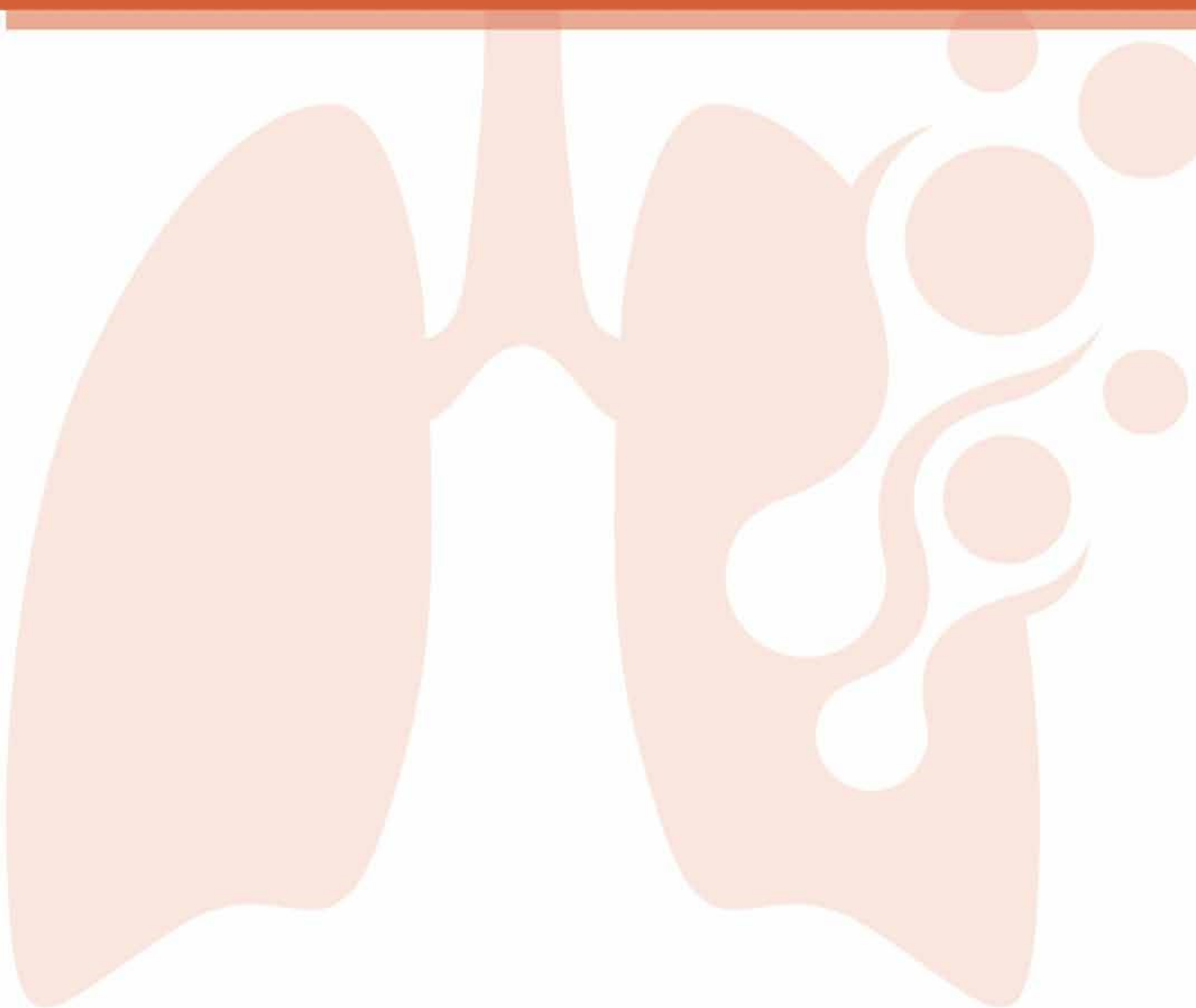
Therapeutics and COVID-19

Living guideline

7 December 2021

World Health Organization



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

WHO reference number: WHO/2019-nCoV/therapeutics/2021.4

Sections

1. Summary of the guideline

Info Box

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 increasing with numerous randomized controlled trials (RCTs) underway. This update includes recommendations on convalescent plasma, informed by pooled data from 16 RCTs with 16 236 patients.

New recommendations: The Guideline Development Group (GDG) made a strong recommendation against the use of convalescent plasma in patients with non-severe illness, and a recommendation against its use in patients with severe and critical illness, except in the context of an RCT.

Understanding the new recommendations: When moving from evidence to recommendations against the use of convalescent plasma, the GDG considered a combination of evidence assessing relative benefits and harms, values and preferences, and feasibility issues. The GDG recognized there was no clear benefit for critical outcomes such as mortality and mechanical ventilation for patients with non-severe, severe and critical illness, and significant resource requirements in terms of cost and time for administration. Thus, the strong recommendation against use reflects the GDG's view that drug administration, especially for patients with non-severe illness where there is a low baseline risk of mortality and other important clinical outcomes, is not justified. The GDG believed that although convalescent plasma should not be used in any severity subgroups as part of routine care, there was sufficient uncertainty in patients with severe and critical illness to warrant continuation of RCTs.

Prior recommendations:

Recommended for patients with severe and critical COVID-19:

- a strong recommendation for systemic corticosteroids;
- a strong recommendation for IL-6 receptor blockers (tocilizumab or sarilumab);
- a conditional recommendation for casirivimab and imdevimab, for those having seronegative status.

Recommended for patients with non-severe COVID-19:

- a conditional recommendation for casirivimab and imdevimab, for those at highest risk of severe disease.

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

- a conditional recommendation against systemic corticosteroids.

Not recommended, regardless of COVID-19 disease severity

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

About this guideline: This living guideline, from the World Health Organization (WHO), incorporates new recommendations on therapies for COVID-19 and provides updates on 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, they also consider 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 with network meta-analyses (LNMA) *(1)(2)(3)*.

Updates and access: This is the seventh update of the living guideline, replacing earlier versions. 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 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 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
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
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 10 November 2021, there have been over 251 million confirmed cases of COVID-19 *(10)*. The pandemic has thus far claimed more than 5.1 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 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)*.

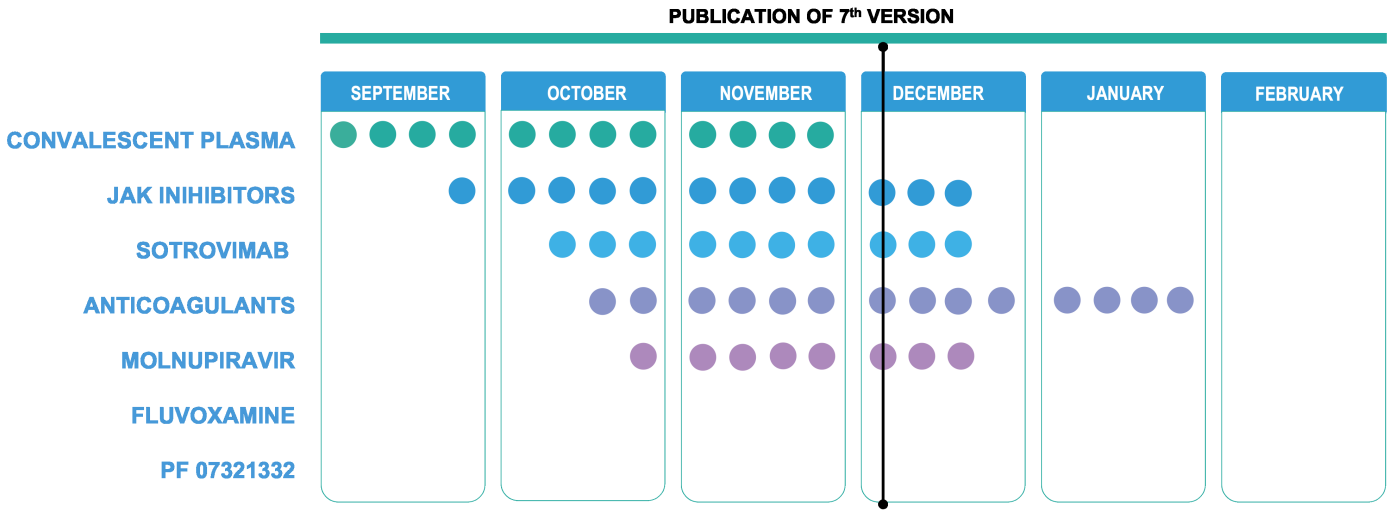
This living guideline responds to emerging evidence from RCTs on existing and new drug treatments for COVID-19. More than 5070 trials investigating interventions for COVID-19 have been registered or are ongoing (see Section 9 for emerging evidence) *(13)*. Among these are large national and international platform trials (such as RECOVERY, WHO SOLIDARITY, REMAP-CAP, and ACTIV) that recruit large numbers of patients in many countries, with a pragmatic and adaptive design *(14)(15)(16)(17)*. These platform trials are currently investigating and reporting on numerous interventions, including antiviral monoclonal antibodies and immunomodulators. This 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 seventh version of the WHO living guideline addresses the use of convalescent plasma in two groups of patients: those with non-severe COVID-19, and those with severe and critical illness. It follows the availability of 16 RCTs in both groups of patients, based on a LNMA on antibodies and cellular therapies for COVID-19 *(2)*. Convalescent plasma administration involves the transfer of endogenously produced neutralizing antibodies in plasma from previously infected and recovered patients into patients with active infection.

Fig. 1 shows other therapeutics in progress for this WHO living guideline, also communicated through the WHO portal *(4)*. In deciding which therapeutics to cover, the WHO considers factors such as the existence of a substantial body of 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 new drugs and update existing recommendations.

Fig 1. COVID-19 therapeutics under assessment



5. Understanding and applying the WHO severity definitions

Info Box

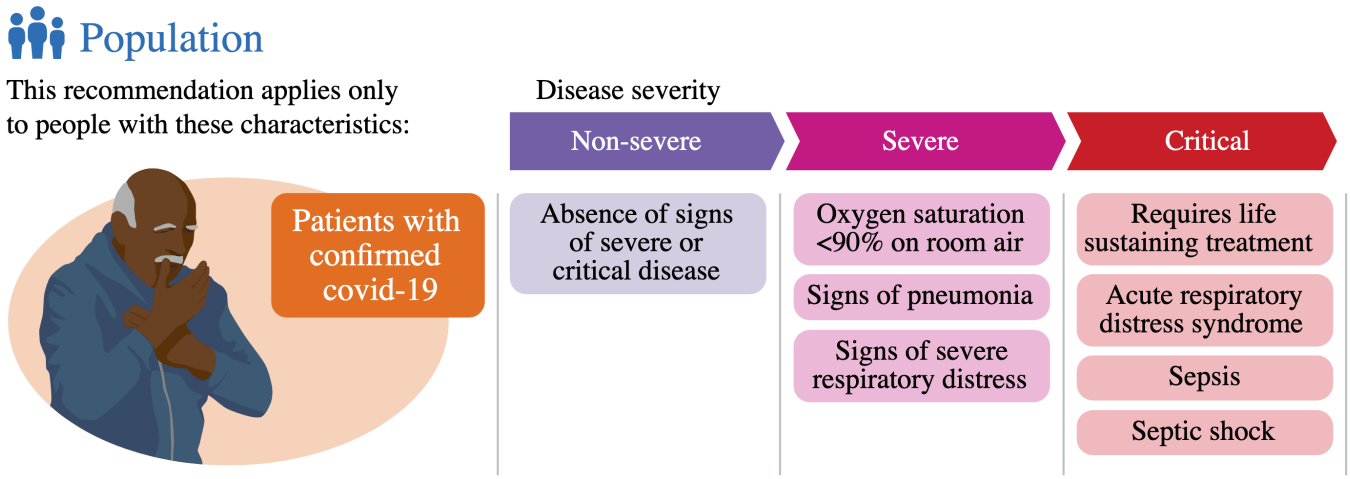
The guideline for COVID-19 therapeutics applies to all patients with COVID-19. However, for some drugs recommendations may differ for different patient populations, for example, based on the severity of COVID-19 disease. The GDG used the WHO severity definitions based on clinical indicators, adapted from WHO COVID-19 disease severity categorization (see below) *(6)*. These definitions avoid reliance on access to health care to define patient subgroups.

WHO severity definitions

- **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;
  - in adults, signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, respiratory rate > 30 breaths per minute), and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs (inability to breastfeed or drink, lethargy or reduced level of consciousness, convulsions) in addition to the signs of pneumonia.
- **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 used to define 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, a saturation of 90–94% on room air is abnormal (in the patient with normal lungs) and can be an early sign of severe disease, if the patient is on a downward trend. Generally, if there is any doubt, the GDG suggested erring on the side of considering the illness as severe.

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



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

6. Recommendations for therapeutics

6.1 Convalescent plasma

For patients with non-severe COVID-19 (who do not meet criteria for severe or critical infection)

Recommendation against

New

We recommend against administering convalescent plasma for treatment of COVID-19. *(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, as detailed in 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 critical/severe 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:	No convalescent plasma

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. Table 1 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 *(18)(19)*. 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** No convalescent plasma	**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 patients 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 patients in 3 studies. [3] (Randomized controlled)	6 per 1000 Difference:	4 per 1000 **2 fewer per 1000** (CI 95% 5 fewer — 5 more)	**Moderate** Due to serious risk of bias [4]	Convalescent plasma probably does not impact mechanical ventilation.
Transfusion-related acute lung injury (TRALI) within 28 days	Based on data from 1,365 patients 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 patients 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 patients 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:** [20], [23], [24], [21].
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:** [21], [24], [20].
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:** [26], [22], [25], [21].
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:** [22], [20], [25], [26].
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:** [20], [27], [23], [22], [26], [25], [28], [29].
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

New

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/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, as detailed in 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/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/critical was also informed by the feasibility (patients are already hospitalized) and baseline risk of mortality and requiring life support interventions (higher in severe/critical). 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 and critical COVID-19
Intervention: Convalescent plasma
Comparator: No convalescent plasma

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** No convalescent plasma	**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 patients 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 patients 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 patients 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 patients 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 patients 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** No convalescent plasma	**Intervention** Convalescent plasma	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Time to symptom improvement	Lower better Based on data from: 472 patients in 3 studies. [11] (Randomized controlled)	**15** (Mean) Difference:	**15** (Mean) **MD 0 fewer** (CI 95% 10.4 fewer — 33.6 more)	**Low** Due to very serious imprecision [12]	Convalescent plasma may not impact time to symptom improvement.
Length of hospital stay	Measured by: days Lower better Based on data from: 1015 patients 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 patients 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:** [30], [31], [32], [23], [33], [28], [25], [26], [27], [29].
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:** [30], [22], [26], [32], [29].
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:** [26], [21], [22], [25].
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:** [22], [26], [25], [20].
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:** [28], [25], [26], [23], [22], [27], [20], [29].
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:** [26],
12. **Imprecision: very serious.**
13. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [25], [30], [26], [29], [33], [31], [32].
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:** [29], [25], [27].

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.

6.1.1 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 *(34)*. 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 *(35)*.

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 *(36)*). 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 *(37)*.

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 *(38)*). 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.
- 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.

6.2 Casirivimab and imdevimab (neutralizing monoclonal antibodies) (published 24 September 2021)

Info Box

Recommendations concerning neutralizing monoclonal antibodies (casirivimab and imdevimab) for patients with non-severe, severe and 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 and imdevimab recommendations in this seventh version of the guideline.

For patients with non-severe COVID-19 (who do not meet criteria for severe or critical infection)

Conditional recommendation

We suggest treatment with casirivimab and imdevimab, conditional to those at highest risk of hospitalization. *(Conditional recommendation for)*

- *Whereas casirivimab and imdevimab achieves a substantial reduction in the relative risk of hospitalization, the absolute benefit will be trivial or unimportant 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 and 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 and 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 and 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 and imdevimab probably reduces the risk of hospitalization and duration of symptoms. Casirivimab and 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 *(39)*. 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 and imdevimab and only those at higher risk (e.g. unvaccinated, older, or immunosuppressed) would choose the treatment.

The limited availability of casirivimab and 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 and 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 and 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 and imdevimab be reserved for those at highest risk of hospitalization.

Major feasibility challenges include limited production of casirivimab and 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) *(40)*. 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) *(41)* – and subcutaneous administration, which has been used in the prophylactic trial *(42)*. 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 and 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 and 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 and imdevimab
Comparator: No casirivimab and imdevimab

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 and imdevimab or usual care *(41)*. All trials were registered and presented in pre-prints when the data were reviewed by the GDG. Table 2 shows trial characteristics.

The GRADE Summary of Findings table shows the relative and absolute effects of casirivimab and 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 and 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** No casirivimab and imdevimab	**Intervention** Casirivimab and 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 patients 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 and 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 patients 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 and imdevimab probably do not have an important effect on mechanical ventilation.
Admission to hospital	Odds Ratio 0.29 (CI 95% 0.17 — 0.48) Based on data from 4722 patients in 4 studies. (Randomized controlled)	42 per 1000 Difference:	13 per 1000 **29 fewer per 1000** (CI 95% 35 fewer — 21 fewer)	Moderate Due to serious indirectness [3]	Casirivimab and imdevimab probably reduce admission to hospital.

Outcome Timeframe	**Study results and measurements**	**Comparator** No casirivimab and imdevimab	**Intervention** Casirivimab and imdevimab	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Allergic reactions	Based on data from 15 406 patients 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 [4]	Casirivimab and imdevimab probably do not result in an important increase in allergic reactions.
Adverse effects leading to drug discontinuation	Based on data from 5284 patients in 4 studies. (Randomized controlled)	**2** per 1000 Difference:	**1** per 1000 **1 fewer per 1000** (CI 95% 2 fewer — 1 more)	**High**	Casirivimab and imdevimab do not result in an important increase in adverse effects leading to drug discontinuation.
Time to symptom improvement	Lower better Based on data from: 3084 patients 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 [5]	Casirivimab and imdevimab probably reduce time to symptom improvement.
Duration of hospitalization (not in hospital at baseline)	Lower better Based on data from: 111 patients 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 [6]	Casirivimab and 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 and 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 and 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. **Imprecision: serious.**
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: very serious.**

For patients with severe or critical COVID-19

Conditional recommendation

We suggest treatment with casirivimab and imdevimab, under the condition that the patient has seronegative status.
(Conditional recommendation for)

- *With benefits of casirivimab and 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 and 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 and imdevimab. 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 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 and 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 and 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 and 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 and 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 unimportant) and indirectness (variants may emerge in which casirivimab and 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 and 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 and 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 and 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 *(43)(44)(45)*. 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 and 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 and 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) *(41)*. 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 and 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 and 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 and 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 and 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 and 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 and 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 and imdevimab
Comparator:	No casirivimab and imdevimab

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 *(46)*. The trial was registered and presented in pre-prints when the data was reviewed by the GDG. Table 2 shows trial characteristics.

The GRADE Summary of Findings table shows the relative and absolute effects of casirivimab and 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

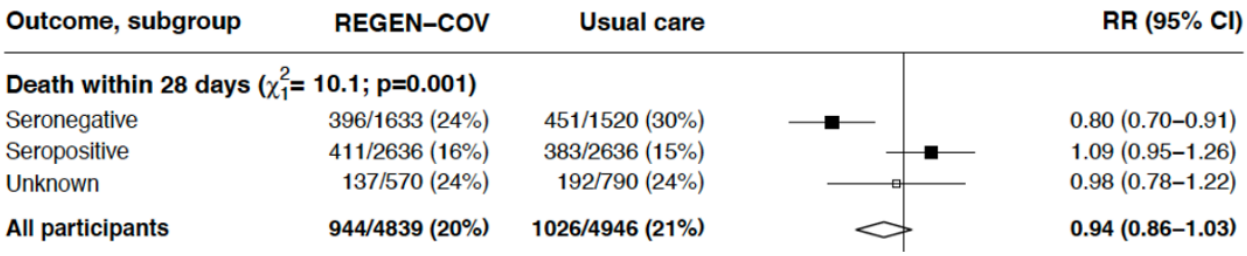
A highly credible subgroup effect demonstrated that casirivimab and imdevimab likely reduces mortality in patients who

are seronegative but not in those who are seropositive.

The credibility of the subgroup effect was evaluated using the ICEMAN tool *(47)*. 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 *(46)*.

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



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** No casirivimab and imdevimab	**Intervention** Casirivimab and imdevimab	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Mortality Severe disease	Relative risk 0.85 (CI 95% 0.76 — 0.95) Based on data from 2823 patients in 1 study. (Randomized controlled)	260 per 1000 Difference:	221 per 1000 **39 fewer per 1000** (CI 95% 62 fewer — 13 fewer)	Moderate Due to concerns with imprecision and indirectness [1]	Casirivimab and imdevimab probably reduce mortality.
Mortality Critical disease	Relative risk 0.85 (CI 95% 0.76 — 0.95) Based on data from 2823 patients 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 and imdevimab probably reduce mortality.
Mechanical ventilation	Relative risk 0.87 (CI 95% 0.77 — 0.98) Based on data from 2410 patients 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 and imdevimab may reduce mechanical ventilation.

Outcome Timeframe	Study results and measurements	Comparator No casirivimab and imdevimab	Intervention Casirivimab and imdevimab	Certainty of the evidence (Quality of evidence)	Plain language summary
Duration of hospitalization	Based on data from: 3153 patients in 1 study. (Randomized controlled)	The median duration of hospital stay was 4 days shorter with casirivimab and 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 and imdevimab
Comparator: No casirivimab and imdevimab

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 *(46)*. The trial was registered and presented in preprints when the data was reviewed by the GDG. Table 2 shows trial characteristics.

The GRADE Summary of Findings table shows the relative and absolute effects of casirivimab and 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 No casirivimab and imdevimab	Intervention Casirivimab and 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 patients 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]	Casirivimab and 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 patients 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** No casirivimab and imdevimab	**Intervention** Casirivimab and imdevimab	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Allergic reactions	Based on data from 15 406 patients 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 and imdevimab probably do not result in an important increase in allergic reactions.
Adverse effects leading to drug discontinuation	Based on data from 5284 patients in 4 studies. (Randomized controlled)	2 per 1000 Difference:	1 per 1000 **1 fewer per 1000** (CI 95% 2 fewer — 1 more)	High	Casirivimab and imdevimab do not result in an important increase in adverse effects leading to drug discontinuation.
Duration of hospitalization	Based on data from: 9785 patients 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.**

6.2.1 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 *(48)* and have demonstrated antiviral activity in rhesus macaques and Syrian golden hamsters *(49)*. 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 *(42)*. 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 *(50)*. Data available also suggest that when delivered in combination, activity remains for currently circulating variants of concern *(51)*.

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.

6.3 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 seventh version of the guideline.

For patients with severe and 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 (4), and we recommend patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers.

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)(52)(53)*.

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

Certainty of the Evidence

Certainty of evidence was rated as high for mortality and need for mechanical ventilation. Certainty in duration of mechanical ventilation was rated as low due to serious risk of bias due to concerns regarding lack of blinding in included trials, and for imprecision as the lower limit of the confidence interval suggested no effect. Certainty in duration of hospitalization was rated as low due to serious risk of bias from lack of blinding in included trials, and for inconsistency related to differences in point estimates and lack of overlap in confidence intervals.

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

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

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 SAEs. The GDG anticipated little variation in values and preferences between patients for this intervention.

Resources and other considerations

Resource implications, equity and human rights

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

At a time of drug shortage, it may be necessary to prioritize use of IL-6 receptor 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 invasive mechanical ventilation (IMV). Additional trial data from REMAP-CAP (see research evidence summary) 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.

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 COVID-19 (severe and critical)

Intervention: IL-6 inhibitor
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) *(9)*. 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 *(8)*.

The evidence summary for mortality was based on 27 RCTs and 10 930 participants from the PMA *(9)*. 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 (less than 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 *(9)*. 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) *(7)(8)*.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** IL-6 inhibitor	**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 patients 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 inhibitors reduce mortality.
Mechanical ventilation	Odds Ratio 0.72 (CI 95% 0.57 — 0.9)	**86** per 1000	**63** per 1000	**High**	IL-6 inhibitors reduce need for mechanical ventilation.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** IL-6 inhibitor	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
	Based on data from 5686 patients in 9 studies. [2] (Randomized controlled)	Difference:	**23 fewer per 1000** (CI 95% 35 fewer — 8 fewer)		
Adverse events leading to drug discontinuation	Odds Ratio 0.5 (CI 95% 0.03 — 9.08) Based on data from 815 patients 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 inhibitors on adverse events leading to discontinuation is uncertain.
Bacterial infections	Odds Ratio 0.95 (CI 95% 0.72 — 1.29) Based on data from 3548 patients 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 inhibitors may not increase secondary bacterial infections.
Duration of mechanical ventilation	Lower better Based on data from: 1189 patients 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 inhibitors may reduce duration of mechanical ventilation.
Duration of hospitalization	Lower better Based on data from: 6665 patients 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 inhibitors 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.

6.3.1 Mechanism of action

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

Tocilizumab and sarilumab are monoclonal antibodies approved for use in rheumatoid arthritis. They antagonize the membrane bound and soluble forms of the IL-6 receptor (IL-6R/sIL-6R). Tocilizumab is approved for intravenous use in rheumatoid arthritis and sarilumab for subcutaneous use, although in COVID-19 both have been studied intravenously. At the studied doses in COVID-19, both medicines are expected to achieve very high levels of receptor occupancy based upon studies in rheumatoid arthritis *(29)*. IL-6 inhibitors 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.

6.4 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 seventh 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 *(54)(55)*. 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 before the next iteration of this guideline.

Only in research settings

We recommend not to use ivermectin in patients with COVID-19 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.

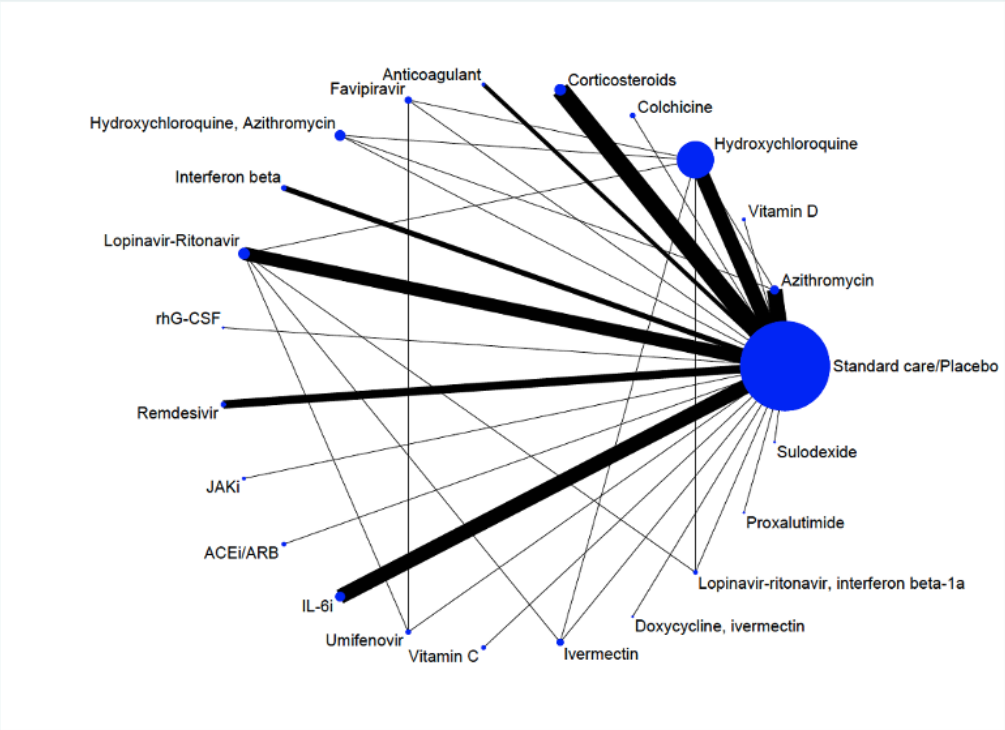
Justification

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. Fig. 3 is the network map for mortality

from the accompanying LNMA informing this guideline. Within the map, the size of the nodes (blue circles) correlates with the number of patients randomized to that intervention across all included trials; it is clear that the size of the ivermectin node is much smaller than other interventions which have been subjected to WHO guidelines, such as corticosteroids, hydroxychloroquine and lopinavir/ritonavir. The width of the line connecting two specific interventions correlates with the number of patients and number of events in this comparison across all trials; again, the lines connecting ivermectin to standard of care, as well as to the comparators lopinavir/ritonavir and hydroxychloroquine, are much thinner compared with drugs that have been assessed previously in this guideline.

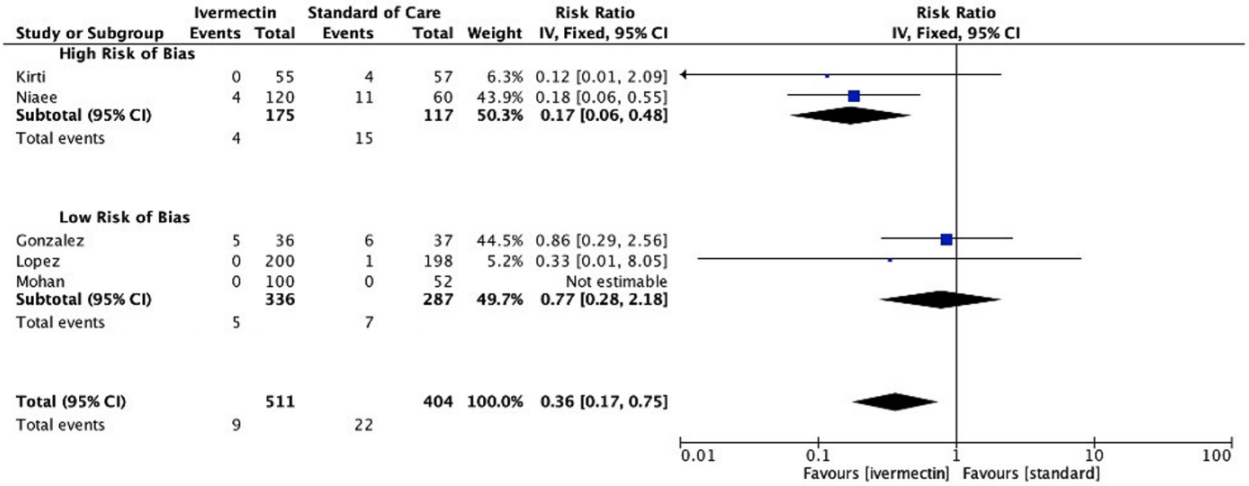
Fig. 3. Network map from the living network meta-analysis informing this guideline



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 *(56)(57)(58)(59)(60)(61)(62)*. 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 *(56)(57)* were at high risk of bias, due to inadequate blinding. One of these two trials *(56)* 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. 4), 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 *(54)* due to a lack of detailed description of blinding or randomization and the lack of a publicly available study protocol (figure not shown).

Fig. 4. 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 *(63)*. 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.

Uncertainties

Please see end of document for residual uncertainties (Section 9).

Clinical Question/PICO

Population: Patients with COVID-19 (all disease severities)
Intervention: Ivermectin
Comparator: Usual 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 3 on trial characteristics). We excluded a number of quasi-RCTs *(64)(65)(66)(67)*.

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 *(47)*.

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 1419 patients in 7 studies. [1] (Randomized controlled)	70 per 1000 Difference:	14 per 1000 **56 fewer per 1000** (CI 95% 63 fewer — 44 fewer)	Very low Due to serious risk of bias and very serious imprecision [2]	The effect of ivermectin on mortality is uncertain.
Mechanical ventilation	Odds Ratio 0.51 (CI 95% 0.12 — 1.77) Based on data from 687 patients in 5 studies. (Randomized controlled)	20 per 1000 Difference:	10 per 1000 **10 fewer per 1000** (CI 95% 18 fewer — 15 more)	Very low Due to very serious imprecision and publication bias [3]	The effect of ivermectin on mechanical ventilation is uncertain.
Viral clearance 7 days	Odds Ratio 1.62 (CI 95% 0.95 — 2.86) Based on data from 625 patients 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Ivermectin	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
		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 patients in 1 study (Randomized controlled)	50 per 1000 Difference:	18 per 1000 **32 fewer per 1000** (CI 95% 47 fewer — 23 more)	**Very low** Due to extremely serious imprecision [5]	The effect of ivermectin on hospital admission is uncertain.
Serious adverse events	Odds Ratio 3.07 (CI 95% 0.77 — 12.09) Based on data from 584 patients in 3 studies. (Randomized controlled)	9 per 1000 Difference:	27 per 1000 **18 more per 1000** (CI 95% 2 fewer — 89 more)	**Low** Due to very serious imprecision [6]	Ivermectin may increase the risk of serious adverse events leading to drug discontinuation.
Time to clinical improvement	Measured by: days Lower better Based on data from: 633 patients in 2 studies. (Randomized controlled)	11 days (Mean) Difference:	10.5 days (Mean) **MD 0.5 fewer** (CI 95% 1.7 fewer — 1.1 more)	**Low** Due to very serious imprecision [7]	Ivermectin may have little or no difference on time to clinical improvement.
Duration of hospitalization	Measured by: days Lower better Based on data from: 252 patients in 3 studies. (Randomized controlled)	12.8 days (Mean) Difference:	11.7 days (Mean) **MD 1.1 fewer** (CI 95% 2.3 fewer — 0.1 more)	**Very low** Due to serious imprecision, inconsistency and serious risk of bias [8]	The effect of ivermectin on hospital length of stay is uncertain.
Time to viral clearance	Measured by: days Lower better Based on data from: 559 patients 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.

6.4.1 Mechanism of action

Ivermectin is an antiparasitic agent that interferes with nerve and muscle function of helminths through binding glutamate-gated chloride channels *(68)*. 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 *(69)(70)(71)*. Ivermectin had no impact on SARS-CoV-2 viral RNA in the Syrian golden hamster model of SARS-CoV-2 infection *(72)*. 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 *(73)(74)(75)(76)(77)*. 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 *(78)*, and has benefits in murine models of atopic dermatitis and allergic asthma *(79)(80)*. 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 *(81)*, 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 *(72)*. 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.

6.5 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 seventh version of the guideline.

Recommendation against

We recommend against administering hydroxychloroquine or chloroquine for treatment of COVID-19. *(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 less than 70 years versus those aged 70 years and 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 infection (all disease severities)
Intervention:	Hydroxychloroquine + usual care
Comparator:	Usual 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 (Table 4). 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. under 70 years] vs older adults [e.g. 70 years or older]), illness severity (non-severe vs severe vs critical COVID-19) and based on whether or not it was co-administered with azithromycin.

The panel also requested a subgroup analysis based on high dose vs low dose hydroxychloroquine. A categorical

approach to hydroxychloroquine dosing proved impossible because the trials used varying loading doses, continuation doses and durations. Therefore, in collaboration with a pharmacology expert (Professor Andrew Owen), we modelled the expected serum concentrations over time. We hypothesized that higher trough concentrations early in the treatment course (e.g. trough concentration on Day 3) might be more effective than lower early trough concentrations. We also hypothesized that higher maximum serum concentrations (e.g. peak concentration on the last day) might result in higher risk of adverse effects than lower maximum serum concentrations. In our pharmacokinetic model, the cumulative dose was highly correlated with all measures of serum concentrations on Day 3 and the final day of treatment, and therefore we decided to use cumulative dose as the primary analysis. Day 3 trough concentration was least strongly correlated with total cumulative dose (R2 = 0.376) and therefore we performed a sensitivity subgroup analysis with predicted Day 3 trough concentrations for efficacy outcomes.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Hydroxychloroquine	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Mortality	Odds Ratio 1.11 (CI 95% 0.95 — 1.31) Based on data from 10 859 patients 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 patients in 5 studies. (Randomized controlled)	105 per 1000 Difference:	123 per 1000 **18 more per 1000** (CI 95% 16 fewer — 70 more)	**Moderate** Due to borderline risk of bias and serious imprecision [3]	Hydroxychloroquine probably does not reduce mechanical ventilation.
Viral clearance 7 days	Odds Ratio 1.08 (CI 95% 0.25 — 4.78) Based on data from 280 patients in 4 studies. [4] (Randomized controlled)	483 per 1000 Difference:	502 per 1000 **19 more per 1000** (CI 95% 294 fewer — 334 more)	**Very low** Due to very serious imprecision [5]	The effect of hydroxychloroquine on viral clearance is very uncertain.
Admission to hospital	Odds Ratio 0.39 (CI 95% 0.12 — 1.28) Based on data from 465 patients 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 patients 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Hydroxychloroquine	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Diarrhoea	Odds Ratio 1.95 (CI 95% 1.4 — 2.73) Based on data from 979 patients 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 patients 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 patients 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 patients in 5 studies. (Randomized controlled)	11 days (Mean) Difference:	9 days (Mean) **MD 2 fewer** (CI 95% 4 fewer — 0.1 more)	**Very low** Due to serious risk of bias, imprecision, and indirectness [11]	The effect of hydroxychloroquine on time to clinical improvement is uncertain.
Duration of hospitalization	Lower better Based on data from: 5534 patients 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 patients 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 patients 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.**

6.6 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/ritonavirsivir, remdesivir and hydroxychloroquine in hospitalized patients with COVID-19 *(15)*. No changes were made for the lopinavir/ritonavir recommendation in this seventh version of the guideline.

Recommendation against

We recommend against administering lopinavir/ritonavir for treatment of COVID-19. *(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 (Table 5). 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 patients 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 patients 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 patients 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 patients 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Lopinavir/ ritonavir	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Diarrhoea	Odds Ratio 4.28 (CI 95% 1.99 — 9.18) Based on data from 370 patients 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 patients 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 patients in 1 study. (Randomized controlled)	11 days (Mean) Difference:	10 days (Mean) **MD 1 fewer** (CI 95% 4.1 fewer — 3.2 more)	Very low Due to serious risk of bias and very serious imprecision [9]	The effect of lopinavir/ ritonavir improves on time to clinical improvement is very uncertain.
Duration of hospitalization	Lower better Based on data from: 5239 patients 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.

6.7 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 seventh version of the guideline.

Conditional recommendation against

We suggest against administering remdesivir in addition to usual care. *(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 Low

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 Substantial variability is expected or uncertain

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 Important issues, or potential issues not investigated

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) *(82)*. 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 + usual care
Comparator: Usual care

Summary

Evidence summary
Based on 4 RCTs with 7333 participants *(15)(82)(83)(84)*, 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 (Table 6).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 *(47)*.

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 patients 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 patients 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 patients 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)	483 per 1000	498 per 1000		

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Remdesivir	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
	Based on data from 196 patients in 1 study. (Randomized controlled)	Difference:	**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 patients 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 patients 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.
Time to clinical improvement	Measured by: days Lower better Based on data from: 1882 patients 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 patients 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 patients 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.

6.7.1 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 *(85)(86)*.

6.8 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, including links to MAGICapp. 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 seventh 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 *(87)* 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 inhibitors, 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 and critical COVID-19

Strong recommendation for

We recommend systemic corticosteroids rather than no 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 — Substantial net benefits of the recommended alternative

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 *(88)(89)*. 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 — No substantial variability expected

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 — No important issues with the recommended alternative

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 *(90)*. 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 *(91)*.

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 and critical COVID-19 (updated baseline mortality risk)
Intervention: Steroids

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)(92)*. 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) *(93)*; dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID19, CoDEX) *(94)(95)*; 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) *(96)*; 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) *(97)*.

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 *(93)*. An additional trial, which randomized hospitalized patients with suspected SARS-CoV-2 infection, published on 12 August 2020 (MetCOVID) *(98)*, 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 *(47)*, 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** Steroids	**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 patients in 7 studies. [1] Follow up: 28 days.	160 per 1000 Difference:	126 per 1000 **34 fewer per 1000** (CI 95% 48 fewer — 16 fewer)	**Moderate** Due to serious risk of bias [2]	Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with critical illness due to COVID-19.
Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (CI 95% 0.59 — 0.93) Based on data from 5481 patients in 2 studies. Follow up: 28 days.	116 per 1000 Difference:	86 per 1000 **30 fewer per 1000** (CI 95% 48 fewer — 8 fewer)	**Moderate** Due to serious risk of bias [3]	Systemic corticosteroids probably reduce the need of mechanical ventilation.
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5403 patients 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 patients 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 patients 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 patients 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 patients 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Steroids	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1813 patients 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 patients in 1 study. (Randomized controlled)	13 days	12 days CI 95%	Low Due to serious risk of bias and serious imprecision [10]	Steroids may result in an important reduction in the duration of hospitalizations.

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

For patients with non-severe COVID-19 infection (absence of criteria for severe or critical infection)

Conditional recommendation against

We suggest not to use 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 *(99)(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.

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: Steroids
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** Steroids	**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 patients 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 patients 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 patients 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 patients 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.

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard care	**Intervention** Steroids	**Certainty of the evidence** (Quality of evidence)	**Plain language summary**
Hyperglycaemia	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8938 patients in 24 studies.	286 per 1000 Difference:	332 per 1000 **46 more per 1000** (CI 95% 23 more — 72 more)	Moderate Due to serious indirectness [7]	Corticosteroids probably increase the risk of hyperglycaemia.
Hypernatremia	Relative risk 1.64 (CI 95% 1.32 — 2.03) Based on data from 5015 patients in 6 studies.	40 per 1000 Difference:	66 per 1000 **26 more per 1000** (CI 95% 13 more — 41 more)	Moderate Due to serious indirectness [8]	Corticosteroids probably increase the risk of hypernatremia.
Neuromuscular weakness	Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6358 patients in 8 studies.	69 per 1000 Difference:	75 per 1000 **6 more per 1000** (CI 95% 10 fewer — 27 more)	Low Due to serious indirectness and serious imprecision [9]	Corticosteroids may not increase the risk of neuromuscular weakness.
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1813 patients in 7 studies.	35 per 1000 Difference:	28 per 1000 **7 fewer per 1000** (CI 95% 21 fewer — 22 more)	Low Due to serious indirectness and serious imprecision [10]	Corticosteroids may not increase the risk of neuropsychiatric effects.
Duration of hospitalization	Measured by: days Lower better Based on data from: 6425 patients in 1 study. (Randomized controlled)	13 days	12 days	Low Due to serious risk of bias and serious imprecision [11]	Steroids may result in an important reduction in the duration of hospitalizations.

1. Systematic review [1]. **Baseline/comparator:** Primary study [15]. We derived baseline risk for mortality and mechanical ventilation from the control arm of the WHO SOLIDARITY trial.
2. **Risk of bias: serious.** Lack of blinding. **Imprecision: serious.**
3. **Risk of bias: serious.** Lack of blinding.
4. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [1].
5. **Indirectness: serious. Imprecision: serious.**
6. **Indirectness: serious. Imprecision: serious.**
7. **Indirectness: serious.**
8. **Indirectness: serious.**
9. **Indirectness: serious. Imprecision: serious.**
10. **Indirectness: serious. Imprecision: serious.**
11. **Risk of Bias: serious.** Lack of blinding. **Imprecision: serious.** Confidence interval includes no benefit.

7. Methods: how this guideline was created

This living WHO guideline was developed according to standards and methods for trustworthy guidelines, making use of an innovative process to achieve efficiency in dynamic updating of recommendations. The methods are aligned with the *WHO Handbook for guideline development* and according to a pre-approved protocol (planning proposal) by the Guideline Review Committee (GRC) *(99)*.

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 six versions of this WHO *Therapeutics and COVID-19: living guideline*, addressing corticosteroids, remdesivir, hydroxychloroquine, lopinavir/ritonavir, ivermectin, IL-6 receptor blockers, and a combination of casirivimab and imdevimab (neutralizing monoclonal antibodies) 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 *(100)*. The aim is for a 6-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*) *(101)(99)*.

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. 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. 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 two occasions to address convalescent plasma. The first meeting, held on 27 May 2021, reviewed 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). At the second meeting, held on 23 September 2021, the GDG reviewed analyses, including pre-specified subgroup analyses presented in summary of findings tables, and considered an individual patient perspective and feasibility issues specific to this intervention, and formulated recommendations for both patients with non-severe illness and severe and critical illness.

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 *(47)*.

Step 4: Final recommendations
The GRADE approach provided the framework for establishing evidence certainty and generating both the direction and strength of recommendations *(102)(103)*. While *a priori* voting rules informed procedures if the GDG failed to reach consensuswhenconsensus was reached on decisions of the GDG, there was no 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) *(104)*;
- quality/certainty of the evidence *(102)(105)*;
- values and preferences of patients *(106)*;
- resources and other considerations (including considerations of feasibility, applicability, equity) *(106)*;
- 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 *(104)*;
- 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 *(103)(106)*.

When possible, we used researchevidence 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 7 and 8 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 7) and severe and critical illness (Table 8).

Table 7. 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 8. 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.

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 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 commentsfrom such individuals or organizations on a draft guideline may be helpful in anticipating and dealing with controversy, identifying factual erross, 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 guideline review committee (GRC).

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.

The guideline is available via:

- 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.

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 *(101)*. It accommodates dynamic updating of evidence and recommendations that can focus on what is new while keeping existing recommendations, as appropriate, within the guideline.

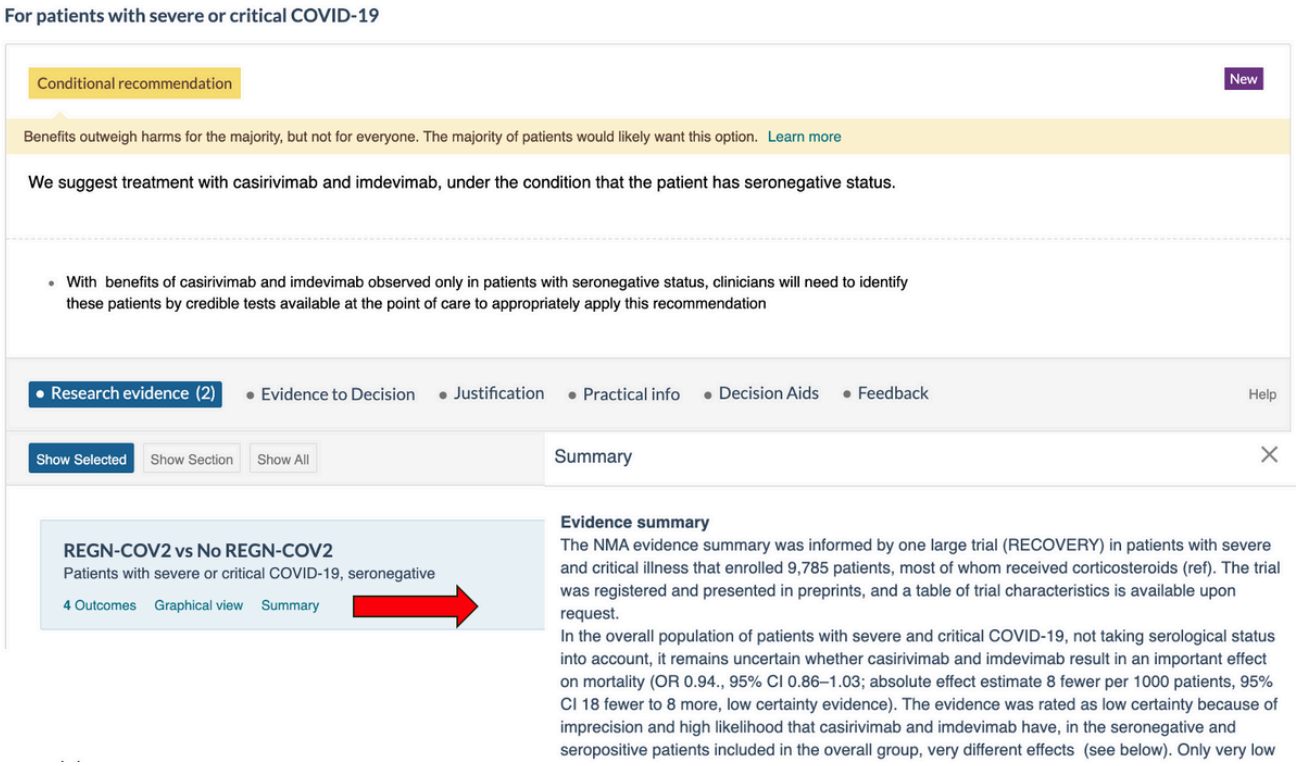
The purpose of the online formats and additional tools, such as the infographics, is to make it easier to navigate and make use of the guideline in busy clinical practice. The online multilayered formats are designed to allow end-users to find recommendations first and then drill down to find supporting evidence and other information pertinent to applying the recommendations in practice, including tools for shared decision-making (clinical encounter decision aids) *(101)*.

Fig. 5 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. 5).
- ***Evidence to decision:*** The absolute benefits and harms are summarised, 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 idenfity patients in practice.
- ***Decision aids:*** Tools for shared decision-making in clinical encounters *(19)*.

Fig. 5. Example of how research evidence is available one click away, here with narrative evidence summary giving additional details to GRADE Summary of Findings table



Additional educational modules and implementation tools for health workers can be found via:

- 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 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.
- 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, 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 values and preferences of patients with COVID-19 infection. Here we outline key uncertainties for convalescent plasma identified by the GDG, adding to those for casirivimab and imdevimab, ivermectin, corticosteroids, remdesivir, hydroxychloroquine, lopinavir/ritonavir, and IL-6 inhibitors 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

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 and 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 (*despite the strong recommendation, there are a number of uncertainties that persist):

- 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 and effects on:

- 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 and effects on:

- 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 5070 RCTs as of 22 November 2021 – 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 convalescent plasma)
The committee includes representatives from various WHO departments at headquarters and the regions and has been approved by the WHO Director of the Country Readiness Department, and the WHO Chief Scientist. The WHO Secretariat meets on a regular basis to discuss when to trigger guideline updates based on evidence updates from the WHO rapid review team, and other sources of evidence and selects the members of the **Guideline Development Group** (GDG) for the living guideline.

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The WHO Therapeutics Steering Committee is fully responsible for decisions about guidance production and convening the GDG.

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