Interventions for preventing and treating COVID-19: protocol for a living mapping of research and a living systematic review

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ABSTRACT

Objective: To provide researchers and decision-makers with a detailed and up-to date summary of all ongoing studies evaluating the effectiveness of interventions for preventing and treating COVID-19 and to develop and maintain a living evidence synthesis of the effectiveness of these interventions.

Design: We will perform a living mapping of ongoing randomized trials, followed by living systematic reviews with pairwise meta-analyses and when possible, network meta-analyses focusing on two main questions: 1) the effectiveness of preventive interventions for COVID-19 and 2) the effectiveness of treatment interventions for COVID-19. We will evaluate the impact of these treatments considering the severity of the disease (i.e., mild, moderate, severe and critical diseases).

Living network meta-analysis is a novel approach in which multiple treatments (three or more) are compared by using both direct comparisons within randomised controlled trials and indirect comparisons across trials based on a common comparator. Hence, with living network meta-analyses, we will be able to contribute evidence to evaluate the effectiveness of interventions for specific outcomes related to COVID-19. We will also systematically contact authors of trials with results available to request individual- participant data.

Methods: We will systematically search clinical trial registries and electronic bibliographic databases to identify all ongoing and completed randomized controlled trials evaluating the effectiveness of interventions for preventing the spread of COVID-19 (e.g., vaccination, prophylactic interventions, personal protective equipment, models of practice and organization of care, etc.) or treating COVID-19 (e.g., specific therapeutic agents for COVID-19 such as anti-infectious agents, specific immunomodulators, non-specific immunomodulators, supportive management for patients admitted to the intensive care unit, general treatments for viral infection, models of practice and organization of care etc.). Screening, data extraction and risk of bias assessment will be performed in duplicate. The living systematic review will be updated at least once a week if new evidence is available.

Conclusion: Our work will provide an updated synthesis of available evidence. Our results will be essential for healthcare providers, researchers, the public and other decision-makers for preventing COVID-19, caring for patients with COVID-19, planning future trials and managing the pandemic on a public health level. Our analyses and the underlying database will be available publicly on a website that will be updated regularly.

1 BACKGROUND

In December 2019, a novel coronavirus outbreak was documented in Wuhan, Hubei Province, China. Over the first 6 weeks of the new decade, 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.

The estimated number of people who will be infected with SARS-CoV-2 by one contagious person — the baseline reproduction number, R0 — is estimated at 2.4 to 3.3[1]. In other words, with an R0 of about 3, about two-thirds of all transmissions must be prevented to bring the epidemic under control. At the time of writing, the cumulative incidence of COVID-19 cases is following an almost exponential trend in most European countries and the United States[2].

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)[3]. Although frail older patients are at higher risk, young and otherwise healthy patients can have severe forms as well[4].

Currently, there are no specific therapeutic agents for COVID-19 that have demonstrated a beneficial effect. Nevertheless, some treatments were tested during the outbreak in China, and the *Chinese clinical guidance for COVID-19 pneumonia diagnosis and treatment* (7th edition) recommends that alpha-interferon, lopinavir/ritonavir, ribavirin, chloroquine phosphate, and umifénovir[5] are potential treatment options. Recently, the World Health Organization suggested a handful of antiviral treatments for research prioritization[6]. For instance, remdesivir was considered the most promising candidate based on the in vitro and in vivo data available for coronaviruses. Likewise, lopinavir/ritonavir, alone or in combination with interferon beta1b, was considered a suitable alternative for rapid implementation in clinical trials. Recently, promising results were also highlighted for tocilizumab and

hydroxychloroquine. For patients with extensive lung lesions and severely ill patients with elevated interleukin 6 (IL-6) levels, the *Chinese clinical guidance for COVID-19 pneumonia diagnosis and treatment* (7th edition) recommends tocilizumab.

To address this pandemic, researchers are working to accelerate the development of diagnostic tests, preventive interventions and therapeutic interventions. Many randomized trials have been established to evaluate candidate therapeutic agents that may effectively reduce symptoms and avoid deaths. This emerging situation requires the optimal planning and conduct of trials as well as strategies for the appropriate translation of research into practice. Therefore, decision-makers and researchers urgently need a complete, high-quality and up-to-date synthesis of data from all ongoing research studies as soon as they are available. To this end, we will perform a living mapping of ongoing randomized trials followed by a living systematic review and network meta-analysis of randomized trials.

Our living mapping of ongoing research will allow us to monitor in real-time new evidence that becomes available for treating and preventing COVID-19. In this way, we will also be able to identify gaps and deficiencies within the existing evidence body early to help identify and prioritize future research efforts. Gathering any available piece of information as soon as it becomes available will enable the conduct of a living systematic review with pairwise comparisons and network meta-analyses (NMAs) as a next step.

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

We will consider the following specific research areas/topics/questions:

A) The effectiveness of interventions for preventing the spread of COVID-19

We will particularly consider the following preventive interventions aimed at reducing the secondary transmission of COVID-19 in healthcare providers and the community, particularly vaccination, prophylactic interventions, personal protective equipment, models of practice and organization of care (e.g., checklists, training, dedicated staff to ensure compliance to preventive interventions, organization of patient transportation), and movement control strategies.

B) The effectiveness of interventions for treating COVID-19

The following interventions will be considered:

1. Specific therapeutic agents for COVID-19 such as anti-infectious agents, specific immunomodulators, non-specific immunomodulators
2. Supportive interventions for patients admitted to the ICU such as high-flow nasal canula, non-invasive ventilation, protective mechanical ventilation and extracorporeal membrane oxygenation (ECMO)
3. General treatments for viral infection such as vitamin C, zinc, selenium etc.
4. Models of practice and organization of care (e.g., checklists, training, dedicated staff to ensure compliance with preventive interventions, organization of patient transportation, etc.)

We will consider both the treatments and treatment combinations. We will evaluate the impact of these treatments regimens considering the severity of the disease (i.e., mild, moderate, severe and critical diseases).

The different treatment regimens and preventive interventions considered in this living mapping and systematic review will evolve over time as the research field is continuously evolving.

2 METHODS

The process is described in the figure.

2.1 Criteria for considering studies for this review

2.1.1 Types of studies

We will include randomized controlled trials and quasi-randomized trials.

Observational analysis of routinely collected data that explicitly emulated a target trial to evaluate the effectiveness of interventions for preventing the spread of COVID-19 or for treating COVID-19 will be retrieved. We will include in the synthesis only emulated trials at low risk of bias as evaluated by Cochrane Risk of Bias tool for observational studies (i.e., ROBINS[5]).

Early-phase clinical trials, single arm trials and observational studies will be identified and cited on a website to inform the research community but will not be included in the review.

Systematic review and meta-analyses of COVID-19 prevention/treatments will be retrieved and the references will be screened.

We will exclude studies about prognosis, systematic reviews and meta-analyses, diagnostic test accuracy studies, and modelling studies.

2.1.2 Types of participants

For each research question, we will consider different participants.

For preventive interventions, we will consider

- The local community
- Healthcare providers

For treatment interventions, we will consider

- Suspected, probable or confirmed COVID-19 patients (see classification in appendix 1[9]).

We will distinguish patients according to the severity of the disease (i.e., mild, moderate, severe and critical diseases).

2.1.3 Types of interventions

A) The effectiveness of interventions for preventing SARS-CoV-2

We will particularly consider the following preventive interventions aimed at reducing human-to-human transmission of COVID-19 in healthcare and in the community:

- vaccination
- prophylactic interventions, such as pharmacologic treatment provided to people exposed to COVID-19 patients
- personal protective equipment
- models of practice and organization of care (e.g., checklist in ICU, training, dedicated staff to ensure compliance with preventive interventions, organization of patients' transportation, etc.)
- movement control strategies (e.g., self-isolation, quarantine, enforced lockdown).

B) The effectiveness of interventions for treating COVID-19

1. Evaluation of the effectiveness of specific therapeutic agents for COVID-19.

   Specific therapeutic agents will consist of

   a. anti-infectious agents including antiviral treatments such as remdesivir, lopinavir-ritonavir, oseltamivir, favipiravir and umifenovir; chloroquine and hydroxychloroquine; azithromycin, etc.
   b. specific immunomodulators such as interferon alpha, interferon beta, nivolumab, tocilizumab, etc.

c. non-specific immunomodulators such as corticosteroids, polyclonal antibodies, convalescent plasma, etc.

2. Evaluation of the effectiveness of supportive treatments for patients admitted to the ICU, such as high-flow nasal canula, non-invasive ventilation, protective mechanical ventilation, ECMO
3. Evaluation of the effectiveness of general treatments for viral infection such as vitamin C, zinc, selenium etc.
4. Evaluation of the effectiveness of models of practice and organization of care

Appendix 2 provides a list of interventions currently evaluated in trials registered on the WHO International Clinical Trials Registry Platform.

We will evaluate the effectiveness of these treatments considering the severity of the disease and comorbidities in subgroup analysis (ref WHO[4,10]). Particularly we will consider the following:

- **Mild disease** — clinical symptoms are mild with no sign of pneumonia on imaging
- **Moderate disease —** fever and respiratory symptoms with radiological findings of pneumonia and requiring oxygen (3 L/min>oxygen <5 L/min)
- **Severe disease —** cases meeting any of the following criteria:
    - respiratory distress (≧ 30 breaths/min)
    - oxygen saturation ≤ 93% at rest in ambient air or oxygen saturation ≤97% with $O_2 \geq 5$ L/min.
    - PaO_2/FiO_2 ≦ 300 mmHg (l mmHg=0.133 kPa). PaO_2/FiO_2 in high-altitude areas (> 1,000 m above sea level) will be corrected by the following formula: PaO2/FiO2 x [atmospheric pressure (mmHg)/760]
    - chest imaging showing obvious lesion progression within 24-48 hr
- **Critical disease —** cases meeting any of the following criteria
    - respiratory failure and requiring mechanical ventilation

- shock
- other organ failure that requires ICU care

The treatments and preventive interventions considered in this living mapping and 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.

2.2 Outcome measures

We based our outcome selection on the CORE outcome sets developed by the WHO[11] 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.

We will consider the following **primary outcomes**:

- Prevention of COVID-19
    1. Incidence of symptomatic or asymptomatic secondary COVID-19

- Treatment of COVID-19
    1. Clinical progression measured on the WHO Clinical Progression Scale (Appendix 2)

2. Hospitalization
3. Admission to an ICU
4. All-cause mortality at hospital discharge, at 28 and 60 days

We will consider the following **secondary outcomes**:

- Treatment of COVID-19
    1. Time to 2019-nCoV RT-PCR negativity
    2. Incidence of patients receiving oxygen by mask or nasal prongs
    3. Incidence of patients receiving oxygen by non-invasive or high-flow ventilation
    4. Incidence of intubation/mechanical ventilation
    5. Incidence of ECMO

We will consider the following **safety outcomes**:

1. Incidence of serious adverse events (SAEs)
2. Incidence of AEs

2.3 Search strategy and study selection

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.

The search strategy was developed with Robin Featherstone, Information Specialist, at Cochrane Editorial & Methods Department. The search strategy will be updated and modified to rely on the Cochrane living registry of available COVID-19 studies.

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.

2.3.1. Priority sources

- 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.

- **PubMed** (https://pubmed.ncbi.nlm.nih.gov)

We will use the following search to identify randomized trials:

Search	Query
#9	#8 Filters: **Publication date from 2020/01/01**
#8	Search: **#4 AND #7**
#7	Search: **#5 NOT #6**
#6	Search: **animals[mh] NOT humans[mh]**
#5	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]**
#4	Search: **#1 OR #2 OR #3**
#3	Search: **severe acute respiratory syndrome coronavirus 2[Supplementary Concept]**
#2	Search: **COVID-19[Supplementary Concept]**

Search	Query
#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])**

To identify observational studies, we will use the following search:

Search	Query
#9	#8 Filters: **Publication date from 2020/01/01**
#8	Search: **#6 NOT #7**
#7	Search: **animals[mh] NOT humans[mh]**
#6	Search: **#4 NOT #5**
#5	Search: **editorial[pt] OR comment[pt] OR letter[pt] OR newspaper article[pt]**
#4	Search: **#1 OR #2 OR #3**
#3	Search: **severe acute respiratory syndrome coronavirus 2[Supplementary Concept]**
#2	Search: **COVID-19[Supplementary Concept]**
#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])**

We will update the search strategies in PubMed to incorporate the names of the drugs we identify in our work when appropriate.

- **MedRχiv** (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.

2.3.2. Secondary sources

These sources will be searched as a quality control, and if no studies are identified over 8 weeks, these sources will be abandoned.

- **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 will screen studies listed under "treatment".
- **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)
- **ClinicalTrials.gov** (https://clinicaltrials.gov/ct2/home), using the term "COVID-19" to check all trials listed on the WHO platform
- **The EU clinical trial register** (https://www.clinicaltrialsregister.eu/) using the term "COVID-19" to check all trials listed on the WHO platform
- We will regularly contact investigators of ongoing studies to update the status of their study and obtain results.

- We will screen other sources such as the EPPI-Centre living map of evidence (http://eppi.ioe.ac.uk/COVID19_MAP/COVID_map_v5.html), Meta-evidence developed by Campbell UK & Ireland (http://meta-evidence.co.uk/).

We will use an Excel spreadsheet to document search dates and numbers of hits identified. Screening will be done in duplicate.

2.4 Data extraction

Two reviewers will independently read each preprint, publication, protocol, or other study report available; evaluate the completeness of the data availability; and assess the risk of bias. We will design and use a structured data extraction form to ensure consistency of information. 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 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.

All data will be extracted in duplicate, with consensus in case of disagreement.

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. These data will be curated and stored. We will re-analyse the outcomes. Furthermore, if possible, we will conduct individual-participant data NMAs.

2.5 Risk of bias assessment

The risk of bias of each study will be assessed with the Cochrane risk of bias tool RoB 2 for randomized controlled trials and ROBINS for emulated trials[7,8].

2.6 Living systematic review approach

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.

To achieve this goal, we will progressively increase the size of the team involved in screening and data extraction.

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 each task, 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), watching an online

video providing the correction for the exercise and contacting the team leader to ask about difficulties; 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 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)

We will consider the following tasks

1) Research mapping: screening and extracting data from registries
2) Screening databases from title/abstract to full text
3) Extracting data
4) Grading the evidence

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

The process will also evolve over time according to the difficulties encountered.

We will also set up a scientific committee that will meet weekly to discuss and agree on evolutions of the protocol.

2.7 Quantitative synthesis

2.7.1 Characteristics of eligible studies and evolution of evidence

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[12]. Using a contribution matrix,[13] we will show the effect of each piece of evidence in the full body of evidence and how new evidence affects the existing results.

2.7.2 Pairwise meta-analysis

For each direct comparison with at least two studies providing data, we will synthesize the results using as effect measures the odds ratio (OR) or relative risk (RR) for dichotomous data, mean difference for continuous outcomes measured on the same scale and standardized mean difference (SMD) if the same outcome is measured in different scales. 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 (τ^2): 1) a separate τ^2 for every comparison between two interventions and 2) a common τ^2 for studies comparing the same types of interventions. Visual inspection of forest plots, prediction intervals (the interval within which the effect of a future study is expected to lie[14]) and comparison of τ^2 with appropriate empirical distributions[15,16] will be used to assess the presence of important statistical heterogeneity.

2.7.3 Assessment of the transitivity assumption

Transitivity is the fundamental assumption of NMA and needs careful examination to reassure that results will be valid[17]. 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 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.

2.7.4 Network meta-analysis

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 (τ^2) 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, we will use the surface under the cumulative ranking curve (SUCRA)[18].

2.7.5 Assessment of incoherence

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[19],

the side-splitting method[20] and the design-by-treatment interaction model[21]. Tests for incoherence are known to have low power, so we will interpret the results of the tests with caution.

2.7.6 Exploring heterogeneity and incoherence

If we find substantial heterogeneity or incoherence, we will use subgroup analyses and meta-regressions to explore the impact of the characteristics age, disease severity, comorbidity status, country where care is delivered, and time after the beginning of the outbreak. The characteristics explored will evolve and consider new knowledge on COVID-19. We will also explore heterogeneity using available individual- participant data.

2.7.7 Bias due to missing results

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.[22]

We will use the comparison-adjusted funnel plot[12] (a modified funnel plot appropriate for NMA) and appropriate network meta-regression models[23] 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[24].

2.7.8 Implementation

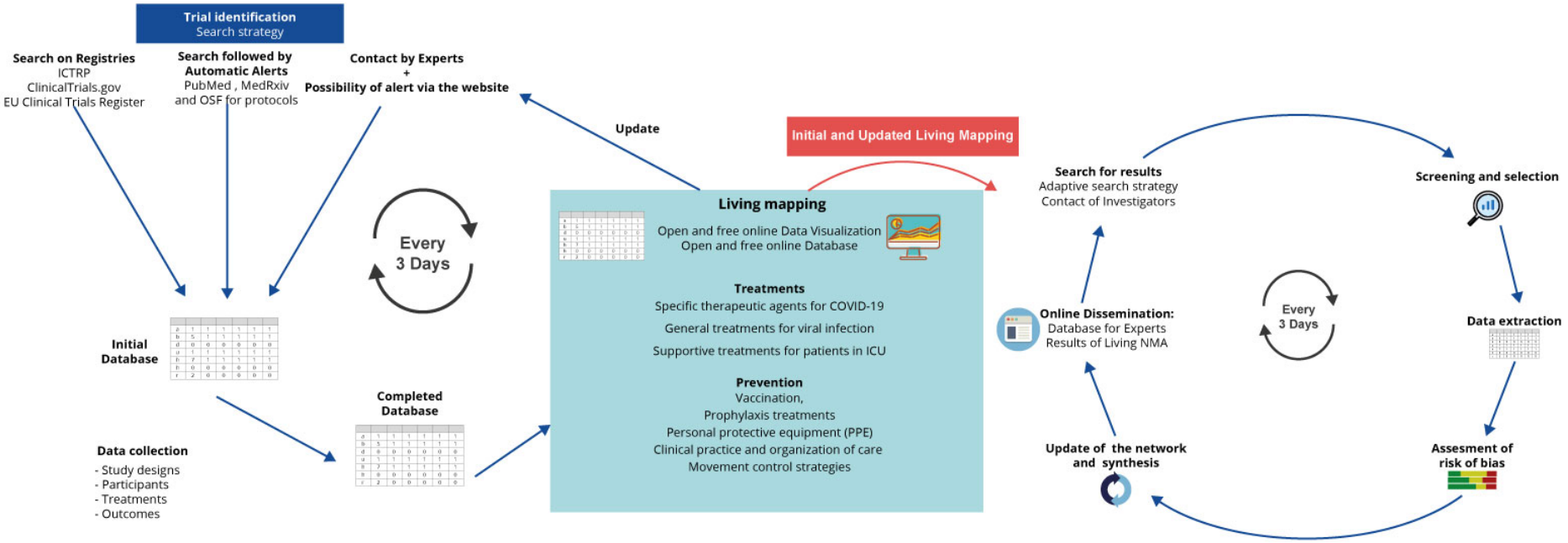
We will run analyses and produce graphical displays using R (netmeta package[25]) and Stata (network[26] and network graphs packages[27]). Network meta-regressions will be run in a Bayesian environment using r2jags[28].

2.7.9 Evaluation of the confidence in the network evidence

To evaluate the confidence in the NMA results 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[29,30]. 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.

For pairwise comparisons, we will rely on the GRADE approach[31] and report summary of findings tables.

Figure: Description of the process



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Appendix 1. CASE DEFINITIONS

(https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200316-sitrep-56-COVID-19.pdf?sfvrsn=9fda7db2_2)

Suspect case

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease (e.g., cough, shortness of breath), AND with no other etiology that fully explains the clinical presentation AND a history of travel to or residence in a country/area or territory reporting local transmission of COVID-19 disease during the 14 days prior to symptom onset.

OR

B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID19 case (see definition of contact) in the last 14 days before onset of symptoms;

OR

C. A patient with severe acute respiratory infection (fever and at least one sign/symptom of respiratory disease (e.g., cough, shortness breath) AND requiring hospitalization AND with no other etiology that fully explains the clinical presentation.

Probable case

A suspect case for whom testing for COVID-19 is inconclusive.

- Inconclusive being the result of the test reported by the laboratory

Confirmed case

A person with laboratory confirmation of COVID-19 infection, regardless of clinical signs and symptoms.

Appendix 2. Pharmacological treatment and non-pharmacological interventions of COVID-19. The list will be modified according to the evolution of the field. This list was established from the treatment evaluated in registered randomized controlled trials.

	Treatment type	Treatment name
Drugs	Antiviral, non-specific	Interferons Immunoglobulin Interleukin-2
	Antiviral, broad spectrum	Favipiravir Ribavirin Triazavirin Umifenovir Sofosbuvir+daclatasvir Sofosbuvir+ledipasvir Umifenovir+ribavirin Xiyanping
	Antiviral, antiretrovirals	ASC09 Azvudine Danoprevir Darunavir Darunavir+cobicistat Lopinavir+ritonavir Remdesivir Danoprevir+ritonavir ASC09+ritonavir
	Other antiviral	Baloxavir marboxil Oseltamivir
	Antiviral combination (when combining antivirals from different groups)	interferon alpha+lopinavir umifenovir+interferon alpha Lopinavir+ritonavir+ribavirin+interferon beta1 ASC09F+oseltamivir Ritonavir+oseltamivir lopinavir+ritonavir+xiyanping Lopinavir+ritonavir+interferon beta1
	Antimalaria	Chloroquine sulphate Hydroxychloroquine sulphate Dihydroartemisinin
	Antibiotics	Carrimycin
	Antiparasitics	Suramin sodium
	Non-specific anti-inflammatory	Methylprednisolone Other corticosteroids
	Immunosuppressant	Fingolimod

		Leflunomide Thalidomide
	Immunosuppressant+antiviral	Thalidomide+umifenovir
	Kinase inhibitors	Jakotinib hydrochloride Ruxolitinib
	Monoclonal antibodies	Adalimumab Bevacizumab Camrelizumab Eculizumab Mepolizumab PD-1 monoclonal antibody Sarilumab Tocilizumab Adamumab + tozumab Ixekizumab
	Antiviral+ monoclonal antibodies	Favipiravir+tocilizumab
	Antiviral+antimalaria	Darunavir+cobicistat+hydroxychloroquine Favipiravir+chloroquine phosphate
	Immunomodulator	CD24
	ACE inhibitor	Losartan
	Anticoagulant	Enoxaparin sodium
	Antiviral+antihistamine	Ebastine+interferon alpha
	Mucolytic	Acetylcysteine Bromhexine hydrochloride
	Other	Aviptadil (vasoactive intestinal peptide) Bismuth potassium citrate (may inhibit SARS-CoV1 helicase) Dipyridamole (antiplatelet) Pirfenidone (treat idiopathic pulmonary fibrosis) Polyinosinic-polycytidylic acid rhG-CSF Thymosin Tranilast Ulinastatin (sepsis management) Vitamin C Sodium Aescinate (vasoactive, organ protective) Tetrandrine (calcium channel blocker, anti-inflammatory) Lipoic acid injection (antioxidant) PUL-042 inhalation solution Noscapine (narcotine derivative) T89 (improving oxygen saturation)

Non-drug	Advanced Therapy Medicinal Products (ATMPs)	Aerosol inhalation of viral macrophage inflammatory protein Ankylosaurus; M1 macrophage target Convalescent plasma treatment Biological preparation of human placenta Umbilical cord mesenchymal stem cells Inactivated mycobacterium vaccine mRNA-1273 NK cells Recombinant cytokine gene-derived protein injection Washed microbiota transplantation
	Respiratory support	High-flow therapy with nasal cannulae Bag-valve mask oxygenation
	Organ support	Renal replacement therapy Artificial liver therapy Ozonated autohemotherapy
Prevention	Protective device	Medical mask N95 respirator
Post-COVID-19 management	Rehabilitation	Shadowboxing Pulmonary rehabilitation Lung rehabilitation training Ultra short-wave electrotherapy

Appendix 3. WHO Clinical Progression Scale, measured daily over the course of the study

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	**0**
Ambulatory	Asymptomatic; viral RNA detected	**1**
	Symptomatic; Independent	**2**
	Symptomatic; Assistance needed	**3**
Hospitalized: Mild disease	Hospitalized; no oxygen therapy	**4**
	Hospitalized; oxygen by mask or nasal prongs	**5**
Hospitalized: Severe disease	Hospitalized; Oxygen by NIV or High flow	**6**
	Intubation & Mechanical ventilation, pO_2/FIO_2 ≥150 or SpO_2/FIO_2≥200	**7**
	Mechanical ventilation pO_2/FIO_2<150 (SpO_2/FIO_2 <200) **or** vasopressors	**8**
	Mechanical ventilation pO_2/FIO_2<150 **and** vasopressors, dialysis, or ECMO	**9**
Death	Dead	**10**

Notes.

1. If hospitalized for isolation only, record status as for ambulatory patient
2. If pO_2 not available, use SpO_2/FIO_2 ratio with a cutoff of 200 [18]