Interventions for preventing and treating COVID-19: living systematic reviews and network meta-analyses

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# Background

## Description of the condition

In December 2019, a novel coronavirus outbreak was documented in Wuhan, Hubei Province, China. This coronavirus, known as SARS-CoV-2, spread from China to several countries of the world, and WHO declared COVID-19 a pandemic on March 11, 2020.

At the time of writing (September, 2020), the cumulative incidence of COVID-19 cases is following an almost exponential trend over the world with around 900,000 death (Coronavirus Symptoms (COVID-19) - Worldometer).

COVID-19 can cause various clinical manifestations from non-specific flu-like symptoms (fever, dry cough, fatigue) to severe hypoxemia, multiorgan failure, and death. Severe forms usually manifest a week after the onset of symptoms. Most people with COVID-19 show only mild or uncomplicated illness, but approximately 14% exhibit severe disease that requires hospitalization and oxygen support; 5% require admission to an intensive care unit (ICU) (Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020). Although frail older patients are at higher risk, young and otherwise healthy patients can have severe forms as well (*Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)*, 2020).

## 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. Therefore, we aim to evaluate:

1. Interventions for preventing the spread of COVID-19
2. Interventions for treating COVID-19
3. Post-acute care interventions for COVID-19 patients
4. Models of practice and organization of care aiming to improve patients’ health care

The different research questions will be addressed in detail in specific sub-protocols of this ‘master’ protocol.

## How the intervention might work

Descriptions will be provided 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. To help decision makers facing this emerging situation, we set up the COVID-NMA project. This project aims to provide a complete, high-quality and up-to-date synthesis of evidence as soon as results are available as well as a living mapping of registered randomized controlled trials. This evidence synthesis will allow evidence-based decisions. The living mapping will inform the planning of future research.

Here we describe the protocol for the evidence synthesis.

# Objectives

To assess and rank where appropriate ﻿the relative effects of interventions for the prevention and treatment of COVID-19. ﻿

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.

All our results are made publicly available on a website (<https://covid-nma.com/>) updated every week.

# Methods

## General principles

Our goal is to provide decision makers 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 intervention for preventing and treating COVID-19 and to set up the specific research questions as soon as new evidence is available. Further, we are linking the living evidence synthesis to a living research mapping of all RCTs registered and identified on the WHO International Clinical Trials Registry Platform (ICTRP) (<https://www.who.int/ictrp/en/>), an international registry that assembles information on clinical trials registered in 17 primary registries. This approach allows having a clear understanding of the upcoming evidence and contacting investigators of ongoing trials to inform them of the outcomes considered in the review as well as requesting in advance their protocol. We also set-up a strong process to ensure both quality and rapidity. We will search, screen and extract data every day. The updated synthesis will be reported at least every week and all results available on a website <https://covid-nma.com/>.

### Steering committee

A steering committee of epidemiologists, methodologists, statisticians and clinicians with content expertise will be set-up. 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

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 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 bias methods group for risk of bias)
6. We will set-up working groups on different domains to improve our process such as a specific working group with trialists; a working group with guideline developers.

### 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.

## Criteria for considering studies for this review

### Types of studies

The criteria for study selection have evolved. These changes are detailed in Appendix 1.

We will include randomized controlled trials whatever the trial design, including cluster-randomized trials 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, diagnostic test accuracy studies, and modelling studies.

We have no restriction on language.

### Types of participants

The type of participants will be described in each sub-protocol.

### Types of interventions

For each research question, we will consider different interventions. Briefly, eligible interventions will include:

* Interventions for preventing SARS-CoV-2 (vaccination, prophylactic interventions, personal protective equipment, models of practice and organization of care)
* Interventions for treating COVID-19 (anti-infectious agents, specific and non-specific immunomodulators, supportive treatments for patients admitted to the ICU, general treatments for viral infection)
* Post-acute care interventions
* Models of practice and organization of care for improving patients’ health care

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.

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.

Interventions will be described in each sub-protocol.

### Types of outcome measures

We based our outcome selection on the CORE outcome sets developed by the WHO (WHO Working Group on the Clinical Characterization of COVID-19 infection) and on the meta-COS for research in COVID-19 hospitalized patients identified through the COMET initiative (<http://www.comet-initiative.org/Studies/Details/1538>).

The outcomes considered will evolve over time to take into account the new CORE outcome set being developed by the COMET initiative (<http://www.comet-initiative.org/Studies/Details/1538>) and any other important outcome that may arise over time.

The primary and secondary outcomes will be defined in the specific sub-protocol for each research question

#### Primary outcomes

See each specific sub-protocol

#### Secondary outcomes

See each specific sub-protocol

## Search methods for identification of studies

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/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 was developed with Robin Featherstone, Information Specialist, at the Cochrane Editorial & Methods Department. The search was updated on September 4, 2020 following an evaluation of the sensitivity of the L.OVE platform which demonstrated that it allowed identifying 100% of the RCTs identified through the initial extensive search strategy.

From September 4, 2020, we search only the following secondary sources and stop searching PubMed, CNKI, ﻿﻿MedRχiv and Chinaxiv.

* **The L.OVE platform** (<https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d>). Details of this platform is available in Appendix 3.
* **The Cochrane COVID-19 Study register**(<https://covid-19.cochrane.org/>)

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

We recognize 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 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.

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 regularly 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 we will retrieve the Clinical Study Report (CSR) of eligible studies. We will also search the FDA website to identify FDA approval documents.

### Electronic searches

Details are available in Appendix 2 and a description of the L.OVE platform in Appendix 3.

## Data collection and analysis

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 at least every week.

### Selection of studies

W﻿e 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. Screening of records and abstracts will be done in duplicate independently. Disagreements will be resolved by a third reviewer. For Pubmed we will be using Rayyan and for MedRxiv an xml table. Secondary sources are screened by one reviewer once a week.

### Data extraction and management

All data will be extracted in duplicate, with consensus in case of disagreement. Two reviewers 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 are discussed by the two reviewers and the consensus is recorded. As soon the consensus is validated, data related to the characteristics of the study and risk of bias assessment are available online. ﻿

Information extracted will include study characteristics (such as first author, publication year and journal), number of participants randomised, patient characteristics (such as mild or severe clinical presentation), intervention details (such as class and type of treatments), 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, t-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 standard errors (SE). When these are not provided, we will attempt to obtain them using the tools provided in Tierney 2007.

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 NMAs. 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 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 analys﻿es and update the forest plots available online weekly.

### Assessment of risk of bias in included studies

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 primary and secondary ﻿outcomes recorded at all time points﻿. We are recording the judgement but not systematically the answer to each signalling question. Risk of ﻿Bias is assessed by researchers with a master degree in epidemiology (currently 4 people) or members of Cochrane rapid response (the number of people involved varies). They all have been previously trained in clinical epidemiology and systematic reviews. They all participated in a training phase where they had to read the training material and perform data extraction and RoB assessment with a team of experienced researcher. The quality of the data is checked by members of the Bias Methods group who will regularly check a random sample of the data extracted.

The Cochrane RoB 2 tool is structured into 5 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 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 arising from 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’.

The risk of bias assessment will be taken into account in the evaluation of the confidence (or certainty) of the evidence as follows:

To evaluate the confidence in the results of the pairwise comparisons for the primary 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](https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012208.pub2/references" \l "CD012208-bbs2-0065)). We will include the primary outcomes (listed in [Primary outcomes](file:///Users/Laura/Downloads/CRIT_OUTCOMES_PRIMARY)) in the 'Summary of findings' tables.

To evaluate the confidence in the NMA for the primary outcomes, we will use the CINeMA tool that considers the following domains: within-study bias, across-studies bias, indirectness, imprecision, heterogeneity and incoherence ([CINeMA](file:///Users/Laura/Downloads/417549144345308038), [Nikolakopoulou 2019](file:///Users/Laura/Downloads/417549530246179823)). 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.

### Measures of treatment effect

Details will be provided in each sub-protocol.

### Unit of analysis issues

Details will be provided in each sub-protocol.

### 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 assumptions.

### Assessment of heterogeneity and transitivity

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.). The data will be presented 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 et al., 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.

Visual inspection of forest plots, prediction intervals (**the interval within which the effect of a future study is expected to lie** (Riley et al., 2011)) and comparison of with appropriate empirical distributions (Rhodes et al., 2015; Turner et al., 2012) will be used 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. To avoid intransitive 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. 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 (Higgins et al., 2019).

We will use the comparison-adjusted funnel plot (Chaimani et al., 2013) (a modified funnel plot appropriate for NMA) and appropriate network meta-regression models

(Chaimani and Salanti, 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 et al., 2014).

### Data synthesis

The main analysis ﻿will include RCTs only. 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 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 (τ2): 1) a separate τ2 for every comparison between two interventions and 2) a common τ2 for studies comparing the same types of interventions.

For the sets of studies for which transitivity is likely plausible, we will perform random-effects NMAs to compare the different interventions or combination regimens and potentially obtain their ranking. We will assume a common heterogeneity parameter (τ2) 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 et al., 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 (R2jags).

The conceptual evaluation of transitivity will be supplemented 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 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 and incoherence

Pre-specified subgroup analyses will be detailed in each subprotocol.

### Sensitivity analysis

We will perform sensitivity analyses by 1) excluding studies at high risk of bias, 2) excluding preprints. 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 et al., 2018; Mavridis et al., 2015; White et al., 2008).

# Acknowledgements

This work received some funding from the Agence Nationale de la Recherche (ANR), the World Health Organization (WHO), the German Federal Ministry of Health, Cochrane France, the Center of Research in Epidemiology and StatisticS (CRESS), the Centre d’Epidémiologie Clinique (GHU Cochin, Hôtel Dieu), Assistance Publique Hôpitaux de Paris (APHP) and Université de Paris and the CNRS (Centre National de la Recherche Scientifique).

# References

Bucher, H.C., Guyatt, G.H., Griffith, L.E., Walter, S.D., 1997. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J.Clin.Epidemiol. 50, 683–691.

Chaimani, A., Higgins, J.P.T., Mavridis, D., Spyridonos, P., Salanti, G., 2013. Graphical tools for network meta-analysis in STATA. PLoS.One. 8, e76654.

Chaimani, A., Mavridis, D., Higgins, J.P.T., Salanti, G., White, I.R., 2018. Allowing for informative missingness in aggregate data meta-analysis with continuous or binary outcomes: Extensions to metamiss. Stata J. 18, 716–740.

Chaimani, A., Salanti, G., 2015. Visualizing assumptions and results in network meta-analysis: The network graphs package. Stata J. 15, 905–950.

Chaimani, A., Salanti, G., 2012. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. Res.Synth.Meth. 3, 161–176.

CINeMA: Confidence in Network Meta-Analysis [Software]. Institute of Social and Preventive Medicine, University of Bern, 2017.

Clinical management of severe acute respiratory infection when COVID-19 is suspected [WWW Document], 2020. URL https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected (accessed 4.6.20).

Coronavirus disease 2019 (COVID-19)Situation Report –56, 2020.

Coronavirus Symptoms (COVID-19) - Worldometer [WWW Document], n.d. URL https://www.worldometers.info/coronavirus/coronavirus-symptoms/ (accessed 4.6.20).

Dias, S., Welton, N.J., Caldwell, D.M., Ades, A.E., 2010. Checking consistency in mixed treatment comparison meta-analysis. Stat.Med. 29, 932–944. https://doi.org/10.1002/sim.3767

Hernán, M.A., Robins, J.M., n.d. Causal inference: What if.

Higgins, J.P.T., Chandler, J., Cumpston, M., Li, T., Page, M.J., Welch, V.A., (editors), 2019. Cochrane Handbook for Systematic Reviews of Interventions, 2nd ed. John Wiley & Sons, Ltd, Chichester (UK).

Higgins, J.P.T., Jackson, D., Barrett, J.K., Lu, G., Ades, A.E., White, I.R., 2012. Consistency and insconsistency in network meta-analysis: concepts and models for multi-arm studies. Res.Synth.Meth. 3, 98–110.

Mavridis, D., Welton, N.J., Sutton, A., Salanti, G., 2014. A selection model for accounting for publication bias in a full network meta-analysis. Stat. Med. 33, 5399–5412. https://doi.org/10.1002/sim.6321

Mavridis, D., White, I.R., Higgins, J.P.T., Cipriani, A., Salanti, G., 2015. Allowing for uncertainty due to missing continuous outcome data in pairwise and network meta-analysis. Stat. Med. 34, 721–741. https://doi.org/10.1002/sim.6365

Nikolakopoulou, A., Higgins, J.P., Papakonstantinou, T., Chaimani, A., Giovane, C.D., Egger, M., Salanti, G., 2019. Assessing Confidence in the Results of Network Meta-Analysis (Cinema). bioRxiv 597047. https://doi.org/10.1101/597047

Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. Zhonghua Liu Xing Bing Xue Za Zhi Zhonghua Liuxingbingxue Zazhi 41, 145–151. https://doi.org/10.3760/cma.j.issn.0254-6450.2020.02.003

Papakonstantinou, T., Nikolakopoulou, A., Rucker, G., Chaimani, A., Schwarzer, G., Egger, M., Salanti, G., 2018. Estimating the contribution of studies in network meta-analysis: paths, flows and streams. F1000Research.

Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), 2020.

Rhodes, K.M., Turner, R.M., Higgins, J.P.T., 2015. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. J. Clin. Epidemiol. 68, 52–60. https://doi.org/10.1016/j.jclinepi.2014.08.012

Riley, R.D., Higgins, J.P.T., Deeks, J.J., 2011. Interpretation of random effects meta-analyses. BMJ 342, d549.

RKI - Coronavirus SARS-CoV-2 - SARS-CoV-2 Steckbrief zur Coronavirus-Krankheit-2019 (COVID-19) [WWW Document], n.d. URL https://www.rki.de/DE/Content/InfAZ/N/Neuartiges\_Coronavirus/Steckbrief.html#doc13776792bodyText3 (accessed 4.6.20).

Rucker, G., Schwarzer, G., 2013. netmeta: An R package for network meta-analysis. R Proj. Website.

Salanti, G., 2012. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Res.Synth.Meth. 3, 80–97.

Salanti, G., Ades, A.E., Ioannidis, J.P., 2011. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J.Clin.Epidemiol. 64, 163–171. https://doi.org/10.1016/j.jclinepi.2010.03.016

Schünemann, H.J., Higgins, J.P., Vist, G.E., Glasziou, P., Akl, E.A., Skoetz, N., Guyatt, G.H., 2019. 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, pp. 375–402.

Sterne, J.A., Hernán, M.A., Reeves, B.C., Savović, J., Berkman, N.D., Viswanathan, M., Henry, D., Altman, D.G., Ansari, M.T., Boutron, I., Carpenter, J.R., Chan, A.-W., Churchill, R., Deeks, J.J., Hróbjartsson, A., Kirkham, J., Jüni, P., Loke, Y.K., Pigott, T.D., Ramsay, C.R., Regidor, D., Rothstein, H.R., Sandhu, L., Santaguida, P.L., Schünemann, H.J., Shea, B., Shrier, I., Tugwell, P., Turner, L., Valentine, J.C., Waddington, H., Waters, E., Wells, G.A., Whiting, P.F., Higgins, J.P., 2016. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355, i4919. https://doi.org/10.1136/bmj.i4919

Sterne, J.A.C., Savović, J., Page, M.J., Elbers, R.G., Blencowe, N.S., Boutron, I., Cates, C.J., Cheng, H.-Y., Corbett, M.S., Eldridge, S.M., Emberson, J.R., Hernán, M.A., Hopewell, S., Hróbjartsson, A., Junqueira, D.R., Jüni, P., Kirkham, J.J., Lasserson, T., Li, T., McAleenan, A., Reeves, B.C., Shepperd, S., Shrier, I., Stewart, L.A., Tilling, K., White, I.R., Whiting, P.F., Higgins, J.P.T., 2019. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366, l4898. https://doi.org/10.1136/bmj.l4898

Su, Y.-S., Yajima, M., 2009. R2jags: A Package for Running jags from R.

Tallarita, M., Iorio, M.D., Baio, G., 2019. A comparative review of network meta-analysis models in longitudinal randomized controlled trial. Stat. Med. 38, 3053–3072. https://doi.org/10.1002/sim.8169

Tierney, J.F., Stewart, L.A., Ghersi, D., Burdett, S., Sydes, M.R., 2007. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 8, 16. https://doi.org/10.1186/1745-6215-8-16

Turner, R.M., Davey, J., Clarke, M.J., Thompson, S.G., Higgins, J.P., 2012. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. Int. J. Epidemiol. 41, 818–827. https://doi.org/10.1093/ije/dys041

White, I.R., 2015. Network meta-analysis. Stata J. 15, 951–985.

White, I.R., Higgins, J.P.T., Wood, A.M., 2008. Allowing for uncertainty due to missing data in meta-analysis--part 1: two-stage methods. Stat. Med. 27, 711–727. https://doi.org/10.1002/sim.3008

WHO Working Group on the Clinical Characterization of COVID-19 infection, n.d. A Candidate Core Outcome Measure Set for Clinical Research During the SARS-CoV-2/COVID-19 Pandemic. submitted.

# Appendices

**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. Search strategy**

**Current search strategy:**

On September 4, 2020, we decided to search only the following secondary sources and stop searching PubMed, CNKI, ﻿﻿MedRχiv and Chinaxiv.

* **The L.OVE platform** (<https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d>). Details of this platform is available in Appendix 3.
* **The Cochrane COVID-19 Study register**(<https://covid-19.cochrane.org/>)

This was decided after we demonstrated that the L.OVE platform allowed identifying 100% of the RCTs identified through our initial search.

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 (<https://retractionwatch.com/retracted-coronavirus-covid-19-papers/>).

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 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.

**Initial search strategy**

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

The following primary sources were searched daily

* **PubMed** ([https://pubmed.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/))
* **CNKI (**China National Knowledge Infrastructure, [https://www.cnki.net/)](https://clicktime.symantec.com/3PygCBMYSDCur5T41Qb26mb6H2?u=https%3A%2F%2Fwww.cnki.net%2F%29) **database** and ([http://journal.yiigle.com/](https://clicktime.symantec.com/3EGC7swzbbszNGuZR5zrfad6H2?u=http%3A%2F%2Fjournal.yiigle.com%2F) )
* **MedRχiv** ([https://www.medrxiv.org](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 will only screen the sources published on MedRχiv (i.e., titles in blue rather than red).
* **Chinaxiv** (<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.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d>). Details of this platform is available in Appendix 3.
* **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](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** | |
| **Search** | **Query** |
| #10 | #8 Filters: **Publication date from 2020/01/01** |
| #9 | Search: **#4 AND #7** |
| #8 | Search: **#5 NOT #6** |
| #7 | Search: **animals[mh] NOT humans[mh]** |
| #6 | Search: **randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]** |
| #5 | Search: **#1 OR #2 OR #3 OR #4﻿** |
| #4 | Search: **severe acute respiratory syndrome coronavirus 2[Supplementary Concept]** |
| #3 | Search: **COVID-19[Supplementary Concept]** |
| #2 | Search: "﻿nCoV 19"[tiab] OR nCoV19[tiab] OR SARSCoV2[tiab] OR "SARSCoV-2"[tiab] OR "SARS-CoV2"[tiab] OR "new CoV"[tiab] OR "novel CoV"[tiab] OR "SARS coronavirus2"[tiab] OR "SARS coronavirus 2"[tiab] OR "coronavirus 19"[tiab] OR coronavirus19[tiab] |
| #1 | Search: **"2019 nCoV"[tiab] OR 2019nCoV[tiab] OR "2019 novel coronavirus"[tiab] OR "COVID 19"[tiab] OR COVID19[tiab] OR "new coronavirus"[tiab] OR "novel coronavirus"[tiab] OR "SARS CoV-2"[tiab] OR (Wuhan[tiab] AND coronavirus[tiab])** |

**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”

#13 “COVID-19”

#14 “coronavirus”

#15 OR/#1-#14

**Appendix 3. Methods & report 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:

**Search methods**

**Search strategy**

All of the evidence organized in the L·OVE platform is retrieved in real-time from Epistemonikos Database (See Epistemonikos Database methods [here](https://www.epistemonikos.org/en/about_us/methods)).

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](https://github.com/dperezrada/keywords2vec) to the corpus of documents available in [Epistemonikos Database](https://www.epistemonikos.org/" \t "_blank).
* 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 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"

**Search sources**

To complement the searches in the 10 sources routinely performed in Epistemonikos Database (See Epistemonikos Database methods [here](https://www.epistemonikos.org/en/about_us/methods)), we conduct searches in the following sources:

* PubMed (updated several times a day)
* EMBASE (updated weekly)
* ICTRP 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)
* Cochrane Resources on Coronavirus (COVID-19) (targeted searches)
* Oxford COVID-19 Evidence Service (targeted searches)
* NICE Rapid Guideline and Summaries on COVID-19 (targeted searches)
* Coronavirus disease (COVID-19) - European Medicines Agency (EMA) (targeted searches)
* Coronavirus Disease 2019 (COVID-19) - U.S. Food & Drug Administration (FDA) (targeted searches)
* SSRN’s Coronavirus and Infectious Disease Research page (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 classify the articles in the following categories:

1. Systematic reviews  
   According to [Epistemonikos Database criteria](https://www.epistemonikos.org/en/about_us/methods" \t "_blank) for systematic review.
2. Primary studies  
   Primary study is an umbrella term that encompasses any study design, qualitative or quantitative, where data is 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 displays all articles not yet classified or not fulfilling the definitions for the categories above.