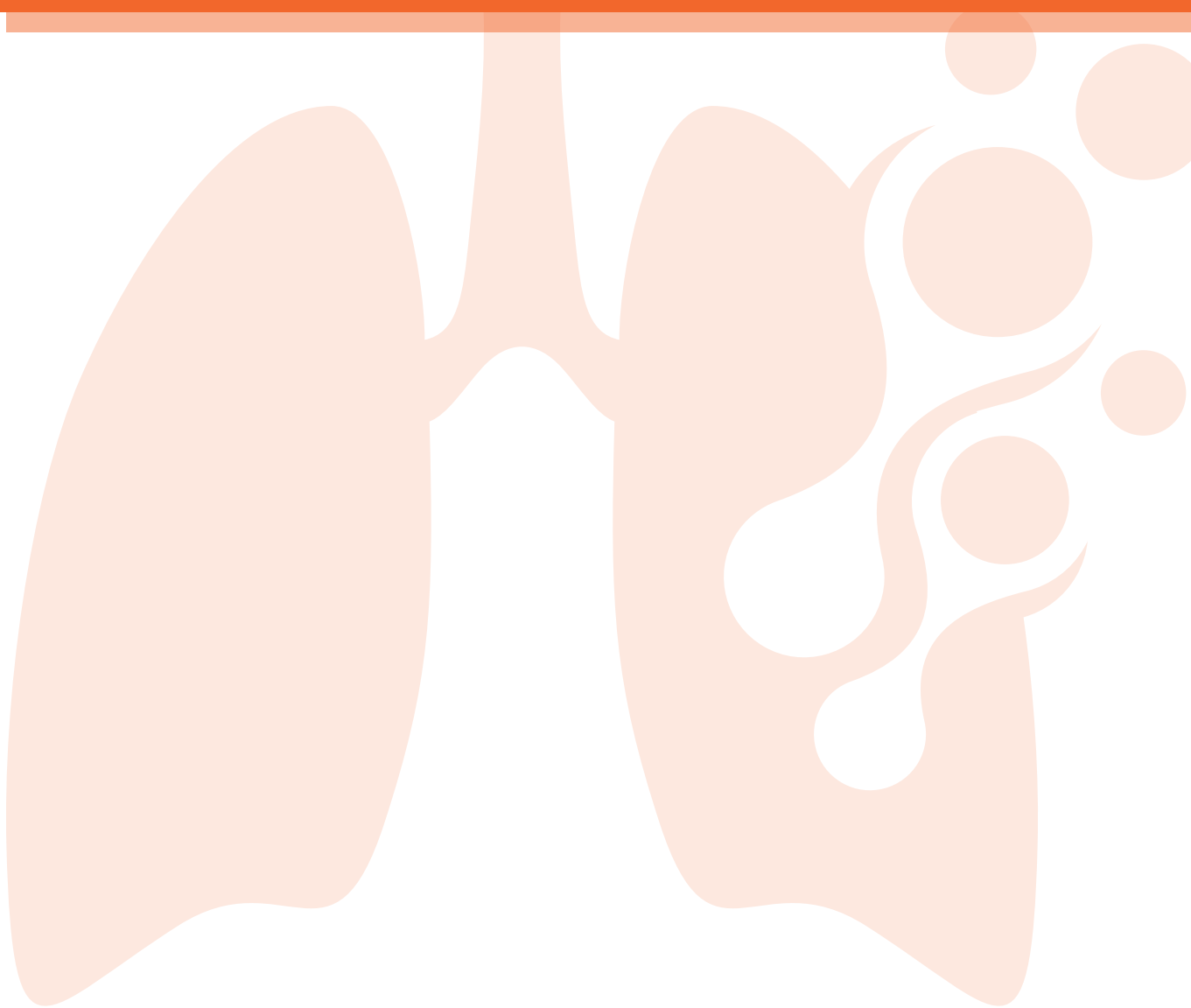
Therapeutics and COVID-19

LIVING GUIDELINE
20 NOVEMBER 2020

World Health Organization



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WHO reference number: WHO/2019-nCov/remdesivir/2020.1

1. SUMMARY: WHAT IS THIS LIVING GUIDELINE?

Clinical question: What is the role of drugs in the treatment of patients with COVID-19?

Target audience: The target audience is clinicians and health care decision-makers.

Current practice: Current practice to treat COVID-19 is variable, reflecting large-scale uncertainty. Numerous randomized controlled trials (RCTs) of many different drugs are underway to inform practice. This version of the World Health Organization (WHO) living guideline contains new information and recommendations on remdesivir. It follows the preprint publication of results from the WHO SOLIDARITY trial on 15 October 2020 *(1)*, which also reported results on hydroxychloroquine and lopinavir-ritonavir. Remdesivir is increasingly used to treat patients hospitalized with COVID-19 and is of considerable interest to all stakeholder groups.

Recommendations: The panel made a conditional recommendation against the use of remdesivir in hospitalized patients with COVID-19, regardless of disease severity. This guidance adds to recommendations published in the previous version: a strong recommendation for systemic corticosteroids in patients with severe and critical COVID-19, and a conditional recommendation against systemic corticosteroids in patients with non-severe COVID-19.

How this guideline was created: This living guideline is an innovation from WHO, driven by the urgent need for global collaboration to provide trustworthy and evolving COVID-19 guidance informing policy and practice world-wide. WHO has partnered with the non-profit Magic Evidence Ecosystem Foundation (MAGIC) for methodologic support and development and dissemination of living guidance for COVID-19 drug treatments, based on a living systematic review and network analysis *(2)*. An international Guideline Development Group (GDG) of content experts, clinicians, patients, ethicists and methodologists produced recommendations following standards for trustworthy guideline development using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. No conflict of interest was identified for any panel member.

The latest evidence: The recommendation on remdesivir was informed by results from a systematic review and network meta-analysis (NMA) that pooled data from four randomized trials with 7333 participants hospitalized for COVID-19. The resulting GRADE evidence summary suggested that remdesivir has possibly no effect on mortality (odds ratio 0.90, 95% confidence interval [CI] 0.70 - 1.12; absolute effect estimate 10 fewer deaths per 1000 patients, 95% CI from 29 fewer - 11 more deaths per 1000 patients; low certainty evidence); and possibly no effect on the other important outcomes identified by the panel, with similar low to very low certainty of evidence. The panel judged the overall credibility of subgroup analyses assessing differences in mortality by severity of illness to be insufficient to make subgroup recommendations.

Understanding the recommendations: When moving from evidence to the conditional recommendation against the use of remdesivir in hospitalized patients with COVID-19, the panel emphasized the evidence suggesting no important effect on mortality, need for mechanical ventilation, time to clinical improvement, and other patient-important outcomes. Considering the low or very low certainty evidence for all outcomes, the panel concluded that the evidence did not prove that remdesivir has no benefit; rather, there is no evidence based on currently available data that it does improve patient-important outcomes. The panel placed low value on small and uncertain benefits in the presence of the remaining possibility of important harms. In addition, the panel considered contextual factors such as resources, feasibility, acceptability and equity for countries and health care systems.

Info box

This living WHO guideline on therapeutics for COVID-19 now includes a conditional recommendation against the use of remdesivir, triggered by results from the WHO SOLIDARITY trial *(1)*. Recommendations for hydroxychloroquine and lopinavir will follow. The first version of the living WHO guideline (published 2 September 2020) provides recommendations for corticosteroids.

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 guideline is therefore written, disseminated and updated in MAGICapp, with a format and structure aiming to make it user-friendly and easy to navigate while accommodating for dynamically updated evidence and recommendations, focusing on what is new while keeping existing recommendations within the guideline.

Please visit the WHO website for the latest version of the guidance, also available in the BMJ as Rapid Recommendations together with the living NMA, a major evidence source for the guidelines *(2)*.

At the time of publication (20 November 2020), the updated living NMA that informs this recommendation has been made available in the Annex (while undergoing peer review in the BMJ); and the systematic review and meta-analysis of adverse effects from remdesivir is also available as a preprint *(3)*.

2. ABBREVIATIONS

ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
CI	confidence interval
COVID-19	coronavirus disease 2019
eGFR	estimated glomerular filtration rate
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
MAGIC	Magic Evidence Ecosystem Foundation
MD	mean difference
NMA	network meta-analysis
PICO	population, intervention, comparator, outcome
RCT	randomized controlled trial
SAE	serious adverse event
WHO	World Health Organization

3. BACKGROUND

As of 11 November 2020, over 50 million people worldwide have been diagnosed with COVID-19, according to the WHO dashboard *(4)*. The pandemic has so far claimed more than 1.2 million lives, and many areas of the world are experiencing a resurgence in cases. The COVID-19 pandemic – and the explosion of both research and misinformation – has highlighted the need for trustworthy, accessible and regularly updated (living) guidance to place emerging findings into context and provide clear recommendations for clinical practice.

This living guideline responds to emerging evidence from RCTs on existing and new drug treatments for COVID-19. More than 2800 trials on COVID-19 interventions have been registered or are ongoing (see section on emerging evidence) *(5)*. Among these are large national and international platform trials (e.g. RECOVERY, WHO SOLIDARITY and DISCOVERY) that recruit very large numbers of patients in many countries, with a pragmatic and adaptive design *(1, 6)*. These platform trials are currently investigating and reporting on drugs such as remdesivir, corticosteroids, hydroxychloroquine and lopinavir-ritonavir, with other interventions underway (e.g. convalescent plasma, immune-modulatory therapies). This rapidly evolving evidence landscape requires trustworthy interpretation and expeditious clinical practice guidelines to inform clinicians, patients, governments, ministries and health administrators.

3.1 What triggered this version of the guideline?

This second version of the WHO living guideline addresses the use of remdesivir in patients with COVID-19. It follows the pre-print publication of the WHO SOLIDARITY trial on 15 October 2020, reporting results on treatment with remdesivir, hydroxychloroquine and lopinavir-ritonavir in hospitalized patients with COVID-19 *(1)*. The role of these drugs in clinical practice has remained uncertain, with limited prior trial evidence. The WHO SOLIDARITY trial adds 11 266 randomized patients (2570 to remdesivir, 954 to hydroxychloroquine, 1411 to lopinavir-ritonavir, 6331 to usual care) and holds the potential to change practice *(1)*.

The WHO GDG started with developing trustworthy recommendations on remdesivir, and plans recommendations on hydroxychloroquine and lopinavir-ritonavir to follow shortly. Remdesivir is a novel monophosphoramidate adenosine analogue prodrug which is metabolized to an active tri-phosphate form that inhibits viral RNA synthesis. Remdesivir has in vitro and in vivo antiviral activity against several viruses, including SARS-CoV-2. Remdesivir is widely used in many countries, with several guidelines recommending its use in patients with severe or critical COVID-19 *(7, 8)*.

3.2 Who made this guideline?

As detailed in the Methods section, the WHO convened a standing GDG with 28 clinical content experts, 4 patient-partners and one ethicist, headed by a clinical chair (Dr Michael Jacobs) and methods chair (Dr Bram Rochwerg). WHO selected GDG members to ensure global geographical representation, gender balance, and appropriate technical and clinical expertise. No conflict of interest was identified for any panel member. MAGIC provided methodological experts with high-level expertise in standards and methods for systematic reviews and guideline development, including GRADE; in addition MAGIC offered innovations in processes (BMJ Rapid Recommendations) and platforms (MAGICapp) for developing living guidance in user-friendly formats. The methodological experts were not involved in the formulation of recommendations. MAGIC also worked with the BMJ to coordinate the simultaneous scientific publication of the living WHO guidelines *(9)*.

3.3 How to use this guideline

This is a living guideline from the WHO. Recommendations will be updated, and new recommendations will be added on other therapies for COVID-19, including hydroxychloroquine and lopinavir-ritonavir *(9)*. The guideline is written, disseminated and updated in MAGICapp, with a format and structure aiming to make it user-friendly and easy to navigate. It accommodates dynamic updating of evidence and recommendations that can focus on what is new while keeping existing recommendations, as appropriate, within the guideline. Section 4 outlines the key methodological aspects of the living guideline process.

The guideline is available via: the WHO website; online, multilayered formats (through MAGICapp), PDF-formats; and as BMJ Rapid Recommendations and WHO Academy app *(9)*. The purpose of the online formats and additional tools, such as the infographics made by the BMJ, is to make it easier to navigate and make use of the guideline in busy clinical practice. The online, multilayered formats are designed to allow end users to find recommendations first and then drill down to find supporting evidence and other information pertinent to applying the recommendations in practice, including tools for shared decision-making (encounter decision aids).

4. METHODS: HOW THIS GUIDELINE WAS CREATED

The living WHO guideline is developed according to standards and methods for trustworthy guidelines, making use of an innovative process to achieve efficiency in dynamic updating of recommendations. The methods are aligned with the WHO Handbook for guideline development and according to a pre-approved protocol (planning proposal) by the WHO Guideline Review Committee (https://www.who.int/publications/guidelines/guidelines_review_committee/en/).

Related guidelines
This living WHO guidance for COVID-19 treatments will be related to the larger, more comprehensive guidance for Clinical management of COVID-19: interim guidance, which has a wider scope of content *(10)*. The first WHO living guidance published, Corticosteroids for COVID-19: living guidance, was well received by stakeholders and disseminated via the BMJ and MAGICapp.

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 an ambitious timeframe from trials that trigger the guideline development process to WHO publication, within 1 month, while maintaining standards and methods for trustworthy guidelines (WHO Handbook of guideline development).

Here we outline the stepwise approach we take to improve efficiency and timeliness of the living, trustworthy guidance, in the development and dissemination of the recommendations. To do so, various processes occurred simultaneously.

Stepwise approach
Step 1: Evidence monitoring and mapping and triggering of evidence synthesis
Comprehensive daily monitoring of all emerging RCTs occurs on a continuous basis, within the context of the living systematic review and NMA, using experienced information specialists, who look at all relevant information sources for new RCTs addressing interventions for COVID-19. Once practice-changing evidence is identified, such as in this case the SOLIDARITY trial pre-print, the WHO Therapeutics Steering Committee triggered the guideline development process, with the Guidance Support Collaboration Committee (see acknowledgements), PICO development and construction of evidence summaries addressing the intervention of interest initiated.

The trigger for producing or updating specific recommendations is based on the following:

- likelihood to change practice;
- sufficient RCT data on therapeutics to inform the high-quality evidence synthesis living systematic review; and
- relevance to a global audience.

Step 2: Convening the GDG
The pre-selected expert panel (see Acknowledgments) convened on five occasions over a 2-week period. The first meeting, held 13 October 2020, reviewed the basics of GRADE methodology; including formulating PICO questions and subgroups of interests, assessment of certainty of evidence, incorporating patients' values and preferences, and prioritization of patient-important outcomes. The second meeting, held on 20 October 2020, finalized the outcome prioritization, PICOs and pre-specified subgroups for this specific question. At the third meeting, held on 23 October 2020, a Q&A session was held with the individual study investigators and biostatisticians: SOLIDARITY (Drs Ana Maria Henao Restrepo and Richard Peto); ACTT-1 (Drs Lori Dodd and John Beigel); and RECOVERY (Drs Peter Horby and Jonathan Emberson). At the fourth meeting, held on 27 October 2020, evidence summaries were shown to the GDG panel, including pre-specified subgroup analysis and preliminary recommendations were drafted. An additional fifth meeting was convened on 5 November 2020, to review a post hoc subgroup analysis and allow for final deliberation on values and preference statements, as well as recommendations.

Step 3: Evidence synthesis
The living systematic review/NMA team, as requested by the WHO Therapeutics Steering Committee and coordinated by the Guidance Support Collaboration Committee, was ready to perform an independent systematic review to examine the benefits and harms of the intervention. The systematic review team is multidisciplinary and made up of systematic review experts, clinical experts, clinical epidemiologists, graduate students and biostatisticians. The team has expertise in GRADE methodology and rating certainty of evidence specifically in NMAs. The NMA team was informed by the deliberations from the initial two GDG meetings in order to guide the NMA, specifically focusing on the outcomes and subgroups prioritized by the panel. After the fourth meeting, the NMA team continued with a post hoc subgroup analysis using a Bayesian approach and meta-regression. This was shown to the panel at the last panel meeting.

Step 4: Final recommendations
The GRADE approach provided the framework for establishing evidence certainty and generating both the direction and strength of recommendations. Although *a priori* voting procedures were established at the outset, in case consensus was not reached, these procedures were not necessary for this recommendation, which reached consensus amongst the panel.

The following key factors were used to formulate transparent and trustworthy recommendations:

- absolute benefits 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 have 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;
- recommendations will be rated as either conditional or strong, as defined by GRADE. If the panel members disagree regarding the evidence assessment or strength of recommendations, WHO will apply voting according to established methods.

Step 5: External and internal review: The WHO guideline was then reviewed by pre-specified external reviewers (see Acknowledgements) and then approved by the WHO Publication Review Committee.

5. THE EVIDENCE

This section outlines what information the GDG panel requested and used in making their recommendation for remdesivir.

Benefits and harms: relative effects of remdesivir on patient-important outcomes
The GDG panel requested an update of the living NMA of RCTs of drug treatments for COVID-19, based around important clinical questions to be addressed in the recommendations. The GDG members prioritized outcomes (rating from 1 [not important] to 9 [critical]), taking a patient's perspective (Table 1). The panel's questions were structured using the PICO format (see evidence profile under the recommendations).

Table 1. Panel outcome rating from a patient perspective

Outcome	Mean	SD	Range
Death at 28 days	9.0	0.0	9-9
Need for invasive mechanical ventilation	8.4	0.8	7-9
Duration of invasive mechanical ventilation	7.7	1.0	5-9
Time to clinical improvement	7.2	1.5	4-9
Serious adverse effect leading to drug discontinuation	7.1	1.4	4-9
Time to symptom resolution	6.6	1.5	3-9
Duration of oxygen support	6.6	1.3	5-9
Duration of hospitalization	6.4	1.3	3-8
Hepatitis (increased liver enzymes)	5.3	1.8	2-9
Duration of viral shedding	4.9	2.4	2-9
Nausea/vomiting	4.5	1.7	2-9
Diarrhea	4.3	1.5	2-8

Note: 1: not important, 9: critically important.

Based on 4 trials with 7333 participants *(1, 11-13),* the NMA provided relative estimates of effect for patient-important outcomes (Table 2). Of note, none of the included studies enrolled children or adolescents under the age of 19 years old.

Table 2. Summary of trials and trial characteristics informing the remdesivir recommendation

Study	N	Country	Mean age (years)	Severity (as per WHO criteria)	% IMV (at baseline)	Treatments (dose and duration)	Outcomes
Biegel (ACTT-1)	1063	United States, Europe, Asia	58.9	Non-severe (11.3%) Severe[a] (88.7%)	44.1%	Remdesivir IV (100 mg/day for 10 days)	-Mortality -Adverse events -Time to clinical improvement
Spinner (SIMPLE MODERATE)*	596	United States, Europe, Asia	56-58	Non-severe (100%)	0%	Remdesivir IV (200 mg at day 1, then 100 mg for 4 days or 9 days)	-Mortality -Time to clinical improvement -Duration of hospitalization -Mechanical ventilation -Adverse events
Pan (SOLIDARITY)	5451	Worldwide	< 50 35% 50-70 47% > 70 18%	Non-severe (24%) Severe[b] (67%) Critical (9%)	8.9%	Remdesivir IV (200 mg at day 1, then 100 mg day 2-10)	-Mortality -Mechanical ventilation
Wang	237	China	65	Severe[c] (100%)	16.1%	Remdesivir IV (100 mg/day for 10 days)	-Mortality -Mechanical ventilation -Adverse events -Viral clearance -Duration of hospitalization -Duration of ventilation -Time to clinical improvement

Notes: IMV – invasive mechanical ventilation; IV – intravenous; N – number; NR (not reported); Sx – symptom.
Severity criteria based on WHO definitions unless otherwise stated: [a] defined severe as SpO_2 < 94% on room air OR respiratory rate > 24 breaths /min; [b] defined severe as requiring oxygen support; [c] defined severe as SpO_2 < 94% on room air
*Only SIMPLE MODERATE was included in the analysis, as SIMPLE SEVERE *(14)* did not have a placebo/usual care arm.

Subgroup analysis

The GDG panel requested subgroup analyses based on age (considering children vs adults vs older people), illness severity (non-severe vs severe vs critical COVID-19 – see subgroup analysis under 7.1 Recommendations for details), and duration of remdesivir therapy (5 days vs longer than 5 days). The GDG discussed other potential subgroups of interest including time from onset of symptoms until initiation of therapy, and concomitant medications (especially corticosteroids), however recognized these analyses would not be possible without access to individual participant data. To this last point, the panel recognized that usual care is likely variable between centres, regions and evolved over time. However, given all of the data comes from RCTs, use of these co-interventions that comprise usual care should be balanced between study patients randomized to either the intervention or usual care arms.

Following the panel's request, the NMA team performed subgroup analyses in order to assess for effect modification which, if present, could mandate distinct recommendations by subgroups. From the data available from the included trials, subgroup analysis was only possible for severity of illness and the outcome of mortality. This subgroup analysis was performed using a random effects frequentist analysis based on the three WHO severity definitions. A post hoc Bayesian analysis was also performed, which incorporated meta-regression using study as a random effect. This latter approach has the advantage of more accurately accounting for within-study differences but can only compare two subgroups at a time. The panel used a pre-specified framework incorporating the ICEMAN tool to assess the credibility of subgroup findings *(15)*.

Baseline risk estimates (prognosis of patients with COVID-19): informing absolute estimates of effect

The evidence summaries that informed the guideline recommendation reported the anticipated absolute effects of remdesivir compared with usual care across all patient-important outcomes, with explicit judgments of certainty in the evidence for each outcome. The absolute effects of treatment are informed by the prognosis (i.e. baseline risk estimates) combined with the relative estimates of effects (e.g. risk ratios, odds ratio) obtained from the NMA.

The control arm of the WHO SOLIDARITY trial *(1),* performed across a wide variety of countries and geographical regions, was identified by the GDG panel as representing the most relevant source of evidence to make the baseline risk estimates for the outcomes of mortality and mechanical ventilation. The rationale for selecting the WHO

SOLIDARITY trial was to reflect the overall prognosis of the global population for which the WHO guideline recommendations are made. In view of the study designs, the GDG determined that for other outcomes using the median or mean of all patients randomized to usual care across the included studies would provide the most reliable estimate of baseline risk.

Values and preferences

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

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

- Mortality would be the outcome most important to patients, followed by need and duration of mechanical ventilation, time to clinical improvement, and serious intervention-related adverse events.
- Most patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on the outcomes listed above. This was particularly so when evidence suggested treatment effects, if they do exist, are small, and the possibility of important harm remains.
- In an alternative situation with larger benefits and less uncertainty regarding both benefits and harms, more patients would be inclined to choose the intervention.

The GDG acknowledged, however, that values and preferences are likely to vary. There will be patients inclined to use a treatment in which evidence has not excluded important benefit, particularly when the underlying condition is potentially fatal. On the other hand, there will be those who have a high threshold of likely benefit before they will choose the intervention. Although the GDG focused on an individual patient perspective, they also considered a population perspective in which feasibility, acceptability, equity and cost are important considerations.

6. WHO DO THE RECOMMENDATIONS APPLY TO?

The guideline for COVID-19 therapeutics applies to hospitalized patients with COVID-19. For some drugs (such as corticosteroids), recommendations may differ based on the severity of COVID-19 disease. The GDG elected to use the WHO severity definitions based on clinical indicators, adapted from WHO COVID-19 disease severity categorization (see below) *(10)*. These definitions avoid reliance on access to health care to define patient subgroups. The infographic illustrates these three disease severity groups and key characteristics to apply in practice.

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.

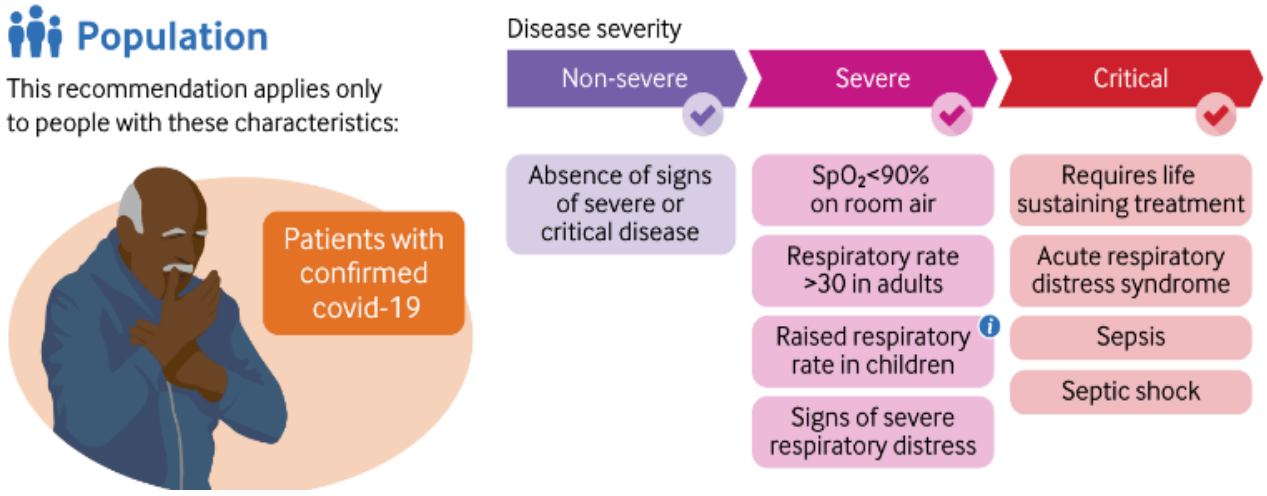
Severe COVID-19: Defined by any of:

- oxygen saturation < 90% on room air;
- respiratory rate > 30 breaths/min in adults and children > 5 years old; ⩾ 60 breaths/min in children < 2 months old;
  ⩾ 50 in children 2–11 months old; and ⩾ 40 in children 1–5 years old;
- signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).

Non-severe COVID-19: Defined as absence of any criteria for 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 judgment to determine whether a low oxygen

saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, a saturation > 90–94% on room air is abnormal (in patient with normal lungs) and can be an early sign of severe disease, if the patient is on a downward trend. Generally, if there is any doubt, the panel suggested erring on the side of considering the illness as severe.



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7. RECOMMENDATIONS FOR THERAPEUTICS

7.1 Remdesivir

Hospitalized patients with COVID-19, regardless of disease severity

Conditional recommendation

We suggest against administering remdesivir in addition to standard care.

Evidence to decision

Benefits and harms	**Possibly no benefit, or little difference, compared with usual care alone**

The GDG panel found a lack of evidence that remdesivir improved outcomes that matter to patients such as reduced mortality, need for mechanical ventilation, time to clinical improvement and others. However, the low certainty evidence for these outcomes, especially mortality, does not prove that remdesivir is ineffective; rather, there is insufficient evidence to confirm that it does improve patient-important outcomes.

There was no evidence of increased risk of severe adverse events (SAEs) from the trials. However, further pharmacovigilance is needed because SAEs are commonly underreported and rare events could be missed, even in large RCTs.

A subgroup analysis indicated that remdesivir treatment possibly increased mortality in the critically ill and possibly reduced mortality in the non-severely and severely ill. The panel judged the overall credibility of this subgroup effect (evaluated using the ICEMAN tool) to be insufficient to make subgroup recommendations. The overall low certainty evidence on the benefits and harms of remdesivir, driven by risk of bias and imprecision limitations in the included studies, also contributed to the judgment.

Certainty of the evidence	Low

The evidence is based on a linked systematic review and network meta-analysis of 4 RCTs; pooling data from 7333 patients hospitalized with various severities of COVID-19 and variably reporting the outcomes of interest to the guideline panel. The panel agreed that there was low certainty in the estimates of effect for all patient-important outcomes across benefits and harms, mostly driven by risk of bias and imprecision (wide confidence intervals which don't exclude important benefit or harm). There was very low certainty evidence for viral clearance and delirium.

Preference and values	Substantial variability is expected or uncertain

Applying the agreed values and preferences (see Evidence section), the GDG inferred that most patients would be reluctant to use remdesivir given the evidence left high uncertainty regarding effects on mortality and the other prioritized outcomes. This was particularly so as any beneficial effects of remdesivir, if they do exist, are likely to be small and the possibility of important harm remains. The panel acknowledged, however, that values and preferences are likely to vary, and there will be patients and clinicians who choose to use remdesivir given the evidence has not excluded the possibility of benefit.

Resources implications, feasibility, equity and other considerations	Important issues, or potential issues not investigated

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

Justification

When moving from evidence to the conditional recommendation against the use of remdesivir for patients with COVID-19, the panel emphasized the evidence of possibly no effect on mortality, need for mechanical ventilation, recovery from symptoms and other patient-important outcomes, albeit of low certainty; it also noted the anticipated variability in patient values and preferences, and other contextual factors, such as resource-considerations, accessibility, feasibility and impact on health equity (see summary of these factors under Evidence to decision).

Importantly, given the low certainty evidence for these outcomes, the panel concluded that the evidence did not prove that remdesivir has no benefit; rather, there is no evidence based on currently available data that it does improve patient-important outcomes. Especially given the costs and resource implications associated with remdesivir, but consistent with the approach that should be taken with any new drug, the panel felt the responsibility should be on demonstrating evidence of efficacy, which is not established by the currently available data. The panel noted that there was no evidence of increased risk of SAEs in patients receiving remdesivir, at least from the included trials. Further pharmacovigilance is required to confirm this, as SAEs are commonly underreported and rare events would be missed, even in large RCTs.

Subgroup analysis

The panel carefully considered a potential subgroup effect across patients with different levels of disease severity, suggesting a possible increase in mortality in the critically ill and a possible reduction in mortality in the non-severely and severely ill. For this analysis, critical illness was defined as those requiring invasive or non-invasive ventilation; severe illness as those requiring oxygen therapy (but not meeting critical illness criteria); and non-severe as all others. Patients requiring high-flow nasal cannula represented a small proportion and were characterized as either severe (SOLIDARITY) or critical (ACTT-1, Wang). The analysis focused on within-study subgroup comparisons across the different severities, and therefore the SIMPLE-MODERATE trial could not be included in the subgroup analysis as it only enrolled patients with non-severe COVID-19. The panel reviewed the results of both the random effects frequentist analysis and the post hoc Bayesian analysis which incorporated meta-regression using study as a random effect.

The GDG panel judged the credibility in the subgroup analysis assessing differences in mortality by severity of illness to be insufficient to make subgroup recommendations. Important factors influencing this decision included a lack of *a priori* hypothesized direction of subgroup effect by trial investigators, little or no previously existing supportive evidence for the subgroup finding, and relatively arbitrary cut points used to examine the subgroups of interest. The overall low certainty evidence for the benefits and harms of remdesivir, driven by risk of bias and imprecision limitations, also contributed to the judgment. The panel highlighted that despite the conditional recommendation against remdesivir, they support further enrolment into RCTs evaluating remdesivir, especially to provide higher certainty of evidence for specific subgroups of patients.

The panel had *a priori* requested analyses of other important subgroups of patients including children and older persons, but there were no data to address these groups specifically. None of the included RCTs enrolled children, and although older people were included in the trials, their outcomes were not reported separately. Also, there are no pharmacokinetic or safety data on remdesivir for children. Given this, the applicability of this recommendation to children is currently uncertain.

Practical information

The GDG made a conditional recommendation against using remdesivir for treatment of hospitalized patients with COVID-19. If administration of remdesivir is considered, it should be noted that its use is contraindicated in those with liver (ALT > 5 times normal at baseline) or renal (eGFR < 30 mL/minute) dysfunction. To date, it can only be administered intravenously, and it has relatively limited availability.

PICO

Population: patients with COVID-19 (all disease severities)
Intervention: remdesivir + usual care
Comparator: usual care

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Standard care	Remdesivir	**Certainty of the evidence** (Quality of evidence)	**Plain text summary**
Mortality	Odds ratio: 0.90 (95% CI 0.70 - 1.12) Based on data from 7333 patients in 4 studies	**106** per 1000	**96** per 1000 Difference: **10 fewer per 1000** (95% CI 29 fewer - 11 more)	**Low** Due to serious risk of bias and serious imprecision	Remdesivir possibly has no effect on mortality.
Mechanical ventilation	Odds ratio: 0.89 (95% CI 0.76 - 1.03) Based on data from 6549 patients in 4 studies	**105** per 1000	**95** per 1000 Difference: **10 fewer per 1000** (95% CI 23 fewer - 3 more)	**Low** Due to serious risk of bias and serious imprecision	Remdesivir possibly has no effect on mechanical ventilation.
Serious adverse events leading to discontinuation	Odds ratio: 1.00 (95% CI 0.37 - 3.83) Based on data from 1894 patients in 3 studies	**15** per 1000	**15** per 1000 Difference: **0 fewer per 1000** (95% CI 9 fewer - 40 more)	**Low** Due to very serious imprecision	Remdesivir possibly has no effect on serious adverse events leading to discontinuation.
Viral clearance 7 days	Odds ratio: 1.06 (95% CI 0.06 - 17.56) Based on data from 196 patients in 1 study	**483** per 1000	**498** per 1000 Difference: **15 more per 1000** (95% CI 430 fewer - 460 more)	**Very Low** Due to very serious imprecision	The effect of remdesivir on viral clearance is uncertain.
Acute kidney injury	Odds ratio: 0.85 (95% CI 0.51 - 1.41) Based on data from 1281 patients in 2 studies	**56** per 1000	**48** per 1000 Difference: **8 fewer per 1000** (95% CI 27 fewer - 21 more)	**Low** Due to serious imprecision and serious indirectness	Remdesivir possibly has no effect on acute kidney injury.

Delirium	Odds ratio: 1.22 (95% CI 0.48 - 3.11) Based on data from 1048 patients in 1 study	**16** per 1000 **19** per 1000 Difference: **3 more per 1000** (95% CI 8 fewer - 32 more)	**Very low** Due to very serious imprecision and serious indirectness	The effect of remdesivir on delirium is uncertain.
Time to clinical improvement	Measured by: Scale: lower better Based on data from 1882 patients in 3 studies	**11.0** Days mean **9.0** Days mean Difference: **MD 2.0 lower** (95% CI 4.2 lower - 0.9 higher)	**Low** Due to serious imprecision and serious indirectness	Remdesivir possibly has no effect on time to clinical improvement.
Duration of hospitalization	Measured by: Scale: lower better Based on data from 1882 patients in 3 studies	**12.8** Days mean **12.3** Days mean Difference: **MD 0.5 lower** (95% CI 3.3 lower - 2.3 higher)	**Low** Due to serious imprecision and serious indirectness	Remdesivir possibly has no effect on duration of hospitalization.
Duration of ventilation	Measured by: Scale: lower better Based on data from 440 patients in 2 studies	**14.7** Days mean **13.4** Days mean Difference: **MD 1.3 lower** (95% CI 4.1 lower - 1.5 higher)	**Low** Due to very serious imprecision	Remdesivir possibly has no effect on duration of ventilation.

Source: Siemieniuk et al., 2020 *(2)*.

8. UNCERTAINTIES, EMERGING EVIDENCE AND FUTURE RESEARCH

The guideline recommendations for COVID-19 therapeutics demonstrate remaining uncertainties concerning treatment effects for all outcomes of importance to patients. There is also a need for better evidence on prognosis and values and preferences of patients with COVID-19. Here we outline key uncertainties for remdesivir identified by the GDG, adding to those for corticosteroids in the first version of the living guideline. These uncertainties may inform future research, i.e. the production of more relevant and reliable evidence to inform policy and practice. We also outline emerging evidence in the rapidly changing landscape of trials for COVID-19.

Ongoing uncertainties and opportunities for future research

Remdesivir and its effects on:

- critical outcomes of interest, particularly those that impact resource allocation, such as the need for mechanical ventilation, duration of mechanical ventilation and duration of hospitalization;
- specific subgroups, such as different severities of illness, different time (days) since onset of illness, children and older adults, pregnant women, and duration of therapy;
- long-term outcomes such as mortality at extended endpoints or long-term quality of life;
- long-term safety and rare but important side-effects;
- patient-reported outcomes such as symptom burden;
- outcomes, when used in combination with other agents, such as, but not limited to, corticosteroids;
- impact on viral shedding, viral clearance, patient infectivity.

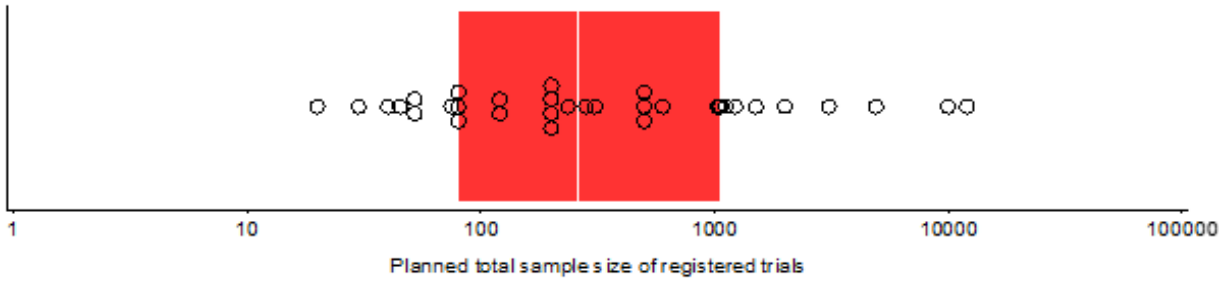
Emerging evidence

The unprecedented volume of planned and ongoing studies for COVID-19 interventions – 2801 RCTs as of 1 November 2020 – implies that more reliable and relevant evidence will emerge to inform policy and practice *(5)*. An overview of registered and ongoing trials for COVID-19 therapeutics is available from the Infectious Diseases Data Observatory, through their living systematic review of COVID-19 clinical trial registrations *(5)* and the WHO website (https://www.covid-nma.com/dataviz/).

Whereas most of these studies are small and of variable methodological quality, a number of large, international platform trials (e.g. RECOVERY, SOLIDARITY and DISCOVERY) are better equipped to provide robust evidence for a number of potential treatment options *(1)*. Such trials can also adapt their design, recruitment strategies and selection of interventions based on new insights, exemplified by the uncertainties outlined above.

For remdesivir 36 trials have been registered and 6 are completed. The median (25th, 75th percentile) planned sample size of these trials is 260 (80, 1062) (Figure 1). Further details of all registered trials are in Supplementary Table 1 in the WHO living guideline on COVID-19 therapeutics published in the BMJ *(9)*.

Figure 1. Sample size of remdesivir randomized controlled trials



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WHO Therapeutics Steering Committee
The committee includes representatives from various WHO departments at headquarters and the regions and has been approved by the WHO Director of the Country Readiness Department and the WHO Chief Scientist. The WHO Secretariat meets on a regular basis to discuss when to trigger guideline updates based on evidence updates from the WHO rapid review team, and other sources of evidence and selects the members of the **Guideline Development Group** (GDG) for living guidance.

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The WHO Therapeutics Steering Committee is fully responsible for decisions about guidance production and convening the GDG.

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ANNEX

Please note that this annex contains the preprint version of this meta-analysis, as used by the Guideline Development Group in its deliberations. The final peer-reviewed version will be available in due course in the BMJ.

Drug treatments for covid-19: living systematic review and network meta-analysis version 3

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Abstract

Objective To compare the effects of treatments for coronavirus disease 2019 (covid-19).
Design Living systematic review and network meta-analysis.
Data sources WHO covid-19 database, a comprehensive multilingual source of global covid-19 literature, up to 27 October 2020 and six additional Chinese databases up to 16 October 2020.
Study selection Randomised clinical trials in which people with suspected, probable, or confirmed covid-19 were randomised to drug treatment or to standard care or placebo. Pairs of reviewers independently screened potentially eligible articles.
Methods After duplicate data abstraction, a bayesian network meta-analysis was conducted. Risk of bias of the included studies was assessed using a modification of the Cochrane risk of bias 2.0 tool, and the certainty of the evidence using the grading of recommendations assessment, development and evaluation (GRADE) approach. For each outcome, interventions were classified in groups from the most to the least beneficial or harmful following GRADE guidance.
Results 85 trials enrolling 41 669 patients met inclusion criteria; 50 (58.8 %) trials and 25 081 (60.2%) patients are new from the previous iteration. 75 randomised controlled trials were eligible for analysis performed on 21 October 2020; 43 (50.6%) of these trials met the threshold inclusion in the analyses with at least 100 participants or 20 events. Compared with standard care, corticosteroids probably reduce death (risk difference 17 fewer per 1000 patients, 95% credible interval 34 fewer to 1 more, moderate certainty), mechanical ventilation (29 fewer per 1000 patients, 54 fewer to 1 more, moderate certainty), and days free from mechanical ventilation (2.6 fewer, 0.2 fewer to 5.0 fewer, moderate certainty). The impact of remdesivir on mortality, mechanical ventilation, length of hospital stay, and duration of symptoms is uncertain, but it probably does not substantially increase adverse effects leading to drug discontinuation (0 more per 1000, 9 fewer to 40 more, moderate certainty). Azithromycin, hydroxychloroquine, lopinavir/ritonavir, interferon-beta, and tocilizumab may not reduce risk of death or have an effect on any other patient-important outcome. The certainty in effects for all other interventions was low or very low.
Conclusion Corticosteroids probably reduce mortality and mechanical ventilation in patients with covid-19 compared with standard care, whereas azithromycin, hydroxychloroquine, interferon-beta, and tocilizumab may not reduce either. Whether or not remdesivir confers any patient-important benefit remains uncertain.
Systematic review registration This review was not registered. The protocol is included as a supplement.
Readers' note This article is a living systematic review that will be updated to reflect emerging evidence. Updates may occur for up to two years from the date of original publication. This version is the 2nd update of the original article published on 30 July 2020 (*BMJ* 2020;370:m2980), and previous versions can be found as data supplements.

Introduction

As of 13 November 2020, more than 55 million people have been infected with severe acute respiratory syndrome coronavirus virus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (covid-19); of these, more than 1.3 million have died.[1] Despite global efforts to identify effective interventions for the prevention and treatment of covid-19, which have resulted in 2400 trials completed or underway,[2] evidence for effective treatment remains limited.

Faced with the pressures of a global pandemic, healthcare workers around the world are prescribing drugs off-label for which there is only very low quality evidence. Timely evidence summaries and associated guidelines could ameliorate the problem.[3] Clinicians, patients, guideline bodies, and government agencies are also facing the challenges of interpreting the results from trials that are being published at a rate never encountered previously. This environment makes it necessary to produce well developed summaries that distinguish more trustworthy evidence from less trustworthy evidence.

Living systematic reviews deal with the main limitation of traditional reviews—that of providing an overview of the relevant evidence only at a specific time.[4] This is crucial in the context of covid-19, in which the best evidence is constantly changing. The ability of a living network meta-analysis to present a complete, broad, and updated view of the evidence makes it the best type of evidence synthesis to inform the development of practice recommendations. Network meta-analysis, rather than pairwise meta-analysis, provides useful information about the comparative effectiveness of treatments that have not been tested head to head. The lack of such direct comparisons is certain to limit inferences in the covid-19 setting. Moreover, the incorporation of indirect evidence can strengthen evidence in comparisons that were tested head to head.[5]

In this living systematic review and network meta-analysis we compare the effects of drug treatments for covid-19. This review is part of the *BMJ* Rapid Recommendations project, a collaborative effort from the MAGIC Evidence Ecosystem Foundation (www.magicproject.org) and *The BMJ*.[6] This living systematic review and network meta-analysis will directly inform *BMJ* Rapid Recommendations[6] on covid-19 treatments, initiated to provide trustworthy, actionable, and living guidance to clinicians and patients soon after new and potentially practice-changing evidence becomes available. The first covid-19 *BMJ* Rapid Recommendation considered the role of remdesivir[7] and subsequent WHO living guidance considered corticosteroids[8] (box 1). This living network meta-analysis is the third version. The previous versions are available in the supplementary material.

Box start

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

- Rochwerg B, Agarwal A, Zeng L, et al. Remdesivir for severe covid-19: a clinical practice guideline. *BMJ* 2020;370:m2924, doi:10.1136/bmj.m2924
  - Rapid Recommendation on remdesivir for covid-19
- Lamontagne F, Agoritsas T, Macdonald H, et al. A living WHO guideline on drugs for covid-19. *BMJ* 2020;370:m3379, doi:10.1136/bmj.m3379
  - Living WHO *BMJ* Rapid Recommendations guidance on drugs for covid-19
- World Health Organization. Corticosteroids for COVID-19. Living guidance 2 September 2020. https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1

• Siemieniuk RAC, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ* 2020;370:m2980, doi:10.1136/bmj.m2980

- Review and network meta-analysis of all available randomised trials that assessed drug treatments for covid-19

• MAGICapp (https://app.magicapp.org/#/guideline/j1W7rn)

- Expanded version of the methods, processes, and results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

Box end

Methods

A protocol provides the detailed methods of this systematic review, including all updates (see supplementary file). We report this living systematic review following the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist for network meta-analyses.[9] A living systematic review is a cumulative synthesis that is updated regularly as new evidence becomes available.[10] The linked *BMJ* Rapid Recommendations guideline panels approved all major decisions relevant to data synthesis.

Eligibility criteria

We included randomised clinical trials in people with suspected, probable, or confirmed covid-19 that compared drugs for treatment against one another or against no intervention, placebo, or standard care. We included trials regardless of publication status (peer reviewed, in press, or preprint) or language. No restrictions were applied based on severity of illness or setting and we included trials of Chinese medicines if the drug comprised one or more specific molecules with a defined molecular weight dosing.

We excluded randomised controlled trials evaluating vaccination, blood products, nutrition, traditional Chinese herbal medicines that include more than one molecule or a molecule without specific molecular weighted dosing, and non-drug supportive care interventions. Trials that evaluated these interventions were identified and categorised separately.

Information sources

We perform daily searches from Monday to Friday in the World Health Organization (WHO) covid-19 database for eligible studies – a comprehensive multilingual source of global literature on covid-19. Prior to its merge with the WHO covid-19 database on 9 October 2020, we performed daily searches from Monday to Friday in the US Centers for Disease Control and Prevention (CDC) COVID-19 Research Articles Downloadable Database for eligible studies.[11] The database includes, but is not limited to the following 25 bibliographic and grey literature sources: Medline (Ovid and PubMed), PubMed Central, Embase, CAB Abstracts, Global Health, PsycInfo, Cochrane Library, Scopus, Academic Search Complete, Africa Wide Information, CINAHL, ProQuest Central, SciFinder, the Virtual Health Library, LitCovid, WHO covid-19 website, CDC covid-19 website, Eurosurveillance, China CDC Weekly, Homeland Security Digital Library, ClinicalTrials.gov, bioRxiv (preprints), medRxiv (preprints), chemRxiv (preprints), and SSRN (preprints).

The daily searches are designed to match the update schedule of the database and to capture eligible studies the day of or the day after publication. To identify randomised controlled trials, we filtered the results from the CDC's database through a validated and highly sensitive machine learning model.[12] We tracked preprints of randomised controlled trials until publication and

updated data to match that in the peer reviewed publication when discrepant and reconciled corrections and retractions existed.

In addition, we search six Chinese databases monthly: Wanfang, Chinese Biomedical Literature, China National Knowledge Infrastructure, VIP, Chinese Medical Journal Net (preprints), and ChinaXiv (preprints). We adapted the search terms for covid-19 developed by the CDC to the Chinese language. For the Chinese literature search, we also included search terms for randomised trials. The supplementary file includes the Chinese literature search strategy.

We monitor living evidence retrieval services on an ongoing basis. These included the Living Overview of the Evidence (L-OVE) COVID-19 Repository by the Epistemonikos Foundation[13] and the Systematic and Living Map on COVID-19 Evidence by the Norwegian Institute of Public Health, in collaboration with the Cochrane Canada Centre at McMaster University.[14]

We searched all English information sources from 1 December 2019 to 27 October 2020, and the Chinese literature from conception of the databases to 16 October 2020.

Study selection

Using a systematic review software, Covidence,[15] pairs of reviewers, following training and calibration exercises, independently screened all titles and abstracts, followed by full texts of trials that were identified as potentially eligible. A third reviewer adjudicated conflicts.

Data collection

For each eligible trial, pairs of reviewers, following training and calibration exercises, extracted data independently using a standardised, pilot tested data extraction form. Reviewers collected information on trial characteristics (trial registration, publication status, study status, design), patient characteristics (country, age, sex, smoking habits, comorbidities, setting and type of care, and severity of covid-19 symptoms for studies of treatment), and outcomes of interest (means or medians and measures of variability for continuous outcomes and the number of participants analysed and the number of participants who experienced an event for dichotomous outcomes). Reviewers resolved discrepancies by discussion and, when necessary, with adjudication by a third party. We updated the data collected from included preprints as soon as the peer review publication became available.

Outcomes of interest were selected based on importance to patients and were informed by clinical expertise in the systematic review team and in the linked guideline panel responsible for the WHO-*BMJ* Rapid Recommendations.[8] The panel includes unconflicted clinical and methodology experts, recruited to ensure global representation, and patient-partners. All panel members rated outcomes from 1 to 9 based on importance to individual patients (9 being most important), and we included any outcome rated 7 or higher by any panel member. Selected outcomes included mortality (closest to 90 days), mechanical ventilation (total number of patients, over 90 days), adverse events leading to discontinuation (within 28 days), viral clearance (closest to 7 days, 3 days either way), admission to hospital, duration of hospital stay, intensive care unit (ICU) length of stay, duration of mechanical ventilation, time to symptom resolution or clinical improvement, time to viral clearance, and days free from mechanical

ventilation (within 28 days). Viral clearance at seven days and time to viral clearance were included because both may be surrogates for transmissibility, although this is uncertain.[16]

Because of the inconsistent reporting observed across trials, we used a hierarchy for the outcome mechanical ventilation in which we considered the total number of patients who received ventilation over the study, if available, and the number of patients ventilated at the time point at which most of the patients were mechanically ventilated, if that is the only way in which this outcome was reported.

Risk of bias within individual studies

For each eligible trial, reviewers, following training and calibration exercises, used a revision of the Cochrane tool for assessing risk of bias in randomised trials (RoB 2.0)[17] to rate trials as either at i) low risk of bias, ii) some concerns—probably low risk of bias, iii) some concerns—probably high risk of bias, or iv) high risk of bias, across the following domains: bias arising from the randomisation process; bias owing to departures from the intended intervention; bias from missing outcome data; bias in measurement of the outcome; bias in selection of the reported results, including deviations from the registered protocol; bias due to competing risks; and bias arising from early termination for benefit. We rated trials at high risk of bias overall if one or more domains were rated as some concerns—probably high risk of bias or as high risk of bias and as low risk of bias if all domains were rated as some concerns—probably low risk of bias or low risk of bias. Reviewers resolved discrepancies by discussion and, when not possible, with adjudication by a third party.

Data synthesis

We conducted the network meta-analysis using a bayesian framework.[18] In this report, we conducted a network meta-analysis of drug treatments for covid-19 that included all patients, regardless of severity of disease.

Summary measures

We summarised the effect of interventions on dichotomous outcomes using the odds ratio and corresponding 95% credible interval. For continuous outcomes, we used the mean difference and corresponding 95% credible interval in days for ICU length of stay, length of hospital stay, and duration of mechanical ventilation because we expected similar durations across randomised controlled trials. For time to symptom resolution and time to viral clearance, we first performed the analyses using the relative effect measure ratio of means and corresponding 95% credible interval before calculating the mean difference in days because we expected substantial variation between studies.[19]

Treatment nodes

Treatments were grouped into common nodes based on molecule and not on dose or duration. For intervention arms with more than one drug, we created a separate node. Chloroquine and hydroxychloroquine were included in the same node for covid-19 specific effects and separated for disease independent adverse effects. We drew network plots using the *networkplot* command of Stata version 15.1 (StataCorp, College Station, TX), with thickness of lines between nodes and size of the nodes based on the inverse of the variance of the direct comparison.[20]

Statistical analysis

For most outcomes, we conducted network meta-analyses and pairwise meta-analyses using a bayesian framework with the same priors for the variance and effect parameters.[18] In previous versions, we used fixed effects for some outcomes because data was sparse or dominated by a single trial. In this update, we used random effects for all outcomes. We used a plausible prior for variance parameter and a uniform prior for the effect parameter suggested in a previous study based on empirical data.[21] For all analyses, we used three Markov chains with 100 000 iterations after an initial burn-in of 10 000 and a thinning of 10. We used node splitting models to assess local incoherence and to obtain indirect estimates.[22] All network meta-analyses were performed using the *gemtc* package of R version 3.6.3 (RStudio, Boston, MA)[23] and all pairwise meta-analyses using the *bayesmeta* package.[18]

In the first iteration of this living network meta-analysis, some treatment nodes with few total participants and few total events resulted in highly implausible and extremely imprecise effect estimates. We therefore decided to include only treatments that included at least 100 patients or had at least 20 events, based on our impression of the minimum number of patients/events to possibly provide meaningful results.

Certainty of the evidence

We assessed the certainty of evidence using the grading of recommendations assessment, development and evaluation (GRADE) approach for network meta-analysis.[5 24 25] Two people with experience in using GRADE rated each domain for each comparison separately and resolved discrepancies by consensus. We rated the certainty for each comparison and outcome as high, moderate, low, or very low, based on considerations of risk of bias, inconsistency, indirectness, publication bias, intransitivity, incoherence (difference between direct and indirect effects), and imprecision.[25] Judgments of imprecision for this systematic review were made using a minimally contextualised approach, with a null effect as the threshold of importance.[26] The minimally contextualised approach considers only whether credible intervals include the null effect and thus does not consider whether plausible effects, captured by credible intervals, include both important and trivial effects.[26] To evaluate certainty of no benefit (or no effect), we used a 2% risk difference threshold of the 95% credible interval for mortality and mechanical ventilation. In other words, if the entire 95% credible interval was within 2% of the null effect, we would not rate down for imprecision. We decided on this preliminary threshold based on a survey of the authors. In future updates, it will be guided by a survey of patients and guideline panellists. We created GRADE evidence summaries (Summary of Findings tables) in the MAGIC Authoring and publication platform (www.magicapp.org) to provide user friendly formats for clinicians and patients and to allow re-use in the context of clinical practice guidelines for covid-19.

Interpretation of results

To facilitate interpretation of the results, we calculated absolute effects for outcomes in which the summary measure was an odds ratio or ratio of means. When available, we inferred baseline risk in the usual care group for each outcome from representative observational data (supplementary material). For mortality, we used data from the CDC on patients who were

hospitalized with covid-19.[27 28] For mechanical ventilation, duration of invasive mechanical ventilation, duration of hospitalization, and ICU length of stay we used baseline risks from the International Severe Acute Respiratory and Emerging Infection COVID-19 database.[29] For all other outcomes, we used the median from all studies in which participants received standard of care to calculate the baseline risk for each outcome, with each study weighed equally. We calculated absolute effects using the transitive risks model[30] using *R2jags* package in R.[31]

For each outcome, we classified treatments in groups from the most to the least effective using the minimally contextualised framework, which focuses on the treatment effect estimates and the certainty of the evidence.[25]

Subgroup and sensitivity analysis

Subgroup analyses were performed for specific interventions of interest at the direction of the linked WHO living guideline panel.[8] In this iteration, we performed subgroup analyses for remdesivir, hydroxychloroquine, and lopinavir/ritonavir. The panel requested subgroup analyses by age (children vs. non-elderly adults vs. elderly) and severity (non-severe vs. severe vs. critical). We performed bayesian hierarchical meta-regression with study as a random effect.

Patient and public involvement

Patients were involved in outcome selection, interpretation of results, and the generation of parallel recommendations, as part of the *BMJ* Rapid Recommendations initiative.

Results

After screening 15 130 titles and abstracts and 300 full texts, 106 unique randomised controlled trials from 94 publications were identified that evaluated drug treatments as of 27 October 2020 (fig 1).[32-76] Searches of living evidence retrieval services identified 19 additional eligible randomised controlled trials.[77-81] Fifty-nine randomized trials have been published in peer reviewed journals, 28 only as preprints, and 17 within two meta-analyses. Most of the trials were registered (98/106; 93%), published in English (89/94; 95%), and evaluated treatment in patients admitted to hospital with covid-19 (95/106; 90%). Just over one third of the trials were conducted in China (33/106; 39%), with the remainder distributed globally. Of the 106 included drug trials, the three most commonly studied drugs were (hydroxy)chloroquine (31/106; 29%), followed by corticosteroids (11/106; 10%) and lopinavir/ritonavir (8/106; 7.5%). Several randomised controlled trials were not eligible to be included in the analysis: four trials that evaluated different durations or doses of the same drug, because both arms would have been classified within the same treatment node[35 43 60 82]; two trials with insufficient data[83-85]; and four trials that reported no outcomes of interest.[81 86-88] Seventy-five randomised controlled trials were eligible for the analysis. To mitigate results with highly implausible and extremely imprecise estimates, we included 43 (57.3%) of these trials reporting on treatments with at least 100 patients or 20 events. Table 1 presents the characteristics of the included studies. Additional study characteristics, outcome data, and risk of bias assessments for each study are available in the supplementary file.

Of the randomised controlled trials included in the analyses, seven did not have publicly accessible protocols or registrations.[66 79 86 88-91] Of the trials with publicly accessible protocols or registrations, 55 reported results for one or more of our outcomes of interest that were not

prespecified in protocols or registrations. No other discrepancies between the reporting of our outcomes of interest in trial reports and protocols or registrations were noted. One trial did not report outcomes in the groups as randomised; the authors shared outcome data with us in the groups as randomised.[51]

Eleven studies were initially posted as preprints and subsequently published after peer review.[35 47 92 48 72 81 93-97] The supplementary material presents the differences between study preprint and peer reviewed publications. Six studies had discrepancies in outcome reporting between the preprint and peer-reviewed publication. No substantiative differences were found for the other five studies.

All analyses reached convergence based on trace plots and a Brooks-Gelman-Rubin statistic less than 1.05, except comparisons including umifenovir for mortality and tocilizumab for adverse events leading to discontinuation because no patients randomised to either of these drugs died.

Risk of bias in included studies

The supplementary material presents the assessment of risk of bias of the included studies for each outcome. Nine studies were judged at low risk of bias in all domains.[17 33 35 40 56 61 85 98 99] All other studies had probably high or high risk of bias in at least one of the domains.

Effects of the interventions

The supplementary material presents the network plots depicting the interventions included in the network meta-analysis of each outcome. Figure 2 presents a summary of the effects of the interventions on the outcomes. The supplementary file also presents detailed relative and absolute effect estimates and certainty of the evidence for all comparisons and outcomes. We did not detect statistical incoherence in any of the network meta-analyses.

Mortality

Seventy-two randomised controlled trials including 40 083 participants reported mortality (Table 1). Thirty-eight trials with 37 730 participants met the threshold of analysing treatments with a minimum of 100 patients or 20 events and were included in the network-meta analysis. The treatment nodes included were azithromycin, colchicine, corticosteroids, favipiravir, hydroxychloroquine, hydroxychloroquine plus azithromycin, interferon beta, lopinavir-ritonavir, remdesivir, rhG-CSF, tocilizumab, umifenovir, and standard care. Random effects network meta-analysis showed that corticosteroids (odds ratio 0.85, 95% credible interval 0.71 to 1.01; risk difference 17 fewer per 1000, 95% credible interval 34 fewer to 1 more; moderate certainty) probably reduce deaths compared to standard care (fig 2). Evidence was less certain for remdesivir (odds ratio 0.90, 0.70 to 1.12; risk difference 12 fewer per 1000, 35 fewer to 14 more; low certainty) and lopinavir-ritonavir (odds ratio 0.90, 0.73 to 1.09; risk difference 12 fewer per 1000, 31 fewer to 10 more; low certainty). Patients randomised to hydroxychloroquine (odds ratio 1.10, 0.90 to 1.35; risk difference 11 more per 1000, 11 fewer to 38 more; low certainty of no benefit) and interferon beta (odds ratio 1.02, 0.70 to 1.32; risk difference 2 more per 1000, 35 fewer to 35 more; low certainty) did not have a lower risk of death than those randomised to standard care. 95% credible intervals included both substantial benefit and harm for azithromycin, colchicine, favipiravir, hydroxychloroquine plus azithromycin, and tocilizumab

(all very low certainty).Very low certainty evidence suggests that rhG-CSF may reduce risk of death compared to standard care. Fixed effects network meta-analysis led to similar results for all treatments compared with standard care: corticosteroids (odds ratio 0.86, 0.77 to 0.95), hydroxychloroquine (odds ratio 1.08, 0.96 to 1.22), interferon beta (odds ratio 1.08, 0.89 to 1.30), lopinavir-ritonavir (odds ratio 0.89, 0.80 to 1.00) and remdesivir (odds ratio 0.92, 0.80 to 1.07).

Mechanical ventilation

Forty randomised controlled trials including 33 727 participants reported mechanical ventilation (Table 1). Twenty-one trials with 32 162 participants met the threshold of analysing treatments with a minimum of 100 patients or 20 events and were included in the network-meta analysis. The treatment nodes included were azithromycin, corticosteroids, hydroxychloroquine, hydroxychloroquine plus azithromycin, interferon beta, lopinavir-ritonavir, remdesivir, rhG-CSF, and standard care (fig 2). Random effects network-meta analysis showed that, compared with standard care, corticosteroids probably reduce risk of mechanical ventilation (odds ratio 0.72, 0.50 to 1.01; risk difference 29 fewer per 1000, 54 fewer to 1 fewer; moderate certainty for risk of bias). Certainty was lower for remdesivir (odds ratio 0.68, 0.41 to 1.00; risk difference 33 fewer per 1000, 65 fewer to 1 more; low certainty) and hydroxychloroquine (odds ratio 1.20, 0.83 to 1.81; risk difference 20 more per 1000, 18 fewer to 76 more; low certainty for risk of bias and imprecision). Evidence for was less certain for azithromycin, hydroxychloroquine plus azithromycin, interferon beta, lopinavir-ritonavir, and tocilizumab, and rhG-CSF (all very low certainty). Fixed effects network meta-analysis led to similar results for all treatments compared with standard care: corticosteroids (odds ratio 0.73, 0.61 to 0.86), remdesivir (odds ratio 0.88, 0.76 to 1.03), hydroxychloroquine (odds ratio 1.16, 0.97 to 1.38), azithromycin (odds ratio 1.13, 0.79 to 1.64), hydroxychloroquine plus azithromycin (odds ratio 1.59, 0.86 to 2.89), interferon beta (odds ratio 0.97, 0.80 to 1.18), and lopinavir-ritonavir (odds ratio 1.16, 0.98 to 1.36).

Adverse events leading to discontinuation

Thirty-two randomised controlled trials including 4698 participants reported adverse effects leading to discontinuation of the study drug (Table 1). Six trials with 1946 participants met the threshold of analysing treatments with a minimum of 100 patients or 20 events and were included in the network-meta analysis. The treatment nodes included were hydroxychloroquine, remdesivir, tocilizumab, and standard care. Moderate certainty evidence showed that remdesivir did not result in a substantial increase in adverse effects leading to drug discontinuation compared with standard care (odds ratio 1.00, 0.37 to 3.83; risk difference 0 more per 1000, 9 fewer to 40 more). Certainty in evidence for hydroxychloroquine and tocilizumab was very low (fig 2).

Viral clearance at 7 days (3 days either way)

Twenty-four randomised controlled trials including 1857 participants measured viral clearance with polymerase chain reaction cut-off points (Table 1). Fourteen trials with 1186 participants met the threshold of analysing treatments with a minimum of 100 patients or 20 events and were included in the network-meta analysis. The treatment nodes included were corticosteroids, favipiravir, hydroxychloroquine, interferon gamma, interferon kappa plus trefoil

factor 2, lopinavir-ritonavir, remdesivir, and standard care. We did not find any convincing evidence that any of the interventions increased the rate of viral clearance (fig 2). The certainty of the evidence was low for remdesivir compared with standard care, and very low for all other comparisons.

Admission to hospital

Three randomised controlled trials including 603 participants reported admission to hospital in patients who were outpatients at baseline (Table 1). One study of hydroxychloroquine versus placebo was included.[98] There were too few events to make any inferences (odds ratio 0.39, 0.12 to 1.28; risk difference 26 fewer per 1000, 38 fewer to 12 more; low certainty) (fig 2).

Venous thromboembolism

One study including 20 participants[100] reported venous thromboembolism in patients who received an anticoagulant as the active drug. No treatment node contained information on at least 100 patients, therefore no analyses were conducted for this outcome.

Clinically-important bleeding

One study including 20 participants[100] reported clinically-important bleeding in patients who received an anticoagulant as the active drug. No treatment node contained information on at least 100 patients, therefore no analyses were conducted for this outcome.

Duration of hospital stay

Thirty-nine randomised controlled trials including 22 807 participants reported duration of hospital stay (Table 1). Twenty trials with 21 440 participants meeting the threshold of analysing treatments with a minimum of 100 patients or 20 events were included in the network meta-analysis. The treatment nodes included were azithromycin, colchicine, corticosteroids, hydroxychloroquine, hydroxychloroquine plus azithromycin, lopinavir-ritonavir, remdesivir, rhG-CSF, tocilizumab, and standard care. Compared with standard care, duration of hospitalisation was shorter in patients who received colchicine (mean difference −1.57 days, −2.78 to −0.32; low certainty). There was no evidence that azithromycin (very low certainty), corticosteroids (very low certainty), hydroxychloroquine (very low certainty), hydroxychloroquine plus azithromycin (low certainty), lopinavir-ritonavir (low certainty), tocilizumab (very low certainty), or remdesivir (low certainty), rhG-CSF (low certainty) impact length of stay (fig 2).

ICU length of stay

Nine randomised controlled trials including 890 participants reported length of ICU stay (Table 1). Two studies randomised at least 100 patients to receive corticosteroids.[70 80] Compared with standard care, length of ICU stay was shorter in patients who received corticosteroids (mean difference −3.83 days, −5.88 to −1.78; low certainty) (fig 2).

Duration of mechanical ventilation

Six randomised controlled trials including 857 participants reported duration of mechanical ventilation (Table 1). Three studies with 739 participants meeting the threshold of analysing treatments with a minimum of 100 patients or twenty events were included in the network-meta analysis. The treatment nodes included corticosteroids, remdesivir, and standard care. There was

no evidence that corticosteroids (mean difference −1.41 days, −3.44 to 0.62; low certainty) and remdesivir (mean difference −1.28 days, −4.06 to 1.47; low certainty) reduce duration of mechanical ventilation (fig 2).

Ventilator-free days

Five randomised controlled trials including 1036 participants reported ventilator-free days (Table 1). Three studies with 962 participants meeting the threshold of analysing treatments with a minimum of 100 patients were included in the network-meta analysis. The treatment nodes included were azithromycin, corticosteroids, tocilizumab, and standard care. Compared to standard care, corticosteroids (mean difference 2.62 days, 0.24 to 4.97; moderate certainty) may increase ventilator-free days. There was no evidence that tocilizumab (low certainty) and azithromycin (very low certainty) increase ventilator-free days (fig 2).

Time to symptom resolution

Thirty-two randomised controlled trials including 4424 participants reported time to symptom resolution (Table 1). Thirteen trials including 3285 participants meeting the threshold of analysing treatments with a minimum of 100 patients were analysed. The treatment nodes included were hydroxychloroquine, lopinavir-ritonavir, remdesivir, rhG-CSF, tocilizumab, and standard care. There was no evidence that remdesivir (moderate certainty), hydroxychloroquine (low certainty), and lopinavir-ritonavir (low certainty) led to shorter symptom duration than in patients who received standard care (fig 2).

Time to viral clearance

Twenty-two randomised controlled trials including 1459 participants reported time to viral clearance (Table 1). At least 100 patients across five trials received hydroxychloroquine and standard care. The certainty of the evidence was very low (fig 2).

Subgroups

Remdesivir have different effects in patients by severity of disease (ratio of odds ratios (ROR) 1.80, CI 1.27 2.59, probability of ROR≤1 = 0.0003). The effects of remdesivir on mortality the three subgroups are: non-severe disease (OR 0.71, 0.33 to 1.46), severe disease (OR 0.73, 0.49 to 1.03), critical disease (OR 1.30, 0.89 to 1.97). Using established criteria, we felt that this subgroup effect had low-to-moderate credibility (supplementary material). No other subgroup was notable for any subgroup effects.

Discussion

This living systematic review and network meta-analysis provides a comprehensive overview of the evidence for drug treatments of covid-19 up to 21 October 2020 and a comprehensive list of drug trials to 27 October 2020. The certainty of the evidence for most of the comparisons was very low. Corticosteroids probably reduce the risk of death, mechanical ventilation, and increase ventilator-free days results driven almost entirely by the RECOVERY trial.[50]

Whether or not remdesivir has any effect on mortality is uncertain. If one believes the subgroup effect, remdesivir may reduce or have no effect mortality in patients with non-critical disease and may increase or have no effect on mortality in patients with critical illness. The subgroup effect however has only moderate credibility and whether or not remdesivir reduces or

increases mortality in any subgroup is uncertain. Direct evidence from randomised controlled trials in patients with covid-19 has so far provided little definitive evidence about adverse effects for most interventions, apart from remdesivir which probably has low risk for adverse effects leading to discontinuation.

No other drug was found to have an impact on any patient with at least moderate certainty for any other outcome. Based on three small trials, colchicine may reduce duration of hospitalization (low certainty) and based on a single small trial, rhG-CSF might reduce mortality and mechanical ventilation in patients with lymphopenia (low certainty).

Compared with the second iteration, there are several important updates (box 2). We now have evidence from several large scale international trials on remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon beta. Unfortunately, the trials showed that none of these interventions had a meaningful effect on any patient important outcomes.

Box start

Box 2. Summary of changes since last iteration

- Fifty-seven additional randomised trials (25 081 participants)
- Azithromycin, colchicine, interferon beta, interferon gamma, interferon kappa plus trefoil factor 2, rhG-CSF, tocilizumab are new interventions included in the analyses, but certainty is low or very low for the effects of these interventions
- We changed the previous analyses that were performed in fixed effects to random effects
- New evidence suggests that remdesivir may not reduce mortality (low certainty) or time to symptom resolution (moderate certainty). Previously, the evidence suggested a benefit on these outcomes with remdesivir.
- New evidence that glucocorticoids probably reduce length of ICU stay (low certainty) and increase ventilator-free days (moderate certainty)
- Evidence for other interventions is similar to the previous version

Box end

Strengths and limitations of this review

Our search strategy and eligibility criteria were comprehensive, without restrictions on language of publication or publication status. To ensure expertise in all areas, our team is composed of clinical and methods experts who have undergone training and calibration exercises for all stages of the review process. To minimise problems with counterintuitive results, we anticipated challenges that arise in network meta-analysis when data are sparse.[20] Many of the results for comparisons with sparse data were uninformative and were sometimes implausible. For that reason, we decided to report evidence on treatments for which at least 100 people were randomised or for which there were at least 20 events. In the future, when more data from more treatments are available, our classification of interventions from the most to the least effective will facilitate clear interpretation of results.

The main limitation of the data is that only nine studies were judged to be at low risk of bias. The primary limitation of the evidence is lack of blinding, which might introduce bias through differences in co-interventions between randomisation groups. We chose to consider the treatment arms that did not receive an active experimental drug (ie, placebo or standard care) within the same node: it is possible that the unblinded standard care groups received systematically different co-interventions than groups randomised to receive a placebo. Direct comparisons in which the evidence is dominated by unblinded studies were rated down, consistent with GRADE, for risk of bias and that is reflected in the rating of the quality of

evidence from the network estimate.[101] Many of the data also had reporting concerns. For some outcomes, the method in which the researchers measured and reported outcomes proved inconsistent across studies. This led the team to propose a hierarchy for the outcome mechanical ventilation, as described in the methods.

The living nature of our systematic review and network meta-analysis could conceivably (at least temporarily) amplify publication bias, because studies with promising results are more likely to be published and are published sooner than studies with negative results. The inclusion of preprints, many of which have negative results, might mediate this risk. Industry sponsored trials such as those for remdesivir and other patented drugs could be particularly at risk of publication bias, and positive results for these drugs might require more cautious interpretation than generic drugs tested in randomised controlled trials independent of industry influence. However, the inclusion of preprints in our network meta-analysis might introduce bias from simple errors and the reporting limitations of preprints. We include preprints because of the urgent need for information and because so many of the studies on covid-19 are published first as preprints. So far, there did not appear to be any major differences between preprints and peer-reviewed manuscripts.

Our living systematic review and network meta-analysis will continue to inform the development of the WHO living guidelines and *BMJ* Rapid Recommendations.[8] An important difference in the methods for assessing the certainty of the evidence does, however, exist between the two. In this living systematic review and network meta-analysis, we use a minimally contextualised approach for rating the certainty of the evidence, whereas the guideline panels use a fully contextualised approach in which the thresholds of importance of magnitudes of effects depend on all other outcomes and factors involved in the decision.[26] The contextualisation explains differences in the certainty of the evidence between the two. The limitations of potentially misleading results when the network is sparse, and the desirability of focusing on direct estimates from larger studies when this is the case, explain differences in the details of the estimates of effect in this network meta-analysis and in the associated guidelines for remdesivir.[7 8]

To date, we are aware of two other similar efforts to ours.[102 103] We decided to proceed independently to ensure that the results fully inform clinical decision making for the associated living guidance.[8] We also include a more comprehensive search for the evidence and several differences in analytical methods, which we believe are best suited for this process. It is also important to evaluate the reproducibility and replicability of results from different scientific approaches.

We will periodically update this living systematic review and network meta-analysis. We from several new randomised trials that examined tocilizumab were published after our statistical analysis and trials on all drugs are being published at an increasingly faster rate. The changes from each version will be highlighted for readers and the most updated version will be the one available in the publication platform. Previous versions will be archived in the supplementary material. This living systematic review and network meta-analysis will also be accompanied by an interactive infographic and a website for users to access the most updated results in a user-friendly format (magicapp.org).

Conclusions

Evidence from this living systematic review and network meta-analysis suggests that corticosteroids probably reduce mortality, mechanical ventilation, and ventilator-free days in patients with severe covid-19. Whether or not remdesivir has any impact on any outcome remains uncertain. Hydroxychloroquine, lopinavir/ritonavir, and interferon beta may not reduce mortality or mechanical ventilation, and they seem unlikely to have any other benefits. The effects of most drug interventions are currently highly uncertain, and no definitive evidence exists that other interventions result in important benefits and harms for any outcomes.

Box start

What is already known on this topic

Despite huge efforts to identify effective drug interventions for coronavirus disease 2019 (covid-19), evidence for effective treatment remains limited

What this study adds

This living systematic review and network meta-analysis provides a comprehensive overview and assessment of the evidence published as of 21 October 2020 and will be updated periodically

The certainty of the evidence for most interventions tested thus far is low or very low

In patients with severe covid-19, glucocorticoids probably decrease mortality, mechanical ventilation. No other drug has compelling evidence of benefit.

Box end

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Ethical approval: Not applicable. All the work was developed using published data.

Data sharing: No additional data available.

RACS affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: The infographic and MAGICapp decision aids (available at www.magicapp.org/) were created to facilitate conversations between healthcare providers and patients or their surrogates. The MAGICapp decision aids were co-created with people who have lived experience of covid-19.

Table 1 Study characteristics

Study	Publication status, registration No	No of participants	Country	Mean age (years)	Men (%)	Type of care, comorbidities	Severity	Mechanical ventilation at baseline (%)	Treatments (dose and duration)	Outcomes
Abbaspour Kasgari 2020[74]‡	Published, IRCT20200328046886N1	48	Iran	52.5	37.5	Inpatient; ischemic heart disease (22.9%); diabetes (37.5%); chronic obstructive pulmonary disease (2.1%)	Mild/moderate (100%)	NR	Sofosbuvir-daclatasvir (400 mg and 60 mg once daily for 14 days, ribavirin (600 mg twice daily for 14 days); standard care	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay; intensive care unit length of stay; duration of ventilation
Abd-Elsalam 2020[54]	Published, NCT04353336	194	Egypt	40.7	58.8	Inpatient	NR	NR	Hydroxychloroquine (200 mg twice daily for 15 days); standard care	Mortality; mechanical ventilation; duration of hospital stay; time to symptom or clinical improvement; time to viral clearance
Altay 2020[104]‡	Preprint, NCT04573153	100	Turkey	35.6	60.0	Outpatient; diabetes (5.0%); hypertension (2.0%)	Mild/moderate (100%)	0	Serine (24 g/day total, given twice daily, for 14 days), N-acetylcysteine (5.1 g/day total, given twice daily, for 14 days), nicotinamide riboside (2 g/day total, given twice daily, for 14 days), L-carnitine tartrate (7.46 g/day total, given twice daily, for 14 days); placebo	Mortality; time to symptom or clinical improvement

Angus 2020; REMAP-CAP[70]	Published, NCT02735707	403	Australia, Canada, Ireland, France, Netherlands, New Zealand, UK, USA	59.9	71.1	Inpatient; intensive care (100%); cardiovascular disease (7.3%); diabetes (32.1%); asthma or chronic obstructive pulmonary disease (16.2%); respiratory disease (19.5%)	Severe (100%)	100	Hydrocortisone (50 mg four times daily for 7 days); hydrocortisone (50 mg four times daily while in shock for up to 28 days); standard care	Mortality; mechanical ventilation; duration of hospital stay; ICU length of stay
Ansarin 2020[105]‡	Published, IRCT202003117046797N4	78	Iran	59.8	55.1	Inpatient; diabetes (33.3%); hypertension (50.0%)	NR	NR	Bromhexine hydrochloride (8 mg three times daily for 14 days); standard care	Mortality; mechanical ventilation; duration of hospital stay
Beigel 2020; ACTT-1[106]	Published, NCT04280705	1062	USA, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore	58.9	64.4	Inpatient; coronary artery disease (11.9%); congestive heart failure (5.6%); diabetes (30.6%); hypertension (50.7%); asthma (11.4%); chronic oxygen requirement (2.2%); chronic respiratory disease (7.6%)	Severe (90.1%)	45.0	Remdesivir (100 mg/day for 10 days); placebo	Mortality; mechanical ventilation; adverse effects leading to discontinuation; duration of hospital stay; duration of ventilation; time to symptom or clinical improvement
Cao 2020; LOTUS China[37]	Published, ChiCTR2000029308	199	China	58.0	60.3	Inpatient; cerebrovascular disease (6.5%); diabetes (11.6%)	Severe (100%)	16.1	Lopinavir-ritonavir (400 mg and 100 mg twice daily for 14 days); standard care	Mortality; mechanical ventilation; viral clearance; duration of hospital stay; intensive care unit length of stay; duration of ventilation; time to symptom or clinical

										improvement
Cao 2020[38]‡	Published, ChiCTR-OPN-2000029580	43	China	63.0	58.5	Inpatient; coronary artery disease (7.3%); diabetes (19.5%); hypertension (39.0%)	Severe (100%)	12.2	Ruxolitinib (5 mg twice daily); placebo	Mortality; mechanical ventilation; duration of hospital stay; duration of ventilation; time to symptom or clinical improvement; time to viral clearance
Castillo 2020‡; Pilot Covidiol[55]	Published, NCT04366908	76	Spain	53.0	59.2	Inpatient; cardiovascular disease (4.0%); diabetes (10.5%); hypertension (34.2%); previous lung disease (7.9%)	NR	NR	Calcifediol (0.532 mg on day 1, then 0.266 mg on day 3 and 7, and then weekly until discharge or ICU admission); standard care	Mortality; adverse events leading to discontinuation
Cavalcanti, 2020[107]	Published, NCT04322123	667	Brazil	50.3	58.4	Inpatient; intensive care (13.8%); heart failure (1.5%); diabetes (19.1%); hypertension (38.3%); asthma (6.0%); chronic obstructive pulmonary disease (1.8%)	Mild/Moderate (100%)	0	Hydroxychloroquine (400 mg twice daily for 7 days); hydroxychloroquine (400 mg twice daily for 7 days), azithromycin (500 mg/day for 7 days); standard care	Mortality; mechanical ventilation; duration of hospital stay
Chen 2020[39]	Preprint, ChiCTR2000029559	62	China	44.7	46.8	Inpatient; NR	Mild/moderate (100%)	NR	Hydroxychloroquine (200 mg twice daily for 5 days); standard care	Time to symptom or clinical improvement
Chen 2020[39]	Preprint, ChiCTR2000030254	240	China	NR	46.6	NR; diabetes (11.4%); hypertension (28.0%)	Mild/moderate (88.6%); severe (10.2%); critical (1.3%)	NR	Favipiravir (600 mg twice daily for 7 days); umifenovir (200 mg three times daily for 7 days)	Mortality; time to symptom or clinical improvement

Chen 2020[33]	Published, NCT04261517	30	China	48.6	70.0	Inpatient; diabetes (6.7%); hypertension (26.7%); chronic obstructive pulmonary disease (3.3%)	Mild/moderate (100%)	NR	Hydroxychloroquine (400 mg/day for 5 days); standard care	Mortality; adverse events leading to discontinuation; viral clearance; time to symptom or clinical improvement; time to viral clearance
Chen 2020[35]	Preprint, ChiCTR2000030054	48	China	46.9	45.8	Inpatient; diabetes (18.8%); hypertension (16.7%)	Mild/moderate (100%)	NR	Chloroquine (500 mg/day for 10 days); hydroxychloroquine (200 mg twice daily for 10 days); standard care	Mortality; adverse events leading to discontinuation; viral clearance; duration of hospital stay; time to symptom or clinical improvement; time to viral clearance
Chen 2020[39]	Preprint, NCT04384380	33	Taiwan	32.9	57.6	Inpatient	Mild/Moderate (100%)	0	Hydroxychloroquine (200 mg twice daily for 7 days); standard care	Mortality; time to viral clearance
Cheng 2020[110]	Published, ChiCTR2000030007	200	China	45.0	56.0	Inpatient	Critical (0%)	27.0	Granulocyte colony-stimulating factor (5 µg/kg/day for 3 days); standard care	Mortality; mechanical ventilation; viral clearance; duration of hospital stay; time to symptom or clinical improvement
Corral-Gudino 2020; GLUCOCOVID[51]	Preprint, 2020-001934-37	63	Spain	69.8	61.9	Inpatient; heart disease (12.7%); diabetes (17.5%); hypertension (47.6%); respiratory condition (7.9%)	Critical (0%)	0	Methylprednisolone (40 mg twice daily for 3 days, then 20 mg twice daily for 3 days); standard care	Mortality; mechanical ventilation
Cruz 2020‡; ATENEA-Co-300[111]	Preprint, IG/CIGB300I/CV/2001	20	Cuba	45.4	70.0	Inpatient; hypertension (25.0%)	Mild/moderate (90%); severe (10%)	NR	Anti-CK2 synthetic peptide (2.5 mg/kg/day for 5 days); standard care	Time to viral clearance
Dabbous 2020[112]	Preprint, NCT04349241	100	Egypt	36.4	50.0	Inpatient	Mild/moderate (100%)	NR	Favipiravir (600 mg twice daily for 10 days); standard care	Mortality; viral clearance; duration of hospital stay; time to viral clearance

Davoodi 2020[113]‡	Published, IRCT2019072704434N1	60	Iran	57.7	59.3	Outpatient; diabetes (27.8%); lung disease (1.9%)	Mild/Moderate (100%)	0	Febuxostat (80 mg/day for 5 days); hydroxychloroquine (200 mg twice daily for 5 days)	Mortality; admission to hospital
Davoudi-Monfared 2020[42 95]	Published, IRCT20100228003449N28	92	Iran	58.7	54.3	Inpatient; ischemic heart disease (28.4%); diabetes (27.2%); hypertension (38.3%); asthma (1.2%); chronic obstructive pulmonary disease (1.2%)	Severe (100%)	29.6	Interferon beta-1a (44 μg/ml three times weekly for 14 days); standard care	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay; intensive care unit length of stay; duration of ventilation; time to symptom or clinical improvement
de Alencar 2020[99]‡	Published, U1111-1250-356	140	Brazil	58.5	59.3	Inpatient; diabetes (37.8%); hypertension (46.7%)	Severe (100%)	0.7	N-acetylcysteine (14 g in the first 4 hours, then 7 g in the next 16 hours); placebo	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay; intensive care unit length of stay
Deftereos 2020; GRECCO-19[114]	Published, NCT04326790	110	Greece	64.0	58.1	Inpatient; atrial fibrillation (10.5%); coronary artery disease (13.3%); valvulopathy (4.8%); diabetes (20.0%); hypertension (44.8%); chronic obstructive pulmonary disease (4.8%)	NR	2.9	Colchicine (0.5 mg twice daily for 21 days); standard care	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay
Delgado-Enciso 2020‡; TX-COVID19[115]	Preprint, RPCEC00000309	84	Mexica	47.1	53.6	Outpatient; diabetes (11.9%); hypertension (19.1%); asthma (6.0%)	Mild/moderate (100%)	NR	Electrolyzed saline (15 ml/day for 7 days with successive increases up to 30 ml/day if indicated); standard care	Mortality; admission to hospital; adverse events leading to discontinuation

Dequin 2020; CAPE COVID[56]	Published, NCT02517489	149	France	62.2	69.8	Inpatient; intensive care (100%); cerebrovascular disease (4.0%); diabetes (18.1%); asthma (3.4%); chronic obstructive pulmonary disease (4.0%)	Critical (100%)	81.2	Hydrocortisone (200 mg/day for 7 days, followed by 100 mg once daily for 4 days, and 50 mg once daily for 3 days)	Mortality; mechanical ventilation
Doi 2020* [82]	Published, jRCTs041190120	89	Japan	50.0	61.4	Inpatient	NR	NR	Favipiravir (800 mg twice daily for 10 days starting on day 1 of enrolment); favipiravir (800 mg twice daily for 10 days starting on day 6 of enrolment)	Mortality; mechanical ventilation; viral clearance; duration of hospital stay; time to symptom or clinical improvement; time to viral clearance
Duarte 2020[82]‡	Preprint, NCT04355936	82	Argentina	61.9	61.5	Inpatient; stroke (7.7%); diabetes (11.5%); hypertension (30.8%); asthma (1.3%); chronic obstructive pulmonary disease (11.5%)	NR	0	Telmisartan (80 mg twice daily for 14 days); standard care	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay
Edalatifard 2020[116]	Published, IRCT20200404046947N1	68	Iran	58.5	62.9	Inpatient; cardiovascular disease (17.7%); diabetes (35.5%); hypertension (32.3%); respiratory condition (9.7%)	Severe (100%)	37.1	Methylprednisolone (250 mg/day for 3 days); standard care	Mortality; mechanical ventilation; time to symptom or clinical improvement
Esquivel-Moynelo 2020; ESPERANZA[71]	Preprint, RPCEC00000307	79	Cuba	38.0	54.0	Inpatient; cardiac disease (6.4%); diabetes (4.8%); hypertension (22.2%);	Mild/moderate (100%)	NR	Interferon gamma (0.5 MIU twice a week for 14 days); standard care	Mortality; viral clearance; time to viral clearance

						asthma (6.4%)				
Farahani 2020[85]*	Preprint, IRCT20200406046963N1	29	Iran	64.0	65.5	Inpatient	Mild/moderate (0%)	NR	Methylprednisolone (1000 mg/day for 3 days), prednisolone (1 mg/kg with tapering of dose over 10 days); standard care	Mortality; mechanical ventilation; intensive care unit length of stay
Fu 2020[117]	Published, ChiCTR2000030262	80	China	35.3	63.8	Inpatient; diabetes (3.8%); hypertension (5.0%)	Mild/moderate (100%)	NR	Interferon kappa (2 mg/day for 6 days), trefoil factor 2 (5 mg/day for 6 days); standard care	Mortality; adverse events leading to discontinuation; viral clearance; duration of hospital stay; time to viral clearance
Furtado 2020; COALITION II[118]	Published, NCT04321278	447	Brazil	60.2	64.0	Inpatient; heart failure (5.6%); previous stroke (4.0%); previous myocardial infarction (4.5%); diabetes (38.0%); hypertension (60.9%); chronic obstructive pulmonary disease (6.7%)	Severe (100%)	50.3	Azithromycin (500 mg/day for 10 days); standard care	Mortality; mechanical ventilation; duration of hospital stay; ventilator-free days
Goldman 2020[43]*	Published, NCT04292899	402	USA, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, Taiwan	61.5	63.7	Inpatient; diabetes (22.7%); hypertension (49.9%); asthma (12.3%)	Severe (100%)	30.7	Remdesivir (100 mg/day for 5 days); remdesivir (100 mg/day for 10 days)	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay; time to symptom or clinical improvement
Guvenmez 2020[89]	Published	24	Turkey	58.8	62.5	Inpatient; NR	NR	0	Lincomycin (600 mg twice daily for 5 days); azithromycin (250 mg/day for 5 days)	Viral clearance
Horby 2020; RECOVERY[10 92]	Published, NCT04381936	6425	UK	66.2	63.6	Inpatient; heart disease (27.3%); diabetes (24.1%); chronic lung disease (21.0%); tuberculosis (0.4%)	NR	15.7	Dexamethasone (6 mg/day for 10 days); standard care	Mortality; mechanical ventilation; duration of hospital stay

Horby 2020; RECOVERY[96 119]	Published, NCT04381936	4716	UK	65.3	62.2	Inpatient; heart disease (25.7%); diabetes (27.2%); chronic lung disease (22.2%); tuberculosis (0.3%)	NR	16.8	Hydroxychloroquine (400 mg twice daily for 10 days); standard care	Mortality; mechanical ventilation; duration of hospital stay
Horby 2020; RECOVERY[97]	Published, NCT04381936	5040	UK	66.2	61.1	Inpatient; heart disease (26.0%); diabetes (27.5%); chronic lung disease (23.1%); tuberculosis (0.3%)	NR	4.1	Lopinavir-ritonavir (400 mg and 100 mg twice daily for 10 days); standard care	Mortality; mechanical ventilation; duration of hospital stay
Hu 2020[120]‡	Published, ChiCTR2000030058	10	China	54.9	30.0	Inpatient; hypertension (10.0%); chronic obstructive pulmonary disease (10.0%)	Mild/moderate (100%)	0	Leflunomide (20 mg/day for 10 days); standard care	Mortality; viral clearance; time to symptom or clinical improvement; time to viral clearance
Huang 2020[77]	Published, ChiCTR2000029542	22	China	44.0	59.1	Inpatient; cerebrovascular disease (4.5%); diabetes (9.1%); hypertension (18.2%)	Mild/moderate (63.6%); severe (36.4%)	NR	Chloroquine (500 mg twice daily for 10 days); lopinavir-ritonavir (400 mg and 100 mg twice daily for 10 days)	Viral clearance; duration of hospital stay; time to symptom or clinical improvement; time to viral clearance
Huang 2020[93]‡	Published, ChiCTR2000029387	101	China	42.5	45.5	Inpatient	Mild/moderate (100%)	NR	Ribavirin (400-600 mg three times daily for 14 days), interferon-alfa (5 mg twice daily for 14 days); lopinavir-ritonavir (400 mg and 100 mg twice daily for 14 days), interferon-alfa (5 mg twice daily for 14 days); ribavirin (400-600 mg three times daily for 14 days), lopinavir-ritonavir (400 mg and 100 mg twice daily for 14 days), interferon-alfa (5 mg twice daily for 14 days)	Mortality; adverse events leading to discontinuation; viral clearance; duration of hospital stay; time to symptom or clinical improvement; time to viral clearance
Hung 2020[44]‡	Published, NCT04276688	127	China	51.3	53.5	Inpatient; coronary artery disease (7.9%); cerebrovascular disease (1.6%);	Mild/moderate (100%)	0	Lopinavir-ritonavir (400 mg and 100 mg twice daily for 14 days), ribavarin (400 mg twice daily for 14 days), interferon	Mortality; mechanical ventilation; adverse effects leading to discontinuation;

						diabetes (13.4%); hypertension (28.4%); obstructive sleep apnoea (1.6%); tuberculosis (1.6%)			beta-1b (1-3 mlL every other day); lopinavir-ritonavir (400 mg and 100 mg twice daily for 14 days)	duration of hospital stay; time to symptom or clinical improvement; time to viral clearance
Ivaschenko 2020[72 73]	Published, NCT04434248	60	Russia	50.7	50.0	Inpatient; NR	Mild/moderate (100%)	0	Favipiravir (600 mg twice daily for 14 days); favipiravir (800 mg twice daily for 14 days); standard care	Mortality; mechanical ventilation; adverse events leading to discontinuation; viral clearance; time to symptom or clinical improvement
Jeronimo 2020; Metcovid[59]	Published, NCT04343729	416	Brazil	55.0	65.3	Inpatient; intensive care (35.4%); heart disease (6.6%); diabetes (29.1%); hypertension (48.4%); asthma (2.4%); chronic obstructive pulmonary disease (0.5%); tuberculosis (2.1%)	NR	33.9	Methylprednisolone (0.5 mg/kg twice daily for 5 days); placebo	Mortality; mechanical ventilation; viral clearance; duration of hospital stay
Kimura 2020[121]‡	Published, NCT0447538	54	USA	38.2	53.3	Outpatient; heart disease (4.4%); diabetes (6.7%); hypertension (24.4%); chronic lung disease (15.6%)	NR	NR	Hypertonic saline (250 ml twice daily); hypertonic saline with surfactant (250 ml and 2.5 mg twice daily); standard care	Time to symptom or clinical improvement
Lemos 2020‡; HESACOVID[100]	Published, REBEC RBR-949z6v	20	Brazil	56.5	80.0	Inpatient; cardiovascular disease (10.0%); diabetes (35.0%); hypertension (35.0%)	Critical (100%)	100	Enoxaparin (1 mg/kg/day to 1 mg/kg twice daily for 14 days based on age and creatinine clearance; maximum dose was 140 mg twice daily); standard care	Mortality; venous thromboembolism; clinically-important bleeding; duration of hospital stay; ventilator-free days
Li 2020; ELACOI[83]	Published, NCT04252885	86	China	49.4	46.5	Inpatient; cardiovascular disease (2.3%); diabetes (2.3%); hypertension (10.5%)	Mild/moderate (100%)	0	Lopinavir-ritonavir (200 mg and 50 mg twice daily for 7 to 14 days); umifenovir (200 mg three times daily for 7 to 14 days); standard care	Mortality; adverse effects leading to discontinuation; viral clearance; time to viral clearance

Li 2020[60]*	Preprint, ChiCTR2000029638	96	China	53.6	46.8	Inpatient; cerebrovascular disease (5.3%); heart disease (7.5%); diabetes (9.6%); hypertension (19.2%); chronic obstructive pulmonary disease (1.1%); tuberculosis (3.2%)	Mild/moderate (87.2%); severe (12.8%)	25.5	Recombinant super-combinant interferon (12 MIU twice daily for 28 days); interferon alpha (5 MIU twice daily for 28 days)	Mortality; mechanical ventilation; adverse events leading to discontinuation; viral clearance; duration of hospital stay; time to symptom or clinical improvement; time to viral clearance
Li 2020[122]‡	Published, NCT04273763	18	China	52.0	77.8	Inpatient; diabetes (11.1%); hypertension (33.3%)	Mild/moderate (100%)	0	Bromhexine hydrochloride (32 mg three times daily for 14 days); standard care	Mortality; mechanical ventilation; adverse events leading to discontinuation; time to symptom or clinical improvement
Lopes 2020 [61]	Preprint, RBR-8jyhxh	38	Brazil	50.8	40.0	Inpatient; cardiovascular disease (40.0%); diabetes (31.4%); respiratory condition (14.3%)	Critical (0%)	2.6	Colchicine (0.5 mg three times daily for 5 days, then 0.5 mg twice daily for 5 days); placebo	Mortality; adverse events leading to discontinuation; duration of hospital stay; intensive care unit length of stay
Lou 2020[80]	Preprint, ChiCTR2000029544	30	China	52.5	72.4	Inpatient; cardiovascular disease (13.8%); diabetes (6.9%); hypertension (20.7%)	NR	0	Baloxavir marboxil (80 mg/day for up to 3 doses on days 1, 4, and 7); favipiravir (600 mg three times daily for 14 days); standard care	Mortality; mechanical ventilation; viral clearance; time to symptom or clinical improvement; time to viral clearance
Lyngbakken 2020*; NO COVID-19[81]	Published, NCT04316377	53	Norway	62.0	66.0	Inpatient; coronary heart disease (9.4%); diabetes (17.0%); hypertension (32.1%); chronic obstructive pulmonary disease or asthma (26.4%)	Mild/moderate (0%)	0	Hydroxychloroquine (400 mg twice daily for 7 days); standard care	NA

Mansour 2020[62]‡	Preprint, U1111-1250-1843	60	Brazil	51.6	53.3	Inpatient; diabetes (46.7%); hypertension (50.0%); asthma (3.3%)	Severe (100%)	NR	Icatibant (30 mg three times daily for 4 days); C1 esterase/kallikrein inhibitor (20 IU/kg on day 1 and 4); standard care	Mortality; duration of hospital stay; intensive care unit length of stay
Mehboob 2020[75]‡	Preprint, NCT04468646	18	Pakistan	53.3	61.1	Inpatient; carotid artery bypass grafting (5.6%); ischemic heart disease (33.3%); diabetes (38.9%); hypertension (50.0%)	Mild/moderate (27.8%); severe (33.3%); critical (38.9%)	NR	Aprepitant (80 mg/day for 3-5 days); standard care	Mortality
Miller 2020‡; CARDEA[63]	Published, NCT04345614	30	USA	59.3	46.7	Inpatient; diabetes (40.0%); hypertension (46.7%)	Severe (86.7%); critical (13.3%)	13.3	Auxora (1.6 mg/kg given in 4 hours for 3 days); standard care	Mortality; mechanical ventilation; time to symptom or clinical improvement
Mitja 2020[83]†	Published, NCT04304053	353	Spain	41.6	31.4	Outpatient; cardiovascular disease (12.0%); respiratory condition (5.8%)	Mild/moderate (100%)	0	Hydroxychloroquine (400 mg/day for 7 days); standard care	Mortality; mechanical ventilation; admission to hospital; time to symptom or clinical improvement
Mitja 2020†; BCN PEP-CoV-2[84]	Preprint, NCT04304053	352	Spain	42.0	29.0	Outpatient; NR	Mild/moderate (100%)	0	Hydroxychloroquine (400 mg/day for 7 days), cobicistat-boosted darunavir (800 mg/150 mg/day for 7 days); standard care	Mortality; mechanical ventilation; admission to hospital; time to symptom or clinical improvement
Nojomi 2020[123]‡	Preprint, IRCT20180725040596N2	100	Iran	56.4	60.0	Inpatient; coronary heart disease (9.0%); diabetes (28.0%); hypertension (39.0%); asthma (2.0%)	Mild/moderate (77.0%); severe (23.0%)	NR	Hydroxychloroquine (400 mg/ day for 1 day), lopinavir-ritonavir (400 mg twice daily for up to 14 days); hydroxychloroquine (400 mg twice daily for 7 to 14 days), umifenovir (200 mg three times daily for 7 to 14 days)	Mortality; mechanical ventilation; duration of hospital stay; time to symptom or clinical improvement

Pan 2020; SOLIDARITY[124]	Preprint, NCT04315948	5475	Albania, Argentina, Austria, Belgium, Brazil, Canada,	NR	62.9	Inpatient; heart disease (20.9%); diabetes (25.2%); asthma (5.1%); chronic lung disease (5.4%)	NR	8.9	Remdesivir (100 mg/day for 10 days); standard care	Mortality; mechanical ventilation
		1854	Colombia, Egypt, Finland, France, Honduras, India,		59.9	Inpatient; heart disease (20.9%); diabetes (21.8%); asthma (4.7%); chronic lung disease (6.9%)		9.0	Hydroxychloroquine (200 mg twice daily for 10 days); standard care	Mortality; mechanical ventilation
		2791	Indonesia, Iran, Ireland, Italy, Kuwait, Lebanon, Lithuania,		59.7	Inpatient; heart disease (20.9%); diabetes (24.0%); asthma (4.4%); chronic lung disease (6.6%)		8.2	Lopinavir-ritonavir (200 mg and 50 mg twice daily for 14 days); standard care	Mortality; mechanical ventilation
		4127	Luxembourg, Macedonia, Malaysia, Norway, Pakistan, Phillipines, Peru, Saudi Arabia, South Africa, Spain, Switzerland		63.0	Inpatient; heart disease (21.5%); diabetes (25.0%); asthma (4.2%); chronic lung disease (5.4%)		6.6	Interferon beta-1a (44 µg three times daily for 6 days; patients on high-flow oxygen, ventilators, or ECMO were given 10 µg/day for 6 days); standard care	Mortality; mechanical ventilation
Rahmani 2020[64]	Published, IRCT20100228003449N27	80	Iran	60.5	59.1	Inpatient; ischemic heart disease (30.0%); diabetes (31.8%); hypertension (56.1%); asthma (4.6%); chronic obstructive pulmonary disease (4.6%)	Severe (100%)	1.5	Interferon beta-1b (250 µg every other day for 14 days); standard care	Mortality; mechanical ventilation; duration of hospital stay; intensive care unit length of stay; time to symptom or clinical improvement
Ren 2020[125]‡	Published, ChiCTR2000029853	20	China	52.0	60.0	Inpatient; cardiovascular disease (5.0%); diabetes	Mild/moderate (100%)	0	Azvudine (5 mg/day until discharge); standard care	Mortality; adverse events leading to discontinuation; viral

						(5.0%); hypertension (5.0%)				clearance; duration of hospital stay; time to viral clearance
Rosas 2020; COVACTA[80]	Preprint, NCT04320615	452	Canada, Denmark, France, Germany, Italy, Netherlands, Spain, UK, USA	60.8	69.9	Inpatient; intensive care (56.4%); cardiovascular impairment (28.1%); diabetes (38.1%); hypertension (62.1%); chronic lung disease (16.2%)	Severe (100%)	37.7	Tocilizumab (8 mg/kg, max 800 mg up to two times in 24 hours); placebo	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay; intensive care unit length of stay; ventilator-free days; time to symptom or clinical improvement
Sadeghi 2020[65]‡	Published, IRCT20200128046294N2	70	Iran	58.0	51.5	Inpatient; heart failure (15.2%); diabetes (42.4%); hypertension (34.9%); asthma (3.0%); chronic pulmonary disease (22.7%)	Mild/moderate (0%)	0	Sofosbuvir-declatasvir (400 mg and 60 mg once daily for 14 days); standard care	Mortality; mechanical ventilation; duration of hospital stay; time to symptom or clinical improvement
Salehzadeh 2020[126]	Preprint, IRCT20200418047126N1	100	Iran	56.1	41.0	Inpatient; ischemic heart disease (15.0%); diabetes (11.0%); hypertension (11.0%); chronic obstructive pulmonary disease (4.0%)	NR	NR	Colchicine (1 mg/day for 6 days); placebo	Mortality; duration of hospital stay
Sekhavati 2020[66]	Published	111	Iran	57.1	46.0	Inpatient	NR	NR	Azithromycin (500 mg/day for 5 days); standard care	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay; intensive care unit length of stay
Silva Borba 2020*; CloroCOVID-19[35][127]	Published, NCT04323527	81	Brazil	51.1	75.3	Inpatient; intensive care (45.7%); cardiovascular disease (9.1%); diabetes (25.5%); hypertension (45.5%); asthma	Severe (100%)	NR	Chloroquine (600 mg twice daily for 10 days); chloroquine (450 mg/day for 5 days)	Mortality

						(7.4%); tuberculosis (3.6%)				
Skipper 2020[68]	Published, NCT04308668	491	USA, Canada	40.0	45.8	Outpatient; cardiovascular disease (1.2%); diabetes (3.9%); hypertension (11.0%); asthma (10.4%); chronic lung disease (0.4%)	Mild/moderate (100%)	0	Hydroxychloroquine (600 mg/day for 5 days); placebo	Mortality; admission to hospital
Spinner 2020[67]	Published, NCT04292730	596	France, Germany, Hong Kong, Italy, Netherlands, Korea, Singapore, Spain, Switzerland, Taiwan, UK, USA	57.0	61.1	Inpatient; cardiovascular disease (56.3%); diabetes (39.7%); hypertension (42.5%); asthma (13.9%)	Mild/moderate (100%)	0.9	Remdesivir (100 mg/day for 10 days); remdesivir (100 mg/day for 5 days); standard care	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay; time to symptom or clinical improvement
Sterne 2020; DEXA-COVID 19[58]	Data from meta-analysis, NCT04325061	19	Spain	60.7	68.4	Inpatient; NR	Critical (100%)	100	Dexamethasone (20 mg/day for 5 days, then 10 mg/day for 5 days); standard care	Mortality
Sterne 2020; COVID STEROID[58]	Data from meta-analysis, NCT04348305	29	Denmark	59.4	79.3	Inpatient; NR	Critical (100%)	51.7	Hydrocortisone (200 mg/day for 7 days); placebo	Mortality
Sterne 2020; Steroids-SARI[58]	Data from meta-analysis, NCT04244591	47	China	64.6	74.5	Inpatient; NR	Critical (100%)	57.5	Methylprednisolone (40 mg twice daily for 5 days); standard care	Mortality
Sun 2020[79]‡	Published	66	China	49.5	66.7	Inpatient; cardiovascular disease (1.5%); diabetes (9.1%); hypertension (18.2%)	Mild/moderate (100%)	NR	Diammonium glycyrrhizinate (150 mg three times daily)	Mortality
Tang 2020[47 128]	Published, ChiCTR2000029868	150	China	46.1	55.0	Inpatient; diabetes (14.0%); hypertension (6.0%)	Mild/moderate (99.0%); severe (1.0%)	NR	Hydroxychloroquine (800 mg/day for 14 to 21 days); standard care	Mortality; adverse effects leading to discontinuation; viral

										clearance; time to symptom or clinical improvement; time to viral clearance
Tomazini 2020; CoDEX[68]	Published, NCT04327401	299	Brazil	61.4	62.5	Inpatient; intensive care (100%); heart failure (7.7%); diabetes (42.1%); hypertension (66.2%)	Critical (100%)	100	Dexamethasone (20 mg/day for 5 days, then 10 mg/day for 5 days); standard care	Mortality; mechanical ventilation; ventilator-free days; duration of ventilation
Ulrich 2020; TEACH[129]	Published, NCT04369742	128	USA	66.2	59.4	Inpatient; non-hypertensive cardiovascular disease (25.6%); diabetes (32.0%); hypertension (57.8%); asthma (15.6%); chronic obstructive pulmonary disease (7.0%)	Mild/moderate (0%)	1.56	Hydroxychloroquine (200 mg twice daily for 5 days); placebo	Mortality; mechanical ventilation; viral clearance; duration of hospital stay
Vlaar 2020‡; PANAMO[76]	Published, NCT04333420	30	Netherlands	60.5	73.3	Inpatient; intensive care (60.0%); diabetes (26.7%); hypertension (30.0%)	Severe (100%)	60.0	IFX-1 (800 mg/day for up to 7 times within 22 days); standard care	Mortality; adverse events leading to discontinuation
Wang 2020[70]	Published, NCT04257656	237	China	65.0	59.3	Inpatient; cardiovascular disease (7.2%); diabetes (23.7%); hypertension (43.2%)	Severe (100%)	16.1	Remdesivir (100 mg/day for 10 days); placebo	Mortality; mechanical ventilation; adverse events leading to discontinuation; viral clearance; duration of hospital stay; duration of ventilation; time to symptom or clinical improvement
Wang 2020[86]*	Published	20	China	47.0	45.0	Inpatient; NR	Mild/moderate (100%)	NR	Vitamin C (10 g/60 kg twice daily); standard care	NA
Wang 2020[88]*	Published	60	China	NR	38.3	Inpatient; NR	Mild/moderate (100%)	NR	Lopinavir-ritonavir (2 tablets twice daily); standard care	NA

Wang 2020[69]	Preprint, ChiCTR2000029765	65	China	63.0	50.8	Inpatient; diabetes (15.4%); hypertension (30.8%)	Mild/moderate (56.9%); severe (43.1%)	15.4	Tocilizumab (400 mg for up to two times in 24 hours); standard care	Duration of hospital stay; time to symptom or clinical improvement; time to viral clearance
Wang 2020[130]‡	Published, ChiCTR2000030058	50	China	55.8	45.8	Inpatient; coronary artery disease (2.1%); diabetes (4.2%); hypertension (25.0%); chronic obstructive pulmonary disease (4.2%)	Mild/moderate (81.25%); severe (14.6%); critical (4.2%)	NR	Leflunomide (50 mg twice daily for 1.5 days, then 20 mg/day for 8 days); standard care	Mortality; adverse events leading to discontinuation; viral clearance; duration of hospital stay; time to viral clearance
Wu 2020[131]‡	Published, ChiCTR20000300001	52	China	58.0	50.0	Inpatient; cardiovascular disease (15.4%); cerebrovascular disease (7.7%); diabetes (15.4%); hypertension (28.8%); chronic obstructive pulmonary disease (5.8%)	NR	NR	Triazavirin (250 mg three times daily for 7 days in mildly ill patients, 250 mg four times daily for 7 days in severe or critically ill patients); placebo	Mortality; adverse events leading to discontinuation; viral clearance; time to symptom or clinical improvement; time to viral clearance
Yethindra 2020[91]	Published	30	Kyrgyzstan	36.5	60.0	Inpatient; cardiovascular disease (0%)	Mild/moderate (100%)	NR	Umifenovir (200 mg three times daily for 1 to 5 days); standard care	Mortality; time to symptom or clinical improvement
Yuan 2020[87]*	Preprint, ChiCTR2000029431	21	China	61.0	42.9	Inpatient; NR	Mild/moderate (100%)	NR	^{99}mTC-methylene diphosphate (5 ml/day for 7 days); standard care	NA
Zhang 2020[78]‡	Preprint, NCT04264533	56	China	67.4	66.7	Inpatient; intensive care (100%); coronary heart disease (22.2%); diabetes (29.6%); hypertension (44.4%); chronic lung disease (5.6%)	Mild/moderate (0%)	100	Vitamin C (12 g/50 ml given at 12 ml/hour for 7 days); placebo	Mortality; mechanical ventilation; adverse events leading to discontinuation; duration of hospital stay; intensive care unit length of stay; ventilator-free days; duration of

										ventilation
Zhao 2020[132]‡	Published, NCT04310228	26	China	73.5	53.9	Inpatient; coronary artery disease (23.1%); diabetes (11.5%); hypertension (42.3%)	Mild/moderate (46.2%); severe (50.0%); critical (3.9%)	3.9	Favipiravir (600 mg twice daily for 7 days); tocilizumab (4-8 mg/kg in 100 ml for 1 hr); favipiravir (600 mg twice daily for 7 days), tocilizumab (4-8 mg/kg in 100 ml for 1 hr)	Mortality; mechanical ventilation
Zheng 2020[49 94]‡	Published, ChiCTR2000029496	89	China	46.7	47.2	Inpatient; chronic bronchitis (2.0%)	Mild/moderate (94.4%); severe (5.6%)	NR	Novaferon (20 μg twice daily for 7 to 10 days); novaferon, lopinavir-ritonavir (200 mg and 50 mg twice daily for 7 to 10 days); lopinavir-ritonavir (200 mg and 50 mg twice daily for 7 to 10 days)	Adverse events leading to discontinuation; viral clearance; time to viral clearance
Zhong 2020[46]‡	Preprint, ChiCTR2000029851	17	China	63.0	76.5	Inpatient; cardiovascular disease (5.9%); diabetes (23.5%); hypertension (47.1%)	Critical (100%)	94.1	Alpha lipoic acid (1200 mg/day for 7 days); placebo	Mortality; adverse events leading to discontinuation
Zhou 2020[90]‡	Published	104	China	52.1	57.7	Inpatient	Mild/moderate (100%)	NR	Diammonium glycyrrhizinate (150 mg three times daily for 14 days), lopinavir-ritonavir (500 mg twice daily for 14 days); lopinavir-ritonavir (500 mg twice daily for 14 days)	Adverse events leading to discontinuation

NR=not reported
NA=not applicable
*Not eligible to be included in the network meta-analysis.
†Not included in the current iteration of the network meta-analysis but will be included in a future iteration.
‡This study was part of a treatment node with less than 100 participants or less than 20 events.

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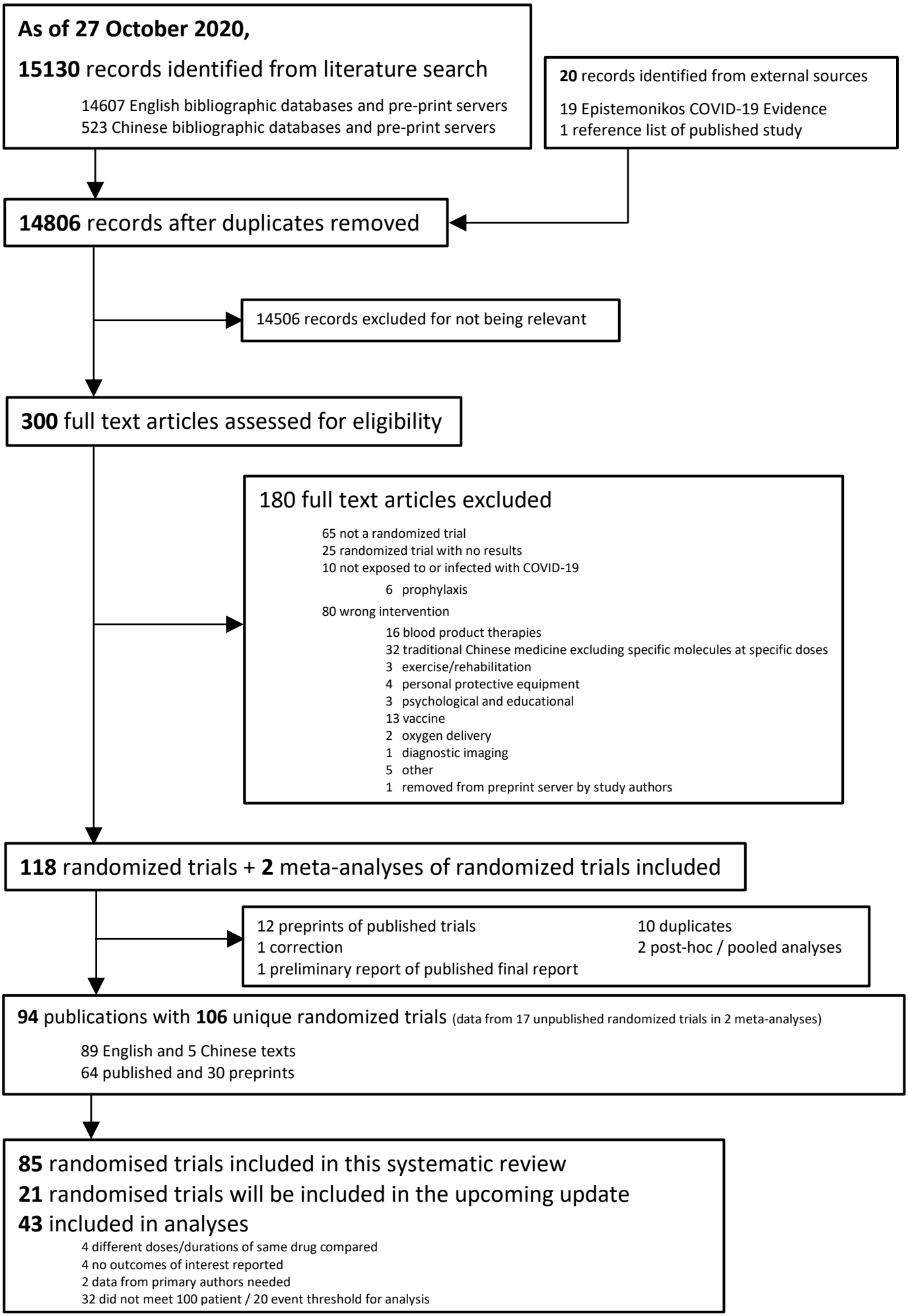

Figure 1. Study selection

	Mortality	Mechanical ventilation	Adverse events	Admission to hospital	Viral clearance at 7 days	Duration of hospitalization	ICU length of stay	Duration of mechanical ventilation	Time to symptom resolution	Time to viral clearance	Ventilator free days
Standard care*	130 per 1,000	116 per 1,000	15 per 1,000	43 per 1,000	484 per 1,000	13 days	13 days	15 days	11 days	10 days	11 days
Azithromycin	6 (-40 to 62)	1 (-60 to 90)				0.4 (-2.9 to 3.9)					-1.7 (-5.1 to 1.8)
Colchicine	-106 (-129 to 42)					-1.6 (-2.8 to -0.3)**					
Corticosteroids	-17 (-34 to 1)***	-29 (-54 to 1)****			5 (-426 to 458)	-0.9 (-3.4 to 1.7)	-3.8 (-5.9 to -1.8)	-1.4 (-3.4 to 0.62)			2.6 (0.2 to 5.0)
Favipiravir	63 (-113 to 773)				81 (-301 to 399)						
Hydroxychloroquine	11 (-11 to 38)***	20 (-18 to 76)****	16 (-11 to 192)**	-26 (-38 to 12)**	18 (-293 to 334)	0.1 (-1.9 to 2.0)			-2.0 (-4.0 to 0.1)	-0.7 (-4.3 to 4.8)**	
Hydroxychloroquine + azithromycin	-48 (-103 to 66)	58 (-32 to 216)				0.6 (-1.2 to 2.4)**					
Interferon beta	2 (-35 to 35)	-13 (-60 to 45)									
Interferon gamma					436 (-215 to 516)						
Interferon kappa+ treefoil factor 2					290 (-334 to 503)						
Lopinavir-ritonavir	-12 (-31 to 10)	10 (-31 to 60)****			-235 (-449 to 164)	-0.4 (-1.7 to 0.6)**			-1.0 (-4.1 to 3.2)		
rhG-CSF	-102 (-124 to -41)***	-96 (-108 to -68)				-0.7 (-2.3 to 1.0)**			-0.8 (-4.5 to 4.6)		
Remdesivir	-12 (-35 to 14)***	-33 (-65 to 1)****	0 (-9 to 40)		14 (-429 to 460)	-0.2 (-1.9 to 1.2)**		-1.3 (-4.1 to 1.5)	-2.0 (-4.2 to 0.9)		
Tocilizumab	5 (-46 to 81)	-35 (-80 to 54)	-8 (-15 to 300)**			-2.5 (-6.9 to 1.8)	-4.5 (-13.8 to 4.9)		-1.8 (-5.0 to 3.4)		4.7 (-4.2 to 13.9)
Umifenovir	-130 (-130 to 870)										
	Most beneficial	Intermediate benefit	Not different from SC	Harmful							
High/ moderate certainty											
Low/ very low certainty											
*Numbers presented are absolute risk differences (95% CI) per 1000 patients or mean difference (95% CI) when compared to standard care											
** The best estimate of effect was obtained from direct evidence											
*** Fixed effects NMA estimates (vs standard care): Corticosteroids, -18 (-30 to -7); Hydroxychloroquine, 10 (-5 to 29); Lopinavir-Ritonavir, -14 (-26 to 0); Remdesivir, -10 (-26 to 9)											
**** Fixed effects NMA estimates (vs standard care): Corticosteroids, -57 (-85 to -27); Hydroxychloroquine, 30 (-5 to 66); Lopinavir-Ritonavir, 29 (-3 to 63); Remdesivir, -24 (-51 to 5)											
Empty cells: there was no evidence for the specific intervention											
rSG-CSF: Recombinant human granulocyte colony-stimulating factor											

Fig 2. Summary of effects compared with standard care