Interleukin-1 Blocking Agents for the Treatment of COVID-19: A Living Systematic Review of Therapeutic Efficacy and Safety Outcomes

Dr. Giulia Rossi[1]*, Dr. Marco Bianchi[1], Dr. Luca Romano[1], Dr. Elena Conti[1], Dr. Andrea Ferrari[1], Dr. Marta De Luca[1]
[1]University of Milan Hospital, Milan, Italy

1. Université de Paris, France
2. Centre of Research in Epidemiology and StatisticS (CRESS UMR1153), Methods team, France
3. Laboratoire d'Informatique de Grenoble (LIG), CNRS, France
4. IRCCS Fondazione Don Carlo Gnocchi, Italy
5. Laboratoire Bordelais de Recherche en Informatique (LaBRI), Université Bordeaux I, France
6. Epistemonikos Foundation, Chile
7. McMaster University, Canada
8. Center for Health Regulatory Policies, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Italy
9. Centre Max Weber, CNRS, France
10. Centre of Research in Epidemiology and StatisticS (CRESS UMR1153), Eren team, France
11. Cochrane Response
12. Cochrane Germany, Cochrane Germany Foundation, Freiburg, Germany
13. Bordeaux Pharmacoepi - ADERA, France
14. Laboratoire d'Informatique, de Modélisation et d'Optimisation des Systèmes (LIMOS), CNRS, Université Clermont Auvergne
15. Université Toulouse 3 – Paul Sabatier - Institut de Recherche en Informatique de Toulouse – IRIT UMR 5505, France
16. Cochrane France
17. Institut des Systèmes Complexes de Paris IDF (ISC-PIF), CNRS, France
18. WHO Collaborating Centre for Guideline Implementation and Knowledge Translation & Chinese GRADE Centre, Lanzhou University, China
19. Laboratoire de recherche en Informatique (LRI), CNRS, Université Paris-Saclay, France
20. Laboratoire d'InfoRmatique en Image et Systèmes d'information (LIRIS), CNRS, Université Claude Bernard Lyon 1, France
21. Evidence Synthesis Ireland, Cochrane Ireland and HRB-Trials Methodology Research Network, National University of Ireland, Galway, Ireland
22. Centre for Evidence Based Medicine Odense (CEBMO), University of Southern Denmark and Odense University Hospital, Denmark
23. French National Research Institute for Agriculture, Food and Environment (INRAE), France
24. Service de Neurochirurgie, Hôpital d'Instruction des Armées Percy (HIA), France
25. The Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES), Centre for Clinical Brain Sciences, University of Edinburgh, Scotland
26. Cochrane Editorial and Methods Department, Cochrane Central

27. Department of Anesthesia, Intensive Care and Emergency, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Department of Pathophysiology and Transplantation, University of Milan, Italy
28. Cochrane South Africa, South African Medical Research Council
29. Department of Primary Education, University of Ioannina, Greece
30. Institute for Evidence in Medicine, Medical Center & Faculty of Medicine, University of Freiburg, Freiburg, Germany
31. Cochrane Review Group on Drugs and Alcohol; International GRADE Working Group; Department of Epidemiology, Lazio Regional Health Service, Italy
32. Research Methodology Division, School of Public Health and Preventive Medicine, Monash University, Australia
33. Health Research Board-Trials Methodology Research Network (HRB-TMRN), NUI Galway, Ireland
34. UC Evidence Center, Cochrane Chile Associated Center, Pontificia Universidad Católica de Chile, Santiago, Chile
35. Population Health Sciences, Bristol Medical School, University of Bristol, UK; NIHR CLAHRC West, University Hospitals Bristol and Weston NHS Foundation Trust, UK
36. Bristol Medical School, Bristol Population Health Science Institute, University of Bristol, UK
37. Nottingham Ningbo GRADE Centre, The Nottingham China Health Institute, the University of Nottingham Ningbo, China
38. Laboratoire d'Informatique pour la Mécanique et les Sciences de l'Ingénieur (LIMSI), CNRS, France

BACKGROUND

Description of the condition

In December 2019, a novel coronavirus outbreak began in Wuhan, Hubei Province, China. This coronavirus, named SARS-CoV-2, quickly spread around the world, such that on March 11 2020, the WHO declared COVID-19 a pandemic. The COVID-19 pandemic has now spread across the globe and in many countries during the first and subsequent waves has increased in an almost exponential manner (Worldometer 2020). The clinical spectrum of SARS-CoV-2 pneumonia ranges from mild to critically ill cases. Approximately 15% of patients infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) suffer severe pneumonia COVID-19 (Guan 2020). Enormous efforts are focusing on finding treatments to reduce the risk of invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia.

It has been proposed that high-risk COVID-19 patients may develop a “cytokine storm”(Mehta 2020a) characterized by increased production of pro-inflammatory peptides responsible for long-term damage, lung tissue fibrosis, and multiple organ failure (Pedersen 2020). Interleukin-1 (IL-1) is a cytokine produced by multiple cells such as macrophages and monocytes in response to infections and tissue damage. IL-1 blood levels which reflect the host inflammatory response were shown to be increased in patients with COVID-19 pneumonia (Huang 2020).

Description of the intervention

IL-1 blocking agents are a class of therapeutics whose compounds are directed against either the IL-1 peptide or the IL-1 receptor. Two IL-1 blocking agents are currently available. One (anakinra) is a recombinant protein that inhibits the IL-1 receptor while the other (canakinumab) is a human anti-IL-1ß monoclonal antibody. Both can be administered subcutaneously or intravenously. Other IL-1 blocking agents might become available in the future.

How the intervention might work

IL-1 blockers are beneficial in inflammation-associated pathologies, such as rheumatoid arthritis (Mertens 2009) and possibly also in the subgroup of patients with severe sepsis where the inflammasome pathway is involved (Shakoory 2016). Similar benefits were reported in children with secondary macrophage activation syndrome, including cases triggered by viral infections (Mehta 2020b).

Compared to corticosteroids, a classic anti-inflammatory drug, the immunosuppressive effect of IL-1 blockers is deemed less intense (Khan 2020). This might be important for COVID-19 patients, who are characterized by a significant immune system dysfunction and are at high risk for infectious complications (Campochiaro 2020).
IL-1 produced by macrophages/monocytes can in turn elicit secretion of IL-6 and IL-8 in other cells (Giavridis 2018). Early prevention of IL-1 receptor activation with IL-1 blocking agents is expected to reduce the downstream secretion of IL-6 and IL-8 thereby curbing the spread of the cytokine storm. Investigators have hypothesized that IL-1 blockers will prove valuable host-directed therapy for COVID-19 patients through the control of inflammation and the promotion of disease tolerance.

Why it is important to do this review

Given the urgent need for an effective treatment for COVID-19, patients worldwide have received several off-label or compassionate-use treatments including costly immune-modulating compounds (Shen 2020, Grein 2020, Touret 2020) such as IL-1 blockers (Huet 2020).

Policy makers, scientific experts and other stakeholders need high-quality up-to-date evidence evaluating the effectiveness of IL-1 blocking agents for the treatment of COVID 19. This is a high priority question, for which there is uncertainty in the existing evidence. Likely, emerging evidence will impact what we currently know, as the evidence base for this potential therapeutic intervention grows; thus, a living systematic review is an optimal approach to tracking the impact of Il-1 use in COVID patients.
The published Cochrane review will be updated as soon as new evidence substantially changes the conclusions or certainty of the evidence of the review or at least twice a year (i.e., every six months) if no substantial changes occur. The process of the living systematic review is described in Appendix 1.

OBJECTIVES

To assess the effects of IL-1 blocking agents compared to placebo, standard of care or no treatment on outcomes in patients with COVID-19.

This review is part of a larger project: the COVID-NMA project (Boutron 2020a). The COVID-NMA project aims to provide decision-makers with a complete, high-quality and up-to-date synthesis of evidence on interventions for the prevention and treatment of COVID 19. For this purpose, we perform a living mapping of all registered randomized controlled trials and a living evidence synthesis of data from RCTs. We developed a master protocol on the effect of all interventions for the prevention and treatment of COVID-19 (first published on April 8, 2020; an update on May 11, 2020, June 17, 2020, and September 8, 2020) (Boutron 2020b). We set-up a platform (https://covid-nma.com) where all our results are made available and updated weekly.

This protocol is a sub-protocol of the master protocol considering one type of interventions of the COVID-NMA project and using pairwise meta-analysis only.

This living review focuses only on SARS-COV2 and will not consider studies evaluating treatment with IL-1 blocking agents for other coronavirus infections affecting humans.

METHODS

Criteria for considering studies for this review

Types of studies

We will include RCTs including cluster-randomized and crossover trials.

Early-phase clinical trials, single-arm trials, non-randomized studies and modelling studies of interventions for COVID-19 will not be included in the review.

We will exclude studies about prognosis, systematic reviews and meta-analyses and diagnostic test accuracy studies.

We have no restriction on language.

Types of participants

Participants will be:

- Suspected (presenting acute respiratory illness), probable (a suspect case for whom testing for COVID-19 is inconclusive) or confirmed (having received laboratory confirmation of COVID-19 infection) COVID-19 patients (see full classification in Appendix 2 (WHO 2020b).
- Children or adults with no restriction in age.

Of note, trials involving patients with non-respiratory manifestations of COVID-19 can be included in this review.

For the preplanned subgroup analysis, participants will be classified as mild, moderate, severe, critical or mixed according to the classification detailed in the data collection and analysis section.

Types of interventions

We will include the following IL-1 blocking agents:

- Canakinumab (human monoclonal antibody against IL-1 beta)
- Anakinra (human IL-1 receptor antagonist)

The list of included IL-1 blocking agents could expand over time if new IL-1 inhibitors are evaluated in the context of COVID-19.

Overall, 16 randomized controlled trials evaluating these treatments have been registered, as of September 30, 2020. The table below indicates the number of registered RCTs and the number of RCTs recruiting or completed per type of IL-1 blocking agent:

Treatment	Total number of registered trials	Number of trials recruiting	completed
Canakinumab	3	1	0
Anakinra	13	10	0
	16	11	0

Type of comparator

We will include as comparator placebo, no treatment or standard of care whatever the definition used for standard of care.

Types of outcome measures

Our outcome selection is based on 1) the CORE outcome sets developed by the WHO (Marshall 2020), 2) the results of the research mapping that will describe the outcomes assessed in ongoing trials and 3) the clinical relevance to patients (i.e., patient-important outcomes).

Critical outcomes

The following outcomes with related time points reported as Days (D) of follow-up will be considered:

1. Clinical improvement (D7 / D14 / D28 / D60 / D90) defined as a hospital discharge or improvement on the scale used by trialists to evaluate clinical progression and recovery. We will describe the scale and the threshold used to define improvement where appropriate.
2. WHO Clinical Progression Score level 6 or above (i.e., NIV/High Flow 02 OR Mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) OR Death) (D7 / D14 / D28 / D60 / D90)

3. WHO Clinical Progression Score level 7 or above (i.e., Mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) OR death (D7 / D14 / D28 / D60 / D90)
4. All-cause mortality (D7 / D14 / D28 / D60 / D90)

We will consider the following safety outcomes:

1. Incidence of any adverse events
2. Incidence of serious adverse events (SAEs)

For each time point, we will consider time of randomisation as day 0 (D0). However, if not reported, we will consider D0 as reported by the authors.

For the analysis, we will group different time points within temporal ranges (e.g., D14-28). Further, when outcomes are reported as assessed at time points other than those selected by the review, we will choose the closest (e.g., D15 for D14).

Of note D90 will include all assessment performed at D90 and above (i.e., >D90)

We will present all critical outcomes in the summary of findings table.

Important outcomes

1. Time to clinical improvement
2. Time to WHO Clinical Progression Score level 6 or above
3. Time to WHO Clinical Progression Score level 7 or above
4. Time to death

Search methods for identification of studies

We will use the search strategies defined in the master protocol and outlined in Appendix 3 to identify randomized trials evaluating treatments for COVID-19.

The initial search strategy was developed with Robin Featherstone, Information Specialist, at the Cochrane Editorial & Methods Department and evolved following assessment of secondary sources. The search was updated on September 4, 2020 following an evaluation of the sensitivity of the L·OVE platform, which identified all RCTs identified through the initial extensive search strategy.

Electronic searches

- The **L-OVE platform** (https://app.iloveevidence.com/covid19), searched every working day since September 4, 2020. Details of the methods used by the L·OVE database are detailed here (https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?population=5e6fdab269c00e4ac072701c&section=methods).

- The **Cochrane COVID-19 Study Register** (https://covid-19.cochrane.org/), searched every working day since September 4, 2020
- **CNKI (**China National Knowledge infrastructure, https://www.cnki.net/) **database** and (http://journal.yiigle.com/): searched on April 17, 2020.
- **MedRχiv** (https://www.medrxiv.org): MedRχiv is a free online archive and distribution server for complete but unpublished manuscripts (preprints) in the medical, clinical, and related health sciences. A curated list of records on COVID-19 and SARS-CoV-2 is available at https://connect.biorxiv.org/relate/content/181. Note that this list also includes sources listed in bioRχiv, but we only screened the sources published on MedRχiv. Searched every working day from March 1, 2020 to September 4, 2020
- **Chinaxiv** (http://chinaxiv.org/) Chinaxiv is a free online archive and distribution server for complete but unpublished manuscripts (preprints) in Chinese. Searched every working day from March 1, 2020 to September 4, 2020
- **LitCOVID** (https://www.ncbi.nlm.nih.gov/research/coronavirus/), a curated database that tracks scientific evidence on COVID-19 published in PubMed. The hub is updated daily and studies are categorized by domain (e.g., "transmission" or "treatment" (https://www.nature.com/articles/d41586-020-00694-1). We screened studies listed under "treatment" from March 1, 2020 to June 1, 2020. We decided to stop searching LitCOVID as it did not identify any trials that were not already identified in the primary source.
- **WHO database of publications on coronavirus disease** (COVID-19) (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov) from March 1, 2020 to August 28th, 2020. We decided to stop searching these secondary sources as they did not identify any trials that were not already identified in the primary source.
- We screened other sources such as the **EPPI-Centre living map of evidence** (http://eppi.ioe.ac.uk/COVID19_MAP/COVID_map_v5.html) and **Meta-evidence**, developed by Campbell UK & Ireland (http://meta-evidence.co.uk/) from March 1, 2020 to August 28th, 2020. We decided to stop searching these secondary sources as they did not identify any trials that were not already identified in the primary source.

References will not be checked as the living search process identifies COVID-19 trial records prospectively from the point of trial registration.

We will also search the **Retraction Watch Database** for retracted studies (https://retractionwatch.com/retracted-coronavirus-covid-19-papers/).

Data will be extracted on preprint where no peer-review publication is available.We recognise that preprint are not peer-reviewed and are living documents that can be updated or published. We developed a preprint tracker in collaboration with a research team from the French National Centre for Scientific Research (CNRS), which systematically informs us when a preprint is updated or published. As soon as an update is identified, we record the data and run the analysis if needed.

Searching other resources

We will search the following trial registries for unpublished and ongoing studies:

- The **World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP**, https://www.who.int/ictrp/en/), to identify ongoing and completed clinical trials on COVID-19. We will use the *List By Health Topic*: 2019-nCoV / COVID-19 filter and retrieve all studies identified.
- We will contact investigators of ongoing studies to update the status of their study and obtain results.

We will also search the **EMA clinical data website** https://clinicaldata.ema.europa.eu/web/cdp/home) to identify trials submitted to the EMA, and search for the Clinical Study Report (CSR) of eligible studies. We will also search the **FDA website** to identify FDA approval trials.

Data collection and analysis

We will search, screen and extract data daily. The updated synthesis will be reported online at least every week.

In addition, we will update the published Cochrane review at least every six months or when information is published that might introduce more data or lead to change in the certainty of evidence. We will wait until the accumulating evidence changes one or more of the following components of the review before incorporating it and re-publishing the review:

- The findings of one or more critical outcomes
- The certainty (e.g. GRADE rating) of one or more critical outcomes
- New settings, population, interventions, comparisons or outcome studied
- New serious adverse events

Selection of studies

We will search and screen the citations retrieved daily. We will use an Excel spreadsheet to document search dates and numbers of hits identified. Screening of records and abstracts will be done in duplicate independently. A third reviewer will resolve disagreements.

Data extraction and management

All data will be extracted in duplicate. Two reviewers will independently read each preprint, publication, protocol, or other study reports, evaluate the completeness of the data availability, and assess the risk of bias. We will design and use a specific structured online data extraction form to ensure consistency of extraction of information. All discrepancies automatically identified by the online tool are discussed by the two reviewers to find a consensus. When consensus is reached, data related to the characteristics of the study and risk of bias assessment are made available online.

Information extracted will include study characteristics (such as first author, publication year and journal), number of participants randomised, patient characteristics (such as the severity of clinical presentation), intervention details (such as dose), outcome measures, and risk of bias assessment.

For dichotomous outcomes, we will extract the number of events and number of total participants in each study arm. For time-to-event outcomes, we will extract hazard ratios (HR) and standard errors (SE). When these are not provided, we will attempt to obtain them using the tools provided in Tierney 2007. When several analyses are reported, we will extract results obtained from the intention to treat (ITT) analysis whenever these are available. If ITT results are not available, a modified ITT analysis will be used.

We will contact trial authors and ask them to supply information that we need but are unable to retrieve from the available study reports. These data will be requested by a personalized email sent by the WHO, with whom we are collaborating on COVID-NMA.

Study and participant characteristics, risk of bias data as well as outcome data will be made publicly available on a dedicated website as soon as they are extracted.

Every week, all the complementary data obtained from authors and all the updates or publications of preprint are recorded by one reviewer and systematically checked by a second reviewer. The data available online are updated accordingly.

Once a week, all the data for new studies, or updates of studies previously identified, are sent to the statistical analysis team who will perform the relevant analysesand update the forest plots available online.

Assessment of risk of bias in included studies

Risk of Bias 2

Each study will be assessed with the Cochrane 'Risk of Bias 2' (RoB 2) tool for randomized controlled trials (Sterne 2019).

We assess Risk of Bias for critical and important outcomes recorded at all time points. We are recording judgements for each domain using the online data extraction tool we developed. Risk of Bias is assessed by researchers with a epidemiological training (currently 4 people) or members of Cochrane Response (the number of people involved varies). All have been previously trained in clinical epidemiology and systematic reviews. All have participated in a training program where they had to read the training material and perform data extraction and RoB assessment with a team of experienced researchers. The quality of the data is checked by members of the Cochrane Bias Methods Group who will regularly check a random sample of the data extracted.

The Cochrane RoB 2 tool is structured into five domains: 1) risk of bias arising from the randomization process, 2) risk of bias due to deviations from intended interventions, 3) risk of bias due to missing outcome data, 4) risk of bias in measurement of the outcome, 5) risk of bias in the selection of the reported result. Within each domain, a series of 'signaling questions' elicit information relevant to risk of bias assessment. The response options to the signaling questions are: “Yes”; “Probably yes”; “Probably no”; “No”; and “No information”. A risk of bias judgement for each domain is generated by an algorithm, based on answers to the signaling questions. Judgement can be 'Low', ‘Some concerns’ or 'High' risk of bias. Overall risk of bias will be considered as “low risk of bias” if all domains are at ‘low risk’; “some concerns” if at least one domain is ‘some concern’ and no domain ‘high risk of bias’; and “high risk of bias” if there is at least one domain ‘high risk’, or several domains

with ‘some concerns’. In the context of this protocol, we are interested in quantifying the effect of assignment to the interventions at baseline, regardless of whether the interventions are received as intended (i.e., the ‘intention-to-treat effect’).

For cluster trials if any, we will also rely on the extension of the RoB tool 2.0 for cluster trial.

While we are relying on the signalling questions to assess each domain and justify our assessment, we are not recording the answer of systematic reviewers / obtaining consensus for the signalling questions. This is done only at the domain level.

Co-interventions that could differ between intervention groups and have an impact on study outcomes that we will consider are use of:

- remdesivir; and other antivirals
- corticosteroids
- anticoagulants and
- other immunotherapies.

The risk of bias assessment will be considered in the evaluation of the confidence (or certainty) of the evidence.

Measures of treatment effect

For dichotomous outcomes, we will use the risk ratio accompanied by the 95% confidence interval (CI) as measure of effect and the hazard ratio with 95% CI for time-to-event outcomes.

Unit of analysis issues

Different comparisons from multi-arm trials will be analyzed separately. If multi-arm trials appear in meta-analyses synthesizing different drugs, we will merge the different drug arms to avoid double-counting the participants in the control arm.

We do not expect to identify any cross-over trials. If we identify eligible cluster-randomized trials, we will extract results that properly account for the cluster design (such as based on a multilevel model or on generalized estimating equations). If such an analysis is not reported, we will try to obtain an estimate of the intraclass correlation coefficient and calculate data required for the meta analyses taking the design effect into consideration.

Dealing with missing data

For missing outcome data, we will extract the number of participants who dropped out before the completion of the study and how missing outcome data were handled by the study authors. We will assess the appropriateness of any imputation methods used to account for early dropouts in our risk of bias assessments. To assess the potential impact of missing outcome data on the results, we will conduct sensitivity analyses, making different assumption on different proportions of missing data.

Assessment of heterogeneity

At each update, we will first generate descriptive statistics for study and population characteristics and we will examine the distribution of important clinical and methodological variables (such as age, disease severity, pre-existing conditions and comorbidities, location etc.). Visual inspection of forest plots, the I-square statistic, prediction intervals (the interval within which the effect of a future study is expected to lie (Riley 2011) and comparison of $\tau 2$ with appropriate empirical distributions (Turner 2012) will be used to assess the presence of important statistical heterogeneity.

Assessment of reporting biases

We will assess the selective non-reporting or under-reporting of results in the studies identified according to the framework proposed in Chapter 13 of the Cochrane Handbook (Higgins 2019).

We will use funnel plots (in the presence of at least ten studies per meta-analysis) and statistical tests (such as the Egger's test) to assess the potential for small-study effects. If asymmetry is found, we will explore possible reasons for the apparent association between study size and study effect.

Data synthesis

The primary analysis will include RCTs only and will be performed both at drug level and class level unless there is substantial heterogeneity among RCTs comparing different drugs. All eligible RCTs will be included in the primary analysis, whatever the RoB assessment.

For each direct comparison with at least two studies providing data, we will present effect estimates with 95% confidence intervals (CIs). We will use the random-effects model to incorporate the anticipated clinical and methodological heterogeneity across studies.

In the presence of excessive heterogeneity across studies, we will not synthesize them quantitatively but only qualitatively and no diamonds will be presented in the forest plots.

Subgroup analysis and investigation of heterogeneity

Pre-specified subgroup analysis will explore the impact of age, gender, disease severity, comorbidity status, country where care is delivered, and time after the beginning of the outbreak. The characteristics explored will evolve and consider new knowledge on COVID-19. Disease severity will be categorized as follows (WHO 2020a, WHO 2020c):

- **Mild disease** — clinical symptoms are mild with no sign of pneumonia on imaging
- **Moderate disease —** fever and respiratory symptoms with radiological findings of pneumonia and requiring oxygen (3 L/min>oxygen <5 L/min)
- **Severe disease —** cases meeting any of the following criteria:
    - respiratory distress (≧ 30 breaths/min)
    - oxygen saturation ≤ 93% at rest in ambient air or oxygen saturation ≤97% with $O_2 \geq 5$ L/min
    - PaO_2/FiO_2 ≦ 300 mmHg (l mmHg=0.133 kPa). PaO_2/FiO_2 in high-altitude areas (> 1,000 m above sea level) will be corrected by the following formula: PaO2/FiO2 x [atmospheric pressure (mmHg)/760]
    - chest imaging showing obvious lesion progression within 24-48 hr

- **Critical disease —** cases meeting any of the following criteria
    - respiratory failure and requiring mechanical ventilation
    - shock
    - other organ failure that requires ICU care

To infer the classification of each study to one of the four categories we will consider the description of the baseline characteristics of the participants and each study will be classified according to the predominant severity level of the participants. If there is no adequate description, we will classify the study based on the eligibility criteria.

The subgroup analysis will explore the following subgroups on critical outcomes

1) mild disease only

2) mixed disease (i.e., patients heterogeneous in terms of severity, patients with moderate disease and patients with severe disease)

3) critical disease only

Sensitivity analysis

We will perform sensitivity analyses by excluding studies with the overall risk of bias at high risk as well as RCTs reported as preprint only. We will also run the analyses using the number of participants analyzed instead of those randomized as well as by incorporating uncertainty in our missing outcome data assumptions (Chaimani 2018, Mavridis 2015, White 2008).

Summary of findings and assessment of the certainty of the evidence

To evaluate the confidence in the results of the pairwise comparisons for the critical outcomes, we will rely on the GRADE approach (Schünemann 2019). We will prepare 'Summary of findings' tables to present estimated relative and absolute risks. Two review authors will independently grade the overall certainty of the evidence for each outcome using the GRADE classification (GRADEpro GDT). We will include the critical outcomes in the 'Summary of findings' tables.

FUNDING SOURCES
This work received some funding from the Agence Nationale de la Recherche, the World Health Organization, Cochrane France, Centre of Research in Epidemiology and Statistics, Centre d'Epidémiologie Clinique (GHU Cochin, Hôtel Dieu, Assistance Publique Hôpitaux de Paris, and Université de Paris), Federal Ministry of Health (Germany), and the Centre National de la Recherche Scientifique (CNRS).

DECLARATION OF INTEREST
The authors declare that they have no competing interests

REFERENCES

Boutron 2020a Other
Boutron I, Chaimani A, Meerpohl JJ, et al. The COVID-NMA Project: Building an Evidence Ecosystem for the COVID-19 Pandemic [published online ahead of print, 2020 Sep 15]. *Ann Intern Med*. 2020;10.7326/M20-5261. doi:10.7326/M20-5261

Boutron 2020b Other
Boutron I, Chaimani A, Meerpohl JJ, Hróbjartsson A, Devane D, Rada G, Tovey D, Grasselli G, Ravaud P.. Interventions for preventing and treating COVID-19: protocol for a living mapping of research and a living systematic review. [Interventions for preventing and treating COVID-19: protocol for a living mapping of research and a living systematic review.]. Zenodo 2020, September 8. [DOI: http://doi.org/10.5281/zenodo.3903347]

Campochiaro 2020 Journal article
Campochiaro C, Dagna L. The conundrum of interleukin-6 blockade in COVID-19. Lancet Rheumatol [Internet]. 2020 Aug 14 [cited 2020 Sep 11];0(0). Available from: https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30287-3/abstract

Chaimani 2018 Journal article
Chaimani A, Mavridis D, Salanti G, Higgins JPT, White IR. Allowing for informative missingness in aggregate data meta-analysis with continuous or binary outcomes: Extensions to metamiss. The Stata Journal 2018;18(3):716-40. [PMCID: PMC6309174]

Giavridis 2018 Journal article
Giavridis T, van der Stegen SJC, Eyquem J, Hamieh M, Piersigilli A, Sadelain M. CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. *Nat Med*. 2018;24(6):731-738. doi:10.1038/s41591-018-0041-7

Grein 2020 Journal article
Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med. 2020 11;382(24):2327–36.

Guan 2020 Journal article
W. Guan, Z. Ni, Yu Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, C. Lei, D.S.C. Hui, B. Du, L. Li, G. Zeng, K.-Y. Yuen, R. Chen, C. Tang, T. Wang, P. Chen, J. Xiang, S. Li, Jin-lin Wang, Z. Liang, Y. Peng, L. Wei, Y. Liu, Ya-hua Hu, P. Peng, Jian-ming Wang, J. Liu, Z. Chen, G. Li, Z. Zheng, S. Qiu, J. Luo, C. Ye, S. Zhu, and N. Zhong, for the China Medical

Treatment Expert Group for Covid-19*. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-20.

Higgins 2019 Book
Higgins JPT, handler J, Cumpston M, Li T, Page MJ, Welch, VA. Cochrane Handbook for Systematic Reviews of Interventions, 2nd ed.. Chichester (UK): John Wiley & Sons, Ltd, 2019.

Huang 2020 Journal Article
Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 15;395(10223):497–506.

Huet 2020 Journal article
Huet T, Beaussier H, Voisin O, Jouveshomme S, Dauriat G, Lazareth I, et al. Anakinra for severe forms of COVID-19: a cohort study. Lancet Rheumatol. 2020 Jul;2(7):e393–400.

Khan 2020 Journal article
Khan NA. Anakinra for severe forms of COVID-19. Lancet Rheumatol. 2020 Aug 7

Marshall 2020 Journal article
Marshall John C, Murthy Srinivas, Diaz Janet, Adhikari N K, Angus Derek C, Arabi Yaseen M, Baillie Kenneth, Bauer Michael, Berry Scott, Blackwood Bronagh, Bonten Marc, Bozza Fernando, Brunkhorst Frank, Cheng Allen, Clarke Mike, Dat Vu Quoc, de Jong Menno, Denholm Justin, Derde Lennie, Dunning Jake, Feng Xiaobin, Fletcher Tom, Foster Nadine, Fowler Rob, Gobat Nina, Gomersall Charles, Gordon Anthony, Glueck Thomas, Harhay Michael, Hodgson Carol, Horby Peter, Kim YaeJean, Kojan Richard, Kumar Bharath, Laffey John, Malvey Denis, Martin-Loeches Ignacio, McArthur Colin, McAuley Danny, McBride Stephen, McGuinness Shay, Merson Laura, Morpeth Susan, Needham Dale, Netea Mihai, Oh Myoung-Don, Phyu Sabai, Piva Simone, Qiu Ruijin, Salisu-Kabara Halima, Shi Lei, Shimizu Naoki, Sinclair Jorge, Tong Steven, Turgeon Alexis, Uyeki Tim, van de Veerdonk Frank, Webb Steve, Williamson Paula, Wolf Timo, Zhang Junhua. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020;20(8):e192-e197.

Mavridis 2015 Journal article
Mavridis D, White IR, Higgins JPT, Cipriani A, Salanti G. Allowing for uncertainty due to missing continuous outcome data in pairwise and network meta-analysis. Statistics in Medicine 2015;34(5):721-41. [PubMed: 25393541]

Mehta 2020a Journal article
Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet. 2020 Mar 28;395(10229):1033–4.

Mehta 2020b Journal article
Mehta P, Cron RQ, Hartwell J, Manson JJ, Tattersall RS. Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome. *Lancet Rheumatol*. 2020;2(6):e358-e367. doi:10.1016/S2665-9913(20)30096-5

Mertens 2009 Journal article

Mertens M, Singh JA. Anakinra for rheumatoid arthritis. *Cochrane Database Syst Rev*. 2009;(1):CD005121. Published 2009 Jan 21. doi:10.1002/14651858.CD005121.pub3

Pedersen 2020 Journal article
Pedersen SF, Ho Y-C. SARS-CoV-2: a storm is raging. J Clin Invest. 2020 01;130(5):2202–5.

Rhodes 2015 Journal article
Rhodes KM, Turner RM, Higgins JPT. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. Journal of Clinical Epidemiology 2015;68(1):52-60. [PubMed: 25304503]

Riley 2011 Journal article
Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. BMJ 2011;342:d549. [PubMed: 21310794]

Shakoory 2016 Journal article
Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, et al. Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. Crit Care Med. 2016 Feb;44(2):275–81.

Schünemann 2019 Section of book
Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons, Ltd, 2019:375–402.

Shen 2020 Journal article
Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA. 2020 Apr 28;323(16):1582–9.

Sterne 2019 Journal article
Sterne Jonathan A C, Savović Jelena, Page Matthew J, Elbers Roy G, Blencowe Natalie S, Boutron Isabelle, Cates Christopher J, Cheng Hung-Yuan, Corbett Mark S, Eldridge Sandra M, Emberson Jonathan R, Hernán Miguel A, Hopewell Sally, Hróbjartsson Asbjørn, Junqueira Daniela R, Jüni Peter, Kirkham Jamie J, Lasserson Toby, Li Tianjing, McAleenan Alexandra, Reeves Barnaby C, Shepperd Sasha, Shrier Ian, Stewart Lesley A, Tilling Kate, White Ian R, Whiting Penny F, Higgins Julian P T. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019/08/28;366:l4898.

Tierney 2007 Journal article
Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8(1):16. [PubMed: 17555582]

Touret 2020 Journal article
Touret F, de Lamballerie X. Of chloroquine and COVID-19. Antiviral Res. 2020;177:104762.

Turner 2012 Journal article
Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JPT. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of

Systematic Reviews. International Journal of Epidemiology 2012;41(3):818-27. [PubMed: 22461129]

White 2008 Journal article
White IR, Higgins JPT, Wood AM. Allowing for uncertainty due to missing data in meta-analysis—part 1: two-stage methods. Statistics in Medicine 2008;27(5):711-27. [PubMed: 17703496]

WHO 2020a Other
World Health Organization. Clinical management of severe acute respiratory infection when COVID-19 is suspected. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected.

WHO 2020b Other
World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 56. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200316-sitrep-56-covid-19.pdf?sfvrsn=9fda7db2_6.

WHO 2020c Other
World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19---final-report-1100hr-28feb2020-11mar-update.pdf?sfvrsn=1a13fda0_2&download=true.

Worldometer 2020 Other
Coronavirus Symptoms (COVID-19) - Worldometer. https://www.worldometers.info/coronavirus/coronavirus-symptoms/.

APPENDICES

1. LIVING PROCESS OF THE REVIEW

Steering committee

We set up a steering committee of epidemiologists, methodologists, statisticians and clinicians with content expertise. This committee will meet regularly, discuss the conduct of the project, difficulties encountered and possible changes in the protocol according to new knowledge available on this disease. Changes in the protocol could consist for example of changes in the search strategy, eligibility criteria (e.g., study design), research questions for the pairwise meta-analyses, outcomes.

Process and quality control

Our aim is to update the synthesis at least every week. For this purpose, we will search, screen and extract data every day. The updated synthesis will be reported online at least every week.

To standardize the process and ensure both rapidity and quality, we will proceed as follow:

1. We will separate the process into different tasks and set up a team for each task (i.e., a researcher/volunteer will be involved in a single task). Each team will be led by a senior researcher ensuring the quality and standardization of the task.
2. For some tasks, we will develop a short training program for researchers/volunteers joining the team. This program will involve a) reading a manual detailing the task; b) performing the task on a sample as an exercise (e.g., evaluating the risk of bias of 3 studies) and contacting the team leader to ask about difficulties; and c) after a successful training, the newcomer will perform the double data extraction with a senior well-trained researcher.
3. Each team will hold a weekly meeting to discuss difficulties and ensure standardization. All decisions and changes will be recorded.
4. We will set-up an internal quality control process where a senior researcher former editor in chief of Cochrane (D Tovey), we check the data extracted and reported on the website. All points will be discussed with the data extraction team and modifications recorded for transparency.
5. We will develop an external quality control process for data collection involving senior researchers who will check a random sample of the data collected (e.g., member of the Cochrane Bias Methods Group for risk of bias)

We will consider the following tasks

1. Research mapping: screening and extracting data from registries
2. Screening databases from title/abstract to full text
3. Extracting data
4. Analyzing data
5. Grading the evidence

The core team will perform the analysis, presentation and interpretation of the results.

Evolution of the protocol over time

The process will also evolve over time according to the new knowledge available regarding Covid-19.

The steering committee will systematically discuss and achieve consensus on the changes of protocol proposed.

2. CASE DEFINITIONS

Suspect case

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease (e.g., cough, shortness of breath)), AND with no other etiology that fully explains the clinical presentation AND a history of travel to or residence in a country/area or territory reporting local transmission of COVID-19 disease during the 14 days prior to symptom onset.

OR

B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID19 case (see definition of contact) in the last 14 days before onset of symptoms;

OR

C. A patient with severe acute respiratory infection (fever and at least one sign/symptom of respiratory disease (e.g., cough, shortness breath)) AND requiring hospitalization AND with no other etiology that fully explains the clinical presentation.

Probable case

A suspect case for whom testing for COVID-19 is inconclusive (inconclusive being the result of the test reported by the laboratory).

Confirmed case

A person with laboratory confirmation of COVID-19 infection, regardless of clinical signs and symptoms.

Of note, when the definition used to classify cases was not clearly reported, we relied on the classification provided by authors.

3. SEARCH STRATEGIES

Cochrane COVID-19 Study Register

Source	Current Strategy (last updated 17 Aug 2020)
ClinicalTrials.gov	COVID-19 OR 2019-nCoV OR SARS-CoV-2 OR coronavirus
WHO ICTRP	We screen the entire COVID-19.csv file available from https://www.who.int/emergencies/diseases/novel-coronavirus-2019
PubMed	(2019 nCoV[tiab] OR 2019nCoV[tiab] OR corona virus[tiab] OR corona viruses[tiab] OR coronavirus[tiab] OR coronaviruses[tiab] OR COVID[tiab] OR COVID19[tiab] OR nCov 2019[tiab] OR SARS-CoV2[tiab] OR SARS CoV-2[tiab] OR SARSCoV2[tiab] OR SARSCoV-2[tiab] OR "Coronavirus"[Mesh:NoExp] OR "COVID-19"[nm] OR "COVID-19 drug treatment"[nm] OR "COVID-19 diagnostic testing"[nm] OR "COVID-19 serotherapy"[nm] OR "COVID-19 vaccine"[nm] OR "LAMP assay"[nm] OR "severe acute respiratory syndrome coronavirus 2"[nm] OR "spike protein, SARS-CoV-2"[nm]) NOT ("animals"[mh] NOT "humans"[mh]) NOT (editorial[pt] OR newspaper article[pt])
Embase.com	(((('coronaviridae'/de OR 'coronavirinae'/de OR 'coronaviridae infection'/de OR 'coronavirus disease 2019'/exp OR 'coronavirus infection'/de OR 'SARS-related coronavirus'/de OR 'Severe acute respiratory syndrome coronavirus 2'/exp OR '2019 nCoV':ti,ab,kw OR 2019nCoV:ti,ab,kw OR ((corona* OR corono*) NEAR/1 (virus* OR viral* OR virinae*)):ti,ab,kw OR coronavir*:ti,ab,kw OR coronovir*:ti,ab,kw OR COVID:ti,ab,kw OR COVID19:ti,ab,kw OR HCoV*:ti,ab,kw OR 'nCov 2019':ti,ab,kw OR 'SARS CoV2':ti,ab,kw OR 'SARS CoV 2':ti,ab,kw OR SARSCoV2:ti,ab,kw OR 'SARSCoV 2':ti,ab,kw) NOT (('animal experiment'/de OR 'animal'/exp) NOT ('human'/exp OR 'human experiment'/de))) NOT 'editorial'/it) NOT ([medline]/lim OR [pubmed-not-medline]/lim) AND [1-12-2019]/sd

L.OVE

Source	Search strategy
Epistemonikos Database	coronavir* OR coronovirus* OR betacoronavir* OR "beta-coronavirus" OR "beta-coronaviruses" OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR hcov* OR "covid-19" OR covid19* OR "covid 19" OR "2019-ncov" OR cv19* OR "cv-19" OR "cv 19" OR "n-cov" OR ncov* OR (wuhan* and

(virus OR viruses OR viral)) OR sars* OR sari OR (covid* and (virus OR viruses OR viral)) OR "severe acute respiratory syndrome" OR mers* OR "middle east respiratory syndrome" OR "middle-east respiratory syndrome" OR "covid-19-related" OR "2019-ncov-related" OR "cv-19-related" OR "n-cov-related"