For numbered affiliations see end of article.

Correspondence to: Bram Rochwerg rochwerg@mcmaster.ca or Michael Jacobs michael.jacobs@ucl.ac.uk

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RAPID RECOMMENDATIONS

# A living WHO guideline on drugs for covid-19

Bram Rochwerg, [1, 2, a, c] Reed AC Siemieniuk, [1, 2, a, *] Thomas Agoritsas, [1, 3, 4, *, b] François Lamontagne, [5, *, b] Lisa Askie, [6] Lyubov Lytvyn, [1, *] Arnav Agarwal, [7, *] Yee-Sin Leo, [8, a, b, c] Helen Macdonald, [9, *] Linan Zeng, [1, *] Wagdy Amin, [10, a, c] Erlina Burhan, [11, a, c] Frederique Jacquerioz Bausch, [12, a, c] Carolyn S Calfee, [13, b, c] Maurizio Cecconi, [14, a, b, c] Duncan Chanda, [15, a, c] Bin Du, [16, a, c] Heike Geduld, [17, a, b, c] Patrick Gee, [18, a, b, c] Nerina Harley, [19, c] Madiha Hashimi, [20, a, c] Beverly Hunt, [21, c] Sushil K Kabra, [22, a, c] Seema Kanda, [23, a, b, c] Leticia Kawano-Dourado, [24, a, b, c] Yae-Jean Kim, [25, a, b, c] Niranjan Kissoon, [26, a, b, c] Arthur Kwizera, [27, a, b, c] Imelda Mahaka, [28, a, c] Hela Manai, [29, a, b, c] Greta Mino, [30, a, c] Emmanuel Nsutebu, [31, a, c] Natalia Pshenichnaya, [32, a, c] Nida Qadir, [33, a, b, c] Saniya Sabzwari, [34, a, c] Rohit Sarin, [35, a, b, c] Manu Shankar-Hari, [36, c] Michael Sharland, [37, a, c] Yinzhong Shen, [38, a, b, c] Shalini Sri Ranganathan, [39, a, c] Joao P Souza, [40, a, c] Miriam Stegemann, [41, c] An De Sutter, [42, c] Sebastian Ugarte, [43, a, c] Sridhar Venkatapuram, [44, a, c] Vu Quoc Dat, [45, a, c] Dubula Vuyiseka, [46, a, c] Ananda Wijewickrama, [47, a, c] Brittany Maguire, [48, *] Dena Zeraatkar, [1, *] Jessica J Bartoszko, [1, *] Long Ge, [1, 49, *] Romina Brignardello-Petersen, [1, *] Andrew Owen, [50, *] Gordon Guyatt, [1, 2, *] Janet Diaz, [6, *, d] Michael Jacobs, [51, a, c, d] Per Olav Vandvik [4, 52, *, d]

## ABSTRACT

### CLINICAL QUESTION

What is the role of drug interventions in the treatment of patients with covid-19?

### NEW RECOMMENDATION

Increased attention on ivermectin as a potential treatment for covid-19 triggered this recommendation. The panel made a recommendation against ivermectin in patients with covid-19 regardless of disease severity, except in the context of a clinical trial.

### PRIOR RECOMMENDATIONS

(*a*) a strong recommendation against the use of hydroxychloroquine in patients with covid-19, regardless of disease severity; *(b)* a strong recommendation against the use of lopinavir-ritonavir in patients with covid-19, regardless of disease severity; *(c)* a strong recommendation for systemic corticosteroids in patients with severe and critical covid-19; (*d*) a conditional recommendation against systemic corticosteroids in patients with non-severe covid-19, and (*e*) a conditional recommendation against remdesivir in hospitalised patients with covid-19.

### HOW THIS GUIDELINE WAS CREATED

This living guideline is from the World Health Organization (WHO) and provides up to date covid-19 guidance to inform policy and practice worldwide. Magic Evidence Ecosystem Foundation (MAGIC) provided methodological support. A living systematic review with network analysis informed the recommendations. An international guideline development group (GDG) of content experts, clinicians, patients, an ethicist and methodologists produced recommendations following standards for trustworthy guideline development using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

### UNDERSTANDING THE NEW RECOMMENDATION

There is insufficient evidence to be clear to what extent, if any, ivermectin is helpful or harmful in treating covid-19. There was a large degree of uncertainty in the evidence about ivermectin on mortality, need for mechanical ventilation, need for hospital admission, time to clinical improvement, and other patient-important outcomes. There is potential for harm with an increased risk of adverse events leading to study drug discontinuation. Applying pre-determined values and preferences, the panel inferred that almost all well informed patients would want to receive ivermectin only in the context of a randomised trial, given that the evidence left a very high degree of uncertainty on important effects.

### UPDATES

This is a living guideline. It replaces earlier versions (4 September, 20 November, and 17 December 2020) and supersedes the *BMJ* Rapid Recommendations on remdesivir published on 2 July 2020. The previous versions can be found as data supplements. New recommendations will be published as updates to this guideline.

### READERS NOTE

This is the fourth version (update 3) of the living guideline (*BMJ* 2020;370:m3379). When citing this article, please consider adding the update number and date of access for clarity.

This living guideline responds to emerging evidence from randomised controlled trials (RCTs) on existing and new drug treatments for covid-19. Although case numbers are falling in some regions, they are rising in others. Vaccines are linked to falling case numbers and hospitalisations, but most people remain unvaccinated. It is unclear how long protection following vaccination or natural infection will last, or how this might alter with the emergence of new variants. Therefore, the potential for drugs to treat people infected with covid-19 remains of interest and is the focus of this guideline. A linked guideline addresses the role of drugs in the prevention of covid-19 among people who are not infected.[1]

More than 3800 trials on covid-19 interventions have been registered or are ongoing (see section on

emerging evidence[2]). Among these are large national and international platform trials (such as RECOVERY, WHO SOLIDARITY, DISCOVERY, REMAP-CAP and ACTIV) that recruit large numbers of patients in many countries, with a pragmatic and adaptive design.[3 4] These platform trials are currently investigating and reporting on numerous interventions, including antiviral monoclonal antibodies and immunomodulators. This rapidly evolving evidence landscape requires trustworthy interpretation and expeditious clinical practice guidelines to inform clinicians and health care decision-makers.

A living network meta-analysis associated with this guideline will incorporate new trial data as the evidence base increases and allows for analysis of comparative effectiveness of multiple covid-19 treatments.[5] This network meta-analysis and other related publications are included in box 1. We also use additional relevant evidence on safety, prognosis, and patient values and preferences related to covid-19 treatments to inform the living guidance.

**Box 1: Linked resources in this *BMJ* Rapid Recommendations cluster**

- Siemieniuk RAC, Rochwerg B, Agoritsas T, et al. A living WHO guideline on drugs for covid-19 [Update 3]. *BMJ* 2020;370:m3379
- World Health Organization. *Therapeutics and COVID-19. Living guideline*. 31 March 2021. https://www.who.int/publications/i/item/therapeutics-and-covid-19-living-guideline.
- MAGICapp (https://app.magicapp.org/#/guideline/nBkO1E)
  - Expanded version of the methods, processes, and results with multilayered recommendations, evidence summaries, and decision aids for use on all devices
- Siemieniuk RAC, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis [Update 3]. *BMJ* 2020;370:m2980, doi:10.1136/bmj.m2980
- Izcovich A, Siemieniuk RAC, Bartoszko JJ, et al. Adverse effects of remdesivir, hydroxychloroquine, and lopinavir/ritonavir when used for COVID-19: systematic review and meta-analysis of randomized trials. Preprint available at: https://www.medrxiv.org/content/10.1101/2020.11.16.20232876v1

## What triggered this version of the guideline?

This is the fourth version of this guideline, and it addresses the use of ivermectin in patients with covid-19. It was triggered by increased international attention on ivermectin as a potential treatment.

## How to use this guideline

This is a living guideline, so the recommendations included here will be updated, and new recommendations will be added for other drugs for covid-19. The infographic provides a summary of the recommendations and includes links to the MAGICapp for more details on the evidence and rationale for the recommendation, as well as patient decision aids. Box 2 outlines key methodological aspects of the guideline process.

**Box 2: How this living guideline was created (see MAGICapp for full details https://app.magicapp.org/#/guideline/nBkO1E)**

This guideline was developed by WHO and the MAGIC Evidence Ecosystem Foundation (MAGIC), with support from *The BMJ*. It is driven by an urgent need for trustworthy and living guidance to rapidly inform policy and practice worldwide during the covid-19 pandemic. WHO has partnered with MAGIC for their methodologic support in the development and dissemination of living guidance for covid-19 drug treatments, in the form of *BMJ* Rapid Recommendations, to provide patients, clinicians, and policy makers with up to date, evidence based, and user friendly guidelines.

**Standards, methods, and processes for living and trustworthy guidance**

The panel produced the recommendations following standards for trustworthy guideline development using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, in compliance with the *WHO Handbook for Guideline Development 2nd Edition*,[6] the Institute of Medicine, and the Guideline International Network (G-I-N).[7] Details are provided in the WHO guideline (https://www.who.int/publications/i/item/therapeutics-and-covid-19-living-guideline) and MAGICapp (https://app.magicapp.org/#/guideline/nBkO1E).

**Selection and support of the panel**

For the ivermectin recommendation, WHO convened an international guideline development panel (GDG) with 34 individuals, of whom 28 were content experts (clinicians, methodologists, scientists) and four were patients who had survived covid-19. The methods chair (methodological expertise) and a clinical chair (content expertise) guided the panel discussions. Panel members were invited by WHO, after consultation with the methods chair and MAGIC, with the aim of achieving gender, geography, expertise, and patient representation balance in the panel. No relevant conflict of interest was identified for any panel member.

As recommended by the WHO handbook, the panel aimed to create a recommendation based on consensus but elected, at the beginning of the first panel meeting, to call a vote if a consensus could not be reached. These procedures proved unnecessary for this recommendation.

**Guideline perspective, outcomes, and values and preferences**

The target audience for this guidance consists primarily of clinicians, but secondarily of patients and healthcare decision makers. The panel considered an individual patient perspective but also took account of contextual factors (such as resources, feasibility, acceptability, equity) to accommodate global re-use and adaptation for countries and healthcare systems.

During a pandemic, access to healthcare may vary over time and between different countries. The panel defined covid-19 by clinical severity, and mutually exclusive definitions are provided in box 3.

There were insufficient published data to provide the GDG with an informative systematic review of studies describing patients' experiences or values and preferences on treatment decisions for covid-19 drug treatments. The GDG therefore relied on their own judgments of what well informed patients would value after carefully balancing the benefits, harms, and burdens of treatment and their subsequent treatment preferences. The GDG included four patient representatives who had lived experience with covid-19.

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

- Most patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on the outcomes they consider important. This was particularly so when evidence suggested treatment effects, if they 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.

**Sources of evidence**

To create recommendations, the panel relied on evidence synthesised in a living network meta-analysis led by MAGIC.[5] While the investigators responsible for the meta-analyses rate the certainty of the evidence, this is re-assessed independently by the guideline panel.

**Derivation of absolute effects for drug treatments**

The control arm of the WHO SOLIDARITY trial, performed across a wide variety of countries and geographical regions, was identified by the GDG as generally representing the most relevant source of evidence for baseline risk estimates for mortality and mechanical ventilation. 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 hospitalised with covid-19. Given ivermectin has been proposed for use and is 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 determined that for other outcomes using the median or mean of all patients randomised to usual care across the included studies would provide the most reliable estimate of baseline risk.

Of note, baseline risks, and thus absolute effects, may vary significantly geographically and over time. As such, users of this guideline may prefer estimating absolute effects by using local event rates.

### Who do the recommendations apply to?

This guideline applies to all patients with covid-19. For some drugs, such as corticosteroids, recommendations differ based on the severity of covid-19 disease. The GDG elected to use the WHO severity definitions based on clinical indicators, adapted from WHO covid-19 severity categorisation (see box 3).[8] These definitions avoid reliance on access to healthcare to define patient subgroups. The infographic illustrates these three disease severity groups and key characteristics to apply in practice.

**Box 3: WHO definitions of disease severity for covid-19**

- *Critical covid-19*—Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
- *Severe covid-19*—Defined by any of:
  - Oxygen saturation ‹90% on room air*
  - Respiratory rate ›30 breaths per minute 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 signs of severe or critical covid-19.

*The panel noted that the oxygen saturation threshold of 90% to define severe covid-19 was arbitrary and should be interpreted cautiously when defining disease severity. For example, clinicians must use their judgment to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, a saturation ›90-94% is abnormal, and can be an early sign of severe disease, if the patient is on a downward trend. Generally, if there is any doubt, the panel suggested erring on the side of considering the illness as severe.

## The guidance

### Ivermectin

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. Ivermectin is an antiparasitic agent that interferes with nerve and muscle function of helminths through binding glutamate-gated chloride channels.[9] We currently lack persuasive evidence of a mechanism of action for ivermectin in covid-19; any observed clinical benefit would be unexplained.

Evidence underpinning the recommendation comes from the linked systematic review and network meta-analysis.[5] Compared with previous drugs evaluated as part of this living guideline (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, across multiple small trials. The evidence is outlined in box 4.

**Box 4: Ivermectin trial data**

The LNMA pooled data from 16 RCTs with 2407 participants.[5] 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 (table 1). We excluded a number of quasi-RCTs. None of the included RCTs enrolled children under 15 or pregnant women but there is no rationale to suggest they would respond differently.

Although 16 RCTs contributed to the evidence summary informing this drug, only five directly compared ivermectin with standard care and reported mortality.[10 -14] Of these five RCTs, two were at high risk of bias, due to inadequate blinding.[10 11] One of these two trials also started enrolling and randomising patients before the protocol being publicly posted, another factor that contributes to an increased risk of bias.[10] The potential impact of risk of bias is exemplified by subgroup analyses for mortality based on trial risk of bias. As shown in the forest plot (fig 1), 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 consider only the trials at low risk of bias (which together contribute nearly two thirds of the evidence).

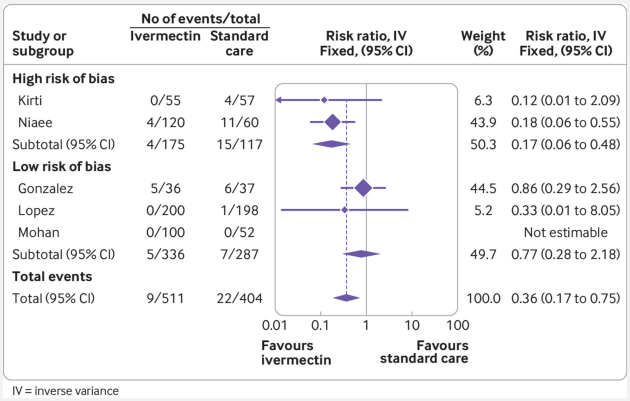


Fig 1 | Forest plot showing direct comparison of ivermectin versus standard care for mortality with subgroup analysis by risk of bias

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 with standard 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 due to a lack of detailed description of blinding or randomisation and the lack of a publicly available study protocol (figure not shown).[15]

In addition to concerns related to risk of bias, there are serious concerns related to imprecision for the outcome of mortality. 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.[16] 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 randomised to ivermectin (1.76%) and 22 deaths across all 404 patients randomised to standard care (5.45%). This is an extremely small number of events on which to base conclusions, and far below the optimal information size. Furthermore, the evidence informing this comparison is from multiple small trials, adding to the risk of unrecognised 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.

### Understanding the recommendation on ivermectin

We recommend not to use ivermectin in patients with covid-19 except in the context of a clinical trial, regardless of disease severity or duration of symptoms.

*Balance of benefit and harm*—For most important outcomes, the panel considered the evidence to be of very low certainty. A 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 (box 4). The picture was similar for other important outcomes, including mechanical ventilation, hospital admission, duration of hospitalisation, and viral clearance. The very low certainty of evidence was a critical factor in the recommendation. Ivermectin may have little or no effect on time to clinical improvement (low certainty evidence) and may increase the risk of adverse effects leading to drug discontinuation (low certainty evidence). 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.

Subgroup analyses indicated no effect modification based on dose. We were unable to examine subgroups based on patient age or severity of illness due to insufficient trial data. Therefore, we assumed similar effects in all subgroups.

*Values and preferences*—The GDG inferred that almost all well-informed patients would not want to receive ivermectin, given the evidence left a very high degree of uncertainty in effect on critical outcomes and there was a possibility of harms, such as adverse events associated with treatment. The panel did not expect there would be much variation among patients in values and preferences when it came to this intervention.

*Resource implications, feasibility, equity, and human rights*—Although the cost of ivermectin 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 supply away from pathologies for which it is clearly indicated, potentially contributing to drug shortages, especially for helminth control and elimination programmes. If corticosteroids are used in the treatment of covid-19, empiric treatment with ivermectin may still be considered in areas where strongyloidiasis is endemic, albeit not for treatment of covid-19 itself.

### Hydroxychloroquine (published 17 December 2020)

The recommendation addressing hydroxychloroquine was informed by results from a systematic review and network meta-analysis that pooled data from 30 RCTs with 10 921 participants. Of note, none of the included RCTs enrolled children or adolescents under the age of 19 years. Given this, the applicability of this recommendation to children is currently uncertain.

### Understanding the recommendation on hydroxychloroquine

We recommend against using hydroxychloroquine or chloroquine in addition to usual care for the treatment of patients with covid-19, regardless of disease severity or duration of symptoms (strong recommendation).

*Balance of benefit and harm*—Hydroxychloroquine and chloroquine probably do not reduce mortality or mechanical ventilation and may not reduce duration of hospitalisation. 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 or 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 healthcare resources are limited. Whether and to what degree hydroxychloroquine increases the risk of cardiac toxicity, including life threatening arrhythmias, when used in patients with covid-19 is uncertain.

Subgroup analyses indicated no effect modification based on severity of illness (comparing either critical versus severe/non-severe or non-severe versus critical/severe) or age (comparing those aged <70 years versus those ≥70 years). Further, the cumulative dose and predicted day 3 serum trough concentrations (lowest predicted blood concentration on day 3) 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 versus hydroxychloroquine alone. There was no evidence that the addition of azithromycin modified the effect of hydroxychloroquine for any outcome (very low certainty).

*Values and preferences*—Applying the agreed values and preferences (box 2), 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 that there was a risk of adverse events including diarrhoea and nausea/vomiting. The panel did not expect there would be much variation in values and preferences among patients when it came to this intervention.

*Resource implications, feasibility, equity, and human rights*—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.

### Lopinavir-ritonavir (published 17 December 2020)

The recommendation addressing lopinavir-ritonavir was informed by the same systematic review and network meta-analysis, including data from seven RCTs with 7429 participants. None of the included

RCTs enrolled children or adolescents under the age of 19 years, so the applicability of this recommendation to children is uncertain.

### Understanding the recommendation on lopinavir-ritonavir

We recommend against using lopinavir-ritonavir in addition to usual care for the treatment of patients with covid-19, regardless of disease severity and duration of symptoms (strong recommendation).

*Balance of benefit and harm*—The GDG panel found a lack of evidence that lopinavir-ritonavir improved patient-important outcomes such as reduced mortality, need for mechanical ventilation, time to clinical improvement, and others. For mortality and need for mechanical ventilation, this was based on moderate certainty evidence; for the other outcomes, this was based on low or very low certainty evidence.

There was low certainty evidence that lopinavir-ritonavir may increase the risk of diarrhoea and nausea or vomiting, a finding consistent with the indirect evidence evaluating its use in patients with HIV infection. Diarrhoea and vomiting may increase the risk of hypovolaemia, hypotension, and acute kidney injury, especially in settings where healthcare 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 versus severe/non-severe or non-severe versus critical/severe) or age (comparing those aged <70 years versus those ≥70 years). As there was no evidence of a statistical subgroup effect, we did not formally evaluate credibility. 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.

*Values and preferences*—Applying the agreed values and preferences (box 2), the GDG inferred that almost all well informed patients would not want to receive lopinavir-ritonavir given that 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 or vomiting. The panel did not expect there would be much variation in values and preferences between patients for this intervention.

*Resource implications, feasibility, equity, and human rights*—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 healthcare 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.

### Remdesivir (published 20 November 2020)

The recommendation addressing remdesivir was informed by the same systematic review and network meta-analysis, including data from four RCTs with 7333 participants hospitalised for covid-19.[5 17-19] Of note, none of the included RCTs enrolled children or adolescents under the age of 19 years, 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 (see box 1 for links).

### Understanding the recommendation on remdesivir

We suggest against administering remdesivir in addition to usual care for the treatment of patients hospitalised with covid-19, regardless of disease severity (weak or conditional recommendation).

When moving from evidence to the conditional recommendation against the use of remdesivir for patients with covid-19, the panel emphasised the evidence of possibly no effect on mortality, need for mechanical ventilation, time to clinical improvement, 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 below).

*Balance of benefit and harm*—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 serious adverse events in patients receiving remdesivir, at least from the included trials. Further pharmacovigilance is required, because serious adverse events are commonly underreported and rare events could be missed, even in large RCTs.

Data from the network meta-analysis indicated that a subgroup of people with non-critical disease might benefit from remdesivir. However, the panel judged the credibility in this subgroup analysis to be insufficient to make subgroup recommendations.[18] Important factors influencing this decision included a lack of a priori hypothesised direction of subgroup effect by trial investigators, little or no previously existing supportive evidence for the subgroup finding, and relatively arbitrary cut points used to examine the subgroups of interest. The overall low certainty evidence for the benefits and harms of remdesivir, driven by risk of bias and imprecision limitations, also contributed to the judgment (see WHO guidance and MAGICapp linked from box 1 for full details). 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 people, but there were no data to address these groups specifically.

*Values and preferences*— Applying the agreed values and preferences (box 2), the panel inferred that most patients would be reluctant to use remdesivir, given the evidence left high uncertainty regarding effects on mortality and the other prioritised 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 that the evidence has not excluded the possibility of benefit.

*Resource implications, feasibility, equity, and human rights*—A novel therapy typically requires higher certainty evidence of important benefits than is 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, currently, remdesivir is administered only by the intravenous route and global availability is limited.

*Practical issues*—Its use is contraindicated in those with liver dysfunction (ALT >5 times normal at baseline) or renal dysfunction (eGFR <30 mL/minute). To date, it can only be administered intravenously, and it has relatively limited availability.

### Corticosteroids (published 4 September 2020)

On 17 July 2020 the panel reviewed evidence from eight RCTs (7184 patients)[19-23] evaluating systemic corticosteroids versus usual care in treatment of covid-19, seven of which reported mortality data by subgroup of illness severity. Mortality data from one trial, GLUCOCOVID, were not incorporated in the summary of finding for mortality because the mortality outcome data were not available by subgroup. The panel did not consider transdermal or inhaled administration of corticosteroids, high dose or long-term regimens, or prophylaxis. The panel did not reach consensus on recommendation 1, which required a vote. The second recommendation was made by consensus. The WHO guideline publication and MAGICapp provides details about the evidence, such as characteristics of trials, subgroup analyses performed, and underlying panel discussions to inform recommendations (see box 1 for link).

### Understanding the recommendations on corticosteroids

**Recommendation 1:** We recommend systemic corticosteroids rather than no systemic corticosteroids for the treatment of patients with severe and critical covid-19 (strong recommendation)

*Who does it apply to?* This recommendation applies to patients with severe and critical covid-19. The panel judged that all or almost all fully informed patients with severe covid-19 would choose to take systemic corticosteroids. The recommendation should apply to patients with severe and critical covid-19 even if they cannot be hospitalised or receive oxygen because of resource limitations.

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. In considering potential contraindications to short term systemic corticosteroids in such patients, clinicians must determine if they warrant depriving a patient of a potentially lifesaving therapy. Clinicians should exercise caution in use of corticosteroids in patients with diabetes or underlying immunocompromise. 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.

*Balance of benefit and harm*—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% reduction in patients with severe covid-19 who were not critically ill. Systemic corticosteroids compared with no corticosteroid therapy probably reduce the risk of 28-day mortality in critically ill patients with covid-19 (moderate certainty evidence; relative risk 0.80 (95% confidence interval 0.70 to 0.91); absolute effect estimate 87 fewer deaths per 1000 patients (95% CI 124 fewer to 41 fewer)). In patients with severe covid-19, systemic corticosteroids also probably reduce the risk of death (moderate certainty evidence; relative risk 0.80 (0.70 to 0.92); absolute effect estimate 67 fewer deaths per 1000 patients (100 fewer to 27 fewer)). The effects of systemic corticosteroids on other outcomes are described in the summary of findings.

Overall, the panel has high certainty that the adverse effects when considered together are sufficiently limited in importance and frequency and suggested that corticosteroids administered in these doses for 7-10 days 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 (23 more to 72 more)) and hypernatraemia (moderate certainty evidence; 26 more per 1000 patients (13 more to 41 more)). 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.

*Values and preferences*—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.

*Resource implications, feasibility, equity, and human rights*—Systemic corticosteroids are low cost, easy to administer, and readily available globally.[24] Dexamethasone and prednisolone are among the most commonly listed medicines in national essential medicines lists; listed by 95% of countries. 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 administered for up to 7-10 days led the panel to conclude that the acceptability of this intervention was high.

**Recommendation 2:** We suggest not to use corticosteroids in the treatment of patients with non-severe covid-19 (weak or conditional recommendation)

*Who does it apply to?* This recommendation applies to patients with non-severe disease regardless of their hospitalisation status. The panel noted that patients with non-severe covid-19 would not normally require acute care in hospital or respiratory support, but in some jurisdictions these patients may be hospitalised for isolation purposes only, in which case they should not be treated with systemic corticosteroids. Several specific circumstances were considered.

- Systemic corticosteroids should not be stopped for patients with non-severe covid-19 who are already treated with systemic corticosteroids for other reasons (such as patients with chronic obstructive pulmonary disease or chronic autoimmune disease).
- If the clinical condition of patients with non-severe covid-19 worsens (that is, increase in respiratory rate, signs of respiratory distress or hypoxaemia) they should receive systemic corticosteroids (see recommendation 1).
- Pregnancy: antenatal corticosteroid therapy may be administered 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 are available. 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 those of her family, and available healthcare resources.

- 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.

*Balance of benefit and harm*—Systemic corticosteroids may increase the risk of 28 day mortality (low certainty evidence; relative risk 1.22 (95% CI 0.93 to 1.61); absolute effect estimate 39 more per 1000 patients (95% CI 12 fewer to 107 more)). The certainty of the evidence for this specific subgroup was downgraded due to serious imprecision (that is, the evidence does not allow to rule out a mortality reduction) and risk of bias due to lack of blinding. The effects of systemic corticosteroids on other outcomes are described in the summary of findings (infographic and links to MAGICapp).

*Values and preferences*—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.

*Resource implications, feasibility, equity, and human rights*—To help guarantee access to systemic corticosteroids for patients with severe and critical covid-19, it is reasonable to avoid their administration to patients who, given the current evidence, do not seem to derive any benefit from this intervention

## 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. Here we outline key uncertainties for ivermectin identified by the GDG, adding to those for corticosteroids in the first version, remdesivir in the second version, and hydroxychloroquine and lopinavir-ritonavir in the third version of the living guideline. These uncertainties may inform future research—that is, 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.

### 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, patients 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 hospitalisation, need for invasive mechanical ventilation and time to clinical or symptom improvement. Also, a better characterisation of potential harms with ivermectin in patients with covid-19 is important.

### Hydroxychloroquine and lopinavir-ritonavir

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

### Remdesivir

Remaining uncertainties include 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 hospitalisation
- Specific subgroups, such as different severities of illness, different time (days) since onset of illness, children and older adults, pregnant women, duration of therapy
- Long term outcomes (such as 1-year endpoint) examining mortality 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

Remaining uncertainties include effects on:

- Long term mortality and functional outcomes in covid-19 survivors
- Patients with non-severe covid-19 (that is, pneumonia without hypoxaemia)
- 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 versus systemic corticosteroids alone
- Immunity and the risk of a subsequent infection, which may affect the risk of death after 28 days
- 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.[2] An overview of registered and ongoing trials for covid-19 therapeutics is available from the Infectious Diseases Data Observatory, through their living systematic review of covid-19 clinical trial registrations[2] and WHO website https://www.covid-nma.com/dataviz/. Concerning ivermectin and covid-19, more than 66 RCTs planning to enrol more than 12 000 participants (range 24-2724) are registered or ongoing.[2]

Although most of these studies are small and of variable methodological quality, some large, international platform trials (such as RECOVERY, SOLIDARITY, and DISCOVERY) are better equipped to provide robust evidence for several potential treatment options. Such trials can also adapt their design, recruitment strategies, and selection of interventions based on new insights.

**How patients were involved in the creation of this article**

The guideline panel included four patients who have had covid-19. Their perspectives were crucial in considering the values and preferences

associated with ivermectin, hydroxychloroquine, lopinavir-ritonavir, remdesivir, and corticosteroids.

## AUTHOR AFFILIATIONS


1 Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada
2 Department of Medicine, McMaster University, Hamilton, Ontario, Canada
3 Division of General Internal Medicine & Division of Clinical Epidemiology, University Hospitals of Geneva, Geneva, Switzerland
4 MAGIC Evidence Ecosystem Foundation, Oslo, Norway
5 Université de Sherbrooke, Centre de recherche due CHU de Sherbrooke, Quebec, Canada
6 World Health Organization, Geneva, Switzerland
7 Department of Medicine, University of Toronto, Toronto, Ontario, Canada
8 National Center for Infectious Diseases, Singapore
9 , London, UK
10 Ministry of Health and Population, Cairo, Egypt
11 Infection Division, Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Universitas Indonesia
12 Geneva University Hospital, Switzerland
13 University of California, San Francisco, USA
14 Department of Anesthesia and Intensive Care Medicine, Humanitas Clinical and Research Center - IRCCS, Via Manzoni 56, 20089 Rozzano (MI), Italy
15 Adult Infectious Disease Centre, University Teaching Hospital, Lusaka, Zambia
16 Peking Union Medical College Hospital, Beijing, China
17 Division of Emergency Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa
18 USA
19 Royal Melbourne Hospital and Epworth Healthcare, Melbourne , Australia
20 Ziauddin University, Karachi, Pakistan
21 St Thomas' Hospital, London, UK
22 All India Institute of Medical Sciences, New Delhi, India
23 McMaster University (alumnus)
24 Pulmonary Division, Heart Institute (InCor)- HCFMUSP, Medical School, University of Sao Paulo, São Paulo, Brazil and Research Institute, Hospital do Coração (HCor), São Paulo, Brazil
25 Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea
26 Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada
27 Department of Anaesthesia and Critical Care, College of Health Sciences, Makerere University, Kampala, Uganda
28 Zimbabwe
29 Emergency Medical Services, Faculty of Medicine, Tunis, Tunisia
30 Alcivar Hospital in Guayaquil, Ecuador
31 Sheikh Shakhbout Medical City, Abu Dhabi
32 Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow, Russia
33 Division of Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA
34 Aga Khan University, Karachi, Pakistan
35 National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India
36 Guy's and St Thomas' NHS Foundation Trust, London, UK
37 St. George's University Hospital, UK
38 Shanghai Public Health Clinical Center, Fudan University, Shanghai, China
39 University of Colombo, Sri Lanka
40 University of Sao Paulo, Brazil
41 Charité - Universitätsmedizin Berlin, Germany
42 University of Gent, Belgium
43 Faculty of Medicine Andres Bello University, Indisa Clinic, Santiago, Chile);
44 King's College, London, UK
45 Department of Infectious Diseases, Hanoi Medical University, Hanoi, Vietnam
46 University of Stellenbosch, South Africa
47 Ministry of Health, Sri Lanka
48 Infectious Diseases Data Observatory (IDDO), Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK
49 Evidence Based Social Science Research Centre, School of Public Health, Lanzhou University, Lanzhou, China and the Department of Social Medicine and Health Management, School of Public Health, Lanzhou University, Lanzhou, China
50 Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, England
51 Royal Free London NHS Foundation Trust
52 Department of Health Economics and Health Management, Institute for Health and Society, University of Oslo, Oslo, Norway
* . Not panel member; resource for methodology, systematic review, and content support
a Remdesivir, hydroxychloroquine, and lopinavir-ritonavir panel member
b Corticosteroid panel member
c ivermectin panel member
d co-senior author


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## Appendix 3. Table of registered ongoing trials for remdesivir

## Appendix 4. Table of registered ongoing trials for ivermectin

Table 1 | Characteristics of included trials for ivermectin

| Study | Publication status | Registration | No of participants | Country | Mean age (years) | % Male | Severity |
|---|---|---|---|---|---|---|---|
| Ahmed, 2020 | Published | NR | 72 | Bangladesh | 42.0 | 46.0 | Non-severe |
| Babalola, 2021 | Preprint | ISRCTN40302986 | 63 | Nigeria | 44.3 | 69.4 | Non-severe |
| Bukhari, 2021 | Preprint | NCT04392713 | 100 | Pakistan | 40.5 | 84.8 | Non-severe |
| Chaccour, 2020 | Published | NCT04390022 | 24 | Spain | 26.0 | 50.0 | Non-severe |
| Chachar, 2020 | Published | NR | 50 | Pakistan | 41.8 | 62.0 | Non-severe |
| Elgazzar, 2020 | Preprint | NR | 400 | Egypt | 57.1 | 70.3 | Non-severe, severe |
| Kirti, 2021 | Preprint | CTRI /2020/08/027225 | 115 | India | 52.5 | 72.3 | Non-severe, severe |
| Krolewiecki, 2020 | Preprint | NCT004381884 | 45 | Argentina | 40.9 | 55.6 | Non-severe |
| Mahmud, 2020 | Data from trial registration | NCT04523831 | 400 | Bangladesh | 39.6 | 58.8 | Non-severe |
| Mohan, 2021 RIVET-COV | Preprint | CTRI /2020/06/026001 | 157 | India | 35.3 | 88.8 | Non-severe |
| Niaee, 2020 | Preprint | IRCT 20200408046987N1 | 180 | Iran | 56.0 | 50.0 | Non-severe, severe |
| Raad, 2020 | Data from a meta-analysis | ChiCTR2000033627 | ~100 | Lebanon | NR | NR | Non-severe |
| Rezai, 2021 | Data from meta-analysis | IRCT 20111224008507N3 | ~103 | Iran | NR | NR | Non-severe, severe |
| Schwartz, 2021 | Data from authors (unpublished) | NCT04429711 | 94 | Israel | 39.5 | 80.9 | Non-severe |
| Lopez, 2021 | Data from authors (unpublished) | NCT04405843 | 398 | Colombia | 37 | 40.5 | Non-severe |
| Gonzalez, 2021 | Preprint | NCT04391127 | 106 | Mexico | 53 | 62.2 | Severe |