Hi Dr. Hahn and Anand and Michael, I share this so confidentially. Yikes...and I thought of it long and hard as the group submitted last night to BMJ after revisions...so I am part of the large international research group and one of the senior researchers in this network meta-analysis as seen in the list of authors. You would know the one reason why I stand out among this group of some the world’s top researchers which I am proud of and made the personal decision to reveal it. I was told that had I not played such a prominent role in this project started in Feb before I came on deck, that they would have not wanted me in it and I expected this since coming to DC and experiencing the push back which is so terrible. But a lot of the work I did so folk had no choice and some was my own work...anyway, I share this submission (embargoed) so highly confidentially, please share with no one not even in people who work or report to you...please. But I weighed the balance and this is so important and such an emergency and while I have not done this before and will not again, I share this embargoed so that you are primed of what we found if it could help your decision-making to help the USA and the globe as the US leads the world, rightly. You two are an example. So I trust you and Michael, I trust him as a brother. This is for your eyes only but can inform your decision-making behind the scenes as it will be in print maybe one week.

I draw your attention to “Time to symptom resolution”...we included 13 RCTs for that outcome enrolling 2,282 participants. Remember, with Network meta-analysis (NMA), the approach is not simple pair-wise modelling of a treatment to its comparator but we include the indirect evidence in the models (briefly, in NMA we may have evidence of A vs C and B vs C where C is the common comparator e.g. placebo, but not A vs B (head to head) that we are interested in and NMA allows us to speculate mathematically ‘if’ they were actually compared and we include the direct and that indirect evidence in the model...anyway, we found that in patients who received remdesivir (MD -2.58 days CI -4.32 to -0.84, moderate certainty), hydroxychloroquine (MD -4.53 days CI -5.98 to -2.99, low certainty), and lopinavir-ritonavir (MD -1.22 days CI -2.00 to -0.37, low certainty) had a shorter symptom duration than standard care. For hydroxy there was no other benefit and there was apparent risk of adverse events.

Again, I would never do this but do it here for we have lives on the line and we are searching for a treatment or combination and I want to help the administration and you two as the top regulators in this push. I am so confident in you and the team in beating this virus and the whole administration...yes, it is wearing on us for this is tough, and we are being fought by the other side and media which is horrendous for we have a very serious emergency and the people the public seek just simple, honest, direct guidance and allow them to be informed so they can make common sense ‘best’ decisions for themselves.

Dr. Paul E. Alexander, PhD
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Time to symptom resolution. Thirteen RCTs enrolling 2,282 participants reported time to symptom resolution. At least 100 patients received hydroxychloroquine, lopinavir-ritonavir, and remdesivir. Patients who received remdesivir (MD -2.58 days CI -4.32 to -0.54, moderate certainty), hydroxychloroquine (MD -4.53 days CI -5.98 to -2.99, low certainty), and lopinavir-ritonavir (MD -1.22 days CI -3.00 to -0.37, low certainty) had a shorter symptom duration than standard care.
Pharmacologic treatment for COVID-19: living systematic review and network meta-analysis

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Pharmacologic treatment for COVID-19: living systematic review and network meta-analysis

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Competing Interests declaration
All authors will complete the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and will declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influeneed the submitted work.

Ethics approval: Not applicable. All the work was developed using published data.
Transparency declaration
RS 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.

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

Role of the funding source
This study was conducted with the support of project grant from the Canadian Institutes of Health Research (CIHR-IRSC: 0515001521).
What is already known/what this paper adds

Despite huge efforts to identify effective pharmacologic interventions for COVID-19 disease, evidence for effective treatment remains limited.

This living systematic review and network meta-analysis provides a comprehensive picture and assessment of the evidence published as of 8 July 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 and mechanical ventilation. Hydroxychloroquine, lopinavir-ritonavir, and remdesivir may reduce time to symptom resolution.
Abstract

Objectives: To compare the effects of therapies for treatment of COVID-19.

Design: Living systematic review and network meta-analysis (NMA).

Data sources: U.S. Centers for Disease Control and Prevention (CDC) COVID-19 Research Articles Downloadable Database, which includes 25 electronic databases up to 8 July 2020.

Study selection: We included randomized clinical trials (RCTs), which persons with suspected, probable, or confirmed COVID-19 were randomized to pharmacologicals or standard care/placebo for treatment. Pairs of reviewers independently screened titles and abstracts, and full texts, of potentially eligible articles.

Methods: After duplicate data abstraction, we conducted a Bayesian-random effects network meta-analysis for each outcome of interest. We assessed the risk of bias of the included studies using a modification of the Cochrane Risk of Bias Tool, and the certainty of the evidence using the GRADE approach for NMA. We classified interventions in groups from the most to the least effective/harmful following GRADE guidance using a minimally contextualized approach.

Results: We included 25 RCTs. The certainty in the evidence for the majority of comparisons is very low because of risk of bias (lack of blinding) and very serious imprecision. Glucocorticoids were the only intervention with evidence for a reduction in death compared to standard care (37 fewer per 1000 patients, 95% credible interval [CI] 53 fewer to 11 fewer, moderate certainty) and mechanical ventilation (31 fewer per 1000 to 47 fewer to 9 fewer, moderate certainty). Three drugs may reduce symptom duration compared to standard care: hydroxychloroquine (-4.5 days, low certainty), remdesivir (-2.6 days, moderate certainty), and lopinavir-ritonavir (-1.2 days, low certainty). Hydroxychloroquine may increase the risk of adverse events when compared to the other interventions and remdesivir probably does not substantially increase the risk of adverse effects. No other interventions included enough patients to meaningfully interpret adverse effects leading to drug discontinuation.

Conclusion: Glucocorticoids probably reduce mortality and mechanical ventilation compared to standard care. The effectiveness of most interventions is very uncertain because most of the RCTs so far have been small and have important study limitations.

Protocol: The protocol is included as a supplement.
Background

As of 18 July 2020, over 14.1 million people have been infected with COVID-19; of these, 600,000 have died. Despite huge efforts to identify effective interventions for its prevention and treatment—which have resulted in almost 1500 trials completed or under way—evidence of effective treatment remains limited.

Faced with the pressures of a global pandemic, healthcare workers around the world are prescribing medications off-label for which there is only very low-quality evidence. The result—this appears to be certainly the case for the very well-publicized example of hydroxychloroquine—may be no benefit and appreciably more harm. Timely evidence summaries and associated guidelines may ameliorate the problem. 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 seen before. This environment makes it necessary to produce well-developed summaries that distinguish more from less trustworthy evidence.

Living systematic reviews (SRs) and network meta-analyses (NMAs) address the main limitation of traditional reviews—that of providing a picture of the relevant evidence only at a specific timepoint. This is crucial in the context of COVID-19, in which the picture is constantly changing. The ability of living NMA to present a complete, broad, and updated view of the evidence makes it ideal to inform the development of practice recommendations. NMA, rather than pairwise meta-analysis provides useful information about the comparative effectiveness of treatments that were not 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.

The objective of this living SR and NMA is to compare the effects of pharmacologic therapies for treatment of COVID-19. This SR is part of the BMJ Rapid Recommendations project, a collaborative effort from the MAGIC Evidence Ecosystem Foundation (www.magicproject.org) and the BMJ. Our living NMA will directly inform BMJ Rapid Recommendations on COVID-19 treatments, triggered to provide trustworthy, actionable, and living guidance to clinicians and patients soon after new and potentially practice-changing evidence becomes available.

Methods

A protocol provides the detailed methods of this SR, including all updates (available as supplementary material). We report this living SR following the guidelines of the PRISMA checklist for NMA. A living systematic review is a cumulative synthesis that is updated regularly as new evidence becomes available. The linked BMJ Rapid Recommendations the guideline panels approved all decisions relevant to data synthesis.

Eligibility criteria

We included randomized clinical trials (RCT) in persons exposed to COVID-19 or with suspected, probable or confirmed COVID-19 that compared pharmaceuticals 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 pre-print) or language. We applied no restriction based on severity of illness or setting and included trials of Chinese medicines if the drug was one or more specific molecules with a defined molecular weight dosing.
We excluded RCTs 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. RCTs including patients with COVID-19 that evaluated these interventions were identified and categorized separately.

Information sources
We perform daily searches Monday to Friday in the U.S. Center for Disease Control and Prevention (CDC) COVID-19 Research Articles Downloadable Database for eligible studies—the most comprehensive database of COVID-19 research articles. The database includes 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, Trade and 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 day after their publication. We filtered the results from the CDC’s database through a validated and highly sensitive machine learning model to identify RCTs.15 We tracked preprints of RCTs until publication and updated data to match that in the peer-reviewed publication when discrepant and reconciled corrections and retractions.

In addition, we searched six Chinese databases on a biweekly basis: Wanfang, CBM, CNKI, 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 randomized trials. The Supplementary material 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 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.

We searched all English information sources from 1 December 2019 and until 8 July 2020 and Chinese literature from the conception of the databases to 26 June 2020.

Study selection
Using a web-based software, Covidence,16 pairs of trained and calibrated reviewers 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 analyzed and the number of participants that experienced an event for dichotomous outcomes).

Outcomes of interest were selected based on their importance to patients and were informed by clinical expertise in the SR team and in the linked guideline panel responsible for the BMJ Rapid Recommendations. The panel includes unconflicted clinical experts, recruited to ensure global representation, and patient-partners. Outcomes were rated from 1-9 based on importance to individual patients (9 being most important) and any outcome rated 7 or lower by any panel member was included. 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), duration of hospitalization, ICU length of stay, time to symptom resolution or clinical improvement, and time to viral clearance. Outcomes of interest for prophylaxis of COVID-19 include mortality, infection with COVID-19, hospitalization, adverse events leading to discontinuation, and time to symptom resolution or clinical improvement. Time to viral clearance was included because it may be a surrogate of transmissibility, although this is uncertain.13

Because of the inconsistent reporting observed across trials, in the updates we will use a hierarchy for the outcome mechanical ventilation in which we will include information from the total number of patients who received ventilation over a time period if available (as done for this analysis) but we will also include the number at the time point in which most of the patients were mechanically ventilated if this is the only way in which this outcome is reported.

Reviewers resolved discrepancies by discussion and, when necessary, by adjudication by a third party.

We update the data collected from included studies when they were published as preprints and as soon as the peer-review publication becomes available. Studies initially included as preprints.

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 randomized trials (RoB 2.0)14 to rate trials as either low risk of bias, 'some concerns - probably low risk of bias', 'high risk of bias' or 'high risk of bias', across the following domains: bias arising from the randomization process, bias due to departures from the intended intervention, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported results, including deviations from the registered protocol, and bias arising from early termination for benefit. We rated trials as high risk of bias overall if one or more domains were rated at 'some concerns - probably high risk of bias' or 'high risk of bias' and at low risk of bias if all domains were rated at 'some concerns - probably low risk of bias' or 'low risk of bias'. Reviewers resolved discrepancies by discussion and, when not possible, by adjudication by a third party.

Data synthesis
We conducted NMA using a Bayesian framework. In this report, we conducted an NMA for pharmacological treatments of COVID-19 that included all patients, regardless of severity of disease.

a. Summary measures
We summarized the effect of interventions on dichotomous outcomes using the odds ratio (OR) and its 95% credible intervals (CI). For continuous outcomes, we used the mean difference (MD) and its 95% CI in days for ICU length of stay and duration of mechanical ventilation because we expected similar durations across studies. For time to symptom resolution and length of hospital stay, we first performed the analyses using the relative effects measure ratio of means (ROM) and its 95% CI before calculating MD in days because we expected substantial variation between studies.

b. Treatment nodes
Treatments were grouped into common nodes based on molecule but not dose or duration. For intervention arms with more than one medication, we created a separate node and included drugs from the same class within the same node. Hydroxychloroquine and hydroxychloroquine were included in the same node for COVID-19 specific effects and separated for adverse effects. We drew network plots using the network plot command of Stata version 15.1 (StataCorp, College Station, Texas, USA) with thickness of edges of the nodes based on the number of studies.

c. Statistical analysis
For most outcomes, we conducted random-effects NMAs using a Bayesian framework with the same priors for the variance and effect parameters. For networks where the outcome were particularly sparse, we conducted fixed-effects NMAs. We will use a plausible prior for variance parameter, and uniform prior for the effect parameter suggested by Turner et al 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 NMAs were performed using the open-source package of R version 4.0.0 (RStudio, Boston, MA).

Some treatment nodes with very few total participants and very few total events resulted in highly implausible and extremely imprecise effect estimates. We therefore decided to include only treatments that achieved a total of at least 100 patients or had at least 20 events. For this iteration, the analyses included treatment nodes with fewer than 100 patients and 20 events, but the results are not reported.

Certainty of the evidence
We assessed the certainty of evidence using the GRADE approach for NMA. People with GRADE experience 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, probability bias, imprecision, incoherence (difference between direct and indirect effects), and imprecision. Judgments of imprecision for this SR were made using a minimally contextualized approach, with a null effect as the threshold of importance. The minimally contextualized 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.
publication platform (www.medicapp.org) to provide user-friendly formats for clinicians and patients, and 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 OR or RoM. For the outcomes mortality and mechanical ventilation, we used baseline risks from the International Severe Acute Respiratory and Emerging Infection COVID-19 database.26 For all other outcomes, we used the mean or median from all studies in which participants received standard of care for each outcome. We calculated absolute effects using the transitive risk model27 using R2jags package in R.28

For each outcome, we classified treatments in groups from the most to the least effective using the minimally important difference framework that focuses on the treatment effect estimates and the certainty of the evidence.29

Subgroup and sensitivity analysis
When a comparison was dominated by a single study (defined as >90% contribution in fixed effects), we conducted a post-hoc sensitivity analysis with a fixed effects model for that comparison.28 We planned to perform subgroup analyses of preprints vs peer reviewed studies and high vs. low risk of bias. We will perform additional subgroup analyses in the future if directed by the independent Rapid Recommendation guideline panels; in this case there was no such direction.

Results
Following screening of 6,516 titles and abstracts, and 109 full-texts, we identified 25 unique RCTs that evaluated pharmacological treatments as of 8 July 2020 (Figure 1).30-54 Searches of living evidence retrieval services identified one additional eligible RCT.55 Fifteen RCTs have been published in peer-reviewed journals; and ten only as preprints. Most trials were registered (23/25; 92%), published in English (23/25; 92%) and evaluated treatment in hospitalized patients with COVID-19 (24/25; 96%). Nearly two-thirds were conducted in China (16/25; 64%). Of the 25 included pharmacological trials, 6 evaluated treatment against active comparator(s), 9 evaluated treatment against standard care or placebo and 8 evaluated different durations/doses of the same treatment. Our MRC was performed on 26 June 2020 and includes 19 RCTs.31 32 34-39 41 42 43 44 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 Material.

The RCTs not included in the analysis are: 1) two RCTs evaluating different durations of the same drug because both arms would have been classified within the same treatment node;32 50 2) one RCT evaluating lincosycin vs azithromycin,38 which was excluded because neither arm was connected to the network; 3) three RCTs, evaluating colchicine,37 febuxostat,38 and methylprednisolone39 all versus standard care were excluded because they were identified after, or the data was available after the analysis was completed.

Two trials did not have publicly accessible protocols or registrations.26 29 Of the trials with publicly accessible protocols or registrations, 16 reported results for one or more of our outcomes of interest that were not prespecified in protocols/registrations. No other discrepancies
between the reporting of our outcomes of interest in trial reports and protocols/registrations were noted.

Three studies were initially posted as preprints and subsequently published after peer review. In one study, mortality was not reported in the preprint but was reported in the peer reviewed paper. There were no substantive differences between the preprint and peer reviewed publications for the other two studies. One RCT did not report outcomes in the groups as randomized; the authors shared outcome data with us in the groups as randomized.

All analyses reached convergence based on trace plots and Brooks-Gelman-Rubin statistic <1.05. For glucocorticoids, there were two RCTs with substantial differences in size (RECOVERY enrolled 6425 patients and GLUCCOVID 6352), thus we performed a fixed effects analysis for the direct pairwise analysis for this the outcomes that were reported in both RCTs (mortality and mechanical ventilation). This analysis was separate from the network meta-analyses, which were all random effects. Due to the lack of sufficient data, we did not conduct any separate subgroup or sensitivity analyses specified in the protocol (see Supplementary Material).
As of July 8, 2020:

6516 records identified from literature search

- 6145 English bibliographic databases and pre-print servers
- 371 Chinese bibliographic databases and pre-print servers

1 Epistemonikos COVID-19 Evidence

6468 records after duplicates removed

- 6359 records excluded for not being relevant

109 full text articles assessed for eligibility

78 full text articles excluded

- 34 not a randomized trial
- 14 randomized trial with no results
- 5 not exposed to or infected with COVID-19
- 2 prophylaxis
- 25 wrong intervention
- 2 blood products
- 15 traditional Chinese medicine that were not specific molecules at specific doses
- 2 exercise rehabilitation
- 2 personal protective equipment
- 1 diagnostic imaging
- 1 psychological and educational
- 2 other

31 randomized trials included

- 3 preprints of published trials
- 1 correction
- 2 duplicates

25 unique randomized trials included

- 23 English and 2 Chinese trials
- 15 published and 10 preprints

Figure 1: Study Selection
Risk of bias in included studies

The supplementary material presents the assessment of risk of bias of the included studies per outcome. Two studies were judged at low risk of bias in all domains. All other studies had probably high or high risk of bias in the domains of randomization or deviation from the intended interventions.

Effects of the interventions

The supplementary material presents the network plots depicting the interventions included in the NMA of each outcome. Table 2 presents a summary of the effects of the interventions on the outcomes. The supplementary material 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 NMAs.

a. Mortality

The 15 RCTs including 8,654 participants addressed mortality. The treatment nodes included in the NMA were glucocorticoids, hydroxychloroquine, lopinavir-ritonavir, remdesivir, umifenovir, and standard care. The network estimates did not reveal a convincing reduction for any of these interventions compared to standard care. The certainty of the evidence was low for the comparison between remdesivir and standard care, and very low for all other comparisons (Table 2). For glucocorticoids, the direct estimate was more credible than the network estimate (moderate certainty vs. very low certainty) because the direct estimate was more precise. The network estimate, which considers heterogeneity of the entire network, was RR 0.84 CI 0.52 to 1.36. The direct meta-analysis of two RCTs for glucocorticoids versus standard care suggested a probable mortality reduction with glucocorticoids: RR 0.88 CI 0.80 to 0.97, RD 37 fewer per 1000 CI 63 fewer to 11 fewer, moderate certainty for risk of bias.

b. Mechanical ventilation

Eight RCTs that enrolled 1,956 participants reported mechanical ventilation in patients who were not receiving mechanical ventilation at baseline. The treatment nodes included in the NMA were glucocorticoids, remdesivir, and standard care (Table 2). The network estimate for glucocorticoids was very low certainty because of very serious imprecision RR 0.71 CI 0.29 to 1.73. The direct pairwise direct meta-analysis for glucocorticoids versus standard care resulted in higher certainty and suggested a probable reduction with glucocorticoids versus standard care: RR 0.74 CI 0.59 to 0.93, RD 30 fewer per 1000 CI 48 fewer to 8 fewer, moderate certainty for risk of bias.

c. Adverse events leading to discontinuation

Eleven RCTs that enrolled 1,875 participants reported adverse effects leading to discontinuing the study drug. The treatment nodes included in the NMA were hydroxychloroquine, remdesivir, and standard care. There was moderate certainty evidence that remdesivir did not incur any additional harm beyond standard care and low certainty evidence that hydroxychloroquine increased the risk of adverse events compared with standard care (Table 2).

d. Viral clearance at 7 days (+/- 3 days)

All ten RCTs that cumulatively enrolled 856 participants measured viral clearance with PCR cutoff points. The treatment nodes included in the NMA were hydroxychloroquine, lopinavir-ritonavir, remdesivir, and standard care. There was no
convincing evidence that any of the interventions increased the rate of viral clearance (Table 2). The certainty of the evidence was low for the comparison between remdesivir and standard care, and very low for all other comparisons.

e. Duration of hospitalization
Eight RCTs enrolling 855 participants reported duration of hospitalization. The treatment nodes included in the NMA were lopinavir-ritonavir, remdesivir, and standard care. Patients who received lopinavir-ritonavir had fewer days of hospitalization than patients who received standard care; but the effect estimate included no difference: RD -1.42 days CI -0.03 to 0.02 (low certainty; Table 2). Remdesivir did not appear to reduce duration of hospitalization (low certainty).

f. ICU length of stay
Two RCTs enrolling 280 participants studied lopinavir-ritonavir (99 patients) and interferon beta 1 (42 patients) versus standard care (139 patients) reported length of ICU stay. Interferon standard care was the only treatment node with at least 100 patients and therefore no analyses were performed for this outcome.

g. Duration of mechanical ventilation
Three RCTs and enrolling 557 participants reported duration of mechanical ventilation. The treatment nodes included in the meta-analysis were remdesivir and standard care. Moderate certainty evidence that remdesivir reduces the duration of mechanical ventilation compared to standard care, MD -5.15 days CI -8.28 to -2.02 (Table 2).

h. Time to symptom resolution
Thirteen RCTs enrolling 2,828 participants reported time to symptom resolution. At least 100 patients received hydroxychloroquine, lopinavir-ritonavir, and remdesivir. Patients who received remdesivir (MD -2.32 days CI -4.32 to -0.32, moderate certainty), hydroxychloroquine (MD -4.53 days CI -5.98 to -2.99, low certainty), and lopinavir-ritonavir (MD -1.22 days CI -2.00 to -0.37, low certainty) had a shorter symptom duration than standard care.

i. Time to viral clearance
Ten RCTs enrolling 684 participants revealed no convincing evidence that any of the interventions reduced the time to viral clearance; at least 100 patients received hydroxychloroquine, lopinavir-ritonavir, and remdesivir. The certainty of the evidence was very low for all comparisons (Table 2).

Discussion
This living SR and NMA provides a comprehensive picture of the evidence for pharmacologic treatments of COVID-19 up to 8 July 2020. The certainty of the evidence for the majority of the comparisons is very low. The only intervention that probably reduced mortality and mechanical ventilation is glucocorticoids, result driven entirely by the RECOVERY trial. Remdesivir is the only intervention in which moderate certainty exists supporting benefits for both time to symptom resolution and duration of mechanical ventilation, but it remains uncertain whether remdesivir has any impact on mortality and other outcomes important to patients. Remdesivir was the only intervention where all of the data came from RCTs sponsored by a pharmaceutical company. Direct evidence from RCTs in patients with COVID-19 has so far provided

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little definitive evidence about adverse effects for most interventions.

Hydroxychloroquine may increase the risk of adverse events leading to drug discontinuation when compared to the other interventions. Notably, this iteration of the living NMA did not include three recently published large RCTs on hydroxychloroquine versus standard care. RECOVERY, the largest hydroxychloroquine RCT, suggests that hydroxychloroquine may not reduce mortality and may increase length of hospital stay. These data will be included in the next update. There was no convincing evidence that the other interventions resulted in benefits or harms when compared to standard of care.

Strengths and limitations of our review
Our search strategy and eligibility criteria were comprehensive, without restrictions of language of publication, and provide a full picture of the current evidence. To ensure expertise in all areas, our team is composed of clinical and method experts trained and calibrated for all stages of the review process. In order to minimize problems with counterintuitive results, the data analysis plan anticipated challenges that arise in NMA when data is sparse. We assessed the certainty of the evidence using the GRADE approach and interpreted the results considering absolute effects. 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 that randomized at least 100 patients. 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 systematic review is the very low quality of the evidence as a result of the current sparse data available. As the many ongoing trials are completed, we anticipate that the effect estimates will quickly become both plausible and informative as the quality of the evidence rises. Only two studies were judged to be at low risk of bias. The most common limitation was lack of blinding, including the largest trials.

Another limitation in this SR is the limited quality of reporting. For some outcomes, the method in which the researchers measured and reported outcomes proved inconsistent across studies did not match across studies, and thus such studies could not be included in the NMA. This led the team to propose a hierarchy for the outcome mechanical ventilation as described in the methods. We expect that the relative effect will not vary importantly across methods of measurements.

The living nature of our NMA 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 medications may be particularly at risk for publication bias and positive results for these medications may require more cautious interpretation than generic medications tested in RCTs independent of industry influence. However, the inclusion of preprints in our NMA may introduce bias from simple errors and 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.
For comparisons with sufficient data, the primary limitation of the evidence is lack of blinding, which may introduce bias through differences in co-interventions between randomization groups. We chose to consider the treatment arms that did not receive an active experimental drug (i.e., placebo or standard care) within the same node: it is possible that the unblinded standard care groups received systematically different co-interventions than in studies that were blinded.

It is also possible that study-level meta-analysis may not detect important subgroup modification that would otherwise be detected within trial comparisons. 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. For example, the RECOVERY trial suggested that patients with more severe disease may obtain a greater benefit from dexamethasone than patients with less severe disease.

Our living NMA is informing the development of the BMJ Rapid Recommendations. There is, however, an important difference in the methods for assessing the certainty of the evidence between the two. In this SR and living NMA, we are using a minimally contextualized approach for rating the certainty of the evidence, whereas the BMJ Rapid Recommendations are using a fully contextualized approach in which the thresholds of importance of magnitudes of effects depend on all other outcomes and factors involved in the decision. The contextualization explains potential 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 NMA and in the associated remdesivir guidelines.

To date, we are aware of no other efforts similar to ours. We decided to proceed independently to ensure that the results fully inform clinical decision-making for the associated living guidance in BMJ Rapid Recommendations. We are also including a more comprehensive search for the evidence, and several differences in analytic 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 SR and living NMA. The changes from each version will be highlighted for readers and the most up-to-date version will be the one available on the publication platform. Previous versions will be archived in the supplementary material. The SR and living NMA will also be accompanied by interactive infographics and a website for users to access the most updated results in a user-friendly format.

Conclusions
The evidence suggests that glucocorticoids probably reduce mortality and mechanical ventilation in patients with severe COVID-19. Remdesivir probably reduces length of hospital stay. The effects of most pharmacologic interventions is currently highly uncertain, and no definitive evidence exists that other interventions result in important benefits and harms for any outcomes.
Acknowledgments
We appreciate the input and early contributions of Dr. Kevin Cheung.
<table>
<thead>
<tr>
<th>Study</th>
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<th>Authors</th>
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<th>Country</th>
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<th>Gender</th>
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Table 1: Study characteristics
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<td>Tocilizumab</td>
<td>Placebo</td>
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**Notes:**
- Phase 1 study included 10 mg/kg/week i.v. for 4 weeks.
- Phase 2 study included 10 mg/kg/week i.v. for 4 weeks.
- Phase 3 study included 10 mg/kg/week i.v. for 4 weeks.

**References:**
- Canadian Clinical Trials Registry (CCRT) [link]
- ClinicalTrials.gov [link]

**Authors:**
- John Doe, MD
- Jane Smith, PhD

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**Keywords:**
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- Safety

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- All authors declare no conflicts of interest.

**Ethical Approval:**
- Institutional Review Board (IRB) approval was obtained.

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