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RAPID RECOMMENDATIONS

A living WHO guideline on drugs for covid-19

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ABSTRACT UPDATES

This is the eighth version (seventh update) of a living guideline. It replaces earlier versions (4 September 2020, 20 November 2020, 17 December 2020, 31 March 2021, 6 July 2021, 23 September 2021, and 6 December 2021). The previous versions can be found as data supplements. New recommendations will be published as updates to this guideline.

CLINICAL QUESTION

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

CONTEXT

The evidence base for therapeutics for covid-19 is increasing with numerous recently completed randomised controlled trials (RCTs). This update adds new recommendations on Janus kinase (JAK) inhibitors based on three RCTs with 2659 participants for baricitinib, two RCTs with 475 participants for ruxolitinib, and one RCT with 289 participants for tofacitinib. It also adds a recommendation for sotrovimab (monoclonal antibody) based on one RCT with 1057 participants, that was completed before the emergence of the omicron variant.

NEW RECOMMENDATIONS

The Guideline Development Group (GDG) made:

- A strong recommendation for the use of baricitinib as an alternative to interleukin-6 (IL-6) receptor blockers, in combination with corticosteroids, in patients with severe or critical covid-19
- A conditional recommendation against the use of ruxolitinib and tofacitinib for patients with severe or critical covid-19
- A conditional recommendation for the use of sotrovimab in patients with non-severe covid-19, restricted to those at highest risk of hospitalisation.

Following the publication of a previous conditional recommendation for casirivimab- imdevimab, pre-clinical evidence has emerged suggesting that this monoclonal antibody combination lacks neutralisation activity against the omicron variant in vitro. Sotrovimab has been reported to retain activity against omicron in pseudovirus assays but with higher concentrations being required for neutralisation. More data are required to ascertain whether efficacy against the omicron variant will be maintained at the studied doses of monoclonal antibodies, and these living guidelines will be updated when additional data becomes available.

UNDERSTANDING THE NEW RECOMMENDATIONS

When moving from evidence to recommendations, the GDG considered a combination of evidence assessing relative benefits and harms, values and preferences, and feasibility issues. The strong recommendation for baricitinib in those with severe or critical illness reflects moderate certainty evidence for benefits on mortality, duration of mechanical ventilation, and hospital length of stay, with no observed increase in adverse events leading to drug discontinuation. Baricitinib and IL-6 receptor blockers have similar effects; when both are available, choose one based on issues including cost and clinician experience. The conditional recommendation against the use of ruxolitinib and tofacitinib was driven by low certainty evidence from small trials, failing to demonstrate benefit, and suggesting a possible increase in serious adverse events for tofacitinib. A conditional recommendation for the monoclonal antibody sotrovimab in patients with non-severe illness reflects substantial reduction in risk of hospitalisation in those at higher risk, and trivial benefits in those at lower risk. There were insufficient data to recommend one monoclonal antibody

treatment over another, and evidence on their efficacy for emerging variants is likely to influence future recommendations.

PRIOR RECOMMENDATIONS

- Recommended for patients with severe or critical covid-19—a strong recommendation for systemic corticosteroids; a strong recommendation for IL-6 receptor blockers (tocilizumab or sarilumab); and a conditional recommendation for casirivimab-imdevimab, for those having seronegative status.
- Recommended for patients with non-severe covid-19—a conditional recommendation for casirivimab-imdevimab, for those at highest risk of severe illness.
- Not recommended for patients with non-severe covid-19—a conditional recommendation against systemic corticosteroids; and a strong recommendation against convalescent plasma.
- Not recommended for patients with severe or critical covid-19—a recommendation against convalescent plasma, except in the context of a clinical trial.
- Not recommended, regardless of covid-19 illness severity—a conditional recommendation against remdesivir; a strong recommendation against hydroxychloroquine; a strong recommendation against lopinavir/ritonavir; and a recommendation against ivermectin, except in the context of a clinical trial.

ABOUT THIS GUIDELINE

This living guideline from the World Health Organization (WHO) incorporates three new recommendations on two therapies for covid-19, and updates existing recommendations. The GDG typically evaluates a therapy when WHO judges sufficient evidence is available to make a recommendation. While the GDG takes an individual patient perspective in making recommendations, it also considers resource implications, acceptability, feasibility, equity, and human rights. This guideline was developed according to standards and methods for trustworthy guidelines. MAGIC Evidence Ecosystem Foundation provides methodological support, including the coordination of living systematic reviews with network meta-analyses to inform the recommendations.

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This living guideline responds to emerging evidence from randomised controlled trials (RCTs) on existing and new drug treatments for covid-19. Vaccines are linked to limiting hospitalisations, but it is unclear how long protection following vaccination or natural infection will last, or how this might change 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.

More than 5000 trials on covid-19 interventions have been registered or are ongoing (see section on emerging evidence¹). Although most of these studies are small and of variable methodological quality, some large, international platform trials have provided robust evidence. Such trials can also adapt their design, recruitment strategies, and selection of interventions based on new insights. Examples include RECOVERY, WHO SOLIDARITY, REMAP-CAP, and ACTIV, which recruit large numbers of patients in many countries.²⁻⁵ An overview of ongoing trials is available from the Infectious Diseases Data Observatory, through their living systematic review of covid-19 clinical trial registrations¹ and the World Health Organization (WHO) website (<https://www.covid-nma.com/dataviz/>).

However, existing and emerging evidence demonstrates 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.

Moreover, the rapidly evolving evidence landscape requires trustworthy interpretation and expeditious clinical practice guidelines to inform clinicians and health care decision-makers.

Several living network meta-analyses associated with this guideline incorporate emerging trial data and allow for analysis of comparative effectiveness of multiple covid-19 treatments.^{6,7} Box 1 includes these network meta-analyses and other related publications. To inform the living guidance, we also use additional relevant evidence on safety, prognosis, and patient values and preferences related to covid-19 treatments.

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

Versions of this guidance

- This article and infographic: Agarwal A, Rochweg B, Siemieniuk RAC, et al. A living WHO guideline on drugs for covid-19 [Update 7]. *BMJ* 2020;370:m3379, doi:10.1136/bmj.m3379
- WHO PDF: World Health Organization. *Therapeutics and COVID-19. Living guideline*. January 2022. <https://www.who.int/teams/health-care-readiness-clinical-unit/covid-19/therapeutics>
- MAGICapp (<https://app.magicapp.org/#/guideline/nBkO1E>)
 - Expanded version of the guideline, including methods, processes, and results with multi-layered recommendations, evidence summaries, and decision aids for use on all devices

Linked research

- Siemieniuk RAC, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis [Update 3]. *BMJ* 2021;370:m2980, doi:10.1136/bmj.m2980
 - The data on Janus kinase inhibitors are available in appendix 7 on bmj.com and at the living systematic review website: <https://www.covid19nma.com/>
- Siemieniuk RAC, Bartoszko JJ, Díaz Martínez JP, et al. Antibody and cellular therapies for treatment of covid-19: a living systematic review and network meta-analysis. *BMJ* 2021;374:n2231, doi:10.1136/bmj.n2231
- Zeraatkar D, Cusano E, Diaz Martinez JP, et al. Tocilizumab and sarilumab alone or in combination with corticosteroids for COVID-19: a systematic review and network meta-analysis. *medRxiv* 2021; doi:10.1101/2021.07.05.21259867v1
- 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. *medRxiv* 2020; doi:10.1101/2020.11.16.20232876v1
- Lamontagne F, Agoritsas T, Siemieniuk R, et al. A living WHO guideline on drugs to prevent covid-19. *BMJ* 2021;372:n526. doi:10.1136/bmj.n526

What triggered this version of the guideline and what is coming next?

This eighth version of the WHO living guideline was triggered by new data on three Janus kinase (JAK) inhibitors (baricitinib, ruxolitinib, and tofacitinib) and the monoclonal antibody sotrovimab. The evidence was summarised in two parallel living network meta-analyses: one on drug treatments, and a second on antibodies and cellular therapies for covid-19.^{6,7}

Other therapeutics in progress for this WHO living guideline include new antiviral treatments (molnupiravir and nirmatrelvir) and fluvoxamine. In deciding which therapeutics to cover in the future, the WHO considers factors including the extent of the evidence to inform recommendations and makes a judgment on whether and when additional evidence may be anticipated. A WHO standing

steering committee evaluates possibilities for new drug recommendations and updates to existing drug recommendations.

How this guideline was created, and how to use it

This is a living guideline. The recommendations and evidence included here will be updated, and new recommendations will be added for other treatments for covid-19. The guideline is developed according to standards and methods for trustworthy guidelines, making use of an innovative process to achieve efficiency in dynamic updating of recommendations. The methods are aligned with the *WHO Handbook for Guideline Development* and according to a pre-approved protocol (planning proposal) by the Guideline Review Committee (GRC).⁸ A box at the end of the article outlines key methodological aspects of the guideline process.

The infographic provides a summary of the recommendations and includes links to MAGICapp for more information, as well as patient decision aids. Specific uncertainties regarding the therapeutics are listed with each drug and may inform future research.

Who do the recommendations apply to?

This guideline applies to all patients with covid-19. Recommendations may differ based on the severity of covid-19, according to WHO severity definitions (see [box 2](#)).⁹ These definitions avoid reliance on access to healthcare to define patient subgroups.

Box 2: WHO definitions of illness 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*
 - Signs of pneumonia
 - Signs of severe respiratory distress (in adults, accessory muscle use, inability to complete full sentences, respiratory rate > 30 breaths per minute; and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs including inability to breastfeed or drink, lethargy, convulsions, or reduced level of consciousness).
- *Non-severe covid-19*—Defined as the absence of any criteria for severe or critical covid-19.

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

The recommendations

Janus kinase (JAK) inhibitors (Update 7, published 14 January 2022)

JAK inhibitors are a class of drugs which inhibit intracellular signalling in response to numerous interleukins, interferons, colony stimulating factors, and hormones. As a consequence, they interfere with many cellular responses, including antiviral responses, angiotensin-converting enzyme 2 (ACE2) expression, T cell function and differentiation, and macrophage activation. Baricitinib, ruxolitinib, and tofacitinib are three of at least nine JAK inhibitors. Their inherent differences, as well as variation in dosing and administration and pharmacokinetics, limit class-wide recommendations, and the GDG decided to make separate recommendations for individual drugs.

Evidence underpinning the recommendations is outlined in [box 3](#).

Box 3: JAK inhibitor data (<https://app.magicapp.org/#/guideline/nBkO1E/rec/E5AOaN>)

Baricitinib for severe or critical covid-19

The living network meta-analysis for baricitinib was informed by three RCTs that enrolled 2659 patients across illness severities.¹⁰⁻¹² All trials were registered, and two were published in peer reviewed journals; one was a preprint. All three trials enrolled patients in the inpatient setting. None of the included trials enrolled children or pregnant women (see appendix 8 on bmj.com).

For patients with severe or critical covid-19, pooled data showed baricitinib probably reduces mortality (odds ratio (OR) 0.62, 95% confidence interval (CI) 0.44 to 0.85), with an absolute difference of 45 fewer deaths per 1000 patients (95% CI 68 fewer to 17 fewer; moderate certainty). Treatment reduces hospital length of stay (mean difference (MD) 1.4 fewer days, 95% CI 2.4 fewer to 0.4 fewer days; high certainty), and probably reduces duration of mechanical ventilation (MD 3.2 fewer days, 95% CI 5.9 fewer to 0.5 fewer days; moderate certainty). Treatment probably results in little or no increase in serious adverse events leading to discontinuation (absolute difference 5 more per 1000 patients, 95% CI 18 fewer to 28 more; moderate certainty).

Ruxolitinib and tofacitinib for severe or critical covid-19


The living network meta-analysis for ruxolitinib was informed by two RCTs that enrolled 475 patients across illness severities.¹³⁻¹⁴ Both trials were registered; one was published in a peer reviewed journal, and one was a trial registration only. Both trials enrolled patients in the inpatient setting; neither enrolled children or pregnant women.

Evidence for tofacitinib was informed by one RCT that enrolled 289 inpatients; the trial was registered and published in a peer reviewed journal.¹⁵ Children and pregnant women were excluded.

For both of these drugs, the certainty of evidence was rated as very low, primarily due to serious concerns regarding imprecision; the small trials failed to demonstrate differences in outcomes of interest, including mortality, mechanical ventilation, and hospital length of stay.

Subgroup analysis

- Four pre-specified subgroup analyses were undertaken for JAK inhibitors as a class rather than for individual drugs: age (younger adults <70 years v older adults >70 years); severity of illness at time of treatment initiation (non-severe v severe v critical); concomitant use of corticosteroids at baseline; and concomitant use of remdesivir at baseline. No evidence of subgroup effects was identified on the relative risk of critical outcomes across all pre-specified effect modifiers.

thebmj Visual summary 

Treatments for covid-19

Overview of rapid recommendations


See an interactive version of this graphic online
<https://bit.ly/BMJrrcovid>


Population


This recommendation applies only to people with these characteristics:




Interventions

 Strong recommendations in favour

 Weak or conditional recommendations in favour

 Weak or conditional recommendations against

 Strong recommendations against

Disease severity	
Non-severe	Severe
Absence of signs of severe or critical disease	<p>Oxygen saturation <90% on room air</p> <p>Signs of pneumonia</p> <p>Signs of severe respiratory distress</p>
	<p>Requires life sustaining treatment</p> <p>Acute respiratory distress syndrome</p> <p>Sepsis</p> <p>Septic shock</p>
	<p>Corticosteroids</p> <p>IL-6 receptor blockers or Baricitinib</p> <p>Depending on availability as well as clinical and contextual factors</p>
<p>Casirivimab and imdevimab</p> <p>For those with highest risk of hospital admission</p> <p>Sotrovimab</p> <p>For those with highest risk of hospital admission</p>	<p>Casirivimab and imdevimab</p> <p>For those with seronegative status for SARS-CoV-2 antibodies</p>
<p>Corticosteroids</p>	<p>Ruxolitinib and tofacitinib</p> <p>Should be considered only if neither baricitinib nor IL-6 receptor blockers are available</p>
	<p>Remdesivir</p>
	<p>Ivermectin</p> <p>Should be considered only in the context of a clinical trial</p>
	<p>Convalescent plasma</p> <p>Should be considered only in the context of a clinical trial</p>
<p>Convalescent plasma</p>	
	<p>Hydroxychloroquine</p>
	<p>Lopinavir-ritonavir</p>

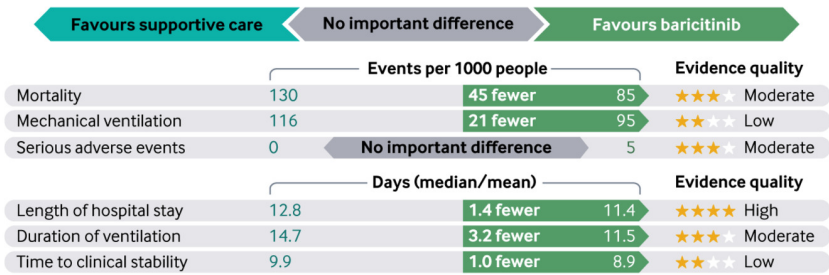
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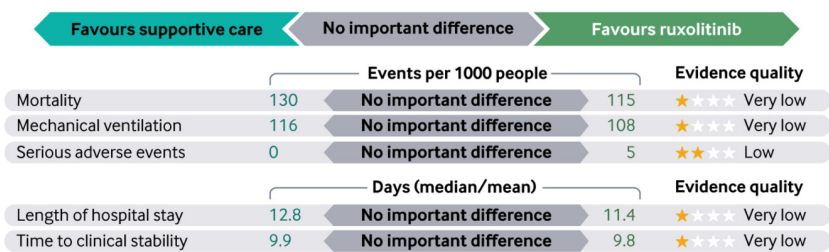
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Visual summary of recommendation

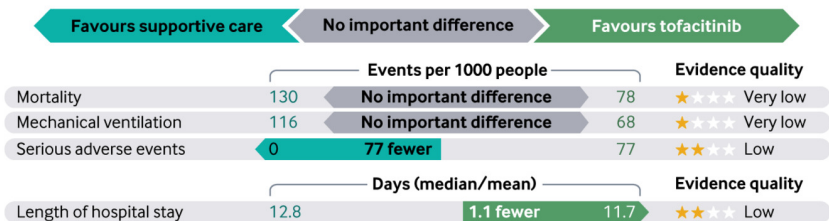
Evidence profile | Baricitinib | Patients with severe or critical covid-19



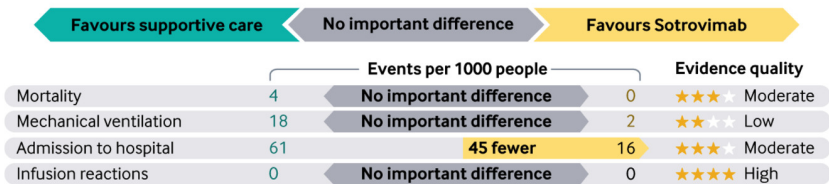
Evidence profile | Ruxolitinib | Patients with severe or critical covid-19



Evidence profile | Tofacitinib | Patients with severe or critical covid-19



Evidence profile | Sotrovimab | Patients with non-severe covid-19



Key practical issues

Baricitinib

Administered as a pill, but can be crushed and administered by a nasogastric or gastrostomy tube

Must be adjusted for patients who have renal impairment

Has not been studied in patients with severe hepatic impairment

May cause leucopenia, lymphopenia, thrombocytosis, anaemia, clotting abnormalities, hepatic impairment, and secondary infection

Sotrovimab

Administered by intravenous infusion

Patients should be clinically monitored during infusion and observed for at least one hour after infusion is complete

Values and preferences

Baricitinib

The panel inferred that most patients would want to receive baricitinib. The benefit on mortality was deemed of critical importance to patients and the panel was reassured by the moderate certainty evidence of little or no increase in serious adverse events

Ruxolitinib or tofacitinib

The panel inferred that, given the uncertain benefits and the possibility of serious adverse effects, the majority of patients would not want ruxolitinib or tofacitinib. However, a minority of patients might choose to receive them if neither baricitinib nor IL-6 receptor blockers were available.

Sotrovimab

The panel inferred that almost all well informed patients with a low risk of hospital admission would decline sotrovimab and only those at highest risk (such as unvaccinated, older, or immunosuppressed) would choose to receive this treatment



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<https://bit.ly/BMJrcovid>

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Recommendation 1: We recommend treatment with baricitinib for patients with severe or critical covid-19 (strong recommendation).

Understanding the recommendation

Evidence of improved survival and decreased length of hospital stay, coupled with no evidence of serious adverse events, drove the

strong recommendation for baricitinib. The GDG acknowledged that some serious adverse events such as invasive fungal infections may not have been accurately captured during the relatively short follow-up period in the included trials.

The GDG carefully considered whether to make a recommendation or to wait for new data (expected soon on patients randomised to

baricitinib or no baricitinib in the RECOVERY trial). However, given that moderate to high certainty evidence already show the benefits with baricitinib, the panel made an immediate strong recommendation for use of the drug, with readiness to update the recommendation as necessary once RECOVERY trial data are publicly available.

The GDG has previously made a strong recommendation for the use of interleukin-6 (IL-6) receptor blockers (tocilizumab or sarilumab) in patients with severe or critical covid-19. Based on their mechanism of action as immune modulators, both baricitinib and IL-6 receptor blockers should have fairly similar benefits. Combining them may unacceptably increase harms, including secondary bacterial and fungal infections. In the absence of evidence of incremental benefit, the GDG advises that clinicians do not administer the drugs together.

The GDG looked at evidence comparing baricitinib and IL-6 receptor blockers, for which there are no head-to-head comparisons. Indirect comparisons generated from the living network meta-analysis provided low certainty evidence. This did not justify recommending one drug over the other. Therefore, when both agents are available, clinicians should choose between them based on other considerations. These might include experience and comfort using the drugs; local institutional policies; route of administration (baricitinib is oral; IL-6 receptor blockers are intravenous); and cost.

Balance of benefits and harms—In patients with severe or critical illness, there is moderate certainty evidence that baricitinib reduces mortality and duration of mechanical ventilation, and high certainty evidence for reduced hospital length of stay. The trials provided moderate certainty evidence for little or no increase in harm, specifically drug discontinuation. Some serious adverse events such as fungal infections may not have been accurately captured during the relatively short follow-up period in the included trials. This risk may vary in different parts of the world according to the local prevalence of infections such as tuberculosis. This risk may also be less important, given the short course of baricitinib used for the treatment of covid-19.

Values and preferences—The GDG inferred that almost all well informed patients with severe or critical covid-19 would choose to receive baricitinib due to the likely reduction in mortality, and moderate certainty evidence of little or no increase in serious adverse events.

Applicability—None of the included RCTs for baricitinib enrolled children, or pregnant or lactating women; therefore, the applicability of this recommendation remains uncertain. The GDG did not have reason to believe that patients in these groups with covid-19 would respond differently; decisions regarding the use of JAK inhibitors in these groups should be guided by discussion between the individual and their healthcare provider.

Practical issues—As baricitinib is administered orally once daily, hospitalised patients should find it easy to accept this treatment. In patients who cannot swallow tablets, baricitinib can be crushed, dispersed in water, or given via a nasogastric tube. The recommended dose is 4 mg daily orally in adults with eGFR ≥ 60 mL/min/1.73 m² for a duration of 14 days or until hospital discharge, whichever is first. The optimal duration of treatment is unknown, and the proposed duration reflects what was used in the trials providing evidence on treatment effects of baricitinib.

Dose adjustments may be needed for patients with leucopenia, renal impairment, or hepatic impairment, all of which should be monitored during treatment, and for patients taking strong organic

anion transporter 3 (OAT3) inhibitors such as probenecid, where drug interactions warrant dose reductions.

Baricitinib, like IL-6 receptor blockers, should be initiated at the same time as systemic corticosteroids; there are currently no data to suggest that specific timing during hospitalisation or the course of illness is beneficial.

Additional considerations regarding practical issues are summarised in MAGICapp.

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

At a time of drug shortage, it may be necessary to prioritise use through clinical triage such as selecting patients with the highest baseline risk for mortality (for instance, those with critical illness over those with severe illness), in whom the absolute benefit of treatment is greatest. Other suggestions for prioritisation, which lack direct evidence, include focusing on patients with an actively deteriorating clinical course, and avoiding baricitinib in those with established multi-organ failure (in whom the benefit is likely to be smaller).

Recommendation 2: We suggest not to use ruxolitinib or tofacitinib for patients with severe or critical covid-19 (conditional or weak recommendation).

Understanding the recommendation

Low to very low certainty evidence for mortality and duration of mechanical ventilation and a possible increase in serious adverse events, particularly for tofacitinib, drove the weak recommendation not to use ruxolitinib or tofacitinib in patients with severe or critical covid-19. Clinicians should consider using ruxolitinib or tofacitinib only if neither baricitinib nor IL-6 receptor blockers (tocilizumab or sarilumab) are available. The GDG emphasized the need for more trial evidence to better inform the recommendations; this is anticipated through ongoing trials for these JAK inhibitors.

Benefits and harms—Low to very low certainty evidence from small trials failed to demonstrate benefits for mortality or duration of mechanical ventilation, and suggested tofacitinib may increase adverse events leading to drug discontinuation. When more evidence is available, the GDG acknowledged that these drugs may prove to have similar benefits as baricitinib.

Values and preferences—Most well informed patients would decline ruxolitinib or tofacitinib. However, a minority might choose to receive one or the other drug if neither baricitinib nor IL-6 receptor blockers are available, given the possibility of benefit has not been excluded, and a class effect of JAK inhibitors might exist.

Applicability—None of the included RCTs enrolled children; therefore, the applicability of this recommendation to children remains uncertain. Uncertainty also remains with regards to the administration of ruxolitinib or tofacitinib to pregnant or lactating women.

Practical issues—Both drugs are administered orally twice daily; therefore, treatment should be acceptable to hospitalised patients with severe or critical covid-19. In patients unable to swallow whole tablets, treatment can be dispersed in water to be taken orally or via nasogastric tube.

The GDG referred to treatment regimens in the included trials, available via MAGICapp, to guide the administration of these agents in the absence of other available information. If ruxolitinib or tofacitinib is administered, like with IL-6 receptor blockers, it should be given with systemic corticosteroids; specific timing during hospitalisation or the course of illness is not specified.

Resource implications, equity, and human rights—Efforts to ensure access to drugs should focus on those that are currently recommended.

Specific uncertainties, emerging evidence, and future research (for all JAK inhibitors)

- Incremental benefit for patients receiving baricitinib and IL-6 blockers together, rather than either drug individually.
- Impact of tofacitinib and ruxolitinib relative to that of baricitinib.
- Safety and efficacy in children and pregnant and lactating women.

Sotrovimab (Update 7, published 14 January 2022)

Sotrovimab is a single human monoclonal antibody that binds to a highly conserved epitope in the SARS-CoV-2 spike protein, preventing the virus from entering cells. Monoclonal antibodies such as sotrovimab and casirivimab-imdevimab are expected to have similar benefits against the SARS-CoV-2 virus. However, their action against the spike protein may render them less effective against emerging variants of the virus such as omicron, where the spike protein is altered.

Evidence underpinning the recommendation is outlined in [box 4](#).

Box 4: Sotrovimab data (<https://app.magicapp.org/#/guide-line/nBk01E/rec/LA69PM>)

For non-severe covid-19

The living network meta-analysis summary was informed by one trial (COMET-ICE) that enrolled 1057 non-hospitalised patients with symptomatic covid-19 (≤ 5 days after the onset of symptoms) and at least one risk factor for illness progression. Of the 1057 randomised patients, the living network meta-analysis team had access to data for 1044 patients. Included patients were randomised to receive a single infusion of sotrovimab at a dose of 500 mg, or placebo.¹⁶ Median age of patients was 53 years; 46% were male. Median duration of follow-up in the intention-to-treat population was 72 days. Vaccinated patients were excluded from the trial.

The trial data on sotrovimab provided moderate certainty evidence for a reduction in hospitalisation (OR 0.19, 95% CI 0.06 to 0.51; absolute difference 45 fewer per 1000 patients, 95% CI 54 fewer to 27 fewer), with little or no impact on mortality (OR 0.11, 95% CI 0.01 to 2.60; absolute difference 4 fewer deaths per 1000 patients, 95% CI 4 fewer to 6 more; moderate certainty). Sotrovimab may have little or no impact on mechanical ventilation (OR 0.11, 95% CI 0.01 to 2.60; absolute difference 16 fewer per 1000 patients, 95% CI 18 fewer to 27 more; low certainty) and results in little or no increase in infusion reactions (absolute difference 0 fewer per 1000, 95% CI 13 fewer to 13 more; high certainty). No data were available regarding time to clinical improvement.

- **Indirect comparison to casirivimab-imdevimab**
 - The living network meta-analysis provided moderate certainty evidence for little or no difference in mortality, mechanical ventilation, and hospitalisation, and high certainty evidence for

little or no difference in infusion reactions. No data were available regarding time to clinical improvement.

- **Subgroup analysis**

- Four pre-specified subgroup analyses were requested by the GDG: age (children v adults <70 years v older adults >70 years); severity of illness at time of treatment initiation (non-severe v severe v critical); time of symptom onset; and serological status (seropositive v seronegative). No data were available to conduct these analyses.

Recommendation: We suggest treatment with sotrovimab for patients with non-severe covid-19, conditional to those at highest risk of hospitalisation (conditional or weak recommendation).

Understanding the recommendation

A combination of evidence, values and preferences, and feasibility contributed to the conditional recommendation for the use of sotrovimab in individuals with non-severe covid-19, restricted to those at highest risk of hospitalisation. Typical characteristics of individuals at highest risk include those who are unvaccinated, older people, or those with immunodeficiencies or chronic diseases such as diabetes.

Although there is moderate certainty evidence of a substantial relative risk reduction in hospitalisation, only a minority of patients who are at highest risk are likely to achieve sufficient benefit to compensate for the risks and other disadvantages of this therapy. Other limitations include a lack of reliable tools to identify high risk patients, delivering a parenteral therapy to patients who are typically cared for in the community, and limited availability of the drug.

Another combination of monoclonal antibodies, casirivimab-imdevimab, is also conditionally recommended in patients with non-severe covid-19 at highest risk of hospitalisation. The GDG advised that clinicians do not administer the drugs together, given an absence of evidence of incremental benefit of the drugs when given together, and the low likelihood of incremental benefit mechanistically.

The GDG then considered how to choose between the two drugs. No trials provide head-to-head comparisons. With alpha and delta variants, there may be little or no difference in the agents' impact on critical outcomes, according to an indirect comparison from the network meta-analysis (see [box 4](#)). Now and in the future, the choice of monoclonal antibodies will depend on emerging information regarding effectiveness with different variants and their availability, as well as clinical and contextual factors. Of note, the trials included in the living network meta-analysis were conducted before the emergence of the omicron variant. The GDG is now fully considering how the omicron variant may impact efficacy, with recommendations to be updated once sufficient evidence is available.

Pre-clinical evidence has recently emerged, suggesting that casirivimab-imdevimab lacks neutralisation activity against the omicron variant in vitro.¹⁷ Sotrovimab has been reported to retain activity against omicron in pseudo-virus assays, but with higher concentrations being required for neutralisation.¹⁸ More data are required to ascertain whether efficacy against the omicron variant will be maintained at the studied doses of monoclonal antibodies, and recommendations will be updated when additional data becomes available.

Balance of benefits and harms—In patients with non-severe illness, moderate certainty evidence showed sotrovimab probably reduces hospitalisation, with little or no impact on mortality and mechanical ventilation. There was high certainty evidence of little or no increase in infusion reactions. Indirect comparison data with casirivimab-imdevimab versus sotrovimab provides moderate certainty evidence of little or no difference on mortality, mechanical ventilation and hospitalisation, and high certainty of no difference in infusion reactions.

Values and preferences—The GDG inferred that almost all well informed patients with a low risk of hospitalisation would decline sotrovimab, and only those at highest risk would choose to receive treatment. In the absence of research evidence, during a previous survey (see recommendation for casirivimab-imdevimab), the GDG expressed the view that most patients with a risk of hospitalisation above 10%, and thus an absolute risk reduction of approximately 6%, would choose to receive treatment; conversely, most of those below the risk threshold would decline treatment. The same risk thresholds were used here.

Applicability—The included trial enrolled only non-pregnant adults; the applicability to children and pregnant women remains uncertain. The GDG had no reason to believe that children or pregnant women with covid-19 would respond differently to treatment with sotrovimab. However, for children, as the risk of hospitalisation is generally extremely low; the GDG therefore inferred that, in the absence of immunosuppression or another major risk factor, children should not receive the intervention.

The GDG did not provide a recommendation for sotrovimab in severe or critical illness. A recently published RCT randomised 546 adults hospitalised with covid-19 to two neutralizing monoclonal antibody therapies (sotrovimab and BRII-196 plus BRII-198) or placebo.¹⁹ The results did not demonstrate benefits from these antibodies therapies, including a subgroup analysis on patients with seropositive versus seronegative status. Although the role of sotrovimab in severe or critical covid-19 is not supported by the new trial, it was not assessed by the GDG, as they focused on patients with non-severe covid-19 where evidence was available at the time of recommendation development; this trial, and any other new evidence that is publicly available, will be fully considered by the GDG for future recommendations for sotrovimab.

Practical issues—The authorised dose for sotrovimab is one single intravenous infusion of 500 mg over 30 minutes, administered as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset. Sotrovimab is available as a concentrated solution and must be diluted before administration. Patients should be clinically monitored during the infusion and observed for at least one hour after the infusion is completed.

Additional considerations regarding practical issues are summarized in MAGICapp.

Resource implications, equity, human rights, acceptability and feasibility—Sotrovimab is unlikely to be available for all individuals who, given the option, would choose to receive the treatment. This further supports the recommendation that sotrovimab be reserved for those at highest risk of hospitalisation.

Additional challenges include the requirement for intravenous administration to patients who would normally be treated at home. Specialised clinics may be required to ensure safe and effective administration of sotrovimab. For the intervention to achieve substantial use, healthcare systems will need to address these

challenges, which have the potential to exacerbate health inequity in low- and middle-income countries.

Specific uncertainties, emerging evidence, and future research

- Accurate clinical prediction guides to establish the individual patient risk of hospitalisation in patients presenting with non-severe covid-19, to effectively identify patients who would most benefit from this intervention.
- Efficacy and safety for severe or critical seronegative covid-19 patients, for patients infected with emerging variants, and in children and pregnant women.

Convalescent plasma (Update 6, published 6 December 2021)

Overview

Treatment with convalescent plasma involves the transfer of endogenously produced neutralising antibodies present within the plasma from previously infected and recovered patients into patients with active infection. The concentrations (titre) of neutralising antibodies present within convalescent plasma are highly variable between donors, and various methodologies to measure antibody levels are available.

Evidence—Data were derived from 16 trials enrolling 16 236 patients across illness severities, of which four RCTs with 1602 patients informed estimates for outcomes in non-severe illness. See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendation (<https://app.magicapp.org/#/guideline/nBkO1E/section/LG5NRE>).

Recommendation 1: We recommend not to use convalescent plasma for patients with non-severe covid-19 (strong recommendation).

Understanding the recommendation

A combination of evidence, values and preferences, and feasibility contributed to the strong recommendation against convalescent plasma in patients with non-severe covid-19. The GDG noted that, although not demonstrated in the evidence summary, there remains a potential for harms with blood product transfusion. Most importantly, given there was no benefit demonstrated for any of the critical or important outcomes for non-severe covid-19, the GDG did not see any justification for the resources (including time and cost) that would be associated with administration of convalescent plasma.

The included RCTs enrolled non-pregnant women and men. The GDG did not have reason to believe that children or pregnant women with covid-19 would respond any differently to treatment with convalescent plasma; the GDG therefore inferred that children and pregnant women should not receive the intervention either.

Balance of benefits and harms—In patients with non-severe illness, convalescent plasma does not have an important impact on mortality. Convalescent plasma probably does not affect mechanical ventilation. There were no data evaluating the risk of hospitalisation with convalescent plasma; the impact is therefore very uncertain. Convalescent plasma probably does not result in important increases in risks of transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), or allergic reactions.

The certainty for mortality was high, whereas it was moderate for mechanical ventilation because of serious risk of bias. Certainty was rated as moderate for TRALI and TACO due to serious risk of

bias, and for allergic reactions due to concerns regarding risk of bias and imprecision.

Values and preferences—Applying the agreed values and preferences, the GDG inferred that almost all well informed patients with non-severe covid-19 would choose against receiving convalescent plasma.

Acceptability and applicability—Although blood transfusion is acceptable to most, there is a subset of the population who will not accept allogenic blood transfusions. There are also regulatory challenges in most jurisdictions related to blood product transfusions. The applicability of this recommendation to children or pregnant women is currently uncertain, as the included RCTs enrolled non-pregnant adults.

Practical issues—Issues include, though are not limited to, the identification and recruitment of potential donors, collection of plasma, storage and distribution of plasma, and infusion of convalescent plasma into recipients.

Resource implications, feasibility, equity, and human rights—The GDG noted that convalescent plasma use is associated with significant resource requirements, including identification of potential donors, testing of donors to ensure adequate titres of anti-SARS-CoV-2 antibodies, collection of donor plasma, storage of plasma, transportation of plasma to recipient location, and administration of plasma. These resources and feasibility issues are compounded for those with non-severe illness, who are most often outpatients. Also, this process is costly and time consuming. Given the number of patients with non-severe illness and the low event rate in this subgroup of patients, mobilising the use of convalescent plasma on a large scale would be of questionable feasibility.

Recommendation 2: We recommend not to use convalescent plasma for patients with severe or critical covid-19, except in the context of a clinical trial (recommended only in research settings).

Understanding the recommendation

Given low certainty evidence suggesting a small or no effect on mortality, mechanical ventilation, or time to symptom improvement, with possible associated harms (although not demonstrated in the evidence summary, there is always a potential for harms with blood product transfusion), the GDG agreed further research addressing these patient-important outcomes would be valuable. A recommendation to use a drug only in the setting of clinical trials is appropriate when there is low certainty evidence, and future research has potential to reduce uncertainty about the effects of the intervention, and for doing so at a reasonable cost.

Balance of benefits and harms—In patients with severe or critical covid-19, convalescent plasma may not result in an important impact on mortality, mechanical ventilation, time to symptom improvement, length of hospital stay, or ventilator-free days. Convalescent plasma probably does not result in important increases in risks of TRALI, TACO, or allergic reactions. However, there is always potential for harms with blood product transfusions.

The certainty for mortality was rated as low due to concerns with indirectness, risk of bias, and imprecision. The GDG rated down certainty as low for mechanical ventilation, length of hospital stay, and ventilator-free days because of serious risk of bias and serious imprecision, and rated certainty as low for time to symptom improvement due to very serious imprecision. As in patients with non-severe covid-19, certainty was rated as moderate for TRALI and TACO due to serious risk of bias, and moderate for allergic reactions due to concerns regarding risk of bias and imprecision.

Values and preferences—Applying the agreed values and preferences, the GDG inferred that almost all well informed patients would choose against receiving convalescent plasma.

Resource implications, acceptability and feasibility, equity, human rights, and practical issues—Resource implications and feasibility issues were largely similar to those noted for patients with non-severe covid-19. Although convalescent plasma may be easier to administer to hospitalised patients with severe or critical covid-19, it still represents a resource-demanding intervention with several practical challenges to limit its feasibility.

Specific uncertainties, emerging evidence, and future research

- Effects in severe or critical illness (low to moderate certainty evidence for most patient-important outcomes).
- Long term mortality and functional outcomes in covid-19 survivors.
- Safety and efficacy in children, and pregnant and lactating women.
- Effects of high titre convalescent plasma on mortality and other patient-important outcomes.
- Effects in patients with seronegative antibody status.

Casirivimab-imdevimab (neutralising monoclonal antibodies) (Update 5, published 23 September 2021)

Overview

Casirivimab and imdevimab are two fully human antibodies (REGN10933 and REGN10987) that bind to the SARS-CoV-2 spike protein and have demonstrated antiviral activity in animal models. It has been postulated that administration of a combination of casirivimab and imdevimab might have differential effects in patients who have produced their own anti-SARS-CoV-2 spike protein antibodies (hereafter seropositive) compared with those who have not (hereafter seronegative); it was hypothesised that effects might be larger for, or restricted to, seronegative individuals who have not yet mounted an effective natural antibody response.

WHO has noted that, as per pre-clinical evidence, there is a predicted lack of efficacy for casirivimab and imdevimab with the omicron variant, and that other monoclonal antibodies may retain efficacy in this setting.²⁰ Recommendations are planned to be updated when sufficient evidence addressing this is available.

A conditional recommendation for sotrovimab in non-severe illness for patients at highest risk for hospitalisation has been published following recommendations for casirivimab-imdevimab (see above) and should be considered when interpreting evidence and recommendations for this treatment.

Evidence—For patients with non-severe illness, data were derived from four RCTs with 4722 patients, all coming from a larger adaptive randomised master trial. For patients with severe or critical illness, one large trial (RECOVERY) enrolling 9785 patients, most of whom received corticosteroids, informed estimates. See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendation (<https://app.magicapp.org/#/guideline/nBkO1E/section/LG5NRE>).

Recommendation 1: We suggest treatment with casirivimab-imdevimab for patients with non-severe covid-19, conditional to those at highest risk of hospitalisation (conditional or weak recommendation).

Understanding the recommendation

A combination of evidence, values and preferences, and feasibility contributed to the conditional recommendation for the use of casirivimab-imdevimab restricted to patients with non-severe covid-19 at highest risk of hospitalisation. Although there is moderate certainty evidence of a substantial relative risk reduction in hospitalisation, only a minority of patients at highest risk are likely to achieve important benefit. In routine care of those with non-severe covid-19, there exists a lack of tools to accurately identify those at highest risk. This limitation, combined with the limited availability of the drug and need for parenteral administration for a group of patients who are typically cared for in the community, presents challenges for care that healthcare systems need to address.

Balance of benefits and harms—In non-severely ill patients, casirivimab-imdevimab probably reduces the risk of hospitalisation and duration of symptoms (both moderate certainty); however, the absolute benefit will be trivial in absolute terms for all but those at highest risk, for whom the intervention should be reserved. The GDG identified a risk beyond 10% of being hospitalised for covid-19 to represent a threshold at which most people would want treatment with casirivimab-imdevimab. In the absence of credible tools to predict risk for hospitalisation in people with covid-19, typical characteristics of people at highest risk include lack of vaccination, older people, or those with immunodeficiencies or chronic diseases such as diabetes.

The lack of an empirically developed and validated risk prediction tool for establishing patients' risk of hospitalisation represents the major source of indirectness for which the GDG rated down the certainty of the evidence. In addition, the GDG felt that there was some indirectness because of the possible emergence of variants in which effectiveness of the treatment may be reduced, now predicted for omicron, as noted above. Casirivimab-imdevimab is unlikely to have serious adverse effects (high certainty evidence), including allergic reactions (moderate certainty due to imprecision). We found no evidence of subgroup effects with age or time from onset of illness for any outcomes.

Values and preferences—The GDG inferred that almost all well informed patients at typical low risk of hospitalisation would decline casirivimab-imdevimab, and only those at higher risk would choose to receive treatment.

Applicability—Available trials only enrolled adults; the applicability of this recommendation to children is therefore uncertain. The GDG did not have reason to believe that children with covid-19 would respond any differently to treatment with casirivimab-imdevimab. However, given the risk of hospitalisation in children is extremely low, the GDG inferred that, in the absence of immunosuppression or another significant risk factor, children should not receive the intervention. Lack of data precluded the GDG from making specific recommendations for other special populations, such as pregnant women.

Practical issues—Regarding monitoring, although available trials have not convincingly shown that casirivimab-imdevimab results in allergic reactions, the possibility remains. Casirivimab-imdevimab should be administered through an intravenous line containing a sterile in-line or add-on 0.2 µm filter. Following infusion, patients should undergo monitoring for allergic reactions.

Resource implications, acceptability, feasibility, equity, and human rights—Major feasibility challenges include limited production of casirivimab-imdevimab and, for outpatients, the requirement for parenteral administration.

Casirivimab-imdevimab is unlikely to be available for all individuals who would choose to receive treatment, supporting the recommendation to reserve them for those at highest risk of hospitalisation.

Regarding intravenous administration, it is likely that specialised clinics with adequate amounts of the antibodies and staff to ensure safe and effective administration of the intervention will be required. For the intervention to achieve substantial use, health systems will have to address these challenges.

The trials used different doses of the monoclonal antibody combination, and health systems will face the choice of which dose to use; this can be informed, in part, by system values and preferences. If one's priority is to ensure giving as many people as possible the opportunity to benefit from treatment, one might use the lowest effective dose offered in the studies of non-severe patients, 1200 mg total dose (600 mg of each antibody). If one's priority is to ensure effectiveness in every individual who receives treatment and minimise the risk of emergence of resistance, one might use a higher total dose of 2400 mg (1200 mg of each antibody).

Similar considerations apply to choosing between intravenous and subcutaneous administration, the former used in the four trials included in the living network meta-analysis, and the latter used in a recent trial; one may balance priorities of maximum effectiveness and faster ability to achieve maximum drug concentrations with intravenous therapy, with widespread accessibility with subcutaneous therapy. Volumes that can be administered subcutaneously are limited to the lowest dose, which is a total dose of 1200 mg (600 mg of each antibody).

Recommendation 2: We suggest treatment with casirivimab-imdevimab for patients with severe or critical covid-19, conditional to those with seronegative status (conditional or weak recommendation).

Understanding the recommendations

In patients with severe or critical illness, the conditional recommendation in favour reflects the likelihood that benefits are restricted to patients who have seronegative status. In order to translate trial findings into clinical practice, assessment of serological status will need to be integrated into a clinical decision pathway before treatment is administered. This implies rapid identification of serological status at the time of presentation of severe or critical illness to guide use in this population. Several rapid and relatively inexpensive tests with adequate performance characteristics are available and should see increasing use in settings in which casirivimab-imdevimab is available for administration to these patients.

Balance of benefits and harms—A credible subgroup effect based on RECOVERY trial data demonstrated that casirivimab-imdevimab probably reduces mortality and mechanical ventilation in patients with seronegative status. For mortality among patients with seronegative status, the absolute effects range from 39 fewer per 1000 (95% CI 62 fewer to 13 fewer) in severe illness, to 69 fewer (110 fewer to 23 fewer) in critical illness. Evidence for mortality for patients in the seronegative status subgroup was rated as moderate due to imprecision (the confidence intervals included effects as small as 14 in 1000, which some patients may perceive as unimportant) and indirectness (variants may emerge in which casirivimab-imdevimab antibodies may have reduced effect).

In patients with seronegative status, the intervention possibly reduces the need for mechanical ventilation (absolute effect 42 fewer per 1000 (95% CI 74 fewer to 6 fewer)). The GDG noted risk of

bias from lack of blinding as an additional concern, resulting in low certainty evidence.

In all patients with severe or critical covid-19, casirivimab-imdevimab may not have an impact on mortality, and the impact on mechanical ventilation and duration of hospitalisation is very uncertain. Evidence for mortality was of low certainty because of imprecision and high likelihood that casirivimab-imdevimab has, in patients with seronegative and seropositive status included in the overall group, very different effects. In this population, the evidence regarding the impact of the intervention on need for mechanical ventilation and duration of hospitalisation was, given additional concerns with risk of bias, very low certainty. Aside from the credible subgroup effect for serological status, we found no evidence of subgroup effects on age, time from onset of illness, and severity in patients with severe or critical covid-19.

Values and preferences—The GDG inferred that most, if not all, well informed patients with severe or critical covid-19 and seronegative status would choose to receive casirivimab-imdevimab. Other patients—those with seropositive status or whose status is uncertain—are likely to decline the intervention.

Applicability—None of the included randomised trials including RECOVERY enrolled children; therefore, the applicability of this recommendation to children is uncertain. Fortunately, very few children become critically ill with covid-19. For those who do and have seronegative status, it is possible they may benefit from casirivimab-imdevimab. Lack of data precluded the GDG from making specific recommendations for other special populations, such as pregnant women.

Practical issues—Regarding monitoring, although available trials have not convincingly shown that casirivimab-imdevimab results in allergic reactions, the possibility remains. Casirivimab-imdevimab should be administered through an intravenous line containing a sterile in-line or add-on 0.2 µm filter. Following infusion, patients should undergo monitoring for allergic reactions.

Resource implications, acceptability, feasibility, equity, and human rights—Given the cost and availability of casirivimab-imdevimab, and the challenges associated with serological testing, the obstacles to ensuring access to low- and middle-income countries may prove formidable. Thus, the GDG's suggestion that patients who are seronegative receive the intervention may exacerbate health inequity. On the other hand, given the demonstrated benefits for patients, the recommendations should provide a stimulus to engage all possible mechanisms to improve global access to the intervention and associated testing. Individual countries may formulate their guidelines, considering available resources and prioritise treatment options accordingly.

Dosing of casirivimab-imdevimab differed in trials for non-severe covid-19; a single intravenous dose of 8000 mg was used in the RECOVERY trial for severe or critical covid-19. Clinical trials and pharmacokinetic studies in non-severe covid-19 have provided supporting data for similar effects on decreasing the need for hospitalisation with total doses of 1200 mg, 2400 mg, 4000 mg, and 8000 mg. Thus, using doses lower than used in the RECOVERY trial (8000 mg total dose) for treatment of severely and critically ill patients may achieve the same benefit; on the other hand, it is theoretically plausible but untested that pharmacokinetic differences in patients with severe or critical illness, when compared with non-severe illness, may reduce drug exposure. This would increase the risk of suboptimal drug exposure in some individuals, which, in turn, could increase the risk of therapeutic failure and

the emergence of viral resistance. In the absence of clinical data on treatment of severe or critical covid-19 patients with doses lower than 8000 mg, the choice of dose depends on system values and preferences, with due consideration to maximising effectiveness and minimising emergence of resistance with higher doses, compared with lower doses maximising accessibility in the face of low drug availability and high cost.

Diagnostic testing to identify patients with seronegative status at the time patients present with severe or critical covid-19 warrants healthcare systems making available rapid serological tests with adequate performance characteristics. Rapid serological tests with performance characteristics similar to the reference standard test used to characterise seronegative patients in the RECOVERY trial (that is, Oxford fluorescent-based ELISA assay for serum IgG against the SARS-CoV-2 spike protein, with an arbitrary cut-off determined from a group of positive controls) are available and potentially affordable.

Specific uncertainties, emerging evidence, and future research

- Accurate clinical prediction guides to establish the individual patient risk of hospitalisation in patients presenting with non-severe covid-19, to effectively identify patients that would most benefit from this intervention.
- Dosing and administration routes in non-severe, and in severe or critical covid-19 patients.
- Safety and efficacy in children and pregnant women.

Interleukin-6 (IL-6) receptor blockers (Update 4, published 6 July 2021)

Overview

IL-6 receptor blockers tocilizumab and sarilumab are monoclonal antibodies approved for use in rheumatoid arthritis. Elevated IL-6 concentrations are associated with severe outcomes in covid-19, including respiratory failure and death. IL-6 receptor blockers antagonise membrane-bound and soluble forms of the IL-6 receptor, blocking the cytokine's activation and regulation of the immune response to infection.

WHO has made a strong recommendation for JAK inhibitors, specifically baricitinib, in patients with severe or critical covid-19. An IL-6 receptor blocker and baricitinib should not be given together and should be viewed as alternatives (see discussion for JAK inhibitors above).

Evidence—In addition to the linked network meta-analysis (see [box 1](#)), this recommendation was also informed by an independent prospective meta-analysis from the WHO Rapid Evidence Appraisal for covid-19 group.²¹ The network meta-analysis included 30 RCTs with 10 618 participants, and these data were used by the GDG for all outcomes other than mortality. All trials included patients with severe or critical covid-19: 37% were published in peer reviewed journals, 3% were available as preprints, and 60% were completed but unpublished. We used the prospective meta-analysis for mortality because it included additional data that was unpublished at the time. The prospective meta-analysis pooled data from 22 RCTs with 10 156 participants.²¹ See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendation (<https://app.magicapp.org/#/guideline/nBk01E/section/LG5NRE>).

Recommendation: We recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab) for patients with severe or critical covid-19 (strong recommendation).

Understanding the recommendation

Of note, corticosteroids have previously been strongly recommended in patients with severe or critical covid-19, and we recommend that patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers, alternatively baricitinib (see above).

Balance of benefits and harms—There was high certainty evidence for a clinically important reduction in mortality and need for mechanical ventilation. The effects of IL-6 receptor blockers on duration of both hospitalisation and mechanical ventilation are uncertain (low certainty evidence; serious risk of bias due to lack of blinding and serious inconsistency).

There was uncertainty about the risk of serious adverse effects (low certainty evidence). The risk of bacterial infections with immunomodulatory IL-6 receptor blocker therapy may be similar to usual care. However, the GDG had some concerns that, given the short term follow-up of most trials and the challenges associated with accurately capturing adverse events such as bacterial or fungal infections, that the evidence summary may under-represent the risks of treatment with IL-6 receptor blockers. Furthermore, the trials of IL-6 receptor blockers that inform this recommendation were mostly performed in high-income countries, where the risk of infectious complications may be less than in some other parts of the world; the generalisability of the data on these adverse events is therefore unclear.

Values and preferences—The GDG inferred that almost all well informed patients with severe or critical covid-19 infection would want to receive IL-6 receptor blockers, given the reduction in mortality and mechanical ventilation, despite low certainty around evidence for serious adverse events. A minority of the GDG felt that a significant proportion of patients might decline the intervention due to the uncertainties around harms, and taking into account the small reduction in mortality.

Applicability—None of the included RCTs enrolled children or pregnant women. Although this resulted in uncertain applicability, the GDG did not have reason to believe that children or pregnant women with COVID-19 would respond any differently to treatment with IL-6 receptor blockers.

Practical issues—IL-6 receptor blockers require intravenous administration but only require one, or at most two, doses. See MAGICapp for practical information, including considerations if IL-6 receptor blockers are considered in children and pregnant women.

Resource implications, acceptability, feasibility, equity, and human rights—IL-6 receptor blockers require intravenous administration but only require one, or at most two, doses.

Compared with other treatments for covid-19, IL-6 receptor blockers are expensive. The recommendation does not consider cost-effectiveness. Access to these drugs is challenging in many parts of the world, and this recommendation could exacerbate health inequity. However, this strong recommendation should provide a stimulus to improve global access to these treatments.

At a time of drug shortage, many jurisdictions have suggested triaging use of IL-6 receptor blockers. Strategies for this include prioritising patients with the highest baseline risk for mortality (those with critical illness over those with severe illness), in whom

the absolute benefit of treatment is therefore greatest. The relative effects (odds ratio 0.87) for reduction in mortality with IL-6 receptor blockers result in 28 fewer deaths per 1000 patients (95% confidence interval 9 to 47 fewer deaths) in critically ill patients, compared with 12 fewer deaths per 1000 patients (4 to 19 fewer deaths) in severely ill patients.

Other suggestions, which lack direct evidence, include prioritising patients who are deteriorating despite corticosteroid treatment, and avoiding use in those with established multi-organ failure (in whom the benefit is likely to be smaller). Finally, sarilumab is not indicated for use in children; therefore, there could be a preference for tocilizumab in this subgroup.

Specific uncertainties, emerging evidence, and future research

- Long term mortality and functional outcomes in covid-19 survivors.
- Safety data, including nosocomial infections.
- Data in children, pregnant patients, and those with immunocompromise.
- Patients with non-severe covid-19.
- Immunity and the risk of subsequent infection, which may affect the risk of death after 28 days.
- Outcomes by different IL-6 receptor blocker dosing, and optimal timing of drug initiation.

Ivermectin (Update 3, published 31 March 2021)

Overview

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

No changes were made for the ivermectin recommendation in this version of the guideline. We are aware of a few new, relatively small trials published since our recommendation was made, and that one key trial has since been retracted, given concerns about research fraud.^{22,23} However, the updated evidence summary from the living network meta-analysis is consistent with our previous recommendation. This updated evidence summary will be fully considered by the GDG in an upcoming iteration of the guideline.

Evidence—The living systematic review and network meta-analysis pooled data from 16 trials with 2407 participants. Of the included trials, 75% examined patients with non-severe illness, and 25% included patients with both severe and non-severe illness. None of the included trials enrolled children or pregnant women; the applicability of the evidence to these subgroups is therefore uncertain, though there is no rationale to suggest they would respond differently. See MAGICapp for detailed description of the mechanism of action, evidence, and subgroup analyses underpinning the recommendation (<https://app.magicapp.org/#/guideline/nBk01E/section/LG5NRE>).

Recommendation: We recommend not to use ivermectin for patients with covid-19, regardless of illness severity, except in the context of a clinical trial (recommended only in research settings).

Understanding the recommendation

Balance of benefits and harms—For most prioritised outcomes, the GDG 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 seemed to suggest benefit with ivermectin; similar judgements were made for other outcomes, including mechanical ventilation, hospital admission, duration of hospitalisation, and viral clearance. Very low certainty 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 events leading to drug discontinuation (low certainty evidence). A recommendation to only use a drug in the setting of clinical trials is appropriate when there is very low certainty evidence, and when future research has large potential for reducing uncertainty about the effects of the intervention and at a reasonable cost.

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

Values and preferences—The GDG inferred that almost all well informed patients would not want to receive ivermectin, given available evidence left a very high degree of uncertainty in effects on critical outcomes and the possibility of harms, such as adverse events associated with treatment.

Resource implications, acceptability, feasibility, equity, and human rights—Although the cost of ivermectin may be low per patient, the GDG raised concerns about diverting attention and resources away from care likely to provide a benefit, such as corticosteroids in patients with severe covid-19, and other supportive care interventions. Also, use of ivermectin for covid-19 would divert 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 strongyloidiasis-endemic areas, albeit not for treatment of covid-19 itself.

Specific uncertainties, emerging evidence, and future research

- Effects in inpatients and outpatients, in varying illness severities, and with different dosing regimens.
- Potential harms associated with ivermectin.

Hydroxychloroquine (Update 2, published 17 December 2020)

Overview

Evidence—The recommendation addressing hydroxychloroquine was informed by results from the living network meta-analysis, pooling data from 30 RCTs with 10 921 participants. None of the included trials enrolled children or adolescents; the applicability to this subgroup is therefore uncertain. See MAGICapp for detailed description of the evidence and subgroup analyses underpinning the recommendation (<https://app.magicapp.org/#/guide-line/nBkO1E/section/j197zj>).

Recommendation: We recommend not to use hydroxychloroquine or chloroquine for patients with covid-19, regardless of illness severity (strong recommendation).

Understanding the recommendation

Balance of benefits and harms—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 v severe and non-severe illness, or non-severe v critical and severe illness) 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, the GDG inferred that almost all well informed patients would not want to receive hydroxychloroquine, given the evidence suggesting probably no effect on mortality or need for mechanical ventilation and that there was a risk of adverse events including diarrhoea and nausea/vomiting.

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 GDG 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 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.

Specific uncertainties, emerging evidence, and future research

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

Lopinavir-ritonavir (Update 2, published 17 December 2020)

The recommendation was informed by 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. See MAGICapp for detailed description of the evidence and subgroup analyses underpinning the recommendation (<https://app.magicapp.org/#/guide-line/nBkO1E/section/EgyLXL>).

Recommendation: We recommend not to use lopinavir-ritonavir for patients with covid-19, regardless of illness severity (strong recommendation).

Understanding the recommendation

Balance of benefits and harms—The GDG 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 illness course. The GDG therefore felt that the evidence applies to all patients with covid-19.

Values and preferences—Applying the agreed values and preferences, 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 GDG 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.

Specific uncertainties, emerging evidence, and future research

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

Remdesivir (Update 1, published 20 November 2020)

The recommendation addressing remdesivir includes data from four RCTs with 7333 participants hospitalised for covid-19. See MAGICapp for detailed description of the evidence and subgroup analyses underpinning the recommendation and practical information on how to administer remdesivir (<https://app.magicapp.org/#/guideline/nBk01E/section/Egzoxn>).

Recommendation: We suggest not to use remdesivir for patients with covid-19, regardless of illness severity (conditional or weak recommendation).

Understanding the recommendation on remdesivir

When moving from evidence to the conditional recommendation against the use of remdesivir for patients with covid-19, the GDG 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 benefits and harms—The GDG 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 illness might benefit from remdesivir. However, the GDG judged the credibility in this subgroup analysis to be insufficient to make subgroup recommendations. 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 GDG 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 GDG 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, 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 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 GDG 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.

Applicability—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.

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.

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.

Specific uncertainties, emerging evidence, and future research

- 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.

Systemic corticosteroids (Original publication, published 4 September 2020)

On 17 July 2020 the GDG reviewed evidence from eight RCTs (7184 patients) 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 GDG did not consider transdermal or inhaled administration of corticosteroids, high dose or long term regimens, or prophylaxis. The GDG did not reach consensus on recommendation 1, which required a vote. The second recommendation was made by consensus. See MAGICapp for detailed description of the evidence and subgroup analyses underpinning the recommendation and practical information on how to administer systemic corticosteroids (<https://app.magicapp.org/#/guideline/nBk01E/section/nByvRL>).

Whereas the recommendations remain unchanged, the evidence summary available via MAGICapp for corticosteroids was updated before the fifth iteration of the living guideline. The baseline risk estimates for mortality are now based on the WHO SOLIDARITY trial (as for other drugs in this guideline)⁴ rather than the initial ISARIC cohort study that likely overestimates current mortality risks at the global level.²⁴ This update was also needed to inform the baseline risk for mortality in the evidence summary informing the strong recommendation for IL-6 inhibitors in addition to standard care for patients with severe or critical covid-19, where corticosteroids provide a relative reduction in mortality by 21%.

Recommendation 1: We recommend treatment with systemic corticosteroids for patients with severe or critical covid-19 (strong recommendation).

Understanding the recommendation

Balance of benefits and harms—Ultimately, the GDG made its recommendation on the basis of the moderate certainty evidence of a 28-day mortality reduction of 3.4% in severe or critical covid-19 combined. Systemic corticosteroids compared with no corticosteroid therapy probably reduce the risk of 28-day mortality in these patients (moderate certainty evidence; relative risk 0.79 (95% confidence interval 0.70 to 0.90); absolute effect estimate 34 fewer deaths per 1000 patients (95% CI 48 fewer to 16 fewer)). Therapy also probably reduces the need for mechanical ventilation (moderate certainty evidence, relative risk 0.74 (0.59 to 0.930; absolute effect estimate 30 fewer cases per 1000 patients (48 fewer to 8 fewer)). The effects of systemic corticosteroids on other outcomes are described in the summary of findings.

Overall, the GDG 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 GDG was reassured by their overall safety profile.

Values and preferences—The GDG 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 were 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.

Applicability—This recommendation applies 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 GDG 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.

Acceptability and practical issues—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 GDG to conclude that the acceptability of this intervention was high.

Resource implications, feasibility, equity, and human rights—Systemic corticosteroids are low cost, easy to administer, and readily available globally. 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.

Recommendation 2: We suggest not to use systemic corticosteroids for patients with non-severe covid-19 (conditional or weak recommendation).

Understanding the recommendation

Balance of benefits and harms—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 conditional recommendation was driven by likely variation in patient values and preferences. The GDG 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.

Applicability—This recommendation applies to patients with non-severe illness regardless of their hospitalisation status. The GDG 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* hyper-infection associated with corticosteroid therapy, diagnosis or empiric treatment may be considered in endemic areas if steroids are used.

Resource implications, feasibility, equity, and human rights—To help guarantee access to systemic corticosteroids for patients with severe or 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

Specific uncertainties, emerging evidence, and future research

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 or 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.

How this living guideline was created (see MAGICapp for full details <https://app.magicapp.org/#/guideline/nBk01E>)

Standards, methods, and processes for living and trustworthy guidance

The Guideline Development Group (GDG) 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*,⁸ the Institute of Medicine, and the Guideline International Network (G-I-N).²⁵

Selection and support of the GDG

WHO convened a Guideline Development Group (GDG) with content experts (clinicians, methodologists, scientists) and patients who previously had covid-19. The methods chair (methodological expertise) and a clinical chair (content expertise) guided the GDG discussions. GDG members were invited by WHO, with the aim of achieving gender, geography, expertise, and patient representation balance as well as relevant technical and clinical expertise. No relevant conflict of interest was identified for any GDG member or other contributors to the guideline development process. The GDG aimed to create a recommendation based on consensus with a provision for voting that proved unnecessary for this recommendation.

Guideline perspective, outcomes, and values and preferences

The target audience for this guidance consists of clinicians, patients, and healthcare decision makers. The GDG defined covid-19 by clinical severity (box 2). The GDG considered an individual patient perspective, but also took account of contextual factors (such as resources, feasibility, acceptability, and equity) to accommodate global re-use and adaptation for countries and healthcare systems, and to recognise system challenges in implementing recommendations.

There were insufficient published data to provide the GDG with an evidence-based description of patient experiences, or values and preferences regarding treatment decisions for covid-19 drug treatments. The GDG therefore relied on their own judgments of what well informed patients would value after carefully balancing the benefits, harms, and burdens of treatment. These judgments on values and preferences were also informed through the experiences of former patients with covid-19, represented in the GDG.

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 treatment 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 treatment.

Sources of evidence

To create recommendations, the GDG relied on evidence synthesised in two living network meta-analyses coordinated by MAGIC.^{6 7}

Derivation of absolute effects for drug treatments

For patients with non-severe illness, we used the median of the control arm of the RCTs that contributed to the evidence. For patients with severe or critical illness, the GDG identified the control arm of the WHO SOLIDARITY trial, performed across a wide variety of countries and geographical regions, as representing the most relevant source of evidence for baseline risk estimates for mortality and mechanical ventilation.⁴ Systemic corticosteroids now represent standard of care in patients with severe or critical covid-19 (see strong recommendation issued by WHO in September 2020). Therefore, the baseline risk estimates in the evidence summaries for Janus kinase (JAK) inhibitors, convalescent plasma and interleukin-6 (IL-6) receptor blockers were adjusted for treatment effects of corticosteroids for the outcome of mortality and mechanical ventilation.⁴ For other outcomes, we used the median of the control arm of the RCTs that contributed to the evidence. Baseline risks, and thus absolute effects, may vary significantly geographically and over time. Thus, users of this guideline may prefer estimating absolute effects by using local event rates.

How patients were involved in the creation of this article

The GDG included four patients who previously had covid-19. Their perspectives were crucial in considering the values and preferences associated with the various treatments.

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b systemic corticosteroids Guideline Development Group member

c ivermectin IL-6 receptor blocker Guideline Development Group member

d IL-6 receptor blocker Guideline Development Group member

e casirivimab-imdevimab Guideline Development Group member

f convalescent plasma Guideline Development Group member

g janus kinase inhibitor Guideline Development Group member

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Main infographic: Summary of recommendations and evidence

Appendix 7: Data on JAK inhibitors from living network meta-analysis

Appendix 8: Details on trial data for baricitinib