Comparative effectiveness of pharmacological interventions for Covid-19: a living systematic review and network meta-analysis

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Review question

Our aim is to suggest clinical recommendations by assessing the comparative acceptability, efficacy, safety, and tolerability of pharmacological interventions for the treatment of Covid-19.

Searches

We will search the following electronic databases:

• Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library.

• MEDLINE, accessed via OVID.

• Embase, accessed via OVID.

The searches will cover from the inception of each database and will be updated on a daily basis using auto?alerts when possible. We will develop search strategies including a combination of controlled vocabulary and free text terms. We will revise the strategy appropriately for each database to take account of differences in controlled vocabulary and syntax rules. We will apply no restriction on language of publication.

We will also search medRxiv Health Sciences and bioRxiv Biology, which provide open access to preprints of preliminary reports of work that have not been peer-reviewed.

In addition to the source and strategies described above, we will screen registers of ongoing studies such as ClinicalTrials.gov and ISRCTN. A similar process will be undertaken twice monthly for the European Clinical Trials Registry.

In the context of living systematic review, we will follow key conferences are to be held and will search conference proceedings when published.

Types of study to be included

We will include randomised controlled trials.

Condition or domain being studied

SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. It started spreading in December 2019, and was declared a pandemic by the World Health Organisation on 11th March 2020. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multiorgan failure, and death. There are no registered treatments for coronavirus infections, but some studies, including randomised trials and cohort studies, have already been completed and many more are rapidly developing in an unprecedented effort made by the scientific community.

Participants/population

We will include people affected by COVID-19, as defined by the authors of the studies. There will be no limits

in terms of gender or ethnicity.

Intervention(s), exposure(s)
We will include studies evaluating interventions for the treatment of people affected by COVID-19, including pharmacological interventions (e.g. antibiotics, antibodies, antimalarial, antiviral, antiretroviral, immunosuppressors/modulators, kinase inhibitors) and their combinations.

Comparator(s)/control
Any active treatment, placebo, or standard of care.

Main outcome(s)
All-cause mortality.

* Measures of effect

Risk ratio with 95% CIs. We will consider grouping outcomes according to the timepoint in which they were measured in categories (e.g. short term, medium term, long term).

Additional outcome(s)
We will give priority according to Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (Jin et al., 2020):

Length of hospital stay, 2019-nCoV RT-PCR negativity, PaO2/FiO2, Duration of mechanical ventilation, radiological imaging, Adverse events, Severe adverse events

* Measures of effect

Risk ratio with 95% CIs for dichotomous outcomes and Standardised Mean Difference with 95% CI for continuous outcomes. We will consider grouping outcomes according to the timepoint in which they were measured in categories (e.g. short term, medium term, long term).

Data extraction (selection and coding)
At least two review authors will independently screen titles and abstracts retrieved by the search strategy. Full-texts of potentially relevant studies will then be assessed independently by at least two authors and disagreements will be resolved through discussion with a third member of the review team.

We will use a data collection form to extract study characteristics and outcome data, which has been piloted on at least one study in the review. Two review authors will independently extract study characteristics and outcome data from included studies, as follows:

Methods: first author or acronym, year of publication, study design.

Participants: diagnosis, sample size, mean age, gender distribution, severity of illness, setting.

Interventions: number of patients allocated to each arm, drug name, dose, duration of the interventions and follow-up.

Outcomes: primary and secondary outcomes evaluated.

Adverse events (AEs): AEs occurring during the course of the study.

Notes: country, funding source; investigational drug versus comparator.

Risk of bias (quality) assessment
At least two review authors will independently assess the risk of bias of each study, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019). The following domains will be assessed: random sequence generation, allocation concealment, blinding of personnel and participants, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. We will judge each potential source of bias as high, low or unclear. We will report the 'Risk of bias' judgements across different studies for each of the domains listed. Where information on risk of bias relates

to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table. A judgment of high risk of bias in one or more domain will be considered as a 'high risk' study, a judgment of low risk of bias in most of the domains will be considered as a 'low risk' study, and a judgment of unclear risk of bias in most of the domains as an 'unclear risk' study. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Strategy for data synthesis

Dichotomous outcomes will be analysed by calculating the relative risk (RR) for each trial with the uncertainty in each result being expressed by its 95% confidence interval (CI).

Continuous outcomes will be analysed by calculating the mean difference (MD) with the relative 95% CI when the study used the same instruments for assessing the outcome. We will use the standardised mean difference (SMD) when studies used different instruments.

We will perform pairwise meta-analyses for primary and secondary outcomes using a random-effects model in RevMan for every treatment comparison (DerSimonian 1986).

We will perform network meta-analysis (NMA) for the primary outcome. NMA is a method of synthesising information from a network of trials addressing the same question but involving different interventions (Cipriani 2013). NMA combines direct evidence and indirect evidence across a network of randomised trials into a single effect size, and it can increase the precision in the estimates while randomisation is respected. We will perform NMA using a random-effects model within a frequentist setting assuming equal heterogeneity across all comparisons, and we will account for correlations induced by multi-arm studies. The models will enable us to estimate the probability of each intervention being the best, given the relative effect sizes as estimated in NMA. We will perform NMA in Stata 16 using the 'mvmeta' command and Stata routines available at http://www.mtm.uoi.gr (Chaimani 2014; White 2011; White 2012).

Results of meta-analysis and NMA will be applied when reasonable and presented as summary relative effect sizes OR or SMD) for each possible pair of treatments.

We will use the GRADE approach to rating the certainty of the evidence.

The systematic review will be updated every month. As soon as new studies are included, their basic study characteristics are extracted and provided online. We will keep the living systematic review up to date for 2020.

Analysis of subgroups or subsets

No subgroup analysis planned at present.

Contact details for further information

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Organisational affiliation of the review

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Type and method of review
Intervention, Meta-analysis, Network meta-analysis, Prospective meta-analysis (PMA), Systematic review

Anticipated or actual start date
27 March 2020

Anticipated completion date
31 January 2021

Funding sources/sponsors
None

Conflicts of interest

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English, Italian

Country
England, Italy

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
COVID-19; Humans; Network Meta-Analysis; severe acute respiratory syndrome coronavirus 2

Date of registration in PROSPERO
22 April 2020

Date of first submission
20 April 2020

Stage of review at time of this submission
The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add

publication details in due course.

Versions

22 April 2020

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