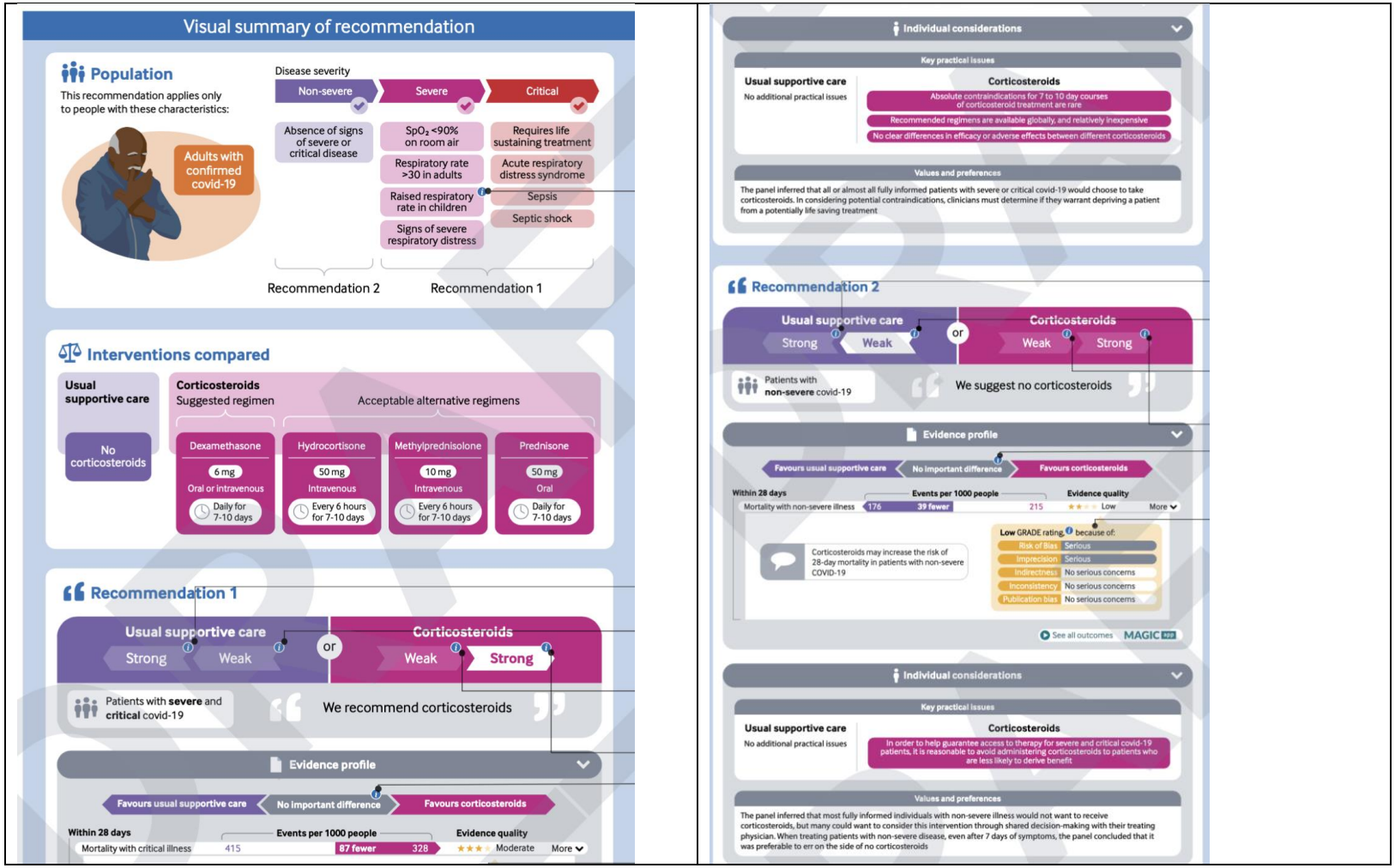
A living WHO guideline on drugs for the treatment and prevention of covid-19

Infographic 1 (Screenshots here. now with BMJ for final technical editing, through interactions with MAGIC, will check consistence with WHO guidance)



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Abstract

Clinical question: What is the role of systemic corticosteroids in the treatment of patients with covid-19?

New recommendation/s: This living guidance contains a strong recommendation for systemic corticosteroids in patients with severe and critical covid-19 and a weak/conditional recommendation against systemic corticosteroids in patients with non-severe COVID-19. Corticosteroids are inexpensive and on the WHO list of essential medicines.

Understanding the recommendations: The panel made a strong recommendation for use because there is a lower risk of death among people treated with systemic corticosteroids (moderate certainty evidence) and they believe that all or almost all fully informed patients with severe and critical covid-19 would choose this treatment. In contrast, the panel concluded that patients with non-severe covid-19 would decline this treatment because they would be unlikely to benefit and may be harmed. Moreover, taking both a public health and a patient perspective, the panel warned that indiscriminate use of any therapy for covid-19 would potentially rapidly deplete global resources and deprive patients who may benefit from it most as potentially life-saving therapy.

The evidence: A living systematic review and network meta-analysis, supported by a prospective meta-analysis with data from eight randomized trials (7184 participants), found that systemic corticosteroids probably reduce 28-day mortality in patients with critical covid-19 (moderate certainty evidence; 87 fewer deaths per 1000 patients, 95% CI 124 fewer to 41 fewer), and also in those with severe disease (moderate certainty evidence; 67 fewer deaths per 1000 patients, 95% CI 100 fewer to 27 fewer). In contrast, systemic corticosteroids may increase the risk of death in patients without severe covid-19 (low certainty evidence; absolute effect estimate 39

more per 1000 patients, 95% CI 12 fewer to 107 more). Systemic corticosteroids probably reduce the need for invasive mechanical ventilation and harms are likely to be minor (indirect evidence).

How this guideline was created: This guideline reflects an innovation from the WHO and the MAGIC Evidence Ecosystem Foundation, driven by an urgent need for global collaboration to provide trustworthy and living covid-19 guidance. A standing international panel of content experts, patients, clinicians and methodologists (no conflicts of interest declared) produce recommendations. The panel follows standards, methods, processes and platforms for trustworthy guideline development using the GRADE approach. We apply an individual patient perspective while considering contextual factors (i.e. resources, feasibility, acceptability, equity) for countries and health care systems.

Updates: This is a living guideline. Work is underway on evaluating new evidence on corticosteroids and for other covid-19 drugs (e.g. remdesivir and hydroxychloroquine) and recommendations will be published as updates to this guideline.

Readers note: This is version 1 of the living guideline, published on XXXX (*BMJ* 2020;insert version number). Updates will be labelled as version 2, 3 etc. When citing this article, please cite the version number.

Submitted: August 28

Accepted: August 31?

Provenance (standard note appearing at the end of BMJ publications)**:**

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 by WHO, and internal review at The BMJ. Post-publication review on bmj.com on rapid responses and through MAGICapp.

MAIN TEXT

As of 12 August 2020 (update with final numbers from WHO), 20 162 474 people worldwide have been diagnosed with covid-19, according to the international World Health Organization (WHO) dashboard.[1] The pandemic has claimed 737 417 lives, and a resurgence in the number of new cases and continued growth is some countries has threatened high- and low-resource countries alike.

The covid-19 pandemic—which can also be characterised as an infodemic, given the explosion of research combined with misinformation and hoaxes—has demonstrated a need for trustworthy, accessible, and regularly updated (living) guidance to place emerging findings into context and give clear recommendations for clinical practice. This living guideline responds to emerging evidence on existing and new drug treatments for covid-19 from trials (see Infectious Diseases Data Observatory for registered and ongoing trials, see table for corticosteroids-trials in appendix 4 on bmj.com, insert 2 refs). The living network meta-analysis associated with this guideline will incorporate new trial data as the evidence base increases and allow for analysis of comparative effectiveness of

multiple covid-19 treatments.[2] This network meta-analysis and other related publications are included in **Box 1**. We will also include other relevant evidence on long term safety, prognosis and patient values and preferences related to covid-19 treatments to inform the living guidance.

BOX 1: Linked publications (work with BMJ, WHO and JAMA to get final references right)

Guidance:
Lamontagne F, Agoritsas T, MacDonald H, et al. A living WHO guideline on drugs for the treatment and prevention of COVID-19. BMJ 2020…

World Health Organization. Corticosteroids for COVID-19. Interim guidance. Insert link to guidance on WHO website

MAGICapp (Per to insert widget link)

Systematic reviews:

Siemieniuk RAC, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ 2020 (insert right details and doi)

Sterne J…..Prospective meta-analysis of randomized trials for corticosteroids for covid-19. JAMA (insert right title and details)

How to use this guideline?

This is a living guideline and so the recommendations included here will be updated, and new recommendations will be added on other therapies for covid-19. The infographic provides a summary of the recommendations and supporting evidence, 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.

The standing guideline panel applied the WHO severity definitions based on clinical indicators,[3] in order to align with other WHO guidance to define covid-19.[4] These definitions avoid reliance on access to health care to define patient subgroups. **Table 1** is adapted from WHO covid-19 disease severity categorization. This guideline is presented by drug and by patient population. The evidence related to the effect of each drug may lead the panel to adapt the specific population one drug would apply to.

Box 3 lists the information that has emerged since the panel created recommendations (for corticosteroids; July 17 2020) but before the guideline went to press. Rapid responses on bmj.com will highlight evidence that have emerged since this version of the guideline was published. As new evidence emerges the WHO, MAGIC and BMJ Rapid Recommendations team will make a judgment on

whether and to what extent it may alter or add to existing recommendations and will update and publish guidance as the evidence itself if published. Updates currently in progress include recommendations on the use of hydroxychloroquine and remdesivir.

Box 3: Updates to this Living Guideline

New evidence which has emerged after initial publication

Date	Trigger	Action
August 12 2020	Metcovid (insert ref)	This additional trial on corticosteroids was published after the panel created recommendations on July 17. The trial data - pertaining to critically ill participants - was considered by the panel and deemed not to change the recommendation.

Table 1: WHO definitions of disease severity for covid-19

Critical covid-19	Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock or other conditions that would normally require the provision of life-sustaining therapies, such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
Severe covid-19	Defined by any of: • oxygen saturation < 90% on room air. • respiratory rate > 30 breaths per minute in adults and children > 5 years old; ≥ 60 in children less than 2 months; ≥ 50 in children 2–11 months; and ≥ 40 in children 1–5 years old.

	• signs of severe respiratory distress (i.e. 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.
Caution: The panel noted that the oxygen saturation threshold of 90% to define severe covid-19 was arbitrary and should be interpreted cautiously when used for determining which patients should be offered systemic corticosteroids. For example, clinicians must use their judgement to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient suffering from chronic lung disease. Similarly, a saturation above 90–94% on room air may be abnormal if the clinician suspects that this number is on a downward trend. Generally, if there is any doubt, the panel suggested erring on the side of considering the illness as severe.	

What triggered this version of the guideline?

A preliminary report of the RECOVERY trial June 2020, suggested that dexamethasone reduced mortality, with a subgroup analysis suggesting the benefit to be restricted to patients with severe and critical covid-19.[5] This evidence was complemented by new data from six randomized trials of corticosteroids reporting mortality data by subgroup in a prospective meta-analysis of randomized trials for corticosteroid therapy for covid-19 (ref JAMA). The data were made immediately available for the guideline panel, allowing the

WHO guidance to be peer-reviewed and published simultaneously with the prospective meta-analysis and 3 of the individual trials (refs JAMA).

Box 3: How this living guideline was created (see MAGICapp for details, MAGIC team to insert widget)

This guideline represents an innovation from the WHO, MAGIC Evidence Ecosystem Foundation (MAGIC) and The BMJ. It is driven by an urgent need for global collaboration to provide trustworthy and living guidance, rapidly informing policy and practice worldwide during an outbreak of an emerging infectious disease, such as this 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 the most up to date, evidence based and user-friendly information and adaptation.

Standards, methods and processes for living and trustworthy guidance

The panel produced the recommendations through an innovative process, following standards for trustworthy guideline development using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, in full compliance with the *WHO*

Handbook for guideline development 2nd edition,[6] the Institute of Medicine and the Guideline International Network (G-I-N).[7] Details are provided in MAGICapp (MAGIC team to insert widget).

Selection and support of the panel

An international, guideline development panel was composed of 23 individuals, of whom 21 were content experts (clinicians, methodologists, scientists) and 2 were patients who survived covid-19.[6] The Methods Chair (methodological expertise) and a Clinical Chair (content expertise) guided the panel discussions. Four resource persons with methodologic expertise assisted the Methods Chair, and 15 observers (12 from WHO, 3 from MAGIC) attended the panel meetings but did not directly participate in discussions. Following consultation with the Methods Chair and MAGIC, invitations were sent out to candidate panel members by the WHO with the aim of achieving balance within the panel in terms of gender, geography, expertise, patient representation. No conflict of interest was identified for any panel member. As per the *WHO Handbook*, the panel aimed to create a recommendation based on consensus but elected, at the beginning of the first panel meeting, to call a vote if a consensus could not be reached. Before discussions started, the panel determined that a simple majority would provide the direction of the recommendation and that 80% would be required to make a strong recommendation.

Guideline perspective, outcomes, values and preferences

The target audience for this guidance consists primarily of clinicians, but secondarily of patients and health care decision-makers. The panel considered an individual patient perspective but also took contextual factors (e.g. resources, feasibility, acceptability, equity) into account to accommodate global re-use and adaptation for countries and health care systems. During all discussions which occurred via email and during both meetings, the Methods Chair actively reminded the panel that guidelines were designed to inform the care of the average patient and, therefore, that they should attempt to consider the values and preferences of the average patient.

During a pandemic, access to health care may vary over time and between different countries. The panel defined covid-19 by clinical severity and mutually exclusive definitions are provided above in **Table 1**. For example, the panel assumes that critical illness due to covid-19 is incompatible with life, unless life-sustaining therapies are instituted and severe patients are treated in hospitals and receive oxygen or non-invasive ventilation, if available.

Ahead of the first meeting, panel members, including two COVID-19 survivors, were asked to consider a list of outcomes and deemed relevant to COVID-19 research. They were asked to consider the importance of each outcome and whether they agreed with a hierarchy ranging from “critically important” to “not very important”. In doing so, each member was asked to consider the perspective of the patients and were instructed to make their recommendation on the basis not on their own values and preferences, but rather on those of

COVID-19 patients around the world. One source of their information in this regard would be conversations with patient panel members as the discussion proceeded. Another would be their own experience in shared decision-making with patients and families.

Sources of evidence

To create recommendations, the panel relied on evidence synthesized in a living network meta-analysis led by MAGIC[2], which is iteratively tracking the development of evidence from randomized controlled trials (RCTs); where relevant prospective meta-analysis of RCTs conducted by a WHO clinical research working group (insert ref JAMA)[8]; relevant additional published evidence such as about the safety of systemic corticosteroids in distinct but relevant patient populations.[9] The lead investigators responsible for each meta-analysis rated the certainty of the evidence independently, followed by re-assessment by the guideline panel.

Derivation of absolute effects for drug treatments

Using the pooled relative risk from the meta-analyses and the best available current evidence of prognosis in patients with covid-19 (e.g. pooled control event rates for each subgroup from included trials), we calculated the absolute effect estimates that were presented to the guideline panel members in the form of GRADE evidence summaries.

Of note, baseline risks, and thus absolute effects, may vary significantly geographically and over time. As such, users of this guideline may prefer estimating absolute effects by using local event rates. Taking corticosteroids as an example, if the baseline event rate in one area is much lower, the expected benefit from steroids will also be lower in absolute terms. Notwithstanding, the panel attributed a high value to even a small reduction in mortality and concluded that the recommendations for corticosteroids apply across baseline event rates.

The guidance

Systemic corticosteroids

On 17 July 2020, the panel reviewed evidence from eight RCTs (7184 patients) evaluating systemic corticosteroids versus usual care in covid-19,[5] of which seven reported mortality data by subgroup. Mortality data from one trial, GLUCOCOVID, were not incorporated in the Summary of Finding for mortality because the mortality outcome data was not available by subgroup). The guideline was triggered by the publication of the RECOVERY trial and complemented by data on mortality specifically for the subgroup of critically ill patients from 6 new trials synthesized in the prospective meta-analysis (insert ref JAMA). The panel did not consider transdermal or inhaled administration, high-dose or long-term regimens, or prophylaxis. **Box 4** outlines the evidence. The panel did not reach consensus on recommendation one and this was made by vote. The second recommendation was made by consensus. More details on the underlying panel discussions can be found in the WHO guidance (see **Box 1** for link).

Box 4: Outline of the evidence on systemic corticosteroids

While six trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalized patients with covid-19 and reported mortality data by subgroup, whereas the smaller GLUCOCOVID trial, which also enrolled hospitalized, patients did not. The panel considered the results of a subgroup analysis of the RECOVERY trial suggesting that the relative

effects of systemic corticosteroids varied as a function of the level of respiratory support received at randomization. On the basis of the peer-reviewed criteria for credible subgroup effects,[10] the panel determined that the subgroup effect was sufficiently credible to warrant separate recommendations for severe and non-severe covid-19.

Population - There were data from 1703 critically ill patients in seven trials. RECOVERY, the largest of the seven trials randomized 6425 hospitalized patients in the United Kingdom (2104 were randomized to dexamethasone and 4321 were randomized to usual care). At the time of randomization, 16% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without non-invasive ventilation), and 24% were receiving neither.[5] The mortality data from six other smaller trials included approximately 700 critically ill patients (definitions of critical illness varied across studies) enrolled up to 9 June 2020, approximately four-fifths were invasively mechanically ventilated; approximately one-half were randomized to receive corticosteroid therapy, and one-half randomized to no corticosteroid therapy. For patients with severe and non-severe covid-19, data was only available by relevant subgroup in RECOVERY (3883 patients with severe and 1535 patients with non-severe covid-19). Because the mortality data from one trial (GLUCOCOVID, n=63) was not reported separately for severe and non-severe covid-19,[11] the panel reviewed only the data pertaining to the outcome of mechanical ventilation from this trial.

Interventions – RECOVERY evaluated the effects of dexamethasone 6 mg given once daily (oral or intravenous) for up to 10 days. Other corticosteroid regimens included: dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID,

CoDEX); hydrocortisone 200 mg daily for 4 to 7 days followed by 100 mg daily for 2 to 4 days and then 50 mg daily for 2 to 3 days (one trial, CAPE-COVID); hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP); methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI); and methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (one trial, GLUCOCOVID).[2] Seven of the trials were conducted in individual countries (Brazil, China, Denmark, France, Spain) whilst REMAP-CAP was an international study (recruiting in 14 European countries, Australia, Canada, New Zealand, Saudi Arabia and United Kingdom).

Outcomes - All trials reported mortality 28 days after randomization, except for one trial at 21 days and the another at 30 days.

The recommendations

#1: We recommend systemic corticosteroids rather than no systemic corticosteroids for the treatment of patients with severe and critical covid-19 (strong recommendation, based on moderate certainty evidence).

Understanding the recommendation

Who it applies to - This recommendation applies to patients with severe and critical covid-19. The panel judged that all or almost all fully informed patients with severe covid-19 would choose to take systemic corticosteroids. The recommendation should apply to patients with severe and critical covid-19 even if they cannot be hospitalized 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 life-saving therapy. Clinicians should exercise caution in use of corticosteroids in patients with diabetes or underlying immunocompromise. The panel was confident that clinicians using these guidelines would be aware of additional potential side effects and contraindications to systemic corticosteroid therapy, which may vary geographically in function of endemic microbiological flora.

Balance of benefit and harm - Ultimately, the panel made its recommendation on the basis of the moderate certainty evidence of a 28-day mortality reduction of 8.7% in the critically ill and 6.7% in patients with severe covid-19 who were not critically ill, respectively. *S*ystemic corticosteroids compared with no corticosteroid therapy probably reduce the risk of 28-day mortality (moderate certainty evidence; RR 0.80, 95% CI 0.70–0.91; absolute effect estimate 87 fewer deaths per 1000 patients, 95% CI 124 fewer to 41 fewer). In patients with severe COVID-19, systemic corticosteroids also probably reduce the risk of death (moderate certainty evidence; RR 0.80, 95% CI 0.70–0.92; absolute effect estimate 67 fewer deaths per 1000 patients, 95% CI 100 fewer to 27 fewer). The effects of systemic corticosteroids on other outcomes are described in the summary of findings (See Infographic and link to MAGICapp [insert widget link]).

Overall, the panel has, however, high certainty that the adverse effects when considered together are sufficiently limited in importance and frequency that, while generally of low certainty, these data were reassuring and suggested that corticosteroids are not associated with an increased risk of adverse events, beyond likely increasing the incidence of hyperglycaemia (moderate certainty evidence; absolute effect estimate 46 more per 1000 patients, 95% CI 23 more to 72 more) and hypernatremia (moderate certainty evidence; 26 more per 1000 patients, 95% CI 13 more to 41 more). In contrast with new agents proposed for covid-19, clinicians have a vast experience of systemic corticosteroids and the panel was reassured by their overall safety profile.

Values and preferences - The panel took an individual patient perspective to values and preferences but, given the burden of the pandemic for health care 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.[12] Dexamethasone and prednisolone are among the most commonly listed medicines in national essential medicines lists; listed by 95% of countries. Accordingly, systemic corticosteroids are among a relatively small number of interventions for covid-

19 that have the potential to reduce inequities and improve equity in health. Those considerations influenced the strength of this recommendation.

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

Recommendation #2: We suggest not to use corticosteroids in the treatment of patients with non-severe covid-19 (weak/ conditional recommendation, based on low certainty evidence).

Who it applies to - This recommendation applies to patients with non-severe disease regardless of their hospitalization status. The panel noted that patients with non-severe covid-19 would not normally require acute care in hospital or respiratory support, but that in some jurisdictions, these patients may be hospitalized for isolation purposes only, in which case they should not be treated with systemic corticosteroids. 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 (e.g. patients with chronic obstructive pulmonary disease need not discontinue a course of systemic oral corticosteroids; or other chronic autoimmune diseases).
- If the clinical condition of patients with non-severe covid-19 worsens (i.e. increase in respiratory rate, signs of respiratory distress or hypoxaemia) they should receive systemic corticosteroids (see recommendation #1).
- 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 is 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 harm
- s for the woman and the preterm newborn should be discussed with the woman to ensure an informed decision, as this assessment may vary depending on the woman's clinical condition, her wishes and that of her family, and available health care resources.
- 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; RR 1.22, 95% CI 0.93–1.61; 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 (i.e. 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 (See Infographic and link to MAGICapp [insert widget link])

Values and preferences – The weak/ conditional recommendation was driven by likely variation in patient values and preferences. The panel judged that most individuals with non-severe illness would decline systemic corticosteroids. However, many may want them following shared decision-making with their treating physician. [6]

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 appear to derive any benefit from this intervention

Practical issues for corticosteroids (check content in Infographic 1 consistent with WHO guidance as in text below)

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

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

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

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

Timing - The timing of therapy from onset of symptoms was discussed by the panel. The RECOVERY investigators reported a subgroup analysis suggesting that the initiation of therapy 7 days or more after symptom onset may be more beneficial than treatment initiated within 7 days of treatment onset. A post hoc subgroup analysis within the PMA did not support this hypothesis. While some panel members believed that postponing systemic corticosteroids until after viral replication is contained by the immune system may

be reasonable, many noted that, in practice, it is often impossible to ascertain symptom onset and that signs of severity frequently appear late (i.e. denote a co-linearity between severity and timing). The panel concluded that, given the evidence, it was preferable to err on the side of administering corticosteroids when treating patients with severe or critical COVID-19 (even if within 7 days of symptoms onset) and to err on the side of not giving corticosteroids when treating patients with non-severe disease (even if after 7 days of symptoms onset)."R

Uncertainty

The following uncertainties remain

- Long-term effect of systemic corticosteroids on mortality and functional outcomes in covid-19 survivors are unknown and will be the subject of future analyses of the evidence considered by the panel.
- The clinical effects of systemic corticosteroids in patients with non-severe covid-19 (i.e. pneumonia without hypoxaemia) remain unclear and may be studied further.
- As additional therapies emerge for covid-19, notably 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 to systemic corticosteroids vs. systemic corticosteroids alone.

- Other uncertainties include:
    - The impact of systemic corticosteroids on immunity and the risk of a subsequent infection, which may impact the risk of death after 28 days.
    - Steroid preparation, dosing and optimal timing of drug initiation.
    - Generalizability of study results to populations that were underrepresented in the trials considered by the panel (e.g. children, immunocompromised patients, patients with tuberculosis).
    - Generalizability in resource-limited settings (i.e. low- and middle-income countries).
    - Effect on viral replication.

Tables, Boxes and Infographics

Table 1: WHO definition of disease severity

Box 1: Linked resources for this BMJ Rapid Recommendations

Box 2: How this recommendation was created

Box 3: Updates to this living guideline

Box 4: Outline of the evidence on systemic corticosteroids.

Add appendix 2 WHO guidance: Characteristics of patients and trials included in systematic review of effects of systemic corticosteroids for COVID-19

Infographic 1: Will display PICO and SoF (identical with WHO guidance, check final numbers)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Plain text summary**
		Usual care	Corticosteroids		
Mortality in patients with critical illness 28 days	Relative risk 0.79 (95% CI 0.70–0.90) Data from 1703 patients in 7 studies	415 per 1000	328 per 1000	**Moderate** Due to serious risk of bias (lack of blinding)	Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with critical illness due to COVID-19
		Difference: **87 fewer per 1000 (95% CI 124 fewer – 41 fewer)**			

	Follow up: 28 days				
Mortality in patients with severe illness 28 days	Relative risk 0.80 (95% CI 0.70–0.92) Data from 3883 patients in 1 study Follow up: 28 days	334 per 1000	267 per 1000 Difference: **67 fewer per 1000** **(95% CI 100 fewer – 27 fewer)**	**Moderate** Due to serious risk of bias (lack of blinding)	Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with severe COVID-19
Mortality in patients with non-severe illness 28 days	Relative risk 1.22 (95% CI 0.93–1.61) Data from 1535 patients in 1 study Follow-up: 28 days	176 per 1000	215 per 1000 Difference: 39 more per 1000 **(95% CI 12 fewer – 107 more)**	**Low** Due to serious risk of bias (lack of blinding) and imprecision	Systemic corticosteroids may increase the risk of 28-day mortality in patients with non-severe COVID-19
		116 per 1000	86 per 1000		

Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (95% CI 0.59–0.93) Data from 5481 patients in 2 studies Follow up: 28 days	Difference: **30 fewer per 1000 (95% CI 48 fewer – 8 fewer)**		**Moderate** Due to serious risk of bias (risk of bias due to lack of blinding)	Systemic corticosteroids probably reduce the risk of mortality
Duration of hospitalization	Data from 6425 patients in 1 study Follow up: not reported	13 Days (median)	12 Days (median)	**Low** Due to serious risk of bias (lack of blinding) and imprecision (CI includes no benefit)	Steroids may result in an important reduction in the duration of hospitalizations
		Difference: **1 lower**			
Time to symptom resolution	Not reported				
Duration of intensive care unit stay	Not reported				
Duration of mechanical ventilation	Not reported				

Serious adverse events (indirect evidence from ARDS, community-acquired pneumonia and sepsis populations)				
Gastrointestinal bleeding	Relative risk 1.06 (95% CI 0.85–1.33) (5403 patients, 30 studies)	48 per 1000 | 51 per 1000 Difference: **3 more per 1000 (95% CI 7 fewer – 16 more)**	**Low** Due to serious indirectness and serious imprecision	Corticosteroids may not increase the risk of gastrointestinal bleeding
Super-infections	Relative risk 1.01 (95% CI 0.90–1.13) (6027 patients, 32 studies)	186 per 1000 | 188 per 1000 Difference: **2 more per 1000 (95% CI 19 fewer – 24 more)**	**Low** Due to serious indirectness and serious imprecision	Corticosteroids may not increase the risk of super-infections
Hyperglycaemia	Relative risk 1.16 (95% CI 1.08–1.25) (8938 patients, 24 studies)	286 per 1000 | 332 per 1000 Difference: **46 more per 1000 (95% CI 23 more – 72 more)**	**Moderate** Due to serious indirectness	Corticosteroids probably increase the risk of hyperglycaemia

Hypernatraemia	Relative risk 1.64 (95% CI 1.32–2.03) (5015 patients, 6 studies)	40 per 1000 | 66 per 1000 Difference: **26 more per 1000 (95% CI 13 more – 41 more)**	**Moderate** Due to serious indirectness	Corticosteroids probably increase the risk of hypernatraemia
Neuromuscular weakness	Relative risk 1.09 (95% CI 0.86–1.39) (6358 patients, 8 studies)	69 per 1000 | 75 per 1000 Difference: **6 more per 1000 (95% CI 10 fewer – 27 more)**	**Low** Due to serious indirectness and serious imprecision	Corticosteroids may not increase the risk of neuromuscular weakness
Neuropsychiatric effects	Relative risk 0.81 (95% CI 0.41–1.63) (1813 patients, 7 studies)	35 per 1000 | 28 per 1000 Difference: **7 fewer per 1000 (95% CI 21 fewer – 22 more)**	**Low** Due to serious indirectness and serious imprecision	Corticosteroids may not increase the risk of neuropsychiatric effects
Stroke	Relative risk 2.07 (95% CI 0.45–9.61)	4 per 1000 | 8 per 1000 Difference: **4 more per 1000 (95% CI 2 fewer – 34 more)**	**Very low** Due to serious indirectness and	Whether or not corticosteroids impact the risk of stroke is uncertain

	(1105 patients, 3 studies)			very serious imprecision	
Myocardial infarction	Relative risk 0.91 (95% CI 0.45–1.82) (1080 patients, 3 studies)	30 per 1000	27 per 1000 Difference: **3 fewer per 1000 (95% CI 17 fewer – 25 more)**	**Very low** Due to serious indirectness and very serious imprecision	Whether or not corticosteroids impact the risk of myocardial infarction is uncertain

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References: To be updated based on final WHO guidance and JAMA publications (see Box 1)

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