SARS-CoV-2 and arbovirus infection: a rapid systematic review

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INTRODUCTION

Since the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged, the coronavirus disease (COVID-19) has spread worldwide. On March 11, 2020, the World Health Organization declared the outbreak of the COVID-19 disease to be a pandemic event and a Public Health Emergency of International Concern. In the meantime, its epidemiological picture has been constantly changing. Up to July 9, 2020, almost 12 million cases had been confirmed, with 545,481 deaths, in 213 countries and territories around the world, as reported to the World Health Organization (WHO).1,2

Amidst this pandemic, the world still needs to deal with the burden of various other diseases that present overlapping occurrences. Whether these are communicable or non-communicable, much remains to be learned regarding how to manage them all, so as to simultaneously mitigate issues relating to healthcare system saturation. In particular, countries located in tropical and subtropical regions, where arboviral diseases occur abundantly, are still dealing with these old endemics, which for some countries are epidemic diseases.3-6

Individuals affected by these various diseases may present clinical features that range from subclinical to severe forms, such as encephalitic or hemorrhagic forms, with very significant fatality rates.3 It has been estimated that more than two billion people live in environments suitable for arbovirus dissemination.7

Throughout the world, epidemiologists have been warning of temporal coincidence between endemic peaks and outbreaks relating to arboviruses and COVID-19.8,9 The constantly evolving knowledge of COVID-19 and its characteristics suggests that it and arboviral diseases share similarities with regard to clinical manifestations and laboratory findings.4,5 So far, dengue fever

ABSTRACT

BACKGROUND: The numbers of cases of arboviral diseases have increased in tropical and subtropical regions while the coronavirus disease (COVID-19) pandemic overwhelms healthcare systems worldwide. The clinical manifestations of arboviral diseases, especially dengue fever, can be very similar to COVID-19, and misdiagnoses are still a reality. In the meantime, outcomes for patients and healthcare systems in situations of possible synergism have not yet been clarified.

OBJECTIVE: We set out to conduct a systematic review to understand and summarize the evidence relating to clinical manifestations, disease severity and prognoses among patients coinfected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and arboviruses.

METHODS: We conducted a rapid systematic review with meta-analysis, on prospective and retrospective cohorts, case-control studies and case series of patients with confirmed diagnoses of SARS-CoV-2 and arboviral infection. We followed the Cochrane Handbook recommendations. We searched EMBASE, MEDLINE, Cochrane Library, LILACS, Scopus and Web of Science to identify published, ongoing and unpublished studies. We planned to extract data and assess the risk of bias and the certainty of evidence of the studies included, using the Quality in Prognosis Studies tool and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.

RESULTS: We were able to retrieve 2,407 citations using the search strategy, but none of the studies fulfilled the inclusion criteria.

CONCLUSION: The clinical presentations, disease severity and prognoses of patients coinfected with SARS-CoV-2 and arboviruses remain unclear. Further prospective studies are necessary in order to provide useful information for clinical decision-making processes.

PROTOCOL REGISTRATION NUMBER IN THE PROSPERO DATABASE: CRD42020183460

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Severe acute respiratory syndrome coronavirus 2 [supplementary concept].
Arbovirus infections.
Coinfection.
Syndemic.
Prognosis.

AUTHORS’ KEY WORDS:
COVID-19.
Severity.
Burden.
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Testing.
Dengue fever.
is the arboviral disease that has been found to share the largest number of clinical features with COVID-19, including the excessive systemic inflammatory response that is induced by both diseases. The effects of these diseases when a patient is infected with only one of them is already known, albeit more so with regard to arboviral diseases than to COVID-19. However, there still is a lack of information on the impact of coinfection with these diseases on patients’ clinical manifestations, the potential for severe disease and the prognosis. This knowledge is of vital importance for enabling adequate medical approaches towards these types of cases and, consequently, for applying the most appropriate treatment.

OBJECTIVE
The aim of this rapid systematic review was to summarize the evidence that exists concerning the impact of coinfection relating to SARS-CoV-2 and arboviruses, with regard to clinical features, disease severity and prognoses among coinfected patients.

METHODS

Protocol and registration
The protocol for this rapid systematic review was registered within the PROSPERO (International Prospective Register of Systematic Reviews) platform, under the protocol number CRD42020183460. Additionally, we developed and published a protocol on the SciELO preprints platform (https://preprints.scielo.org/index.php/scielo/preprint/view/346).

This study was developed at the Cochrane Brazil Center and it followed the Cochrane methodology.10

Eligibility criteria

Types of studies
Cohort studies, case-control studies and case series that described the clinical presentation, severity or prognosis of patients coinfected with SARS-CoV-2 and arboviruses were deemed to be eligible for inclusion.

Types of participants
Patients of any age who tested positive for SARS-CoV-2 infection and positive for any type of arboviral infection were included.

Types of comparators
Patients mono-infected with SARS-CoV-2 were used as comparators.

Outcome measurements
The primary outcomes evaluated were mortality rate, length of hospital stay and disease severity.

The secondary outcomes evaluated were clinical characteristics, length of intensive care unit stay, need for invasive mechanical ventilation, hospitalization rate and time taken to achieve clinical improvement.

Information sources and search strategy
We developed a search strategy (Appendix 1) to retrieve eligible studies from the following databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, BVS Portal, Scopus, Web Of Science, SciELO and LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde). Additional COVID-19 specific databases such as Epistemonikos COVID-19 LOVE platform, ClinicalTrial.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) were also searched for ongoing studies.

To improve the range of studies that we identified, we applied specific search strategies within large open-source databases, such as Mendeley Data and Figshare. Lastly, we applied the snowballing technique, in which the reference lists of the studies selected were also screened to identify possible published papers for inclusion in this review. There were no restrictions relating to languages or publication site. All studies published before May 18, 2020 were considered within this search strategy.

Study selection and data extraction
The titles and abstracts of citations identified through the search strategy described above were screened for eligibility by one author of this review. When duplicated citations were found, only one of them was considered for inclusion. If reports using the same participants but with different outcome measurements or different assessment time points were found, these reports would be considered as parts of only one study. Studies that clearly did not fulfill the eligibility criteria would be excluded and the remaining articles would be fully read and assessed by two authors for inclusion in the review. Disagreements between the authors, relating to this matter, would be resolved by a third author. To optimize the screening process and selection of studies, the Rayyan QCRI11 software was used.

We planned that two authors of this review would independently conduct the data extraction from the studies included. After that, they would together discuss any conflicts found among their results or discrepancies within this process. If necessary, a third author would mediate and resolve any conflicts. The data would be extracted through a Microsoft Excel file and would comprise information relating to study design and setting, demographic and clinical characteristics, time points used for the assessments, epidemiological characteristics, outcomes, numbers of participants, means, standard deviations, standard errors, medians, interquartile ranges, minimums, maximums, 95% confidence intervals (CI) (for continuous outcomes) and p-values, among other information.
Risk of bias in individual studies and risk of bias across studies
We planned to perform critical appraisals on the studies included, using the Quality in Prognosis Studies (QUIPS) tool, and to assess the certainty of evidence using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation). 4,13,14

Summary measurements and synthesis of results
We planned to assess the possibility of pooling the results from the studies included into meta-analyses when at least two studies were sufficiently homogeneous in terms of design, participants and outcome measurements. If insufficient information or heterogeneous studies were found, we planned to summarize the results through a qualitative synthesis.

If the response of interest was provided by a continuous variable, we planned to perform the analysis in terms of the mean difference (MD) or the standardized mean difference (SMD; via Hedge’s g and Cohen’s d). Hazard ratios (unadjusted crude or adjusted) or odds ratios (OR) were to be pooled in cases of a dichotomous response, for hospital admission, intensive care unit admission and/or respiratory support and mortality. All the other parameters, such as standard deviations (for MD or SMD), numbers of events, relative risks or odds ratios, were planned to be pooled. In all cases, we planned to use the generic inverse variance method with a random-effects model.

Dealing with missing data
For studies that did not provide the mean and the associated standard deviation (SD) parameters, we planned to use the information and results reported in the text or tables and to provide an inference from those findings. Additionally, we planned to contact the principal investigators of the studies included, to ask for additional data or to clarify specific concerns relating to the studies. In the absence of any response from those authors, we planned to present the data in a descriptive manner, so as to avoid making undue inferences.

Assessment of heterogeneity
We planned to use Cochran’s Q test to assess the presence of heterogeneity. We took P-values < 0.1 to be the threshold for indicating that heterogeneity was present. In addition, we planned to assess statistical heterogeneity by examining the Higgins I² statistic, following these thresholds: < 25%, no heterogeneity; 25% to 49%, low heterogeneity; 50% to 74%, moderate heterogeneity; and ≥ 75%, high heterogeneity.

RESULTS
The search strategy developed retrieved 2,407 records (Figure 1). After removal of duplicates and screening of the citations, we were not able to find a single study that fulfilled the eligibility criteria of this systematic review.
It is noteworthy that presence of skin rashes and exanthema has been well established as having high predictive value as signs and symptoms for COVID-19.24-27 Skin rashes and exanthema are also present within the development of some arboviral diseases, especially dengue fever. A study conducted in Pakistan21 reported a misdiagnosed COVID-19 case: after two serologically negative tests for SARS-CoV-2, antibody testing for dengue fever showed positive immunoglobulin M (IgM) titers and borderline NS1 antigen results. On the other hand, a study conducted in Thailand22 reported a case that was initially misdiagnosed as dengue fever due to the presence of a skin rash with petechiae, which was later correlated with the COVID-19 disease. In the same way, two cases reported from Singapore20 were initially misdiagnosed as dengue fever through rapid tests for dengue fever that provided false-positive results. As the health condition of these patients gradually worsened, they were tested for SARS-CoV-2 and confirmed as positive cases of COVID-19.

Unfortunately, most cases of arboviral diseases relate to individuals living in low-income countries, where access to the healthcare system is difficult and of poor quality, due to lack of resources. Even worse, this scenario is faced within situations in which the healthcare system is in a fragile state, which is the reality for the majority of tropical countries.8,28

Figure 1. Flow diagram of the study selection process, conducted on June 20, 2020.
Ideally, rapid, sensitive, accurate and accessible tools for diagnosing the different types of arboviral diseases and COVID-19 should be considered vital. Moreover, allocation of resources to manage and respond adequately to the pandemic should be well balanced.28,30

Nevertheless, knowledge of the impact of this type of coinfection on patients is still unclear. Much remains in the realm of the unknown. Overlapping of these diseases would affect the healthcare system, which is already overwhelmed. The expression of these diseases among patients and healthcare systems in the form of a possible syndemic31,32 remains unclear. Therefore, we undertook a systematic search of the literature to look for outcomes from coinfection between SARS-CoV-2 and arboviruses, including their clinical presentations, disease severity and prognoses, in order to provide support for decision-makers in future scenarios of a possible syndemic.

Thinking about this matter is of vital importance, for several reasons. One of these is that there remains a need to understand what impact these types of coinfections have on the clinical manifestations, disease severity and prognoses of coinfected patients. It has already been established that both COVID-19 and dengue fever induce cytokine storms, multi-organ failure and shock.33 How the immune system responds to simultaneous occurrence of these diseases is a matter that has not been clarified yet.

Given the lack of evidence found, we call on researchers to conduct studies on arboviral infections within the context of the COVID-19 pandemic. Prospective cohort studies are strongly recommended within this scenario. Our research has revealed a possibly substantial public health threat that needs to be addressed. This also highlights the importance for healthcare professionals who are on the front line of providing care for patients to consider the possibility of coinfection of SARS-CoV-2 and arboviruses, especially in tropical and subtropical regions. We hope that this review may help healthcare professionals to broaden their approach to diagnosis and treatment, and that this may stimulate more vital research, in a timely manner.

CONCLUSION
The clinical presentation, disease severity and prognoses of patients coinfected with SARS-CoV-2 and arboviruses remain unclear. Given that no eligible studies have been found to date through this systematic review, no conclusions relating to this research question can be drawn. Since this study is an ongoing systematic review, we hope to find evidence that can fill the gap in scientific information, in our subsequent publication updates.

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APPENDIX 1. Search strategies

COCHRANE LIBRARY
#1 (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARS-CoV2 or ncov*) OR (SARS-CoV2) 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 'covid19'/exp OR (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARS-CoV2 or ncov*) OR (SARS-CoV2) 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 (SARS-CoV2 or ncov*) OR (SARS-CoV2) 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)

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PORTAL REGIONAL BVS
MH:"Infecções por Coronavírus" OR (Infecções por Coronavírus) OR (Infecciones por Coronavirus) OR (Coronavirus Infections) OR (COVID-19) OR (COVID 19) OR (Pneumonia da China 2019-2020) OR (Pneumonia do Mercado de Frutos do Mar de Wuhan) OR (Pneumonia por Coronavírus de Wuhan) OR (Pneumonia por Novo Coronavirus de 2019-2020) OR (2019-pn2019-nCoV) OR (2019-ncov) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARS-CoV2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus de Wuhan) OR (Coronavirus do Oriente Médio) 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)

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