 fewer — 3.2 fewer)	**High** 2	Nirmatrelvir-ritonavir does not result in an important reduction in hospital admission
Mortality Moderate risk	Odds ratio 0.04 (CI 95% 0 — 0.67) Based on data from 2,224 participants in 1 studies.	**3** per 1000	**0.1** per 1000	**High** 3	Nirmatrelvir-ritonavir does not result in an important reduction on mortality

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the evidence** (Quality of evidence)	**Summary**
	(Randomized controlled)	Difference:	**2.9 fewer per 1000** (CI 95% 3 fewer — 1 fewer)		
Admission to hospital Moderate risk	Odds ratio 0.15 (CI 95% 0.06 — 0.36) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	**30** per 1000 Difference:	**5** per 1000 **25 fewer per 1000** (CI 95% 28 fewer — 19 fewer)	**High**	Nirmatrelvir-ritonavir reduces hospital admission
Mortality High risk	Odds ratio 0.04 (CI 95% 0 — 0.67) Based on data from 2,224 participants in 1 studies. (Randomized controlled)	**6** per 1000 Difference:	**0** per 1000 **6 fewer per 1000** (CI 95% 6 fewer — 2 fewer)	**Moderate** Due to serious imprecision [4]	Nirmatrelvir-ritonavir probably reduces mortality.
Admission to hospital High risk	Odds ratio 0.15 (CI 95% 0.06 — 0.36) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	**60** per 1000 Difference:	**9** per 1000 **51 fewer per 1000** (CI 95% 56 fewer — 38 fewer)	**High**	Nirmatrelvir-ritonavir reduces hospital admission
Mechanical ventilation				No data [5]	The effect of nirmatrelvir-ritonavir is very uncertain
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.29 — 0.8) Based on data from 2,224 participants in 1 studies. (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**High**	Nirmatrelvir-ritonavir does not result in an important increase in adverse effects leading to drug discontinuation
Time to symptom resolution	Lower better Based on data from 662 participants in 1 studies. (Randomized controlled)	**9** (Median) Difference:	**9** (Median) **MD 0 fewer** (CI 95% 3 fewer — 4.4 more)	**Low** Due to very serious imprecision [6]	Nirmatrelvir-ritonavir may not reduce time to symptom resolution

1, 3. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 12 events total, all in one study. All 12 deaths occurred in the placebo group. **Publication bias: no serious.**
2. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
4. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: serious.** There were only 12 events total, all in one

study. All 12 deaths occurred in the placebo group. **Publication bias: no serious.**
5. **Risk of Bias: no serious.** The single trial reporting mechanical ventilation was not blinded. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Very few events (24 total), resulted in wide credible intervals that include important and unimportant effects. **Publication bias: no serious.**
6. **Imprecision: very serious.** Credible interval includes both important benefit and important harm.

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Molnupiravir
Comparator: Nirmatrelvir-ritonavir

Summary

Evidence summary

The LNMA for molnupiravir was informed by 12 RCTs which enrolled 31 512 patients to molnupiravir or a control with non-severe COVID-19. All RCTs were registered; nine RCTs with 29 556 patients (93.8% of total) were published in peer-reviewed journals; the rest were data shared from authors from unpublished trials. None of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of molnupiravir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

Subgroup analyses

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1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
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Studies did not enrol children. All studies enrolled individuals with time from symptom onset < 5 days. Data regarding serological status were not reported. There was no credible relative effect modification by vaccination status (although the absolute benefit is much lower in patients who have been vaccinated).

Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84) (Randomized controlled)	**0.02** per 1000 Difference:	**0.02** per 1000 **0 fewer per 1000** (CI 95% 0.02 fewer — 0.08 more)	**High** 1	There is little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir.
Admission to hospital Low risk	Odds ratio 4.37 (CI 95% 1.82 — 10.28) (Randomized controlled)	**0.7** per 1000 Difference:	**3.05** per 1000 **2.35 more per 1000** (CI 95% 0.57 more — 6.45 more)	**High** 2	There is little or no difference in admission to hospital between nirmatrelvir-ritonavir and molnupiravir.

Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Moderate risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84) (Randomized controlled)	**0.1** per 1000 Difference:	**0.1** per 1000 **0 fewer per 1000** (CI 95% 0.08 fewer — 0.38 more)	**High** 3	There is little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir.
Admission to hospital Moderate risk	Odds ratio 4.37 (CI 95% 1.82 — 10.28) (Randomized controlled)	**5** per 1000 Difference:	**21** per 1000 **16 more per 1000** (CI 95% 4 more — 44 more)	**Moderate** Due to serious imprecision [4]	Nirmatrelvir-ritonavir probably reduces admission to hospital more than molnupiravir.
Mortality High risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84) (Randomized controlled)	**0.23** per 1000 Difference:	**0.22** per 1000 **0.01 fewer per 1000** (CI 95% 0.18 fewer — 0.88 more)	**High**	There is little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir.
Admission to hospital High risk	Odds ratio 4.37 (CI 95% 1.82 — 10.28) (Randomized controlled)	**9** per 1000 Difference:	**38** per 1000 **29 more per 1000** (CI 95% 7 more — 76 more)	**Moderate** Due to serious imprecision [5]	Nirmatrelvir-ritonavir probably reduces admission to hospital more than molnupiravir.
Adverse effects leading to drug discontinuation	Odds ratio 0.81 (CI 95% 0.05 — 10.07) (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **2 fewer per 1000** (CI 95% 16 fewer — 4 more)	**Moderate** Due to serious risk of bias [6]	There is probably little or no difference in adverse effects leading to drug discontinuation between nirmatrelvir-ritonavir and molnupiravir.
Time to symptom resolution	Lower better (Randomized controlled)	**9** (Median) Difference:	**6.5** (Median) **MD 2.5 fewer** (CI 95% 6.8 fewer — 0.9 more)	**Low** Due to serious risk of bias and imprecision [7]	Molnupiravir may reduce duration of symptoms more than nirmatrelvir-ritonavir.

1, 3. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**
2. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
4. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (2 fewer per 1000).
5. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
6. **Risk of Bias: serious.** The molnupiravir studies were not blinded.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
7. **Risk of Bias: serious.** All three molnupiravir trials were at high risk of bias for deviations from intended intervention (lack of blinding). One trial was at high risk of bias for possible inadequate randomization concealment. **Inconsistency: no serious.**

Indirectness: no serious. Imprecision: serious. Publication bias: no serious.

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Nirmatrelvir-ritonavir
Comparator: Remdesivir

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**0.33** per 1000 Difference:	**0.1** per 1000 **0.23 fewer per 1000** (CI 95% 0.3 fewer — 0.02 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.
Admission to hospital Low risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**1** per 1000 Difference:	**0.6** per 1000 **0.4 fewer per 1000** (CI 95% 0.94 fewer — 3.82 more)	**High** [1]	There is little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.
Mortality Moderate risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**2** per 1000 Difference:	**0.6** per 1000 **1.4 fewer per 1000** (CI 95% 1.84 fewer — 0.1 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.
Admission to hospital Moderate risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**8** per 1000 Difference:	**5** per 1000 **3 fewer per 1000** (CI 95% 8 fewer — 30 more)	**Moderate** Due to serious imprecision [2]	There is probably little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.
Mortality High risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**4** per 1000 Difference:	**1.2** per 1000 **2.8 fewer per 1000** (CI 95% 3.68 fewer — 0.2 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.
Admission to hospital High risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**16** per 1000 Difference:	**10** per 1000 **6 fewer per 1000** (CI 95% 15 fewer — 57 more)	**Low** Due to very serious imprecision [3]	There may be little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.

Outcome Timeframe	Study results and measurements	Comparator Remdesivir	Intervention Nirmatrelvir-ritonavir	Certainty of the evidence (Quality of evidence)	Summary
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.04 — 5.67) (Randomized controlled)	**4** per 1000 Difference:	**0** per 1000 **3 fewer per 1000** (CI 95% 19 fewer — 4 more)	**High**	There is no little or no difference in adverse effects leading to drug discontinuation between remdesivir and nirmatrelvir-ritonavir.
Time to symptom resolution	Lower better (Randomized controlled)	**8.6** (Median) Difference:	**7.8** (Median) **MD 0.8 more** (CI 95% 3.5 fewer — 5.5 more)	**Very low** Due to very serious imprecision and serious intransitivity [4]	The relative impact of nirmatrelvir-ritonavir compared to remdesivir on duration of symptoms is uncertain.

1. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
2. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (2 fewer per 1000).
3, 4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**

Mechanism of action of nirmatrelvir-ritonavir

Nirmatrelvir inhibits the SARS-CoV-2 protease (3CLpro), thereby preventing cleavage of the viral polyprotein which is needed for viral proteins to become functional *[23]*. Inhibition of the protease renders the virus unable to replicate. Nirmatrelvir is co-administered with ritonavir, an inhibitor of HIV protease, but used in this context to boost the pharmacokinetics of nirmatrelvir without exerting any direct antiviral activity itself *[24]*. Therefore, the combination should be considered as antiviral monotherapy. Nirmatrelvir was developed as an orally deliverable analogue of an intravenous prodrug (lufotrelvir; PF-07304814). The drug was originally developed for SARS-CoV, and has been subsequently re-purposed for SARS-CoV-2.

Nirmatrelvir exhibited antiviral activity against SARS-CoV-2 in differentiated normal human bronchial epithelial cells with an EC_{50} of 0.06 micromolar and an EC_{90} of 0.18 micromolar *[24]*. In healthy volunteers, plasma maximum concentrations of nirmatrelvir were 2210 ng/mL with a half-life of 6 hours following a 300/100 mg dose of nirmatrelvir-ritonavir, and steady-state pharmacokinetics were achieved on Day 2 *[25]* (an EC_{90} of 0.18 micromolar equates to approximately 90 ng/mL). High doses (300 mg/kg) of unboosted nirmatrelvir were active against murine-adapted SARS-CoV-2 in mice but with maximum concentrations higher than those achieved at 300/100 mg doses in healthy human volunteers *[24]*. High doses (250 mg/kg) of unboosted nirmatrelvir also had efficacy in SARS-CoV-2-infected Syrian golden hamsters but no pharmacokinetic data are available in this species *[26]*. Based upon the genome sequence of Omicron, there appears to be no molecular basis for a loss of activity. Nirmatrelvir retains activity against all SARS-CoV-2 lineages studied *in vitro* to date *[27][28]* but in vivo data are currently unavailable.

Much more data are required to ascertain the rate at which resistance will emerge for nirmatrelvir. Single amino acid changes introduced into the protease sequence can reduce activity of nirmatrelvir by between 23.6- and 39-fold *[25]*. Mouse hepatitis virus (used as a betacoronavirus surrogate) acquired several mutations under a selective pressure *in vitro*, and these reduced nirmatrelvir activity by between 4- and 91-fold *[25]*. Two amino substitutions were described in clinical trials, one of which did not impact nirmatrelvir activity.

Major differences in sequence across new variants have occurred in the viral spike protein and not the 3CLpro protease that is targeted by nirmatrelvir. Accordingly, nirmatrelvir activity across variants has been stable in comparison to monoclonal antibodies that target the spike protein (NIH Open Data Portal; *[29][30]*). Therefore, there is no known molecular of pharmacokinetic-pharmacodynamic basis for a change in activity of nirmatrelvir since initial RCTs were conducted.

Through its impact on metabolism and clearance, ritonavir is a perpetrator of many drug-drug interactions that will require careful consideration. Short durations of therapy needed in COVID-19 may make drug interactions easier to manage than they are for HIV, but twice daily administration means that the ritonavir dose is double that used in most modern antiretroviral regimens. The

impact of ritonavir on metabolism may also outlast dosing by several days. The Liverpool COVID-19 drug interaction checker may constitute a valuable tool for management of drug interactions with nirmatrelvir-ritonavir *[20]*.

Remdesivir (updated 10 November 2023)

The recommendations for remdesivir were initially published on 20 November 2020 and updated on 22 April 2022. In the November 2023 version of the guideline, the GDG made new recommendations for patients with non-severe COVID-19 at low and moderate risk of hospitalization. The recommendation for those at high risk is unchanged.

For patients with non-severe COVID-19 at high risk of hospitalization

Conditional recommendation for

We suggest treatment with remdesivir *(conditional recommendation for)*.

- *See Section 6 regarding identifying patients at high risk for hospitalization.*
- *Several therapeutic options are available: see decision support tool that displays benefits and harms of nirmatrelvir-ritonavir, molnupiravir and remdesivir.*
- *The GDG concluded that nirmatrelvir-ritonavir may represent a superior choice to remdesivir because of the practical difficulty that arises from the intravenous administration of remdesivir.*
- *Remdesivir is likely to be the desirable option in patients for whom nirmatrelvir-ritonavir or molnupiravir are not options. For nirmatrelvir, this will be patients who are using drugs with problematic interactions with nirmatrelvir-ritonavir. For molnupiravir, these will be individuals in whom concerns regarding mutagenesis are particularly great, which would include pregnancy and children. For both drugs, it will include those for whom, for whatever reason, the drugs are unavailable.*
- *Remdesivir should be administered as soon as possible after onset of symptoms, ideally within 7 days.*

Practical info

Route, dosage and duration: Additional considerations are available in three summaries of practical issues (remdesivir for COVID-19, administration of remdesivir for COVID-19, safety and monitoring in patients receiving remdesivir for COVID-19). Here follows a brief summary of the key points:

- The recommended dose for remdesivir is one dose daily for 3 consecutive days as intravenous infusion, as per the regimen evaluated in large trials informing the recommendation. Remdesivir is given as 200 mg intravenously on Day 1, followed by 100 mg intravenously on Days 2 and 3.
- Administration should be as early as possible in the time course of the disease. In the included studies, remdesivir was administered within 7 days of disease onset.
- It may be reasonable to monitor patients for a brief period following infusion. Any health care workers administering the infusions should follow recommended infection prevention and control recommendations in the outpatient setting.
- One should use caution when administering remdesivir to patients with significant liver or kidney disease.
- The GDG noted that there is insufficient evidence to make a recommendation around the use of remdesivir in children and further studies are needed.
- Additionally, the trials did not enrol pregnant or breastfeeding individuals. The decision regarding use of this therapeutic should be made between the pregnant person and their health care provider while discussing whether the potential benefit justifies the potential risk to the pregnant individual and fetus (see Research evidence and WHO information sheet).

Evidence to decision

Benefits and harms

In patients with non-severe COVID-19 at high risk of hospitalization, remdesivir probably results in 44 fewer admissions per 1000 patients (95% CI 56 fewer to 9 fewer), with probably little or no impact on mortality, mechanical ventilation and time to symptom resolution. The impact on adverse events leading to discontinuation is uncertain.

The planned subgroup analyses for remdesivir versus standard care including age, time of symptom onset and disease severity could not be performed in the absence of subgroup data reported publicly or provided

by investigators. There were eight children (12 years or more of age) enrolled in the PINETREE trial [29]; none died or were hospitalized.

Relative to both nirmatrelvir/ritonavir and molnupiravir, there is little or no difference in mortality. Remdesivir may reduce admission to hospital more than molnupiravir; there may be little or no difference when compared to nirmatrelvir-ritonavir.

Certainty of the evidence

The evidence summary was informed by seven trials with 5138 patients with non-severe COVID-19 included in the updated NMA. All trials compared remdesivir with standard care, with or without a placebo. Only one trial with 584 patients enrolled outpatients *[31]*, and the rest enrolled in-patients.

Relative to standard of care, the GDG rated certainty of evidence as: moderate for decreased admission to hospital (due to serious imprecision), mortality and mechanical ventilation; and very low for adverse effects leading to drug discontinuation.

Relative to both nirmatrelvir-ritonavir and molnupiravir, because of very low baseline risk, the GDG rated certainty in mortality with remdesivir as high. Due to very serious imprecision, admission to hospital was rated as low certainty.

Values and preferences

Applying the agreed values and preferences (see Section 10), the GDG inferred that most patients with non-severe COVID-19 would choose to receive remdesivir rather than no antiviral agent but an appreciable minority would decline or, because of feasibility issues consequent on the need for intravenous administration, would not have remdesivir available.

The GDG concluded that because of the need for 3 days of intravenous administration with remdesivir, patients for whom nirmatrelvir-ritonavir was available and not contraindicated would choose that drug over remdesivir.

The GDG concluded that because of the possible toxicity of molnupiravir and the possible superiority of remdesivir in reducing hospitalization, the majority of patients would choose remdesivir over molnupiravir.

Resources and other considerations

Acceptability and feasibility

Remdesivir is administered as one intravenous infusion daily over 3 consecutive days, representing a feasibility challenge in outpatients aiming to avoid hospital admission. Furthermore, remdesivir is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. This reinforces that remdesivir should be reserved for those at high risk, and is an important consideration in choices between remdesivir and both nirmatrelvir-ritonavir and molnupiravir.

Obstacles to access in LMICs due to cost, feasibility and availability are of concern *[32]*. Challenges in shared decision-making and in communicating the harms versus benefits of remdesivir may also be increased in LMICs. For example, those with socioeconomic disadvantages tend to have less access to services, including diagnostic testing and treatments in the first 7 days of symptoms, and thus less access to the interventions. Therefore, if patients at highest risk receive the intervention, this may exacerbate health inequities. It is important that countries integrate the COVID-19 clinical care pathway in the parts of the health system that may provide care for patients with non-severe COVID-19 (i.e. primary care, community care settings).

The recommendations should provide a stimulus to engage all possible mechanisms to improve global access to the intervention. Individual countries may formulate their guidelines considering available resources and prioritize treatment options accordingly.

Access to SARS-CoV-2 diagnostics: Since this recommendation emphasizes the need to administer treatment with remdesivir within 7 days of symptom onset, increasing access and ensuring appropriate use of diagnostic tests is essential. Thus, availability and use of reliable and timely SARS-CoV-2 diagnostic tests (including the use of nucleic acid amplification tests [NAAT)]and antigen-based rapid detection tests [Ag-RDTs]) are needed to improve access to drugs, especially those targeting the early phase of disease. The appropriate use of Ag-RDTs by individuals and trained professionals can improve early diagnosis and earlier

access to clinical care, particularly in the community and in primary health care settings. National programmes should optimize their testing systems to reflect local epidemiology, response objectives, available resources and needs of their populations.

Justification

In this update of the guideline, the GDG was informed by additional trials that further confirmed the benefits of remdesivir in reducing hospitalizations for patients at high risk of being hospitalized. When moving from evidence to the maintained conditional recommendation to use remdesivir in patients with non-severe COVID-19 at high risk of hospitalization, the GDG emphasized these benefits, along with uncertain but apparently little or no serious adverse effects attributable to the drug. Feasibility and complexity of administration (e.g. 3 consecutive days of intravenous administration) were also considered, and supported the conditional recommendation for use in high-risk patients.

Costs and access were also important considerations, and the GDG recognized that this recommendation could exacerbate health inequities, further supporting a conditional recommendation.

Alternative or combination therapy

In the high-risk non-severe population the GDG has made a conditional recommendation for molnupiravir and a strong recommendation for nirmatrelvir-ritonavir. Indirect comparisons in high-risk patients found remdesivir may reduce hospitalization when compared with molnupiravir; and found little or no difference when compared with nirmaltrelvir-ritonavir (both low certainty). Without direct data and low certainty in indirect comparisons, the GDG chose not to make comparative recommendations between drugs, but rather remarked that nirmatrelvir-ritonavir may be superior based on its efficacy compared with standard care and that ultimately, remdesivir should be reserved for specific subpopulations.

There is no evidence for combining antiviral therapies; the GDG therefore advised against this.

Applicability

Only one of the trials included children (12 years of age and older), and the numbers were extremely small; therefore the applicability of this recommendation to children remains uncertain. Uncertainty also remains with regard to administration of remdesivir to pregnant or lactating individuals. The decision regarding use of this therapeutic should be made between the pregnant individual and their health care provider while discussing whether the potential benefit justifies the potential risk to the pregnant individual and fetus (see Research evidence and Practical info tabs).

The GDG also had concerns about whether the drug would retain efficacy against emerging variants of concern. Surveillance is needed for SARS-CoV-2 strains with reduced susceptibility to remdesivir and further research examining the role of combination therapy in severely immunocompromised patients. Until further data are available, we have no reason to believe that activity against known variants will be diminished.

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Remdesivir
Comparator: Standard care

Summary

Seven trials with 5138 patients with non-severe COVID-19 were included in the updated NMA (see Table). All of the trials compared remdesivir with standard care with or without a placebo. Five trials were not included because they enrolled patients with exclusively severe COVID-19, or did not report any outcomes for patients with non-severe disease separately. Only one trial with 584 patients enrolled outpatients *[31]*; the rest were inpatients. Two trials enrolled some patients from LMICs. All of the trials used a 200 mg intravenous loading dose, followed by 100 mg intravenously daily thereafter. Duration of therapy ranged from 3 to 10 days. All of the included trials were publicly pre-registered and are published in peer-reviewed journals. Most of the trials were judged to be at low risk of bias.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.66 (CI 95% 0.32 — 1.36) Based on data from 2,946 participants in 6 studies. (Randomized controlled)	**0.5** per 1000 Difference:	**0.33** per 1000 **0.17 fewer per 1000** (CI 95% 0.34 fewer — 0.18 more)	**High**	Remdesivir has little or no impact on mortality.
Admission to hospital Low risk	Odds ratio 0.25 (CI 95% 0.07 — 0.85) Based on data from 562 participants in 1 studies. (Randomized controlled)	**5** per 1000 Difference:	**1** per 1000 **4 fewer per 1000** (CI 95% 5 fewer — 1 fewer)	**High**	Remdesivir does not result in an important reduction in hospitalization.
Mortality Moderate risk	Odds ratio 0.66 (CI 95% 0.32 — 1.36) Based on data from 2,946 participants in 6 studies. (Randomized controlled)	**3** per 1000 Difference:	**2** per 1000 **1 fewer per 1000** (CI 95% 2 fewer — 1 more)	**Moderate** Due to serious imprecision [1]	Remdesivir may have little or no impact on mortality.
Admission to hospital Moderate risk	Odds ratio 0.25 (CI 95% 0.07 — 0.85) Based on data from 562 participants in 1 studies. (Randomized controlled)	**30** per 1000 Difference:	**8** per 1000 **22 fewer per 1000** (CI 95% 28 fewer — 4 fewer)	**Moderate** Due to serious imprecision [2]	Remdesivir probably reduces hospitalization
Mortality High risk	Odds ratio 0.66 (CI 95% 0.32 — 1.36) Based on data from 2,946 participants in 6 studies. (Randomized controlled)	**6** per 1000 Difference:	**4** per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 2 more)	**Moderate** Due to serious imprecision [3]	Remdesivir may have little or no impact on mortality.
Admission to hospital High risk	Odds ratio 0.25 (CI 95% 0.07 — 0.85) Based on data from 562 participants in 1 studies. (Randomized controlled)	**60** per 1000 Difference:	**16** per 1000 **44 fewer per 1000** (CI 95% 56 fewer — 9 fewer)	**Moderate** Due to serious imprecision [4]	Remdesivir probably reduces hospitalization
Mechanical ventilation	Odds ratio 0.7 (CI 95% 0.37 — 1.78) Based on data from 2,952 participants in 5 studies. (Randomized controlled)	**29** per 1000 Difference:	**20** per 1000 **9 fewer per 1000** (CI 95% 18 fewer — 21 more)	**Moderate** Due to serious imprecision [5]	Remdesivir probably has little or no impact on mechanical ventilation
Adverse events leading to discontinuation	Odds ratio 3.67 (CI 95% 1.18 — 18.25) Based on data from 1,846	**0** per 1000	**4** per 1000	**Very low** Due to serious risk of bias, imprecision,	The impact on adverse events leading to discontinuation is uncertain

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the evidence** (Quality of evidence)	**Summary**
	participants in 4 studies. (Randomized controlled)	Difference:	**4 more per 1000** (CI 95% 0 more — 17 more)	and indirectness [6]	
Time to symptom resolution	Lower better Based on data from 1,200 participants in 3 studies. (Randomized controlled)	**9** (Mean) Difference:	**8.6** (Mean) **MD 0.4 fewer** (CI 95% 1.5 fewer — 2.8 more)	**Low** Due to serious inconsistency, imprecision, and concerns with risk of bias [7]	Remdesivir may have little or no impact on time to symptom resolution

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.**
2. **Imprecision: serious.** .
3. **Imprecision: serious.**
4. **Imprecision: serious.** The total sample size does not meet the optimal information size; few events (23 total events)..
5. **Imprecision: serious.** Wide confidence intervals.
6. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
7. **Inconsistency: serious. Imprecision: serious.**

Clinical question/ PICO

Population: Patients with non-severe COVID-19

Intervention: Molnupiravir

Comparator: Remdesivir

Summary

Evidence summary

The LNMA for molnupiravir was informed by 12 RCTs which enrolled 31 512 patients to molnupiravir or a control with non-severe COVID-19. All RCTs were registered; nine RCTs with 29 556 patients (93.8% of total) were published in peer-reviewed journals; the rest were data shared from authors from unpublished trials. None of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of molnupiravir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

Subgroup analyses

Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

Studies did not enrol children. All studies enrolled individuals with time from symptom onset < 5 days. Data regarding serological status were not reported. There was no credible relative effect modification by vaccination status (although the absolute benefit is much lower in patients who have been vaccinated).

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**0.33** per 1000 Difference:	**0.1** per 1000 **0.23 fewer per 1000** (CI 95% 0.3 fewer — 0.02 fewer)	**High**	There is little or no difference in mortality between remdesivir and molnupiravir.
Admission to hospital Low risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**1** per 1000 Difference:	**2.62** per 1000 **1.62 more per 1000** (CI 95% 0.21 fewer — 8.45 more)	**High** [1]	There is little or no difference in admission to hospital between remdesivir and molnupiravir.
Mortality Moderate risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**2** per 1000 Difference:	**0.58** per 1000 **1.42 fewer per 1000** (CI 95% 1.84 fewer — 0.12 fewer)	**High** [2]	There is little or no difference in mortality between remdesivir and molnupiravir.
Admission to hospital Moderate risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**8** per 1000 Difference:	**21** per 1000 **13 more per 1000** (CI 95% 2 fewer — 63 more)	**Low** Due to very serious imprecision [3]	There may be little or no difference in admission to hospital between remdesivir and molnupiravir.
Mortality High risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**4** per 1000 Difference:	**1.16** per 1000 **2.84 fewer per 1000** (CI 95% 3.68 fewer — 0.24 fewer)	**High**	There is little or no difference in mortality between remdesivir and molnupiravir.
Admission to hospital High risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**16** per 1000 Difference:	**41** per 1000 **25 more per 1000** (CI 95% 3 fewer — 118 more)	**Low** Due to very serious imprecision [4]	Remdesivir may reduce admission to hospital more than molnupiravir.
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.04 — 5.67) (Randomized controlled)	**4** per 1000 Difference:	**0** per 1000 **3 fewer per 1000** (CI 95% 19 fewer — 4 more)	**Moderate** Due to serious risk of bias [5]	There is probably little or no difference in adverse effects leading to drug discontinuation between remdesivir and molnupiravir.

Outcome Timeframe	Study results and measurements	Comparator Remdesivir	Intervention Molnupiravir	Certainty of the evidence (Quality of evidence)	Summary
Time to symptom resolution	Lower better (Randomized controlled)	**8.6** (Median) Difference:	**6.8** (Median) **MD 1.8 fewer** (CI 95% 4.9 fewer — 0.9 more)	**Low** Due to concern with risk of bias, imprecision, and intransitivity [6]	Molnupiravir may reduce duration of symptoms more than remdesivir.

1. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
2. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**
3. **Imprecision: very serious.** Credible interval includes a large benefit for remdesivir relative to molnupiravir..
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**
5. **Risk of Bias: serious.** The molnupiravir studies were not blinded.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
6. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Nirmatrelvir-ritonavir
Comparator: Remdesivir

Outcome Timeframe	Study results and measurements	Comparator Remdesivir	Intervention Nirmatrelvir-ritonavir	Certainty of the evidence (Quality of evidence)	Summary
Mortality Low risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**0.33** per 1000 Difference:	**0.1** per 1000 **0.23 fewer per 1000** (CI 95% 0.3 fewer — 0.02 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.
Admission to hospital Low risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**1** per 1000 Difference:	**0.6** per 1000 **0.4 fewer per 1000** (CI 95% 0.94 fewer — 3.82 more)	**High** [1]	There is little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.
Mortality Moderate risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**2** per 1000 Difference:	**0.6** per 1000 **1.4 fewer per 1000** (CI 95% 1.84 fewer — 0.1 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Admission to hospital Moderate risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**8** per 1000 Difference:	**5** per 1000 **3 fewer per 1000** (CI 95% 8 fewer — 30 more)	**Moderate** Due to serious imprecision [2]	There is probably little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.
Mortality High risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**4** per 1000 Difference:	**1.2** per 1000 **2.8 fewer per 1000** (CI 95% 3.68 fewer — 0.2 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.
Admission to hospital High risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**16** per 1000 Difference:	**10** per 1000 **6 fewer per 1000** (CI 95% 15 fewer — 57 more)	**Low** Due to very serious imprecision [3]	There may be little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.04 — 5.67) (Randomized controlled)	**4** per 1000 Difference:	**0** per 1000 **3 fewer per 1000** (CI 95% 19 fewer — 4 more)	**High**	There is no little or no difference in adverse effects leading to drug discontinuation between remdesivir and nirmatrelvir-ritonavir.
Time to symptom resolution	Lower better (Randomized controlled)	**8.6** (Median) Difference:	**7.8** (Median) **MD 0.8 more** (CI 95% 3.5 fewer — 5.5 more)	**Very low** Due to very serious imprecision and serious intransitivity [4]	The relative impact of nirmatrelvir-ritonavir compared to remdesivir on duration of symptoms is uncertain.

1. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
2. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (2 fewer per 1000).
3, 4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**

For patients with non-severe COVID-19 at moderate risk of hospitalization

Conditional recommendation against

We suggest not to use remdesivir *(conditional recommendation against)*.

- *See Section 6 regarding identifying patients at moderate risk of hospitalization.*
- *The GDG concluded that nirmatrelvir-ritonavir represents a superior choice because it is easier to administer than a 3- day course of intravenous remdesivir.*
- *The conditional recommendation against represents the panel's view that remdesivir will represent a good choice only in those in whom nirmatrelvir-ritonavir is unavailable or involves problematic interactions, and even then only in a minority of such individuals.*
- *Remdesivir should be administered as soon as possible after onset of symptoms, ideally within 7 days.*

Practical info

Given the conditional recommendation against using remdesivir for patients with non-severe COVID-19 at moderate risk of hospitalization, practical considerations were felt to be less relevant here. See practical info for use of remdevisir in patients with COVID-19 at high risk of hospitalization if needed.

Evidence to decision

Benefits and harms	In patients with non-severe COVID-19 at moderate risk of hospitalization, remdesivir probably results in 22 fewer admissions per 1000 patients (95% CI 28 fewer to 4 fewer) with probably little or no impact on mortality, mechanical ventilation and time to symptom resolution. The impact on adverse events leading to discontinuation is uncertain. The planned subgroup analyses for remdesivir versus standard care including age, time of symptom onset and disease severity could not be performed in the absence of subgroup data reported publicly or provided by investigators. There were eight children (12 years or more of age) enrolled in the PINETREE trial *[31]*; none died or were hospitalized. Relative to nirmatrelvir-ritonavir, there is little or no difference in mortality with remdesivir and may be little or no difference in admission to hospital. Relative to molnupiravir, there is little or no difference in mortality with remdesivir. Molnupiravir may reduce admission to hospital compared with remdesivir in patients at high and moderate risk of hospitalization.
Certainty of the evidence	The evidence summary was informed by seven trials with 5138 patients with non-severe COVID-19, included in the updated NMA. All of the trials compared remdesivir with standard care with or without a placebo. Only one trial with 584 patients enrolled outpatients *[31]*; the rest of the trials enrolled inpatients. Certainty of evidence was rated as: moderate for decreased admission to hospital (due to serious imprecision), mortality, and mechanical ventilation; and very low for adverse effects leading to drug discontinuation.
Values and preferences	Applying the agreed values and preferences (see Section 10), the GDG inferred that most patients with non-severe COVID-19 would either choose not to receive remdesivir or, because of feasibility issues consequent on the need for intravenous administration, would not have remdesivir available. A minority of patients would have the drug available and would choose to receive it rather than no antiviral agent.
Resources and other considerations	Issues related to resources, acceptability and feasibility are outlined in the section on remdesivir for use in patients with COVID-19 at high risk of hospitalizations and also apply to patients at moderate risk.

Justification

When considering remdesivir in patients with non-severe COVID-19 at moderate risk of hospitalization, the GDG emphasized the limited benefits of decreased need for hospitalization, uncertainty in adverse effects, and the challenge of identifying patients at moderate risk in the absence of credible risk prediction tools. The GDG also carefully considered issues related to resource use, feasibility of administration (e.g. the complexity of 3 consecutive days of intravenous administration) and recognized that widespread use of remdesivir could exacerbate health inequities.

Clinical question/ PICO

Population: Patients with non-severe COVID-19

Intervention: Remdesivir

Comparator: Standard care

Summary

Seven trials with 5138 patients with non-severe COVID-19 were included in the updated NMA (see Table). All of the trials compared remdesivir with standard care with or without a placebo. Five trials were not included because they enrolled patients with exclusively severe COVID-19, or did not report any outcomes for patients with non-severe disease separately. Only one trial with 584 patients enrolled outpatients *[31]*; the rest were inpatients. Two trials enrolled some patients from LMICs. All of the trials used a 200 mg intravenous loading dose, followed by 100 mg intravenously daily thereafter. Duration of therapy ranged from 3 to 10 days. All of the included trials were publicly pre-registered and are published in peer-reviewed journals. Most of the trials were judged to be at low risk of bias.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.66 (CI 95% 0.32 — 1.36) Based on data from 2,946 participants in 6 studies. (Randomized controlled)	**0.5** per 1000 Difference:	**0.33** per 1000 **0.17 fewer per 1000** (CI 95% 0.34 fewer — 0.18 more)	**High**	Remdesivir has little or no impact on mortality.
Admission to hospital Low risk	Odds ratio 0.25 (CI 95% 0.07 — 0.85) Based on data from 562 participants in 1 studies. (Randomized controlled)	**5** per 1000 Difference:	**1** per 1000 **4 fewer per 1000** (CI 95% 5 fewer — 1 fewer)	**High**	Remdesivir does not result in an important reduction in hospitalization.
Mortality Moderate risk	Odds ratio 0.66 (CI 95% 0.32 — 1.36) Based on data from 2,946 participants in 6 studies. (Randomized controlled)	**3** per 1000 Difference:	**2** per 1000 **1 fewer per 1000** (CI 95% 2 fewer — 1 more)	**Moderate** Due to serious imprecision [1]	Remdesivir may have little or no impact on mortality.
Admission to hospital Moderate risk	Odds ratio 0.25 (CI 95% 0.07 — 0.85) Based on data from 562 participants in 1 studies. (Randomized controlled)	**30** per 1000 Difference:	**8** per 1000 **22 fewer per 1000** (CI 95% 28 fewer — 4 fewer)	**Moderate** Due to serious imprecision [2]	Remdesivir probably reduces hospitalization

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality High risk	Odds ratio 0.66 (CI 95% 0.32 — 1.36) Based on data from 2,946 participants in 6 studies. (Randomized controlled)	**6** per 1000 Difference:	**4** per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 2 more)	**Moderate** Due to serious imprecision [3]	Remdesivir may have little or no impact on mortality.
Admission to hospital High risk	Odds ratio 0.25 (CI 95% 0.07 — 0.85) Based on data from 562 participants in 1 studies. (Randomized controlled)	**60** per 1000 Difference:	**16** per 1000 **44 fewer per 1000** (CI 95% 56 fewer — 9 fewer)	**Moderate** Due to serious imprecision [4]	Remdesivir probably reduces hospitalization
Mechanical ventilation	Odds ratio 0.7 (CI 95% 0.37 — 1.78) Based on data from 2,952 participants in 5 studies. (Randomized controlled)	**29** per 1000 Difference:	**20** per 1000 **9 fewer per 1000** (CI 95% 18 fewer — 21 more)	**Moderate** Due to serious imprecision [5]	Remdesivir probably has little or no impact on mechanical ventilation
Adverse events leading to discontinuation	Odds ratio 3.67 (CI 95% 1.18 — 18.25) Based on data from 1,846 participants in 4 studies. (Randomized controlled)	**0** per 1000 Difference:	**4** per 1000 **4 more per 1000** (CI 95% 0 more — 17 more)	**Very low** Due to serious risk of bias, imprecision, and indirectness [6]	The impact on adverse events leading to discontinuation is uncertain
Time to symptom resolution	Lower better Based on data from 1,200 participants in 3 studies. (Randomized controlled)	**9** (Mean) Difference:	**8.6** (Mean) **MD 0.4 fewer** (CI 95% 1.5 fewer — 2.8 more)	**Low** Due to serious inconsistency, imprecision, and concerns with risk of bias [7]	Remdesivir may have little or no impact on time to symptom resolution

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.**
2. **Imprecision: serious.** .
3. **Imprecision: serious.**
4. **Imprecision: serious.** The total sample size does not meet the optimal information size; few events (23 total events)..
5. **Imprecision: serious.** Wide confidence intervals.
6. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
7. **Inconsistency: serious. Imprecision: serious.**

Clinical question/ PICO

Population: Patients with non-severe COVID-19

Intervention: Molnupiravir

Comparator: Remdesivir

Summary

Evidence summary

The LNMA for molnupiravir was informed by 12 RCTs which enrolled 31 512 patients to molnupiravir or a control with non-severe COVID-19. All RCTs were registered; nine RCTs with 29 556 patients (93.8% of total) were published in peer-reviewed journals; the rest were data shared from authors from unpublished trials. None of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of molnupiravir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

Subgroup analyses

Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

Studies did not enrol children. All studies enrolled individuals with time from symptom onset < 5 days. Data regarding serological status were not reported. There was no credible relative effect modification by vaccination status (although the absolute benefit is much lower in patients who have been vaccinated).

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**0.33** per 1000 Difference:	**0.1** per 1000 **0.23 fewer per 1000** (CI 95% 0.3 fewer — 0.02 fewer)	**High**	There is little or no difference in mortality between remdesivir and molnupiravir.
Admission to hospital Low risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**1** per 1000 Difference:	**2.62** per 1000 **1.62 more per 1000** (CI 95% 0.21 fewer — 8.45 more)	**High** [1]	There is little or no difference in admission to hospital between remdesivir and molnupiravir.
Mortality Moderate risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**2** per 1000 Difference:	**0.58** per 1000 **1.42 fewer per 1000** (CI 95% 1.84 fewer — 0.12 fewer)	**High** [2]	There is little or no difference in mortality between remdesivir and molnupiravir.
Admission to hospital Moderate risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**8** per 1000 Difference:	**21** per 1000 **13 more per 1000** (CI 95% 2 fewer — 63 more)	**Low** Due to very serious imprecision [3]	There may be little or no difference in admission to hospital between remdesivir and molnupiravir.

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality High risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**4** per 1000 Difference:	**1.16** per 1000 **2.84 fewer per 1000** (CI 95% 3.68 fewer — 0.24 fewer)	**High**	There is little or no difference in mortality between remdesivir and molnupiravir.
Admission to hospital High risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**16** per 1000 Difference:	**41** per 1000 **25 more per 1000** (CI 95% 3 fewer — 118 more)	**Low** Due to very serious imprecision [4]	Remdesivir may reduce admission to hospital more than molnupiravir.
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.04 — 5.67) (Randomized controlled)	**4** per 1000 Difference:	**0** per 1000 **3 fewer per 1000** (CI 95% 19 fewer — 4 more)	**Moderate** Due to serious risk of bias [5]	There is probably little or no difference in adverse effects leading to drug discontinuation between remdesivir and molnupiravir.
Time to symptom resolution	Lower better (Randomized controlled)	**8.6** (Median) Difference:	**6.8** (Median) **MD 1.8 fewer** (CI 95% 4.9 fewer — 0.9 more)	**Low** Due to concern with risk of bias, imprecision, and intransitivity [6]	Molnupiravir may reduce duration of symptoms more than remdesivir.

1. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
2. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**
3. **Imprecision: very serious.** Credible interval includes a large benefit for remdesivir relative to molnupiravir..
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**
5. **Risk of Bias: serious.** The molnupiravir studies were not blinded.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
6. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Nirmatrelvir-ritonavir
Comparator: Remdesivir

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**0.33** per 1000 Difference:	**0.1** per 1000 **0.23 fewer per 1000** (CI 95% 0.3 fewer — 0.02 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.
Admission to hospital Low risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**1** per 1000 Difference:	**0.6** per 1000 **0.4 fewer per 1000** (CI 95% 0.94 fewer — 3.82 more)	**High** [1]	There is little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.
Mortality Moderate risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**2** per 1000 Difference:	**0.6** per 1000 **1.4 fewer per 1000** (CI 95% 1.84 fewer — 0.1 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.
Admission to hospital Moderate risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**8** per 1000 Difference:	**5** per 1000 **3 fewer per 1000** (CI 95% 8 fewer — 30 more)	**Moderate** Due to serious imprecision [2]	There is probably little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.
Mortality High risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**4** per 1000 Difference:	**1.2** per 1000 **2.8 fewer per 1000** (CI 95% 3.68 fewer — 0.2 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.
Admission to hospital High risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**16** per 1000 Difference:	**10** per 1000 **6 fewer per 1000** (CI 95% 15 fewer — 57 more)	**Low** Due to very serious imprecision [3]	There may be little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.04 — 5.67) (Randomized controlled)	**4** per 1000 Difference:	**0** per 1000 **3 fewer per 1000** (CI 95% 19 fewer — 4 more)	**High**	There is no little or no difference in adverse effects leading to drug discontinuation between remdesivir and nirmatrelvir-ritonavir.
Time to symptom resolution	Lower better (Randomized controlled)	**8.6** (Median)	**7.8** (Median)	**Very low** Due to very serious imprecision and	The relative impact of nirmatrelvir-ritonavir compared to remdesivir on

Outcome Timeframe	Study results and measurements	Comparator Remdesivir	Intervention Nirmatrelvir-ritonavir	Certainty of the evidence (Quality of evidence)	Summary
		Difference:	**MD 0.8 more** (CI 95% 3.5 fewer — 5.5 more)	serious intransitivity [4]	duration of symptoms is uncertain.

1. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
2. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (2 fewer per 1000).
3, 4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**

For patients with non-severe COVID-19 at low risk of hospitalization

Strong recommendation against

We recommend not to use remdesivir *(strong recommendation against).*

- *See Section 6 regarding identifying patients at low risk.*
- *The marginal benefits of remdesivir for patients at low risk of hospitalization (those expected to have a 0.5% risk of hospital admission) suggest most patients would not want to use this treatment.*
- *Given considerations regarding resources and equity, the GDG concluded that health care systems may reasonably not offer this drug to patients at low risk of hospitalization.*

Practical info

Given the strong recommendation against using remdesivir for patients with non-severe COVID-19 at low risk of hospitalization, practical considerations were felt to be less relevant here.

Evidence to decision

Benefits and harms

In patients with non-severe COVID-19 at low risk of hospitalization, remdesivir does not result in important reductions in admissions and probably has little or no impact on mortality, mechanical ventilation and time to symptom resolution. The impact on adverse events leading to discontinuation is uncertain (absolute risk difference 4 more per 1000 [CI 95% 0 more to 17 more]).

Certainty of the evidence

The evidence summary was informed by seven trials with 5138 patients with non-severe COVID-19, included in the updated NMA. All of the trials compared remdesivir with standard care with or without a placebo. Only one trial with 584 patients enrolled outpatients *[31]*; the rest of the trials enrolled inpatients.

Certainty of evidence was rated as: high for decreased admission to hospital, mortality and mechanical ventilation; and very low for adverse effects leading to drug discontinuation.

Values and preferences

Applying the agreed values and preferences (see Section 10), the GDG inferred that almost all well-informed patients with a low risk of hospitalization would decline remdesivir.

Resources and other considerations

Issues related to resources, acceptability and feasibility are outlined in the section on remdesivir for use in patients with COVID-19 at high risk of hospitalization and also apply to patients at low risk.

Justification

When moving from evidence to a strong recommendation against the use of remdesivir in patients with non-severe COVID-19 at low risk of hospitalization, the GDG emphasized the negligible benefits of decreased need for hospitalization (largely because of the very low risk of hospitalization among untreated patients), uncertainty in adverse effects, and the feasibility issues related to intravenous administration of remdesivir (three consecutive days of intravenous administration). The GDG also recognized that widespread use of remdesivir could exacerbate health inequities.

Clinical question/ PICO

Population: Patients with non-severe COVID-19

Intervention: Remdesivir

Comparator: Standard care

Summary

Seven trials with 5138 patients with non-severe COVID-19 were included in the updated NMA (see Table). All of the trials compared remdesivir with standard care with or without a placebo. Five trials were not included because they enrolled patients with exclusively severe COVID-19, or did not report any outcomes for patients with non-severe disease separately. Only one trial with 584 patients enrolled outpatients *[31]*; the rest were inpatients. Two trials enrolled some patients from LMICs. All of the trials used a 200 mg intravenous loading dose, followed by 100 mg intravenously daily thereafter. Duration of therapy ranged from 3 to 10 days. All of the included trials were publicly pre-registered and are published in peer-reviewed journals. Most of the trials were judged to be at low risk of bias.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.66 (CI 95% 0.32 — 1.36) Based on data from 2,946 participants in 6 studies. (Randomized controlled)	**0.5** per 1000 Difference:	**0.33** per 1000 **0.17 fewer per 1000** (CI 95% 0.34 fewer — 0.18 more)	**High**	Remdesivir has little or no impact on mortality.
Admission to hospital Low risk	Odds ratio 0.25 (CI 95% 0.07 — 0.85) Based on data from 562 participants in 1 studies. (Randomized controlled)	**5** per 1000 Difference:	**1** per 1000 **4 fewer per 1000** (CI 95% 5 fewer — 1 fewer)	**High**	Remdesivir does not result in an important reduction in hospitalization.
Mortality Moderate risk	Odds ratio 0.66 (CI 95% 0.32 — 1.36) Based on data from 2,946 participants in 6 studies. (Randomized controlled)	**3** per 1000 Difference:	**2** per 1000 **1 fewer per 1000** (CI 95% 2 fewer — 1 more)	**Moderate** Due to serious imprecision [1]	Remdesivir may have little or no impact on mortality.
Admission to hospital Moderate risk	Odds ratio 0.25 (CI 95% 0.07 — 0.85) Based on data from 562 participants in 1 studies. (Randomized controlled)	**30** per 1000 Difference:	**8** per 1000 **22 fewer per 1000** (CI 95% 28 fewer — 4 fewer)	**Moderate** Due to serious imprecision [2]	Remdesivir probably reduces hospitalization

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality High risk	Odds ratio 0.66 (CI 95% 0.32 — 1.36) Based on data from 2,946 participants in 6 studies. (Randomized controlled)	**6** per 1000 Difference:	**4** per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 2 more)	**Moderate** Due to serious imprecision [3]	Remdesivir may have little or no impact on mortality.
Admission to hospital High risk	Odds ratio 0.25 (CI 95% 0.07 — 0.85) Based on data from 562 participants in 1 studies. (Randomized controlled)	**60** per 1000 Difference:	**16** per 1000 **44 fewer per 1000** (CI 95% 56 fewer — 9 fewer)	**Moderate** Due to serious imprecision [4]	Remdesivir probably reduces hospitalization
Mechanical ventilation	Odds ratio 0.7 (CI 95% 0.37 — 1.78) Based on data from 2,952 participants in 5 studies. (Randomized controlled)	**29** per 1000 Difference:	**20** per 1000 **9 fewer per 1000** (CI 95% 18 fewer — 21 more)	**Moderate** Due to serious imprecision [5]	Remdesivir probably has little or no impact on mechanical ventilation
Adverse events leading to discontinuation	Odds ratio 3.67 (CI 95% 1.18 — 18.25) Based on data from 1,846 participants in 4 studies. (Randomized controlled)	**0** per 1000 Difference:	**4** per 1000 **4 more per 1000** (CI 95% 0 more — 17 more)	**Very low** Due to serious risk of bias, imprecision, and indirectness [6]	The impact on adverse events leading to discontinuation is uncertain
Time to symptom resolution	Lower better Based on data from 1,200 participants in 3 studies. (Randomized controlled)	**9** (Mean) Difference:	**8.6** (Mean) **MD 0.4 fewer** (CI 95% 1.5 fewer — 2.8 more)	**Low** Due to serious inconsistency, imprecision, and concerns with risk of bias [7]	Remdesivir may have little or no impact on time to symptom resolution

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.**
2. **Imprecision: serious.** .
3. **Imprecision: serious.**
4. **Imprecision: serious.** The total sample size does not meet the optimal information size; few events (23 total events)..
5. **Imprecision: serious.** Wide confidence intervals.
6. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
7. **Inconsistency: serious. Imprecision: serious.**

Clinical question/ PICO

Population: Patients with non-severe COVID-19

Intervention: Molnupiravir

Comparator: Remdesivir

Summary

Evidence summary

The LNMA for molnupiravir was informed by 12 RCTs which enrolled 31 512 patients to molnupiravir or a control with non-severe COVID-19. All RCTs were registered; nine RCTs with 29 556 patients (93.8% of total) were published in peer-reviewed journals; the rest were data shared from authors from unpublished trials. None of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of molnupiravir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

Subgroup analyses

Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

Studies did not enrol children. All studies enrolled individuals with time from symptom onset < 5 days. Data regarding serological status were not reported. There was no credible relative effect modification by vaccination status (although the absolute benefit is much lower in patients who have been vaccinated).

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**0.33** per 1000 Difference:	**0.1** per 1000 **0.23 fewer per 1000** (CI 95% 0.3 fewer — 0.02 fewer)	**High**	There is little or no difference in mortality between remdesivir and molnupiravir.
Admission to hospital Low risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**1** per 1000 Difference:	**2.62** per 1000 **1.62 more per 1000** (CI 95% 0.21 fewer — 8.45 more)	**High** [1]	There is little or no difference in admission to hospital between remdesivir and molnupiravir.
Mortality Moderate risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**2** per 1000 Difference:	**0.58** per 1000 **1.42 fewer per 1000** (CI 95% 1.84 fewer — 0.12 fewer)	**High** [2]	There is little or no difference in mortality between remdesivir and molnupiravir.
Admission to hospital Moderate risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**8** per 1000 Difference:	**21** per 1000 **13 more per 1000** (CI 95% 2 fewer — 63 more)	**Low** Due to very serious imprecision [3]	There may be little or no difference in admission to hospital between remdesivir and molnupiravir.

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality High risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**4** per 1000 Difference:	**1.16** per 1000 **2.84 fewer per 1000** (CI 95% 3.68 fewer — 0.24 fewer)	**High**	There is little or no difference in mortality between remdesivir and molnupiravir.
Admission to hospital High risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**16** per 1000 Difference:	**41** per 1000 **25 more per 1000** (CI 95% 3 fewer — 118 more)	**Low** Due to very serious imprecision [4]	Remdesivir may reduce admission to hospital more than molnupiravir.
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.04 — 5.67) (Randomized controlled)	**4** per 1000 Difference:	**0** per 1000 **3 fewer per 1000** (CI 95% 19 fewer — 4 more)	**Moderate** Due to serious risk of bias [5]	There is probably little or no difference in adverse effects leading to drug discontinuation between remdesivir and molnupiravir.
Time to symptom resolution	Lower better (Randomized controlled)	**8.6** (Median) Difference:	**6.8** (Median) **MD 1.8 fewer** (CI 95% 4.9 fewer — 0.9 more)	**Low** Due to concern with risk of bias, imprecision, and intransitivity [6]	Molnupiravir may reduce duration of symptoms more than remdesivir.

1. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
2. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**
3. **Imprecision: very serious.** Credible interval includes a large benefit for remdesivir relative to molnupiravir..
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**
5. **Risk of Bias: serious.** The molnupiravir studies were not blinded.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
6. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Nirmatrelvir-ritonavir
Comparator: Remdesivir

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**0.33** per 1000 Difference:	**0.1** per 1000 **0.23 fewer per 1000** (CI 95% 0.3 fewer — 0.02 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.
Admission to hospital Low risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**1** per 1000 Difference:	**0.6** per 1000 **0.4 fewer per 1000** (CI 95% 0.94 fewer — 3.82 more)	**High** [1]	There is little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.
Mortality Moderate risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**2** per 1000 Difference:	**0.6** per 1000 **1.4 fewer per 1000** (CI 95% 1.84 fewer — 0.1 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.
Admission to hospital Moderate risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**8** per 1000 Difference:	**5** per 1000 **3 fewer per 1000** (CI 95% 8 fewer — 30 more)	**Moderate** Due to serious imprecision [2]	There is probably little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.
Mortality High risk	Odds ratio 0.3 (CI 95% 0.08 — 0.95) (Randomized controlled)	**4** per 1000 Difference:	**1.2** per 1000 **2.8 fewer per 1000** (CI 95% 3.68 fewer — 0.2 fewer)	**High**	There is little or no difference in mortality between remdesivir and nirmatrelvir-ritonavir.
Admission to hospital High risk	Odds ratio 0.6 (CI 95% 0.06 — 4.84) (Randomized controlled)	**16** per 1000 Difference:	**10** per 1000 **6 fewer per 1000** (CI 95% 15 fewer — 57 more)	**Low** Due to very serious imprecision [3]	There may be little or no difference in admission to hospital between remdesivir and nirmatrelvir-ritonavir.
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.04 — 5.67) (Randomized controlled)	**4** per 1000 Difference:	**0** per 1000 **3 fewer per 1000** (CI 95% 19 fewer — 4 more)	**High**	There is no little or no difference in adverse effects leading to drug discontinuation between remdesivir and nirmatrelvir-ritonavir.
Time to symptom resolution	Lower better (Randomized controlled)	**8.6** (Median)	**7.8** (Median)	**Very low** Due to very serious imprecision and	The relative impact of nirmatrelvir-ritonavir compared to remdesivir on

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the evidence** (Quality of evidence)	**Summary**
		Difference:	**MD 0.8 more** (CI 95% 3.5 fewer — 5.5 more)	serious intransitivity [4]	duration of symptoms is uncertain.

1. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
2. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (2 fewer per 1000).
3, 4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**

Mechanism of action of remdesivir

Remdesivir was developed for treatment of hepatitis C virus infection, and was also studied in Ebola and Marburg virus infections before being repurposed for SARS-CoV-2. Remdesivir is a nucleoside drug. Its mechanism of action involves chain termination, which is different to lethal mutagenesis: the drug is incorporated preferentially to the endogenous adenosine nucleoside by the SARS-CoV-2 polymerase during replication of the RNA genome. Unlike many other chain-terminating nucleoside drugs used for other viruses, remdesivir elicits delayed chain termination because RNA synthesis is terminated after the addition of three more nucleotides, rather than at the point of remdesivir incorporation *[33]*.

Under a selective pressure in vitro, SAR-CoV-2 resistance to remdesivir emerged and was associated with mutations (e.g. E802D and V792I) within the sequence coding for the polymerase *[34][35]*. The E802D mutation was reported in a case study describing an immunocompromised patient receiving remdesivir who experienced recrudescence of high-grade viral shedding following a transient virological response to the drug *[36]*. Moreover, the V792I mutation has also been documented in two transplant recipients with persistent SARS-CoV-2 infection *[37]*. The clinical significance of these observations if remdesivir were widely used in an outpatient setting is unclear.

Major changes in sequence across new variants have occurred in the viral spike protein and not the RNA polymerase that is targeted by remdesivir. Accordingly, remdesivir activity across variants has been stable in comparison to monoclonal antibodies that target the spike protein (NIH OpenData Portal) *[29][30]*. Therefore, there is no known molecular, pharmacokinetic or pharmacodynamic basis for a change in activity of remdesivir since initial RCTs were conducted.

Molnupiravir (updated 10 November 2023)

The recommendations for molnupiravir were initially published on 3 March 2022. In this 14th version of the guideline, the panel maintained a conditional recommendation for use of molnupiravir in patients with non-severe COVID-19 at high risk of hospitalization (updated risk estimate of 6%) and provided additional recommendations against its use in moderate and low-risk patients.

For patients with non-severe COVID-19 at high risk of hospitalization

Conditional recommendation for

We suggest treatment with molnupiravir *(conditional recommendation for)*.

- *See Section 6 regarding identifying patients at high risk for hospitalization.*
- *Several therapeutic options are available: see decision support tool that displays benefits and harms of nirmatrelvir-ritonavir, molnupiravir and remdesivir among patients at high risk of hospitalization.*
- *The longer term harms of molnupiravir remain unknown in the absence of clinical evidence, both for individual patients and at the population level. These include potential mutagenesis, emergence of resistance, and emergence of new variants (see Mechanism of action section).*
- *Use of molnupiravir should be accompanied by mitigation strategies such as avoiding the drug in younger adults, children and pregnant patients, active pharmacovigilance programmes, and monitoring viral polymerase and spike sequences (see Justification section).*
- *The GDG considered that nirmatrelvir-ritonavir represents a superior choice to molnupiravir (due to greater reduction in hospitalization and because of safety concerns with molnupiravir.*
- *The GDG considered that remdesivir represents a superior choice to molnupiravir because it possibly has a greater reduction in hospitalization in high-risk patients.*

Practical info

Route, dosage and duration: Additional considerations are available in three summaries of practical issues (molnupiravir for COVID-19, administration of molnupiravir for COVID-19, safety and monitoring for patients receiving molnupiravir for COVID-19). Here follows a brief summary of the key points:

- The recommended dose for molnupiravir is 800 mg tablet every 12 hours daily for 5 days, as per the regimen evaluated in large trials informing the recommendation.
- Administration should be as early as possible in the time course of the disease. In the included studies, molnupiravir was administered within 5 days of disease onset.

Evidence to decision

Benefits and harms	In patients with non-severe COVID-19 at high risk of hospitalization, molnupiravir probably reduces admission to hospital, mortality and time to symptom resolution. Molnupiravir may have no important effect on mechanical ventilation or adverse effects leading to drug discontinuation. However, potential long-term harms of molnupiravir remain uncertain and, in the absence of clinical data, remain a matter of concern. Potential harms include emergence of resistance, and the potential harm coming from the potential risk of molnupiravir-induced mutagenesis. These considerations (see Justification section) were based on molnupiravir's mechanism of action and available pre-clinical data (see Mechanism of action section). Nirmatrelvir-ritonavir probably reduces hospitalization to a greater extent than molnupiravir and is not associated with the possible serious toxicity that may occur with molnupiravir. There is little or no difference in mortality between remdesivir and molnupiravir. However, remdesivir may result in a larger reduction in admission to hospital compared with molnupiravir.
Certainty of the evidence	The evidence summary was informed by nine trials with 30 332 participants included in the LNMA. Certainty of evidence of molnupiravir against standard care was rated as: moderate for decreased hospitalization (rated down due to serious imprecision); moderate for mortality (rated down due to serious imprecision); moderate for time to symptom resolution (rated down due to serious risk of bias); low for mechanical ventilation (rated down due to very serious imprecision); and high for adverse effects leading to drug discontinuation.

	Certainty of evidence for mortality of molnupiravir against both nirmatrelvir-ritonavir and remdesivir was rated as high; certainty for admission to hospital was rated as moderate for the comparison with nirmatrelvir-ritonavir, and low for the comparison with remdesivir.
Values and preferences	Applying the agreed values and preferences (see Section 10), the GDG inferred that the majority of well-informed patients with high risk of hospitalization would choose molnupiravir.
Resources and other considerations	**Acceptability and feasibility** Molnupiravir is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. This reinforces that molnupiravir should be reserved for those at high risk. Obstacles to access in LMICs due to cost and availability are of concern [*30*]. Challenges in shared decision-making and in communicating the harms versus benefits of molnupiravir may also be increased in LMICs. For example, those with socioeconomic disadvantages tend to have less access to services, including diagnostic testing and treatments, in the first 5 days of symptoms, and thus less access to the interventions. Therefore, if patients at high risk receive the intervention this may exacerbate health inequity. It is important that countries integrate the COVID-19 clinical care pathway in the parts of the health system that may provide care for patients with non-severe COVID-19 (i.e. primary care, community care settings). The recommendations should provide a stimulus to engage all possible mechanisms to improve global access to the intervention. In promoting access, WHO has prequalified generic versions of molnupiravir and nirmatrelvir-ritonavir. In addition, there are additional applications under review for both products. Individual countries may formulate their guidelines considering available resources and prioritize treatment options according. **Access to SARS-CoV-2 diagnostics:** Since this recommendation emphasizes the need to administer treatment with molnupiravir within 5 days of symptom onset, increasing access and ensuring appropriate use of diagnostic tests is essential. Thus, availability and use of reliable and timely COVID-19 diagnostic tests (including the use of NAAT and Ag-RDTs) is needed to improve access to drugs, especially those targeting the early phase of disease. The appropriate use of Ag-RDTs by individuals and trained professionals can improve early diagnosis and earlier access to clinical care, particularly in the community and in primary health care settings. National programmes should optimize their testing systems to reflect local epidemiology, response objectives, available resources and the needs of their populations.

Justification

When moving from evidence to a conditional recommendation for molnupiravir in patients with non-severe COVID-19 at high risk of hospitalization, the GDG emphasized the moderate certainty evidence demonstrating a reduction in absolute risk for hospitalization and death without an increased risk of adverse effects. The GDG did not anticipate important variability in patient values and preferences. A combination of safety concerns based on preclinical data, values and preferences, and feasibility contributed to the conditional recommendation.

Primarily, only a minority of patients who are at high risk are likely to achieve sufficient absolute benefit to compensate for the risks and other limitations and disadvantages of therapy.

- Molnupiravir is mutagenic in mammalian cells *in vitro,* but there is no evidence of mutagenicity in animal models or humans. The GDG therefore acknowledged uncertainty regarding longer term genetic toxicity and potential for malignancy associated with molnupiravir.
- Given evidence from rat pups of an impact on growth plate thickness, molnupiravir should not be used in children. Similarly, since molnupiravir elicited embryo-fetal lethality and teratogenicity in offspring when given to pregnant animals, it should not be used in pregnant or breastfeeding individuals.
- The GDG acknowledged that spermatogenesis may also be especially prone to the mutagenic effects of molnupiravir, but that there was uncertainty regarding the consequences to children conceived by fathers receiving or having recently received molnupiravir.

Applicability

The applicability of this recommendation to children, breastfeeding and pregnant individuals is currently uncertain, as the included RCTs enrolled only non-pregnant adults. However, the GDG concluded that molnupiravir should not be offered to children,

breastfeeding or pregnant individuals with COVID-19. In addition, men planning to conceive should be oriented on the potential for temporary genotoxic effect on sperm cell production. The unknown long-term risk of genotoxicity is likely to be higher in younger patients as compared with older patients, thus its use in younger adults not at high risk should be avoided.

Mitigation strategies:

- Decisions around treatment with molnupiravir must be done using a shared decision-making model, ensuring the clinician is well educated on the potential benefits and harms of therapy and able to explain these to the patient in order to make well-informed decisions. See Practical information section.
- Active sequence monitoring of SARS-CoV-2 detected in clinical respiratory samples (i.e. may include polymerase and spike) should be arranged for patients receiving therapy, including higher risk individuals (immunocompromised).
- Pharmacovigilance: use of molnupiravir should be accompanied by a robust, active pharmacovigilance programme.
- Molnupiravir should not be given to pregnant or breastfeeding individuals or to children. In case of doubt about pregnancy, a pregnancy test should be performed prior to treatment initiation. If a person of child bearing potential is considered for treatment, counselling regarding birth control during treatment and for 4 days after the last dose of molnupiravir should be facilitated.
- Men planning to conceive should be oriented on the potential for temporary genotoxic effect on sperm cell production, and those who are sexually active with females should be counselled to use birth control during treatment and for at least 3 months after the last dose of molnupiravir *[38]*.
- The unknown long-term risk of mutagenesis is likely to be higher in younger patients as compared with older patients; thus use in younger adults who are not at high risk should be limited.

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Molnupiravir
Comparator: Standard care

Summary

Evidence summary

The LNMA for molnupiravir was informed by 12 RCTs which enrolled 31 512 patients to molnupiravir or a control with non-severe COVID-19. All RCTs were registered; nine RCTs with 29 556 patients (93.8% of total) were published in peer-reviewed journals; the rest were data shared from authors from unpublished trials. None of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of molnupiravir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

Subgroup analyses

Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

Studies did not enrol children. All studies enrolled individuals with time from symptom onset < 5 days. Data regarding serological status were not reported. There was no credible relative effect modification by vaccination status (although the absolute benefit is much lower in patients who have been vaccinated).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.21 (CI 95% 0.06 — 0.59) Based on data from 30,332 participants in 9 studies. (Randomized controlled)	**0.5** per 1000 Difference:	**0.1** per 1000 **0.4 fewer per 1000** (CI 95% 0.5 fewer	**High** 1	Molnupiravir does not have an important impact on mortality

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
			— 0.2 more)		
Admission to hospital Low risk	Odds ratio 0.64 (CI 95% 0.39 — 0.93) Based on data from 30,221 participants in 8 studies. (Randomized controlled)	**5** per 1000 Difference:	**3** per 1000 **1.8 fewer per 1000** (CI 95% 3.1 fewer — 0.4 fewer)	**High** 2	Molnupiravir does not result in an important reduction in hospital admission
Mortality Moderate risk	Odds ratio 0.21 (CI 95% 0.06 — 0.59) Based on data from 30,332 participants in 9 studies. (Randomized controlled)	**3** per 1000 Difference:	**0.6** per 1000 **2.4 fewer per 1000** (CI 95% 2.8 fewer — 1.2 fewer)	**High** 3	Molnupiravir does not have an important impact on mortality
Admission to hospital Moderate risk	Odds ratio 0.64 (CI 95% 0.39 — 0.93) Based on data from 30,221 participants in 8 studies. (Randomized controlled)	**30** per 1000 Difference:	**19** per 1000 **11 fewer per 1000** (CI 95% 18 fewer — 2 fewer)	**Moderate** Due to serious imprecision [4]	Molnupiravir probably does not result in an important reduction in hospital admission.
Mortality High risk	Odds ratio 0.21 (CI 95% 0.06 — 0.59) Based on data from 30,332 participants in 9 studies. (Randomized controlled)	**6** per 1000 Difference:	**1** per 1000 **5 fewer per 1000** (CI 95% 6 fewer — 3 fewer)	**Moderate** Due to serious imprecision [5]	Molnupiravir probably has a marginal effect on mortality
Admission to hospital High risk	Odds ratio 0.64 (CI 95% 0.39 — 0.93) Based on data from 30,221 participants in 8 studies. (Randomized controlled)	**60** per 1000 Difference:	**39** per 1000 **21 fewer per 1000** (CI 95% 37 fewer — 4 fewer)	**Moderate** Due to serious imprecision [6]	Molnupiravir probably reduces hospital admission
Mechanical ventilation	Odds ratio 0.39 (CI 95% 0.12 — 1.19) Based on data from 2,746 participants in 3 studies. (Randomized controlled)	**29** per 1000 Difference:	**14** per 1000 **15 fewer per 1000** (CI 95% 25 fewer — 7 more)	**Low** Due to very serious imprecision [7]	There may be no important effect of molnupiravir on mechanical ventilation
Adverse effects leading to drug discontinuation	Odds ratio 0.91 (CI 95% 0.36 — 3.48) Based on data from 5,383 participants in 9 studies. (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 3 more)	**High**	There is no important difference in adverse effects leading to drug discontinuation
Time to symptom	Lower better	**9**	**6.3**	**Moderate** Due to serious risk	Molnupiravir probably reduces duration of

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
resolution	Based on data from 22,245 participants in 5 studies. (Randomized controlled)	(Median) Difference:	(Median) **MD 2.7 fewer** (CI 95% 3.8 fewer — 1.5 fewer)	of bias [8]	symptoms
Malignancy		In vitro and animal studies suggest the possibility of carcinogenesis		**Very low** No human data with long-term follow-up	The effect of molnupiravir on cancer is uncertain

1, 3. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**
2. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
4. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (2 fewer per 1000).
5. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**
6. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
7. **Risk of Bias: no serious.** The single trial reporting mechanical ventilation was not blinded. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Very few events (24 total), resulted in wide credible intervals that include important and unimportant effects. **Publication bias: no serious.**
8. **Risk of Bias: serious.** All three trials were at high risk of bias for deviations from intended intervention (lack of blinding). One trial was at high risk of bias for possible inadequate randomization concealment.

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Molnupiravir
Comparator: Nirmatrelvir-ritonavir

Summary

Evidence summary

The LNMA for molnupiravir was informed by 12 RCTs which enrolled 31 512 patients to molnupiravir or a control with non-severe COVID-19. All RCTs were registered; nine RCTs with 29 556 patients (93.8% of total) were published in peer-reviewed journals; the rest were data shared from authors from unpublished trials. None of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of molnupiravir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

Subgroup analyses

Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

Studies did not enrol children. All studies enrolled individuals with time from symptom onset < 5 days. Data regarding serological status were not reported. There was no credible relative effect modification by vaccination status (although the absolute benefit is much lower in patients who have been vaccinated).

Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84) (Randomized controlled)	**0.02** per 1000 Difference:	**0.02** per 1000 **0 fewer per 1000** (CI 95% 0.02 fewer — 0.08 more)	**High** 1	There is little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir.
Admission to hospital Low risk	Odds ratio 4.37 (CI 95% 1.82 — 10.28) (Randomized controlled)	**0.7** per 1000 Difference:	**3.05** per 1000 **2.35 more per 1000** (CI 95% 0.57 more — 6.45 more)	**High** 2	There is little or no difference in admission to hospital between nirmatrelvir-ritonavir and molnupiravir.
Mortality Moderate risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84) (Randomized controlled)	**0.1** per 1000 Difference:	**0.1** per 1000 **0 fewer per 1000** (CI 95% 0.08 fewer — 0.38 more)	**High** 3	There is little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir.
Admission to hospital Moderate risk	Odds ratio 4.37 (CI 95% 1.82 — 10.28) (Randomized controlled)	**5** per 1000 Difference:	**21** per 1000 **16 more per 1000** (CI 95% 4 more — 44 more)	**Moderate** Due to serious imprecision [4]	Nirmatrelvir-ritonavir probably reduces admission to hospital more than molnupiravir.
Mortality High risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84) (Randomized controlled)	**0.23** per 1000 Difference:	**0.22** per 1000 **0.01 fewer per 1000** (CI 95% 0.18 fewer — 0.88 more)	**High**	There is little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir.
Admission to hospital High risk	Odds ratio 4.37 (CI 95% 1.82 — 10.28) (Randomized controlled)	**9** per 1000 Difference:	**38** per 1000 **29 more per 1000** (CI 95% 7 more — 76 more)	**Moderate** Due to serious imprecision [5]	Nirmatrelvir-ritonavir probably reduces admission to hospital more than molnupiravir.
Adverse effects leading to drug	Odds ratio 0.81 (CI 95% 0.05 — 10.07)	**0** per 1000	**0** per 1000	**Moderate** Due to serious risk	There is probably little or no difference in adverse effects leading to drug

Outcome Timeframe	Study results and measurements	Comparator Nirmatrelvir-ritonavir	Intervention Molnupiravir	Certainty of the evidence (Quality of evidence)	Summary
discontinuation	(Randomized controlled)	Difference:	**2 fewer per 1000** (CI 95% 16 fewer — 4 more)	of bias [6]	discontinuation between nirmatrelvir-ritonavir and molnupiravir.
Time to symptom resolution	Lower better (Randomized controlled)	**9** (Median) Difference:	**6.5** (Median) **MD 2.5 fewer** (CI 95% 6.8 fewer — 0.9 more)	**Low** Due to serious risk of bias and imprecision [7]	Molnupiravir may reduce duration of symptoms more than nirmatrelvir-ritonavir.

1, 3. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**
2. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
4. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (2 fewer per 1000).
5. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
6. **Risk of Bias: serious.** The molnupiravir studies were not blinded.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
7. **Risk of Bias: serious.** All three molnupiravir trials were at high risk of bias for deviations from intended intervention (lack of blinding). One trial was at high risk of bias for possible inadequate randomization concealment. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Molnupiravir
Comparator: Remdesivir

Summary

Evidence summary

The LNMA for molnupiravir was informed by 12 RCTs which enrolled 31 512 patients to molnupiravir or a control with non-severe COVID-19. All RCTs were registered; nine RCTs with 29 556 patients (93.8% of total) were published in peer-reviewed journals; the rest were data shared from authors from unpublished trials. None of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of molnupiravir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

Subgroup analyses

Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

Studies did not enrol children. All studies enrolled individuals with time from symptom onset < 5 days. Data regarding serological status were not reported. There was no credible relative effect modification by vaccination status (although the absolute benefit is much lower in patients who have been vaccinated).

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**0.33** per 1000 Difference:	**0.1** per 1000 **0.23 fewer per 1000** (CI 95% 0.3 fewer — 0.02 fewer)	**High**	There is little or no difference in mortality between remdesivir and molnupiravir.
Admission to hospital Low risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**1** per 1000 Difference:	**2.62** per 1000 **1.62 more per 1000** (CI 95% 0.21 fewer — 8.45 more)	**High** [1]	There is little or no difference in admission to hospital between remdesivir and molnupiravir.
Mortality Moderate risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**2** per 1000 Difference:	**0.58** per 1000 **1.42 fewer per 1000** (CI 95% 1.84 fewer — 0.12 fewer)	**High** [2]	There is little or no difference in mortality between remdesivir and molnupiravir.
Admission to hospital Moderate risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**8** per 1000 Difference:	**21** per 1000 **13 more per 1000** (CI 95% 2 fewer — 63 more)	**Low** Due to very serious imprecision [3]	There may be little or no difference in admission to hospital between remdesivir and molnupiravir.
Mortality High risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**4** per 1000 Difference:	**1.16** per 1000 **2.84 fewer per 1000** (CI 95% 3.68 fewer — 0.24 fewer)	**High**	There is little or no difference in mortality between remdesivir and molnupiravir.
Admission to hospital High risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**16** per 1000 Difference:	**41** per 1000 **25 more per 1000** (CI 95% 3 fewer — 118 more)	**Low** Due to very serious imprecision [4]	Remdesivir may reduce admission to hospital more than molnupiravir.

Outcome Timeframe	Study results and measurements	Comparator Remdesivir	Intervention Molnupiravir	Certainty of the evidence (Quality of evidence)	Summary
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.04 — 5.67) (Randomized controlled)	**4** per 1000 Difference:	**0** per 1000 **3 fewer per 1000** (CI 95% 19 fewer — 4 more)	**Moderate** Due to serious risk of bias [5]	There is probably little or no difference in adverse effects leading to drug discontinuation between remdesivir and molnupiravir.
Time to symptom resolution	Lower better (Randomized controlled)	**8.6** (Median) Difference:	**6.8** (Median) **MD 1.8 fewer** (CI 95% 4.9 fewer — 0.9 more)	**Low** Due to concern with risk of bias, imprecision, and intransitivity [6]	Molnupiravir may reduce duration of symptoms more than remdesivir.

1. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
2. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**
3. **Imprecision: very serious.** Credible interval includes a large benefit for remdesivir relative to molnupiravir..
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**
5. **Risk of Bias: serious.** The molnupiravir studies were not blinded.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
6. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**

For patients with non-severe COVID-19 at moderate risk of hospitalization

Conditional recommendation against

We suggest against treatment with molnupiravir *(conditional recommendation against)*.

- *See Section 6 regarding identifying patients at moderate risk of hospitalization.*
- *The GDG considered that nirmatrelvir-ritonavir represents a superior choice to molnupiravir because it probably has a greater reduction in hospitalization and because of concerns about possible harms of molnupiravir.*
- *In moderate risk patients for whom nirmatrelvir-ritonavir is not an option where a choice exists between molnupiravir and remdesivir, key considerations will be the potential toxicity of molnupiravir, its possible reduction in duration of symptoms, and the burden of remdesivir in requiring 3 days of intravenous injections.*

Practical info

Given the conditional recommendation against using molnupiravir for patients with non-severe COVID-19 at moderate risk of hospitalizations, practical considerations were felt to be less relevant here. See practical info for use of molnupiravir in patients with COVID-19 at high risk of hospitalization if needed.

Evidence to decision

Benefits and harms	Although molnupiravir has a similar relative effect on the main outcomes of interest, the absolute effects are smaller in those at moderate risk.

In patients with non-severe COVID-19 at moderate risk, molnupiravir does not have an important impact on mortality and probably results in little or no reduction in hospital admission. Molnupiravir may not have an important effect on mechanical ventilation while it probably reduces duration of symptoms.

Long-term harms of molnupiravir, in the absence of clinical data, remain uncertain and a matter of concern. Potential harms include emergence of resistance, and the potential harm coming from the risk of molnupiravir-induced mutagenesis. These considerations (see Justification section) were based on molnupiravir's mechanism of action and available pre-clinical data (see Mechanism of action section).

Relative to nirmatrelvir-ritonavir, in moderate risk patients, molnupiravir has little or no difference in mortality, probably has less benefit in reducing hospitalization, and may reduce duration of symptoms.

Relative to remdesivir, in moderate risk patients, molnupiravir has little or no difference in mortality, may have little or no difference in reducing hospitalization, and may reduce duration of symptoms.

Certainty of the evidence

Certainty of evidence against standard care in moderate risk patients was rated as: high for decreased hospitalization, mortality and adverse effects leading to drug discontinuation; moderate for time to symptom resolution (rated down due to serious risk of bias); low for mechanical ventilation (rated down due to very serious imprecision); and very low for effect on malignancy (no human data).

In moderate risk patients, certainty of evidence of molnupiravir relative to nirmatrelvir-ritonavir was rated as high for mortality, moderate for reducing hospitalization, and low for duration of symptoms.

In moderate risk patients, certainty of evidence of molnupiravir relative to remdesivir was rated high for mortality, low for reducing hospitalization, and low for duration of symptoms.

Values and preferences

The GDG believes that most patients at moderate risk of hospitalization would be reluctant to use a medication for which the evidence left high uncertainty regarding absolute effects on outcomes they consider important.

Resources and other considerations

Acceptability and feasibility

Molnupiravir is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. This reinforces that molnupiravir should be reserved for those at high risk of hospitalization.

Justification

In moderate risk patients, benefits of molnupiravir in reducing hospitalization are small, though possibly important to a majority of patients, and the drug probably reduces duration of symptoms. In the judgment of the GDG, concerns regarding toxicity will be, for the majority of patients, sufficient to more than counterbalance these benefits. There is likely, however, to be an appreciable proportion of the moderate risk population who will perceive the benefits as outweighing the possible toxicity risk.

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Molnupiravir
Comparator: Standard care

Summary

Evidence summary

The LNMA for molnupiravir was informed by 12 RCTs which enrolled 31 512 patients to molnupiravir or a control with non-severe COVID-19. All RCTs were registered; nine RCTs with 29 556 patients (93.8% of total) were published in peer-reviewed journals; the rest were data shared from authors from unpublished trials. None of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of molnupiravir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

Subgroup analyses

Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

Studies did not enrol children. All studies enrolled individuals with time from symptom onset < 5 days. Data regarding serological status were not reported. There was no credible relative effect modification by vaccination status (although the absolute benefit is much lower in patients who have been vaccinated).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.21 (CI 95% 0.06 — 0.59) Based on data from 30,332 participants in 9 studies. (Randomized controlled)	**0.5** per 1000 Difference:	**0.1** per 1000 **0.4 fewer per 1000** (CI 95% 0.5 fewer — 0.2 more)	**High** 1	Molnupiravir does not have an important impact on mortality
Admission to hospital Low risk	Odds ratio 0.64 (CI 95% 0.39 — 0.93) Based on data from 30,221 participants in 8 studies. (Randomized controlled)	**5** per 1000 Difference:	**3** per 1000 **1.8 fewer per 1000** (CI 95% 3.1 fewer — 0.4 fewer)	**High** 2	Molnupiravir does not result in an important reduction in hospital admission
Mortality Moderate risk	Odds ratio 0.21 (CI 95% 0.06 — 0.59) Based on data from 30,332 participants in 9 studies. (Randomized controlled)	**3** per 1000 Difference:	**0.6** per 1000 **2.4 fewer per 1000** (CI 95% 2.8 fewer — 1.2 fewer)	**High** 3	Molnupiravir does not have an important impact on mortality
Admission to hospital Moderate risk	Odds ratio 0.64 (CI 95% 0.39 — 0.93) Based on data from 30,221 participants in 8 studies. (Randomized controlled)	**30** per 1000 Difference:	**19** per 1000 **11 fewer per 1000** (CI 95% 18 fewer — 2 fewer)	**Moderate** Due to serious imprecision [4]	Molnupiravir probably does not result in an important reduction in hospital admission.
Mortality High risk	Odds ratio 0.21 (CI 95% 0.06 — 0.59) Based on data from 30,332 participants in 9 studies. (Randomized controlled)	**6** per 1000 Difference:	**1** per 1000 **5 fewer per 1000** (CI 95% 6 fewer — 3 fewer)	**Moderate** Due to serious imprecision [5]	Molnupiravir probably has a marginal effect on mortality

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Admission to hospital High risk	Odds ratio 0.64 (CI 95% 0.39 — 0.93) Based on data from 30,221 participants in 8 studies. (Randomized controlled)	**60** per 1000 Difference:	**39** per 1000 **21 fewer per 1000** (CI 95% 37 fewer — 4 fewer)	**Moderate** Due to serious imprecision [6]	Molnupiravir probably reduces hospital admission
Mechanical ventilation	Odds ratio 0.39 (CI 95% 0.12 — 1.19) Based on data from 2,746 participants in 3 studies. (Randomized controlled)	**29** per 1000 Difference:	**14** per 1000 **15 fewer per 1000** (CI 95% 25 fewer — 7 more)	**Low** Due to very serious imprecision [7]	There may be no important effect of molnupiravir on mechanical ventilation
Adverse effects leading to drug discontinuation	Odds ratio 0.91 (CI 95% 0.36 — 3.48) Based on data from 5,383 participants in 9 studies. (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 3 more)	**High**	There is no important difference in adverse effects leading to drug discontinuation
Time to symptom resolution	Lower better Based on data from 22,245 participants in 5 studies. (Randomized controlled)	**9** (Median) Difference:	**6.3** (Median) **MD 2.7 fewer** (CI 95% 3.8 fewer — 1.5 fewer)	**Moderate** Due to serious risk of bias [8]	Molnupiravir probably reduces duration of symptoms
Malignancy		In vitro and animal studies suggest the possibility of carcinogenesis		**Very low** No human data with long-term follow-up	The effect of molnupiravir on cancer is uncertain

1, 3. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**
2. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
4. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (2 fewer per 1000).
5. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**
6. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
7. **Risk of Bias: no serious.** The single trial reporting mechanical ventilation was not blinded. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Very few events (24 total), resulted in wide credible intervals that include important and unimportant effects. **Publication bias: no serious.**
8. **Risk of Bias: serious.** All three trials were at high risk of bias for deviations from intended intervention (lack of blinding). One trial was at high risk of bias for possible inadequate randomization concealment.

Clinical question/ PICO

Population: Patients with non-severe COVID-19

Intervention: Molnupiravir

Comparator: Nirmatrelvir-ritonavir

Summary

Evidence summary

The LNMA for molnupiravir was informed by 12 RCTs which enrolled 31 512 patients to molnupiravir or a control with non-severe COVID-19. All RCTs were registered; nine RCTs with 29 556 patients (93.8% of total) were published in peer-reviewed journals; the rest were data shared from authors from unpublished trials. None of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of molnupiravir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

Subgroup analyses

Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

Studies did not enrol children. All studies enrolled individuals with time from symptom onset < 5 days. Data regarding serological status were not reported. There was no credible relative effect modification by vaccination status (although the absolute benefit is much lower in patients who have been vaccinated).

Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84) (Randomized controlled)	**0.02** per 1000 Difference:	**0.02** per 1000 **0 fewer per 1000** (CI 95% 0.02 fewer — 0.08 more)	**High** 1	There is little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir.
Admission to hospital Low risk	Odds ratio 4.37 (CI 95% 1.82 — 10.28) (Randomized controlled)	**0.7** per 1000 Difference:	**3.05** per 1000 **2.35 more per 1000** (CI 95% 0.57 more — 6.45 more)	**High** 2	There is little or no difference in admission to hospital between nirmatrelvir-ritonavir and molnupiravir.
Mortality Moderate risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84) (Randomized controlled)	**0.1** per 1000 Difference:	**0.1** per 1000 **0 fewer per 1000** (CI 95% 0.08 fewer — 0.38 more)	**High** 3	There is little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir.
Admission to hospital	Odds ratio 4.37 (CI 95% 1.82 — 10.28)	**5**	**21**	**Moderate** Due to serious	Nirmatrelvir-ritonavir probably reduces

Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Moderate risk	(Randomized controlled)	per 1000 Difference:	per 1000 **16 more per 1000** (CI 95% 4 more — 44 more)	imprecision [4]	admission to hospital more than molnupiravir.
Mortality High risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84) (Randomized controlled)	**0.23** per 1000 Difference:	**0.22** per 1000 **0.01 fewer per 1000** (CI 95% 0.18 fewer — 0.88 more)	**High**	There is little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir.
Admission to hospital High risk	Odds ratio 4.37 (CI 95% 1.82 — 10.28) (Randomized controlled)	**9** per 1000 Difference:	**38** per 1000 **29 more per 1000** (CI 95% 7 more — 76 more)	**Moderate** Due to serious imprecision [5]	Nirmatrelvir-ritonavir probably reduces admission to hospital more than molnupiravir.
Adverse effects leading to drug discontinuation	Odds ratio 0.81 (CI 95% 0.05 — 10.07) (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **2 fewer per 1000** (CI 95% 16 fewer — 4 more)	**Moderate** Due to serious risk of bias [6]	There is probably little or no difference in adverse effects leading to drug discontinuation between nirmatrelvir-ritonavir and molnupiravir.
Time to symptom resolution	Lower better (Randomized controlled)	**9** (Median) Difference:	**6.5** (Median) **MD 2.5 fewer** (CI 95% 6.8 fewer — 0.9 more)	**Low** Due to serious risk of bias and imprecision [7]	Molnupiravir may reduce duration of symptoms more than nirmatrelvir-ritonavir.

1, 3. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**
2. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
4. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (2 fewer per 1000).
5. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
6. **Risk of Bias: serious.** The molnupiravir studies were not blinded.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
7. **Risk of Bias: serious.** All three molnupiravir trials were at high risk of bias for deviations from intended intervention (lack of blinding). One trial was at high risk of bias for possible inadequate randomization concealment. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Molnupiravir

Comparator: Remdesivir

Summary

Evidence summary

The LNMA for molnupiravir was informed by 12 RCTs which enrolled 31 512 patients to molnupiravir or a control with non-severe COVID-19. All RCTs were registered; nine RCTs with 29 556 patients (93.8% of total) were published in peer-reviewed journals; the rest were data shared from authors from unpublished trials. None of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of molnupiravir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

Subgroup analyses

Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

Studies did not enrol children. All studies enrolled individuals with time from symptom onset < 5 days. Data regarding serological status were not reported. There was no credible relative effect modification by vaccination status (although the absolute benefit is much lower in patients who have been vaccinated).

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**0.33** per 1000 Difference:	**0.1** per 1000 **0.23 fewer per 1000** (CI 95% 0.3 fewer — 0.02 fewer)	**High**	There is little or no difference in mortality between remdesivir and molnupiravir.
Admission to hospital Low risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**1** per 1000 Difference:	**2.62** per 1000 **1.62 more per 1000** (CI 95% 0.21 fewer — 8.45 more)	**High** [1]	There is little or no difference in admission to hospital between remdesivir and molnupiravir.
Mortality Moderate risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**2** per 1000 Difference:	**0.58** per 1000 **1.42 fewer per 1000** (CI 95% 1.84 fewer — 0.12 fewer)	**High** [2]	There is little or no difference in mortality between remdesivir and molnupiravir.
Admission to hospital Moderate risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**8** per 1000 Difference:	**21** per 1000 **13 more per 1000**	**Low** Due to very serious imprecision [3]	There may be little or no difference in admission to hospital between remdesivir and molnupiravir.

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
			(CI 95% 2 fewer — 63 more)		
Mortality High risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**4** per 1000 Difference:	**1.16** per 1000 **2.84 fewer per 1000** (CI 95% 3.68 fewer — 0.24 fewer)	**High**	There is little or no difference in mortality between remdesivir and molnupiravir.
Admission to hospital High risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**16** per 1000 Difference:	**41** per 1000 **25 more per 1000** (CI 95% 3 fewer — 118 more)	**Low** Due to very serious imprecision [4]	Remdesivir may reduce admission to hospital more than molnupiravir.
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.04 — 5.67) (Randomized controlled)	**4** per 1000 Difference:	**0** per 1000 **3 fewer per 1000** (CI 95% 19 fewer — 4 more)	**Moderate** Due to serious risk of bias [5]	There is probably little or no difference in adverse effects leading to drug discontinuation between remdesivir and molnupiravir.
Time to symptom resolution	Lower better (Randomized controlled)	**8.6** (Median) Difference:	**6.8** (Median) **MD 1.8 fewer** (CI 95% 4.9 fewer — 0.9 more)	**Low** Due to concern with risk of bias, imprecision, and intransitivity [6]	Molnupiravir may reduce duration of symptoms more than remdesivir.

1. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
2. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**
3. **Imprecision: very serious.** Credible interval includes a large benefit for remdesivir relative to molnupiravir..
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**
5. **Risk of Bias: serious.** The molnupiravir studies were not blinded.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
6. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**

For patients with non-severe COVID-19 at low risk of hospitalization

Strong recommendation against

We recommend against treatment with molnupiravir *(strong recommendation against)*.

- *See Section 6 regarding identifying patients at low risk.*
- *The marginal benefits of molnupiravir for patients at low risk of hospitalization (those expected to have a 0.5% risk of hospital admission) suggest most patients would not want to use this treatment.*
- *Given considerations regarding resources and equity, the GDG concluded that health care systems may reasonably not offer this drug to patients at low risk of hospitalization.*

Practical info

Given the strong recommendation against using molnupiravir for patients with non-severe COVID-19 at low risk of hospitalizations, practical considerations were felt to be less relevant here.

Evidence to decision

Benefits and harms	Because COVID-19 patients at low risk are extremely unlikely to be either hospitalized or die as a result of COVID-19, the GDG judged that any possible benefits of molnupiravir would be trivial. Long-term harms of molnupiravir, in the absence of clinical data, remain uncertain and a matter of concern. Potential harms include emergence of resistance, and the potential harm coming from the risk of molnupiravir-induced mutagenesis. These considerations (see Justification section) were based on molnupiravir's mechanism of action and available pre-clinical data (see Mechanism of action section).
Certainty of the evidence	Certainty of evidence against standard care in low-risk patients was rated as: high for decreased hospitalization, mortality and adverse effects leading to drug discontinuation; moderate for time to symptom resolution (rated down due to serious risk of bias); and very low for effect on malignancy (no human data).
Values and preferences	The GDG believes that all or almost all patients at low-risk of hospitalization would decline use of a medication with high certainty evidence of a trivial benefit and serious concerns about possible long-term harms.
Resources and other considerations	**Acceptability and feasibility** Molnupiravir is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. This reinforces that molnupiravir should be reserved for those at high risk of hospitalization.

Justification

In low-risk patients, benefits of molnupiravir in reducing hospitalization are trivial. Although the drug probably reduces the duration of symptoms, the GDG considered that, for all or almost all patients, the toxicity will be sufficient to more than counterbalance this benefit.

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Molnupiravir
Comparator: Standard care

Summary

Evidence summary

The LNMA for molnupiravir was informed by 12 RCTs which enrolled 31 512 patients to molnupiravir or a control with non-severe COVID-19. All RCTs were registered; nine RCTs with 29 556 patients (93.8% of total) were published in peer-reviewed journals; the rest were data shared from authors from unpublished trials. None of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of molnupiravir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

Subgroup analyses

Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

Studies did not enrol children. All studies enrolled individuals with time from symptom onset < 5 days. Data regarding serological status were not reported. There was no credible relative effect modification by vaccination status (although the absolute benefit is much lower in patients who have been vaccinated).

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.21 (CI 95% 0.06 — 0.59) Based on data from 30,332 participants in 9 studies. (Randomized controlled)	**0.5** per 1000 Difference:	**0.1** per 1000 **0.4 fewer per 1000** (CI 95% 0.5 fewer — 0.2 more)	**High** 1	Molnupiravir does not have an important impact on mortality
Admission to hospital Low risk	Odds ratio 0.64 (CI 95% 0.39 — 0.93) Based on data from 30,221 participants in 8 studies. (Randomized controlled)	**5** per 1000 Difference:	**3** per 1000 **1.8 fewer per 1000** (CI 95% 3.1 fewer — 0.4 fewer)	**High** 2	Molnupiravir does not result in an important reduction in hospital admission
Mortality Moderate risk	Odds ratio 0.21 (CI 95% 0.06 — 0.59) Based on data from 30,332 participants in 9 studies. (Randomized controlled)	**3** per 1000 Difference:	**0.6** per 1000 **2.4 fewer per 1000** (CI 95% 2.8 fewer — 1.2 fewer)	**High** 3	Molnupiravir does not have an important impact on mortality
Admission to hospital Moderate risk	Odds ratio 0.64 (CI 95% 0.39 — 0.93) Based on data from 30,221 participants in 8 studies. (Randomized controlled)	**30** per 1000 Difference:	**19** per 1000 **11 fewer per 1000** (CI 95% 18 fewer — 2 fewer)	**Moderate** Due to serious imprecision [4]	Molnupiravir probably does not result in an important reduction in hospital admission.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality High risk	Odds ratio 0.21 (CI 95% 0.06 — 0.59) Based on data from 30,332 participants in 9 studies. (Randomized controlled)	**6** per 1000 Difference:	**1** per 1000 **5 fewer per 1000** (CI 95% 6 fewer — 3 fewer)	**Moderate** Due to serious imprecision [5]	Molnupiravir probably has a marginal effect on mortality
Admission to hospital High risk	Odds ratio 0.64 (CI 95% 0.39 — 0.93) Based on data from 30,221 participants in 8 studies. (Randomized controlled)	**60** per 1000 Difference:	**39** per 1000 **21 fewer per 1000** (CI 95% 37 fewer — 4 fewer)	**Moderate** Due to serious imprecision [6]	Molnupiravir probably reduces hospital admission
Mechanical ventilation	Odds ratio 0.39 (CI 95% 0.12 — 1.19) Based on data from 2,746 participants in 3 studies. (Randomized controlled)	**29** per 1000 Difference:	**14** per 1000 **15 fewer per 1000** (CI 95% 25 fewer — 7 more)	**Low** Due to very serious imprecision [7]	There may be no important effect of molnupiravir on mechanical ventilation
Adverse effects leading to drug discontinuation	Odds ratio 0.91 (CI 95% 0.36 — 3.48) Based on data from 5,383 participants in 9 studies. (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 3 more)	**High**	There is no important difference in adverse effects leading to drug discontinuation
Time to symptom resolution	Lower better Based on data from 22,245 participants in 5 studies. (Randomized controlled)	**9** (Median) Difference:	**6.3** (Median) **MD 2.7 fewer** (CI 95% 3.8 fewer — 1.5 fewer)	**Moderate** Due to serious risk of bias [8]	Molnupiravir probably reduces duration of symptoms
Malignancy		In vitro and animal studies suggest the possibility of carcinogenesis		**Very low** No human data with long-term follow-up	The effect of molnupiravir on cancer is uncertain

1, 3. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**

2. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).

4. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (2 fewer per 1000).

5. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**

6. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).

7. **Risk of Bias: no serious.** The single trial reporting mechanical ventilation was not blinded. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Very few events (24 total), resulted in wide credible intervals that include

important and unimportant effects. **Publication bias: no serious.**
8. **Risk of Bias: serious.** All three trials were at high risk of bias for deviations from intended intervention (lack of blinding). One trial was at high risk of bias for possible inadequate randomization concealment.

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Molnupiravir
Comparator: Nirmatrelvir-ritonavir

Summary

Evidence summary

The LNMA for molnupiravir was informed by 12 RCTs which enrolled 31 512 patients to molnupiravir or a control with non-severe COVID-19. All RCTs were registered; nine RCTs with 29 556 patients (93.8% of total) were published in peer-reviewed journals; the rest were data shared from authors from unpublished trials. None of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings.

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5. Vaccination status (unvaccinated versus vaccinated).

Studies did not enrol children. All studies enrolled individuals with time from symptom onset < 5 days. Data regarding serological status were not reported. There was no credible relative effect modification by vaccination status (although the absolute benefit is much lower in patients who have been vaccinated).

Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84) (Randomized controlled)	**0.02** per 1000 Difference:	**0.02** per 1000 **0 fewer per 1000** (CI 95% 0.02 fewer — 0.08 more)	**High** 1	There is little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir.
Admission to hospital Low risk	Odds ratio 4.37 (CI 95% 1.82 — 10.28) (Randomized controlled)	**0.7** per 1000 Difference:	**3.05** per 1000 **2.35 more per 1000** (CI 95% 0.57 more — 6.45 more)	**High** 2	There is little or no difference in admission to hospital between nirmatrelvir-ritonavir and molnupiravir.
Mortality Moderate risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84)	**0.1** per 1000	**0.1** per 1000	**High** 3	There is little or no difference in mortality between nirmatrelvir-

Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
	(Randomized controlled)	Difference:	**0 fewer per 1000** (CI 95% 0.08 fewer — 0.38 more)		ritonavir and molnupiravir.
Admission to hospital Moderate risk	Odds ratio 4.37 (CI 95% 1.82 — 10.28) (Randomized controlled)	**5** per 1000 Difference:	**21** per 1000 **16 more per 1000** (CI 95% 4 more — 44 more)	**Moderate** Due to serious imprecision [4]	Nirmatrelvir-ritonavir probably reduces admission to hospital more than molnupiravir.
Mortality High risk	Odds ratio 0.96 (CI 95% 0.2 — 4.84) (Randomized controlled)	**0.23** per 1000 Difference:	**0.22** per 1000 **0.01 fewer per 1000** (CI 95% 0.18 fewer — 0.88 more)	**High**	There is little or no difference in mortality between nirmatrelvir-ritonavir and molnupiravir.
Admission to hospital High risk	Odds ratio 4.37 (CI 95% 1.82 — 10.28) (Randomized controlled)	**9** per 1000 Difference:	**38** per 1000 **29 more per 1000** (CI 95% 7 more — 76 more)	**Moderate** Due to serious imprecision [5]	Nirmatrelvir-ritonavir probably reduces admission to hospital more than molnupiravir.
Adverse effects leading to drug discontinuation	Odds ratio 0.81 (CI 95% 0.05 — 10.07) (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **2 fewer per 1000** (CI 95% 16 fewer — 4 more)	**Moderate** Due to serious risk of bias [6]	There is probably little or no difference in adverse effects leading to drug discontinuation between nirmatrelvir-ritonavir and molnupiravir.
Time to symptom resolution	Lower better (Randomized controlled)	**9** (Median) Difference:	**6.5** (Median) **MD 2.5 fewer** (CI 95% 6.8 fewer — 0.9 more)	**Low** Due to serious risk of bias and imprecision [7]	Molnupiravir may reduce duration of symptoms more than nirmatrelvir-ritonavir.

1, 3. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**

2. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).

4. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (2 fewer per 1000).

5. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).

6. **Risk of Bias: serious.** The molnupiravir studies were not blinded.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

7. **Risk of Bias: serious.** All three molnupiravir trials were at high risk of bias for deviations from intended intervention (lack of blinding). One trial was at high risk of bias for possible inadequate randomization concealment. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**

Clinical question/ PICO

Population: Patients with non-severe COVID-19

Intervention: Molnupiravir

Comparator: Remdesivir

Summary

Evidence summary

The LNMA for molnupiravir was informed by 12 RCTs which enrolled 31 512 patients to molnupiravir or a control with non-severe COVID-19. All RCTs were registered; nine RCTs with 29 556 patients (93.8% of total) were published in peer-reviewed journals; the rest were data shared from authors from unpublished trials. None of the included studies enrolled children or pregnant individuals. The appendix summarizes study characteristics and risk of bias ratings.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of molnupiravir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

Subgroup analyses

Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

Studies did not enrol children. All studies enrolled individuals with time from symptom onset < 5 days. Data regarding serological status were not reported. There was no credible relative effect modification by vaccination status (although the absolute benefit is much lower in patients who have been vaccinated).

Outcome Timeframe	**Study results and measurements**	**Comparator** Remdesivir	**Intervention** Molnupiravir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**0.33** per 1000 Difference:	**0.1** per 1000 **0.23 fewer per 1000** (CI 95% 0.3 fewer — 0.02 fewer)	**High**	There is little or no difference in mortality between remdesivir and molnupiravir.
Admission to hospital Low risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**1** per 1000 Difference:	**2.62** per 1000 **1.62 more per 1000** (CI 95% 0.21 fewer — 8.45 more)	**High** 1	There is little or no difference in admission to hospital between remdesivir and molnupiravir.
Mortality Moderate risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**2** per 1000 Difference:	**0.58** per 1000 **1.42 fewer per 1000** (CI 95% 1.84 fewer — 0.12 fewer)	**High** 2	There is little or no difference in mortality between remdesivir and molnupiravir.

Outcome Timeframe	Study results and measurements	Comparator Remdesivir	Intervention Molnupiravir	Certainty of the evidence (Quality of evidence)	Summary
Admission to hospital Moderate risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**8** per 1000 Difference:	**21** per 1000 **13 more per 1000** (CI 95% 2 fewer — 63 more)	**Low** Due to very serious imprecision [3]	There may be little or no difference in admission to hospital between remdesivir and molnupiravir.
Mortality High risk	Odds ratio 0.29 (CI 95% 0.08 — 0.94) (Randomized controlled)	**4** per 1000 Difference:	**1.16** per 1000 **2.84 fewer per 1000** (CI 95% 3.68 fewer — 0.24 fewer)	**High**	There is little or no difference in mortality between remdesivir and molnupiravir.
Admission to hospital High risk	Odds ratio 2.62 (CI 95% 0.79 — 9.53) (Randomized controlled)	**16** per 1000 Difference:	**41** per 1000 **25 more per 1000** (CI 95% 3 fewer — 118 more)	**Low** Due to very serious imprecision [4]	Remdesivir may reduce admission to hospital more than molnupiravir.
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.04 — 5.67) (Randomized controlled)	**4** per 1000 Difference:	**0** per 1000 **3 fewer per 1000** (CI 95% 19 fewer — 4 more)	**Moderate** Due to serious risk of bias [5]	There is probably little or no difference in adverse effects leading to drug discontinuation between remdesivir and molnupiravir.
Time to symptom resolution	Lower better (Randomized controlled)	**8.6** (Median) Difference:	**6.8** (Median) **MD 1.8 fewer** (CI 95% 4.9 fewer — 0.9 more)	**Low** Due to concern with risk of bias, imprecision, and intransitivity [6]	Molnupiravir may reduce duration of symptoms more than remdesivir.

1. **Imprecision: no serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
2. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: no serious.** There were only 24 events total in the molnupiravir studies. **Publication bias: no serious.**
3. **Imprecision: very serious.** Credible interval includes a large benefit for remdesivir relative to molnupiravir..
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**
5. **Risk of Bias: serious.** The molnupiravir studies were not blinded.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
6. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**

Mechanism of action of molnupiravir

Molnupiravir is an orally available antiviral, which was originally designed as an influenza treatment, although not approved. The drug inhibits replication of SARS-CoV-2 with an *in vitro* potency broadly, similar to remdesivir, and was re-purposed early in development as an antiviral for SARS-CoV-2 *[39][40]*. Molnupiravir is an orally available prodrug of ß-D-N4-hydroxycytidine (NHC). It is a nucleoside drug, but the mechanism of action involves lethal mutagenesis of the virus. This contrasts with chain termination seen with other antiviral nucleoside analogues (e.g. remdesivir and those used in HIV or HCV) *[41]*. NHC is incorporated by the SARS-CoV-2 RdRp, instead of either C or U nucleosides, into the genomic or subgenomic RNA during copying of the RNA template genome. The resultant NHC-containing RNAs are then themselves used as a template for production of subsequent RNAs which are mutated and therefore do not form functional viruses *[41][42]*.

Molnupiravir is given orally twice daily unlike remdesivir, which is given by intravenous infusion once daily. In healthy volunteers, molnupiravir (800 mg) achieves maximum plasma concentrations of its active metabolite at 3600 ng/mL *[43]*. This is higher than that of remdesivir (2200 ng/mL) *[44]*. However, the intracellular half-life of molnupiravir's active metabolite is shorter in human cell lines (3h) compared with that of remdesivir's active metabolite (35h) *[43]*.

High doses of molnupiravir (250 mg/kg twice daily) have been shown to be effective in SARS-CoV-2-infected Syrian golden hamsters; however, the animal plasma pharmacokinetics were not reported to benchmark against those seen in humans *[45]*. Evidence of antiviral activity is also available from a study in SARS-CoV-2-infected ferrets at lower doses *[46]*. When molnupiravir was combined with favipiravir in infected Syrian golden hamsters, the efficacy was greater than when either drug was given alone *[47]*.

Major differences in sequence across new variants have occurred in the viral spike protein and not the RNA polymerase that is targeted by molnupiravir. Accordingly, molnupiravir activity across variants has been stable in comparison to monoclonal antibodies that target the spike protein (NIH Open Data Portal; *[29][30]*). Therefore, there is no known molecular, pharmacokinetic and pharmacodynamic basis for a change in activity of molnupiravir since initial RCTs were conducted.

Emergence of resistance: For other viruses, the speed with which resistance to drugs emerges is varied. The barrier to resistance for a given drug with a given virus is generally considered to increase with the number of mutations that are required to emerge. Insufficient data are currently available to ascertain how high the barrier of resistance is with SARS-CoV-2 for molnupiravir. Based on experiences with other nucleoside antiviral drugs (some have a high barrier to resistance and some have a low barrier to resistance), molnupiravir will place a selective pressure for viral resistance mutations within an individual, with the potential to spread at a population level. Non-clinical and/or clinical data are therefore needed, but are not currently available for molnupiravir.

Resistance occurs through inherent variability in viral sequences that happen spontaneously as the virus replicates. Chance variations become selected, known as selective pressure, when they confer a survival advantage in the presence of the drug. Sometimes, there is a fitness cost to the virus and secondary mutations can subsequently be selected to restore fitness. The major uncertainty relates to how quickly resistance will emerge rather than whether it will emerge. There may be a higher risk of resistance in immunocompromised patients because of a longer tail of replication in this group. There may also be a higher risk of resistance in patients with poor adherence where the virus is exposed to suboptimal drug concentrations. The rate at which resistance emerges will be slower if drugs are given in combination because more mutations will be required to confer resistance to multiple drugs than will be required for one drug. Of note, animal studies have also demonstrated drug combinations to be more effective. The risk of resistance to individual patients is drug failure due to compromised efficacy. If resistance is transmitted, there is a risk of efficacy failure at a population level and subsequent attempts to combine the drug may be futile because of “functional monotherapy” with the partner agent. The genetic barrier to resistance cannot be estimated without data.

Emergence of new variants: It has been proposed that random mutagenesis arising from the molnupiravir mechanism of action might increase diversity in the viral sequences that may result in more rapid emergence of new variants or resistant variants *[48]*. Unlike the considerations for resistance, there is no conceptual basis for molnupiravir placing a selective pressure on emergence of new variants. Sequence variation is lower given molnupiravir is only incorporated in place of two of the four nucleotide bases in the genome than it would be if incorporated in place of any nucleotide. In addition, when considering the more rapid evolution of new variants as a result of the lethal mutagenesis mechanism it is also important to consider that overall replication of the virus is constrained in the patient during the period of therapeutic drug exposure. In February 2023, a preprint described the results of a systematic investigation of global sequencing databases for a signature of molnupiravir mutagenesis *[49]*. A mutational signature with elevated G-to-A and C-to-T mutations was described that appeared almost exclusively in sequences from 2022, after introduction, and in countries and age groups with widespread usage of molnupiravir. No direct causality between molnupiravir use and emergence of these mutations was established but it is highly plausible given the mechanism of action of the drug and the chronology of the emergence of these mutations that the two are linked. Notwithstanding, there is no current evidence that these signature mutations result in any change in phenotype of the virus (new variants or resistance). As such, there remains no direct evidence to support or refute the variants hypothesis and the risk is currently unquantifiable.

The rate of resistance emergence and the risk of additional diversity in the viral genome leading to new variants, were acknowledged to be higher with a higher number of patients receiving the intervention.

Non-clinical safety: The GDG reviewed the publicly available data on non-clinical safety of molnupiravir from the FDA meeting documents for molnupiravir Emergence Use Authorization (30 November 2021) *[50]*. The following safety concerns were highlighted:

- Genetic toxicology data demonstrated that molnupiravir is mutagenic *in vitro,* but there was no evidence of mutagenicity in animal models. The GDG acknowledged uncertainties in the available data and concluded that based upon the available information molnupiravir may or may not be carcinogenic in humans.
- An increase in thickness of growth plate associated with decreased bone formation was observed in rapidly growing rats but not in mice, rats or dogs. The GDG determined that molnupiravir should not therefore be administered to paediatric patients.
- Importantly, low concentrations of NHC (0.09% maternal exposures) were detectable in 10-day old rat pups suggesting that NHC is present in breastmilk. The GDG determined molnupiravir should not be administered to breastfeeding women.
- In developmental and reproductive toxicology assessments, reduced fetal body weights were observed in rats and rabbits, with higher exposures also being associated with embryo-fetal lethality and teratogenicity in rats. Accordingly, molnupiravir should not be administered during pregnancy.
- There was an absence of available data relating to spermatogenesis, which may be particularly prone to the effect of a mutagen in adult males. No data are available to quantify the consequences of this for embryo/fetus conceived by fathers who were receiving or had recently received molnupiravir.

Systemic corticosteroids (published 2 September 2020)

The recommendation for corticosteroids was initially published on 22 September 2020, with evidence summaries updated in the guideline's 6th version, but no subsequent changes.

For patients with non-severe COVID-19

Conditional recommendation against

We suggest not to use systemic corticosteroids *(conditional recommendation against)*.

Practical info

With the conditional recommendation against the use of corticosteroids in patients with non-severe COVID-19 the following practical information applies in situations where such treatment is to be considered:

Route: Systemic corticosteroids may be administered both orally and intravenously. Of note, while the bioavailability of dexamethasone is very high (i.e. similar concentrations are achieved in plasma after oral and intravenous intake), critically ill patients may be unable to absorb any nutrients or medications due to intestinal dysfunction. Clinicians therefore may consider administering systemic corticosteroids intravenously rather than orally if intestinal dysfunction is suspected.

Duration: While most patients received corticosteroids in the form of dexamethasone 6 mg daily for up to 10 days, the total duration of regimens evaluated in the seven trials varied between 5 and 14 days, and treatment was generally discontinued at hospital discharge (i.e. the duration of treatment could be less than the duration stipulated in the protocols).

Dose: The once daily dexamethasone formulation may increase adherence. A dose of 6 mg of dexamethasone is equivalent (in terms of glucocorticoid effect) to 150 mg of hydrocortisone (e.g. 50 mg every 8 hours), or 40 mg of prednisone, or 32 mg of methylprednisolone (e.g. 8 mg every 6 hours or 16 mg every 12 hours). It would be prudent to monitor glucose levels in patients with severe and critical COVID-19, regardless of whether the patient is known to have diabetes.

Timing: The timing of therapy from onset of symptoms was discussed by the panel. The RECOVERY investigators reported a subgroup analysis suggesting that the initiation of therapy 7 days or more after symptom onset may be more beneficial than treatment initiated within 7 days of treatment onset. A post hoc subgroup analysis within the prospective meta-analysis (PMA) did not support this hypothesis. While some panel members believed that postponing systemic corticosteroids until after viral replication is contained by the immune system may be reasonable, many noted that, in practice, it is often impossible to ascertain symptom onset and that

signs of severity frequently appear late (i.e. denote a co-linearity between severity and timing). The panel concluded that, given the evidence, it was preferable to err on the side of administering corticosteroids when treating patients with severe or critical COVID-19 (even if within 7 days of symptoms onset) and to err on the side of not giving corticosteroids when treating patients with non-severe disease (even if after 7 days of symptoms onset).

Other endemic infections that may worsen with corticosteroids should be considered. For example, for *Strongyloides stercoralis* hyperinfection associated with corticosteroid therapy, diagnosis or empiric treatment may be considered in endemic areas if steroids are used.

Evidence to decision

Benefits and harms	The panel made its recommendation on the basis of low certainty evidence suggesting a potential increase of 3.9% in 28-day mortality among patients with COVID-19 who are not severely ill. The certainty of the evidence for this specific subgroup was downgraded due to serious imprecision (i.e. the evidence does not allow to rule out a mortality reduction) and risk of bias due to lack of blinding. In making a conditional recommendation against the indiscriminate use of systemic corticosteroids, the panel inferred that most fully informed individuals with non-severe illness would not want to receive systemic corticosteroids, but many could want to consider this intervention through shared decision-making with their treating physician *[6][52]*. **Note:** WHO recommends antenatal corticosteroid therapy for pregnant individuals at risk of preterm birth from 24 to 34 weeks' gestation when there is no clinical evidence of infection in the pregnant individual, and adequate childbirth and newborn care is available. However, in cases where the pregnant individual presents with mild or moderate COVID-19, the clinical benefits of antenatal corticosteroid might outweigh the risks of potential harm to the individual. In this situation, the balance of benefits and harms for the patient and the preterm newborn should be discussed with the patient to ensure an informed decision, as this assessment may vary depending on the patient's clinical condition, their wishes and that of their family, and available health care resources.
Certainty of the evidence	See Benefits and Harms section.
Values and preferences	The conditional recommendation was driven by likely variation in patient values and preferences. The panel judged that most individuals with non-severe illness would decline systemic corticosteroids. However, many may want this intervention after shared decision-making with their treating physician.
Resources and other considerations	**Resource implications, feasibility, equity and human rights** The panel also considered that in order to help guarantee access to systemic corticosteroids for patients with severe and critical COVID-19, it is reasonable to avoid administering this intervention to patients who, given the current evidence, would not appear to derive any benefit from this intervention.

Justification

This recommendation was achieved by consensus.

Applicability

This recommendation applies to patients with non-severe disease regardless of their hospitalization status. The panel noted that patients with non-severe COVID-19 would not normally require acute care in hospital or respiratory support, but that in some jurisdictions, these patients may be hospitalized for isolation purposes only, in which case they should not be treated with systemic corticosteroids. The panel concluded that systemic corticosteroids should not be stopped for patients with non-severe COVID-19 who are already treated with systemic corticosteroids for other reasons (e.g. patients with chronic obstructive pulmonary disease or other chronic autoimmune diseases need not discontinue a course of systemic oral corticosteroid). If the clinical condition of patients with non-severe COVID-19 worsens (i.e. increase in respiratory rate, signs of respiratory distress or hypoxaemia) they should receive systemic corticosteroids (see recommendation for severe and critical COVID-19).

Clinical question/ PICO

Population: Patients with non-severe COVID-19

Intervention: Systemic corticosteroids

Comparator: Standard care

Summary

Evidence summary
Please see evidence summary above (placed under recommendation for patients with severe and critical COVID-19 to find more information about the eight RCTs pooled into two systematic reviews with meta-analysis. It also provides information about additional systematic reviews used to inform safety outcomes and results of subgroup analyses resulting in separate recommendations for patients with non-severe COVID-19 and those with severe and critical illness.

The GRADE Summary of Findings table shows the relative and absolute effects of systemic corticosteroids compared with standard care for the outcomes of interest in patients with non-severe COVID-19, with certainty ratings.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Systemic corticosteroids	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality 28 days	Relative risk 1.22 (CI 95% 0.93 — 1.61) Based on data from 1,535 participants in 1 studies. [1] Follow up: 28 days.	**23** per 1000 Difference:	**28** per 1000 **5 more per 1000** (CI 95% 2 fewer — 14 more)	**Low** Due to serious risk of bias and serious imprecision [2]	Systemic corticosteroids may increase the risk of 28-day mortality in patients with non-severe COVID-19.
Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (CI 95% 0.59 — 0.93) Based on data from 5,481 participants in 2 studies. Follow up: 28 days.	**116** per 1000 Difference:	**86** per 1000 **30 fewer per 1000** (CI 95% 48 fewer — 8 fewer)	**Moderate** Due to serious risk of bias [3]	Systemic corticosteroids probably reduce the need for mechanical ventilation.
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 participants in 30 studies. [4]	**48** per 1000 Difference:	**51** per 1000 **3 more per 1000** (CI 95% 7 fewer — 16 more)	**Low** Due to serious indirectness and serious imprecision [5]	Corticosteroids may not increase the risk of gastrointestinal bleeding.
Super-infections	Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 participants in 32 studies.	**186** per 1000 Difference:	**188** per 1000 **2 more per 1000** (CI 95% 19 fewer — 24 more)	**Low** Due to serious indirectness, Due to serious imprecision [6]	Corticosteroids may not increase the risk of super-infections.
Hyperglycaemia	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 participants in 24 studies.	**286** per 1000 Difference:	**332** per 1000 **46 more per 1000** (CI 95% 23 more — 72 more)	**Moderate** Due to serious indirectness [7]	Corticosteroids probably increase the risk of hyperglycaemia.
Hypernatremia	Relative risk 1.64	**40**	**66**	**Moderate**	Corticosteroids probably

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Systemic corticosteroids	Certainty of the evidence (Quality of evidence)	Summary
	(CI 95% 1.32 — 2.03) Based on data from 5,015 participants in 6 studies.	per 1000 Difference:	per 1000 **26 more per 1000** (CI 95% 13 more — 41 more)	Due to serious indirectness [8]	increase the risk of hypernatremia.
Neuromuscular weakness	Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 participants in 8 studies.	**69** per 1000 Difference:	**75** per 1000 **6 more per 1000** (CI 95% 10 fewer — 27 more)	**Low** Due to serious indirectness and serious imprecision [9]	Corticosteroids may not increase the risk of neuromuscular weakness.
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 participants in 7 studies.	**35** per 1000 Difference:	**28** per 1000 **7 fewer per 1000** (CI 95% 21 fewer — 22 more)	**Low** Due to serious indirectness and serious imprecision [10]	Corticosteroids may not increase the risk of neuropsychiatric effects.
Duration of hospitalization	Measured by: days Lower better Based on data from 6,425 participants in 1 studies. (Randomized controlled)	**13** days	**12** days	**Low** Due to serious risk of bias and serious imprecision [11]	Steroids may result in an important reduction in the duration of hospitalizations.

1. Systematic review [1] **Comparator:** Primary study [15]. We derived baseline risk for mortality and mechanical ventilation from the control arm of the WHO SOLIDARITY trial.
2. **Risk of Bias: serious.** lack of blinding. **Imprecision: serious.**
3. **Risk of Bias: serious.** lack of blinding.
4. **Supporting references:** [1],
5, 6, 9, 10. **Indirectness: serious. Imprecision: serious.**
7, 8. **Indirectness: serious.**
11. **Risk of Bias: serious.** lack of blinding. **Imprecision: serious.** confidence interval includes no benefit.

Fluvoxamine (published 14 July 2022)

The recommendation for fluvoxamine was initially published on 14 July 2022, with no subsequent changes.

For patients with non-severe COVID-19

Only in research settings

We recommend not to use fluvoxamine, except in the context of a clinical trial *(recommended only in research settings)*.

Practical info

The GDG made a recommendation against using fluvoxamine for treatment of patients with COVID-19 outside the setting of a clinical trial and therefore practical considerations are less relevant for this drug.

Evidence to decision

Benefits and harms

In patients with non-severe COVID-19, fluvoxamine probably has little or no effect on mortality and may have little or no effect on mechanical ventilation and hospitalization, with no data reported for time to symptom resolution and adverse effects leading to drug discontinuation. The GDG concluded that the balance between benefits and potential harms does not favour treatment.

The planned subgroup analyses for fluvoxamine versus standard care for age and time of symptom onset did not support any differences in relative effects, whereas disease severity could not be assessed since trials only enrolled patients with non-severe COVID-19.

Certainty of the evidence

The evidence summary was informed by three trials with 2225 participants included in the LNMA. The largest trial (n=1480) exclusively enrolled patients in Brazil [*79*].

Certainty of evidence was rated as moderate for mortality (due to serious indirectness), and low for mechanical ventilation (due to serious indirectness, imprecision, and some concerns regarding risk of bias) and hospitalization (due to serious imprecision and risk of bias). Acknowledging that its evaluation of the certainty of the evidence may differ from other published meta-analyses [*80*], panel members pointed out that early stopping due to apparent benefit may have biased the results of the largest trial. They argued that, although the stopping rules were pre-specified, the decision was based on the effect estimate on a composite outcome of questionable importance, meanwhile the number of important events was lower. The panel also raised concerns regarding the uncertain applicability of this trial conducted in a single country.

Values and preferences

Given the agreed upon values and preferences statement (see Section 10), the GDG inferred that almost all well-informed patients would choose not to receive fluvoxamine therapy for COVID-19 based on the available evidence. The GDG did not believe that other considerations, such as feasibility, acceptability, equity and cost, would impact this specific recommendation. Specifically, the GDG did not consider the potential role of fluvoxamine as an antidepressant for this guideline of medications for COVID-19.

Resources and other considerations

The panel acknowledged that effective therapeutic alternatives for non-severe COVID-19 were expensive, which could limit their availability in resource-constrained areas. However, although fluvoxamine is relatively inexpensive, compared with other drugs used for COVID-19, and widely available, including in low-income settings, the evidence does not justify the use of fluvoxamine for non-severe COVID-19 anywhere. Although the cost of fluvoxamine may be low, the GDG panel raised concerns regarding the risk of diverting attention and resources away from interventions that are more likely to provide a benefit. To avoid the risk of writing recommendations that would risk perpetuating and legitimizing unequal access to more effective drugs, the panel believed that it would be preferable to emphasize the need for more equitable access to effective therapeutic options.

Justification

When moving from evidence to the recommendation not to use fluvoxamine in patients with non-severe COVID-19 except in the context of a clinical trial, the GDG emphasized the lack of a clear mechanism of action and the low certainty evidence suggesting little to no effect on hospitalization and mechanical ventilation, moderate certainty evidence of little or no effect on mortality, as well as the absence of reliable data on serious adverse effects attributable to the drug known for significant pharmacological interactions. The panel noted that in the largest trial more patients discontinued the investigational product in the fluvoxamine group than in the placebo group. Noting that effective therapeutic alternatives exist for non-severe COVID-19, the GDG did not anticipate important variability in patient values and preferences. The panel also did not believe that other considerations, such as resource considerations, accessibility, feasibility, and equity (see summary of these factors under Evidence to Decision) impacted this specific recommendation.

Applicability

None of the included studies enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. However, the panel did not see a reason to assume that children with COVID-19 would respond any differently to treatment with fluvoxamine.

Clinical question/ PICO

Population: Patients with non-severe COVID-19

Intervention: Fluvoxamine

Comparator: No fluvoxamine

Summary

The LNMA for fluvoxamine was informed by three RCTs which enrolled 2225 patients with non-severe illness in outpatient settings. All three RCTs were registered, and two were published in a peer-reviewed journal. All three studies were conducted in outpatients. None of the included studies enrolled children. The Table shows characteristics of the RCTs.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of fluvoxamine compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[1]*.

Based on data from the TOGETHER trial *[55]*, no credible subgroup effects were observed on the primary outcome by age (children vs adults vs older adults) and time from symptom onset (0–3 days vs 4–7 days). Planned subgroup analyses for disease severity, age and chronic conditions (absolute effects), serological status and vaccination status were precluded by lack of available data.

Outcome Timeframe	**Study results and measurements**	**Comparator** No fluvoxamine	**Intervention** Fluvoxamine	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality	Odds ratio 0.68 (CI 95% 0.33 — 1.32) Based on data from 1,649 participants in 2 studies. (Randomized controlled)	**4** per 1000 Difference:	**3** per 1000 **1 fewer per 1000** (CI 95% 3 fewer — 1 more)	**Moderate** Due to serious indirectness [1]	There is probably little or no difference in mortality
Hospital admission High risk	Odds ratio 0.7 (CI 95% 0.34 — 1.23) Based on data from 2,196 participants in 3 studies. (Randomized controlled)	**35** per 1000 Difference:	**25** per 1000 **10 fewer per 1000** (CI 95% 23 fewer — 8 more)	**Low** Due to very serious imprecision [2]	Fluvoxamine may reduce hospitalization
Hospital admission Higher risk	Odds ratio 0.7 (CI 95% 0.34 — 1.23) Based on data from 2,196 participants in 3 studies. (Randomized controlled)	**60** per 1000 Difference:	**43** per 1000 **17 fewer per 1000** (CI 95% 39 fewer — 13 more)	**Low** Due to very serious imprecision [3]	Fluvoxamine may reduce hospitalization
Hospital admission Highest risk	Odds ratio 0.7 (CI 95% 0.34 — 1.23) Based on data from 2,196 participants in 3 studies. (Randomized controlled)	**100** per 1000 Difference:	**72** per 1000 **28 fewer per 1000** (CI 95% 64 fewer — 20 more)	**Low** Due to very serious imprecision [4]	Fluvoxamine may reduce hospitalization
Mechanical ventilation	Odds ratio 0.73 (CI 95% 0.38 — 1.4) Based on data from 1,649 participants in 2 studies. (Randomized controlled)	**18** per 1000 Difference:	**13** per 1000 **5 fewer per 1000** (CI 95% 11 fewer — 7 more)	**Low** Due to serious indirectness and imprecision [5]	There may be little or no difference in mechanical ventilation

Outcome Timeframe	Study results and measurements	Comparator No fluvoxamine	Intervention Fluvoxamine	Certainty of the evidence (Quality of evidence)	Summary
Adverse effects leading to drug discontinuation				No data	The effect of fluvoxamine is unknown
Time to symptom resolution				No data	The effect of fluvoxamine is unknown

1. **Indirectness: serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, which are not easily identifiable. For these patients, it is plausible that fluvoxamine may have an important impact on mortality.
2, 3, 4. **Imprecision: very serious.** The credible interval includes both important harm and important benefit.
5. **Indirectness: serious.** Some patients may be at substantially higher risk of mechanical ventilation. **Imprecision: serious.**

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Fluvoxamine
Comparator: Nirmatrelvir-ritonavir

Outcome Timeframe	Study results and measurements	Comparator Nirmatrelvir-ritonavir	Intervention Fluvoxamine	Certainty of the evidence (Quality of evidence)	Summary
Mortality	(Randomized controlled)	**0** per 1000 Difference:	**3** per 1000 **3 more per 1000** (CI 95% 1 more — 5 more)	**Very low** Due to serious indirectness, imprecision, and serious risk of bias [1]	The impact on mortality is very uncertain
Hospital admission	Odds ratio 4.54 (CI 95% 1.32 — 12.78) (Randomized controlled)	**5** per 1000 Difference:	**22** per 1000 **17 more per 1000** (CI 95% 2 more — 55 more)	**Low** Due to serious imprecision and risk of bias [2]	Nirmatrelvir-ritonavir may reduce hospitalization more than fluvoxamine
Mechanical ventilation				No data [3]	The effect on mechanical ventilation is unknown
Adverse effects				No data	The effect on adverse

Outcome Timeframe	Study results and measurements	Comparator Nirmatrelvir-ritonavir	Intervention Fluvoxamine	Certainty of the evidence (Quality of evidence)	Summary
leading to drug discontinuation					effects is unknown
Time to symptom resolution				No data	The effect on time to symptom resolution is unknown

1. **Risk of Bias: serious.** The EPIC-HR study was stopped early for benefit. **Indirectness: serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, which are not easily identifiable. For these patients, it is plausible that fluvoxamine may have an important impact on mortality. **Imprecision: serious.** There were very few events.
2. **Risk of Bias: serious.** The nirmatrelvir-ritonavir study (EPIC-HR) was stopped early for benefit. **Imprecision: serious.**
3. **Inconsistency: no serious. Indirectness: serious.** Some patients may be at substantially higher risk of mechanical ventilation. **Imprecision: serious. Publication bias: no serious.**

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Fluvoxamine
Comparator: Molnupiravir

Outcome Timeframe	Study results and measurements	Comparator Molnupiravir	Intervention Fluvoxamine	Certainty of the evidence (Quality of evidence)	Summary
Mortality	Odds ratio 5.74 (CI 95% 0.95 — 56.11) (Randomized controlled)	**0.4** per 1000 Difference:	**2** per 1000 **1.6 more per 1000** (CI 95% 0.02 fewer — 21.56 more)	**Low** Due to serious indirectness and imprecision [1]	There may be little or no difference in mortality
Hospital admission	Odds ratio 1.31 (CI 95% 0.52 — 2.98) (Randomized controlled)	**19** per 1000 Difference:	**25** per 1000 **6 more per 1000** (CI 95% 9 fewer — 36 more)	**Low** Due to very serious imprecision [2]	There may be little or no difference in hospital admission
Mechanical ventilation	Odds ratio 1.77 (CI 95% 0.19 — 10.6) (Randomized controlled)	**8** per 1000 Difference:	**14** per 1000 **6 more per 1000** (CI 95% 6 fewer — 71 more)	**Very low** Due to serious indirectness and very serious imprecision [3]	The effect on mechanical ventilation is uncertain

Outcome Timeframe	Study results and measurements	Comparator Molnupiravir	Intervention Fluvoxamine	Certainty of the evidence (Quality of evidence)	Summary
Adverse effects leading to drug discontinuation				No data	The effect on adverse effects is unknown
Time to symptom resolution				No data	The effect on time to symptom resolution is unknown

1. **Indirectness: serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, which are not easily identifiable. For these patients, it is plausible that fluvoxamine may have an important impact on mortality. **Imprecision: serious.** There were very few events.
2. **Imprecision: very serious.** The credible interval includes both important harm and important benefit.
3. **Indirectness: serious.** Some patients may be at substantially higher risk of mechanical ventilation. **Imprecision: very serious.**

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Fluvoxamine
Comparator: Remdesivir

Outcome Timeframe	Study results and measurements	Comparator Remdesivir	Intervention Fluvoxamine	Certainty of the evidence (Quality of evidence)	Summary
Mortality	Odds ratio 0.87 (CI 95% 0.27 — 2.85) (Randomized controlled)	**3** per 1000 Difference:	**3** per 1000 **0 fewer per 1000** (CI 95% 2 fewer — 6 more)	**Low** Due to serious indirectness and serious imprecision [1]	There may be little or no difference in mortality
Hospital admission	Odds ratio 2.76 (CI 95% 0.62 — 12.07) (Randomized controlled)	**9** per 1000 Difference:	**24** per 1000 **15 more per 1000** (CI 95% 3 fewer — 90 more)	**Low** Due to very serious imprecision [2]	Remdesivir may reduce hospitalization more than fluvoxamine
Mechanical ventilation	Odds ratio 1.63 (CI 95% 0.19 — 11.23) (Randomized controlled)	**8** per 1000 Difference:	**13** per 1000 **5 more per 1000** (CI 95% 6 fewer — 75 more)	**Very low** Due to serious indirectness and very serious imprecision [3]	The effect on mechanical ventilation is uncertain

Outcome Timeframe	Study results and measurements	Comparator Remdesivir	Intervention Fluvoxamine	Certainty of the evidence (Quality of evidence)	Summary
Adverse effects leading to drug discontinuation				No data	The effect on adverse effects is unknown
Time to symptom resolution				No data	The effect on time to symptom resolution is unknown

1. **Indirectness: serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, which are not easily identifiable. For these patients, it is plausible that fluvoxamine may have an important impact on mortality. **Imprecision: serious.** There were very few events.
2. **Imprecision: very serious.**
3. **Indirectness: serious.** Some patients may be at substantially higher risk of mechanical ventilation. **Imprecision: very serious.**

Mechanism of action of fluvoxamine

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) approved as an antidepressant. The antidepressant effects of fluvoxamine are related to inhibition of the serotonin transporter in the brain, which serves to increase the concentrations of serotonin in the synaptic cleft. In COVID-19, several putative anti-inflammatory or antiviral mechanisms of action have been proposed *[56][57]*. First, anti-inflammatory properties have been postulated as a result of serotonin transporter inhibition in platelets and/or lungs, but this is based upon indirect evidence from non-COVID-19 disease models. Secondly, host-directed antiviral properties have been proposed via agonism of the sigma-1 receptor, for which some evidence exists from other viruses for an involvement in RNA replication, but there are currently no published preclinical studies that directly demonstrate or refute a mechanism in COVID-19. Therefore, plausibility requires interpretation of indirect evidence for anti-inflammatory or antiviral mechanisms, which are currently unproven preclinically and not directly related to the mechanism and site of action in depression.

Sotrovimab (updated 13 January 2023)

The recommendation for sotrovimab was initially published on 14 January 2022. Updated evidence supporting the previous strong recommendation against use of sotrovimab for patients with non-severe COVID-19 was published in the 13th version of the guideline, following the availability of data showing *in vitro* neutralization activity is diminished with sotrovimab with currently circulating SARS-CoV-2 variants and subvariants (e.g. Omicron). No subsequent changes have been made.

For patients with non-severe COVID-19

Strong recommendation against

We recommend against treatment with sotrovimab *(strong recommendation against).*

- *The GDG considered in vitro data demonstrating that neutralization of currently circulating variants of SARS-CoV-2 and their subvariants with sotrovimab is diminished.*
- *There was consensus among the panel that the meaningful reduction of in vitro neutralization activity strongly suggests absence of clinical effectiveness of monoclonal antibodies such as sotrovimab.*
- *There was also consensus regarding the need for clinical trial evidence in order to confirm clinical effectiveness of new monoclonal antibodies that reliably neutralize circulating strains in vitro.*

Practical info

Given the strong recommendation against using sotrovimab for patients with non-severe COVID-19, practical considerations were felt to be less relevant here.

Evidence to decision

Benefits and harms

On the basis of clinical trial evidence that remains available via the LNMA *[2]*, in the 8th version of this guideline, GDG had previously made a conditional recommendation for use of sotrovimab to patients with non-severe COVID-19 at highest risk of hospitalization. At the time, the panel acknowledged that the emergence of future variants could reduce the clinical effectiveness of sotrovimab.

In the 12th version of this guideline, rather than new clinical trial evidence, the change in recommendation was triggered by new *in vitro* evidence demonstrating that sotrovimab has very diminished *in vitro* neutralization activity to currently circulating subvariants of SARS-CoV-2. There was consensus among the panel that it is highly unlikely that the clinical effectiveness of sotrovimab would persist in the absence of adequate *in vitro* neutralization of the circulating variants. Accordingly, the panel concluded that the evidence upon which the previous recommendation hinged was no longer applicable.

In the 13th version of the guideline, the GDG reviewed additional *in vitro* neutralization data that emerged after the change in the guideline for sotrovimab and casirivimab-imdevimab, and that included information on new variants. This incremental evidence supported the change in recommendation and strengthened the GDG's confidence that the strong recommendation not to use sotrovimab (and casirivimab-imdevimab) was applicable to the current SARS-CoV-2 ecology. More information on the interpretation of the results of in vitro neutralization data can be found in the Mechanism of action section and in correspondence published in the *Lancet [58]*.

Certainty of the evidence

In light *in vitro* evidence, the GDG concluded that the clinical effects of sotrovimab for COVID-19 caused by the currently circulating variants and subvariants of SARS-CoV-2 are highly uncertain.

The existing trial evidence identified in the LNMA *[2]* was judged to be at moderate certainty for reduced hospitalization and high certainty for absence of infusion reactions, with no or small differences in mortality or mechanical ventilation. With the new circulating SARS-CoV-2 variants, this trial evidence would be rated as very low, meaning that the benefits of sotrovimab cannot be determined by trials performed before the new variants occurred.

Values and preferences

Applying the agreed upon values and preferences (see Section 10), the GDG inferred that, in the absence of compelling evidence of clinical effectiveness for the currently circulating SARS-CoV-2 variants, almost all well-informed patients would choose not to receive sotrovimab.

Resources and other

Acceptability and feasibility

considerations	The strong recommendation against the use of sotrovimab is further supported by the challenges with availability and feasibility, such as limited production, intravenous administration and requirement for expertise to offer such treatment while oral antiviral therapies are also available.

Justification

Although previous clinical trial evidence available via the LNMA *[2]* remains accurate, the panel concluded that it is no longer applicable to COVID-19 caused by the SARS-CoV-2 variants that are currently circulating globally. The panel surmised that the likelihood of COVID-19 caused by former variants was extremely low and that accordingly, evidence of sotrovimab's clinical effectiveness for COVID-19 was nonexistent.

Of note, the panel applied the same rationale to the recommendation for casirivimab-imdevimab.

Reliance on in vitro evidence

The GDG agreed that large high-quality clinical trials generally provide the best evidence of clinical effectiveness for therapeutic interventions. The GDG also continues to base its recommendations strictly on critically important outcomes. From the perspective of clinical guidelines, mechanistic studies and surrogate outcomes are useful to identify candidate therapies for clinical trials, but are of no use in confirming clinical effectiveness. The panel concluded that the emerging evidence demonstrating the reduced neutralization of current variants by sotrovimab in vitro would likely have justified not launching clinical trials and now renders the results of previous trials inapplicable. In vitro assays were deemed sufficient to rule out a clinical effect. Notwithstanding, proof of potent in vitro neutralization would not be sufficient to confirm clinical effectiveness. Therefore, the GDG will only consider making recommendations for new monoclonal antibodies once they have been rigorously evaluated in clinical trials.

Mechanism of action of sotrovimab

- Sotrovimab (VIR-7831; GSK4182136) is a single human monoclonal antibody that binds to a conserved epitope of the SARS-CoV-2 spike protein, preventing the virus from entering cells.
- Antiviral activity in a Syrian golden hamster model of SARS-CoV-2 infection was demonstrated at 5 mg/kg IP but with a version of the antibody that was not Fc-engineered *[60]*. Neutralization of SARS-CoV-2 (USA WA1/2020) was achieved in Vero E6 cells with an EC90 value of 0.19 µg/mL *[59]*. Sotrovimab serum concentrations in COMET-ICE (single 500 mg IV infusion) provided geometric mean Cmax (at the end of a 1 hr IV infusion) of 117.6 µg/mL (N=129, CV% 40) and a geometric mean Day 29 serum concentration of 24.5 µg/mL *[59]*. Population mean serum concentrations are therefore expected to be 129-fold higher after 29 days than the concentrations needed *in vitro* to neutralize the original strain of SARS-CoV-2.
- Information in the FDA Emergency Use Authorization states “no change” in activity of sotrovimab against Alpha, Beta, Gamma, Epsilon, Iota, Kappa, Delta (including with K417N), Lambda and Mu in pseudo-typed virus-like particle neutralization assays *[59]*. Sotrovimab has been reported to retain activity against BA.1 Omicron in pseudovirus assays but with higher concentrations being required for neutralization compared with the wild-type virus *[61]*.
- The FDA summarized the reported *in vitro* neutralization data (EC90) available for BA.2 Omicron and its interpretation in the context of the pharmacokinetics of sotrovimab in humans *[62]*. The presented data show the EC90 to be between 25.3- and 48.1-fold higher for BA.2 Omicron than for pre-Omicron variants. In the associated analysis, assuming a 6.5% or 12% penetration of antibody from serum into the lung (as described for other monoclonal antibodies), it was shown that concentrations required for robust neutralization were unlikely to be achieved in the lung. Furthermore, the independent safety monitoring committee for the COMET-TAIL trial recommended early termination of the 250 mg intramuscular (IM) sotrovimab arm due to a higher rate of hospitalization than either 500 mg IM or 500 mg intravenous (IV) arms. Since the serum neutralization of 500 mg IV sotrovimab against the Omicron BA.2 variant (serum concentration divided by the *in vitro* EC90) is expected to be lower than that observed with 250 mg IM sotrovimab against the Delta variant, it is unlikely to be effective in treating patients with the Omicron BA.2 variant. *In vitro* neutralization activities have been demonstrated to be broadly similar between BA.2, BA.2.12.1, BA.4 and BA.5 *[63][64][65][66]*, and similar or further reduced for BQ.1 and BQ.1.1 *[67][68][69]*). Therefore, the presented analysis is relevant to many of the currently dominant Omicron sub-lineages.
- An E340A amino acid substitution in the conserved epitope of the spike protein emerged rapidly under a selective pressure with sotrovimab in cell culture, and subsequent characterization using a pseudovirus assay resulted in a >100-fold reduction in susceptibility to sotrovimab *[59]*. Sixteen other substitutions introduced into the epitope were also described as reducing neutralization by sotrovimab by between 5.4 and > 297-fold *[59]*.
- The GDG members surmised that monoclonal antibodies most likely need to penetrate the respiratory tract to achieve clinical effectiveness. On the basis of available empirical and quantitative pharmacology evidence for other monoclonal antibodies, the GDG estimates that the likely lung-to-serum ratio is 6.5–12.0% *[70][71][53][54][72]*. Considering all available *in vitro* neutralization experiments, when serum concentrations are corrected for penetration into the lung, the target concentrations (defined by the effective concentration required for 90% neutralization [EC90] of viral particles) are unlikely to be achieved.
- The GDG has considered but rejected the suggestion that target concentrations neutralizing 50% of viral particles in serum

can reliably predict clinical effectiveness *[66][58]*. EC90 is at least nine times higher than EC50. Not fully neutralizing the virus population not only carries the risk of inefficacy but also increases the likelihood of emergence of selected resistance. Emergence of selected resistance has already been widely documented with sotrovimab use against susceptible variants, particularly in the context of immunocompromised patients *[73][74][75][76][77][78]*.

Colchicine (published 14 July 2022)

The recommendation for colchicine was initially published on 14 July 2022, with no subsequent changes.

For patients with non-severe COVID-19

Strong recommendation against

We recommend against treatment with colchicine *(strong recommendation against)*.

Practical info

The GDG made a strong recommendation against using colchicine for treatment of patients with non-severe COVID-19 and therefore practical considerations are less relevant.

Evidence to decision

Benefits and harms	In patients with non-severe COVID-19, colchicine probably has little or no impact on mortality and mechanical ventilation, may have little or no impact on hospitalizations, and may increase the likelihood of adverse effects leading to drug discontinuation. The panel discussed the risk of drug interactions and colchicine's narrow therapeutic window, particularly in patients with or at risk of hepatic and renal failure. Colchicine toxicity can be severe, and sometimes fatal. The planned subgroup analyses for colchicine versus standard care did not show different relative effects for disease severity, and age (children, adults, older) with no data reported from illness onset.
Certainty of the evidence	The evidence summary on colchicine was informed by a systematic review including 13 trials with 18 172 participants. The evidence was most abundant for mortality with incomplete reporting for other outcomes (e.g. five trials with 598 participants for adverse effects). A single trial of 4488 participants [*83*], which contributed almost all of the evidence on hospitalizations, was stopped prematurely. Certainty of evidence was rated as: moderate for mortality and mechanical ventilation (rated down for indirectness); low for admission to hospital (rated down for imprecision and risk of bias); and low for adverse effects leading to drug discontinuation (rated down for imprecision and risk of bias).
Values and preferences	Given the agreed upon values and preferences statement (see Section 10), the GDG inferred that almost all well-informed patients would choose not to receive colchicine based on available evidence regarding relative benefits and harms. The GDG did not believe that other considerations, such as feasibility, acceptability, equity, and cost, impacted this specific recommendation.
Resources and other considerations	The panel acknowledged that effective therapeutic alternatives for non-severe COVID-19 were expensive, which could limit their availability in resource-constrained areas. However, although colchicine is relatively inexpensive, compared with other drugs used for COVID-19, and widely available, including in low-income settings, the evidence does not justify the use of colchicine for non-severe COVID-19 anywhere. Although the cost of colchicine may be low, the GDG raised concerns regarding the risk of diverting attention and resources away from interventions that are more likely to provide a benefit. To avoid writing recommendations that would risk perpetuating and legitimizing unequal access to more effective drugs, the

panel believed that it would be preferable to emphasize the need for more equitable access to effective therapeutic options.

Justification

When moving from evidence to the strong recommendation against the use of colchicine for patients with non-severe COVID-19, the GDG emphasized the moderate certainty evidence of no effect on mortality and mechanical ventilation, and the low certainty evidence of no effect on hospitalizations, but possible harm associated with treatment. Specifically, the panel recognized the risks of diarrhoea, cytopenia and other toxicities, particularly among patients with, or at risk of, renal failure, as potentially important to patients with non-severe COVID-19. Noting that effective therapeutic alternatives exist for non-severe COVID-19, the GDG did not anticipate important variability in patient values and preferences. The panel also did not believe that other considerations, such as resource considerations, accessibility, feasibility, and equity impacted this specific recommendation.

Applicability

None of the included studies enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. However, the panel did not see a reason to assume that children with COVID-19 would respond any differently to treatment with colchicine.

Clinical question/ PICO

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

Summary

The systematic review for colchicine included 13 trials that enrolled 18 172 patients. All but three trials were registered. None of the studies enrolled children. The Table shows characteristics of the RCTs.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of colchicine compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[1]*.

Based on data from the COLCORONA trial *[79]*, no credible subgroup effects were observed on the primary outcome by age (children vs adults vs older adults) and disease severity (non-severe vs severe). Planned subgroup analyses for time from symptom onset, age and chronic conditions (absolute effects), serological status and vaccination status were precluded by lack of available data.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Colchicine	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality	Odds ratio 0.84 (CI 95% 0.5 — 1.17) Based on data from 17,914 participants in 10 studies. (Randomized controlled)	**4** per 1000 Difference:	**3** per 1000 **1 fewer per 1000** (CI 95% 2 fewer — 1 more)	**Moderate** Due to serious indirectness [1]	Colchicine probably has little or no impact on mortality
Admission to hospital Risk in trials	Odds ratio 0.68 (CI 95% 0.27 — 1.57) Based on data from 4,949 participants in 3 studies. (Randomized controlled)	**35** per 1000 Difference:	**24** per 1000 **11 fewer per 1000** (CI 95% 25 fewer — 19 more)	**Moderate** Due to serious imprecision [2]	Colchicine probably has little or no impact on hospital admission
Admission to hospital Higher risk	Odds ratio 0.68 (CI 95% 0.27 — 1.57) Based on data from 4,949	**60** per 1000	**42** per 1000	**Moderate** Due to serious imprecision [3]	Colchicine probably has little or no impact on hospital admission

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Colchicine	**Certainty of the evidence** (Quality of evidence)	**Summary**
	participants in 3 studies. (Randomized controlled)	Difference:	**18 fewer per 1000** (CI 95% 43 fewer — 31 more)		
Admission to hospital Highest risk	Odds ratio 0.68 (CI 95% 0.27 — 1.57) Based on data from 4,949 participants in 3 studies. (Randomized controlled)	**100** per 1000 Difference:	**70** per 1000 **30 fewer per 1000** (CI 95% 71 fewer — 49 more)	**Low** Due to very serious imprecision [4]	Colchicine may have little or no impact on hospital admission
Mechanical ventilation	Odds ratio 0.75 (CI 95% 0.37 — 1.26) Based on data from 12,746 participants in 5 studies. (Randomized controlled)	**9** per 1000 Difference:	**7** per 1000 **2 fewer per 1000** (CI 95% 6 fewer — 2 more)	**Moderate** Due to serious indirectness [5]	Colchicine probably has little or no impact on mechanical ventilation
Adverse effects leading to drug discontinuation	Based on data from 598 participants in 5 studies. (Randomized controlled)	**0** per 1000 Difference:	**34** per 1000 **34 more per 1000** CI 95%	**Low** Due to serious risk of bias and serious imprecision [6]	Colchicine may increase the risk of adverse effects leading to drug discontinuation

1. **Indirectness: serious.**
2, 3. **Imprecision: serious.** The upper credible interval includes a small and unimportant effect on hospitalization (4 fewer per 1000).
4. **Imprecision: very serious.**
5. **Indirectness: serious. Imprecision: no serious.** Credible interval includes modest benefit.
6. **Risk of Bias: serious. Imprecision: serious.**

Mechanism of action of colchicine

Colchicine is an anti-inflammatory drug used to treat gout, recurrent pericarditis, familial Mediterranean fever, and other inflammatory indications. There are several proposed mechanisms of action that are theorized to obviate inflammation-associated pathology seen in COVID-19 *[80][81]*, which include a reduction in chemotaxis of neutrophils, inhibition of inflammasome signalling, and decreased production of cytokines such as interleukin-1b (IL-1b). There are no published data at the time of publication from animal models of SARS-CoV-2 infection to support or refute pre-clinical efficacy or harm of colchicine in associated disease pathology. The mechanism of action is postulated to be similar to that for the indications for which colchicine is already approved, but plausibility of effect in COVID-19 requires assumptions around similarities between COVID-19 and other diseases to be accepted. There are marked differences between trials in terms of the doses and schedules that have been investigated in COVID-19. Within the studies included in the NMA, doses ranged between 0.5 and 2 mg per day, course durations ranged between 6 and 30 days, some studies used once daily dosing, some used twice daily dosing, and others used three times daily dosing. In addition, some studies used dosing schedules which changed throughout the course, starting with one dose or schedule and then changing to a different dose or schedule after a predetermined interval. The pharmacokinetics of colchicine are dose linear between 0.5 mg and 1.5 mg *[82][83]* but the substantive variation between studies included in the NMA precludes a robust interpretation of differences in outcome associated with dose and schedule.

8. Recommendations for patients with severe and critical COVID-19

Heparins (published August 2025)

Heparins, which include unfractionated heparin and low-molecular weight heparin (referred to collectively as 'heparin'), are widely used anticoagulants that have been studied due to the increased risk of venous thromboembolic events in hospitalized patients with COVID-19 compared to other diagnoses *[198]*. In addition, heparins may have immunomodulatory effects due to inhibitory actions on neutrophils and inflammatory mediators, reduction in vascular permeability, and other mechanisms *[199]*. Therefore, heparins have been studied in COVID-19 at doses higher than the usual prophylactic doses used to prevent venous thromboembolism in hospitalized patients.

Heparins for patients with severe or critical COVID-19

New

Conditional recommendation for

We suggest administering prophylactic dose heparin instead of therapeutic or intermediate dose heparin for severe or critical COVID-19 (heparin includes unfractionated or low molecular weight heparin) (C*onditional recommendation).*

- *The panel recognized that standard care for hospitalized patients with COVID-19 would include a heparin to prevent venous thromboembolic events (prophylaxis). and therefore did not consider the question of heparin (at any dose) compared to no heparin.*
- *The recommendation is consistent with the current standard of care for venous thromboembolism prophylaxis in the majority of hospitalized patients.The majority of trials that informed this recommendation evaluated unfractionated or low-molecular-weight heparin. The panel therefore judged that this recommendation applies to both types of heparins.*
- *The panel judged that this recommendation does not apply to patients with an established indication for therapeutic anticoagulation, for example, confirmed venous thromboembolism.*

Practical info

Prophylactic dosing of heparins includes dalteparin 400 units daily, enoxaparin 40 mg daily, tinzaparin 4500 units daily, and unfractionated heparin 5000 units twice daily (all subcutaneous), with dose adjustment for elevated body mass index.

Evidence to decision

Benefits and harms

In patients hospitalized with severe or critical COVID-19, therapeutic heparin, when compared to intermediate or prophylactic dose heparin, probably results in a small reduction in thromboembolic events (moderate certainty), with possibly little or no increase in major bleeding (low certainty). Effects on 28-day all-cause mortality and progression to invasive mechanical ventilation or death by 28 days are both uncertain (very low certainty).

Intermediate dose heparin, when compared to prophylactic dose heparin, may have little or no effect on 28-day mortality and thromboembolic events (both low certainty) and probably has little or no effect on major bleeding (moderate certainty). The effect on progression to invasive mechanical ventilation or death by 28 days is uncertain (very low certainty).

Certainty of the evidence

For the comparison between therapeutic and intermediate or prophylactic dose heparin, certainty of evidence for thromboembolic events was rated as moderate due to imprecision and some potential subjectivity in assessment across trials. Certainty in major bleeding was rated as low due to serious imprecision and concerns regarding indirectness based on potential subjectivity and lack of outcome adjudication. Also, there was variability in how this outcome was operationalized across trials including implications for patients. Certainty in the outcomes of mortality and progression to invasive mechanical ventilation or death was rated as very low given extremely serious imprecision, with confidence intervals encompassing large beneficial and large harmful effects.

For the comparison between intermediate and prophylactic dose heparin, certainty of evidence for mortality was rated as low due to very serious imprecision, with very wide confidence intervals encompassing important benefit and harm. Certainty in thromboembolic events was rated as low due to serious imprecision

and indirectness based on potential subjectivity in assessment across trials. Certainty in major bleeding was rated as moderate based on potential subjectivity and lack of outcome adjudication and similar concerns re: variability mentioned above. Certainty in progression to invasive mechanical ventilation or death by 28 days was rated as very low due to extremely serious imprecision, with confidence intervals encompassing large beneficial and large harmful effects.

Values and preferences

Applying the agreed values and preferences (see Section 10), the GDG inferred that, given very low certainty evidence informing mortality and progression to invasive mechanical ventilation or death and moderate certainty evidence of a small reduction in thromboembolic events, the majority of well-informed patients would choose to not receive therapeutic dose heparin over intermediate or prophylactic dose. They further inferred that, given low to moderate certainty of comparable effects between intermediate and prophylactic dose heparin (except for very low certainty evidence for the outcome of progression to invasive mechanical ventilation or death), the majority of well-informed patients would choose to receive prophylactic dose heparin.

The GDG anticipated, however, that because of the residual possibility of benefit with therapeutic and intermediate dose heparins and substantial uncertainty regarding effects on several patient-important outcomes, that a minority of well-informed patients would choose to receive these regimens instead.

Resources and other considerations

Resource implications, feasibility, equity and human rights

The panel took an individual patient perspective, but also considered issues related to resource use and health system implications. Compared to therapeutic and intermediate-dose heparins, prophylactic-dose heparins (either unfractionated heparin or low molecular weight heparins) are lower in cost and require fewer resources for administration and monitoring, making their use more feasible in low-resource settings.

Heparins, irrespective of dose, are widely available in most healthcare settings internationally, although the specific medications may vary. Both low-molecular-weight heparins and unfractionated heparin are on the WHO Essential Medicines List.

Low molecular weight heparins are easier to administer than unfractionated heparin (which demands either continuous or intermittent intravenous infusions [for treatment], or more frequent subcutaneous administration [for prophyaxis]). Low molecular weight heparins require less monitoring (generally not required, compared to activated partial thromboplastin time monitoring required for unfractionated heparin), and have a lower risk of heparin-induced thrombocytopenia. Use of low molecular weight heparins may therefore reduce health inequities and increase feasibility n low-resource settings.

Acceptability

Prophylactic-dose heparins are easy to administer and well-established as part of standard care to prevent venous thromboembolism in hospitalized patients. The lack of need for laboratory monitoring and generally favourable safety profile of prophylactic-dose heparin, compared to intermediate or therapeutic dosing, led the panel to conclude that the acceptability of this intervention was high.

Justification

The GDG was informed by a systematic review and prospective meta-analysis (PMA) of 22 randomized trials evaluating therapeutic, intermediate, and prophylactic dose anticoagulation strategies among patients hospitalized with severe or critical COVID-19.*[206]* The PMA pooled data from several trials that allowed patents in the non-therapeutic heparin comparator group to receive intermediate and prophylactic dose, based on clinician discretion. The PMA categorized such trials according to the dose received by the majority of patients. From a clinical perspective, the panel felt that the first task was to determine a recommendation for therapeutic dosing compared to non-therapeutic (i.e., either intermediate or prophylactic) dosing of heparin. If relevant, the panel was prepared to consider evidence regarding intermediate compared to prophylactic heparin. Trials included in the PMA were categorized accordingly, with trial data taken from the PMA.

To address this, the GDG re-pooled data from the systematic review and prospective meta-analysis. One analysis combined intermediate and prophylactic dose categories and compared the combination against therapeutic dose anticoagulation. A second analysis compared intermediate and prophylactic dose categories. Re-analysed data (forest plots) are available in Annex A.

When comparing therapeutic dose to intermediate or prophylactic dose heparin, the GDG emphasized moderate certainty of a small reduction in thromboembolic events balanced against low or very low certainty evidence regarding effects on mortality, progression to

invasive mechanical ventilation or death, and major bleeding as a relevant adverse event. Given only small anticipated benefit regarding thromboembolic events and substantial uncertainty regarding effects on other patient-important outcomes, they anticipated that a majority of patients would choose to receive intermediate or prophylactic dose over therapeutic dose heparin.

When comparing intermediate to prophylactic dose heparin, the GDG emphasized low certainty of little or no effect on mortality and thromboembolic events and very low certainty of effects on progression to invasive mechanical ventilation or death. Therefore, the GDG anticipated that a majority of patients would choose to receive prophylactic dose over intermediate dose heparin. They also considered that prophylactic dose heparin represented standard of care for a large proportion of hospitalized patients and would be easily implemented from a feasibility and resource perspective.

Subgroup considerations

The GDG acknowledged that the multi-platform randomized controlled trials *[201][202]* reported divergent effects in non-critically ill patients (benefit of therapeutic heparin compared to intermediate or prophylactic dose heparin) compared to critically ill patients (no benefit from therapeutic heparin compared to intermediate or prophylactic dose heparin) *[203]*. The GDG therefore considered the possibility of subgroup analysis of severe versus critical illness. However, there was no statistical evidence of a subgroup effect when comparing (a) therapeutic dose vs. intermediate or prophylactic dose heparin, or (b) intermediate vs. prophylactic dose heparin. In each case, the subgroup test for difference p value ≤ 0.20, and the panel therefore inferred that the ICEMAN tools should not be employed, and that a recommendation should be made encompassing all disease severities.

Applicability
None of the included studies enrolled children, and therefore the applicability of this recommendation to children is uncertain. However, the panel did not see a reason to assume that children with COVID-19 would respond any differently to differing heparin dosing intensities.

Clinical question/ PICO

Population: Patients with severe or critical COVID-19
Intervention: Therapeutic dose heparin
Comparator: Intermediate or prophylactic dose heparin

Summary

Evidence summary

A systematic review and prospective meta-analysis (PMA) of randomized trials evaluating therapeutic versus intermediate versus prophylactic heparin synthesized data from 22 trials and 11 733 participants *[200]*; full details of the included trials are available in the PMA supplement. In several trials, including the two largest *[201][202]*, patients assigned to the non-therapeutic heparin comparator group could receive either prophylactic or intermediate dosing. From a clinical perspective, the panel felt that the first task was to determine a recommendation for therapeutic dosing compared to non-therapeutic (i.e., either intermediate or prophylactic) dosing of heparin. If relevant, the panel was prepared to consider evidence regarding intermediate compared to prophylactic heparin.

In this guideline, the meta-analysis of therapeutic compared to intermediate or prophylactic heparin was was informed by 14 RCTs with 7 821 participants *[206]*. All trials enrolled hospitalized patients with severe or critical illness; 12 were published and 2 were completed but unpublished.

The GRADE Summary of Findings table shows the relative and absolute effects of therapeutic compared with intermediate or prophylactic heparin for the outcomes of interest in patients with severe or critical COVID-19, with certainty ratings. See Section 7 for sources of baseline risk estimates informing absolute estimates of effect.

Subgroup analysis
The GDG requested a subgroup analysis based on disease severity (severe versus critical); there was no evidence of a subgroup effect (interaction p-value 0.20) for the outcome of 28-day mortality.

Outcome Timeframe	**Study results and measurements**	**Comparator** Intermediate or prophylactic dose heparin	**Intervention** Therapeutic dose heparin	**Certainty of the evidence** (Quality of evidence)	**Summary**
All-cause mortality 28 days	Relative risk 0.91 (CI 95% 0.74 — 1.13) Based on data from 7,821	**130** per 1000	**118** per 1000	**Very low** Due to extremely serious imprecision	We are unsure of the effect of therapeutic dose heparin on mortality compared with

Outcome Timeframe	Study results and measurements	Comparator Intermediate or prophylactic dose heparin	Intervention Therapeutic dose heparin	Certainty of the evidence (Quality of evidence)	Summary
	participants in 14 studies. (Randomized controlled)	Difference:	**12 fewer per 1000** (CI 95% 34 fewer — 17 more)	[1]	intermediate or prophylactic dose.
Progression to invasive mechanical ventilation or death 28 days	Relative risk 0.94 (CI 95% 0.76 — 1.17) Based on data from 7,339 participants in 13 studies. (Randomized controlled)	**161** per 1000 Difference:	**151** per 1000 **10 fewer per 1000** (CI 95% 39 fewer — 27 more)	**Very low** Due to extremely serious imprecision [2]	We are unsure of the effect of therapeutic dose heparin on invasive mechanical ventilation or mortality compared with intermediate or prophylactic dose.
Thromboembolic events	Relative risk 0.57 (CI 95% 0.46 — 0.7) Based on data from 7,812 participants in 14 studies. (Randomized controlled)	**54** per 1000 Difference:	**31** per 1000 **23 fewer per 1000** (CI 95% 29 fewer — 16 fewer)	**Moderate** Due to some imprecision and potential subjectivity in assessment [3]	Therapeutic dose heparin probably reduces thromboembolic events compared with intermediate or prophylactic dose.
Major bleeding	Relative risk 1.71 (CI 95% 1.14 — 2.55) Based on data from 7,824 participants in 14 studies. (Randomized controlled)	**11** per 1000 Difference:	**19** per 1000 **8 more per 1000** (CI 95% 2 more — 17 more)	**Low** Due to serious imprecision and some indirectness [4]	Therapeutic dose heparin may result in little to no increase in major bleeding compared with intermediate or prophylactic dose.

1, 2. **Imprecision: extremely serious.**
3. **Imprecision: serious.**
4. **Indirectness: serious. Imprecision: serious.**

Clinical question/ PICO

Population: Patients with severe or critical COVID-19
Intervention: Intermediate dose heparin
Comparator: Prophylactic dose heparin

Summary

Evidence summary

Information on the source systematic review and PMA is presented in the evidence summary for ‘Therapeutic dose heparin vs Intermediate or prophylactic dose heparin’. Given the low-certainty evidence favouring intermediate or prophylactic heparin, evidence was synthesized to inform the question of intermediate compared to prophylactic heparin.

In this guideline, the meta-analysis of intermediate versus prophylactic heparin was informed by 10 RCTs with 3 897 participants. All trials enrolled hospitalized patients with severe or critical illness; 9 were published and 1 was completed but unpublished. *[206]*

The GRADE Summary of Findings table shows the relative and absolute effects of intermediate compared to prophylactic heparin for the outcomes of interest in patients with severe or critical COVID-19, with certainty ratings. See Section 7 for sources of baseline risk estimates informing absolute estimates of effect.

Subgroup analysis
The GDG requested a subgroup analysis based on disease severity (severe versus critical); there was no evidence of a subgroup effect (interaction p-value 0.32) for the outcome of 28-day mortality.

Outcome Timeframe	**Study results and measurements**	**Comparator** Prophylactic dose heparin	**Intervention** Intermediate dose heparin	**Certainty of the evidence** (Quality of evidence)	**Summary**
All-cause mortality 28 days	Relative risk 0.99 (CI 95% 0.86 — 1.14) Based on data from 3,897 participants in 10 studies. (Randomized controlled)	**110** per 1000 Difference:	**109** per 1000 **1 fewer per 1000** (CI 95% 15 fewer — 15 more)	**Low** Due to very serious imprecision [1]	There may be little to no difference in mortality between intermediate and prophylactic dose heparin.
Progression to invasive mechanical ventilation or death 28 days	Relative risk 0.84 (CI 95% 0.6 — 1.19) Based on data from 3,373 participants in 8 studies. (Randomized controlled)	**131** per 1000 Difference:	**110** per 1000 **21 fewer per 1000** (CI 95% 52 fewer — 25 more)	**Very low** Due to extremely serious imprecision [2]	We are unsure of the effect on mortality or invasive mechanical ventilation of intermediate dose heparin compared to prophylactic dose.
Thromboembolic events	Relative risk 0.67 (CI 95% 0.38 — 1.16) Based on data from 3,847 participants in 10 studies. (Randomized controlled)	**39** per 1000 Difference:	**26** per 1000 **13 fewer per 1000** (CI 95% 24 fewer — 6 more)	**Low** Due to serious imprecision and potential subjectivity in assessment [3]	Intermediate dose heparin treatment possibly has little to no effect on thromboembolic events compared to prophylactic dose.
Major bleeding	Relative risk 1.21 (CI 95% 0.84 — 1.73) Based on data from 3,713 participants in 9 studies. (Randomized controlled)	**11** per 1000 Difference:	**13** per 1000 **2 more per 1000** (CI 95% 2 fewer — 8 more)	**Moderate** Due to serious indirectness [4]	Intermediate dose heparin treatment probably causes little to no difference in major bleeding compared to prophylactic dose.

1. **Imprecision: very serious.**
2. **Imprecision: extremely serious.**
3. **Imprecision: serious.**
4. **Indirectness: serious.**

Systemic corticosteroids (published 2 September 2020)

The recommendation for corticosteroids was initially published on 22 September 2020, with evidence summaries updated in the guideline's 6th version, but no subsequent changes.

For patients with severe or critical COVID-19

Strong recommendation for

We recommend treatment with systemic corticosteroids for severe or critical COVID-19 *(strong recommendation for)*.

Practical info

Route: Systemic corticosteroids may be administered both orally and intravenously. Of note, while the bioavailability of dexamethasone is very high (that is, similar concentrations are achieved in plasma after oral and intravenous intake), critically ill patients may be unable to absorb any nutrients or medications due to intestinal dysfunction. Clinicians therefore may consider administering systemic corticosteroids intravenously rather than orally if intestinal dysfunction is suspected.

Duration: While more patients received corticosteroids in the form of dexamethasone 6 mg daily for up to 10 days, the total duration of regimens evaluated in the seven trials varied between 5 and 14 days, and treatment was generally discontinued at hospital discharge (i.e. the duration of treatment could be less than the duration stipulated in the protocols).

Dose: The once daily dexamethasone formulation may increase adherence. A dose of 6 mg of dexamethasone is equivalent (in terms of glucocorticoid effect) to 150 mg of hydrocortisone (i.e. 50 mg every 8 hours), 40 mg of prednisone, or 32 mg of methylprednisolone (8 mg every 6 hours or 16 mg every 12 hours).

Monitoring: It would be prudent to monitor glucose levels in patients with severe and critical COVID-19, regardless of whether the patient is known to have diabetes.

Timing: The timing of therapy from onset of symptoms was discussed by the panel. The RECOVERY investigators reported a subgroup analysis suggesting that the initiation of therapy 7 days or more after symptom onset may be more beneficial than treatment initiated within 7 days of symptom onset. A post hoc subgroup analysis within the PMA did not support this hypothesis. While some panel members believed that postponing systemic corticosteroids until after viral replication is contained by the immune system may be reasonable, many noted that, in practice, it is often impossible to ascertain symptom onset and that signs of severity often appear late (i.e. denote a co-linearity between severity and timing). The panel concluded that, given the evidence, it was preferable to err on the side of administering corticosteroids when treating patients with severe or critical COVID-19 (even if within 7 days of symptoms onset) and to err on the side of not giving corticosteroids when treating patients with non-severe disease (even if after 7 days of symptoms onset).

Evidence to decision

Benefits and harms

Panel members who voted for a conditional recommendation argued that the trials evaluating systemic corticosteroids for COVID-19 reported limited information regarding potential harm. Between the two panel meetings, indirect evidence regarding the potential harmful effects of systemic corticosteroids from studies in sepsis, ARDS and community-acquired pneumonia (CAP) was added to the summary of findings table *[84][85]*. While generally of low certainty, these data were reassuring and suggested that corticosteroids are not associated with an increased risk of adverse events, beyond likely increasing the incidence of hyperglycaemia (moderate certainty evidence; absolute effect estimate 46 more per 1000 patients, 95% CI: 23 more to 72 more) and hypernatraemia (moderate certainty evidence; 26 more per 1000 patients, 95% CI: 13 more to 41 more). Panel members also noted that, given the expected effect of systemic corticosteroids on mortality, most patients would not refuse this intervention to avoid adverse events believed to be markedly less important to most patients than death.

In contrast with new agents proposed for COVID-19, clinicians have a vast experience of systemic corticosteroids and the panel was reassured by their overall safety profile. Moreover, the panel was confident that clinicians using these guidelines would be aware of additional potential side-effects and contraindications to systemic corticosteroid therapy, which may vary geographically in function of endemic microbiological flora. Notwithstanding, clinicians should exercise caution in use of corticosteroids in patients with diabetes or underlying immunocompromise.

Ultimately, the panel made its recommendation on the basis of the moderate certainty evidence of a 28-day

mortality reduction of 8.7% in the critically ill and 6.7% in patients with severe COVID-19 who were not critically ill, respectively. In the 5th version of this living guideline, mortality baseline risk estimates were updated based on the WHO SOLIDARITY trial, considered to represent the best source of prognosis across countries facing the COVID-19 pandemic. This resulted in an overall 3.3% reduction in 28-day mortality for patients with severe or critical COVID-19, still with moderate certainty evidence and considered by the panel to represent a clear benefit to patients, with no impact on the established recommendations.

Certainty of the evidence

See Benefits and Harms section.

Values and preferences

The panel took an individual patient perspective to values and preferences but, given the burden of the pandemic for health care systems globally, also placed a high value on resource allocation and equity. The benefits of corticosteroids on mortality were deemed of critical importance to patients, with little or no anticipated variability in their preference to be offered treatment if severely ill from COVID-19.

Resources and other considerations

Resource implications, feasibility, equity and human rights

In this guideline, the panel took an individual patient perspective, but also placed a high value on resource allocation. In such a perspective, attention is paid to the opportunity cost associated with the widespread provision of therapies for COVID-19. In contrast to other candidate treatments for COVID-19 that, generally, are expensive, often unlicensed, difficult to obtain and require advanced medical infrastructure, systemic corticosteroids are low cost, easy to administer, and readily available globally *[86]*. Dexamethasone and prednisolone are among the most commonly listed medicines in national essential medicines lists; listed by 95% of countries. Dexamethasone was first listed by WHO as an essential medicine in 1977, while prednisolone was listed 2 years later *[87]*.

Accordingly, systemic corticosteroids are among a relatively small number of interventions for COVID-19 that have the potential to reduce inequities and improve equity in health. Those considerations influenced the strength of this recommendation.

Acceptability

The ease of administration, the relatively short duration of a course of systemic corticosteroid therapy, and the generally benign safety profile of systemic corticosteroids for up to 7–10 days led the panel to conclude that the acceptability of this intervention was high.

Justification

This recommendation was achieved after a vote, which concerned the strength of the recommendation in favour of systemic corticosteroids. Of the 23 voting panel members, 19 (83%) voted in favour of a strong recommendation, and 4 (17%) voted in favour of a conditional recommendation. The reasons for the four cautionary votes, which were shared by some panel members who voted in favour of a strong recommendation, are summarized below.

Applicability

Panel members who voted for a conditional recommendation argued that many patients who were potentially eligible for the RECOVERY trial were excluded from participating in the evaluation of corticosteroids by their treating clinicians and that without detailed information on the characteristics of excluded patients, this precluded, in their opinion, a strong recommendation. Other panel members felt that such a proportion of excluded patients was the norm rather than the exception in pragmatic trials and that, while detailed information on the reasons for excluding patients were not collected, the main reasons for refusing to offer participation in the trial were likely related to safety concerns of stopping corticosteroids in patients with a clear indication for corticosteroids (confirmed as per personal communication from the RECOVERY Principal Investigator). Panel members noted that there are few absolute contraindications to a 7–10 day course of corticosteroid therapy, that recommendations are intended for the average patient population, and that it is understood that even strong recommendations should not be applied to patients in whom the intervention is contraindicated as determined by the treating clinician.

Eventually, the panel concluded that this recommendation applies to patients with severe and critical COVID-19 regardless of hospitalization status. The underlying assumption is that these patients would be treated in hospitals and receive respiratory support in the form of oxygen; non-invasive or invasive ventilation if these options were available. Following GRADE guidance, in making a

strong recommendation, the panel has inferred that all or almost all fully informed patients with severe COVID-19 would choose to take systemic corticosteroids. It is understood that even in the context of a strong recommendation, the intervention may be contraindicated for certain patients. Absolute contraindications for 7–10 day courses of systemic corticosteroid therapy are rare. In considering potential contraindications, clinicians must determine if they warrant depriving a patient of a potentially life-saving therapy.

The applicability of the recommendation is less clear for populations that were under-represented in the considered trials, such as children, patients with tuberculosis, and those who are immunocompromised. Notwithstanding, clinicians will also consider the risk of depriving these patients of potentially life-saving therapy. In contrast, the panel concluded that the recommendation should definitely be applied to certain patients who were not included in the trials, such as patients with severe and critical COVID-19 who could not be hospitalized or receive oxygen because of resource limitations.

The recommendation does not apply to the following uses of corticosteroids: transdermal or inhaled administration, high-dose or long-term regimens, or prophylaxis.

Clinical question/ PICO

Population: Patients with severe or critical COVID-19
Intervention: Systemic corticosteroids
Comparator: Standard care

Summary

Evidence summary
This guideline was triggered on 22 June 2020 by the publication of the preliminary report of the RECOVERY trial, later published as a peer-reviewed paper *[14]*. Corticosteroids are listed in the WHO Model List of Essential Medicines, readily available globally at a low cost, and of considerable interest to all stakeholder groups. The guideline panel was informed by combining two meta-analyses which pooled data from eight randomized trials (7184 participants) of systemic corticosteroids for COVID-19 *[1][88]*. The panel discussions were also informed by two other meta-analyses, which were already published and pooled data about the safety of systemic corticosteroids in distinct but relevant patient populations.

The GRADE Summary of Findings table shows the relative and absolute effects of systemic corticosteroids compared with standard care for the outcomes of interest in patients with severe and critical COVID-19, with certainty ratings. Below we provide more details about the trials and meta-analysis as well as a subgroup analysis that informed the recommendation. See Section 7 for sources of baseline risk estimates informing absolute estimates of effect.

On 17 July 2020, the panel reviewed evidence from eight RCTs (7184 patients) evaluating systemic corticosteroids versus standard care in COVID-19. RECOVERY, the largest of the seven trials, from which mortality data were available by subgroup (severe and non-severe), evaluated the effects of dexamethasone 6 mg given once daily (oral or intravenous) for up to 10 days in 6425 hospitalized patients in the United Kingdom (2104 were randomized to dexamethasone and 4321 were randomized to standard care) *[14]*. At the time of randomization, 16% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation; 60% were receiving oxygen only (with or without non-invasive ventilation); and 24% were receiving neither.

The data from seven other smaller trials included 63 non-critically ill patients and approximately 700 critically ill patients (definitions of critical illness varied across studies). For the latter, patients were enrolled up to 9 June 2020, and approximately four-fifths were invasively mechanically ventilated; approximately half were randomized to receive corticosteroid therapy, and half randomized to no corticosteroid therapy. Corticosteroid regimens included: methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (GLUCOCOVID) *[89]*; dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID19, CoDEX) *[90][91]*; hydrocortisone 200 mg daily for 4 to 7 days followed by 100 mg daily for 2 to 4 days and then 50 mg daily for 2 to 3 days (one trial, CAPE-COVID) *[92]*; hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP) *[16]*; methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI) *[93]*.

Seven of the trials were conducted in individual countries (Brazil, China, Denmark, France, Spain) whilst REMAP-CAP was an international study (recruiting in 14 European countries, Australia, Canada, New Zealand, Saudi Arabia and the United Kingdom). All trials reported mortality 28 days after randomization, except for one trial at 21 days and another at 30 days. Because the mortality data from one trial (GLUCOCOVID, n=63) were not reported by subgroup, the panel reviewed only the data pertaining to the outcome of mechanical ventilation from this trial *[89]*. An additional trial, which randomized hospitalized patients with suspected SARS-CoV-2 infection, published on 12 August 2020 (MetCOVID) *[94]*, was included as a supplement in the PMA publication, as it was registered after the searches of trial registries were performed. The supplement showed that inclusion would not change results other than reduce inconsistency.

Subgroup analyses
While all other trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalized patients with COVID-19. The panel considered the results of a subgroup analysis of the RECOVERY trial suggesting that the relative effects of systemic corticosteroids varied as a function of the level of respiratory support received at randomization. On the basis of the peer-reviewed criteria for credible subgroup effects *[95]*, the panel determined that the subgroup effect was sufficiently credible to warrant separate recommendations for severe and non-severe COVID-19.

However, acknowledging that during a pandemic, access to health care may vary considerably over time as well as between different countries, the panel decided against defining patient populations concerned by the recommendations on the basis of access to health interventions (i.e. hospitalization and respiratory support). Thus, the panel attributed the effect modification in the RECOVERY trial to illness severity.

The panel also acknowledged the existence of variable definitions for severity and use of respiratory support interventions. The WHO clinical guidance for COVID-19 published on 27 May 2020 (version 3) defined severity of COVID-19 by clinical indicators, but modified the oxygen saturation threshold from 94% to 90%, in order to align with previous WHO guidance *[6]*. See Section 5 for the WHO severity criteria and Infographic for three disease severity groups for which the recommendations apply in practice.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Systemic corticosteroids	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality 28 days	Relative risk 0.79 (CI 95% 0.7 — 0.9) Based on data from 1,703 participants in 7 studies. [1] Follow up: 28 days.	**160** per 1000 Difference:	**126** per 1000 **34 fewer per 1000** (CI 95% 48 fewer — 16 fewer)	**Moderate** Due to serious risk of bias [2]	Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with critical illness due to COVID-19.
Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (CI 95% 0.59 — 0.93) Based on data from 5,481 participants in 2 studies. Follow up: 28 days.	**116** per 1000 Difference:	**86** per 1000 **30 fewer per 1000** (CI 95% 48 fewer — 8 fewer)	**Moderate** Due to serious risk of bias [3]	Systemic corticosteroids probably reduce the need of mechanical ventilation.
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5,403 participants in 30 studies.	**48** per 1000 Difference:	**51** per 1000 **3 more per 1000** (CI 95% 7 fewer — 16 more)	**Low** Due to serious indirectness, Due to serious imprecision [4]	Corticosteroids may not increase the risk of gastrointestinal bleeding.
Super-infections	Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 participants in 32 studies.	**186** per 1000 Difference:	**188** per 1000 **2 more per 1000** (CI 95% 19 fewer — 24 more)	**Low** Due to serious indirectness, Due to serious imprecision [5]	Corticosteroids may not increase the risk of super-infections.
Hyperglycaemia	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 participants in 24 studies.	**286** per 1000 Difference:	**332** per 1000 **46 more per 1000** (CI 95% 23 more — 72 more)	**Moderate** Due to serious indirectness [6]	Corticosteroids probably increase the risk of hyperglycaemia.
Hypernatremia	Relative risk 1.64 (CI 95% 1.32 — 2.03) Based on data from 5,015 participants in 6 studies.	**40** per 1000 Difference:	**66** per 1000 **26 more per 1000**	**Moderate** Due to serious indirectness [7]	Corticosteroids probably increase the risk of hypernatremia.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Systemic corticosteroids	Certainty of the evidence (Quality of evidence)	Summary
			(CI 95% 13 more — 41 more)		
Neuromuscular weakness	Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6,358 participants in 8 studies.	**69** per 1000 Difference:	**75** per 1000 **6 more per 1000** (CI 95% 10 fewer — 27 more)	**Low** Due to serious indirectness, Due to serious imprecision [8]	Corticosteroids may not increase the risk of neuromuscular weakness.
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1,813 participants in 7 studies.	**35** per 1000 Difference:	**28** per 1000 **7 fewer per 1000** (CI 95% 21 fewer — 22 more)	**Low** Due to serious indirectness, Due to serious imprecision [9]	Corticosteroids may not increase the risk of neuropsychiatric effects.
Duration of hospitalization	Measured by: days Lower better Based on data from 6,425 participants in 1 studies. (Randomized controlled)	**13** days	**12** days CI 95%	**Low** Due to serious risk of bias and serious imprecision [10]	Steroids may result in an important reduction in the duration of hospitalizations.

1. Systematic review [1] **Comparator:** Primary study [15]. Baseline risk estimate for mortality updated as of May 2021: now from WHO SOLIDARITY (considered the best source) with 14.6% mortality at 28 days in severe and critically ill patients. This estimate adjusted for 50% receiving corticosteroids as standard of care in SOLIDARITY.
2, 3. **Risk of Bias: serious.** Lack of blinding.
4, 5, 8, 9. **Indirectness: serious. Imprecision: serious.**
6, 7. **Indirectness: serious.**
10. **Risk of Bias: serious.** Lack of blinding. **Imprecision: serious.** Confidence interval includes no benefit.

Interleukin-6 receptor blockers (published 6 July 2021)

The recommendation for interleukin-6 (IL-6) receptor blockers was initially published on 6 July 2021, and updated on 15 September 2022 to reflect that that IL-6 receptor blockers and baricitinib may be given together. No changes have been made.

For patients with severe or critical COVID-19

Strong recommendation for

We recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab) for severe or critical COVID-19 *(strong recommendation for).*

- *Corticosteroids have previously been strongly recommended in patients with severe and critical COVID-19, and we recommend patients meeting these severity criteria should receive both corticosteroids and IL-6 receptor blockers.*
- *The JAK inhibitor baricitinib is now recommended for the treatment of patients with severe and critical COVID-19. IL-6 receptor blockers and baricitinib may be given together.*

Practical info

Route: IL-6 receptor blockers are administered intravenously for the treatment of patients with severe or critical COVID-19; subcutaneous administration is not used in this case. IL-6 receptor blocker therapy should be administered in combination with systemic corticosteroids, which may be administered both orally and intravenously, with due consideration to their high bioavailability but possible malabsorption in the case of intestinal dysfunction with critical illness.

Duration: Tocilizumab and sarilumab are administered as single intravenous doses, typically over 1 hour. A second dose may be administered 12 to 48 hours after the first dose; this was offered variably in major clinical trials at the discretion of treating clinicians if a clinical response was felt to be inadequate. Duration of concurrent systemic corticosteroids is typically up to 10 days, though may vary between 5 and 14 days.

Dose: Tocilizumab is dosed at 8 mg per kilogram of actual body weight, up to a maximum of 800 mg. Sarilumab is most commonly dosed at 400 mg, consistent with what was used in REMAP-CAP. Renal dose adjustment is not currently warranted for either drug.

Monitoring: Routine bloodwork including neutrophil count, platelets, transaminases and total bilirubin should be checked prior to initiation of therapy. All patients should be monitored for signs and symptoms of infection, given the increased risk with immunosuppression in addition to systemic corticosteroids. Patients on longer term IL-6 receptor blocker therapy are at risk of active tuberculosis, invasive fungal infections and opportunistic pathogens. Risks and benefits of therapy should be considered carefully in patients with any active, severe infection other than COVID-19; caution is advised when considering the use of tocilizumab in patients with a history of recurring or chronic infections or with underlying conditions which may predispose them to infections.

Timing: IL-6 receptor blockers should be initiated with systemic corticosteroids; specific timing during hospitalization or the course of illness is not specified. That being said, IL-6 receptor blockers have been administered early in the course of hospitalization in the included trials and clinicians may consider this approach if possible. See section on resource implications, equity and human rights.

Evidence to decision

Benefits and harms

IL-6 receptor blockers reduce mortality and need for mechanical ventilation based on high certainty evidence. Low certainty evidence suggests they may also reduce duration of mechanical ventilation and hospitalization *[3][96][97]*. The RECOVERY trial demonstrated reduced risk of death also in patients already receiving corticosteroids and IL-6 receptor blockers., resulting in an updated recommendation to allow the combination of IL-6 receptor blockers and baricitinib in the 12th version of this WHO guideline.

The evidence regarding the risk of serious adverse events (SAEs) is uncertain. Low certainty evidence suggested that the risk of bacterial infections in the context of immunosuppression treatment with IL-6 receptor blockers may be similar to standard care *[1]*. However the GDG had some concerns that, given the short-term follow-up of most trials and the challenges associated with accurately capturing adverse events such as bacterial or fungal infection, the evidence summary may under-represent the risks of treatment with IL-6 receptor blockers. Furthermore, the trials of IL-6 receptor blockers that inform this recommendation were mostly performed in high-income countries where the risk of certain infectious complications may be less than in some other parts of the world, and so the generalizability of the data on adverse events is unclear. We did not have any data examining differential risk of harm based on whether patients received one or two doses of IL-6 receptor blocker.

Subgroup analyses indicated no effect modification based on IL-6 receptor blocker drug (sarilumab or tocilizumab) or disease severity (critical vs severe) and therefore this recommendation applies to all adult patients with either severe or critical COVID-19 *[95]*. We were unable to examine subgroups based on elevation of inflammatory markers or age due to insufficient trial data (see Research evidence). Subgroup analyses evaluating baseline steroid use found greater benefit of IL-6 receptor blockers in patients receiving steroids compared with those who were not (p=0.026), demonstrating that steroid use does not abolish and might enhance the beneficial effect of IL-6 receptor blockers. Since steroids are already strongly recommended in patients with severe and critical COVID-19, we did not formally evaluate the credibility of this subgroup analysis as there would be no rationale for a subgroup recommendation for patients not receiving corticosteroids.

Certainty of the evidence

Certainty of evidence was rated as high for mortality and need for mechanical ventilation. Certainty in duration of mechanical ventilation was rated as low due to serious risk of bias due to concerns regarding lack of blinding in included trials, and for imprecision as the lower limit of the confidence interval suggested no

effect. Certainty in duration of hospitalization was rated as low due to serious risk of bias from lack of blinding in included trials, and for inconsistency related to differences in point estimates and lack of overlap in confidence intervals.

Certainty in SAEs was rated as very low due to risk of bias related to lack of blinding and ascertainment bias, and very serious imprecision due to very wide confidence intervals which did not rule out important benefit or harm; certainty in risk of bacterial or fungal infections was rated as low due to similar concerns regarding serious risk of bias and serious imprecision.

Certainty in evidence was rated as moderate when comparing the effect on mortality between tocilizumab and sarilumab due to issues with imprecision.

Values and preferences

Applying the agreed values and preferences (see Section 10), the majority of the GDG inferred that almost all well-informed patients would want to receive IL-6 receptor blockers. The benefit of IL-6 receptor blockers on mortality was deemed of critical importance to patients, despite the very low certainty around SAEs. The GDG anticipated little variation in values and preferences between patients for this intervention.

Resources and other considerations

Resource implications, equity and human rights

The GDG noted that, compared with some other candidate treatments for COVID-19, IL-6 receptor blockers are more expensive and the recommendation does not take account of cost-effectiveness. Currently, access to these drugs is challenging in many parts of the world, and without concerted effort is likely to remain so, especially in resource-poor areas. It is therefore possible that this strong recommendation for IL-6 receptor blockers could exacerbate health inequity. On the other hand, given the demonstrated benefits for patients, it should also provide a stimulus to engage all possible mechanisms to improve global access to these treatments. Individual countries may formulate their guidelines considering available resources and prioritize treatment options accordingly.

At a time of drug shortage, it may be necessary to prioritize use of IL-6 receptor blockers through clinical triage *[6]*. Many jurisdictions have suggested mechanisms for triaging use of these treatments. These include prioritizing patients with the highest baseline risk for mortality (e.g. those with critical disease over those with severe disease), in whom the absolute benefit of treatment is therefore greatest. For example, despite consistent relative effects (OR 0.86 for mortality) with IL-6 receptor blockers, the absolute risk reduction for mortality in the critically ill would be 31 fewer deaths per 1000 (95% CI 11 to 47 fewer deaths) and in the severely ill would be 13 fewer deaths per 1000 (95% CI 5 to 19 fewer deaths).

Other suggestions for prioritization, which lack direct evidence, include focusing on patients with an actively deteriorating clinical course and avoiding IL-6 receptor blocker therapy in those with established multi-organ failure (in whom the benefit is likely to be smaller).

Acceptability and feasibility

As IL-6 receptor blockers require intravenous administration, this treatment would be primarily indicated for patients with severe and critical COVID-19 who require hospitalization. IL-6 receptor blockers are relatively easy to administer, and only require one, or at most, two doses.

Justification

When moving from evidence to the strong recommendation to use IL-6 receptor blockers (tocilizumab or sarilumab) in patients with severe or critical COVID-19, the GDG emphasized the high certainty evidence of improved survival and reduction in need for mechanical ventilation. Additional trial data from REMAP-CAP (see Research evidence section) provided more conclusive evidence regarding the equivalence of tocilizumab and sarilumab.

The GDG acknowledged the uncertain data regarding SAEs and bacterial infections, but felt that the evidence of benefit for the two most important patient outcomes warranted a strong recommendation. Costs and access were important considerations and it was recognized that this recommendation could exacerbate health inequities. Hopefully this strong recommendation will provide impetus to address these concerns and ensure access across regions and countries. The GDG did not anticipate important variability in patient values and preferences, and judged that other contextual factors would not alter the recommendation (see Evidence to Decision).

Subgroup analyses
The GDG did not find any evidence of a subgroup effect across patients with different levels of disease severity (severe vs critical), or by IL-6 receptor blocker drug (tocilizumab vs sarilumab).

There were insufficient data to assess subgroup effect by elevation of inflammatory markers or age. Although the GDG considered a subgroup analysis of patients receiving corticosteroids at baseline as compared with those that were not, the panel did not see a need to consider subgroup recommendations for IL-6 receptor blockers in those not receiving corticosteroids as all severe and critical COVID-19 patients should be receiving corticosteroids. Taken together, the GDG felt that the recommendation applies to both tocilizumab and sarilumab and all adult patients with severe or critical COVID-19.

The role of IL-6 receptor blockers and baricitinib

The GDG had previously made a strong recommendation for use of IL-6 receptor blockers (tocilizumab and sarilumab) or baricitinib as alternative agents administered in addition to corticosteroids for patients with severe or critical COVID-19. The GDG had elected to refrain from recommending combining these three immunosuppressive drugs until clear evidence of incremental benefit emerged. The RECOVERY trial has now provided this evidence that combining corticosteroids, IL-6 receptor blockers and baricitinib provides incremental survival benefit *[98]*. Specifically, in RECOVERY 2659 patients received baricitinib along with corticosteroids and IL-6 receptor blockers. The effect of baricitinib in this subgroup was consistent with the beneficial effect of baricitinib in patients who were not treated with IL-6 receptor blockers *[98]*. Although these three immunosuppressIve drugs are recommended and may be administered jointly, the panel anticipated that there would be situations where clinicians may opt for less aggressive immunosuppressive therapy and/or to combine medications in a stepwise fashion in patients who are deteriorating. However, since the drugs have not undergone direct comparisons, if this situation arises, the GDG felt that clinicians should choose between baricitinib and IL-6 receptor blockers on the basis of experience and comfort using the drugs; local institutional policies; route of administration (baricitinib is oral; IL-6 receptor blockers are intravenous); and cost.

Applicability
None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. However, the GDG had no reason to think that children with COVID-19 would respond any differently to treatment with IL-6 receptor blockers. This is especially true given tocilizumab is used in children safely for other indications including polyarticular juvenile rheumatoid arthritis, systemic onset of juvenile chronic arthritis, and chimeric antigen receptor T-cell induced cytokine release syndrome. Sarilumab is not approved in children, so if an IL-6 receptor blocker is used in this population, tocilizumab is preferred. The GDG also recognized that in many settings children are commonly admitted to hospital with acute respiratory illnesses caused by other pathogens; as a result, it may be challenging to determine who is ill with severe COVID-19, even with a positive test, and therefore likely to benefit from IL-6 receptor blockade. There were similar considerations in regard to pregnant individuals, with no data directly examining this population, but no rationale to suggest they would respond differently than other adults. The drug may, however, cross the placental membrane, although it is uncertain what effect transient immunosuppression in the fetus may have and this should be weighed against the potential benefit for the pregnant individual.

Clinical question/ PICO

Population: Patients with severe or critical COVID-19
Intervention: IL-6 receptor blockers
Comparator: Standard care

Summary

Evidence summary

The LNMA *[8]* on IL-6 receptor blockers was informed by 30 RCTs with 10 618 participants and provided relative estimates of effect for all patient-important outcomes except mortality, which came from the prospective meta-analysis (PMA) *[97]*. Of the trials included in the LNMA, all were registered and examined patients with severe or critical illness related to COVID-19 (trial characteristics table available upon request). Of the trials, 37% were published in peer-reviewed journals, 3% were available as preprints and 60% were completed but unpublished.

The evidence summary for mortality was based on 27 RCTs and 10 930 participants from the PMA *[97]*. We used the PMA for mortality as it included some additional unpublished data that reported on this outcome. The GDG recognized that standard care is likely variable between centres and regions, and has evolved over time. However, given all of the data come from RCTs, use of these co-interventions that comprise standard care would be expected to be balanced between study patients randomized to either the intervention or standard care arms.

The GRADE Summary of Findings table shows the relative and absolute effects of IL-6 receptor blockers compared with standard care for the outcomes of interest in patients with severe and critical COVID-19, with certainty ratings. See Section 7 for sources of baseline

risk estimates informing absolute estimates of effect.

Subgroup analysis
All included RCTs evaluated IL-6 receptor blockers exclusively in severely or critically ill adults with COVID-19 requiring hospitalization. The GDG requested subgroup analyses based on age (< 70 years versus older), disease severity (severe versus critical), levels of inflammatory markers and baseline corticosteroid use for the following outcomes: mortality, need for and duration of mechanical ventilation, duration of hospitalization, and risks of SAEs and bacterial infections.

Based on subgroup analyses, the GDG determined that there was no subgroup effect across any pre-specified outcomes of interest based on disease severity. The GDG considered the results of a subgroup analysis of all included RCTs based on systemic corticosteroid use for the outcome of mortality. The analysis suggested that the relative effects of IL-6 receptor blockers varied as a function of the use of systemic corticosteroids at baseline. Crucially, steroids did not abolish and may even enhance the beneficial effect of IL-6 receptor blockers on mortality. For reasons described below, the GDG did not formally evaluate the credibility of this subgroup analysis.

When comparing tocilizumab and sarilumab, based on the PMA, there was no evidence of a subgroup effect *[97]*. However, there were more data, and therefore greater precision, for tocilizumab+steroids versus steroids alone (OR 0.77, 95% CI 0.68–0.87) as compared with sarilumab+steroids versus steroids alone (OR 0.92, 95% CI 0.61–1.38). In addition to these subgroup data, the GDG reviewed head-to-head data from REMAP-CAP investigators which demonstrated no difference between tocilizumab as compared with sarilumab in a population of patients all receiving corticosteroids (36.5% mortality with tocilizumab, 33.9% mortality with sarilumab). The NMA estimate of tocilizumab+steroids versus sarilumab+steroids, incorporating both direct and indirect data, provided moderate certainty data of no difference between the drugs (OR 1.07, 95% CI 0.86–1.34) *[1][3]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** IL-6 receptor blockers	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality (severe and critically ill patients)	Odds ratio 0.86 (CI 95% 0.79 — 0.95) Based on data from 10,930 participants in 27 studies. [1] (Randomized controlled)	**130** per 1000 Difference:	**114** per 1000 **16 fewer per 1000** (CI 95% 24 fewer — 6 fewer)	**High**	IL-6 receptor blockers reduce mortality.
Mechanical ventilation	Odds ratio 0.72 (CI 95% 0.57 — 0.9) Based on data from 5,686 participants in 9 studies. [2] (Randomized controlled)	**86** per 1000 Difference:	**63** per 1000 **23 fewer per 1000** (CI 95% 35 fewer — 8 fewer)	**High**	IL-6 receptor blockers reduce need for mechanical ventilation.
Adverse events leading to drug discontinuation	Odds ratio 0.5 (CI 95% 0.03 — 9.08) Based on data from 815 participants in 2 studies. [3] (Randomized controlled)	**9** per 1000 Difference:	**5** per 1000 **4 fewer per 1000** (CI 95% 0 more — 67 more)	**Very low** Due to serious risk of bias and very serious imprecision [4]	The effect of IL-6 receptor blockers on adverse events leading to discontinuation is uncertain.
Bacterial infections	Odds ratio 0.95 (CI 95% 0.72 — 1.29) Based on data from 3,548 participants in 18 studies. (Randomized controlled)	**101** per 1000 Difference:	**96** per 1000 **5 fewer per 1000** (CI 95% 26 fewer — 26 more)	**Low** Due to serious risk of bias and serious imprecision [5]	IL-6 receptor blockers may not increase secondary bacterial infections.
Duration of mechanical	Lower better Based on data from 1,189	**14.7** (Mean)	**13.5** (Mean)	**Low** Due to serious risk of bias and serious	IL-6 receptor blockers may reduce duration of mechanical ventilation.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention IL-6 receptor blockers	Certainty of the evidence (Quality of evidence)	Summary
ventilation	participants in 10 studies. (Randomized controlled)	Difference:	**MD 1.2 lower** (CI 95% 2.3 lower — 0.1 lower)	imprecision [6]	
Duration of hospitalization	Lower better Based on data from 6,665 participants in 9 studies. (Randomized controlled)	**12.8** (Mean) Difference:	**8.3** (Mean) **MD 4.5 lower** (CI 95% 6.7 lower — 2.3 lower)	**Low** Due to serious risk of bias and serious inconsistency [7]	IL-6 receptor blockers may reduce duration of hospitalization.

1. **Comparator:** Primary study [15]. Baseline risk for mortality and mechanical ventilation were derived from the WHO SOLIDARITY trial for patients with severe and critical COVID-19, adjusted for corticosteroids as part of standard of care (16% baseline risk x RR 0.79 for corticosteroids = 13%). The control arm of the WHO SOLIDARITY trial, performed across a wide variety of countries and geographical regions, was identified by the GDG panel as generally representing the most relevant source of evidence for baseline risk estimates for mortality and mechanical ventilation for severely and critically ill patients with COVID-19.
2. Systematic review [3] **Comparator:** Primary study Baseline risk for mortality and mechanical ventilation were derived from the WHO SOLIDARITY trial for patients with severe and critical COVID-19, adjusted for corticosteroids as part of standard of care (16% baseline risk x RR 0.79 for corticosteroids = 13%). The control arm of the WHO SOLIDARITY trial, performed across a wide variety of countries and geographical regions, was identified by the GDG panel as generally representing the most relevant source of evidence for baseline risk estimates for mortality and mechanical ventilation for severely and critically ill patients with COVID-19.
3. **Comparator:** We used the median event rate for all patients randomized to usual care across included studies. **Supporting references:** [3],
4. **Risk of Bias: serious.** We downgraded for some concerns regarding risk of bias due to lack of blinding and ascertainment bias. **Imprecision: very serious.** We downgraded due to very wide confidence intervals crossing the null.
5. **Risk of Bias: serious.** We downgraded for some concerns regarding risk of bias due to lack of blinding and ascertainment bias. **Imprecision: serious.** Downgraded due to wide confidence intervals crossing the null.
6. **Risk of Bias: serious.** We downgraded for some concerns regarding risk of bias due to lack of blinding. **Imprecision: serious.** We downgraded as the lower limit of the confidence interval was close to the null.
7. **Risk of Bias: serious.** We downgraded for some concerns regarding risk of bias due to lack of blinding. **Inconsistency: serious.** Downgraded due to differences in point estimates and lack of overlap in confidence intervals.

Clinical question/ PICO

Population: Patients with COVID-19 infection (all disease severities)
Intervention: IL-6 receptor blockers
Comparator: Standard care

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention IL-6 receptor blockers	Certainty of the evidence (Quality of evidence)	Summary
Mortality [1] (severely ill patients)	Odds ratio 0.86 (CI 95% 0.79 — 0.95) Based on data from 10,930 participants in 27 studies. (Randomized controlled)	**100** per 1000 Difference:	**87** per 1000 **13 fewer per 1000** (CI 95% 19 fewer — 5 fewer)	**High**	IL-6 inhibitors reduce mortality.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** IL-6 receptor blockers	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality [2] (critically ill patients)	Odds ratio 0.86 (CI 95% 0.79 — 0.95) Based on data from 10,930 participants in 27 studies. (Randomized controlled)	**300** per 1000 Difference:	**269** per 1000 **31 fewer per 1000** (CI 95% 47 fewer — 11 fewer)	**High**	IL-6 inhibitors reduce mortality.
Mechanical ventilation	Odds ratio 0.72 (CI 95% 0.57 — 0.9) Based on data from 5,686 participants in 9 studies. (Randomized controlled)	**116** per 1000 Difference:	**86** per 1000 **30 fewer per 1000** (CI 95% 46 fewer — 10 fewer)	**High**	IL-6 inhibitors reduce need for mechanical ventilation.
Adverse events leading to drug discontinuation	Odds ratio 0.5 (CI 95% 0.03 — 9.08) Based on data from 815 participants in 2 studies. (Randomized controlled)	**9** per 1000 Difference:	**5** per 1000 **4 fewer per 1000** (CI 95% 9 fewer — 67 more)	**Very low** Due to serious risk of bias and very serious imprecision [3]	The effect of IL-6 inhibitors on adverse events leading to discontinuation is uncertain.
Bacterial infections	Odds ratio 0.95 (CI 95% 0.72 — 1.29) Based on data from 3,548 participants in 18 studies. (Randomized controlled)	**101** per 1000 Difference:	**96** per 1000 **5 fewer per 1000** (CI 95% 26 fewer — 26 more)	**Low** Due to serious risk of bias and serious imprecision [4]	IL-6 inhibitors may not increase secondary bacterial infections.
Duration of mechanical ventilation	Lower better Based on data from 1,189 participants in 10 studies. (Randomized controlled)	**14.7** (Mean) Difference:	**13.5** (Mean) **MD 1.2 lower** (CI 95% 2.3 lower — 0.1 lower)	**Low** Due to serious risk of bias and serious imprecision [5]	IL-6 inhibitors may reduce duration of mechanical ventilation.
Duration of hospitalization	Lower better Based on data from 6,665 participants in 9 studies. (Randomized controlled)	**12.8** (Mean) Difference:	**8.3** (Mean) **MD 4.5 lower** (CI 95% 6.7 lower — 2.3 lower)	**Low** Due to serious risk of bias and serious inconsistency [6]	IL-6 inhibitors may reduce duration of hospitalization.

1, 2. Source: pairwise meta-analysis

3. **Risk of Bias: serious.** We downgraded for some concerns regarding risk of bias due to lack of blinding and ascertainment bias. **Imprecision: very serious.** We downgraded due to very wide confidence intervals crossing the null.

4. **Risk of Bias: serious.** We downgraded for some concerns regarding risk of bias due to lack of blinding and ascertainment bias. **Imprecision: serious.** Downgraded due to wide confidence intervals crossing the null.

5. **Risk of Bias: serious.** We downgraded for some concerns regarding risk of bias due to lack of blinding. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** We downgraded as the lower limit of the confidence interval was close to the null. **Publication bias: no serious.**

6. **Risk of Bias: serious.** We downgraded for some concerns regarding risk of bias due to lack of blinding. **Inconsistency: serious.** Downgraded due to differences in point estimates and lack of overlap in confidence intervals.

Clinical question/ PICO

Population: Patients with severe and critical COVID-19
Intervention: Baricitinib
Comparator: Interleukin-6 receptor blockers

Outcome Timeframe	**Study results and measurements**	**Comparator** IL-6 receptor blockers	**Intervention** Baricitinib	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality	Odds ratio 0.77 (CI 95% 0.53 — 1.1) Based on data from 2,659 participants in 3 studies. (Randomized controlled)	**118** per 1000 Difference:	**96** per 1000 **22 fewer per 1000** (CI 95% 52 fewer — 9 more)	**Low** Due to serious imprecision and ongoing recruitment in a large RCT [1]	Baricitinib may reduce mortality.
Mechanical ventilation	Odds ratio 1.01 (CI 95% 0.61 — 1.6) Based on data from 2,434 participants in 2 studies. (Randomized controlled)	**94** per 1000 Difference:	**96** per 1000 **2 more per 1000** (CI 95% 38 fewer — 44 more)	**Low** Due to very serious imprecision [2]	There may be little or no difference on mechanical ventilation.
Adverse effects leading to drug discontinuation	Based on data from 2,309 participants in 4 studies. (Randomized controlled)	**0** per 1000 Difference:	**1** per 1000 **1 more per 1000** (CI 95% 11 fewer — 15 more)	**Moderate** Due to serious imprecision [3]	There is probably little to no difference in adverse effects leading to discontinuation.
Hospital length of stay	Lower better Based on data from 2,652 participants in 3 studies. (Randomized controlled)	**8.1** days (Median) Difference:	**11.2** days (Mean) **MD 3.1 more** (CI 95% 3.8 fewer — 9.9 more)	**Very low** Due to serious risk of bias, serious inconsistency, and very serious imprecision [4]	The impact on hospital length of stay is very uncertain.
Duration of mechanical ventilation	Lower better Based on data from 328 participants in 2 studies. (Randomized controlled)	**13.8** days (Median) Difference:	**11.6** days (Mean) **MD 2.2 fewer** (CI 95% 5.3 fewer — 0.7 fewer)	**Low** Due to serious risk of bias and imprecision [5]	Baricitinib may reduce duration of mechanical ventilation.
Time to clinical stability	Lower better Based on data from 2,558 participants in 2 studies. (Randomized controlled)	**8.4** days (Median) Difference:	**8.9** days (Mean) **MD 0.5 more** (CI 95% 2.3 fewer — 3.2 more)	**Low** Due to serious risk of bias and imprecision [6]	There may not be an important impact on time to clinical stability.

1. **Imprecision: serious.** The credible interval includes no important difference.
2. **Risk of Bias: no serious.** Most of the data on interleukin-6 receptor blockers comes from trials that were unblinded. **Imprecision: very serious.** The credible interval includes important benefit and important harm.
3. **Imprecision: serious.** The credible interval includes small but important harm.

4. **Risk of Bias: serious.** Most of the data on interleukin-6 receptor blockers comes from trials that were unblinded. **Inconsistency: serious.** The trials that studied interleukin-6 receptor blockers had discrepant results: some increased length of stay, others reduced length of stay. **Imprecision: very serious.** The credible interval includes important benefit and important harm.
5. **Risk of Bias: serious.** Most of the data on interleukin-6 receptor blockers comes from trials that were unblinded. **Imprecision: serious.** The credible interval includes no important difference.
6. **Risk of Bias: serious.** Most of the data on interleukin-6 receptor blockers comes from trials that were unblinded. **Imprecision: serious.** Credible interval includes important harm and important benefit (using a minimal important difference threshold of 1 day).

Mechanism of action of IL-6 receptor blockers

IL-6 is a pleiotropic cytokine which activates and regulates the immune response to infections. Elevated IL-6 concentrations are associated with severe outcomes in COVID-19, including respiratory failure and death, although the role of IL-6 in disease pathogenesis is unclear.

Tocilizumab and sarilumab are monoclonal antibodies approved for use in rheumatoid arthritis. They antagonize the membrane bound and soluble forms of the IL-6 receptor (IL-6R/sIL-6R). Tocilizumab is approved for intravenous use in rheumatoid arthritis and sarilumab for subcutaneous use, although in COVID-19 both have been studied intravenously. At the studied doses in COVID-19, both medicines are expected to achieve very high levels of receptor occupancy based upon studies in rheumatoid arthritis *[21]*. IL-6 receptor blockers are being repurposed in terms of indication but not in terms of the primary pharmacological mechanism of action. Efficacy in COVID-19 depends upon the importance of IL-6 signalling in the pathophysiology of the disease, rather than upon whether the doses used achieve target concentrations.

Statins (published August 2025)

Statins are a class of medicines which competitively inhibit hydroxymethylglutaryl-CoA (HMG-CoA) reductase, causing reductions in cholesterol synthesis and other downstream changes in lipid regulation. They have other actions on anti-inflammatory pathways and on stabilisation of atherosclerotic plaques. They are frequently used in the primary and secondary treatment of cardiovascular disease.

Strong recommendation against

New

We recommend not to use statins for severe or critical COVID-19 *(strong recommendation against).*

- *This recommendation does not apply to individuals already receiving a statin for an alternate indication.*

Practical info

The GDG made a strong recommendation against using statins for treatment of patients with severe or critical COVID-19 and therefore practical considerations are not relevant for this drug.

Evidence to decision

Benefits and harms	In patients with severe or critical COVID-19, statins may reduce mortality (low certainty). Treatment may have little or no effect on mechanical ventilation (low certainty), and probably result in little or no increase in adverse effects leading to drug discontinuation (moderate certainty). Effects on hospital length of stay and time to clinical stability are very uncertain (very low certainty).
Certainty of the evidence	The evidence summary on statins in patients with severe or critical COVID-19 was informed by five trials with 3,704 participants included in the LNMA study *[1]*.

Certainty of evidence was rated as low for mortality and mechanical ventilation (both rated down for very serious imprecision), as moderate for adverse effects leading to drug discontinuation (rated down for serious imprecision), and as very low for hospital length of stay (due to very serious imprecision and serious inconsistency) and time to clinical stability (no data available).

Values and preferences Applying the agreed upon values and preferences (see Section 10), the GDG inferred that all or almost all well-informed patients with severe or critical COVID-19 would be disinclined to receive statins, in light of high uncertainty regarding several patient-important outcomes and the availability of other candidate therapies with more certain benefits. The GDG anticipated little variation in values and preferences between patients for this intervention.

Resources and other considerations Statins are orally administered, widely available internationally, and are affordable relative to the majority of other candidate therapies.

Justification

When moving from evidence to a strong recommendation against the use of statins in patients with severe or critical COVID-19, the GDG emphasized the low or very low certainty available to inform key patient-important outcomes (mortality, mechanical ventilation, hospital length of stay and time to clinical stability). The GDG also emphasized strong recommendations in favour of use for systemic corticosteroids, IL-6 receptor blockers and baricitinib for severe or critical illness, and a conditional recommendation in favour of remdesivir for patients with severe illness. Despite the 1.4% absolute reduction in risk of all-cause death, the panel were concerned that the 95%CI included the possibility of significant harm. It was noted that a larger and more certain benefit could be derived from therapies applicable to the same patient groups (i.e. systemic corticosteroids, IL-6 receptor blockers and baricitinib which importantly have moderate to high certainty in reduced mortality). In light of the potential for harm, the panel surmised that a strong rather than a conditional recommendation against, was justified.

Clinical question/ PICO

Population: Patients with severe or critical COVID-19
Intervention: Statins
Comparator: Standard care

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Statins	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality	Odds ratio 0.88 (CI 95% 0.67 — 1.18) Based on data from 3,638 participants in 4 studies. (Randomized controlled)	**130** per 1000 Difference:	**116** per 1000 **14 fewer per 1000** (CI 95% 39 fewer — 20 more)	**Low** Due to very serious imprecision [1]	Statins may reduce mortality.
Mechanical ventilation	Odds ratio 0.93 (CI 95% 0.68 — 1.24) Based on data from 2,937 participants in 3 studies. (Randomized controlled)	**116** per 1000 Difference:	**109** per 1000 **7 fewer per 1000** (CI 95% 34 fewer — 24 more)	**Low** Due to very serious imprecision [2]	Statins may have little or no effect on mechanical ventilation.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Statins	Certainty of the evidence (Quality of evidence)	Summary
Adverse effects leading to drug discontinuation	Based on data from 2,908 participants in 2 studies. (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 more per 1000** (CI 95% 0 more — 35 more)	**Moderate** Due to serious imprecision [3]	Statins probably result in little or no increase in adverse effects leading to discontinuation.
Hospital length of stay	Lower better Based on data from 3,008 participants in 4 studies. (Randomized controlled)	**12.8** days (Median) Difference:	**11.2** days (Mean) **MD 1.6 fewer** (CI 95% 4.7 fewer — 1.4 fewer)	**Very low** Due to very serious imprecision and serious inconsistency [4]	We are very unsure if statins have an effect on duration of hospitalization.
Time to clinical stability	Lower better Based on data from 0 participants in studies. (Randomized controlled)	**9.9** days (Median)	CI 95%	**Very low** No data [5]	The effect of statins on time to clinical stability is unknown.

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Credible interval includes important benefit and harm.. **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Credible interval includes important benefit and important harm. **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The credible interval includes an important increase in adverse effects. **Publication bias: no serious.**
4. **Inconsistency: serious.** Point estimates vary widely. **Indirectness: no serious. Imprecision: very serious.** Credible interval includes important benefit and important harm. **Publication bias: no serious.**
5. **Imprecision: extremely serious.**

SGLT-2 inhibitors (published August 2025)

Sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors) are a class of medicines used to lower high blood glucose levels in people with type 2 diabetes.

Strong recommendation against

New

We recommend not to use SGLT-2 inhibitors for severe or critical COVID-19 (strong recommendation against).

- *This recommendation does not apply to individuals already receiving an SGLT-2 inhibitor for an alternate indication.*

Practical info

The GDG made a strong recommendation against using SGLT-2 inhibitors for treatment of patients with severe or critical COVID-19 and therefore practical considerations are not relevant for this drug.

Evidence to decision

Benefits and harms	In patients with severe or critical COVID-19, SGLT-2 inhibitors may reduce all-cause mortality (low certainty). Therapy has little or no effect on hospital length of stay, and does not increase serious adverse effects (high certainty).
Certainty of the evidence	The evidence summary on SGLT-2 in patients with severe or critical COVID-19 was informed by three trials with 6,096 participants *[208]*. Certainty of evidence was rated as high for hospital length of stay and serious adverse effects leading to drug discontinuation; and as low for mortality at 28 days, rated down for very serious imprecision.
Values and preferences	Applying the agreed upon values and preferences (see Section 10), the GDG inferred that all or almost all well-informed patients with severe or critical COVID-19 would not want to receive SGLT-2 inhibitors. The GDG anticipated little variation in values and preferences between patients for this intervention.
Resources and other considerations	SGLT-2 inhibitors are orally administered, widely available internationally, and are affordable relative to the majority of other candidate therapies.

Justification

When moving from evidence to a strong recommendation against the use of SGLT-2 inhibitors in patients with severe or critical COVID-19, the GDG emphasized the low certainty evidence available supporting a reduction in mortality, and were concerned that the 95%CI included the possibility of significant harm (increased mortality). It was noted that a larger and more certain benefit could be derived from therapies applicable to the same patient groups (i.e. systemic corticosteroids, IL-6 receptor blockers and baricitinib which importantly have moderate to high certainty in reduced mortality).

In addition, whereas included trials did not show a significantly increased risk of serious adverse events, the residual risk of known harms associated with SGLT-2 inhibitors—such as diabetic ketoacidosis, volume depletion, and acute kidney injury—may be heightened in the context of acute illness and hemodynamic instability typical of severe or critical COVID-19. In light of the potential for harm, the panel surmised that a strong rather than a conditional recommendation against, was justified.

Clinical question/ PICO

Population: Patients with severe or critical COVID-19
Intervention: SGLT-2 inhibitors
Comparator: Usual care

Summary

Data on serious adverse events have not been meta-analyzed due to heterogeneity of reporting in the 3 trials. They are summarised per-study below:

	Absolute effect estimates (per 1000) for serious adverse events experienced by 28 days	
study	**Standard care**	**SGLT2 inhibitor**
DARE-19 *[187]*	130 (81/625)	104 (65/625)
RECOVERY *[188]*	0 (0/2158)	0 (0/2113)
ACTIV4A	42 (12/288)	21 (6/287)

Outcome Timeframe	Study results and measurements	Comparator Usual care	Intervention SGLT-2 inhibitors	Certainty of the evidence (Quality of evidence)	Summary
Mortality 28 days	Relative risk 0.93 (CI 95% 0.79 — 1.08) Based on data from 6,096 participants in 3 studies. (Randomized controlled)	**130** per 1000 Difference:	**121** per 1000 **9 fewer per 1000** (CI 95% 27 fewer — 10 more)	**Low** Due to very serious imprecision [1]	SGLT-2 inhibitors may reduce all-cause mortality
Hospital length of stay	Lower better Based on data from 6,096 participants in 3 studies. (Randomized controlled)	Difference:	**MD 0.13 fewer** (CI 95% 0.58 fewer — 0.32 more)	**High**	SGLT2 inhibitors have little or no effect on hospital length of stay.

1. **Imprecision: very serious.** Wide confidence intervals.

Janus kinase inhibitors (updated 16 September 2022)

The recommendation on JAK inhibitors was initially published on 14 January 2022, and updated on 15 September 2022 to reflect that baricitinib, IL-6 receptor blockers and corticosteroids may be given together. No subsequent changes have been made.

For patients with severe or critical COVID-19

Strong recommendation for

We recommend treatment with baricitinib for severe or critical COVID-19 *(strong recommendation for).*

- *Corticosteroids and IL-6 receptor blockers (tocilizumab and sarilumab) are also recommended,* ***and may be administered in combination*** *with baricitinib to patients with severe or critical COVID-19.*
- *The panel acknowledged that given that the clinical trials were not representative of the global population and that the risk-benefit may be less advantageous, particularly in areas where certain infectious diseases such as HIV infections, tuberculosis and certain fungal infections are endemic or in patients with an increased risk of opportunistic infections.*
- *The panel anticipated that there would be situations where clinicians may opt for less aggressive immunosuppressive therapy and/or to combine medications in a stepwise fashion in patients who are deteriorating.*
- *None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children remains uncertain.*

Practical info

Additional considerations are available in a summary of practical issues. Useful information can also be found in the United States Food and Drug Administration (FDA) fact sheet for health care providers, based on the emergency use authorization (EUA) of baricitinib *[99]*. Here follows a brief summary of key points:

Route, dosage and duration:

- The recommended dose is 4 mg daily orally in adults with eGFR ≥ 60 mL/min/1.73 m^2.
- A duration of 14 days´ treatment or until hospital discharge, whichever is first. The optimal duration of treatment is unknown, and the proposed duration reflects what was used in the trials providing evidence on treatment effects of baricitinib.

Dose regimen adjustment:

- Patients with leukopenia, renal impairment or hepatic impairment (note: these parameters should be monitored during treatment).
- Patients taking strong organic anion transporter 3 (OAT3) inhibitors (e.g. probenecid), there are drug interactions which warrant dose reductions.

Timing: Baricitinib (like IL-6 receptor blockers) should be initiated at the same time as systemic corticosteroids; specific timing during hospitalization or the course of illness is not specified.

Evidence to decision

Benefits and harms

In patients with severe or critical illness, baricitinib reduces mortality and probably reduces duration of mechanical ventilation and hospital length of stay. It probably results in little or no increase in SAEs.

Subgroup analyses were undertaken for JAK inhibitors as a class (rather than on individual drugs) and revealed no evidence of a subgroup effect on relative risk in younger (< 70 years) versus older patients; those with critical versus severe COVID-19; those receiving and not receiving corticosteroids at baseline; and those receiving and not receiving remdesivir or IL-6 blockers at baseline.

Certainty of the evidence

Certainty of evidence was rated as: high for decreased mortality (although the panel acknowledged that the relatively short follow-up period close to 28 days is possibly insufficient to capture all relevant events); moderate for reduction in hospital length of stay, mechanical ventilation and SAEs, all rated down for serious imprecision; and low for time to clinical stability, rated down for very serious imprecision.

The GDG noted in particular that the risk of serious infections (bacterial and fungal) may vary considerably in different parts of the world according to the background prevalence of infections (such as tuberculosis). This may not be so important given the short course of baricitinib used for treatment of COVID-19, but evidence is limited given the limited geographic spread of the included trials and short follow-up periods.

Values and preferences

Applying the agreed upon values and preferences (see Section 10), the GDG inferred that almost all well-informed patients with severe or critical COVID-19 would want to receive baricitinib due to the likely reduction in mortality, and moderate certainty evidence of little or no increase in SAEs. The benefit of baricitinib on mortality was deemed of critical importance to patients and the GDG was reassured by the moderate certainty evidence of little or no increase in SAEs. The GDG anticipated little variation in values and preferences between patients for this intervention.

Resources and other considerations

Resource implications, equity and human rights

Compared with some other candidate treatments for COVID-19, baricitinib is expensive. The recommendation does not take account of cost-effectiveness. Access to these drugs is challenging in many parts of the world and, without concerted effort, is likely to remain so, especially in resource-poor areas. It is therefore possible that this strong recommendation could exacerbate health inequity. The GDG was also sensitive to the fact that allowing the combined use of the JAK inhibitor baricitinib and IL-6 receptor blockers would likely further reduce the availability of these medications. The GDG strongly reinforces the need to improve drug availability, particularly in resource-constrained areas.

On the other hand, given the demonstrated benefits for patients, it should also provide a stimulus to engage all possible mechanisms to improve global access to these treatments. Individual countries may formulate their guidelines considering available resources and prioritize treatment options accordingly. On 17 December 2021, WHO published the 7th Invitation to Manufacturers of therapeutics against COVID-19 to submit an Expression of Interest (EOI) for Product Evaluation to the WHO Prequalification Unit, which includes baricitinib.

At a time of drug shortage, it may be necessary to prioritize use of baricitinib through clinical triage *[6]*, such as prioritizing patients with the highest baseline risk for mortality (e.g. those with critical disease over those with severe disease), in whom the absolute benefit of treatment is therefore greatest. Other suggestions for prioritization, which lack direct evidence, include focusing on patients with an actively deteriorating clinical course, and avoiding baricitinib in those with established multi-organ failure (in whom the benefit is likely to be smaller).

Acceptability and feasibility

As baricitinib is administered orally once daily, hospitalized patients should find it easy to accept this treatment. In patients who cannot swallow tablets, baricitinib can be crushed, dispersed in water, and given via a nasogastric tube (see Practical info).

Justification

In the 12th version of the guideline, the GDG confirmed the existing strong recommendation to use baricitinib in patients with severe or critical COVID-19. The update was based on additional data from 8156 patients enrolled in the RECOVERY trial, which confirmed the survival (now high certainty evidence) and other benefits, with little or no SAEs, of a drug that may be administered easily *[98]*. The GDG acknowledged that some SAEs, such as fungal infections, may not have been accurately captured during the relatively short follow-up period in the included trials. Because of different mechanisms of action, the GDG considered baricitinib separately from other JAK inhibitors (as outlined below).

Costs and access remain important considerations and the GDG recognizes that this recommendation could exacerbate health inequities. This strong recommendation further strengthens the impetus to address these concerns and maximize access across regions and countries. The GDG did not anticipate important variability in patient values and preferences, and judged that other contextual factors would not alter the recommendation (see Evidence to Decision).

The role of IL-6 receptor blockers and baricitinib

The GDG had previously made a strong recommendation for the use of IL-6 receptor blockers (tocilizumab and sarilumab) or baricitinib as alternative agents administered in addition to corticosteroids for patients with severe or critical COVID-19. The GDG had elected to refrain from recommending combining these three immunosuppressive drugs until clear evidence of incremental benefit emerged. The RECOVERY trial has now provided evidence that combining corticosteroids, IL-6 receptor blockers and baricitinib provides incremental survival benefit *[98]*. Specifically, in RECOVERY, 2659 patients received baricitinib along with corticosteroids and IL-6 receptor blockers. The effect of baricitinib in this subgroup was consistent with the beneficial effect of baricitinib in patients who were not treated with IL-6 receptor blockers *[98]*. Although these three immunosuppressIve drugs are recommended and may be administered jointly, the panel anticipated that there would be situations where clinicians may opt for less aggressive immunosuppressive therapy and/or to combine medications in a stepwise fashion in patients who are deteriorating. However, since the drugs have not undergone direct comparisons, if this situation arises, the GDG felt that clinicians should choose between baricitinib and IL-6 receptor blockers on the basis of experience and comfort using the drugs; local institutional policies; route of administration (baricitinib is oral; IL-6 receptor blockers are intravenous); and cost.

Applicability

None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children remains uncertain. Uncertainty also remains with regard to administration of baricitinib to pregnant or lactating individuals. The decision regarding use of this therapeutic should be made between the pregnant individual and their health care provider while discussing whether the potential benefit justifies the potential risk to the pregnant individual and fetus (see Research evidence and Practical info).

Clinical question/ PICO

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

Summary

Evidence summary

The LNMA for baricitinib was informed by four RCTs which enrolled 10 815 patients across disease severities *[100][101][102][98]*. All RCTs were registered, and three were published in peer-reviewed journals *[101][102][98]*; one study was a pre-print *[100]*. All RCTs enrolled patients in in-patient settings. None of the included studies enrolled children or pregnant individuals. The Table shows characteristics of the RCTs.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of baricitinib compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[1]*.

Baseline risk estimates

For severe and critical illness, for the critical outcome of mortality, the applied baseline risk estimate was 13% (130 in 1000). As for other related recommendations in this guideline, the estimate is derived from the SOLIDARITY trial for severe and critical patients adjusted for treatment effects of corticosteroids. For other outcomes, we used the median of the control arm of the RCTs that contributed to the evidence (see Section 6).

Subgroup analysis

Four pre-specified subgroup analyses were undertaken for JAK inhibitors as a class rather than for individual drugs:
1. Age: younger adults (< 70 years) versus older adults (≥ 70 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Concomitant use of corticosteroids at baseline.
4. Concomitant use of remdesivir at baseline.

No evidence of subgroup effects was identified on the relative risk of critical outcomes across all pre-specified effect modifiers.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Baricitinib	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality	Odds ratio 0.83 (CI 95% 0.74 — 0.93) Based on data from 10,815 participants in 4 studies. (Randomized controlled)	**130** per 1000 Difference:	**110** per 1000 **20 fewer per 1000** (CI 95% 30 fewer — 8 fewer)	**High**	Baricitinib reduces mortality.
Mechanical ventilation	Odds ratio 0.89 (CI 95% 0.8 — 0.99) Based on data from 8,412 participants in 3 studies. (Randomized controlled)	**116** per 1000 Difference:	**105** per 1000 **11 fewer per 1000** (CI 95% 21 fewer — 1 fewer)	**Moderate** Due to serious imprecision [1]	Baricitinib probably reduces mechanical ventilation.
Adverse effects leading to drug discontinuation	Based on data from 1,611 participants in 2 studies. (Randomized controlled)	**0** per 1000 Difference:	**5** per 1000 **5 more per 1000** (CI 95% 0 fewer — 28 more)	**Moderate** Due to serious imprecision [2]	Baricitinib probably results in little or no increase in adverse effects leading to discontinuation
Hospital length of stay	Lower better Based on data from 2,652 participants in 3 studies. (Randomized controlled)	**12.8** days (Median) Difference:	**11.4** days (Mean) **MD 1.4 fewer** (CI 95% 2.4 fewer — 0.4 fewer)	**Moderate** Due to serious imprecision [3]	Baricitinib probably reduces duration of hospitalization.
Duration of mechanical ventilation	Lower better Based on data from 328 participants in 2 studies. (Randomized controlled)	**14.7** days (Median) Difference:	**11.5** days (Mean) **MD 3.2 fewer** (CI 95% 5.9 fewer — 0.5 fewer)	**Moderate** Due to serious imprecision [4]	Baricitinib probably reduces duration of mechanical ventilation.
Time to clinical stability	Lower better Based on data from 2,558	**9.9** days (Median)	**8.9** days (Mean)	**Low** Due to very serious imprecision [5]	Baricitinib may reduce time to clinical stability.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Baricitinib	Certainty of the evidence (Quality of evidence)	Summary
	participants in 2 studies. (Randomized controlled)	Difference:	**MD 1 fewer** (CI 95% 2.9 fewer — 1.1 more)		

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Credible interval includes an important decrease and no important difference. **Publication bias: no serious.**
2. **Imprecision: serious.** The credible interval includes an important increase in adverse effects.
3. **Imprecision: serious.**
4. **Imprecision: serious.** The credible interval includes no important difference.
5. **Imprecision: very serious.** Credible interval includes important harm and important benefit (using a minimal important difference threshold of 1 day).

Clinical question/ PICO

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

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Baricitinib	Certainty of the evidence (Quality of evidence)	Summary
Mortality (with IL6-RB)	Odds ratio 0.79 (CI 95% 0.63 — 0.97) Based on data from 2,659 participants in 1 studies. (Randomized controlled)	**130** per 1000 Difference:	**106** per 1000 **24 fewer per 1000** (CI 95% 44 fewer — 3 fewer)	**Moderate** Due to serious imprecision [1]	Baricitinib probably reduces mortality.
Mortality (without IL6-RB)	Odds ratio 0.85 (CI 95% 0.74 — 0.97) Based on data from 8,187 participants in 4 studies. (Randomized controlled)	**130** per 1000 Difference:	**113** per 1000 **17 fewer per 1000** (CI 95% 30 fewer — 3 fewer)	**Moderate** Due to serious imprecision [2]	Baricitinib probably reduces mortality.

1, 2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes no important difference. **Publication bias: no serious.**

For patients with severe or critical COVID-19

Conditional recommendation against

We suggest not to use ruxolitinib or tofacitinib for severe or critical COVID-19 (*conditional recommendation against)*.

- *Clinicians should consider using these drugs only if neither baricitinib nor IL-6 receptor blockers (tocilizumab or sarilumab) are available.*
- *The GDG emphasized the need for more trial evidence to better inform the recommendations.*

Practical info

Route, dosage and duration: We refer to the table of trial characteristics (ruxolitinib and tofacitinib) to guide the administration of these agents, in the absence of other available information.

Timing: Ruxolitinib or tofacitinib (like IL-6 receptor blockers) should be initiated with systemic corticosteroids; specific timing during hospitalization or the course of illness is not specified.

Evidence to decision

Benefits and harms	The effects of ruxolitinib or tofacitinib on mortality, need for mechanical ventilation and hospital length of stay remain uncertain. Tofacinib may increase adverse events leading to drug discontinuation. Subgroup analyses were undertaken for JAK inhibitors as a class (rather than on individual drugs) and revealed no evidence of a subgroup effect on relative risk in younger (< 70 years) versus older patients; those receiving and not receiving corticosteroids; those with severe versus critical COVID-19; and those receiving and not receiving remdesivir.
Certainty of the evidence	Due to serious imprecision due to small cohorts (ruxolitinib: two RCTs, 475 patients; tofacitinib: one RCT, 289 patients) with few events and serious indirectness (pertaining to RCTs for ruxolitinib, most patients did not receive corticosteroids), certainty of evidence was rated as low or very low for all prioritized outcomes for both drugs.
Values and preferences	Applying the agreed values and preferences (see Section 10), the GDG inferred that, given the low or very low certainty evidence on mortality and the other prioritized benefit outcomes and the remaining possibility of SAEs, the majority of well-informed patients would not want to receive ruxolitinib or tofacitinib. The GDG anticipated, however, that because benefit has not been excluded, and because a class effect of JAK inhibitors might exist (such that baricitinib provides indirect evidence of benefit for the other JAK inhibitors), a minority of well-informed patients would choose to receive one or other drug in circumstances in which neither baricitinib nor IL-6 receptor blockers (tocilizumab or sarilumab) were available.
Resources and other considerations	**Resource implications, equity and human rights** The GDG noted that, given the recommendation against use of ruxolitinib or tofacitinib, efforts to ensure access to drugs should focus on those that are currently recommended. **Acceptability and feasibility** As ruxolitinib and tofacitinib are administered orally twice daily, this treatment should be easy to accept for hospitalized patients with severe and critical COVID-19. In patients unable to swallow whole tablets, they can be dispersed in water to take orally or via nasogastric tube (see Practical info).

Justification

When moving from evidence to the conditional recommendation not to use ruxolitinib or tofacitinib in patients with severe or critical COVID-19, the GDG emphasized the low to very low certainty evidence for mortality, duration of mechanical ventilation and possible increase in SAEs (particularly for tofacitinib).

The GDG emphasized the need for more trial evidence to better inform the recommendations; this is anticipated through ongoing trials for these JAK inhibitors.

Applicability

None of the included RCTs enrolled children; therefore, the applicability of this recommendation to children remains uncertain. Uncertainty also remains with regard to the administration of ruxolitinib or tofacitinib to pregnant or lactating individuals.

Clinical question/ PICO

Population: Patients with severe or critical COVID-19
Intervention: Ruxolitinib
Comparator: Standard care

Summary

Evidence summary

The LNMA on ruxolitinib was informed by two RCTs that enrolled 475 patients across non-severe, severe and critical illness subgroups *[103][104]*. Both RCTs were registered, one was published in a peer-reviewed journal, and one was a trial registration only. Both RCTs enrolled patients in in-patient settings. None of the included studies enrolled children or pregnant individuals. The Table shows the characteristics of the RCTs.

For patients with severe and critical COVID-19, the GRADE Summary of Findings table for ruxolitinib shows the relative and absolute effects compared with standard care for the outcomes of interest, with certainty ratings. See Section 6 for sources of baseline risk estimates informing absolute estimates of effect.

Subgroup analysis

The GDG pre-specified several subgroup analyses of interest across all JAK inhibitors of interest; of these, no significant relative subgroup effects were found. Please see the Summary accompanying the recommendation for baricitinib for more details.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Ruxolitinib	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality	Odds ratio 0.87 (CI 95% 0.27 — 2.85) Based on data from 472 participants in 2 studies. (Randomized controlled)	**130** per 1000 Difference:	**115** per 1000 **15 fewer per 1000** (CI 95% 91 fewer — 169 more)	**Very low** Due to serious indirectness and very serious imprecision [1]	The effect of ruxolitinib is very uncertain.
Mechanical ventilation	Odds ratio 0.87 (CI 95% 0.36 — 2.04) Based on data from 472 participants in 2 studies. (Randomized controlled)	**116** per 1000 Difference:	**108** per 1000 **8 fewer per 1000** (CI 95% 71 fewer — 94 more)	**Very low** Due to serious indirectness and very serious imprecision [2]	The effect of ruxolitinib is very uncertain.
Adverse effects leading to drug discontinuation	Based on data from 484 participants in 1 studies. (Randomized controlled)	**0** per 1000 Difference:	**5** per 1000 **2 more per 1000** (CI 95% 0 more — 15 more)	**Low** Due to very serious imprecision [3]	Ruxolitinib may not cause an important increase in adverse effects leading to drug discontinuation.
Hospital length of stay	Lower better Based on data from 472	**12.8** days (Median)	**11.4** days (Mean)	**Very low** Due to serious indirectness and	The impact of ruxolitinib on hospital length of stay is very uncertain.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Ruxolitinib	**Certainty of the evidence** (Quality of evidence)	**Summary**
	participants in 2 studies. (Randomized controlled)	Difference:	**MD 0.1 more** (CI 95% 2.1 fewer — 2.4 more)	very serious imprecision [4]	
Duration of mechanical ventilation	Based on data from 3 participants in 1 studies. (Randomized controlled)	**14.7** days (Median)		**Very low** Insufficient data [5]	The effect of ruxolitinib on mechanical ventilation is unknown.
Time to clinical stability	Lower better Based on data from 472 participants in 2 studies. (Randomized controlled)	**9.9** days (Median) Difference:	**9.8** days (Mean) **MD 0.1 fewer** (CI 95% 2.5 fewer — 2.8 more)	**Very low** Due to serious indirectness and very serious imprecision [6]	The impact of ruxolitinib on time to clinical stability is very uncertain.

1, 2. **Indirectness: serious.** Most patients probably did not receive corticosteroids at baseline. Concomitant use of corticosteroids potentiates the beneficial effect interleukin-6 receptor blockers. Interleukin-6 is downstream in the Janus kinase pathway. Therefore, the effect of ruxolitinib may have been larger had most patients received steroids. Further, the ruxolitinib trial probably included many patients with non-severe disease. A beneficial effect of Janus kinase inhibitors may be limited to patients with severe or critical disease. **Imprecision: very serious.** The credible interval includes important harm and important benefit.
3. **Imprecision: very serious.** There was only one event in the single trial that reported this outcome, of 424 patients enrolled in the study.
4. **Indirectness: serious.** Most patients probably did not receive corticosteroids at baseline. Concomitant use of corticosteroids potentiates the beneficial effect interleukin-6 receptor blockers. Interleukin-6 is downstream in the Janus kinase pathway. Therefore, the effect of ruxolitinib may have been larger had most patients received steroids. Further, the ruxolitinib trial probably included many patients with non-severe disease. A beneficial effect of Janus kinase inhibitors may be limited to patients with severe or critical disease. **Imprecision: very serious.** The credible interval includes important benefit and important harm.
5. **Risk of Bias: serious. Indirectness: serious. Imprecision: very serious.**
6. **Indirectness: serious.** Most patients probably did not receive corticosteroids at baseline. Concomitant use of corticosteroids potentiates the beneficial effect interleukin-6 receptor blockers. Interleukin-6 is downstream in the Janus kinase pathway. Therefore, the effect of ruxolitinib may have been larger had most patients received steroids. Further, the ruxolitinib trial probably included many patients with non-severe disease. A beneficial effect of Janus kinase inhibitors may be limited to patients with severe or critical disease. **Imprecision: very serious.** Credible interval includes important harm and important benefit (using a minimal important difference threshold of 1 day).

Clinical question/ PICO

Population: Patients with severe or critical COVID-19
Intervention: Tofacitinib
Comparator: Standard care

Summary

Evidence summary

The LNMA for tofacitinib was informed by one RCT that enrolled 289 patients across non-severe, severe and critical illness subgroups *[105]*. The trial was registered and published in a peer-reviewed journal; it excluded children and pregnant individuals. The Table shows the characteristics of the RCT.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table for tofacitinib shows the relative and absolute effects compared with standard care for the outcomes of interest, with certainty ratings. See Section 6 for sources of baseline risk estimates informing absolute estimates of effect.

Subgroup analysis

The GDG pre-specified several subgroup analyses of interest across all JAK inhibitors of interest; of these, no significant relative subgroup effects were found. Please see the Summary accompanying the recommendation for baricitinib for more details.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tofacitinib	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality	Odds ratio 0.47 (CI 95% 0.11 — 1.63) Based on data from 289 participants in 1 studies. (Randomized controlled)	**130** per 1000 Difference:	**78** per 1000 **52 fewer per 1000** (CI 95% 113 fewer — 69 more)	**Very low** Due to extremely serious imprecision [1]	The effect of tofacitinib is uncertain.
Mechanical ventilation	Odds ratio 0.5 (CI 95% 0.17 — 1.37) Based on data from 289 participants in 1 studies. (Randomized controlled)	**116** per 1000 Difference:	**68** per 1000 **48 fewer per 1000** (CI 95% 94 fewer — 35 more)	**Very low** Due to extremely serious imprecision [2]	The effect of tofacitinib is uncertain.
Adverse effects leading to drug discontinuation	Based on data from 284 participants in 1 studies. (Randomized controlled)	**0** per 1000 Difference:	**77** per 1000 **77 more per 1000** (CI 95% 17 more — 138 more)	**Low** Due to very serious imprecision [3]	Tofacitinib may increase adverse effects leading to drug discontinuation.
Hospital length of stay	Lower better Based on data from 289 participants in 1 studies. (Randomized controlled)	**12.8** days (Median) Difference:	**11.7** days (Mean) **MD 1.1 fewer** (CI 95% 2.8 fewer — 0.6 more)	**Low** Due to very serious imprecision [4]	Tofacitinib may reduce duration of hospitalization.
Duration of mechanical ventilation	(Randomized controlled)	**14.7** days (Median)		**Very low** No data	The impact of tofacitinib on duration of mechanical ventilation is unknown.
Time to clinical stability	(Randomized controlled)	**9.9** days (Median)		**Very low** No data	The effect of tofacitinib on time to clinical stability is unknown.

1. **Imprecision: extremely serious.** The credible interval includes important benefit and important harm. There were only 12 events total.

2. **Imprecision: extremely serious.** Credible interval includes important benefit and important harm. There were only 18 events in total.
3. **Imprecision: very serious.** Very few events: only 21 in total (16/142 in tofacitinib arm and 5/142 in placebo arm).
4. **Imprecision: very serious.** Credible interval includes no important difference.

Mechanism of action of Janus kinase inhibitors

Type I and type II cytokine receptors are a family of receptors employed by over 50 interleukins, interferons, colony stimulating factors, and hormones *[106]*. The intracellular signalling triggered by these receptors is mediated by JAKs, a small family of kinases including JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). Type I cytokines include IL-2, IFN-γ, IL-12, and TNFb, and type II cytokines include IL-4, IL-5, IL-6, IL-10, and IL-13.

JAK inhibitors are a class of drugs which inhibit intracellular signalling through multifactorial effects on cytokine signalling. As a consequence, they interfere with many cellular responses, including antiviral responses, angiotensin-converting enzyme 2 (ACE2) expression, T cell function and differentiation, and macrophage activation *[106]*.

Baricitinib, ruxolitinib and tofacitinib are three of at least nine JAK inhibitors. These three drugs are all generally considered to be non-specific JAK inhibitors, but differences in the specificity and potency for different JAKs are evident. Baricitinib has been described as a JAK1/JAK2 inhibitor, ruxolitinib as JAK1/JAK2 > TYK2, and tofacitinib as JAK3/JAK1 > JAK2/TYK2; other differences have also been previously described *[106][107][108]*.

Studies evaluating JAK inhibitors for the treatment of COVID-19 have been conducted at doses that are as high or higher than those approved for other indications, such as rheumatoid arthritis, myelofibrosis and ulcerative colitis. Therefore, plausibility is contingent upon the role of cytokine signalling in COVID-19, and not on whether the pharmacokinetics at the studied dose is sufficient to inhibit the target proteins. There are notable differences in the approved doses, schedules, pharmacokinetics, contraindications, and indications of these drugs for other indications. Collectively, these differences limit the confidence to consider a class-wide recommendation with currently available data.

Remdesivir (updated 16 September 2022)

The recommendations on remdesivir in severe and critical illness were initially published on 20 November 2020, and were updated on 16 September 2022, with no subsequent substantial changes.

For patients with severe COVID-19

Conditional recommendation for

We suggest treatment with remdesivir for severe COVID-19 *(conditional recommendation for).*

Practical info

Route, dosage and duration: Additional considerations are available in three summaries of practical issues (remdesivir for COVID-19, administration of remdesivir for COVID-19, safety and monitoring in patients receiving remdesivir for COVID-19). Here follows a brief summary of the key points:

- The recommended dose for remdesivir is one dose daily as intravenous infusion. Remdesivir is given as 200 mg intravenously on Day 1, followed by 100 mg intravenously on Days 2–10. Shorter regimens of 5 days are described in the smaller trials and local practice may be followed.
- Administration should be as early as possible in the time course of the disease.
- One should use caution when administering remdesivir to patients with significant liver or kidney disease.
- The GDG noted that there is insufficient evidence to make a recommendation around use in children and further studies are needed.

- Additionally, the trials did not enrol pregnant or breastfeeding individuals. The decision regarding use of this therapeutic should be made between the pregnant individual and their health care provider while discussing whether the potential benefit justifies the potential risk to the pregnant individual and fetus (see Research evidence and WHO information sheet).

Evidence to decision

Benefits and harms	In patients with severe COVID-19, remdesivir possibly reduces mortality and probably reduces the need for mechanical ventilation and probably has little or no impact on time to symptom improvement. The drug was well tolerated and adverse events were rare. The GDG critically evaluated the credibility of the data for severe and critical subgroups and the need to make separate recommendations (see Justification). It was felt that remdesivir would have an important effect in the severe subgroup and a conditional recommendation could be made for this group. Subgroup analysis based on age was not possible due to lack of trial level data. The GDG noted with concern the dearth of paediatric data and a strong call for research in this area was made. The lack of data regarding the effect in immunocompromised patients was also highlighted. While there is limited evidence in vaccinated populations, the GDG felt that the data were sufficient to conditionally recommend the use of remdesivir. The timing of initiation of therapy was not well reported across the studies and there was no clear subgroup effect based on time.
Certainty of the evidence	Certainty of evidence was rated as: low for decreased mortality (rated down from high for imprecision and inconsistency given the ongoing uncertainty regarding credibility of the severity of illness subgroup effect modification); moderate for reduction in need for invasive mechanical ventilation; and moderate for little or no impact on time to symptom improvement.
Values and preferences	Applying the agreed upon values and preferences (see Section 10), the GDG inferred that the majority of well-informed patients with severe COVID-19 would want to receive remdesivir due to the possible reduction in mortality and need for invasive mechanical ventilation. The benefit of remdesivir on mortality was deemed of critical importance to patients and the GDG was reassured by the safety of the drug. The GDG anticipated little variation in values and preferences between patients for this intervention.
Resources and other considerations	**Acceptability and feasibility** Remdesivir is administered as one intravenous infusion daily over 10 consecutive days, and rather than in an outpatient setting, this is more easily operationalized in hospitalized patients with severe disease. Obstacles to access in LMICs due to cost, feasibility and availability are of concern *[32]*. Challenges in shared decision-making and in communicating the harms versus benefits of remdesivir may also be increased in LMICs. The recommendations should provide a stimulus to engage all possible mechanisms to improve global access to the intervention. As an example of this, on 17 December 2021, WHO published the 7th invitation to Manufacturers of therapeutics against COVID-19 to submit an Expression of Interest (EOI) for Product Evaluation to the WHO Pre-qualification Unit. If this evaluation demonstrates that a product and its corresponding manufacturing (and clinical) site(s) meet WHO recommended standards, it will be included in the list of medicinal products that are considered to be acceptable for procurement by UN organizations and others. Individual countries may formulate their guidelines considering available resources and prioritize treatment options accordingly.

Justification

When moving from evidence to the conditional recommendation to use remdesivir in patients with severe COVID-19, the GDG emphasized the benefits on survival and reduction in need for invasive mechanical ventilation and the likelihood of little or no SAEs attributable to the drug. The GDG acknowledged that some SAEs, may not have been accurately captured during the relatively short follow-up period in the included trials. Of note, although the GDG has recommended for other antiviral drugs in non-severe patients, remdesivir is the only one with a recommendation for use in severe patients.

The GDG did not anticipate important variability in patient values and preferences although the low certainty of evidence and ongoing uncertainty in effect contributed to the conditional recommendation (see Evidence to Decision). There were insufficient trial level data

to examine subgroups based on age, or to consider patients requiring non-invasive ventilation (those on bilevel ventilation or high-flow nasal cannula) as a separate subgroup of interest.

Credibility of subgroup effect based on severity of disease

When making the recommendation for treatment with remdesivir, the GDG carefully considered the credibility of subgroup findings based on severity of disease. When patients with severe and critical COVID-19 were considered together, pooled analysis demonstrated that remdesivir probably had little or no impact on mortality (OR 0.95, 95% CI 0.84 to 1.07). When considered separately, remdesivir possibly has an important reduction on mortality (OR 0.89, 95% CI 0.78 to 1.02) in those with severe COVID-19, while possibly having no impact on mortality in those with critical COVID-19 (OR 1.15, 95% CI 0.89 to 1.51).

The GDG used the ICEMAN tool to assess the credibility of this subgroup finding as this was crucial to informing the direction of the recommendation. The probability of an OR for subgroup interaction < 1 in the Bayesian model demonstrated a p-value of 0.03; this is one-sided and can be considered equivalent to a p-value of 0.06 for subgroup interaction. Based on this, the GDG considered chance to be a potential explanation of the apparent effect modification. This lowered the credibility of the subgroup finding as opposed to if the p-value for interaction had been smaller. That being said, the GDG considered a number of factors which increased the credibility of this subgroup finding. This subgroup analysis was based entirely on within-trial comparisons rather than between-trial comparisons which increased the credibility. The effect modification was mostly similar between included trials although predominantly driven by the largest SOLIDARITY study. There was uncertainty regarding whether the direction of effect modification was correctly hypothesized *a priori* – earlier in the pandemic one may have hypothesized that sicker patients (critical) may benefit more from intervention than those that are less sick (severe). However, now that our understanding of COVID-19 disease course has improved, it fits that those earlier in their disease trajectory (severe, but not yet critical) may have more viral replication and therefore benefit more from an antiviral therapy. Ultimately, the GDG decided that the direction of effect modification was probably correctly hypothesized, which increased the credibility of the subgroup finding. Only a small number of effect modifiers were considered and a random effect model was used, both factors which increased the credibility of the subgroup finding. After accounting for all of these individual factors, the GDG ultimately decided the credibility for this subgroup finding based on severity of illness was moderate and therefore to consider separate recommendations for each, while still recognizing remaining uncertainty.

Applicability

None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children remains uncertain. Uncertainty also remains with regard to administration of remdesivir to pregnant or lactating people. The decision regarding use of this therapeutic should be made between the pregnant individual and their health care provider while discussing whether the potential benefit justifies the potential risk to the mother and fetus (see Research evidence and Practical info).

As the pandemic evolves, and similar to other COVID-19 interventions, there is ongoing uncertainty related to the effect of remdesivir based on variants and individual immune status.

Clinical question/ PICO

Population: Patients with severe or critical COVID-19
Intervention: Remdesivir
Comparator: No remdesivir

Summary

The GRADE Summary of Findings table shows the relative and absolute effects of remdesivir in patients with severe and critical COVID-19 compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA that included five RCTs which enrolled 7643 participants *[3]*. The planned subgroup analyses were limited by available data but did demonstrate sufficient credibility of a subgroup effect to inform specific recommendations for severe versus critical disease. Therefore these Summary of Findings tables are presented separately.

Outcome Timeframe	**Study results and measurements**	**Comparator** No remdesivir	**Intervention** Remdesivir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality	Odds ratio 0.95 (CI 95% 0.84 — 1.07) Based on data from 7,643	**130** per 1000	**124** per 1000	**Moderate** Due to serious imprecision [1]	Remdesivir probably has little or no impact on mortality

Outcome Timeframe	**Study results and measurements**	**Comparator** No remdesivir	**Intervention** Remdesivir	**Certainty of the evidence** (Quality of evidence)	**Summary**
	participants in 5 studies. (Randomized controlled)	Difference:	**6 fewer per 1000** (CI 95% 18 fewer — 8 more)		
Mechanical ventilation	Odds ratio 0.88 (CI 95% 0.78 — 0.99) Based on data from 6,905 participants in 5 studies. (Randomized controlled)	**116** per 1000 Difference:	**104** per 1000 **12 fewer per 1000** (CI 95% 23 fewer — 1 fewer)	**Moderate** Due to serious imprecision [2]	Remdesivir probably reduces mechanical ventilation
Adverse events leading to drug discontinuation	Odds ratio 1.35 (CI 95% 0.31 — 9.27) Based on data from 3,251 participants in 4 studies. (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 25 more)	**Moderate** Due to serious imprecision [3]	Remdesivir probably does not increase risk of adverse events leading to drug discontinuation.
Length of hospital stay	Lower better Based on data from 8,365 participants in 3 studies. (Randomized controlled)	**12.8** days (Mean) Difference:	**12.4** days (Mean) **MD 0.4 fewer** (CI 95% 1 fewer — 0.2 more)	**Low** Due to serious risk of bias and imprecision [4]	Remdesivir may have little or no impact on length of hospital stay
Time to symptom improvement	Lower better Based on data from 2,599 participants in 2 studies. (Randomized controlled)	**9.9** days (Mean) Difference:	**9.3** days (Mean) **MD 0.6 fewer** (CI 95% 1.7 fewer — 0.6 more)	**Moderate** Due to serious imprecision [5]	Remdesivir probably has little or no impact on time to symptom improvement

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Does not meet optimal information size. **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Credible interval includes no important difference. **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**
4. **Risk of Bias: serious.** The largest trial (SOLIDARITY) was not blinded. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Credible interval includes important benefit. **Publication bias: no serious.**
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Credible interval includes important benefit. **Publication bias: no serious.**

Clinical question/ PICO

Population: Patients with severe COVID-19

Intervention: Remdesivir

Comparator: No remdesivir

Summary

The LNMA for remdesivir in severe COVID-19 was informed by five RCTs which enrolled 6631 patients. All RCTs were published in peer-reviewed journals. None of the included studies enrolled children or pregnant individuals. The Table shows characteristics of the RCTs.

For patients with severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of remdesivir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

The planned subgroup analyses were limited by available data but demonstrated low to moderate credibility of a subgroup effect based on severe versus critical disease and therefore these are presented separately and with separate recommendations. We were unable to perform subgroup analysis by age given the sparsity of data.

Outcome Timeframe	**Study results and measurements**	**Comparator** No remdesivir	**Intervention** Remdesivir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality	Odds ratio 0.89 (CI 95% 0.78 — 1.02) Based on data from 6,631 participants in 5 studies. (Randomized controlled)	**130** per 1000 Difference:	**117** per 1000 **13 fewer per 1000** (CI 95% 26 fewer — 2 more)	**Low** Due to serious imprecision and inconsistency [1]	Remdesivir may reduce mortality
Mechanical ventilation	Odds ratio 0.87 (CI 95% 0.77 — 0.99) Based on data from 6,620 participants in 5 studies. (Randomized controlled)	**116** per 1000 Difference:	**102** per 1000 **14 fewer per 1000** (CI 95% 24 fewer — 1 fewer)	**Moderate** Due to serious imprecision [2]	Remdesivir probably reduces mechanical ventilation
Time to symptom improvement	Lower better Based on data from 2,599 participants in 2 studies. (Randomized controlled)	**9.9** days (Mean) Difference:	**9.2** days (Mean) **MD 0.7 fewer** (CI 95% 1.8 fewer — 0.6 more)	**Moderate** Due to serious imprecision [3]	Remdesivir probably has little or no impact on time to symptom improvement

1. **Inconsistency: serious.** There is only low-to-moderate credibility of a subgroup effect between severe and critical disease. If there is no effect modification, then it is more likely that there is no difference in . **Indirectness: no serious. Imprecision: serious.** Does not meet optimal information size. **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Credible interval includes no important difference. **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Credible interval includes important benefit. **Publication bias: no serious.**

For patients with critical COVID-19

Conditional recommendation against

We suggest not to use remdesivir for critical COVID-19 *(conditional recommendation against)*.

Practical info

Given the conditional recommendation against using remdesivir for patients with critical COVID-19, practical considerations were felt to be less relevant here. See practical info for use of remdevisir in patients with non-severe or severe COVID-19 if needed.

Evidence to decision

Benefits and harms	In patients with critical COVID-19, remdesivir possibly has little or no effect on mortality, need for mechanical ventilation and has an uncertain effect on time to symptom improvement. The drug was well tolerated and adverse events were rare. Subgroup analysis based on age was not possible due to lack of trial level data. The GDG considered the potential of small subgroup effects in immunocompromised patients and critically ill patients with prolonged detection of SARS-CoV-2 RNA in blood specimens; however, given the paucity of data and concerns for harm, it was felt that a conditional recommendation against the use of remdesivir was appropriate.
Certainty of the evidence	Certainty of evidence was rated as: low for no impact on mortality or invasive mechanical ventilation (rated down from high for imprecision and inconsistency given the ongoing uncertainty regarding credibility of the severity of illness subgroup effect modification); and very low for no impact on time to symptom improvement.
Values and preferences	Applying the agreed upon values and preferences (see Section 10), the GDG inferred that the majority of well-informed patients with critical COVID-19 would not want to receive remdesivir due to little or no impact on patient important outcomes including mortality and need for invasive mechanical ventilation. The GDG anticipated little variation in values and preferences between patients for this intervention.
Resources and other considerations	**Acceptability and feasibility** Remdesivir is administered as one intravenous infusion daily over 10 consecutive days, and rather than in an outpatient setting, this is more easily operationalized in hospitalized patients with critical disease. Obstacles to access in LMICs due to cost, feasibility and availability are of concern *[32]*. Challenges in shared decision-making and in communicating the harms versus benefits of remdesivir may also be increased in LMICs.

Justification

When moving from evidence to the conditional recommendation against remdesivir in patients with critical COVID-19, the GDG emphasized the lack of benefit on survival or other patient important outcomes. The GDG recognized there is ongoing uncertainty, and there may still be a subset of patients that would benefit (e.g. immunocompromised, persistent viraemia) but there is insufficient evidence to make recommendations specific to these subsets of critical patients.

The GDG did not anticipate important variability in patient values and preferences although the low certainty of evidence and ongoing uncertainty in effect contributed to the conditional recommendation (see Evidence to Decision). There were insufficient trial level data to examine subgroups based on age, or to consider patients requiring non-invasive ventilation (those on bilevel ventilation or high-flow nasal cannula) as a separate subgroup of interest.

Credibility of subgroup effect based on severity of disease

When making the recommendation for treatment with remdesivir, the GDG carefully considered the credibility of subgroup findings based on severity of disease. When patients with severe and critical COVID-19 were considered together, pooled analysis demonstrated that remdesivir probably had little or no impact on mortality (OR 0.95, 95% CI 0.84–1.07). When considered separately, remdesivir possibly has an important reduction on mortality (OR 0.89, 95% CI 0.78–1.02) in those with severe COVID-19, while possibly having no impact on mortality in those with critical COVID-19 (OR 1.15, 95% CI 0.89–1.51).

The GDG used the ICEMAN tool to assess the credibility of this subgroup finding as this was crucial to informing the direction of the recommendation. The probability of an OR for subgroup interaction < 1 in the Bayesian model demonstrated a p-value of 0.03; this is one-sided and can be considered equivalent to a p-value of 0.06 for subgroup interaction. Based on this, the GDG considered chance to be a potential explanation of the apparent effect modification. This lowered the credibility of the subgroup finding as opposed to if the p-value for interaction had been smaller. That being said, the GDG considered a number of factors which increased the credibility of this subgroup finding. This subgroup analysis was based entirely on within-trial comparisons rather than between-trial comparisons

which increased the credibility. The effect modification was mostly similar between included trials although predominantly driven by the largest SOLIDARITY study. There was uncertainty regarding whether the direction of effect modification was correctly hypothesized *a priori* – earlier in the pandemic one may have hypothesized that sicker patients (critical) may benefit more from intervention than those that are less sick (severe). However, now that our understanding of COVID-19 disease course has improved, it fits that those earlier in their disease trajectory (severe, but not yet critical) may have more viral replication and therefore benefit more from an antiviral therapy. Ultimately, the GDG decided that the direction of effect modification was probably correctly hypothesized, which increased the credibility of subgroup finding. The probability of an OR for subgroup interaction < 1 in the Bayesian model demonstrated a p-value of 0.03, this is one-sided and can be considered equivalent to a p-value of 0.06 for subgroup interaction. Based on this, the GDG considered chance a likely or unclear explanation of the apparent effect modification. This lowered the credibility of the subgroup finding as opposed to if the p-value for interaction had been smaller. Only a small number of effect modifiers were considered and a random effect model was used, both factors which increased the credibility of the subgroup finding. After accounting for all of these individual factors, the GDG ultimately decided the credibility for this subgroup finding based on severity of illness was moderate and therefore to consider separate recommendations for each, while still recognizing remaining uncertainty.

Applicability

None of the included RCTs enrolled children or pregnant individuals, and therefore the applicability of this recommendation to children remains uncertain. As the pandemic evolves, and similar to other COVID-19 interventions, there is ongoing uncertainty related to the effect of remdesivir based on variants and individual immune status.

Clinical question/ PICO

Population: Patients with severe or critical COVID-19

Intervention: Remdesivir

Comparator: No remdesivir

Summary

The GRADE Summary of Findings table shows the relative and absolute effects of remdesivir in patients with severe and critical COVID-19 compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA that included five RCTs which enrolled 7643 participants *[3]*. The planned subgroup analyses were limited by available data but did demonstrate sufficient credibility of a subgroup effect to inform specific recommendations for severe versus critical disease. Therefore these Summary of Findings tables are presented separately.

Outcome Timeframe	**Study results and measurements**	**Comparator** No remdesivir	**Intervention** Remdesivir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality	Odds ratio 0.95 (CI 95% 0.84 — 1.07) Based on data from 7,643 participants in 5 studies. (Randomized controlled)	**130** per 1000 Difference:	**124** per 1000 **6 fewer per 1000** (CI 95% 18 fewer — 8 more)	**Moderate** Due to serious imprecision [1]	Remdesivir probably has little or no impact on mortality
Mechanical ventilation	Odds ratio 0.88 (CI 95% 0.78 — 0.99) Based on data from 6,905 participants in 5 studies. (Randomized controlled)	**116** per 1000 Difference:	**104** per 1000 **12 fewer per 1000** (CI 95% 23 fewer — 1 fewer)	**Moderate** Due to serious imprecision [2]	Remdesivir probably reduces mechanical ventilation
Adverse events leading to drug discontinuation	Odds ratio 1.35 (CI 95% 0.31 — 9.27) Based on data from 3,251 participants in 4 studies. (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 25 more)	**Moderate** Due to serious imprecision [3]	Remdesivir probably does not increase risk of adverse events leading to drug discontinuation.

Outcome Timeframe	Study results and measurements	Comparator No remdesivir	Intervention Remdesivir	Certainty of the evidence (Quality of evidence)	Summary
Length of hospital stay	Lower better Based on data from 8,365 participants in 3 studies. (Randomized controlled)	**12.8** days (Mean) Difference:	**12.4** days (Mean) **MD 0.4 fewer** (CI 95% 1 fewer — 0.2 more)	**Low** Due to serious risk of bias and imprecision [4]	Remdesivir may have little or no impact on length of hospital stay
Time to symptom improvement	Lower better Based on data from 2,599 participants in 2 studies. (Randomized controlled)	**9.9** days (Mean) Difference:	**9.3** days (Mean) **MD 0.6 fewer** (CI 95% 1.7 fewer — 0.6 more)	**Moderate** Due to serious imprecision [5]	Remdesivir probably has little or no impact on time to symptom improvement

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Does not meet optimal information size. **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Credible interval includes no important difference. **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**
4. **Risk of Bias: serious.** The largest trial (SOLIDARITY) was not blinded. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Credible interval includes important benefit. **Publication bias: no serious.**
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Credible interval includes important benefit. **Publication bias: no serious.**

Clinical question/ PICO

Population: Patients with critical COVID-19

Intervention: Remdesivir

Comparator: No remdesivir

Summary

The LNMA for remdesivir in critical COVID-19 was informed by three RCTs which enrolled 1012 patients. All RCTs were published in peer-reviewed journals. None of the included studies enrolled children or pregnant individuals. The Table shows characteristics of the RCTs.

For patients with critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of remdesivir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

The planned subgroup analyses were limited by available data but demonstrated low to moderate credibility of a subgroup effect based on severe versus critical disease and therefore these are presented separately and with separate recommendations. We were unable to perform subgroup analysis by age given the sparsity of data.

Outcome Timeframe	Study results and measurements	Comparator No remdesivir	Intervention Remdesivir	Certainty of the evidence (Quality of evidence)	Summary
Mortality	Odds ratio 1.15 (CI 95% 0.89 — 1.51) Based on data from 1,012 participants in 3 studies.	**386** per 1000 Difference:	**420** per 1000 **34 more per 1000**	**Low** Due to serious imprecision and inconsistency [1]	Remdesivir may have little or no impact on mortality

Outcome Timeframe	**Study results and measurements**	**Comparator** No remdesivir	**Intervention** Remdesivir	**Certainty of the evidence** (Quality of evidence)	**Summary**
	(Randomized controlled)		(CI 95% 27 fewer — 101 more)		
Invasive mechanical ventilation Patients receiving non-invasive ventilation or high-flow oxygen at baseline	Odds ratio 0.97 (CI 95% 0.61 — 1.54) Based on data from 285 participants in 1 studies. (Randomized controlled)	**316** per 1000 Difference:	**309** per 1000 **7 fewer per 1000** (CI 95% 96 fewer — 100 more)	**Low** Due to very serious imprecision [2]	Remdesivir may have little or no impact on invasive mechanical ventilation
Time to symptom improvement	Lower better Based on data from 2,599 participants in 1 studies. (Randomized controlled)	**9.9** days (Mean) Difference:	**10.3** days (Mean) **MD 0.4 more** (CI 95% 4.3 fewer — 8.7 more)	**Very low** Due to extremely serious imprecision [3]	The impact of remdesivir is very uncertain

1. **Inconsistency: serious. Indirectness: no serious. Imprecision: serious.** Does not meet optimal information size. **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Credible interval includes important benefit and important harm. **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious. Publication bias: no serious.**

9. Recommendations against therapeutics applicable across disease severities

VV116 (updated August 2025)

In November 2023, the panel confirmed the recommendation made against the use of VV116 except in the context of a clinical trial. For the August 2025 guideline, the GDG considered new evidence from one additional trial, but made no change to the recommendation.

For patients with COVID-19, regardless of disease severity

Updated evidence, no change in recommendation

Only in research settings

We recommend not to use VV116 for any severity of COVID-19, except in the context of a clinical trial *(recommended only in research settings)*.

Practical info

The GDG made a recommendation against using VV116 for treatment of patients with non-severe, severe or critical COVID-19 outside the setting of a clinical trial and therefore practical considerations are less relevant for this drug.

Evidence to decision

Benefits and harms

VV116 is an oral antiviral that is chemically related to remdesivir. The effects of VV116 on admission to hospital, mortality and use of invasive mechanical ventilation, remain uncertain because of very low certainty of evidence addressing each of these outcomes. In fact, hospital admission was not reported in either of the included studies, whereas mortality was reported in both but there were no events. VV116 may have little or no effect on time to symptom resolution (low certainty) and has little to no effect on adverse effects leading to drug discontinuation (high certainty).

Subgroup analyses based on age, and serological status or vaccine status was not possible due to lack of data (see Research evidence). Therefore, we assumed similar effects in all subgroups. Both included studies were done in non-severe patients, however the panel was comfortable to generalize this recommendation to patients with any disease severity and any duration of symptoms, pending further data.

Certainty of the evidence

For most key outcomes, including mortality, mechanical ventilation and hospital admission, the GDG considered the evidence to be very low certainty. Evidence was rated as very low certainty primarily because of extremely serious imprecision for mortality, and no data for others (hospital admission and need for invasive mechanical ventilation). Evidence for time to symptom resolution was rated as low certainty because of very serious imprecision.

For more details, see the Justification section for this recommendation.

Values and preferences

Applying the agreed values and preferences (see Section 10), the GDG inferred that almost all well-informed patients would want to receive VV116 only in the context of a randomized trial; the evidence left a very high degree of uncertainty in effect on mortality, need for mechanical ventilation, need for hospitalization and other critical outcomes of interest, although harms were unlikely. The panel anticipated little variation in values and preferences between patients when it came to this intervention.

Resources and other considerations

The cost of VV116 is uncertain. The lack of availability of this novel intervention, especially in low-income settings, may influence the ability to administer this drug, even if it proves useful in patients with non-severe disease. The drug is administered orally which makes operationalization easier than other intravenous options (e.g. remdesivir).

Justification

The GDG emphasized the high degree of uncertainty in the most critical outcomes such as mortality and need for hospital admission. The panel adopted this perspective despite the fact that VV116 does not seem to be associated with increased adverse effects. The GDG did not anticipate important variability in patient values and preferences. Other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity did not alter the recommendation.
Compared with other drugs evaluated for this guideline, there are far fewer RCT data available for VV116. The GDG judged it was appropriate to maintain its recommendation against use outside the context of a clinical trial after reviewing most recently available data, informed by the LNMA *[1]*, in light of persistent uncertainties for critical outcomes.

Subgroup analyses

A lack of within-trial comparisons prevented subgroup analyses based on pre-identified variables such as age, serological status or COVID-19 vaccination status. The panel judged that the recommendation against VV116 except in the context of clinical trials is applicable across disease severity, vaccination status, and age groups.

Applicability

The included RCTs did not enrol children. However, the panel had no reason to think that children with COVID-19 would respond differently to treatment with VV116. There were similar considerations for pregnant individuals, with no data directly examining this population, but no rationale to suggest they would respond differently to other adults. The recommendation therefore pertains to all these populations.

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: VV116
Comparator: Standard care

Summary

Evidence summary

The LNMA for VV116 was informed by two RCTs which enrolled 2,191 patients with non-severe illness. The RCTs were both registered and published in peer-reviewed journals. The Table summarizes study characteristics for VV116 versus standard care.

The GRADE Summary of Findings table shows the relative and absolute effects of VV116 compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *[3]*.

Subgroup analysis

Five pre-specified subgroup analyses were requested by the GDG:

1. Age: children (≤ 19 years) versus adults (20–60 years) versus older adults (≥ 60 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time from symptom onset.
4. Serological status (seropositive versus seronegative).
5. Vaccination status (unvaccinated versus vaccinated).

The studies did not enrol children, pregnant individuals, or patients with severe or critical illness. The study enrolled unvaccinated individuals with time from symptom onset < 5 days. Data regarding serological status were not reported.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** VV116	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio (CI 95% — 1,000) Based on data from 2,118 participants in 2 studies. (Randomized controlled)	**0.5** per 1000 Difference:	**0** per 1000 **0.5 fewer per 1000** (CI 95% 0.5 fewer — 989.6 more)	**Very low** Due to extremely serious imprecision [1]	The effect of VV116 on mortality is very uncertain

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** VV116	**Certainty of the evidence** (Quality of evidence)	**Summary**
Admission to hospital Low risk		**5** per 1000		No data	The effect of VV116 on admission to hospital is unknown
Mortality Moderate risk	Odds ratio (CI 95% — 1,000) Based on data from 2,118 participants in 2 studies. (Randomized controlled)	**3** per 1000 Difference:	**0** per 1000 **3 fewer per 1000** (CI 95% 3 fewer — 987.13 more)	**Very low** Due to extremely serious imprecision [2]	The effect of VV116 on mortality is very uncertain
Admission to hospital Moderate risk		**30** per 1000		No data	The effect of VV116 on admission to hospital is unknown
Mortality High risk	Odds ratio (CI 95% — 1,000) Based on data from 2,118 participants in 2 studies. (Randomized controlled)	**6** per 1000 Difference:	**0** per 1000 **6 fewer per 1000** (CI 95% 6 fewer — 984 more)	**Very low** Due to extremely serious imprecision [3]	The effect of VV116 on mortality is very uncertain
Admission to hospital High risk		**60** per 1000		No data	The effect of VV116 on admission to hospital is unknown
Mechanical ventilation				No data [4]	The effect of VV116 on mechanical ventilation is unknown
Adverse effects leading to drug discontinuation	Odds ratio Based on data from 2,118 participants in 2 studies. (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** CI 95% 2 more	**High**	There is little or no difference in adverse effects leading to drug discontinuation
Time to symptom resolution	Lower better Based on data from 2,118 participants in 2 studies. (Randomized controlled)	**9** (Median) Difference:	**8.4** (Median) **MD 0.6 fewer** (CI 95% 2.9 fewer — 2.2 more)	**Very low** Due to very serious imprecision and serious risk of bias [5]	The effect of VV116 on time to symptom resolution is uncertain

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** There were no deaths in the trial. **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** There were no events in the trial. **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious.** The baseline risk across the entire population is very low, meaning that any impact on mortality will be very small. There are some people with much higher baseline risk, who are not easily identifiable. For these patients, VV116 may have an important impact on mortality. **Imprecision: extremely serious.** There were no deaths in the trial. **Publication bias: no serious.**
4. **Risk of Bias: no serious.** The single trial reporting mechanical ventilation was not blinded. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Very few events (24 total), resulted in wide credible intervals that include important and unimportant effects. **Publication bias: no serious.**
5. **Risk of Bias: serious.** Not blinded. **Imprecision: very serious.** Credible interval includes both important benefit and important harm.

Mechanism of action of VV116

VV116 is a nucleoside prodrug for which the mechanism of action involves chain-termination (like remdesivir), which should not be confused with mutagenesis as for molnupiravir. Although the mechanism of action is the same for VV116 and remdesivir there are notable and important differences between the two medicines. First, the prodrug moiety for VV116 is chemically very different to that of remdesivir, and when hydrolysed it also releases the active nucleoside analogue which is also chemically different to the nucleoside released when remdesivir is hydrolysed *[109]*. Second, the active nucleoside has a different *in vitro* antiviral activity to that of remdesivir *[109]*, and also exhibits a different pharmacokinetic profile *[110][44]*. Finally, VV116 is dosed orally (600 mg BID day 1; 300 mg BID days 2–5) whereas remdesivir is dosed intravenously (200 mg BID day 1; 100 mg BID days 2–5) *[111]*. Based upon this knowledge, the GDG concluded that while the mechanism of action is plausible for VV116, there are major gaps in knowledge that cannot be inferred from prior knowledge of remdesivir. In particular, non-clinical safety data for VV116 and its active nucleoside were not available, and only pharmacokinetic data for Chinese participants were available for discussion by the GDG. Regional differences in pharmacokinetics cannot be ruled out.

Ivermectin (updated 10 November 2023)

The recommendation for ivermectin across disease severities was initially published on 31 March 2021. In this 14th version of the guideline (10 Nov 2023), the GDG considered new trial evidence that resulted in updated recommendations for patients with non-severe illness. The evidence for patients with severe and critical illness was not reconsidered in this update, meaning that the summary of findings table for all patients with COVID-19 still applies to patients with several and critical illness.

For patients with non-severe COVID-19

Strong recommendation against

We recommend not to use ivermectin *strong recommendation against).*

Practical info

The GDG made a strong recommendation against using ivermectin for treatment of patients with non-severe COVID-19 and therefore practical considerations are not relevant for this drug.

Evidence to decision

Benefits and harms	The absolute benefits of ivermectin on hospital admission vary from being of low certainty among patients at high risk of hospitalization to trivial (high certainty) in patients at low risk. Ivermectin does not result in an

important reduction in mortality (high certainty) and probably does not result in an important reduction in mechanical ventilation, time to symptom resolution and duration of hospitalization, while probably increasing the risk of SAEs leading to drug discontinuation (all moderate certainty).

Subgroup analyses indicated no effect modification based on dose. We were unable to examine subgroups based on patient age or severity of illness due to insufficient trial data (see Research evidence), and similar effects were inferred for all subgroups.

Certainty of the evidence

The evidence summary was informed by 13 trials with 3396 participants included in the LNMA [29]. One new large trial that randomized participants to ivermectin or placebo was included from the evidence base for the initial recommendation.

Certainty of evidence varied between risk groups for hospitalization, was high for mortality, and moderate for mechanical ventilation and adverse events leading to drug discontinuation. For high certainty evidence, confidence arose from the very low risk of adverse outcomes, with the very narrow confidence intervals excluding important benefit. Where uncertainty existed in the usual application of GRADE criteria, for example uncertainty that may ordinarily have warranted a conditional recommendation (for instance, the remaining possibilities of important decrease in hospitalization for high-risk patients and reduction in duration of illness), the panel was influenced by the lack of a plausible biological basis for ivermectin's effect. This increased the panel's confidence in lack of benefit beyond the GRADE rating.

Values and preferences

Applying the agreed values and preferences (see Section 10), the GDG inferred that the all or almost all of well-informed patients would not want to receive ivermectin given the very low likelihood of important benefit.

Resources and other considerations

Ivermectin is a relatively inexpensive drug and is widely available, including in low-income settings, providing an incentive to use the medication. Given both the published evidence summarized in the evidence profile, and the lack of a plausible biological mechanism for action against the virus, the GDG concluded that the drug is very likely to be ineffective. Use of ivermectin runs the risk of diverting attention and resources away from care likely to provide a benefit such as nirmatrelvir/ritonavir, remdesivir and molnupiravir as well as supportive care interventions. Also, use of ivermectin for COVID-19 would divert drug supply away from pathologies for which it is clearly indicated, potentially contributing to drug shortages, especially for helminth control and elimination programmes.

Justification

The GDG were informed by new trial evidence that reduced the high degree of uncertainty informing the previous recommendation to continue with ivermectin within the context of RCTs. When moving from evidence to a strong recommendation against the use of ivermectin in patients with COVID-19, the GDG emphasized the very low likelihood of benefit given both the evidence from randomized trials and the lack of biological basis for any effect of ivermectin on the virus, combined with probable (although modest) harm associated with treatment. Regarding the merits of the strong recommendation, more important than the harms is the temptation to use a low cost easily accessible drug in low-income settings, diverting effort away from optimizing the likelihood of administration of one of interventions known to benefit. The GDG did not anticipate important variability in patient values and preferences.

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Ivermectin
Comparator: Standard care

Summary

Thirteen trials with 3396 participants were included (see Table). One new trial was included from our last update, which randomized 1358 participants to ivermectin or placebo *[112]*. Four other trials were excluded because they did not report any relevant outcomes and one was excluded because it included patients with severe COVID-19. The included trials enrolled patients from around the world,

including many from LMICs. Other than the new TOGETHER trial, the other trials were small (average number of participants was 170). There were a range of treatment durations, from a single dose to several doses over 4 weeks. A range of doses was provided, including 6 mg and 12 mg fixed doses as well as 0.1 mg/kg to 1.2 mg/kg weight-based doses. The vast majority of patients were included in trials judged to be at low risk of bias.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Ivermectin	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality Low risk	Odds ratio 0.73 (CI 95% 0.37 — 1.34) Based on data from 3,050 participants in 9 studies. (Randomized controlled)	**0.5** per 1000 Difference:	**0.37** per 1000 **0.13 fewer per 1000** (CI 95% 0.31 fewer — 0.17 more)	**High**	Ivermectin does not result in an important reduction in mortality
Admission to hospital Low risk	Odds ratio 0.67 (CI 95% 0.36 — 1.16) Based on data from 2,316 participants in 4 studies. (Randomized controlled)	**6** per 1000 Difference:	**4** per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 1 more)	**High**	Ivermectin does not result in an important reduction in hospital admission
Mortality Moderate risk	Odds ratio 0.73 (CI 95% 0.37 — 1.34) Based on data from 3,050 participants in 9 studies. (Randomized controlled)	**3** per 1000 Difference:	**2.19** per 1000 **0.81 fewer per 1000** (CI 95% 1.89 fewer — 1.02 more)	**High**	Ivermectin does not result in an important reduction in mortality
Admission to hospital Moderate risk	Odds ratio 0.67 (CI 95% 0.36 — 1.16) Based on data from 2,316 participants in 4 studies. (Randomized controlled)	**30** per 1000 Difference:	**20** per 1000 **10 fewer per 1000** (CI 95% 19 fewer — 5 more)	**Moderate** Due to serious imprecision [1]	Ivermectin probably does not result in an important reduction in hospital admission
Mortality High risk	Odds ratio 0.73 (CI 95% 0.37 — 1.34) Based on data from 3,050 participants in 9 studies. (Randomized controlled)	**6** per 1000 Difference:	**4.39** per 1000 **1.61 fewer per 1000** (CI 95% 3.77 fewer — 2.02 more)	**High** [2]	Ivermectin does not result in an important reduction in mortality
Admission to hospital High risk	Odds ratio 0.67 (CI 95% 0.36 — 1.16) Based on data from 2,316 participants in 4 studies. (Randomized controlled)	**60** per 1000 Difference:	**41** per 1000 **19 fewer per 1000** (CI 95% 38 fewer — 9 more)	**Low** Due to very serious imprecision [3]	Ivermectin may reduce hospital admission

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Ivermectin	Certainty of the evidence (Quality of evidence)	Summary
Mechanical ventilation	Odds ratio 0.74 (CI 95% 0.38 — 1.37) Based on data from 2,806 participants in 9 studies. (Randomized controlled)	**29** per 1000 Difference:	**22** per 1000 **7 fewer per 1000** (CI 95% 18 fewer — 10 more)	**Moderate** Due to serious imprecision [4]	Ivermectin probably not result in an important reduction in mechanical ventilation
Adverse events leading to discontinuation	Odds ratio 6.82 (CI 95% 1.81 — 49.9) Based on data from 1,332 participants in 6 studies. (Randomized controlled)	**0** per 1000 Difference:	**10** per 1000 **10 more per 1000** (CI 95% 1 more — 47 more)	**Moderate** Due to serious imprecision [5]	Ivermectin probably results in an increase in adverse events leading to discontinuation
Time to symptom resolution	Lower better Based on data from 2,816 participants in 5 studies. (Randomized controlled)	**10.7** (Mean) Difference:	**9.73** (Mean) **MD 0.97 lower** (CI 95% 2.38 lower — 0.62 higher)	**Moderate** Due to serious imprecision [6]	Ivermectin probably does not reduce duration of symptoms
Duration of hospitalization	Lower better Based on data from 383 participants in 3 studies. (Randomized controlled)	**10.88** (Mean) Difference:	**10.03** (Mean) **MD 0.85 fewer** (CI 95% 2.63 fewer — 1 more)	**Moderate** Due to serious imprecision [7]	Ivermectin probably does not reduce duration of hospitalization

1, 5, 6, 7. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** 64 events. **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.**

For patients with severe or critical COVID-19

Only in research settings

We recommend not to use ivermectin, except in the context of a clinical trial *(recommended only in research settings).*

- *A recommendation to only use a drug in the setting of clinical trials is appropriate when there is very low certainty evidence and future research has a large potential for reducing uncertainty about the effects of the intervention and for doing so at reasonable cost.*
- *A strong recommendation against use of ivermectin in patients with non-severe COVID-19 was published in October 2023, given new trial evidence.*

Practical info

The GDG made a recommendation against using ivermectin for treatment of patients with COVID-19 outside the setting of a clinical trial and therefore practical considerations are less relevant for this drug.

Evidence to decision

Benefits and harms	The effects of ivermectin on mortality, mechanical ventilation, hospital admission, duration of hospitalization and viral clearance remain uncertain because of very low certainty of evidence addressing each of these outcomes. Ivermectin may have little or no effect on time to clinical improvement (low certainty evidence). Ivermectin may increase the risk of SAEs leading to drug discontinuation (low certainty evidence). Subgroup analyses indicated no effect modification based on dose. We were unable to examine subgroups based on patient age or severity of illness due to insufficient trial data (see Research evidence). Therefore, we assumed similar effects in all subgroups. This recommendation applies to patients with any disease severity and any duration of symptoms.
Certainty of the evidence	For most key outcomes, including mortality, mechanical ventilation, hospital admission, duration of hospitalization and viral clearance, the GDG considered the evidence of very low certainty. Evidence was rated as very low certainty primarily because of very serious imprecision for most outcomes: the aggregate data had wide confidence intervals and/or very few events. There were also serious concerns related to risk of bias for some outcomes, specifically lack of blinding, lack of trial pre-registration, and lack of outcome reporting for one trial that did not report mechanical ventilation despite pre-specifying it in their protocol (publication bias). For more details, see the Justification section. For other outcomes, including SAEs and time to clinical improvement, the certainty of the evidence was low.
Values and preferences	Applying the agreed values and preferences (see Section 10), the GDG inferred that almost all well-informed patients would want to receive ivermectin only in the context of a randomized trial, given that the evidence left a very high degree of uncertainty in effect on mortality, need for mechanical ventilation, need for hospitalization and other critical outcomes of interest and there was a possibility of harms, such as treatment-associated SAEs. The panel anticipated little variation in values and preferences between patients when it came to this intervention.
Resources and other considerations	Ivermectin is a relatively inexpensive drug and is widely available, including in low-income settings. The low cost and wide availability do not, in the GDG's view, mandate the use of a drug in which any benefit remains very uncertain and ongoing concerns regarding harms remain. Although the cost may be low per patient, the GDG raised concerns about diverting attention and resources away from care likely to provide a benefit such as corticosteroids in patients with severe COVID-19 and other supportive care interventions. Also, use of ivermectin for COVID-19 would divert drug supply away from pathologies for which it is clearly indicated, potentially contributing to drug shortages, especially for helminth control and elimination programmes. Other endemic infections that may worsen with corticosteroids should be considered. If steroids are used in the treatment of COVID-19, empiric treatment with ivermectin may still be considered in Strongyloidiasis endemic areas, at the discretion of clinicians overseeing treatment, albeit not for treatment of COVID-19 itself.

Justification

When moving from evidence to a recommendation on the use of ivermectin in patients with COVID-19 only in the context of a clinical trial, the GDG emphasized the high degree of uncertainty in the most critical outcomes such as mortality and need for mechanical ventilation. It also noted the evidence suggesting possible harm associated with treatment, with increased adverse events. The GDG did not anticipate important variability in patient values and preferences. Other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity did not alter the recommendation.

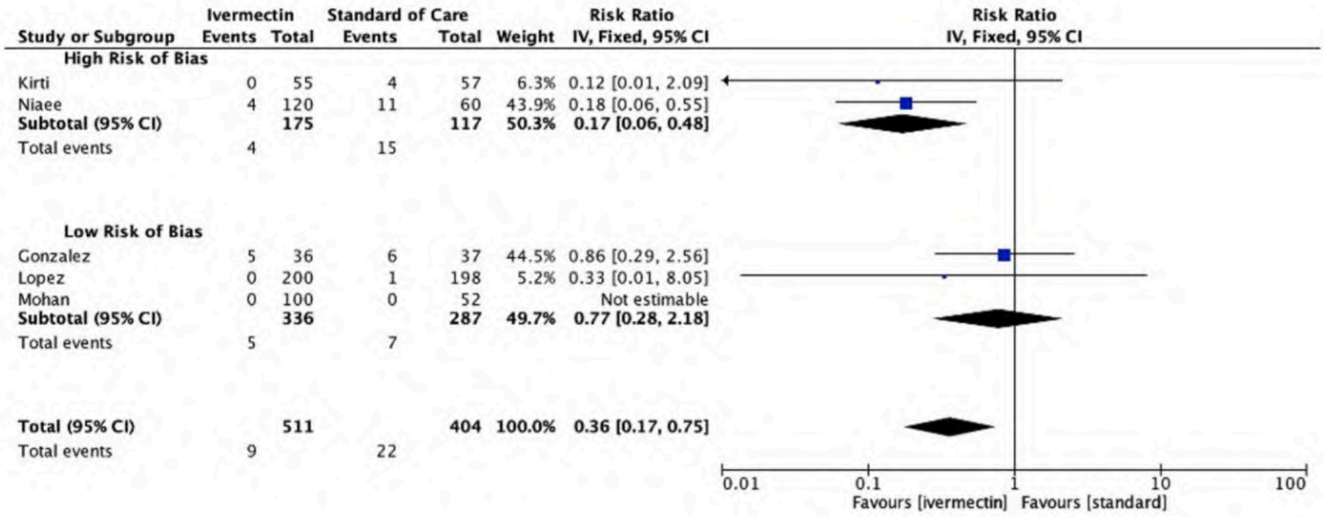
Compared with previous drugs evaluated as part of the WHO *Therapeutics and COVID-19: living guideline*, currently there are far fewer RCT data available for ivermectin. The existing data on ivermectin also have a substantially higher degree of uncertainty, with included trials having enrolled substantially fewer patients with far fewer events.

High degree of uncertainty

The certainty in effect estimates for ivermectin on the main outcomes of interest, including mortality, is very low and therefore the effect of ivermectin on these outcomes remains uncertain. There are two domains that contribute to this uncertainty: serious risk of bias and

serious imprecision. Although 16 RCTs contributed to the evidence summary informing this drug, only five directly compared ivermectin with standard care and reported mortality *[113][114][115][116][117][118][119]*. Of note, and in keeping with our methodology, the LNMA team excluded quasi-randomized trials, or any RCT that did not use explicit randomization techniques. Of these five RCTs, two *[113][114]* were at high risk of bias, due to inadequate blinding. One of these two trials *[113]* also started enrolling and randomizing patients prior to the protocol being publicly posted, another factor that contributes to an increased risk of bias. The potential impact of risk of bias is exemplified by subgroup analyses for mortality based on trial risk of bias. As demonstrated in the forest plot (Fig. 2), the pooled estimate across all five RCTs that directly compare ivermectin with standard care suggests a reduction in mortality with ivermectin, but this effect is not apparent if we only consider the trials at low risk of bias (which together contribute nearly two-thirds of the evidence). This finding increases the degree of uncertainty regarding the true effect of ivermectin on mortality. Consistent with the direct evidence, a similar phenomenon is observed with the indirect evidence comparing ivermectin with standard of care (via comparisons against hydroxychloroquine and lopinavir/ritonavir). The indirect evidence suggesting a reduction in mortality with ivermectin is driven almost entirely by one study which is at high risk of bias *[120]* due to a lack of detailed description of blinding or randomization and the lack of a publicly available study protocol (figure not shown).

Fig. 2. Forest plot demonstrating direct comparison of ivermectin versus standard of care for mortality with subgroup analysis by risk of bias



IV: inverse variance.

In addition to concerns related to risk of bias, for the outcome of mortality, there are very serious concerns related to imprecision. According to GRADE, imprecision is evaluated based on both a confidence interval approach and an evaluation of information size (event number), ensuring there is adequate information on which to make informed judgments *[121]*. In this case, despite confidence intervals that suggest benefit with ivermectin, the information size is very low. For mortality (and ignoring the concerns related to risk of bias discussed above), there were nine deaths across all 511 patients randomized to ivermectin (1.76%) and 22 deaths across all 404 patients randomized to standard care (5.45%). This is an extremely small number of events on which to base conclusions, and far below the optimal information size. In fact, performing a theoretical exercise in which a change of three events (deaths) is made from those randomized to standard care to those randomized to ivermectin eliminates any statistical significance, a finding that suggests that results could reasonably be due to chance alone. Furthermore, the evidence informing this comparison is from multiple small trials, adding to the risk of unrecognized imbalances in study arms. Given the strong likelihood that chance may be playing a role in the observed findings, the panel believed there was very serious imprecision, further lowering the overall certainty in findings.

This combination of serious risk of bias and very serious imprecision contributed to very low certainty of evidence for mortality despite a point estimate and confidence interval that appear to suggest benefit with ivermectin. As a result, the panel concluded that the effect of ivermectin on mortality is uncertain. Similar considerations were applied to the other critical outcomes including mechanical ventilation, hospital admission, and duration of hospitalization and resulted in very low certainty for these outcomes as well.

Subgroup analyses

We conducted subgroup analysis only for effect by ivermectin dose and the panel did not find any evidence of a subgroup effect (see Research evidence). A lack of within-trial comparisons prevented subgroup analyses by age or disease severity. Therefore, the panel did not make any subgroup recommendation for this drug. In other words, the recommendation against ivermectin except in the context of clinical trials is applicable across disease severity, age groups, and all dose regimens of ivermectin.

Applicability

None of the included RCTs enrolled children under 15, and therefore the applicability of this recommendation to children is currently uncertain. However, the panel had no reason to think that children with COVID-19 would respond any differently to treatment with ivermectin. There were similar considerations for pregnant individuals, with no data directly examining this population, but no rationale to suggest they would respond differently to other adults.

Clinical question/ PICO

Population: Patients with COVID-19 (all disease severities)
Intervention: Ivermectin
Comparator: Standard care

Summary

Evidence summary

The LNMA on ivermectin was based on 16 RCTs and 2407 participants. Of the included studies, 75% examined patients with non-severe disease and 25% included both severe and non-severe patients. A number of the included studies did not report on our outcomes of interest. Of the studies, 25% were published in peer-reviewed journals, 44% were available as preprints and 31% were completed but unpublished (see Table on trial characteristics). We excluded a number of quasi-RCTs *[122][123][124][125]*.

The GRADE Summary of Findings table shows the relative and absolute effects of ivermectin compared with standard care for the outcomes of interest in patients with COVID-19, with certainty ratings. See Section 10 for sources of baseline risk estimates informing absolute estimates of effect.

Subgroup analysis

The NMA team performed subgroup analyses which could result in distinct recommendations by subgroups. From the available data, subgroup analyses were only possible by dose of ivermectin and considering the outcomes of mortality, mechanical ventilation, admission to hospital, and adverse events leading to drug discontinuation. The ivermectin dose subgroup analyses were performed from the direct comparison of ivermectin versus standard care. For these analyses, meta-regression was used to evaluate the effect of cumulative dose as a continuous variable, and further adding a co-variate for single vs multiple dosing regimens. This approach was based on input from the pharmacology experts (led by Professor Andrew Owen) who performed pharmacokinetic simulations across trial doses, and found that cumulative ivermectin dose was expected to correlate with key pharmacokinetic parameters when single- and multiple-dose studies were segregated. It should be noted that the included trials did not directly assess the pharmacokinetics of ivermectin, and our approach was based upon simulations validated, where possible, against published pharmacokinetics in humans. The panel used a pre-specified framework incorporating the ICEMAN tool to assess the credibility of subgroup findings *[95]*.

The GDG panel requested subgroup analyses based on: age (considering children vs younger adults vs older adults [70 years or older]); illness severity (non-severe vs severe vs critical COVID-19); time from onset of symptoms; and use of concomitant medications. However, there was insufficient within-trial data to perform any of these subgroup analyses, based on our pre-specified protocol. The panel recognized that standard care is likely variable between centres and regions, and has evolved over time. However, given all of the data come from RCTs, use of these co-interventions that comprise standard care should be balanced between study patients randomized to either the intervention or standard care arms.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Ivermectin	**Certainty of the evidence** (Quality of evidence)	**Summary**
Hospital admission (outpatients only)	Odds ratio 0.36 (CI 95% 0.08 — 1.48) Based on data from 398 participants in 1 studies. (Randomized controlled)	**50** per 1000 Difference:	**18** per 1000 **32 fewer per 1000** (CI 95% 47 fewer — 23 more)	**Very low** Due to extremely serious imprecision [1]	The effect of ivermectin on hospital admission is uncertain.
Mortality	Odds ratio 0.19 (CI 95% 0.09 — 0.36) Based on data from 1,419 participants in 7 studies. [2] (Randomized controlled)	**70** per 1000 Difference:	**14** per 1000 **56 fewer per 1000** (CI 95% 63 fewer — 44 fewer)	**Very low** Due to serious risk of bias and very serious imprecision [3]	The effect of ivermectin on mortality is uncertain.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Ivermectin	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mechanical ventilation	Odds ratio 0.51 (CI 95% 0.12 — 1.77) Based on data from 687 participants in 5 studies. (Randomized controlled)	**20** per 1000 Difference:	**10** per 1000 **10 fewer per 1000** (CI 95% 18 fewer — 15 more)	**Very low** Due to very serious imprecision and publication bias [4]	The effect of ivermectin on mechanical ventilation is uncertain.
Viral clearance 7 days	Odds ratio 1.62 (CI 95% 0.95 — 2.86) Based on data from 625 participants in 6 studies. (Randomized controlled)	**500** per 1000 Difference:	**618** per 1000 **118 more per 1000** (CI 95% 13 fewer — 241 more)	**Low** Due to serious inconsistency and imprecision [5]	Ivermectin may increase or have no effect on viral clearance.
Serious adverse events leading to discontinuation	Odds ratio 3.07 (CI 95% 0.77 — 12.09) Based on data from 584 participants in 3 studies. (Randomized controlled)	**9** per 1000 Difference:	**27** per 1000 **18 more per 1000** (CI 95% 0 more — 89 more)	**Low** Due to very serious imprecision [6]	Ivermectin may increase the risk of serious adverse events leading to drug discontinuation.
Time to clinical improvement	Measured by: days Lower better Based on data from 633 participants in 2 studies. (Randomized controlled)	**11** days (Mean) Difference:	**10.5** days (Mean) **MD 0.5 fewer** (CI 95% 1.7 fewer — 1.1 more)	**Low** Due to very serious imprecision [7]	Ivermectin may have little or no difference on time to clinical improvement.
Duration of hospitalization	Measured by: days Lower better Based on data from 252 participants in 3 studies. (Randomized controlled)	**12.8** days (Mean) Difference:	**11.7** days (Mean) **MD 1.1 fewer** (CI 95% 2.3 fewer — 0.1 more)	**Very low** Due to serious imprecision, inconsistency and serious risk of bias [8]	The effect of ivermectin on hospital length of stay is uncertain.
Time to viral clearance	Measured by: days Lower better Based on data from 559 participants in 4 studies. (Randomized controlled)	**7.3** days (Mean) Difference:	**5.7** days (Mean) **MD 1.6 fewer** (CI 95% 4.1 fewer — 3 more)	**Very low** Due to very serious imprecision and serious risk of bias [9]	We are uncertain whether ivermectin improves or worsens time to viral clearance.

1. **Imprecision: extremely serious.** Credible interval includes important benefit and harm.
2. Systematic review [1] **Comparator:** We elected to use the control arm of the WHO SOLIDARITY trial, reflecting usual care across countries participating in the trial.
3. **Risk of Bias: serious.** The large trial contributing most of the effect estimate was driven by studies that were not blinded. **Imprecision: very serious.** The number of total events was very small.
4. **Imprecision: very serious.** Very few events and credible intervals that include both important benefit and harm. **Publication bias: serious.**
5. **Inconsistency: serious.** The point estimates varied widely and credible intervals do not substantially overlap. **Imprecision: serious.** Credible interval includes no effect.
6. **Imprecision: very serious.** Credible interval includes little to no difference.
7. **Imprecision: very serious.**

8. **Risk of Bias: serious.** Result driven by one study that was not blinded. **Inconsistency: serious.** Despite overlapping confidence intervals, point estimates discrepant. **Imprecision: serious.** Credible intervals include no difference.
9. **Risk of Bias: serious.** Concerns around risk of bias. **Imprecision: very serious.** Credible interval includes important benefit and important harm.

Mechanism of action of ivermectin

Ivermectin is an antiparasitic agent that interferes with nerve and muscle function of helminths through binding glutamate-gated chloride channels *[126]*. Based on *in vitro* experiments, some have postulated that ivermectin may have a direct antiviral effect against SARS-CoV-2. However, in humans the concentrations needed for *in vitro* inhibition are unlikely to be achieved by the doses proposed for COVID-19 *[127][128][129]*. The proposed mechanism remains unclear: multiple targets have been proposed based upon either analogy to other viruses with very different life cycles, or, like several hundred other candidates, simulations indicating molecular docking with multiple viral targets including spike, RdRp and 3CLpro *[130][131][132][133][134]*. No direct evidence for any mechanism of antiviral action against SARS-CoV-2 currently exists.

Some have also proposed, based predominantly upon research in other indications, that ivermectin has an immunomodulatory and/or anti-inflammatory effect, but while several putative mechanisms have been proposed, again the mechanism in COVID-19 remains unclear.

Three published studies have investigated ivermectin in the Syrian golden hamster model of SARS-CoV-2 infection *[135][136][137]*. In two of these studies, no impact on virus was evident comparing the ivermectin group with the control group, while in one study an impact on the virus on Day 3 was noted but not at 6 days post infection. In terms of disease outcomes in these studies, one study indicated no effect of ivermectin, one study indicated an effect more pronounced in female hamsters, and one study indicated an effect but only males were studied.

Convalescent plasma (published 7 December 2021)

The recommendations for convalescent plasma across disease severities were initially published on 7 December 2021. No subsequent changes have been made.

For patients with non-severe COVID-19

Strong recommendation against

We recommend against treatment with convalescent plasma *(strong recommendation against)*.

Practical info

The GDG made a strong recommendation against using convalescent plasma for the treatment of patients with non-severe COVID-19 and a recommendation against using convalescent plasma in those with severe or critical COVID-19 outside the context of a clinical trial. Given this, we will not go into detail regarding the many practical issues related to convalescent plasma including but not limited to: identification and recruitment of potential donors, collection of plasma, storage and distribution of plasma, and infusion of convalescent plasma into recipients.

Evidence to decision

Benefits and harms	In non-severe patients, convalescent plasma does not result in an important impact on mortality. Convalescent plasma probably does not impact mechanical ventilation. There were no data evaluating the risk of hospitalization with convalescent plasma and therefore the impact is very uncertain.

	Convalescent plasma probably does not result in important increases in risks of transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), or allergic reactions.
Certainty of the evidence	The certainty in mortality was high, whereas mechanical ventilation was moderate due to serious risk of bias. Certainty was rated as moderate for TRALI and TACO due to serious risk of bias, and for allergic reactions due to concerns regarding risk of bias and imprecision.
Values and preferences	The GDG inferred that, in keeping with the agreed upon values and preferences (see Section 10), almost all well-informed patients would choose against receiving convalescent plasma based on available evidence regarding relative benefits and harms. From a population perspective, feasibility, acceptability, equity and cost are other important elements to take into account.
Resources and other considerations	**Acceptability and feasibility** The GDG noted that convalescent plasma use is associated with significant resource requirements including identification of potential donors, testing of donors to ensure adequate titres of anti-SARS-CoV-2 antibodies, collection of donor plasma, storage of plasma, transportation of plasma to recipient location, and administration of plasma. These resources and feasibility issues are compounded for those with non-severe disease who are most often outpatients. Also, this process is costly and time-consuming. Given the number of patients with non-severe disease and the low event rate in this subgroup of patients, mobilizing the use of convalescent plasma on a large scale would be of questionable feasibility. For patients with non-severe illness, the GDG considered that resource and feasibility issues may be amplified in outpatient setting, and mobilizing the use of convalescent plasma on a large scale would likely be of questionable feasibility. Although blood transfusion is acceptable to most, there is a subset of the population that will not accept allogenic blood transfusion. There are also regulatory challenges in most jurisdictions related to blood product transfusion.

Justification

A combination of the evidence, values and preferences, and feasibility contributed to the strong recommendation against convalescent plasma in patients with non-severe COVID-19. Most importantly, given there was no benefit demonstrated in any of the critical or important outcomes for either non-severe or severe or critical COVID-19, the GDG did not see any justification for the resources (including time and cost) that would be associated with administration of convalescent plasma. The recommendation also took into account possible associated harms (although not demonstrated in the evidence summary, there is always a potential for harms with blood product transfusion), the low baseline risk of mortality, mechanical ventilation, and hospitalization in non-severe illness, and feasibility challenges with the administration of convalescent plasma.

Titres

Titres of neutralizing antibodies varied substantially between included trials, with over half of the trials not reporting or considering recipient titres at all. In fact, the largest trial (RECOVERY) did not report on donor antibody titres at all. Even when titres were reported, the method for testing and the volume of plasma infused varied. This made it impossible to provide any analysis based on donor titre levels or assess for credible subgroup effects.

Applicability

The applicability of this recommendation to children or pregnant individuals is currently uncertain, as the included RCTs enrolled non-pregnant adults. The GDG had no reason to think that children with COVID-19 would respond any differently to treatment with convalescent plasma. However, the risk of hospitalization in children is generally extremely low and the GDG inferred that in the absence of immunosuppression or another significant risk factor children should not receive the intervention.

Clinical question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Convalescent plasma

Comparator: Standard care

Summary

Evidence summary

The LNMA on convalescent plasma included 16 RCTs that enrolled 16 236 patients across non-severe, severe and critical illness subgroups. All RCTs were registered, and 80% were published in peer-reviewed journals; 20% were pre-prints. 99% of participants were enrolled from inpatient settings; of them, 15% were admitted to the intensive care unit. 1% of patients were enrolled from outpatient settings. None of the included studies enrolled children or pregnant individuals. The Table shows characteristics of the RCTs, of which two trials used comparisons with plasma as placebo and were not included in the evidence summaries. We are aware of two additional published RCTs comparing convalescent plasma with standard care or placebo *[139][140]*. These trials were not incorporated in the latest analysis presented to the GDG, based on which recommendations were made.

For patients with non-severe COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of convalescent plasma compared with standard care for the outcomes of interest, with certainty ratings. This evidence summary was informed by the LNMA *[2]* pooling data from 1602 patients in 4 RCTs for the outcome of mortality and fewer data available for other outcomes, except for allergic reactions (8 RCTs, 243 patients). See Section 7 for sources of baseline risk estimates informing absolute estimates of effect.

Subgroup analysis

We pre-specified the following subgroup analyses of interest:

1. Age: younger adults (< 70 years) versus older adults (> 70 years).
2. Severity of illness (at time of treatment initiation): non-severe versus severe and critical.
3. Treatment dose: higher titre versus lower titre plasma.

The subgroup analyses were performed on patients across all disease severities. The majority of subgroups did not have sufficient data across outcomes of interest to pursue subgroup analyses.

Of those that did, we found no significant subgroup effects for severity of illness (p=0.80) and age (p=0.84) on mortality, and of severity of illness (p=0.17) on mechanical ventilation.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Convalescent plasma	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality closest to 90 days	Odds ratio 0.83 (CI 95% 0.43 — 1.46) Based on data from 1,602 participants in 4 studies. [1] (Randomized controlled)	**3** per 1000 Difference:	**2** per 1000 **1 fewer per 1000** (CI 95% 2 fewer — 1 more)	**High** [2]	Convalescent plasma does not result in an important impact on mortality.
Mechanical ventilation closest to 90 days	Odds ratio 0.71 (CI 95% 0.18 — 1.77) Based on data from 705 participants in 3 studies. [3] (Randomized controlled)	**6** per 1000 Difference:	**4** per 1000 **2 fewer per 1000** (CI 95% 5 fewer — 5 more)	**Moderate** Due to serious risk of bias [4]	Convalescent plasma probably does not impact mechanical ventilation.
Transfusion-related acute lung injury (TRALI) within 28 days	Based on data from 1,365 participants in 4 studies. [5] (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 5 fewer — 6 more)	**Moderate** Due to serious risk of bias [6]	Convalescent plasma probably does not result in an important increase in TRALI.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Convalescent plasma	**Certainty of the evidence** (Quality of evidence)	**Summary**
Transfusion-associated circulatory overload (TACO) within 28 days	Based on data from 1,442 participants in 4 studies. [7] (Randomized controlled)	**0** per 1000 Difference:	**5** per 1000 **5 more per 1000** (CI 95% 3 fewer — 12 more)	**Moderate** Due to serious risk of bias [8]	Convalescent plasma probably does not result in an important increase in TACO.
Allergic reactions within 28 days	Odds ratio 3.25 (CI 95% 1.27 — 9.3) Based on data from 15,243 participants in 8 studies. [9] (Randomized controlled)	**3** per 1000 Difference:	**10** per 1000 **7 more per 1000** (CI 95% 1 more — 24 more)	**Low** Due to concerns with risk of bias and imprecision [10]	Convalescent plasma probably does not result in an important increase in allergic reactions.

1. **Supporting references:** [142], [144], [141], [145],
2. **Risk of Bias: no serious.** The GDG did not rate down for risk of bias due to lack of blinding. .
3. **Supporting references:** [142], [141], [145],
4. **Risk of Bias: serious. Imprecision: no serious.** The GDG did not rate down for imprecision, because the credible interval excludes an important benefit and important harm.
5. **Supporting references:** [146], [142], [143], [147],
6. **Risk of Bias: serious.** Most patients were enrolled in unblinded studies. **Imprecision: no serious.** GDG decided not to rate down for imprecision, because credible interval excludes an important effect and baseline risk is very low.
7. **Supporting references:** [146], [141], [143], [147],
8. **Risk of Bias: serious.** Most patients were enrolled in unblinded studies. **Imprecision: no serious.** GDG decided not to rate down for imprecision, because credible interval excludes an important effect, and baseline risk is very low.
9. **Supporting references:** [148], [146], [149], [144], [141], [143], [150], [147],
10. **Risk of Bias: serious.** 2 trials (491 patients; 3% of total) were at low risk of bias vs. 6 trials (14 910 patients) at high risk of bias. **Imprecision: serious.** GDG agreed the credible interval includes some concern regarding allergic reactions, though acknowledges that the baseline risk is low.

For patients with severe or critical COVID-19

Only in research settings

We recommend not to use convalescent plasma for treatment of COVID-19, except in the context of a clinical trial *(recommended only in research settings)*.

Practical info

The GDG made a recommendation against using convalescent plasma in those with severe or critical COVID-19 outside the context of a clinical trial and a strong recommendation against using convalescent plasma for treatment of patients with non-severe COVID-19. Many practical issues exist related to convalescent plasma, including but not limited to: identification and recruitment of potential donors; collection of plasma; storage and distribution of plasma; and infusion of convalescent plasma into recipients.

Evidence to decision

Benefits and harms	In severe or critical patients, convalescent plasma may not result in an important impact on mortality, mechanical ventilation, time to symptom improvement, length of hospital stay or ventilator-free days.

Convalescent plasma probably does not result in important increases in risks of TRALI, TACO or allergic reactions. However, there is always potential for harms with blood product transfusion although not demonstrated in the evidence summary.

Certainty of the evidence

The certainty in mortality was low due to concerns with indirectness, risk of bias and imprecision. The GDG rated down certainty to low for mechanical ventilation, length of hospital stay and ventilator-free days due to serious risk of bias and serious imprecision, and to low for time to symptom improvement due to very serious imprecision.

Certainty was rated as moderate for TRALI and TACO due to serious risk of bias, and for allergic reactions due to concerns regarding risk of bias and imprecision.

Values and preferences

The GDG inferred that, in addition to the agreed upon values and preferences (see Section 10), almost all well-informed patients would choose against receiving convalescent plasma based on available evidence regarding relative benefits and harms. From a population perspective, feasibility, acceptability, equity and cost are other important elements to take into account (see Section 10).

Resources and other considerations

Acceptability and feasibility

The GDG noted that convalescent plasma use is associated with significant resource requirements including identification of potential donors, testing of donors to ensure adequate titres of anti-SARS-CoV-2 antibodies, collection of donor plasma, storage of plasma, transportation of plasma to recipient location, and administration of plasma. Also, this process is costly and time-consuming.

Although blood transfusion is acceptable to most, there is a subset of the population that will not accept allogenic blood transfusion. There are also regulatory challenges in most jurisdictions related to blood product transfusion.

Justification

After substantial discussion, the GDG decided to make a recommendation against convalescent plasma in patients with severe or critical COVID-19, except in the context of clinical trials. Given the low certainty evidence suggesting a small or no effect on mortality, mechanical ventilation, and time to symptom improvement, with possible associate harms (although not demonstrated in the evidence summary, there is always a potential for harms with blood product transfusion) the panel agreed further research addressing these patient-important outcomes would be valuable. This research focus on severe or critical COVID-19 was also informed by the feasibility (patients are already hospitalized) and baseline risk of mortality and requiring life support interventions (higher in severe or critical COVID-19). The panel identified high titre products as the highest priority for future research as well as the need of reporting on donor titre and volume infused which can give an idea of dilution of titres in the recipient. Similarly, the panel identified seronegative COVID-19 patients as the highest priority for future convalescent plasma research.

A recommendation to only use a drug in the setting of clinical trials is appropriate when there is low certainty evidence, and future research has a potential for reducing uncertainty about the effects of the intervention and for doing so at a reasonable cost.

Clinical question/ PICO

Population: Patients with severe or critical COVID-19
Intervention: Convalescent plasma
Comparator: Standard care

Summary

Evidence summary for convalescent plasma

Please see summary for patients with non-severe COVID-19 above. It provides details about the LNMA and 16 included trials across disease severities, as well as subgroup analyses that did not detect credible effects based on age, severity of illness, or dosage of convalescent plasma.

The GRADE Summary of Findings table shows the relative and absolute effects of convalescent plasma compared with usual standard for the outcomes of interest for patients with severe and critical COVID-19, with certainty ratings. This evidence summary was informed by the LNMA *[2]*, pooling data from from 14 366 patients in 10 studies for the outcome of mortality, with fewer data available for other outcomes.

Baseline risk estimates

For severe and critical illness, for the critical outcome of mortality, the applied baseline risk estimate was 13% (130 in 1000). As for other related recommendations in this guideline, the estimate is derived from the SOLIDARITY trial for severe and critical patients adjusted for treatment effects of corticosteroids. For other outcomes, we used the median of the control arm of the RCTs that contributed to the evidence (see Section 7).

Subgroup analysis

We pre-specified the following subgroup analyses of interest:

1. Age: younger adults (< 70 years) versus older adults (> 70 years).
2. Severity of illness (at time of treatment initiation): non-severe versus severe and critical.
3. Treatment dose: higher titre versus lower titre plasma.

The majority of subgroups did not have sufficient data across outcomes of interest to pursue subgroup analyses.

Of those that did, we found no significant subgroup effects for severity of illness (p=0.80) and age (p=0.84) on mortality, and of severity of illness (p=0.17) on mechanical ventilation.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Convalescent plasma	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality closest to 90 days	Odds ratio 0.92 (CI 95% 0.7 — 1.12) Based on data from 14,366 participants in 10 studies. [1] (Randomized controlled)	**130** per 1000 Difference:	**121** per 1000 **9 fewer per 1000** (CI 95% 35 fewer — 13 more)	**Very low** Due to concerns with indirectness, risk of bias, and imprecision [2]	Convalescent plasma may have a small or no effect on mortality.
Mechanical ventilation closest to 90 days	Odds ratio 0.92 (CI 95% 0.46 — 1.68) Based on data from 623 participants in 5 studies. [3] (Randomized controlled)	**86** per 1000 Difference:	**80** per 1000 **6 fewer per 1000** (CI 95% 45 fewer — 50 more)	**Low** Due to serious risk of bias and serious imprecision [4]	Convalescent plasma may not impact mechanical ventilation.
Transfusion-related acute lung injury (TRALI) within 28 days	Based on data from 1,365 participants in 4 studies. [5] (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 5 fewer — 6 more)	**Moderate** Due to serious risk of bias [6]	Convalescent plasma probably does not result in an important increase in TRALI.
Transfusion-associated circulatory overload (TACO) within 28 days	Based on data from 1,442 participants in 4 studies. [7] (Randomized controlled)	**0** per 1000 Difference:	**5** per 1000 **5 more per 1000** (CI 95% 3 fewer —	**Moderate** Due to serious risk of bias [8]	Convalescent plasma probably does not result in an important increase in TACO.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Convalescent plasma	**Certainty of the evidence** (Quality of evidence)	**Summary**
			12 more)		
Allergic reactions within 28 days	Odds ratio 3.25 (CI 95% 1.27 — 9.3) Based on data from 15,243 participants in 8 studies. [9] (Randomized controlled)	**3** per 1000 Difference:	**10** per 1000 **7 more per 1000** (CI 95% 1 more — 24 more)	**Low** Due to concerns with risk of bias and imprecision [10]	Convalescent plasma probably does not result in an important increase in allergic reactions.
Time to symptom improvement	Lower better Based on data from 472 participants in 3 studies. [11] (Randomized controlled)	**15** (Mean) Difference:	**15** (Mean) **MD 0 fewer** (CI 95% 10.4 fewer — 33.6 more)	**Low** Due to very serious imprecision [12]	Convalescent plasma may not impact time to symptom improvement.
Length of hospital stay	Measured by: days Lower better Based on data from 1,015 participants in 7 studies. [13] (Randomized controlled)	**11.7** days (Mean) Difference:	**11** days (Mean) **MD 0.7 fewer** (CI 95% 2.3 fewer — 1 more)	**Low** Due to serious risk of bias and serious imprecision [14]	Convalescent plasma may not impact length of hospital stay.
Ventilator-free days within 28 days	Measured by: days High better Based on data from 2,859 participants in 3 studies. [15] (Randomized controlled)	**13.7** days (Mean) Difference:	**13** days (Mean) **MD 0.7 fewer** (CI 95% 1.8 fewer — 0.4 more)	**Low** Due to serious risk of bias and serious imprecision [16]	Convalescent plasma may not impact the number of ventilator-free days.

1. **Supporting references:** [148], [152], [146], [149], [154], [153], [144], [151], [150], [147],
2. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.** Credible intervals include both important benefit and important harm.
3. **Supporting references:** [152], [146], [151], [143], [150],
4. **Risk of Bias: serious. Imprecision: serious.** The GDG decided the credible intervals warranted downgrading only once for imprecision.
5. **Supporting references:** [147], [146], [142], [143],
6, 8. **Risk of Bias: serious.** Most patients were enrolled in unblinded studies. **Imprecision: no serious.** GDG decided not to rate down for imprecision, because credible interval excludes an important effect, and baseline risk is low.
7. **Supporting references:** [147], [146], [141], [143],
9. **Supporting references:** [141], [143], [150], [147], [148], [146], [149], [144],
10. **Risk of Bias: serious.** 2 trials (491 patients; 3% of total) were at low risk of bias vs. 6 trials (14 910 patients) at high risk of bias. **Imprecision: serious.** GDG agreed the credible interval includes some concern regarding allergic reactions, though acknowledges the baseline risk is low.
11. **Supporting references:** [146],
12. **Imprecision: very serious.**
13. **Supporting references:** [150], [147], [152], [154], [153], [146], [151],
14. **Risk of Bias: serious.** All studies except one were not adequately blinded. **Imprecision: serious.** Credible interval does not exclude small but important benefit.
15. **Supporting references:** [150], [148], [147],
16. **Risk of Bias: serious.** Almost all patients were randomized to trials that were not blinded. **Imprecision: serious.** Credible interval

does not exclude important benefit.

Mechanism of action of convalescent plasma

The proposed primary mechanism of action for convalescent plasma involves the transfer of endogenously produced neutralizing antibodies present within the plasma from previously infected and recovered patients into patients with active infection *[155]*. Therefore, the underlying plausibility for this mechanism of action depends upon whether sufficient antibody concentrations remain following the dilution from donor to recipient. As such, the neutralizing antibody titre within the donor plasma as well as the volume administered are likely to be important. Data generated in Syrian golden hamsters have demonstrated efficacy of convalescent plasma against SARS-CoV-2 at a titre of 1:2560, but not at a titre of 1:320, when given at a volume of 1 mL, which extrapolates based on average blood volume to a human dosing volume of 300 mL *[156]*.

At the extremes of the studies which have investigated convalescent plasma clinically and reported the dose in terms of neutralizing antibody titre and volume administered, administration of 200 mL would be expected to result in an average dilution of 25-fold whereas administration of 1000 mL would be expected to result in an average dilution of 5-fold from those titres present in the circulation of the donor themselves (assuming an average human blood volume of 5 L *[157]*). It should be further recognized that the concentrations (titre) of neutralizing antibodies present within convalescent plasma are highly variable between donors and that there are different methodologies available to measure it *[158]*.

Antibody titre, methodology employed, and the volume of convalescent plasma administered all vary widely across the studies that have investigated this approach in COVID-19. It should be further noted that in some trials, the antibody titre reported for eligibility was higher than the reported antibody titre in the donor plasma that was used because of the differences in methodology used for the two assessments (e.g. total IgG for donor eligibility with subsequent assessment of the specific neutralizing antibody titre *[159]*). There is clear uncertainty surrounding the dose of neutralizing antibodies given in different trials and this uncertainty is summarized as follows:

For trials in severe/critical patients:

- No cut-off in neutralizing antibody titre of the donor was applied in 9/16 studies.
- Antibody titre of the donor plasma was not recorded in 12/16 trials, meaning the titre may have been high or may have been low. However, in three of the trials in which donor titre was not recorded, a lower cut-off was applied at a titre of either 1:160 (for two trials) or 1:400.
- The largest trial (RECOVERY) did not report donor antibody titres although only donors with a titre above 1:100 were eligible.
- One (1/16) trial did not provide information on what volume of plasma was administered meaning volume could have been high or could have been low.
- Both volume and donor titre were only known for 6/16 trials. Donor titres were 1:80, 1:87, 1:300, 1:320, 1:526 and 1:640 with volumes of 300, 500, 400–600, approx. 480, 750–975 and 300 mL, respectively (estimated dose range of 6-fold).

For trials in non-severe patients:

- Only three trials were conducted in non-severe patients using antibody titres of 1:40, 1:292 and 1:3200 with volumes administered of 250–300 mL, 400 mL and 250 mL, respectively (estimated dose range of 100-fold).
- Two trials studied both non-severe and severe/critical patients, one of which didn't record antibody titre, and the other which used 200–250 +/- 75 mL of plasma with a titre of 1:160.

Lopinavir-ritonavir (published 17 December 2020)

The recommendation for lopinavir-ritonavir was initially published on 17 December 2020. No subsequent changes have been made.

For patients with COVID-19, regardless of disease severity

Strong recommendation against

We recommend not to use lopinavir-ritonavir *(strong recommendation against)*.

Remark: This recommendation applies to patients with any disease severity and any duration of symptoms.

Practical info

Given the strong recommendation against using lopinavir-ritonavir, practical considerations were felt to be less relevant here.

Evidence to decision

Benefits and harms

The GDG panel found a lack of evidence that lopinavir-ritonavir improved outcomes that matter to patients such as reduced mortality, need for mechanical ventilation, time to clinical improvement and others. For mortality and need for mechanical ventilation this was based on moderate certainty evidence, for the other outcomes low or very low certainty evidence.

There was low certainty evidence that lopinavir-ritonavir may increase the risk of diarrhoea and nausea and vomiting, a finding consistent with the indirect evidence evaluating its use in patients with HIV. Diarrhoea and vomiting may increase the risk of hypovolaemia, hypotension and acute kidney injury, especially in settings where health care resources are limited. There was an uncertain effect on viral clearance and acute kidney injury.

Subgroup analysis indicated no effect modification based on severity of illness (comparing either critical vs severe/non-severe or non-severe vs critical/severe) or age (comparing those aged < 70 years versus those 70 years and older). As there was no evidence of a statistical subgroup effect, we did not formally evaluate using the ICEMAN tool.

Certainty of the evidence

The evidence is based on a linked systematic review and NMA of seven RCTs; pooling data from 7429 patients hospitalized with various severities of COVID-19 and variably reporting the outcomes of interest to the guideline panel *[1]*. The panel agreed that there was moderate certainty for mortality and need for mechanical ventilation, low certainty for diarrhoea, nausea and duration of hospitalization and very low certainty in the estimates of effect for viral clearance, acute kidney injury and time to clinical improvement. Most outcomes were lowered for risk of bias and imprecision (wide confidence intervals which do not exclude important benefit or harm).

Values and preferences

Applying the agreed values and preferences (see Section 10), the GDG inferred that almost all well-informed patients would not want to receive lopinavir-ritonavir given the evidence suggested there was probably no effect on mortality or need for mechanical ventilation and there was a risk of adverse events including diarrhoea and nausea and vomiting. The panel did not expect there would be much variation in values and preferences between patients when it came to this intervention.

Resources and other considerations

Although the cost of lopinavir-ritonavir is not as high as some other investigational drugs for COVID-19, and the drug is generally available in most health care settings, the GDG raised concerns about opportunity costs and the importance of not drawing attention and resources away from best supportive care or the use of corticosteroids in severe COVID-19.

Justification

When moving from evidence to the strong recommendation against the use of lopinavir-ritonavir for patients with COVID-19, the panel emphasized the moderate certainty evidence of probably no reduction in mortality or need for mechanical ventilation. It also noted the evidence suggesting possible harm associated with treatment, with increased nausea and diarrhoea. The GDG did not anticipate

important variability in patient values and preferences, and other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity would not alter the recommendation (see summary of these factors under Evidence to Decision).

Subgroup analysis
The panel did not find any evidence of a subgroup effect across patients with different levels of disease severity, or between adults and older adults and therefore did not make any subgroup recommendation for this drug. Although the trials did not report subgroup effects by time from symptom onset, many of the trials enrolled patients early in the disease course. The strong recommendation is applicable across disease severity and age groups.

Applicability
None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. However, the panel had no reason to think that children with COVID-19 would respond any differently to treatment with lopinavir-ritonavir. There were similar considerations in regards to pregnant individuals, with no data directly examining this population, but no rationale to suggest they would respond differently than other adults. In patients using lopinavir-ritonavir for HIV infection, it should generally be continued while receiving care for COVID-19.

Uncertainties
Please see Section 12 for residual uncertainties. The GDG panel felt that it was unlikely future studies would identify a subgroup of patients that are likely to benefit from lopinavir-ritonavir.

Additional considerations
In patients who have undiagnosed or untreated HIV, use of lopinavir-ritonavir alone may promote HIV resistance to important antiretrovirals. Widespread use of lopinavir-ritonavir for COVID-19 may cause drug shortages for people living with HIV.

Clinical question/ PICO

Population: Patients with COVID-19 (all disease severities)
Intervention: Lopinavir-ritonavir
Comparator: Standard care

Summary

Evidence summary
The LNMA on lopinavir-ritonavir was based on 7 RCTs with 7429 participants. Of note, none of the included studies enrolled children or adolescents under the age of 19 years old (see Table). The GRADE Summary of Findings table shows the relative and absolute effects of lopinavir-ritonavir compared with standard care for the outcomes of interest in patients with COVID-19 across all disease severities, with certainty ratings. See Section 7 for sources of baseline risk estimates informing absolute estimates of effect.

Subgroup analysis
For lopinavir-ritonavir, the GDG panel requested subgroup analyses based on age (considering children vs younger adults [e.g. under 70 years] vs older adults [e.g. 70 years or older]), and illness severity (non-severe vs severe vs critical COVID-19). The GDG discussed other potential subgroups of interest including time from onset of symptoms until initiation of therapy and concomitant medications, but recognized that these analyses would not be possible without access to individual participant data and/or more detailed reporting from the individual trials.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Lopinavir-ritonavir	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality	Odds ratio 1 (CI 95% 0.82 — 1.2) Based on data from 8,061 participants in 4 studies. [1] (Randomized controlled)	**106** per 1000 Difference:	**106** per 1000 **0 fewer per 1000** (CI 95% 17 fewer — 19 more)	**Moderate** Due to borderline risk of bias and imprecision [2]	Lopinavir-ritonavir probably has no effect on mortality.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Lopinavir-ritonavir	Certainty of the evidence (Quality of evidence)	Summary
Mechanical ventilation	Relative risk 1.16 (CI 95% 0.98 — 1.36) Based on data from 7,579 participants in 3 studies. (Randomized controlled)	**105** per 1000 Difference:	**122** per 1000 **17 more per 1000** (CI 95% 2 fewer — 38 more)	**Moderate** Due to borderline risk of bias and imprecision [3]	Lopinavir-ritonavir probably does not reduce mechanical ventilation.
Viral clearance	Odds ratio 0.35 (CI 95% 0.04 — 1.97) Based on data from 171 participants in 2 studies. [4] (Randomized controlled)	**483** per 1000 Difference:	**246** per 1000 **237 fewer per 1000** (CI 95% 447 fewer — 165 more)	**Low** Due to very serious imprecision [5]	The effects of lopinavir-ritonavir on viral clearance is very uncertain.
Acute kidney injury	Relative risk Based on data from 259 participants in 2 studies. (Randomized controlled)	**45** per 1000 Difference:	**25** per 1000 **20 fewer per 1000** (CI 95% 70 fewer — 20 more)	**Very low** Due to serious risk of bias and very serious imprecision [6]	The effect of lopinavir-ritonavir on acute kidney injury is uncertain.
Diarrhoea	Odds ratio 4.28 (CI 95% 1.99 — 9.18) Based on data from 370 participants in 4 studies. (Randomized controlled)	**67** per 1000 Difference:	**235** per 1000 **168 more per 1000** (CI 95% 58 more — 330 more)	**Moderate** Due to serious risk of bias and imprecision; upgraded due to large magnitude of effect [7]	Lopinavir-ritonavir may increase the risk of diarrhoea.
Nausea/vomiting	Relative risk Based on data from 370 participants in 4 studies. (Randomized controlled)	**17** per 1000 Difference:	**177** per 1000 **160 more per 1000** (CI 95% 100 more — 210 more)	**Moderate** Due to serious risk of bias and imprecision [8]	Lopinavir-ritonavir may increase the risk of nausea/vomiting.
Time to clinical improvement	Lower better Based on data from 199 participants in 1 studies. (Randomized controlled)	**11** days (Mean) Difference:	**10** days (Mean) **MD 1 fewer** (CI 95% 4.1 fewer — 3.2 more)	**Very low** Due to serious risk of bias and very serious imprecision [9]	The effect of lopinavir-ritonavir improves on time to clinical improvement is very uncertain.
Duration of hospitalization	Lower better Based on data from 5,239 participants in 2 studies. (Randomized controlled)	**12.8** days (Mean) Difference:	**12.5** days (Mean) **MD 0.3 lower** (CI 95% 3 lower — 2.5 higher)	**Low** Due to serious risk of bias and imprecision [10]	Lopinavir-ritonavir may have no effect on duration of hospitalization.

1. **Comparator:** Primary study [15]. Baseline risk for mortality and mechanical ventilation were derived from the WHO SOLIDARITY trial for patients with severe and critical COVID-19. **Supporting references:** [1],
2. **Imprecision: serious.** The 95% CI crosses the minimally important difference (2% reduction in mortality).
3. **Imprecision: serious.** Wide confidence intervals.

4. **Comparator:** We used the median event rate for all patients randomized to usual care across included studies. **Supporting references:** [1],
5. **Imprecision: very serious.** Wide confidence intervals.
6. **Risk of Bias: serious. Imprecision: very serious.** Wide confidence intervals.
7, 8. **Risk of Bias: serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results. **Imprecision: serious.** Few patients and events. **Upgrade: large magnitude of effect.**
9. **Risk of Bias: serious. Imprecision: very serious.** Wide confidence intervals, low number of patients.
10. **Risk of Bias: serious. Imprecision: serious.** Wide confidence intervals.

Hydroxychloroquine (published 17 December 2020)

The recommendation for hydroxychloroquine was initially published on 17 December 2020. No subsequent changes have been made.

For patients with COVID-19, regardless of disease severity

Strong recommendation against

We recommend not to use hydroxychloroquine or chloroquine *(strong recommendation against)*.

This recommendation applies to patients with any disease severity and any duration of symptoms.

Practical info

The GDG made a strong recommendation against using hydroxychloroquine or chloroquine for treatment of patients with COVID-19. The use of hydroxychloroquine may preclude the use of other important drugs that also prolong the QT interval, such as azithromycin and fluoroquinolones. Concomitant use of drugs that prolong the QT interval should be done with extreme caution.

Evidence to decision

Benefits and harms

Hydroxychloroquine and chloroquine probably do not reduce mortality or mechanical ventilation and may not reduce duration of hospitalization. The evidence does not exclude the potential for a small increased risk of death and mechanical ventilation with hydroxychloroquine. The effect on other less important outcomes, including time to symptom resolution, admission to hospital, and duration of mechanical ventilation, remains uncertain.

Hydroxychloroquine may increase the risk of diarrhoea and nausea/vomiting; a finding consistent with evidence from its use in other conditions. Diarrhoea and vomiting may increase the risk of hypovolaemia, hypotension and acute kidney injury, especially in settings where health care resources are limited. Whether or not and to what degree hydroxychloroquine increases the risk of cardiac toxicity, including life-threatening arrhythmias, is uncertain.

Subgroup analyses indicated no effect modification based on severity of illness (comparing either critical vs severe/non-severe or non-severe vs critical/severe) or age (comparing those aged < 70 years vs older). Further, the cumulative dose and predicted Day 3 serum trough concentrations did not modify the effect for any outcome. Therefore, we assumed similar effects in all subgroups.

We also reviewed evidence comparing the use of hydroxychloroquine plus azithromycin vs hydroxychloroquine alone. There was no evidence that the addition of azithromycin modified the effect of hydroxychloroquine for any outcome (very low certainty).

Certainty of the evidence	For the key outcomes of mortality and mechanical ventilation, the panel considered the evidence to be of moderate certainty. There were residual concerns about lack of blinding in the largest trials and the imprecision. For example, the credible interval around the pooled effect leaves open the possibility of a very small reduction in mortality. The quality of evidence was low for diarrhoea and nausea/vomiting because of lack of blinding in many of the trials and because the total number of patients enrolled in trials reporting these outcomes was smaller than the optimal information size (although the credible interval laid entirely on the side of harm for both outcomes). For all other outcomes, the certainty of the evidence was low or very low. The primary concerns with the data were imprecision (credible intervals included both important benefit and important harm) as well as risk of bias (lack of blinding).
Values and preferences	Applying the agreed values and preferences (see Section 10), the GDG inferred that almost all well-informed patients would not want to receive hydroxychloroquine given the evidence suggesting there was probably no effect on mortality or need for mechanical ventilation and there was a risk of adverse events including diarrhoea and nausea and vomiting. The panel did not expect there would be much variation in values and preferences between patients when it came to this intervention.
Resources and other considerations	Hydroxychloroquine and chloroquine are relatively inexpensive compared with other drugs used for COVID-19 and are already widely available, including in low-income settings. Despite this, the panel felt that almost all patients would choose not to use hydroxychloroquine or chloroquine because the harms outweigh the benefits. Although the cost may be low per patient, the GDG panel raised concerns about diverting attention and resources away from care likely to provide a benefit such as corticosteroids in patients with severe COVID-19 and other supportive care interventions.

Justification

When moving from evidence to the strong recommendation against the use of hydroxychloroquine or chloroquine for patients with COVID-19, the panel emphasized the moderate certainty evidence of probably no reduction in mortality or need for mechanical ventilation. It also noted the evidence suggesting possible harm associated with treatment, with increased nausea and diarrhoea. The GDG did not anticipate important variability in patient values and preferences, and other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity (see summary of these factors under Evidence to decision).

Subgroup analyses

The panel did not find any evidence of a subgroup effect across patients with different levels of disease severity, between adults and older adults, and by different doses, and therefore did not make any subgroup recommendation for this drug. In other words, the strong recommendation is applicable across disease severity, age groups, and all doses and dose schedules of hydroxychloroquine.

The trials included patients from around the world, with all disease severities, and treated in different settings (outpatient and inpatient). Although the trials did not report subgroup effects by time from symptom onset, many of the trials enrolled patients early in the disease course. The GDG panel therefore felt that the evidence applies to all patients with COVID-19.

Applicability

Special populations

None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. However, the panel had no reason to think that children with COVID-19 would respond any differently to treatment with hydroxychloroquine. There were similar considerations in regards to pregnant individuals, with no data directly examining this population, but no rationale to suggest they would respond differently than other adults. Hydroxychloroquine crosses the placental barrier and there are concerns that it may lead to retinal damage in neonates. Although hydroxychloroquine has been used in pregnant individuals with systemic autoimmune diseases, such as systemic lupus erythematosus, pregnant individuals may have even more reasons than other patients to be reluctant to use hydroxychloroquine for COVID-19.

In combination with azithromycin

There was no evidence from the NMA that the addition of azithromycin modified the effect of hydroxychloroquine for any outcome. As there were no trial data suggesting that azithromycin favourably modifies the effect of hydroxychloroquine, the recommendation against hydroxychloroquine and chloroquine applies to patients whether or not they are concomitantly receiving azithromycin.

Uncertainties
Please see Section 12 for residual uncertainties. The GDG panel felt that it was unlikely future studies would identify a subgroup of patients that are likely to benefit from hydroxychloroquine or chloroquine.

Clinical question/ PICO

Population: Patients with COVID-19 (all disease severities)
Intervention: Hydroxychloroquine
Comparator: Standard care

Summary

Evidence summary
The LNMA on hydroxychloroquine was based on 30 RCTs with 10 921 participants, providing relative estimates of effect for patient-important outcomes (see Table). Five of the trials (414 total participants) randomized some patients to chloroquine.

The GRADE Summary of Findings table shows the relative and absolute effects of hydroxychloroquine compared with standard care for the outcomes of interest in patients with COVID-19, with certainty ratings. See Section 7 for sources of baseline risk estimates informing absolute estimates of effect.

Subgroup analysis
For hydroxychloroquine, the GDG panel requested subgroup analyses based on age (considering children vs younger adults [e.g. < 70 years] vs older adults [e.g. 70 years or older]), illness severity (non-severe vs severe vs critical COVID-19) and based on whether or not it was co-administered with azithromycin.

The panel also requested a subgroup analysis based on high dose vs low dose hydroxychloroquine. A categorical approach to hydroxychloroquine dosing proved impossible because the trials used varying loading doses, continuation doses and durations. Therefore, in collaboration with a pharmacology expert (Professor Andrew Owen), we modelled the expected serum concentrations over time. We hypothesized that higher trough concentrations early in the treatment course (e.g. trough concentration on Day 3) might be more effective than lower early trough concentrations. We also hypothesized that higher maximum serum concentrations (e.g. peak concentration on the last day) might result in higher risk of adverse effects than lower maximum serum concentrations. In our pharmacokinetic model, the cumulative dose was highly correlated with all measures of serum concentrations on Day 3 and the final day of treatment, and therefore we decided to use cumulative dose as the primary analysis. Day 3 trough concentration was least strongly correlated with total cumulative dose (R2 = 0.376) and therefore we performed a sensitivity subgroup analysis with predicted Day 3 trough concentrations for efficacy outcomes.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Hydroxychloroquine	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality	Odds ratio 1.11 (CI 95% 0.95 — 1.31) Based on data from 10,859 participants in 29 studies. [1] (Randomized controlled)	**106** per 1000 Difference:	**116** per 1000 **10 more per 1000** (CI 95% 5 fewer — 28 more)	**Moderate** Due to borderline risk of bias and imprecision [2]	Hydroxychloroquine probably does not reduce mortality.
Mechanical ventilation	Odds ratio 1.2 (CI 95% 0.83 — 1.81) Based on data from 6,379 participants in 5 studies. (Randomized controlled)	**105** per 1000 Difference:	**123** per 1000 **18 more per 1000** (CI 95% 16 fewer — 70 more)	**Moderate** Due to borderline risk of bias and serious imprecision [3]	Hydroxychloroquine probably does not reduce mechanical ventilation.
Viral clearance 7 days	Odds ratio 1.08 (CI 95% 0.25 — 4.78) Based on data from 280 participants in 4 studies. [4] (Randomized controlled)	**483** per 1000 Difference:	**502** per 1000 **19 more per 1000** (CI 95% 294 fewer	**Very low** Due to very serious imprecision [5]	The effect of hydroxychloroquine on viral clearance is very uncertain.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Hydroxychloroquine	**Certainty of the evidence** (Quality of evidence)	**Summary**
			— 334 more)		
Admission to hospital	Odds ratio 0.39 (CI 95% 0.12 — 1.28) Based on data from 465 participants in 1 studies. (Randomized controlled)	**47** per 1000 Difference:	**19** per 1000 **28 fewer per 1000** (CI 95% 41 fewer — 12 more)	**Very low** Due to very serious imprecision and serious indirectness [6]	The effect of hydroxychloroquine on admission to hospital is uncertain.
Cardiac toxicity	Based on data from 3,287 participants in 7 studies. (Randomized controlled)	**46** per 1000 Difference:	**56** per 1000 **10 more per 1000** (CI 95% 0 more — 30 more)	**Very low** Due to serious imprecision, risk of bias, and indirectness [7]	The effect of hydroxychloroquine on cardiac toxicity is uncertain.
Diarrhoea	Odds ratio 1.95 (CI 95% 1.4 — 2.73) Based on data from 979 participants in 6 studies. (Randomized controlled)	**149** per 1000 Difference:	**255** per 1000 **106 more per 1000** (CI 95% 48 more — 174 more)	**Low** Due to serious imprecision and risk of bias [8]	Hydroxychloroquine may increase the risk of diarrhoea.
Nausea/vomiting	Odds ratio 1.74 (CI 95% 1.26 — 2.41) Based on data from 1,429 participants in 7 studies. (Randomized controlled)	**99** per 1000 Difference:	**161** per 1000 **62 more per 1000** (CI 95% 23 more — 110 more)	**Low** Due to serious imprecision and serious risk of bias [9]	Hydroxychloroquine may increase the risk of nausea and vomiting.
Delirium	Odds ratio 1.59 (CI 95% 0.77 — 3.28) Based on data from 423 participants in 1 studies. (Randomized controlled)	**62** per 1000 Difference:	**95** per 1000 **33 more per 1000** (CI 95% 14 fewer — 116 more)	**Very low** Due to very serious imprecision and serious indirectness [10]	The effect of hydroxychloroquine on delirium is uncertain.
Time to clinical improvement	Lower better Based on data from 479 participants in 5 studies. (Randomized controlled)	**11** days (Mean) Difference:	**9** days (Mean) **MD 2 fewer** (CI 95% 4 fewer — 0.1 more)	**Very low** Due to serious risk of bias, imprecision, and indirectness [11]	The effect of hydroxychloroquine on time to clinical improvement is uncertain.
Duration of hospitalization	Lower better Based on data from 5,534 participants in 5 studies. (Randomized controlled)	**12.8** days (Mean) Difference:	**12.9** days (Mean) **MD 0.1 more** (CI 95% 1.9 fewer — 2 more)	**Low** Due to serious imprecision and serious risk of bias [12]	Hydroxychloroquine may have no effect on duration of hospitalization.
Time to viral	Lower better	**9.7**	**10.6**	**Very low** Due to serious risk	The effect of hydroxychloroquine on

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Hydroxychloroquine	Certainty of the evidence (Quality of evidence)	Summary
clearance	Based on data from 440 participants in 5 studies. (Randomized controlled)	days (Mean) Difference:	days (Mean) **MD 0.7 fewer** (CI 95% 4.3 fewer — 4.8 more)	of bias and very serious imprecision [13]	time to viral clearance is uncertain.
Adverse events leading to drug discontinuation	Based on data from 210 participants in 3 studies. (Randomized controlled)	Two of 108 patients randomized to hydroxychloroquine discontinued treatment because of adverse effects. None of 102 patients did so in the placebo/standard care group.		**Very low** Due to extremely serious imprecision [14]	The effect of hydroxychloroquine on adverse events leading to drug discontinuation is uncertain.

1. Systematic review [1] **Comparator:** Primary study Baseline risk for mortality and mechanical ventilation were derived from the WHO SOLIDARITY trial for patients with severe and critical COVID-19.
2. **Imprecision: serious.** The 95% CI crosses the minimally important difference (2% reduction in mortality). .
3. **Imprecision: serious.** Wide confidence intervals.
4. We used the median event rate for all patients randomized to usual care across included studies. **Supporting references:** [1],
5. **Imprecision: very serious.** Wide confidence intervals.
6. **Indirectness: serious. Imprecision: very serious.**
7. **Risk of Bias: serious.** Unblinded studies -> cardiac toxicity differential detection. **Indirectness: serious.** Studies measured serious cardiac toxicity differently. **Imprecision: serious.**

8, 9. **Risk of Bias: serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results. **Imprecision: serious.** OIS not met. **Upgrade: large magnitude of effect.**

10. **Indirectness: serious.** This outcome was not collected systematically and the definition of delirium was not specified. **Imprecision: very serious.**
11. **Risk of Bias: serious. Indirectness: serious.** Studies measured clinical improvement differently. **Imprecision: serious.**
12. **Risk of Bias: serious. Imprecision: serious.** Wide confidence intervals.
13. **Risk of Bias: serious. Imprecision: very serious.**
14. **Imprecision: extremely serious.**

Casirivimab-imdevimab (updated 13 January 2023)

The recommendation for casirivimab-imdevimab was initially published on 24 September 2021, and was updated on 3 March 2022, with no subsequent changes.

For all patients with COVID-19, regardless of disease severity

Strong recommendation against

We recommend against treatment with casirivimab-imdevimab *(strong recommendation against).*

- *The GDG considered in vitro data demonstrating that casirivimab-imdevimab does not neutralize the currently circulating variants of SARS-CoV-2 and their subvariants.*
- *There was consensus among the panel that the meaningful reduction of in vitro neutralization activity strongly suggests absence of clinical effectiveness of monoclonal antibodies such as sotrovimab and casirivimab-imdevimab.*
- *There was also consensus regarding the need for clinical trial evidence in order to confirm clinical effectiveness of new monoclonal antibodies that reliably neutralize circulating strains in vitro.*

Practical info

Given the strong recommendation against using casirivimab-imdevimab for all patients with COVID-19, practical considerations were felt to be less relevant here.

Evidence to decision

Benefits and harms

On the basis of clinical trial evidence that remains available via the LNMA *[1]*, the GDG had previously made a conditional recommendation to administer casirivimab-imdevimab to patients with non-severe COVID-19 (driven by benefits in reduction of hospital admission) as well as seronegative patients with severe and critical illness (driven by reductions in mortality and mechanical ventilation) as shown in previous GRADE Summary of Findings tables. At the time, the panel acknowledged that the emergence of future variants could reduce the clinical effectiveness of casirivimab-imdevimab.

Rather than new clinical trial evidence, the change in recommendation was triggered by new *in vitro* evidence demonstrating that casirivimab-imdevimab has very diminished *in vitro* neutralization activity to currently circulating subvariants of SARS-CoV-2. There was consensus among the panel that it is highly unlikely that the clinical effectiveness of casirivimab-imdevimab would persist in the absence of adequate *in vitro* neutralization of the circulating variants. Accordingly, the panel concluded that the evidence upon which the previous recommendations hinged was no longer applicable.

The GDG reviewed additional *in vitro* neutralization data that emerged after the change in the guideline for sotrovimab and casirivimab-imdevimab and that included information on new variants. This incremental evidence supports the change in recommendation and strengthens the GDG's confidence that the strong recommendation not to use casirivimab-imdevimab (and sotrovimab) is applicable to the current SARS-CoV-2 ecology. More information on the interpretation of the results of *in vitro* neutralization data can be found in the Mechanism of action section and in correspondence published in the *Lancet [58]*.

Certainty of the evidence

In light of the recent *in vitro* evidence, the GDG concluded that the clinical effects of casirivimab-imdevimab for COVID-19 caused by the currently circulating variants and subvariants of SARS-CoV-2 are highly uncertain. Trials performed before these variants occurred provided overall moderate certainty evidence for modest benefits and negligible harms, as demonstrated in GRADE Summary of Findings tables available in previous versions of this living guideline.

Values and preferences

Applying the agreed upon values and preferences (see Section 10), the GDG inferred that, in the absence of compelling evidence of clinical effectiveness for the currently circulating SARS-CoV-2 variants, almost all well-informed patients would choose to not receive casirivimab-imdevimab.

Resources and other considerations

Acceptability and feasibilty

The strong recommendation against the use of casirivimab-imdevimab is further supported by the challenges with availability and feasibility, such as limited production, intravenous administration and requirement for expertise to offer such treatment while oral options are also available.

Justification

Although previous clinical trial evidence available via the LNMA *[2]* remains accurate, the panel concluded that it is no longer applicable to COVID-19 caused by the SARS-CoV-2 variants that are currently circulating globally. The panel surmised that the likelihood of COVID-19 caused by former variants was extremely low and that, accordingly, evidence of casirivimab-imdevimab clinical effectiveness for COVID-19 was nonexistent.

Of note, the panel applied the same rationale to the recommendation for sotrovimab.

Reliance on *in vitro* evidence

The GDG agreed that large high-quality clinical trials generally provide the best evidence of clinical effectiveness for therapeutic interventions. The GDG also continues to base its recommendations strictly on predefined patient-important outcomes. From the perspective of clinical practice guidelines, mechanistic studies and surrogate outcomes are useful to identify candidate therapies for clinical trials, but are of no use in confirming clinical effectiveness. The panel concluded that the emerging evidence demonstrating that casirivimab-imdevimab did not comparatively neutralize current variants *in vitro* would have justified not launching clinical trials

and now renders the results of previous trials inapplicable. *In vitro* assays were deemed sufficient to rule out a clinical effect. Notwithstanding, proof of potent *in vitro* neutralization would not be sufficient to confirm clinical effectiveness. Therefore, the GDG will only consider making recommendations for new monoclonal antibodies once they have been rigorously evaluated in clinical trials.

Mechanism of action of casirivimab and imdevimab

Casirivimab and imdevimab are two fully human antibodies (REGN10933 and REGN10987). Their mechanism of action is very plausible: they bind to the SARS-CoV-2 spike protein *[160]* and have demonstrated antiviral activity in rhesus macaques and Syrian golden hamsters *[161]*. Pharmacokinetic data in patients with non-severe COVID-19 show that antiviral concentrations of both antibodies against pre-Omicron variants are achieved and maintained for at least 28 days after intravenous administration of the combination at a total dose of 1200 mg (600 mg each antibody) or above *[162]*. Pre-Omicron antiviral concentrations are also achieved and maintained using a subcutaneous total dose of 1200 mg (600 mg of each antibody) in uninfected individuals for prophylaxis *[163]*. Half-lives range from 25 to 37 days for both antibodies.

It was postulated that administration might have differential effects in patients who have produced their own anti-SARS-CoV-2 spike protein antibodies (hereafter seropositive) compared with those who have not (hereafter seronegative). It was hypothesized that effects might be larger, or restricted to, seronegative individuals who have not yet mounted an effective antibody response.

Data describing the *in vitro* neutralization of different variants by monocolonal antibodies are collated on the NIH NCATS OpenData Portal *[164]*. Several reports have demonstrated that *in vitro* neutralization of pseudovirus containing the BA.1 Omicron spike protein and *in vitro* neutralization of authentic BA.1 Omicron virus is dramatically reduced or lost for casirivimab and imdevimab. Furthermore, the combination of casirivimab and imdevimab had no impact upon subgenomic viral RNA in the lungs or nasal turbinate of K18 human ACE2 transgenic mice infected with BA.1 Omicron *[165]*. Reductions for *in vitro* neutralizing activity have been reported for casirivimab and/or imdevimab against BA.2, BA.4 and BA.5 Omicron sub-lineages *[63][64][65]*, and serum from patients that received the combination also does not neutralize BA.2, BA.4 and BA.5 sub-lineages *[166]*. Furthermore, neither casirivumab nor imdevimab neutralize BQ.1 or BQ.1.1 sublineages *[68][69]*). Therefore, currently available preclinical data do not support activity of the casirivimab and imdevimab combination against currently circulating Omicron sub-lineages.

10. Methods: how this guideline was created

This living WHO guideline was developed according to standards and methods aligned with the *WHO Handbook for guideline development* and according to a pre-approved protocol (planning proposal) by the WHO Guideline Review Committee (GRC) *[52]*. This guideline is living – dynamically updated and globally disseminated once new evidence warrants a consideration of a change in recommendations *[167]*.

Related guidelines

- Previous versions of this WHO *Therapeutics and COVID-19: living guideline* can be accessed via the WHO website *[4]*.
- This therapeutic guideline is related to the WHO *COVID-19 Clinical management: living guideline*, which addresses non-pharmacological aspects of patient care *[6]*.
- Guidelines regarding the use of drugs to prevent (rather than treat) COVID-19 are included in a separate document, *WHO Living guideline: Drugs to prevent COVID-19*, that can be accessed via the WHO website and the BMJ *[8]*.

Stepwise approach

Here we outline the approach, involving simultaneous processes, taken to improve efficiency and timeliness of development and dissemination of living, trustworthy guidance.

Step 1: Evidence monitoring and mapping and triggering of evidence synthesis

Emerging evidence is monitored within the context of the living systematic review and NMA, using experienced information specialists, who review multiple information sources on new RCTs. Once practice-changing evidence or increasing international interest are identified, the WHO therapeutics steering committee triggers the guideline development process if they consider all of the following pertain:

- likelihood to change practice;
- sufficient RCT data on therapeutics to inform the high-quality evidence synthesis living systematic review;
- relevance to a global audience.

Step 2: Convening the GDG

WHO selected GDG members to ensure global geographical representation, gender balance, and appropriate technical and clinical expertise, and patient perspectives. For each intervention, the technical unit collected and managed written declarations of interests (DOIs) on an annual basis, and verbal declarations at each meeting. Web searches were performed to seek additional interests that could be perceived to affect an individual's objectivity and independence during the development of the recommendations. The WHO technical team found no conflicts of interests in any of the panel members.

The GDG (see Section 13) convened in online meetings which involved a review of the basics of GRADE methodology including formulating population, intervention, comparator, outcome (PICO) questions and subgroups of interests, and prioritization of patient-important outcomes (see Step 4 below). The GDG subsequently reviewed analyses, including pre-specified subgroup analyses presented in summary of findings tables, considered an individual patient perspective and feasibility issues specific to this intervention, and formulated recommendations. The GDG also reviewed the mechanism of actions and non-clinical evidence around safety.

Step 3: Evidence synthesis

The living systematic review/NMA team, as requested by the WHO Therapeutics Steering Committee, performed an independent systematic review to examine the benefits and harms of the interventions *[1]*. The systematic review team includes systematic review experts, clinical experts, clinical epidemiologists and biostatisticians. Team members have expertise in GRADE methodology and rating certainty of evidence specifically in NMAs, including direct and indirect comparisons of treatment alternatives. The NMA team considered deliberations from the initial GDG meeting, specifically focusing on the outcomes and subgroups prioritized by the GDG and produced GRADE evidence summaries to inform development of recommendations. In situations where no head-to-head comparisons of therapeutics were available from RCTs, indirect comparisons were used. The methods team rated credibility of subgroups using the ICEMAN tool *[95]*. The technical unit collected and managed DOIs and found no systematic review team member to have a conflict of interest.

Step 4: Final recommendations

The GRADE approach provided the framework for establishing evidence certainty and generating both the direction and strength of recommendations *[169][170]*. Methods and clinical co-chairs facilitated deliberations to reach final recommendations. *A priori* voting rules informed procedures if the GDG failed to reach consensus by discussion; co-chairs were not eligible to vote in this setting. For recommendations revised or added in the current version, there was no need for voting.

The following key factors informed transparent and trustworthy recommendations:

- absolute benefits and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE summary of findings tables) *[171]*;
- quality/certainty of the evidence *[169][172]*;
- values and preferences of patients *[173]*;
- resources and other considerations (including considerations of feasibility, applicability, equity) *[173]*;
- effect estimates and confidence intervals for each outcome, with an associated rating of certainty in the evidence, as presented in summary of findings tables. If such data are not available, the GDG reviews narrative summaries *[171]*;
- recommendations are rated as either conditional or strong, as defined by GRADE. If the GDG members disagree regarding the evidence assessment or strength of recommendations, WHO will apply voting according to established rules *[170][173]*.

When possible, we used research evidence to inform discussion around these key factors. If not available, discussion of these factors was informed by expert opinion, supported by surveys of the GDG members as outlined below.

Benefits and harms
The GDG members prioritized outcomes (rating from 9 [critical] to 1 [not important]) in patients with non-severe COVID-19 and in patients with severe and critical COVID-19, taking a patient perspective (Tables 1 and 2 below). The GDG's questions were structured using the PICO format (see evidence profile under the recommendations). The prioritization was performed through a survey, most lately in May 2021, followed by a GDG discussion. These prioritized outcomes were used to update the LNMA *[2]*.

Selecting and rating the importance of outcomes
GDG members prioritized outcomes from the perspective of patients with non-severe illness (Table 1) and severe and critical illness (Table 2).

Table 1. GDG outcome rating from the perspective of patients with non-severe illness

Outcome	Mean	SD	Range
Admission to hospital	8.5	0.7	7-9
Death	8.1	1.9	3-9
Quality of life	7.5	1.3	5-9
Serious adverse effects (e.g. adverse events leading to drug discontinuation)	7.4	1.8	3-9
Time to symptom resolution	7.3	1.7	4-9
Duration of hospitalization	6.6	0.9	5-8
Duration of oxygen support	6.6	1.2	5-9
Need for invasive mechanical ventilation	5.9	2.3	1-8
New non-SARS-CoV-2 infection	5.6	2.1	3-9
Time to viral clearance	5.5	2.4	1-9
Duration of invasive mechanical ventilation	5.4	2.1	1-8

SD: standard deviation.
Note: 7 to 9 – critical; 4 to 6 – important; 1 to 3 – of limited importance.

Table 2. GDG outcome rating from the perspective of patients with severe and critical illness

Outcome	Mean	SD	Range
Death	9.0	0	9
Need for invasive mechanical ventilation	8.2	0.9	6-9
Duration of invasive mechanical ventilation	7.6	0.9	6-9
Quality of life	6.9	1.3	5-9

Duration of hospitalization	6.7	1.2	4-9
Serious adverse effects (e.g. adverse events leading to drug discontinuation)	6.7	1.8	3-9
Time to symptom resolution	6.5	1.6	4-9
New non-SARS-CoV-2 infection	6.4	1.8	3-9
Duration of oxygen support	6.3	1.3	4-9
Time to viral clearance	4.7	2.3	1-9

SD: standard deviation.
Note: 7 to 9 – critical; 4 to 6 – important; 1 to 3 – of limited importance.

Derivation of absolute effects for drug treatments

The GDG specified a reduction of 1.5% (15 per 1000) as the threshold for an important reduction in hospitalization.

Non-severe COVID-19: We applied the pooled relative effect (typically odds ratio) from the LNMA to pre-specified estimates of baseline risk where these had been established. For patients with non-severe illness, we used the median of the control arm of the RCTs that contributed to the evidence *[1][2]*. In the 15th version of the guideline, the risk estimates for non-severe COVID-19 have been adjusted to align with the major reduction of risk of hospitalization and death than has occurred in the last period. Specific deliberations based on risk groups are presented for each recommendation.

- Risk estimates for hospitalization for non-severe COVID-19 were 6% for high-risk patients, 3% for moderate risk patients, and 0.5% for low-risk patients.
- Risk estimates for mortality amongst patients with non-severe illness were 0.6% (high risk), 0.3% (moderate risk) and 0.05% (low risk).

These categorizations were developed based on observational data. However reliably identifying those at high risk is challenging because of the changing global context, evolution of the virus and patterns of COVID-19 vaccination. This highlights the importance of validation of models to local context. Before widespread Omicron variant circulation, a living systematic review of 232 risk prediction models for COVID-19 identified two promising risk prediction tools *[18]*. These tools concur that typical characteristics of people at high risk include those with older age, immunosuppression and/or chronic diseases, with lack of COVID-19 vaccination as an additional risk factor to consider.

Severe and critical COVID-19: For patients with severe and critical illness, the GDG identified the control arm of the WHO SOLIDARITY trial, performed across a wide variety of countries and geographical regions, as representing the most relevant source of evidence for baseline risk estimates for mortality and mechanical ventilation. Systemic corticosteroids now represent standard of care in patients with severe and critical COVID-19 (see strong recommendation issued by WHO September 2020). Therefore, the baseline risk estimates in the evidence summaries for JAK inhibitors, convalescent plasma and IL-6 receptor blockers were adjusted for treatment effects of corticosteroids for the outcome of mortality and mechanical ventilation. The applied baseline risk estimate for mortality was 13% (130 deaths per 1000 patients). For other outcomes, we used the median of the control arm of the RCTs that contributed to the evidence.

The GDG acknowledged that these risks, and thus absolute effects, may vary significantly geographically and over time. Users of this guideline may prefer estimating absolute effects by using local event rates.

Values and preferences

We had insufficient information to provide the GDG with an evidence-based description of patient experiences or values and preferences regarding treatment decisions for COVID-19 drug treatments. The GDG therefore relied on their own judgments of what well-informed patients would value after carefully balancing the benefits, harms, and burdens of treatment. Judgments on values and preferences were crucially informed through the experiences of former COVID-19 patients, represented in the GDG.

The GDG agreed that the following values and preferences would be typical of well-informed patients:

- Most patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on outcomes they consider important. This was particularly so when evidence suggested treatment effects, if they do exist, are small, and the possibility of important harm remains.
- In an alternative situation with larger benefits and less uncertainty regarding both benefits and harms, more patients would be inclined to choose the intervention.

In addition to taking an individual patient perspective, the GDG also considered a population perspective in which feasibility, acceptability, equity and cost were important considerations.

Specific deliberations on values and preferences and associated feasibility and resource related considerations are presented for each recommendation.

Step 5: External and internal review
An external review group reviewed the final guideline document to identify factual errors, and to comment on clarity of language, contextual issues and implications for implementation. The technical unit collected and managed DOIs of the external reviewers and found no external reviewer to have a conflict of interest. However, for certain therapeutics, pharmaceutical company technical representative may be asked to comment on a new drug from the industry perspectives, in line with the *WHO Handbook for guideline development* (page 70), as comments from such individuals or organizations on a draft guideline may be helpful in anticipating and dealing with controversy, identifying factual errors, and promoting engagement with all stakeholders. Comments on contextual issues were considered taking into account their interests. The conflict of interest of such individuals will be transparent, as their affiliation will appear in the acknowledgement section.

Each version was reviewed and approved by the WHO Guideline Review Committee.

11. How to access and use this guideline

This is a living guideline from WHO. The recommendations included here will be updated, and new recommendations will be added for other drugs for COVID-19.

How to access the guideline:

- WHO website in PDF format *[4]*: This is a full read out of the MAGICapp content for those without reliable web access. It can also be downloaded directly from MAGICapp (see cogwheel on top right).
- MAGICapp in online, multilayered formats: This is the fullest version of the guideline, as detailed below.
- BMJ Rapid Recommendations *[5]*: Designed with clinical readers in mind and including an interactive infographic to summarize all treatments included.

How to navigate this guideline

The guideline is written and updated in MAGICapp, with a format and structure that ensures user-friendliness and ease of navigation *[168]*. It accommodates dynamic updating of evidence and recommendations that can focus on what is new while keeping existing recommendations, as appropriate, within the guideline.

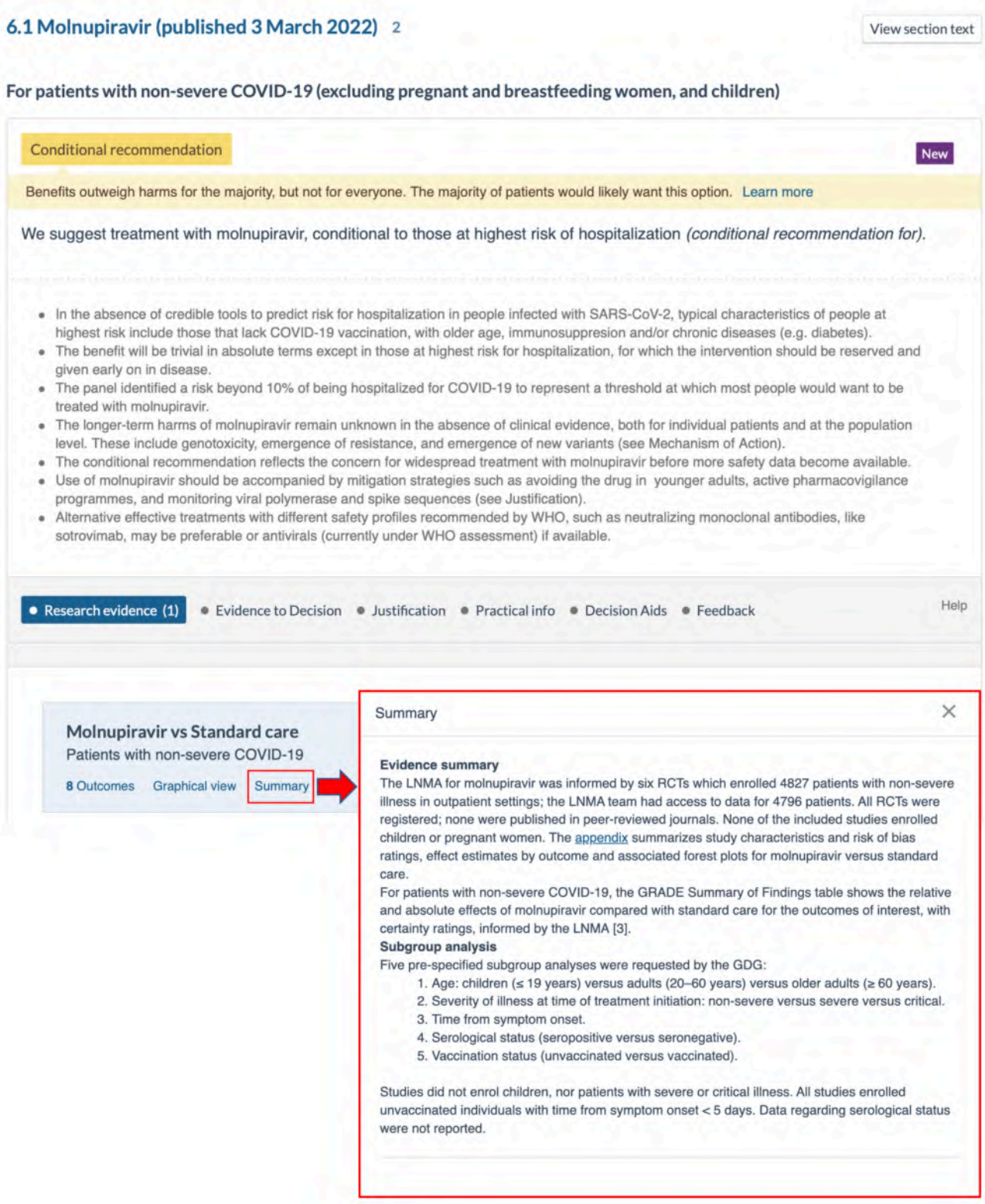
The purpose of the online formats and additional tools, such as the infographics, is to make it easier to navigate and make use of the guideline in busy clinical practice. The online multilayered formats are designed to allow end-users to find recommendations first and then drill down to find supporting evidence and other information pertinent to applying the recommendations in practice, including tools for shared decision-making (clinical encounter decision aids) *[168]*.

Fig. 3 shows how the online multilayered formats are designed to allow end-users to find recommendations first and then drill down to find supporting information pertinent to applying the recommendations in practice. End-users will also need to understand what is meant by strong and conditional recommendations (displayed immediately below) and certainty of evidence (the extent to which the estimates of effect from research represent true effects from treatment).

For each recommendation additional information is available through the following tabs:

- ***Research evidence:*** Readers can find details about the research evidence underpinning the recommendations as GRADE Summary of Findings tables and narrative evidence summaries (shown in Fig. 3).
- ***Evidence to decision:*** The absolute benefits and harms are summarized, along with other factors such as the values and preferences of patients, practical issues around delivering the treatment as well as considerations concerning resources, applicability, feasibility, equity and human rights. These latter factors are particularly important for those in need of adapting the guidelines for the national or local context.
- ***Justification:*** Explanation of how the GDG considered and integrated evidence to decision factors when creating the recommendations, focusing on controversial and challenging issues.
- ***Practical information:*** For example, dosing, duration and administration of drugs, or how to apply tests to identify patients in practice.
- ***Decision aids:*** Tools for shared decision-making in clinical encounters.

Fig. 3. Example of how research evidence is available one click away, with narrative evidence summary giving additional details to GRADE Summary of Findings table



Additional educational modules and implementation tools for health workers:

- WHO Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation provides algorithms and practical tools for clinicians working in acute care hospitals managing adult and paediatric patients with acute respiratory infection, including severe pneumonia, acute respiratory distress syndrome, sepsis and septic shock. This includes information on screening, testing, monitoring and treatments.
- Safety monitoring of molnupiravir for treatment of mild to moderate COVID-19 infection in low and middle-income countries using cohort event monitoring: a WHO study.

This living guideline from WHO is also used to inform the activities of the WHO Prequalification of Medicinal Products.

12. Uncertainties, emerging evidence and future research

The guideline recommendations for COVID-19 therapeutics demonstrate remaining uncertainties concerning treatment effects for all outcomes of importance to patients. There is also a need for better evidence on prognosis and on values and preferences of patients with COVID-19

Uncertainties that are frequently common across therapeutics are summarized here, with some specific uncertainties for molnupiravir detailed below:

For drugs recommended in non-severe illness: the lack of accurate clinical prediction guides to establish the individual patient risk of hospitalization in order to best identify patients that would most benefit from interventions; data regarding emergence of resistance and efficacy against new variants; safety and efficacy in children and in immunocompromised, vaccinated, or pregnant patients and other specific subgroups of patients; optimal duration of therapies; head-to-head comparisons of recommended treatments; and relative effectiveness of combination therapy and longer term outcomes.

For molnupiravir, the GDG identified additional uncertainties, including long-term impact on mutagenesis and cancer risk; the relative intracellular nucleotide ratios of endogenous: molnupiravir cell lines and animal models to assess genetic toxicity; how readily mutations arise under a selective pressure with NHC *in vitro* and molnupiravir in animal models and patients with SARS-CoV-2 infection; if mutations arising under selective pressure *in vitro* and *in vivo* (including in humans) confer a decreased antiviral activity for NHC; and if they arise in the spike protein and/or confer an increase in replicative potential/transmission.

For drugs recommended in severe or critical illness: safety and efficacy in children and in immunocompromised, vaccinated, or pregnant patients and other specific subgroups of patients; long term mortality and functional outcomes in COVID-19 survivors; and immunity and the risk of a subsequent infection, which may affect the risk of death after 28 days.

Emerging evidence
Hundreds of RCTs for COVID-19 are currently recruiting implying that evidence will continue to emerge which could inform policy and practice, see https://www.who.int/clinical-trials-registry-platform.

13. Authorship, contributions, acknowledgements

WHO would like to thank the collaborative efforts of all those involved to make this process rapid, efficient, trustworthy and transparent.

The committee includes representatives from various WHO departments at headquarters and the regions and has been approved by the WHO Director of the Country Readiness Department, and the WHO Chief Scientist. The WHO Secretariat meets on a regular basis to discuss when to trigger guideline updates based on evidence updates from the WHO rapid review team, and other sources of evidence and selects the members of the Guideline Development Group (GDG) for the living guideline.

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The WHO Therapeutics Steering Committee is fully responsible for decisions about guidance production and convening the GDG.

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Heparin (1 April 2025)

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SGLT2 and simvastatin (25 June 2024)

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The WHO Therapeutics Steering Committee is fully responsible for decisions about guidance production and convening the GDG.

Guideline Development Group (GDG) - (For list of GDG members of previous recommendations, see here.)

Indirect comparisons (31 August 2023)

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Guideline Development Group (GDG) for the updates (May 2023) on molnupiravir and nimatrelvir recommendations and a new recommendation on VV116. For list of GDG members of previous recommendations, see here.

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Guideline Development Group (GDG) for the updates (15 July 2022 and 9 December 2022) on remdesivir recommendation. For list of GDG members of previous recommendations, see here.

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Guideline Development Group (GDG) for the updates (2 June 2022 and 9 December 2022) on sotrovimab recommendation. For list of GDG members of previous recommendations, see here.

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Guideline Development Group (GDG) for the updates (2 June 2022 and 9 December 2022) on baricitinib recommendation. For list of GDG members of previous recommendations, see here.

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Guideline Development Group (GDG) for molnupiravir recommendation. For list of GDG members of previous recommendations, see here.
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Guideline Development Group (GDG) for sotrovimab recommendation. For list of GDG members of previous recommendations, see here.
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Guideline Development Group (GDG) for convalescent plasma guideline. For list of GDG members of previous recommendations, see here.
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Observer Sade Ogunsala (World Health Organization) for colchicine and fluvoxamine recommendations.

Special thanks to WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group for their publication: Association of administration of interleukin-6 antagonists with mortality and other outcomes among hospitalized patients with COVID-19: a prospective meta-analysis *[97]*.

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Annex A

Re-analysis of: WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group; Vale CL, Godolphin PJ, Fisher DJ, et al. Anticoagulation among patients hospitalized for COVID-19 : a systematic review and prospective meta-analysis. *Ann Intern Med.* 2025;178(1):59-69.*[206]*

The GDG used these data in reaching judgements on the used of heparin in severe and critical COVID-19 (link).

Figure 1: Effects of therapeutic dose versus intermediate or prophylactic dose anticoagulation on 28-day mortality, random effects model.

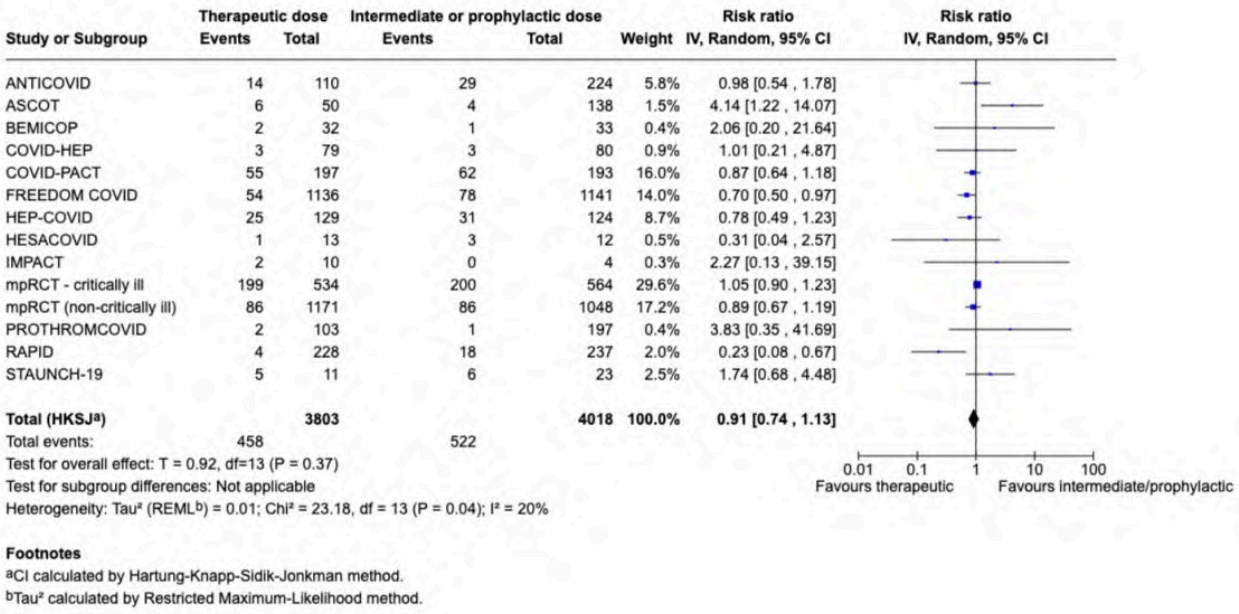
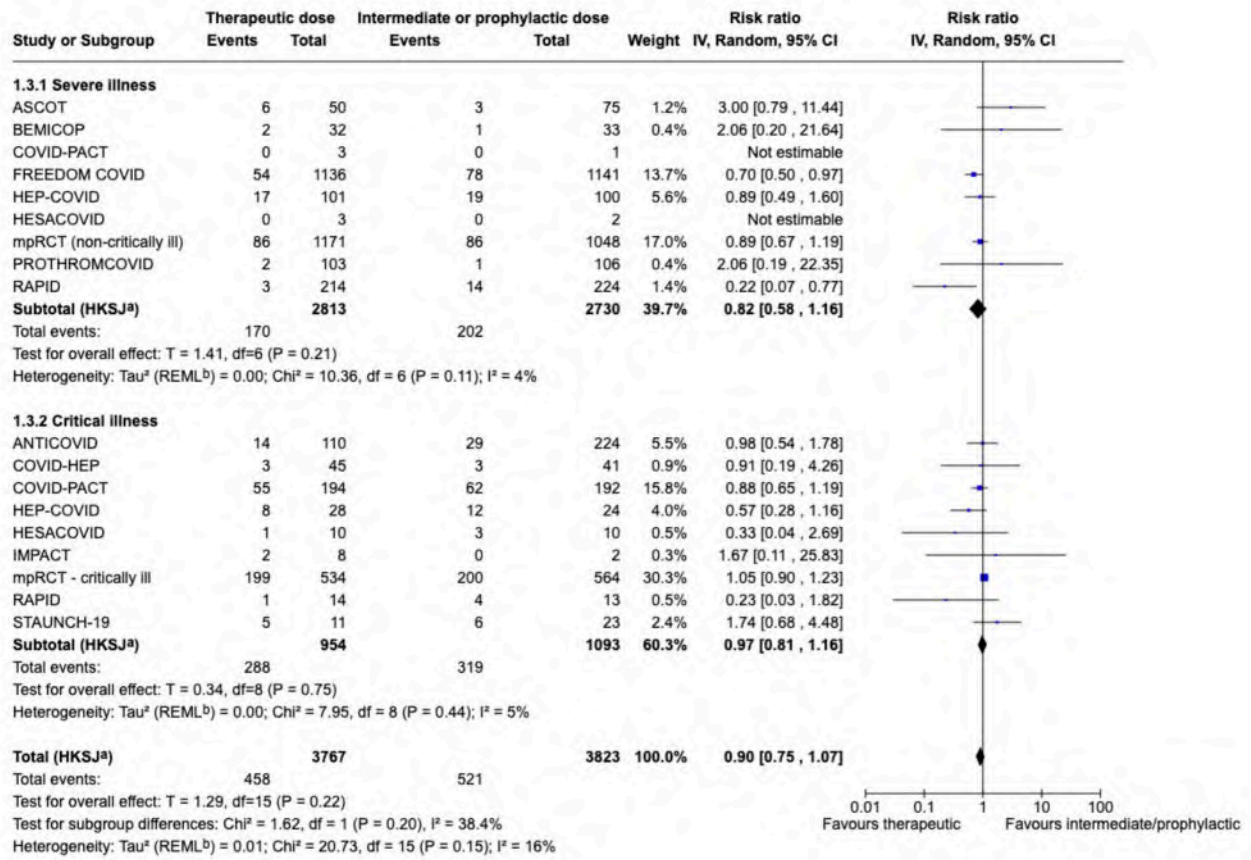


Figure 2: Effects of therapeutic dose versus intermediate or prophylactic dose anticoagulation on 28-day mortality, random effects model, with subgroups by disease severity.



The GDG reviewed the following forest plots comparing intermediate versus prophylactic dose anticoagulation when moving from evidence to recommendations:

Figure 3: Effects of intermediate versus prophylactic dose anticoagulation on 28-day mortality, random effects model.

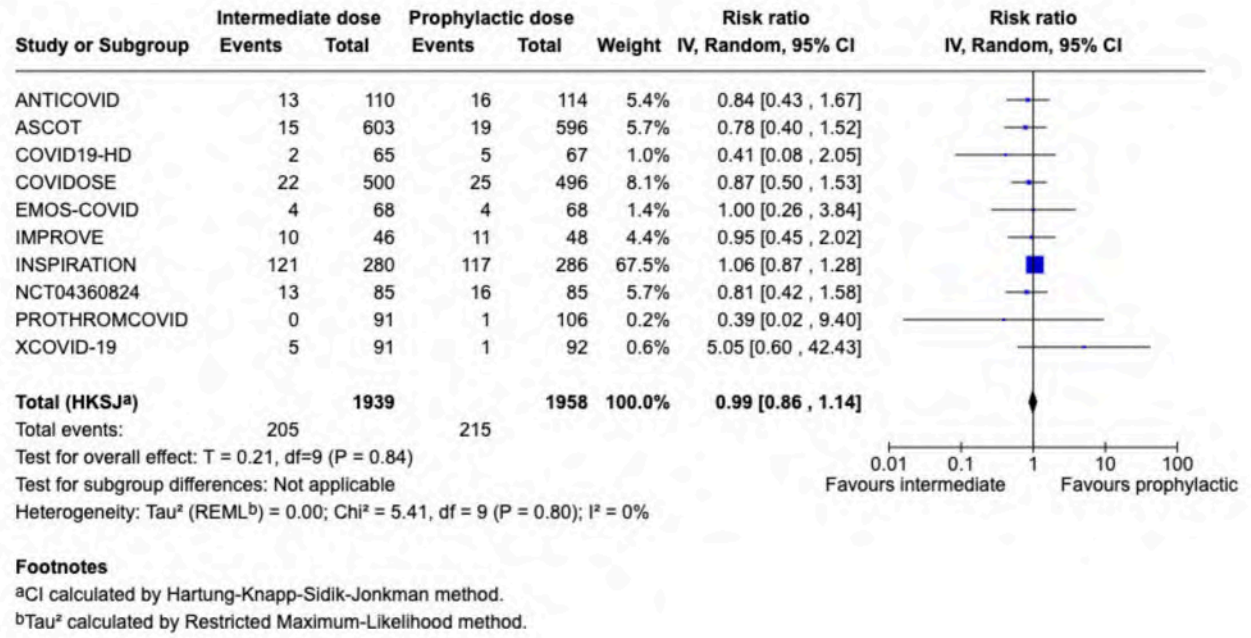
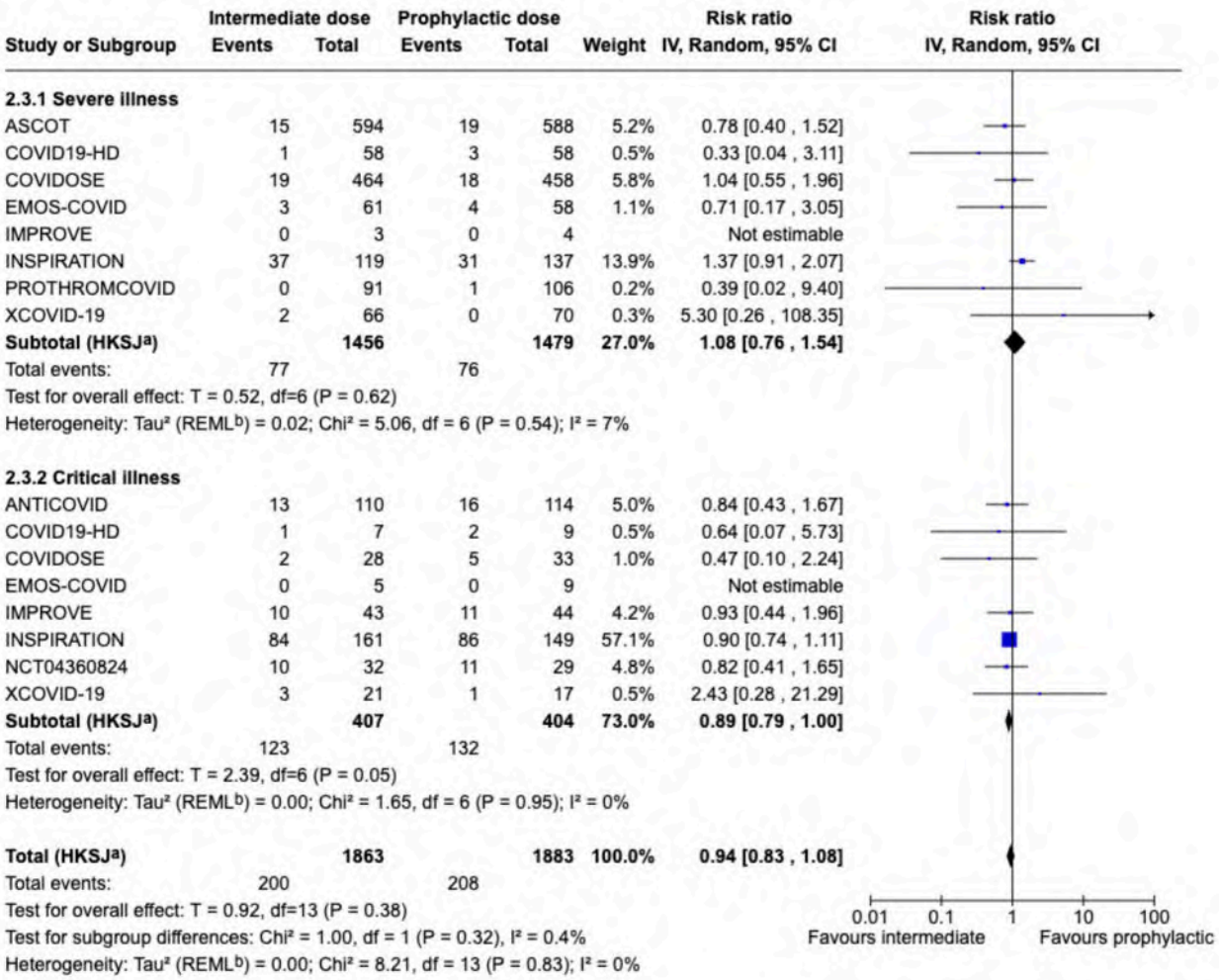
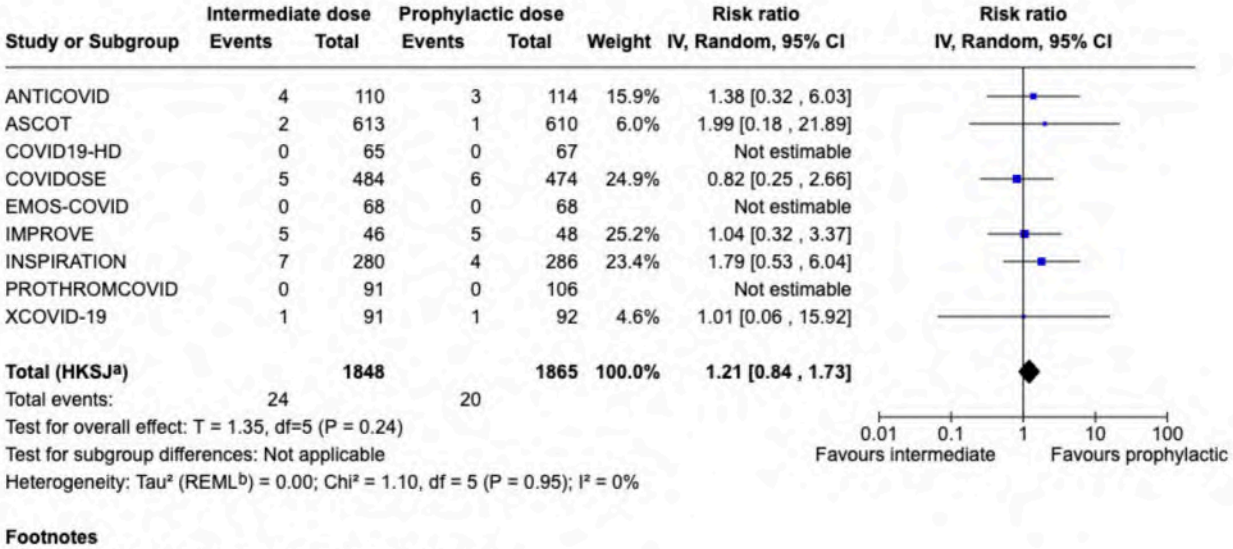


Figure 4: Effects of intermediate versus prophylactic dose anticoagulation on 28-day mortality, random effects model, with subgroups by disease severity.



The GDG considered effects of dosing strategies on major bleeding when developing recommendations.

Figure 5: Effects of intermediate versus prophylactic dose anticoagulation on major bleeding, random effects model.



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