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Cite this as: *BMJ* 2020;370:m3379
<http://dx.doi.org/10.1136/bmj.m3379>

Published: 4 September 2020

RAPID RECOMMENDATIONS

A living WHO guideline on drugs for covid-19

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ABSTRACT

CLINICAL QUESTION

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

NEW RECOMMENDATION

Pre-prints of four randomised trials (from a larger adaptive randomised master protocol) among patients with non-severe illness, and the RECOVERY trial among severe and critically ill patients, triggered this guideline update. This resulted in a conditional recommendation to use a combination of casirivimab and imdevimab in non-severe patients for those at highest risk of severe disease. The RECOVERY trial included a crucial subgroup analysis demonstrating differential benefits (effect modification) associated with serological status. The Guideline Development Group (GDG) made a second conditional recommendation to use casirivimab-imdevimab in patients with severe and critical infection, if the individual has seronegative status.

PRIOR RECOMMENDATIONS

(a) A strong recommendation for interleukin-6 receptor blockers (tocilizumab or sarilumab) in patients with severe or critical covid-19; (b) a recommendation not to use ivermectin in patients with covid-19, regardless of disease severity, except in the context of a clinical trial; (c) a strong recommendation against the use of hydroxychloroquine in patients with covid-19, regardless of disease severity; (d) a strong recommendation against the use of lopinavir-ritonavir in patients with covid-19, regardless of disease severity; (e) a strong recommendation for systemic corticosteroids in patients with severe and critical covid-19; (f) a conditional recommendation against systemic corticosteroids in patients with non-severe covid-19; and (g) a conditional recommendation against remdesivir in hospitalised patients with covid-19.

HOW THIS GUIDELINE WAS CREATED

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

UNDERSTANDING THE NEW RECOMMENDATION

In patients with non-severe illness, pooled data showed casirivimab-imdevimab had trivial or no effects on mortality or need for mechanical ventilation, due to very low baseline risk. Evidence demonstrated a likely reduction in need for hospitalisation; the absolute benefit will be greater in those at highest risk of hospitalisation. When moving from evidence to the conditional recommendation to use casirivimab-imdevimab in those at highest risk, the GDG recognised the limited availability, in relation to the large number of patients with non-severe disease, of the medicine and the very small benefits in reducing hospitalisation for low risk patients. Although there is no established decision tool to identify those at highest risk of hospitalisation, factors that substantially increase risk include no prior vaccination, older age, immunosuppression, and the presence of chronic conditions.

In patients with severe or critical illness the conditional recommendation reflects the likelihood that any benefits are restricted to patients who are seronegative. A credible subgroup effect demonstrated that, in patients who are seronegative (that is, absence of their own anti-SARS-CoV-2 spike protein antibodies despite active infection), casirivimab-imdevimab probably reduces mortality

and may reduce the need for mechanical ventilation. Rapid identification of serological status at the time of presentation of severe or critical illness is necessary. Several rapid, relatively inexpensive tests with adequate performance characteristics are available.

UPDATES

This is a living guideline. It replaces earlier versions (4 September, 20 November, 17 December 2020, 31 March 2021, and 6 July 2021) and supersedes the *BMJ* Rapid Recommendations on remdesivir published on 2 July 2020. The previous versions can be found as data supplements. New recommendations will be published as updates to this guideline.

READERS NOTE

This is the sixth version (update 5) of the living guideline (*BMJ* 2020;370:m3379). When citing this article, please consider adding the update number and date of access for clarity.

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

More than 4200 trials on covid-19 interventions have been registered or are ongoing (see section on emerging evidence²). Among these are large national and international platform trials (such as RECOVERY, WHO SOLIDARITY, REMAP-CAP, and ACTIV) that recruit large numbers of patients in many countries, with pragmatic and adaptive designs.³⁻⁶ These platform trials are currently investigating and reporting on numerous interventions, including antiviral monoclonal antibodies and immunomodulators. This rapidly evolving evidence landscape requires trustworthy interpretation and expeditious clinical practice guidelines to inform clinicians and healthcare 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.^{7,8} Box 1 includes these network meta-analyses and other related publications. We also use additional relevant evidence on safety, prognosis, and patient values and preferences related to covid-19 treatments to inform the living guidance.

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

- Rochwerf B, Agarwal A, Siemieniuk RAC, et al. A living WHO guideline on drugs for covid-19 [Update 5]. *BMJ* 2020;370:m3379, doi:10.1136/bmj.m3379
- World Health Organization. *Therapeutics and COVID-19. Living guideline*. September 2021. <https://www.who.int/publications/i/item/therapeutics-and-covid-19-living-guideline>.
- MAGICapp (<https://app.magicapp.org/#/guideline/nBkO1E>)
 - Expanded version of the guideline, including methods, processes, and results with multilayered recommendations, evidence summaries, and decision aids for use on all devices
- Siemieniuk RAC, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis [Update 3]. *BMJ* 2020;370:m2980, doi:10.1136/bmj.m2980
- 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, Díaz Martínez 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

What triggered this version of the guideline?

This is the sixth version of this guideline, and it addresses the use of a combination of casirivimab and imdevimab in two groups of patients: those with non-severe covid-19, and those with severe and critical illness. It was triggered by the availability of pre-prints of four randomised trials (from a larger adaptive randomised master protocol) addressing patients with non-severe illness,^{9,10} and of the RECOVERY trial addressing severe and critically ill patients.¹¹

How to use this guideline

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

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

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

Standards, methods, and processes for living and trustworthy guidance

The 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*,¹² the Institute of Medicine, and the Guideline International Network (G-I-N).¹³ Details are provided in the WHO guideline (<https://www.who.int/publications/i/item/therapeutics-and-covid-19-living-guideline>) and MAGICapp (<https://app.magicapp.org/#/guideline/nBkO1E>).

Selection and support of the GDG

For the two recommendations on the combination of casirivimab and imdevimab, WHO convened a GDG with 40 individuals, of whom 36 were content experts (clinicians, methodologists, scientists) and four were 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. No relevant conflict of interest was identified for any GDG member.

As recommended by the WHO handbook,¹² 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 considered an individual patient perspective but also took account of contextual factors (such as resources, feasibility, acceptability, equity) to accommodate global re-use

and adaptation for countries and healthcare systems, and recognised system challenges in implementing recommendations regarding casirivimab and imdevimab.

During a pandemic, access to healthcare may vary over time and between different countries. The GDG defined covid-19 by clinical severity (box 3).

There were insufficient published data to provide the GDG with an evidence-based description of patients' experiences or values and preferences regarding treatment decisions for covid-19 drug treatments. The GDG therefore relied on their own judgments of what well informed patients would value after carefully balancing the benefits, harms, and burdens of treatment. These judgments on values and preferences were also informed through the experiences of former covid-19 patients, 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 medication for which the evidence left high uncertainty regarding effects on the outcomes they consider important. This was particularly so when evidence suggested treatment effects, if they exist, are small and the possibility of important harm remains.
- In an alternative situation with larger benefits and less uncertainty regarding both benefits and harms, more patients would be inclined to choose the intervention.

Although the GDG focused on an individual patient perspective, they also considered a population perspective in which feasibility, acceptability, equity, and cost are important considerations to contextualise recommendations in health care systems around the world.

For the specific recommendations on casirivimab-imdevimab, the GDG considered the limited availability of the drug in relation to the number of infected individuals a major concern for patients with non-severe illness. GDG members completed a survey in which they provided their view regarding the magnitude of reduction in hospitalisation that would prompt patients to use casirivimab-imdevimab. The GDG responses

suggested that most patients with a risk of hospitalisation above 10%, and thus an absolute risk reduction of approximately 6%, would choose to receive treatment, while a majority of those below that risk level would decline treatment. Large majorities of patients with risks substantially higher than 10% would choose to receive treatment, and large majorities of those with substantially lower risks would decline.

For patients with severe and critical illness, both limited availability of the intervention and the requirement for serological testing as part of clinical decision-making to identify seronegative patients (that is, absence of their own anti-SARS-CoV-2 spike protein antibodies despite active infection) proved important considerations.

Sources of evidence

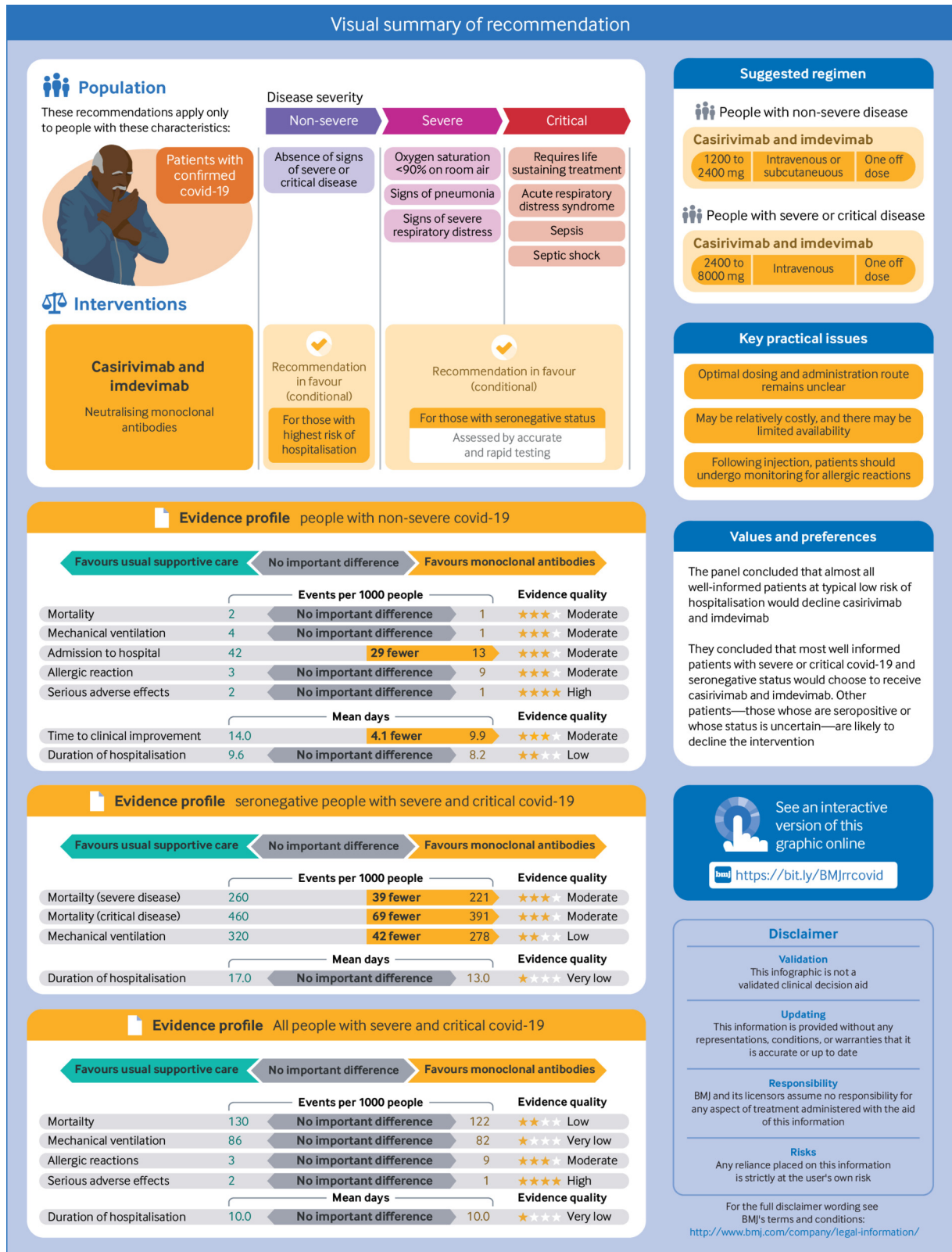
To create recommendations, the GDG relied on evidence synthesised in two living network meta-analyses led by MAGIC.^{7 8}

Derivation of absolute effects for drug treatments

For patients with non-severe covid-19, the median of the control arm of the four randomised trials that contributed to the evidence provided baseline (untreated patient) risks. For hospital admission, the incidence in untreated patients provided a baseline risk of 4.2%.

For patients with severe and critical covid-19, 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.⁵ Systemic corticosteroids now represent standard of care in patients with severe and critical covid-19 (see strong recommendation issued by WHO September 2020). Therefore, the baseline risk estimates in the casirivimab-imdevimab evidence summaries were adjusted for treatment effects of corticosteroids for the outcome of mortality and mechanical ventilation.⁵ Incidence of these outcomes proved substantially higher in seronegative patients as per the RECOVERY trial; these rates informed absolute estimates of effect in this population.¹¹

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.



Who do the recommendations apply to?

This guideline applies to all patients with covid-19. For some drugs, recommendations may differ based on the severity of covid-19. The GDG elected to use the WHO severity definitions based on clinical indicators, adapted from WHO covid-19 severity categorisation (see

box 3).¹⁴ These definitions avoid reliance on access to healthcare to define patient subgroups. The infographic illustrates these three disease severity groups and key characteristics to apply in practice.

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

- **Critical covid-19**—Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
- **Severe covid-19**—Defined by any of:
 - Oxygen saturation <90% on room air*
 - Signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).
- **Non-severe covid-19**—Defined as absence of any signs of severe or critical covid-19.

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

The guidance**Casirivimab-imdevimab (neutralising monoclonal antibodies)**

Casirivimab and imdevimab are two fully human antibodies (REGN10933 and REGN10987) that bind to the SARS-CoV-2 spike protein¹⁵ and have demonstrated anti-viral activity in animal models.

It has been postulated that administration of a combination of casirivimab and imdevimab may 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.

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

Box 4: Casirivimab-imdevimab trial data**Patients with non-severe illness**

The living network meta-analyses pooled data from four RCTs with 4722 patients with non-severe illness, coming from a larger adaptive randomised master protocol.^{9 10} Pooled data showed that a combination of casirivimab and imdevimab probably reduces admission to hospital (moderate certainty evidence), the outcome the GDG rated of the highest importance for patients with non-severe covid-19. The relative reduction in hospitalisation (odds ratio 0.29 (95% CI 0.17 to 0.48)) results in 29 fewer hospitalisations per 1000 patients (95% CI 35 fewer to 21 fewer) when using the baseline risk of hospitalisation in the four trials (4.2%). Evidence certainty was rated down to moderate because of concerns about decreased efficacy against emerging SARS-CoV-2 variants. The absolute benefit in hospital reduction is greatest in those at highest risk for hospitalisation, and lower for the majority of the population at low risk. Casirivimab-imdevimab probably also reduces duration of hospitalisation (best estimate 4.1 fewer days (95% CI 1.8 to 5.7), moderate certainty evidence). The intervention results in very few allergic reactions and severe adverse events.

The absolute risk of mortality in the overall trial population was very low (2 in 1000), and it is still possible that there is a small but important mortality reduction in patients at greatest risk of hospitalisation. The conclusion is similar for mechanical ventilation based on 3432 patients, with a very low baseline risk for ventilation of 4 in 1000.

• **Subgroup analysis**

- In patients with non-severe covid-19, the GDG determined that there was no subgroup effect across all pre-specified outcomes of interest based on age or time from onset of illness.

Patients with severe illness

The living network meta-analyses were informed by one large trial (RECOVERY) which enrolled 9785 patients with severe or critical illness, most of whom received corticosteroids.¹¹

In the overall population of patients with severe and critical covid-19, including both seronegative and seropositive individuals, it remains uncertain whether casirivimab-imdevimab results in an important effect on mortality (odds ratio 0.94 (95% CI 0.86 to 1.03); absolute effect estimate 8 fewer per 1000 patients (95% CI 18 fewer to 4 more), low certainty evidence). The evidence was rated as low certainty because of imprecision and indirectness: a high likelihood that casirivimab-imdevimab has, in the seronegative and seropositive patients included in the overall group, very different effects (see below). The evidence on need for mechanical ventilation and duration of hospitalisation was rated as very low certainty, adding risk of bias due to lack of blinding as another concern.

• **Subgroup analysis**

- A highly credible subgroup effect demonstrated that casirivimab-imdevimab likely reduces mortality in patients who are seronegative but not in those who are seropositive.¹¹
- Based on data from 2823 patients in the RECOVERY trial, the anticipated relative risk of death in seronegative patients receiving casirivimab-imdevimab is 0.85 (95% CI 0.76 to 0.95) with an absolute effect of 39 fewer per 1000 (95% CI 62 fewer to 13 fewer, moderate certainty evidence due to concerns with imprecision and indirectness due to possible new SARS-CoV-2 variants in the future where benefit may change). In the seronegative patients, the intervention may reduce the need for mechanical ventilation (relative risk 0.87 (95% CI 0.77 to 0.98); absolute effect 42 fewer per 1000 (74 fewer to 6 fewer), low certainty).
- The credibility of the subgroup effect was evaluated using the ICEMAN tool¹⁶ and was strongly supported by: an a priori hypothesis with a specified direction, a small number of such hypotheses, evidence based on a within-study comparison, a suggestion of a similar subgroup effect in mechanical ventilation, and an interaction P value of 0.001. [Figure 1](#) presents the forest plot from the RECOVERY trial publication and depicts the point estimate and confidence interval around the effects on mortality in the seropositive and seronegative patients.¹¹ It demonstrates benefit in the seronegative, a point estimate suggesting harm in the seropositive, and no overlap in the confidence intervals, a result corresponding to the P = 0.001 in the test of interaction.
- Very low certainty evidence raises the possibility of shorter hospitalisation in seronegative patients. Aside from the reported subgroup effects on serological status, we found no evidence of subgroup effects on age, time from onset of illness, and severity (comparing severe and critically ill patients).

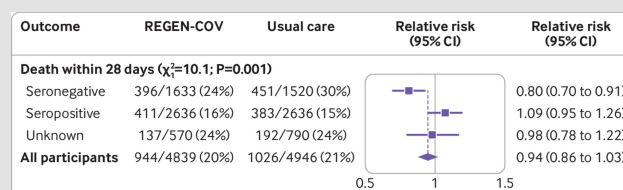


Fig 1 | Mortality, in seropositive and seronegative patients with severe and critical covid-19. Adapted from RECOVERY Collaborative Group 2021¹¹

Understanding the recommendations on casirivimab-imdevimab

Recommendation 1: Among patients with non-severe covid-19, we suggest treatment with casirivimab-imdevimab, conditional to those at highest risk of hospitalisation.

A combination of the evidence, values and preferences and feasibility contribute to the conditional recommendation for the use of casirivimab-imdevimab only in 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 who are 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 of hospitalisation. 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, present challenges for care that healthcare systems need to address.

Balance of benefit and harm—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 or unimportant 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 and 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. 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 on 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 (for example, unvaccinated, older, or immunosuppressed) would choose the treatment.

Resource implications, 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, and this can be informed by 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).¹⁷ If one's priority is on ensuring effectiveness in every individual who receives treatment, and minimising the risk of emergence of resistance, one might use a higher total intravenous 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-analyses,^{9–11} and the latter used in a recent trial¹⁸; 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 1200 mg (600 mg of each antibody).

Applicability—The applicability of this recommendation to children is uncertain, as the randomised trials exclusively enrolled adults. The GDG had no reason to think that children with covid-19 would respond any differently to treatment with casirivimab-imdevimab. However, the risk of hospitalisation in children is extremely low, and the GDG inferred that, in the absence of immunosuppression or another significant risk factor, that children should not receive the intervention.

Practical information—Regarding monitoring, although the available trials have not convincingly shown that casirivimab-imdevimab results in allergic reactions, the possibility remains. Administer 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.

Recommendation 2: Among patients with severe or critical covid-19, we suggest treatment with casirivimab-imdevimab, conditional to those with seronegative status.

In patients with severe or critical illness, the conditional recommendation in favour reflects the likelihood that any benefits are restricted to patients who have seronegative status. In order to translate the trial findings into clinical practice, assessment of serological status will need to become 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 the RECOVERY trial data demonstrated that casirivimab-imdevimab probably reduces mortality and mechanical ventilation in patients who are seronegative.¹¹ For mortality among patients who are seronegative, the absolute effects range from 39 fewer per 1000 (95% CI 62 fewer to 13 fewer) in the severely ill to 69 fewer (110 fewer to 23 fewer) in the critically ill. Evidence for mortality for the seronegative subgroup was rated as moderate due to imprecision (the confidence intervals include effects as small as 14 in 1000 that some patients may perceive as unimportant) and indirectness (variants may emerge in which casirivimab-imdevimab antibodies may have reduced effect).

In seronegative patients, 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 the overall population of patients with severe and 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 the seronegative and seropositive patients 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 and 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 who are seropositive or whose status is uncertain—are likely to decline the intervention.

Resource implications, 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-to-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 and critical covid-19.¹¹ 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 severe and critical patients, when compared with non-severe, may reduce drug exposure.¹¹ This would increase the risk of sub-optimal 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 and critical covid-19 patients with doses lower than 8000 mg, the choice of dose depends on 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 warrant rapid serological tests with adequate performance characteristics. Healthcare systems would need to implement such tests. Rapid serological tests with performance characteristics similar to the reference standard test used to characterise seronegative patients in the RECOVERY trial¹¹ (that is, the 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.

Applicability—None of the included randomised trials including RECOVERY enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. Fortunately, very few children become critically ill with covid-19. For those who do and are seronegative, 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 information—In terms of monitoring, although the available trials have not convincingly shown that casirivimab-imdevimab results in allergic reactions, the possibility remains. Administer 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.

Interleukin-6 receptor blockers (published 06 July 2021)

The recommendation addressing IL-6 receptor blockers was informed by results from the same living systematic review and network meta-analysis, and an independent prospective meta-analysis from the WHO Rapid Evidence Appraisal for covid-19 group.¹⁹ The living 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, unpublished data. The prospective meta-analysis pooled data from 22 RCTs with 10 156 participants.¹⁹ (see MAGICapp for detailed description of evidence and subgroup analyses underpinning the recommendation <https://app.magicapp.org/#/guideline/nBk01E>).

Understanding the recommendation on IL-6 receptor blockers

We recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab) for patients with severe or critical covid-19. Of note, corticosteroids have previously been strongly recommended in patients with severe and critical covid-19, and we recommend patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers.

Balance of benefit and harm—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 infection, the evidence summary may under-represent the risks of treatment with IL-6 receptor blockers. Furthermore, the trials of IL-6 receptor blockers that inform this recommendation were mostly performed in high income countries where the risk of infectious complications may be less than in some other parts of the world, and so the generalisability of the data on these adverse events is 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 the low certainty around 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 account of the small reduction in mortality.

Resource implications, 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 take account of 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 disease over those with severe disease), 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 (95% confidence interval 9 to 47 fewer deaths) in critically ill patients compared with 12 fewer deaths per 1000 (4 to 19 fewer deaths) in the severely ill.

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 to be used in children, and therefore there could be a preference for tocilizumab in this subgroup.

Ivermectin (published 31 March 2021)

The recommendation addressing ivermectin was informed by results from a systematic review and network meta-analysis that pooled data from 16 RCTs with 2407 participants. Of the included trials, 75% examined patients with non-severe disease and 25% included both severe and non-severe patients. None of the included RCTs enrolled children under 15 years old or pregnant women. Given this, the applicability of this recommendation to children is uncertain, though there is no rationale to suggest they would respond differently.

No changes were made for the ivermectin recommendation in this sixth 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.^{20 21} However, the updated evidence summary from the living network meta-analysis is consistent with our previously made recommendation. This updated evidence summary will be fully considered by the GDG for the next iteration of this guideline.

Understanding the recommendation on ivermectin

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

Balance of benefit and harm—For most important outcomes, the 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 seem to suggest benefit

with ivermectin. The picture was similar for other important outcomes, including mechanical ventilation, hospital admission, duration of hospitalisation, and viral clearance. The very low certainty of evidence was a critical factor in the recommendation.

Ivermectin may have little or no effect on time to clinical improvement (low certainty evidence) and may increase the risk of adverse effects leading to drug discontinuation (low certainty evidence). A recommendation to only use a drug in the setting of a clinical trials is appropriate when there is very low certainty evidence and future research has a large potential for reducing uncertainty about the effects of the intervention and for doing so at reasonable cost.

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

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

Resource implications, feasibility, equity, and human rights—Although the cost of ivermectin may be low per patient, the GDG 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.

Hydroxychloroquine (published 17 December 2020)

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

Understanding the recommendation on hydroxychloroquine

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

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

Hydroxychloroquine may increase the risk of diarrhoea and nausea or vomiting, a finding consistent with evidence from its use in other conditions. Diarrhoea and vomiting may increase the risk of hypovolaemia, hypotension, and acute kidney injury, especially in

settings where healthcare resources are limited. Whether and to what degree hydroxychloroquine increases the risk of cardiac toxicity, including life-threatening arrhythmias, when used in patients with covid-19 is uncertain.

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

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

Values and preferences—Applying the agreed values and preferences (box 2), the GDG inferred that almost all well informed patients would not want to receive hydroxychloroquine given the evidence suggesting there was probably no effect on mortality or need for mechanical ventilation and that there was a risk of adverse events including diarrhoea and nausea/vomiting. The GDG did not expect there would be much variation in values and preferences among patients when it came to this intervention.

Resource implications, feasibility, equity, and human rights—Hydroxychloroquine and chloroquine are relatively inexpensive compared with other drugs used for covid-19 and are already widely available, including in low income settings. Despite this, the 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.

Lopinavir-ritonavir (published 17 December 2020)

The recommendation addressing lopinavir-ritonavir was informed by the same systematic review and network meta-analysis, including data from seven RCTs with 7429 participants. None of the included RCTs enrolled children or adolescents under the age of 19 years, so the applicability of this recommendation to children is uncertain.

Understanding the recommendation on lopinavir-ritonavir

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

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

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

Subgroup analysis indicated no effect modification based on severity of illness (comparing either critical versus severe/non-severe or non-severe versus critical/severe) or age (comparing those aged <70 years versus those ≥70 years). As there was no evidence of a statistical subgroup effect, we did not formally evaluate credibility. Although the trials did not report subgroup effects by time from symptom onset, many of the trials enrolled patients early in the disease course. The GDG therefore felt that the evidence applies to all patients with covid-19.

Values and preferences—Applying the agreed values and preferences (box 2), the guideline 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.

Remdesivir (published 20 November 2020)

The recommendation addressing remdesivir was informed by the same systematic review and network meta-analysis, including data from four RCTs with 7333 participants hospitalised for covid-19. Of note, none of the included RCTs enrolled children or adolescents under the age of 19 years, and, although older people were included in the trials, their outcomes were not reported separately. Also, there is no pharmacokinetic or safety data on remdesivir for children. Given this, the applicability of this recommendation to children is currently uncertain.

Understanding the recommendation on remdesivir

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

When moving from evidence to the conditional recommendation against the use of remdesivir for patients with covid-19, the 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 benefit and harm—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 disease 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 ([box 2](#)), the guideline 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.

Resource implications, feasibility, equity, and human rights—A novel therapy typically requires higher certainty evidence of important benefits than is currently available for remdesivir, preferably supported wherever possible by cost effectiveness analysis. In the absence of this information, the GDG raised concerns about opportunity costs and the importance of not drawing attention and resources away from best supportive care or the use of corticosteroids in severe covid-19. It was noted that, currently, remdesivir is administered only by the intravenous route and global availability is limited.

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

Corticosteroids (published 4 September 2020)

On 17 July 2020 the 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.

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)⁵ rather than the initial ISARIC cohort study that likely overestimates current mortality risks

at the global level.²² 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%.

Understanding the recommendations on corticosteroids

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

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

The applicability of the recommendation is less clear for populations that were under-represented in the considered trials, such as children, patients with tuberculosis, and those who are immunocompromised. In considering potential contraindications to short term systemic corticosteroids in such patients, clinicians must determine if they warrant depriving a patient of a potentially lifesaving therapy. Clinicians should exercise caution in use of corticosteroids in patients with diabetes or underlying immunocompromise. The 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.

Balance of benefit and harm—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 and 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 0.93); 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 was deemed of critical importance to patients, with little or no anticipated variability in their preference to be offered treatment if severely ill from covid-19.

Resource implications, feasibility, equity, and human rights—Systemic corticosteroids are low cost, easy to administer, and readily available globally. Dexamethasone and prednisolone are among the most commonly listed medicines in national essential medicines lists; listed by 95% of countries. Accordingly, systemic corticosteroids are among a relatively small number of interventions for covid-19 that have the potential to reduce inequities and improve equity in health. Those considerations influenced the strength of this recommendation.

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

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

Who does it apply to? This recommendation applies to patients with non-severe disease regardless of their hospitalisation status. The 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* hyperinfection associated with corticosteroid therapy, diagnosis or empiric treatment may be considered in endemic areas if steroids are used.

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

Values and preferences—The weak or conditional recommendation was driven by likely variation in patient values and preferences. The 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.

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

Uncertainties, emerging evidence, and future research

The guideline recommendations for covid-19 therapeutics demonstrate remaining uncertainties concerning treatment effects for all outcomes of importance to patients. There is also a need for better evidence on prognosis and values and preferences of patients with covid-19.

Here we outline key uncertainties for casirivimab-imdevimab identified by the GDG, adding to those for corticosteroids in the first version, remdesivir in the second version, hydroxychloroquine and lopinavir-ritonavir in the third version, ivermectin in the fourth version, and IL-6 receptor blockers in the fifth version of the living guideline. These uncertainties may inform future research—that is, the production of more relevant and reliable evidence to inform policy and practice. We also outline emerging evidence in the rapidly changing landscape of trials for covid-19.

Casirivimab-imdevimab

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

IL-6 receptor blockers

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

Ivermectin

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

improvement. Also, a better characterisation of potential harms with ivermectin in patients with covid-19 is important.

Hydroxychloroquine and lopinavir-ritonavir

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

Remdesivir

Remaining uncertainties include effects on:

- Critical outcomes of interest, particularly those that impact resource allocation, such as the need for mechanical ventilation, duration of mechanical ventilation, and duration of hospitalisation.
- Specific subgroups, such as different severities of illness, different time (days) since onset of illness, children and older adults, pregnant women, duration of therapy.
- Long term outcomes (such as 1-year endpoint) examining mortality or long term quality of life.
- Long term safety and rare but important side effects.
- Patient-reported outcomes such as symptom burden.
- Outcomes when used in combination with other agents such as, but not limited to, corticosteroids.
- Impact on viral shedding, viral clearance, patient infectivity.

Corticosteroids

Remaining uncertainties include effects on:

- Long term mortality and functional outcomes in covid-19 survivors.
- Patients with non-severe covid-19 (that is, pneumonia without hypoxaemia).
- When used in combination with additional therapies for covid-19, such as novel immunomodulators. It will become increasingly important to ascertain how these interact with systemic corticosteroids. All investigational therapies for severe and critical covid-19 (including remdesivir) should be compared with systemic corticosteroids or evaluated in combination with systemic corticosteroids versus systemic corticosteroids alone.
- Immunity and the risk of a subsequent infection, which may affect the risk of death after 28 days.
- By different steroid preparation, dosing, and optimal timing of drug initiation.

Emerging evidence

The unprecedented volume of planned and ongoing studies for covid-19 interventions—over 4200 RCTs as of 26 May 2021—implies that more reliable and relevant evidence will emerge to inform policy and practice.² An overview of registered and ongoing trials for covid-19 therapeutics is available from the Infectious Diseases Data Observatory, through their living systematic review of covid-19 clinical trial registrations² and WHO website (<https://www.covid-nma.com/dataviz/>).

Although most of these studies are small and of variable methodological quality, some large, international platform trials (such as RECOVERY and SOLIDARITY) are better equipped to provide

robust evidence for several potential treatment options. Such trials can also adapt their design, recruitment strategies, and selection of interventions based on new insights.

How patients were involved in the creation of this article

The guideline GDG included four patients who previously had covid-19. Their perspectives were crucial in considering the values and preferences associated with IL-6 receptor blockers, ivermectin, hydroxychloroquine, lopinavir-ritonavir, remdesivir, and corticosteroids.

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

Competing interests: All GDG members have completed the WHO interest disclosure form. All authors have completed the *BMJ* Rapid Recommendations interest of disclosure form. The WHO, MAGIC and *The BMJ* judged that no GDG member had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the GDG to make fully informed decisions. MAGIC and *The BMJ* assessed declared interests from other co-authors of this publication and found no relevant conflicts of interests.

Provenance and peer review: This publication was commissioned by *The BMJ* in partnership with WHO and the MAGIC Evidence Ecosystem Foundation, in the context of the *BMJ* Rapid Recommendations. Pre-publication internal and external peer-review managed by WHO, and internal review at *The BMJ*. Post-publication review through rapid responses on *bmj.com* and through MAGICapp.

We thank all the following collaborators who contributed to this endeavour, as detailed in the WHO guidance (see link in box 1)

- World Health Organisation (WHO) Secretariat for Therapeutics and COVID-19

- External reviewers for WHO

We also thank

- The living systematic review and network meta-analysis team, led by investigators Reed Siemieniuk and Romina Brignardello-Petersen at McMaster University, Canada

- *BMJ* editorial team of Greg Cotton (technical editor), Navjoyt Ladher (head of education), and Will Stahl-Timmins (data graphics designer) for their work on this living guideline publication in *The BMJ*

- Brittany Maguire, Philippe Guerin, Lorenzo Arena and Sumayyah Rathan for providing up to date data on ivermectin trials from the Infectious Diseases Data Observatory (IDDO) living systematic review for covid-19 clinical trial registration (<https://www.iddo.org/research-themes/covid-19/live-systematic-clinical-trial-review>)

- Andrew Owen (University of Liverpool, UK) for contributions on pharmacological considerations and analyses

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