Therapeutics and COVID-19

World Health Organization

Sections

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: The evidence base for therapeutics for COVID-19 is increasing rapidly, and some treatments of proven benefit have emerged. Numerous randomized trials of many drugs are underway to further inform practice. This version of the WHO living guideline contains new information and a recommendation on interleukin-6 (IL-6) receptor blockers, including both tocilizumab and sarilumab *(1)(2)(3)*. Publication of the RECOVERY and REMAP-CAP trials addressing IL-6 receptor blockers as a potential treatment for COVID-19 triggered this recommendation.

Recommendations: In this update, the panel makes a strong recommendation to use IL-6 receptor blockers (tocilizumab or sarilumab) in patients with severe or critical COVID-19.

Previous recommendations include:

- 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;
- a conditional recommendation against remdesivir in hospitalized patients with COVID-19;
- a strong recommendation against hydroxychloroquine in patients with COVID-19 of any severity;
- a strong recommendation against lopinavir/ritonavir in patients with COVID-19 of any severity;
- a recommendation against ivermectin in patients with COVID-19 of any severity, except in the context of a clinical trial.

How this guideline was created: 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 or other contributors to the guideline development process. This living guideline represents 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 drugs to prevent and treat COVID-19 *(4)*. These guidelines are also published in the BMJ *(6)*, supported by a living systematic review with network meta-analysis (NMA) that informs the recommendations *(7)(8)*. WHO also partnered with investigators to conduct a prospective meta-analysis (PMA) of randomized trials for IL-6 receptor blocker therapy for COVID-19 *(9)*, in order to rapidly provide additional data and inform guidance development.

The latest evidence: The guideline panel's recommendation on IL-6 receptor blockers (including both tocilizumab and sarilumab) was informed by combining results from a living systematic review and NMA that pooled data from 30 randomized controlled trials (RCTs) with 10 618 participants *(8)*, and a PMA that pooled data from 27 RCTs with 10 930 participants *(9)*, both including only inpatients with severe or critical COVID-19. IL-6 receptor blockers reduce mortality (high certainty evidence, 27 studies, 10 930 patients; odds ratio [OR] 0.86, 95% CI 0.79–0.95; absolute effect estimate 16 fewer deaths per 1000 patients, 95% CI 24 fewer to 6 fewer) and need for invasive mechanical ventilation (IMV) (high certainty evidence, 9 studies, 5686 patients; OR 0.72, 95% CI 0.57-0.90; absolute effect estimate 23 fewer IMV per 1000 patients, 95% CI 35 fewer to 8 fewer). IL-6 receptor blockers may reduce duration of mechanical ventilation (low certainty evidence, 10 studies, 1189 patients; mean difference [MD] 1.2 fewer days, 95% CI 2.3 fewer to 0.1 fewer) and duration of hospitalization (low certainty evidence, 9 studies, 6665 patients; MD 4.5 fewer days, 95% CI 6.7 fewer to 2.3 fewer).

Treatment with IL-6 receptor blockers may not increase secondary bacterial infections (low certainty, 18 studies, 3548 patients; OR 0.95, 95% CI 0.72–1.29; absolute effect estimate 5 fewer per 1000 patients, 95% CI 26 fewer to 26 more). The GDG noted that most of the trials informing this recommendation were performed in high-income settings where the background infection rates differ from many other parts of the world, and so the generalizability of this data is uncertain. The effect on serious adverse events (SAEs) was uncertain (very low certainty evidence due to concerns related serious risk of bias and very serious imprecision from a very low number of events and wide CIs in pooled estimates).

There were no subgroup effects for mortality or other outcomes of interest based on disease severity (critical disease versus severe disease). No within-trial comparisons were possible for levels of inflammatory markers or age. Subgroup analyses evaluating baseline steroid use found greater benefit of IL-6 receptor blockers in patients receiving steroids compared with those who were not (p=0.026), demonstrating that steroid use does not abolish and might enhance the beneficial effect of IL-6 receptor blockers. Since steroids are already strongly recommended in patients with severe and critical COVID-19, we did not formally evaluate the credibility of this subgroup analysis as there would be no rationale for a subgroup recommendation for patients not receiving corticosteroids.

When comparing tocilizumab and sarilumab, based on the PMA, there was no evidence of subgroup effect although data examining tocilizumab were more extensive and therefore more precise. In addition to this subgroup data, the GDG reviewed head-to-head data from REMAP-CAP investigators which demonstrated no difference between tocilizumab and sarilumab in a population of patients all receiving corticosteroids. Finally, the NMA estimate of tocilizumab+steroids versus sarilumab+steroids, incorporating both direct and indirect data, provided moderate certainty data of no different effect between drugs.

Understanding the recommendations: When moving from evidence to the recommendation to use IL-6 receptor blockers (tocilizumab or sarilumab) in severe and critical COVID-19, the panel emphasized the high certainty in improved survival and reduction in the need for IVM. The data only provided low or very low certainty data on the potential harms from treatment. Based on the data presented, the panel decided there was sufficient information to make a strong recommendation for administering either tocilizumab or sarilumab. The panel believed that most well-informed patients would choose to use a drug that improved survival, even if some uncertainty regarding adverse events was present. The panel recognized important resources and access issues around IL-6 receptor blockers.

Info Box

This WHO *Therapeutics and COVID-19: living guideline* now includes a strong recommendation to use IL-6 receptor blockers (tocilizumab or sarilumab) in patients with severe or critical COVID-19. This guideline update was initiated in response to publication of the RECOVERY *(1)* and REMAP-CAP studies *(2)*. The guideline was finalized when new trial data from REMAP-CAP (1020 patients randomized to direct comparison between tocilizumab and sarilumab) were made available to WHO *(3)*.

The section text provides 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 on remdesivir; the third version, published 17 December 2020, provides recommendations on hydroxychloroquine and lopinavir/ritonavir; and the fourth version, published 31 March 2021, provides recommendations on ivermectin *(4)*. This update does not include changes to the recommendations for any of these other drugs.

This living guideline will incorporate new recommendations on other therapies for COVID-19 and updates on existing recommendations. The guideline is therefore written, disseminated, and updated here in MAGICapp, with a user-friendly format and easy to navigate structure that accommodates dynamically updated evidence and recommendations, focusing on what is new while keeping existing recommendations within the guideline.

Please visit the WHO website for the latest version of the guidance *(4)*, also available in the BMJ as Rapid Recommendations *(6)*, together with the living network meta-analysis (LNMA) *(7)*, a major evidence source for the guidelines. For the recommendation on IL-6 receptor blockers, a focused update of the LNMA is available *(8)*, whereas a complementary PMA and the most recent REMAP-CAP results have been published in JAMA *(9)*.

Guidelines with recommendations on prophylaxis against COVID-19 have been published separately *(10)*.

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2. Abbreviations

ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
CAP	community-acquired pneumonia
CI	confidence interval
COVID-19	coronavirus disease 2019
DOI	declaration of interests
eGFR	estimated glomerular filtration rate
GDG	guideline development group
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	guideline review committee
IL-6	interleukin-6
LNMA	living network meta-analysis
MAGIC	Magic Evidence Ecosystem Foundation
MD	mean difference
NMA	network meta-analysis
OIS	optimal information size
OR	odds ratio
PICO	population, intervention, comparator, outcome
PMA	prospective meta-analysis
RCT	randomized controlled trial
RR	relative risk/risk ratio
SAE	serious adverse event
WHO	World Health Organization

3. Background

As of 1 July 2021, over 182 million people worldwide have been diagnosed with COVID-19, according to the WHO dashboard *(11)*. The pandemic has thus far claimed more than 3.9 million lives *(11)*, and although some areas of the world are seeing a drop in case counts, other areas are experiencing a resurgence in cases. Vaccination is beginning to have a substantial impact on case numbers and hospitalizations in a few countries, but limitations in global access to vaccines mean that many populations remain vulnerable *(11)(12)*. Even in vaccinated individuals, uncertainties remain about duration of protection and efficacy of current vaccines against emerging SARS-CoV-2 variants.

Taken together, there remains a need for more effective treatments for COVID-19. The COVID-19 pandemic – and the explosion of both research and misinformation – has highlighted the need for trustworthy, accessible and regularly updated living guidance to place emerging findings into context and provide clear recommendations for clinical practice *(13)*.

This living guideline responds to emerging evidence from RCTs on existing and new drug treatments for COVID-19. More than 3800 trials investigating interventions for COVID-19 have been registered or are ongoing (see section on emerging evidence) *(14)*. Among these are large national and international platform trials (such as RECOVERY, WHO SOLIDARITY, REMAP-CAP and ACTIV) that recruit large numbers of patients in many countries, with a pragmatic and adaptive design *(15)(16)(17)(18)*. These platform trials are currently investigating and reporting on numerous interventions, including antiviral monoclonal antibodies and immunomodulators. This rapidly evolving evidence landscape requires trustworthy interpretation and expeditious clinical practice guidelines to inform clinicians and health care decision-makers.

3.1 What triggered this version of the guideline?

This fifth version of the WHO living guideline addresses the use of IL-6 receptor blockers (tocilizumab and sarilumab) in patients with severe and critical COVID-19. It follows the publication of the RECOVERY and REMAP-CAP RCTs addressing IL-6 receptor blockers as a potential therapeutic option for COVID-19, which suggested the benefit of this class of drugs *(1)(2)*. It was finalized when data from the direct comparison between tocilizumab and sarilumab from REMAP-CAP became available to WHO *(3)*.

IL-6 receptor blockers are used in the treatment of autoimmune diseases such as rheumatoid arthritis. Given the inflammatory cascade and the potential role of IL-6 signalling in the pathogenesis of severe and critical COVID-19, IL-6 receptor blockers are plausible treatments.

3.2 Who made this guideline?

For the IL-6 receptor blocker recommendation, WHO convened an international Guideline Development Group with 34 individuals, of whom 28 were content experts (clinicians, methodologists, scientists) and 4 were patients who had survived COVID-19. The methods chair (methodological expertise) and a clinical chair (content expertise) guided the GDG discussions.

WHO selected GDG members to ensure global geographical representation, gender balance, and appropriate technical and clinical expertise. No GDG member had a conflict of interest. In addition to distribution of a DOI form, during the meeting, the WHO secretariat described the declarations of interests (DOI) process and an opportunity was given to GDG to declare any interests not provided in written form. Web searches also did not identify any conflicts. The MAGIC Evidence Ecosystem Foundation provided methodological experts with high-level expertise in standards and methods for systematic reviews and guideline development, including GRADE. These experts helped to support each of the recommendations. In addition, MAGIC offered innovations in processes (BMJ Rapid Recommendations) and platforms (MAGICapp) for developing living guidance in user-friendly formats. 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 *(6)*.

3.3 How to access and use this guideline

This is a living guideline from WHO. The recommendations included here will be updated, and new recommendations will be added for other drugs for COVID-19.

The guideline is written, disseminated and updated in MAGICapp, with a format and structure that ensures user-friendliness and ease of navigation *(19)*. 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. In addition, the methodologic support team, under the coordination of the Guideline Collaboration Committee (see Section 9), worked with the BMJ to develop the presentation, communication and coordinate the simultaneous scientific publication of the living WHO guidelines *(6)*.

The guideline is available via:

- WHO website in PDF format *(4)*
- MAGICapp in online, multilayered formats
- WHO Academy app
- BMJ Rapid Recommendations *(6)*

The purpose of the online formats and additional tools, such as the infographics, is to make it easier to navigate and make use of the guideline in busy clinical practice. The online multilayered formats are designed to allow end-users to find recommendations first and then drill down to find supporting evidence and other information pertinent to applying the recommendations in practice, including tools for shared decision-making (clinical encounter decision aids) *(19)*.

4. Methods: how this guideline was created

This living WHO guideline was developed according to standards and methods for trustworthy guidelines, making use of an innovative process to achieve efficiency in dynamic updating of recommendations *(4)*. The methods are aligned with the WHO Handbook for guideline development and according to a pre-approved protocol (planning proposal) by the Guideline Review Committee (GRC) *(20)*.

Related guidelines
This living WHO guidance for COVID-19 treatments is related to the larger, more comprehensive guidance for COVID-19 Clinical management: living guidance, which has a wider scope of content and has been regularly updated *(21)*. The first four versions of this WHO *Therapeutics and COVID-19: living guideline*, addressing corticosteroids, remdesivir, hydroxychloroquine, lopinavir/ritonavir and ivermectin, can be accessed via the WHO website *(4)*. Guidelines regarding the use of drugs to prevent (rather than treat) COVID-19 are included in a separate document, WHO Living guideline: Drugs to prevent COVID-19, that can be accessed via the WHO website and the BMJ *(10)*.

Timing
This guidance is living; dynamically updated and globally disseminated once new evidence warrants a change in recommendations *(22)*. The aim is for a 1 month timeframe from the public availability of trial data that trigger the guideline development process to WHO publication, while maintaining standards for trustworthy guidelines (*WHO Handbook for Guideline Development*) *(19)(20)*.

Stepwise approach
Here we outline the approach, involving simultaneous processes, taken to improve efficiency and timeliness of development and dissemination of living, trustworthy guidance.

Step 1: Evidence monitoring and mapping and triggering of evidence synthesis
Comprehensive daily monitoring of all emerging RCTs occurs on a continuous basis, within the context of the living systematic review and NMA, using experienced information specialists, who review all relevant information sources for new RCTs addressing interventions for COVID-19. Once practice-changing evidence, or increasing international interest, are identified, the WHO Therapeutics Steering Committee triggers the guideline development process. The trigger for producing or updating specific recommendations is based on the following (any of the three may initiate a recommendation):

- likelihood to change practice;
- sufficient RCT data on therapeutics to inform the high-quality evidence synthesis living systematic review;
- relevance to a global audience.

Step 2: Convening the GDG
The pre-selected expert GDG (see Section 9) convened on three occasions to address IL-6 receptor blockers. The first meeting, held 4 February 2021, reviewed the basics of GRADE methodology including formulating population, intervention, comparator, outcome (PICO) questions and subgroups of interests, and prioritization of patient-important outcomes. At this meeting the GDG finalized the PICOs and pre-specified subgroups of interest, and reviewed evidence summaries and pre-specified subgroup analyses. Subsequent to the meeting, the GDG participated, through email correspondence, in an outcome prioritization exercise. At the second meeting, held on 29 April 2021, the GDG reviewed pre-specified subgroup analyses, and considered an individual patient perspective and contextual factors for countries and health care systems, and a recommendation was drafted. At the third meeting, held on 3 June 2021, the GDG were presented with updated evidence summaries including most recent data from REMAP-CAP and created a final recommendation for IL-6 receptor blockers, with full consensus.

Step 3: Evidence synthesis
The living systematic review/NMA team, as requested by the WHO Therapeutics Steering Committee, performed an independent systematic review to examine the benefits and harms of the intervention *(7)*. The systematic review team includes systematic review experts, clinical experts, clinical epidemiologists and biostatisticians. Team members have expertise in GRADE methodology and rating certainty of evidence specifically in NMAs. The NMA team considered deliberations from the initial GDG meeting, specifically focusing on the outcomes and subgroups prioritized by the GDG.

For the IL-6 receptor blocker guideline, the GDG also considered data from a WHO-sponsored PMA which included some previously unpublished data evaluating sarilumab that was subsequently included in the NMA *(9)*. The PMA investigators carefully evaluated risk of bias in the included trials using the Cochrane 2.0 tool, and this was used to inform the GRADE certainty assessment. This PMA was used to summarize the data evaluating the outcome of mortality.

To conduct the subgroup analyses based on age, IL-6 drug (tocilizumab versus sarilumab), disease severity (severe versus critical illness related to COVID-19) and baseline steroid use, Professor Andrew Owen (see Section 9) provided hypothesized direction on analyses. Credibility of subgroups were rated by the methods team based on the ICEMAN tool *(23)*.

Step 4: Final recommendations

The GRADE approach provided the framework for establishing evidence certainty and generating both the direction and strength of recommendations *(24)(25)*. While *a priori* voting rules informed procedures if the GDG failed to reach consensus, these procedures proved unnecessary for this recommendation.

The following key factors informed transparent and trustworthy recommendations:

- absolute benefits and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE summary of findings tables) *(26)*;
- quality/certainty of the evidence *(24)(27)*;
- values and preferences of patients *(28)*;
- resources and other considerations (including considerations of feasibility, applicability, equity) *(28)*;
- effect estimates and confidence intervals for each outcome, with an associated rating of certainty in the evidence, as presented in summary of findings tables. If such data are not available, the GDG reviews narrative summaries *(26)*;
- recommendations are rated as either conditional or strong, as defined by GRADE. If the GDG members disagree regarding the evidence assessment or strength of recommendations, WHO will apply voting according to established rules *(25)(28)*.

Step 5: External and internal review

The WHO guideline was reviewed by pre-specified external reviewers (see Section 9) and approved by the WHO GRC.

5. The latest evidence

This section outlines what information the GDG requested and used in making their recommendation for IL-6 receptor blockers. In addition to the RECOVERY and REMAP-CAP trial publications from February 2021 *(1)(2)*, new trial data from 1020 patients randomized head-to-head to either tocilizumab or sarilumab in REMAP-CAP were made available to the WHO on 1 June 2021 *(3)*. This new evidence, synthesized through the LNMA and the PMA *(7)(8)(9)*, reduced uncertainties regarding potential differential effects between IL-6 receptor blocker drugs (see section 7.1).

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

Tocilizumab and sarilumab are monoclonal antibodies approved for use in rheumatoid arthritis. They antagonize the membrane bound and soluble forms of the IL-6 receptor (IL-6R/sIL-6R). Tocilizumab is approved for intravenous use in rheumatoid arthritis and sarilumab for subcutaneous use, although in COVID-19 both have been studied intravenously. At the studied doses in COVID-19, both medicines are expected to achieve very high levels of receptor occupancy based upon studies in rheumatoid arthritis *(29)*. IL-6 inhibitors are being repurposed in terms of indication but not in terms of the primary pharmacological mechanism of action. Efficacy in COVID-19 depends upon the importance of IL-6 signalling in the pathophysiology of the disease, rather than upon whether the doses used achieve target concentrations.

Benefits and harms
The GDG members prioritized outcomes (rating from 1 [not important] to 9 [critical]) taking a patient perspective. The GDG prioritized outcomes (Table 1). The GDG's questions were structured using the PICO format (see evidence profile under the recommendations). These prioritized outcomes were used to update the LNMA *(7)(8)*.

Table 1. GDG outcome rating from an inpatient perspective

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

SD: standard deviation.
Note: 1: not important, 9: critically important.

Evidence summary

The evidence summary was based on 30 trials and 10 618 participants for which the NMA *(8)* provided relative estimates of effect for all patient-important outcomes except mortality, which came from the PMA *(9)*. Of the trials included in the NMA, all were registered and examined patients with severe or critical illness related to COVID-19 (trial characteristics table available upon request). Of the trials, 37% were published in peer-reviewed journals, 3% were available as preprints and 60% were completed but unpublished *(8)*. The evidence summary for mortality was based on 27 trials and 10 930 participants from the PMA *(9)*. We used the PMA for mortality as it included some additional unpublished data that reported on this outcome. The GDG recognized that usual care is likely variable between centres and regions, and has evolved over time. However, given all of the data come from RCTs, use of these co-interventions that comprise usual care would be expected to be balanced between study patients randomized to either the intervention or usual care arms.

Based on pooled data, IL-6 receptor blockers reduce mortality (high certainty evidence, 27 studies, 10 930 patients; odds ratio [OR] 0.86, 95% CI 0.79–0.95; absolute effect estimate 16 fewer deaths per 1000 patients, 95% CI 24 fewer to 6 fewer) (9) and need for IMV (high certainty evidence, 9 studies, 5686 patients; OR 0.72, 95% CI 0.57–0.90; absolute effect estimate 23 fewer IMV per 1000 patients, 95% CI 35 fewer to 8 fewer) (8). IL-6 receptor blockers may reduce duration of both mechanical ventilation (low certainty evidence, 10 studies, 1189 patients; mean difference [MD] 1.2 fewer days, 95% CI 2.3 fewer to 0.1 fewer) and hospitalization (low certainty evidence, 9 studies, 6665 patients; MD 4.5 fewer days, 95% CI 6.7 fewer to 2.3 fewer) (8).

Treatment with IL-6 receptor blockers may not increase secondary bacterial infections (low certainty, 18 studies, 3548 patients; OR 0.95, 95% CI 0.72–1.29; absolute effect estimate 5 fewer per 1000 patients, 95% CI 26 fewer to 26 more). The effect on SAEs was uncertain (very low certainty evidence) due to concerns related to serious risk of bias and very serious imprecision from a very low number of events and, in some cases, wide confidence intervals (8).

Subgroup analysis

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

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

When comparing tocilizumab and sarilumab, based on the PMA, there was no evidence of a subgroup effect (9). However, there were more data, and therefore greater precision, for tocilizumab+steroids versus steroids alone (OR 0.77, 95% CI 0.68–0.87) as compared to sarilumab+steroids versus steroids alone (OR 0.92, 95% CI 0.61–1.38). In addition to these subgroup data, the GDG reviewed head-to-head data from REMAP-CAP investigators which demonstrated no difference between tocilizumab as compared with sarilumab in a population of patients all receiving corticosteroids (36.5% mortality with tocilizumab, 33.9% mortality with sarilumab). The NMA estimate of tocilizumab+steroids versus sarilumab+steroids, incorporating both direct and indirect data, provided moderate certainty data of no difference between the drugs (OR 1.07, 95% CI 0.86–1.34) (7)(8).

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 IL-6 receptor blockers compared with usual care across all patient-important outcomes. 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 ratios [RR], OR) obtained from the living NMA and PMA.

The control arm of the WHO SOLIDARITY trial (16), performed across a wide variety of countries and geographical regions, was identified by the GDG as generally representing the most relevant source of evidence for baseline risk estimates for mortality and mechanical ventilation for severely and critically ill patients with COVID-19. 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. The GDG judged 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.

Systemic corticosteroids now represent standard of care in patients with severe and critical COVID-19 (see strong recommendation issued by WHO September 2020) (4). Therefore, the baseline risk estimates in the IL-6 receptor blocker evidence summaries were adjusted for treatment effects of corticosteroids for mortality and mechanical ventilation. This warranted an update of the evidence summaries for corticosteroids, with SOLIDARITY (16) replacing the original United Kingdom cohort study informing the initial (and considerably higher) baseline risk estimates for mortality (30).

Values and preferences

We had insufficient information to provide the GDG with a trustworthy description of patient experiences or values and preferences regarding treatment decisions for COVID-19 drug treatments. The GDG therefore relied on their own judgments of what well-informed patients would value after carefully balancing the benefits, harms and burdens of treatment. The GDG included four patient-partners who had lived experience with COVID-19.

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

- Most patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on outcomes they consider important. This was particularly so when evidence suggested treatment effects, if they do exist, are small, and the possibility of important harm remains.
- In an alternative situation with larger benefits and less uncertainty regarding both benefits and harms, more patients would be inclined to choose the intervention.

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?

Info Box

The guideline for COVID-19 therapeutics applies to all patients with COVID-19. For some drugs (such as corticosteroids), recommendations may differ based on the severity of COVID-19 disease. The GDG used the WHO severity definitions based on clinical indicators, adapted from WHO COVID-19 disease severity categorization (see below) *(21)*. 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 GDG noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously when used to define disease severity. For example, clinicians must use their judgment to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, a saturation 90–94% on room air is abnormal (in patient with normal lungs) and can be an early sign of severe disease, if patient is on a downward trend. Generally, if there is any doubt, the GDG suggested erring on the side of considering the illness as severe.
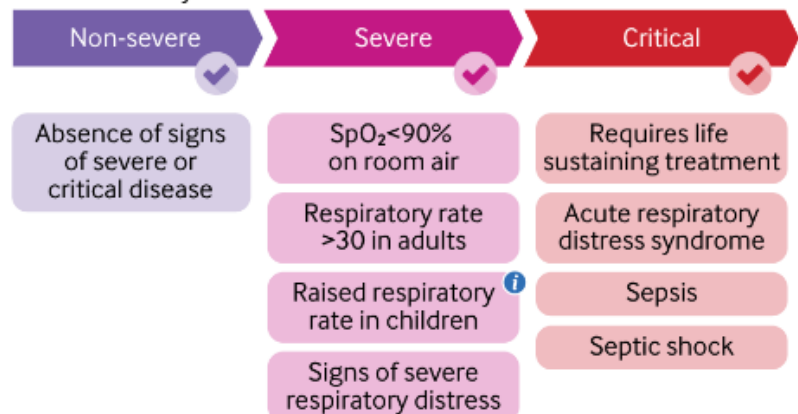
The infographic illustrates these three disease severity groups and key characteristics to apply in practice.

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

7. Recommendations for therapeutics

7.1 IL-6 receptor blockers

> Recommended   New
>
> We recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab) for patients with severe or critical COVID-19 infection.
>
> --
>
> *Corticosteroids have previously been strongly recommended in patients with severe and critical COVID-19 (4), and we recommend patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers.*

Practical info

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

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

Dose: Tocilizumab is dosed at 8 mg per kilogram of actual body weight, up to a maximum of 800 mg. Sarilumab is most commonly dosed at 400 mg, consistent with what was used in REMAP-CAP (3). Renal dose adjustment is not currently warranted for either drug.

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

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

Evidence to Decision

> **Benefits and harms**
>
> IL-6 receptor blockers reduce mortality and need for mechanical ventilation based on high certainty evidence. Low certainty evidence suggests they may also reduce duration of mechanical ventilation and hospitalization (8)(9).
>
> The evidence regarding the risk of SAEs is uncertain. Low certainty evidence suggested that the risk of bacterial infections in the context of immunosuppression treatment with IL-6 receptor blockers may be similar to usual care (8). However the GDG had some concerns that, given the short-term follow-up of most trials and the challenges associated with accurately capturing adverse events such as bacterial or fungal infection, the evidence summary may under-represent the risks of treatment with IL-6 receptor blockers. Furthermore, the trials of IL-6 receptor blockers that inform this recommendation were mostly performed in high-income countries where the risk of certain infectious complications may be less than in some

other parts of the world, and so the generalizability of the data on adverse events is unclear. We did not have any data examining differential risk of harm based on whether patients received one or two doses of IL-6 receptor blocker.

Subgroup analyses indicated no effect modification based on IL-6 receptor blocker drug (sarilumab or tocilizumab) or disease severity (critical vs severe) and therefore this recommendation applies to all adult patients with either severe or critical COVID-19 *(23)*. We were unable to examine subgroups based on elevation of inflammatory markers or age due to insufficient trial data (see Section 5). Subgroup analyses evaluating baseline steroid use found greater benefit of IL-6 receptor blockers in patients receiving steroids compared with those who were not (p=0.026), demonstrating that steroid use does not abolish and might enhance the beneficial effect of IL-6 receptor blockers. Since steroids are already strongly recommended in patients with severe and critical COVID-19, we did not formally evaluate the credibility of this subgroup analysis as there would be no rationale for a subgroup recommendation for patients not receiving corticosteroids.

Certainty of the evidence

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

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

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

Preference and values

Applying the agreed values and preferences (see Section 5), the majority of the GDG inferred that almost all well-informed patients would want to receive IL-6 receptor blockers. The benefit of IL-6 receptor blockers on mortality was deemed of critical importance to patients, despite the very low certainty around SAEs. The GDG anticipated little variation in values and preferences between patients for this intervention.

Resources and other considerations

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

At a time of drug shortage, it may be necessary to prioritize use of IL-6 receptor blockade through clinical triage *(21)*. Many jurisdictions have suggested mechanisms for triaging use of these treatments. These include prioritizing patients with the highest baseline risk for mortality (e.g. those with critical disease over those with severe disease), in whom the absolute benefit of treatment is therefore greatest. For example, despite consistent relative effects (OR 0.86 for mortality) with IL-6 receptor blockers, the absolute risk reduction for mortality in the critically ill would be 31 fewer deaths per 1000 (95% CI 11 to 47 fewer deaths) and in the severely ill would be 13 fewer deaths per 1000 (95% CI 5 to 19 fewer deaths).

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

Acceptability and feasibility

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

Justification

When moving from evidence to the strong recommendation to use IL-6 receptor blockers (tocilizumab or sarilumab) in patients with severe or critical COVID-19, the GDG emphasized the high certainty evidence of improved survival and reduction in need for IVM. Additional trial data from REMAP-CAP (see latest evidence section) *(3)* provided more conclusive evidence regarding the equivalence of tocilizumab and sarilumab.

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

Subgroup analyses

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

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

Applicability

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

Clinical question/ PICO

Population:	Patients with COVID-19 infection (severe and critical)
Intervention:	IL-6 inhibitor
Comparator:	Standard care

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention IL-6 inhibitor	Certainty of the evidence (Quality of evidence)	Plain text summary
Mortality (severe and critically ill patients)	Odds ratio 0.86 (CI 95% 0.79—0.95) Based on data from 10 930 patients in 27 studies. [1] (Randomized controlled)	**130** per 1000	**114** per 1000 Difference: **16 fewer** per 1000 (CI 95% 24 fewer — 6 fewer)	High	IL-6 inhibitors reduce mortality.
Mechanical ventilation	Odds ratio 0.72 (CI 95% 0.57—0.90) Based on data from 5686 patients in 9 studies. [2] (Randomized controlled)	**86** per 1000	**63** per 1000 Difference: **23 fewer** per 1000 (CI 95% 35 fewer — 8 fewer)	High	IL-6 inhibitors reduce need for mechanical ventilation.
Adverse events leading to drug discontinuation	Odds ratio 0.5 (CI 95% 0.03—9.08) Based on data from 815 patients in 2 studies. [3] (Randomized controlled)	**9** per 1000	**5** per 1000 Difference: **4 fewer** per 1000 (CI 95% 9 fewer — 67 more)	Very low Due to serious risk of bias and very serious imprecision [4]	The effect of IL-6 inhibitors on adverse events leading to discontinuation is uncertain.
Bacterial infections	Odds ratio 0.95 (CI 95% 0.72—1.29) Based on data from 3548 patients in 18 studies. [3] (Randomized controlled)	**101** per 1000	**96** per 1000 Difference: **5 fewer** per 1000 (CI 95% 26 fewer — 26 more)	Low Due to serious risk of bias and serious imprecision [5]	IL-6 inhibitors may not increase secondary bacterial infections.
Duration of mechanical ventilation	Lower better Based on data from: 1189 patients in 10 studies. [3] (Randomized controlled)	**14.7** (Mean)	**13.5** (Mean) Difference: **MD 1.2 lower** (CI 95% 2.3 lower — 0.1 lower)	Low Due to serious risk of bias and serious imprecision [6]	IL-6 inhibitors may reduce duration of mechanical ventilation.
Duration of hospitalization	Lower better Based on data from: 6665 patients in 9 studies. [3] (Randomized controlled)	**12.8** (Mean)	**8.3** (Mean) Difference: **MD 4.5 lower** (CI 95% 6.7 lower — 2.3 lower)	Low Due to serious risk of bias and serious inconsistency [7]	IL-6 inhibitors may reduce duration of hospitalization.

1. Systematic review (9). **Baseline/comparator:** Primary study (16). Baseline risk for mortality and mechanical ventilation were derived from the WHO SOLIDARITY trial for patients with severe and critical COVID-19, adjusted for corticosteroids as part of standard of care (16% baseline risk x RR 0.79 for corticosteroids = 13%). The control arm of the WHO SOLIDARITY trial, performed across a wide variety of countries and geographical regions, was identified by the GDG panel as generally representing the most relevant source of evidence for baseline risk estimates for mortality and mechanical ventilation for severely and critically ill patients with COVID-19.

2. Systematic review (8). **Baseline/comparator:** Primary study (16). Baseline risk for mortality and mechanical ventilation were derived from the WHO SOLIDARITY trial for patients with severe and critical COVID-19, adjusted for corticosteroids as part of standard of care (16% baseline risk x RR 0.79 for corticosteroids = 13%). The control arm of the WHO

SOLIDARITY tria, performed across a wide variety of countries and geographical regions, was identified by the GDG panel as generally representing the most relevant source of evidence for baseline risk estimates for mortality and mechanical ventilation for severely and critically ill patients with COVID-19.

3. Systematic review (8). **Baseline/comparator:** Control arm of reference used for intervention. We used the median event rate for all patients randomized to usual care across included studies.

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

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

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

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

7.2 Ivermectin (published 31 March 2021)

The fourth version of the WHO living guideline addressed the use of ivermectin in patients with COVID-19. It followed the increased international attention on ivermectin as a potential therapeutic option. While ivermectin is also being investigated for prophylaxis, the guideline only addressed its role in the treatment of COVID-19.

Ivermectin is relatively inexpensive and accessible, and some countries had already witnessed its widespread use in the treatment of COVID-19; in other countries, there was increasing pressure to do so (31). In response to this international attention, the WHO GDG provided recommendations on ivermectin for treatment of COVID-19.

Mechanism of action
Ivermectin is an antiparasitic agent that interferes with nerve and muscle function of helminths through binding glutamate-gated chloride channels (32). Based on in vitro experiments, some have postulated that ivermectin may have a direct antiviral effect against SARS-CoV-2. However, in humans the concentrations needed for in vitro inhibition are unlikely to be achieved by the doses proposed for COVID-19 (33)(34)(35). Ivermectin had no impact on SARS-CoV-2 viral RNA in the Syrian golden hamster model of SARS-CoV-2 infection (36). The proposed mechanism remains unclear: multiple targets have been proposed based upon either analogy to other viruses with very different life cycles, or, like several hundred other candidates, simulations indicating molecular docking with multiple viral targets including spike, RdRp and 3CLpro (37)(38)(39)(40)(41). No direct evidence for any mechanism of antiviral action against SARS-CoV-2 currently exists.

Some have proposed, based predominantly upon research in other indications, that ivermectin has an immunomodulatory effect, but again the mechanism remains unclear. Historical data showed that ivermectin improved survival in mice given a lethal dose of lipopolysaccharide (42), and has benefits in murine models of atopic dermatitis and allergic asthma (43)(44). For SARS-CoV-2, one hypothesis suggests immunomodulation mediated by allosteric modulation of the alpha-7 nicotinic acetylcholine receptor (indirectly by modulating the activity of ligands of the receptor). Although investigators have demonstrated this action in vitro, concentrations used in these experiments have been even higher than those required for an antiviral effect (45), and therefore very unlikely to be achieved in humans. In the Syrian golden hamster model of SARS-CoV-2 infection, ivermectin resulted in some changes in pulmonary immune phenotype consistent with allosteric modulation of the alpha-7 nicotinic acetylcholine receptor (36). However, ivermectin did not appear to rescue body weight loss which is a hallmark of disease in this model, and drug concentrations were not measured to extrapolate to those achieved in humans. Taken together, there remains great uncertainty regarding the relevance of any immunomodulatory or anti-inflammatory action of ivermectin.

Benefits and harms
The GDG members prioritized outcomes (rating from 1 [not important] to 9 [critical]) taking a patient's perspective. The panel prioritized outcomes from both an inpatient (same as for IL-6 inhibitor) and outpatient (Table 1) perspective. The panel's questions were structured using the PICO format (see evidence profile under the recommendations). These prioritized outcomes were used to update the LNMA.

Evidence summary

The evidence summary was based on 16 trials and 2407 participants for which the NMA provided relative estimates of effect for patient-important outcomes. Of the included trials, 75% examined patients with non-severe disease and 25% included both severe and non-severe patients. A number of the included trials did not report on our outcomes of interest. Of the trials, 25% were published in peer-reviewed journals, 44% were available as preprints and 31% were completed but unpublished (See Table on trial characteristics). We excluded a number of quasi-RCTs *(46)(47)(48)(49)*.

Subgroup analysis

The NMA team performed subgroup analyses which could result in distinct recommendations by subgroups. From the available data, subgroup analyses were only possible by dose of ivermectin and considering the outcomes of mortality, mechanical ventilation, admission to hospital, and adverse events leading to drug discontinuation. The ivermectin dose subgroup analyses were performed from the direct comparison of ivermectin versus usual care. For these analyses, meta-regression was used to evaluate the effect of cumulative dose as a continuous variable, and further adding a co-variate for single vs multiple dosing regimens. This approach was based on input from the pharmacology experts (led by Professor Andrew Owen) who performed pharmacokinetic simulations across trial doses, and found that cumulative ivermectin dose was expected to correlate with key pharmacokinetic parameters when single- and multiple-dose studies were segregated. It should be noted that the included trials did not directly assess the pharmacokinetics of ivermectin, and our approach was based upon simulations validated where possible against published pharmacokinetics in humans. The panel used a pre-specified framework incorporating the ICEMAN tool to assess the credibility of subgroup findings *(23)*.

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

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 ivermectin compared with usual care across all patient-important outcomes. The absolute effects of treatment are informed by the prognosis (i.e. baseline risk estimates) combined with the relative estimates of effects (e.g. RR, OR) obtained from the NMA.

The control arm of the WHO SOLIDARITY trial *(16)*, performed across a wide variety of countries and geographical regions, was identified by the GDG panel as generally representing the most relevant source of evidence for baseline risk estimates for mortality and mechanical ventilation. 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. However, the SOLIDARITY trial only enrols patients who are hospitalized with COVID-19. Since ivermectin has been proposed for use and often studied in outpatients, on this occasion the panel used the median of risk in the standard care arms of the included trials for baseline risk estimates for these outcomes. When applying the evidence to a particular patient or setting, for any medication with a convincing effect, clinicians should consider the individual's risk of mortality and need for mechanical ventilation. In view of the study designs, the GDG judged 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

We had insufficient information to provide the GDG with a trustworthy description of patient experiences or values and preferences regarding treatment decisions for COVID-19 drug treatments. The GDG therefore relied on their own judgments of what well-informed patients would value after carefully balancing the benefits, harms and burdens of treatment. The GDG included four patient-partners who had lived experience with COVID-19.

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

- Most patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on outcomes they consider important. This was particularly so when evidence suggested treatment effects, if they do exist, are small, and the possibility of important harm remains.
- In an alternative situation with larger benefits and less uncertainty regarding both benefits and harms, more patients would be inclined to choose the intervention.
- 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.

Info Box

The recommendation concerning ivermectin was published on 31 March 2021 as the fourth version of the WHO living guideline and in the BMJ as Rapid Recommendations. No changes were made for the ivermectin recommendation in this fifth version of the guideline. Please view the section text for a summary of the evidence requested to inform the recommendation.

Only in research settings

We recommend not to use ivermectin in patients with COVID-19 except in the context of a clinical trial.

- -

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

A recommendation to only use a drug in the setting of clinical trials is appropriate when there is very low certainty evidence and future research has a large potential for reducing uncertainty about the effects of the intervention and for doing so at reasonable cost.

Practical info

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

Evidence to Decision

Benefits and harms

The effects of ivermectin on mortality, mechanical ventilation, hospital admission, duration of hospitalization and viral clearance remain uncertain because of very low certainty of evidence addressing each of these outcomes. Ivermectin may have little or no effect on time to clinical improvement (low certainty evidence). Ivermectin may increase the risk of SAEs leading to drug discontinuation (low certainty evidence).

Subgroup analyses indicated no effect modification based on dose. We were unable to examine subgroups based on patient age or severity of illness due to insufficent trial data (see section text). Therefore, we assumed similar effects in all subgroups. This recommendation applies to patients with any disease severity and any duration of symptoms.

Certainty of the evidence

For most key outcomes, including mortality, mechanical ventilation, hospital admission, duration of hospitalization and viral clearance, the GDG considered the evidence of very low certainty. Evidence was rated as very low certainty primarily because of very serious imprecision for most outcomes: the aggregate data had wide confidence intervals and/or very few events. There were also serious concerns related to risk of bias for some outcomes, specifically lack of blinding, lack of trial pre-registration, and lack of outcome reporting for one trial that did not report mechanical ventilation despite pre-specifying it in their protocol (publication bias).

For more details, see the Justification section for this recommendation. For other outcomes, including SAEs and time to clinical improvement, the certainty of the evidence was low.

Preference and values

Applying the agreed values and preferences (see Section 5), the GDG inferred that almost all well-informed patients would want to receive ivermectin only in the context of a randomized trial, given that the evidence left a very high degree of uncertainty in effect on mortality, need for mechanical ventilation, need for hospitalization and other critical outcomes of interest and there was a possibility of harms, such as treatment-associated SAEs. The panel anticipated little variation in values and preferences between patients when it came to this intervention.

> **Resources**
>
> Ivermectin is a relatively inexpensive drug and is widely available, including in low-income settings. The low cost and wide availability do not, in the GDG's view, mandate the use of a drug in which any benefit remains very uncertain and ongoing concerns regarding harms remain. Although the cost may be low per patient, the GDG raised concerns about diverting attention and resources away from care likely to provide a benefit such as corticosteroids in patients with severe COVID-19 and other supportive care interventions. Also, use of ivermectin for COVID-19 would divert drug supply away from pathologies for which it is clearly indicated, potentially contributing to drug shortages, especially for helminth control and elimination programmes. Other endemic infections that may worsen with corticosteroids should be considered. If steroids are used in the treatment of COVID-19, empiric treatment with ivermectin may still be considered in Strongyloidiasis endemic areas, at the discretion of clinicians overseeing treatment, albeit not for treatment of COVID-19 itself.

Justification

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

Compared with previous drugs evaluated as part of the WHO *Therapeutics and COVID-19: living guideline*, currently there are far fewer RCT data available for ivermectin. The existing data on ivermectin also have a substantially higher degree of uncertainty, with included trials having enrolled substantially fewer patients with far fewer events. Fig. 1 is the network map for mortality from the accompanying LNMA informing this guideline. Within the map, the size of the nodes (blue circles) correlates with the number of patients randomized to that intervention across all included trials; it is clear that the size of the ivermectin node is much smaller than other interventions which have been subjected to WHO guidelines, such as corticosteroids, hydroxychloroquine and lopinavir/ritonavir. The width of the line connecting two specific interventions correlates with the number of patients and number of events in this comparison across all trials; again, the lines connecting ivermectin to standard of care, as well as to the comparators lopinavir/ritonavir and hydroxychloroquine, are much thinner compared with drugs that have been assessed previously in this guideline.

Fig. 1. Network map from the living network meta-analysis informing this guideline
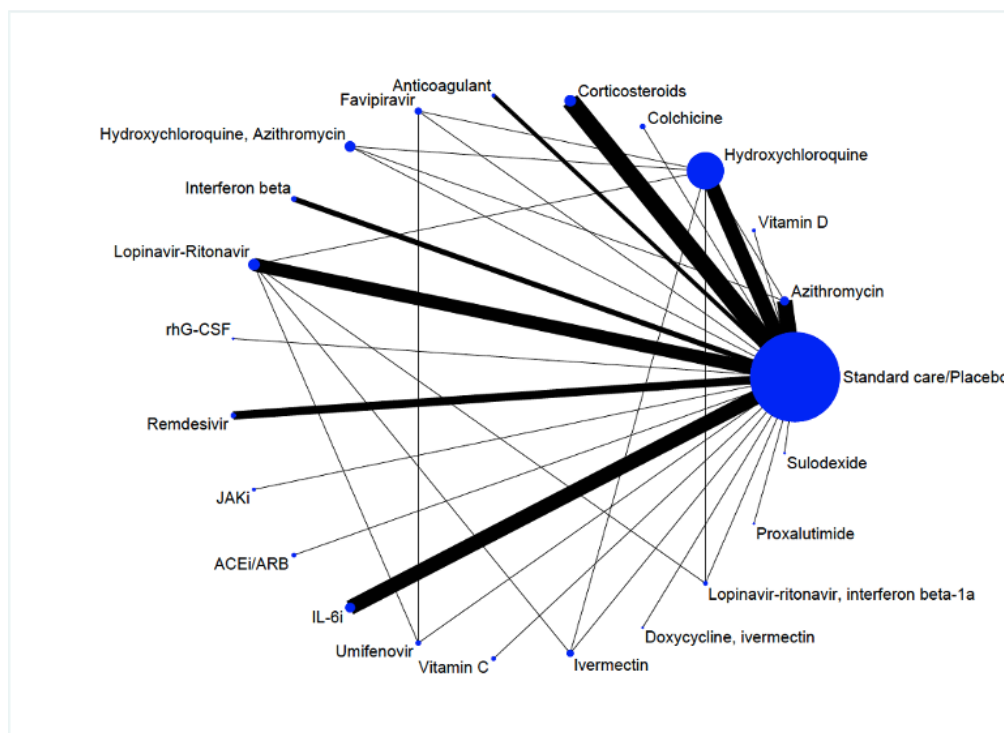

Drugs for which this guideline has already addressed with recommendations include corticosteroids, remdesivir, hydroxychloroquine and lopinavir/ritonavir.

High degree of uncertainty

The certainty in effect estimates for ivermectin on the main outcomes of interest, including mortality, is very low and therefore the effect of ivermectin on these outcomes remains uncertain. There are two domains that contribute to this uncertainty: serious risk of bias; and serious imprecision. Although 16 RCTs contributed to the evidence summary informing this drug, only five directly compared ivermectin with standard of care and reported mortality *(50)(51)(52)(53)(54)*. Of note, and in keeping with our methodology, the LNMA team excluded quasi-randomized trials, or any RCT that did not use explicit randomization techniques. Of these five RCTs, two *(50)(51)* were at high risk of bias, due to inadequate blinding. One of these two trials *(50)* also started enrolling and randomizing patients prior to the protocol being publicly posted, another factor that contributes to an increased risk of bias. The potential impact of risk of bias is exemplified by subgroup analyses for mortality based on trial risk of bias. As demonstrated in the forest plot (Fig. 2), the pooled estimate across all five RCTs that directly compare ivermectin with standard care suggests a reduction in mortality with ivermectin, but this effect is not apparent if we only consider the trials at low risk of bias (which together contribute nearly two-thirds of the evidence). This finding increases the degree of uncertainty regarding the true effect of ivermectin on mortality. Consistent with the direct evidence, a similar phenomenon is observed with the indirect evidence comparing ivermectin to standard of care (via comparisons against hydroxychloroquine and lopinavir/ritonavir). The indirect evidence suggesting a reduction in mortality with ivermectin is driven almost entirely by one study which is at high risk of bias *(55)* due to a lack of detailed description of blinding or randomization and the lack of a publicly available study protocol (figure not shown).

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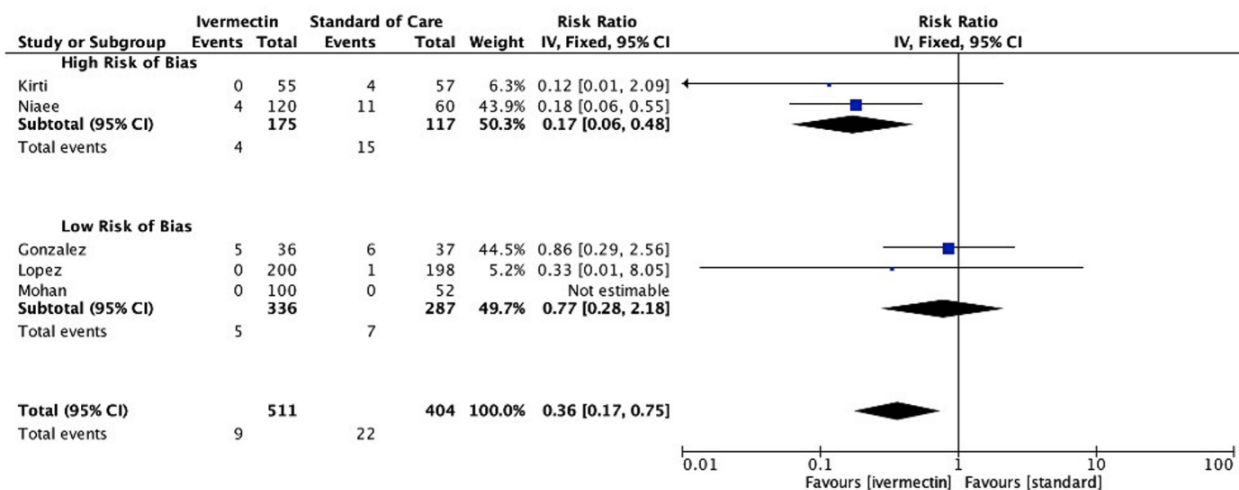
IV: inverse variance.

In addition to concerns related to risk of bias, for the outcome of mortality, there are very serious concerns related to imprecision. According to GRADE, imprecision is evaluated based on both a confidence interval approach and an evaluation of information size (event number), ensuring there is adequate information on which to make informed judgments *(56)*. In this case, despite confidence intervals that suggest benefit with ivermectin, the information size is very low. For mortality (and ignoring the concerns related to risk of bias discussed above), there were nine deaths across all 511 patients randomized to ivermectin (1.76%) and 22 deaths across all 404 patients randomized to standard of care (5.45%). This is an extremely small number of events on which to base conclusions, and far below the optimal information size. In fact, performing a theoretical exercise in which a change of three events (deaths) is made from those randomized to standard of care to those randomized to ivermectin eliminates any statistical significance, a finding that suggests that results could reasonably be due to chance alone. Furthermore, the evidence informing this comparison is from multiple small trials, adding to the risk of unrecognized imbalances in study arms. Given the strong likelihood that chance may be playing a role in the observed findings, the panel believed there was very serious imprecision further lowering the overall certainty in findings.

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

Subgroup analyses

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

Applicability

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

Uncertainties

Please see end of document for residual uncertainties (Section 8).

Clinical question/ PICO

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

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Ivermectin	Certainty of the evidence (Quality of evidence)	Plain text summary
Mortality	Odds ratio 0.19 (CI 95% 0.09—0.36) Based on data from 1419 patients in 7 studies. [1] (Randomized controlled)	**70** per 1000	**14** per 1000 Difference: **56 fewer** per 1000 (CI 95% 63 fewer — 44 fewer)	**Very low** Due to serious risk of bias and very serious imprecision [2]	The effect of ivermectin on mortality is uncertain.
Mechanical ventilation	Odds ratio 0.51 (CI 95% 0.12—1.77) Based on data from 687 patients in 5 studies. [1] (Randomized controlled)	**20** per 1000	**10** per 1000 Difference: **10 fewer** per 1000 (CI 95% 18 fewer — 15 more)	**Very low** Due to very serious imprecision and publication bias [3]	The effect of ivermectin on mechanical ventilation is uncertain.
Viral clearance 7 days	Odds ratio 1.62 (CI 95% 0.95—2.86) Based on data from 625 patients in 6 studies. [1] (Randomized controlled)	**500** per 1000	**618** per 1000 Difference: **118 more** per 1000 (CI 95% 13 fewer — 241 more)	**Low** Due to serious inconsistency and imprecision [4]	Ivermectin may increase or have no effect on viral clearance.
Hospital admission (outpatients only)	Odds ratio 0.36 (CI 95% 0.08—1.48) Based on data from 398 patients in 1 studies. [1] (Randomized controlled)	**50** per 1000	**18** per 1000 Difference: **32 fewer** per 1000 (CI 95% 47 fewer — 23 more)	**Very low** Due to extreme imprecision [5]	The effect of ivermectin on hospital admission is uncertain.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Ivermectin	Certainty of the evidence (Quality of evidence)	Plain text summary
Serious adverse events	Odds ratio 3.07 (CI 95% 0.77—12.09) Based on data from 584 patients in 3 studies. [1] (Randomized controlled)	**9** per 1000	**27** per 1000 Difference: **18 more** per 1000 (CI 95% 2 fewer — 89 more)	**Low** Due to very serious imprecision [6]	Ivermectin may increase the risk of serious adverse events leading to drug discontinuation.
Time to clinical improvement	Measured by: days Lower better Based on data from: 633 patients in 2 studies. [1] (Randomized controlled)	**11** days (Mean)	**10.5** days (Mean) Difference: **MD 0.5 fewer** (CI 95% 1.7 fewer — 1.1 more)	**Low** Due to very serious imprecision [7]	Ivermectin may have little or no difference on time to clinical improvement
Duration of hospitalization	Measured by: days Lower better Based on data from: 252 patients in 3 studies. [1] (Randomized controlled)	**12.8** days (Mean)	**11.7** days (Mean) Difference: **MD 1.1 fewer** (CI 95% 2.3 fewer — 0.1 more)	**Very low** Due to serious imprecision, inconsistency and serious risk of bias [8]	The effect of ivermectin on hospital length of stay is uncertain.
Time to viral clearance	Measured by: days Lower better Based on data from: 559 patients in 4 studies. [1] (Randomized controlled)	**7.3** days (Mean)	**5.7** days (Mean) Difference: **MD 1.6 fewer** (CI 95% 4.1 fewer — 3 more)	**Very low** Due to very serious imprecision and serious risk of bias [9]	We are uncertain whether ivermectin improves or worsen time to viral clearance

1. Systematic review (7). **Baseline/comparator:** Control arm of reference used for intervention. As ivermectin has been proposed for use and often studied in outpatients, on this occasion the panel used the median of risk in the standard care arms of the included trials for baseline risk estimate for mortality and mechanical ventilation, rather than the WHO SOLIDARITY trial as the source.
2. **Risk of bias: Serious.** The large trial contributing most of the effect estimate was driven by studies that were not blinded. **Imprecision: Very serious.** The number of total events was very small.
3. **Imprecision: Very serious.** Very few events and credible intervals that include both important benefit and harm. **Publication bias: Serious.**
4. **Inconsistency: Serious.** The point estimates varied widely and credible intervals do not substantially overlap. **Imprecision: Serious.** Credible interval includes no effect.
5. **Imprecision: Very serious.** Credible interval includes important benefit and harm.
6. **Imprecision: Very serious.** Credible interval includes little to no difference.
7. **Imprecision: Very serious.**
8. **Risk of bias: Serious.** Result driven by one study that was not blinded. **Inconsistency: Serious.** Despite overlapping confidence intervals, point estimates discrepant. **Imprecision: Serious.** Credible intervals include no difference.
9. **Risk of bias: Serious.** Concerns around risk of bias. **Imprecision: Very serious.** Credible interval includes important benefit and important harm.

7.3 Hydroxychloroquine (published 17 December 2020)

The third version of the WHO living guideline addressed the use of hydroxychloroquine (and lopinavir/ritonavir) in patients with COVID-19. It followed the pre-print publication of the WHO SOLIDARITY trial on 15 October, 2020, reporting results on treatment

with remdesivir, hydroxychloroquine and lopinavir/ritonavir in hospitalized patients with COVID-19 *(16)*. 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 had the potential to change practice *(15)(16)*.

The evidence
The evidence summary for hydroxychloroquine 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.

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

Geographic region	Region of the Americas	Region of the Americas
		(12 trials, 2358 patients)
	South-East Asia Region	South-East Asea and Western Pacific Regions
	Western Pacific Region	
		(7 trials, 731 patients)
	European Region	European Region
		(10 trials, 7638 patients)
		Eastern Mediterranean Region
	Eastern Mediterranean Region	(1 trial, 194 patients)
Severity of illness[a]	Non-severe	Mild/Moderate
		(10 trials, 2436 patients)
	Severe	Severe (1 trial, 479 patients)
	Critically ill	Critically ill (0 trials, 0 patients)
Mechanically ventilated at baseline[b]	Mean (range), %	3.23 (0-16.8)
Age[c]	Mean (range of means), years	50.8 (32.9-77)
Sex[d]	Mean (range of means), % women	46.9 (30-71)
Loading doses Day 1[e]	Mean (range of means), mg	1010 (800-1600)
Total cumulative doses[f]	Mean (range), mg	4000 (2000-11 200)
Duration of therapy[g]	Median (range), days	7 (4-16)
Type of care	n (%) inpatient	Inpatient: 9549 (87.4)
	n (%) outpatient	Outpatient: 1372 (12.6)
Trial participants	Median (range)	364 (2-4716)
Concomitant use of corticosteroids[h]	Mean (range across trials that report this), %	12.61 (8-19.5)

Notes:

[a] 19 trials did not report the disease severity of patients.

[b] 19 trials did not report the proportion of mechanical ventilation at baseline.

[c] 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 ≥ 12, 18, or 40.

[d] 14 trials did not report the sex of patients.

[e] 10 trials did not use a loading dose.

[f] 1 trial reported range of treatment duration.

[g] 1 trial reported range of treatment duration.

[h] 23 trials did not report the concomitant use of corticosteroids.

Baseline risk

The absolute effects of treatment are informed by the prognosis (i.e. baseline risk estimates) combined with the relative estimates of effects (e.g. RR, OR) obtained from the NMA.

The control arm of the WHO SOLIDARITY Trial *(16)*, 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.

Subgroup analysis

For hydroxychloroquine, the GDG panel requested subgroup analyses based on age (considering children vs younger adults [e.g. under 70 years] vs older adults [e.g. 70 years or older]), illness severity (non-severe vs severe vs critical COVID-19) and based on whether or not it was co-administered with azithromycin.

The panel also requested a subgroup analysis based on high dose vs low dose hydroxychloroquine. A categorical approach to hydroxychloroquine dosing proved impossible because the trials used varying loading doses, continuation doses and durations. Therefore, in collaboration with a pharmacology expert (Professor Andrew Owen), we modelled the expected serum concentrations over time. We hypothesized that higher trough concentrations early in the treatment course (e.g. trough concentration on Day 3) might be more effective than lower early trough concentrations. We also hypothesized that higher maximum serum concentrations (e.g. peak concentration on the last day) might result in higher risk of adverse effects than lower maximum serum concentrations. In our pharmacokinetic model, the cumulative dose was highly correlated with all measures of serum concentrations on Day 3 and the final day of treatment, and therefore we decided to use cumulative dose as the primary analysis. Day 3 trough concentration was least strongly correlated with total cumulative dose ($R^2 = 0.376$) and therefore we performed a sensitivity subgroup analysis with predicted Day 3 trough concentrations for efficacy outcomes.

Info Box

The recommendation concerning hydroxychloroquine was published 17 December 2020 as the third version of the WHO living guideline and in the BMJ as Rapid Recommendations. No changes were made for the hydroxychloroquine recommendation in this fifth version of the guideline. Please view the section text for a summary of the evidence requested to inform the recommendation, triggered by the WHO SOLIDARITY trial.

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.

Practical info

The GDG made a strong recommendation against using hydroxychloroquine or chloroquine for treatment of patients with COVID-19. The use of hydroxychloroquine may preclude the use of other important drugs that also prolong the QT interval, such as azithromycin and fluoroquinolones. Concomitant use of drugs that prolong the QT interval should be done with extreme caution.

Evidence to Decision

Benefits and harms

Hydroxychloroquine and chloroquine probably do not reduce mortality or mechanical ventilation and may not reduce duration of hospitalization. The evidence does not exclude the potential for a small increased risk of death and mechanical ventilation with hydroxychloroquine. The effect on other less important outcomes, including time to symptom resolution, admission to hospital, and duration of mechanical ventilation, remains uncertain.

Hydroxychloroquine may increase the risk of diarrhoea and nausea/vomiting; a finding consistent with evidence from its use in other conditions. Diarrhoea and vomiting may increase the risk of hypovolaemia, hypotension and acute kidney injury, especially in settings where health care resources are limited. Whether or not and to what degree hydroxychloroquine increases the risk of cardiac toxicity, including life-threatening arrhythmias, is uncertain.

Subgroup analyses indicated no effect modification based on severity of illness (comparing either critical vs severe/non-severe or non-severe vs critical/severe) or age (comparing those aged < 70 years vs those > 70 years old). Further, the cumulative dose and predicted Day 3 serum trough concentrations did not modify the effect for any outcome. Therefore, we assumed similar effects in all subgroups.

We also reviewed evidence comparing the use of hydroxychloroquine plus azithromycin vs hydroxychloroquine alone. There was no evidence that the addition of azithromycin modified the effect of hydroxychloroquine for any outcome (very low certainty).

Certainty of the evidence

For the key outcomes of mortality and mechanical ventilation, the panel considered the evidence to be of moderate certainty. There were residual concerns about lack of blinding in the largest trials and the imprecision. For example, the credible interval around the pooled effect leaves open the possibility of a very small reduction in mortality. The quality of evidence was low for diarrhoea and nausea/vomiting because of lack of blinding in many of the trials and because the total number of patients enrolled in trials reporting these outcomes was smaller than the optimal information size (although the credible interval laid entirely on the side of harm for both outcomes).

For all other outcomes, the certainty of the evidence was low or very low. The primary concerns with the data were imprecision (credible intervals included both important benefit and important harm) as well as risk of bias (lack of blinding).

Preference and values

Applying the agreed values and preferences (see 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 and vomiting. The panel did not expect there would be much variation in values and preferences between patients when it came to this intervention.

Resources and other considerations

Hydroxychloroquine and chloroquine are relatively inexpensive compared with other drugs used for COVID-19 and are already widely available, including in low-income settings. Despite this, the panel felt that almost all patients would choose not to use hydroxychloroquine or chloroquine because the harms outweigh the benefits. Although the cost may be low per patient, the GDG panel raised concerns about diverting attention and resources away from care likely to provide a benefit such as corticosteroids in patients with severe COVID-19 and other supportive care interventions.

Justification

When moving from evidence to the strong recommendation against the use of hydroxychloroquine or chloroquine for patients with COVID-19, the panel emphasized the moderate certainty evidence of probably no reduction in mortality or need for mechanical ventilation. It also noted the evidence suggesting possible harm associated with treatment, with increased nausea and diarrhoea. The GDG did not anticipate important variability in patient values and preferences, and other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity (see summary of these factors under Evidence to decision).

Subgroup analyses

The panel did not find any evidence of a subgroup effect across patients with different levels of disease severity, between adults and older adults, and by different doses, and therefore did not make any subgroup recommendation for this drug. In other words, the strong recommendation is applicable across disease severity, age groups, and all doses and dose schedules of hydroxychloroquine.

The trials included patients from around the world, with all disease severities, and treated in different settings (outpatient and inpatient). Although the trials did not report subgroup effects by time from symptom onset, many of the trials enrolled patients early in the disease course. The GDG panel therefore felt that the evidence applies to all patients with COVID-19.

Applicability

Special populations

None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. However, the panel had no reason to think that children with COVID-19 would respond any differently to treatment with hydroxychloroquine. There were similar considerations in regards to pregnant women, with no data directly examining this population, but no rationale to suggest they would respond differently than other adults. Hydroxychloroquine crosses the placental barrier and there are concerns that it may lead to retinal damage in neonates. Although hydroxychloroquine has been used in pregnant women with systemic autoimmune diseases, such as systemic lupus erythematosus, pregnant women may have even more reasons than other patients to be reluctant to use hydroxychloroquine for COVID-19.

In combination with azithromycin

There was no evidence from the NMA that the addition of azithromycin modified the effect of hydroxychloroquine for any outcome. As there were no trial data suggesting that azithromycin favourably modifies the effect of hydroxychloroquine, the recommendation against hydroxychloroquine and chloroquine applies to patients whether or not they are concomitantly receiving azithromycin.

Uncertainties

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

Clinical question/ PICO

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

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Hydroxychloro quine	Certainty of the evidence (Quality of evidence)	Plain text summary
Mortality	Odds ratio 1.11 (CI 95% 0.95−1.31) Based on data from 10 859 patients in 29 studies. [1] (Randomized controlled)	**106** per 1000	**116** per 1000 Difference: **10 more** per 1000 (CI 95% 5 fewer − 28 more)	Moderate Due to borderline risk of bias and imprecision [2]	Hydroxychloroquine probably does not reduce mortality.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Hydroxychloroquine	Certainty of the evidence (Quality of evidence)	Plain text summary
Mechanical ventilation	Odds ratio 1.2 (CI 95% 0.83—1.81) Based on data from 6379 patients in 5 studies. [1] (Randomized controlled)	105 per 1000	123 per 1000 Difference: **18 more** per 1000 (CI 95% 16 fewer — 70 more)	Moderate Due to borderline risk of bias and serious imprecision [3]	Hydroxychloroquine probably does not reduce mechanical ventilation.
Viral clearance 7 days	Odds ratio 1.08 (CI 95% 0.25—4.78) Based on data from 280 patients in 4 studies. [4] (Randomized controlled)	483 per 1000	502 per 1000 Difference: **19 more** per 1000 (CI 95% 294 fewer — 334 more)	Very low Due to very serious imprecision [5]	The effect of hydroxychloroquine on viral clearance is very uncertain.
Admission to hospital	Odds ratio 0.39 (CI 95% 0.12—1.28) Based on data from 465 patients in 1 studies. [4] (Randomized controlled)	47 per 1000	19 per 1000 Difference: **28 fewer** per 1000 (CI 95% 41 fewer — 12 more)	Very low Due to very serious imprecision and serious indirectness [6]	The effect of hydroxychloroquine on admission to hospital is uncertain.
Cardiac toxicity	Based on data from 3287 patients in 7 studies. [4] (Randomized controlled)	46 per 1000	56 per 1000 Difference: **10 more** per 1000 (CI 95% 0 more — 30 more)	Very low Due to serious imprecision, risk of bias, and indirectness [7]	The effect of hydroxychloroquine on cardiac toxicity is uncertain.
Diarrhoea	Odds ratio 1.95 (CI 95% 1.4—2.73) Based on data from 979 patients in 6 studies. [4] (Randomized controlled)	149 per 1000	255 per 1000 Difference: **106 more** per 1000 (CI 95% 48 more — 174 more)	Low Due to serious imprecision and risk of bias [8]	Hydroxychloroquine may increase the risk of diarrhoea.
Nausea/ vomiting	Odds ratio 1.74 (CI 95% 1.26—2.41) Based on data from 1429 patients in 7 studies. [4] (Randomized controlled)	99 per 1000	161 per 1000 Difference: **62 more** per 1000 (CI 95% 23 more — 110 more)	Low Due to serious imprecision and serious risk of bias [9]	Hydroxychloroquine may increase the risk of nausea and vomiting.
Delirium	Odds ratio 1.59 (CI 95% 0.77—3.28) Based on data from 423 patients in 1 studies. [4] (Randomized controlled)	62 per 1000	95 per 1000 Difference: **33 more** per 1000 (CI 95% 14 fewer — 116 more)	Very low Due to very serious imprecision and serious indirectness [10]	The effect of hydroxychloroquine on delirium is uncertain.
Time to clinical improvement	Lower better Based on data from: 479 patients in 5 studies. [4] (Randomized controlled)	11 days (Mean)	9 days (Mean) Difference: **MD 2 fewer**	Very low Due to serious risk of bias, imprecision, and indirectness [11]	The effect of hydroxychloroquine on time to clinical improvement is uncertain.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Hydroxychloroquine	Certainty of the evidence (Quality of evidence)	Plain text summary
Duration of hospitalization	Lower better Based on data from: 5534 patients in 5 studies. [4] (Randomized controlled)	(CI 95% 4 fewer — 0.1 more) **12.8** days (Mean) Difference: **MD 0.1 more** (CI 95% 1.9 fewer — 2 more)	**12.9** days (Mean)	Low Due to serious imprecision and serious risk of bias [12]	Hydroxychloroquine may have no effect on duration of hospitalization.
Time to viral clearance	Lower better Based on data from: 440 patients in 5 studies. [4] (Randomized controlled)	**9.7** days (Mean) Difference: **MD 0.7 fewer** (CI 95% 4.3 fewer — 4.8 more)	**10.6** days (Mean)	Very low Due to serious risk of bias and very serious imprecision [13]	The effect of hydroxychloroquine on time to viral clearance is uncertain.
Adverse events leading to drug discontinuation	Based on data from: 210 patients in 3 studies. [4] (Randomized controlled)	Two of 108 patients randomized to hydroxychloroquine discontinued treatment because of adverse effects. None of 102 patients did so in the placebo/standard care group.		Very low Due to extremely serious imprecision [14]	The effect of hydroxychloroquine on adverse events leading to drug discontinuation is uncertain.

1. Systematic review (7). **Baseline/comparator:** Primary study (16). Baseline risk for mortality and mechanical ventilation were derived from the WHO SOLIDARITY trial for patients with severe and critical COVID-19.
2. **Imprecision: Serious.** The 95% CI crosses the minimally important difference (2% reduction in mortality). .
3. **Imprecision: Serious.** Wide confidence intervals.
4. Systematic review (7). **Baseline/comparator:** Control arm of reference used for intervention. We used the median event rate for all patients randomized to usual care across included studies.
5. **Imprecision: Very serious.** Wide confidence intervals.
6. **Indirectness: Serious. Imprecision: Very serious.**
7. **Risk of Bias: Serious.** Unblinded studies -> cardiac toxicity differential detection. **Indirectness: Serious.** Studies measured serious cardiac toxicity differently. **Imprecision: Serious.**
8. **Risk of Bias: Serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results. **Imprecision: Serious.** OIS not met. **Upgrade: Large magnitude of effect.**
9. **Risk of Bias: Serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results. **Imprecision: Serious.** OIS not met. **Upgrade: Large magnitude of effect.**
10. **Indirectness: Serious.** This outcome was not collected systematically and the definition of delirium was not specified. **Imprecision: Very serious.**
11. **Risk of Bias: Serious. Indirectness: Serious.** Studies measured clinical improvement differently. **Imprecision: Serious.**
12. **Risk of Bias: Serious. Imprecision: Serious.** Wide confidence intervals.
13. **Risk of Bias: Serious. Imprecision: Very serious.**
14. **Imprecision: Very serious.**

7.4 Lopinavir/ritonavir (published 17 December 2020)

The third version of the WHO living guideline addressed the use of lopinavir/ritonavir (and hydroxychloroquine, see above) in patients with COVID-19. It followed the pre-print publication of the WHO SOLIDARITY trial on 15 October 2020, reporting results on treatment with remdesivir, hydroxychloroquine and lopinavir/ritonavir in hospitalized patients with COVID-19 (16). 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 had the potential to change practice *(15)(16)*.

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

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

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

NR: Not reported.

Notes:

^a 2 trials did not report the disease severity of patients.

^b 3 trials did not report the proportion of mechanical ventilation at baseline.

^c 2 trials did not report the age of patients.

^d No trial reported loading dose.

^e 1 trial did not report cumulative doses; 2 trials only reported range of treatment duration.

^f 1 trial did not report the duration of therapy; 2 trials used a range of treatment duration.

^g 2 trials did not report the concomitant use of corticosteroids.

Baseline risk
The absolute effects of treatment are informed by the prognosis (i.e. baseline risk estimates) combined with the relative estimates of effects (e.g. RR, OR) obtained from the NMA.

The control arm of the WHO SOLIDARITY trial (16), 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.

Subgroup analysis
For lopinavir/ritonavir, the GDG panel requested subgroup analyses based on age (considering children vs younger adults [e.g. under 70 years] vs older adults [e.g. 70 years or older]), and illness severity (non-severe vs severe vs critical COVID-19). The GDG discussed other potential subgroups of interest including time from onset of symptoms until initiation of therapy and concomitant medications, but recognized that these analyses would not be possible without access to individual participant data and/or more detailed reporting from the individual trials.

Info Box

The recommendation concerning lopinavir/ritonavir was published 17 December 2020 as the third version of the WHO living guideline and in the BMJ as Rapid Recommendations. No changes were made for the lopinavir/ritonavir recommendation in this fifth version of the guideline. Please view the section text for a summary of the evidence requested to inform the recommendation, triggered by the WHO SOLIDARITY trial.

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 outcomes that matter to patients such as reduced mortality, need for mechanical ventilation, time to clinical improvement and others. For mortality and need for mechanical ventilation this was based on moderate certainty evidence, for the other outcomes low or very low certainty evidence.

There was low certainty evidence that lopinavir/ritonavir may increase the risk of diarrhoea and nausea and vomiting, a finding consistent with the indirect evidence evaluating its use in patients with HIV. Diarrhoea and vomiting may increase the risk of hypovolaemia, hypotension and acute kidney injury, especially in settings where health care resources are limited. There was an uncertain effect on viral clearance and acute kidney injury.

Subgroup analysis indicated no effect modification based on severity of illness (comparing either critical vs severe/non-severe or non-severe vs critical/severe) or age (comparing those aged < 70 years versus those 70 years and older). As there was no evidence of a statistical subgroup effect, we did not formally evaluate using the ICEMAN tool.

Certainty of the evidence

The evidence is based on a linked systematic review and NMA of seven RCTs; pooling data from 7429 patients hospitalized with various severities of COVID-19 and variably reporting the outcomes of interest to the guideline panel (7). The panel agreed that there was moderate certainty for mortality and need for mechanical ventilation, low certainty for diarrhoea, nausea and duration of hospitalization and very low certainty in the estimates of effect for viral clearance, acute kidney injury and time to clinical improvement. Most outcomes were lowered for risk of bias and imprecision (wide confidence intervals which do not exclude important benefit or harm).

Preference and values

Applying the agreed values and preferences (see 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 when it came to this intervention.

Resources and other considerations

Although the cost of lopinavir/ritonavir is not as high as some other investigational drugs for COVID-19, and the drug is generally available in most health care settings, the GDG raised concerns about opportunity costs and the importance of not drawing attention and resources away from best supportive care or the use of corticosteroids in severe COVID-19.

Justification

When moving from evidence to the strong recommendation against the use of lopinavir/ritonavir for patients with COVID-19, the panel emphasized the moderate certainty evidence of probably no reduction in mortality or need for mechanical ventilation. It also noted the evidence suggesting possible harm associated with treatment, with increased nausea and diarrhoea. The GDG did not anticipate important variability in patient values and preferences, and other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity would not alter the recommendation (see summary of these factors under Evidence to decision).

Subgroup analysis

The panel did not find any evidence of a subgroup effect across patients with different levels of disease severity, or between adults and older adults and therefore did not make any subgroup recommendation for this drug. Although the trials did not report subgroup effects by time from symptom onset, many of the trials enrolled patients with patients early in the disease course. The strong recommendation is applicable across disease severity and age groups.

Applicability

None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. However, the panel had no reason to think that children with COVID-19 would respond any differently to treatment with lopinavir/ritonavir. There were similar considerations in regards to pregnant women, with no data directly examining this population, but no rationale to suggest they would respond differently than other adults. In patients using lopinavir/ritonavir for HIV infection, it should generally be continued while receiving care for COVID-19.

Uncertainties

Please see end of document for residual uncertainties (Section 8). The GDG panel felt that it was unlikely future studies would identify a subgroup of patients that are likely to benefit from lopinavir/ritonavir.

Additional considerations

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

Clinical question/ PICO

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

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Lopinavir/ ritonavir	Certainty of the evidence (Quality of evidence)	Plain text summary
Mortality	Odds ratio 1 (CI 95% 0.82—1.2) Based on data from 8061 patients in 4 studies. [1] (Randomized controlled)	**106** per 1000	**106** per 1000 Difference: **0 fewer** per 1000 (CI 95% 17 fewer — 19 more)	**Moderate** Due to borderline risk of bias and imprecision [2]	Lopinavir/ritonavir probably has no effect on mortality
Mechanical ventilation	Relative risk 1.16 (CI 95% 0.98—1.36) Based on data from 7579 patients in 3 studies. [1] (Randomized controlled)	**105** per 1000	**122** per 1000 Difference: **17 more** per 1000 (CI 95% 2 fewer — 38 more)	**Moderate** Due to borderline risk of bias and imprecision [3]	Lopinavir/ritonavir probably does not reduce mechanical ventilation
Viral clearance	Odds ratio 0.35 (CI 95% 0.04—1.97) Based on data from 171 patients in 2 studies. [4] (Randomized controlled)	**483** per 1000	**246** per 1000 Difference: **237 fewer** per 1000 (CI 95% 447 fewer — 165 more)	**Low** Due to very serious imprecision [5]	the effects of lopinavir/ ritonavir on viral clearance is very uncertain
Acute kidney injury	Relative risk Based on data from 259 patients in 2 studies. [4] (Randomized controlled)	**45** per 1000	**25** per 1000 Difference: **20 fewer** per 1000 (CI 95% 70 fewer — 20 more)	**Very low** Due to serious risk of bias and very serious imprecision [6]	The effect of lopinavir/ ritonavir on acute kidney injury is uncertain
Diarrhoea	Odds ratio 4.28 (CI 95% 1.99—9.18) Based on data from 370 patients in 4 studies. [4] (Randomized controlled)	**67** per 1000	**235** per 1000 Difference: **168 more** per 1000 (CI 95% 58 more — 330 more)	**Moderate** Due to serious risk of bias and imprecision; upgraded due to large magnitude of effect [7]	Lopinavir/ritonavir may increase the risk of diarrhoea.
Nausea/ vomiting	Relative risk Based on data from 370 patients in 4 studies. [4] (Randomized controlled)	**17** per 1000	**177** per 1000 Difference: **160 more** per 1000 (CI 95% 100 more — 210 more)	**Moderate** Due to serious risk of bias and imprecision [8]	Lopinavir/ritonavir may increase the risk of nausea/vomiting

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Lopinavir/ ritonavir	Certainty of the evidence (Quality of evidence)	Plain text summary
Time to clinical improvement	Lower better Based on data from: 199 patients in 1 studies. [4] (Randomized controlled)	**11** days (Mean) Difference: **MD 1 fewer** (CI 95% 4.1 fewer — 3.2 more)	**10** days (Mean)	**Very low** Due to serious risk of bias and very serious imprecision [9]	The effect of lopinavir/ritonavir improves on time to clinical improvement is very uncertain
Duration of hospitalization	Lower better Based on data from: 5239 patients in 2 studies. [4] (Randomized controlled)	**12.8** days (Mean) Difference: **MD 0.3 lower** (CI 95% 3 lower — 2.5 higher)	**12.5** days (Mean)	**Low** Due to serious risk of bias and imprecision [10]	Lopinavir/ritonavir may have no effect on duration of hospitalization

1. Systematic review (7). **Baseline/comparator:** Primary study (16). Baseline risk for mortality and mechanical ventilation were derived from the WHO SOLIDARITY trial for patients with severe and critical COVID-19.

2. **Imprecision: Serious.** The 95% CI crosses the minimally important difference (2% reduction in mortality).

3. **Imprecision: Serious.** Wide confidence intervals.

4. Systematic review (7). **Baseline/comparator:** Control arm of reference used for intervention. We used the median event rate for all patients randomized to usual care across included studies.

5. **Imprecision: Very serious.** Wide confidence intervals.

6. **Risk of bias: Serious. Imprecision: Very serious.** Wide confidence intervals.

7. **Risk of bias: Serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results. **Imprecision: Serious.** Few patients and events. **Upgrade: Large magnitude of effect.**

8. **Risk of bias: Serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results. **Imprecision: Serious.** Few patients and events. **Upgrade: Large magnitude of effect.**

9. **Risk of bias: Serious. Imprecision: Very serious.** Wide confidence intervals, low number of patients.

10. **Risk of bias: Serious. Imprecision: Serious.** Wide confidence intervals.

7.5 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 pre-print publication of the WHO SOLIDARITY trial on 15 October 2020, reporting results on treatment with remdesivir, hydroxychloroquine and lopinavir/ritonavir in hospitalized patients with COVID-19 (16). 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 had the potential to change practice (15)(16).

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 (57)(58).

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 *(16)(59)(60)(61)*, 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
Beigel (ACTT-1)	1063	United States, Europe, Asia	58.9	Non-severe (11.3) Severe[a] (88.7)	44.1	Remdesivir IV (100 mg/ day for 10 days)	- Mortality - Adverse effects - Time to clinical improvement
Spinner (SIMPLE MODERATE*)	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 - Mechanical ventilation - Adverse effects - Duration of hospitalization - Time to clinical improvement
Pan (SOLIDARITY)	5451	Worldwide	< 50: 35% 50-70: 47% >70: 18%	Non-severe (24) Severe[b] (67) Critical (9)	8.9	Remdesivir IV (200 mg at day 1, then 100 mg day 2-10)	- Mortality - Mechanical ventilation
Wang	237	China	65	Severe[c] (100)	16.1	Remdesivir IV (100 mg/ day for 10 days)	- Mortality - Mechanical ventilation - Duration of ventilation - Adverse effects - Duration of hospitalization - Time to clinical improvement - Viral clearance

IMV: invasive mechanical ventilation; IV: intravenous; n: number.

Notes:
Severity criteria based on WHO definitions unless otherwise stated:
a: defined severe as SpO$_2$ < 94% on room air OR respiratory rate > 24 breaths per minute.
b: defined severe as requiring oxygen support.
c: defined severe as SpO$_2$ < 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), and duration of remdesivir therapy (5 days vs longer than 5 days). The GDG discussed other potential subgroups of interest including time from onset of symptoms until initiation of therapy, and concomitant medications (especially corticosteroids), however recognized these analyses would not be possible without access to individual participant data. To this last point, the panel recognized that usual care is likely variable between centres, regions and evolved over time. However, given all of the data come from RCTs, use of these co-interventions that comprise usual care should be balanced between study patients randomized to either the intervention or usual care arms.

Following the panel's request, the NMA team performed subgroup analyses in order to assess for effect modification which, if present, could mandate distinct recommendations by subgroups. From the data available from the included trials, subgroup analysis was only possible for severity of illness and the outcome of mortality. This subgroup analysis was performed using a random effects frequentist analysis based on the three WHO severity definitions. A post hoc Bayesian analysis was also performed, which incorporated meta-regression using study as a random effect. This latter approach has the advantage of more accurately accounting for within-study differences but can only compare two subgroups at a time. The panel used a pre-specified framework incorporating the ICEMAN tool to assess the credibility of subgroup findings *(23)*.

Info Box

The recommendation concerning remdesivir was published 20 November 2020 as the second version of the WHO living guideline and in the BMJ as Rapid Recommendations. No changes were made for the remdesivir recommendation in this fifth version of the guideline. Please view the section text for a summary of the evidence requested to inform the recommendation, triggered by the WHO SOLIDARITY trial.

Conditional recommendation against

We suggest against administering remdesivir in addition to usual care.

Practical info

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

Evidence to Decision

Benefits and harms

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

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

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

Certainty of the evidence

Low

The evidence is based on a linked systematic review and NMA of four RCTs; pooling data from 7333 patients hospitalized with various severities of COVID-19 and variably reporting the outcomes of interest to the guideline panel *(7)*. The panel agreed that there was low certainty in the estimates of effect for all patient-important outcomes across benefits and harms, mostly driven by risk of bias and imprecision (wide confidence intervals which do not exclude important benefit or harm). There was very low certainty evidence for viral clearance and delirium.

Preference and values

Substantial variability is expected or uncertain

Applying the agreed values and preferences (see 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 summary of these factors under Evidence to Decision).

Importantly, given the low certainty evidence for these outcomes, the panel concluded that the evidence did not prove that remdesivir has no benefit; rather, there is no evidence based on currently available data that it 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) *(16)* or critical (ACTT-1) *(61)*. The analysis focused on within-study subgroup comparisons across the different severities, and therefore the SIMPLE-MODERATE trial could not be included in the subgroup analysis as it only enrolled patients with non-severe COVID-19. The panel reviewed the results of both the random effects frequentist analysis and the post hoc Bayesian analysis which incorporated meta-regression using study as a random effect.

The GDG panel judged the credibility in the subgroup analysis assessing differences in mortality by severity of illness to be insufficient to make subgroup recommendations. Important factors influencing this decision included a lack of *a priori* hypothesized direction of subgroup effect by trial investigators, little or no previously existing supportive evidence for the subgroup finding, and relatively arbitrary cut points used to examine the subgroups of interest. The overall low certainty evidence for the benefits and harms of remdesivir, driven by risk of bias and imprecision limitations, also contributed to the

judgment. The panel highlighted that despite the conditional recommendation against remdesivir, they support further enrolment into RCTs evaluating remdesivir, especially to provide higher certainty of evidence for specific subgroups of patients.

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

Clinical question/ PICO

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

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

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Remdesivir	Certainty of the evidence (Quality of evidence)	Plain text summary
Delirium	Odds ratio 1.22 (CI 95% 0.48–3.11) Based on data from 1048 patients in 1 studies. [4] (Randomized controlled)	**16** per 1000 Difference: **3 more** per 1000 (CI 95% 8 fewer — 32 more)	**19** per 1000	**Very low** Due to very serious imprecision and serious indirectness [8]	We are uncertain whether remdesivir increases or decreases delirium
Time to clinical improvement	Measured by: days Lower better Based on data from: 1882 patients in 3 studies. [4] (Randomized controlled)	**11** days Difference: **MD 2 lower** (CI 95% 4.2 lower — 0.9 higher)	**9** days	**Low** Due to serious imprecision and serious indirectness [9]	Remdesivir possibly has little or no effect on time to clinical improvement.
Duration of hospitalization	Measured by: days Lower better Based on data from: 1882 patients in 3 studies. [4] (Randomized controlled)	**12.8** days Difference: **MD 0.5 lower** (CI 95% 3.3 lower — 2.3 higher)	**12.3** days	**Low** Due to serious imprecision and serious indirectness [10]	Remdesivir possibly has little or no effect on duration of hospitalization.
Duration of ventilation	Measured by: days Lower better Based on data from: 440 patients in 2 studies. [4] (Randomized controlled)	**14.7** days Difference: **MD 1.3 lower** (CI 95% 4.1 lower — 1.5 higher)	**13.4** days	**Low** Due to very serious imprecision [11]	Remdesivir possibly has little or no effect on duration of ventilation.

1. Systematic review (7). **Baseline/comparator:** Primary study (16). Baseline risk for mortality and mechanical ventilation were derived from the WHO SOLIDARITY trial for patients with severe and critical COVID-19.

2. **Risk of bias: Serious.** We rated two trials as high risk of bias due to high or probably high risk of bias in deviations from the intended intervention. **Imprecision: Serious.** The 95% CI crosses the minimally important difference (2% reduction in mortality).

3. **Risk of bias: Serious. Imprecision: Serious.** Wide confidence intervals.

4. Systematic review (7). **Baseline/comparator:** Control arm of reference used for intervention. We used the median event rate for all patients randomized to usual care across included studies.

5. **Imprecision: Very serious.** Wide confidence intervals.

6. **Imprecision: Very serious.** Wide confidence intervals.

7. **Indirectness: Serious.** Studies used change in serum creatinine rather than patient-important measures of acute kidney injury. **Imprecision: Serious.** Wide 95% credible intervals.

8. **Indirectness: Serious.** Differences between the outcomes of interest and those reported (e.g short-term/surrogate,not patient-important). **Imprecision: Very serious.**

9. **Indirectness: Serious. Imprecision: Serious.**

10. **Indirectness: Serious. Imprecision: Serious.** Wide confidence intervals.

11. **Imprecision: Very serious.** Wide confidence intervals.

7.6 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 (15). Corticosteroids are listed in the WHO Model List of Essential Medicines, readily

available globally at a low cost, and of considerable interest to all stakeholder groups. The guideline panel was informed by combining two meta-analyses which pooled data from eight randomized trials (7184 participants) of systemic corticosteroids for COVID-19 *(7)(62)*. 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 versus usual care in COVID-19. RECOVERY, the largest of the seven trials, from which mortality data were available by subgroup (severe and non-severe), evaluated the effects of dexamethasone 6 mg given once daily (oral or intravenous) for up to 10 days in 6425 hospitalized patients in the United Kingdom (2104 were randomized to dexamethasone and 4321 were randomized to usual care) *(15)*. 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) *(63)*; dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID19, CoDEX) *(64)(65)*; 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) *(66)*; hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP) *(17)*; methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI) *(67)*.

Seven of the trials were conducted in individual countries (Brazil, China, Denmark, France, Spain) whilst REMAP-CAP was an international study (recruiting in 14 European countries, Australia, Canada, New Zealand, Saudi Arabia and the United Kingdom). All trials reported mortality 28 days after randomization, except for one trial at 21 days and another at 30 days. Because the mortality data from one trial (GLUCOCOVID, n=63) were not reported by subgroup, the panel reviewed only the data pertaining to the outcome of mechanical ventilation from this trial *(63)*. An additional trial, which randomized hospitalized patients with suspected SARS-CoV-2 infection, published on 12 August 2020 (MetCOVID) *(68)*, was included as a supplement in the PMA publication, as it was registered after the searches of trial registries were performed. The supplement showed that inclusion would not change results other than reduce inconsistency.

Subgroup 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 *(23)*, the panel determined that the subgroup effect was sufficiently credible to warrant separate recommendations for severe and non-severe COVID-19.

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

The panel also acknowledged the existence of variable definitions for severity and use of respiratory support interventions. The WHO clinical guidance for COVID-19 published on 27 May 2020 (version 3) defined severity of COVID-19 by clinical indicators, but modified the oxygen saturation threshold from 94% to 90%, in order to align with previous WHO guidance *(21)*. See Section 6 for the WHO severity criteria and Infographic for three disease severity groups for which the recommendations apply in practice.

Info Box

The recommendations for corticosteroids were first published as WHO living guidelines 2 September 2020, and as BMJ Rapid Recommendations 5 September 2020, including links to MAGICapp. 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.

Whereas the recommendations remain unchanged, the evidence summary for corticosteroids in patients with COVID-19 was updated before this fifth iteration of this living guideline. The baseline risk estimates for mortality are now based on the WHO SOLIDARITY trial (as for other drugs in this guideline) *(16)* rather than the initial ISARIC cohort study *(30)* that likely overestimates current mortality risks at the global level. This update was also needed to inform the baseline risk for mortality in the evidence summary informing the strong recommendation for IL-6 inhibitors, in addition to standard of care for patients with severe or critical COVID-19, where corticosteroids provide a relative reduction in mortality by 21%.

Recommended | Updated evidence, no change in recommendation

We recommend systemic corticosteroids rather than no corticosteroids.

Practical info

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

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

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

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

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

Evidence to Decision

Benefits and harms | Substantial net benefits of the recommended alternative

Panel members who voted for a conditional recommendation argued that the trials evaluating systemic corticosteroids for COVID-19 reported limited information regarding potential harm. Between the two panel meetings, indirect evidence regarding the potential harmful effects of systemic corticosteroids from studies in sepsis, ARDS and community-acquired pneumonia (CAP) was added to the summary of findings table *(69)(70)*. While generally of low certainty, these data were reassuring and suggested that corticosteroids are not associated with an increased risk of adverse events, beyond likely

increasing the incidence of hyperglycaemia (moderate certainty evidence; absolute effect estimate 46 more per 1000 patients, 95% CI: 23 more to 72 more) and hypernatraemia (moderate certainty evidence; 26 more per 1000 patients, 95% CI: 13 more to 41 more). Panel members also noted that, given the expected effect of systemic corticosteroids on mortality, most patients would not refuse this intervention to avoid adverse events believed to be markedly less important to most patients than death.

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

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

Preference and values

`No substantial variability expected`

The panel took an individual patient perspective to values and preferences but, given the burden of the pandemic for healthcare 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 *(71)*. 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 *(72)*.

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

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

Justification

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

Applicability

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

Eventually, the panel concluded that this recommendation applies to patients with severe and critical COVID-19 regardless of hospitalization status. The underlying assumption is that these patients would be treated in hospitals and receive respiratory support in the form of oxygen; non-invasive or invasive ventilation if these options were available. Following GRADE guidance, in making a strong recommendation, the panel has inferred that all or almost all fully informed patients with severe COVID-19 would choose to take systemic corticosteroids. It is understood that even in the context of a strong recommendation, the intervention may be contraindicated for certain patients. Absolute contraindications for 7–10 day courses of systemic corticosteroid therapy are rare. In considering potential contraindications, clinicians must determine if they warrant depriving a patient of a potentially life-saving therapy.

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

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

Clinical question/ PICO

Population: Patients with severe and critical COVID-19 (updated baseline mortality risk)
Intervention: Steroids
Comparator: Standard care

Summary

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 *(23)*, 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 *(15)*. 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) were not reported separately for severe and non-severe COVID-19 *(63)*, 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) (7). 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 United Kingdom).
Outcomes: All trials reported mortality 28 days after randomization, except for one trial at 21 days and another at 30 days.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Steroids	Certainty of the evidence (Quality of evidence)	Plain text summary
Mortality 28 days	Relative risk 0.79 (CI 95% 0.7—0.9) Based on data from 1703 patients in 7 studies. [1] (Randomized controlled)	**160** per 1000	**126** per 1000 Difference: **34 fewer** per 1000 (CI 95% 48 fewer — 16 fewer)	Moderate Due to serious risk of bias [2]	Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with critical illness due to COVID-19.
Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (CI 95% 0.59—0.93) Based on data from 5481 patients in 2 studies. [1] (Randomized controlled)	**116** per 1000	**86** per 1000 Difference: **30 fewer** per 1000 (CI 95% 48 fewer — 8 fewer)	Moderate Due to serious risk of bias [3]	Systemic corticosteroids probably reduce the need of mechanical ventilation
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85—1.33) Based on data from 5403 patients in 30 studies. [4] (Randomized controlled)	**48** per 1000	**51** per 1000 Difference: **3 more** per 1000 (CI 95% 7 fewer — 16 more)	Low Due to serious indirectness, Due to serious imprecision [5]	Corticosteroids may not increase the risk of gastrointestinal bleeding.
Super-infections	Relative risk 1.01 (CI 95% 0.9 — 1.13) Based on data from 6,027 patients in 32 studies. [4] (Randomized controlled)	**186** per 1000	**188** per 1000 Difference: **2 more** per 1000 (CI 95% 19 fewer — 24 more)	Low Due to serious indirectness, Due to serious imprecision [6]	Corticosteroids may not increase the risk of super-infections.
Hyperglycaemia	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8,938 patients in 24 studies. [4] (Randomized controlled)	**286** per 1000	**332** per 1000 Difference: **46 more** per 1000 (CI 95% 23 more — 72 more)	Moderate Due to serious indirectness [7]	Corticosteroids probably increase the risk of hyperglycaemia.
Hypernatremia	Relative risk 1.64 (CI 95% 1.32 — 2.03) Based on data from	**40**	**66**	Moderate Due to serious indirectness [8]	Corticosteroids probably increase the risk of hypernatremia.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Steroids	Certainty of the evidence (Quality of evidence)	Plain text summary
	5,015 patients in 6 studies. [4] (Randomized controlled)	per 1000	per 1000		
		Difference: **26 more** per 1000 (CI 95% 13 more − 41 more)			
Neuromuscular weakness	Relative risk 1.09 (CI 95% 0.86 − 1.39) Based on data from 6,358 patients in 8 studies. [4] (Randomized controlled)	69 per 1000	75 per 1000	Low Due to serious indirectness, Due to serious imprecision [9]	Corticosteroids may not increase the risk of neuromuscular weakness.
		Difference: **6 more** per 1000 (CI 95% 10 fewer − 27 more)			
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41 − 1.63) Based on data from 1,813 patients in 7 studies. [4] (Randomized controlled)	35 per 1000	28 per 1000	Low Due to serious indirectness, Due to serious imprecision [10]	Corticosteroids may not increase the risk of neuropsychiatric effects.
		Difference: **7 fewer** per 1000 (CI 95% 21 fewer − 22 more)			
Duration of hospitalization	Measured by: days Lower better Based on data from: 6,425 patients in 1 studies. [4] (Randomized controlled)	13 days	12 days	Low Due to serious risk of bias, Due to serious imprecision [11]	Steroids may result in an important reduction in the duration of hospitalizations
		CI 95%			

1. Systematic review (7). **Baseline/comparator:** Primary study (16). Baseline risk estimate for mortality updated May 2021: Now from WHO SOLIDARITY (as considered the best source) with 14.6% mortality at 28 days in severe and critically ill patients. This estimate adjusted for 50% receiving corticosteroids as standard of care in SOLIDARITY.

2. **Risk of bias: Serious.** Lack of blinding.

3. Systematic review (7). **Baseline/comparator:** Control arm of reference used for intervention. We used the median event rate for all patients randomized to usual care across included studies.

4. **Risk of bias: Serious.** Lack of blinding.
5. **Indirectness: Serious. Imprecision: Serious.**
6. **Indirectness: Serious. Imprecision: Serious.**
7. **Indirectness: Serious.**
8. **Indirectness: Serious.**
9. **Indirectness: Serious. Imprecision: Serious.**
10. **Indirectness: Serious. Imprecision: Serious.**
11. **Risk of bias: Serious.** Lack of blinding. **Imprecision: Serious.** Confidence interval includes no benefit.

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

Conditional recommendation against	Updated evidence, no change in recommendation
We suggest not to use corticosteroids.	

Practical info

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

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

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

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

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

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

Evidence to Decision

Benefits and harms

The panel made its recommendation on the basis of low certainty evidence suggesting a potential increase of 3.9% in 28-day mortality among patients with COVID-19 who are not severely ill. The certainty of the evidence for this specific subgroup was downgraded due to serious imprecision (i.e. the evidence does not allow to rule out a mortality reduction) and risk of bias due to lack of blinding. In making a conditional recommendation against the indiscriminate use of systemic corticosteroids, the panel inferred that most fully informed individuals with non-severe illness would not want to receive systemic corticosteroids, but many could want to consider this intervention through shared decision-making with their treating physician *(20)(21)*.

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

Preference and values

The weak or conditional recommendation was driven by likely variation in patient values and preferences. The panel judged that most individuals with non-severe illness would decline systemic corticosteroids. However, many may want them after shared decision-making with their treating physician.

Resources and other considerations

Resource implications, feasibility, equity and human rights
The panel also considered that in order to help guarantee access to systemic corticosteroids for patients with severe and critical COVID-19, it is reasonable to avoid administering this intervention to patients who, given the current evidence, would not appear to derive any benefit from this intervention.

Justification

This recommendation was achieved by consensus.

Applicability

This recommendation applies to patients with non-severe disease regardless of their hospitalization status. The panel noted that patients with non-severe COVID-19 would not normally require acute care in hospital or respiratory support, but that in some jurisdictions, these patients may be hospitalized for isolation purposes only, in which case they should not be treated with systemic corticosteroids. The panel concluded that systemic corticosteroids should not be stopped for patients with non-severe COVID-19 who are already treated with systemic corticosteroids for other reasons (e.g. patients with chronic obstructive pulmonary disease or other chronic autoimmune diseases need not discontinue a course of systemic oral corticosteroid). If the clinical condition of patients with non-severe COVID-19 worsens (i.e. increase in respiratory rate, signs of respiratory distress or hypoxaemia) they should receive systemic corticosteroids (see first recommendation in Section 7.6).

Clinical question/ PICO

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

Summary

Outline of the evidence on systemic corticosteroids

See Summary of the evidence profile for patients with severe and critical COVID-19.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Steroids	Certainty of the evidence (Quality of evidence)	Plain text summary
Mortality 28 days	Relative risk 1.22 (CI 95% 0.93—1.61) Based on data from 1535 patients in 1 study. [1] (Randomized controlled)	**23** per 1000 Difference: **5 more** per 1000 (CI 95% 2 fewer — 14 more)	**28** per 1000	**Low** Due to serious risk of bias and serious imprecision [2]	Systemic corticosteroids may increase the risk of 28-day mortality in patients with non-severe COVID-19
Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (CI 95% 0.59—0.93) Based on data from 5481 patients in 2 studies. [1] (Randomized controlled)	**116** per 1000 Difference: **30 fewer** per 1000 (CI 95% 48 fewer — 8 fewer)	**86** per 1000	**Moderate** Due to serious risk of bias [3]	Systemic corticosteroids probably reduce the need for mechanical ventilation
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85—1.33)	**48** per 1000	**51** per 1000	**Low** Due to serious indirectness and	Corticosteroids may not increase the risk of gastrointestinal bleeding.

Outcome Timeframe	Study results and measurements	Comparator Standard care	Intervention Steroids	Certainty of the evidence (Quality of evidence)	Plain text summary
	Based on data from 5403 patients in 30 studies. [4] (Randomized controlled)	Difference: **3 more** per 1000 (CI 95% 7 fewer — 16 more)		serious imprecision [5]	
Super-infections	Relative risk 1.01 (CI 95% 0.9—1.13) Based on data from 6027 patients in 32 studies. [4] (Randomized controlled)	**186** per 1000 Difference: **2 more** per 1000 (CI 95% 19 fewer — 24 more)	**188** per 1000	Low Due to serious indirectness, Due to serious imprecision [6]	Corticosteroids may not increase the risk of super-infections.
Hyperglycaemia	Relative risk 1.16 (CI 95% 1.08—1.25) Based on data from 8938 patients in 24 studies. [4] (Randomized controlled)	**286** per 1000 Difference: **46 more** per 1000 (CI 95% 23 more — 72 more)	**332** per 1000	Moderate Due to serious indirectness [7]	Corticosteroids probably increase the risk of hyperglycaemia.
Hypernatremia	Relative risk 1.64 (CI 95% 1.32—2.03) Based on data from 5015 patients in 6 studies. [4] (Randomized controlled)	**40** per 1000 Difference: **26 more** per 1000 (CI 95% 13 more — 41 more)	**66** per 1000	Moderate Due to serious indirectness [8]	Corticosteroids probably increase the risk of hypernatremia.
Neuromuscular weakness	Relative risk 1.09 (CI 95% 0.86—1.39) Based on data from 6358 patients in 8 studies. [4] (Randomized controlled)	**69** per 1000 Difference: **6 more** per 1000 (CI 95% 10 fewer — 27 more)	**75** per 1000	Low Due to serious indirectness and serious imprecision [9]	Corticosteroids may not increase the risk of neuromuscular weakness.
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41—1.63) Based on data from 1813 patients in 7 studies. [4] (Randomized controlled)	**35** per 1000 Difference: **7 fewer** per 1000 (CI 95% 21 fewer — 22 more)	**28** per 1000	Low Due to serious indirectness and serious imprecision [10]	Corticosteroids may not increase the risk of neuropsychiatric effects.
Duration of hospitalization	Measured by: days Lower better Based on data from: 6425 patients in 1 studies. [4] (Randomized controlled)	**13** days	**12** days	Low Due to serious risk of bias and serious imprecision [11]	Steroids may result in an important reduction in the duration of hospitalizations

1. Systematic review (7). **Baseline/comparator:** Primary study (16). We derived baseline risk for mortality and mechanical ventilation from the control arm of the WHO SOLIDARITY trial.

2. **Risk of bias: Serious.** Lack of blinding. **Imprecision: Serious.**

3. **Risk of bias: Serious.** Lack of blinding.

4. Systematic review (7). **Baseline/comparator:** Control arm of reference used for intervention.

5. **Indirectness: Serious. Imprecision: Serious.**

6. **Indirectness: Serious. Imprecision: Serious.**
7. **Indirectness: Serious.**
8. **Indirectness: Serious.**
9. **Indirectness: Serious. Imprecision: Serious.**
10. **Indirectness: Serious. Imprecision: Serious.**
11. **Risk of bias: Serious.** Lack of blinding. **Imprecision: Serious.** Confidence interval includes no benefit.

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 IL-6 receptor blockers identified by the GDG, adding to those for ivermectin, corticosteroids, remdesivir and hydroxychloroquine and lopinavir/ritonavir 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

*IL-6 receptor blockers (*despite the strong recommendation, there are a number of uncertainties that persist):

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

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

Hydroxychloroquine
Although some uncertainty remains, the GDG panel felt that further research was unlikely to uncover a subgroup of patients that 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 and effects on:

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

Corticosteroids and effects on:

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

Emerging evidence

The unprecedented volume of planned and ongoing studies for COVID-19 interventions – over 3300 RCTs as of 1 July 2021 – implies that more reliable and relevant evidence will emerge to inform policy and practice *(14)*. An overview of registered and ongoing trials for COVID-19 therapeutics and prophylaxis is available from the Infectious Diseases Data Observatory, through their living systematic review of COVID-19 clinical trial registrations *(14)*, the WHO website and other repositories, such as the COVID-NMA initiative.

Whereas most of these studies are small and of variable methodological quality, a number of large, international platform trials (e.g. RECOVERY, SOLIDARITY and DISCOVERY) are better equipped to provide robust evidence for a number of potential treatment options *(15)(16)(17)(18)*. Such trials can also adapt their design, recruitment strategies and selection of interventions based on new insights, exemplified by the uncertainties outlined above.

9. Authorship, contributions, acknowledgements

Authorship, contributions, acknowledgements

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 Emergencies Programme, Geneva); John Appiah (Lead, Case Management, WHO Regional Office for Africa); Lisa Askie (Quality Assurance of Norms and Standards Department); Silvia Bertagnolio (Communicable and Noncommunicable Diseases Division/Clinical Team for COVID-19 Response); Sophie Harriet Dennis (Infection Prevention and Control and Clinical Management); Nathan Ford (Department of HIV/AIDS and Global Hepatitis Programme); Chiori Kodama (WHO Regional Office for the Eastern Mediterranean); Marta Lado Castro-Rial (Clinical Team for COVID-19 Response, Health Emergencies Programme, Geneva); Lorenzo Moja (Health Products Policy and Standards Department); Olufemi Oladapo (Sexual and Reproductive Health and Research Department); Dina Pfeifer (WHO Regional Office for Europe/Health Emergencies Programme); Jacobus Preller (Clinical Team for COVID-19 Response, Health Emergencies Programme, Geneva; Pryanka Relan (Clinical Team for COVID-19 Response, Health Emergencies Programme, Geneva); Ludovic Reveiz (Evidence and Intelligence for Action in Health Department, Incident Management Systems for COVID-19, Pan American Health Organization); Vaseeharan Sathiyamoorthy (Research for Health, Science Division); Archana Seahwag (Clinical Team for COVID-19 Response, Health Emergencies Programme, Geneva); Anthony Solomon (Neglected Tropical Diseases); Juan Soriano Ortiz (Clinical Team for COVID-19 Response, Health Emergencies Programme, Geneva); Pushpa Wijesinghe (Lead, Case Management, Regional Office for South-East Asia). Supporting project officer: Anne Colin (Clinical Team for COVID-19 Response, Health Emergencies Programme, Geneva).

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

We would like to acknowledge the **Guidance Support Collaboration Committee** which provided the coordination between WHO and MAGIC to allow the rapid development of the WHO guidance and its dissemination: Thomas Agoritsas (MAGIC, University Hospitals of Geneva); Janet Diaz (World Health Organization), Fiona Godlee (British Medical Journal); Gordon Guyatt (McMaster University, Canada); Navjoyt Ladher (British Medical Journal); François Lamontagne (Université de Sherbrooke, Canada); Srinivas Murthy (University of British Columbia, Canada); Bram Rochwerg (McMaster University, Canada); Archana Seahwag (World Health Organization); Per Olav Vandvik (MAGIC, University of Oslo).

Guideline Development Group (GDG)
Wagdy Amin (Ministry of Health and Population, Egypt); Frederique Bausch (Geneva University Hospital, Switzerland); Erlina Burhan (Infection Division Department of Pulmonology and Respiratory Medicine Faculty of Medicine Universitas Indonesia); Carolyn S Calfee (University of California, San Francisco); Maurizio Cecconi (Humanitas Research Hospital Milan, Italy); Duncan Chanda (Adult Infectious Disease Centre, University Teaching Hospital, Lusaka, Zambia); Vu Quoc Dat (Department of Infectious Diseases, Hanoi Medical University, Hanoi, Viet Nam); Bin Du (Peking Union Medical College Hospital); Heike Geduld (Emergency Medicine, Stellenbosch University, South Africa); Patrick Gee (patient panel member, United States of America); Nerina Harley (Royal Melbourne Hospital and Epworth Healthcare, Melbourne, Australia); Madiha Hashmi (Ziauddin University, Karachi, Pakistan); Manai Hela (Emergency Medical Service Tunis, Tunisia); Beverley Hunt (Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom); Sushil Kumar Kabra (All India Institute of Medical Sciences, New Delhi, India); Seema Kanda (patient panel member, Ontario, Canada); Leticia Kawano-Dourado (Research Institute, Hospital do Coração, São Paulo, Brazil); Yae-Jean Kim (Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea); Niranjan Kissoon (Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Arthur Kwizera (Makerere College of Health Sciences, Kampala, Uganda); Yee Sin Leo (National Centre for Infectious Diseases, Singapore); Imelda Mahaka (patient panel member, Pangaea Harare, Zimbabwe); Greta Mino (Alcivar Hospital in Guayaquil, Ecuador); Emmanuel Nsutebu (Sheikh Shakhbout Medical City, Abu Dhabi); Natalia Pshenichnaya (Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow, Russian Federation); Nida Qadir (Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California, Los Angeles, United States of America); Saniya Sabzwari (Aga Khan University, Karachi, Pakistan); Rohit Sarin (National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India); Yinzhong Shen (Shanghai Public Health Clinical Center, Fudan University, Shanghai, China); Shalini Sri Ranganathan (University of Colombo, Sri Lanka); Joao Paulo Souza, University of São Paulo, Brazil); Miriam Stegeman (Charité - Universitätsmedizin Berlin, Germany); Ann De Sutter (University of Gent,

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