metaEvidence.org-COVID - Methods used to populate and perform dynamic meta-analysis using the metaEvidence plateform.

metaEvidence.org Team

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1 Background

In domains of intensive therapeutic research, such as in COVID-19, the exploitation of the produced evidence for the development of therapeutic strategies is being confronted to several types of problems.

These problems cover the profusion of results, the existence of contradictory results due, among others, to the lack of statistical power of certain studies, the heterogeneity across study quality and the possibility of selective publication of results (and publication bias).

A common solution to these problems is a systematic review and meta-analysis. However, in contexts of intensive research, the classical meta-analytic approach poses itself new problems. The time needed to complete them plus the time required for the publication (reviewing) leads to the fact that many published meta-analyses are already outdated on the day of their publication. Quite frequently, several meta-analyses on the same subject are published, leading to a new profusion of potentially contradictory results.

Some of these problems can be solved by shifting from the traditional approach based on scientific publications to a dynamic approach in which meta-analysis are continuously updated as new results become available, and with a direct online access to theirs results. With this virtualization, meta-analyses take the form of knowledge bases, accessible online, continuously updated according to a pre-established methodology in full compliance with the principles of meta-analysis. This paradigm shift leads to the replacement of the traditional scientific publication as the medium for disseminating evidence by a completely new ecosystem(1–3).

www.metaEvidence.org – COVID19 is an emerging online resource that provides direct access to all the results about efficacy and safety of potential drugs for COVID-19, annotated by their risk of bias and synthesized by meta-analysis.

The underlying knowledge base is populated by scientific biocurators who supervise automatic tools based on artificial intelligence algorithms. These proprietary robots search trials on bibliographic databases; perform scientific watching in search of new results by monitoring RSS feeds of journals and tweeter for example, and give assistance for data extraction.

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The online interface, www.metaEvidence.org, allows the user to navigate interactively through the large number of results produced by the studies and to obtain a synthetic view.

This project implements the concept of scientific biocuration, developed more than 10 years ago in the field of genetic among others, to the field of treatment evaluation and health technology assessment.

Biocuration is carried out continuously. New results are integrated as they become available, within a target time of less than 24 hours. Thus, unlike the classic meta-analysis publications, this system provides access to a evidence synthesis constantly updated in real time.

MetaEvidence is the result of the research work of the meta-research and biocuration team of the Pharmacology and Toxicology Department of the university hospital of Lyon and the University of Lyon (UMR CNRS 5558 LBBE). This project implements the concepts of intensive biocuration and meta-analysis automation.

This project does not directly produce practice guidelines. It is intended for health professionals and decision makers who develop these recommendations. metaEvidence.org provides to concerned people the up-to-date evidence synthesis needed to develop treatment strategies and practice guidelines.

This document describes the adaptation of this general concept to the field of COVID-19 and describes the generic method used to build the COVID-19 knowledge base and produce meta-analysis results.

2 Objective

To synthesize by a dynamic systematic review and meta-analysis the best available evidence resulting from randomized controlled trials (RCTs) about the efficacy and safety of all potential treatment of COVID-19.

We preferentially included high quality randomized trials (RCT). Where no such studies existed, we included the best evidence available from observational studies (OBS).

3 Method

The procedures for these reviews and meta-analysis followed established best methods and Cochrane standards(4) used in the evolving science of systematic review research in general. They were reported on the online interface www.metaEvidence.org accordingly to the suggested PRISMA or STROBE guidelines standards(5,6) when appropriate.

All specific dynamic systematic reviews and meta-analysis available on the metaEvidence web site were performed accordingly to this global platform protocol, tailored to each specificity of these reviews (bibliographic search in particular).

4 Study search strategy

The search strategy aimed to identify all clinical studies relating to the evaluation of a specific potential treatment for COVID-19, as soon there are released. Several methods were used to ensure that all relevant literature, both published and unpublished, was identified.

In a dynamic meta-analysis, the research approach of the studies is somewhat different from that used in a classical meta-analysis. Emphasis is placed on the real-time detection of new results, which in the context of COVID-19, may come from publication channels different from traditional biomedical journals (preprints, press releases, etc.).

4.1 Bibliographic sources

The following electronic bibliographic databases were continuously searched for relevant published literature using appropriate, comprehensive search strategies:

- Pubmed
- LitCovid hub
- Scopus
- Web of Science

Each database was incrementally searched as far back as possible (last 24 hours), using automatic software robots. Detected hits are pushed to biocurators that manually selected relevant evidence.

Search strategies of relevant clinical keywords (MESH, EMTREE and text) were developed through reference to published strategies, and by iterative searching, whereby keywords identified in references retrieved by initial scoping searches were used to extend the search strategy and so increase the sensitivity of retrieval.

The reference list of manuscripts included in the analysis were searched for additional relevant publications, as well those of published meta-analysis or systematic reviews.

Pre-publication manuscripts (aka preprints) were searching in preprint servers (SSRN, F1000, PeerJ, Biorxiv, Medrxiv, and Chinxiv).

We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch) to detect ongoing or unpublished trials.

4.2 Continuous search

In the context of a dynamic meta-analysis that needs to be updated immediately after the availability of new results, the search methods of classical meta-analysis are not enough.

To instantly detect new results, automatic RSS and Tweeter feed screening tools have been implemented. Each item published through these channels is subject to text analysis to detect those announcing new clinical trial results. These tools use a self-learning algorithm based on a Naive Bayes classifier.

The searched RSS feeds encompass biomedical journals, preprints archives, stored Pubmed Query run daily, registries of clinical trials (like clinicalTrials.gov, WHO registry, etc.) and web sites dedicated into medical or pharma news.

The Twitter accounts to follow were determined by an algorithm using the presence in their history of known posts about clinical trial in COVID19.

This list will be updated in future by searching Tweeter account posting about the new trials when there is available.

4.3 Search restrictions

No language or date restrictions were applied to the main searches.

For articles in foreign languages, the selection phase on title and abstract was based on the English abstract almost always available. In the other cases, machine translation tools (Google, DeepL) were used to detect potentially eligible studies. For this studies, the help of a native speaker was sought among the students of the university or hospital. As a last resort, a translation is requested from a professional translator.

4.4 Conference proceedings}

Classically, research carried out for a meta-analysis must use abstracts from conference proceedings. In the present context, this type of research has no relevance and will not be carried out for at least 6 months.

After this delay, specific searches were undertaken to identify relevant conference abstracts and posters presented in the past three years at key scientific conferences in the field of infectious diseases conferences:

- Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)
- European Society of Clinical Microbiology and Infectious Diseases (ESCMID)
- Asia Pacific Society of Infection Control (APSIC)

5 Selection of studies

Abstracts of studies identified in the above search were examined by a biocurator and an automatic classification algorithm. Each abstract is analyzed by this automatic classification algorithm that determines an index of relevance of the abstract for meta-analysis. This automatic classification algorithm is based on naïve Bayes classifier.

We obtained the full text reports of studies that are potentially relevant. Studies under consideration were assessed for whether they fulfil the inclusion criteria and methodological quality without regard to their results.

Where two biocurators disagree on the inclusion of a study, a third biocurator was invited to determine the inclusion of the study.

The process of study selection was documented and reported using a PRISMA flow diagram (not yet implemented).

5.1 Inclusion and exclusion criteria

To be included in this review, trials or observational studies had to meet the following pre-defined eligibility criteria

Studies were eligible if:

- they were randomized clinical trials (including cluster randomized trial) or observational studies if less than 2 randomized clinical trial are available or if they provide valuable information (other drugs, populations)
- they investigate a therapy of any kind (drug or other) in the treatment of COVID-19, whatever the condition (hospitalized patients with mild, severe or critical condition, outpatients, prophylaxis, etc.),
- they had a comparator group,
- they reported an effect measure, adjusted or not, such as odds ratio (OR), risk ratio (RR) hazard ratio (HR) or there was enough information to calculate an unadjusted OR,
- co-interventions were intended to be administered equally in both trial arms by protocol.

Studies were excluded if:

- they were cross over studies (because validity assumption of the crossover studies is not met in COVID given the rapid evolution of the disease)
- they were considered methodologically unsound
- they had no or inappropriate comparator group
- they were very badly reported (key information for the risk of bias assessment or data extraction are missing)
- they were impossible to confirm the origin of the article in the case of prepublications outside a preprints site
- they were suspicious in relation to the origin of data.

All inclusion criteria and no exclusion criterion should be met for studies to get into the final meta-analysis.

The list of excluded studies with reason of their exclusion is given in a specific section.

Additionally, mainly for observational studies, if the data source of two or more studies overlapped (period, population, or exclusion criteria), the most recent study was included.

6 Data extraction

Data extraction was carried out using the metaEvidence plateform and assistance tools.

Data collected included the following:

- General information: author, title, source, publication date, country, language, duplicate publications.
- Study characteristics: trial design, aims, setting and dates, source of participants, inclusion/exclusion criteria, comparability of groups, subgroup analysis, treatment crossovers, compliance with assigned treatment, length of follow-up.
- Participant characteristics: age, gender, participants lost to follow up, type of treatment
- Interventions: type, dose, and cycles of treatment; duration of follow-up.
- Outcomes: death, clinical improvement, clinical worsening, PCR-negative conversion, serious adverse events, withdrawals due to adverse events.

For the results, the following data were extracted.

For time-to-event data, we extracted the hazard ratio and its confidence interval in order to compute the standard error; if these are not reported, we will attempt to estimate the log (HR) and its standard error using the methods described by Parmar (7).

For dichotomous outcomes, we extracted the relative treatment effect directly with the measure used in the paper (risk ratio, odds ratio) and its confidence interval. If these are not reported we extracted the number of patients with the outcome of interest and the number of people assessed at the endpoint in each treatment arm, in order to estimate the odds ratio (OR).

For continuous outcomes, we extracted the final value and standard deviation of the outcome of interest and the number of patients assessed at the endpoint in

7 Endpoints

We based our thinking about relevant endpoint on the core outcomes as pre-defined by the Core Outcome Measures in Effectiveness Trials Initiative for Covid-19 patients (COMET 2020, http://www.comet-initiative.org/Studies/Details/1538).

Endpoints were classified as critical (very important), important or minor according the GRADE approach (8–10).

Only clinically relevant endpoints were taken into consideration. Among biological endpoints only the viral load and the negative PCR conversion were recorded.

8 Risk of bias assessment

Risk of bias assessment was conducted by using the ROB 2.0 (11,12) for RCTs and ROBINS-I (13) for observational studies.

Data on risk of bias were presented for all included studies, and results were interpreted in light of risk of bias; studies were not being excluded on the grounds of risk of bias.

Studies with low risk with some concerns were categorized as being above the quality threshold, while studies with high (or critical for observational studies) of bias were considered below quality threshold and sensitivity analysis were conducted to compare results from studies above and below this quality threshold.

However, the Web site offers a choice of 3 scenarios of analysis to the users: “all evidence”, “best evidence” and “top evidence”. In the “all evidence analysis”, all the studies are pooled together irrespective to their risk of bias (the pooled estimates will have a ROB corresponding to the worst ROB of the pooled studies). The “top evidence analysis” retains only studies above quality threshold (low or some concerns for RCTs). In the “best evidence analysis”, only the studies with the lowest risk of bias are pooled (even there are below the quality threshold, except for studies at critical risk of bias).

Study risk of bias	**All evidence analysis**	**Top evidence analysis**	**Best evidence analysis**
Low	X	X	X (if available)
Some concerns (moderate)	X		X (if there are not studies at low risk)
High (serious)	X		X (are not studies at low or moderate risk)
Critical	X		Never considered

8.1 Observational studies}

Risk of bias were assessed with the Cochrane Risk of Bias Tool for Randomized Trials or with the Risk of Bias Tool for Non-Randomized Studies of Interventions (ROBINS-I) (13).

ROBINS-I was used to assessing seven domains of bias:

- Bias due to confounding,
- Bias in selection of participants into the study,
- Bias in classification of exposures,
- Bias due to departures from intended exposures,
- Bias due to missing data,
- Bias in measurement of outcomes, and
- Bias in selection of reported results

(see https://sites.google.com/site/riskofbiastool/).

Each study was rated as critical, serious, moderate or low risk of bias based on a judgment of the gathered information. The overall assessment is based on the responses to individual domains. If there is insufficient detail reported in the study, the risk of bias will be classified as ‘no information’ and the original study authors will be contacted for more information. We expected an evolving quality over the time, the fist study being of less quality than the following, leading to exclude a large proportion of early studies.

Assessments were performed independently by two biocurators with discrepancies resolved through discussion with a third biocurator. A summary table presenting risk of bias assessments for each study is provided on the web site.

8.2 RCTs

Risk of bias for all randomized studies were assessed using the Cochrane Collaboration's tool for assessing risk of bias ROB2.0 (11).

This tool addresses the following domains:

- Bias arising from the randomization process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

We judged each of the five risk of bias domains using the categories "low risk", "high risk" or "some concerns" of bias.

Study overall risk of bias was determined as being the level of the worst domain (weak link principle).

Any disagreements about methodological quality were resolved by consultation among all biocurators.

9 Meta-analysis strategy

The meta-analysis was performed by using only the reported treatment effect size or from summary data. No attempt was done to obtain the individual patient data.

If the relative treatment effect was not reported in the study, we calculated the odds ratios (OR) and its 95% confidence intervals (95% CI) from the reported numbers of events and effectives of each group.

The inverse variance method with a random effect model was used to calculate a pooled OR for each outcome.

If an arm in a multi-arm trial were to be included in the same meta-analysis, the number of events and the number of participants in that arm is divided by the number of treatment comparisons made. This method avoids multiple use of participants in the pooled estimate of treatment effect while retaining information from each arm of the trial. It is compromising the precision of the pooled estimate slightly.

We will use trial definitions for all outcomes.

10 Assessment of heterogeneity

Heterogeneity was assessed by means of the I-squared statistic (14,15). When considerable heterogeneity is present (>50%), an attempt was made to explain the differences based on the clinical and methodological differences of the included studies. In the online interface, results with substantial heterogeneity are identified with a warning sign.

In an attempt to explain possible heterogeneity between studies, several sub-group or sensitivity analyses are provided to the users : by the type of design (RCT or observational), level of risk of bias, type of comparator groups, type of drugs (for meta-analysis performed on a class)

11 Dealing with missing data

No attempt was made to contact study authors to obtain any missing data.

Analyses were conducted on an intention-to-treat basis where possible; alternatively, data were analyzed as reported.

Loss to follow up were reported and assessed as a potential source of bias in the risk of bias assessment.

12 Publication bias

In the online interface, publication could be examined visually from funnel plots. Funnel plots are rendered only if there is enough studies (more than 5). The Egger's regression is reported to test the funnel plot asymmetry with along with the results of the trim and fill method to determine the number of missing studies and to adjust for publication bias if their were more than 5 studies (16–18).

13 Sensitivity analysis

Several sensitivity analyses are reported to determine the robustness of the results to methodological assumptions made in conducting the meta-analysis:

- restricting the analysis to RCTs
- restricting the analysis to the “top evidences”
- restricting the analysis to the “best evidences”
- restricting the analysis to published studies in a peer reviewed journal.

14 Software considerations

All analyses were conducted in our proprietary meta-analysis platform metaEvidence.org. Cross validation with R script using standard meta-analysis package (meta) were performed.

15 Evidence degree of certainty

We rated the certainty of the evidence from studies using the Grading of Recommendations Assessment, Development and Evaluation working group methodology (GRADE).

Degree of certainty considers the overall risk of bias, the heterogeneity of the meta-analysis, the directness of the evidence regarding the clinical question, the imprecision of the estimates, the reporting bias and the type 1 error risk control. This former criterion is not considered in the original GRADE approach and represent the point of adaptation.

Clinical relevance and importance for decision-making of endpoints were determined as follows, after consultation of the scientific committee:

Endpoint importance	Endpoints
Critical endpoint	• Death • Clinical worsening (including death)
Important	• Clinical improvement (given that deaths are not taken into consideration in this endpoint) • Serious adverse events
Not important	• Radiographic improvement or worsening • Viral load or PCR-negative conversion or other biological parameters (CRP level, etc.)

16 Funding

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17 Availability of data and materials

All the data used and analyzed are available on the metaEvidence.org site.

18 Project committees

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19 Bibliography