Therapeutics and COVID-19

LIVING GUIDELINE

16 SEPTEMBER 2022

World Health Organization

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WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 2 years after the date of publication.

Contact

WHO Emerging Diseases Clinical Assessment and Response Network

EDCARN@who.int

Sections

1. Summary of the guideline

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

Context: The evidence base for therapeutics for COVID-19 is evolving with numerous randomized controlled trials (RCTs) recently completed and underway. The emerging SARS-CoV-2 variants (e.g. Omicron) and subvariants are also changing the role of therapeutics. This update provides updated recommendations for remdevisir, addresses the use of combination therapy with corticosteroids, interleukin-6 (IL-6) receptor blockers and Janus kinase (JAK) inhibitors in patients with severe or critical COVID-19, and modifies previous recommendations for the neutralizing monoclonal antibodies sotrovimab and casirivimab-imdevimab in patients with non-severe COVID-19.

New recommendations:

- a conditional recommendation for remdesivir in patients with severe COVID-19, and a conditional recommendation against remdesivir in patients with critical COVID-19;
- concerning the concomitant use of IL-6 receptor blockers (tocilizumab or sarliumab), and the JAK inhibitor baricitinib, these drugs may now be combined, in addition to corticosteroids in patients with severe or critical COVID-19;
- strong recommendations against the use of sotrovimab and casirivimab-imdevimab in patients with COVID-19, replacing the previous conditional recommendations for their use.

Understanding the new recommendations: When moving from new evidence to updated recommendations, the GDG considered a combination of evidence assessing relative benefits and harms, values and preferences, and feasibility issues.

For remdesivir, new trial data were added to a previous subgroup analysis and provided sufficiently trustworthy evidence to demonstrate benefits in patients with severe COVID-19, but not critical COVID-19. Added to existing drugs strongly recommended for these patients, the GDG considered benefits of remdesivir to be modest and of moderate certainty for key outcomes such as mortality and mechanical ventilation, resulting in a conditional recommendation.

For baricitinib, the GDG considered clinical trial evidence (RECOVERY) demonstrating reduced risk of death also in patients already receiving corticosteroids and IL-6 receptor blockers. The GDG acknowledged that the clinical trials were not representative of the world population and that the risk-benefit may be less advantageous, particularly in areas where certain pathogens like HIV, tuberculosis, and fungal infections are endemic. 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. The decision to combine the medications will depend on their availability, and the clinician's perception of the risk-benefit associated with combination immunosuppressive therapy, particularly in patient populations at risk of opportunistic infections who may have been underrepresented in clinical trials.

When making a strong recommendation against the use of monoclonal antibodies for patients with COVID-19 the GDG considered in vitro neutralization data demonstrating whether sotrovimab and casirivimab-imdevimab evaluated in clinical trials have meaningfully reduced neutralization activity of the currently circulating variants of SARS-CoV-2 and their subvariants. There was consensus among the panel that the absence of in vitro neutralization activity strongly suggests absence of clinical effectiveness of these monoclonal antibodies. However, there was also consensus regarding the need for clinical trial evidence in order to confirm clinical efficacy of new monoclonal antibodies that reliably neutralize the circulating strains in vitro. Whether emerging new variants and subvariants might be susceptible to sotrovimab or casirivimab-imdevimab, or other anti-SARS-CoV-2 monoclonal antibodies cannot be predicted.

Prior recommendations, unchanged from previous:

Recommended for patients with severe or critical COVID-19:

- a strong recommendation for systemic corticosteroids;
- a strong recommendation for interleukin-6 (IL-6) receptor blockers (tocilizumab or sarilumab);
- a strong recommendation for the JAK inhibitor baricitinib.

Recommended for patients with non-severe COVID-19 at highest risk of hospitalization:

- a strong recommendation for nirmatrelvir-ritonavir;
- a conditional recommendation for molnupiravir;
- a conditional recommendation for remdesivir.

Not recommended for patients with non-severe COVID-19:

- a conditional recommendation against systemic corticosteroids;
- a strong recommendation against convalescent plasma;
- a recommendation against fluvoxamine, except in the context of a clinical trial;
- a strong recommendation against colchicine.

Not recommended for patients with non-severe COVID-19 at low risk of hospitalization:

- a conditional recommendation against nirmatrelvir-ritonavir.

Not recommended for patients with severe and critical COVID-19:

- a recommendation against convalescent plasma, except in the context of a clinical trial;
- a conditional recommendation against the JAK inhibitors ruxolitinib and tofacitinib.

Not recommended, regardless of COVID-19 disease severity:

- a strong recommendation against hydroxychloroquine;
- a strong recommendation against lopinavir-ritonavir;
- a recommendation against ivermectin, except in the context of a clinical trial.

About this guideline: This living guideline from the World Health Organization (WHO) incorporates new evidence to dynamically update recommendations for COVID-19 therapeutics. The GDG typically evaluates a drug 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)(3)(4)*.

Updates and access: This is the 12th version (11th update) of the living guideline. It replaces earlier versions, latest published 14 July 2022. The current guideline and its earlier versions are available through the WHO website *(4)*, the BMJ *(5)*, and MAGICapp (online and also as PDF outputs for readers with limited internet access). The living guideline is written, disseminated, and updated in an online platform (MAGICapp), with a user-friendly format and easy-to-navigate structure that accommodates dynamically updated evidence and recommendations, focusing on what is new while keeping existing recommendations updated within the guideline. This format should also facilitate adaptation, which is strongly encouraged by WHO to contextualise recommendations in a health care system perspective to maximize country impact.

This living WHO guideline for therapeutics for COVID-19 is related to the larger, more comprehensive guideline for COVID-19 clinical management *(6)*. Guidelines for the use of drugs 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)*.

2. Abbreviations

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
IL-6	interleukin-6
IMV	invasive mechanical ventilation
JAK	Janus kinase
LNMA	living network meta-analysis
LMIC	low- and middle-income countries
MAGIC	Magic Evidence Ecosystem Foundation
MD	mean difference
OIS	optimal information size
OR	odds ratio
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
WHO	World Health Organization

3. Introduction

Info Box

As of August 2022, there have been over 572 million confirmed cases of COVID-19 *(9)*. The pandemic has thus far claimed approximately 6.39 million lives *(9)*. Vaccination is having a substantial impact on hospitalizations and death in a number of high-income countries, but limitations in global access to COVID-19 vaccines mean that many populations remain vulnerable *(9)(10)*. Even in vaccinated individuals, uncertainties remain about the duration of protection and effectiveness of current vaccines – and the efficacy of existing treatments for COVID-19 – against emerging SARS-CoV-2 variants and subvariants.

Taken together, there remains a need for more effective treatments for COVID-19. The COVID-19 pandemic – and the explosion of both research and misinformation – has highlighted the need for trustworthy, accessible, and regularly updated living guidance to place emerging findings into context and provide clear recommendations for clinical practice *(11)*.

This living guideline responds to emerging evidence from RCTs on existing and new drug treatments for COVID-19. More than 5000 trials investigating interventions for COVID-19 have been registered and are ongoing or completed (see Section 9 for emerging evidence and linked appendix) *(12)*. Among these are large national and international platform trials (such as ACCT, RECOVERY, WHO SOLIDARITY, REMAP-CAP, and ACTIV), which recruit large numbers of patients in many countries, with a pragmatic and adaptive design *(13)(15)(16)(17)*. An overview of ongoing trials is available from the Infectious Diseases Data Observatory, through their living systematic review of COVID-19 clinical trial registrations *(12)* and the WHO website.

Several LNMAs associated with this guideline incorporate emerging trial data and allow for analysis of comparative effectiveness of multiple COVID-19 treatments. To inform the living guidance, we also use additional relevant evidence on safety, prognosis, and patient values and preferences related to COVID-19 treatments. A recently updated living systematic review of 232 risk prediction models in hospitalized patients with COVID-19 identified two promising risk prediction tools that could inform recommendations in this 11th version of the guideline; these include the Jehi diagnostic model and the 4C mortality model (see Section 6.1 for more details) *(14)*.

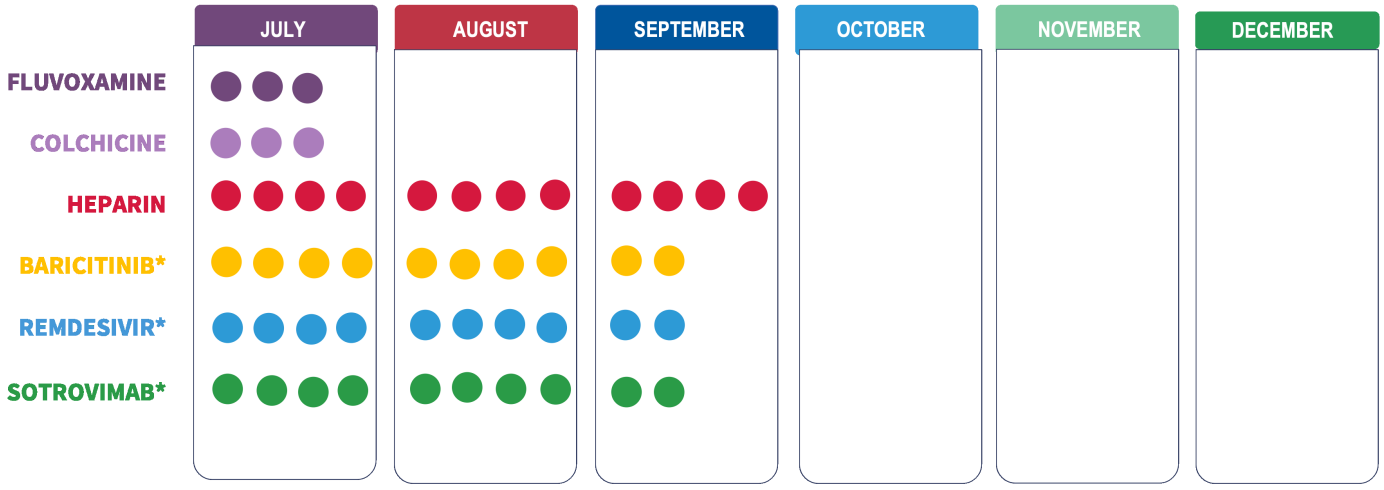
4. What triggered this update and what is coming next?

This 12th version of the WHO living guideline was triggered by:

- The publication of a large RCT (RECOVERY), confirming the benefits of the JAK inhibitor baricitinib in patients with severe or critical COVID-19, also in patients receiving corticosteroids and IL-6 receptor blockers.
- The availability of data from in vitro SARS-CoV-2 neutralization assays, suggesting that monoclonal antibodies (sotrovimab and casirivimab-imdevimab) are not effective for patients with non-severe COVID-19 in the current stage of the pandemic, with the predominant Omicron variants.
- New RCTs on the effects of remdesivir in patients with severe and critical COVID-19.

Fig. 1 shows other therapeutics in progress for this WHO living guideline, also communicated through the WHO portal *(4)*. Each dot represents a week of time. 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 WHO has a standing Steering Committee (see Section 10) to evaluate possibilities for new drug recommendations and updates to existing drug recommendations.

Fig. 1. COVID-19 therapeutics under assessment as of 31 August 2022



5. Understanding and applying the WHO severity definitions

Info Box

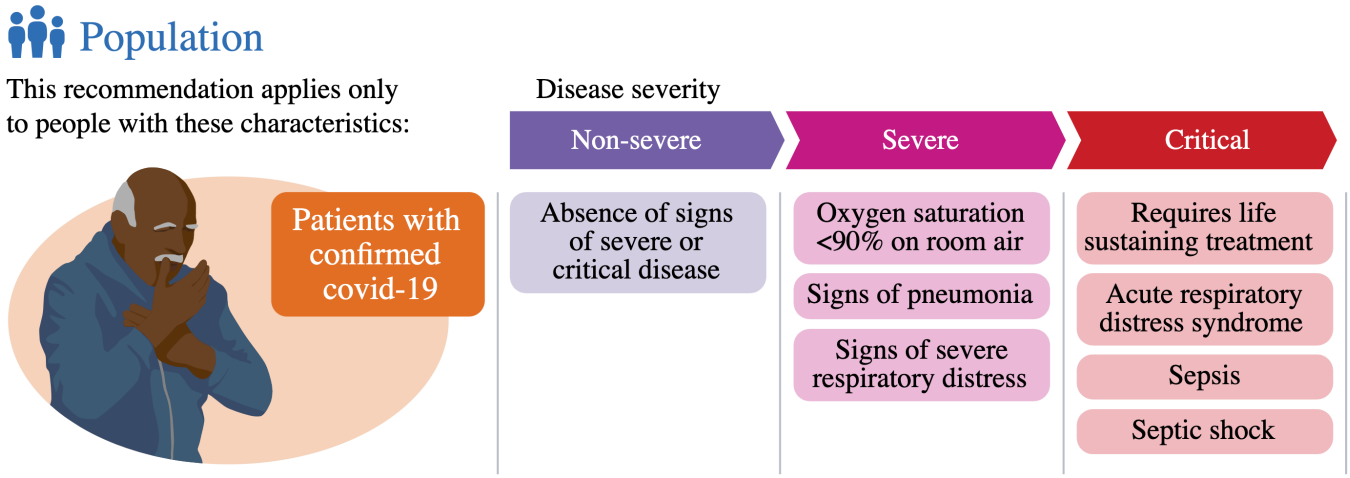
This guideline applies to all patients with COVID-19. Recommendations may differ based on the severity of COVID-19, according to WHO severity definitions (see below) *(6)*. These definitions avoid reliance on access to health care to define patient subgroups.

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. Recommendations for therapeutics

6.1 Overview of drugs, recommendations and key issues to consider when applying them

Updated

Info Box

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 choose between therapeutics

Several therapeutical 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 and monoclonal antibodies), co-administered medication, duration of treatment, and time from onset of symptoms to starting treatment. Some can be used in combination (i.e. as for severe or critical COVID-19) 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 the various therapeutics in trials, indirect comparisons from the LNMA have been used (see Section 7 - Methods) to inform use of one drug over another with a related mechanism of action. 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 highest risk of hospitalisation.

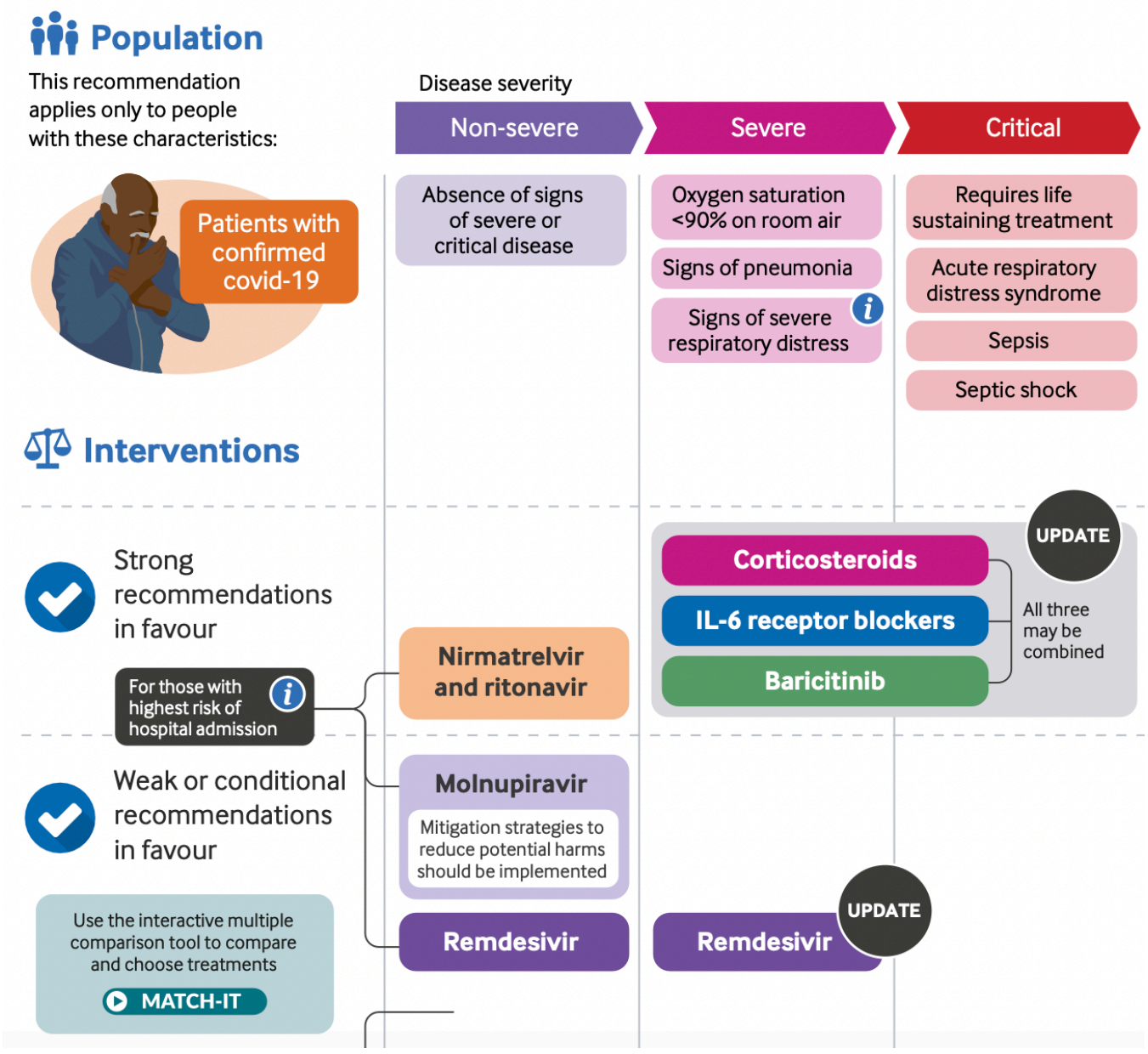
How to identify patients with non-severe COVID-19 at highest risk of hospitalization.

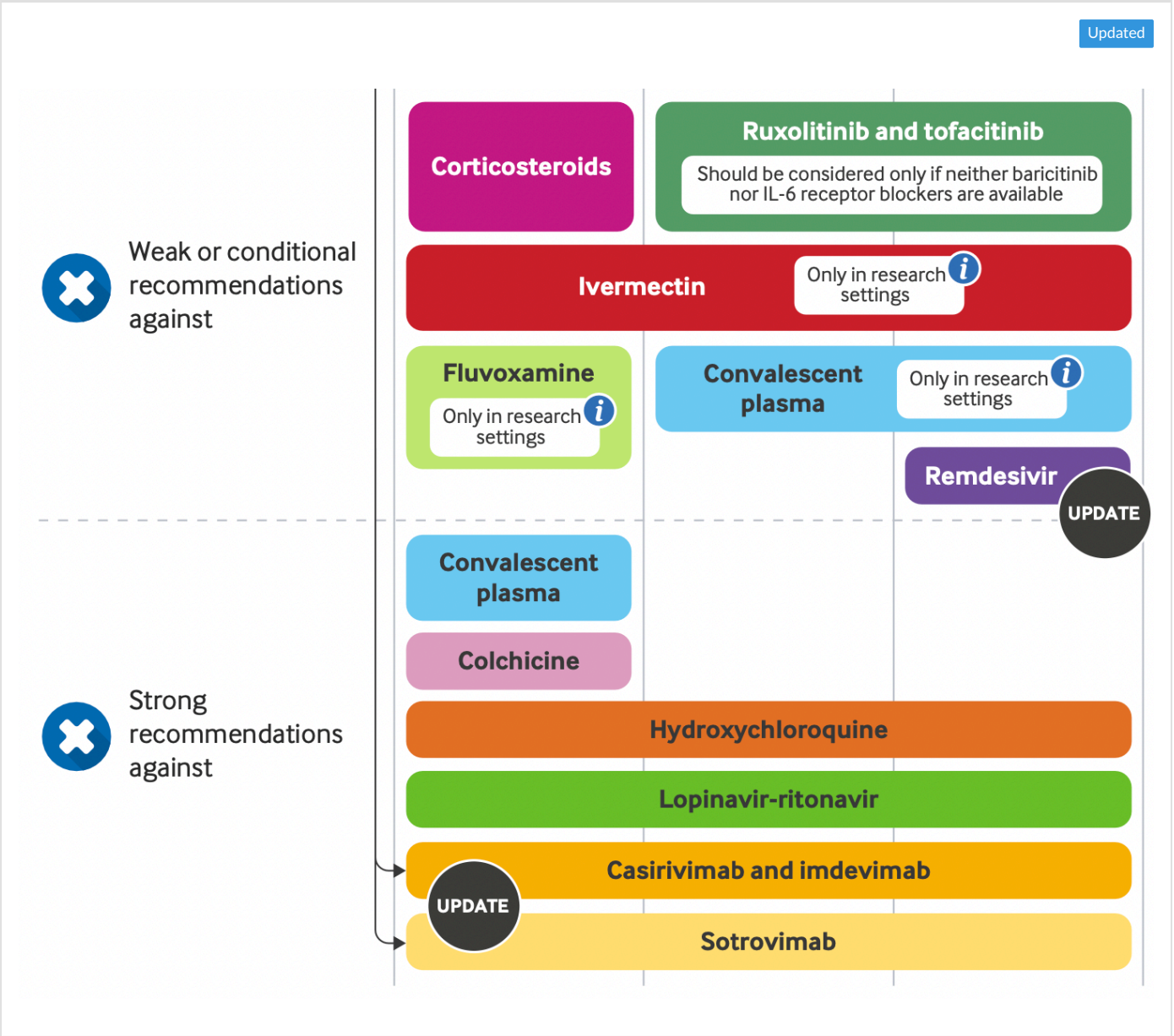
Several recommendations for drugs are only for those at highest risk for hospitalization because the benefit would be trivial (in absolute terms) if everyone with non-severe COVID-19 were to receive treatment; instead, some treatments should be reserved for those at highest risk of hospitalization and given early in the disease course. The panel identified a risk beyond 10% of being hospitalized for COVID-19 to represent a threshold at which most patients with non-severe illness would want to be treated (see Section 7).

Reliably identifying those at highest risk is challenging because of the changing global context with evolution of the virus and patterns of COVID-19 vaccination, thus raising importance of validation of models to local context. A living systematic review of 232 risk prediction models for COVID-19 identified two promising risk prediction tools *(14)* before Omicron circulation. These tools concur that typical characteristics of people at highest risk include those with older age, immunosuppression and/or chronic diseases, with lack of COVID-19 vaccination as an additional risk factor to consider.

Updated

Info Box





6.2 Remdesivir (updated 16 September 2022)

Info Box

An initial conditional recommendation was made on 20 November 2020, suggesting not to use remdesivir for patients with COVID-19, regardless of illness severity. This was based on data from four RCTs which were available at the time, with 7333 participants hospitalized for COVID-19. In the 10th iteration of the guideline, a new recommendation was made for the use of remdesivir for patients with non-severe illness. In this 12th iteration of the guideline, new recommendations for patients with severe or critical COVID-19 are provided, given new trial data providing sufficiently trustworthy evidence for a subgroup effect demonstrating modest benefit in patients with severe, but not critical COVID-19.

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

Conditional recommendation for

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

- *See Section 6.1 for help to identify patients at highest 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 represents a superior choice because it may have greater efficacy in preventing hospitalization than the alternatives, has fewer concerns with respect to harms than does molnupiravir; and is easier to administer than a 3 day course of intravenous remdesivir.*
- *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 women. 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 mother and fetus (see Research evidence and WHO information sheet).

Evidence To Decision

Benefits and harms

In patients with non-severe COVID-19, remdesivir probably reduces admission to hospital and and may have little or no impact on mortality. The effect of remdesivir on mechanical ventilation and time to symptom resolution is very uncertain. Treatment probably does not increase the likelihood of adverse effects leading to drug discontinuation.

The balance between benefits and potential harms favours treatment, but only in the highest risk group. This is because absolute benefit of remdesivir on hospital admission depends on a given patient's prognosis. The GDG defined a threshold of a 6% absolute reduction in hospital admission to represent what most patients would value as an important benefit. Remdesivir would exert such a benefit in patients at highest risk of hospitalization (above 10% baseline risk), such as older people, or those with immunodeficiencies and/or chronic diseases, further enhanced by lacking vaccination. The conditional recommendation for the use of remdesivir in those at highest risk (above 10% baseline risk) reflects this threshold: 73 fewer hospitalizations per 1000 patients.

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 *(15)*; however, none died or were hospitalized.

Certainty of the Evidence

The evidence summary was informed by five trials with 2709 participants included in the LNMA, with one trial informing the outcome of hospital admission *(1)(15)*.

Certainty of evidence was rated as: moderate for decreased admission to hospital (due to serious imprecision); low for mortality (due to serious imprecision and indirectness); very low for mechanical ventilation (due to very serious imprecision and serious indirectness); and moderate for adverse effects leading to drug discontinuation.

Limitations in available empirically developed risk prediction tools for establishing patients' risk of hospitalization represent the major source of indirectness for which the GDG rated down the certainty of the evidence *(14)(24)*. See Section 6.1 for more details.

Values and preferences

Applying the agreed values and preferences (see Section 7), the GDG inferred that almost all well-informed patients with a low risk of hospitalization would decline remdesivir, and only those at highest risk would choose to receive treatment.

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 highest risk.

Obstacles to access in LMICs due to cost, feasibility and availability are of concern *(30)*. 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 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. As an example of this, on 17 December 2021, WHO published the 8th 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.

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

When moving from evidence to the conditional recommendation to use remdesivir in patients with non-severe COVID-19, the GDG emphasized the benefits of decreased need for hospitalization, along with little or no serious adverse effects attributable to the drug. Feasibility and complexity of administration were also carefully considered, and led to the recommendation for use only in the highest risk patients. Typical characteristics of people at highest risk include older people, or those with immunodeficiencies and/or chronic diseases with being unvaccinated further contributing to risk.

Costs and access were important considerations, and the GDG recognizes that this recommendation could exacerbate health inequities. The GDG did not anticipate important variability in patient values and preferences (see Evidence to Decision).

Alternative or combination therapy

The GDG has previously made a a conditional recommendation for molnupiravir in the highest risk non-severe population, a strong recommendation for nirmatrelvir-ritonavir (see Section 6.7) and a conditional recommendation against nirmatrelvir-ritonavir in the lower risk non-severe population. Indirect comparisons in higher and highest risk patients found remdesivir may reduce hospitalization when compared with molnupiravir (low certainty); and found little or no difference when compared with nirmaltrelvir-ritonanivir (low certainty). Without direct data and low certainty confidence in indirect comparisons the GDG chose not to make comparative recommendations between drugs, but rather remark that nirmatrelvir-ritonavir may be superior based on its efficacy compared with standard of care and that ultimate choice be based on practical issues such as administration and potential drug-drug interactions.

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

Applicability

Only one of the included 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 women. 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 tabs).

The GDG also had concerns about whether the drug would retain efficacy against emerging variants of concern such as Omicron BA.1 or BA.2. 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: No remdesivir

Summary

The LNMA for remdesivir was informed by five RCTs which enrolled 2731 patients with non-severe illness in outpatient settings; data was available for 2709 patients. All RCTs were registered; and four were published in peer-reviewed journals *(15)(15)(31)(32)*. One of the included studies enrolled children 12 years of age and over; none included pregnant women. 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 remdesivir compared with standard care for the outcomes of interest, with certainty ratings, informed by the LNMA *(3)*.

The PINETREE trial was the only study to report subgroups within the non-severe subgroup *(15)*. The planned subgroup analyses were limited by available data but did not detect credible subgroup effects for serological status and age. As all patients were unvaccinated, randomized within 7 days of symptom onset, and did not receive therapeutic co-interventions; these subgroup analyses could not be performed. Of note, for age, 1.4% (n=8) were between 12 and 18 years old in the PINETREE trial, and none died or were hospitalized; no subgroup effect was noted for > 60 vs ≤ 60 years old patients (p=0.78).

Outcome Timeframe	**Study results and measurements**	**Comparator** No remdesivir	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Odds ratio 0.68 (CI 95% 0.39 — 1.21) Based on data from 2,709 participants in 5 studies. (Randomized controlled)	6 per 1000 Difference:	4 per 1000 **2 fewer per 1000** 4 fewer — 1 more	**Low** Due to serious indirectness and imprecision [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)	**Plain language summary**
Mechanical ventilation	Odds ratio 0.42 (CI 95% 0.08 — 1.96) Based on data from 261 participants in 2 studies. (Randomized controlled)	8 per 1000 Difference:	3 per 1000 **5 fewer per 1000** (CI 95% 7 fewer — 8 more)	**Very low** Due to very serious imprecision and serious indirectness [2]	The impact of remdesivir on mechanical ventilation is uncertain
Admission to hospital Risk in trials	Odds ratio 0.25 (CI 95% 0.06 — 0.88) Based on data from 562 participants in 1 studies. (Randomized controlled)	35 per 1000 Difference:	9 per 1000 **26 fewer per 1000** (CI 95% 33 fewer — 4 fewer)	**Moderate** Due to serious imprecision [3]	Remdesivir probably reduces hospitalization
Admission to hospital Higher risk	Odds ratio 0.25 (CI 95% 0.06 — 0.88) 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 — 7 fewer)	**Moderate** Due to serious imprecision [4]	Remdesivir probably reduces hospitalization
Admission to hospital Highest risk	Odds ratio 0.25 (CI 95% 0.06 — 0.88) Based on data from 562 participants in 1 studies. (Randomized controlled)	100 per 1000 Difference:	27 per 1000 **73 fewer per 1000** (CI 95% 93 fewer — 11 fewer)	**Moderate** Due to serious imprecision [5]	Remdesivir probably reduces hospitalization
Adverse effects leading to drug discontinuation	Based on data from 1,379 participants in 4 studies. (Randomized controlled)	0 per 1000 Difference:	9 per 1000 **9 more per 1000** (CI 95% 0 more — 21 more)	**Moderate** Due to serious imprecision [6]	There is probably little or no difference in adverse effects leading to drug discontinuation
Time to symptom resolution	Lower better Based on data from 138 participants in 1 studies. (Randomized controlled)	9 days (Median) Difference:	7.2 days (Mean) **MD 1.8 fewer** (CI 95% 5.7 fewer — 3.5 more)	**Very low** Due to extremely serious imprecision [7]	The impact of remdesivir on time to symptom resolution is uncertain

1. **Indirectness: serious.** Some patients may be at substantially higher risk of death. There may be an important difference in mortality in these patients. **Imprecision: serious.** Does not meet optimal information size; few events (50 total events).
2. **Indirectness: serious.** Some patients may be at substantially higher risk of mechanical ventilation. There may be an important difference in mechanical ventilation in these patients. **Imprecision: very serious.** Credible interval includes important benefit and important harm. Does not meet optimal information size; few events (11 total).
3. **Imprecision: serious.** The total sample size does not meet the optimal information size; few events (23 total events).

4. **Imprecision: serious.** The total sample size does not meet the optimal information size; few events (23 total events).
5. **Imprecision: serious.** The total sample size does not meet the optimal information size; few events (23 total events).
6. **Imprecision: serious.**
7. **Imprecision: extremely serious.**

Clinical Question/ PICO

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

Outcome Timeframe	**Study results and measurements**	**Comparator** Molnupiravir	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Odds ratio 6.55 (CI 95% 1.3 — 53.23) (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** 0 fewer — 0 fewer	**Low** Due to serious indirectness and imprecision [1]	There may be little or no difference in mortality
Mechanical ventilation	Odds ratio 1.08 (CI 95% 0.12 — 9) (Randomized controlled)	8 per 1000 Difference:	9 per 1000 **1 more per 1000** (CI 95% 13 fewer — 16 more)	**Low** Due serious risk of bias and indirectness [2]	The there may be little or no difference in mechanical ventilation
Admission to hospital Risk in trials	Odds ratio 0.48 (CI 95% 0.11 — 1.93) (Randomized controlled)	19 per 1000 Difference:	9 per 1000 **10 fewer per 1000** (CI 95% 17 fewer — 17 more)	**Moderate** Due to serious imprecision [3]	There may be little or no difference in hospital admission
Admission to hospital Higher risk	Odds ratio 0.48 (CI 95% 0.11 — 1.93) (Randomized controlled)	33 per 1000 Difference:	16 per 1000 **17 fewer per 1000** (CI 95% 29 fewer — 29 more)	**Low** Due to very serious imprecision [4]	Remdesivir may reduce hospital admission more than molnupiravir
Admission to hospital Highest risk	Odds ratio 0.48 (CI 95% 0.11 — 1.93) (Randomized controlled)	57 per 1000 Difference:	28 per 1000 **29 fewer per 1000** (CI 95% 50 fewer — 47 more)	**Low** Due to very serious imprecision [5]	Remdesivir may reduce hospital admission more than molnupiravir

Outcome Timeframe	**Study results and measurements**	**Comparator** Molnupiravir	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Adverse effects leading to drug discontinuation	(Randomized controlled)	0 per 1000 Difference:	9 per 1000 **9 more per 1000** (CI 95% 3 fewer — 21 more)	Very low Due to serious risk of bias, imprecision and indirectness [6]	The impact on adverse events leading to drug discontinuation is uncertain
Time to symptom resolution	Lower better (Randomized controlled)	5.6 days (Median) Difference:	7.9 days (Mean) **MD 2.3 more** (CI 95% 1.9 fewer — 7.8 more)	Very low Due to extremely serious imprecision [7]	The impact on time to symptom resolution is very uncertain

1. **Indirectness: serious.** Some patients may be at substantially higher risk of death. There may be an important difference in mortality in these patients. **Imprecision: serious.** Few events: 50 total events for remdesivir vs. control and 11 events for molnupiravir vs. control.
2. **Risk of bias: serious.** The evidence for molnupiravir was at high risk of bias. **Inconsistency: no serious. Indirectness: serious.** Some patients may be at substantially higher risk of mechanical ventilation. There may be an important difference in mechanical ventilation in these patients. **Imprecision: no serious. Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Credible interval includes important benefit and important harm. **Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Credible interval includes important benefit and important harm. **Publication bias: no serious.**
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Credible interval includes important benefit and important harm. **Publication bias: no serious.**
6. **Risk of bias: serious. Inconsistency: no serious. Indirectness: serious. Imprecision: serious. Publication bias: no serious.**
7. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious. Publication bias: no serious.**

Clinical Question/ PICO

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

Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days	(Randomized controlled)	0 per 1000 Difference:	3 per 1000 **3 more per 1000** 2 more — 5 more	Very low Due to serious risk of bias, indirectness, and imprecision [1]	The impact on mortality is uncertain
Mechanical				No data	The impact on

Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
ventilation					mechanical ventilation is unknown
Hospital admission Risk in trials	Odds ratio 1.64 (CI 95% 0.33 — 7.57) (Randomized controlled)	**6** per 1000 Difference:	**9** per 1000 **3 more per 1000** (CI 95% 4 fewer — 38 more)	**Low** Due to serious risk of bias and imprecision [2]	There may be little or no difference in hospital admission
Hospital admission Higher risk	Odds ratio 1.64 (CI 95% 0.33 — 7.57) (Randomized controlled)	**9** per 1000 Difference:	**15** per 1000 **6 more per 1000** (CI 95% 6 fewer — 55 more)	**Low** Due to serious risk of bias and imprecision [3]	There may be little or no difference in hospital admission
Hospital admission Highest risk	Odds ratio 1.64 (CI 95% 0.33 — 7.57) (Randomized controlled)	**16** per 1000 Difference:	**26** per 1000 **10 more per 1000** (CI 95% 11 fewer — 94 more)	**Low** Due to serious risk of bias and imprecision [4]	There may be little or no difference in hospital admission
Adverse events leading to drug discontinuation	(Randomized controlled)	**0** per 1000	**9** per 1000	**Very low** Due to very serious imprecision, serious risk of bias, serious indirectness, and very serious risk of bias [5]	The impact on adverse effects leading to drug discontinuation is uncertain
Time to symptom resolution				No data	The effect of nirmatrelvir-ritonavir is unknown

1. **Risk of bias: serious. Indirectness: serious.** Some patients may be at substantially higher risk of death. There may be an important difference in mortality in these patients. **Imprecision: serious.** Few events: 50 total events for remdesivir vs. control and 11 events for molnupiravir vs. control.
2. **Risk of bias: serious.** The EPIC-HR study of nirmatrelvir-ritonavir was stopped early for benefit. **Imprecision: serious.** Credible interval includes no difference and important harm.
3. **Risk of bias: serious.** The EPIC-HR study of nirmatrelvir-ritonavir was stopped early for benefit. **Imprecision: serious.** Credible interval includes no difference and important harm.
4. **Risk of bias: serious.** The EPIC-HR study of nirmatrelvir-ritonavir was stopped early for benefit. **Imprecision: serious.** Credible interval includes no difference and important harm.
5. **Risk of bias: very serious. Indirectness: serious. Imprecision: very serious.**

For patients with severe COVID-19

Conditional recommendation for

New

We suggest treatment with remdesivir *(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 women. 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 mother 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 pediatric 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 7), 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 *(30)*. 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 8th 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 serious adverse events attributable to the drug. The GDG acknowledged that some serious adverse events, 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 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 anti-viral 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 women. 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 tabs).

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)	**Plain language 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.
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	Lower better	9.9	9.3	Moderate	Remdesivir probably has little or no impact on

Outcome Timeframe	Study results and measurements	Comparator No remdesivir	Intervention Remdesivir	Certainty of the Evidence (Quality of evidence)	Plain language summary
symptom improvement	Based on data from 2,599 participants in 2 studies. (Randomized controlled)	days (Mean) Difference:	days (Mean) **MD 0.6 fewer** (CI 95% 1.7 fewer — 0.6 more)	Due to serious imprecision [5]	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 women. 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)	Plain language 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

Outcome Timeframe	**Study results and measurements**	**Comparator** No remdesivir	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
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

New

We suggest not to use remdesivir *(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 7), 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 *(30)*. 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 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 anti-viral 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 woman, 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)	**Plain language 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.
Length of hospital stay	Lower better Based on data from 8,365 participants in 3 studies. (Randomized	12.8 days (Mean) Difference:	12.4 days (Mean) **MD 0.4 fewer**	Low Due to serious risk of bias and imprecision [4]	Remdesivir may have little or no impact on length of hospital stay

Outcome Timeframe	**Study results and measurements**	**Comparator** No remdesivir	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	controlled)		(CI 95% 1 fewer — 0.2 more)		
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 women. 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)	**Plain language summary**
Mortality	Odds ratio 1.15 (CI 95% 0.89 — 1.51) Based on data from 1,012 participants in 3 studies. (Randomized	**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)	**Plain language summary**
	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.**

6.2.1 Mechanism of action

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)*.

Emergence of antiviral resistance: 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)(173)*. 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 *(35)*. Moreover, the V792I mutation has also been documented in two transplant recipients with persistant SARS-CoV-2 infection *(174)*. The clinical significance of these observations if remdesivir were widely used in an outpatient setting is unclear.

6.3 Janus kinase inhibitors (updated 16 September 2022)

Info Box

The existing strong recommendation concerning baricitinib, for patients with severe or critical COVID-19, was updated by the GDG on 2 August 2022 as the 12th version of the WHO living guideline and in the BMJ as Rapid Recommendations. It follows the availability of new clinical trial evidence for baricitinib administered in combination with corticosteroids and IL-6 receptor blockers suggesting that the incremental survival benefit afforded by baricitinib exists even among patients also treated with corticosteroids and IL-6 receptor blockers *(169)*.

Baricitinib, for patients with severe or critical COVID-19

Strong recommendation for

Updated

We recommend treatment with baricitinib *(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 (see Section 6.1 1 and 6.1 5).*
- *The panel acknowledged that given that the clinical trials were not representative of the world population and that the risk-benefit may be less advantageous, particularly in areas where certain infectious diseases 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 *(53)*. 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 of total 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 serious adverse events.

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 serious adverse events, 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 7), 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 serious adverse events. 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 serious adverse events. 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 8th 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 multiorgan 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 this update, 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 serious adverse events, of a drug that may be administered easily *(169)*. The GDG acknowledged that some serious adverse events, 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 this evidence that combining corticosteroids, IL-6 receptor blockers and baricitinib provides incremental survival benefit *(169)*. 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 *(169)*. Although these three immunosuppresslve 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 women. 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 tabs).

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 *(62)(54)(55)(169)*. All RCTs were registered, and three were published in peer-reviewed journals *(54)(55)(169)*; one study was a pre-print *(62)*. All RCTs enrolled patients in in-patient settings. None of the included studies enrolled children or pregnant women. 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 7).

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)	**Plain language 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	9.9 days (Median)	8.9 days (Mean)	Low Due to very serious	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)	**Plain language summary**
	2,558 participants in 2 studies. (Randomized controlled)	Difference:	**MD 1 fewer** (CI 95% 2.9 fewer — 1.1 more)	imprecision [5]	

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 - IL-6 subgroups
Intervention: Baricitinib
Comparator: Standard care

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Baricitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain language 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. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes no important difference. **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval includes no important difference. **Publication bias: no serious.**

Ruxolitinib and tofacitinib, for patients with severe or critical COVID-19

Conditional recommendation against

We suggest not to use ruxolitinib or tofacitinib (*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 7), 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 serious adverse effects, 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 serious adverse events (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 regards to the administration of ruxolitinib or toficitinib to pregnant or lactating women.

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 *(56)(57)*. 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 women. The Table shows characteristics of the RCTs.

For patients with severe and critical COVID-19, the GRADE Summary of Findings tables for ruxolitinib shows the relative and absolute effects compared with usual care for the outcomes of interest, with certainty ratings. See Section 7 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)	**Plain language 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Ruxolitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
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 participants in 2 studies. (Randomized controlled)	12.8 days (Median) Difference:	11.4 days (Mean) **MD 0.1 more** (CI 95% 2.1 fewer — 2.4 more)	Very low Due to serious indirectness and very serious imprecision [4]	The impact of ruxolitinib on hospital length of stay is very uncertain.
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. **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.
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 *(67)*. The trial was registered and published in a peer-reviewed journal; it excluded children and pregnant women. Table shows 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 7 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)	**Plain language 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**	Low Due to very serious imprecision [3]	Tofacitinib may increase adverse effects leading to drug discontinuation.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Tofacitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			(CI 95% 17 more — 138 more)		
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.

6.3.1 Mechanism of action

Type I and type II cytokine receptors are a family of receptors employed by over 50 interleukins, interferons, colony stimulating factors, and hormones *(68)*. The intracellular signalling triggered by these receptors is mediated by Janus kinases (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 *(68)*.

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 *(68)(58)(59)*.

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.

6.4 Sotrovimab (updated 16 September 2022)

Info Box

An updated recommendation concerning sotrovimab for patients with non-severe COVID-19 was published on 15 September 2022 in the 12th version of the WHO living guideline. Previously, a conditional recommendation was provided for patients with non-severe COVID-19 at highest risk of hospitalisation. Following the emergence of currently circulating SARS-CoV-2 variants and subvariants (e.g. Omicron) now dominating COVID-19 worldwide, and availability of evidence showing sotrovimab lacks related in vitro neutralization activity, the GDG made a strong recommmendation against the use of sotrovimab.

For patients with non-severe COVID-19

Strong recommendation against

Updated

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

- *Several other therapeutic options for patients with non-severe COVID-19 at highest risk of hospitalization are available: see decision support tool that displays benefits and harms of nirmatrelvir-ritonavir, molnupiravir, and remdesivir.*
- *The GDG considered in vitro data demonstrating that sotrovimab 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.*
- *However, there was also consensus regarding the need for clinical trial evidence in order to confirm any clinical effectiveness of new monoclonal antibodies that reliably neutralize the 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 *(3)*, the GDG had previously made a conditional recommendation to administer sotrovimab to patients with non-severe COVID-19 at highest risk of hospitalisation. At the time, the panel acknowledged that the emergence of future variants could reduce the clinical effectiveness of sotrovimab.

Rather than new clinical trial evidence, the change in recommendation was triggered by new in vitro evidence demonstrating that sotrovimab does not neutralize the currently circulating variants and 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.

Certainty of the Evidence

In light of the recent 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 [74] 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 can not be determined by trials performed before the new variants occurred.

Values and preferences

Applying the agreed upon values and preferences (see Section 7), 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 not choose to receive sotrovimab.

Resources and other considerations

Acceptability and feasibility

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

Justification

Although previous clinical trial evidence available via the LNMA *(3)* 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 utility in the evaluation of clinical effectiveness. The panel concluded that the emerging evidence demonstrating that sotrovimab did not 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.

6.4.1 Mechanism of action

- 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 [75]. Neutralization of SARS-CoV-2 (USA WA1/2020) was achieved in Vero E6 cells with an EC90 value of 0.19 µg/mL [76]. 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 [76]. 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 state “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 [76]. 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 [72].
- The FDA have 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 (https://www.fda.gov/media/157556/download). 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 500mg 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 [170][171][172], which makes the presented analysis 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 [76]. Sixteen other substitutions introduced into the epitope were also described as reducing neutralization by sotrovimab by between 5.4 and > 297-fold [76]. Therefore, resistance to sotrovimab can emerge under experimental conditions. Additionally, 4 of the first 1000 consecutive patients treated with sotrovimab during a Delta wave in Australia are reported to have developed E340 mutations in their viral sequences, and remained culture positive for 12–24 days after dosing [80].

6.5 Casirivimab-imdevimab (updated 16 September 2022)

Info Box

An updated recommendation concerning the neutralizing antibodies casirivimab-imdevimab for patients with COVID-19 was published on 15 September 2022 in this 12th version of the WHO living guideline. Previously, a conditional recommendation was provided for patients with non-severe COVID-19 at highest risk of hospitalization and also for patients with severe and critical illness provided they were seronegative. Following the emergence of the currently circulating SARS-CoV-2 variants and subvariants (e.g. Omicron) now dominating COVID-19 worldwide, and availability of evidence from in vitro SARS-CoV-2 neutralization assays, the GDG made a strong recommendation against the use of casirivimab-imdevimab for all patients with COVID-19 as casirivimab-imdevimab lacks sufficient in vitro neutralization activity against the Omicron variant and subvariants.

For all patients with COVID-19

Strong recommendation against

Updated

We recommend against treatment with casirivimab-imdevimab *(strong recommendation against).*

- *Several other therapeutic options exist for patients with COVID-19 across the severity spectrum: see decision support tool for patients with non-severe COVID-19.*
- *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.*
- *However, there was also consensus regarding the need for clinical trial evidence in order to confirm any clinical effectiveness of new monoclonal antibodies that reliably neutralize the 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 *(3)*, 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 does not neutralize the currently circulating variants and 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.

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 7), 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 their challenges with availability and feasibility, such as limited production, intravenous administration and requirement for expertise to offer such treatment while also oral options are available.

Justification

Although previous clinical trial evidence available via the LNMA *(3)* 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 utility in the evaluation of clinical effectiveness. The panel concluded that the emerging evidence demonstrating that casirivimab-imdevimab did not neutralize current variants in vitro would have justified not launching clinical trials and now renders the results 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.

6.5.1 Mechanism of action

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 *[111]* and have demonstrated antiviral activity in rhesus macaques and Syrian golden hamsters *[112]*. 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 *[42]*. 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 *[105]*. 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 (https://opendata.ncats.nih.gov/variant/activity). 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 (https://www.biorxiv.org/content/10.1101/2022.01.23.477397v1.full.pdf+html). Similar reductions for in vitro neutralising activity have been reported for casirivimab and/or imdevimab against BA.2, BA.4 and BA.5 Omicron sub-lineages *[170][171][172]*. Therefore, currently available preclinical data do not support activity of the casirivimab and imdevimab combination against currently circulating Omicron sub-lineages.

6.6 Fluvoxamine (published 14 July 2022)

Info Box

The recommendation concerning fluvoxamine for patients with non-severe COVID-19 was published on 14 July 2022, in the eleventh version of the WHO living guideline and in the BMJ as Rapid Recommendations. It follows the availability of three RCTs, as per the LNMA on drug therapies *(1)*. No changes were made for the recommendation in this twelfth version of the guideline.

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)*.

- *Several therapeutic options are recommended for patients with non-severe COVID-19 including nirmatrelvir-ritonavir, molnupiravir, and remdesivir.*
- *For choosing between the therapeutic options, see Section 6.1 and the decision support tool, which displays benefits and harms of the options.*

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 performed since trials only enrolled patients with non-severe COVID-19.

Certainty of the Evidence

The evidence summary was informed by 3 trials with 2225 participants included in the LNMA. The largest trial (n=1480) exclusively enrolled patients in Brazil *(16)*.

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 *(19)*, 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 7), 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

Special populations: 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 *(16)*, 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)	**Plain language 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
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 [2]	There may be little or no difference in mechanical ventilation
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 [3]	Fluvoxamine may reduce hospitalization
Hospital admission	Odds ratio 0.7 (CI 95% 0.34 — 1.23) Based on data from	60 per 1000	43 per 1000	**Low** Due to very serious	Fluvoxamine may reduce hospitalization

Outcome Timeframe	**Study results and measurements**	**Comparator** No fluvoxamine	**Intervention** Fluvoxamine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Higher risk	2,196 participants in 3 studies. (Randomized controlled)	Difference:	**17 fewer per 1000** (CI 95% 39 fewer — 13 more)	imprecision [4]	
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 [5]	Fluvoxamine may reduce hospitalization
Adverse effects leading to drug discontinuation	Based on data from 0 participants in studies.			No data	The effect of fluvoxamine is unknown
Time to symptom resolution	Based on data from 0 participants in studies.			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. **Indirectness: serious.** Some patients may be at substantially higher risk of mechanical ventilation. **Imprecision: serious.**
3. **Imprecision: very serious.** The credible interval includes both important harm and important benefit.
4. **Imprecision: very serious.** The credible interval includes both important harm and important benefit.
5. **Imprecision: very serious.** The credible interval includes both important harm and important benefit.

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)	**Plain language summary**
Mortality		**0** per 1000	**3** per 1000	**Very low** Due to serious	The impact on mortality is very uncertain

Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Fluvoxamine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	(Randomized controlled)	Difference:	**3 more per 1000** (CI 95% 1 more — 5 more)	indirectness, imprecision, and serious risk of bias [1]	
Mechanical ventilation				No data [2]	The effect on mechanical ventilation is unknown
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 [3]	Nirmatrelvir-ritonavir may reduce hospitalization more than fluvoxamine
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. **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. **Inconsistency: no serious. Indirectness: serious.** Some patients may be at substantially higher risk of mechanical ventilation. **Imprecision: serious. Publication bias: no serious.**
3. **Risk of bias: serious.** The nirmatrelvir-ritonavir study (EPIC-HR) was stopped early for benefit. **Imprecision: 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)	**Plain language 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
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 [2]	The effect on mechanical ventilation is uncertain
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 [3]	There may be little or no difference in hospital admission
Adverse effects leading to drug discontinuation	Based on data from 0 participants in studies.			No data	The effect on adverse effects is unknown
Time to symptom resolution	Based on data from 0 participants in studies.			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. **Indirectness: serious.** Some patients may be at substantially higher risk of mechanical ventilation. **Imprecision: very serious.**
3. **Imprecision: very serious.** The credible interval includes both important harm and important benefit.

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)	**Plain language 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
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 [2]	The effect on mechanical ventilation is uncertain
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 [3]	Remdesivir may reduce hospitalization more than fluvoxamine
Adverse effects leading to drug discontinuation	Based on data from 0 participants in studies.			No data	The effect on adverse effects is unknown
Time to symptom resolution	Based on data from 0 participants in studies.			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. **Indirectness: serious.** Some patients may be at substantially higher risk of mechanical ventilation. **Imprecision: very serious.**
3. **Imprecision: very serious.**

6.6.1 Mechanism of action

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 *(17)(18)*. 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.

6.7 Colchicine (published 14 July 2022)

Info Box

The recommendation concerning colchicine for patients with non-severe COVID-19 was published on 14 July 2022, in the eleventh version of the WHO living guideline and in the BMJ as Rapid Recommendations. It follows the availability of 13 RCTs that enrolled 18 172 patients, as per the LNMA on drug therapies *(1)*. No changes were made for the recommendation in this twelfth version of the guideline.

For patients with non-severe COVID-19

Strong recommendation against

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

- *Several therapeutic options are recommended for patients with non-severe COVID-19 including nirmatrelvir-ritonavir, molnupiravir, and remdesivir.*
- *For choosing between the therapeutic options, see Section 6.1 and the decision support tool, which displays benefits and harms of the options.*

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 *(23)*, 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 7), 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 (see summary of these factors under Evidence to Decision) impacted this specific recommendation.

Applicability

Special populations: 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 *(23)*, 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)	**Plain language 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
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 [2]	Colchicine probably has little or no impact on mechanical ventilation
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 [3]	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 participants in 3 studies. (Randomized controlled)	60 per 1000 Difference:	42 per 1000 **18 fewer per 1000** (CI 95% 43 fewer — 31 more)	**Moderate** Due to serious imprecision [4]	Colchicine probably has little or no impact on hospital admission
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 [5]	Colchicine may have little or no impact on hospital admission
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. **Indirectness: serious. Imprecision: no serious.** Credible interval includes modest benefit.
3. **Imprecision: 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 (4 fewer per 1000).
5. **Imprecision: very serious.**
6. **Risk of bias: serious. Imprecision: serious.**

6.7.1 Mechanism of action

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 *(20)(25)*, 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 when the guideline was pubished 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 *(26)(21)* but the substantive variation between studies included in the NMA precludes a robust interpretation of differences in outcome associated with dose and schedule.

6.8 Nirmatrelvir-ritonavir (published 22 April 2022)

Info Box

Recommendations concerning nirmatrelvir-ritonavir for patients with non-severe COVID-19 were published on 22 April 2022 as the tenth version of the WHO living guideline and in the BMJ as Rapid Recommendations. It follows the availability of two RCTs, as per the LNMA on drug therapies *(1)*. No changes were made for the nirmatrelvir-ritonavir recommendation in this twelfth version of the guideline.

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

Strong recommendation for

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

- *See Section 6.1 for help to identify patients at highest risk.*
- *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 represents a superior choice because it may have greater efficacy in preventing hospitalization than the alternatives, has fewer concerns with respect to harms than does molnupiravir; and is easier to administer than intravenous remdesivir and the antibodies.*
- *The strong recommendation in favour does not apply to pregnant women, children, or those with possible dangerous drug interactions (many drugs interact with nirmatrelvir-ritonavir, see mechanism of action).*
- *Nirmatrelvir-ritonavir should be administered as soon as possible after onset of symptoms, ideally within 5 days.*

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). 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 reduction is 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 time course of the disease. In the included studies, nirmatrelvir-ritonavir was administered within 5 days of disease onset.
- The GDG concluded that nirmatrelvir-ritonavir should not be offered to children, breastfeeding or pregnant women with COVID-19.

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 *(22)*.

Evidence To Decision

Benefits and harms

In highest risk patients in whom an appreciable decrease in hospitalization with nirmatrelvir-ritonavir is likely, the benefits clearly outweigh the harms, thus warranting the strong recommendation in favour of the drug.

In patients with non-severe COVID-19, nirmatrelvir-ritonavir likely reduces admission to hospital (moderate certainty evidence). It may have little or no impact on mortality (low certainty evidence). There are no data reported for time to symptom resolution or mechanical ventilation. Treatment does not increase the likelihood of adverse effects leading to drug discontinuation (high certainty evidence), though diarrhoea and dysgeusia (loss of taste) have occurred more frequently with nirmatrelvir-ritonavir as compared with placebo.

The GDG acknowledged that there was a paucity of information relating to emergence of resistance and much more data were needed to inform the recommendation.

Certainty of the Evidence

The evidence summary on nirmatrelvir-ritonavir was informed by two trials (EPIC-SR and EPIC-HR) with 3100 participants included in the LNMA study *(1)(29)(23)*.

Certainty of evidence was rated as: moderate for decreased hospitalization (rated down due to concerns regarding imprecision and risk of bias); low for mortality (rated down due to serious imprecision and indirectness) and high for adverse

effects leading to drug discontinuation. We did not rate the certainty of the evidence for diarrhoea and dysgeusia.

Limitations in available empirically developed risk prediction tools for establishing patients' risk of hospitalization represent the major source of indirectness for which the GDG rated down the certainty of the evidence *(24)*.

Values and preferences

Applying the agreed upon values and preferences (see Section 7), the GDG inferred that almost all well-informed patients with a higher 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 nirmatrelvir-ritonavir be reserved for those at higher risk.

Obstacles to access in low- and middle-income countries (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 patients at higher 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. 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 Prequalification 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 according

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

Moderate certainty evidence of a substantial relative risk reduction in hospitalization, and high certainty evidence of no adverse effects requiring drug discontinuation, motivated the strong recommendation in individuals at higher risk of hospitalization. Such individuals are likely to achieve an important reduction in the absolute risk of hospitalization in comparison with those not receiving nirmatrelvir-ritonavir.

Alternative or combination therapy

The GDG has previously made a conditional recommendation for molnupiravir (see Section 6.6) in the highest risk non-severe population, and in this guideline update a conditional recommendation for remdesivir (see Section 6.5). Indirect comparisons in higher and highest risk patients found nirmatrelvir-ritonavir may reduce hospitalization when compared with molnupiravir (low certainty); however, found little or no difference when compared with remdesivir (low certainty). Without direct data comparisons and low certainty confidence in indirect comparisons, the GDG chose not to make comparative recommendations between drugs, but rather remark that nirmatrelvir-ritonavir may be superior based on its efficacy compared with standard of care (moderate certainty) and then ultimate choice based on practical issues, such as ease of administration and risk profiles.

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

Applicability

The applicability of this recommendation to children, breastfeeding and pregnant women is currently uncertain, as the included RCTs enrolled only non-pregnant adults. The GDG concluded that nirmatrelvir-ritonavir should not be offered to children, breastfeeding or pregnant women with COVID-19.

Clinical Question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Nirmatrelvir-ritonavir
Comparator: No nirmatrelvir-ritonavir

Summary

The LNMA for nirmatrelvir-ritonavir was informed by two RCTs (EPIC-SR and HR) which enrolled 3100 patients with non-severe illness in outpatient settings. The two RCTs were registered; and one was published in a peer-reviewed journal *(23)*. None of the included studies enrolled children or pregnant women. 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 nirmatrelvir-ritonavir 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 did not detect credible subgroup effects for serological status and age (children were not enrolled). As all patients were unvaccinated and were randomized within 5 days of symptom onset, and no patients received therapeutic co-interventions, these subgroup analyses could not be performed.

Outcome Timeframe	**Study results and measurements**	**Comparator** No nirmatrelvir-ritonavir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days	Odds ratio 0.04 (CI 95% 0 — 0.67) Based on data from 3,100 participants in 2 studies. (Randomized controlled)	6 per 1000 Difference:	0 per 1000 **6 fewer per 1000** (CI 95% 6 fewer — 2 fewer)	**Low** Due to serious imprecision and indirectness [1]	Nirmatrelvir-ritonavir may have a small effect on mortality
Mechanical ventilation	Based on data from 0 participants in studies.			No data	The effect of nirmatrelvir-ritonavir is unknown
Admission to hospital Risk in trials	Odds ratio 0.15 (CI 95% 0.06 — 0.38) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	35 per 1000 Difference:	5 per 1000 **30 fewer per 1000** (CI 95% 33 fewer — 21 fewer)	**Moderate** Due to concerns with risk of bias and imprecision [2]	Nirmatrelvir-ritonavir probably reduces hospitalization
Admission to hospital Higher risk	Odds ratio 0.15 (CI 95% 0.06 — 0.38) 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 — 36 fewer)	**Moderate** Due to concerns with risk of bias and imprecision [3]	Nirmatrelvir-ritonavir probably reduces hospitalization

Outcome Timeframe	**Study results and measurements**	**Comparator** No nirmatrelvir-ritonavir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Admission to hospital Highest risk	Odds ratio 0.15 (CI 95% 0.06 — 0.38) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	**100** per 1000 Difference:	**16** per 1000 **84 fewer per 1000** (CI 95% 93 fewer — 59 fewer)	**Moderate** Due to concerns with risk of bias and imprecision [4]	Nirmatrelvir-ritonavir probably reduces hospitalization
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.29 — 0.8) Based on data from 2,246 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 has little or no risk of adverse effects leading to drug discontinuation
Time to symptom resolution	Based on data from 0 participants in studies.			No data	The effect of nirmatrelvir-ritonavir is unknown

1. **Indirectness: serious.** Some patients may be at substantially higher risk of death. Nirmatrelvir-ritonavir probably reduces mortality in these patients. **Imprecision: serious.** There were only 12 events (all in the placebo group); and only one study.
2. **Risk of bias: serious.** The study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.
3. **Risk of bias: serious.** The study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.
4. **Risk of bias: serious.** The study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.

Clinical Question/ PICO

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

Outcome Timeframe	**Study results and measurements**	**Comparator** Molnupiravir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days	Odds ratio 0 (CI 95% 0 — 0.29) (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000**	**Moderate** Due to serious indirectness [1]	There is probably little or no difference in mortality

Outcome Timeframe	**Study results and measurements**	**Comparator** Molnupiravir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			(CI 95% 0 fewer — 0 fewer)		
Mechanical ventilation	Based on data from 0 participants in studies.			No data	The effect of nirmatrelvir-ritonavir is unknown
Admission to hospital Risk in trials	Odds ratio 0.29 (CI 95% 0.1 — 0.88) (Randomized controlled)	**19** per 1000 Difference:	**6** per 1000 **13 fewer per 1000** (CI 95% 17 fewer — 2 fewer)	**Low** Due to risk of bias and imprecision [2]	Nirmatrelvir-ritonavir may reduce hospitalization more than molnupiravir
Admission to hospital Highest risk	Odds ratio 0.29 (CI 95% 0.1 — 0.88) (Randomized controlled)	**57** per 1000 Difference:	**17** per 1000 **40 fewer per 1000** (CI 95% 51 fewer — 6 fewer)	**Low** Due to risk of bias and imprecision [3]	Nirmatrelvir-ritonavir may reduce hospitalization more than molnupiravir
Admission to hospital Higher risk	Odds ratio 0.29 (CI 95% 0.1 — 0.88) (Randomized controlled)	**33** per 1000 Difference:	**17** per 1000 **40 fewer per 1000** (CI 95% 51 fewer — 6 fewer)	**Low** Due to risk of bias and imprecision [4]	Nirmatrelvir-ritonavir may reduce hospitalization more than molnupiravir
Adverse effects leading to drug discontinuation	(Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**High**	There is little or no difference in the risk of adverse effects leading to drug discontinuation.
Time to symptom resolution	Based on data from 0 participants in studies.			No data	The effect of nirmatrelvir/ritonavir is unknown

1. **Indirectness: serious.** Some patients may be at substantially higher risk of death. There may be an important difference in mortality in these patients.
2. **Risk of bias: serious.** The nirmatrelvir-ritonavir study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.
3. **Risk of bias: serious.** The nirmatrelvir-ritonavir study was stopped early for benefit. **Imprecision: serious.** The total

sample size does not meet the optimal information size.
4. **Risk of bias: serious.** The nirmatrelvir-ritonavir study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.

Clinical Question/ PICO

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

Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days	(Randomized controlled)	0 per 1000 Difference:	3 per 1000 **3 more per 1000** 2 more — 5 more	Very low Due to serious risk of bias, indirectness, and imprecision [1]	The impact on mortality is uncertain
Mechanical ventilation				No data	The impact on mechanical ventilation is unknown
Hospital admission Risk in trials	Odds ratio 1.64 (CI 95% 0.33 — 7.57) (Randomized controlled)	6 per 1000 Difference:	9 per 1000 **3 more per 1000** (CI 95% 4 fewer — 38 more)	Low Due to serious risk of bias and imprecision [2]	There may be little or no difference in hospital admission
Hospital admission Higher risk	Odds ratio 1.64 (CI 95% 0.33 — 7.57) (Randomized controlled)	9 per 1000 Difference:	15 per 1000 **6 more per 1000** (CI 95% 6 fewer — 55 more)	Low Due to serious risk of bias and imprecision [3]	There may be little or no difference in hospital admission
Hospital admission Highest risk	Odds ratio 1.64 (CI 95% 0.33 — 7.57) (Randomized controlled)	16 per 1000 Difference:	26 per 1000 **10 more per 1000** (CI 95% 11 fewer — 94 more)	Low Due to serious risk of bias and imprecision [4]	There may be little or no difference in hospital admission
Adverse events leading to drug discontinuation	(Randomized controlled)	0 per 1000	9 per 1000	Very low Due to very serious imprecision, serious risk of	The impact on adverse effects leading to drug discontinuation is uncertain

Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
				bias, serious indirectness, and very serious risk of bias [5]	
Time to symptom resolution				No data	The effect of nirmatrelvir-ritonavir is unknown

1. **Risk of bias: serious. Indirectness: serious.** Some patients may be at substantially higher risk of death. There may be an important difference in mortality in these patients. **Imprecision: serious.** Few events: 50 total events for remdesivir vs. control and 11 events for molnupiravir vs. control.
2. **Risk of bias: serious.** The EPIC-HR study of nirmatrelvir-ritonavir was stopped early for benefit. **Imprecision: serious.** Credible interval includes no difference and important harm.
3. **Risk of bias: serious.** The EPIC-HR study of nirmatrelvir-ritonavir was stopped early for benefit. **Imprecision: serious.** Credible interval includes no difference and important harm.
4. **Risk of bias: serious.** The EPIC-HR study of nirmatrelvir-ritonavir was stopped early for benefit. **Imprecision: serious.** Credible interval includes no difference and important harm.
5. **Risk of bias: very serious. Indirectness: serious. Imprecision: very serious.**

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

Conditional recommendation against

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

- *In the GDG's assessment, only a minority of low-risk patients will choose to consider using nirmatrelvir-ritonavir.*
- *Trials on antivirals included patients with some risk factors for hospital admission, resulting in a baseline risk of 3% that the GDG applied to generate the recommendation. The risk of hospitalization is likely to be lower in the general population.*
- *Clinicians should not consider nirmatrelvir-ritonavir in pregnant women, children, or those with possible dangerous drug interactions (note: many drugs interact with nirmatrelvir-ritonavir).*

Practical Info

Route, dosage and duration: Additional considerations are available in a summary of practical issues.

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 *(22)*.

Evidence To Decision

Benefits and harms

In patients with non-severe COVID-19, nirmatrelvir-ritonavir probably reduces admission to hospital. However, in low risk patients, the absolute benefit is very small and unlikely to be important to most patients. Nirmatrelvir-ritonavir probably has little or no impact on mortality. Highly relevant to patients at low risk of hospitalization, studies have reported no data for

time to symptom resolution. EPIC-SR did, however, report a very closely related outcome: time to 4 consecutive days of mild or no symptoms. For this analysis, the median time was 13.0 (95% CI 12 to 15) days for nirmatrelvir-ritonavir, and 13.0 (95% CI 11 to 14) days for placebo (p=0.47). Treatment does not increase the likelihood of adverse effects leading to drug discontinuation, though diarrhoea and dysgeusia have occurred more frequently with nirmatrelvir-ritonavir, as compared with placebo.

Certainty of the Evidence

The evidence summary on nirmatrelvir-ritonavir was informed by two trials (EPIC-SR and EPIC HR) with 3100 participants included in the LNMA study *(1)(29)(23)*.

Certainty of evidence was rated as: moderate for decreased hospitalization (rated down due to concerns regarding serious imprecision and risk of bias); low for mortality (rated down due to serious imprecision and indirectness) and high for adverse effects leading to drug discontinuation. We did not rate certainty of evidence for diarrhoea and dysgeusia.

Values and preferences

The GDG believes that most low risk patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on outcomes they consider important. This consideration is particularly relevant for shortening of the duration of symptoms, for which we have no direct evidence supporting a positive impact of nirmatrelvir-ritonavir.

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 be reserved for those at highest risk.

Justification

Most patients who contract COVID-19 are at very low risk of hospitalization (under 1%) and at a vanishingly small risk of mortality. Such patients will experience trivial benefits with use of nirmatrelvir-ritonavir. The panel inferred that most such patients would be uninterested in using the drug for these trivial benefits. Thus, for most patients, sufficient risk - and thus sufficient benefit of nirmatrelvir-ritonavir - to make nirmatrelvir-ritonavir use an attractive option will require presence of at least one if not a combination of risk factors. This is particularly true in low-income settings in which resource constraints and feasibility issues will make nirmatrelvir-ritonavir use less attractive.

The GDG, nevertheless, was cognizant that there are likely to be an appreciable number of individuals who place a high value on very small reductions in the risk of hospitalization and who would thus choose use of nirmatrelvir-ritonavir; therefore, a conditional rather than strong recommendation was made.

Clinical Question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Nirmatrelvir-ritonavir
Comparator: No nirmatrelvir-ritonavir

Summary

The LNMA for nirmatrelvir-ritonavir was informed by two RCTs (EPIC-SR and HR) which enrolled 3100 patients with non-severe illness in outpatient settings. The two RCTs were registered; and one was published in a peer-reviewed journal *(23)*. None of the included studies enrolled children or pregnant women. 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 nirmatrelvir-ritonavir 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 did not detect credible subgroup effects for serological status and age (children were not enrolled). As all patients were unvaccinated and were randomized within 5 days of symptom onset, and no patients received therapeutic co-interventions, these subgroup analyses could not be performed.

Outcome Timeframe	**Study results and measurements**	**Comparator** No nirmatrelvir-ritonavir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days	Odds ratio 0.04 (CI 95% 0 — 0.67) Based on data from 3,100 participants in 2 studies. (Randomized controlled)	6 per 1000 Difference:	0 per 1000 **6 fewer per 1000** (CI 95% 6 fewer — 2 fewer)	**Low** Due to serious imprecision and indirectness [1]	Nirmatrelvir-ritonavir may have a small effect on mortality
Mechanical ventilation	Based on data from 0 participants in studies.			No data	The effect of nirmatrelvir-ritonavir is unknown
Admission to hospital Risk in trials	Odds ratio 0.15 (CI 95% 0.06 — 0.38) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	35 per 1000 Difference:	5 per 1000 **30 fewer per 1000** (CI 95% 33 fewer — 21 fewer)	**Moderate** Due to concerns with risk of bias and imprecision [2]	Nirmatrelvir-ritonavir probably reduces hospitalization
Admission to hospital Higher risk	Odds ratio 0.15 (CI 95% 0.06 — 0.38) 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 — 36 fewer)	**Moderate** Due to concerns with risk of bias and imprecision [3]	Nirmatrelvir-ritonavir probably reduces hospitalization
Admission to hospital Highest risk	Odds ratio 0.15 (CI 95% 0.06 — 0.38) Based on data from 3,078 participants in 2 studies. (Randomized controlled)	100 per 1000 Difference:	16 per 1000 **84 fewer per 1000** (CI 95% 93 fewer — 59 fewer)	**Moderate** Due to concerns with risk of bias and imprecision [4]	Nirmatrelvir-ritonavir probably reduces hospitalization
Adverse effects leading to drug discontinuation	Odds ratio 0.48 (CI 95% 0.29 — 0.8) Based on data from 2,246 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 has little or no risk of adverse effects leading to drug discontinuation

Outcome Timeframe	Study results and measurements	Comparator No nirmatrelvir-ritonavir	Intervention Nirmatrelvir-ritonavir	Certainty of the Evidence (Quality of evidence)	Plain language summary
Time to symptom resolution	Based on data from 0 participants in studies.			No data	The effect of nirmatrelvir-ritonavir is unknown

1. **Indirectness: serious.** Some patients may be at substantially higher risk of death. Nirmatrelvir-ritonavir probably reduces mortality in these patients. **Imprecision: serious.** There were only 12 events (all in the placebo group); and only one study.
2. **Risk of bias: serious.** The study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.
3. **Risk of bias: serious.** The study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.
4. **Risk of bias: serious.** The study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.

Clinical Question/ PICO

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

Outcome Timeframe	Study results and measurements	Comparator Molnupiravir	Intervention Nirmatrelvir-ritonavir	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality 28 days	Odds ratio 0 (CI 95% 0 — 0.29) (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**Moderate** Due to serious indirectness [1]	There is probably little or no difference in mortality
Mechanical ventilation	Based on data from 0 participants in studies.			No data	The effect of nirmatrelvir-ritonavir is unknown
Admission to hospital Risk in trials	Odds ratio 0.29 (CI 95% 0.1 — 0.88) (Randomized controlled)	**19** per 1000 Difference:	**6** per 1000 **13 fewer per 1000** (CI 95% 17 fewer — 2 fewer)	**Low** Due to risk of bias and imprecision [2]	Nirmatrelvir-ritonavir may reduce hospitalization more than molnupiravir

Outcome Timeframe	**Study results and measurements**	**Comparator** Molnupiravir	**Intervention** Nirmatrelvir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Admission to hospital Highest risk	Odds ratio 0.29 (CI 95% 0.1 — 0.88) (Randomized controlled)	57 per 1000 Difference:	17 per 1000 **40 fewer per 1000** (CI 95% 51 fewer — 6 fewer)	**Low** Due to risk of bias and imprecision [3]	Nirmatrelvir-ritonavir may reduce hospitalization more than molnupiravir
Admission to hospital Higher risk	Odds ratio 0.29 (CI 95% 0.1 — 0.88) (Randomized controlled)	33 per 1000 Difference:	17 per 1000 **40 fewer per 1000** (CI 95% 51 fewer — 6 fewer)	**Low** Due to risk of bias and imprecision [4]	Nirmatrelvir-ritonavir may reduce hospitalization more than molnupiravir
Adverse effects leading to drug discontinuation	(Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**High**	There is little or no difference in the risk of adverse effects leading to drug discontinuation.
Time to symptom resolution	Based on data from 0 participants in studies.			No data	The effect of nirmatrelvir/ritonavir is unknown

1. **Indirectness: serious.** Some patients may be at substantially higher risk of death. There may be an important difference in mortality in these patients.
2. **Risk of bias: serious.** The nirmatrelvir-ritonavir study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.
3. **Risk of bias: serious.** The nirmatrelvir-ritonavir study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.
4. **Risk of bias: serious.** The nirmatrelvir-ritonavir study was stopped early for benefit. **Imprecision: serious.** The total sample size does not meet the optimal information size.

Clinical Question/ PICO

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

Outcome Timeframe	**Study results and measurements**	**Comparator** Nirmatrelvir-ritonavir	**Intervention** Remdesivir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 28 days	(Randomized controlled)	0 per 1000 Difference:	3 per 1000 **3 more per 1000** 2 more — 5 more	**Very low** Due to serious risk of bias, indirectness, and imprecision [1]	The impact on mortality is uncertain
Mechanical ventilation				No data	The impact on mechanical ventilation is unknown
Hospital admission Risk in trials	Odds ratio 1.64 (CI 95% 0.33 — 7.57) (Randomized controlled)	6 per 1000 Difference:	9 per 1000 **3 more per 1000** (CI 95% 4 fewer — 38 more)	**Low** Due to serious risk of bias and imprecision [2]	There may be little or no difference in hospital admission
Hospital admission Higher risk	Odds ratio 1.64 (CI 95% 0.33 — 7.57) (Randomized controlled)	9 per 1000 Difference:	15 per 1000 **6 more per 1000** (CI 95% 6 fewer — 55 more)	**Low** Due to serious risk of bias and imprecision [3]	There may be little or no difference in hospital admission
Hospital admission Highest risk	Odds ratio 1.64 (CI 95% 0.33 — 7.57) (Randomized controlled)	16 per 1000 Difference:	26 per 1000 **10 more per 1000** (CI 95% 11 fewer — 94 more)	**Low** Due to serious risk of bias and imprecision [4]	There may be little or no difference in hospital admission
Adverse events leading to drug discontinuation	(Randomized controlled)	0 per 1000	9 per 1000	**Very low** Due to very serious imprecision, serious risk of bias, serious indirectness, and very serious risk of bias [5]	The impact on adverse effects leading to drug discontinuation is uncertain
Time to symptom resolution				No data	The effect of nirmatrelvir-ritonavir is unknown

1. **Risk of bias: serious. Indirectness: serious.** Some patients may be at substantially higher risk of death. There may be an important difference in mortality in these patients. **Imprecision: serious.** Few events: 50 total events for remdesivir vs.

control and 11 events for molnupiravir vs. control.
2. **Risk of bias: serious.** The EPIC-HR study of nirmatrelvir-ritonavir was stopped early for benefit. **Imprecision: serious.** Credible interval includes no difference and important harm.
3. **Risk of bias: serious.** The EPIC-HR study of nirmatrelvir-ritonavir was stopped early for benefit. **Imprecision: serious.** Credible interval includes no difference and important harm.
4. **Risk of bias: serious.** The EPIC-HR study of nirmatrelvir-ritonavir was stopped early for benefit. **Imprecision: serious.** Credible interval includes no difference and important harm.
5. **Risk of bias: very serious. Indirectness: serious. Imprecision: very serious.**

6.8.1. Mechanism of action

Nirmatrelvir inhibits the SARS-CoV-2 protease (3CLpro), thereby preventing cleavage of the viral polyprotein which is needed for viral proteins to become functional *(25)*. Inhibition of the protease renders the virus unable to replicate. Nirmatrelvir is co-administered with ritonavir, a HIV protease inhibitor, used in this context to boost the pharmacokinetics of nirmatrelvir but without exerting any direct antiviral activity itself *(26)*. 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 repurposed 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 *(26)*. 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 nimatrelvir-ritonavir, and steady-state pharmacokinetics were achieved on day 2 *(27)* (an EC_{90} of 0.18 micromolar equates to approximately 90 ng/mL). High doses (300 mg/kg) of unboosted nimatrelvir was 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 *(26)*. High doses (250 mg/kg) of unboosted nimatrelvir also had efficacy in SARS-CoV-2-infected Syrian golden hamsters but no pharmacokinetic data are available in this species *(28)*. Based upon genome sequence of Omicron, there appears to be no molecular basis for a loss of activity. Nimatrelvir retains activity against BA.1 Omicron in vitro *(29)* 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 *(27)*. 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 *(27)*. Two amino substitutions were described in clinical trials, one of which did not impact nirmatrelvir activity.

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 *(22)*.

6.9 Molnupiravir (published 3 March 2022)

Info Box

Recommendations concerning molnupiravir for patients with non-severe COVID-19 were published on 3 March 2022 as the ninth version of the WHO living guideline and in the BMJ as Rapid Recommendations. It follows the availability of six RCTs, as per the LNMA on drug therapies *(1)*. No changes were made to the molnupiravir recommendation in this twelfth version of the guideline.

For patients with non-severe COVID-19 at highest risk of hospitalization (excluding pregnant and breastfeeding women, and children)

Conditional recommendation for

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

- *See Section 6.1 for help to identify patients at highest risk for hospitalization.*
- *Several therapeutic options are available: see decision support tool that displays benefits and harms of nirmatrelvir-ritonavir, molnupiravir and remdesivir.*
- *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 genotoxicity, emergence of resistance, and emergence of new variants (see Mechanism of action).*
- *The conditional recommendation reflects the concern for widespread treatment with molnupiravir before more safety data become available.*
- *Use of molnupiravir should be accompanied by mitigation strategies such as avoiding the drug in younger adults, active pharmacovigilance programmes, and monitoring viral polymerase and spike sequences (see Justification).*

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, molnupiravir probably reduces admission to hospital and time to symptom resolution, and may reduce mortality. The effect of molnupiravir on mechanical ventilation is very uncertain. Treatment does not increase the likelihood of adverse effects leading to drug discontinuation.

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

The balance between benefits and potential harms was close, but favoured treatment in the highest risk group, if implemented with other mitigation strategies to avoid harm at individual and population level (see Mitigation strategies section). There is a risk that monotherapy with molnupiravir (as for other antiviral monotherapies) may be associated with emergence of drug resistance, as has been seen with other antivirals (see Mechanism of action section).

The absolute benefits of molnupiravir on hospital admission depend on the prognosis. The GDG defined a threshold of a 6% absolute reduction in hospital admission to represent what most patients would value as an important benefit. Molnupiravir would exert such a benefit in patients at highest risk of hospitalization (above 10% baseline risk), such as those that lack COVID-19 vaccination, older people, or those with immunodeficiencies and/or chronic diseases. The conditional recommendation for the use of molnupiravir in those at highest risk reflects this threshold: 60 fewer hospitalizations per 1000 patients, and a greater anticipated absolute survival benefit, although this was not possible to quantify in the absence of data.

The planned subgroup analyses could not be performed in the absence of subgroup data reported publicly or provided by investigators.

Certainty of the Evidence

The evidence summary was informed by six trials with 4796 participants included in the LNMA, including the MOVe-OUT study *(36)*.

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

Limitations in available empirically developed risk prediction tools for establishing patients' risk of hospitalization represent the major source of indirectness for which the GDG rated down the certainty of the evidence *(24)*. In addition, the GDG felt that there was some indirectness because of the possible emergence of variants (including Omicron) for which the effectiveness of currently available monoclonal antibodies may be reduced.

The GDG decided against rating certainty down for imprecision for outcomes where low event rates reflected very low baseline risks (e.g. mortality).

Values and preferences

Applying the agreed values and preferences (see Section 7), the GDG inferred that almost all well-informed patients with a low risk of hospitalization would decline molnupiravir, and only those at highest risk (e.g. unvaccinated, older, or immunosuppressed) would choose to receive treatment.

In the absence of research evidence, in a previous survey (see recommendation for casirivimab-imdevimab), the GDG expressed the view that most patients with a risk of hospitalization above 10%, and thus an absolute risk reduction of approximately 6%, would choose to receive treatment, whereas most of those below that risk level would decline treatment. A similar survey was completed by the GDG for this recommendation; the GDG expressed the view that most patients would consider a reduction in the absolute risk of death of 3 per 1000 (increase in survivors from 995 to 998 per 1000 patients) to be 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 highest 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 highest 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. 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 Prequalification Unit, which included molnupiravir. 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.

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 programs should optimize their testing systems to reflect local epidemiology, response objectives, available resources and needs of their populations.

Justification

A combination of the evidence, safety concerns based on preclinical data, values and preferences, and feasibility contributed to the conditional recommendation for the use of molnupiravir only in patients with non-severe COVID-19 at highest risk of hospitalization. Typical characteristics of people at highest risk include those who are unvaccinated, older people, or those with immunodeficiencies and/or chronic diseases (e.g. diabetes).

Only a minority of patients who are at highest risk are likely to achieve sufficient benefit to compensate for the risks, and other limitations and disadvantages of therapy. These include a lack of reliable tools to identify high-risk patients, limited availability of the drug, and the safety concerns summarized below.

- The GDG had concerns about the risk of emergent resistance with a new antiviral deployed as monotherapy (see Mechanism of action section). Significant uncertainty exists regarding how quickly resistance will emerge; in the absence of sufficient clinical data, the GDG concluded large uncertainties remain.
- Concerning the risk of the drug promoting the emergence of new variants, the GDG noted that there was a low likelihood that the drug would result in a selective pressure for a new variant; large uncertainty remains in the absence of sufficient clinical data.
- 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 women.
- 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 women, 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 women with COVID-19. In addition, men planning to conceive should be oriented on the potential for temporary genotoxic effect on sperm cell production (see Mitigation strategies section). 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 a high risk should be avoided.

The GDG also had concerns about whether the drug would retain efficacy against emerging variants of concern such as Omicron. While there is no molecular basis for a loss of efficacy, the GDG noted that the higher viral loads and associated disease severity may impact the effectiveness of molnupiravir. This represents another area of uncertainty, given currently available data did not include patients with newer variants, including Omicron (see Section 9).

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 six RCTs which enrolled 4827 patients with non-severe illness in outpatient settings; the LNMA team had access to data for 4796 patients. All RCTs were registered; none were published in peer-reviewed journals. None of the included studies enrolled children or pregnant women. The appendix

summarizes study characteristics and risk of bias ratings, effect estimates by outcome and associated forest plots for molnupiravir versus standard care.

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 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).

Studies did not enrol children, nor patients with severe or critical illness. All studies 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** Molnupiravir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Odds ratio 0.06 (CI 95% 0 — 0.4) Based on data from 4,796 participants in 6 studies. (Randomized controlled)	6 per 1000 Difference:	0 per 1000 **6 fewer per 1000** (CI 95% 6 fewer — 4 fewer)	**Low** Due to serious imprecision and indirectness [1]	Molnupiravir may have a small effect on mortality
Mechanical ventilation	Odds ratio 1 (CI 95% 0.02 — 59.74) Based on data from 1,220 participants in 1 studies. (Randomized controlled)	8 per 1000 Difference:	8 per 1000 **0 fewer per 1000** (CI 95% 8 fewer — 317 more)	**Very low** Due to serious risk of bias and extremely serious imprecision [2]	The effect of molnupiravir on mechanical ventilation is very uncertain
Admission to hospital Risk in trials	Odds ratio 0.54 (CI 95% 0.3 — 0.89) Based on data from 4,688 participants in 5 studies. (Randomized controlled)	35 per 1000 Difference:	19 per 1000 **16 fewer per 1000** (CI 95% 24 fewer — 4 fewer)	**Moderate** Due to serious imprecision [3]	Molnupiravir probably reduces hospital admission
Admission to hospital Higher risk	Odds ratio 0.54 (CI 95% 0.3 — 0.89) Based on data from 4,688 participants in 5 studies. (Randomized controlled)	60 per 1000 Difference:	33 per 1000 **27 fewer per 1000** (CI 95% 41 fewer — 6 fewer)	**Moderate** Due to serious imprecision [4]	Molnupiravir probably reduces hospital admission
Admission to	Odds ratio 0.54 (CI 95% 0.3 — 0.89)	100	57	**Moderate** Due to serious	Molnupiravir probably reduces hospital

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Molnupiravir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
hospital Highest risk	Based on data from 4,688 participants in 5 studies. (Randomized controlled)	per 1000 Difference:	per 1000 **43 fewer per 1000** (CI 95% 68 fewer — 10 fewer)	imprecision [5]	admission
Adverse effects leading to drug discontinuation	Based on data from 4,796 participants in 6 studies. (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 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 3,078 participants in 3 studies. (Randomized controlled)	**9** (Median) Difference:	**5.6** (Mean) **MD 3.4 fewer** (CI 95% 4.8 fewer — 1.7 fewer)	**Moderate** Due to serious risk of bias [6]	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. **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, who are not easily identifiable. For these patients, molnupiravir may have an important impact on mortality. **Imprecision: serious.** There were only 11 events total (10 in the control arms and 1 in the molnupiravir arms).
2. **Risk of bias: serious.** The single trial reporting mechanical ventilation was not blinded. **Imprecision: extremely serious.** Very few events, resulted in very large credible intervals that include important and unimportant effects.
3. **Imprecision: 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 (4 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.** 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.

Mitigation strategies to address safety concerns

Info Box

With the safety concerns related to molnupiravir (see Mechanism of action section), the WHO recognizes the need to mitigate risks, both for individual patients and at the population level.

The conditional recommendation takes into account one such strategy: limiting the intervention to patients that are at higher risk of hospitalization or death. Typical characteristics of people at highest risk include those with older age, immunodeficiencies and/or chronic diseases (e.g. diabetes) and lack of COVID-19 vaccination. See WHO recommendations for further information on COVID-19 vaccination Strategic Advisory Group of Experts on Immunization for more details.

Other mitigation strategies include:

- 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.
    - Molnupiravir should not be given to pregnant or breastfeeding women or to children. In case of doubt about pregnancy, a pregnancy test should be performed prior to treatment initiation. If a woman of child bearing age 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 genotoxicity 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.
- 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.

6.9.1 Mechanism of action

Molnupiravir 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 mutagensis 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 predicted to be mutated and therefore not believed to 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 (800mg) 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 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)*.

Molnupiravir retains activity against Alpha and Beta variants in vivo *(48)*, and the Delta and Omicron variants in vitro *(49)(50)*. No data are currently available demonstrating activity against the Delta or Omicron variants in vivo, and while there appears to be no molecular basis for a loss of activity, there is residual uncertainty around whether a higher replication or transmission rate may impact efficacy of the drug.

Emergence of resistance: The emergence of resistance to drugs used for other viruses is varied; with some resistance emerges readily, and with others emerging more slowly. 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 *(51)*. Unlike in 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. There is no direct evidence to support or refute the variants hypothesis and as such 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 publically available data on non-clinical safety of molnupiravir from the FDA meeting documents for molnupiravir Emergence Use Authorization (30 November 2021) *(52)*. 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 breast milk. The GDG determined molnupiravir should not be administered to breastfeeding women.
- In developmental and reproductive toxicology assessments, reduced foetal body weights were observed in rats and rabbits, with higher exposures also being associated with embryo-foetal 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/foetus conceived by fathers who were receiving or had recently received molnupiravir.

6.10 Convalescent plasma (published 7 December 2021)

Info Box

Recommendations concerning convalescent plasma for patients with non-severe, severe and critical COVID-19 were published on 7 December 2021 as the seventh version of the WHO living guideline and in the BMJ as Rapid Recommendations. It follows the availability of 16 RCTs across disease severities, as per the LNMA on antibody and cellular therapies *(3)*. No changes were made to the convalescent plasma recommendations in this twelfth version of the guideline.

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 addition to the agreed upon values and preferences (see Section 7), 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 7).

For patients with non-severe illness, the GDG considered that resource and feasibility issues may be amplified in the outpatient setting, and mobilizing the use of convalescent plasma on a large scale would likely be of questionable feasibility.

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.

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 women 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 in-patient settings; of them, 15% were admitted to the intensive care unit (ICU). 1% of patients were enrolled from outpatient settings. None of the included studies enrolled children or pregnant women. The Table shows characteristics of the RCTs, of which two trials used comparisons to plasma as placebo and were not included in the evidence summaries. We are aware of two additional published RCTs comparing convalescent plasma to standard care or placebo *(69)(70)*. 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 usual care for the outcomes of interest,with certainty ratings. This evidence summary was informed by the LNMA *(3)* pooling data from 1602 patients in 4 RCTs for the outcome of mortality and less 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)	**Plain language 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.
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. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [75],

[71], [72], [74],
2. **Risk of bias: no serious.** The GDG did not rate down for risk of bias due to lack of blinding. .
3. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [71], [72], [75],
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. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [88], [72], [76], [73],
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. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [76], [73], [71], [88],
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. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [79], [88], [74], [71], [78], [73], [76], [77],
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. 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 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 for 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 7), 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 7).

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 care for the outcomes of interest for patients with severe and critical COVID-19, with certainty ratings. This evidence summary was informed by the LNMA *(3)*, pooling data from from 14 366 patients in 10 studies for the outcome of mortality, with less 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)	**Plain language 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 — 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	3 per 1000 Difference:	10 per 1000 **7 more per 1000**	**Low** Due to concerns with risk of bias and imprecision [10]	Convalescent plasma probably does not result in an important increase in allergic reactions.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Convalescent plasma	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	controlled)		(CI 95% 1 more — 24 more)		
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. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [76], [80], [82], [79], [77], [88], [81], [74], [83], [78],
2. **Risk of bias: serious. Indirectness: serious. Imprecision: serious.** Credible intervals include both important benefit and important harm.
3. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [80], [76], [73], [79], [82],
4. **Risk of bias: serious. Imprecision: serious.** The GDG decided the credible intervals warranted downgrading only once for imprecision.
5. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [73], [76], [72], [88],
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 low.
7. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [88], [71], [76], [73],
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.
9. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [78], [73], [76], [71], [79], [88], [77], [74],
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. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [76],
12. **Imprecision: very serious.**
13. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [80], [88], [81], [82], [83], [79], [76],

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. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [79], [88], [77],
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.

6.10.1 Mechanism of action

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 *(84)*. 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 *(85)*.

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 *(86)*). 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 *(87)*.

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 *(88)*). There is clear uncertainty surrounding the dose of neutralizing antibodies given in different trials and this uncertainty is summarised 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 3 of the trials in which donor titre was not recorded, a lower cut-off was applied at a titre of either 1:160 (for 2 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.

6.11 Interleukin-6 receptor blockers (published 6 July 2021)

Info Box

Therecommendation concerning IL-6 receptor blockers (tocilizumab or sarilumab) was published on 6 July 2021 as the fifth version of the WHO living guideline.. It followed the publication of RECOVERY and REMAP-CAP trial publications in February 2021, and new trial data from 1020 patients randomized head-to-head to either tocilizumab or sarilumab in REMAP-CAP being made available to the WHO on 1 June 2021. .

In this twelfth iteration of the guideline (September 15 2022), WHO has updated the strong recommendation for baricitinib in patients with severe and critical COVID-19, reflecting that IL-6 receptor blockers and baricitinib may be given together.

For patients with severe or critical COVID-19

Strong recommendation for

Updated

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

- *Corticosteroids have previously been strongly recommended in patients with severe and critical COVID-19 (see Section 6.15), and we recommend patients meeting these severity criteria should now 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 (see Section 6.3). 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 *(4)(98)(99)*. The RECOVERY trial demonstrating 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 twelfth iteration 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 usual 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 *(96)*. 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 serious adverse events 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 7), 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 serious adverse events. 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 blockade 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 (see previous strong recommendation below). 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 baricitinib or 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 *(169)*. 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 *(169)*. Although these three immunosuppresslve 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 women, 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 mother.

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)	**Plain language 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	8.1 days (Median)	11.2 days (Mean)	Very low Due to serious risk of bias,	The impact on hospital length of stay is very uncertain.

Outcome Timeframe	**Study results and measurements**	**Comparator** IL-6 receptor blockers	**Intervention** Baricitinib	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	2,652 participants in 3 studies. (Randomized controlled)	Difference:	**MD 3.1 more** (CI 95% 3.8 fewer — 9.9 more)	serious inconsistency, and very serious imprecision [4]	
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).

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) *(99)*. 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 *(99)*. We used the PMA for mortality as it included some additional unpublished data that reported on this outcome. The GDG recognized that usual 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 usual care would be expected to be balanced between study patients randomized to either the intervention or usual care arms.

The GRADE Summary of Findings table shows the relative and absolute effects of IL-6 receptor blockers compared with usual 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 *(99)*. 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)(4)*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** IL-6 receptor blockers	**Certainty of the Evidence** (Quality of evidence)	**Plain language 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** IL-6 receptor blockers	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
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 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 [6]	IL-6 receptor blockers 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 [7]	IL-6 receptor blockers may reduce duration of hospitalization.

1. . **Baseline/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 [4] . **Baseline/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. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. We used the median event rate for all patients randomized to usual care across included studies. **Supporting references:** [4],
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: MOCK-UP Stratified baseline risk_Patients withCOVID-19 infection (all disease severities)
Intervention: IL-6 inhibitor
Comparator: Standard care

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** IL-6 inhibitor	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality (critically ill patients) [1]	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.
Mortality (severely ill patients) [2]	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.
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. Source: pairwise meta-analysis
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.

6.11.1 Mechanism of action

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 *(29)*. 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.

6.12 Ivermectin (published 31 March 2021)

Info Box

The recommendation concerning ivermectin was published on 31 March 2021 as the fourth version of the WHO living guideline and in the BMJ as Rapid Recommendations. It followed the increased international attention on ivermectin as a potential therapeutic option. No changes were made to the ivermectin recommendation in this twelfth version of the guideline.

We are aware of a few new, relatively small trials published since our recommendation was made and that one key trial has since been retracted given concerns about research fraud *(100)(101)*. However, the updated evidence summary from the LNMA is consistent with our previously made recommendation. This updated evidence summary will be fully considered by the GDG in subsequent iterations of the guideline.

For patients with COVID-19, regardless of disease severity

Only in research settings

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

Remark: This recommendation applies to patients with any disease severity and any duration of symptoms.

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.

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 this recommendation. 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 7), 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

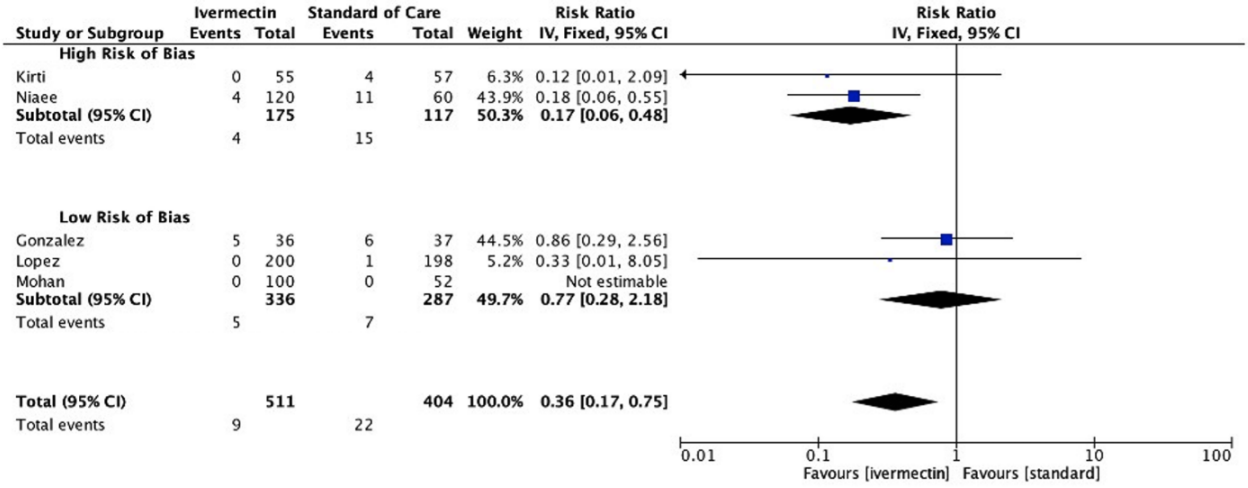
When moving from evidence to a recommendation on the use of ivermectin in patients with COVID-19 only in the context of a clinical trial, the GDG emphasized the high degree of uncertainty in the most critical outcomes such as mortality and need for mechanical ventilation. It also noted the evidence suggesting 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 of care and reported mortality *(119)(102)(103)(104)(105)(106)(107)*. 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 *(119)(102)* were at high risk of bias, due to inadequate blinding. One of these two trials *(119)* 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 to 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 *(100)* 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 *(126)*. 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 of 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 of 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 women, 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 *(108)(109)(110)(111)*.

The GRADE Summary of Findings table shows the relative and absolute effects of ivermectin compared to usual 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

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 usual 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 *(96)*.

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 usual 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 usual care should be balanced between study patients randomized to either the intervention or usual care arms.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Ivermectin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Odds ratio 0.19 (CI 95% 0.09 — 0.36) Based on data from 1,419 participants in 7 studies. [1] (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 [2]	The effect of ivermectin on mortality is uncertain.
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 [3]	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 [4]	Ivermectin may increase or have no effect on viral clearance.
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 [5]	The effect of ivermectin on hospital admission is uncertain.
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.	12.8 days (Mean)	11.7 days (Mean)	**Very low** Due to serious imprecision, inconsistency and	The effect of ivermectin on hospital length of stay is uncertain.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Ivermectin	Certainty of the Evidence (Quality of evidence)	Plain language summary
	(Randomized controlled)	Difference:	**MD 1.1 fewer** (CI 95% 2.3 fewer — 0.1 more)	serious risk of bias [8]	
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. Systematic review [1] . **Baseline/comparator:** Control arm of reference used for intervention. We elected to use the control arm of the WHO SOLIDARITY trial, reflecting usual care across countries participating in the trial.
2. **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.
3. **Imprecision: very serious.** Very few events and credible intervals that include both important benefit and harm. **Publication bias: serious.**
4. **Inconsistency: serious.** The point estimates varied widely and credible intervals do not substantially overlap. **Imprecision: serious.** Credible interval includes no effect.
5. **Imprecision: extremely serious.** Credible interval includes important benefit and harm.
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.

6.12.1 Mechanism of action

Ivermectin is an antiparasitic agent that interferes with nerve and muscle function of helminths through binding glutamate-gated chloride channels *(112)*. 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 *(113)(114)(115)*. Ivermectin had no impact on SARS-CoV-2 viral RNA in the Syrian golden hamster model of SARS-CoV-2 infection *(116)*. 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 *(117)(118)(119)(120)(140)*. No direct evidence for any mechanism of antiviral action against SARS-CoV-2 currently exists.

Some have proposed, based predominantly upon research in other indications, that ivermectin has an immunomodulatory effect, but again the mechanism remains unclear. Historical data showed that ivermectin improved survival in mice given a lethal dose of lipopolysaccharide *(121)*, and has benefits in murine models of atopic dermatitis and allergic asthma *(122)(123)*. For SARS-CoV-2, one hypothesis suggests immunomodulation mediated by allosteric modulation of the alpha-7 nicotinic acetylcholine receptor (indirectly by modulating the activity of ligands of the receptor). Although investigators have demonstrated this action in vitro, concentrations used in these experiments have been even higher than those required for an antiviral effect *(124)*, and therefore very unlikely to be achieved in humans. In the Syrian golden hamster model of SARS-CoV-2 infection, ivermectin resulted in some changes in pulmonary immune phenotype consistent with allosteric modulation of the alpha-7 nicotinic acetylcholine receptor *(116)*. However, ivermectin did not appear to rescue body weight loss which is a hallmark of disease in this model, and drug concentrations were not measured to extrapolate to those achieved in humans. Taken together, there remains great uncertainty regarding the relevance of any immunomodulatory or anti-inflammatory action of ivermectin.

6.13 Hydroxychloroquine (published 17 December 2020)

Info Box

The recommendation concerning hydroxychloroquine was published 17 December 2020 as the third version of the WHO living guideline and in the BMJ as Rapid Recommendations. It followed the pre-print publication of the WHO SOLIDARITY trial on 15 October 2020, reporting results on treatment with hydroxychloroquine, remdesivir and lopinavir/ritonavir in hospitalized patients with COVID-19 *(15)*. No changes were made to the hydroxychloroquine recommendation in this twelfth version of the guideline.

For patients with COVID-19, regardless of disease severity

Strong recommendation against

We recommend not to use hydroxychloroquine or chloroquine *(strong recommendation against)*.

Remark: 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 7), 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 women, 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 women with systemic autoimmune diseases, such as systemic lupus erythematosus, pregnant women 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 end of document for residual uncertainties (Section 9). 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 usual 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)	**Plain language 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Hydroxychloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
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 — 334 more)	**Very low** Due to very serious imprecision [5]	The effect of hydroxychloroquine on viral clearance is very uncertain.
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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Hydroxychloroquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
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 clearance	Lower better Based on data from 440 participants in 5 studies. (Randomized controlled)	9.7 days (Mean) Difference:	10.6 days (Mean) **MD 0.7 fewer** (CI 95% 4.3 fewer — 4.8 more)	Very low Due to serious risk of bias and very serious imprecision [13]	The effect of hydroxychloroquine on 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] . **Baseline/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. Systematic review. We used the median event rate for all patients randomized to usual care across included studies. **Baseline/comparator:** Control arm of reference used for intervention. **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. **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.**
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.**

6.14 Lopinavir-ritonavir (published 17 December 2020)

Info Box

The recommendation concerning lopinavir-ritonavir was published 17 December 2020 as the third version of the WHO living guideline and in the BMJ as Rapid Recommendations. It followed the pre-print publication of the WHO SOLIDARITY trial on 15 October 2020, reporting results on treatment with lopinavir-ritonavir, remdesivir and hydroxychloroquine in hospitalized patients with COVID-19 *(15)*. No changes were made to the lopinavir-ritonavir recommendation in this twelfth version of the guideline.

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.

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 7), 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 women, 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 end of document for residual uncertainties (Section 9). 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 usual 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)	**Plain language 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.
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.	11 days (Mean)	10 days (Mean)	Very low Due to serious risk of bias and very serious	The effect of lopinavir-ritonavir improves on time to clinical improvement is very

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Lopinavir-ritonavir	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	(Randomized controlled)	Difference:	**MD 1 fewer** (CI 95% 4.1 fewer — 3.2 more)	imprecision [9]	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. Systematic review. **Baseline/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. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. 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. **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.**
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.

6.15 Systemic corticosteroids (published 2 September 2020)

Info Box

The recommendations for corticosteroids were first published as WHO living guidelines 2 September 2020, and as BMJ Rapid Recommendations 5 September 2020. It followed the publication of the preliminary report of the RECOVERY trial, later published as a peer-reviewed paper *(13)*. No changes were made to the corticosteroids recommendations in this twelfth version of the guideline.

Whereas the recommendations remain unchanged, the evidence summary for corticosteroids in patients with COVID-19 was updated before the sixth iteration of this living guideline. The baseline risk estimates for mortality are now based on the WHO SOLIDARITY trial (as for other drugs in this guideline) *(15)* rather than the initial ISARIC cohort study *(129)* that likely overestimates current mortality risks at the global level. The update was also needed to inform the baseline risk for mortality in the evidence summary informing the strong recommendation for IL-6 receptor blockers, in addition to standard of care for patients with severe or critical COVID-19, where corticosteroids provide a relative reduction in mortality by 21%.

For patients with severe or critical COVID-19

Strong recommendation for

We recommend treatment with systemic corticosteroids *(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 (that is, 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 (that is, 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 (that is, 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 *(130)(131)*. 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 fifth iteration 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.

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 was 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 *(132)*. 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 *(133)*.

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 (updated baseline mortality risk)
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 *(13)*. 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)(134)*. 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 usual 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 usual 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 usual care) *(13)*. 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) *(135)*; dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID19, CoDEX) *(136)(137)*; 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) *(138)*; 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) *(139)*.

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 *(135)*. An additional trial, which randomized hospitalized patients with suspected SARS-CoV-2 infection, published on 12 August 2020 (MetCOVID) *(140)*, 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 *(96)*, 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)	**Plain language 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Systemic corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
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** (CI 95% 13 more — 41 more)	**Moderate** Due to serious indirectness [7]	Corticosteroids probably 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, 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] . **Baseline/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. **Risk of bias: serious.** Lack of blinding.
3. **Risk of bias: serious.** Lack of blinding.
4. **Indirectness: serious. Imprecision: serious.**
5. **Indirectness: serious. Imprecision: serious.**
6. **Indirectness: serious.**
7. **Indirectness: serious.**
8. **Indirectness: serious. Imprecision: serious.**
9. **Indirectness: serious. Imprecision: serious.**
10. **Risk of bias: serious.** Lack of blinding. **Imprecision: serious.** Confidence interval includes no benefit.

For patients with non-severe COVID-19 infection

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 apply 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 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 (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 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 *(141)(6)*.

Note: WHO recommends antenatal corticosteroid therapy for pregnant women at risk of preterm birth from 24 to 34 weeks' gestation when there is no clinical evidence of maternal infection, and adequate childbirth and newborn care is available. However, in cases where the woman presents with mild or moderate COVID-19, the clinical benefits of antenatal corticosteroid might outweigh the risks of potential harm to the mother. In this situation, the balance of benefits and harms for the woman and the preterm newborn should be discussed with the woman to ensure an informed decision, as this assessment may vary depending on the woman's clinical condition, her wishes and that of her family, and available health care resources.

Certainty of the Evidence

See Benefits and Harms section.

Values and preferences

The weak or 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 them 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 usual 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)	**Plain language 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 (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** (CI 95% 13 more — 41 more)	**Moderate** Due to serious indirectness [8]	Corticosteroids probably 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Systemic corticosteroids	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
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] . **Baseline/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. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [1],
5. **Indirectness: serious. Imprecision: serious.**
6. **Indirectness: serious. Imprecision: serious.**
7. **Indirectness: serious.**
8. **Indirectness: serious.**
9. **Indirectness: serious. Imprecision: serious.**
10. **Indirectness: serious. Imprecision: serious.**
11. **Risk of bias: serious.** lack of blinding. **Imprecision: serious.** confidence interval includes no benefit.

7. Methods: how this guideline was created

This living WHO guideline was developed according to standards and methods for trustworthy guidelines, making use of an innovative process to achieve efficiency in dynamic updating of recommendations. The methods are aligned with the *WHO Handbook for guideline development* and according to a pre-approved protocol (planning proposal) by the Guideline Review Committee (GRC) *(141)*.

Related guidelines
This living WHO guideline for COVID-19 treatments is related to the larger, more comprehensive guidance for *COVID-19 Clinical management: living guideline*, which has a wider scope of content and has been regularly updated *(6)*. The first eleven versions of this WHO *Therapeutics and COVID-19: living guideline*, addressing corticosteroids, remdesivir, hydroxychloroquine, lopinavir/ritonavir, ivermectin, IL-6 receptor blockers, casirivimab-imdevimab (neutralizing monoclonal antibodies), convalescent plasma, JAK inhibitors, sotrovimab, molnupiravir, remdesivir,nirmatrelvir-ritonavir, colchicin and fluvoxamine can be accessed via the WHO website *(4)*.

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)*.

Timing
This guideline is living – dynamically updated and globally disseminated once new evidence warrants a change in recommendations *(162)*. The aim is for a six-week timeframe from the public availability of trial data that trigger the guideline development process to WHO publication, while maintaining standards for trustworthy guidelines (*WHO Handbook for guideline development*) *(141)(142)*.

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
Comprehensive daily monitoring of all emerging RCTs occurs on a continuous basis, within the context of the living systematic review and network meta-analysis (NMA), using experienced information specialists, who review all relevant information sources for new RCTs addressing interventions for COVID-19. Incorporating pre-print data, which have not yet undergone peer review, promote rapid data sharing in a public health emergency and its inclusion can accelerate the assessment and clinical use of COVID-19 therapeutic interventions. Guidelines are periodically updated to assess data that have undergone peer review in the intervening period and new data. Once practice-changing evidence, or increasing international interest, are identified, the WHO Therapeutics Steering Committee triggers the guideline development process. The trigger for producing or updating specific recommendations is based on the following (any of the three may initiate a recommendation):

- 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 representatives. For each intervention, the technical unit collected and managed declarations of interests (DOIs) and found no GDG member and co-chairs to have a conflict of interest. In addition to the distribution of a DOI form, during the meeting, the WHO Secretariat described the DOI process and an opportunity was given to GDG members to declare any interests not provided in written form. No verbal conflicts were declared. Web searches did not identify any additional interests that could be perceived to affect an individual's objectivity and independence during the development of the recommendations.

The pre-selected expert GDG (see Section 10) convened on 02 June 2022 to address baricitinib and sotrovimab and on 15 July 2022 to address remdesivir. The meeting 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, the LNMA team performed indirect comparisons and produced additional GRADE evidence summaries that the GDG used to inform recommendations. The methods team rated credibility of subgroups using the ICEMAN tool *(96)*. The technical unit collected and managed declarations of interests (DOIs) and found no SR 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 *(143)(144)*. 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 iteration, 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) *(145)*;
- quality/certainty of the evidence *(143)(146)*;
- values and preferences of patients *(147)*;
- resources and other considerations (including considerations of feasibility, applicability, equity) *(147)*;
- 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 *(145)*;
- 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 *(144)(147)*.

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 *(3)*.

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

For patients with non-severe illness, we used the median of the control arm of the RCTs that contributed to the evidence, identified in the LNMA *(1)(3)*. For admission to hospital, the GDG defined a 10% (100 admissions per 1000 patients) threshold for a baseline risk that would reflect an important absolute benefit for the therapeutics under consideration (i.e., 60 fewer admissions per 1000 patients).

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.

Specific deliberations on baseline risk are presented for each recommendation.

The GDG acknowledged that baseline risks, and thus absolute effects, may vary significantly geographically and over time. Thus, 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 declarations of interests (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 (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.

The guideline was then reviewed and approved by the WHO GRC and the Publication Review Committee.

8. 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.
- WHO Academy app: Mobile application available for health workers and public on Apple Store and Google Play with a full Case Management section which includes Guidance, Training and Tools, including the latest training modules on Therapeutics for COVID-19. Includes treatment and other guidelines and training materials from WHO on COVID-19 for use offline.
- WHO COVID-19 Clinical Care Pathway is a new tool that summarizes these recommendations in a concise and easy to understand manner for health workers. It links this guideline to WHO guidelines on Diagnostic testing for SARS-CoV-2 and Antigen-detection in the diagnosis of SARS-CoV-2 infection to aid in implementation.

How to navigate this guideline

The guideline is written, disseminated, and updated in MAGICapp, with a format and structure that ensures user-friendliness and ease of navigation *(142)*. It accommodates dynamic updating of evidence and recommendations that can focus on what is new while keeping existing recommendations, as appropriate, within the guideline.

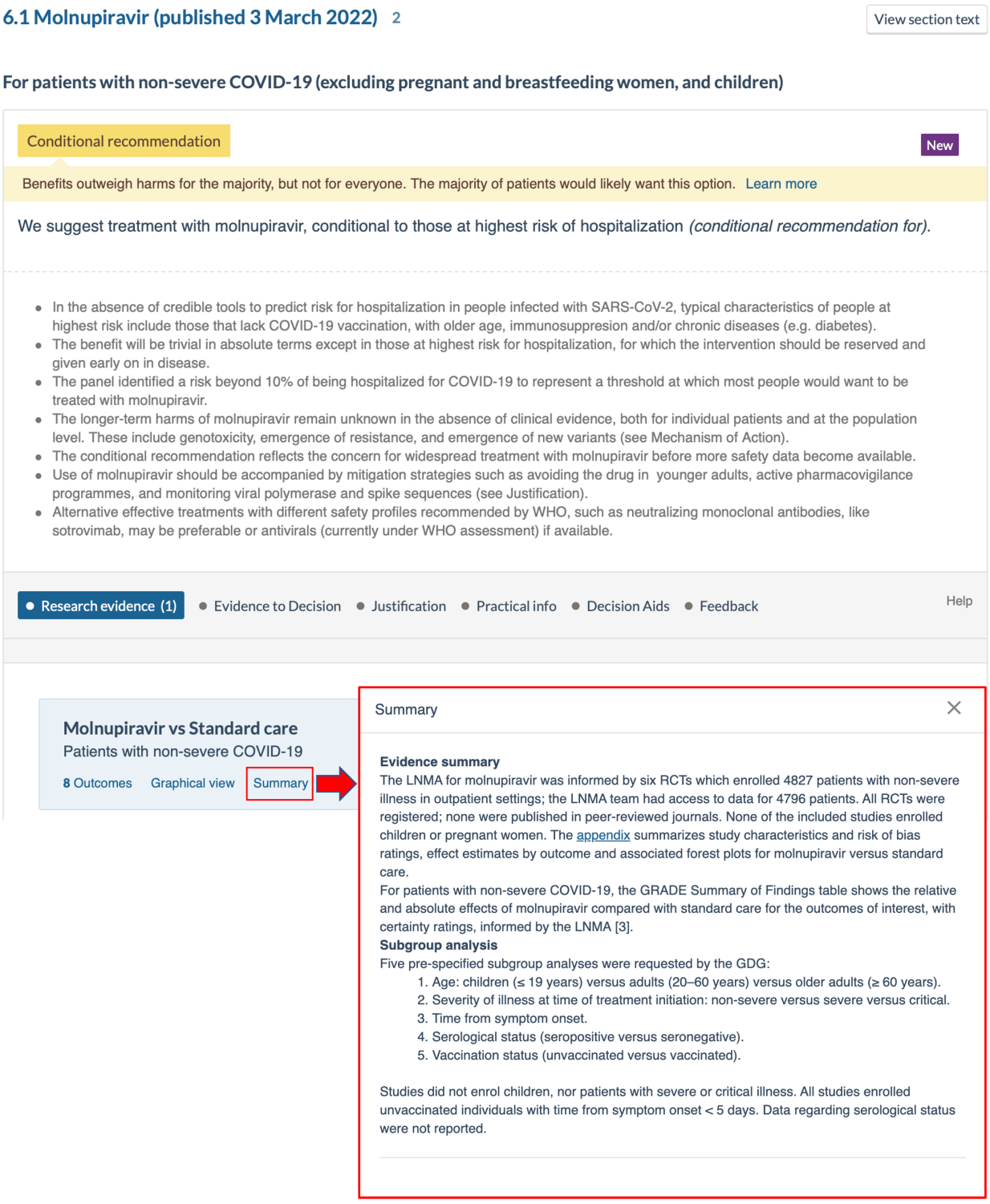
The purpose of the online formats and additional tools, such as the infographics, is to make it easier to navigate and make use of the guideline in busy clinical practice. The online multilayered formats are designed to allow end-users to find recommendations first and then drill down to find supporting evidence and other information pertinent to applying the recommendations in practice, including tools for shared decision-making (clinical encounter decision aids) *(142)*.

Fig. 4 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, focussing 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 COVID-19 essential supplies forecasting tool (COVID-ESFT) assists governments, partners, and other stakeholders to forecast the necessary volume of personal protective equipment, diagnostic test equipment, consumable medical supplies, biomedical equipment for case management, and essential drugs for supportive care and treatment of COVID-19.
- 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.
- WHO Openwho.org clinical management course series hosts a full course series on COVID-19 which covers a holistic pathway of care for a patient, from screening and triage to rehabilitation, testing and treatments and palliative care.
- 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.

9. 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.

Here we outline an update of the key uncertainties for remdesivir, sotrovimab and casirivimab-imdevimab identified by the GDG, adding to those for remdesivir, sotrovimab and casirivimab-imdevimab and nirmatrelvir-ritonavir, molnupiravir, JAK inhibitors, convalescent plasma, ivermectin, corticosteroids, hydroxychloroquine, lopinavir-ritonavir, and IL-6 receptor blockers identified when recommendations were initially formulated in previous versions of the living guideline. These uncertainties may inform future research, i.e. the production of higher certainty and more relevant evidence to inform policy and practice. We also outline emerging evidence in the rapidly changing landscape of trials for COVID-19.

Ongoing uncertainties and opportunities for future research

Remdesivir

- accurate clinical prediction guides to establish the individual patient risk of hospitalization in patients presenting with non-severe COVID-19 in order to best identify patients that would most benefit from this intervention;
- resistance and efficacy against newer variants of interest;
- efficacy in immunocompromised, vaccinated, children, pregnant patients, and other specific subgroups of patients;
- optimal duration of therapy;
- combination therapy with other COVID-19 drugs, and head-to-head comparison against other antiviral agents.

JAK inhibitors

- safety and efficacy of combination therapy of baricitinib with corticosteroids and IL-6 receptor blockers on longer term outcomes;
- safety and efficacy in areas where certain infections such as HIV infections, tuberculosis, and certain fungal infections are endemic;
- relative benefits of tofacitinib and ruxolitinib to baricitinib;
- safety and efficacy in children, and pregnant and lactating women.

Sotrovimab and casirivimab-imdevimab

- clinical effectiveness with emerging variants;
- if in vitro evidence of effectiveness with emerging variants, then dosing and administration routes in non-severe and severe/critical COVID-19 patients;
- safety and efficacy in children and pregnant women;
- accurate clinical prediction guides to establish the individual patient risk of hospitalization in patients presenting with non-severe COVID-19 in order to best identify patients that would most benefit from this intervention.

Fluvoxamine

The panel's recommendation reflects the panel's perception that the current evidence does not justify using fluvoxamine to treat COVID-19. However, the panel has not implied that fluvoxamine was proven to be ineffective. Decisions to further investigate the effects of fluvoxamine for COVID-19 will likely hinge on how stakeholders perceive the opportunity cost of investigating the effects of fluvoxamine over other candidate therapies. The panel discussions illuminated the following knowledge gaps:

- What are the effects of fluvoxamine in patients who suffer from a combination of non-severe COVID-19 at risk of deteriorating and significant symptoms of anxiety?
- What are the side-effects of fluvoxamine therapy in patients with non-severe COVID-19 at risk of deteriorating?
- What proportion of patients with non-severe COVID-19 at risk of deteriorating would be ineligible due to risk of pharmacological interactions?

The panel surmised that, in the future, investigators would have to carefully consider whether fluvoxamine could still be compared with placebo or no treatment given that effective treatments are available. If the rationale to further investigate fluvoxamine is its advantageous cost and availability, non-inferiority designs may be considered.

Nirmatrvelvir-ritonavir

- accurate clinical prediction guides to establish the individual patient risk of hospitalization in patients presenting with non-severe

COVID-19 in order to best identify patients that would most benefit from this intervention;
- resistance and efficacy against newer variants of interest;
- efficacy in immunocompromised, vaccinated, children, pregnant patients, and other specific subgroups of patients;
- optimal duration of therapy;
- combination therapy with other COVID-19 drugs, and head-to-head comparison against other antiviral agents.

Colchicine

The GDG panel believed that it was unlikely future studies would identify subgroups of patients who may benefit from colchicine.

Molnupiravir

- need for clinical data to investigate safety and applicability concerns (including in children, lactating or pregnant women, and men; and long-term impact on mutagenesis and cancer risk);
- accurate clinical prediction guides to establish the individual patient risk of hospitalization in patients presenting with non-severe COVID-19 in order to best identify patients that would most benefit from this intervention;
- data to inform individual and population-level concerns, such as the emergence of resistance and efficacy against new variants;
- comparative effectiveness of molnupiravir compared with other treatment options (e.g. monoclonal antibodies or other antivirals) in the non-severe population, including combination therapy;
- 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, in vivo or in humans:
  - confer a decreased antiviral activity for NHC;
  - arise in the spike protein and/or do they confer an increase in replicative potential/transmission.

Convalescent plasma

- effects in severe and critical illness (low to moderate certainty evidence for most patient-important outcomes);
- long-term mortality and functional outcomes in COVID-19 survivors;
- safety and efficacy in children, pregnant, and lactating women;
- effects of high-titre convalescent plasma on mortality and other patient-important outcomes;
- effects in patients with seronegative antibody status.

IL-6 receptor blockers

- long-term mortality and functional outcomes in COVID-19 survivors;
- safety data in terms of nosocomial infections;
- data in children, pregnant patients and those that are already immunocompromised;
- patients with non-severe COVID-19;
- immunity and the risk of a subsequent infection, which may impact the risk of death after 28 days;
- outcomes by different IL-6 receptor blocker dosing and optimal timing of drug initiation.

Ivermectin
Given the very low certainty in estimates for most critical outcomes of interest, the GDG felt that further high-quality clinical trials examining this drug would be essential before any recommendation for use as part of clinical care. This includes further RCTs examining both inpatients and outpatients and those with varying disease severities and using different ivermectin dosing regimens. The focus of these studies should be on outcomes important to patients such as mortality, quality of life, need for hospitalization, need for invasive mechanical ventilation and time to clinical or symptom improvement. Also, a better characterization of potential harms with ivermectin in patients with COVID-19 would be important.

Hydroxychloroquine
Although some uncertainty remains, the GDG panel felt that further research was unlikely to uncover a subgroup of patients that would benefit from hydroxychloroquine on the most important outcomes (mortality, mechanical ventilation) given the consistent results in trials across disease severity and location.

Lopinavir-ritonavir
Although some uncertainty remains, the GDG panel felt that further research was unlikely to uncover a subgroup of patients that would benefit from lopinavir-ritonavir on the most important outcomes (mortality, mechanical ventilation) given the consistent results in trials across disease severity and location.

Corticosteroids

- long-term mortality and functional outcomes in COVID-19 survivors;
- patients with non-severe COVID-19 (i.e. pneumonia without hypoxaemia);
- outcomes, when used in combination with additional therapies for COVID-19, such as novel immunomodulators. It will become increasingly important to ascertain how these interact with systemic corticosteroids. All investigational therapies for severe and critical COVID-19 (including remdesivir) should be compared with systemic corticosteroids or evaluated in combination with systemic corticosteroids vs systemic corticosteroids alone;
- immunity and the risk of a subsequent infection, which may impact the risk of death after 28 days;
- outcomes, by different steroid preparation, dosing, and optimal timing of drug initiation.

Emerging evidence

The unprecedented volume of planned and ongoing studies for COVID-19 interventions – over 5000 RCTs as of May 2022 – implies that more reliable and relevant evidence will emerge to inform policy and practice *(12)* (see appendix). An overview of registered and ongoing trials for COVID-19 therapeutics and prophylaxis is available from the Infectious Diseases Data Observatory, through their living systematic review of COVID-19 clinical trial registrations *(12)*, the WHO website and other repositories, such as the COVID-NMA initiative.

Whereas most of these studies are small and of variable methodological quality, a number of large, international platform trials (e.g. RECOVERY, SOLIDARITY, and DISCOVERY) are better equipped to provide robust evidence for a number of potential treatment options *(13)(15)(16)(17)*. Such trials can also adapt their design, recruitment strategies, and selection of interventions based on new insights, exemplified by the uncertainties outlined above.

10. Authorship, contributions, acknowledgements

Authorship, contributions, acknowledgements

WHO would like to thank the collaborative efforts of all those involved to make this process rapid, efficient, trustworthy and transparent.

WHO Therapeutics Steering Committee (updated for baricitinib, sotrovimab and remdesivir updates)
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.

Janet V Diaz (Lead, Clinical Team for COVID-19 Response, Health Emergencies Programme, Geneva); John Appiah (Lead, Case Management, WHO Regional Office for Africa); Lisa Askie (Quality Assurance of Norms and Standards Department); Silvia Bertagnolio (Communicable and Noncommunicable Diseases Division/Clinical Team for COVID-19 Response); Chiori Kodama (WHO Regional Office for the Eastern Mediterranean); Krutika Kuppalli (Clinical Team for COVID-19 Response, Health Emergencies Programme, Geneva); Marta Lado Castro-Rial (Clinical Team for COVID-19 Response, Health Emergencies Programme, Geneva); Lorenzo Moja (Health Products Policy and Standards Department); Olufemi Oladapo (Sexual and Reproductive Health and Research Department); Dina Pfeifer (WHO Regional Office for Europe/Health Emergencies Programme); J Pryanka Relan (Clinical Team for COVID-19 Response, Health Emergencies Programme, Geneva); Ludovic Reveiz (Evidence and Intelligence for Action in Health Department, Incident Management Systems for COVID-19, Pan American Health Organization); Vaseeharan Sathiyamoorthy (Research for Health, Science Division); Anthony Solomon (Neglected Tropical Diseases); Pushpa Wijesinghe (Lead, Case Management, Regional Office for South-East Asia). Supporting project officers: Julie Viry and Anne Colin (Clinical Team for COVID-19 Response, Health Emergencies Programme, Geneva).

The WHO Therapeutics Steering Committee is fully responsible for decisions about guidance production and convening the GDG. Special thanks to the WHO Pharmacovigilance team for their support and contributions to this update: Noha Iessa and Shanti Pal.

Guideline Development Group (GDG) for the update on remdesivir recommendation. For list of GDG members of previous recommendations, see here.

Wagdy Amin (Ministry of Health and Population, Egypt); Andre Ricardo Araujo Da Silva (Departamento de Materno Infantil, Universidade Federal Fluminense, Brazil); Maurizio Cecconi (Humanitas Research Hospital Milan, Italy); Binila Chacko (Division of Critical Care Medicine at Christian Medical College, Vellore, India); Vu Quoc Dat (Department of Infectious Diseases, Hanoi Medical University, Hanoi, Viet Nam); Heike Geduld (Emergency Medicine, Stellenbosch University, South Africa); Patrick Gee (patient panel member, Virginia, United States); Madiha Hashmi (Ziauddin University, Karachi, Pakistan); Beverley Hunt (King's College London, United Kingdom); Fyezah Jehan (Aga Khan University, Pakistan); Sushil Kumar Kabra (All India Institute of Medical Sciences, New Delhi, India); Yee-Sin Leo (National Centre for Infectious Diseases, Singapore); Hela Manai (Emergency Medical Service Tunis, Tunisia); Marc Mendelson (Division of Infectious Diseases & HIV Medicine at Groote Schuur Hospital, University of Cape Town, South Africa); Giovanni Battista Migliori (Pulmonology, Istituti Clinici Scientifii Maygeri, Italy); Natalia Pshenichnaya (Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow, Russian Federation); Rohit Sarin (National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India); Ronald Swanstrom (Department of Biochemistry & Biophysics of the University of North Carolina, United States); Tim Uyeki (Influenza Division, U.S. Centers for Disease Control and Prevention, United States).

Guideline Development Group (GDG) for the update on sotrovimab recommendation. For list of GDG members of previous recommendations, see here.

Wagdy Amin (Ministry of Health and Population, Egypt); Andre Ricardo Araujo Da Silva (Departamento de Materno Infantil, Universidade Federal Fluminense, Brazil); Diptesh Aryal (Mediciti Hospital, Nepal); Erlina Burhan (Infection Division Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Universitas Indonesia); Maurizio Cecconi (Humanitas Research Hospital Milan, Italy); Duncan Chanda (Institute for Medical Research and Training, Zambia); Heike Geduld (Emergency Medicine, Stellenbosch University, South Africa); Nerina Harley (Royal Melbourne Hospital and Epworth Healthcare, Melbourne, Australia); Beverley Hunt (King's College London, United Kingdom); Fabian Alberto Jaimes Barragan (Antioquia University Medellin, Colombia); Sushil Kumar Kabra (All India Institute of Medical Sciences, New Delhi, India); Niranjan Kissoon (Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Rakesh Lodha (Department of Paediatrics, All India Institute of Medical Sciences, India); Giovanni Battista Migliori (Pulmonology, Istituti Clinici Scientifii Maygeri, Italy); Natalia Pshenichnaya (Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow, Russian Federation); Nida Qadir (Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California, Los Angeles, United States); Saniya Sabzwari (Aga Khan University, Karachi, Pakistan); Manu Shankar-Hari (King's College London, United Kingdom);Yinzhong Shen (Shanghai Public Health Clinical Center, Fudan University, Shanghai, China); Shalini Sri Ranganathan (University of Colombo, Sri Lanka); Miriam Stegemann (Charité - Universitätsmedizin Berlin, Germany); Ronald Swanstrom (Department of Biochemistry & Biophysics of the University of North Carolina, United States); Tim Uyeki

(Influenza Division, U.S. Centers for Disease Control and Prevention, United States); Sridhar Venkatapuram (King's College London, United Kingdom).

Guideline Development Group (GDG) for the update on baricitinib recommendation. For list of GDG members of previous recommendations, see here.

Wagdy Amin (Ministry of Health and Population, Egypt); Andre Ricardo Araujo Da Silva (Departamento de Materno Infantil, Universidade Federal Fluminense, Brazil); Diptesh Aryal (Mediciti Hospital, Nepal); Erlina Burhan (Infection Division Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Universitas Indonesia); Maurizio Cecconi (Humanitas Research Hospital Milan, Italy); Duncan Chanda (Institute for Medical Research and Training, Zambia); Heike Geduld (Emergency Medicine, Stellenbosch University, South Africa); Nerina Harley (Royal Melbourne Hospital and Epworth Healthcare, Melbourne, Australia); Beverley Hunt (King's College London, United Kingdom); Fabian Alberto Jaimes Barragan (Antioquia University Medellin, Colombia); Sushil Kumar Kabra (All India Institute of Medical Sciences, New Delhi, India); Niranjan Kissoon (Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Rakesh Lodha (Department of Paediatrics, All India Institute of Medical Sciences, India); Giovanni Battista Migliori (Pulmonology, Istituti Clinici Scientifii Maygeri, Italy); Natalia Pshenichnaya (Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow, Russian Federation); Nida Qadir (Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California, Los Angeles, United States); Saniya Sabzwari (Aga Khan University, Karachi, Pakistan); Manu Shankar-Hari (King's College London, United Kingdom); Yinzhong Shen (Shanghai Public Health Clinical Center, Fudan University, Shanghai, China); Shalini Sri Ranganathan (University of Colombo, Sri Lanka); Miriam Stegemann (Charité - Universitätsmedizin Berlin, Germany); Ronald Swanstrom (Department of Biochemistry & Biophysics of the University of North Carolina, United States); Tim Uyeki (Influenza Division, U.S. Centers for Disease Control and Prevention, United States); Sridhar Venkatapuram (King's College London, United Kingdom).

Guideline Development Group (GDG) for fluvoxamine recommendation. For list of GDG members of previous recommendations, see here.

Andre Ricardo Araujo Da Silva (Departamento de Materno Infantil, Universidade Federal Fluminense, Brazil); Diptesh Aryal (Mediciti Hospital, Nepal); Erlina Burhan (Infection Division Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Universitas Indonesia); Maurizio Cecconi (Humanitas Research Hospital Milan, Italy); Nerina Harley (Royal Melbourne Hospital and Epworth Healthcare, Melbourne, Australia); David Hui (Stanley Ho Centre for Emerging Infectious Diseases, Chinese University of Hong Kong, Hong Kong SAR, China); Beverley Hunt (King's College London, United Kingdom); Fabian Alberto Jaimes Barragan (Antioquia University Medellin, Colombia); Sushil Kumar Kabra (All India Institute of Medical Sciences, New Delhi, India); Seema Kanda (patient panel member, Ontario, Canada); Yae Jean Kim (Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea); Niranjan Kissoon (Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Sanjeev Krishna (St George's University of London, United Kingdom); Yee-Sin Leo (National Centre for Infectious Diseases, Singapore); Rakesh Lodha (Department of Paediatrics, All India Institute of Medical Sciences, India); Hela Manai (Emergency Medical Service Tunis, Tunisia);Marc Mendelson (Division of Infectious Diseases & HIV Medicine at Groote Schuur Hospital, University of Cape Town, South Africa); Giovanni Battista Migliori (Pulmonology, Istituti Clinici Scientifii Maygeri, Italy); Emmanuel Nsutebu (Sheikh Shakhbout Medical City, Abu Dhabi, United Arab Emirates); Natalia Pshenichnaya (Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow, Russian Federation); Nida Qadir (Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California, Los Angeles, United States); Rohit Sarin (National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India); Yinzhong Shen (Shanghai Public Health Clinical Center, Fudan University, Shanghai, China); Shalini Sri Ranganathan (University of Colombo, Sri Lanka); Miriam Stegemann (Charité - Universitätsmedizin Berlin, Germany); Ronald Swanstrom (Department of Biochemistry & Biophysics of the University of North Carolina, United States); Tim Uyeki (Influenza Division, U.S. Centers for Disease Control and Prevention, United States); Sridhar Venkatapuram (King's College London, United Kingdom).

Guideline Development Group (GDG) for colchicine recommendation. For list of GDG members of previous recommendations, see here.

Andre Ricardo Araujo Da Silva (Departamento de Materno Infantil, Universidade Federal Fluminense, Brazil); Diptesh Aryal (Mediciti Hospital, Nepal); Erlina Burhan (Infection Division Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Universitas Indonesia); Maurizio Cecconi (Humanitas Research Hospital Milan, Italy); Nerina Harley (Royal Melbourne Hospital and Epworth Healthcare, Melbourne, Australia); David Hui (Stanley Ho Centre for Emerging Infectious Diseases, Chinese University of Hong Kong, Hong Kong SAR, China); Beverley Hunt (King's College London, United Kingdom); Fabian Alberto Jaimes Barragan (Antioquia University Medellin, Colombia); Sushil Kumar Kabra (All India Institute of Medical Sciences, New Delhi, India); Seema Kanda (patient panel member, Ontario, Canada); Yae Jean Kim (Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea); Niranjan Kissoon (Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Sanjeev Krishna (St George's University of London, United Kingdom); Yee-Sin Leo (National Centre for Infectious Diseases, Singapore); Rakesh Lodha (Department of Paediatrics, All India Institute of Medical Sciences, India); Hela Manai (Emergency Medical Service Tunis, Tunisia); Marc Mendelson (Division of Infectious Diseases & HIV Medicine at Groote Schuur Hospital, University of Cape Town, South Africa); Giovanni Battista Migliori (Pulmonology, Istituti Clinici Scientifii Maygeri, Italy); Emmanuel Nsutebu (Sheikh Shakhbout Medical

City, Abu Dhabi, United Arab Emirates); Natalia Pshenichnaya (Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow, Russian Federation); Nida Qadir (Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California, Los Angeles, United States); Rohit Sarin (National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India); Yinzhong Shen (Shanghai Public Health Clinical Center, Fudan University, Shanghai, China); Shalini Sri Ranganathan (University of Colombo, Sri Lanka); Miriam Stegemann (Charité - Universitätsmedizin Berlin, Germany); Ronald Swanstrom (Department of Biochemistry & Biophysics of the University of North Carolina, United States); Tim Uyeki (Influenza Division, U.S. Centers for Disease Control and Prevention, United States); Sridhar Venkatapuram (King's College London, United Kingdom).

Guideline Development Group (GDG) for the update on remdesivir recommendation. For list of GDG members of previous recommendations, see here.

Wagdy Amin (Ministry of Health and Population, Egypt); Erlina Burhan (Infection Division Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Universitas Indonesia); Carolyn S Calfee (University of California, San Francisco, United States); Maurizio Cecconi (Humanitas Research Hospital Milan, Italy); Duncan Chanda (Institute for Medical Research and Training, Zambia); Vu Quoc Dat (Department of Infectious Diseases, Hanoi Medical University, Hanoi, Viet Nam); Heike Geduld (Emergency Medicine, Stellenbosch University, South Africa); Frederique Jacquerioz Bausch (Department of Primary Care, University Hospital of Geneva, Switzerland); Fabian Alberto Jaimes Barragan (Antioquia University Medellin, Colombia); Sushil Kumar Kabra (All India Institute of Medical Sciences, New Delhi, India); Niranjan Kissoon (Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Sanjeev Krishna (St George's University of London, United Kingdom); Yee-Sin Leo (National Centre for Infectious Diseases, Singapore); Rakesh Lodha (Department of Paediatrics, All India Institute of Medical Sciences, India); Hela Manai (Emergency Medical Service Tunis, Tunisia);Natalia Pshenichnaya (Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow, Russian Federation); Saniya Sabzwari (Aga Khan University, Karachi, Pakistan); Rohit Sarin (National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India); Manu Shankar-Hari (King's College London, United Kingdom); Yinzhong Shen (Shanghai Public Health Clinical Center, Fudan University, Shanghai, China); Shalini Sri Ranganathan (University of Colombo, Sri Lanka); Miriam Stegemann (Charité - Universitätsmedizin Berlin, Germany); Ronald Swanstrom (Department of Biochemistry & Biophysics of the University of North Carolina, United States); Tim Uyeki (Influenza Division, U.S. Centers for Disease Control and Prevention, United States); Sridhar Venkatapuram (King's College London, United Kingdom).

Guideline Development Group (GDG) for nirmatrelvir-ritonavir recommendation. For list of GDG members of previous recommendations, see here.

Wagdy Amin (Ministry of Health and Population, Egypt); Erlina Burhan (Infection Division Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Universitas Indonesia); Carolyn S Calfee (University of California, San Francisco, United States); Maurizio Cecconi (Humanitas Research Hospital Milan, Italy); Duncan Chanda (Institute for Medical Research and Training, Zambia); Vu Quoc Dat (Department of Infectious Diseases, Hanoi Medical University, Hanoi, Viet Nam); Stephen Freedman (Department of Pediatrics, Cumming School of Medicine, University of Calgary, Canada); Heike Geduld (Emergency Medicine, Stellenbosch University, South Africa); Beverley Hunt (King's College London, United Kingdom); Fabian Alberto Jaimes Barragan (Antioquia University Medellin, Colombia); Sushil Kumar Kabra (All India Institute of Medical Sciences, New Delhi, India); Niranjan Kissoon (Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Sanjeev Krishna (St George's University of London, United Kingdom); Arthur Kwizera (Makerere University College of Health Sciences, Mulago National Referral Hospital ICU, Uganda); Yee-Sin Leo (National Centre for Infectious Diseases, Singapore); Thiago Lisboa (Coraçao Hospital, Sao Paulo, Brazil); Rakesh Lodha (Department of Paediatrics, All India Institute of Medical Sciences, India); Emmanuel Nsutebu (Sheikh Shakhbout Medical City, Abu Dhabi, United Arab Emirates); Natalia Pshenichnaya (Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow, Russian Federation); Saniya Sabzwari (Aga Khan University, Karachi, Pakistan); Rohit Sarin (National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India); Manu Shankar-Hari (King's College London, United Kingdom); Yinzhong Shen (Shanghai Public Health Clinical Center, Fudan University, Shanghai, China); Shalini Sri Ranganathan (University of Colombo, Sri Lanka); Ronald Swanstrom (Department of Biochemistry & Biophysics of the University of North Carolina, United States); Tim Uyeki (Influenza Division, U.S. Centers for Disease Control and Prevention, United States); Sridhar Venkatapuram (King's College London, United Kingdom).

Guideline Development Group (GDG) for molnupiravir recommendation. For list of GDG members of previous recommendations, see here.

Wagdy Amin (Ministry of Health and Population, Egypt); Maurizio Cecconi (Humanitas Research Hospital Milan, Italy); Duncan Chanda (Institute for Medical Research and Training, Zambia); Vu Quoc Dat (Department of Infectious Diseases, Hanoi Medical University, Hanoi, Viet Nam); Ann De Sutter (Ghent Faculty of Medicine and Health Science, Belgium); Heike Geduld (Emergency Medicine, Stellenbosch University, South Africa); Patrick Gee (patient panel member, Virginia, United States); Matthias Gotte (University of Alberta, Canada); Nerina Harley (Royal Melbourne Hospital and Epworth Healthcare, Melbourne, Australia); Beverley Hunt (King's College London, United Kingdom); Frederique Jacquerioz Bausch (Department of Primary Care, University Hospital of Geneva, Switzerland); Fabian Alberto Jaimes Barragan (Antioquia University Medellin, Colombia); Fyezah Jehan (Aga Khan University, Pakistan); Sushil Kumar Kabra (All India Institute of Medical Sciences, New Delhi, India); Yae Jean Kim (Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea); Niranjan Kissoon (Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Sanjeev Krishna (St George's University of London, United Kingdom); Arthur Kwizera (Makerere University College of Health Sciences, Mulago National Referral Hospital ICU, Uganda); Yee-Sin Leo (National Centre for Infectious Diseases, Singapore); Thiago Lisboa (Coraçao Hospital, Sao Paulo, Brazil); Imelda Mahaka (Pangaea Zimbabwe AIDS Trust, Harare,

Zimbabwe); Hela Manai (Emergency Medical Service Tunis, Tunisia); Emmanuel Nsutebu (Sheikh Shakhbout Medical City, Abu Dhabi, United Arab Emirates); Natalia Pshenichnaya (Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow, Russian Federation); Rohit Sarin (National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India); Manu Shankar-Hari (King's College London, United Kingdom); Yinzhong Shen (Shanghai Public Health Clinical Center, Fudan University, Shanghai, China); Shalini Sri Ranganathan (University of Colombo, Sri Lanka); Miriam Stegemann (Charité - Universitätsmedizin Berlin, Germany); Ronald Swanstrom (Department of Biochemistry & Biophysics of the University of North Carolina, United States); Tim Uyeki (Influenza Division, U.S. Centers for Disease Control and Prevention, United States); Sridhar Venkatapuram (King's College London, United Kingdom); Ananda Wijewickrama (Ministry of Health, Sri Lanka).

Guideline Development Group (GDG) for JAK inhibitors recommendation. For list of GDG members of previous recommendations, see here.
Wagdy Amin (Ministry of Health and Population, Egypt); Carolyn S Calfee (University of California, San Francisco, United States); Duncan Chanda (Institute for Medical Research and Training, Zambia); Vu Quoc Dat (Department of Infectious Diseases, Hanoi Medical University, Hanoi, Viet Nam); Ann De Sutter (Ghent Faculty of Medicine and Health Science, Belgium); Beverley Hunt (King's College London, United Kingdom); Heike Geduld (Emergency Medicine, Stellenbosch University, South Africa); Yae Jean Kim (Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea); Sanjeev Krishna (St George's University of London, United Kingdom); Yee-Sin Leo (National Centre for Infectious Diseases, Singapore); Natalia Pshenichnaya (Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow, Russian Federation); Saniya Sabzwari (Aga Khan University, Karachi, Pakistan); Rohit Sarin (National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India); Yinzhong Shen (Shanghai Public Health Clinical Center, Fudan University, Shanghai, China); Shalini Sri Ranganathan (University of Colombo, Sri Lanka); Miriam Stegemann (Charité - Universitätsmedizin Berlin, Germany); Sridhar Venkatapuram (King's College London, United Kingdom); Ananda Wijewickrama (Ministry of Health, Sri Lanka).

Guideline Development Group (GDG) for sotrovimab recommendation. For list of GDG members of previous recommendations, see here.
Wagdy Amin (Ministry of Health and Population, Egypt); Fabian Alberto Jaimes Barragan (Antioquia University Medellin, Colombia); Duncan Chanda (Institute for Medical Research and Training, Zambia); Vu Quoc Dat (Department of Infectious Diseases, Hanoi Medical University, Hanoi, Vietnam); Ann De Sutter (Ghent Faculty of Medicine and Health Science, Belgium); Heike Geduld (Emergency Medicine, Stellenbosch University, South Africa); Nerina Harley (Royal Melbourne Hospital and Epworth Healthcare, Melbourne, Australia); Beverley Hunt (King's College, London, United Kingdom); Fyezah Jehan (Aga Khan University, Pakistan); Sushil Kumar Kabra (All India Institute of Medical Sciences, New Delhi, India); Yae Jean Kim (Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea); Niranjan Kissoon (Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Sanjeev Krishna (St George's University of London, United Kingdom); Yee-Sin Leo (National Centre for Infectious Diseases, Singapore); Thiago Lisboa (Coraçao Hospital, Sao Paulo, Brazil); Natalia Pshenichnaya (Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow, Russian Federation); Rohit Sarin (National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India); Manu Shankar-Hari (King's College London, United Kingdom), Yinzhong Shen (Shanghai Public Health Clinical Center, Fudan University, Shanghai, China); Shalini Sri Ranganathan (University of Colombo, Sri Lanka); Ronald Swanstrom (University of North Carolina, United States); Miriam Stegemann (Charité - Universitätsmedizin Berlin, Germany); Sridhar Venkatapuram (King's College London, United Kingdom).

Guideline Development Group (GDG) for convalescent plasma guideline. For list of GDG members of previous recommendations, see here.
Wagdy Amin (Ministry of Health and Population, Egypt); Erlina Burhan (Infection Division Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Universitas Indonesia); Carolyn S Calfee (University of California, San Francisco, United States); Maurizio Cecconi (Humanitas Research Hospital Milan, Italy); Vu Quoc Dat (Department of Infectious Diseases, Hanoi Medical University, Hanoi, Viet Nam); Heike Geduld (Emergency Medicine, Stellenbosch University, South Africa); Patrick Gee (patient panel member, United States); Nerina Harley (Royal Melbourne Hospital and Epworth Healthcare, Melbourne, Australia); Madiha Hashmi (Ziauddin University, Karachi, Pakistan); Sushil Kumar Kabra (All India Institute of Medical Sciences, New Delhi, India); Seema Kanda (patient panel member, Ontario, Canada); Leticia Kawano-Dourado (Research Institute, Hospital do Coração, São Paulo, Brazil); Niranjan Kissoon (Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Greta Mino (Alcivar Hospital in Guayaquil, Ecuador); Natalia Pshenichnaya (Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow, Russian Federation); Nida Qadir (Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California, Los Angeles, United States); Saniya Sabzwari (Aga Khan University, Karachi, Pakistan); Rohit Sarin (National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India); Yinzhong Shen (Shanghai Public Health Clinical Center, Fudan University, Shanghai, China); Shalini Sri Ranganathan (University of Colombo, Sri Lanka); Miriam Stegemann (Charité - Universitätsmedizin Berlin, Germany); Sridhar Venkatapuram (King's College, London, United Kingdom); Ananda Wijewickrama (Ministry of Health, Sri Lanka).

Methods chairs
Gordon Guyatt (casirivimab-imdevimab, JAK inhibitors, nirmatrelvir-ritonavir); Bram Rochwerg (IL-6 receptor blockers, ivermectin, remdesivir and lopinavir-ritonavir, convalescent plasma, molnupiravir, remdesivir update); Reed Siemieniuk (hydroxychloroquine); Francois Lamontagne (corticosteroids, sotrovimab and sotrovimab update, colchicine, fluvoxamine, casirivimab-imdevimab update,

baricitinib update, hydroxychloroquine prophylaxis).

Clinical chairs
Michael Jacobs (casirivimab-imdevimab, IL-6 receptor blockers, ivermectin, remdesivir, hydroxychloroquine, lopinavir-ritonavir, JAK inhibitors, remdesivir update); Yee-Sin Leo (corticosteroids); Leticia Kawano-Dourado (convalescent plasma, sotrovimab, molnupiravir); Miriam Stegemann (fluvoxamine, colchicine, baricitinib update, sotrovimab update); Heike Geduld (remdesivir update).

Methods resource persons
Arnav Agarwal (University of Toronto, Canada); Thomas Agoritsas (University Hospitals of Geneva, Switzerland); Romina Brignardello-Petersen (McMaster University, Canada); Gordon H Guyatt (McMaster University, Canada); George Tomlinson (Department of Medicine, University Health Network, Toronto, Canada); Per Olav Vandvik (MAGIC, University of Oslo Norway); Linan Zeng (West China Second University Hospital, Sichuan University, Chengdu, China; McMaster University, Canada).

Guideline Support Collaboration Committee which provides the coordination between WHO and MAGIC to allow the rapid development of the WHO guideline and its dissemination into the various publication platforms: Thomas Agoritsas (MAGIC, University Hospitals of Geneva); Janet Diaz (World Health Organization); Helen Macdonald (British Medical Journal); Gordon Guyatt (McMaster University, Canada); Per Olav Vandvik (MAGIC, University of Oslo); Julie Viry (World Health Organization).

Temporary advisors:

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External reviewers

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Meta-analysis teams

Special thanks to the McMaster University LNMA team: Arnav Agarwal (University of Toronto, Canada); Thomas Agoritsas (MAGIC; University Hospitals of Geneva, Switzerland); Jessica J Bartoszko (McMaster University, Canada); Romina Brignardello-Petersen (McMaster University, Canada); Derek K Chu (McMaster University, Canada); Rachel Couban (McMaster University, Canada); Andrea Darzi (McMaster University, Canada); Tahira Devji (McMaster University, Canada); Bo Fang (Chongqing Medical University, China);

Carmen Fang (William Osler Health Network, Canada); Signe Agnes Flottorp (University of Oslo, Norway); Farid Foroutan (McMaster University, Canada); Long Ge (Lanzhou University, China); Gordon H Guyatt (McMaster University, Canada); Mi Ah Han (Chosun University, Republic of Korea); Diane Heels-Ansdell (McMaster University, Canada); Kimia Honarmand (Western University, Canada); Liangying Hou (Lanzhou University, China); Xiaorong Hou (Chongqing Medical University, China); Quazi Ibrahim (McMaster University, Canada); Ariel Izcovich (Servicio de Clinica Médica del Hospital Alemán, Argentina); Elena Kum (McMaster University, Canada); Francois Lamontagne (Université de Sherbrooke, Canada); Qin Liu (Chongqing Medical University, China); Mark Loeb (McMaster University, Canada); Maura Marcucci (McMaster University, Canada); Shelley L McLeod (Sinai Health, Canada); Sharhzad Motaghi, (McMaster University, Canada); Srinivas Murthy (University of British Columbia, Canada); Reem A Mustafa (McMaster University, Canada); John D Neary (McMaster University, Canada); Hector Pardo-Hernandez (Sant Pau Biomedical Research Institute, Spain); Anila Qasim (McMaster University, Canada); Gabriel Rada (Epistemonikos Foundation, Chile); Irbaz Bin Riaz (Mayo Clinic Rochester, United States of America); Bram Rochwerg (McMaster University, Canada); Behnam Sadeghirad (McMaster University, Canada); Nigar Sekercioglu (McMaster University, Canada); Lulu Sheng (Chongqing Medical University, China); Reed AC Siemieniuk (McMaster University, Canada); Ashwini Sreekanta (McMaster University, Canada); Charlotte Switzer (McMaster University, Canada); Britta Tendal (Monash University, Australia); Lehana Thabane (McMaster University, Canada); George Tomlinson (University of Toronto, Canada); Tari Turner (Monash University, Australia); Per Olav Vandvik (MAGIC; University of Oslo, Norway); Robin WM Vernooij (University Medical Center Utrecht, Netherlands); Andrés Viteri-García (Epistemonikos Foundation, Chile); Ying Wang (McMaster University, Canada); Liang Yao (McMaster University, Canada); Zhikang Ye (McMaster University, Canada); Dena Zeraatkar (McMaster University, Canada) *(1)(3)(4)*.

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Manu Shankar-Hari; Claire L Vale; Peter J Godolphin; David Fisher; Julian PT Higgins; Francesca Spiga; Jelena Savović; Jayne Tierney; Nor Arisah Misnan; Gabriel Baron; Julie S Benbenishty; Lindsay R Berry; Niklas Broman; Alexandre Biasi Cavalcanti; Roos Colman; Stefanie L De Buyser; Lennie PG Derde; Pere Domingo; Sharifah Faridah Syed Omar; Ana Fernandez-Cruz; Thijs Feuth; Felipe Garcia; Rosario Garcia-Vicuna; Isidoro Gonzalez-Alvaro; Anthony C Gordon; Richard Haynes; Olivier Hermine; Peter W Horby; Nora K Horick; Kuldeep Kumar: Bart N Lambrecht; Martin J Landray; Lorna Leal; David J Lederer; Elizabeth Lorenzi; Xavier Mariette; Nicolas Merchante; Nor Arisah Misnan; Shalini V Mohan; Michael C Nivens; Jarmo Oksi; Jose A Perez-Molina; Reuven Pizov; Raphael Porcher; Simone Postma; Reena Rajasuriar; Athimalaipet V Ramanan; Pankti D Reid; Abraham Rutgers; Aranzazu Sancho-Lopez; Todd B Seto; Sumathi Sivapalasingam; Arvinder Singh Soin; Natalie Staplin; John H Stone; Garth W Strohbehn; Jonas Sunden-Cullberg; Julian Torre-Cisneros; Larry W Tsai; Hubert van Hoogstraten; Tom van Meerten; Viviane Cordeiro Veiga; Peter Westerwheel; Srinivas Murthy; Janet V Diaz; John C Marshall; Jonathan A C Sterne.

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