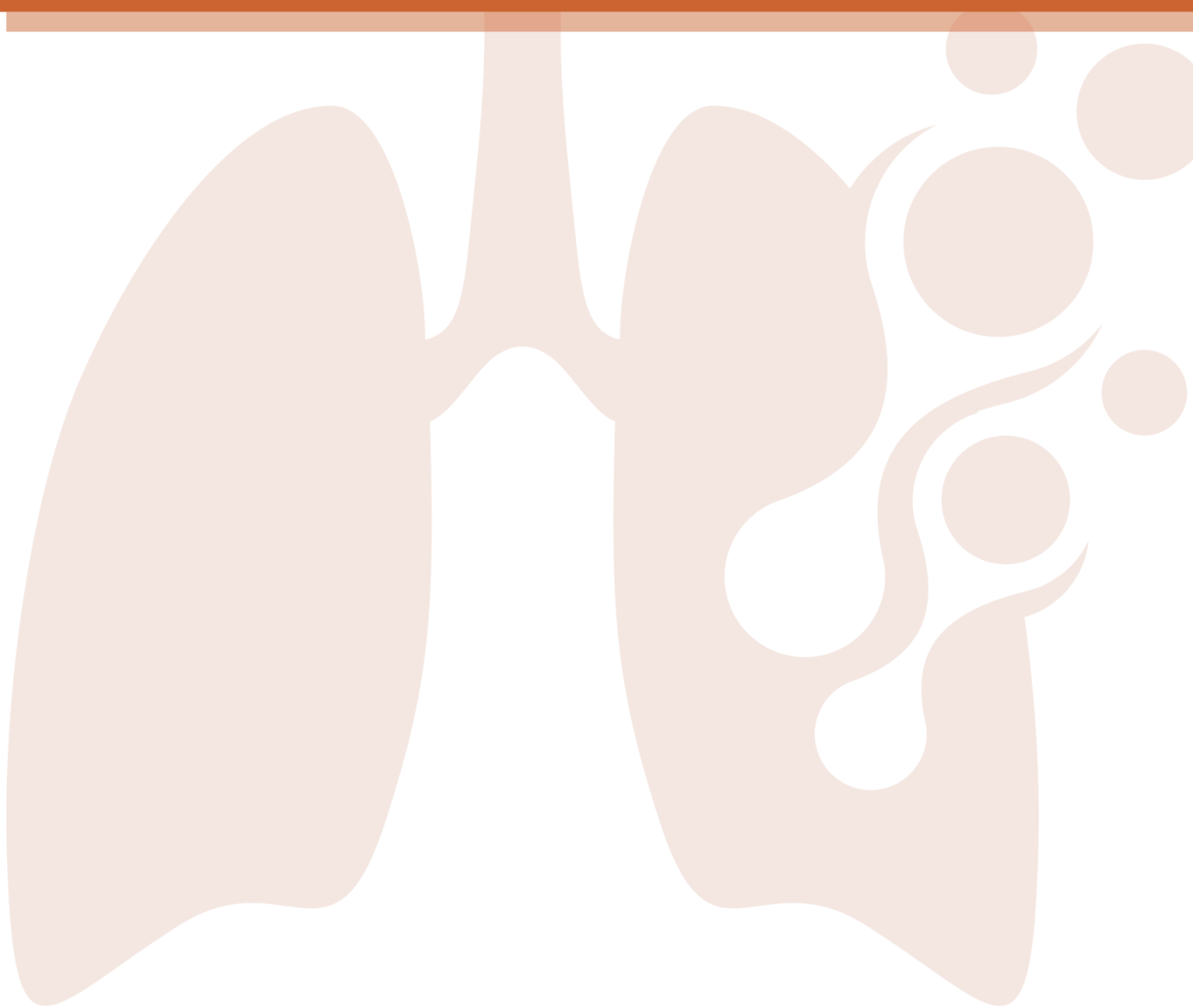
Therapeutics and COVID-19

LIVING GUIDELINE
31 MARCH 2021

World Health Organization



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WHO reference number: WHO/2019-nCoV/therapeutics/2021.1

Contents

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 audiences are 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 ivermectin *(1)*. Increased international attention on ivermectin as a potential treatment for COVID-19 triggered this recommendation.

Recommendations: In this update, the panel makes a recommendation not to use ivermectin in patients with COVID-19 except in the context of a clinical trial. 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.

How this guideline was created: 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. These guidelines are also published in the BMJ *(2)*, supported by two living systematic reviews with network analysis that inform the recommendations *(3, 4)*. 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.

The latest evidence: Results from a living systematic review and network meta-analysis (NMA) that pooled data from 16 randomized controlled trials (RCTs) with 2407 participants, including both inpatients and outpatients with COVID-19, informed the recommendation on ivermectin *(3)*. The effects of ivermectin on mortality, need for invasive mechanical ventilation, hospital admission, duration of hospitalization and time to viral clearance all remain very uncertain (all very low certainty evidence). The uncertainty results from important concerns related to risk of bias in the included studies, and imprecision from a very low number of events and, in some cases, wide confidence intervals (CIs) in pooled estimates.

Ivermectin may increase the risk of serious adverse events (SAEs) leading to drug discontinuation (odds ratio [OR] 3.07; 95% CI: 0.77–12.09; low certainty evidence) and may have little or no impact on time to clinical improvement (mean difference [MD] 0.5 fewer days; 95% CI: 1.7 fewer days to 1.1 more days; low certainty evidence). There was no credible subgroup effect based on dose. Subgroup analyses were not performed examining between-study differences in age or illness severity as per our pre-defined decision to limit subgroup analysis to within-study comparisons.

Understanding the recommendations: When moving from evidence to the recommendation not to use ivermectin except in the context of a clinical trial, the panel emphasized the large degree of uncertainty in the evidence on mortality, need for mechanical ventilation, need for hospital admission, time to clinical improvement, and other patient-important outcomes. There remains potential for harms with an increased risk of adverse events leading to study drug discontinuation. The panel believed that most well-informed patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects. The panel considered contextual factors such as resources, feasibility, acceptability, and equity for countries and health care systems were unlikely to alter the recommendation.

Info Box

This WHO *Therapeutics and COVID-19: living guideline* now includes a recommendation not to use ivermectin except in the context of a clinical trial. The guideline was initiated in response to international attention on ivermectin as a potential treatment for COVID-19. 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 *(5)*; the second version published 20 November 2020 provides recommendations for remdesivir *(6)*; the third version published 12 December 2020 provides recommendations for hydroxychloroquine and lopinavir/ritonavir *(7)*. This update does not include changes for any of these 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 *(1)*, also available in the BMJ as Rapid Recommendations *(2)*, together with the living network meta-analysis (LNMA) *(3)*, a major evidence source for the guidelines. The updated LNMA informing the recommendation on ivermectin has been published in the BMJ, with the updated guideline in the BMJ pending *(3)*.

2. Abbreviations

ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
CAP	community-acquired pneumonia
CI	confidence interval
COVID-19	coronavirus disease 2019
eGFR	estimated glomerular filtration rate
GDG	guideline development group
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	guideline review committee
LNMA	living network meta-analysis
MAGIC	Magic Evidence Ecosystem Foundation
MD	mean difference
NMA	network meta-analysis
OIS	optimal information size
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 20 March 2021, over 121 million people worldwide have been diagnosed with COVID-19, according to the WHO dashboard *(8)*. The pandemic has thus far claimed more than 2.6 million lives, 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 *(9)*. 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 *(10)*.

This living guideline responds to emerging evidence from randomized controlled trials (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 8 – emerging evidence) *(11)*. Among these are national and international platform trials (e.g. RECOVERY, WHO SOLIDARITY, DISCOVERY, REMAP-CAP and ACTIV) that recruit large numbers of patients in many countries, with a pragmatic and adaptive design *(12, 13)*. These platform trials are currently investigating and reporting on 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 fourth version of the WHO living guideline addresses the use of ivermectin in patients with COVID-19. It follows the increased international attention on ivermectin as a potential therapeutic option. While ivermectin is also being investigated for prophylaxis, this guideline only addresses its role in the treatment of COVID-19. Ivermectin is relatively inexpensive and accessible, and some countries have already witnessed its widespread use in the treatment of COVID-19; in other countries, there is increasing pressure to do so *(14)*.

In response to this international attention, the WHO GDG now provides recommendations on ivermectin for treatment of COVID-19. Ivermectin is an antiparasitic agent that interferes with nerve and muscle function of helminths through binding glutamate-gated chloride channels *(15)*. We currently lack persuasive evidence of a mechanism of action for ivermectin in COVID-19, and any observed clinical benefit would be unexplained (see Section 5).

3.2 Who made this guideline

WHO selected GDG members that represent all WHO regions, has equal gender balance and includes specialists in infectious diseases, pulmonary medicine, intensive care, emergency care, primary care, ethics and four patient panel members, headed by a clinical chair (Dr Michael Jacobs) and a methods chair (Dr Bram Rochwerg). Declaration of interest forms were collected, assessed and managed by the WHO secretariat according to WHO standard procedures. No panel members were assessed to have a conflict of interest. GDG member bios can be found on the WHO website. Evidence summaries were prepared by the systematic review team (see Section 9). Methodologic support, with high-level expertise in GRADE, was provided by the MAGIC Evidence Ecosystem Foundation (MAGIC) (see Section 9). The methodological experts were not involved in the formulation of recommendations.

3.3 How to use this guideline

This is a living guideline from WHO. The guideline is written, disseminated and updated in MAGICapp, with a format and structure that ensures user-friendliness and ease of navigation *(16)*. 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 (MAGIC), under the coordination of the Guideline Collaboration Committee (see Section 9), worked with the BMJ to coordinate the simultaneous scientific publication of the living WHO guidelines *(2)*.

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

- WHO website in PDF format
- WHO Academy app

- BMJ Rapid Recommendations *(2)*

The purpose of the MAGICapp 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) *(16)*.

4. Methods: how this guideline was created

The team developed this living WHO guideline according to standards and methods for trustworthy guidelines, making use of an innovative process to achieve efficiency in dynamic updating of recommendations *(1)*. 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 *(18)*.

Related guidelines

This living WHO guidance for COVID-19 treatments will be related to the larger, more comprehensive guidance for Clinical management of COVID-19: interim guidance, which has a wider scope of content and has been updated and is available on MAGICapp *(17)*. The first three WHO living guidelines, addressing corticosteroids *(5)*, remdesivir *(6)*, hydroxychloroquine and lopinavir/ritonavir *(7)*, were disseminated via the WHO website, BMJ and MAGICapp.

Timing

This guidance will be living: dynamically updated and globally disseminated once new evidence warrants a change in recommendations *(19)*. The aim is for a timeframe from trials that trigger guideline development process to WHO publication within one month, while maintaining standards for trustworthy guidelines (WHO Handbook of guideline development) *(18, 19)*.

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 panel (see Section 9) convened on two occasions to address this drug. 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 panel finalized the PICOs and pre-specified subgroups of interest. Subsequent to the meeting, the panel participated, through email correspondence, in an outcome prioritization exercise. At the second meeting, held on 4 March 2021, the GDG panel reviewed evidence summaries, including pre-specified subgroup analysis, and a recommendation was drafted.

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. 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 panel. To conduct the subgroup analysis of high versus low dose of ivermectin, Professor Andrew Owen (see Section 9), provided direction on analysis of different dosing regimens. Based on pharmacokinetic data, Professor Owen and the methods support team recommended analysing cumulative dose as a continuous variable, further adding a co-variate for single vs multiple dosing regimens. This subgroup analysis informed the direct comparison of ivermectin compared with standard of care only, and not the network analysis.

Step 4: Final recommendations

The GRADE approach provided the framework for establishing evidence certainty and generating both the direction and strength of recommendations *(20, 21)*. While a priori voting rules informed procedures if the panel 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) *(22)*;
- quality/certainty of the evidence *(20, 23)*;
- values and preferences of patients *(24)*;
- resources and other considerations (including considerations of feasibility, applicability, equity) *(24)*;
- 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 panel reviews narrative summaries;
- recommendations are rated as either conditional or strong, as defined by GRADE. If the panel members disagree regarding the evidence assessment or strength of recommendations, WHO will apply voting according to established rules.

Step 5: External and internal review

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

5. The latest evidence

This section outlines what information the GDG panel requested and used in making their recommendation for ivermectin.

Mechanism of action

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 *(25-27)*. Ivermectin had no impact on SARS-CoV-2 viral RNA in the Syrian golden hamster model of SARS-CoV-2 infection *(28)*. 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 *(29-33)*. 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 *(34)*, and has benefits in murine models of atopic dermatitis and allergic asthma *(35, 36)*. 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 *(37)*, 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 *(28)*. 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 (Table 1) and outpatient (Table 2) 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.

Table 1. Panel outcome rating from an inpatient perspective

Outcome	Mean	SD	Range
Death	9.0	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-CoV2 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.

Table 2. Panel outcome rating from an outpatient perspective

Outcome	Mean	SD	Range
Admission to hospital	8.5	0.7	7-9
Death	8.1	1.9	3-9
Quality of life	7.5	1.3	5-9
Serious adverse effects (e.g. adverse events leading to drug discontinuation)	7.4	1.8	3-9
Time to symptom resolution	7.3	1.7	4-9
Duration of hospitalization	6.6	0.9	5-8
Duration of oxygen support	6.6	1.2	5-9
Need for invasive mechanical ventilation	5.9	2.3	1-8
New non-SARS-CoV2 infection	5.6	2.1	3-9
Time to viral clearance	5.5	2.4	1-9
Duration of invasive mechanical ventilation	5.4	2.1	1-8

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

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 *(38-41)*.

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 *(42)*.

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. risk ratios [RR], OR) obtained from the NMA.

The control arm of the WHO SOLIDARITY trial *(13)*, 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 patients' 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

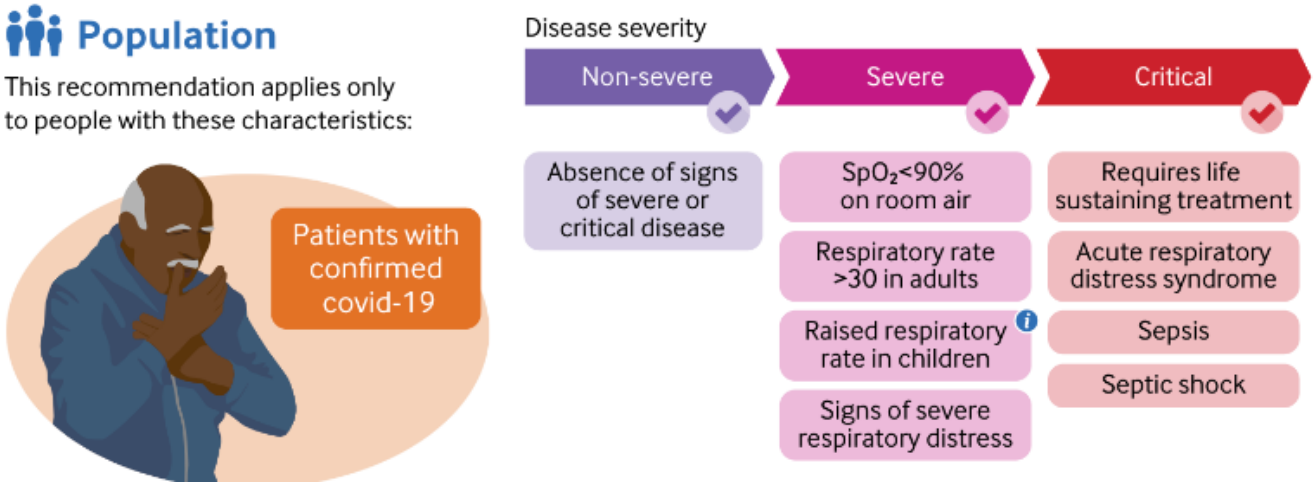
The guideline for COVID-19 therapeutics applies to all patients with COVID-19. For some drugs (such as corticosteroids), recommendations may differ based on the severity of COVID-19 disease. The GDG used the WHO severity definitions based on clinical indicators, adapted from WHO COVID-19 disease severity categorization (see below) *(17)*. These definitions avoid reliance on access to health care to define patient subgroups.

WHO Severity definitions

- **Critical COVID-19** – Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
- **Severe COVID-19** – Defined by any of:
  - Oxygen saturation <90% on room air;
  - Respiratory rate > 30 breaths/min in adults and children > 5 years old; ≥ 60 breaths/min in children < 2 months old; ≥ 50 in children 2–11 months old; and ≥ 40 in children 1–5 years old;
  - Signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).
- **Non-severe COVID-19** – Defined as absence of any criteria for severe or critical COVID-19.

Caution: The panel noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously when used 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 panel suggested erring on the side of considering the illness as severe.

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



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

7. Recommendations for therapeutics

7.1 Ivermectin

Only in research settings

New

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 a 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 dicontinuation (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 5). 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 panel 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 and other considerations

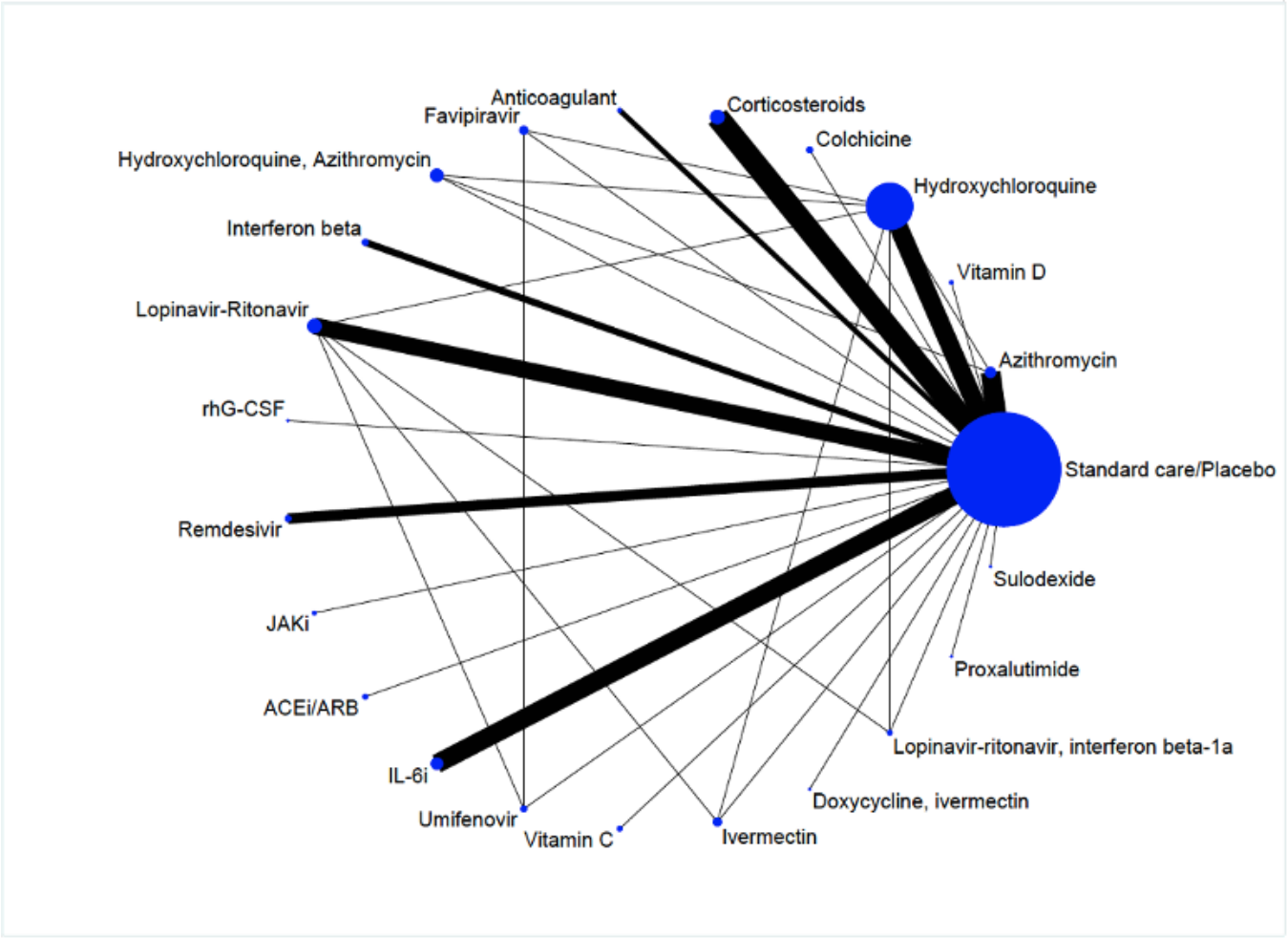
Ivermectin is a relatively inexpensive drug and is widely available, including in low-income settings. The low cost and wide availability do not, in the panel's view, mandate the use of a drug in which any benefit remains very uncertain and ongoing concerns regarding harms remain. Although the cost may be low per patient, the GDG 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. 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 panel 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 Living Guidelines for Therapeutics in COVID-19 (see below), 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

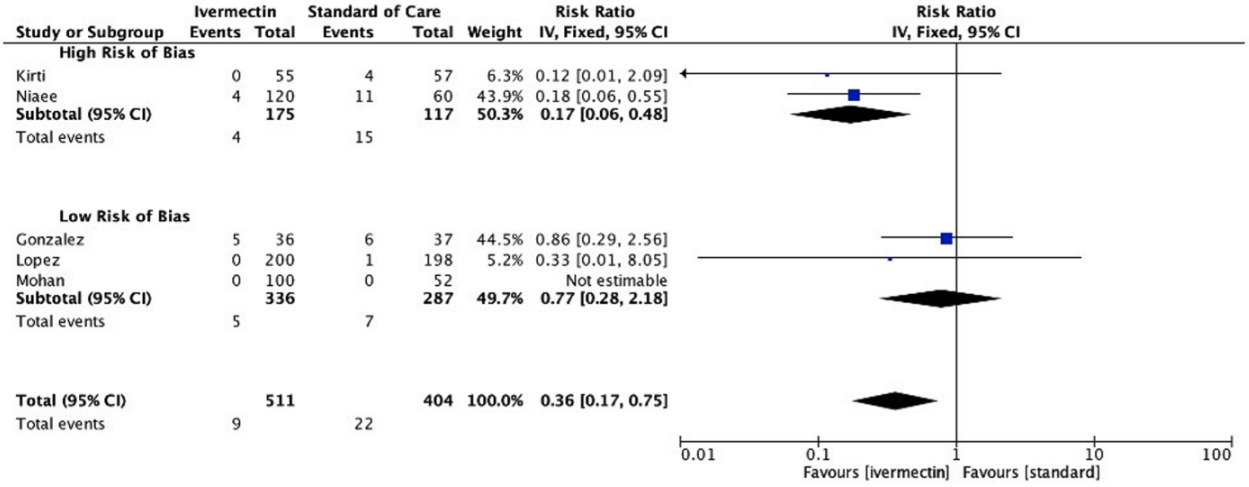


Drugs for which this guideline has already addressed with recommendations include corticosteroids, remdesivir, hydroxychloroquine and lopinavir/ritonavir.

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 *(43-47)*. 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 *(43, 44)* were at high risk of bias, due to inadequate blinding. One of these two trials *(43)* 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 *(48)* 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 *(49)*. 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 5). 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

Summary

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 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 1,419 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. (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. (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. (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.
Serious adverse events	Odds ratio 3.07 (CI 95% 0.77 - 12.09) Based on data from 584 patients in 3 studies. (Randomized controlled)	9 per 1000	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.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 Ivermectin	Certainty of the evidence (Quality of evidence)	Plain text summary
Time to clinical improvement	Measured by: days Lower better Based on data from: 633 patients in 2 studies. (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. (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. (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 *(3)*. **Baseline/comparator:** Control arm of reference used for intervention. We elected to use the control arm of the WHO solidarity trial, reflecting usual care across countries participating in the trial.
2. **Risk of bias: Serious.** The large trial contributing most of the effect estimate was driven by studies that were not blinded.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** The number of total events was very small.. **Publication bias: No serious.**
3. **Inconsistency: No serious. Indirectness: No serious. 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.. **Indirectness: No serious. Imprecision: Serious.** Credible interval includes no effect.. **Publication bias: No serious.**
5. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Credible interval includes important benefit and harm.. **Publication bias: No serious.**
6. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Credible interval includes little to no difference.. **Publication bias: No serious.**
7. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious. Publication bias: No serious.**
8. **Risk of bias: Serious.** Result driven by one study that was not blinded.. **Inconsistency: Serious.** Despite overlapping confidence intervals, point estimates discrepant.. **Indirectness: No serious. Imprecision: Serious.** Credible intervals include no difference.. **Publication bias: No serious.**
9. **Risk of bias: Serious.** Concerns around risk of bias.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Credible interval includes important benefit and important harm.. **Publication bias: No serious.**

7.2 Hydroxychloroquine (published December 17 2020)

The third version of the WHO living guideline addressed the use of hydroxychloroquine (and lopinavir/ritonavir, see below) 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 *(50)*. 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, 6,331 to usual care) and had the potential to change practice *(13, 50)*.

The evidence

The evidence summary for hydroxychloroquine was based on 30 trials and 10 921 participants for which the NM provided relative estimates of effect for patient-important outcomes (Table 3). Five of the trials (414 total participants) randomized some patients to chloroquine.

Table 3. Summary of trials and trial characteristics informing the hydroxychloroquine recommendation

(trials = 30, total patients = 10 921)

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

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. risk ratio, odds ratio) obtained from the NMA.

The control arm of the WHO SOLIDARITY Trial *(13)*, 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) 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 categorica 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 th 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) migh result in higher risk of adverse effects than lower maximum serum concentrations. In our pharmacokinetic model, the cumulative dose was highly correlated with all measures of serum concentrations on Day 3 and the final day of treatment, and therefore we decided to use cumulative dose as the primary analysis. Day 3 trough concentration was least strongly correlated with total cumulative dose (R2 = 0.376) and therefore we performed a sensitivity subgroup analysis with predicted Day 3 trough concentrations for efficacy outcomes.

Info Box

The recommendation concerning hydroxychloroquine was published December 17 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 fourth 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 versus 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

Summary

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	Hydroxychloroquine	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**	**Absolute effect estimates** Standard care	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 6,379 patients in 5 studies. (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. (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 [4]	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. (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 [5]	The effect of hydroxychloroquine on admission to hospital is uncertain.
Cardiac toxicity	Based on data from 3,287 patients in 7 studies. (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 [6]	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. (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 [7]	Hydroxychloroquine may increase the risk of diarrhoea.
Nausea/ vomiting	Odds ratio 1.74 (CI 95% 1.26 - 2.41) Based on data from 1,429 patients in 7 studies. (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 risk of bias [8]	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. (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 [9]	The effect of hydroxychloroquine on delirium is uncertain.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Hydroxychloroquine	**Certainty of the evidence** (Quality of evidence)	**Plain text summary**
Time to clinical improvement	Lower better Based on data from: 479 patients in 5 studies. (Randomized controlled)	11 days (Mean)	9 days (Mean) Difference: MD 2 fewer (CI 95% 4 fewer - 0.1 more)	Very Low Due to serious risk of bias, imprecision, and indirectness [10]	The effect of hydroxychloroquine on time to clinical improvement is uncertain.
Duration of hospitalization	Lower better Based on data from: 5,534 patients in 5 studies. (Randomized controlled)	12.8 days (Mean)	12.9 days (Mean) Difference: MD 0.1 more (CI 95% 1.9 fewer - 2 more)	Low Due to serious imprecision and serious risk of bias [11]	Hydroxychloroquine may have no effect on duration of hospitalization.
Time to viral clearance	Lower better Based on data from: 440 patients in 5 studies. (Randomized controlled)	9.7 days (Mean)	10.6 days (Mean) Difference: MD 0.7 fewer (CI 95% 4.3 fewer - 4.8 more)	Very Low Due to serious risk of bias and very serious imprecision [12]	The effect of hydroxychloroquine on time to viral clearance is uncertain.
Adverse events leading to drug discontinuation	Based on data from: 210 patients in 3 studies. (Randomized controlled)	Two of 108 patients randomized to hydroxychloroquine discontinued treatment because of adverse effects. None of 102 patients did so in the placebo/standard care group.		Very Low Due to extremely serious imprecision [13]	The effect of hydroxychloroquine on adverse events leading to drug discontinuation is uncertain.

1. Systematic review *(3)*. **Baseline/comparator:** Control arm of reference used for intervention. We elected to use the control arm of the WHO solidarity trial, reflecting usual care across countries participating in the trial.
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. . **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** The 95% CI crosses the minimally important difference (2% reduction in mortality). . **Publication bias: No serious.**
3. **Risk of bias: Serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
4. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals. **Publication bias: No serious.**
5. **Inconsistency: No serious. Indirectness: Serious. Imprecision: Very Serious. Publication bias: No serious.**
6. **Risk of bias: Serious.** unblinded studies -> cardiac toxicity differential detection. **Inconsistency: No serious. Indirectness: Serious.** Studies measured serious cardiac toxicity differently.. **Imprecision: Serious.**
7. **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.**
8. **Risk of bias: Serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** OIS not met.. **Publication bias: No serious. Upgrade: Large magnitude of effect.**
9. **Indirectness: Serious.** This outcome was not collected systematically and the definition of delirium was not specified.. **Imprecision: Very Serious.**
10. **Risk of bias: Serious. Inconsistency: No serious. Indirectness: Serious.** Studies measured clinical improvement

differently.. **Imprecision: Serious. Publication bias: No serious.**

11. **Risk of bias: Serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals.
12. **Risk of bias: Serious. Imprecision: Very Serious.**
13. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious. Publication bias: No serious.**

7.3 Lopinavir/ritonavir (published December 17 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 *(50)*. 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, 6,331 to usual care) and had the potential to change practice *(13, 50)*.

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 4).

Table 4. Summary of trials and trial characteristics informing the lopinavir/ritonavir recommendation

(trials = 7, total patients = 7429)

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

Notes:

[a] 2 trials did not report the disease severity of patients.
[b] 3 trials did not report 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. risk ratio, odds ratio) obtained from the NMA.

The control arm of the WHO SOLIDARITY Trial *(13)*, 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. 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 December 17 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 fourth 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 randomized controlled trials; pooling data from 7429 patients hospitalized with various severities of COVID-19 and variably reporting the outcomes of interest to the guideline panel *(3)*. The panel agreed that there was moderate certainty for mortality and need for mechanical ventilation, low certainty for diarrhoea, nausea and duration of hospitalization and very low certainty in the estimates of effect for viral clearance, acute kidney injury and time to clinical improvement. Most outcomes were lowered for risk of bias and imprecision (wide confidence intervals which 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	Absolute effect estimates Standard care	 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 8,061 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 7,579 patients in 3 studies. [3] (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 [4]	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. (Randomized controlled)	483 per 1000	246 per 1000 Difference: 237 fewer per 1000 (CI 95% 447 fewer - 165 more)	Low Due to serious risk of bias, Due to very serious imprecision [5]	the effects of lopinavir-ritonavir on viral clearance is very uncertain
Acute kidney injury	Relative risk Based on data from 259 patients in 2 studies. (Randomized controlled)	45 per 1000	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, Due to 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. (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. [8] (Randomized controlled)	17 per 1000	177 per 1000 Difference: 160 more per 1000	Moderate Due to serious risk of bias and imprecision [9]	Lopinavir-ritonavir may increase the risk of nausea/vomiting

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	Lopinavir-ritonavir	Certainty of the evidence (Quality of evidence)	Plain text summary
		(CI 95% 100 more - 210 more)			
Time to clinical improvement	Lower better Based on data from: 199 patients in 1 studies. (Randomized controlled)	11 days (Mean)	10 days (Mean) Difference: MD 1 fewer (CI 95% 4.1 fewer - 3.2 more)	Very Low Due to serious risk of bias, Due to very serious imprecision [10]	The effect of lopinavir-ritonavir improves on time to clinical improvement is very uncertain
Duration of hospitalization	Lower better Based on data from: 5,239 patients in 2 studies. (Randomized controlled)	12.8 days (Mean)	12.5 days (Mean) Difference: MD 0.3 lower (CI 95% 3 lower - 2.5 higher)	Low Due to serious risk of bias and imprecision [11]	Lopinavir-ritonavir may have no effect on duration of hospitalization

1. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** *(3)*,
2. **Risk of bias: No serious.** We rated two trials as high risk of bias due to high or probably high risk of bias in deviations from the intended intervention.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** The 95% CI crosses the minimally important difference (2% reduction in mortality).. **Publication bias: No serious.**
3. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** *(3)*,
4. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
5. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals. **Publication bias: No serious.**
6. **Risk of bias: Serious. Inconsistency: No serious. Imprecision: Very Serious.** Wide confidence intervals. **Publication bias: No serious.**
7. **Risk of bias: Serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Few patients and events. **Publication bias: No serious. Upgrade: Large magnitude of effect.**
8. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** *(3)*,
9. **Risk of bias: Serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Few patients and events. **Publication bias: No serious. Upgrade: Large magnitude of effect.**
10. **Risk of bias: Serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals, low number of patients. **Publication bias: No serious.**
11. **Risk of bias: Serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**

7.4 Remdesivir (published Nov 20 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 *(13)*. 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, 6,331 to usual care) and had the potential to change

practice *(13)*.

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-CoV2. Remdesivir is widely used in many countries, with several guidelines recommending its use in patients with severe or critical COVID-19 *(51, 52)*.

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 *(13, 53-55)*, 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 5. 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
Biegel (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 events -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 -Time to clinical improvement -Duration of hospitalization -Mechanical ventilation -Adverse events
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 -Adverse events -Viral clearance -Duration of hospitalization -Duration of ventilation -Time to clinical improvement

IMV: invasive mechanical ventilation; IV: intravenous; N: number; NR: not reported; Sx: symptom.
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. *Notes:*
*Only SIMPLE MODERATE was included in the analysis, as SIMPLE SEVERE did not have a placebo/usual care arm.

Subgroup analysis

The GDG panel requested subgroup analyses based on age (considering children vs adults vs older people), illness severity (non-severe vs severe vs critical COVID – see subgroup under Section 7 - Recommendations for therapeutics section for details), and duration of remdesivir therapy (5 days vs longer than 5 days). The GDG discussed other potential subgroups of interest including time from onset of symptoms until initiation of therapy, concomitant medications (especially corticosteroids) however recognized these analyses would not be possible without access to individual participant data. To this last point, the panel recognized that usual care is likely variable between centres, regions and evolved over time. However, given all of the data comes from RCTs, use of these co-interventions that comprise usual care should be balanced between study patients randomized to either the intervention or usual care arms.

Following the panel's request, the NMA team performed subgroup analyses in order to assess for effect modification which, if present, could mandate distinct recommendations by subgroups. From the data available from the included trials, subgroup analysis was only possible for severity of illness and the outcome of mortality. This subgroup analysis was performed using a random effects frequentist analysis based on the three WHO severity definitions. A post-hoc Bayesian analysis was also performed, which incorporated meta-regression using study as a random effect. This latter approach has the advantage of more accurately accounting for within-study differences but can only compare two subgroups at a time. The panel used a pre-specified framework incorporating the ICEMAN tool to assess the credibility of subgroup findings *(13)*.

Info Box

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

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

Conditional recommendation against

We suggest against administering remdesivir in addition to usual care

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 severe adverse events (SAEs) from the trials.. However, further pharmacovigilance is needed because SAEs are commonly underreported and rare events could be missed, even in large RCTs.

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

Certainty of the evidence Low

The evidence is based on a linked systematic review and NMA of 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 *(3)*. The panel agreed that there was low certainty in the estimates of effect for all patient-important outcomes across benefits and harms, mostly driven by risk of bias and imprecision (wide confidence intervals which 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) *(13)* or critical (ACTT-1) *(55)*. The analysis focused on within-study subgroup comparisons across the different severities, and therefore the SIMPLE-MODERATE trial could not be included in the subgroup analysis as it only enrolled patients with non-severe COVID-19. The panel reviewed the results of both the random effects frequentist analysis and the post-hoc Bayesian analysis which incorporated meta-regression using study as a random effect.

The GDG panel judged the credibility in the subgroup analysis assessing differences in mortality by severity of illness to be

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

The panel had *a priori* requested analyses of other important subgroups of patients including children and older persons, but there were no data to address these groups specifically. None of the included RCTs enrolled children, and although older people were included in the trials, their outcomes were not reported separately. Also, there 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

Summary

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 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 7,333 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 6,549 patients in 4 studies. [3] (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 [4]	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 1,894 patients in 3 studies. [5] (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 [6]	Remdesivir possibly has little or no effect on serious adverse events leading to discontinuation.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Remdesivir	**Certainty of the evidence** (Quality of evidence)	**Plain text summary**
Viral clearance 7 days	Odds ratio 1.06 (CI 95% 0.06 - 17.56) Based on data from 196 patients in 1 studies. [7] (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 [8]	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 1,281 patients in 2 studies. [9] (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 [10]	Remdesivir possibly has little or no effect on acute kidney injury.
Delirium	Odds ratio 1.22 (CI 95% 0.48 - 3.11) Based on data from 1,048 patients in 1 studies. [11] (Randomized controlled)	16 per 1000	19 per 1000 Difference: 3 more per 1000 (CI 95% 8 fewer - 32 more)	Very Low Due to very serious imprecision and serious indirectness [12]	We are uncertain whether remdesivir increases or decreases delirium
Time to clinical improvement	Measured by: days Lower better Based on data from: 1,882 patients in 3 studies. [13] (Randomized controlled)	11 days	9 days Difference: MD 2 lower (CI 95% 4.2 lower - 0.9 higher)	Low Due to serious imprecision and serious indirectness [14]	Remdesivir possibly has little or no effect on time to clinical improvement.
Duration of hospitalization	Measured by: days Lower better Based on data from: 1,882 patients in 3 studies. [15] (Randomized controlled)	12.8 days	12.3 days Difference: MD 0.5 lower (CI 95% 3.3 lower - 2.3 higher)	Low Due to serious imprecision and serious indirectness [16]	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. [17] (Randomized controlled)	14.7 days	13.4 days Difference: MD 1.3 lower (CI 95% 4.1 lower - 1.5 higher)	Low Due to very serious imprecision [18]	Remdesivir possibly has little or no effect on duration of ventilation.

1. Systematic review *(3)*. **Baseline/comparator:** Control arm of reference used for intervention *(50)*.
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. . **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** The 95% CI crosses the minimally important difference (2% reduction in mortality). . **Publication bias: No serious.**
3. Systematic review *(3)* . **Baseline/comparator:** Control arm of reference used for intervention *(50)*.
4. **Risk of bias: Serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence

intervals. **Publication bias: No serious.**
5. Systematic review *(3)*. **Baseline/comparator:** Systematic review *(3)*. Used the median or mean of all patients randomized to usual care across the included studies..
6. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals. **Publication bias: No serious.**
7. Systematic review *(3)*. **Baseline/comparator:** Systematic review *(3)*. Used the median or mean of all patients randomized to usual care across the included studies..
8. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals. **Publication bias: No serious.**
9. Systematic review *(3)*. **Baseline/comparator:** Systematic review *(3)*. Used the median or mean of all patients randomized to usual care across the included studies..
10. **Inconsistency: No serious. Indirectness: Serious.** Studies used change in serum creatinine rather than patient-important measures of acute kidney injury.. **Imprecision: Serious.** Wide 95% credible intervals.. **Publication bias: No serious.**
11. Systematic review *(3)*. **Baseline/comparator:** Systematic review *(3)*. Used the median or mean of all patients randomized to usual care across the included studies..
12. **Indirectness: Serious.** Differences between the outcomes of interest and those reported (e.g short-term/surrogate,not patient-important). **Imprecision: Very Serious.**
13. Systematic review *(3)*. Used the median or mean of all patients randomized to usual care across the included studies.. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Inconsistency: No serious. Indirectness: Serious. Imprecision: Serious. Publication bias: No serious.**
15. Systematic review *(3)*. Used the median or mean of all patients randomized to usual care across the included studies.. **Baseline/comparator:** Control arm of reference used for intervention.
16. **Indirectness: Serious. Imprecision: Serious.** Wide confidence intervals.
17. Systematic review *(3)*. Used the median or mean of all patients randomized to usual care across the included studies.. **Baseline/comparator:** Control arm of reference used for intervention.
18. **Imprecision: Very Serious.** Wide confidence intervals.

7.5 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 *(12)*. 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 *(3, 58)*. 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) *(12)*. 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) *(68)*; dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID19, CoDEX) *(60, 64)*; 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) *(59)*; hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP) *(63)*;

methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI) *(61)*.

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 *(68)*. An additional trial, which randomized hospitalized patients with suspected SARS-CoV-2 infection, published on 12 August 2020 (MetCOVID) *(62)*, was included as a supplement in the prospective meta-analysis (PMA) publication, as it was registered after the searches of trial registries were performed. The supplement showed that inclusion would not change results other than reduce inconsistency.

Subgroup effect for mortality
While all other trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY Trial enrolled hospitalized patients with COVID-19. The panel considered the results of a subgroup analysis of the RECOVERY Trial suggesting that the relative effects of systemic corticosteroids varied as a function of the level of respiratory support received at randomization. On the basis of the peer-reviewed criteria for credible subgroup effects *(42)*, 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% *(16)*, in order to align with previous WHO guidance *(17)*. See Section 6 for the WHO severity criteria and Infographic below for three disease severity groups for which the recommenndations apply in practice.

Info Box

The recommendations for corticosteroids below 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. By 15 November 2020 there was no new evidence to suggest any change in the recommendations, as identified in the living systematic review and NMA informing this living guideline.

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

Recommended

We recommend systemic corticosteroids rather than no corticosteroids

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 five 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 seven days or more after symptom onset may be more beneficial than treatment initiated within seven days of symptom onset. A post hoc subgroup analysis within the prospective meta-analysis 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 *(66, 67)*. 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.

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 *(57)*. 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 *(56)*.

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 critical COVID-19
Intervention: Steroids
Comparator: Standard Care

Summary

Outline of the evidence on systemic corticosteroids
While six trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalized patients with covid-19 and reported mortality data by subgroup, whereas the smaller GLUCOCOVID trial, which also enrolled hospitalized, patients did not. The panel considered the results of a subgroup analysis of the RECOVERY trial suggesting that the relative effects of systemic corticosteroids varied as a function of the level of respiratory support received at randomization. On the basis of the peer-reviewed criteria for credible subgroup effects *(42)*, 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 *(12)*. The mortality data from six other smaller trials included approximately 700 critically ill patients (definitions of critical illness varied across studies) enrolled up to 9 June 2020, approximately four-fifths were invasively mechanically ventilated; approximately one-half were randomized to receive corticosteroid therapy, and one-half randomized to no corticosteroid therapy. For patients with severe and non-severe covid-19, data was only available by relevant subgroup in RECOVERY (3883 patients with severe and 1535 patients with non-severe covid-19). Because the mortality data from one trial (GLUCOCOVID, n=63) was not reported separately for severe and non-severe covid-19 *[68]*, 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) *(3)*. 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 the another at 30 days.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard Care	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 1,703 patients in 7 studies. Follow up: 28 days.	415 per 1000	328 per 1000 Difference: 87 fewer per 1000 (CI 95% 124 fewer - 41 fewer)	**Moderate** Due to serious risk of bias [1]	Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with critical illness due to COVID-19.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard Care	Steroids	**Certainty of the evidence** (Quality of evidence)	**Plain text summary**
Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (CI 95% 0.59 - 0.93) Based on data from 5,481 patients in 2 studies. Follow up: 28 days.	116 per 1000	86 per 1000 Difference: **30 fewer** per 1000 (CI 95% 48 fewer - 8 fewer)	**Moderate** Due to serious risk of bias [2]	Systemic corticosteroids probably reduce the need of mechanical ventilation
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85 - 1.33) Based on data from 5,403 patients in 30 studies.	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 [3]	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.	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 [4]	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.	286 per 1000	332 per 1000 Difference: **46 more** per 1000 (CI 95% 23 more - 72 more)	**Moderate** Due to serious indirectness [5]	Corticosteroids probably increase the risk of hyperglycaemia.
Hypernatremia	Relative risk 1.64 (CI 95% 1.32 - 2.03) Based on data from 5,015 patients in 6 studies.	40 per 1000	66 per 1000 Difference: **26 more** per 1000 (CI 95% 13 more - 41 more)	**Moderate** Due to serious indirectness [6]	Corticosteroids probably increase the risk of hypernatremia.
Neuromuscular weakness	Relative risk 1.09 (CI 95% 0.86 - 1.39) Based on data from 6,358 patients in 8 studies.	69 per 1000	75 per 1000 Difference: **6 more** per 1000 (CI 95% 10 fewer - 27 more)	**Low** Due to serious indirectness, Due to serious imprecision [7]	Corticosteroids may not increase the risk of neuromuscular weakness.
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41 - 1.63) Based on data from 1,813 patients in 7 studies.	35 per 1000	28 per 1000 Difference: **7 fewer** per 1000 (CI 95% 21 fewer - 22 more)	**Low** Due to serious indirectness, Due to serious imprecision [8]	Corticosteroids may not increase the risk of neuropsychiatric effects.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard Care	Steroids	Certainty of the evidence (Quality of evidence)	Plain text summary
Duration of hospitalization	Measured by: days Lower better Based on data from: 6,425 patients in 1 studies. (Randomized controlled)	13 days	12 days CI 95%	Low Due to serious risk of bias, Due to serious imprecision [9]	Steroids may result in an important reduction in the duration of hospitalizations

1. **Risk of bias: Serious.** lack of blinding. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
2. **Risk of bias: Serious.** lack of blinding. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
3. **Inconsistency: No serious. Indirectness: Serious. Imprecision: Serious. Publication bias: No serious.**
4. **Inconsistency: No serious. Indirectness: Serious. Imprecision: Serious. Publication bias: No serious.**
5. **Indirectness: Serious.**
6. **Indirectness: Serious.**
7. **Indirectness: Serious. Imprecision: Serious.**
8. **Indirectness: Serious. Imprecision: Serious.**
9. **Risk of bias: Serious.** lack of blinding. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** confidence interval includes no benefit. **Publication bias: No serious.**

Clinical question/ PICO

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

Summary

Outline of the evidence on systemic corticosteroids
While six trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalized patients with covid-19 and reported mortality data by subgroup, whereas the smaller GLUCOCOVID trial, which also enrolled hospitalized, patients did not. The panel considered the results of a subgroup analysis of the RECOVERY trial suggesting that the relative effects of systemic corticosteroids varied as a function of the level of respiratory support received at randomization. On the basis of the peer-reviewed criteria for credible subgroup effects *(42)*, 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 *(12)*. The mortality data from six other smaller trials included approximately 700 critically ill patients (definitions of critical illness varied across studies) enrolled up to 9 June 2020, approximately four-fifths were invasively mechanically ventilated; approximately one-half were randomized to receive corticosteroid therapy, and one-half randomized to no corticosteroid therapy. For patients with severe and non-severe covid-19, data was only available by relevant subgroup in RECOVERY (3883 patients with severe and 1535 patients with non-severe covid-19). Because the mortality data from one trial (GLUCOCOVID, n=63) was not reported separately for severe and non-severe covid-19

(68), 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) *(3)*. 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 the another at 30 days.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard Care	Steroids	**Certainty of the evidence** (Quality of evidence)	**Plain text summary**
Mortality 28 days	Relative risk 0.8 (CI 95% 0.7 - 0.92) Based on data from 3,883 patients in 1 studies. Follow up: 28 days.	334 per 1000	267 per 1000 Difference: **67 fewer** per 1000 (CI 95% 100 fewer - 27 fewer)	**Moderate** Due to serious risk of bias [1]	Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with severe COVID-19.
Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (CI 95% 0.59 - 0.93) Based on data from 5,481 patients in 2 studies. Follow up: 28 days.	116 per 1000	86 per 1000 Difference: **30 fewer** per 1000 (CI 95% 48 fewer - 8 fewer)	**Moderate** Due to serious risk of bias [2]	Systemic corticosteroids probably reduce the need for mechanical ventilation
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85 - 1.33) Based on data from 5,403 patients in 30 studies.	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 [3]	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.	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 [4]	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.	286 per 1000	332 per 1000 Difference: **46 more** per 1000	**Moderate** Due to serious indirectness [5]	Corticosteroids probably increase the risk of hyperglycaemia.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard Care / Steroids	**Certainty of the evidence** (Quality of evidence)	**Plain text summary**
		(CI 95% 23 more - 72 more)		
Hypernatremia	Relative risk 1.64 (CI 95% 1.32 - 2.03) Based on data from 5,015 patients in 6 studies.	40 per 1000 / 66 per 1000 Difference: 26 more per 1000 (CI 95% 13 more - 41 more)	**Moderate** Due to serious indirectness [6]	Corticosteroids probably increase the risk of hypernatremia.
Neuromuscular weakness	Relative risk 1.09 (CI 95% 0.86 - 1.39) Based on data from 6,358 patients in 8 studies.	69 per 1000 / 75 per 1000 Difference: 6 more per 1000 (CI 95% 10 fewer - 27 more)	**Low** Due to serious indirectness, Due to serious imprecision [7]	Corticosteroids may not increase the risk of neuromuscular weakness.
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41 - 1.63) Based on data from 1,813 patients in 7 studies.	35 per 1000 / 28 per 1000 Difference: 7 fewer per 1000 (CI 95% 21 fewer - 22 more)	**Low** Due to serious indirectness, Due to serious imprecision [8]	Corticosteroids may not increase the risk of neuropsychiatric effects.
Duration of hospitalization	Measured by: days Lower better Based on data from: 6,425 patients in 1 studies. (Randomized controlled)	13 days / 12 days CI 95%	**Low** Due to serious risk of bias, Due to serious imprecision [9]	Steroids may result in an important reduction in the duration of hospitalizations

1. **Risk of bias: Serious.** lack of blinding. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
2. **Risk of bias: Serious.** lack of blinding. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
3. **Inconsistency: No serious. Indirectness: Serious. Imprecision: Serious. Publication bias: No serious.**
4. **Inconsistency: No serious. Indirectness: Serious. Imprecision: Serious. Publication bias: No serious.**
5. **Indirectness: Serious.**
6. **Indirectness: Serious.**
7. **Indirectness: Serious. Imprecision: Serious.**
8. **Indirectness: Serious. Imprecision: Serious.**
9. **Risk of bias: Serious.** lack of blinding. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** confidence interval includes no benefit. **Publication bias: No serious.**

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

Conditional recommendation against

We suggest not to use corticosteroids.

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 (6).

Note: WHO recommends antenatal corticosteroid therapy for pregnant women at risk of preterm birth from 24 to 34 weeks' gestation when there is no clinical evidence of maternal infection, and adequate childbirth and newborn care is available. However, in cases where the woman presents with mild or moderate COVID-19, the clinical benefits of antenatal

corticosteroid might outweigh the risks of potential harm to the mother. In this situation, the balance of benefits and harms for the woman and the preterm newborn should be discussed with the woman to ensure an informed decision, as this assessment may vary depending on the woman's clinical condition, her wishes and that of her family, and available health care resources.

Preference and values

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

Resources and other considerations

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

Justification

This recommendation was achieved by consensus.

Applicability
This recommendation applies to patients with non-severe disease regardless of their hospitalization status. The panel noted that patients with non-severe COVID-19 would not normally require acute care in hospital or respiratory support, but that in some jurisdictions, these patients may be hospitalized for isolation purposes only, in which case they should not be treated with systemic corticosteroids. The panel concluded that systemic corticosteroids should not be stopped for patients with non-severe COVID-19 who are already treated with systemic corticosteroids for other reasons (e.g. patients with chronic obstructive pulmonary disease need not discontinue a course of systemic oral corticosteroids; or other chronic autoimmune diseases). If the clinical condition of patients with non-severe COVID-19 worsens (i.e. increase in respiratory rate, signs of respiratory distress or hypoxaemia) they should receive systemic corticosteroids (see recommendation 1).

Clinical question/ PICO

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

Summary

Outline of the evidence on systemic corticosteroids
While six trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalized patients with covid-19 and reported mortality data by subgroup, whereas the smaller GLUCOCOVID trial, which also enrolled hospitalized, patients did not. The panel considered the results of a subgroup analysis of the RECOVERY trial suggesting that the relative effects of systemic corticosteroids varied as a function of the level of respiratory support received at randomization. On the basis of the peer-reviewed criteria for credible subgroup effects *(42)*, 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 *(12)*. The mortality data from six other smaller trials included approximately 700 critically ill patients (definitions of critical illness varied across studies) enrolled up to 9 June 2020, approximately four-fifths were invasively mechanically ventilated; approximately one-half were randomized to receive corticosteroid therapy, and one-half randomized to no corticosteroid therapy. For patients with severe and non-severe covid-19, data was only available by relevant subgroup in RECOVERY (3883 patients with severe and 1535 patients with non-severe covid-19). Because the mortality data from one trial (GLUCOCOVID, n=63) was not reported separately for severe and non-severe covid-19 *(68)*, 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) *(3)* 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 the another at 30 days.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard Care	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 1,535 patients in 1 studies. Follow up: 28 days.	176 per 1000	215 per 1000 Difference: **39 more** per 1000 (CI 95% 12 fewer - 107 more)	**Low** Due to serious risk of bias, Due to serious imprecision [1]	Systemic corticosteroids may increase the risk of 28-day mortality in patients with non-severe COVID-19
Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (CI 95% 0.59 - 0.93) Based on data from 5,481 patients in 2 studies. Follow up: 28 days.	116 per 1000	86 per 1000 Difference: **30 fewer** per 1000 (CI 95% 48 fewer - 8 fewer)	**Moderate** Due to serious risk of bias [2]	Systemic corticosteroids probably reduce the need for mechanical ventilation
Duration of hospitalization	Based on data from 6,425 patients in 1 studies. Follow up: NR.	13	12 Difference: **1 fewer**	**Low** Due to serious risk of bias, Due to serious imprecision [3]	Steroids may result in an important reduction in the duration of hospitalizations
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85 - 1.33) Based on data from 5,403 patients in 30	48 per 1000	51 per 1000	**Low** Due to serious indirectness, Due to serious	Corticosteroids may not increase the risk of gastrointestinal bleeding.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard Care	 Steroids	Certainty of the evidence (Quality of evidence)	Plain text summary
	studies.	Difference: **3 more** per 1000 (CI 95% 7 fewer - 16 more)		imprecision [4]	
Super-infections	Relative risk 1.01 (CI 95% 0.9 - 1.13) Based on data from 6,027 patients in 32 studies.	**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 [5]	Corticosteroids may not increase the risk of super-infections.
Hyperglycaemia	Relative risk 1.16 (CI 95% 1.08 - 1.25) Based on data from 8,938 patients in 24 studies.	**286** per 1000	**332** per 1000 Difference: **46 more** per 1000 (CI 95% 23 more - 72 more)	**Moderate** Due to serious indirectness [6]	Corticosteroids probably increase the risk of hyperglycaemia.
Hypernatremia	Relative risk 1.64 (CI 95% 1.32 - 2.03) Based on data from 5,015 patients in 6 studies.	**40** per 1000	**66** per 1000 Difference: **26 more** per 1000 (CI 95% 13 more - 41 more)	**Moderate** Due to serious indirectness [7]	Corticosteroids probably increase the risk of hypernatremia.
Neuromuscular weakness	Relative risk 1.09 (CI 95% 0.86 - 1.39) Based on data from 6,358 patients in 8 studies.	**69** per 1000	**75** per 1000 Difference: **6 more** per 1000 (CI 95% 10 fewer - 27 more)	**Low** Due to serious indirectness, Due to serious imprecision [8]	Corticosteroids may not increase the risk of neuromuscular weakness.
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41 - 1.63) Based on data from 1,813 patients in 7 studies.	**35** per 1000	**28** per 1000 Difference: **7 fewer** per 1000 (CI 95% 21 fewer - 22 more)	**Low** Due to serious indirectness, Due to serious imprecision [9]	Corticosteroids may not increase the risk of neuropsychiatric effects.
Duration of hospitalization	Measured by: days Lower better Based on data from: 6,425 patients in 1 studies. (Randomized controlled)	**13** days	**12** days CI 95%	**Low** Due to serious risk of bias, Due to serious imprecision [10]	Steroids may result in an important reduction in the duration of hospitalizations

1. **Risk of bias: Serious.** lack of blinding. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious. Publication bias: No serious.**
2. **Risk of bias: Serious.** lack of blinding. **Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious.**

Publication bias: No serious.

3. **Risk of bias: Serious.** lack of blinding. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** confidence interval includes no benefit. **Publication bias: No serious.**
4. **Inconsistency: No serious. Indirectness: Serious. Imprecision: Serious. Publication bias: No serious.**
5. **Inconsistency: No serious. Indirectness: Serious. Imprecision: Serious. Publication bias: No serious.**
6. **Indirectness: Serious.**
7. **Indirectness: Serious.**
8. **Indirectness: Serious. Imprecision: Serious.**
9. **Indirectness: Serious. Imprecision: Serious.**
10. **Risk of bias: Serious.** lack of blinding. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** confidence interval includes no benefit. **Publication bias: No serious.**

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 ivermectin identified by the GDG, adding to those for 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

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 3000 RCTs as of 1 March 2021 – implies that more reliable and relevant evidence will emerge to inform policy and practice *(11)*. 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 *(11)*, 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 *(10)*. Such trials can also adapt their design, recruitment strategies and selection of interventions based on new insights, exemplified by the uncertainties outlined above.

Concerning ivermectin used to treat COVID-19, more than 66 RCTs planning to enrol more than 12 000 participants (range 24 - 2724) are registered or ongoing *(11)*.

9. Authorship, contributions, acknowledgements

WHO would like to thank the collaborative efforts of all those involved to make this process rapid, efficient, trustworthy and transparent, including in-kind support from the Magic Evidence Ecosystem Foundation (MAGIC) and their partner, the BMJ, to develop and disseminate this living guidance for COVID-19 drug treatments, based on a living systematic review and network meta-analysis from investigators at McMaster University, Canada.

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.

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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).

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Special thanks to Professor Andrew Owen (Department of Molecular and Clinical Pharmacology, University of Liverpool) for his contributions in the pharmacokinetics analysis of ivermectin.

Special thanks to the external reviewers for their insights:
Yaseen Arabi (King Saud Bin Abdulaziz University for Health Sciences, Saudi Arabia); Richard Kojan (Alliance for International Medical Action); Bhargavi Rao, Saschveen Singh, Armand Sprecher, Marcio da Fonseca, Francisco Bartolome (Médecins Sans Frontières).

No conflict of interest was identified for the external reviewers, based on completed WHO declaration forms.

Infographic
Special thanks to the BMJ for providing the infographic for this guideline.

Funding
No specific funding was provided for this guideline, with MAGIC providing pro bono contributions and support to WHO in the context of the COVID-19 pandemic.

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