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

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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 1 March 2021 and six additional Chinese databases up to 20 February 2021. Studies identified as of 12 February 2021 were included in the analysis.

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
196 trials enrolling 76 767 patients were included; 111 (56.6%) trials and 35 098 (45.72%) patients are new from the previous iteration; 113 (57.7%) trials evaluating treatments with at least 100 patients or 20 events met the threshold for inclusion in the analyses. Compared with standard care, corticosteroids probably reduce death (risk difference 20 fewer per 1000 patients, 95% credible interval 36 fewer to 3 fewer, moderate certainty), mechanical ventilation (25 fewer per 1000, 44 fewer to 1 fewer, moderate certainty), and increase the number of days free from mechanical ventilation (2.6 more, 0.3 more to 5.0 more, moderate certainty). Interleukin-6 inhibitors probably reduce mechanical ventilation (30 fewer per 1000, 46 fewer to 10 fewer, moderate certainty) and may reduce length of hospital stay (4.3 days fewer, 8.1 fewer to 0.5 fewer, low certainty), but whether or not they reduce mortality is uncertain (15 fewer per 1000, 30 fewer to 6 more, low certainty). Janus kinase inhibitors may reduce mortality (50 fewer per 1000, 84 fewer to no difference, low certainty), mechanical ventilation (46 fewer per 1000, 74 fewer to 5 fewer, low certainty), and duration of mechanical ventilation (3.8 days fewer, 7.5 fewer to 0.1 fewer, moderate certainty). The impact of remdesivir on mortality and most other outcomes is uncertain. The effects of ivermectin were rated as very low certainty for all critical outcomes, including mortality. In patients with non-severe disease, colchicine may reduce mortality (7 fewer per 1000, 110 fewer to 9 fewer, low certainty) and mechanical ventilation (57 fewer per 1000, 90 fewer to 3 more, low certainty). Azithromycin, hydroxychloroquine, lopinavir-ritonavir, and interferon-beta do not appear to 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 and interleukin-6 inhibitors probably confer important benefits in patients with severe covid-19. Janus kinase inhibitors appear to have promising benefits, but certainty is low. Azithromycin, hydroxychloroquine, lopinavir-ritonavir, and interferon-beta do not appear to reduce risk of death or have an effect on any other patient-important outcome. Whether or not remdesivir, ivermectin, and other drugs confer any patient-important benefit remains uncertain.

SYSTEMATIC REVIEW REGISTRATION
This review was not registered. The protocol is publicly available in the supplementary material.

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 is the fourth version of the original article published on 30 July 2020 (BMJ 2020;370:m2980), and previous versions can be found as data supplements. When citing this paper...
please consider adding the version number and date of access for clarity.

Introduction

As of 28 March 2021, more than 127 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 2.7 million have died.1 Despite global efforts to identify effective interventions for the prevention and treatment of covid-19, which have resulted in 2800 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 informs World Health Organization and BMJ Rapid Recommendations6 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 Subsequent guidance addressed the role of hydroxychloroquine, corticosteroids, lopinavir-ritonavir, and updated guidance for remdesivir (box 1).8 The latest recommendation covers vermeirin. This living network meta-analysis is the fourth version. The previous versions are available in the supplementary material. Drugs for prophylaxis9 10 and antibody-based treatments will be addressed separately.

Methods

A protocol provides the detailed methods of this systematic review, including all updates (see supplementary appendix). 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.11 A living systematic review is a cumulative synthesis that is updated regularly as new evidence becomes available.12 The linked BMJ Rapid Recommendations guideline panels approved all 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 trials evaluating vaccination, blood products and antibody-based antiviral therapies (such as virus-specific monoclonal antibodies), nutrition, traditional Chinese herbal or alternative 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.13 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 supplementary material contains the WHO literature search strategy.

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 trials, we filtered the results from the WHO’s database through a validated and highly sensitive machine learning model.14 We tracked preprints of randomised trials for updates and through publication: when data was discrepant, we used the most recent data.

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 appendix 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 Foundation15 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.16

We searched WHO information sources from 1 December 2019 to 1 March 2021, and the Chinese literature from conception of the databases to 20 February 2021.

Study selection

Using a systematic review software, Covidence, 17 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 who received mechanical ventilation over the number of patients who received mechanical ventilation in which we preferentially used the total number of patients who received mechanical ventilation over the study. We used the number of patients ventilated at the time point that the largest number of the patients were ventilated if the trial reported the number of patients ventilated at specific timepoints.

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)19 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 probably high risk of bias or as high risk of bias and as low risk of bias if all domains were rated as probably low risk of bias or low risk of bias.

For ivermectin, the linked guideline panel also requested a review of the study protocols to check that trial registration occurred prior to patient recruitment. 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.20 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 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.21

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.22
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. In previous versions, we used fixed effects for some outcomes because data was sparse or dominated by a single trial. As per our protocol, 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. 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. All network meta-analyses were performed using the gemtc package of R version 3.6.3 (RStudio, Boston, MA) and all pairwise meta-analyses using the bayesmeta package.

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. 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. We rated down for risk of bias if the interpretation of the effect would change if only studies at low risk of bias would have been considered. For example, if the credible interval of the pooled effect from studies at low risk of bias would have crossed the threshold for imprecision, we rated down for risk of bias. Judgments of imprecision for this systematic review were made using a minimally contextualised approach, with a null effect as the threshold of importance. 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. 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. Interim updates and additional study data will be posted on our website (www.covid19nma.com).

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 hospitalised with covid-19. For mechanical ventilation, duration of invasive mechanical ventilation, duration of hospitalisation, and ICU length of stay we used baseline risks from the International Severe Acute Respiratory and Emerging Infection COVID-19 database. 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 using the R2jags package in R.

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.

Subgroup and sensitivity analysis

Subgroup analyses were performed for specific interventions of interest at the direction of the linked WHO living guideline panel. In this iteration, we performed subgroup analyses for ivermectin and interleukin-6 inhibitors for the pairwise comparison against standard care. Previous iterations included subgroup analyses for corticosteroids, hydroxychloroquine, lopinavir-ritonavir, and remdesivir. The panel requested subgroup analyses by age (children v non-elderly adults v elderly), severity (non-severe v severe v critical), concomitant use of corticosteroids (for interleukin-6 inhibitors), dose (for ivermectin; by cumulative dose and by single v multiple dosing regimens), higher v lower C reactive protein (for interleukin-6 inhibitors), and risk of bias (for ivermectin) for the following outcomes: adverse events leading to discontinuation, hospital admission (for ivermectin), mortality, and mechanical ventilation. We performed bayesian hierarchical meta-regression with study as a random effect. Where possible, we performed within rather than between trial analyses.

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 31 848 titles and abstracts and 611 full texts, 206 unique randomised trials from 189 publications were identified that evaluated drug treatments as of 1 March 2021 (fig 1). A table of excluded full texts is provided in the supplementary appendix. Searches of living evidence retrieval services identified 84 publications of eligible randomised trials, which were reconciled with our formal search strategy when necessary. One hundred and thirty randomised trials have been published in peer reviewed journals, 53 as preprints, 17 within three meta-analyses, three as correspondence from study authors, one as a presentation, one as a conference abstract and one as a clinical trial registry reporting results. Most of the trials were registered (181/206; 88%), published in English (197/206; 96%), and evaluated treatment in patients admitted to hospital with covid-19 (168/206; 82%). China, Iran, Brazil, United States and Spain were the five most common countries in which randomised trials were conducted. Eighty-four different drug treatments were evaluated. The five most common drug treatments evaluated, based on number of randomised trials, were (hydroxy)chloroquine (37/206; 18%), ivermectin (16/206, 7.8%), corticosteroids (14/206; 6.8%), lopinavir-ritonavir (14/206, 6.8%) and interleukin-6 inhibitors (tocilizumab and sarilumab) (11/206; 5.3%).
One hundred and ninety six randomised trials that evaluated drug treatments were identified up until the date of analysis (12 February 2021) (table 1; supplementary appendix). Several of these trials could not be included in the analysis: nine trials that evaluated different durations or doses of the same drug, because both arms would have been classified within the same treatment node; two trials with insufficient data; and ten trials that reported no outcomes of
interest. Of the remaining 175 trials, we analysed 113 (69.8%) reporting on treatments with at least 100 patients or 20 events to avoid implausible and extremely imprecise estimates. Table 1 presents the characteristics of the 196 included studies. Additional study characteristics, outcome data, and risk of bias assessments for each study are available in the supplementary appendix.

Table 1 | Study characteristics. Values are numbers (percentages) of studies unless stated otherwise

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registered</td>
<td>175 (89.3%)</td>
</tr>
<tr>
<td>Publication status:</td>
<td></td>
</tr>
<tr>
<td>Preprint</td>
<td>52 (26.5%)</td>
</tr>
<tr>
<td>Published</td>
<td>121 (61.7%)</td>
</tr>
<tr>
<td>Unpublished</td>
<td>23 (11.7%)</td>
</tr>
<tr>
<td>Median (SD) No of patients</td>
<td>87.5 (145.2)</td>
</tr>
<tr>
<td>Country:</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>38 (19.4%)</td>
</tr>
<tr>
<td>Iran</td>
<td>28 (14.3%)</td>
</tr>
<tr>
<td>Brazil</td>
<td>26 (13.3%)</td>
</tr>
<tr>
<td>United States</td>
<td>26 (13.3%)</td>
</tr>
<tr>
<td>Spain</td>
<td>19 (9.7%)</td>
</tr>
<tr>
<td>Intensity of care:</td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td>33 (16.8%)</td>
</tr>
<tr>
<td>Inpatient</td>
<td>156 (79.6%)</td>
</tr>
<tr>
<td>ICU</td>
<td>8 (4.1%)</td>
</tr>
<tr>
<td>Severity:</td>
<td></td>
</tr>
<tr>
<td>Mild/moderate</td>
<td>57 (29.1%)</td>
</tr>
<tr>
<td>Severe/critical</td>
<td>35 (17.9%)</td>
</tr>
<tr>
<td>Median (SD) percentage of patients mechanically ventilated at baseline</td>
<td>3.9 (37.7)</td>
</tr>
</tbody>
</table>

Table 2 describes the 10 randomised trials that were identified after the data analysis and that will be included in the next update.213–222

Table 2 | Randomised trials identified after data analysis, which will be included in the next update

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication status, registration No</th>
<th>No of participants</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yadegarinia 2020213</td>
<td>Published, NR</td>
<td>34</td>
<td>Umifenovir; standard care</td>
</tr>
<tr>
<td>Balykova 2020214</td>
<td>Published, NCT04542694</td>
<td>39</td>
<td>Favipiravir; standard care</td>
</tr>
<tr>
<td>Thomas 2021215</td>
<td>Published, NCT04342728</td>
<td>214</td>
<td>Zinc, ascorbic acid; zinc, ascorbic acid; standard care</td>
</tr>
<tr>
<td>Baratt-Due 2021217</td>
<td>Preprint, NCT04321616</td>
<td>185</td>
<td>Hydroxychloroquine; remdesivir; standard care</td>
</tr>
<tr>
<td>Punwati 2021222</td>
<td>Published, INA-TX6YSS</td>
<td>754</td>
<td>Lopinavir-ritonavir, azithromycin; lopinavir-ritonavir, doxycycline; hydroxychloroquine, azithromycin</td>
</tr>
<tr>
<td>Jamaati 2021219</td>
<td>Published, IRCT20151227025762N17</td>
<td>50</td>
<td>Dexamethasone; standard care</td>
</tr>
<tr>
<td>Mejdeh 2020220</td>
<td>Published, NR</td>
<td>60</td>
<td>Methisoprinol; standard care</td>
</tr>
<tr>
<td>Balykova 2020216</td>
<td>Published, NR</td>
<td>200</td>
<td>Favipiravir; standard care</td>
</tr>
<tr>
<td>Patel 2021221</td>
<td>Published, ACTRN1262000000454976</td>
<td>33</td>
<td>Zinc; placebo</td>
</tr>
<tr>
<td>Cadegiani 2021218</td>
<td>Published, NR</td>
<td>236</td>
<td>Proxalutamide; placebo</td>
</tr>
</tbody>
</table>

Of the randomised trials included in the analyses, eight did not have publicly accessible protocols or registrations. Of the trials with publicly accessible protocols or registrations, 79 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 stratify reporting of outcomes for those who were truly randomised versus those who were allocated by preference; the authors shared outcome data with us among patients who were truly randomised.64

Thirty five studies were initially posted as preprints and subsequently published after peer review. The supplementary material presents the differences between study preprint and peer reviewed publications. Eighteen studies had discrepancies in outcome reporting between the preprint and peer-reviewed publication. Fourteen studies had discrepancies with patient...
baseline characteristics. Six studies had discrepancies in reporting that led to changes in risk of bias ratings. No substantive differences were found for 11 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 because no patients randomised to either of these drugs died, interleukin-6 inhibitors and doxycycline with ivermectin for adverse events, proxalutamide for hospital admission, and sulodexide for clinically important bleeding.

**Risk of bias in included studies**

The supplementary material presents the assessment of risk of bias of the included studies for each outcome. Thirty-seven studies were judged at low risk of bias in all domains. 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 appendix 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

One hundred and forty eight randomised trials including 71 468 participants reported mortality (supplementary appendix). One hundred and one trials with 67 491 participants met the threshold of analysing treatments with a minimum of 100 patients or 20 events and were included in the network meta-analysis (supplementary appendix). Figure 3 shows the network plot for mortality, with each

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mortality</th>
<th>Mechanical ventilation</th>
<th>Adverse events</th>
<th>Admission to hospital</th>
<th>Viral clearance at 7 days</th>
<th>Duration of hospital stay</th>
<th>ICU length of stay</th>
<th>Duration of mechanical ventilation</th>
<th>Time to symptom resolution</th>
<th>Time to viral clearance</th>
<th>Ventilator free days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard care*</td>
<td>130/1000</td>
<td>116/1000</td>
<td>9/1000</td>
<td>51/1000</td>
<td>500/1000</td>
<td>13 days</td>
<td>13 days</td>
<td>11 days</td>
<td>7 days</td>
<td>12 days</td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>-4 (-59 to 93)</td>
<td>-16 (-55 to 44)</td>
<td>8 (-5 to 59)</td>
<td>-1.9 (-5.7 to 1.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Anakinra</td>
<td>21 (-52 to 155)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Anticoagulants</td>
<td>-2 (-33 to 34)</td>
<td>-6 (-33 to 28)</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Azithromycin</td>
<td>-4 (-25 to 21)</td>
<td>-6 (-33 to 34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Colchicine</td>
<td>-78 (-110 to -9)</td>
<td>-57 (-90 to -3)</td>
<td>-11 (-34 to 42)</td>
<td>-1.7 (-2.8 to 0.7)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>-20 (-36 to -3)</td>
<td>-25 (-44 to -1)</td>
<td></td>
<td></td>
<td>-82 (-269 to 111)</td>
<td>-0.1 (-1.7 to 1.3)</td>
<td>-1.4 (-3.4 to 0.7)</td>
<td></td>
<td></td>
<td>2.6 (0.3 to 5.0)</td>
<td></td>
</tr>
<tr>
<td>Doxycycline + ivermectin</td>
<td>-130 (-130 to -123)</td>
<td>-14 (-74 to 120)</td>
<td></td>
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<tr>
<td>Favipiravir</td>
<td>-4 (-113 to 207)</td>
<td>-14 (-74 to 47)</td>
<td></td>
<td>50 (-96 to 193)</td>
<td>-1.3 (-2.4 to 0.1)</td>
<td></td>
<td></td>
<td>-4.3 (-5.9 to -2.1)</td>
<td>-0.6 (-3.2 to 4.2)</td>
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<td></td>
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<tr>
<td>Hydroxychloroquine</td>
<td>10 (-8 to 30)</td>
<td>15 (-9 to 45)</td>
<td>8 (-1 to 27)</td>
<td>-10 (-31 to 26)</td>
<td>1 (-93 to 109)</td>
<td>0.1 (-1.8 to 2.0)</td>
<td></td>
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<tr>
<td>Hydroxychloroquine + azithromycin</td>
<td>-42 (-96 to 53)</td>
<td>54 (-22 to 174)</td>
<td>9 (-5 to 60)</td>
<td>-1 (-35 to 63)</td>
<td>-35 (-211 to 154)</td>
<td>0.4 (-1.4 to 2.1)</td>
<td></td>
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<td></td>
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<tr>
<td>IL-6</td>
<td>-15 (-30 to 6)</td>
<td>-30 (-46 to 10)</td>
<td>-4 (-9 to 67)</td>
<td>-4.2 (-8.1 to 0.5)</td>
<td></td>
<td></td>
<td></td>
<td>-0.7 (-2.7 to 1.7)</td>
<td>1.6 (0.2 to 3.3)</td>
<td></td>
<td></td>
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<tr>
<td>Interferon beta</td>
<td>2 (-34 to 28)</td>
<td>-7 (-40 to 32)</td>
<td></td>
<td></td>
<td>-0.4 (-1.9 to 1.0)</td>
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<tr>
<td>Interferon gamma</td>
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<tr>
<td>Interferon kappa + trefoil factor 2</td>
<td></td>
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<tr>
<td>Ivermectin</td>
<td>-103 (-117 to 78)</td>
<td>-54 (-100 to 80)</td>
<td>26 (-2 to 187)</td>
<td>-32 (-47 to 23)</td>
<td>118 (-13 to 241)</td>
<td>-0.5 (-1.7 to 1.1)</td>
<td></td>
<td></td>
<td>-0.4 (-3.7 to 2.5)</td>
<td>-2.0 (-4.4 to 2.4)</td>
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<tr>
<td>JAKI</td>
<td>-50 (-84 to 0)</td>
<td>-46 (-74 to -5)</td>
<td></td>
<td></td>
<td></td>
<td>-1.5 (-3.0 to 0.1)</td>
<td>-3.8 (-7.5 to -0.1)</td>
<td>-1.0 (-3.8 to 2.8)</td>
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<tr>
<td>Lopinavir-ritonavir</td>
<td>3 (-17 to 25)</td>
<td>10 (-16 to 41)</td>
<td>46 (9 to 197)</td>
<td>-17 (-39 to 37)</td>
<td>-20 (-165 to 98)</td>
<td>0.7 (-1.1 to 2.7)</td>
<td></td>
<td></td>
<td>0.1 (-2.5 to 3.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir-ritonavir + interferon b1a</td>
<td>62 (-17 to 26)</td>
<td>42 (-17 to 125)</td>
<td>136 (31 to 506)</td>
<td>-93 (-296 to 143)</td>
<td>5.0 (3.7 to 6.3)</td>
<td>1.2 (2.8 to 6.9)</td>
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<tr>
<td>Natazoamide</td>
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<td></td>
<td></td>
<td></td>
<td>63 (3 to 725)</td>
<td>0 (-39 to 151)</td>
<td>159 (-97 to 350)</td>
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<tr>
<td>Peginterferon lambda/2</td>
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<td></td>
<td>206 (-142 to 418)</td>
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<tr>
<td>Prolutamide</td>
<td>-130 (-130 to 118)</td>
<td>-116 (-116 to 111)</td>
<td>-50 (-51 to -38)</td>
<td></td>
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<tr>
<td>rhG-CSF</td>
<td>-102 (-124 to 96)</td>
<td>-107 (-107 to -93)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.7 (-1.8 to 0.3)</td>
<td>-0.8 (-4.6 to 2.2)</td>
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<tr>
<td>Remdesivir</td>
<td>-11 (-33 to 12)</td>
<td>-26 (-51 to -2)</td>
<td>1 (4 to 26)</td>
<td>13 (242 to 262)</td>
<td>0.4 (0.1 to 1.4)</td>
<td>-1.3 (-4.3 to 1.5)</td>
<td>-2.0 (-4.1 to 0.7)</td>
<td></td>
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</tr>
<tr>
<td>Sulodexide</td>
<td>-78 (-119 to 50)</td>
<td>-62 (-105 to 81)</td>
<td>3 (-7 to 62)</td>
<td>-24 (-41 to 20)</td>
<td></td>
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<tr>
<td>Umifenovir</td>
<td>794 (130 to 870)</td>
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<tr>
<td>Vitamin C</td>
<td>50 (-89 to 22)</td>
<td>17 (-41 to 110)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-1.6 (-3.3 to 1.3)</td>
<td></td>
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<tr>
<td>Vitamin D</td>
<td>-11 (-86 to 150)</td>
<td>-63 (-96 to 7)</td>
<td></td>
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</tr>
</tbody>
</table>

Most beneficial Not different from SC Harmful

High/m moderate certainty

Low certainty

Very low certainty

*The expected risk of each outcome with standard care is reported in the grey row. Numbers in the coloured cells are the estimated risk differences (95% CI) per 1000 patients or mean difference (95% CI) in days when compared to standard care

† The best estimate of effect was obtained from direct evidence

‡ For this outcome, higher risk/mean is a benefit

Empty cells: there was no evidence for the specific intervention

IL-6: Interleukin 6 inhibitors (tocilizumab, sarilumab); JAKI: Janus kinase inhibitors (baricitinib, ruxolitinib); rhG-CSF: Recombinant human granulocyte colony-stimulating factor
edge representing a direct comparison between two interventions. The most common interventions were standard care/placebo (95 trials, 36 166 participants), hydroxychloroquine (33 trials, 4902 participants), lopinavir-ritonavir (7 trials, 3557 participants), interleukin-6 inhibitors (9 trials, 3642 participants), azithromycin (6 trials, 2982 participants), and corticosteroids (11 trials, 2975 participants).

Random effects network meta-analysis showed that corticosteroids probably reduce deaths compared with standard care (odds ratio 0.83, 95% credible interval 0.69 to 0.98; moderate certainty) (fig 2). Evidence was less certain for remdesivir (odds ratio 0.90, 0.72 to 1.11; low certainty), interleukin-6 inhibitors (odds ratio 0.87, 0.74 to 1.05; low certainty), colchicine (evidence primarily from patients with non-severe disease; odds ratio 0.37, 0.13 to 0.92; low certainty), and janus kinase (JAK) inhibitors (baricitinib and ruxolitinib, odds ratio 0.58, 0.33 to 1.00; low certainty). Patients randomised to azithromycin (odds ratio 0.97, 0.78 to 1.19; low certainty), hydroxychloroquine (odds ratio 1.09, 0.93 to 1.27; moderate certainty of no benefit), lopinavir-ritonavir (odds ratio 1.02, 0.85 to 1.23; low certainty), full dose anticoagulation (odds ratio 0.98, 0.72 to 1.32; low certainty), and interferon beta (odds ratio 0.99, 0.71 to 1.26; low certainty) did not have a lower risk of death than those randomised to standard care. Although the 95% credible intervals did not include harm for ivermectin and recombinant human granulocyte colony stimulating factor (rh-G-CSF), the evidence was very low certainty because of risk of bias and extremely low total number of events.

Fig 3 | Network plot for mortality. The size of the circles is proportional to the number of patients randomised to that intervention and the size of the lines is proportional to the inverse of the standard error of the effect estimate.

Mechanical ventilation

Eighty seven randomised trials including 56 560 participants reported mechanical ventilation (supplementary appendix). Sixty six trials with 55 174 participants met the threshold of analysing treatments with a minimum of 100 patients or 20 events and were included in the network meta-analysis (supplementary appendix). The most common interventions were standard care (64 trials, 30 339 participants), remdesivir (4 trials, 3433 participants), hydroxychloroquine (11 trials, 3155 participants), lopinavir-ritonavir (4 trials, 3086 participants), interleukin-6 inhibitors (9 trials, 3056 participants), and corticosteroids (8 trials, 2425 participants).

Random effects network meta-analysis showed that, compared with standard care, two interventions probably reduce risk of mechanical ventilation: corticosteroids (odds ratio 0.76, 0.59 to 0.99; moderate certainty) and interleukin-6 inhibitors (odds ratio 0.72, 0.57 to 0.90; moderate certainty) (fig 2). Treatments that may reduce mechanical ventilation, with lower certainty, were remdesivir (odds ratio 0.75, 0.52 to 0.98; low certainty), JAK inhibitors (odds ratio 0.57, 0.33 to 0.95; low certainty), and colchicine (odds ratio 0.48, 0.21 to 1.03; low certainty). Patients randomised to several interventions did not have a lower chance of mechanical ventilation compared to standard care: hydroxychloroquine (odds ratio 1.15, 0.92 to 1.46; low certainty), azithromycin (odds ratio 0.95, 0.69 to 1.28), lopinavir-ritonavir (odds ratio 1.10, 0.84 to 1.42; low certainty). The effect of ivermectin was very uncertain (odds ratio 0.51, 0.13 to 1.86; very low certainty).

Adverse events leading to discontinuation

Fifty nine randomised trials including 10 314 participants reported adverse effects leading to discontinuation of the study drug (supplementary appendix). Twenty five trials with 6999 participants met the threshold of analysing treatments with a minimum of 100 patients or 20 events and were included in the network meta-analysis (supplementary appendix). The most common interventions were standard care (24 trials, 2866 participants), hydroxychloroquine (8 trials, 893 participants), and remdesivir (2 trials, 699 participants). 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, 0.36 to 4.06). Certainty in evidence for all of the other interventions was low or very low (fig 2).

**Viral clearance at 7 days (± 3 days)**

Forty three randomised trials including 5136 participants measured viral clearance with polymerase chain reaction cut-off points (supplementary appendix). Thirty one trials with 4383 participants met the threshold of analysing treatments with a minimum of 100 patients or 20 events and were included in the network meta-analysis (supplementary appendix). The most common interventions were standard care (29 trials, 1741 participants), hydroxychloroquine (10 trials, 756 participants), lopinavir-ritonavir (6 trials, 450 participants), and ivermectin (7 trials, 291 participants). We did not find evidence that any of the interventions increased the rate of viral clearance: hydroxychloroquine (odds ratio 1.01, 0.69 to 1.56; very low certainty), lopinavir-ritonavir (odds ratio 0.92, 0.50 to 1.49; very low certainty), ivermectin (odds ratio 1.62, 0.95 to 2.86; low certainty), and remdesivir (odds ratio 1.06, 0.35 to 3.20) (fig 2).

**Admission to hospital**

Sixteen randomised trials including 8307 participants reported admission to hospital among outpatients at baseline (supplementary appendix). Nine trials with 7655 participants met the threshold of analysing treatments with a minimum of 100 patients or 20 events and were included in the network meta-analysis (supplementary appendix). The most common interventions were standard care (9 trials, 3603 participants), colchicine (1 trial, 2235 participants), hydroxychloroquine (4 trials, 668 participants), and lopinavir-ritonavir (1 trial, 244 participants). There was insufficient evidence to know if any of the interventions reduce hospitalisation (fig 2).

**Venous thromboembolism**

Two trials including a total of 2523 participants reported venous thromboembolism in patients who received full dose anticoagulation versus prophylactic dose anticoagulation (odds ratio 0.57, 0.21 to 1.73; low certainty).

**Clinically important bleeding**

Two trials including 2523 participants reported clinically important bleeding in patients who received full dose anticoagulation versus prophylactic dose anticoagulation (odds ratio 2.00, 0.70 to 5.98; low certainty).

**Duration of hospital stay**

Eighty two randomised trials including 54 277 participants reported duration of hospital stay (supplementary appendix). Fifty eight trials with 52 518 participants met the threshold of analysing treatments with a minimum of 100 patients and were included in the network meta-analysis (supplementary appendix). The most common interventions were standard care (56 trials, 29 443 participants), interleukin-6 inhibitors (9 trials, 3583 participants), remdesivir (4 trials, 3826 participants), hydroxychloroquine (12 trials, 3226 participants), azithromycin (3 trials, 2780 participants), and corticosteroids (5 trials, 2669 participants). Compared with standard care, duration of hospitalisation was shorter in patients who received interleukin-6 inhibitors (mean difference −4.5 days, −6.7 to −2.3; low certainty), colchicine (mean difference −1.7 days, −2.8 to −0.7; low certainty), and favipiravir (mean difference −1.3 days, −2.4 to −0.1; low certainty). There was no evidence that any of the other interventions reduce length of stay, but certainty was low or very low (fig 2).

**ICU length of stay**

Fourteen randomised trials including 1784 participants reported length of ICU stay (supplementary appendix). Three interventions had at least 100 participants including standard care (3 trials, 609 participants), interleukin-6 inhibitors (2 trials, 598 participants), and corticosteroids (1 trial, 278 participants). Most of these trials did not report estimates of variance. Therefore, we did not perform a meta-analysis (fig 2). The REMAP-CAP trial found a large reduction in median duration of ICU stay with interleukin-6 inhibitors (−9 days).14

**Duration of mechanical ventilation**

Thirteen randomised trials including 1138 participants reported duration of mechanical ventilation (supplementary appendix). Four trials with 966 participants met the threshold of analysing treatments with a minimum of 100 patients and were included in the network meta-analysis (supplementary appendix). The included interventions were standard care (4 trials, 521 participants), remdesivir (2 trials, 194 participants), corticosteroids (1 trial, 151 participants), and JAK inhibitors (1 trial, 100 participants). JAK inhibitors probably reduce the duration of mechanical ventilation (−3.8 days, −7.5 to −0.1, moderate certainty). There was no convincing evidence that corticosteroids (mean difference −1.4 days, −3.2 to 0.4; low certainty) or remdesivir (mean difference −1.4 days, −3.2 to 1.5; low certainty) reduce duration of mechanical ventilation (fig 2).

**Ventilator-free days**

Ten randomised trials including 2495 participants reported ventilator-free days (supplementary appendix). Seven studies with 1835 participants met the threshold of analysing treatments with a minimum of 100 patients and were included in the network meta-analysis (supplementary appendix). The most common interventions were standard care (6 trials, 783 participants), interleukin-6 inhibitors (3 trials, 652 participants), azithromycin (2 trials, 155 participants), and corticosteroids (1 trial, 151 participants). Compared with standard care, corticosteroids probably increase ventilator-free days (mean difference 2.6 days, 0.3 to 4.9; moderate certainty). There was no evidence that interleukin-6 inhibitors (low certainty), hydroxychloroquine (very low certainty), or azithromycin (very low certainty) increase ventilator-free days (fig 2).

**Time to symptom resolution**

Fifty nine randomised trials including 9846 participants reported time to symptom resolution (supplementary appendix). Thirty one trials including 7639 participants met the threshold of analysing treatments with a minimum of 100 patients and were included in the network meta-analysis (supplementary appendix). The most common interventions were standard care (29 trials, 3155 participants), remdesivir (3 trials, 1083 participants), interleukin-6 inhibitors (5 trials, 1070 participants), hydroxychloroquine (9 trials, 706 participants), and JAK inhibitors (2 trials, 535 participants). Favipiravir may reduce time to symptom resolution (ratio of mean days between intervention and standard care 0.62, 0.48 to 0.81; low certainty). The 95% credible interval for all other interventions included no effect, and certainty was low or very low for all interventions except remdesivir (ratio of mean days between intervention and standard care, 0.82, 0.64 to 1.06; moderate certainty) (fig 2).

**Time to viral clearance**

Thirty-five randomised trials including 2933 participants reported time to viral clearance (supplementary appendix). Thirteen trials...
Evidence from our analyses suggests that colchicine may reduce mortality in any subgroup is uncertain. Remdesivir only moderate credibility and whether or not remdesivir reduces in patients with critical illness. The subgroup effect however has less severe disease and may increase or have no effect on mortality, remdesivir may reduce or have no effect mortality in patients with non-severe disease remains.

Subgroups

Previous iterations of this living systematic review explored subgroup effects for remdesivir, lopinavir-ritonavir, hydroxychloroquine, and corticosteroids. In this iteration, we explored subgroup effects for ivermectin and interleukin-6 inhibitors (supplementary material). For ivermectin, there was no difference in relative effects for any of the subgroups tested, including cumulative dose, single versus multiple doses of ivermectin, or risk of bias. There was insufficient information to examine the effect of age or severity of illness. For interleukin-6 inhibitors, there was no difference in relative effects between sarilumab and tocilizumab, by disease severity, or concomitant corticosteroid use on mortality, mechanical ventilation, or adverse effects. There was insufficient information to examine the effect of age on any of these outcomes. There was also no credible effect difference between patients with higher versus lower C reactive protein on a composite of mortality and mechanical ventilation.

Discussion

This living systematic review and network meta-analysis provides a comprehensive overview of the evidence for drug treatments of covid-19 up to 12 February 2021 and a comprehensive list of drug trials to 1 March 2021. There are now more than 200 randomised trials examining many different interventions for treating covid-19, and, as a result, the certainty in evidence for multiple interventions is improving.

Corticosteroids probably reduce the risk of death and mechanical ventilation and probably increase ventilator-free days. The evidence for corticosteroids comes primarily from patients who are hypoxic and admitted to hospital. Whether corticosteroids have any important effect on patients with non-severe disease remains uncertain.

Interleukin-6 inhibitors are likely to have some benefits, although the evidence regarding their impact on mortality remains of low certainty. Other meta-analyses using fixed effects (that is, they do not consider between-trial heterogeneity) found a significant mortality reduction. Interleukin-6 inhibitors probably reduce risk of mechanical ventilation and may reduce duration of hospitalisation. The evidence for interleukin-6 inhibitors comes primarily from patients who are admitted to hospital and are hypoxic. The use (or not) of corticosteroids, and baseline C reactive protein levels did not appear to modify their effects, however data available for subgroup analyses was limited.

Whether or not remdesivir has any effect on mortality remains uncertain. If one believes the subgroup effect previously reported, remdesivir may reduce or have no effect mortality in patients with less severe 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. Remdesivir may reduce risk of mechanical ventilation.

Evidence from our analyses suggests that colchicine may reduce mortality, mechanical ventilation, and duration of hospitalisation. These results were driven in large part by the COlCORA study, which enrolled outpatients with non-severe disease. The RECOVERY trial randomised 11 162 inpatients to colchicine or standard care and was not included in this analysis because the study was published after conducting the analysis. Colchicine did not appear to have an effect on mortality in the RECOVERY trial, which was limited to inpatients with mostly severe or critical disease. Substantial uncertainty about the effect of colchicine on patients with non-severe disease remains.

Several small trials have examined the effect of ivermectin, and the pooled result suggests a possible reduction in mortality. However, the data are limited by extremely few events (very serious imprecision) and serious risk of bias (several of the studies were not pre-registered prior to enrolling patients or were not adequately blinded). The effect of ivermectin on all other outcomes was similarly uncertain, with 95% credible intervals that include substantial harm.

Two trials examined the effect of JAK inhibitors and appear to show promising results, JAK inhibitors may reduce mortality, mechanical ventilation, and duration of hospitalisation. They probably reduce the duration of mechanical ventilation. Further trials are needed to confirm these promising effects.

Full dose anticoagulation did not appear to show any important effect. A separate meta-analysis of four trials that examined full dose anticoagulation versus prophylactic dose anticoagulation appeared to show a reduction in mortality in patients with severe but not critical illness; but these trials are not yet published in full and the data available is insufficient to judge whether or not it is a credible subgroup effect.

Several interventions do not appear to have important impact on any patient-important outcomes, including angiotensin-converting enzyme inhibitors, azithromycin, hydroxychloroquine, interferon-beta, lopinavir-ritonavir, vitamin C, and vitamin D. For other interventions, there remains substantial uncertainty.

Box 2: Summary of changes since last iteration

- One hundred and eleven additional randomised trials (35 038 participants)
- Angiotensin-converting enzyme inhibitors, anakinra, full dose anticoagulation, ivermectin, ivermectin plus doxycycline, JAK inhibitors, lopinavir-ritonavir plus interferon-beta, peginterferon lambda, proxalutamide, sulodexide, vitamin C, and vitamin D are new interventions included in the analyses, but certainty is low or very low for the effects of the most of these interventions
- New evidence suggests that azithromycin may not have an impact on any patient-important outcome, when combined with usual care.
- New evidence suggests that interleukin-6 inhibitors probably reduce mechanical ventilation (moderate certainty) and may reduce duration of hospitalisation (low certainty).
- New evidence suggests that JAK inhibitors probably reduce duration of mechanical ventilation (moderate certainty) and may reduce mortality (low certainty), mechanical ventilation (low certainty), and duration of hospitalisation (low certainty).
- New evidence suggests that colchicine may reduce mortality (low certainty) and mechanical ventilation (low certainty) in outpatients with non-severe disease, however our analysis does not include recent
Evidence from the RECOVERY trial, which did not find any effect on mortality in hospitalised patients.

- There is some new evidence on ivermectin and ivermectin plus doxycycline, however whether or not they have an important impact on any patient-important outcome remains very uncertain.
- Evidence for other interventions is similar to the previous version.

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.235 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.

The main limitation of the data is that only thirty-seven 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 randomised groups. We chose to consider the treatment arms that did not receive an active experimental drug (that is, 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.228 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 reduce this risk. 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, differences between preprints and peer reviewed publications have been mostly been limited to additional baseline patient information, clarification on study design, and outcomes reported in the peer reviewed publications. None of these changes would have resulted in a meaningful change to pooled effect estimates or certainty for any outcome.

It is possible that we did not detect important subgroup modification.227 For example, the RECOVERY trial suggested that patients with more severe disease might obtain a greater benefit from dexamethasone than patients with less severe disease.103 Full dose anticoagulation may be beneficial in patients with severe but not critical disease, and harmful in patients with critical disease. However, these subgroup effects only have moderate credibility at best. Users should carefully consider the characteristics of the patients included in the trials for each intervention.

Our living systematic review and network meta-analysis will continue to inform the development of the WHO living guidelines and BMJ Rapid Recommendations.6–8 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.28 The contextualisation explains differences in the certainty of the evidence between the two.

To date, we are aware of two other similar efforts to ours.228 229 Our intention is different in that the results fully inform clinical decision making for the associated living guidance.6 We also include a more comprehensive search for the evidence and several differences in analytical methods, which we believe are best suited for this evidence. For example, some others use fixed rather than random effects meta-analysis and provide estimates for pairwise comparisons only. It is also important to evaluate the reproducibility and replicability of findings from different scientific approaches.

We will periodically update this living systematic review and network meta-analysis. 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. Remdesivir may reduce the need for mechanical ventilation but does not appear to have an impact on mortality. Interleukin-6 inhibitors (sarilumab and tocilizumab) probably reduce mechanical ventilation and ICU length of stay, and may reduce duration of hospitalisation. JAK inhibitors (baricitinib and ruxolitinib) may reduce mortality, mechanical ventilation, duration of hospitalisation. Azithromycin, hydroxychloroquine, lopinavir-ritonavir, and interferon beta seem unlikely to have any benefits. The effects of many other drug interventions are currently highly uncertain (including ivermectin), and no definitive evidence exists that these interventions result in important benefits and harms for any outcomes.

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 1 March 2021 and will be updated periodically
- The certainty of the evidence for most interventions is low or very low, including ivermectin
- In patients with severe covid-19, glucocorticoids probably decrease mortality, mechanical ventilation.
- In patients with severe covid-19, interleukin-6 inhibitors probably reduce mechanical ventilation and ICU length of stay, and may improve ventilator-free days and duration of hospitalisation.
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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.

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