Interventions for the prevention and treatment of COVID-19: a living mapping of research and living network meta-analysis (Protocol)

Boutron I, Chaimani A, Devane D, Meerpohl JJ, Rada G, Hróbjartsson A, Tovey D, Grasselli G, Ravaud P.


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# Interventions for the prevention and treatment of COVID-19: a living mapping of research and living network meta-analysis (Protocol)

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Interventions for the prevention and treatment of COVID-19: a living mapping of research and living network meta-analysis

Isabelle Boutron1,2, Anna Chaimani1,2, Declan Devane3, Joerg J Meerpohl4,5, Gabriel Rada6, Asbjørn Hróbjartsson7, David Tovey1,2, Giacomo Grasselli8, Philippe Ravaud1,2

1Université de Paris, Centre of Research Epidemiology and Statistics (CRESS), INSERM, INRA, F-75004, Paris, France. 2Cochrane France, Paris, France. 3School of Nursing and Midwifery, National University of Ireland Galway, Galway, Ireland. 4Institute for Evidence in Medicine, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany. 5Cochrane Germany, Cochrane Germany Foundation, Freiburg, Germany. 6Department of Internal Medicine and Evidence-Based Healthcare Program, Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile. 7Centre for Evidence-Based Medicine Odense (CEBMO), Odense University Hospital, Odense, Denmark. 8Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

Contact address: Isabelle Boutron, isabelle.boutron@aphp.fr, isabelle.boutron@htd.aphp.fr.

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Abstract

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To provide a living mapping of registered randomized trials, and to assess and rank where appropriate the relative effects of interventions for the prevention and treatment of COVID-19.

Our approach has been described in Boutron 2020 and Nguyen 2020.

As part of the methodological process of living systematic reviews, we will continuously (i.e. every working day) collect and critically appraise results from all eligible RCTs addressing specific clinical outcomes related to COVID-19. We will synthesize the available study results using pairwise meta-analyses and when possible and appropriate, network meta-analyses (NMAs). The interventions and the research questions considered will evolve over time and will be guided by end-users’ needs.

We will report our updated evidence synthesis every week, and will make all results available on a website: www.covid-nma.com.

In addition, we will update this Cochrane Review at least once every six months, or as soon as the certainty of evidence (assessed with the GRADE methodology) changes. We will wait until the accumulating evidence changes one or more of the following aspects of the review, before incorporating it and re-publishing the Cochrane Review:

- the findings of one or more critical outcomes;
- the credibility (e.g. GRADE rating) of one or more critical outcomes;
- new settings, population, interventions, comparisons or outcomes studied; or
- new serious adverse events.

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

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

Description of the condition

SARS-CoV-2 is a novel coronavirus first documented in December 2019 in an outbreak in Wuhan, Hubei, China. COVID-19 is the illness caused by this virus. Over the first six weeks of the new decade, SARS-CoV-2 transmission spread from China to several other countries. The World Health Organization (WHO) declared COVID-19 to be a pandemic on 11 March 2020.

The COVID-19 pandemic spread to most of the world’s countries during its first and subsequent waves, often increasing in an almost exponential manner (Worldometer 2020).

COVID-19 can cause various clinical manifestations, from non-specific flu-like symptoms (fever, dry cough, fatigue) to severe hypoxaemia, multi-organ failure, and death (Novel 2020, Grasselli 2020, Goyal 2020, Guisado-Vasco 2020, Shah 2020, Karagiannidis 2020 WHO 2020, Cunningham 2020). Severe forms usually manifest a week after the onset of symptoms. Most people with COVID-19 show only mild or uncomplicated illness. Although frail, older patients are at higher risk, young and otherwise healthy patients can have severe forms as well.

Description of the intervention

To address this pandemic, researchers are working to accelerate the development of preventive and therapeutic interventions. Many randomized controlled trials (RCTs) have been established to evaluate candidate therapeutic agents that may effectively reduce symptoms and avoid deaths. With this project, we aim to evaluate the following.

1. Interventions for preventing the spread of COVID-19.
2. Interventions for treating COVID-19.

We will address the different research questions in detail in specific sub-protocols of this ‘master’ protocol.

How the intervention might work

We will provide descriptions in the specific sub-protocols.

Why it is important to do this review

This emerging situation requires the optimal planning and conduct of trials, as well as strategies for the appropriate translation of research into practice. We set up the COVID-NMA initiative (www.covid-nma.com) to help decision-makers make evidence-based decisions. Our goal is to provide decision-makers with a complete, high-quality and up-to-date synthesis of evidence, as soon as results are available. For this purpose, we decided to define a very broad research question - ‘all interventions for preventing and treating COVID-19’ - and to set up the specific research questions as soon as new evidence becomes available. We are also linking this ‘living’ evidence synthesis to a ‘living’ research mapping of all RCTs registered and identified on the WHO International Clinical Trials Registry Platform (ICTRP), an international registry that collates information on clinical trials registered in 17 primary registries. This approach allows for a clear understanding of the upcoming evidence and for contacting investigators of ongoing trials to inform them of the outcomes considered in the review, as well as requesting their trial protocols in advance. We also set up a strong process to ensure both the quality and rapidity of results. We will search for, screen and extract data every working day. We will report our updated evidence mapping and evidence synthesis every week, and will make all results available on a website: www.covid-nma.com.

OBJECTIVES

To provide a living mapping of registered randomized trials, and to assess and rank where appropriate the relative effects of interventions for the prevention and treatment of COVID-19.

Our approach has been described in Boutron 2020 and Nguyen 2020.

As part of the methodological process of living systematic reviews, we will continuously (i.e. every working day) collect and critically appraise results from all eligible RCTs addressing specific clinical outcomes related to COVID-19. We will synthesize the available study results using pairwise meta-analyses and when possible and appropriate, network meta-analyses (NMAs). The interventions and the research questions considered will evolve over time and will be guided by end-users’ needs.

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

Criteria for considering studies for this review

Types of studies
The criteria for study selection have evolved. Changes in protocols are detailed in Appendix 1.

We will include randomized controlled trials, whatever the trial design, including cluster-randomized trials and crossover trials.

We will exclude early-phase clinical trials, single-arm trials, non-randomized studies or modelling studies of interventions for COVID-19.

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
For each research question, we will consider different participants, as detailed in each specific sub-protocol.

Types of interventions
For each research question, we will consider different interventions. Briefly, eligible interventions will include the following:

- Preventive interventions
  * Prophylactic pharmacologic treatments for preventing SARS-CoV-2 transmission
  * Vaccination
  * Non-pharmacologic interventions for preventing SARS-CoV-2 transmission (e.g. personal protective equipment)
- Interventions for treating COVID-19 (anti-infectious agents, specific and non-specific immunomodulators, supportive treatments for hospitalized patients, general treatments for viral infection)
- Post-acute care interventions
  * Rehabilitation
  * Any other treatment for long-term effects of COVID-19

The treatments and preventive interventions considered in this systematic review will likely expand over time to take into account new emerging management options and combination regimens. We will update this list according to the results of the mapping of all RCTs registered on ICTRP, which is updated weekly.

Nguyen 2020.

Interventions will be included in the same NMA only when we anticipate that any patient who meets the pre-defined inclusion criteria would, in principle, be equally likely to be randomized to any of the interventions within a network.

Types of outcome measures
Our outcome selection will be based on:

- the CORE outcome sets identified through the COMET initiative, where available (www.comet-initiative.org/Studies/Details/1538);
- the results of the research mapping that will describe the outcomes assessed in ongoing trials; and
- the clinical outcomes relevant to patients (i.e. patient-important outcomes).

The outcomes considered will evolve over time to take into account the new CORE outcome sets being developed by the COMET initiative, and any other important outcomes that may arise over time.

We will describe outcomes as critical (primary) and important (secondary). We will define outcomes in the specific sub-protocols for each research question.

Primary outcomes
See each specific sub-protocol.

Secondary outcomes
See each specific sub-protocol.

Search methods for identification of studies
We will use the search strategies described below to identify randomized trials of interventions for the prevention and treatment of COVID-19.

For this review, it is crucial that we identify relevant results as rapidly as possible. Therefore, we will target databases for which data from clinical trials on COVID-19 can easily be retrieved and use strategies that maximize specificity.

We recognize that information sources are being developed rapidly in the current situation. We will add to or modify our evidence sources based on the availability of new eligible resources. Currency, usability and the credibility of new information sources will all be considered when selecting sources to integrate into our search strategy.

The initial search strategy, described in Appendix 2, was developed with Robin Featherstone, Information Specialist at the Cochrane Editorial & Methods Department. This search strategy was updated on 4 September 2020, following an evaluation of the sensitivity of the Living Overview of Evidence (L-OVE) platform. This evaluation demonstrated that the L-OVE platform identified 100% of the RCTs that were identified through the initial extensive search strategy.

Electronic searches
From 4 September 2020, we will search only the following secondary sources.

- The L-OVE platform (app.loveevidence.com/covid19). Details of this platform are available in Appendix 3.
- The Cochrane COVID-19 Study register (covid-19.cochrane.org).

We will no longer search PubMed, CNKI, MedRxiv and Chinaxiv, which we had previously been searching.

We will regularly contact investigators of ongoing studies to update the status of their study and obtain results.

We will also search the Retraction Watch Database for retracted studies (retractionwatch.com/retracted-coronavirus-covid-19-papers).
We recognize that preprint articles are not peer-reviewed, and are living documents that can be updated or published. In collaboration with a research team from the French National Centre for Scientific Research (Centre National de la Recherche Scientifique; CNRS), we developed a preprint tracker that 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 several databases for unpublished and ongoing studies.

- We will search the WHO ICTRP (www.who.int/ictrp) 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 regularly contact investigators of ongoing studies to update study status and obtain results.
- We will also search the European Medicines Agency (EMA) clinical data website (clinicaldata.eema.europa.eu/web/cdp/home) to identify trials submitted to the EMA, and will retrieve the Clinical Study Reports (CSR) of eligible studies. We will also search the website of the United States Food and Drug Administration (FDA) (www.fda.gov) to identify FDA approval documents.

**Data collection and analysis**

To standardize the process and ensure both rapidity and quality, we will proceed as follows.

1. We will separate the process into different tasks and set up a team for each task (i.e. a researcher or volunteer will be involved in a single task). Each team will be led by a senior researcher, to ensure the quality and standardization of the task.
2. For some tasks, we will develop a short training program for researchers or 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 three studies), and contacting the team leader to ask about difficulties; and c) after a successful training, the newcomer will perform double data extraction with a senior, well-trained researcher.
3. Each team will hold regular meetings to discuss difficulties and ensure standardization. All decisions and changes will be recorded.
4. We will set-up an internal quality control process to 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 (e.g. a member of the Cochrane Bias Methods group), who will check a random sample of the data collected.

We will consider the following tasks:

- grading the certainty of the evidence, using the GRADE approach.
- research mapping: screening and extracting data from registries;
- screening databases from title/abstract to full text;
- extracting data;
- analyzing data; and

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

**Selection of studies**

We will search and screen the citations retrieved on a daily basis. We will use an Excel spreadsheet to document search dates and numbers of hits identified. Two review authors working independently will screen all records retrieved in searches, and will call upon a third review author to resolve disagreements.

**Data extraction and management**

Two review authors working independently will extract all data and will call upon a third review author to resolve disagreements. Two review authors will independently read each preprint, publication, protocol, or other study reports available, 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 information. All discrepancies automatically identified by the online tool will be discussed by the two review authors and their consensus will be recorded. As soon the consensus is validated, data related to the characteristics of the study and ‘Risk of bias’ assessment will be made available online.

Information extracted will include study characteristics (such as first author, publication year and journal), number of participants randomized, patient characteristics, intervention details, 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 continuous outcomes, we will extract means, standard deviations (SDs) and number of total participants per study arm. When SDs are not available but standard errors (SE), Tau statistics or P values are reported, we will extract these and transform to SDs when possible. For time-to-event outcomes, we will extract hazard ratios (HR) and SEs. 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) sample whenever these are available. If ITT results are not available, the modified ITT analysis will be our second choice. When both adjusted and unadjusted analyses are reported, we will extract the latter (to avoid introducing additional methodological heterogeneity across studies) unless the two types of analyses yield substantially different results. If they are different, we will examine each study on a case by case basis.

We will systematically contact authors and ask them to supply 1) information that could not be retrieved from the available study reports and 2) individual-participant data (IPD). These data will be requested by a personalized email sent by the WHO. These data will be curated and stored. In the presence of IPD, we will re-analyze the outcomes. Furthermore, if possible, we will conduct IPD NMA. If acquiring IPD for some of the studies will be deemed feasible, a specific protocol describing the methods to perform IPD meta-analyses and NMA will be prepared.
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 as well as all the updates or publications of preprint will be recorded by one review author and systematically checked by a second review author. The data available online will be updated accordingly.

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

**Assessment of risk of bias in included studies**

We will assess each study with the Cochrane 'Risk of bias 2' (RoB 2) tool for randomized controlled trials (Sterne 2019).

We will assess the risk of bias for critical and important outcomes recorded at all time points. We will record the judgement using the online data extraction tool we developed, but not the answer to each signalling question. Researchers with a master’s degree in epidemiology, or members of Cochrane’s rapid response team, will assess the risk of bias. The members of the team have all previously been trained in clinical epidemiology and systematic reviews. They have also all participated in a training phase where they read the training material and performed data extraction and RoB 2 assessment with a team of experienced researchers. Members of the Cochrane Bias Methods group will regularly check the quality of 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; and 5) risk of bias in selection of the reported result. Within each domain, a series of signalling questions elicit information relevant to ‘Risk of bias’ assessment. The response options to the signalling questions are ‘yes,’ ‘probably yes,’ ‘probably no,’ ‘no’, and ‘no information.’ A ‘Risk of bias’ judgement arising from each domain is generated by an algorithm, based on answers to the signalling questions. Judgements can be ‘low risk of bias,’ ‘some concerns’ or ‘high risk of bias.’ We will consider the overall risk of bias to be ‘low risk of bias’ if all domains are at ‘low risk’; ‘some concerns’ if at least one domain is of ‘some concern’ and no domain is at ‘high risk of bias’; and ‘high risk of bias’ if there is at least one domain considered to be at ‘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. under the ITT principle).

We will define in each sub-protocol the co-interventions that could differ between intervention groups and potentially affect study outcomes.

In assessing the certainty of the evidence with GRADE, we will take our ‘Risk of bias’ assessment into account.

**Measures of treatment effect**

For dichotomous outcomes, we will use as measure of effect the risk ratio (RR) accompanied by the 95% CI. For continuous and time-to-event outcomes we will use the standardized mean difference (SMD), or mean difference (MD), if all studies use the same scale; and the HR, respectively.

**Unit of analysis issues**

In the pairwise meta-analysis, different comparisons from multi-arm trials will be analyzed separately. In the network meta-analyses, we will properly account for the inherent correlation in multi-arm trials.

We do not expect to identify any cross-over trials. Cluster-randomized trials might appear. 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.

**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 describe 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 assumptions.

**Assessment of heterogeneity**

At each update, we will first generate descriptive statistics for study and population characteristics to show the available comparisons, the amount of information and the distribution of important clinical and methodological variables (such as age, disease severity, comorbidities, location etc.). We will present the data by pairwise comparison and network diagrams with nodes representing the interventions being compared and lines representing the available direct comparisons in the studies. We will additionally use colours to represent the risk of bias of the studies in each direct comparison (Chaimani 2013). Using a contribution matrix (Papakonstantinou 2018), we will show the effect of each piece of evidence in the full body of evidence and how new evidence affects the existing results.

We will use visual inspection of forest plots, prediction intervals (the interval within which the effect of a future study is expected to lie) (Riley 2011) and comparison of Tau² with appropriate empirical distributions (Rhodes 2015, Turner 2012) to assess the presence of important statistical heterogeneity.

Transitivity is the fundamental assumption of NMA and needs careful examination to reassure that results will be valid (Salanti 2012). We will investigate the distribution of clinical and methodological characteristics that may act as effect modifiers across treatment comparisons. Such characteristics include age, severity status, comorbidity status, and country where care is delivered. To avoid intrinsically networks, we will evaluate the similarity of studies comparing different sets of interventions and only synthesize them when important clinical and methodological characteristics are sufficiently similar. Similarity will be judged
qualitatively using boxplots (for continuous characteristics) and histograms (for categorical characteristics). We will also investigate whether different studies similarly define the interventions forming the nodes of the networks.

**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 for Systematic Reviews of Interventions* (Higgins 2019).

We will use the comparison-adjusted funnel plot (Chaimani 2013) (a modified funnel plot appropriate for NMA) and appropriate network meta-regression models (Chaimani 2012) to assess the potential for small-study effects in each NMA. If asymmetry is found, we will explore possible reasons for the apparent association between study size and study effect. If publication bias is suspected, we will apply selection models that make assumptions about the probability of publication based on the study results (Mavridis 2014).

**Data synthesis**

The main analysis will include RCTs only. All eligible RCTs will be included in the primary analysis, whatever the RoB 2 assessment

For each direct comparison with at least two studies providing data, we will present effect estimates with 95% CIs. We will use the random-effects model to incorporate the anticipated clinical and methodological heterogeneity across studies. We will use two assumptions for the between-study variance (Tau²): 1) a separate Tau² for every comparison between two interventions; and 2) a common Tau² for studies comparing the same types of interventions.

For the sets of studies for which transitivity is plausible, we will perform random-effects NMAs to compare the different interventions or combination regimens and potentially obtain their ranking. Each outcome will constitute a different network of interventions. We will assume a common heterogeneity parameter (Tau²) for every network of interventions. We will present the results in terms of effect sizes and 95% CIs in league tables and will use colours to represent the confidence in the evidence for every comparison. We will assess the impact of heterogeneity on the results by using prediction intervals. To rank the interventions, in the absence of excessive uncertainty in the relative effects, we will use the surface under the cumulative ranking curve (SUCRA) (Salanti 2011). We will run analyses and produce graphical displays using R (netmeta package (Rucker 2013) and Stata network (White 2015) and network graphs packages (Chaimani 2015). Network meta-regressions will be run in a Bayesian environment using R2jags with self-written models ([R2jags](https://github.com/)).

We will supplement the conceptual evaluation of transitivity with a statistical evaluation of the assumption coherence, which refers to the agreement between direct and indirect evidence. We will use both local and global methods. Local approaches assess coherence in parts of the network but global approaches in the entire network jointly. Specifically, we will use the loop-specific approach (Bucher 1997), the side-splitting method (Dias 2010) and the design-by-treatment interaction model (Higgins 2012). Tests for incoherence are known to have low power, so we will interpret the results of the tests with caution.

**Subgroup analysis and investigation of heterogeneity**

We will detail pre-specified subgroup analyses in each sub-protocol. If we find substantial heterogeneity or incoherence, we will use subgroup analyses and meta-regressions to explore the impact of specific characteristics on the results. The characteristics explored will evolve as we consider new knowledge on COVID-19.

**Sensitivity analysis**

We will perform sensitivity analyses by excluding studies at high risk of bias as well as study reported as preprint. We will also run the analyses using the number of participants analysed, instead of those randomized, and 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 classifications (GRADEpro GDT). We will include the critical outcomes in the 'Summary of findings' tables.

To evaluate the confidence in the NMA for the critical outcomes, we will use the CiNeMa tool that considers the following domains: within-study bias, across-studies bias, indirectness, imprecision, heterogeneity and incoherence (CiNeMA 2017, Nikolaoupolou 2019). For within-study bias and indirectness, CiNeMA calculates the contribution of each study in each network estimate and combines these contributions with the study-specific evaluations (low, moderate, high) to rate the relative effect for each comparison in the network. The domains of imprecision, heterogeneity and incoherence use a pre-specified clinically important size of effect to specify the margin of clinical equivalence between two interventions.

Given that knowledge in the field is still limited, pre-defining a clinically important size of effect is not straightforward. Therefore, we will follow a conservative approach and make our judgements based on the statistical difference between two interventions. However, as more evidence becomes available we will attempt to also use clinically important effect sizes to assess the robustness of our judgements.

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The following individuals participated in this review as members of the COVID-NMA

Names are reported in alphabetical order

Sofa Alawadhi1,2, Sihem Amer-Yahia3, Chiara Arienti4, David Auber5, Camila Ávila6, Aida Bafeta2, Fulvia Baldassarre7, Rita Banzi8, Julien Barnier9, Julia Baudry10, Hanna Bergman11, Claudia Bollig12, Hillary Bonnet1,13, Marinnette Bouet14, Mohand Boughanem15, Isabelle Boutron12,16, Brian Buckley11, Guillaume Cabanac15, Anna Chaiman1,16, Sarah Charpy2, David Chavalarias17, YaoLong Chen18, Astrid Chevanche2, Sarah Cohen-Boulakia12, Elise Cogo11, Françoise Conil20, Emmanuel Coquery20, Mauricia Davidson2,16, Laura De Nale16, Declan Devane21, Elise Diard16, Taoqiu Dkaki15, Bastien Doreau14, Merwan El Asri19, Theodoros Evrenoglou1,16, Alice Fabbr122, Gilles Feron23, Gabriel Ferrand16, Leopold Fezeu10, Mathilde Fouet24, Joly Ghanawi25, Lina Ghosn El Chall16, Robin Featherstone26, Carolina Grañaa2,16, Giacomo Grasselli27, François Grolleau1, Benoit Groz19, Mohand-Said Hacid20, Candrye Hame11, Camilla Hansen22, Nicholas Henschkel1, Ameer Hohlfeld28, Asbjørn Hróbjartsson22, Chantal Julia10, Dimitris Mavridis29, Joerg J Meerpolh12,30, Brice Meyer14, Silvia Minozzi31, Jose G. Moreno15, Nivanta Naidoo2, Van Thu Nguyen16, Theodora Oikonomidi1,16, Matthew Page32, Jennifer Petkovic11, Elizabeth Pienaar28, Olivier Pierre2, Katrin Probyn11, Fiona Quirke33, Gabriel Rada6,34, Philippe Ravaud1,2,16, Pierre Ripoll20, Carolina Riverso2,16, Philippe Rivière20, Marie Sauvaint14, Jelena Savovic35, Christine Schmucker30, Yanina Sguassiero11, Jonathan Sterne36, Farouk Toumani14, David Tovey36, Gemma Villanueva11, Romain Vuillermot20, Jun Xia37, Xuan Yu18, Emina Zoletic1,2, Pierre Zweigenbaum38

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 ID (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 Anesthesiology, 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
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Nguyen 2020

Nikolopoulos 2019

Novel 2020

Papakonstantinou 2018

R2jags

Rhodes 2015

Riley 2011

Rucker 2013

Salanti 2011

Salanti 2012

Schünemann 2019

Shah 2020

Sterne 2019

Tierney 2007

Turner 2012

White 2008

White 2015

WHO 2020

Worldometer 2020

A P P E N D I C E S

Appendix 1. Changes in criteria for considering types of studies

On September 2, 2020, considering the increase in randomized controlled trials with results available, the steering committee decided to update the protocol and exclude non-randomized studies from the living systematic review. From this date, we will consider only randomized controlled trials in the living systematic review.

The protocol initially planned to include both randomized controlled trials and non-randomized studies. The non-randomized studies included in the review had to fulfil the following criteria:
• Study design: interrupted time-series studies, non-randomized studies using causal inference analysis (e.g. propensity score, instrumental variables, inverse probability weighting, etc.) (Hernán 2019) and non-randomized studies using multivariable regression adjustment.

• Participants: inclusion of incident users (all non-randomized studies including prevalent users will be excluded). Incident users are defined as participants who started the treatment when included in the study and follow-up. Prevalent users are defined as participants who were treated before being included in the study and follow-up.

Sample size: non-randomized studies including >150 participants to reassure that accounting for multiple confounders in the analysis would be feasible.

Given that non-randomized studies were only a supplementary source of information and considering the importance of obtaining study results as soon as possible in the current circumstances, we planned to only include non-randomized studies reporting the primary and secondary outcomes of the systematic review adjusted for confounding variables.

We initially planned to include in the synthesis only non-randomized studies at moderate risk of bias as evaluated by Cochrane Risk of Bias tool for non-randomized studies of interventions (i.e. ROBINS-I (Sterne 2016)). RCTs and non-randomized studies were planned to only be combined in the same analysis after careful examination of the risk for violating the homogeneity and transitivity assumptions.

It was planned to consider non-randomized studies until several large RCTs of high quality will be made available. The decision of up to which point non-randomized would provide valuable information is discussed regularly within the steering committee and is also guided by the certainty of evidence from RCTs for the different outcomes.

Appendix 2. Initial search strategy

Appendix 3

Up to September 4, 2020, we searched the following sources:

The following primary sources were searched daily:

- CNKI (China National Knowledge Infrastructure, https://www.cnki.net/) database and (http://journal.yiigle.com/)
- MedRxiv (https://www.medrxiv.org): MedRxiv 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 bioRxiv, but we will only screen the sources published on MedRxiv (i.e. titles in blue rather than red).
- Chinese (http://chinaxiv.org/) Chinaxiv is a free online archive and distribution server for complete but unpublished manuscripts (preprints) in Chinese.

In collaboration with the WHO Collaborative Centre for Guideline Implementation and Knowledge Translation and Chinese GRADE Centre (Lanzhou University, China), the Chinese literature was also be extensively searched.

The following secondary sources were searched as quality control:

- The L·OVE platform (https://app.loveevidence.com/loves/5e6fdb9669c00e4ac072701d). Details of this platform is available in Appendix 7.
- The Cochrane COVID-19 Study register (https://covid-19.cochrane.org/)

The secondary sources searched and abandoned because no trial was identified are listed below:

- 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”. On 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). On 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/). On 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.

The search strategy used is detailed below.
### RCT Search Strategy

<table>
<thead>
<tr>
<th>Search</th>
<th>Query</th>
</tr>
</thead>
<tbody>
<tr>
<td>#10</td>
<td>#8 Filters: Publication date from 2020/01/01</td>
</tr>
<tr>
<td>#9</td>
<td>Search: #4 AND #7</td>
</tr>
<tr>
<td>#8</td>
<td>Search: #5 NOT #6</td>
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<td>#7</td>
<td>Search: animals[mh] NOT humans[mh]</td>
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<tr>
<td>#5</td>
<td>Search: #1 OR #2 OR #3 OR #4</td>
</tr>
<tr>
<td>#4</td>
<td>Search: severe acute respiratory syndrome coronavirus 2[Supplementary Concept]</td>
</tr>
<tr>
<td>#3</td>
<td>Search: COVID-19[Supplementary Concept]</td>
</tr>
</tbody>
</table>

### China National Knowledge Infrastructure Strategy

1. “2019冠状病毒”
2. “新型冠状病毒”
3. “新冠肺炎”
4. “武汉2019”
5. “武汉病毒”
6. “武汉肺炎”
7. “2019-nCoV”
8. “SARS-CoV-2”
9. “Novel coronavirus”
10. “nCoV”
11. “Emerging Coronavirus”
12. “new coronavirus”
14. “coronavirus”
15. OR/#1-#14
Appendix 3. Methods and reporting of the special L-OVE of Coronavirus (COVID-19)

The Living OVerview of Evidence (L-OVE) builds upon the general methods of the L-OVE platform and incorporates the following new methods:

All evidence organized in the L-OVE platform is retrieved in real-time from Epistemonikos Database (See Epistemonikos Database methods here).

The team maintaining the L-OVE platform devised a search strategy for COVID-19 and each of the individual PICO questions available, using the following approach:

- Identification of terms relevant to the population and intervention/test/variable components of the search strategy, applying Word2vec technology to the corpus of documents available in the Epistemonikos Database
- Discussion of terms with content and methods experts to identify relevant, irrelevant and missing terms
- Creation of a sensitive boolean strategy encompassing all the relevant terms
- Iterative analysis of articles missed by the boolean strategy and refinement of the strategy accordingly

The following strategy was used to search for coronavirus infection (COVID-19 and other coronavirus infections affecting humans).

coronavir* OR coronavirus* OR betacoronavir* OR "beta-coronavirus" OR "beta-coronaviruses" OR "corona virus" OR "virus corona" OR "coronavirus" OR "coronaviruses" OR "virus coronaviruses" OR "coronavirus" OR "virus coronaviruses" OR "virus coronaviruses"

Search sources

To complement the searches in the 10 sources routinely performed in the Epistemonikos Database (See Epistemonikos Database methods here), we will conduct searches in the following sources:

- PubMed (updated several times a day)
- EMBASE (updated weekly)
- ITRP Search Portal (targeted searches)
- ClinicalTrials.gov (updated daily)
- ISRCTN registry (updated daily)
- Chinese Clinical Trial Register (updated daily)
- Iranian Registry of Clinical Trials (updated daily)
- EU Clinical Trials Register: Clinical trials for COVID-19 (updated daily)
- NIPH Clinical Trials Search (Japan) (targeted searches)
- Clinical Research Information System (Korea) (targeted searches)
- MedRxiv pre-prints (updated several times a day)
- BioRxiv pre-prints (updated several times a day)
- Microsoft Academic (targeted searches)
- Google Scholar (targeted searches)
- COVID-19: Global literature on coronavirus disease (targeted searches)
- NIHR: Innovation observatory: COVID-19 Updates (targeted searches)
- COVID-19: a living systematic map of the evidence (targeted searches)
- COVID-evidence website (targeted searches)
- Live map of COVID-19 evidence (targeted searches)
- LitCovid (targeted searches)
- COVID-19 Special Collection (JBI) (targeted searches)
- Coronavirus disease (COVID-2019) R&D (targeted searches)
- Coronavirus (COVID-19) Resource Hub (targeted searches)
- Coronavirus Research Repository (Elsevier Connect) (targeted searches)
- Coronavirus (COVID-19) (CDC) (targeted searches)
- Orientación sobre la COVID-19 y últimas investigaciones en las Américas (PAHO) (targeted searches)
- COVID-19. Información confiable para la toma de decisiones (targeted searches)
- Cochrane COVID-19 Study Register (targeted searches)
Eligibility criteria

Type of participants

Articles related to SARS-CoV-2 infection/COVID-19 or other Coronaviruses, such as SARS-CoV and MERS-CoV

Type of intervention/test/factor/variable

Varies depending on the question

Types of articles

We will classify the articles according to the following categories:

1. Systematic reviews - According to the Epistemonikos Database criteria for systematic reviews
2. Primary studies - Primary study is an umbrella term that encompasses any study design, qualitative or quantitative, whereby data are collected from individuals or groups of people. We also include studies that have not yet reported results (e.g. trial registries, ongoing trials, protocols).
3. Broad syntheses - We group in this category different types of articles aiming to make an evidence synthesis of systematic reviews and, sometimes, primary studies (guidelines, overviews of reviews, scoping reviews, policy briefs, among others).
4. Other articles- This category includes all articles not yet classified or not fulfilling the definitions for the categories above.

HISTORY

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CONTRIBUTIONS OF AUTHORS

All authors contributed to the protocol development.

DECLARATIONS OF INTEREST

Isabelle Boutron: I am director of Cochrane France and co-convenor of the Cochrane Bias methods group.

Anna Chaimani: none known

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Asbjørn Hróbjartsson: none known

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Gabriel Rada: none known

David Tovey: I have a part time paid consultancy with the Université de Paris.

Grasselli Giacomo: I received personal fees for lectures from Getinge, Fisher&Paykel, Draeger Medical, Biotest, Thermofisher and MSD; support for travel-meeting expenses from Biotest and Getinge (all outside the present work). I also received an unrestricted research grant from Fisher&Paykel (unrelated to the present work).

Philippe Ravaud: I am a minority shareholder of INATO
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- Assistance Publique Hôpitaux de Paris (APHP), France
- Université de Paris, France
- Centre National de la Recherche Scientifique (CNRS), France

External sources
- Agence Nationale de la Recherche (ANR), France
  - Funding provided to produce review
- World Health Organization (WHO), Switzerland
  - Funding provided to produce review
- Federal Ministry of Health, Germany