

# Therapeutics and COVID-19

LIVING GUIDELINE

17 December 2020



World Health  
Organization



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The first version of this living guideline was assigned the WHO reference number WHO/2019-nCoV/remdesivir/2020.1

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WHO reference number: WHO/2019-nCoV/therapeutics/2020.1

# 1. SUMMARY: WHAT IS THIS LIVING GUIDELINE?

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

**Target audience:** The target audience is clinicians and health care decision-makers.

**Current practice:** Current practice to treat COVID-19 is variable, reflecting large-scale uncertainty. Numerous randomized trials of many different drugs are underway to inform practice. This version of the WHO *Therapeutics and COVID-19: living guideline* contains new information and recommendations on hydroxychloroquine and lopinavir/ritonavir. It follows the preprint publication of results from the WHO SOLIDARITY trial on 15 October 2020 (1) and a peer-reviewed publication on 1 December 2020 (2), which also reported results on remdesivir and interferon-beta.

**Recommendations:** The panel made strong recommendations against the use of hydroxychloroquine and lopinavir/ritonavir in patients with COVID-19, regardless of disease severity. This guidance adds to recommendations published in the [previous version](#) with:

- a strong recommendation for systemic corticosteroids in patients with severe and critical COVID-19;
- a conditional recommendation against systemic corticosteroids in patients with non-severe COVID-19; and
- a conditional recommendation against remdesivir in hospitalized patients with COVID-19.

**How this guideline was created:** This living guideline is an innovation from the World Health Organization (WHO), driven by the urgent need for global collaboration to provide trustworthy and evolving COVID-19 guidance informing policy and practice worldwide. WHO has partnered with the non-profit Magic Evidence Ecosystem Foundation ([MAGIC](#)) for methodologic support and development and dissemination of living guidance for COVID-19 drug treatments, based on a living systematic review and network analysis (3). An international Guideline Development Group (GDG) of content experts, clinicians, patients, ethicists and methodologists produced recommendations following standards for trustworthy guideline development using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. No conflict of interest was identified for any panel member.

**The latest evidence:** The recommendation on hydroxychloroquine was informed by results from a systematic review and network meta-analysis (NMA) that pooled data from 30 trials with 10 921 participants with COVID-19 (3). Lopinavir/ritonavir was informed by the same analysis that pooled data from 7 trials with 7429 participants (3). The trials for both drugs included inpatients and outpatients. The resulting GRADE evidence summary suggested that hydroxychloroquine probably does not reduce mortality (odds ratio 1.11, 95% confidence interval: [CI] 0.95–1.31; absolute effect estimate 10 more deaths per 1000 patients, 95% CI: from 5 fewer – 28 more deaths per 1000 patients; moderate certainty evidence) or need for mechanical ventilation. Lopinavir/ritonavir also probably does not reduce mortality (odds ratio 1.00, 95% CI: 0.82–1.20; absolute effect estimate 0 fewer deaths per 1000 patients, 95% CI: from 17 fewer – 19 more deaths per 1000 patients; moderate certainty evidence) or need for mechanical ventilation. Both hydroxychloroquine and lopinavir/ritonavir may the risk of diarrhoea and nausea/vomiting (low certainty evidence). There was no indication of a credible subgroup effect for either intervention based on disease severity or age, and no credible subgroup effect by dose for hydroxychloroquine.

**Understanding the recommendations:** When moving from the evidence to the strong recommendation against the use of hydroxychloroquine and lopinavir/ritonavir in patients with COVID-19, the panel emphasized the evidence suggesting no reduction in mortality, need for mechanical ventilation, and other patient-important outcomes. There were also potential for harms with both drugs including diarrhoea, nausea/vomiting, and other adverse effects that were not elucidated in the available trials. The panel did not anticipate important variability when it comes to patient values and preferences. In addition, the panel decided that contextual factors such as resources, feasibility, acceptability and equity for countries and health care systems were unlikely to alter the recommendation.

## Info box

This WHO Therapeutics and COVID-19: living guidelines now includes strong recommendations against the use of hydroxychloroquine and lopinavir/ritonavir. This update was initiated after publication of the WHO SOLIDARITY trial (1,2). Please view Section 1 for an executive summary of the guidance. The first version of the living WHO guideline published 2 September 2020 provides recommendations for corticosteroids; the second version published 20 November 2020 provides recommendations for remdesivir, with no changes for either of these drugs made as part of this update.

This is a living guideline, so the recommendations included here will be updated, and new recommendations will be added on other therapies for COVID-19. The guideline is therefore written, disseminated and updated here in MAGICapp, with a format and structure aiming to make it user-friendly and easy to navigate while accommodating for dynamically updated evidence and recommendations, focusing on what is new, while keeping existing recommendations within the guideline.

Please visit the WHO website for the latest version of the guidance, also available in the BMJ as Rapid Recommendations together with the living network meta-analysis (NMA), a major evidence source for the guidelines (3). The updated living NMA informing the recommendation on both hydroxychloroquine and lopinavir/ritonavir has been published in the BMJ (3). The same team performed a systematic review and meta-analysis on adverse effects from these drugs. This paper is currently available as preprint through MedRxiv.

## 2. ABBREVIATIONS

ARDS	acute respiratory distress syndrome
CAP	community-acquired pneumonia
CI	confidence interval
GDG	guideline development group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
MAGIC	Magic Evidence Ecosystem Foundation
NMA	network meta-analysis
PICO	population, intervention, comparator, outcome
PMA	prospective meta-analysis
RCT	randomized controlled trial
SAE	serious adverse event
WHO	World Health Organization

## 3. BACKGROUND

As of 14 December 2020, over 70 million people worldwide have been diagnosed with COVID-19, according to the WHO dashboard (4). The pandemic has so far claimed more than 1.6 million lives, and many areas of the world are experiencing a resurgence in cases. 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 (5).

This living guideline responds to emerging evidence from randomized controlled trials (RCTs) on existing and new drug treatments for COVID-19. More than 2800 trials investigating interventions for COVID-19 have been registered or are ongoing (see section on emerging evidence) (6). Among these are large national and international platform trials (e.g. RECOVERY, WHO SOLIDARITY and DISCOVERY) that recruit very large numbers of patients in many countries, with a pragmatic and adaptive design (2,7). These platform trials are currently investigating and reporting on drugs such as antiviral monoclonal antibodies and immunomodulators. This rapidly evolving evidence landscape requires trustworthy interpretation and expeditious clinical practice guidelines to inform clinicians, patients, governments, ministries and health administrators.

### 3.1 What triggered this version of the guideline?

This third version of the WHO living guideline addresses the use of hydroxychloroquine and lopinavir/ritonavir in patients with COVID-19. It follows the preprint publication and peer-reviewed 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 (1,2). The role of these drugs in clinical practice has remained uncertain, with limited prior trial evidence. The WHO SOLIDARITY trial adds 11 266 randomized patients (2570 to remdesivir, 954 to hydroxychloroquine, and 1411 to lopinavir/ritonavir, 6331 to usual care) and holds the potential to change practice (2).

In response to the release of SOLIDARITY data, the WHO GDG started with developing trustworthy recommendations on remdesivir (published 20 November 2020), and now provides recommendations on hydroxychloroquine and lopinavir/ritonavir. Hydroxychloroquine and chloroquine are anti-inflammatory agents that work through blocking of Toll-like receptors reducing dendritic cell activation. Hydroxychloroquine is used to treat rheumatoid arthritis and systemic lupus erythematosus. Chloroquine is listed in the WHO Model List of Essential Medicines as an antimalarial, for use for the treatment of *P. vivax* infection. Chloroquine has an antiviral effect against many viruses in vitro, including SARS-CoV-2, but a clinically useful antiviral effect has not been shown for any viral infection. Lopinavir is a protease-inhibitor antiretroviral agent, commonly used in combination with ritonavir which increases the serum concentration of lopinavir. This combination drug is used to treat and prevent human immunodeficiency virus (HIV) infection.

### 3.2 Who made this guideline?

As detailed in Section 4. Methods, the WHO convened a standing GDG with 28 clinical content experts, 4 patient-partners and one ethicist, headed by a clinical chair (Dr Michael Jacobs) and two methods chairs (Dr Reed Siemieniuk [hydroxychloroquine] and Dr Bram Rochweg [lopinavir/ritonavir]). WHO selected GDG members to ensure global geographical representation, gender balance, and appropriate technical and clinical expertise. No panel member had a conflict of interest.

The MAGIC Evidence Ecosystem Foundation ([MAGIC](#)) provided methodological experts with high-level expertise in standards and methods for systematic reviews and guideline development, including GRADE; in addition, MAGIC offered innovations in processes ([BMJ Rapid Recommendations](#)) and platforms ([MAGICapp](#)) for developing living guidance in user-friendly formats. The WHO has in place Agreements for Performance of Work with this entity for these two deliverables. The methodological experts were not involved in the formulation of recommendations. MAGIC also worked with the BMJ to coordinate the simultaneous scientific publication of the living WHO guidelines (8).

### 3.3 How to use this guideline

This is a living guideline from the WHO. Recommendations will be updated, and new recommendations will be added on other therapies for COVID-19 (8). The guideline is written, disseminated and updated in [MAGICapp](#), with a format and structure aiming to make it user-friendly and easy to navigate (9). It accommodates dynamic updating of evidence and recommendations that can focus on what is new while keeping existing recommendations, as appropriate, within the guideline. Section 4 outlines key methodological aspects of the living guideline process.

The guideline is available here in MAGICapp in online, multilayered formats and via:

- [WHO website](#) in PDF format
- [WHO Academy app](#)
- [BMJ Rapid Recommendations](#) (8).

The purpose of the MAGICapp online formats and additional tools, such as the infographics made by the BMJ, is to make it easier to navigate and use 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](#)).

## 4. METHODS: HOW THIS GUIDELINE WAS CREATED

The living WHO guideline is 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.

### Related guidelines

This living WHO guideline for COVID-19 treatments will be related to the larger, more comprehensive guidance for [Clinical management of COVID-19: interim guidance](#), which has a wider scope of content and is currently being updated and will also become available on the MAGICapp (9). The first two WHO living guidelines, addressing corticosteroids and remdesivir, were disseminated via the WHO website, [BMJ](#) and MAGICapp.

### Timing

This guidance aims to be trustworthy and living; dynamically updated and globally disseminated once new evidence warrants a change in recommendations for COVID-19 therapeutics (10). We aim for an ambitious timeframe from trials that trigger the guideline development process to WHO publication within 1 month, while maintaining standards and methods for trustworthy guidelines ([WHO handbook of guideline development](#)).

### Stepwise approach

Here we outline the stepwise approach we take to improve efficiency and timeliness of the living, trustworthy guidance, in the development and dissemination of the recommendations. To do so, various processes occurred simultaneously.

#### **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 NMA, using experienced information specialists, who look at all relevant information sources for new RCTs addressing interventions for COVID-19. Once practice-changing evidence is identified, such as in this case, the SOLIDARITY trial preprint, the WHO Therapeutics Steering Committee triggered the guideline development process. With the Guidance Support Collaboration Committee (see Acknowledgements), PICO (population, intervention, comparator, outcome) development and construction of evidence summaries addressing the intervention of interest are initiated.

The trigger for producing or updating specific recommendations is based on the following:

- 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**

The pre-selected expert panel (see Acknowledgments) convened on five occasions. The first meeting, held 13 October 2020, reviewed the basics of GRADE methodology; including formulating PICO questions and subgroups of interests, assessment of certainty of evidence, incorporating patients' values and preferences, and prioritization of patient-important outcomes. The second meeting, held on 20 October 2020, finalized the outcome prioritization, PICOs and pre-specified subgroups for this specific question. At the third meeting, held on 23 October 2020, a Q&A session was held with the individual study investigators and biostatisticians: SOLIDARITY (Drs Ana Maria Henao Restrepo and Richard Peto), ACTT-1 (Drs Lori Dodd and John Beigel) and RECOVERY (Drs Peter Horby and Jonathan Emberson). These first three meetings addressed issues related to remdesivir, hydroxychloroquine and lopinavir/ritonavir. At the fourth meeting, held on 17 November 2020, evidence summaries were shown to the GDG panel, including pre-specified subgroup analysis, and a recommendation for lopinavir/ritonavir was drafted. At the fifth meeting, on 24 November 2020, evidence summaries including subgroup analysis for hydroxychloroquine were shown, and a recommendation addressing this intervention was drafted.

#### **Step 3: Evidence synthesis**

The living systematic review/NMA team, as requested by the WHO Therapeutics Steering Committee and coordinated by the Guidance Support Collaboration Committee, was ready to perform an independent systematic review to examine the benefits and harms of the intervention. The systematic review team is multidisciplinary and made up of systematic review experts, clinical experts, clinical epidemiologists, graduate students and biostatisticians. The team

has expertise in GRADE methodology and rating certainty of evidence specifically in NMAs. The NMA team was informed of the deliberations from the initial two GDG meetings in order to guide the NMA, specifically focusing on the outcomes and subgroups prioritized by the panel. To conduct the subgroup analysis of high vs low dose of hydroxychloroquine, Professor Andrew Owen (see Acknowledgments) was engaged to provide direction on how to analyse different dosing regimens of hydroxychloroquine. Based on pharmacokinetic data of the different dosing regimens, Professor Owen and the methods support team recommended analysing cumulative dose as a continuous variable, with a sensitivity analysis using predicted serum trough concentration on Day 3 (a measure of early dosing) for efficacy outcomes.

#### **Step 4: Final recommendations**

The GDG panel members are responsible for the following critical activities:

- reviewing the evidence synthesis and summary of finding tables (presented by the NMA team) and from the evidence-drafting recommendations;
- advising on the priority questions and scope of guidance;
- advising on the choice of important outcomes for decision-making;
- commenting on the evidence used to inform the guideline;
- advising on the interpretation of the evidence, with explicit consideration of the overall balance of risks and benefits;
- formulating recommendations, taking into account diverse values and preferences according to GRADE.

The GRADE approach provided the framework for establishing evidence certainty and generating both the direction and strength of recommendations (11). Although *a priori* voting procedures were established at the outset, in case consensus was not reached, these procedures were not necessary for this recommendation, which reached consensus amongst the panel.

The following key factors were used to formulate transparent and trustworthy recommendations:

- absolute benefits and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE summary of findings tables) (12);
- quality/certainty of the evidence (13);
- values and preferences of patients (14);
- resources and other considerations (including considerations of feasibility, applicability, equity) (14);
- each outcome will have an effect estimate and CI, with a measure of certainty in the evidence, as presented in summary of findings tables. If such data are not available, narrative summaries will be provided;
- recommendations will be rated as either conditional or strong, as defined by GRADE. If the panel members disagree regarding the evidence assessment or strength of recommendations, WHO will apply voting according to established methods.

#### **Step 5: External and internal review**

The WHO guideline was then reviewed by pre-specified external reviewers (see Acknowledgements) and then approved by the WHO Publication Review Committee.

## **5. THE LATEST EVIDENCE**

This section outlines the information the GDG panel requested and used in making their recommendations for hydroxychloroquine and lopinavir/ritonavir.

### **Benefits and harms**

The GDG panel requested an update of the living NMA of RCTs of drug treatments for COVID-19, based around important clinical questions to be addressed in the recommendations. The GDG members prioritized outcomes (rating from 1 [not important] to 9 [critical]) taking a patient perspective (Table 1). The panel's questions were structured using the PICO format (see evidence profile under the recommendations).

**Table 1. Panel outcome rating from a patient perspective**

Outcome	Mean	SD	Range
Death at 28 days	9.0	0.0	9-9
Need for invasive mechanical ventilation	8.4	0.8	7-9
Duration of invasive mechanical ventilation	7.7	1.0	5-9
Time to clinical improvement	7.2	1.5	4-9
Serious adverse effect leading to drug discontinuation	7.1	1.4	4-9
Time to symptom resolution	6.6	1.5	3-9
Duration of oxygen support	6.6	1.3	5-9
Duration of hospitalization	6.4	1.3	3-8
Hepatitis (increased liver enzymes)	5.3	1.8	2-9
Duration of viral shedding	4.9	2.4	2-9
Nausea/vomiting	4.5	1.7	2-9
Diarrhea	4.3	1.5	2-8

*Note:* 1: not important, 9: critically important.

**For hydroxychloroquine:** The evidence summary was based on 30 trials and 10 921 participants for which the NMA provided relative estimates of effect for patient-important outcomes (Table 2). Five of the trials (414 total participants) randomized some patients to chloroquine.

**For lopinavir/ritonavir:** The evidence summary was based on 7 trials with 7429 participants (Table 3). Of note, none of the included studies enrolled children or adolescents under the age of 19 years old.

**Table 2. Summary of trials and trial characteristics informing the hydroxychloroquine recommendation** (trials = 30, total patients = 10 921)

Geographic region	Region of the Americas South-East Asia Region Western Pacific Region European Region Eastern Mediterranean Region	Region of the Americas (12 trials, 2358 patients) South-East Asia and Western Pacific Regions (7 trials, 731 patients) European Region (10 trials, 7638 patients) Eastern Mediterranean Region (1 trial, 194 patients)
Severity of illness <sup>a</sup>	Non-severe Severe Critically ill	Mild/Moderate (10 trials, 2436 patients) Severe (1 trials, 479 patients) Critically ill (0 trials, 0 patients)
Mechanically ventilated at baseline <sup>b</sup>	Mean (range), %	3.23 (0–16.8)
Age <sup>c</sup>	Mean (range of means), years	50.8 (32.9–77.0)
Sex <sup>d</sup>	Mean (range of means), % women	46.9 (30.0–71.0)
Loading doses Day 1 <sup>e</sup>	Mean (range of means), mg	1010 (800–1600)
Total cumulative doses <sup>f</sup>	Median (range), mg	4000 (2000–11200)
Duration of therapy <sup>g</sup>	Median (range), days	7 (4–16)
Type of care	n (%) inpatient n (%) outpatient	Inpatient: 9549 (87.4) Outpatient: 1372 (12.6)
Trial participants	Median (range)	364 (2–4716)
Concomitant use of corticosteroids <sup>h</sup>	Mean (range across trials that report this), %	12.61 (8.0–19.5)

**Notes:**

<sup>a</sup> 19 trials did not report the disease severity of patients.

<sup>b</sup> 19 trials did not report the proportion of mechanical ventilation at baseline.

<sup>c</sup> Based on 15 trials and 8006 patients. For the other 15 trials: 1 trial did not report the age of patients; and the other 14 trials reported that the age of patients were  $\geq 12$ , 18 or 40.

<sup>d</sup> 14 trials did not report the sex of patients.

<sup>e</sup> 10 trials did not use a loading dose.

<sup>f</sup> 1 trial reported range of treatment duration.

<sup>g</sup> 1 trial reported range of treatment duration.

<sup>h</sup> 23 trials did not report the concomitant use of corticosteroids.



**Table 3. Summary of trials and trial characteristics informing the lopinavir/ritonavir recommendation**  
(trials = 7, total patients = 7429)

Geographic region	Region of the Americas South-East Asia Region Western Pacific Region European Region Eastern Mediterranean Region	Region of the Americas (0 trials, 0 patients) South-East Asia and Western Pacific Regions (5 trials, 535 patients) European Region (2 trials, 6894 patients) Middle East (0 trials, 0 patients)
Severity of illness <sup>a</sup>	Non-severe Severe Critically ill	Mild/Moderate (4 trials, 336 patients) Severe (1 trials, 199 patients) Critically ill (0 trials, 0 patients)
Mechanically ventilated at baseline <sup>b</sup>	Mean (range), %	7.3 (0–16.1)
Age <sup>c</sup>	Mean (range of means), years	52.6 (42.5–66.2)
Sex	Mean (range of means), % women	48.7 (38.9–61.7)
Loading doses Day 1 <sup>d</sup>	Mean (range of means), mg	
Total cumulative doses (lopinavir/ ritonavir) <sup>e</sup>	Median (range), mg	11200/2800(8000–11 200/2000–2800)
Duration of therapy <sup>f</sup>	Median (range), days	14 (10–14)
Type of care	n (%) inpatient n (%) outpatient	Inpatient: 7429 (100) Outpatient: 0 (0)
Trial participants	Median (range)	101 (60–5040)
Concomitant use of corticosteroids <sup>g</sup>	Mean (range across trials that report this), %	17.1 (0–32.3)

**Notes:**

<sup>a</sup> 2 trials did not report the disease severity of patients.

<sup>b</sup> 3 trials did not report proportion of mechanical ventilation at baseline.

<sup>c</sup> 2 trials did not report the age of patients.

<sup>d</sup> No trial reported loading dose.

<sup>e</sup> 1 trial did not report cumulative doses; 2 trials only reported range of treatment duration.

<sup>f</sup> 1 trial did not report the duration of therapy, 2 trials used a range of treatment duration.

<sup>g</sup> 2 trials did not report the concomitant use of corticosteroids.

**Subgroup analysis**

For both hydroxychloroquine and 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 – see subgroup under Section 7.1 Hydroxychloroquine recommendations for details). 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. 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. For hydroxychloroquine alone, the panel also requested an analysis based on whether or not it was co-administered with azithromycin.

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 age examining the outcome of mortality. This subgroup analysis was performed using a Bayesian analysis which incorporated meta-regression using study as a random effect. The panel used a pre-specified framework incorporating the ICEMAN tool to assess the credibility of subgroup findings (15).

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 ( $R^2 = 0.376$ ) and therefore we performed a sensitivity subgroup analysis with predicted Day 3 trough concentrations for efficacy outcomes.

### **Baseline risk estimates (prognosis of patients with COVID-19): informing absolute estimates of effect**

The evidence summaries that informed the guideline recommendation reported the anticipated absolute effects of hydroxychloroquine and lopinavir/ritonavir compared with usual care across all patient-important outcomes, with explicit judgments of certainty in the evidence for each outcome. The absolute effects of treatment are informed by the prognosis (i.e. baseline risk estimates) combined with the relative estimates of effects (e.g. risk ratio, odds ratio) obtained from the NMA.

The control arm of the WHO SOLIDARITY trial (2), performed across a wide variety of countries and geographical regions, was identified by the GDG panel as representing the most relevant source of evidence to make the baseline risk estimates for the outcomes of mortality and mechanical ventilation. The rationale for selecting the WHO SOLIDARITY trial was to reflect the overall prognosis of the global population for which the WHO guideline recommendations are made. When applying the evidence to a particular patient or setting, the individual or setting's risk of mortality and mechanical ventilation should be considered. In view of the study designs, the GDG determined that for other outcomes using the median or mean of all patients randomized to usual care across the included studies would provide the most reliable estimate of baseline risk.

### **Values and preferences**

There were insufficient published data to provide the GDG with an informative systematic review of studies describing patients' experiences or values and preferences on 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 and their subsequent treatment preferences. The GDG included four patient-representatives who had lived experience with COVID-19.

The GDG agreed that the following values and preferences would be representative of those of typical well-informed patients:

- Mortality would be the outcome most important to patients, followed by need and duration of mechanical ventilation, time to clinical improvement, and serious intervention-related adverse events.
- Most patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on the outcomes listed above. 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.

The GDG acknowledged, however, that values and preferences are likely to vary. There will be patients inclined to use a treatment in which evidence has not excluded important benefit, particularly when the underlying condition is potentially fatal. On the other hand, there will be those who have a high threshold for likely benefit before they will choose 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.

## 6. WHO DO THE RECOMMENDATIONS APPLY TO?

The guideline for COVID-19 therapeutics applies to patients with COVID-19. For some drugs (such as corticosteroids), recommendations may differ based on the severity of COVID-19 disease. The GDG elected to use the WHO severity definitions based on clinical indicators, adapted from the WHO COVID-19 disease severity categorization (see below) (16). 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;
  - respiratory rate > 30 breaths/min in adults and children > 5 years old; ≥ 60 breaths/min in children < 2 months old; ≥ 50 in children 2–11 months old; and ≥ 40 in children 1–5 years old;
  - signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).
- **Non-severe COVID-19:** Defined as absence of any criteria for severe or critical COVID-19.

**Caution:** The panel noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously when used for determining 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 > = 90–94% on room air is abnormal (in 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 panel suggested erring on the side of considering the illness as severe.

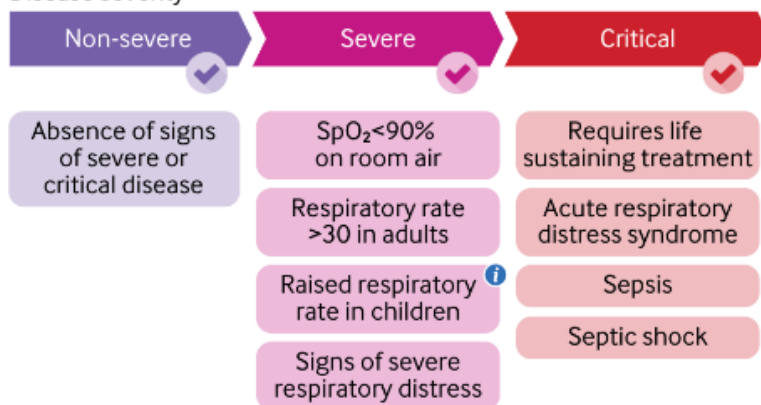
The **infographic** illustrates these three disease severity groups and key characteristics to apply in practice.

### Population

This recommendation applies only to people with these characteristics:



### Disease severity



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

## 7. RECOMMENDATIONS FOR THERAPEUTICS

### 7.1 Hydroxychloroquine

#### Strong recommendation against

We recommend against administering hydroxychloroquine or chloroquine for treatment of COVID-19.

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

#### 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 diarrhea 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 under 70 years vs those 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 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 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 lies 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 Evidence section above), 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/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 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 no reduction in mortality or need for mechanical ventilation. It also noted the evidence suggesting possible harm associated with treatment, with increased nausea/vomiting and diarrhoea. The GDG did not anticipate important variability in patient values and preferences, and judged that other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity would not alter the recommendation (see 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 (outpatients and inpatients). Although the trials did not report subgroup effects by time from symptom onset, several of the trials enrolled patients early in the disease course for early treatment (i.e. as early as 1 day in an outpatient setting). The GDG also noted the challenges in capturing this variable in large platform trials. Taken together, the GDG panel 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 regard 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 was 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.

## Practical information

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.

## Uncertainties

Please see Section 8 for residual uncertainties. The GDG panel felt that it was unlikely future studies would identify a subgroup of patients that are likely to benefit from hydroxychloroquine or chloroquine.

## PICO

Population: Patients with COVID-19 infection (all disease severities)  
Intervention: Hydroxychloroquine + usual care  
Comparator: Usual care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard care	Hydroxychloro- quine		
Mortality	Odds ratio: 1.11 (CI 95% 0.95– 1.31) Based on data from 10 859 patients in 29 studies <sup>a</sup>	<b>106</b> per 1000	<b>116</b> per 1000	<b>Moderate</b> Due to borderline risk of bias and imprecision <sup>b</sup>	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	<b>105</b> per 1000	<b>123</b> per 1000	<b>Moderate</b> Due to borderline risk of bias and serious imprecision <sup>c</sup>	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	<b>483</b> per 1000	<b>502</b> per 1000	<b>Very low</b> Due to very serious imprecision <sup>d</sup>	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 studies	<b>47</b> per 1000	<b>19</b> per 1000	<b>Very low</b> Due to very serious imprecision and serious indirectness <sup>e</sup>	The effect of hydroxychloroquine on admission to hospital is uncertain
Cardiac toxicity	Based on data from 3287 patients in 7 studies	<b>46</b> per 1000	<b>56</b> per 1000	<b>Very low</b> Due to serious imprecision, risk of bias, and indirectness <sup>f</sup>	The effect of hydroxychloroquine on cardiac toxicity is uncertain
Diarrhoea	Odds ratio: 1.95 (CI 95% 1.4–2.73) Based on data from 979 patients in 6 studies	<b>149</b> per 1000	<b>255</b> per 1000	<b>Low</b> Due to serious imprecision and risk of bias <sup>g</sup>	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	<b>99</b> per 1000	<b>161</b> per 1000	<b>Low</b> Due to serious imprecision and risk of bias <sup>h</sup>	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 studies	<b>62</b> per 1000	<b>95</b> per 1000	<b>Very low</b> Due to very serious imprecision and serious indirectness <sup>i</sup>	The effect of hydroxychloroquine on delirium is uncertain
Time to clinical improvement	Measured by: Scale: lower better Based on data from 479 patients in 5 studies	<b>11.0</b> Days mean	<b>9.0</b> Days mean	<b>Very low</b> Due to serious risk of bias, imprecision, and indirectness <sup>j</sup>	The effect of hydroxychloroquine on time to clinical improvement is uncertain

Duration of hospitalization	Measured by: Scale: lower better Based on data from 5534 patients in 5 studies	<b>12.8</b> Days mean	<b>12.9</b> Days mean	<b>Low</b> Due to serious imprecision and serious risk of bias <sup>k</sup>	Hydroxychloroquine may have no effect on duration of hospitalization
Time to viral clearance	Measured by: Scale: lower better Based on data from 440 patients in 5 studies	<b>9.7</b> Days mean	<b>10.6</b> Days mean	<b>Very low</b> Due to serious risk of bias and very serious imprecision <sup>l</sup>	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	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.		<b>Very low</b> Due to extremely serious imprecision <sup>m</sup>	The effect of hydroxychloroquine on adverse events leading to drug discontinuation is uncertain

**Notes:**

<sup>a</sup> Systematic review (3). **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.

<sup>b</sup> **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).

<sup>c</sup> **Risk of bias: Serious. Imprecision: Serious.** Wide confidence intervals.

<sup>d</sup> **Imprecision: Very Serious.** Wide confidence intervals.

<sup>e</sup> **Indirectness: Serious. Imprecision: Very Serious.**

<sup>f</sup> **Risk of bias: Serious.** Unblinded studies – cardiac toxicity differential detection; **Indirectness: Serious.** Studies measured serious cardiac toxicity differently; **Imprecision: Serious.**

<sup>g</sup> **Risk of bias: Serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results;

**Imprecision: Serious.** Optimal information size not met; **Upgrade: Large magnitude of effect.**

<sup>h</sup> **Risk of bias: Serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results;

**Imprecision: Serious.** Optimal information size not met; **Upgrade: Large magnitude of effect.**

<sup>i</sup> **Indirectness: Serious.** This outcome was not collected systematically and the definition of delirium was not specified; **Imprecision: Very Serious.**

<sup>j</sup> **Risk of bias: Serious. Indirectness: Serious.** Studies measured clinical improvement differently; **Imprecision: Serious.**

<sup>k</sup> **Risk of bias: Serious. Imprecision: Serious.** Wide confidence intervals.

<sup>l</sup> **Risk of bias: Serious. Imprecision: Very Serious.**

<sup>m</sup> **Imprecision: Very Serious.**

Source: Siemieniuk et al., 2020 (3).

## 7.2 Lopinavir/ritonavir

### Strong recommendation against

We recommend against administering lopinavir/ritonavir for treatment of COVID-19.

**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 patient-important outcomes 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 under 70 years vs those 70 years and older). As there was no evidence of a statistical subgroup effect, we did not formally evaluate credibility using the ICEMAN tool.

### **Certainty of the evidence**

The evidence is based on a linked systematic review and NMA of 7 RCTs, pooling data from 7429 patients hospitalized with various severities of COVID-19 and variably reporting the outcomes of interest to the guideline panel (3). 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 don't exclude important benefit or harm).

### **Preference and values**

Applying the agreed values and preferences (see Evidence section above), 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 for 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 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 judged that other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity would not alter the recommendation (see 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 regard 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 Section 8 for residual uncertainties. The GDG panel felt that it was unlikely future studies would identify a subgroup of patients that are likely to benefit from lopinavir/ritonavir.

### **Additional considerations**

In patients who have undiagnosed or untreated HIV, use of lopinavir/ritonavir alone may promote HIV resistance to important antiretrovirals. Widespread use of lopinavir/ritonavir for COVID-19 may cause drug shortages for people living with HIV.



**PICO**

Population: Patients with COVID-19 infection (all disease severities)

Intervention: Lopinavir/ritonavir + usual care

Comparator: Usual care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard care	Lopinavir/ ritonavir		
Mortality	Odds ratio: 1.0 (CI 95% 0.82–1.2) Based on data from 8061 patients in 4 studies <sup>a</sup>	<b>106</b> per 1000	<b>106</b> per 1000	<b>Moderate</b> Due to borderline risk of bias and imprecision <sup>b</sup>	Lopinavir/ritonavir probably has no effect on mortality
Mechanical ventilation	Odds ratio: 1.16 (CI 95% 0.98–1.36) Based on data from 7579 patients in 3 studies	<b>105</b> per 1000	<b>120</b> per 1000	<b>Moderate</b> Due to borderline risk of bias and imprecision <sup>c</sup>	Lopinavir/ritonavir probably does not reduce mechanical ventilation
Viral clearance 7 days	Odds ratio: 0.35 (CI 95% 0.04–1.97) Based on data from 171 patients in 2 studies	<b>483</b> per 1000	<b>246</b> per 1000	<b>Very low</b> Due to very serious imprecision <sup>d</sup>	The effect of lopinavir/ritonavir on viral clearance is very uncertain
Acute kidney injury	Based on data from 259 patients in 2 studies	<b>45</b> per 1000	<b>25</b> per 1000	<b>Very low</b> Due to serious risk of bias and very serious imprecision <sup>e</sup>	The effect of lopinavir/ritonavir on acute kidney injury is uncertain
Diarrhoea	Odds ratio: 4.28 (CI 95% 1.99–9.18) Based on data from 370 patients in 4 studies	<b>67</b> per 1000	<b>235</b> per 1000	<b>Low</b> Due to serious risk of bias and imprecision <sup>f</sup>	Lopinavir/ritonavir may increase the risk of diarrhoea
Nausea/ vomiting	Based on data from 370 patients in 4 studies	<b>17</b> per 1000	<b>177</b> per 1000	<b>Low</b> Due to serious risk of bias and imprecision <sup>g</sup>	Lopinavir/ritonavir may increase the risk of nausea/vomiting
Time to clinical improvement	Measured by: Scale: lower better Based on data from 199 patients in 1 study	<b>11.0</b> Days mean	<b>10.0</b> Days mean	<b>Very low</b> Due to serious risk of bias and very serious imprecision <sup>h</sup>	The effect of lopinavir/ritonavir on time to clinical improvement is very uncertain
Duration of hospitalization	Measured by: Scale: lower better Based on data from 5239 patients in 2 studies	<b>12.8</b> Days mean	<b>12.5</b> Days mean	<b>Low</b> Due to serious imprecision and serious risk of bias <sup>i</sup>	Lopinavir/ritonavir may have no effect on duration of hospitalization

Notes:

<sup>a</sup> Systematic review (3). **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.

<sup>b</sup> **Risk of bias: No 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).

<sup>c</sup> **Imprecision: Serious.** Wide confidence intervals.

<sup>d</sup> **Imprecision: Very Serious.** Wide confidence intervals.

<sup>e</sup> **Risk of bias: Serious. Imprecision: Very Serious.**

<sup>f</sup> **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.**

<sup>g</sup> **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.**

<sup>h</sup> **Risk of bias: Serious. Imprecision: Very Serious.**

<sup>i</sup> **Risk of bias: Serious. Imprecision: Serious.** Wide confidence intervals.

Source: Siemieniuk et al., 2020 (3).

## 7.3 Remdesivir (published 20 November 2020)

The second version of the WHO living guideline addressed the use of remdesivir in patients with COVID-19. It followed the preprint 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 (1). The role of these drugs in clinical practice has remained uncertain, with limited prior trial evidence. The WHO SOLIDARITY trial adds 11 266 randomized patients (2570 to remdesivir, 954 to hydroxychloroquine, and 1411 to lopinavir/ritonavir, 6331 to usual care) and has the potential to change practice (1,2).

The WHO GDG started with developing trustworthy recommendations on remdesivir, followed by the now published recommendations on hydroxychloroquine and lopinavir/ritonavir in the third update. 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 (17-18).

### The evidence

The GDG panel requested an update of the living NMA of RCTs of drug treatments for COVID-19, based around important clinical questions to be addressed in the recommendations. The rating of importance of outcomes, selection of estimates for baseline risk and considerations about values and preferences were similar to what is presented in Section 5.

Based on 4 trials with 7333 participants (2, 19-21) the NMA provided relative estimates of effect for patient-important outcomes (Table 4). Of note, none of the included studies enrolled children or adolescents under the age of 19 years old.

**Table 4. Summary of trials and trial characteristics informing the remdesivir recommendation**

Study	N	Country	Mean age (years)	Severity (as per WHO criteria)	% IMV (at baseline)	Treatments (dose and duration)	Outcomes
<b>Biegel (ACTT-1)</b>	1063	United States, Europe, Asia	58.9	Non-severe (11.3%) Severe <sup>a</sup> (88.7%)	44.1%	Remdesivir IV (100 mg/day for 10 days)	-Mortality -Adverse events -Time to clinical improvement
<b>Spinner (SIMPLE MODERATE)*</b>	596	United States, Europe, Asia	56–58	Non-severe (100%)	0%	Remdesivir IV (200 mg at day 1, then 100 mg for 4 days or 9 days)	-Mortality -Time to clinical improvement -Duration of hospitalization -Mechanical ventilation -Adverse events
<b>Pan (SOLIDARITY)</b>	5451	Worldwide	< 50 35% 50–70 47% > 70 18%	Non-severe (24%) Severe <sup>b</sup> (67%) Critical (9%)	8.9%	Remdesivir IV (200 mg at day 1, then 100 mg day 2–10)	-Mortality -Mechanical ventilation
<b>Wang</b>	237	China	65	Severe <sup>c</sup> (100%)	16.1%	Remdesivir IV (100 mg/day for 10 days)	-Mortality -Mechanical ventilation -Adverse events -Viral clearance -Duration of hospitalization -Duration of ventilation -Time to clinical improvement

**Notes:** IMV – invasive mechanical ventilation; IV – intravenous; N – number; NR (not reported); Sx – symptom.

Severity criteria based on WHO definitions unless otherwise stated: <sup>a</sup> defined severe as SpO<sub>2</sub> < 94% on room air OR respiratory rate > 24 breaths /min; <sup>b</sup> defined severe as requiring oxygen support; <sup>c</sup> defined severe as SpO<sub>2</sub> < 94% on room air

\*Only SIMPLE MODERATE was included in the analysis, as SIMPLE SEVERE did not have a placebo/usual care arm.

### 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 – see subgroup in Section 6. Who do the recommendations apply to?) 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, concomitant medications (especially corticosteroids), however 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 comes 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 (15).

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](#). No changes were made for the remdesivir recommendation in this third version of the guideline. Please view Section 5 for a summary of the evidence requested to inform the recommendation, triggered by the WHO SOLIDARITY trial.

Hospitalized patients with COVID-19 infection, regardless of disease severity.

Conditional recommendation against

We suggest against administering remdesivir in addition to usual care.

## **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 does improve patient-important outcomes.

There was no evidence of increased risk of severe adverse events (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 judgement.

### **Certainty of the evidence**

Low

The evidence is based on a linked systematic review and NMA of 4 RCTs; pooling data from 7333 patients hospitalized with various severities of COVID-19 and variably reporting the outcomes of interest to the guideline panel (3). 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 don't 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 Evidence section above), 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 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 does improve 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) or critical (ACTT-1) (2, 19). 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 judgement. 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 are no pharmacokinetic or safety data on remdesivir for children. Given this, the applicability of this recommendation to children is currently uncertain.

## **Practical information**

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 (alanine aminotransferase [ALT] > 5 times normal at baseline) or renal (estimated glomerular filtration rate [eGFR] < 30 mL/min) dysfunction. To date, it can only be administered intravenously, and it has relatively limited availability.

## **PICO**

Population: Patients with COVID-19 infection (all disease severities)  
Intervention: Remdesivir + usual care  
Comparator: Usual care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard care	Remdesivir		
Mortality 28 days	Odds ratio: 0.9 (CI 95% 0.7–1.12) Based on data from 7333 patients in 4 studies <sup>a</sup>	<b>106</b> per 1000	<b>96</b> per 1000	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>b</sup>	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 <sup>c</sup>	<b>105</b> per 1000	<b>95</b> per 1000	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>d</sup>	Remdesivir possibly has little or no effect on mechanical ventilation
Serious adverse events leading to discontinuation	Odds ratio: 1.0 (CI 95% 0.37–3.83) Based on data from 1894 patients in 3 studies <sup>e</sup>	<b>15</b> per 1000	<b>15</b> per 1000	<b>Low</b> Due to very serious imprecision <sup>f</sup>	Remdesivir possibly has little or no effect on serious adverse events leading to discontinuation
Viral clearance 7 days	Odds ratio: 1.06 (CI 95% 0.06–17.56) Based on data from 196 patients in 1 studies <sup>g</sup>	<b>483</b> per 1000	<b>498</b> per 1000	<b>Very low</b> Due to very serious imprecision <sup>h</sup>	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 <sup>i</sup>	<b>56</b> per 1000	<b>48</b> per 1000	<b>Low</b> Due to serious imprecision and serious indirectness <sup>j</sup>	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 studies <sup>k</sup>	<b>16</b> per 1000	<b>19</b> per 1000	<b>Very low</b> Due to very serious imprecision and serious indirectness <sup>l</sup>	We are uncertain whether remdesivir increases or decreases delirium
Time to clinical improvement	Measured by: days Scale: lower better Based on data from 1882 patients in 3 studies <sup>m</sup>	<b>11.0</b> days	<b>9.0</b> days	<b>Low</b> Due to serious imprecision and serious indirectness <sup>n</sup>	Remdesivir possibly has little or no effect on time to clinical improvement
Duration of hospitalization	Measured by: days Scale: lower better Based on data from 1882 patients in 3 studies <sup>o</sup>	<b>12.8</b> days	<b>12.3</b> days	<b>Low</b> Due to serious imprecision and serious indirectness <sup>p</sup>	Remdesivir possibly has little or no effect on duration of hospitalization
Duration of ventilation	Measured by: days Scale: lower better Based on data from 440 patients in 2 studies <sup>q</sup>	<b>14.7</b> days	<b>13.4</b> days	<b>Low</b> Due to very serious imprecision <sup>r</sup>	Remdesivir possibly has little or no effect on duration of ventilation

### Notes:

- <sup>a</sup> Systematic review (3). **Baseline/comparator:** Control arm of reference used for intervention (1).
- <sup>b</sup> **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). <sup>c</sup> Systematic review (3). **Baseline/comparator:** Control arm of reference used for intervention (1).
- <sup>d</sup> **Risk of bias: Serious. Imprecision: Serious.** Wide confidence intervals.
- <sup>e</sup> Systematic review (3). **Baseline/comparator:** Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies.
- <sup>f</sup> **Imprecision: Very Serious.** Wide confidence intervals.
- <sup>g</sup> Systematic review (3). **Baseline/comparator:** Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies.
- <sup>h</sup> **Imprecision: Very Serious.** Wide confidence intervals.
- <sup>i</sup> Systematic review (3). **Baseline/comparator:** Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies.
- <sup>j</sup> **Indirectness: Serious.** Studies used change in serum creatinine rather than patient-important measures of acute kidney injury; **Imprecision: Serious.** Wide 95% credible intervals.
- <sup>k</sup> Systematic review (3). **Baseline/comparator:** Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies.
- <sup>l</sup> **Indirectness: Serious.** Differences between the outcomes of interest and those reported (e.g. short-term/surrogate, not patient-important); **Imprecision: Very Serious.**
- <sup>m</sup> Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies. **Baseline/comparator:** Control arm of reference used for intervention.
- <sup>n</sup> **Indirectness: Serious. Imprecision: Serious.**
- <sup>o</sup> Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies. **Baseline/comparator:** Control arm of reference used for intervention.
- <sup>p</sup> **Indirectness: Serious. Imprecision: Serious.** Wide confidence intervals.
- <sup>q</sup> Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies. **Baseline/comparator:** Control arm of reference used for intervention.
- <sup>r</sup> **Imprecision: Very Serious.** Wide confidence intervals.

### Sources:

Pan et al., 2020 (1); Siemieniuk et al., 2020 (3).

## 7.4 Systemic corticosteroids (published 2 September 2020)

This guideline was triggered on 22 June 2020 by the publication of the preliminary report of the RECOVERY trial, which has now been published as a peer-reviewed paper (7). 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 (22). 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 (3,23). 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.

On 17 July 2020, the panel reviewed evidence from eight RCTs (7184 patients) evaluating systemic corticosteroids vs 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 of Great Britain and Northern Ireland (2104 were randomized to dexamethasone and 4321 were randomized to usual care) (7). 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) (24); dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID19, CoDEX) (25,26); 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) (27); hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP) (28); methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI) (29).

Seven of the trials were conducted in individual countries (Brazil, China, Denmark, France, Spain) while 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 (24). An additional trial, which randomized hospitalized patients with suspected SARS-CoV-2 infection, published on 12 August 2020 (MetCOVID) (30), was included as a supplement in the prospective meta-analysis (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 effect for mortality

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 (15), 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.

However, the panel 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% (16), in order to align with previous WHO guidance (31). See Section 6. Who do the recommendations apply to? for the WHO severity criteria and the three disease severity groups for which the recommendations apply in practice.

The recommendations for corticosteroids below were first published as [WHO living guidance](#) 2 September 2020, and as [BMJ Rapid Recommendations](#) on 5 September, including links to MAGICapp. Please visit the [WHO website](#) guidelines for details (e.g. composition of the guideline panel) and view section text to understand what evidence the panel applied in creating these recommendations. By 15 November 2020 there was no new evidence to suggest any change in the recommendations, as identified in the living systematic review and NMA informing this living guideline.

For patients with severe or critical COVID-19-infection (see disease severity criteria above).

### Recommended

We recommend systemic corticosteroids rather than no corticosteroids.

## 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 (32,33). 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 as a 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.

### 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 (34). 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 (22).

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 underrepresented 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.

### **Practical information**

**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).

### **PICO**

Population: Patients with critical COVID-19  
Intervention: Steroids  
Comparator: Standard care

### **Summary**

**Outline of the evidence on systemic corticosteroids:** While six trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalized patients with COVID-19 and reported mortality data by subgroup, whereas the smaller GLUCOCOVID trial, which also enrolled hospitalized, patients did not. 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 (15), the panel determined that the subgroup effect was sufficiently credible to warrant separate recommendations for severe and non-severe COVID-19.

**Population:** There were data from 1703 critically ill patients in seven trials. RECOVERY, the largest of the seven trials randomized 6425 hospitalized patients in the United Kingdom (2104 were randomized to dexamethasone and 4321 were randomized to usual care). 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 (7). The mortality data from six other smaller trials included approximately 700 critically ill patients (definitions of critical illness varied across studies) enrolled up to 9 June 2020, approximately four-fifths were invasively mechanically ventilated; approximately one-half were randomized to receive corticosteroid therapy, and one-half randomized to no corticosteroid therapy. For patients with severe and non-severe COVID-19, data were only available by relevant subgroup in RECOVERY (3883 patients with severe and 1535 patients with non-severe COVID-19). Because the mortality data from one trial (GLUCOCOVID, n=63) was not reported separately for severe and non-severe COVID-19 (24), the panel reviewed only the data pertaining to the outcome of mechanical ventilation from this trial.

**Interventions:** RECOVERY evaluated the effects of dexamethasone 6 mg given once daily (oral or intravenous) for up to 10 days. Other corticosteroid regimens included: dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID, CoDEX); 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); hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP); methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI); and methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (one trial, GLUCOCOVID) (24). 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).

**Outcomes:** All trials reported mortality 28 days after randomization, except for one trial at 21 days and the another at 30 days.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard Care	Steroids		
Mortality 28 days	Relative risk: 0.79 (CI 95% 0.7–0.9) Based on data from 1703 patients in 7 studies Follow up 28 days	<b>415</b> per 1000	<b>328</b> per 1000	<b>Moderate</b> Due to serious risk of bias <sup>a</sup>	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	<b>116</b> per 1000	<b>86</b> per 1000	<b>Moderate</b> Due to serious risk of bias <sup>b</sup>	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	<b>48</b> per 1000	<b>51</b> per 1000	<b>Low</b> Due to serious indirectness and serious imprecision <sup>c</sup>	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	<b>186</b> per 1000	<b>188</b> per 1000	<b>Low</b> Due to serious indirectness and serious imprecision <sup>d</sup>	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	<b>286</b> per 1000	<b>332</b> per 1000	<b>Moderate</b> Due to serious indirectness <sup>e</sup>	Corticosteroids probably increase the risk of hyperglycaemia
Hypernatraemia	Relative risk: 1.64 (CI 95% 1.32–2.03) Based on data from 5015 patients in 6 studies	<b>40</b> per 1000	<b>66</b> per 1000	<b>Moderate</b> Due to serious indirectness <sup>f</sup>	Corticosteroids probably increase the risk of hypernatraemia
Neuromuscular weakness	Relative risk: 1.09 (CI 95% 0.86–1.39) Based on data from 6358 patients in 8 studies	<b>69</b> per 1000	<b>75</b> per 1000	<b>Low</b> Due to serious indirectness and serious imprecision <sup>g</sup>	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	<b>35</b> per 1000	<b>28</b> per 1000	<b>Low</b> Due to serious indirectness and serious imprecision <sup>h</sup>	Corticosteroids may not increase the risk of neuropsychiatric effects
Duration of hospitalization	Measured by: days Scale: lower better Based on data from 6425 patients in 1 studies	<b>13</b> days	<b>12</b> days	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>i</sup>	Steroids may result in an important reduction in the duration of hospitalizations

**Notes:**

<sup>a</sup> **Risk of bias: Serious.** Lack of blinding.

<sup>b</sup> **Risk of bias: Serious.** Lack of blinding.

<sup>c</sup> **Indirectness: Serious. Imprecision: Serious.**

<sup>d</sup> **Indirectness: Serious. Imprecision: Serious.**

<sup>e</sup> **Indirectness: Serious.**

<sup>f</sup> **Indirectness: Serious.**

<sup>g</sup> **Indirectness: Serious. Imprecision: Serious.**

<sup>h</sup> **Indirectness: Serious. Imprecision: Serious.**

<sup>i</sup> **Risk of bias: Serious.** Lack of blinding; **Imprecision: Serious.** Confidence interval includes no benefit.

**PICO**

Population: Patients with severe COVID-19

Intervention: Steroids

Comparator: Standard care

**Summary**

**Outline of the evidence on systemic corticosteroids:** While six trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalized patients with COVID-19 and reported mortality data by subgroup, whereas the smaller GLUCOCOVID trial, which also enrolled hospitalized, patients did not. 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 (15), the panel determined that the subgroup effect was sufficiently credible to warrant separate recommendations for severe and non-severe COVID-19.

**Population:** There were data from 1703 critically ill patients in seven trials. RECOVERY, the largest of the seven trials randomized 6425 hospitalized patients in the United Kingdom (2104 were randomized to dexamethasone and 4321 were randomized to usual care). 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 (7). The mortality data from six other smaller trials included approximately 700 critically ill patients (definitions of critical illness varied across studies) enrolled up to 9 June 2020, approximately four-fifths were invasively mechanically ventilated; approximately one-half were randomized to receive corticosteroid therapy, and one-half randomized to no corticosteroid therapy. For patients with severe and non-severe COVID-19, data were only available by relevant subgroup in RECOVERY (3883 patients with severe and 1535 patients with non-severe COVID-

19). Because the mortality data from one trial (GLUCOCOVID, n=63) was not reported separately for severe and non-severe COVID-19 (24), the panel reviewed only the data pertaining to the outcome of mechanical ventilation from this trial.

**Interventions:** RECOVERY evaluated the effects of dexamethasone 6 mg given once daily (oral or intravenous) for up to 10 days. Other corticosteroid regimens included: dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID, CoDEX); 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); hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP); methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI); and methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (one trial, GLUCOCOVID) (24). 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).

**Outcomes:** All trials reported mortality 28 days after randomization, except for one trial at 21 days and the another at 30 days.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard care	Steroids		
Mortality 28 days	Relative risk: 0.8 (CI 95% 0.7–0.92) Based on data from 3883 patients in 1 studies Follow up 28 days	<b>334</b> per 1000	<b>267</b> per 1000	<b>Moderate</b> Due to serious risk of bias <sup>a</sup>	Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with 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	<b>116</b> per 1000	<b>86</b> per 1000	<b>Moderate</b> Due to serious risk of bias <sup>b</sup>	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	<b>48</b> per 1000	<b>51</b> per 1000	<b>Low</b> Due to serious indirectness and serious imprecision <sup>c</sup>	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	<b>186</b> per 1000	<b>188</b> per 1000	<b>Low</b> Due to serious indirectness and serious imprecision <sup>d</sup>	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	<b>286</b> per 1000	<b>332</b> per 1000	<b>Moderate</b> Due to serious indirectness <sup>e</sup>	Corticosteroids probably increase the risk of hyperglycaemia
Hypernatraemia	Relative risk: 1.64 (CI 95% 1.32–2.03) Based on data from 5015 patients in 6 studies	<b>40</b> per 1000	<b>66</b> per 1000	<b>Moderate</b> Due to serious indirectness <sup>f</sup>	Corticosteroids probably increase the risk of hypernatraemia

Neuromuscular weakness	Relative risk: 1.09 (CI 95% 0.86–1.39) Based on data from 6358 patients in 8 studies	<b>69</b> per 1000	<b>75</b> per 1000	<b>Low</b> Due to serious indirectness and serious imprecision <sup>g</sup>	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	<b>35</b> per 1000	<b>28</b> per 1000	<b>Low</b> Due to serious indirectness and serious imprecision <sup>h</sup>	Corticosteroids may not increase the risk of neuropsychiatric effects
Duration of hospitalization	Measured by: days Scale: lower better Based on data from 6425 patients in 1 studies	<b>13</b> days	<b>12</b> days	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>i</sup>	Steroids may result in an important reduction in the duration of hospitalizations

**Notes:**

<sup>a</sup> **Risk of bias: Serious.** Lack of blinding.

<sup>b</sup> **Risk of bias: Serious.** Lack of blinding.

<sup>c</sup> **Indirectness: Serious. Imprecision: Serious.**

<sup>d</sup> **Indirectness: Serious. Imprecision: Serious.**

<sup>e</sup> **Indirectness: Serious.**

<sup>f</sup> **Indirectness: Serious.**

<sup>g</sup> **Indirectness: Serious. Imprecision: Serious.**

<sup>h</sup> **Indirectness: Serious. Imprecision: Serious.**

<sup>i</sup> **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.

**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 ruling out a mortality reduction) and risk of bias due to lack of blinding. In making a conditional recommendation against the indiscriminate use of systemic corticosteroids, the panel inferred that most fully informed individuals with non-severe illness would not want to receive systemic corticosteroids, but many could want to consider this intervention through shared decision-making with their treating physician (6).

**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 need not discontinue a course of systemic oral corticosteroids; or other chronic autoimmune diseases). 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 first recommendation).

### Practical information

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

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

**Duration:** While 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.

## PICO

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

## Summary

**Outline of the evidence on systemic corticosteroids:** While six trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalized patients with COVID-19 and reported mortality data by subgroup, whereas the smaller GLUCOCOVID trial, which also enrolled hospitalized, patients did not. 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 (15), the panel determined that the subgroup effect was sufficiently credible to warrant separate recommendations for severe and non-severe COVID-19.

**Population:** There were data from 1703 critically ill patients in seven trials. RECOVERY, the largest of the seven trials randomized 6425 hospitalized patients in the United Kingdom (2104 were randomized to dexamethasone and 4321 were randomized to usual care). 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 (7). The mortality data from six other smaller trials included approximately 700 critically ill patients (definitions of critical illness varied across studies) enrolled up to 9 June 2020, approximately four-fifths were invasively mechanically ventilated; approximately one-half were randomized to receive corticosteroid therapy, and one-half randomized to no corticosteroid therapy. For patients with severe and non-severe covid-19, data was only available by relevant subgroup in RECOVERY (3883 patients with severe and 1535 patients with non-severe covid-19). Because the mortality data from one trial (GLUCOCOVID, n=63) were not reported separately for severe and non-severe COVID-19 (24), the panel reviewed only the data pertaining to the outcome of mechanical ventilation from this trial.

**Interventions:** RECOVERY evaluated the effects of dexamethasone 6 mg given once daily (oral or intravenous) for up to 10 days. Other corticosteroid regimens included: dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID, CoDEX); 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); hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP); methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI); and methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (one trial, GLUCOCOVID) (24). 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).

**Outcomes:** All trials reported mortality 28 days after randomization, except for one trial at 21 days and the another at 30 days.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard care	Steroids		
Mortality 28 days	Relative risk: 1.22 (CI 95% 0.93–1.61) Based on data from 1535 patients in 1 studies Follow up 28 days	<b>176</b> per 1000  Difference: <b>39 more per 1000</b> (CI 95% 12 fewer – 107 more)	<b>215</b> per 1000	<b>Low</b> Due to serious risk of bias, Due to serious imprecision <sup>a</sup>	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	<b>116</b> per 1000  Difference: <b>30 fewer per 1000</b> (CI 95% 48 fewer – 8 fewer)	<b>86</b> per 1000	<b>Moderate</b> Due to serious risk of bias <sup>b</sup>	Systemic corticosteroids probably reduce the need for mechanical ventilation



Duration of hospitalization	Based on data from 6425 patients in 1 study Follow up not reported	<b>13.0</b> <b>12.0</b> Difference: <b>1.0 fewer</b>	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>e</sup>	Steroids may result in an important reduction in the duration of hospitalizations
Gastrointestinal bleeding	Relative risk: 1.06 (CI 95% 0.85–1.33) Based on data from 5403 patients in 30 studies	<b>48</b> per 1000 <b>51</b> per 1000 Difference: <b>3 more per 1000</b> (CI 95% 7 fewer – 16 more)	<b>Low</b> Due to serious indirectness and serious imprecision <sup>d</sup>	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	<b>186</b> per 1000 <b>188</b> per 1000 Difference: <b>2 more per 1000</b> (CI 95% 19 fewer – 24 more)	<b>Low</b> Due to serious indirectness and serious imprecision <sup>e</sup>	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	<b>286</b> per 1000 <b>332</b> per 1000 Difference: <b>46 more per 1000</b> (CI 95% 23 more – 72 more)	<b>Moderate</b> Due to serious indirectness <sup>f</sup>	Corticosteroids probably increase the risk of hyperglycaemia
Hypernatraemia	Relative risk: 1.64 (CI 95% 1.32–2.03) Based on data from 5015 patients in 6 studies	<b>40</b> per 1000 <b>66</b> per 1000 Difference: <b>26 more per 1000</b> (CI 95% 13 more – 41 more)	<b>Moderate</b> Due to serious indirectness <sup>g</sup>	Corticosteroids probably increase the risk of hypernatraemia
Neuromuscular weakness	Relative risk: 1.09 (CI 95% 0.86–1.39) Based on data from 6358 patients in 8 studies	<b>69</b> per 1000 <b>75</b> per 1000 Difference: <b>6 more per 1000</b> (CI 95% 10 fewer – 27 more)	<b>Low</b> Due to serious indirectness and serious imprecision <sup>h</sup>	Corticosteroids may not increase the risk of neuromuscular weakness
Neuro-psychiatric effects	Relative risk: 0.81 (CI 95% 0.41–1.63) Based on data from 1813 patients in 7 studies	<b>35</b> per 1000 <b>28</b> per 1000 Difference: <b>7 fewer per 1000</b> (CI 95% 21 fewer – 22 more)	<b>Low</b> Due to serious indirectness and serious imprecision <sup>i</sup>	Corticosteroids may not increase the risk of neuropsychiatric effects
Duration of hospitalization	Measured by: days Scale: lower better Based on data from 6425 patients in 1 studies	<b>13</b> days <b>12</b> days Difference: <b>null lower</b>	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>j</sup>	Steroids may result in an important reduction in the duration of hospitalizations

**Notes:**

<sup>a</sup> **Risk of bias: Serious.** Lack of blinding; **Imprecision: Serious.**

<sup>b</sup> **Risk of bias: Serious.** Lack of blinding.

<sup>c</sup> **Risk of bias: Serious.** Lack of blinding; **Imprecision: Serious.** Confidence interval includes no benefit.

<sup>d</sup> **Indirectness: Serious. Imprecision: Serious.**

<sup>e</sup> **Indirectness: Serious. Imprecision: Serious.**

<sup>f</sup> **Indirectness: Serious.**

<sup>g</sup> **Indirectness: Serious.**

<sup>h</sup> **Indirectness: Serious. Imprecision: Serious.**

<sup>i</sup> **Indirectness: Serious. Imprecision: Serious.**

<sup>j</sup> **Risk of bias: Serious.** Lack of blinding; **Imprecision: Serious.** Confidence interval includes no benefit.

## 8. 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 hydroxychloroquine and lopinavir/ritonavir identified by the GDG adding to those for corticosteroids and remdesivir in previous versions of the living guideline. These uncertainties may inform future research, i.e. the production of more relevant and reliable 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

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

**Remdesivir:** 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:** 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 – 2801 RCTs as of 1 November 2020 (4) – implies that more reliable and relevant evidence will emerge to inform policy and practice. An overview of registered and ongoing trials for COVID-19 therapeutics is available from [the Infectious Diseases Data Observatory, through their living systematic review of COVID-19 clinical trial registrations](#) (6) and the WHO website (<https://www.covid-nma.com/dataviz/>).

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 (5). Such trials can also adapt their design, recruitment strategies and selection of interventions based on new insights, exemplified by the uncertainties outlined above.

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### **WHO Therapeutics Steering Committee**

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 living guidance.

Janet V Diaz (Lead, Clinical Team for COVID-19 Response, Health Emergency Programme, Geneva); John Appiah (Lead, case management, WHO Regional Office for Africa); Lisa Askie (Quality Assurance of Norms and Standards Department); Silvia Bertagnolio (Communicable and Noncommunicable Diseases Division/Clinical Team for COVID-19 Response); Nedret Emiroglu (Country Readiness Strengthening, Health Emergencies Department); John Grove (Quality Assurance of Norms and Standards Department); Rok Ho Kim (Quality Assurance of Norms and Standards Department); Chiori Kodama (Lead, case management, WHO regional office for the Eastern Mediterranean); Gary Kuniyoshi (WHO Regional Office for the Western Pacific/Health Emergencies Programme); Lorenzo Moja (Health Products Policy and Standards Department); Olufemi Oladapo (Sexual and Reproductive Health and Research Department); Dina Pfeifer (WHO Regional Office for Europe/Health Emergencies Programme); Jacobus Preller (Clinical Team for COVID-19 Response); Pryanka Relan (Integrated Health Services Department/Clinical Team for COVID-19 Response); Ludovic Reveiz (Evidence and Intelligence for Action in Health Department, Incident Management Systems for COVID-19, Pan American Health Organization); Soumya Swaminathan (Office of Chief Scientist); Pushpa Wijesinghe (Lead, case management, Regional Office for South East Asia) Wilson Were (Maternal, Newborn, Child and Adolescent Health and Ageing Department). Supporting project officer: Jacqueline Lee Endt (Health Care Readiness Unit, Health Emergencies Department).

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

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\* Did not participate in deliberations on hydroxychloroquine.

‡ Did not participate in deliberations about remdesivir.

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