A living WHO guideline on drugs for COVID-19

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Sections

Summary of recommendations

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New

The recommendations on corticosteroids for patients with COVID-19 represent the first living WHO guidance, published on September 2 (https://www.who.int/news-room/feature-stories/detail/who-updates-clinical-care-guidance-with-corticosteroid-recommendations), also published as BMJ Rapid Recommendations on September 4 2020 (https://www.bmj.com/content/370/bmj.m3379). This guidance represents a collaboration between the WHO, MAGIC and other collaborators in the evidence ecosystem (https://blogs.bmj.com/bmj/2020/09/04/trustworthy-and-living-guidance-for-covid-19-time-to-join-forces-in-the-evidence-ecosystem/)

Here you can find the same guidance in online, user-friendly formats, directly linked from the BMJ publication.We encourage re-use and adaptation of this living and trustworthy guidance, to reduce duplication and increase efficiency in the evidence ecosystem. Please contact Per Olav Vandvik (CEO of MAGIC per.vandvik@gmail.com) if you want to explore MAGICapp for this purpose, made freely available for organisations interested in tackling the COVID-19 pandemic and infodemic.

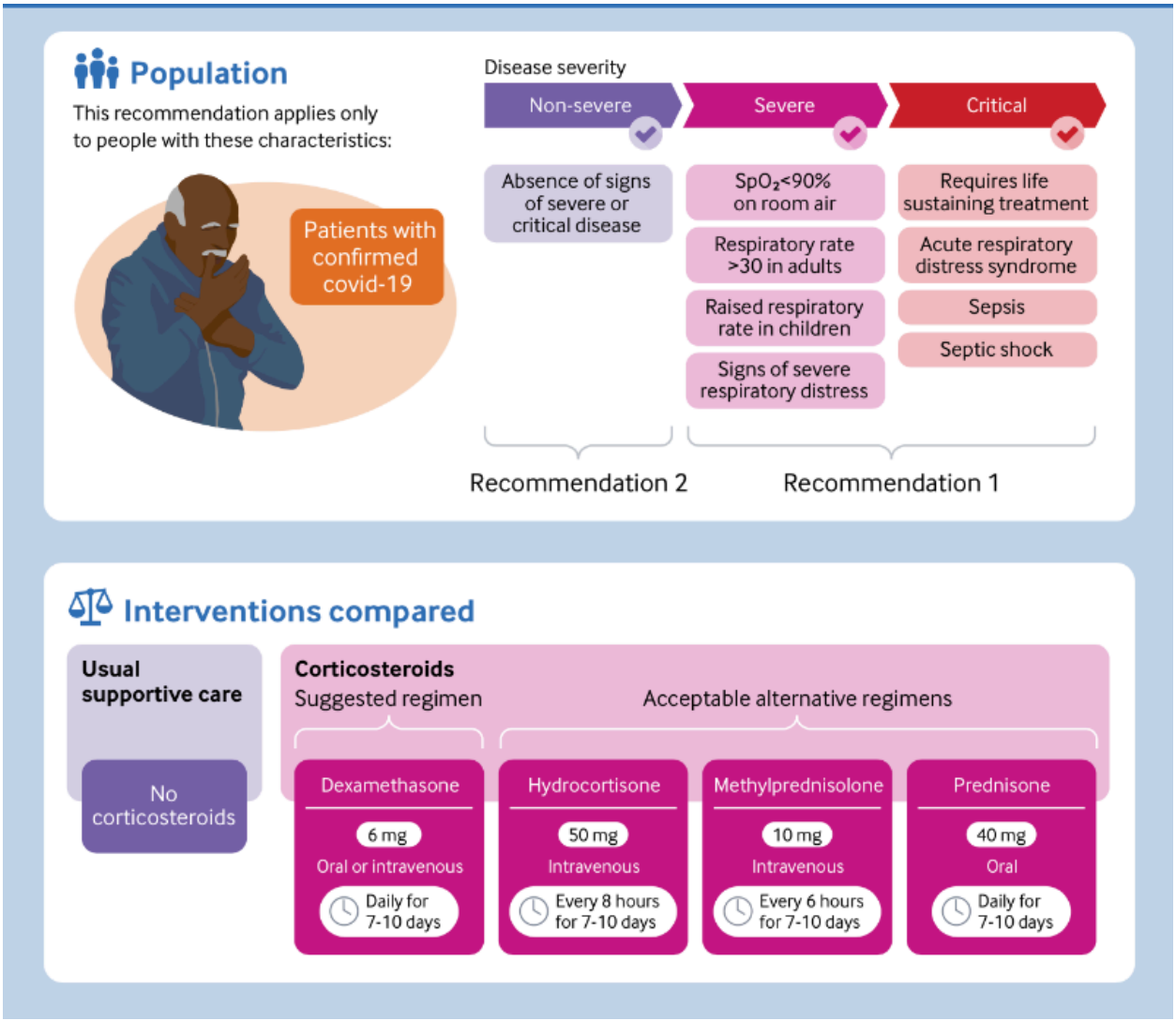
2 - What triggered this version of the guideline?

3 - The guidance

3.1 - Systemic corticosteroids

Info Box

About the patients and corticosteroid treatment options



3.1.1 - Recommendations for steroids in patients with COVID-19 infection

Strong recommendation

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

We recommend systemic corticosteroids rather than no corticosteroids

Weak recommendation against

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

We suggest not to use corticosteroids

4 - How to use this guideline

5 - How this guideline was created

1 - Why this living guideline

As of 1 September 2020, 25 327 098 people worldwide have been diagnosed with covid-19, according to the international World Health Organization (WHO) dashboard.[1] The pandemic has claimed 848 255 lives, and a resurgence in the number of new cases and continued growth is some countries has threatened high resource and low resource countries alike.

The covid-19 pandemic—and its related 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. An overview of registered and ongoing trials is available from the Infectious Diseases Data Observatory (see table of ongoing trials for corticosteroids in appendix 1 on bmj.com).[2] 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.[3] This network meta-analysis and other related publications are included in **box 1** in the BMJ publication (https://www.bmj.com/content/370/bmj.m3379). We will also use additional relevant evidence on long term safety, prognosis, and patient values and preferences related to covid-19 treatments to inform the living guidance.

New

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2 - What triggered this version of the guideline?

A preliminary report of the RECOVERY trial in June 2020 suggested that dexamethasone reduced mortality in covid-19 patients, with a subgroup analysis suggesting the benefit to be restricted to patients with severe and critical covid-19.[4] This evidence was complemented by new data from six randomised trials of corticosteroids reporting mortality data by subgroup in a prospective meta-analysis of randomised trials for corticosteroid therapy for covid-19.[5] 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 three of the individual trials.[6][7][8]

3 - The guidance

On 17 July 2020 the panel reviewed evidence from eight RCTs (7184 patients) evaluating systemic corticosteroids versus usual care in treatment of covid-19,[3] [5]of which seven 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 was not available by subgroup). The panel did not consider transdermal or inhaled administration of corticosteroids, high dose or long-term regimens, or prophylaxis. **Box 4** in the BMJ publication (https://www.bmj.com/content/370/bmj.m3379)outlines the evidence in more detail. The panel did not reach consensus on recommendation 1, which required a vote. The second recommendation was made by consensus. More details on the underlying panel discussions can be found in the WHO guidance document (https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1).

3.1 - Systemic corticosteroids

While six trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalised patients with covid-19 and reported mortality data by subgroup, whereas the smaller GLUCOCOVID trial, which also enrolled hospitalised 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 randomisation. On the basis of the peer reviewed criteria for credible subgroup effects,[9] 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 randomised 6425 hospitalised patients in the United Kingdom (2104 were randomised to dexamethasone and 4321 were randomised to usual care). At the time of randomisation, 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.[4] 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 80% were invasively mechanically ventilated; approximately 50% were randomised to receive corticosteroid therapy, and 50% randomised to no corticosteroid therapy. RECOVERY was the only trial reporting mortality data for patients with severe and non-severe COVID-19 (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,[10] 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 and CoDEX); hydrocortisone 200 mg daily for 4-7 days followed by 100 mg daily for 2-4 days and then 50 mg daily for 2-3 days (one trial, CAPE-COVID); hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP); methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI); and methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (one trial, GLUCOCOVID).[3] Seven of the trials were conducted in individual countries (Brazil, China, Denmark, France, Spain), while REMAP-CAP was an international study (recruiting in 14 European countries, Australia, Canada, New Zealand, Saudi Arabia, and UK).

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

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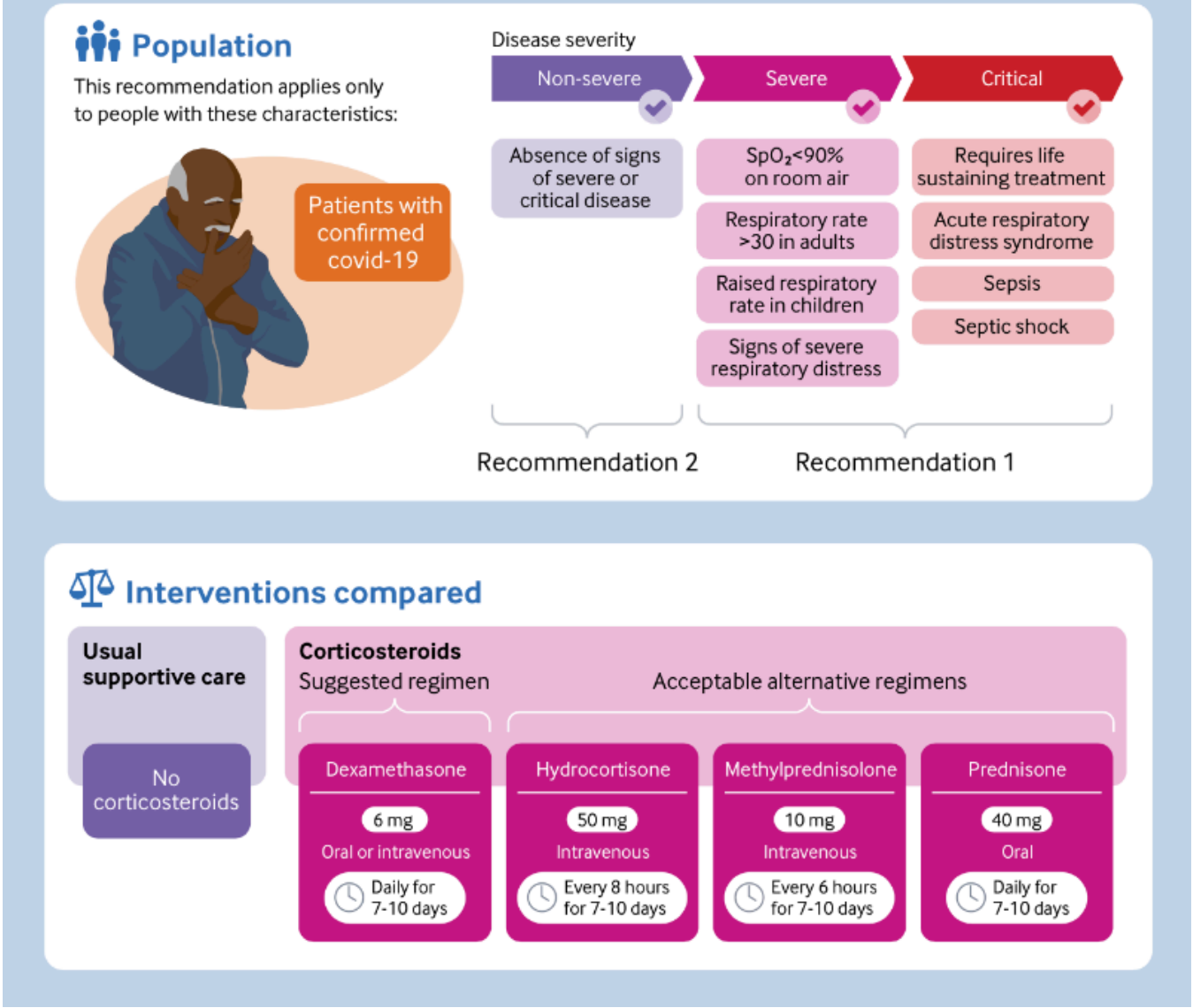
About the patients and corticosteroid treatment options



3.1.1 - Recommendations for steroids in patients with COVID-19 infection

On 17 July 2020, the panel reviewed evidence from eight RCTs (7184 patients) evaluating systemic corticosteroids versus usual care in covid-19,[3][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).

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

Strong recommendation

We recommend systemic corticosteroids rather than no corticosteroids

Practical Info

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

Duration—While more patients received corticosteroids in the form of dexamethasone 6 mg daily for up to 10 days, the total duration of regimens evaluated in the seven trials varied between five and 14 days, and treatment was generally discontinued at hospital discharge (that is, the duration of treatment could be less than the duration stipulated in the protocols).
Dose—The once daily dexamethasone formulation may increase adherence. A dose of 6 mg of dexamethasone is equivalent (in terms of glucocorticoid effect) to 150 mg of hydrocortisone (that is, 50 mg every 8 hours), 40 mg of prednisone, or 32 mg of methylprednisolone (8 mg every 6 hours or 16 mg every 12 hours).

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

Timing—The timing of therapy from onset of symptoms was discussed by the panel. The RECOVERY investigators reported a subgroup analysis suggesting that the initiation of therapy seven days or more after symptom onset may be more beneficial than treatment initiated within seven days of symptom onset. A post hoc subgroup analysis within the prospective meta-analysis did not support this hypothesis. While some panel members believed that postponing systemic corticosteroids until after viral replication is contained by the immune system may be reasonable, many noted that, in practice, it is often impossible to ascertain symptom onset and that signs of severity often appear late (that is, denote a co-linearity between severity and timing). The panel concluded that, given the evidence, it was preferable to err on the side of administering corticosteroids when treating patients with severe or critical covid-19 (even if within 7 days of symptoms onset) and to err on the side of not giving corticosteroids when treating patients with non-severe disease (even if after 7 days of symptoms onset).”

Rationale

Who does it apply to?
This recommendation applies to patients with severe and critical covid-19. The panel judged that all or almost all fully informed patients with severe covid-19 would choose to take systemic corticosteroids. The recommendation should apply to patients with severe and critical covid-19 even if they cannot be hospitalised or receive oxygen because of resource limitations.
The applicability of the recommendation is less clear for populations that were under-represented in the considered trials, such as children, patients with tuberculosis, and those who are immunocompromised. In considering potential contraindications to short term systemic corticosteroids in such patients, clinicians must determine if they warrant depriving a patient of a potentially lifesaving therapy. Clinicians should exercise caution in use of corticosteroids in patients with diabetes or underlying immunocompromise. The panel was confident that clinicians using these guidelines would be aware of additional potential side effects and contraindications to systemic corticosteroid therapy, which may vary geographically in function of endemic microbiological flora.

Balance of benefit and harm
Ultimately, the panel made its recommendation on the basis of the moderate certainty evidence of a 28 day mortality reduction of 8.7% in the critically ill and 6.7% reduction in patients with severe covid-19 who were not critically ill. Systemic corticosteroids compared with no corticosteroid therapy probably reduce the risk of 28 day mortality in critically ill patients with covid-19 (moderate certainty evidence; relative risk (RR) 0.80 (95% confidence interval 0.70 to 0.91); absolute effect estimate 87 fewer deaths per 1000 patients (95% CI 124 fewer to 41 fewer)). In patients with severe covid-19, systemic corticosteroids also probably reduce the risk of death (moderate certainty evidence; RR 0.80 (0.70 to 0.92); absolute effect estimate 67 fewer deaths per 1000 patients (100 fewer to 27 fewer)). The effects of systemic corticosteroids on other

outcomes are described in the summary of findings.

Overall, the panel has high certainty that the adverse effects when considered together are sufficiently limited in importance and frequency and suggested that corticosteroids administered in these doses for 7 to 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 hypernatremia (moderate certainty evidence; 26 more per 1000 patients (13 more to 41 more)). In contrast with new agents proposed for covid-19, clinicians have a vast experience of systemic corticosteroids, and the panel was reassured by their overall safety profile.

Values and preferences
The panel took an individual patient perspective to values and preferences but, given the burden of the pandemic for healthcare systems globally, also placed a high value on resource allocation and equity. The benefits of corticosteroids on mortality was deemed of critical importance to patients, with little or no anticipated variability in their preference to be offered treatment if severely ill from covid-19.

Resource implications, feasibility, equity, and human rights
Systemic corticosteroids are low cost, easy to administer, and readily available globally.17 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.

Clinical Question/ PICO

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

Summary

Outline of the evidence on systemic corticosteroids
While six trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalized patients with covid-19 and reported mortality data by subgroup, whereas the smaller GLUCOCOVID trial, which also enrolled hospitalized, patients did not. The panel considered the results of a subgroup analysis of the RECOVERY trial suggesting that the relative effects of systemic corticosteroids varied as a function of the level of respiratory support received at randomization. On the basis of the peer-reviewed criteria for credible subgroup effects,[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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard Care	Steroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 28 days	Relative risk 0.79 (CI 95% 0.7 - 0.9) Based on data from 1,703 patients in 7 studies. Follow up 28 days	415 per 1000	328 per 1000 Difference: **87 fewer** per 1000 (CI 95% 124 fewer - 41 fewer)	**Moderate** Due to serious risk of bias [1]	Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with critical illness due to COVID-19.
Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (CI 95% 0.59 - 0.93) Based on data from 5,481 patients in 2 studies. Follow up 28 days	116 per 1000	86 per 1000 Difference: **30 fewer** per 1000 (CI 95% 48 fewer - 8 fewer)	**Moderate** Due to serious risk of bias [2]	Systemic corticosteroids probably reduce the risk of mortality
Duration of hospitalization	Based on data from 6,425 patients in 1 studies. Follow up NR	13	12 Difference: **1 fewer**	**Low** Due to serious risk of bias, Due to serious imprecision [3]	Steroids may result in an important reduction in the duration of hospitalizations
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85 - 1.33) Based on data from 5,403 patients in 30 studies.	48 per 1000	51 per 1000 Difference: **3 more** per 1000 (CI 95% 7 fewer - 16 more)	**Low** Due to serious indirectness, Due to serious imprecision [4]	Corticosteroids may not increase the risk of gastrointestinal bleeding.
Super-infections	Relative risk 1.01 (CI 95% 0.9 - 1.13) Based on data from 6,027 patients in 32	186 per 1000	188 per 1000	**Low** Due to serious indirectness, Due to serious	Corticosteroids may not increase the risk of super-infections.

	studies.	Difference: **2 more** per 1000 (CI 95% 19 fewer - 24 more)	imprecision [5]	
Hyperglycaemia	Relative risk 1.16 (CI 95% 1.08 - 1.25) Based on data from 8,938 patients in 24 studies.	**286** per 1000 **332** per 1000 Difference: **46 more** per 1000 (CI 95% 23 more - 72 more)	**Moderate** Due to serious indirectness [6]	Corticosteroids probably increase the risk of hyperglycaemia.
Hypernatremia	Relative risk 1.64 (CI 95% 1.32 - 2.03) Based on data from 5,015 patients in 6 studies.	**40** per 1000 **66** per 1000 Difference: **26 more** per 1000 (CI 95% 13 more - 41 more)	**Moderate** Due to serious indirectness [7]	Corticosteroids probably increase the risk of hypernatremia.
Neuromuscular weakness	Relative risk 1.09 (CI 95% 0.86 - 1.39) Based on data from 6,358 patients in 8 studies.	**69** per 1000 **75** per 1000 Difference: **6 more** per 1000 (CI 95% 10 fewer - 27 more)	**Low** Due to serious indirectness, Due to serious imprecision [8]	Corticosteroids may not increase the risk of neuromuscular weakness.
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41 - 1.63) Based on data from 1,813 patients in 7 studies.	**35** per 1000 **28** per 1000 Difference: **7 fewer** per 1000 (CI 95% 21 fewer - 22 more)	**Low** Due to serious indirectness, Due to serious imprecision [9]	Corticosteroids may not increase the risk of neuropsychiatric effects.

Practical issues	Standard Care	Steroids	Both
 Medication routine		Systemic corticosteroids may be administered orally or intravenously.	
 Medication routine		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.	

 Medication routine		Duration of steroids varies between 5 and 14 days in clinical trials, and treatment is generally discontinued at hospital discharge.
 Medication routine		Regarding the timing of steroids therapy,the panel suggests that it is preferable to err on the side of administering corticosteroids when treating patients with severe or critical COVID-19 and to err on the side of no corticosteroids when treating patients with non-severe disease even after 7 days of symptoms.
 Adverse effects, interactions and antidote		Possible adverse events associated with steroids include: gastrointestinal bleeding, super-infections, hyperglycaemia, hupernatremia, neuromuscular weakness, neuropsychiatric effects etc.

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

Clinical Question/ PICO

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

Summary

Outline of the evidence on systemic corticosteroids

While six trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalized patients with covid-19 and reported mortality data by subgroup, whereas the smaller GLUCOCOVID trial, which also enrolled hospitalized, patients did not. The panel considered the results of a subgroup analysis of the RECOVERY trial suggesting that the relative effects of systemic corticosteroids varied as a function of the level of respiratory support received at randomization. On the basis of the peer-reviewed criteria for credible subgroup effects,[10] the panel determined that the subgroup effect was sufficiently credible to warrant separate recommendations for severe and non-severe covid-19.

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

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

Duration of hospitalization	Based on data from 6,425 patients in 1 studies. Follow up NR	13	12 Difference: **1 fewer**	**Low** Due to serious risk of bias, Due to serious imprecision [3]	Steroids may result in an important reduction in the duration of hospitalizations
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85 - 1.33) Based on data from 5,403 patients in 30 studies.	48 per 1000	51 per 1000 Difference: **3 more** per 1000 (CI 95% 7 fewer - 16 more)	**Low** Due to serious indirectness, Due to serious imprecision [4]	Corticosteroids may not increase the risk of gastrointestinal bleeding.
Super-infections	Relative risk 1.01 (CI 95% 0.9 - 1.13) Based on data from 6,027 patients in 32 studies.	186 per 1000	188 per 1000 Difference: **2 more** per 1000 (CI 95% 19 fewer - 24 more)	**Low** Due to serious indirectness, Due to serious imprecision [5]	Corticosteroids may not increase the risk of super-infections.
Hyperglycaemia	Relative risk 1.16 (CI 95% 1.08 - 1.25) Based on data from 8,938 patients in 24 studies.	286 per 1000	332 per 1000 Difference: **46 more** per 1000 (CI 95% 23 more - 72 more)	**Moderate** Due to serious indirectness [6]	Corticosteroids probably increase the risk of hyperglycaemia.
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Practical issues	Standard Care	Steroids	Both

	Medication routine	Systemic corticosteroids may be administered orally or intravenously.
	Medication routine	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.
	Medication routine	Duration of steroids varies between 5 and 14 days in clinical trials, and treatment is generally discontinued at hospital discharge.
	Medication routine	Regarding the timing of steroids therapy,the panel suggests that it is preferable to err on the side of administering corticosteroids when treating patients with severe or critical COVID-19 and to err on the side of no corticosteroids when treating patients with non-severe disease even after 7 days of symptoms.
	Adverse effects, interactions and antidote	Possible adverse events associated with steroids include: gastrointestinal bleeding, super-infections, hyperglycaemia, hupernatremia, neuromuscular weakness, neuropsychiatric effects etc.

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8. **Indirectness: Serious. Imprecision: Serious.**
9. **Indirectness: Serious. Imprecision: Serious.**

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

Weak recommendation against

We suggest not to use corticosteroids

Practical Info

Rationale

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

- Systemic corticosteroids should not be stopped for patients with non-severe covid-19 who are already treated with systemic corticosteroids for other reasons (such as patients with chronic obstructive pulmonary disease or chronic autoimmune disease).
- If the clinical condition of patients with non-severe covid-19 worsens (that is, increase in respiratory rate, signs of respiratory distress or hypoxaemia) they should receive systemic corticosteroids (see recommendation 1).
- Pregnancy: antenatal corticosteroid therapy may be administered for pregnant women at risk of preterm birth from 24 to 34 weeks' gestation when there is no clinical evidence of maternal infection, and adequate childbirth and newborn care 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 harms for the woman and the preterm newborn should be discussed with the woman to ensure an informed decision, as this assessment may vary depending on the woman's clinical condition, her wishes and that of her family, and available 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; RR 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.

Values and preferences
The weak or conditional recommendation was driven by likely variation in patient values and preferences. The panel judged that most individuals with non-severe illness would decline systemic corticosteroids. However, many may want them after shared decision making with their treating physician.5

Resource implicatios, 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

Clinical Question/ PICO

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

Summary

Outline of the evidence on systemic corticosteroids, across patients with non-severe, severe and critical COVID-19
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.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard Care	Steroids	**Certainty of the Evidence** (Quality of evidence)	**Plain text summary**
Mortality 28 days	Relative risk 1.22 (CI 95% 0.93 - 1.61) Based on data from 1,535 patients in 1 studies. Follow up 28 days	176 per 1000	215 per 1000 Difference: 39 more per 1000 (CI 95% 12 fewer - 107 more)	**Low** Due to serious risk of bias, Due to serious imprecision [1]	Systemic corticosteroids may increase the risk of 28-day mortality in patients with non-severe COVID-19

Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (CI 95% 0.59 - 0.93) Based on data from 5,481 patients in 2 studies. Follow up 28 days	116 per 1000	86 per 1000	**Moderate** Due to serious risk of bias [2]	Systemic corticosteroids probably reduce the risk of mortality
		Difference: **30 fewer** per 1000 (CI 95% 48 fewer - 8 fewer)			
Duration of hospitalization	Based on data from 6,425 patients in 1 studies. Follow up NR	13	12	**Low** Due to serious risk of bias, Due to serious imprecision [3]	Steroids may result in an important reduction in the duration of hospitalizations
		Difference: **1 fewer**			
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85 - 1.33) Based on data from 5,403 patients in 30 studies.	48 per 1000	51 per 1000	**Low** Due to serious indirectness, Due to serious imprecision [4]	Corticosteroids may not increase the risk of gastrointestinal bleeding.
		Difference: **3 more** per 1000 (CI 95% 7 fewer - 16 more)			
Super-infections	Relative risk 1.01 (CI 95% 0.9 - 1.13) Based on data from 6,027 patients in 32 studies.	186 per 1000	188 per 1000	**Low** Due to serious indirectness, Due to serious imprecision [5]	Corticosteroids may not increase the risk of super-infections.
		Difference: **2 more** per 1000 (CI 95% 19 fewer - 24 more)			
Hyperglycaemia	Relative risk 1.16 (CI 95% 1.08 - 1.25) Based on data from 8,938 patients in 24 studies.	286 per 1000	332 per 1000	**Moderate** Due to serious indirectness [6]	Corticosteroids probably increase the risk of hyperglycaemia.
		Difference: **46 more** per 1000 (CI 95% 23 more - 72 more)			
Hypernatremia	Relative risk 1.64 (CI 95% 1.32 - 2.03) Based on data from 5,015 patients in 6 studies.	40 per 1000	66 per 1000	**Moderate** Due to serious indirectness [7]	Corticosteroids probably increase the risk of hypernatremia.
		Difference: **26 more** per 1000 (CI 95% 13 more - 41 more)			
Neuromuscular weakness	Relative risk 1.09 (CI 95% 0.86 - 1.39) Based on data from 6,358 patients in 8 studies.	69 per 1000	75 per 1000	**Low** Due to serious indirectness, Due to serious imprecision [8]	Corticosteroids may not increase the risk of neuromuscular weakness.
		Difference: **6 more** per 1000 (CI 95% 10 fewer - 27 more)			
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41 - 1.63) Based on data from	35	28	**Low** Due to serious indirectness,	Corticosteroids may not increase the risk of neuropsychiatric

	1,813 patients in 7 studies.	per 1000 per 1000 Difference: **7 fewer** per 1000 (CI 95% 21 fewer - 22 more)	Due to serious imprecision [9]		effects.

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

4 - How to use this guideline

This is a living guideline, 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. Section 5 below outlines key methodological aspects of the guideline process.

The standing guideline panel applied the WHO severity definitions based on clinical indicators[11] in order to align with other WHO guidance.[12] These definitions avoid reliance on access to health care to define patient subgroups. Box 3 in the BMJ publication (https://www.bmj.com/content/370/bmj.m3379) shows the definitions is adapted from WHO covid-19 disease severity categorisation. 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.

Table 1 lists the information that has emerged since the panel created recommendations (for corticosteroids; 17 July 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, WHO will make a judgment on the implications for existing recommendations and will update and publish guidance as the evidence itself is published.

Table 1: New evidence which has emerged after initial publication

Date	Trigger	Action
August 12 2020	Metcovid	This additional trial on corticosteroids was published after the panel created recommendations on July 1 pertaining to critically ill participants - was considered by the panel and deemed not to change the rec

5 - How this guideline was created

This guideline was developed by WHO and the MAGIC Evidence Ecosystem Foundation (MAGIC), with support from The BMJ. It is driven by an urgent need for 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 up to date, evidence based, and user friendly guidance.

Standards, methods, and processes for living and trustworthy guidance
The panel produced the recommendations following standards for trustworthy guideline development using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, in compliance with the WHO Handbook for Guideline Development 2nd edition,[13] the Institute of Medicine, and the Guideline International Network (G-I-N).[14] Details are provided in MAGICapp (https://app.magicapp.org/#/guideline/EZYw5n).

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 two were patients who survived covid-19.5 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, and patient representation. No relevant conflict of interest was identified for any panel member. As recommended by the WHO handbook, the panel aimed to create a recommendation based on consensus but elected, at the beginning of the first panel meeting, to call a vote if a consensus could not be reached. 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, and values and preferences
The target audience for this guidance consists primarily of clinicians, but secondarily of patients and healthcare decision makers. The panel considered an individual patient perspective but also took account of contextual factors (such as resources, feasibility, acceptability, equity) to accommodate global re-use and adaptation for countries and healthcare systems. During 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 that they should therefore attempt to consider the values and preferences of the average patient.

During a pandemic, access to healthcare may vary over time and between different countries. The panel defined covid-19 by clinical severity, and mutually exclusive definitions are provided in **box 3,** as provided in the BMJ publication (https://www.bmj.com/content/370/bmj.m3379

Values and preferences of the average patient were considered, ahead of the first meeting, by panel members, including two covid-19 survivors. Asked to consider a list of outcomes deemed relevant to covid-19 research, panel members considered the importance of each outcome and whether they agreed with a hierarchy ranging from “critically important” to “not very important.” Panel members were reminded to consider the perspective of the patients and 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 synthesised in a living network meta-analysis led by MAGIC,[3] on a prospective meta-analysis of RCTs evaluating corticosteroids for critically ill COVID-19 patients commissioned by the WHO,[5] as well as systematic reviews of the safety of similar regimens of systemic corticosteroids in distinct but relevant patient populations.[15][16]While the investigators responsible for meta-analyses rate the certainty of the evidence, this is re-assessed independently 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 (such as 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.

5.1 - More on standards, methods and processes for this living guideline

This section outlines in more detail the applied standards, methods, processes and platforms agreed upon by the WHO and MAGIC to arrive at trustworthy and living guidance for COVID-19 drug treatments. It represents the protocol for the partners to adhere to, as already done for the corticosteroids recommendations, representing the first publication of the living guideline at September 2 by WHO and September 4 by BMJ, in parallel made available here in MAGICapp.

Context: As of 12 August 2020, 20 162 474 people worldwide have been diagnosed with COVID-19, according to the international World Health Organization (WHO) dashboard. 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.

Rationale: This guideline reflects an innovation from the WHO, driven by an urgent need for global collaboration to provide trustworthy and living COVID-19 guidance informing policy and practice worldwide during an outbreak of an emerging infectious disease, such as this pandemic. For this purpose, WHO has partnered with the non-profit Magic Evidence Ecosystem Foundation (MAGIC) for methodologic support, to develop and disseminate living guidance for COVID-19 drug treatments. The COVID-19 pandemic and infodemic warrants increased speed in providing timely guidance after the publication of practice-changing evidence, often through press-releases or pre-prints rather than peer-reviewed journal publications. The need is clear from member states, WHO country and regional offices, and the public.
Target audience: The target audience consists primarily of clinicians caring for patients, and, secondarily, health care decision-makers.
Related guideline: This living WHO guidance for COVID-19 treatments will be a partner guidance to the more comprehensive guidance for Clinical Management of COVID-19, that has wider scope of content.

The WHO guidance on COVID-19 treatments will also be published as BMJ Rapid Recommendations from MAGIC, both supported by a linked living systematic review and network meta-analysis in BMJ and other relevant evidence synthesis (e.g. prospective meta-analysis orchestrated by WHO) published in scientific journals.

Objectives and timing: This guidance aims to be trustworthy and living; dynamically updated and globally disseminated once new evidence warrants a change in recommendations for COVID-19 therapeutics. We aim for a very ambitious time frame from trigger trials to WHO publication without sacrificing standards and methods for trustworthy guidelines (WHO Handbook). We aim to achieve this through increased efficiency at each step of the process established by the WHO and in the BMJ Rapid Recommendations from MAGIC. The guideline panel will have immediate access to unpublished trial data from collaborators through prospective meta-analysis and create WHO guidance to be reviewed and then published as soon as the new trials have undergone peer-review and scientific publication.

Once it becomes relevant, we aim to include comparative effectiveness of drug treatment options, informed by the living systematic review with Network Meta-Analysis (NMA).

Contributors to guideline development

A **WHO therapeutic steering** committee comprised of representatives from various WHO departments at HQ and from the regions. The WHO secretariat meets on a regular basis to discuss when to trigger guideline updates based on evidence synthesis updates from MAGIC collaborators, as well as other sources of evidence synthesis. The steering committee has been approved by the WHO Director of Country Readiness Department, and the WHO Chief Scientist. The technical responsible for this guidance is from the Clinical Unit of the WHO Emergency Programme, lead of COVID19 clinical response.

A **joint steering committee** comprised of representatives from WHO and representatives from MAGIC meets regularly, responsible for decision-making to meet the needs of both parties for the production of guidance for COVID-19. An Agreement for Performance of Work is in place for this collaboration. The BMJ participates to coordinate editorial processes for the BMJ Rapid Recommendations from MAGIC.

The **living systematic review and NMA team** is comprised of MAGIC representatives and their academic partners at McMaster University.

The **guideline development group** (GDG), have been and will be identified and selected according to WHO criteria, to ensure regional representation, gender balance and appropriate technical expertise as well as patient representation. We will facilitate patient and public involvement by including patient experience, via patient-partners and systematic reviews addressing values and preferences to guide outcome choices and relative weights of each outcome, where available.

All GDG members will complete WHO disclosure forms for financial and intellectual conflict of interests. These forms will be reviewed by WHO technical responsible. Any disclosed conflicts will be assessed and managed according to WHO Handbook. MAGIC collaborators will also assess and manage disclosures according to their established criteria for BMJ Rapid

Recommendations. A standing GDG panel is now in place (biographies at WHO website) but will for each new recommendation have to submit new DOI for assessment. The standing GDG panel may also be supplemented by new members to appropriately reflect the target audience for the guidelines (e.g. COVID-19 drugs for prevention and need to include more primary care professionals).

The GDG was and will be reinforced with **methodologic resource persons** to support the chair, provided by MAGIC. These persons have high level expertise in standards and methods for systematic reviews and guideline development, including GRADE, as well as innovations in processes and platforms for living guidance in user-friendly formats. MAGIC will also nominate the Methods chair for the guideline panel.

The external reviewers have been and will continue to be selected according to WHO Handbook, such as leading external organizations involved in public health emergencies (i.e. MSF) and other front-line individuals. They will be asked to provide feedback related to the following, prior to GRC submission: errors of facts, lack of clarity, considerations for implementation, adaptation, and application of recommendations.

The WHO Guideline review committee (GRC) is an independent group of WHO staff, that include representatives from all regions, as well as external members. This is part of WHO internal process of clearance for publications of guidelines. The GRC is responsible for approving the planning proposal and the final guideline to ensure that it meets WHO standards as described in the Handbook, and has clear and actionable recommendations. The GRC can also provide support on processes of guidance development and procedures and on methods for developing high quality guidance. The GRC does not provide guidance on technical content of guidance.

7 steps for trustworthy and living guidance: Methods and processes
Here we describe how the WHO guidance and BMJ Rapid Recommendations aim to meet established standards for how trustworthy guidelines should be developed, aligned with the WHO handbook, the Institute of Medicine and the Guideline International Network (G-I-N) (refs).

Step 1: Evidence monitoring and mapping
The process for identifying potentially practice-changing evidence is based on continuous and comprehensive monitoring of all emerging randomized controlled trials. The monitoring is performed within the context of a living systematic review and NMA *[4]* (see step 3). MAGIC monitors, with the support of experienced information specialists, on a daily basis all relevant information sources for new randomized trials addressing interventions for COVID-19. WHO will contribute with access to unpublished trial data through prospective meta-analysis performed by trustworthy collaborators on a case-by-case basis. Once practice-changing evidence is identified, the joint steering committee is immediately convened to make decisions while newly eligible studies are incorporated into the evidence summaries addressing the intervention of interest.

Step 2: Selection process for **triggering evidence synthesis** and **production of rapid recommendations**
Based on evidence from Step 1, the WHO therapeutic steering committee and the joint steering committee will decide to trigger development of new recommendations or update existing recommendations. The two steering committees jointly determine which clinical questions to pursue, among the identified potentially-practice changing evidence from the living systematic review, or other sources (including unpublished trial data made available for WHO, as exemplified for corticosteroids).

The need for producing or updating specific recommendations will be based on the following:
- Likelihood to change practice
- Sufficient RCT data on therapeutics to inform the high-quality living systematic review.
- Evaluation of such trial data necessary to inform clinical practice
- Relevance to a global audience

Step 3: Evidence synthesis
MAGIC, as requested by the steering committee, coordinates and performs systematic reviews on benefits and harms of COVID-19 drugs, as well as for other topics to the extent they have capacity. Additional systematic reviews on prognosis and values and preferences will be performed as needed.
1. a high-quality living systematic review and NMA will examine the benefits and harms with a focus on outcomes that matter to patients. A large team of systematic review experts, clinical experts, clinical epidemiologists, graduate students and biostatisticians are creating this living review. The team includes the methodologists who developed GRADE methodology for rating quality/ certainty of evidence, including advances in applying that methodology to network meta-analyses *[4]*. A separate protocol describes the living systematic review and NMA addressing drug interventions (Appendix A).
2. a systematic review of observational studies or risk prediction models to identify baseline risk estimates that most closely represent the target population for the clinical question, a key component required to estimate the absolute effects of the intervention required to trade off benefits and harms.
3. a systematic review addressing the preferences and values of patients on the topic, for situations where we anticipate available published studies to better inform panel judgments.
4. Prospective meta-analysis of unpublished trial data, orchestrated by WHO, may feed into the evidence synthesis, as done for the WHO corticosteroids guidance for COVID-19 (ref). These protocols will be made available, if that methodology is chosen before the GDG meeting.

Step 4: Convening the GDG panel and making the recommendations

The GDG members is a standing guideline panel that includes clinicians, content- experts, methodologists and patient-partners ready to immediately convene and start the guidance creation once the need for new recommendations arises. For each recommendation, all panellists will ensure availability and will meet WHO standards for freedom from conflict of interest. The GDG will work on issuing the recommendations.

The GDG is committed to follow all standards for trustworthy guidelines and to utilize a transparent and systematic process to decide on the strength of recommendations - GRADE methodology *[7][8][9][10]*. The GRADE approach will provide the framework for establishing evidence foundations and rating strength of recommendations. For each recommendation systematic and transparent assessments are made across the following key factors:

- Absolute benefit and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE Summary of Findings tables);
- Quality/ certainty of the evidence
- Values and preferences of patients
- Resources and other considerations (including considerations of Feasibility, Applicability, Equity)
- Each outcome will - if data are available through systematic reviews - include an effect estimate and confidence interval, with a measure of certainty in the evidence, as presented in Summary of Findings tables. If such data are not available narrative summaries will be provided.
- A summary of the underlying reasoning and all additional information (e.g. key factors, practical advice, references) will be available online in an interactive format (here at www.magicapp.org). This summary will include descriptions of how theory (e.g. pathophysiology) and clinical experience played into the evidence assessment and recommendation development.
- Recommendations will be rated either weak/ conditional or strong, as defined by GRADE. If the panel members disagree regarding evidence assessment or strength of recommendations, WHO will apply voting according to their established methods.

The GDG panel communicates via online teleconferences and e-mail exchange of written documents. Minutes from teleconferences are audio-recorded, transcribed, and stored for later documentation (available for peer-reviewers on request).

Teleconferences typically occur at three time points, with circulated documents by e-mail in advance:

- At the initiation of the process to provide feedback on the scope of the guideline. The panel will receive a document with the proposed clinical question to be answered by trustworthy recommendations, in the format of PICO questions (e.g. selection of patient-important outcomes) with particular emphasis on need for subgroup analysis (from the living effectiveness and harms systematic review), baseline risk estimates for risk stratification of patients (determining the need for prognosis review) and values and preferences (determining need for surveys, systematic reviews or other evidence sources).
- At the evidence summary stage, with discussion, feedback and agreement on draft GRADE evidence profiles prepared by the clinical co-chair and the methods co-chair, with support from methodologists, based on the living systematic review and baseline risk data.
- At the recommendation formulation phase, with discussion, feedback and agreement on draft recommendations and other content underlying the recommendation (e.g. GRADE SoF-table, key information, rationale, practical advice)

Given the established standing guideline panel and the need for increased speed in providing timely COVID-19 guidance one teleconference may be sufficient, covering the two last steps after agreeing on the scope, question formulation and needs from the systematic review(s) through e-mail and written feedback on documents.

Step 5: Writing of guidance

Following the last teleconference, the final version of the WHO guidance with recommendations will be drafted jointly by the methods chair, the clinical chair and WHO technical officer responsible. The WHO guidance document will be circulated by e-mail specifically requesting feedback from all panel members to document agreement before submission. Additional teleconferences are arranged as needed.

The format of the WHO guidance aims to be user-friendly, while including all relevant populations and drugs for COVID-19 in a living guidance mode. As per contract with MAGIC, future WHO guidance on COVID-19 is planned to be written, published and dynamically updated in the MAGIC authoring and publication platform (MAGICapp). WHO Guidance will articulate actionable recommendations according to their requirements and standards and these will be consistent with the BMJ Rapid Recommendations on COVID-19 drug treatments.

The MAGICapp content will represent the WHO guidance to be disseminated and it will also inform BMJ Rapid Recommendations as a separate publication (see step 7). Guideline panel members and other contributors to the guideline development will be invited as co-authors according to ICMJE criteria, in a process orchestrated by MAGIC.

Step 6: Internal and external review

The draft WHO guidance will be sent to the External Reviewers for input. This will be done according to the WHO Handbook, with written feedback requested within 48 hours, due to necessity to keep to rapid timelines.

For the BMJ Rapid Recommendations reflecting WHO guidance, The BMJ has established a faster editorial process to make the guidance available to readers without undue delay. The first version of the guideline will have rapid editorial and statistical peer review upon manuscript submission. It will then be posted on The BMJ's website (www.bmj.com), open for review by the public and a designated peer-review committee. The peer review committee is typically comprised of reviewers with a range of relevant expertise, including patients, clinicians, and methodologists. All peer reviewers will have access to the guideline, NMA, and any other relevant information in the package. They will be asked for detailed feedback as well as to make an overall judgement on whether they view the guidelines to be trustworthy. The panel co-chairs will, on behalf of panel authors, respond to each peer review report within 30 days for a period of six months after publication of the first version of the guideline. For subsequent updates to the living guidelines, The BMJ will manage the editorial review process and decide on the need for additional peer review based on the size and nature of the update.

Internal review of the guidance will be submitted to the WHO GRC as described in the WHO Handbook. This is an internal group of WHO staff, that are from various WHO departments spanning expertise in content, methods or other public health matters. This group will review the guidance within 24 hours, to keep with rapid predefined timelines. The GRC may have requirements for revisions prior to publication. These will be addressed by the GDG methods and clinical chair, with point by point response to the GRC reviewers. This revised guidance will then be resubmitted to the GRC for additional review and approvals.

Step 7: Dissemination of living guidance and linked evidence synthesis
The GRC approved guidance will be approved by the Technical units Director and Executive Director of WHO for publication on WHO website. Simultaneously, the guidance will be formatted for publication in the BMJ according to previous MAGIC and BMJ collaboration.

- WHO is responsible solely for the publication via WHO's website. As per contract with MAGIC, WHO plans to digitally author, publish and update COVID-19 guidance through the MAGICapp. This allows the publication of PDF-outputs in parallel with online, multilayered formats for clinicians and others users and stakeholders, including those who wish to create national or local adaptation of the recommendations. MAGIC supports WHO in the use of MAGICapp for this purpose.

- MAGIC is responsible for publication in the BMJ according to their established BMJ Rapid Recommendations processes, ideally simultaneously with the WHO guidance publication, or immediately thereafter. Here MAGIC will abide by WHO requirements; WHO will receive the draft publication for comments in the peer-review and proofing phase to approve formulations of relevance to WHO, including their role and contributions in the guideline development. BMJ Rapid Recommendations will link directly to MAGICapp as for previous publications.

Evidence synthesis: The publication of one or more reviews or prospective meta-analyses directly linked to the WHO guidance will also need to be done simultaneously so that references are correct and readers may easily navigate between publications.

- For BMJ Rapid Recommendations the published LNMA will be updated in accordance with the release of WHO guidance, as for previous BMJ Rapid Recommendations (e.g. remdesevir). Other systematic reviews (e.g on prognosis and values/ preferences) will also be published through the BMJ, directly linked to the WHO Guidance.

- Prospective meta-analyses orchestrated by WHO and performed by independent research teams, will be published in other journals, as determined by the authors (e.g. PMA complementing evidence synthesis to inform WHO guidance on corticosteroids published in JAMA).

In situations where the WHO guidance is based on early access to trial data through the PMA, WHO will wait until these are made publicly available (e.g. after peer-review and scientific publication, as for corticosteroids). In these situations, the WHO will work with the trialists, the PMA authors and the designated journal to coordinate with the WHO guidance, BMJ Rapid Recommendations and systematic reviews to be published without undue delay.

Step 8: Living guidance
WHO guidance for COVID-19 on drug treatments represents living guidance, with a commitment to publish updated recommendations based on need of new and practice-changing evidence emerging after the first recommendations published. To achieve this, WHO will use MAGICapp, designed for the purpose of living guidance. Furthermore, the living NMA produced by MAGIC will inform the Steering committee to trigger evidence synthesis and rapid development of new or updated recommendations on a systematic basis according to need arising in the global community *[4]*. These updates will be decided ultimately by the GDG.

BMJ Rapid Recommendations has- through the WHO guidance on corticosteroids – been transformed into a living guidance publication. Here, MAGIC is responsible for the process of triggering updates, in a coordinated process with WHO, through the steering committees (step 2).

References to be inserted

6 - 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 (that is, 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 with systemic corticosteroids versus systemic corticosteroids alone.
- Other uncertainties include:

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

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