Converging pathways: bringing community, student initiatives, and a systematic review project in COVID-19 pandemic

Caminos convergentes: conectando comunidad, iniciativas estudiantiles y un proyecto de revisión sistemática en la pandemia de COVID-19

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Abstract

Introduction: In early January 2020, when the COVID-19 pandemic broke out, in vitro and animal studies showed preliminary positive results for repurposing drugs. Healthcare professionals had to critically assess the vast and emerging literature with an evidence-based approach to best clinical practices. **Objective:** The objective of this paper was to describe and reflect on the integration of a meta-research with a university extension program to promote critical reading of COVID-19 scientific studies among undergraduates. The meta-research aims to map the evidence and to estimate the prevalence of biases in comparative studies evaluating repurposing drugs for the treatment of COVID-19 during the pandemic. **Methods:** We integrated an online training on literature critical appraisal with a systematic review of methods. We searched for "COVID-19" and repurposed drug-related terms in MEDLINE, Embase, Cochrane Library, and LILACS by January 10th, 2022. Two independent researchers reviewed titles and abstracts and comparative studies had data fully extracted, including risk-of-bias. **Results:** A total of 171 students in Brazil signed into the online critical appraisal course. Of those, 24 were invited to collaborate with the meta-research, after robust evidence critical appraisal training. During the COVID-19 pandemic (2020-2021), 30.896 references assessed repurposing drug were identified and 6.246 papers were included. Our preliminary data showed 146 randomized controlled trials (RCT) with the word "randomized" in the title and 146 cohort studies identified by the word "cohort" in the title or abstract. **Conclusions:** The health emergency, there was an important volume of articles on interventions for COVID-19. Our preliminary results suggest that less than 5% of these studies were comparative longitudinal studies, being that most of the pertinent articles represent a challenge to be critically assessed, and probably have low level of evidence for clinical decision making. Our extension activity highlighted the interests of undergraduate healthcare students in developing skills on critical review of scientific articles. Thus, the experience of integrating university extension activity with research allows linking the community with knowledge generation.

Keywords: COVID-19; COVID-19 Drug therapy; Systematic review; Bias; Randomized controlled trial; Observational study.

Resumen

Introducción: al inicio del 2020, cuando inició la pandemia de COVID-19, estudios in vitro y en animales mostraron resultados preliminares positivos en medicamentos reposicionados. Los profesionales de salud tuvieron que evaluar críticamente la vasta y emergente literatura con un enfoque basado en la evidencia para adoptar las mejores prácticas clínicas. El objetivo de este artículo fue describir y reflexionar sobre la integración de un proyecto de meta investigación con un programa de divulgación universitaria para promover la lectura crítica de estudios científicos sobre la COVID-19 entre estudiantes universitarios. **Objetivo:** el objetivo de este artículo fue describir y reflexionar sobre la integración de una metainvestigación con un programa de extensión universitaria para la promoción de la lectura crítica de estudios científicos sobre COVID-19 entre estudiantes de pregrado. El objetivo de la metainvestigación fue mapear las evidencias y estimar las prevalencias de sesgos en estudios comparativos que evalúan fármacos reposicionados para el tratamiento de COVID-19. **Metodología:** integramos un entrenamiento online sobre evaluación crítica de la literatura con un proyecto de revisión sistemática. Se realizaron búsquedas con la palabra "COVID-19" y términos relacionados con la reutilización de fármacos en MEDLINE, EMBASE, Cochrane Library y LILACS hasta el 10 de enero de 2022. Dos investigadores independientes revisaron los títulos y resúmenes y se extrajeron todos los datos de los estudios comparativos, incluido el riesgo de sesgo. **Resultados:** un total de 171 estudiantes de Brasil se inscribieron en el curso de evaluación crítica en línea. De estos, 24 fueron invitados a colaborar con la metainvestigación, después de un entrenamiento robusto en evaluación crítica de la evidencia. Durante la pandemia de COVID-19 (2020 y 2021), se identificaron 30 896 referencias que evaluaban la reutilización de fármacos y 6246 artículos fueron incluidos. Nuestros datos preliminares mostraron 146 ensayos clínicos con la palabra "randomized", y 146 estudios de cohorte identificados con la palabra "cohort" en título o resumen. **Conclusiones:** durante la emergencia sanitaria, hubo un volumen importante de artículos sobre intervenciones para la COVID-19. Nuestros resultados preliminares sugieren que menos del 5 % de estos estudios fueron longitudinales comparativos, lo que sugiere que la mayoría de los artículos representan un desafío para ser evaluados críticamente, y con un probable bajo nivel de evidencia para la toma de decisiones clínicas. Nuestra actividad de extensión puso de manifiesto el interés de los estudiantes de salud, por desarrollar habilidades de revisión crítica de artículos científicos. Así, la experiencia de integrar la actividad de extensión universitaria con la investigación permite la conexión de la comunidad con la generación de conocimiento.

Palabras clave: COVID-19; Tratamiento farmacológico de COVID-19; Revisión sistemática; Sesgo; Ensayo clínico controlado aleatorio; Estudios observacionales.

Introduction

During the COVID-19 pandemic, healthcare professionals faced a challenging situation, they had to make clinical decisions concerning patient care for a new and highly virulent disease. Evidence of possible treatments for COVID-19 emerged at the start of the pandemic in January 2020[1]. In vitro and animal studies showed preliminary positive results for repositioning drugs that were already on the market for other indications, such as ivermectin, hydroxychloroquine, and doxycycline[2,3]. These treatments, still without scientific proof, quickly gained space in the media[4] and healthcare professionals had to critically assess the emerging literature with an evidence-based approach to adopt the best clinical practices. In the early 1990s, evidence-based medicine (EBM) was introduced as an innovative approach to medical practice and education. David Sacket defined EBM as "conscientious, explicit, and judicious use of the best available evidence in decision making on patient care, alongside physician experience and patient preferences"[5]. At that time, it motivated changes in the medical curriculum, which are progressive, and are still ongoing in low-middle income countries[6,7] and even in high-income countries. Often, undergraduate health courses (medical and non-medical) do not offer EBM in their curricula, linked to novel approaches for teaching it such as Problem-Based Learning (PBL)[8]. The evidence on EBM teaching approaches varies in terms of interventions, outcome measures and pedagogical approaches[9]. A systematic review, published in 2023, assessed teaching and learning strategies of EBM and they found that tutorials, lectures, short course and workshops on EBM were the preferred teaching method for healthcare professionals[9]. During the pandemic some physicians prescribed drugs based on their personal professional opinion. It might be influenced by the lack of timely evidence to appropriate decision-making and the fact that clinicians often do not have the methodological training to assess validity, and the prevalence of specific biases in published comparative studies[7]. As soon as the COVID-19 pandemic emerged in early-mid 2020, the need for a critical assessment for clinical decision-making became evident. The media was flooded with information, and the lay public had access to medical publications at a time of fear and hopelessness regarding the emerging burden of COVID-19. Social media has become an important tool for disseminating information, and even health students have used it in a challenging context, with the cancellation of clinical practices and teaching turning online[10,11]. The objective of this paper was to describe and reflect on an experience of integration a university extension program to promote critical reading of COVID-19 scientific studies among undergraduates, with a meta-research aiming to map the evidence and estimate the prevalence of biases in comparative studies evaluating repurposing drugs for the treatment of COVID-19 during the pandemic.

Methods

Researcher training process: studies critical appraisal training

The first part of the work included an online free course to promote critical appraisal of scientific articles. It was offered to undergraduate health students throughout Brazil aiming to fight the pandemic of misinformation, and it was part of the recruitment process for the research team involved in the meta-research.

The course was coordinated and taught by FADQ, and TBR was the monitor. It focused on critical reading of scientific articles in the biomedical literature and to promote the critical analysis of evidence on medications for the treatment of priority public health problems. The course was announced on the Faculdade de Saúde Pública (School of Public Health) of the Universidade de São Paulo (University of Sao Paulo, FSP-USP) and its social media (Instagram, Twitter, Facebook, and LinkedIn), which have more than 69.000 followers. The target population were undergraduate health students, from the third semester on, with a basic knowledge of epidemiology (e.g. discipline of Epidemiology concluded, and/or knowledge about the measure of frequency and association, studies design and their applications).

The course lasted 40 hours and the content included important aspects of EBM and epidemiologic concepts (APPENDIX A). It included flipped classes and problem-based learning. A topic was posted weekly on an educational platform, Google Classroom®, it included an on-demand expositive lecture on YouTube® plus a list of exercises in Google Forms® to apply the concepts. The exercises incorporated problem-based learning from published papers and real situations inspired by epidemiologic and research problems. Thus, the course created settings that offered the opportunity to think about and apply the concepts learned in the recorded lessons. Every week the students and professors met online in a synchronous activity to discuss the concepts and resolve doubts.

After the course was concluded, a subgroup of top-performing students was invited to develop an

undergraduate research ("scientific initiation") project at the Laboratory of Causal Inference in Epidemiology [Laboratório de Inferencia Causal em Epidemiologia] of the FSP-USP (LINCE-USP), as part of the umbrella systematic review reported here. These students received additional training on study methods and tools for critical appraisal, and they met with the supervisor (FADQ) weekly to updates on epidemiological issues and other training activities.

Meta-research (systematic review of methods) methodology

The umbrella systematic review, which was registered in PROSPERO (CRD42022360331)[14], included studies that meet the following inclusion criteria: 1. Having evaluated patients diagnosed with COVID-19 using some of the drugs of interest included in a living systematic review, "Drug treatments for COVID-19: living systematic review and network meta-analysis"[15] from the British Medical Journal, at the time of the search with last update on April 06, 2021, and also repositioned drugs included in the guide suggested by the National Health Institute of the United States 16: Anticoagulants (e.g. heparin, enoxaparin, rivaroxaban); Azithromycin; Canakinumab; Chloroquine; Colchicine; Corticoids systemic; Doxycycline; Angiotensin-converting enzyme inhibitors; Angiotensin II Receptor Type 1 Blockers; Favipavir; Fluvoxamine; Hydroxychloroquine; BTK inhibitors (e.g. ibrutinib, acalabrutinib); IL-6 Receptor Antagonists (sarilimumab and tocilizumab); JAK inhibitors (baracitinib, tofacitinib and ruxolitinib); Beta interferon; Interferon gamma; Ivermectin; Nitazoxanide; Peginterferon lambda; Remdesivir; Recombinant human granulocyte colony-stimulating factor (rhG-CSF); Ritonavir-lopinavir; Sulodexide; Umifenovir; Vitamins (APPENDIX B); 2. Studies including some type of clinical or laboratory efficacy and/or safety endpoint; 3. Publication in journals indexed in English, Portuguese, or Spanish language; 4. For mapping objective, the following study designs and/or their variations were included: Case report, Case series, Cross-sectional study, Case-control study, Cohort, Randomized clinical trial (RCT) and Systematic review (citation in the title or abstract "systematic review"); 5. For full characterization and bias assessment, just comparative studies with a comparator group were included, mainly cohort and RCT.

The exclusion criteria were studies restricted to preventive interventions for COVID-19; studies that did not evaluate COVID-19-related outcomes (e.g., only cancer-related clinical outcomes in oncology patients with COVID-19); and publications of the type: in vitro (e.g., cell) or animal studies, expert opinion, letters (opinion), editorials, preprints, and study protocols.

Information sources

We searched MEDLINE (Via PubMed), Embase, Cochrane Library, and the Latin America Database LILACS (via BVS). We retrieved studies published until January 10th 2022, period that included studies published during the COVID-19 sanitary emergency from early 2020 to end 2021.

Search strategy

We performed a comprehensive search to identify studies that fill in the eligibility criteria, according to this PICO strategy. The search strategy can be found in APPENDIX C.

Study records (Data management and Selection process)

We imported all records obtained via the electronic search into Mendeley software to remove duplicates. The file was exported to Rayyan®. Pairs of reviewers work independently to screen all potential papers by the assessment of titles and abstracts via Rayyan®. Discussion meetings with senior researchers were held to resolve discrepancies or consensus.

Data extraction and management

Non-comparative studies were mapped to record their general characteristics (i.e., study design, population characteristics, effectiveness and/or safety outcomes, and drug of interest). The comparative studies that met eligibility criteria had data fully extracted, detailed below. After reading the complete text, we excluded other studies that did not meet our criteria, and we documented the reason for their exclusion. All data collected in this step was available in a single form at Google Forms®, with different sessions, according to eligibility and study design.

For comparative studies, we performed data extraction by segments. Initially, we extracted data from papers that include "randomized" or "randomised" in their title. Followed for the extraction of studies with the word "cohort" in the title and/or abstract were extracted. The extract data included the following general characteristics: Type of study; Drugs assessed; Posology; Data on COVID-19 diagnosis (e.g. PCR); Context of patient inclusion (e.g. hospital, ambulatorial

setting); Patient severity; Number of centers enrolled; Location of the centers; Single or multiple centers; Country of patients enrolled; First author country of affiliation; Sample process information (e.g. random, consecutive); Subpopulation studied; Protocol registration; Funding; Conflict of interest; Open data; and Data of study protocol (if available).

The following data of outcomes were extracted: mortality, mechanical ventilation, composite outcome: mortality plus mechanical ventilation and primary data reported by the study. From them, we collected the quantitative information according to its characteristics; For binary outcomes, we extracted data from numbers of events intervention and comparator group, number of patients intervention and comparator group, relative measured used and its data with confidence interval, and follow up time.

For continuous outcomes, we extracted data from the type of measure used, the number of the central tendency measure and dispersion (e.g., confidence interval or standard deviation) for the intervention and comparator group, number of patients intervention and comparator group, and follow up time.

Risk of bias in individual studies

The risk of bias was assessed according to each type of study with the standard tool defined by the literature. For observational comparative studies we used Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I)[17] and for RCT we used Risk of Bias (RoB) 2.0[18]. We considered the primary outcome reported by the authors for the assessment of each study.

Two trained reviewers working independently and in duplicate assessed the risk of bias for each study according to the criteria defined and disagreement were resolved by discussion with a third researcher.

Data synthesis

At the time of writing of this manuscript, the analysis has not been completed. We plan to map the papers included in the review, and to present it per type of drug, study design and year of publication.

We have been assessing the risk of bias in the included studies using tools validated in the literature. Based on these tools, we will calculate the proportion of studies with high, moderate, and low risks of bias per domain. We will estimate the inter-rater agreement by calculating the Kappa coefficient of the bias classification. A Kappa of 0.6 or higher will be considered substantial. We will also evaluate the strategy to control confounding in observational studies and describe if appropriate conditioning was made considering the covariates suggested by a Directed Acyclic Graph (DAG).

Results

University extension program – studies critical appraisal training

A total of 171 undergraduate healthcare students from 19 different Brazilian federative units signed into online free course to promote critical reading of scientific articles. All were subscribed to the university system to join formal extension courses at USP. Most of the participant were residents from São Paulo (n=86), followed by Bahia (n=14), Minas Gerais (n=9), Rio de Janeiro, Rio Grande do Sul e Paraiba (each n=8), Ceará and Distrito Federal (n=6), Pernambuco (n=5), Alagoas, Sergipe and Paraná (each n=4), Goiás (n=3), Piauí (n=2) and Amapá, Pará, Rio Grande do Norte, Santa Catarina e Tocantins (each n=1)[11].

Among the participants, twenty-four top performing students, from fourteen different universities, were invited to develop a scientific initiation project at the LINCE-USP. They received additional training on study methods and tools for critical appraisal and collaborated with the meta-research (Figure 1). These students led twenty-three scientific initiation projects nested in this systematic review, which implied in the fulfillment of 480 hours, certified by the USP Research Program. The follow up and monitoring was carried out with weekly meetings of the whole group and individual meetings to review the information collected.

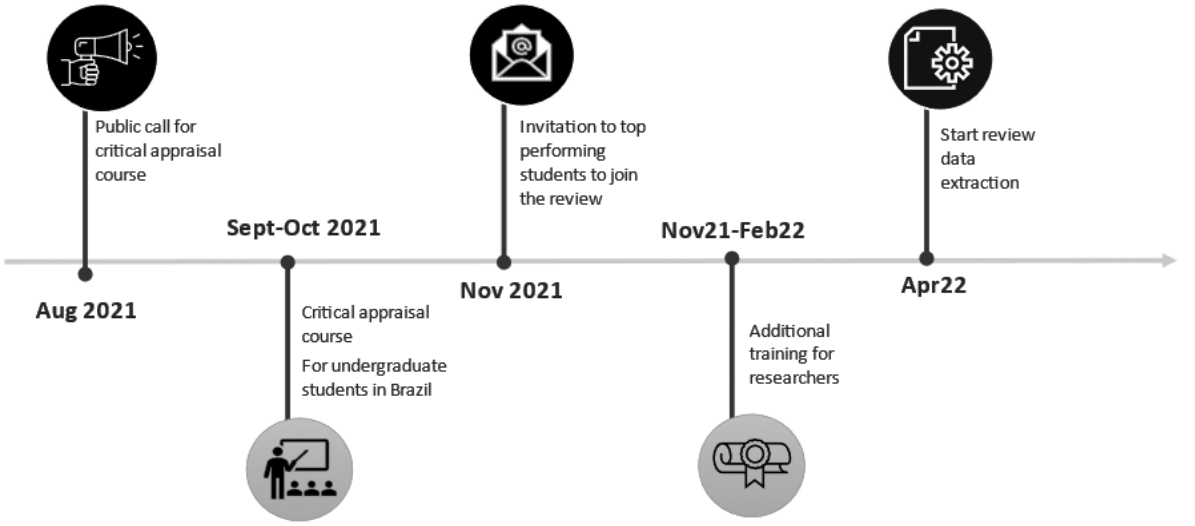

Figure 1. Timeline of project activities.

The projects were presented at the 2022 USP International Symposium on Scientific and Technological Initiation (in Portuguese Simpósio Internacional de Iniciação Científica e Tecnológica da USP), and two of the students were invited to present their results in the international phase of its Symposium. All young researchers sent a report with their results which were approved by the USP Research Program committee.

As an additional integrative activity, we organized a scientific meeting in which the students presented novel topics on causal inference. These presentations were recorded and available on YouTube[12,13].

Meta-research preliminary results

The search identified 15,983 publications in MEDLINE, 15,648 in EMBASE, 2,360 in Cochrane and 439 in Lilacs. Duplicates were removed and 30,896 titles and abstracts were revised via Rayyan by 12 pairs of independent researchers (Figure 2). After discussion with third reviewer or consensus, 6,246 papers were included in the next step of the review: mapping the literature assessing drugs for COVID-19 treatments and selection of comparative studies to data extraction about biases and clinical outcomes. At the time of writing, the analysis has not been completed. However, considering our preliminary classification, 146 papers were randomized controlled trials. Moreover, we identified 146 cohort studies among paper with the term "cohort" in title or abstract.

Discussion

The COVID-19 pandemic was followed by an "infodemic", an information pandemic, through the Internet and social media[19]. This phenomenon was associated with fake news and impacted the public health communication and disease control[20].

Knowledge about the hierarchy of evidence, study design, search in databases, and potential biases is important for literature critical appraisal[21,5]. It is the essence of EBM and Evidence-based Healthcare (EBHC) in which physicians and healthcare professionals use the best scientific studies for turning evidence into their practice, considering patient individual options.

During the COVID-19 pandemic, the topic of EBM has remained prominent on social media and there has been a significant volume of articles on COVID-19 interventions (e,g, drugs, face masks, social distancing, etc). When adding up the number of preprints and published articles, great concern arose about the quality of these papers, because even when they were available in high-impact journals, there was seem significant flaws in the data and conclusions[22]. This situation impacted the lay population, and even more healthcare students who had the challenge of learning during a pandemic about EBM concepts and written in English.

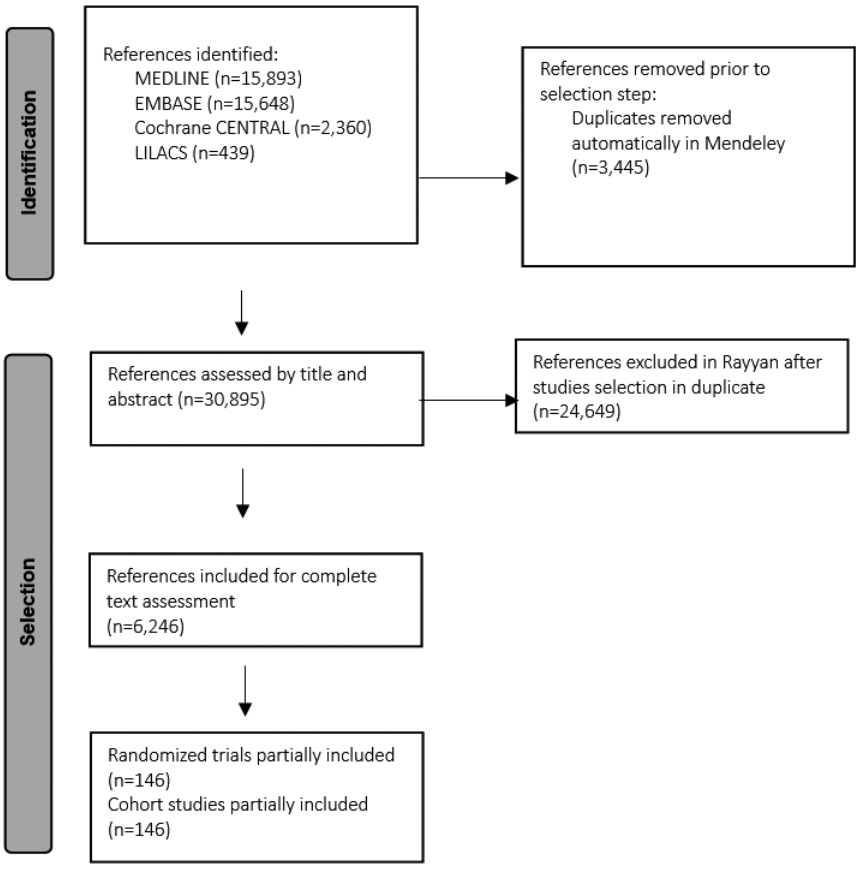

Figure 2. PRISMA flowchart of studies selection.

Fourtassi et al. stated that the COVID-19 global health crisis provided a valuable EBM lesson for undergraduate students to understand and integrate the knowledge[23]. This opportunity to teach students during the pandemic ongoing was a distinguishing feature of our online course, that was announced in social media and had applications of students from several Brazilian Federative Units. This is in line with a concept called EBM PLUS, which states that traditional methods of doing EBM based on probabilistic evidence from RCTs should be extended to incorporate other forms of evidence, such as mechanistic, which includes a wide range of study designs to give greater emphasis to other sources of information, such as that offered by observational studies. This is very useful when rapid decisions need to be made to save lives, as in the case of the COVID-19 pandemic[24].

Prof Guyatt et al. stated in their historical paper published about EBM teaching in 1992 that new skills for physicians are required, such as literature search and its critical appraisal[21]. Our course intended to reduce this gap by training future healthcare professionals from Brazil on studies bias and methods**,** and we aimed to develop new skills in the students and, in contrast from most publications about EBM teaching, we continued the education with a research activity related to literature critical appraisal that solidify the concepts. This also creates a scientific network with different institutions, promoting the concept of collaborative work, which is vital to leverage capabilities and decrease research waste.

The research project described in this manuscript, in which the students took part, included a methodological systematic review, meta-research, to map the published evidence about repositioning drug studies on COVID-19 treatment. This will provide a framework for COVID-19 publication and the scientific community capability to respond quickly to a pandemic situation.

Our systematic review is the first assessing solely repositioning drugs and aiming to quantify specific

biases related to comparative effectiveness research published by January 2022. Other systematic reviews were published assessing general framework or efficacy/safety of repurposed drugs[25-27]. However, the novel aspect of our study relies on our focus on the methodological assessment of the studies and including full pandemic time (until Jan 2022).

During the COVID-19 pandemic, health professionals have had to critically evaluate the literature in order to make evidence-based decision. Especially at the beginning of the pandemic, most of the available studies were observational and evaluated repositioned drugs, while RCTs were being conducted. According with our preliminary data, less than five percent of more than six thousand were longitudinal comparative studies (i.e, RCT or cohort studies), and we only identified 146 RCT. This suggests that most of the evidence was based on observational studies. Another systematic review described efficacy and safety outcomes of drugs repositioned for the treatment of COVID-19[26]. The authors assessed the evidence identified up to April 2020, and in the end included 16 studies, of which 6 were RCTs and 10 observational[26], in line with our preliminary results, which were based on a comprehensive search up to January 2022, which accounted for more than 24 repositioned drugs.

The inherent risk of bias of observational studies, mostly based in real-world data from electronic health records, was typically higher than RCTs, and was mainly related with selection, misclassification and confounding[17].

Outstanding, our work did not cover all the potential causes of misinformation that can occur in times of sanitary emergencies, we focused on internal validity. Other biases were also noted in COVID-19 papers, such as the spin bias, related to a distorted interpretation of research findings that can be related to a misleading conclusion. It seemed that spin occurred in both preprints and published studies on COVID-19[20].

Another example is the confirmation bias, which occurs when information is used to support an individual's ideas, beliefs, or hypotheses, and represents another challenge regarding evidence assessment in sanity emergencies. This bias can occur when interpreting a study, especially when there is uncertainty about a topic with several research questions still to be answered, such as during the beginning of the pandemic with several knowledge gaps about the virus dissemination, clinical features, treatments, and prognosis. During COVID-19 pandemic, social media may have influenced the confirmation bias, inducing polarization[19].

Conclusions

Based on the reported experience, we considered the following lessons:

During the health emergency, there was an expressive volume of articles on interventions for COVID-19. That pandemic of papers makes it unfeasible for a health professional to be updated regarding the evidence on therapeutic alternatives.

Moreover, the fact that only a small number of the studies are experimental suggests that most of the pertinent articles represent challenges to be critically reviewed and considered in clinical practice.

On the other hand, we interpreted the interest of students, from several universities and regions of Brazil, as a generalized felt need for skills on critical review of scientific articles. In this sense, the experience of integrating university extension activity with research allows linking the community with knowledge generation. Moreover, we expected that the offered training contributes to improving the skills to make decisions during public health emergencies and dynamic situations of generation of knowledge.

In conclusion, we describe an innovative project that included an extension activity, for the training of undergraduate students and junior researchers, and its application in mapping and characterizing the evidence on drug repositioning for the treatment of COVID-19. We consider that the project will contribute to knowing the characteristics of research developed in the circumstances of a pandemic, which would help to alert users of biomedical literature about potential biases. Finally, other expected benefits are the promotion of proper reporting of research on comparative studies, development of studies with greater validity, and the reduction of misinformation in future sanitary emergencies.

Authors contribution

FADQ and TBR contributed to the conception and design of the study, the writing of the manuscript draft and last version. FADQ, PCR and TBR contributed to coordination of data collection and analysis. TBR, PCR, DMP, ATSV, LRSM, GPP, JGCBSL, RSA, GAA,

EAB, TSE, RCO, ARTS, APD, LFM, JBM, JSF, PNM, PES, KKG, TPC, FADQ contributed to collection of data and manuscript draft critical review. TBR, PCR, DMP, ATSV, LRSM, GPP, JGCBSL, RSA, GAA, EAB, TSE, RCO, ARTS, APD, LFM, JBM, JSF, PNM, PES, KKG, TPC, FADQ approved the last version of the manuscript.

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Ethical considerations

Not applicable – systematic review.

Conflict of interest

The authors declare no conflict of interest.

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The authors report that they did not use Artificial Intelligence, language models, machine learning or similar technologies to create or assist with the elaboration or editing of any of the contents of this document.

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