SARS-COV-2 AND ARBOVIRUS INFECTIONS: PROTOCOL FOR A RAPID LIVING SYSTEMATIC REVIEW

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Research developed at the Brazilian Cochrane Center

ABSTRACT

Context and objective*:* While cases of COVID-19 disease increase daily worldwide, outbreaks of arboviral infections have affected health systems of countries in tropical regions. The outcomes for patients and health systems of a possible syndemic are not clarified yet. Thus, we aim to systematically review the literature searching for evidence that describes the clinical presentation, severity and prognostic of SARS-CoV-2 and Arboviral coinfection. ***Design and setting****:* Protocol for a rapid living systematic review, that will follow the Cochrane Handbook for Systematic Reviews recommendations. We will include prospective and retrospective cohort, case-control studies and case series of patients with confirmed diagnosis of SARS-CoV-2 and Arboviral infection. We will perform the search strategy with no language restrictions on Medline via PubMed, Embase via Elsevier, Cochrane Library - Cochrane Central Register of Controlled Trials (CENTRAL), Portal Regional BVS - LILACS, Scopus and WebOfScience to identify published, ongoing, and unpublished studies. The selection and extraction will be performed by two authors. We will perform the critical appraisal of included studies with the Newcastle-Ottawa Scale and the certainty of evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Key words: COVID-19; Arbovirus infection; Systematic Review.

INTRODUCTION

The outbreak of Coronavirus Disease (COVID-19) has spread worldwide and the epidemiological picture is constantly evolving. Data updated as of April 29, 2020, count 210 countries and territories around the world involved with almost 3 million confirmed cases and over 200,000 deaths (1).

In the midst of this scenario, countries in tropical regions are also facing the issues of old endemic diseases (2). In Brazil, for example, until mid-March 2020 more than 600,000 probable Dengue cases, almost 18,000 probable Chikungunya cases and over 2,000 probable Zika cases were notified in the year. Mortality data add up to 224 in these human urban arboviruses (3).

Epidemiologists alert to a possible temporal coincidence between Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Dengue outbreaks in Brazil for the first semester of 2020 (4). The recent advances in the understanding of COVID-19 have pointed to high similarity in pathophysiology events, as well as signs and symptoms of SARS-CoV-2 infection and arbovirus infection in general, such as fever and excessive systemic inflammatory response (2).

This finding suggests a possible misdiagnosed scenario that can lead to serious implication of delayed diagnosis, wrong treatment and poor allocation of resources (2,4). However, it is not clear yet how the outcomes of a possible syndemic will be expressed in patients and health systems. Thus, we aim to systematically review the literature searching for evidence that describe the clinical presentation, severity and prognostic of a coinfection SARS-CoV-2 and Arboviruses, in order to provide support for decision-makers in future scenarios of a possible syndemic.

METHODS

Design

This study is a protocol to describe the rationale, hypothesis and planned methods of our systematic review. It was submitted for registration in the PROSPERO "International Prospective Register of Systematic Reviews" platform. Considering the scenario of need for instant evidence to respond to COVID-19 pandemic, we will perform a rapid living systematic review, abbreviating the method by running screens of titles and abstracts through one author. In addition, this study will adopt a living method, continually updating and incorporating new clinical trial registrations and relevant data as they become available

This systematic process will follow the recommendations proposed by the Cochrane Collaboration Handbook (5).

Eligibility Criteria

Types of studies

We will include cohort, case-control studies and case series that describe the clinical presentation, severity and prognostic of a coinfection SARS-CoV-2 and Arboviruses.

Types of participants

We will include patients of any age tested positive for SARS-CoV-2 infection and positive for any type of Arbovirus infection (e.g. Dengue, Zika, Yellow Fever, among others).

Exposure events

Patients coinfected with SARS-CoV-2 and any type of Arboviral infection.

Types of comparators

Patients mono infected with SARS-CoV-2.

Outcome measures
- Primary outcomes: mortality rate; length of hospital stay; disease severity.
- Secondary outcomes: clinical characteristics; length of intensive care unit stay; Need for invasive mechanical ventilation; Hospitalization rate; Time to clinical improvement.

Report characteristics

We will include studies performed since November 2019, with no language restrictions as well as no publication site restrictions.

Data Sources and Searches

We will search for studies on the database that follows: Medline via PubMed, Embase via Elsevier, Cochrane Library - Cochrane Central Register of Controlled Trials (CENTRAL), Portal Regional BVS - LILACS, Scopus and WebOfScince adopting relevant descriptors and synonyms and adapting the search to the specifics of each database to identify published, ongoing, and unpublished studies.

We will also search the following COVID-19 specific databases: Epistemonikos COVID-19 L·OVE platform; ClinicalTrials; The World Health Organization International Clinical Trials Registry Platform (WHO ICTRP); Additionally, we will apply the technique of snowballing, searching the lists of references of the included studies.

Search strategy

The search strategy will be developed with the terms that are related to the SARS-CoV-2 in addition to all terms related to arboviral infection. There will be no language or publishing site restrictions.

Table 1. Search strategy

Number	Combiners	Terms
1	Problem of interest	"COVID-19" [Supplementary Concept OR (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease) OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR (Wuhan coronavirus) OR (Wuhan seafood market pneumonia virus) OR (COVID19 virus) OR (COVID-19 virus) OR (coronavirus disease 2019 virus) OR (SARS-CoV-2) OR (SARS2) OR (2019-nCoV) OR (2019 novel coronavirus)

The search strategy above will be used on Medline via Pubmed and will be adapted to the specifics of each database.

Study Selection

One author (KMM) will select the titles and abstracts of studies for inclusion on this review. If duplicated studies are found, only one of them will be considered for inclusion. When reports using the same participants, but with different outcome measurements or different assessment time points are found, both will be considered as parts of only one study. After removing duplicated studies, KMM will read the study titles and abstracts. Studies that clearly do not fulfill the eligibility criteria will be excluded and the remaining studies will then be fully read and assessed by two authors (APR and ACPNP) for inclusion in the review. Disagreements between authors related to this process will be solved by a third author (KMM). The reasons for the exclusion of studies will be described. To optimize the process of screening and selection of studies the Rayyan software (6) will be used.

Data extraction and management

The data extraction will be conducted by two authors independently (CRRF and FSAR). Discrepancies or disagreements on this process will be discussed and, if necessary, solved by a third author (VFMT). We will develop a form to extract data from included studies, which will be used to insert data related to: (I) Demographic and clinical

characteristics of the patients; (II) Time points used for the assessments; (III) Epidemiological characteristics (IV) Outcome measures; (V) Sources of funding; (VI) Possibility of conflict of interests.

To assess the feasibility of performing a meta-analysis, we will also extract the following data for each primary and secondary outcome measure: (a) Total number of patients (in each group); (b) Number of events in each group (for dichotomous outcomes); (c) Mean, standard deviation, standard error, median, interquartile range, minimum, maximum, 95% confidence interval (CI) (for continuous outcomes); (d) p-value.

Assessment of methodological quality in included studies and certainty of the body of evidence

We will perform the critical appraisal of included studies with the Newcastle-Ottawa Scale (7). The quality of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (8). The critical appraisal and the assessment of the certainty of the evidence will be performed by two authors (NCJ and VTC), and all the disagreements related to the assessment of the critical appraisal or certainty of the evidence will be solved through discussion and, if necessary, by mediation from a third author (VFMT).

Reporting standards

This systematic review protocol was written as per the PRISMA-P guidelines (9).

Data Synthesis and Analysis

When at least two studies are sufficiently homogeneous in terms of design, participants, and outcome measurements, we will assess the possibility of pooling their results into meta-analysis. If insufficient information or heterogeneous studies are found, the results of the studies will be summarized only in qualitative synthesis.

For evaluating prognosis, we will perform analyses according to the recommendations of Cochrane, and the Cochrane Prognosis Methods Group. To perform the meta-analysis we will use R software. When the response of interest is provided by continuous variable we will perform the analysis in terms of mean difference (MD) or Hedge's/Cohen's (SMD). In case of dichotomous response will pool a hazard ratios (unadjusted (crude) or adjusted) or odds ratio with their standard errors for hospital admission, intensive care unit admission and/or respiratory support for adult inpatients with COVID-19 and mortality. All others parameters as standard deviation (for MD or SMD, for instance) and each number of events (RR or OR, for instance) will be pooled. In all cases we will use the generic inverse variance method with random-effects model. The package to be used is the "meta" (version 4.11-0).

Dealing with missing data

For studies that do not provide a mean and associated standard deviation (SD), we will use information and results reported in the text or tables, doing the correct inference. When the parameters established before are not available, the estimate based on other parameters will be made ensuring the correct information.

We will contact the principal investigators of the included studies asking for additional data or to clarify issues about the studies. In the absence of a reply from the authors, we will expose the data in a descriptive manner avoiding imputation.

Assessment of heterogeneity

We will employ the Cochran's Q test to assess the presence of heterogeneity considering a threshold of P value < 0.1 as an indicator of whether heterogeneity is present. In addition, we will assess statistical heterogeneity by examining the Higgins I^2 statistic following these thresholds: < 25%: no (none) heterogeneity; 25% to 49%: low heterogeneity; 50% to 74%: moderate heterogeneity; ≥ 75%: high heterogeneity.

Discussion

The clinical presentation, severity and prognostic of a co-infection related to the SARS-CoV-2 and an Arboviral infection have not been well established yet. However, it is already known that a syndemic scenario would be an additional challenge and burden for the healthcare and economic systems of endemic countries for arboviral diseases (4). In our view, finding reliable evidence for the development of actions to fight COVID-19 situation is an important and urgent strategic objective. Thus, this rapid living review will systematically assess the best available evidence to respond to this scenario and to provide reliable information for decision-makers.

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APPENDIX – Search Strategies

COCHRANE LIBRARY

#1 (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease) OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR (Wuhan coronavirus) OR (Wuhan seafood market pneumonia virus) OR (COVID19 virus) OR (COVID-19 virus) OR (coronavirus disease 2019 virus) OR (SARS-CoV-2) OR (SARS2) OR (2019-nCoV) OR (2019 novel coronavirus)

EMBASE

#1 'covid 19'/exp OR (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease) OR (severe acute respiratory syndrome coronavirus 2) OR (Wuhan coronavirus) OR (Wuhan seafood market pneumonia virus) OR (COVID19 virus) OR (COVID-19 virus) OR (coronavirus disease 2019 virus) OR (SARS-CoV-2) OR (SARS2) OR (2019-nCoV) OR (2019 novel coronavirus)

WEB OF SCIENCE

#1 (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease) OR (severe acute respiratory syndrome coronavirus 2) OR (Wuhan coronavirus) OR (Wuhan seafood market pneumonia virus) OR (COVID19 virus) OR (COVID-19 virus) OR (coronavirus disease 2019 virus) OR (SARS-CoV-2) OR (SARS2) OR (2019-nCoV) OR (2019 novel coronavirus)

SCOPUS

#1 (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease) OR (severe acute respiratory syndrome coronavirus 2) OR (Wuhan coronavirus) OR (Wuhan seafood market pneumonia virus) OR (COVID19 virus) OR (COVID-19 virus) OR (coronavirus disease 2019 virus) OR (SARS-CoV-2) OR (SARS2) OR (2019-nCoV) OR (2019 novel coronavirus)

PORTAL REGIONAL BVS

MH:"Infecções por Coronavirus" OR (Infecções por Coronavirus) OR (Infecciones por Coronavirus) OR (Coronavirus Infections) OR (COVID-19) OR (COVID 19) OR (Doença pelo Novo Coronavírus (2019-nCoV)) OR (Doença por Coronavírus 2019-nCoV) OR (Doença por Novo Coronavírus (2019-nCoV)) OR (Epidemia de Pneumonia por Coronavirus de Wuhan) OR (Epidemia de Pneumonia por Coronavírus de Wuhan) OR (Epidemia de Pneumonia por Coronavírus de Wuhan de 2019-2020) OR (Epidemia de Pneumonia por Coronavírus em Wuhan) OR (Epidemia de Pneumonia por Coronavírus em Wuhan de 2019-2020) OR (Epidemia de Pneumonia por Novo Coronavírus de 2019-2020) OR (Epidemia pelo Coronavírus de Wuhan) OR (Epidemia pelo Coronavírus em Wuhan) OR (Epidemia pelo Novo Coronavírus (2019-nCoV)) OR (Epidemia pelo Novo Coronavírus 2019) OR (Epidemia por 2019-nCoV) OR (Epidemia por Coronavírus de Wuhan) OR (Epidemia por Coronavírus em Wuhan) OR (Epidemia

por Novo Coronavírus (2019-nCoV)) OR (Epidemia por Novo Coronavírus 2019) OR (Febre de Pneumonia por Coronavírus de Wuhan) OR (Infecção pelo Coronavírus 2019-nCoV) OR (Infecção pelo Coronavírus de Wuhan) OR (Infecção por Coronavirus 2019-nCoV) OR (Infecção por Coronavírus 2019-nCoV) OR (Infecção por Coronavírus de Wuhan) OR (Infecções por Coronavírus) OR (Pneumonia do Mercado de Frutos do Mar de Wuhan) OR (Pneumonia no Mercado de Frutos do Mar de Wuhan) OR (Pneumonia por Coronavírus de Wuhan) OR (Pneumonia por Novo Coronavírus de 2019-2020) OR (Surto de Coronavírus de Wuhan) OR (Surto de Pneumonia da China 2019-2020) OR (Surto de Pneumonia na China 2019-2020) OR (Surto pelo Coronavírus 2019-nCoV) OR (Surto pelo Coronavírus de Wuhan) OR (Surto pelo Coronavírus de Wuhan de 2019-2020) OR (Surto pelo Novo Coronavírus (2019-nCoV)) OR (Surto pelo Novo Coronavírus 2019) OR (Surto por 2019-nCoV) OR (Surto por Coronavírus 2019-nCoV) OR (Surto por Coronavírus de Wuhan) OR (Surto por Coronavírus de Wuhan de 2019-2020) OR (Surto por Novo Coronavírus (2019-nCoV)) OR (Surto por Novo Coronavírus 2019) OR (Síndrome Respiratória do Oriente Médio) OR (Síndrome Respiratória do Oriente Médio (MERS)) OR (Síndrome Respiratória do Oriente Médio (MERS-CoV)) OR (Síndrome Respiratória do Oriente Médio por Coronavírus) OR MH:C01.925.782.600.550.200$