Prevention and treatment of COVID-19: a protocol for multiple systematic reviews

Reviews objective

To assess the available interventions for prevention and treatment of COVID-19.

Search strategies

We will conduct highly sensitive searches in PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE, without language or publication status restriction. The searches will cover from inception of each database and will be updated on a daily basis.

The following strategy will be used to search MEDLINE (PubMed):

#1	coronavir*
#2	coronovirus*
#3	"corona virus"
#4	"virus corona"
#5	"corono virus"
#6	"virus corono"
#7	hcov*
#8	"covid-19"
#9	covid19*
#10	"covid 19"
#11	2019-nCoV
#12	cv19*
#13	"cv-19"
#14	"cv 19"
#15	"n-cov"
#16	ncov*
#17	"sars-cov-2"
#18	(wuhan*[tiab] AND (virus OR viruses OR viral OR coronav*))
#19	(covid* AND (virus OR viruses OR viral))
#20	"sars-cov"
#21	"sars cov"
#22	"sars-coronavirus"
#23	"severe acute respiratory syndrome"
#24	"mers-cov"
#25	"mers cov"
#26	"middle east respiratory syndrome"
#27	"middle-east respiratory syndrome"

The MEDLINE strategy will be adapted to the syntax and subject headings of the other databases.

Types of study to be included

We will include prospective or retrospective nonrandomized comparative studies and randomised controlled trials.

Condition or domain being studied

COVID-19, an infection caused by the SARS-CoV-2 coronavirus.

Participants/population

Each review will include studies evaluating interventions for prevention or treatment in people at risk or infected with COVID-19, as defined by the authors of the studies. If we find substantial clinical heterogeneity on how the condition was defined we will explore this using sensitivity analysis. Studies evaluating the effects on animal models or in vitro conditions will be excluded.

Intervention(s), exposure(s)

Each review will include studies evaluating interventions for prevention or treatment in people at risk or infected with COVID-19, including but not limited to: pharmacological interventions (e.g. NSAIDs, antimalarials, anti-IL-6, vaccination, macrolides, antivirals, opioids, etc.), complementary and alternative medicine (herbs and other natural ingredients, acupuncture point therapies, traditional Chinese medicine, etc.), personal protective measures (hand hygiene, facemasks, respiratory etiquette, etc.), public health, health system and nutraceuticals.

Comparator(s)/control

Our primary interest will be in studies evaluating the effect of interventions for prevention or treatment in people at risk or infected with COVID-19, receiving optimal treatment for their condition versus placebo, and in studies comparing against another active intervention considered as standard treatment. Standard treatment will be explicitly defined in each review.

However, we will include any comparison, so the following categories will be used as guide for the analyses and discussion.

Primary comparisons

- Intervention plus standard treatment versus standard treatment .
- Intervention versus standard treatment

Secondary comparisons

- Intervention versus placebo
- Intervention versus non-standard treatment
- Comparison between different interventions, routes of administration or doses.

Context
Main outcome(s):

We will give priority according to Core Outcome Set for Clinical Trials on Coronavirus Disease 2019:

- Mild: Time to 2019-nCoV RT-PCR negativity
- Ordinary: Length of hospital stay, Composite events (total number of patients diagnosed as the types of severec, critical, and all-cause death), Score of clinical symptoms, Time to 2019-nCoV RT-PCR negativity.
- Severe: Composite events (total number of patients diagnosed as type critical and all-cause death), Length of hospital stay, PaO2/FiO2 Duration (d) of mechanical ventilation, Time to 2019-nCoV RT-PCR negativity
  Critical: All-cause mortality
- Rehabilitation: Pulmonary function

If not, we will select outcomes which are critical for decision-making (including patient-reported outcomes for those conditions in which they are relevant) according to the opinion of the authors of the individual review. Clinical guidelines and reports on the topic will also be considered. Surrogate outcomes will not be routinely included. We will prioritise up to seven critical outcomes for the development of 'Summary of Findings' tables. We will consider grouping outcomes according to the timepoint in which they were measured in categories (e.g. short term, medium term, long term).

*** Measures of effect**

For dichotomous outcomes, we will express the estimate of treatment effect of an intervention as risk ratios (RR) together with 95% CIs. For continuous outcomes, we will use mean difference and SD to summarise the data and 95% CIs. Where continuous outcomes are measured using different scales, the treatment effect will be expressed as a standardised mean difference (SMD) with 95% CI. When possible, we will multiply the SMD by a standard deviation that is representative from the pooled studies, for example, the SD from a well-known scale used by several of the studies included in the analysis on which the result is based. In cases where the minimally important difference (MID) is known, we will also present continuous outcomes as MID units or inform the results as the difference in the proportion of patients achieving a minimal important effect between intervention and control (Guyatt GH, Thorlund K, Oxman AD, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. J Clin Epidemiol 2013;66(2):173-83. doi: 10.1016/j.jclinepi.2012.08.001).

Then, these results will be displayed on the 'Summary of Findings Table' as mean difference.

Additional outcome(s)
Not applicable.

*** Measures of effect**
Not applicable.

Data extraction (selection and coding)

The results of the literature search will be uploaded to the software CollaboratronTM (Epistemonikos Foundation. Collaboratron [Software]: https://collaboratron.epistelab.com). References will be de-duplicated by an algorithm comparing unique identifiers (database ID, DOI, trial registry ID), and citation details (i.e. author names, journal, year of publication, volume, number, pages, article title and article abstract).

Two researchers will independently screen the titles and abstracts yielded by the search against the inclusion criteria. We will obtain full reports for all titles that appear to meet the inclusion criteria or where there is any uncertainty. We will resolve disagreements through discussion, or through a third reviewer if the discrepancy cannot be solved.

In order to avoid missing trials in the individual reviews, one senior researcher will perform an additional check to all the included trials selected in the first search. We will record the reasons for excluding trials in any stage of the search.

We will outline the study selection process in a PRISMA flow diagram adapted for the purpose of this project .

Using standardised forms, two reviewers will extract data independently from each included trial. To ensure consistency, we will conduct calibration exercises before starting the review. We will collect information on study design and setting, participant characteristics (including disease severity and age), study eligibility criteria, details of the administered intervention(s), the outcomes assessed, the source of study funding and any conflicts of interest disclosed by the investigators.

We will resolve disagreements by discussion, and one arbiter will adjudicate unresolved disagreements.

Risk of bias (quality) assessment

Two reviewers will independently assess risk of bias using the Cochrane Collaboration tool for assessing risk of bias which considers random sequence generation, allocation concealment, blinding of participants, personnel and outcomes, incomplete outcome data, selective outcome reporting and other sources of bias (Higgins JP, Altman DG. Assessing Risk of Bias in Included Studies. Cochrane Handbook for Systematic Reviews of Interventions 2008;187–241. doi:10.1002/9780470712184.ch8). A judgment will be made from the extracted information, rated as 'high risk' or 'low risk'. In case reported details in a study are insufficient, we will judge the risk of bias as 'unclear' and the original study investigators will be contacted for more information. Disagreements will be resolved first by discussion and then by consulting a third author for arbitration.

We will compute graphic representations of potential bias within and across studies using RevMan 5.3.5 (Review Manager 5.3.5) (Review Manager (RevMan) [Computer program]. Version 5.3.5 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) but other software might be used if preferable by the authors of the individual reviews.

Strategy for data synthesis

We will only conduct a meta-analysis if the included studies are sufficiently homogeneous in terms of design, population, interventions and comparators reporting the same outcome measures.

The results for clinically homogeneous studies will be meta-analysed using RevMan (Review Manager (RevMan) [Computer program]. Version [5.3.5]. Copenhagen: The Nordic Cochrane

Centre, The Cochrane Collaboration, 2014). Meta-analyses will be conducted using the inverse variance method. A random effect model will be used. Separate meta-analyses will be presented for specific populations or interventions if statistically significant heterogeneity is explained by some of these, or if a convincing subgroup effect is found.

For any outcomes where insufficient data are found for a meta-analysis, a narrative synthesis will be presented.

Analysis of subgroups or subsets

The individual reviews will assess specific subgroup analyses relevant for the condition of interest.

Contact details for further information

Gabriel Rada
radagabriel@epistemonikos.org

Organisational affiliation of the review

Epistemonikos Foundation
https://www.epistemonikos.cl/