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Side effects of COVID-19 vaccines: a systematic review and meta-analysis protocol of randomised trials

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ABSTRACT

Introduction SARS-CoV-2 is responsible for a large number of global COVID-19 cases. Strategies such as social isolation, personal hygiene and frequent hand washing have been implemented; however, a protective vaccine is required to achieve sufficient herd immunity to SARS-CoV-2 infection to ultimately control the COVID-19 pandemic. To meet the urgent need for a vaccine, a reduction in the development schedule has been proposed from 10–15 years to 1–2 years. For this reason, this systematic review and meta-analysis protocol aims to compare the side effects, safety and toxicity of COVID-19 vaccines available globally, including their combinations.

Methods and analysis We will select randomised controlled trial-type studies that evaluate the side effects of the COVID-19 vaccine. PubMed, Web of Science, Embase, CINAHL, PsycINFO, LILACS, SCOPUS, ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP), medRxiv.org, biorxiv.org, preprints. org and the Cochrane Library will be searched for eligible studies until December 2021. Three reviewers will independently screen and select studies, assess methodological quality and extract data. A meta-analysis will be performed, if possible, and the Grading of Recommendations, Assessment, Development and Evaluations summary of findings will be presented.

Ethics and dissemination This study will review published data, and thus it is unnecessary to obtain ethical approval. The findings of this systematic review will be published in a peer-reviewed journal.

PROSPERO registration number CRD42021231101.

Strengths and limitations of this study

► Four authors (KSM, APFC, ACAS, CLF) will select the articles independently using titles and abstracts.
► To the best of our knowledge, there are no existing reviews regarding the side effects of COVID-19 vaccines.
► The DerSimonian and Laird method may underestimate the true between-study variance, potentially producing overly narrow CIs for the mean effect. This fact is a limitation, so the collection of studies will be done with care and the assumptions of the analytical methods will be assessed.

INTRODUCTION

SARS-CoV-2 is responsible for a large number of global COVID-19 cases. It is a highly transmissible virus among humans that has become a significant public health issue.[1] Symptoms include fever, dry cough, fatigue, shortness of breath, chills, muscle pain, headache, gastric disorders and weight loss, often leading to death.[2]

Strategies such as social isolation, personal hygiene and frequent hand washing have been implemented; however, a protective vaccine is required to achieve sufficient herd immunity to SARS-CoV-2 infection to ultimately control the COVID-19 pandemic.[3] To meet the urgent need for a vaccine, a reduction in the development schedule has been proposed from 10–15 years to 1–2 years.[4]

SARS-CoV-2 is an RNA virus with a high mutation rate, and that on the envelope surface has three important structural proteins that can be identified: spike protein (S), envelope protein (E) and membrane protein (M). Most innovative vaccines have focused their efforts on inducing an immune response against the S protein. Attenuated virus vaccines are based on weakened microorganisms, effective in stimulating the immune system. The inactivated ones (dead microorganisms) are more stable than the attenuated ones, but they have a short duration of immunological memory that requires the association of adjuvants. mRNA vaccines are stable—and can be easily produced in large quantities. Vaccines against COVID-19 differ in composition and mechanism of action, which may be relevant for their safety and efficacy, being essential for the success and eradication of this infection.[5 6] The viral vector (mRNA) vaccine encodes full-length S protein ectodomains of SARS-CoV-2, which contains both T and B cell epitopes that can

induce cellular and humoral immune responses against viral infection.[7]

Assessing the safety, efficacy and side effects of the vaccine is urgently needed, and has been heavily scrutinised by the leading medical agencies around the world, like the Centers for Disease Control and Prevention and the Food and Drug Administration. Developing any vaccine needs to ensure that safety risks are identified and quantified against potential benefits. Among the potential risks raised in the context of COVID-19, vaccine development is the security and effectiveness of immune responses elicited by a vaccine. Here, this systematic review protocol aims to assess the side effects, safety and toxicity of vaccines against COVID-19.

OBJECTIVES

This systematic review and meta-analysis protocol aims to compare the side effects, safety and toxicity of COVID-19 vaccines available globally, including their combination.

Review question

What are the rates of adverse reactions (local and systemic) to COVID-19 vaccines?

METHODS AND ANALYSIS

The meta-analysis protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.[8 9] This protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO).

Eligibility criteria

The inclusion criteria involved: (1) randomised controlled trial (RCT)-type studies that evaluated the side effects of the COVID-19 vaccine; (2) experiments involving human beings; (3) studies evaluating the safety, immunogenicity and efficacy parameters of the vaccines; (4) studies that presented similar vaccination protocols; (5) studies published since January 2020 until December 2021; and (6) studies published in any language.

The exclusion criteria were as follows: (1) observational studies, and (2) case reports, meeting abstracts, review papers and commentaries.

Patients, intervention, comparison, outcome strategy and types of studies

► Patients: healthy adults aged 18 years or older who were HIV negative and previously SARS-CoV-2 infection free.
► Intervention: COVID-19 vaccine or a combination of vaccines against COVID-19.
► Comparator/control: placebo.
► Outcome: safety, tolerability and immunogenicity of the COVID-19 vaccine or the combination of vaccines against COVID-19.
► Types of studies: RCTs.

Information sources

The following databases will be searched: Medline/PubMed, Web of Science, Embase, CINAHL, PsycINFO, Latin American and Caribbean Health Sciences Literature (LILACS), SCOPUS, ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP), medRxiv.org, biorxiv.org, preprints.org and Cochrane Central Controlled Trials Registry. Furthermore, eligible studies may also be selected from the reference lists of retrieved articles.

Patient and public involvement

The individual patient data will not be presented. A literature search will be carried out from defined databases. No patient will be involved in the study planning and application process during neither the analysis nor the dissemination of results.

Search strategy

Our keyword search will be based on Medical Subject Headings according to the following combination: (COVID-19 OR SARS-CoV-2 OR 2019-nCoV OR coronavirus) AND (vaccines OR vaccination OR COVID-19 vaccine OR SARS-CoV-2 vaccine OR BNT162 vaccine OR mRNA-1273 vaccine OR COVID-19 aAPC vaccine OR INO-4800 vaccine OR LV-SMENP-DC COVID-19 vaccine OR Ad5-nCoV vaccine OR ChAdOx1 COVID-19 vaccine OR MNA SARS-CoV-2 S1 subunit vaccines OR PittCoVacc OR Inactivated novel coronavirus 2019-CoV vaccine Vero cells OR Inactivated Vaccines OR SARS-CoV-2 inactivated vaccines OR Viral Vaccines OR Gam-COVID-Vac vaccine OR Ad26.COV2.S vaccine OR EpiVacCorona vaccine) AND (Toxicity OR Vaccine Immunogenicity OR side effects OR adverse events) AND (randomized controlled trial OR double blind method OR clinical trial) (table 1). A list of vaccines available at WHO was also used.

Study records

Four researchers (KSM, APFC, ACAS, CLF) performed the selection of the studies of interest. Titles and abstracts will be read independently, and duplicate studies will be excluded. The same authors analysed the selected texts to assess the compliance with the inclusion criteria. A fifth reviewer, AKG, solves the discrepancies. The flow chart of this study is shown in figure 1.

Data collection process and management

A standardised data extraction form was developed and tested. Data from each included study will be extracted independently by two reviewers (ACAS and APFC), and any subsequent discrepancies will be resolved through discussion with a third reviewer (AKG). The data extracted will include information on authors, the year of publication, study location, type of study, main objectives, population, type of vaccine, follow-up of participants, rates of systemic events, gastrointestinal symptoms, injection site-related adverse effects and serious vaccine-related adverse events (table 2). Furthermore, participant characteristics

Table 1	Medline search strategy
Search items	
1	COVID-19
2	SARS-CoV-2
3	2019-nCoV
4	Coronavirus
5	Or/1–4
6	vaccines
7	vaccination
8	COVID-19 vaccine
9	SARS-CoV-2 vaccine
10	BNT162 vaccine
11	mRNA-1273 vaccine
12	COVID-19 aAPC vaccine
13	INO-4800 vaccine
14	LV-SMENP-DC COVID-19 vaccine
15	Ad5-nCoV vaccine
16	ChAdOx1 COVID-19 vaccine
17	MNA SARS-CoV-2 S1 subunit vaccines
18	PittCoVacc
19	Inactivated novel coronavirus 2019-CoV vaccine Vero cells
20	Inactivated Vaccines
21	SARS-CoV-2 inactivated vaccines
22	Viral Vaccines
23	Gam-COVID-Vac vaccine
24	Ad26.COV2.S vaccine
25	EpiVacCorona vaccine
26	Or/6–25
27	Toxicity
28	Vaccine Immunogenicity
29	side effects
30	adverse events
31	Or/27–30
32	randomized controlled trial
33	double-blind method
34	clinical trial
35	Or/32–34
36	5 AND 26 AND 31 AND 35

(eg, mean age, gender) and results for immunogenicity will be collected.

The study authors will be contacted in case of missing data and/or to resolve any uncertainties. In addition, any additional information will be recorded. All data entries will be checked twice. If we find a set of articles with similar characteristics based on the information in the data extraction table, we will perform a meta-analysis using a random-effects model. If there are data that are not clear in some articles, the corresponding author will be contacted for possible clarification.

Risk of bias in individual studies

Three authors (KSM, ACAS, APFC) will independently assess the risk of bias in the eligible studies using the Cochrane risk-of-bias tool.[10] The Risk of Bias 2 tool[11] will be used to assess the risk of bias. Bias is assessed as a judgement (high, low or unclear) for individual elements from five domains (selection, performance, attrition, reporting and others).

Data will be entered into the Review Manager software (RevMan V.5.2.3). This software allows the user to enter protocols; complete reviews; include text, characteristics of the studies, comparison tables and study data; and perform meta-analyses. For dichotomous outcomes, we extracted or calculated the OR and 95% CI for each study. In case of heterogeneity ($I^2 \geq 50\%$), the random-effects model will be used to combine the studies to calculate the OR and 95% CI using the DerSimonian-Laird algorithm.[12]

Data synthesis and analysis

Metabias

To grade the strength of evidence from the included data, we will use the Grading of Recommendations, Assessment, Development and Evaluation[13] approach. The summary of the assessment will be incorporated into broader measurements to ensure the judgement of the risk of bias, consistency, directness and precision. The quality of the evidence will be assessed based on the risk of bias, indirectness, inconsistency, imprecision and publication bias.

DISCUSSION

The COVID-19 pandemic represents one of the most significant global public health crises of this generation. Lockdown, quarantine, contact tracing and case isolation are suggested as effective interventions to control the epidemic; however, they may present different results in different contexts because of the specific features of the COVID-19. The lack of implementation of continued interventions or effective treatments further contributes to discovering and using effective and safe vaccines.[14 15]

For all these reasons, scientists worldwide entered a race to find a vaccine candidate useful in fighting the new coronavirus pandemic. Nevertheless, it is essential to note that a vaccine's production is not easy and quick. Before being released to the population, a vaccine must go through three phases of clinical trials that prove its safety and effectiveness. More volunteers are recruited at
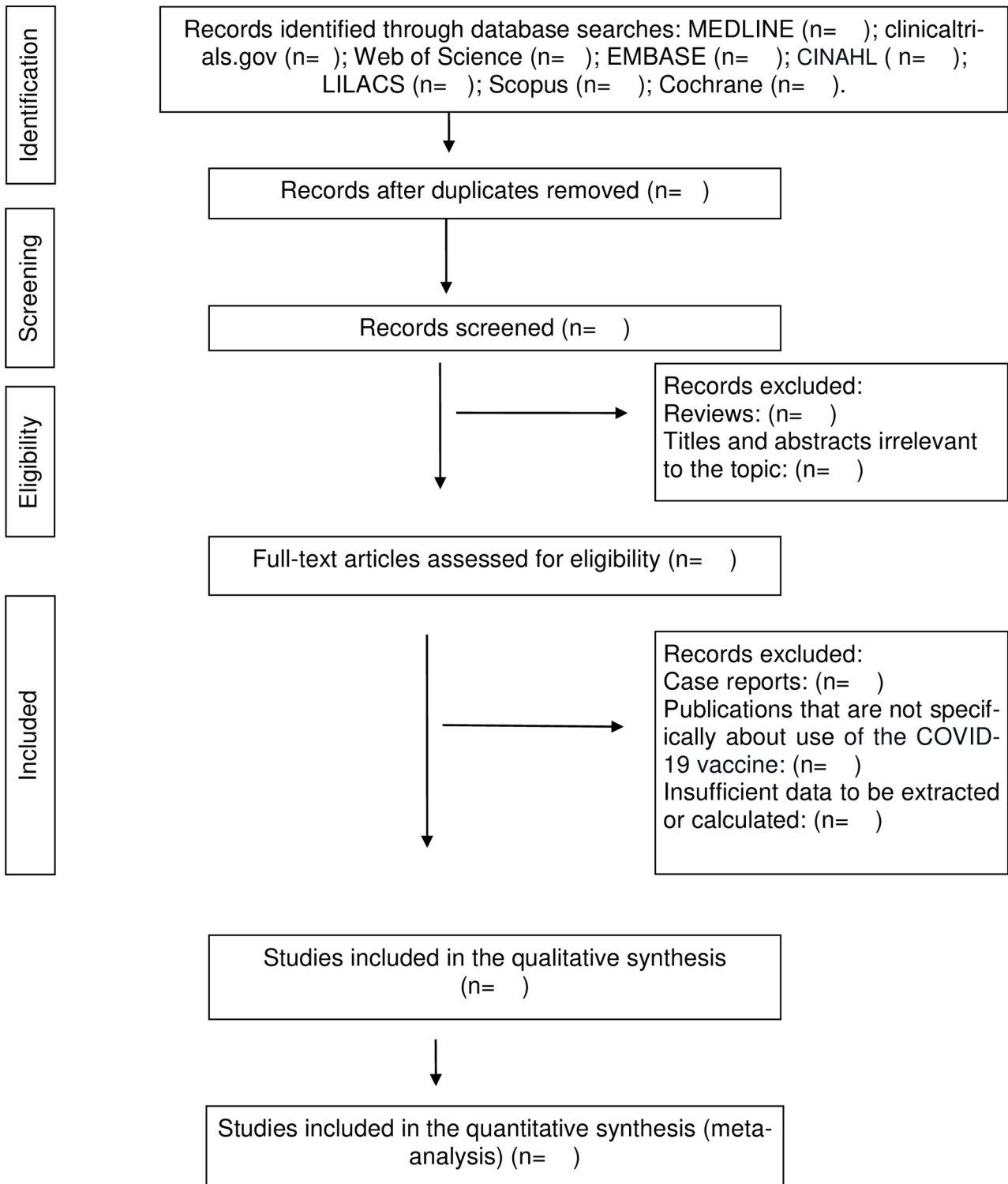
Identification

Screening

Eligibility

Included

Records identified through database searches: MEDLINE (n=   ); clinicaltrials.gov (n=   ); Web of Science (n=   ); EMBASE (n=   ); CINAHL (n=   ); LILACS (n=   ); Scopus (n=   ); Cochrane (n=   ).

Records after duplicates removed (n=   )

Records screened (n=   )

Records excluded:
Reviews: (n=   )
Titles and abstracts irrelevant to the topic: (n=   )

Full-text articles assessed for eligibility (n=   )

Records excluded:
Case reports: (n=   )
Publications that are not specifically about use of the COVID-19 vaccine: (n=   )
Insufficient data to be extracted or calculated: (n=   )

Studies included in the qualitative synthesis (n=   )

Studies included in the quantitative synthesis (meta-analysis) (n=   )

Figure 1 Flow diagram of the search for eligible studies on the side effects, safety, and toxicity of the COVID-19 vaccine: CENTRAL, Cochrane Central Register of Controlled Trials.

Figure 1   Flow diagram of the search for eligible studies on the side effects, safety and toxicity of the COVID-19 vaccine. CENTRAL, Cochrane Central Register of Controlled Trials.

Table 2	Adverse events of COVID-19 vaccines
Adverse events	
Systemic event reactions (10, 11)	Fever or hyperthermia or feverish, headaches, fatigue, vomiting, diarrhoea, muscle pain, joint pain, cough, nausea, dyspnoea, appetite impaired, dizziness, mucosal abnormality, pruritus,[27 28] hypersensitivity, syncope,[27] asthenia, rhinorrhoea, malaise, sore throat (throat irritation), pain in the oropharynx (pharyngalgia), hives, nasal congestion[29 30]
Injection site adverse reactions (10–12)	Pain, induration, redness or erythema, swelling, itch, muscular weakness[27–29]
Serious vaccine-related adverse event	Deaths, hospitalisation,[30] thrombotic complications[31 32]

each stage, and the researchers analyse the test results to ensure that a vaccine can be licensed.[16–18]

One hundred and seventy-three vaccines were in preclinical development and 64 in clinical trials until 20 January 2021. On 31 December 2020, the WHO listed the mRNA vaccine against COVID-19 for emergency use, making this Pfizer/BioNTech immuniser the first to receive WHO emergency validation from the beginning outbreak. Already, in January 2021, emergency approval was granted to nine vaccines by regulatory authorities in different parts of the world.[14 19]

With the starting vaccination, several studies were carried out to ascertain the safety of these vaccines, since they were produced in record time.[20–22] Currently, one systematic review about the thematic showed that of 11 published clinical trials of COVID-19 vaccines included in the study, adverse reactions reported were considered mild to moderate with few severe reactions which were unrelated to the test vaccine. Common adverse events were pain at the site of injection, fever, myalgia, fatigue and headache. Serious adverse events (SAE) were reported in four trials: COVID-19 Vaccine AstraZeneca (AZD1222)—168 SAEs with only three related to the vaccine; Ad26.COV2.S—four with none related to the testing vaccine; five with Comirnaty (BNT162b1) vaccine and one with Covaxin (BBV152) vaccine.[19]

One limitation about the COVID-19 vaccine safety tested until now is that clinical trials of the safety and effectiveness have had low inclusion of vulnerable groups, for example, older persons, the first population to receive the whole vaccine. That's why pharmacovigilance post-marketing is necessary to surveillance of new drugs, as a critical aspect of evaluating medicine safety and effectiveness, particularly in risk groups.

Other prevention approaches are likely to emerge in the coming months, including antiviral agents, drugs may be to decrease disease progression, monoclonal antibodies, hyperimmune globulin and convalescent titre. If proven effective, these approaches could be used in high-risk individuals, including healthcare workers, other essential workers and older adults.[23–26] It is essential to maintain protective measures such as washing hands frequently with soap and water or gel alcohol and covering the mouth with a forearm when coughing or sneezing.

For all the reasons mentioned above, this review is necessary and essential. The latter is a well-defined protocol registered with PROSPERO, well planned to include the largest possible number of vaccines, a significant number of vaccinated patients, thus providing safe and reliable results regarding the use of vaccines.

Ethics and dissemination
This study will review published data, and thus it is unnecessary to obtain ethical approval. The findings of this systematic review will be published in a peer-reviewed journal.

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