

Therapeutics and COVID-19

LIVING GUIDELINE
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Contact

WHO Emerging Diseases Clinical Assessment and Response Network

EDCARN@who.int

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.

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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. This update adds a new recommendation on molnupiravir in patients with non-severe COVID-19, informed by data from 6 RCTs with 4796 patients.

New recommendations: The Guideline Development Group (GDG) suggests administering molnupiravir in patients with non-severe illness, who are at highest risk of hospitalization with implementation of mitigation strategies to reduce potential harms. No recommendation was made in patients with severe or critical illness as there are no data on molnupiravir for this population.

The Omicron variant has resulted in an update to the recommendations for casirivimab-imdevimab. Additional preclinical evidence has emerged demonstrating lack of efficacy of casirivimab-imdevimab against the Omicron BA1 variant (see Mechanism of Action) and reduced neutralizing activity of sotrovimab against the Omicron BA2 variant (see Mechanism of Action). See Section 4 for what drugs are currently under review.

Understanding the new recommendations: When moving from evidence to recommendations, the GDG considered a combination of evidence assessing relative benefits and harms, values and preferences, and feasibility issues. For patients with non-severe illness, the GDG recognized that molnupiravir reduces hospitalization risk and time to symptom resolution, and may have little to no effect on mortality. The effect on need for invasive mechanical ventilation was uncertain. The GDG also acknowledged that only patients at the highest risk of being hospitalized are likely to derive important benefits and would want to receive molnupiravir. This is especially true given the potential for harms associated with molnupiravir. Based on in vitro studies in human cells there is a theoretical risk of malignancy associated with the drug. No evidence for genetic toxicity was uncovered in animals but this has not been evaluated in long-term follow-up or human studies. There are also separate theoretical risks that molnupiravir may induce drug resistance in the virus and/or increase genetic diversity within viral genome sequences that promote the emergence of new variants.

The conditional recommendation for molnupiravir in non-severe illness acknowledges that it is challenging to accurately identify those at highest risk of hospitalization, the limited availability of the drug, and that efficacy against emerging variants remains uncertain. The absence of data on severe and critical COVID-19 prevented the GDG from making any recommendations for these particular risk categories.

Updates to prior recommendations:

- The conditional recommendations for casirivimab-imdevimab in patients with both non-severe (for those at highest risk of hospitalization) and severe or critical COVID-19 (for those with seronegative status) are now restricted to cases where rapid viral genotyping is available and confirms infection with a susceptible SARS-CoV-2 variant (such as Delta). This change follows pre-clinical evidence that casirivimab-imdevimab lacks efficacy against the Omicron BA1 variant.
- Regarding the previous conditional recommendation against remdesivir in patients with COVID-19, new trial data have resulted in an ongoing evidence review by the GDG with an anticipated update of the recommendation in the next iteration of this guideline.

Prior recommendations:

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), in combination with corticosteroids;
- a [strong recommendation](#) for baricitinib as an alternative to IL-6 receptor blockers, in combination with corticosteroids.

Recommended for patients with non-severe COVID-19:

- a [conditional recommendation](#) for sotrovimab, conditional for those at highest risk of hospitalization.

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

- a [conditional recommendation](#) against systemic corticosteroids;
- a [strong recommendation](#) against convalescent plasma.

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 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 a new recommendation on molnupiravir for patients with non-severe COVID-19, and updates existing recommendations. The GDG typically evaluates a drug when 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 systematic reviews and network meta-analyses (LNMA) (1)(2)(3).

Updates and access: This is the ninth update of the living guideline. It replaces earlier versions (2 September 2020, 20 November 2020, 17 December 2020, 31 March 2021, 6 July 2021, 24 September 2021, 7 December 2021 and 14 January 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 living WHO guideline for COVID-19 treatments 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
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
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
TACO	transfusion-associated circulatory overload
TRALI	transfusion-related acute lung injury
WHO	World Health Organization

3. Introduction

Info Box

As of 20 February 2022, there have been over 418 million confirmed cases of COVID-19 (10). The pandemic has thus far claimed approximately 5.8 million lives (10). Vaccination is having a substantial impact on case numbers and hospitalizations in a number of high-income countries, but limitations in global access to vaccines mean that many populations remain vulnerable (10)(11). Even in vaccinated individuals, uncertainties remain about the duration of protection and efficacy of current vaccines – and the efficacy of existing treatments for COVID-19 – against emerging SARS-CoV-2 variants.

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 (12).

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 or are ongoing (see Section 9 for emerging evidence) (13). Among these are large national and international platform trials (such as RECOVERY, WHO SOLIDARITY, REMAP-CAP, and ACTIV), which recruit large numbers of patients in many countries, with a pragmatic and adaptive design (14)(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 (13) and the [WHO website](#).

Several living network meta-analyses 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 for COVID-19 did not identify credible and applicable risk prediction tools that could inform recommendations in this ninth version of the guideline (18).

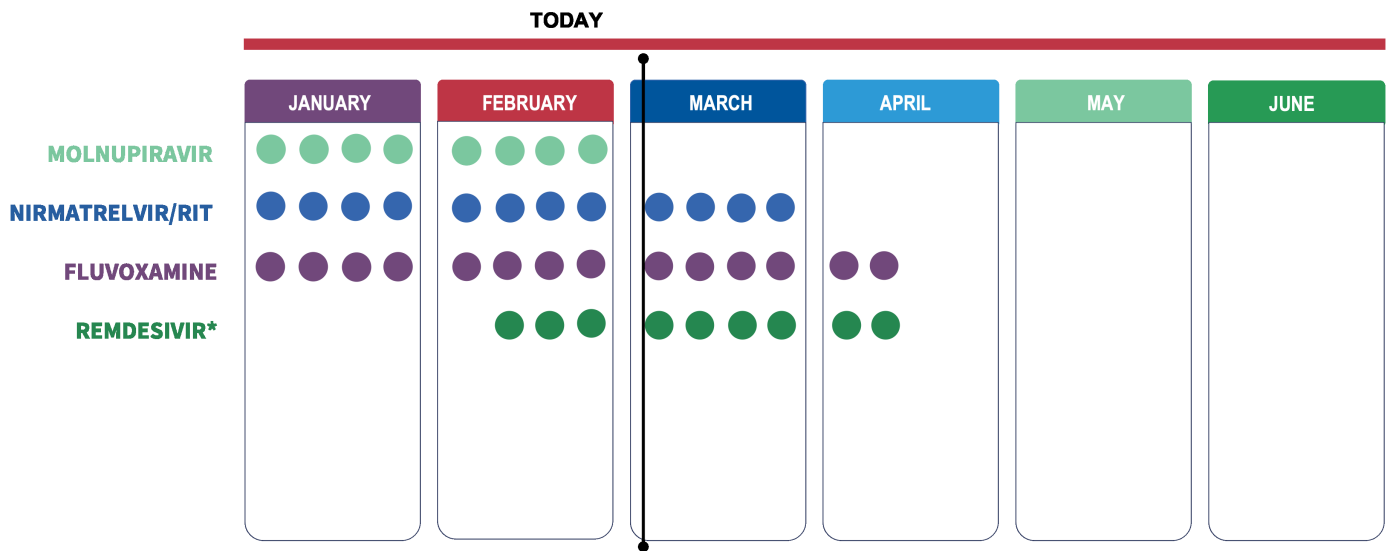
However, existing and evolving evidence demonstrates remaining uncertainties concerning treatment effects for all outcomes of importance to patients. There is also a need for better evidence on prognosis and values and preferences of patients with COVID-19. Moreover, the rapidly evolving evidence landscape requires trustworthy interpretation and expeditious clinical practice guidelines to inform clinicians and health care decision-makers.

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

This ninth version of the WHO living guideline addresses the use of molnupiravir in non-severe COVID-19. It follows the availability of six RCTs, which were incorporated in an update to the LNMA on drug treatments for COVID-19 (2). It also includes updated recommendations for casirivimab-imdevimab, driven by the emergence of the Omicron BA1 variant, and an ongoing evidence review by the GDG for remdesivir with an anticipated update of the recommendation in the next iteration of the guideline.

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



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

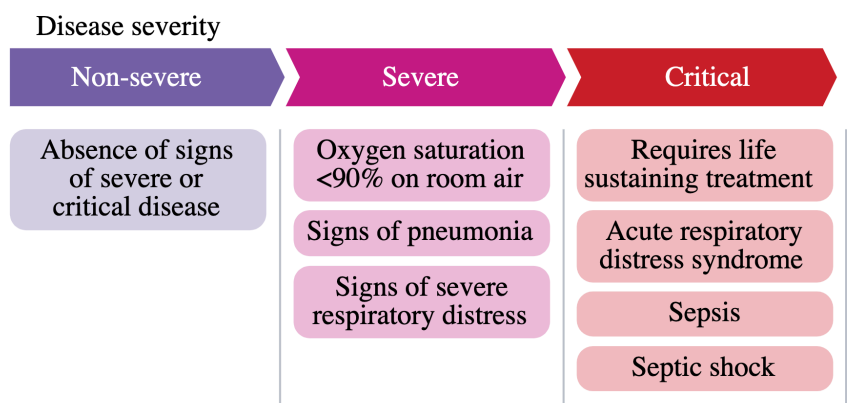
- **Critical COVID-19** – Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
- **Severe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

Population

This recommendation applies only to people with these characteristics:



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

6. Recommendations for therapeutics

6.1 Molnupiravir (published 3 March 2022)

For patients with non-severe COVID-19 (excluding pregnant and breastfeeding women, and children)

Conditional recommendation

New

We suggest treatment with molnupiravir, conditional to those at highest risk of hospitalization (*conditional recommendation for*).

- *In the absence of credible tools to predict risk for hospitalization in people infected with SARS-CoV-2, typical characteristics of people at highest risk include those that lack COVID-19 vaccination, with older age, immunosuppression and/or chronic diseases (e.g. diabetes).*
- *The benefit will be trivial in absolute terms except in those at highest risk for hospitalization, for which the intervention should be reserved and given early on in disease.*
- *The panel identified a risk beyond 10% of being hospitalized for COVID-19 to represent a threshold at which most people would want to be treated with molnupiravir.*
- *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).*
- *Alternative effective treatments with different safety profiles recommended by WHO, such as neutralizing monoclonal antibodies, like sotrovimab, may be preferable or antivirals (currently under WHO assessment) if available.*

Practical Info

Route, dosage and duration: Additional considerations are available in a linked summary of practical issues (accessible [here](#)).

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 (19).

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 (22). 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).

Preference and values

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 low- and middle-income countries (LMICs) due to cost and availability are of concern (20). 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 4796 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 1220 participants in 1 study. (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 4688 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 4688 participants in 5 studies. (Randomized controlled)	60 per 1000	33 per 1000	Moderate Due to serious imprecision ⁴	Molnupiravir probably reduces hospital admission

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Molnupiravir	Certainty of the Evidence (Quality of evidence)	Plain language summary
Admission to hospital Highest risk	Odds Ratio 0.54 (CI 95% 0.3 – 0.89) Based on data from 4688 participants in 5 studies. (Randomized controlled)	Difference: 100 per 1000 Difference: 43 fewer per 1000 (CI 95% 68 fewer – 10 fewer)	27 fewer per 1000 (CI 95% 41 fewer – 6 fewer) 57 per 1000 43 fewer per 1000 (CI 95% 68 fewer – 10 fewer)	Moderate Due to serious imprecision ⁵	Molnupiravir probably reduces hospital admission
Adverse effects leading to drug discontinuation	Based on data from 4796 participants in 6 studies. (Randomized controlled)	0 per 1000 Difference: 0 fewer per 1000 (CI 95% 2 fewer – 2 more)	0 per 1000 0 fewer per 1000 (CI 95% 2 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: 3078 participants in 3 studies. (Randomized controlled)	9 (Median) Difference: MD 3.4 fewer (CI 95% 4.8 fewer – 1.7 fewer)	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

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

New

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 (23).
 - 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.

6.1.1 Mechanism of action

Molnupiravir is an orally available antiviral, which was originally designed as an influenza treatment, although not approved. The drug inhibits replication of SARS-CoV-2 with an in vitro potency broadly, similar to remdesivir, and was re-purposed early in development as an antiviral for SARS-CoV-2 (24)(25).

Molnupiravir is an orally available prodrug of β -D-N4-hydroxycytidine (NHC). It is a nucleoside drug, but the mechanism of action involves lethal mutagenesis of the virus. This contrasts with chain-termination seen with other antiviral nucleoside analogues (e.g. remdesivir and those used in HIV or HCV) (26). 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 (26)(27).

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 (28). This is higher than that of remdesivir (2200 ng/mL) (29). 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) (28).

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 (30). Evidence of antiviral activity is also available from a study in SARS-CoV-2-infected ferrets at lower doses (31). When molnupiravir was combined with favipiravir in infected Syrian golden hamsters, the efficacy was greater than when either drug was given alone (32).

Molnupiravir retains activity against Alpha and Beta variants in vivo (33), and the Delta and Omicron variants in vitro (34)(35). 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 some nucleosides used for other viruses is varied; with some emerging readily, and 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), the drug will place a selective pressure for resistant mutations within an individual, with the potential to spread at a population level.

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. Non-clinical and/or clinical data are therefore needed, and are not currently available for molnupiravir.

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 (36). 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 Emergency Use Authorization (30 November 2021) (37). 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.

6.2 Janus kinase inhibitors (published 14 January 2022)

Info Box

Recommendations concerning janus kinase (JAK) inhibitors, specifically baricitinib, ruxolitinib and tofacitinib, for patients with severe or critical COVID-19 were published on 14 January 2022 as the [eighth version](#) of the WHO living guideline and in the BMJ as [Rapid Recommendations](#). It follows the availability of three RCTs for baricitinib, two RCTs for ruxolitinib, and one RCT for tofacitinib, as per the LNMA on drug therapies (3). No changes were made for the JAK inhibitors recommendations in this ninth version of the guideline.

Baricitinib, for patients with severe or critical COVID-19

Strong recommendation for

We recommend treatment with baricitinib (*strong recommendation for*).

- Along with baricitinib, corticosteroids should also be administered in patients with severe or critical COVID-19 (see Section 6.11).
- IL-6 receptor blockers (tocilizumab or sarilumab) have previously been recommended for the treatment of patients with severe or critical COVID-19 (see Section 6.6). An IL-6 receptor blocker and baricitinib should not be given together, and should be viewed as alternatives. The choice of whether to use baricitinib or an IL-6 receptor blocker depends on availability, as well as clinical and contextual factors (see Justification).

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 (38). 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 m².
- 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 probably reduces mortality and duration of mechanical ventilation, and reduces 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 at baseline.

Certainty of the Evidence

Certainty of evidence was rated as: moderate for decreased mortality (rated down from high for a large ongoing trial that may change estimates of effect and indirectness due to the relatively short follow-up period close to 28 days possibly being insufficient to capture all relevant events); high for reduction in hospital length of stay; moderate for reduction in duration of mechanical ventilation and for little or no increase in serious adverse events, both rated down for serious imprecision; and low for need for mechanical ventilation, 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.

Preference and values

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

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

Acceptability and feasibility

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

Justification

When moving from evidence to the strong recommendation to use baricitinib in patients with severe or critical COVID-19, the GDG emphasized the benefits on survival and decreased length of hospital stay with ease of administration and the likelihood of little or no serious adverse events attributable to the drug. 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 were important considerations and the GDG recognizes that this recommendation could exacerbate health inequities. This strong recommendation will provide 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).

Emerging evidence

The GDG carefully considered the implications of a large trial (RECOVERY) having randomized patients to baricitinib or no baricitinib and the possibility that investigators will report their results in the relatively near future. Uncertainties regarding this trial include the proportion of patients who also received an IL-6 receptor blocker (see below), and when the information will be available. The GDG considered the benefits of baricitinib, supported by moderate to high certainty evidence, sufficient for an immediate strong recommendation for use of the drug, with readiness to update the living guideline as necessary once RECOVERY trial data are published.

The role of IL-6 receptor blockers and baricitinib

The GDG has previously made a strong recommendation for use of IL-6 receptor blockers (tocilizumab and sarilumab) in patients with severe or critical COVID-19. The GDG carefully considered whether, on the basis of the current evidence, baricitinib should be administered as an alternative to IL-6 receptor blockers or in addition to IL-6 receptor blockers. Combining them may unacceptably increase harms, including secondary bacterial and fungal infections. In the absence of evidence of incremental benefit, the GDG advises that clinicians do not administer the drugs together.

The issue then arises regarding the basis for choosing between IL-6 receptor blockers and baricitinib (see Research evidence). The drugs have not undergone direct comparisons, and so the best evidence of their relative effects comes from indirect comparisons generated by the LNMA that informs these guidelines. Baricitinib may reduce mortality relative to IL-6 receptor blockers (low certainty) and may reduce the duration of mechanical ventilation (low certainty). There may be little or no difference in the agents' impact on mechanical ventilation (low certainty), and there is probably little or no difference in adverse events leading to discontinuation (moderate certainty) (see Summary of Findings table in Research evidence).

The GDG felt that the low certainty evidence did not warrant a recommendation favouring the use of baricitinib versus IL-6 receptor blockers on the basis of their impact on patient-important benefits and harms. Therefore, when both agents are available, clinicians should choose between them based on other considerations. These might include 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 three RCTs which enrolled 2659 patients across disease severities (39)(40)(41). All RCTs were registered, and two were published in peer-reviewed journals (40)(41); one study was a pre-print (39). All three 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 0.62 (CI 95% 0.44 – 0.85) Based on data from 2659 participants in 3 studies. (Randomized controlled)	130 per 1000 Difference:	85 per 1000 45 fewer per 1000 (CI 95% 68 fewer – 17 fewer)	Moderate Due to ongoing recruitment in a large RCT	Baricitinib probably reduces mortality.
Mechanical ventilation	Odds Ratio 0.8 (CI 95% 0.52 – 1.19) Based on data from 2434 participants in 2 studies. (Randomized controlled)	116 per 1000 Difference:	95 per 1000 21 fewer per 1000 (CI 95% 52 fewer – 19 more)	Low Due to very serious imprecision ¹	Baricitinib may reduce mechanical ventilation.
Adverse effects leading to drug discontinuation	Based on data from 1611 participants in 2 studies. (Randomized controlled)	0 per 1000 Difference:	5 per 1000 5 more per 1000 (CI 95% 18 fewer – 28 more)	Moderate Due to serious imprecision ²	Baricitinib probably results in little or no increase in serious adverse effects.
Hospital length of stay	Lower better Based on data from: 2652 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)	High	Baricitinib 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 ³	Baricitinib probably reduces duration of mechanical ventilation.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Baricitinib	Certainty of the Evidence (Quality of evidence)	Plain language summary
Time to clinical stability	Lower better Based on data from: 2558 participants in 2 studies. (Randomized controlled)	9.9 days (Median) Difference:	8.9 days (Mean) MD 1 fewer (CI 95% 2.9 fewer – 1.1 more)	Low Due to very serious imprecision ⁴	Baricitinib may reduce time to clinical stability.

1. **Imprecision: very serious.** Credible interval includes an important decrease and increase in mechanical ventilation.
2. **Imprecision: serious.** The credible interval includes an important increase in adverse effects.
3. **Imprecision: serious.** The credible interval includes no important difference.
4. **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 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 2659 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 2434 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 2309 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.

Outcome Timeframe	Study results and measurements	Comparator IL-6 receptor blockers	Intervention Baricitinib	Certainty of the Evidence (Quality of evidence)	Plain language summary
Hospital length of stay	Lower better Based on data from: 2652 participants in 3 studies. (Randomized controlled)	8.1 days (Median) Difference:	11.2 days (Mean) MD 3.1 more (CI 95% 3.8 fewer – 9.9 more)	Very low Due to serious risk of bias, serious inconsistency, and very serious imprecision ⁴	The impact on hospital length of stay is very uncertain.
Duration of mechanical ventilation	Lower better Based on data from: 328 participants in 2 studies. (Randomized controlled)	13.8 days (Median) Difference:	11.6 days (Mean) MD 2.2 fewer (CI 95% 5.3 fewer – 0.7 fewer)	Low Due to serious risk of bias and imprecision ⁵	Baricitinib may reduce duration of mechanical ventilation.
Time to clinical stability	Lower better Based on data from: 2558 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.

- Imprecision: serious.** The credible interval includes no important difference.
- 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.
- Imprecision: serious.** The credible interval includes small but important harm.
- 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.
- 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.
- 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).

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. Tofacitinib 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.

Preference and values

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 tofacitinib 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 (42)(43). 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.
Adverse effects leading to drug discontinuation	Based on data from 484 participants in 1 study. (Randomized controlled)	0 per 1000 Difference:	5 per 1000 2 more per 1000 (CI 95% 11 fewer – 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.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Ruxolitinib	Certainty of the Evidence (Quality of evidence)	Plain language summary
Duration of mechanical ventilation	Lower better Based on data from: 3 participants in 1 study. (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.

- 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.
- 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.
- Imprecision: very serious.** There was only one event in the single trial that reported this outcome, of 424 patients enrolled in the study.
- 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.
- Risk of bias: serious. Indirectness: serious. Imprecision: very serious.**
- 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 (44). 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 study. (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 study. (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 study. (Randomized controlled)	0 per 1000 Difference:	77 per 1000 77 more per 1000 (CI 95% 17 more – 138 more)	Low Due to very serious imprecision ³	Tofacitinib may increase adverse effects leading to drug discontinuation.
Hospital length of stay	Lower better Based on data from: 289 participants in 1 study. (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.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Tofacitinib	Certainty of the Evidence (Quality of evidence)	Plain language summary
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.

6.2.1 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 (45). 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 TNF β , 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 (45).

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 (45)(46)(47).

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.

6.3 Sotrovimab (published 14 January 2022)

Info Box

Recommendations concerning sotrovimab for patients with non-severe COVID-19 were published on 14 January 2022 as the [eighth version](#) of the WHO living guideline and in the BMJ as [Rapid Recommendations](#). It follows the availability of one RCT for non-severe illness, as per the LNMA on antibody and cellular therapies (2). No changes were made for the sotrovimab recommendation in this ninth version of the guideline.

For patients with non-severe COVID-19

Conditional recommendation

We suggest treatment with sotrovimab, conditional to those at highest risk of hospitalization (*conditional recommendation for*).

- *Whereas sotrovimab achieves a substantial reduction in the relative risk of hospitalization, the absolute benefit will be trivial in absolute terms except in those at highest risk for hospitalization, for which the intervention should be reserved.*
- *The panel identified a risk beyond 10% of being hospitalized for COVID-19 to represent a threshold at which most people would want to be treated with sotrovimab.*
- *In the absence of credible tools to predict risk for hospitalization in people infected with COVID-19, 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).*
- *Casirivimab-imdevimab were also conditionally recommended (see Section 6.5) and represent an alternative to sotrovimab; the two drugs should not be given together. The choice of which monoclonal antibodies to use depends on availability, as well as clinical and contextual factors, including emerging information about effectiveness with different variants (see Justification).*
- *Patients with severe or critical COVID-19: based on current evidence, the benefit of sotrovimab in seronegative patients with severe or critical COVID-19 (see casirivimab-imdevimab recommendation in Section 6.5) remains unclear. This means that careful clinical judgment needs to be applied if casirivimab-imdevimab is unavailable and sotrovimab is considered. New trial evidence for sotrovimab in this setting was published after the GDG developed recommendations for this iteration, and will be considered, alongside other publicly available emerging evidence, when developing future recommendations.*

Practical Info

Route, dosage and duration: Additional considerations are available in a [summary of practical issues](#). Here follows a brief summary of key points.

- The authorized dose for sotrovimab is one single intravenous infusion of 500 mg over 30 minutes, administered as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset.
- Sotrovimab is available as a concentrated solution, and must be diluted prior to administration.
- Patients should be clinically monitored during the infusion, and observed for at least 1 hour after the infusion is completed.

Evidence To Decision

Benefits and harms

In patients with non-severe illness, sotrovimab probably reduces hospitalization, with little or no impact on infusion reactions, with no data on time to clinical improvement. Sotrovimab probably has little or no impact on mortality and on mechanical ventilation.

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 one RCT with 1057 patients (COMET-ICE), included in the LNMA (51). This trial provides evidence of moderate certainty for reduced hospitalization (due to serious imprecision), high certainty for absence of infusion reactions, moderate certainty (due to serious indirectness) for no or small difference in mortality and low

certainty (due to serious indirectness and imprecision) for no or small difference in mechanical ventilation.

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. In addition, the GDG felt that there was some indirectness because of the possible emergence of variants for which the effectiveness of currently available monoclonal antibodies may be reduced.

When rating precision, the GDG considered the estimates of the absolute risks. Accordingly, in the context of very low event rates (e.g. very low risk of death among patients with non-severe illness), the GDG did not rate down for imprecision despite relative risks with wide confidence intervals.

Preference and values

Applying the agreed upon values and preferences (see Section 7), the GDG inferred that almost all well-informed patients with a low risk of hospitalization would decline sotrovimab, 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. These thresholds were also used here.

Resources and other considerations

Acceptability and feasibility

The GDG noted that sotrovimab is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. This further supports the guidance that sotrovimab be reserved for those at highest risk of hospitalization.

Additional challenges include the requirement for intravenous administration to patients who would normally be treated at home. Specialized clinics may be required to ensure safe and effective administration of sotrovimab. For the intervention to achieve substantial use, healthcare systems will have to address these challenges.

Given the cost and availability of sotrovimab, and the obstacles to ensuring access in LMICs may prove formidable. For example, those with socioeconomic disadvantages tend to have less frequent access to services in the first five days of symptoms and then less access to the interventions. Thus, the panel's suggestion that patients at highest risk receive the intervention may exacerbate health inequity. On the other hand, given the demonstrated benefits for patients and the still low vaccine coverage in some LMICs and low-income countries (LICs), sotrovimab may be a useful tool to reduce hospitalization from COVID-19 in unvaccinated populations. The recommendations should also provide a stimulus to engage all possible mechanisms to improve global access to the intervention. Individual countries may formulate their guidelines considering available resources and prioritize treatment options accordingly. On 17 December 2021, WHO published the 7th Invitation to Manufacturers of therapeutics against COVID-19 to submit an [Expression of Interest \(EOI\) for Product Evaluation](#) to the WHO Prequalification Unit, which includes sotrovimab.

Justification

A combination of the evidence, values and preferences, and feasibility contributed to the conditional recommendation for the use of sotrovimab only in individuals 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).

Although there is moderate certainty evidence of a substantial relative risk reduction in hospitalization, 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 this therapy. These include a lack of reliable tools to identify high-risk patients, delivering a parenteral therapy to patients who are typically cared for in the community, and limited availability of the drug.

The role of sotrovimab and casirivimab-imdevimab

Another combination of monoclonal antibodies, casirivimab-imdevimab, is also conditionally recommended in patients with non-

severe COVID-19 at highest risk of hospitalization. The GDG advised that clinicians do not administer the drugs together, given an absence of evidence of incremental benefit of the drugs when given together, and the low likelihood of incremental benefit mechanistically.

The GDG then considered how to choose between the two drugs. No trials provide head-to-head comparisons. With Alpha and Delta variants, there may be little or no difference in the agents' impact on critical outcomes, according to an indirect comparison from the LNMA (see GRADE Summary of Findings table in Research evidence).

Now and in the future, the choice of monoclonal antibodies will depend on emerging information regarding effectiveness with different variants and their availability, as well as clinical and contextual factors. Of note, the RCTs included in the LNMA were conducted before the emergence of the Omicron variant. The GDG is now fully considering how the Omicron variant may impact efficacy.

Following the publication of a previous conditional recommendation for casirivimab-imdevimab, pre-clinical evidence has emerged suggesting that this monoclonal antibody combination lacks neutralization activity against the Omicron variant in vitro (48). Sotrovimab has been reported to retain activity against Omicron in pseudo-virus assays, but with higher concentrations being required for neutralization (49). More data are required to ascertain whether efficacy against the Omicron variant will be maintained at the studied doses of monoclonal antibodies, and recommendations will be updated when additional data becomes available.

Applicability

Children and pregnant women: The included RCT enrolled only non-pregnant adults; therefore, the applicability to children and pregnant women remains uncertain. The GDG had no reason to believe that children or pregnant women with COVID-19 would respond differently to treatment with sotrovimab. However, for children, as the risk of hospitalization is generally extremely low, the GDG inferred that, in the absence of immunosuppression or another significant risk factor, children should not receive the intervention.

Severe and critical COVID-19: A recently published RCT randomized 546 adults hospitalized with COVID-19 to two neutralizing monoclonal antibody therapies (sotrovimab and BII-196 plus BII-198) or placebo (50). The results did not demonstrate benefits from these antibodies therapies, including a subgroup analysis on patients with seropositive versus seronegative status. Although the role of sotrovimab in severe and critical COVID-19 is not supported by the new trial, it was not assessed by the GDG, as they focused on patients with non-severe COVID-19 where evidence was available at the time of recommendation development; this trial, and any other new evidence that is publicly available, will be fully considered by the GDG for future recommendations for sotrovimab.

Clinical Question/ PICO

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

Summary

The LNMA for sotrovimab was informed by one RCT (COMET-ICE) that randomized 1057 non-hospitalized patients with symptomatic COVID-19 (≤ 5 days after the onset of symptoms) and at least one risk factor for disease progression. Of the 1057 randomized patients, the LNMA team had access to data for 1044 patients. Included patients were randomized to receive a single infusion of sotrovimab at a dose of 500 mg, or placebo. Median age of patients was 53 years; 46% were male. Median duration of follow-up in the intention-to-treat population was 72 days. Vaccinated patients were excluded from the trial (51).

The GRADE Summary of Findings table shows the relative and absolute effects of sotrovimab compared with standard care (placebo) for the outcomes of interest, with certainty ratings.

Subgroup analysis

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

1. Age: children versus adults (< 70 years) versus older adults (≥ 70 years).
2. Severity of illness at time of treatment initiation: non-severe versus severe versus critical.
3. Time of symptom onset.
4. Serological status.

No data were available in the trial to conduct these analyses.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Sotrovimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality	Odds Ratio 0.11 (CI 95% 0 – 2.6) Based on data from 1044 participants in 1 study. (Randomized controlled)	4 per 1000 Difference:	0 per 1000 4 fewer per 1000 (CI 95% 4 fewer – 6 more)	Moderate Due to serious indirectness and some concerns with imprecision ¹	Sotrovimab probably has little or no impact on mortality.
Mechanical ventilation	Odds Ratio 0.11 (CI 95% 0 – 2.6) Based on data from 1044 participants in 1 study. (Randomized controlled)	18 per 1000 Difference:	2 per 1000 16 fewer per 1000 (CI 95% 18 fewer – 27 more)	Low Due to serious indirectness and serious imprecision ²	Sotrovimab may have little or no impact on mechanical ventilation.
Admission to hospital Risk in trials	Odds Ratio 0.19 (CI 95% 0.06 – 0.51) Based on data from 1044 participants in 1 study. (Randomized controlled)	35 per 1000 Difference:	7 per 1000 28 fewer per 1000 (CI 95% 33 fewer – 17 fewer)	Moderate Due to serious imprecision ³	Sotrovimab probably reduces admission to hospital.
Admission to hospital Higher risk	Odds Ratio 0.19 (CI 95% 0.06 – 0.51) Based on data from 1044 participants in 1 study. (Randomized controlled)	60 per 1000 Difference:	12 per 1000 48 fewer per 1000 (CI 95% 56 fewer – 28 fewer)	Moderate Due to serious imprecision ⁴	Sotrovimab probably reduces admission to hospital.
Admission to hospital Highest risk	Odds Ratio 0.19 (CI 95% 0.06 – 0.51) Based on data from 1044 participants in 1 study. (Randomized controlled)	100 per 1000 Difference:	21 per 1000 79 fewer per 1000 (CI 95% 93 fewer – 46 fewer)	Moderate Due to serious imprecision ⁵	Sotrovimab probably reduces admission to hospital.
Infusion reactions	Based on data from 1044 participants in 1 study. (Randomized controlled)	0 per 1000 Difference:	0 per 1000 0 fewer per 1000 (CI 95% 13 fewer – 13 more)	High	Sotrovimab results in little or no increase in infusion reactions.
Time to clinical improvement				No data	The effect of sotrovimab 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, sotrovimab may have an important impact on mortality. **Imprecision: no serious.** There were only four deaths (all in the placebo group) in the single trial that studied sotrovimab.
2. **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, sotrovimab may have an important impact on mechanical ventilation. **Imprecision: serious.** Very few events – only four patients received invasive mechanical ventilation in the single trial (all in the placebo group).
3. **Imprecision: serious.** Few events (25 total: 4 in the sotrovimab group and 21 in the placebo group); does not meet optimal information size.
4. **Imprecision: serious.** Few events (25 total: 4 in the sotrovimab group and 21 in the placebo group); does not meet optimal information size.
5. **Imprecision: serious.** Few events (25 total: 4 in the sotrovimab group and 21 in the placebo group); does not meet optimal information size.

Clinical Question/ PICO

Population: Patients with non-severe COVID-19
Intervention: Sotrovimab
Comparator: Casirivimab-imdevimab

Outcome Timeframe	Study results and measurements	Comparator Casirivimab- imdevimab	Intervention Sotrovimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality	Odds Ratio 0.53 (CI 95% 0.09 – 2.12) (Randomized controlled)	2 per 1000 Difference:	1 per 1000 1 fewer per 1000 (CI 95% 3 fewer – 0 more)	Moderate Due to serious indirectness and some concerns with imprecision ¹	There is probably little or no difference on mortality.
Mechanical ventilation	Odds Ratio 0 (CI 95% 0 – 0.01) (Randomized controlled)	6 per 1000 Difference:	2 per 1000 4 fewer per 1000 (CI 95% 4 fewer – 0 fewer)	Moderate Due to serious indirectness and some concerns with imprecision ²	There is probably little or no difference on mechanical ventilation.
Admission to hospital	Odds Ratio 0.68 (CI 95% 0.21 – 1.97) (Randomized controlled)	35 per 1000 Difference:	24 per 1000 11 fewer per 1000 (CI 95% 27 fewer – 32 more)	Moderate Due to serious indirectness and some concerns with imprecision ³	There is probably little or no difference in hospitalization.
Infusion reactions	(Randomized controlled)	0 per 1000 Difference:	0 per 1000 0 fewer per 1000 (CI 95% 13 fewer – 13 more)	High	There is little or no difference in infusion reactions.

Outcome Timeframe	Study results and measurements	Comparator Casirivimab- imdevimab	Intervention Sotrovimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
Time to clinical improvement				No data	The effect of sotrovimab 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, the effect on mortality is uncertain. **Imprecision: no serious.** There was only one death (in the placebo group) in the single trial that studied sotrovimab.
2. **Indirectness: serious.** The baseline risk across the entire population is very low, meaning that any impact on mechanical ventilation will be very small. There are some people with much higher baseline risk, which are not easily identifiable. For these patients, whether there is an important difference in mechanical ventilation is uncertain. **Imprecision: no serious.** Very few events – only two patients received invasive mechanical ventilation in the single trial (both in the placebo group).
3. **Indirectness: serious.** Patients at high risk are not easily identified. **Imprecision: no serious.**

6.3.1 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.

Sotrovimab is an Fc-engineered IgG monoclonal antibody that is expected to have a longer half-life than unmodified IgG monoclonal antibodies, but there are no publicly available data regarding its half-life in humans. No published pre-clinical or human pharmacokinetic data were available for review; assessment was therefore based upon public regulatory information and the GSK Product Monograph (52).

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 (52). Neutralization of SARS-CoV-2 (USA WA1/2020) was achieved in Vero E6 cells with an EC90 value of 0.19 µg/mL (53). Sotrovimab serum concentrations in COMET-ICE (single 500 mg IV infusion) provided geometric mean C_{max} (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 (53). 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.

A review manuscript with Vir Biotechnology authors indicates less than 10-fold loss of neutralization for sotrovimab for all tested variants of concern, which did not at the time include Omicron (54).

Information in the [FDA Emergency Use Authorization](#) also 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 (53). Sotrovimab has since been reported to retain activity against Omicron in pseudovirus assays but with higher concentrations being required for neutralization compared the wild-type virus (49). A better understanding of the pharmacokinetic-pharmacodynamic relationship will be need to ascertain the consequences of this reduced activity for efficacy.

Resistance to other monoclonal antibodies deployed as single agents has been described to emerge rapidly in patients but this has not been described clinically for sotrovimab to date. However, an E340A amino acid substitution in the conserved epitope of the spike protein did emerge under a selective pressure in cell culture, and subsequent characterization using a pseudovirus assay resulted in a >100-fold reduction in susceptibility to sotrovimab (53). Sixteen other substitutions introduced into the epitope were also described as reducing neutralization by sotrovimab by between 5.4 and > 297-fold (53). Therefore, resistance to sotrovimab can emerge under experimental conditions but there is uncertainty regarding the speed at which this will occur in patients and the ultimate clinical consequences.

6.4 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 (2). No changes were made for the convalescent plasma recommendations in this ninth version of the guideline.

For patients with non-severe COVID-19

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.

Preference and values

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). One percent 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 (55)(56). 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 to usual care for the outcomes of interest, with certainty ratings. This evidence summary was informed by the LNMA (2) pooling data from 1602 patients in 4 RCTs for the outcome of mortality and 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 1602 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 1365 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 1442 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:** [57], [58], [60], [61].

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:** [57], [58], [61].

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:** [58], [59], [62], [63].

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:** [57],

[59], [62], [63],

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:** [57], [59], [60], [62], [63], [64], [65], [66].

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.

Preference and values

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 to 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 (2), 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 1365 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 1442 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.
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.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Convalescent plasma	Certainty of the Evidence (Quality of evidence)	Plain language summary
Length of hospital stay	Measured by: days Lower better Based on data from: 1015 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: 2859 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:** [60], [62], [63], [64], [65], [66], [67], [68], [69], [70].
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:** [59], [63], [66], [67], [69].
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:** [58], [59], [62], [63].
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:** [57], [59], [62], [63].
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:** [57], [59], [60], [62], [63], [64], [65], [66].
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:** [63].
12. **Imprecision: very serious.**
13. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [62], [63], [66], [67], [68], [69], [70].
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:** [62], [64], [66].
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.

6.4.1 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 (71). 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 (72).

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 mL (73)). 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 (74).

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 (75)). 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.

6.5 Casirivimab-imdevimab (neutralizing monoclonal antibodies) (published 24 September 2021)

Info Box

Recommendations concerning neutralizing monoclonal antibodies (casirivimab-imdevimab) for patients with non-severe, severe or critical COVID-19 were published on 24 September 2021 as the [sixth version](#) of the WHO living guideline and in the BMJ as [Rapid Recommendations](#). It follows the availability of pre-prints of four trials, that are part of the larger adaptive randomized master protocol addressing patients with non-severe illness, and of the RECOVERY trial addressing severe and critically ill patients (9)(10)(11). No changes were made for the casirivimab-imdevimab recommendations in this ninth version of the guideline.

Following the publication of a previous conditional recommendation for casirivimab-imdevimab, additional preclinical evidence has emerged (see Mechanism of action) (76). There is a substantial body of pre-clinical in vitro data, and a confirmatory in vivo evaluation, demonstrating lack of efficacy of casirivimab-imdevimab against the Omicron BA1 variant (see Mechanism of action). As a result, casirivimab-imdevimab is no longer recommended for COVID-19 treatment except in cases where rapid viral genotyping is available and confirms infection with a SARS-CoV-2 variant (such as Delta) that is susceptible to the neutralizing activity of this combination of monoclonal antibodies.

For patients with non-severe COVID-19

Conditional recommendation

Updated

We suggest treatment with casirivimab-imdevimab, conditional to those at highest risk of hospitalization, and where viral genotyping can confirm a susceptible SARS-CoV-2 variant (i.e. excluding Omicron BA1) (*conditional recommendation for*).

- *Whereas casirivimab-imdevimab achieves a substantial reduction in the relative risk of hospitalization, the absolute benefit will be trivial in absolute terms for all but those at highest risk for which the intervention should be reserved.*
- *The panel identified a risk beyond 10% of being hospitalized for COVID-19 to represent a threshold at which most people would want to be treated with casirivimab-imdevimab.*
- *In the absence of credible tools to predict risk for hospitalization in people infected with COVID-19, typical characteristics of people at highest risk include lack of vaccination, older people, or those with immunodeficiencies and/or chronic diseases (e.g. diabetes).*

Practical Info

Dosing and administration route: Intravenous total dose of the monoclonal antibody combination differed in the non-severe trials, ranging from total dose 1200 mg–8000 mg (600 mg–4000 mg each antibody), demonstrating efficacy at all doses, including the lowest tested, 1200 mg total dose (600 mg of each antibody). In the face of limited access and resource considerations, health systems will face choices concerning dose of casirivimab-imdevimab as well as intravenous or subcutaneous injections. Please see the acceptability and feasibility section (under Evidence to Decision) for some deliberations to help in making these choices within the possible range of 1200 mg–2400 mg total dose.

Monitoring: Although the available trials have not convincingly shown that casirivimab-imdevimab results in allergic reactions, the possibility remains. To be administered through an intravenous line containing a sterile in-line or add-on 0.2 micron filter. Following administration, patients should undergo monitoring for severe anaphylaxis.

Evidence To Decision

Benefits and harms

In non-severe patients, casirivimab-imdevimab probably reduces the risk of hospitalization and duration of symptoms. Casirivimab-imdevimab is unlikely to have serious adverse effects, including allergic reactions.

Certainty of the Evidence

Limitations in available empirically developed risk prediction tools for establishing patients' risk of hospitalization represents the major source of indirectness for which the GDG rated down the certainty of the evidence (22). In addition, the GDG felt

that there was some indirectness because of the possible emergence of variants in which effectiveness may be reduced. The GDG thus rated down the certainty of evidence to moderate for hospitalization and duration of symptoms. The GDG rated down evidence certainty to moderate for allergic reactions because of imprecision but considered the finding of no serious adverse effects to represent high certainty evidence.

Preference and values

Applying the agreed values and preferences (see Section 7), the GDG inferred that almost all well-informed patients at typical low risk of hospitalization would decline casirivimab-imdevimab and only those at higher risk (e.g. unvaccinated, older, or immunosuppressed) would choose the treatment.

The limited availability of casirivimab-imdevimab in relation to the number of infected individuals proved a major concern. For non-severe illness, GDG members completed a survey in which they provided their views regarding the magnitude of reduction in hospitalization that would prompt patients to use casirivimab-imdevimab. The panel responses suggested that the majority of patients with a risk of hospitalization above 10%, and thus an absolute risk reduction of approximately 6%, would choose to receive treatment while a majority of those below that risk level would decline treatment. Large majorities of patients with risks substantially higher than 10% would choose to receive treatment and large majorities of those with substantially lower risks would decline.

Resources and other considerations

Acceptability and feasibility

The GDG noted that casirivimab-imdevimab is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. This further supports the guidance that casirivimab-imdevimab be reserved for those at highest risk of hospitalization.

Major feasibility challenges include limited production of casirivimab-imdevimab and, for outpatients, the requirement for intravenous administration. Regarding intravenous administration, it is likely that specialized clinics with adequate amounts of the antibodies and personnel who will ensure safe and effective administration of the intervention will be required. For the intervention to achieve substantial use, health systems will have to address these challenges.

Choosing a dose: Different doses of the monoclonal antibody combination were used in different trials, and health systems will face the choice of which dose to use and this can be informed by values and preferences. If one's priority is to ensure giving as many people as possible the opportunity to benefit from treatment, one might use the lowest effective dose offered in the studies of non-severe patients, 1200 mg total dose (600 mg of each antibody) (77). If one's priority is on ensuring effectiveness in every individual who receives treatment, and minimizing the risk of emergence of resistance, one might use a higher total intravenous dose of 2400 mg (1200 mg of each antibody).

Administration route: A similar value and preference issue arises in choosing between intravenous administration – used in the four trials included in the LNMA (from a larger adaptive randomized master protocol) (78) – and subcutaneous administration, which has been used in the prophylactic trial (79). Intravenous administration will achieve maximum drug concentrations faster than subcutaneous administration; however, both will achieve exposure above the proposed therapeutic threshold. If one's priority is to ensure maximum effectiveness in every individual who receives treatment, one might choose intravenous administration. If one's priority is, in the face of practical difficulties of widespread intravenous administration in the community, to ensure giving as many people as possible the opportunity to benefit from treatment, one might ensure the availability of subcutaneous administration as an alternative. Volumes that can be administered subcutaneously are limited to the lowest dose, which is a total dose 1200 mg (600 mg of each antibody).

Justification

A combination of the evidence, values and preferences, and feasibility contributed to the conditional recommendation for the use of casirivimab-imdevimab only in patients with non-severe COVID-19 at highest risk of hospitalization. Although there is moderate certainty evidence of a substantial relative risk reduction in hospitalization, only a minority of patients who are at highest risk are likely to achieve important benefit. In routine care of those with non-severe COVID-19, there is a lack of tools to reliably identify those at highest risk of hospitalization. This clinical complexity, combined with the limited availability of the drug

and need for parenteral administration route for a group of patients who are typically cared for in the community, present a range of challenges for care that need to be addressed by health care systems.

Applicability

The applicability of this recommendation to children is currently uncertain, as the included RCTs enrolled adults. The GDG had no reason to think that children with COVID-19 would respond any differently to treatment with casirivimab-imdevimab. 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: Casirivimab-imdevimab
Comparator: Standard care

Summary

Evidence summary

For patients with non-severe COVID-19, the LNMA (2) pooled data from four trials that enrolled 4722 patients randomized to casirivimab-imdevimab or usual care (78). All trials were registered and presented in pre-prints when the data were reviewed by the GDG. The [Table](#) shows trial characteristics.

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

Specific considerations regarding baseline risk estimates informing absolute estimates of effect

For hospital admission, the key outcome driving the recommendation in favour of casirivimab-imdevimab, we used a baseline risk of 4.2% (42 in 1000) based on the median of the control arm of the four RCTs contributing to the evidence. These trials recruited patients at elevated risk of being hospitalized to increase statistical power in detecting potential treatment effects. The baseline risk is therefore appreciably higher than the risk for many patients with non-severe COVID-19.

Subgroup analysis

We found no evidence of subgroup effects on age or time from onset of illness in patients with non-severe COVID-19.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Casirivimab- imdevimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality	Odds Ratio 0.57 (CI 95% 0.26 – 1.2) Based on data from 4722 participants in 4 studies. (Randomized controlled)	2 per 1000 Difference:	1 per 1000 1 fewer per 1000 (CI 95% 1 fewer – 0 fewer)	Moderate Due to serious indirectness ¹	Casirivimab-imdevimab do not have an important effect on mortality.
Mechanical ventilation	Odds Ratio 0.22 (CI 95% 0.03 – 1.21) Based on data from 3432 participants in 2 studies. (Randomized controlled)	4 per 1000 Difference:	1 per 1000 3 fewer per 1000 (CI 95% 4 fewer – 1 more)	Moderate Due to serious indirectness ²	Casirivimab-imdevimab probably do not have an important effect on mechanical ventilation.
Admission to	Odds Ratio 0.29 (CI 95% 0.17 – 0.48)	35 per 1000	10 per 1000	Moderate	Casirivimab-imdevimab probably reduce

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Casirivimab- imdevimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
hospital Risk in trials	Based on data from 4722 participants in 4 studies. (Randomized controlled)	Difference:	25 fewer per 1000 (CI 95% 29 fewer – 18 fewer)	Due to serious indirectness ³	admission to hospital.
Admission to hospital Higher risk	Odds Ratio 0.29 (CI 95% 0.17 – 0.48) Based on data from 4722 participants in 4 studies. (Randomized controlled)	60 per 1000 Difference:	18 per 1000 42 fewer per 1000 (CI 95% 49 fewer – 30 fewer)	Moderate Due to serious indirectness ⁴	Casirivimab-imdevimab probably reduce admission to hospital.
Admission to hospital Highest risk	Odds Ratio 0.29 (CI 95% 0.17 – 0.48) Based on data from 4722 participants in 4 studies. (Randomized controlled)	100 per 1000 Difference:	31 per 1000 69 fewer per 1000 (CI 95% 81 fewer – 49 fewer)	Moderate Due to serious indirectness ⁵	Casirivimab-imdevimab probably reduce admission to hospital.
Adverse effects leading to drug discontinuation	Based on data from 5284 participants in 4 studies. (Randomized controlled)	2 per 1000 Difference:	1 per 1000 1 fewer per 1000 (CI 95% 2 fewer – 1 more)	High	Casirivimab-imdevimab do not result in an important increase in adverse effects leading to drug discontinuation.
Allergic reactions	Based on data from 15 406 participants in 4 studies. (Randomized controlled)	3 per 1000 Difference:	9 per 1000 6 more per 1000 (CI 95% 1 fewer – 29 more)	Moderate Due to serious imprecision ⁶	Casirivimab-imdevimab probably do not result in an important increase in allergic reactions.
Time to symptom improvement	Lower better Based on data from: 3084 participants in 2 studies. (Randomized controlled)	14 (Mean) Difference:	9.9 (Mean) MD 4.1 fewer (CI 95% 5.7 fewer – 1.8 fewer)	Moderate Due to serious indirectness ⁷	Casirivimab-imdevimab probably reduce time to symptom improvement.
Duration of hospitalization (not in hospital at baseline)	Lower better Based on data from: 111 participants in 2 studies. (Randomized controlled)	9.6 (Mean) Difference:	8.2 (Mean) MD 1.4 fewer (CI 95% 4.6 fewer – 1.8 more)	Low Due to very serious imprecision ⁸	Casirivimab-imdevimab may not have an important impact on duration of hospitalization.

1. **Indirectness: serious.** There is substantial variability in baseline risk of death between patients. Casirivimab-imdevimab may confer an important benefit in patients at higher risk of death.
2. **Indirectness: serious.** There is substantial variability in baseline risk of mechanical ventilation between patients. Casirivimab-imdevimab may confer an important benefit in patients at higher risk of mechanical ventilation.
3. **Indirectness: serious.** Differences between the population of interest and those studied: the predominant strains currently circulating are not the same as the ones that were circulating during the studies.
4. **Indirectness: serious.** Differences between the population of interest and those studied: the predominant strains currently circulating are not the same as the ones that were circulating during the studies.
5. **Indirectness: serious.** Differences between the population of interest and those studied: the predominant strains currently circulating are not the same as the ones that were circulating during the studies.
6. **Imprecision: serious.**
7. **Indirectness: serious.** Differences between the population of interest and those studied: the predominant strains currently circulating are not the same as the ones that were circulating during the studies.
8. **Imprecision: very serious.**

For patients with severe or critical COVID-19

Conditional recommendation

Updated

We suggest treatment with casirivimab-imdevimab, conditional to those with seronegative status, and where viral genotyping can confirm a susceptible SARS-CoV-2 variant (i.e. excluding omicron BA1) (*conditional recommendation for*).

- *With benefits of casirivimab-imdevimab observed only in patients with seronegative status, clinicians will need to identify these patients by credible tests available at the point of care to appropriately apply this recommendation (see Evidence to Decision section).*
- *Treatment with casirivimab-imdevimab is in addition to the current standard of care, which includes corticosteroids and IL-6 receptor blockers.*

Practical Info

Dosing and administration route: Intravenous dosing of the monoclonal antibody combination in the RECOVERY trial that enrolled severe and critical COVID-19 was a total dose of 8000 mg (4000 mg for each antibody), whereas the dose differed in the four trials in non-severe patients (from a larger adaptive randomized master protocol), ranging from intravenous total dose of 1200 mg–8000 mg. In the face of limited access and resource considerations, health systems will face a choice concerning the dose of casirivimab-imdevimab. Please see the acceptability and feasibility section (under Evidence to Decision) for deliberations to help in making these choices within the possible range of 2400 mg–8000 mg total dose.

Diagnostic testing: Tests to identify patients with seronegative status at the time patients present with severe or critical COVID-19 warrant rapid serological tests with adequate performance characteristics. Health care systems would need to implement such tests, as outlined in the acceptability and feasibility section.

Monitoring: Although the available trials have not convincingly shown that casirivimab-imdevimab results in allergic reactions, the possibility remains. Administer through an intravenous line containing a sterile in-line or add-on 0.2 micron filter. Following infusion, patients should undergo monitoring for allergic reactions.

Evidence To Decision

Benefits and harms

In the overall population of patients with severe and critical COVID-19, casirivimab-imdevimab may not have an impact on mortality and the impact on mechanical ventilation and duration of hospitalization is very uncertain.

A credible subgroup effect demonstrated that casirivimab-imdevimab probably reduces mortality in patients who are seronegative, with the absolute effects ranging from 39 fewer per 1000 (95% CI 62 fewer-13 fewer) in the severely ill to 69

fewer (95% CI 110 fewer-23 fewer) in the critically ill. In seronegative patients, the intervention possibly reduces the need for mechanical ventilation (absolute effect estimate 42 fewer per 1000; 95% CI 74 fewer-6 fewer). Aside from the credible subgroup effect for serological status, we found no evidence of subgroup effects on age or time from onset of illness in the non-severe, or on age, time from onset of illness, and severity in the severe and critically ill.

Certainty of the Evidence

In patients with severe and critical COVID-19, evidence for mortality was of low certainty because of imprecision and high likelihood that casirivimab-imdevimab has, in the seronegative and seropositive patients included in the overall group, very different effects. In this population, the evidence regarding the impact of the intervention on need for mechanical ventilation and duration of hospitalization was very low certainty given additional concerns with risk of bias.

For patients with severe and critical COVID-19 who are seronegative, evidence for mortality was rated as moderate as a result of concerns regarding imprecision (the confidence interval includes effects as small as 14 in 1000 that some patients may perceive as trivial) and indirectness (variants may emerge in which casirivimab-imdevimab antibodies may have reduced effect). For mechanical ventilation, the GDG noted risk of bias from lack of blinding as an additional concern, resulting in low certainty evidence. For duration of hospitalization, the GDG also found very serious imprecision, resulting in very low certainty evidence.

Preference and values

Applying the agreed values and preferences (see Section 7), the GDG inferred that most if not all well-informed patients with severe or critical COVID-19 and seronegative status would choose to receive casirivimab-imdevimab. Other patients – those whose are seropositive or whose status is uncertain – are likely to decline the intervention.

Although the GDG focused on an individual patient perspective, they also considered a population perspective in which feasibility, acceptability, equity and cost are important considerations. In this case, feasibility concerns played an important role in the conditional recommendation. For the severe and critical patients, both limited availability of therapeutics and the requirement for serological testing as part of clinical decision-making to identify the seronegative patients proved important.

Resources and other considerations

Cost and availability

Given the cost and availability of casirivimab-imdevimab, and the challenges associated with serological testing, the obstacles to ensuring access in low- and middle-income countries may prove formidable. Thus, the panel's suggestion that patients who are seronegative receive the intervention may exacerbate health inequity. On the other hand, given the demonstrated benefits for patients, the recommendations should provide a stimulus to engage all possible mechanisms to improve global access to the intervention. Individual countries may formulate their guidelines considering available resources and prioritize treatment options accordingly.

Acceptability and feasibility

Supply of casirivimab-imdevimab is likely to be limited, raising accessibility and possibly rationing challenges. In addition, benefit requires identification of serological status at the time patients present with severe or critical COVID-19. The availability of rapid and accurate serological tests as well as dosing and administration route for the drug are therefore key factors to consider for health care systems.

Rapid serological tests: Tests with performance characteristics similar to the reference standard test used to characterize seronegative patients in the RECOVERY trial, i.e. the Oxford fluorescent-based ELISA assay for serum IgG against the SARS-CoV-2 spike protein, with an arbitrary cut-off determined by a panel of positive controls, are available and potentially affordable. Some lateral flow assays may be suitable and can usually be performed in several minutes (80)(81)(82). Health care systems must, however, gain expertise in choosing and implementing a rapid test or test, choosing those most applicable to their setting..

Choosing a dose: The clinical trial in severe and critical patients (RECOVERY) tested a total dose of 8000 mg (4000 mg of each antibody) casirivimab-imdevimab; clinical trials in non-severe patients have used total doses of 1200 mg–8000 mg (600 mg–4000 mg of each) with similar effects on decreasing the need for hospitalization. Pharmacokinetic profiles of casirivimab-imdevimab in non-severe with COVID-19 are available at total doses of 1200 mg–8000 mg (600 mg–4000 mg of each monoclonal antibody) (78). This study demonstrated that the target therapeutic concentrations were achieved rapidly in serum and maintained for 28 days even at the lowest total dose of 1200 mg (600 mg of each antibody), although serum concentrations of the drug were noted to vary considerably between individuals. Therefore, using doses lower than used in the RECOVERY trial (8000 mg total dose) for treatment of severely and critically ill patients may achieve the same benefit. On the other hand, it is theoretically plausible but untested that pharmacokinetic differences in severe and critical patients, when compared with non-severe, may reduce drug exposure (see Mechanism of action). This would increase the risk of sub-optimal drug exposure in some individuals, which in turn could increase the risk of therapeutic failure and the emergence of viral resistance.

In the absence of clinical data on treatment of severe and critical patients with doses lower than 8000 mg, making a choice on which dose to use can be informed by values and preferences. If one's priority is ensuring effectiveness in every individual who receives treatment, and minimizing the risk of emergence of resistance, one might use the total intravenous dose of 8000 mg (4000 mg of each antibody). If one's priority is, in the face of limited drug availability and high cost, giving as many people as possible an opportunity to benefit from treatment, one might use an intravenous dose as low as a total of 2400 mg (1200 mg of each antibody).

At a time of drug shortage, it may be necessary to prioritize use of casirivimab-imdevimab through clinical triage. One possibility is to prioritize 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 0.85 for mortality) with casirivimab-imdevimab in seronegative patients, the absolute risk reduction for mortality in the critically ill would be 69 fewer deaths per 1000 (95% CI 110 to 23 fewer deaths) and in the severely ill would be 39 fewer deaths per 1000 (95% CI 62 to 13 fewer deaths).

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

Justification

In patients with severe or critical illness, the conditional recommendation in favour of casirivimab-imdevimab use reflects the likelihood that any benefits are restricted to patients who are seronegative. In the RECOVERY trial, which provided all the evidence in severe and critical patients, serological status at baseline was assessed in a pre-planned but retrospective analysis using a laboratory-based anti-spike protein assay. In order to translate the trial findings into clinical practice, assessment of serological status will need to become integrated into a clinical decision pathway *before* treatment is administered. This implies rapid identification of serological status at the time of presentation of severe or critical illness to guide use in this population.

Several rapid and relatively inexpensive tests with adequate performance characteristics are available and should see increasing use in settings in which casirivimab-imdevimab is available for administration to these patients.

Applicability

None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. Fortunately, very few children become critically ill with COVID-19. For those who do and are seronegative, it is possible they may benefit from casirivimab-imdevimab. Lack of data precluded the GDG from making specific recommendations for other special populations, such as pregnant women.

Clinical Question/ PICO

Population:	Patients with severe or critical COVID-19, seronegative
Intervention:	Casirivimab-imdevimab
Comparator:	Standard care

Summary

Evidence summary

The LNMA was informed by one large trial (RECOVERY) in patients with severe and critical illness that enrolled 9785 patients, most of whom received corticosteroids (83). The trial was registered and presented in pre-prints when the data was reviewed by the GDG. The [Table](#) shows trial characteristics.

The GRADE Summary of Findings table shows the relative and absolute effects of casirivimab-imdevimab compared to usual care for the outcomes of interest in patients with severe and critical COVID-19 and seronegative status, with certainty ratings.

Specific considerations regarding baseline risk estimates informing absolute estimates of effect

In severe and critical COVID-19 patients, 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.

To inform baseline risk estimates for mortality in seronegative patients, we identified the control arm of the RECOVERY trial as the best source. For patients with seronegative status, risk of death in both severe (26%; 260 per 1000) and critical (46%; 460 per 1000) illness is substantially higher than for the overall population. Thus, seronegative patients represent a very high risk population, leading to substantial absolute risk reductions in mortality (3.9% in the severe and 6.9% in the critical) despite the modest 15% relative risk reduction.

Subgroup analysis

A highly credible subgroup effect demonstrated that casirivimab-imdevimab likely reduces mortality in patients who are seronegative but not in those who are seropositive.

The credibility of the subgroup effect was evaluated using the ICEMAN tool (84). The credibility of the subgroup effect was strongly supported by: an *a priori* hypothesis with a specified direction; a small number of such hypotheses; evidence based on a within-study comparison; a suggestion of a similar subgroup effect in mechanical ventilation; and an interaction p-value of 0.001.

Fig. 2 presents the forest plot depicting the point estimate and confidence interval around the effects on mortality in patients with seropositive and seronegative status, demonstrating benefit in those with seronegative status, suggesting harm in those with seropositive status, and no overlap in the confidence intervals, a result corresponding to the p=0.001 in the test of interaction (83).

Fig. 2. Mortality, in seropositive and seronegative patients with severe and critical COVID-19

Outcome, subgroup	REGEN-COV	Usual care		RR (95% CI)
Death within 28 days ($\chi^2_1 = 10.1$; p=0.001)				
Seronegative	396/1633 (24%)	451/1520 (30%)		0.80 (0.70–0.91)
Seropositive	411/2636 (16%)	383/2636 (15%)		1.09 (0.95–1.26)
Unknown	137/570 (24%)	192/790 (24%)		0.98 (0.78–1.22)
All participants	944/4839 (20%)	1026/4946 (21%)		0.94 (0.86–1.03)

CI: confidence interval, RR: relative risk.

Very low certainty evidence raises the possibility of shorter hospitalization in seronegative patients. Aside from the reported subgroup effects on serological status, we found no evidence of subgroup effects on age, time from onset of illness, and severity (comparing severe and critically ill patients).

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Casirivimab- imdevimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality Severe disease	Relative Risk 0.85 (CI 95% 0.76 – 0.95)	260 per 1000	221 per 1000	Moderate Due to concerns	Casirivimab-imdevimab probably reduce

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Casirivimab- imdevimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
	Based on data from 2823 participants in 1 study. (Randomized controlled)	Difference:	39 fewer per 1000 (CI 95% 62 fewer – 13 fewer)	with imprecision and indirectness ¹	mortality.
Mortality Critical disease	Relative Risk 0.85 (CI 95% 0.76 – 0.95) Based on data from 2823 participants in 1 study. (Randomized controlled)	460 per 1000 Difference:	391 per 1000 69 fewer per 1000 (CI 95% 110 fewer – 23 fewer)	Moderate Due to concerns with imprecision and indirectness ²	Casirivimab-imdevimab probably reduce mortality.
Mechanical ventilation	Relative Risk 0.87 (CI 95% 0.77 – 0.98) Based on data from 2410 participants in 1 study. (Randomized controlled)	320 per 1000 Difference:	278 per 1000 42 fewer per 1000 (CI 95% 74 fewer – 6 fewer)	Low Due to concerns with risk of bias, imprecision, and indirectness ³	Casirivimab-imdevimab may reduce mechanical ventilation.
Duration of hospitalization	Based on data from: 3153 participants in 1 study. (Randomized controlled)	The median duration of hospital stay was 4 days shorter with casirivimab-imdevimab (13 days vs. 17 days).		Very low Due to serious risk of bias, serious indirectness, and very serious imprecision ⁴	The impact on duration of hospitalization is very uncertain.

1. **Imprecision: serious.** Single study.
2. **Imprecision: serious.** Single study.
3. **Risk of bias: serious. Imprecision: serious.**
4. **Risk of bias: serious. Indirectness: serious. Imprecision: very serious.**

Clinical Question/ PICO

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

Summary

Evidence summary

The NMA evidence summary was informed by one large trial (RECOVERY) in patients with severe and critical illness that enrolled 9785 patients, most of whom received corticosteroids (83). The trial was registered and presented in preprints when the data was reviewed by the GDG. The [Table](#) shows trial characteristics.

The GRADE Summary of Findings table shows the relative and absolute effects of casirivimab-imdevimab compared to usual care for the outcomes of interest in patients with severe and critical COVID-19, with certainty ratings.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Casirivimab- imdevimab	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality Critical or severe disease	Odds Ratio 0.94 (CI 95% 0.86 – 1.03) Based on data from 9785 participants in 1 study. (Randomized controlled)	130 per 1000 Difference:	122 per 1000 8 fewer per 1000 (CI 95% 18 fewer – 4 more)	Low Due to serious indirectness and imprecision ¹	Casirivima-imdevimab may not have an important effect on mortality.
Mechanical ventilation	Odds Ratio 0.95 (CI 95% 0.87 – 1.04) Based on data from 6637 participants in 1 study. (Randomized controlled)	86 per 1000 Difference:	82 per 1000 4 fewer per 1000 (CI 95% 11 fewer – 3 more)	Very low Due to serious risk of bias, indirectness, and imprecision ²	The impact on mechanical ventilation is very uncertain.
Allergic reactions	Based on data from 15 406 participants in 4 studies. (Randomized controlled)	3 per 1000 Difference:	9 per 1000 6 more per 1000 (CI 95% 1 fewer – 29 more)	Moderate Due to serious imprecision ³	Casirivimab-imdevimab probably do not result in an important increase in allergic reactions.
Adverse effects leading to drug discontinuation	Based on data from 5284 participants in 4 studies. (Randomized controlled)	2 per 1000 Difference:	1 per 1000 1 fewer per 1000 (CI 95% 2 fewer – 1 more)	High	Casirivimab-imdevimab do not result in an important increase in adverse effects leading to drug discontinuation.
Duration of hospitalization	Based on data from: 9785 participants in 1 study. (Randomized controlled)	Patients in both groups had the same median duration of hospitalization (10 days).		Very low Due to serious risk of bias and very serious imprecision ⁴	The impact on duration of hospitalization is very uncertain.

1. **Indirectness: serious. Imprecision: serious.**
2. **Risk of bias: serious. Indirectness: serious. Imprecision: serious.**
3. **Imprecision: serious.**
4. **Risk of bias: serious. Imprecision: very serious.**

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 (85) and have demonstrated antiviral activity in rhesus macaques and Syrian golden hamsters (86). Pharmacokinetic data in patients with non-severe COVID-19 show that antiviral concentrations of both antibodies 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). 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 (79). Half-lives range from 25 to 37 days for both antibodies. Data are currently unavailable for the pharmacokinetics of casirivimab and imdevimab in

severe and critical COVID-19, which are important because serum concentrations of other monoclonal antibodies have been reported to be lower during systemic inflammation and correlated with albumin and CRP levels (87). Data available also suggest that when delivered in combination, activity remains for currently circulating variants of concern (88).

While the mechanism is plausible, 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 neutralisation of different variants by monoclonal antibodies are collated on the NIH NCATS OpenData Portal (<https://opendata.ncats.nih.gov/variant/activity>). Several reports have demonstrated that in vitro neutralisation of pseudovirus containing the BA1 omicron spike protein and in vitro neutralisation of authentic BA1 omicron virus is dramatically reduced or lost for casirivumab and imdevimab when studied individually, and completely lost when both monoclonal antibodies are combined. Furthermore, the combination of casirivumab and imdevimab has no impact upon subgenomic viral RNA in the lungs or nasal turbinate of K18 human ACE2 transgenic mice infected with BA1 omicron (<https://www.biorxiv.org/content/10.1101/2022.01.23.477397v1.full.pdf+html>). Therefore, currently available preclinical data do not support activity of the casirivumab and imdevimab combination against the BA1 omicron variant.

6.6 IL-6 receptor blockers (published 6 July 2021)

Info Box

The recommendation concerning IL-6 receptor blockers (tocilizumab or sarilumab) was published on 6 July 2021 as the [fifth version](#) of the WHO living guideline and in the BMJ as [Rapid Recommendations](#). 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. No changes were made for the IL-6 receptor blocker recommendation in this ninth version of the guideline.

WHO has made a strong recommendation for JAK inhibitors, specifically baricitinib, in patients with severe and critical COVID-19. An IL-6 receptor blocker and baricitinib should not be given together and should be viewed as alternatives. These new considerations are provided under 'Justification' for the recommendation for IL-6 receptor blockers, and are unchanged in this ninth version of the guideline.

For patients with severe or critical COVID-19

Strong recommendation for

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 6.11), and we recommend patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers.*
- *Baricitinib, a JAK inhibitor, is now recommended for the treatment of patients with severe and critical COVID-19 (see Section 6.2). An IL-6 receptor blocker and baricitinib should not be given together and should be viewed as alternatives. The choice of whether to use baricitinib or an IL-6 receptor blocker depends on availability as well as clinical and contextual factors (see Justification).*

Practical Info

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

Duration: Tocilizumab and sarilumab are administered as single intravenous doses, typically over 1 hour. A second dose may be administered 12 to 48 hours after the first dose; this was offered variably in major clinical trials at the discretion of treating

clinicians if a clinical response was felt to be inadequate. Duration of concurrent systemic corticosteroids is typically up to 10 days, though may vary between 5 and 14 days.

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

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

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

Evidence To Decision

Benefits and harms

IL-6 receptor blockers reduce mortality and need for mechanical ventilation based on high certainty evidence. Low certainty evidence suggests they may also reduce duration of mechanical ventilation and hospitalization (3)(89)(90).

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 (84). 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.

Preference and values

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

WHO has recently made a strong recommendation for baricitinib in patients with severe and critical COVID-19. Both classes of drugs are immune modulators with overlapping effects on immune responses. There is therefore a reasonable possibility that their effects on COVID-19 will not be additive. Moreover, it is possible that when given together, adverse effects, including secondary bacterial or fungal infection, will be greater. In the absence of evidence of incremental benefit of the drugs when given together, the GDG advises that clinicians do not administer the drugs together.

See justification section for JAK inhibitors and related Summary of Findings table (see Research evidence) for more detailed discussion regarding selecting between therapies.

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 2659 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 2434 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.

Outcome Timeframe	Study results and measurements	Comparator IL-6 receptor blockers	Intervention Baricitinib	Certainty of the Evidence (Quality of evidence)	Plain language summary
Adverse effects leading to drug discontinuation	Based on data from 2309 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: 2652 participants in 3 studies. (Randomized controlled)	8.1 days (Median) Difference:	11.2 days (Mean) MD 3.1 more (CI 95% 3.8 fewer – 9.9 more)	Very low Due to serious risk of bias, serious inconsistency, and very serious imprecision ⁴	The impact on hospital length of stay is very uncertain.
Duration of mechanical ventilation	Lower better Based on data from: 328 participants in 2 studies. (Randomized controlled)	13.8 days (Median) Difference:	11.6 days (Mean) MD 2.2 fewer (CI 95% 5.3 fewer – 0.7 fewer)	Low Due to serious risk of bias and imprecision ⁵	Baricitinib may reduce duration of mechanical ventilation.
Time to clinical stability	Lower better Based on data from: 2558 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.

- Imprecision: serious.** The credible interval includes no important difference.
- 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.
- Imprecision: serious.** The credible interval includes small but important harm.
- 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.
- 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.
- 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:	Interleukin-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) (90). 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 (90). 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 to 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 (90). 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 to sarilumab+steroids versus steroids alone (OR 0.92, 95% CI 0.61–1.38). In addition to these subgroup data, the GDG reviewed head-to-head data from REMAP-CAP investigators which demonstrated no difference between tocilizumab as compared with sarilumab in a population of patients all receiving corticosteroids (36.5% mortality with tocilizumab, 33.9% mortality with sarilumab). The NMA estimate of tocilizumab+steroids versus sarilumab+steroids, incorporating both direct and indirect data, provided moderate certainty data of no difference between the drugs (OR 1.07, 95% CI 0.86–1.34) (1)(3).

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention IL-6 receptor blockers	Certainty of the Evidence (Quality of evidence)	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 5686 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.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention IL-6 receptor blockers	Certainty of the Evidence (Quality of evidence)	Plain language summary
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% 9 fewer – 67 more)	Very low Due to serious risk of bias and very serious imprecision ⁴	The effect of IL-6 receptor blockers on adverse events leading to discontinuation is uncertain.
Bacterial infections	Odds Ratio 0.95 (CI 95% 0.72 – 1.29) Based on data from 3548 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: 1189 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: 6665 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 [3] . **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:** [3].

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

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

6. **Risk of bias: serious.** We downgraded for some concerns regarding risk of bias due to lack of blinding. **Imprecision: serious.** We downgraded as the lower limit of the confidence interval was close to the null.

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

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.

6.7 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 for the ivermectin recommendation in this ninth 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 (91)(92). 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.

Preference and values

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

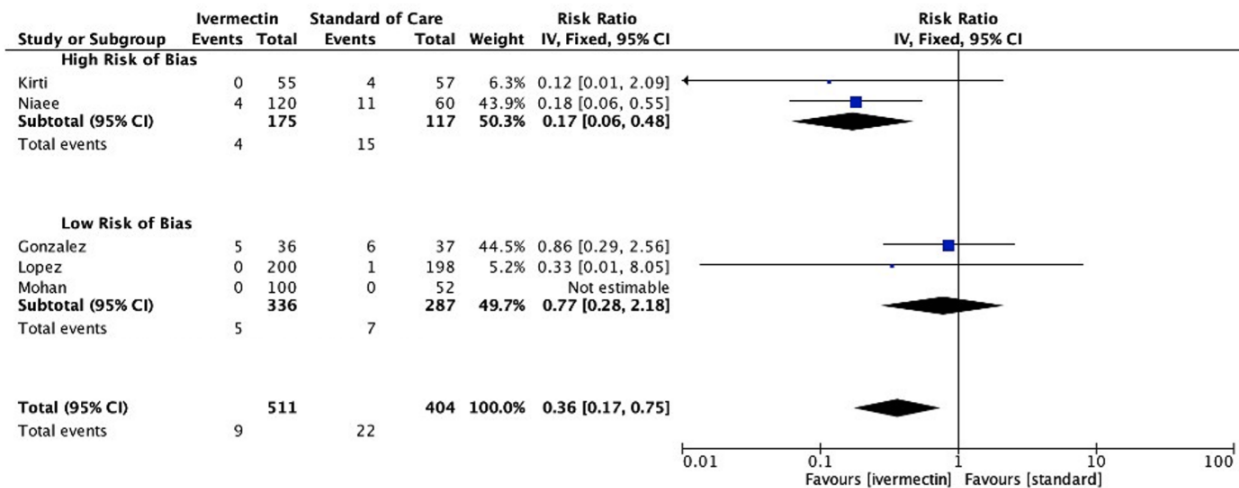
When moving from evidence to a recommendation on the use of ivermectin in patients with COVID-19 only in the context of a clinical trial, the GDG emphasized the high degree of uncertainty in the most critical outcomes such as mortality and need for mechanical ventilation. It also noted the evidence suggesting 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 (93)(94)(95)(96)(97)(98)(99). 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 (93)(94) were at high risk of bias, due to inadequate blinding. One of these two trials (93) 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. 3), 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 (91) due to a lack of detailed description of blinding or randomization and the lack of a publicly available study protocol (figure not shown).

Fig. 3. 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 (100). 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 (101)(102)(103)(104).

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 (84).

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	70 per 1000	14 per 1000	Very low Due to serious risk of bias and very serious imprecision ²	The effect of ivermectin on mortality is uncertain.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Ivermectin	Certainty of the Evidence (Quality of evidence)	Plain language summary
	1419 participants in 7 studies. ¹ (Randomized controlled)				
		Difference:	56 fewer per 1000 (CI 95% 63 fewer – 44 fewer)		
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	10 per 1000	Very low Due to very serious imprecision and publication bias ³	The effect of ivermectin on mechanical ventilation is uncertain.
		Difference:	10 fewer per 1000 (CI 95% 18 fewer – 15 more)		
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	618 per 1000	Low Due to serious inconsistency and imprecision ⁴	Ivermectin may increase or have no effect on viral clearance.
		Difference:	118 more per 1000 (CI 95% 13 fewer – 241 more)		
Hospital admission (outpatients only)	Odds Ratio 0.36 (CI 95% 0.08 – 1.48) Based on data from 398 participants in 1 study. (Randomized controlled)	50 per 1000	18 per 1000	Very low Due to extremely serious imprecision ⁵	The effect of ivermectin on hospital admission is uncertain.
		Difference:	32 fewer per 1000 (CI 95% 47 fewer – 23 more)		
Serious adverse events	Odds Ratio 3.07 (CI 95% 0.77 – 12.09) Based on data from 584 participants in 3 studies. (Randomized controlled)	9 per 1000	27 per 1000	Low Due to very serious imprecision ⁶	Ivermectin may increase the risk of serious adverse events leading to drug discontinuation.
		Difference:	18 more per 1000 (CI 95% 2 fewer – 89 more)		
Time to clinical improvement	Measured by: days Lower better Based on data from: 633 participants in 2 studies. (Randomized controlled)	11 days (Mean)	10.5 days (Mean)	Low Due to very serious imprecision ⁷	Ivermectin may have little or no difference on time to clinical improvement.
		Difference:	MD 0.5 fewer (CI 95% 1.7 fewer – 1.1 more)		
Duration of hospitalization	Measured by: days Lower better Based on data from: 252 participants in 3 studies. (Randomized controlled)	12.8 days (Mean)	11.7 days (Mean)	Very low Due to serious imprecision, inconsistency and serious risk of bias ⁸	The effect of ivermectin on hospital length of stay is uncertain.
		Difference:	MD 1.1 fewer (CI 95% 2.3 fewer – 0.1 more)		

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Ivermectin	Certainty of the Evidence (Quality of evidence)	Plain language summary
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.

6.7.1 Mechanism of action

Ivermectin is an antiparasitic agent that interferes with nerve and muscle function of helminths through binding glutamate-gated chloride channels (105). 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 (106)(107)(108). Ivermectin had no impact on SARS-CoV-2 viral RNA in the Syrian golden hamster model of SARS-CoV-2 infection (109). 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 (110)(111)(112)(113)(114). 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 (115), and has benefits in murine models of atopic dermatitis and allergic asthma (116)(117). 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 (118), 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 (109). 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.

6.8 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 for the hydroxychloroquine recommendation in this ninth version of the guideline.

For patients with COVID-19, regardless of disease severity

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).

Preference and values

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 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

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 Hydroxychloro quine	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 6379 participants in 5 studies. (Randomized controlled)	105 per 1000 Difference:	123 per 1000 18 more per 1000 (CI 95% 16 fewer – 70 more)	Moderate Due to borderline risk of bias and serious imprecision ³	Hydroxychloroquine probably does not reduce mechanical ventilation.
Viral clearance 7 days	Odds Ratio 1.08 (CI 95% 0.25 – 4.78)	483 per 1000	502 per 1000	Very low Due to very	The effect of hydroxychloroquine on

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Hydroxychloro quine	Certainty of the Evidence (Quality of evidence)	Plain language summary
	Based on data from 280 participants in 4 studies. ⁴ (Randomized controlled)	Difference:	19 more per 1000 (CI 95% 294 fewer – 334 more)	serious imprecision ⁵	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 study. (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 3287 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 1429 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 study. (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 Hydroxychloro quine	Certainty of the Evidence (Quality of evidence)	Plain language summary
Duration of hospitalization	Lower better Based on data from: 5534 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.**

6.9 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 for the lopinavir/ritonavir recommendation in this ninth version of the guideline.

For patients with COVID-19, regardless of disease severity

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).

Preference and values

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 to 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 8061 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 7579 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 study.	11 days (Mean)	10 days (Mean)	Very low Due to serious risk of bias and very serious imprecision ⁹	The effect of lopinavir/ ritonavir improves on time to clinical improvement is very uncertain.

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)		
Duration of hospitalization	Lower better Based on data from: 5239 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.

6.10 Remdesivir (published 20 November 2020)

Info Box

The recommendation concerning remdesivir was published 20 November 2020 as the [second 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 remdesivir, hydroxychloroquine and lopinavir/ritonavir in hospitalized patients with COVID-19 (15). No changes were made for the remdesivir recommendation in this ninth version of the guideline. Of note, this recommendation is under review given new trials, and an update is planned in the next iteration of this guideline. The current recommendation provided is based on the initial assessment made by the GDG, and does not represent best current evidence.

For patients with COVID-19, regardless of disease severity

Conditional recommendation against

In review

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

Practical Info

The GDG made a conditional recommendation against using remdesivir for treatment of hospitalized patients with COVID-19. If administration of remdesivir is considered, it should be noted that its use is contraindicated in those with liver (ALT > 5 times normal at baseline) or renal (eGFR < 30 mL/minute) dysfunction. To date, it can only be administered intravenously, and it has relatively limited availability.

Evidence To Decision

Benefits and harms

The GDG panel found a lack of evidence that remdesivir improved outcomes that matter to patients such as reduced mortality, need for mechanical ventilation, time to clinical improvement and others. However, the low certainty evidence for these outcomes, especially mortality, does not prove that remdesivir is ineffective; rather, there is insufficient evidence to confirm that it improves patient-important outcomes.

There was no evidence of increased risk of SAEs from the trials. However, further pharmacovigilance is needed because SAEs are commonly underreported and rare events could be missed, even in large RCTs.

A subgroup analysis indicated that remdesivir treatment possibly increased mortality in the critically ill and possibly reduced mortality in the non-severely and severely ill. The panel judged the overall credibility of this subgroup effect (evaluated using the ICEMAN tool) to be insufficient to make subgroup recommendations. The overall low certainty evidence on the benefits and harms of remdesivir, driven by risk of bias and imprecision limitations in the included studies, also contributed to the judgment.

Certainty of the Evidence

The evidence is based on a linked systematic review and NMA of four RCTs; pooling data from 7333 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 low certainty in the estimates of effect for all patient-important outcomes across benefits and harms, mostly driven by risk of bias and imprecision (wide confidence intervals which do not exclude important benefit or harm). There was very low certainty evidence for viral clearance and delirium.

Preference and values

Applying the agreed values and preferences (see Section 7), the GDG inferred that most patients would be reluctant to use remdesivir given the evidence left high uncertainty regarding effects on mortality and the other prioritized outcomes. This was particularly so as any beneficial effects of remdesivir, if they do exist, are likely to be small and the possibility of important harm remains. The panel acknowledged, however, that values and preferences are likely to vary, and there will be patients and clinicians who choose to use remdesivir given the evidence has not excluded the possibility of benefit.

Resources and other considerations

A novel therapy typically requires higher certainty evidence of important benefits than currently available for remdesivir, preferably supported wherever possible by cost-effectiveness analysis. In the absence of this information, 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. It was noted that remdesivir is administered only by the intravenous route currently, and that global availability is currently limited.

Justification

When moving from evidence to the conditional recommendation against the use of remdesivir for patients with COVID-19, the panel emphasized the evidence of possibly no effect on mortality, need for mechanical ventilation, recovery from symptoms and other patient-important outcomes, albeit of low certainty; it also noted the anticipated 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).

Importantly, given the low certainty evidence for these outcomes, the panel concluded that the evidence did not prove that remdesivir has no benefit; rather, there is no evidence based on currently available data that it improves patient-important outcomes. Especially given the costs and resource implications associated with remdesivir, but consistent with the approach that should be taken with any new drug, the panel felt the responsibility should be on demonstrating evidence of efficacy, which is not established by the currently available data. The panel noted that there was no evidence of increased risk of SAEs in patients receiving remdesivir, at least from the included trials. Further pharmacovigilance is required to confirm this, as SAEs are commonly underreported and rare events would be missed, even in large RCTs.

Subgroup analysis

The panel carefully considered a potential subgroup effect across patients with different levels of disease severity, suggesting a possible increase in mortality in the critically ill and a possible reduction in mortality in the non-severely and severely ill. For this analysis, critical illness was defined as those requiring invasive or non-invasive ventilation; severe illness as those requiring oxygen therapy (but not meeting critical illness criteria); and non-severe as all others. Patients requiring high-flow nasal cannula represented a small proportion and were characterized as either severe (SOLIDARITY) (15) or critical (ACTT-1) (119). The analysis focused on within-study subgroup comparisons across the different severities, and therefore the SIMPLE-MODERATE trial could not be included in the subgroup analysis as it only enrolled patients with non-severe COVID-19. The panel reviewed the results of both the random effects frequentist analysis and the post hoc Bayesian analysis which incorporated meta-regression using study as a random effect.

The GDG panel judged the credibility in the subgroup analysis assessing differences in mortality by severity of illness to be insufficient to make subgroup recommendations. Important factors influencing this decision included a lack of *a priori* hypothesized direction of subgroup effect by trial investigators, little or no previously existing supportive evidence for the subgroup finding, and relatively arbitrary cut points used to examine the subgroups of interest. The overall low certainty evidence for the benefits and harms of remdesivir, driven by risk of bias and imprecision limitations, also contributed to the judgment. The panel highlighted that despite the conditional recommendation against remdesivir, they support further enrolment into RCTs evaluating remdesivir, especially to provide higher certainty of evidence for specific subgroups of patients.

The panel had *a priori* requested analyses of other important subgroups of patients including children and older persons, but there were no data to address these groups specifically. None of the included RCTs enrolled children, and although older people were included in the trials, their outcomes were not reported separately. Also, there is no pharmacokinetic or safety data on remdesivir for children. Given this, the applicability of this recommendation to children is currently uncertain.

Clinical Question/ PICO

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

Summary

Evidence summary

Based on 4 RCTs with 7333 participants (15)(119)(120)(121), the LNMA provided relative estimates of effect for patient-important outcomes. 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 remdesivir compared to usual care for the outcomes of interest in patients 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

The GDG panel requested subgroup analyses based on age (considering children vs adults vs older people), illness severity (non-severe vs severe vs critical COVID), and duration of remdesivir therapy (5 days vs longer than 5 days). The GDG discussed other potential subgroups of interest including time from onset of symptoms until initiation of therapy, and concomitant medications (especially corticosteroids); however, the GDG recognized these analyses would not be possible without access to individual participant data. To this last point, the panel recognized that usual care is likely variable between centres, regions and 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.

Following the panel's request, the NMA team performed subgroup analyses in order to assess for effect modification which, if present, could mandate distinct recommendations by subgroups. From the data available from the included trials, subgroup analysis was only possible for severity of illness and the outcome of mortality. This subgroup analysis was performed using a random effects frequentist analysis based on the three WHO severity definitions. A post hoc

Bayesian analysis was also performed, which incorporated meta-regression using study as a random effect. This latter approach has the advantage of more accurately accounting for within-study differences but can only compare two subgroups at a time. The panel used a pre-specified framework incorporating the ICEMAN tool to assess the credibility of subgroup findings (84).

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Remdesivir	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality 28 days	Odds Ratio 0.9 (CI 95% 0.7 – 1.12) Based on data from 7333 participants in 4 studies. ¹ (Randomized controlled)	106 per 1000 Difference:	96 per 1000 10 fewer per 1000 (CI 95% 29 fewer – 11 more)	Low Due to serious risk of bias and serious imprecision ²	Remdesivir possibly has little or no effect on mortality.
Mechanical ventilation	Odds Ratio 0.89 (CI 95% 0.76 – 1.03) Based on data from 6549 participants in 4 studies. (Randomized controlled)	105 per 1000 Difference:	95 per 1000 10 fewer per 1000 (CI 95% 23 fewer – 3 more)	Low Due to serious risk of bias and serious imprecision ³	Remdesivir possibly has little or no effect on mechanical ventilation.
Serious adverse events leading to discontinuation	Odds Ratio 1 (CI 95% 0.37 – 3.83) Based on data from 1894 participants in 3 studies. ⁴ (Randomized controlled)	15 per 1000 Difference:	15 per 1000 0 fewer per 1000 (CI 95% 9 fewer – 40 more)	Low Due to very serious imprecision ⁵	Remdesivir possibly has little or no effect on serious adverse events leading to discontinuation.
Viral clearance 7 days	Odds Ratio 1.06 (CI 95% 0.06 – 17.56) Based on data from 196 participants in 1 study. (Randomized controlled)	483 per 1000 Difference:	498 per 1000 15 more per 1000 (CI 95% 430 fewer – 460 more)	Very low Due to very serious imprecision ⁶	The effect of remdesivir on viral clearance is uncertain.
Acute kidney injury	Odds Ratio 0.85 (CI 95% 0.51 – 1.41) Based on data from 1281 participants in 2 studies. (Randomized controlled)	56 per 1000 Difference:	48 per 1000 8 fewer per 1000 (CI 95% 27 fewer – 21 more)	Low Due to serious imprecision and serious indirectness ⁷	Remdesivir possibly has little or no effect on acute kidney injury.
Delirium	Odds Ratio 1.22 (CI 95% 0.48 – 3.11) Based on data from 1048 participants in 1 study. (Randomized controlled)	16 per 1000 Difference:	19 per 1000 3 more per 1000 (CI 95% 8 fewer – 32 more)	Very low Due to very serious imprecision and serious indirectness ⁸	We are uncertain whether remdesivir increases or decreases delirium.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Remdesivir	Certainty of the Evidence (Quality of evidence)	Plain language summary
Time to clinical improvement	Measured by: days Lower better Based on data from: 1882 participants in 3 studies. (Randomized controlled)	11 days Difference:	9 days MD 2 lower (CI 95% 4.2 lower – 0.9 higher)	Low Due to serious imprecision and serious indirectness ⁹	Remdesivir possibly has little or no effect on time to clinical improvement.
Duration of hospitalization	Measured by: days Lower better Based on data from: 1882 participants in 3 studies. (Randomized controlled)	12.8 days Difference:	12.3 days MD 0.5 lower (CI 95% 3.3 lower – 2.3 higher)	Low Due to serious imprecision and serious indirectness ¹⁰	Remdesivir possibly has little or no effect on duration of hospitalization.
Duration of ventilation	Measured by: days Lower better Based on data from: 440 participants in 2 studies. (Randomized controlled)	14.7 days Difference:	13.4 days MD 1.3 lower (CI 95% 4.1 lower – 1.5 higher)	Low Due to very serious imprecision ¹¹	Remdesivir possibly has little or no effect on duration of ventilation.

1. Systematic review [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.
2. **Risk of bias: serious.** We rated two trials as high risk of bias due to high or probably high risk of bias in deviations from the intended intervention. **Imprecision: serious.** The 95% CI crosses the minimally important difference (2% reduction in mortality).
3. **Risk of bias: serious. Imprecision: serious.** Wide confidence intervals.
4. Systematic review [1] . **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.
5. **Imprecision: very serious.** Wide confidence intervals.
6. **Imprecision: very serious.** Wide confidence intervals.
7. **Indirectness: serious.** Studies used change in serum creatinine rather than patient-important measures of acute kidney injury. **Imprecision: serious.** Wide 95% credible intervals.
8. **Indirectness: serious.** Differences between the outcomes of interest and those reported (e.g short-term/surrogate, not patient-important). **Imprecision: very serious.**
9. **Indirectness: serious. Imprecision: serious.**
10. **Indirectness: serious. Imprecision: serious.** Wide confidence intervals.
11. **Imprecision: very serious.** Wide confidence intervals.

6.10.1 Mechanism of action

Remdesivir is a novel monophosphoramidate adenosine analogue prodrug which is metabolized to an active tri-phosphate form that inhibits viral RNA synthesis. Remdesivir has in vitro and in vivo antiviral activity against several viruses, including SARS-CoV-2. Remdesivir is widely used in many countries, with several guidelines recommending its use in patients with severe or critical COVID-19 (122)(123).

6.11 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 (14). No changes were made for the corticosteroids recommendations in this ninth 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 (124) 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 (125)(126). 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.

Preference and values

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 (127). 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 (128).

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 (14). Corticosteroids are listed in the WHO Model List of Essential Medicines, readily available globally at a low cost, and of considerable interest to all stakeholder groups. The guideline panel was informed by combining two meta-analyses which pooled data from eight randomized trials (7184 participants) of systemic corticosteroids for COVID-19 (1)(129). 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 to 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) (14). At the time of randomization, 16% were receiving invasive mechanical

ventilation or extracorporeal membrane oxygenation; 60% were receiving oxygen only (with or without non-invasive ventilation); and 24% were receiving neither.

The data from seven other smaller trials included 63 non-critically ill patients and approximately 700 critically ill patients (definitions of critical illness varied across studies). For the latter, patients were enrolled up to 9 June 2020, and approximately four-fifths were invasively mechanically ventilated; approximately half were randomized to receive corticosteroid therapy, and half randomized to no corticosteroid therapy. Corticosteroid regimens included: methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (GLUCOCOVID) (130); dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID19, CoDEX) (131)(132); 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) (133); 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) (134).

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 (130). An additional trial, which randomized hospitalized patients with suspected SARS-CoV-2 infection, published on 12 August 2020 (MetCOVID) (135), 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 (84), 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 1703 participants in 7 studies. ¹ Follow up: 28 days.	160 per 1000	126 per 1000	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 5481 participants in 2 studies.	116 per 1000	86 per 1000	Moderate Due to serious risk of bias ³	Systemic corticosteroids probably reduce the need of mechanical ventilation.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Systemic corticosteroids	Certainty of the Evidence (Quality of evidence)	Plain language summary
	Follow up: 28 days.	Difference:	30 fewer per 1000 (CI 95% 48 fewer – 8 fewer)		
Gastrointestinal bleeding	Relative Risk 1.06 (CI 95% 0.85 – 1.33) Based on data from 5403 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 6027 participants in 32 studies.	186 per 1000 Difference:	188 per 1000 2 more per 1000 (CI 95% 19 fewer – 24 more)	Low Due to serious indirectness, Due to serious imprecision ⁵	Corticosteroids may not increase the risk of super-infections.
Hyperglycaemia	Relative Risk 1.16 (CI 95% 1.08 – 1.25) Based on data from 8938 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 5015 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 6358 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 1813 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: 6425 participants in 1 study.	13 days	12 days	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 (136)(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.

Preference and values

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 to 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 1535 participants in 1 study. 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 5481 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 5403 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 6027 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 8938 participants in 24 studies.	286 per 1000	332 per 1000	Moderate Due to serious indirectness ⁷	Corticosteroids probably increase the risk of hyperglycaemia.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Systemic corticosteroids	Certainty of the Evidence (Quality of evidence)	Plain language summary
Hypernatremia	Relative Risk 1.64 (CI 95% 1.32 – 2.03) Based on data from 5015 participants in 6 studies.	Difference: 40 per 1000 Difference: 26 more per 1000 (CI 95% 13 more – 41 more)	46 more per 1000 (CI 95% 23 more – 72 more) 66 per 1000	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 6358 participants in 8 studies.	69 per 1000 Difference: 6 more per 1000 (CI 95% 10 fewer – 27 more)	75 per 1000	Low Due to serious indirectness and serious imprecision ⁹	Corticosteroids may not increase the risk of neuromuscular weakness.
Neuropsychiatric effects	Relative Risk 0.81 (CI 95% 0.41 – 1.63) Based on data from 1813 participants in 7 studies.	35 per 1000 Difference: 7 fewer per 1000 (CI 95% 21 fewer – 22 more)	28 per 1000	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: 6425 participants in 1 study.	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) (136).

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 eight 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 and sotrovimab 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 (137). 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](#)) (136)(138).

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 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 16 and 22 December 2021 to address molnupiravir. 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 intervention (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. The NMA team considered deliberations from the initial GDG meeting, specifically focusing

on the outcomes and subgroups prioritized by the GDG. The methods team rated credibility of subgroups using the ICEMAN tool (84).

Step 4: Final recommendations

The GRADE approach provided the framework for establishing evidence certainty and generating both the direction and strength of recommendations (139)(140). A *priori* voting rules informed procedures if the GDG failed to reach consensus. 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) (141);
- quality/certainty of the evidence (139)(142);
- values and preferences of patients (143);
- resources and other considerations (including considerations of feasibility, applicability, equity) (143);
- 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 (141);
- 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 (140)(143).

When possible, we used research evidence to inform discussion around these key factors. If not available, discussion of these factors was informed by expert opinion, supported by surveys of the GDG members as outlined below.

Benefits and harms

The GDG members prioritized outcomes (rating from 9 [critical] to 1 [not important]) in patients with non-severe COVID-19 and in patients with severe and critical COVID-19, taking a patient perspective (Tables 1 and 2 below). The GDG's questions were structured using the PICO format (see evidence profile under the recommendations). The prioritization was performed through a survey, most lately in May 2021, followed by a GDG discussion. These prioritized outcomes were used to update the LNMA (2).

Selecting and rating the importance of outcomes

GDG members prioritized outcomes from the perspective of patients with non-severe illness (Table 1) and severe and critical illness (Table 2).

Table 1. GDG outcome rating from the perspective of patients with non-severe illness

Outcome	Mean	SD	Range
Admission to hospital	8.5	0.7	7-9
Death	8.1	1.9	3-9
Quality of life	7.5	1.3	5-9
Serious adverse effects (e.g. adverse events leading to drug discontinuation)	7.4	1.8	3-9
Time to symptom resolution	7.3	1.7	4-9
Duration of hospitalization	6.6	0.9	5-8
Duration of oxygen support	6.6	1.2	5-9
Need for invasive mechanical ventilation	5.9	2.3	1-8
New non-SARS-CoV-2 infection	5.6	2.1	3-9
Time to viral clearance	5.5	2.4	1-9
Duration of invasive mechanical ventilation	5.4	2.1	1-8

SD: standard deviation.

Note: 7 to 9 – critical; 4 to 6 – important; 1 to 3 – of limited importance.

Table 2. GDG outcome rating from the perspective of patients with severe and critical illness

Outcome	Mean	SD	Range
Death	9.0	0	9
Need for invasive mechanical ventilation	8.2	0.9	6-9
Duration of invasive mechanical ventilation	7.6	0.9	6-9
Quality of life	6.9	1.3	5-9
Duration of hospitalization	6.7	1.2	4-9
Serious adverse effects (e.g. adverse events leading to drug discontinuation)	6.7	1.8	3-9
Time to symptom resolution	6.5	1.6	4-9
New non-SARS-CoV-2 infection	6.4	1.8	3-9
Duration of oxygen support	6.3	1.3	4-9
Time to viral clearance	4.7	2.3	1-9

SD: standard deviation.

Note: 7 to 9 – critical; 4 to 6 – important; 1 to 3 – of limited importance.

Derivation of absolute effects for drug treatments

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)(2).

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 in 1000). 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 (138). 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](#)) (138).

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 weak/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. 4).
- **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 (19).

Fig. 4. Example of how research evidence is available one click away, with narrative evidence summary giving additional details to GRADE Summary of Findings table

6.1 Molnupiravir (published 3 March 2022) 2

View section text

For patients with non-severe COVID-19 (excluding pregnant and breastfeeding women, and children)

Conditional recommendation
New

Benefits outweigh harms for the majority, but not for everyone. The majority of patients would likely want this option. [Learn more](#)

We suggest treatment with molnupiravir, conditional to those at highest risk of hospitalization (*conditional recommendation for*).

- In the absence of credible tools to predict risk for hospitalization in people infected with SARS-CoV-2, typical characteristics of people at highest risk include those that lack COVID-19 vaccination, with older age, immunosuppression and/or chronic diseases (e.g. diabetes).
- The benefit will be trivial in absolute terms except in those at highest risk for hospitalization, for which the intervention should be reserved and given early on in disease.
- The panel identified a risk beyond 10% of being hospitalized for COVID-19 to represent a threshold at which most people would want to be treated with molnupiravir.
- 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).
- Alternative effective treatments with different safety profiles recommended by WHO, such as neutralizing monoclonal antibodies, like sotrovimab, may be preferable or antivirals (currently under WHO assessment) if available.

Research evidence (1)
● Evidence to Decision
● Justification
● Practical info
● Decision Aids
● Feedback

Help

Molnupiravir vs Standard care
Patients with non-severe COVID-19

8 Outcomes Graphical view Summary ➔

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.

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.

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 key uncertainties for molnupiravir identified by the GDG, adding to those for JAK inhibitors, sotrovimab, convalescent plasma casirivimab-imdevimab, ivermectin, corticosteroids, remdesivir, 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

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 (eg. 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.

JAK inhibitors

- incremental benefit for patients receiving baricitinib and IL-6 receptor blockers together, rather than either drug individually;
- relative benefits of tofacitinib and ruxolitinib to baricitinib;
- safety and efficacy in children, and pregnant and lactating women.

Sotrovimab

- 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 who would most benefit from this intervention;
- efficacy and safety for severe and critical seronegative COVID-19 patients, for patients infected with emerging variants, as well as in children and pregnant women.

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.

Casirivimab-imdevimab

- accurate clinical prediction guides to establish 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;
- dosing and administration routes in non-severe and severe/critical COVID-19 patients;
- safety and efficacy in children and pregnant women.

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.

Remdesivir

- critical outcomes of interest, particularly those that impact resource allocation, such as the need for mechanical ventilation, duration of mechanical ventilation and duration of hospitalization;
- specific subgroups, such as different severities of illness, different time (days) since onset of illness, children and older adults, pregnant women, and duration of therapy;
- long-term outcomes such as mortality at extended endpoints or long-term quality of life;
- long-term safety and rare but important side-effects;
- patient-reported outcomes such as symptom burden;
- outcomes, when used in combination with other agents, such as, but not limited to, corticosteroids;
- impact on viral shedding, viral clearance, patient infectivity.

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 4 January 2022 – implies that more reliable and relevant evidence will emerge to inform policy and practice (13). 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 (13), 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 (14)(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 molnupiravir)

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 molnupiravir recommendation. For list of GDG members of previous recommendations, see [here](#).

Wagdy Amin (Ministry of Health and Population, Egypt); Fabien Alberto Jaimes Barragan (Antioquia University Medellin, Colombia); Frederique Jacqueroz Bausch (Department of Primary Care, University Hospital of Geneva, Switzerland); 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); Manai Hela (Emergency Medical Service Tunis, Tunisia); 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); Niranjana 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); Emmanuel Nsutebu (Sheikh Shakhboub Medical City, Abu Dhabi); 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); 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); 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); Yee-Sin Leo (National Centre for Infectious Diseases, Singapore).

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); Fabien 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); 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); Niranjana Kissoon (Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Sanjeev Krishna (St George's University of London, United Kingdom); Thiago Lisboa (Coração 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); Yee-Sin Leo (National Centre for Infectious Diseases, Singapore).

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); 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 of America); 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); Niranjana 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); Ananda Wijewickrama (Ministry of Health, Sri Lanka).

Methods chairs

Gordon Guyatt (casirivimab-imdevimab, JAK inhibitors), Bram Rochwerf (IL-6 receptor blockers, ivermectin, remdesivir and lopinavir/ritonavir, convalescent plasma, molnupiravir), Reed Siemieniuk (hydroxychloroquine), Francois Lamontagne (corticosteroids, sotrovimab).

Clinical chairs

Michael Jacobs (casirivimab-imdevimab, IL-6 receptor blockers, ivermectin, remdesivir, hydroxychloroquine, lopinavir/ritonavir, JAK inhibitors), Yee-Sin Leo (corticosteroids), Leticia Kawano-Dourado (convalescent plasma, sotrovimab, molnupiravir).

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).

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Meta-analysis teams

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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 Rochweg (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)(2)(3).

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