

# Vaccine Research in COVID-19: A Living Scoping Review Protocol

**Jieyun Li**

Lanzhou University

**Lufang Feng**

Lanzhou University

**Haitong Zhao**

Lanzhou University

**Kehu Yang**

Lanzhou University

**Cuncun Lu** (✉ [cuncunlu2017@163.com](mailto:cuncunlu2017@163.com))

Lanzhou University <https://orcid.org/0000-0001-9541-9733>

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## Protocol

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# Abstract

**Background:** Coronavirus disease 2019 (COVID-19) has become a global public problem and a pandemic event. Since the epidemic outbreak, deaths and cumulative confirmed positive cases have continued rising rapidly worldwide. Vaccines are regarded as one of the most effective means of preventing and controlling an epidemic. With the spread of COVID-19, a large number amount of literature on vaccines has been published recently. There is a pressing need to map the research activities of COVID-19 vaccines.

**Methods:** Following Arksey and O'Malley's framework and Joanna Briggs Institute (JBI) methodological guidance, a scoping review is proposed to summarize the extent/breadth, range, and nature of evidence in research related to COVID-19 vaccines. Based on the research questions we have developed by ours, a comprehensive search will be performed in Cochrane Library, Embase, PubMed, Web of Science, CNKI, CBM, VIP, and WanFang databases by two independent reviewers. According to our predefined inclusion criteria, pairs of reviewers will independently assess the eligibility of identified studies from the databases. Following literature selection, pairs of reviewers will extract relevant information related to our research questions. The methodological quality and reporting quality of key evidence types (i.e., randomized controlled trials, systematic reviews and meta-analyses) will be evaluated using commonly used tools, if possible. Qualitative synthesis and descriptive statistics will be used to summarize and present the results. In addition, new or updated meta-analysis will be conducted to pool the data available in included primary studies where possible. To track the trends in COVID-19 vaccines research, we plan to update our results every 2~3 months. Preparation of this scoping review protocol referred to PRISMA-P checklist, and the reporting of the following full-text will be using PRISMA-ScR guidelines.

**Discussion:** We believe the results of this scoping review on COVID-19 vaccine will contribute to provide foundational knowledge, and have significant value for the research and practice of COVID-19 vaccines. The findings will also allow us to identify research gaps on this topic and help to guide the future research of COVID-19 vaccines well.

## Background

Since the beginning of 2020, the coronavirus disease 2019 (COVID-19) has swept the whole world, which has brought severe challenges to the politics, economy, and society of all countries [1]. Until November 14, 2020, there were more than 1.30 million deaths worldwide and a total of more than 53.61 million confirmed positive cases [2]. On the premise that the susceptible population has a large base and it is difficult to isolate the source of infection, especially the asymptomatic infection, the vaccine is widely regarded as one of the most effective means to prevent and control the epidemic. In terms of scale and speed, the current global research and development of the COVID-19 vaccines are unprecedented.

Generally speaking, it usually takes 10 to 15 years for a kind of vaccine to be developed and put on the market [3], but this "convention" has been broken as the epidemic continues to spread around the world.

After the genetic information of COVID-19 was made public [4], the global research and development of vaccines showed a high-speed, positive, and cautious trend [5]. According to the data released from the World Health Organization (WHO) on November 12, 2020, there are 212 known vaccines candidates in the world, of which 48 are in clinical evaluation and nine are in phase III clinical stage [6]. Vaccines under this report include the widely used traditional type of vaccines [7], namely the inactivated or attenuated vaccines [8], genetically engineered recombinant subunit adenovirus vector vaccines [9–11], recombinant viral vector vaccines [10, 12], as well as new types of vaccines, ribonucleic acid (RNA) vaccines [13] and deoxyribonucleic acid (DNA) vaccines [14].

In addition to the safety and effectiveness of the vaccine has attracted worldwide attention, the public attitude towards the vaccine and the exploration and research on the accessibility of the vaccine have also been concerned. The public willingness to receive the COVID-19 vaccines in most of the 19 countries surveyed in one published study showed, is not sufficient to meet the requirements of community immunization [15]. At the same time, the study discovered that the accelerated pace of vaccines development may further increase public anxiety and endanger public acceptance [15]. One study suggested that vaccines in remote and poor areas are difficult to ensure cold chain transportation due to their remote geographical location, lack of cold storage conditions, high cold storage costs, and lack of economic capacity. These reasons largely limit the popularity of vaccines [16]. WHO launched “COVID-19 Vaccine implementation Plan” (COVAX) in September, 2020 (<https://www.who.int/initiatives/act-accelerator/covax>), the funds invested by countries joined in the COVAX have been pooled to cooperate in vaccines research production, and procurement agreements, to reduce vaccines’ prices, and promote fair access to vaccines for people in all countries/regions.

With the spread of COVID-19, a large amount of literature on vaccines is being published recently. However, quantity is not the same as quality. On the contrary, too much information may confuse the decisions and choices of health decision-makers, clinicians, and researchers [17]. Meanwhile, overlapped, redundant and useless research may lead to avoidable waste of research [18]. As far as we know, the scientific research quality and integrity of vaccine-related research have not been directly evaluated, but the importance of doing so is self-evident [19]. The dissemination of misinformation may have a considerable impact on the acceptance of the COVID-19 vaccines. So far, it is not clear what evidence is available in the published vaccines’ literature and what decision-making references can be provided by this evidence. Additionally, it is not certain what are the knowledge gaps about the COVID-19 vaccines. Overall, since COVID-19 is new and the outcome of this pandemic is unknown [20], therefore, there is a pressing need to map the status quo and trends of COVID-19 vaccines research.

A scoping review is different from the traditional systematic review [21, 22]. It focuses on a broad range of research issues, can be used for mapping and disseminating the available evidence on a given area. It can not only to summarize the characteristics of existing publications, but clarify key concepts and their relationship, and identify the knowledge gaps in existing research. The methodological research of this method is making a continuous progress [23, 24]. In particular, the reporting guidelines for this comprehensive type of evidence was published in 2018 [24].

Considering the objectives of our research and the advantages of this method, we will undertake a scoping review to synthesize the existing COVID-19 vaccines' literatures. We will provide a comprehensive overview of the evidence and find gaps in knowledge, in order to inform the future vaccines research and clinical practice. Furthermore, the research will support governments and public health officials to spread reliable information of using COVID-19 vaccines, improving the popularization of vaccines knowledge so that the public can receive immunization.

## Methods/design

### Research design

This scoping review will summarize COVID-19 vaccines research activities and describe the extent/breadth, range, and nature of evidence in research related to COVID-19 vaccines. The framework described by Arksey and O'Malley [25] and Joanna Briggs Institute (JBI) [23] methodological guidance has been followed to design this scoping review. The scoping review will involve five stages: 1) identifying the research question; 2) identifying relevant studies; 3) study selection; 4) charting the data; 5) collating, summarizing, and reporting results. The reporting of this protocol is based on the Preferred Reporting Items for Systematic Reviews and Meta Analyses protocols (PRISMA-P) checklist [26] (Additional file 1) and the full text will follow to Preferred Reporting Items for Systematic Reviews and Meta Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines [24]. This protocol has not been registered, because the International Prospective Register of Systematic Reviews (PROSPERO) website does not currently accept scoping reviews. As there are some uncertainties at protocol stage, if there are any deviations from the following full-text, we will report them in detail, as well as the reasons. Meanwhile, given the outbreak and vaccines research are still ongoing, our research team will update the results every 2-3 months.

### Stage 1: identifying the research question

Following Arksey and O'Malley's approach and JBI methodological guidance [25], this scoping review begins by formulating our research questions, which will guide the following processes that include whole of the subsequent literature search and study selection. We will focus on the following questions:

1. The trends in publications of COVID-19 vaccines research (e.g., volume of publications, monthly distribution) and the bibliographic characteristics (e.g., journal, country, study type);
2. The available evidence in the COVID-19 vaccines' literatures and the pivotal points that they focusing on;
3. The scientific quality of the critical evidence types (i.e., randomized controlled trials [RCTs], systematic reviews and meta-analyses) for COVID-19 vaccines, and if they adhering the best practices required by guidelines or tools (e.g., Consolidated Standards of Reporting Trials [CONSORT])

[27], Preferred Reporting Items for Systematic Reviews and Meta Analyses[PRISMA] [24], A Measurement Tool to Assess Systematic Review 2 [AMSTAR 2]) [28];

4. The knowledge gaps in COVID-19 vaccines research, and critical questions that should be focused and addressed in the future.

## Stage 2: identifying relevant studies

This stage will involve the creation of a comprehensive search strategy for identifying literature from the public databases for answering our research questions. Firstly, the potential main search terms have been determined by reading relevant literatures. Then the initial search strategy was established through discussion by the research team. Lastly, our final search strategy was confirmed after improvement and modification through repeating searches (Additional file 2). According to the final search strategy, we will search the eight widely-used databases including Cochrane Library, PubMed, EMBASE, Web of Science, CNKI, WanFang, CBM and VIP. The search will be run by two reviewers independently. The main keywords used in our search strategy include "COVID19", "COVID-19", "COVID2019", "COVID-2019", "2019 novel coronavirus infection", "2019-nCoV", "coronavirus disease 2019", "coronavirus disease-19", "Wuhan coronavirus", "SARS-CoV-2", "2019 novel coronavirus", "Wuhan-Cov", "Wuhan seafood market pneumonia virus", "Wuhan virus", "novel coronavirus pneumonia", "Severe acute respiratory syndrome-related coronavirus", "Novel CoV", "severe acute respiratory syndrome coronavirus 2", "Vaccination Coverage", "Vaccin\*", "Vacuna", "Inoculation", "Immunization Programs", etc. Additionally, we will manually check the reference list of included literatures. Although many published COVID-19 reviews searched preprint servers, e.g., bioRxiv (<https://www.biorxiv.org/>), medRxiv (<https://www.medrxiv.org/>), we will not do so as we only include published papers that have been peer-reviewed (even if the article is retracted after publication), whereas preprint servers manuscripts are not peer-reviewed.

## Stage 3: study selection

Following the recommendations made by Levac et al [29], pairs of reviewers will independently screen the titles, abstracts and full-texts to identify potentially relevant studies. We will use literature management software to complete the literature selection process. After deduplication, an online application Rayyan [30] will be used for screening of abstracts and titles using a process of semi-automation, then Endnote X9 (Thomson Corporation) will be used to assess the eligibility of full-texts. In order to improve the accuracy of the included literature and the consistency of subsequent screening across reviewers, prior to formal screening, the pre-test will be conducted to familiarize the research content and strengthen the understanding for this topic of team members by screening 200 sample records randomly selected. After completing the pre-test, the other records will be screened according to the aforementioned process. Any disagreements during the selection process will be resolved by discussion.

The inclusion and exclusion criteria in our scoping review are as follows: 1) all qualitative, quantitative or mix-method research focusing on COVID-19 vaccines will be included; 2) no limitation on study types, they could be but not limited to guidance documents, basic experiments, clinical studies (e.g., RCTs, cohort studies, cross-sectional studies and case reports), any reviews (e.g., expert reviews, systematic reviews and meta-analyses), conference articles, protocols, and retracted articles (for exploring the issues regarding the integrity of science in the period of COVID-19); 3) we will not limit the research topic for mapping the full landscape for COVID-19 vaccines research, these topics can involve efficacy and safety, cost, public attitudes, views and perceptions, but not limited to that; 4) we will include Chinese and English documents only; 5) we will exclude any news and full-text documents which are not available.

## **Stage 4: charting the data**

A self-developed Excel sheet will be used to extract data, which the relevant information we needed to complete the review. The mainly extracted information including: title, the first author, online or publication date, journal, setting/study location (where the study was conducted), origin/country of corresponding author (where the paper was published), study aim/purpose, study population and sample size, study topic, methodology/method (e.g., framework ), type of vaccines and comparator (if any) and duration of intervention, study type, outcome measures, and important findings or conclusions that relate to our research questions in this scoping review.

Before the formal extraction beginning, pairs of reviewers will pilot the data extraction form by using a sample comprising 10% of the included documents. After the completion of pre-data extraction, the results abstracted by them will be cross-checked and consensus will be sought through discussion, so as to further improve the form until the results are no obvious conflict across data extractors, and then the formal extraction will be completed by pairs of reviewers. Any disagreement will be resolved by discussion within all team members.

In addition, although quality assessment is not required by the scoping review methodology [25], considering the reliability and application of the study conclusion may be affected by the methodology design and reporting of the study; RCTs, systematic reviews and meta-analyses as important types of evidence will be selected to assess their scientific quality, if possible. Thus, four validated tools, risk of bias 2.0 (RoB 2.0) [31] and CONSORT 2010, AMSTAR 2 and PRISMA will be used to assess the methodological quality and reporting quality of RCTs, and systematic reviews and meta-analyses, respectively.

## **Stage 5: collating, summarizing, and reporting results**

We will use the PRISMA flow diagram to report the process for literatures screening, the reasons for excluded and final number of included publications in our scoping review. Qualitative synthesis (thematic analysis method [32]) and descriptive statistics will be used to summarize and present the results.

Descriptive statistics (e.g., frequency and percentage) will be used to report the general characteristics (e.g., journal, country, and study type, volume of publications) of included literatures. According to the research contents reported in included documents and study topics they focused on, the COVID-19 vaccines research will be gathered as different themes and their sub-themes (e.g., efficacy and safety, cost, public attitudes, views, and perceptions). In addition, new or updated meta-analysis will be conducted to pool the data available in included primary studies, if relevant.

## Discussion

Our scoping review is designed for mapping COVID-19 vaccines research activities and to describe the extent/breadth, range, and nature of evidence in research related to COVID-19 vaccines. We believe this scoping review will not only provide meta-data regarding analysis and summary of existing research on COVID-19 vaccines research, but provide profound knowledge and robust evidence for the global research community.

To date, many studies had reported some positive conclusions from the efficacy and safety of COVID-19 vaccines [10, 11, 13]. For example, one study had shown that the upper and lower respiratory tracts in mice and ferrets can be completely protected against SARS-CoV-2 infection by single inoculations of the adenovirus type 5based COVID-19 vaccine (Ad5-nCoV) in mucous membranes and intramuscularly [10]. It also gives us a hint that the different routes of vaccination should be considered in human clinical trials for the development of the SARS-CoV-2 vaccines. In addition to the research on the vaccine itself, the universality and public acceptance of the vaccine also need to be considered. At the same time, to win the battle against the COVID-19 pandemic as soon as possible, some more efforts are needed that involve in increasing cooperation among countries and regions, improving the quality of scientific research, and establishing a comprehensive surveillance system.

Scoping review is a popular approach to address the uncertainty of evidence in a wide research topic [22, 23]. Considering this method allows us to conduct an in-depth exploration of the existing evidence, therefore, we choose this approach to mapping the research activity related to COVID-19 vaccines. This present protocol reports a comprehensive, rigorous, and transparent methodology regarding our scoping review, we will follow this protocol to complete our research. Hopefully, the evidence identified from the literature in our scoping review can provide government and public health officials with reference to the implementation of COVID-19 vaccines. Meanwhile, knowledge gaps identified in the current body of literatures can guide future COVID-19 vaccines research. To our knowledge, this will be the first scoping review of COVID-19 vaccines, and the results of this review will have a significant value for all stakeholders. Nevertheless, we only searched the commonly used Chinese and English databases, and the literatures in Chinese and English will be only included. Given that COVID-19 vaccine is a global problem, some important research reports published with other languages may be missed. This would be a notable limitation of our scoping review.

# Ethics and dissemination

Since the data will be collected from publicly available materials, this study does not require an ethical approval. The results of our scoping review will be disseminated through a peer-reviewed publication, targeting an audience involved in all stakeholders, e.g., medical researchers and clinicians and public health officials.

## Abbreviations

**Ad5-nCoV:** Adenovirus type 5based COVID-19 vaccine; **AMSTAR 2:** A Measurement Tool to Assess Systematic Review 2; **CONSORT:** Consolidated Standards of Reporting Trials; **COVAX:** COVID-19 Vaccine implementation Plan; **COVID-19:** Coronavirus disease 2019; **DNA:** Deoxyribonucleic acid; **JBI:** Joanna Briggs Institute; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta Analyses; **PRISMA-P:** Preferred Reporting Items for Systematic Reviews and Meta Analyses protocols; **PRISMA-ScR:** Preferred Reporting Items for Systematic Reviews and Meta Analyses Extension for Scoping Reviews; **PROSPERO:** International Prospective Register of Systematic Reviews; **RCTs:** Randomized controlled trials; **RNA:** Ribonucleic acid; **RoB 2.0:** Risk of bias 2.0; **SARS-CoV-2:** Severe acute respiratory syndrome-related coronavirus 2; **WHO:** World Health Organization.

## Declarations

## Ethics approval and consent to participate

Research ethics board approval and consent were waived, because the conduct of this research will be based on published literature.

## Consent for publication

Not applicable.

## Availability of data and materials

All data generated or analyzed during this research will be included in the following full-text of the scoping review and/or its supplementary files.

## Competing interests

The authors declare that they have no competing interests.

# Funding

None.

# Authors' contributions

Cuncun Lu developed the research questions, the rest of other authors modified and improved them. Jieyun Li, Lufang Feng, Haitong Zhao and Kehu Yang established the search strategy. Jieyun Li, Lufang Feng and Cuncun Lu drafted the protocol. Jieyun Li, Lufang Feng, Haitong Zhao, Kehu Yang and Cuncun Lu reviewed and approved the final manuscript.

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