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SIDE EFFECTS OF COVID-19 VACCINES: A SYSTEMATIC REVIEW/META-ANALYSIS PROTOCOL OF RANDOMIZED TRIALS

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SIDE EFFECTS OF COVID-19 VACCINES: A SYSTEMATIC REVIEW/META-ANALYSIS PROTOCOL OF RANDOMIZED TRIALS

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ABSTRACT

Objective: This systematic review and meta-analysis protocol aims to compare the side effects, safety, and toxicity of coronavirus disease 2019 (COVID-19) vaccines available globally, including their combinations.

Materials and Methods: We will select randomized controlled trial (RCT)-type studies that evaluated the side effects of the COVID-19 vaccine. PubMed, Web of Science, Embase, CINAHAL, PsycINFO, LILACS, SCOPUS, and the Cochrane Library will be searched for eligible studies. 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 Evaluation (GRADE) 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.

Systematic review registration: CRD42021231101.

Keywords: COVID-19; SARS-Cov-2; COVID-19 vaccine; SARS-CoV-2 vaccine

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The results obtained in this systematic review will, through evidence-based medicine, indicate the rates of adverse reactions (local and systemic) of COVID-19 vaccines.
- Four authors, KSM, APFC, ACS, and 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.
- Potential limitations include a great diversity of existing vaccines, still being tested, and heterogeneity of systemic and local adverse events.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for a large number of global coronavirus disease (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].

COVID-19 vaccine formulations have different compositions, from attenuated virus vaccines to inactive virus vaccines [5]. Attenuated vaccines introduce a mild infection that resembles the actual infection, leading to a robust immune response that can last for years. This type of vaccine's main disadvantage is its potential safety problem since people with compromised immune systems can revert to a virulent strain [6]. Inactivated vaccines are relatively safer, as live pathogens are not involved, but they may be less immunogenic and often require multiple doses to establish immune memory [5].

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 affectivity 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?

MATHERIALS AND METHODS

The meta-analysis protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines [7,8]. This protocol is

registered with the International Prospective Register of Systematic Reviews (CRD42021231101).

Eligibility criteria

The inclusion criteria involved [1] randomized 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; 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: randomized controlled trials (RCT)

Information sources

The following databases will be searched: Medline/PubMed, clinicaltrials.gov, Web of Science, Embase, CINAHAL, Latin American and Caribbean Health Sciences Literature, SCOPUS, and Cochrane Central Controlled Trials Registry. Furthermore, eligible studies may also be selected from the reference lists of retrieved articles.

Search strategy

Our keyword search will be based on Medical Subject Headings (MeSH) 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) AND

(Toxicity OR Vaccine Immunogenicity OR side effects OR adverse events) AND (randomized controlled trial OR double blind method OR clinical trial) (Table 1).

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	Or/6-18
20	Toxicity
21	Vaccine Immunogenicity

22	side effects
23	adverse events
24	Or/20-24
25	randomized controlled trial
26	double-blind method
27	clinical trial
28	Or/25-28
29	5 AND 19 AND 24 AND 28

Study records

Four researchers (KSM, APFC, ACS, and 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 analyzed the selected texts to assess compliance with the inclusion criteria. A fifth reviewer, AKG, solves the discrepancies. The flowchart of this study is shown in Figure 1.

[Insert Figure 1]

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.

Data collection process and management

A standardized data extraction form was developed and tested. Data from each included study will be extracted independently by two reviewers (ACS 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 (GI) symptoms, injection site-related adverse effects, and serious vaccine-related adverse events (Table 2). Furthermore, participant characteristics (e.g., mean age, gender), and results for immunogenicity will be collected.

Table 2 Adverse events of COVID-19 vaccines

ADVERSE EVENTS	
SYSTEMIC EVENTS REACTIONS (9, 10)	Fever or hyperthermia or feverish, headaches, fatigue, vomiting, diarrhea, muscle pain, joint pain, throat pain, cough, nausea, functional gastrointestinal disorder, dyspnea, appetite impaired, dizziness, mucosal anormality, pruritus [9,10], oropharyngeal pain, hypersensitivity, syncope [10], asthenia, heartbeat, rhinorrhea, malaise, sore throat (throat irritation), pain in the oropharynx (pharyngalgia), hives, nasal congestion, sneezing, changes in laboratory variables [11], warmth [12].
INJECTION SITE ADVERSE REACTIONS (9–11)	Pain, induration, redness or erythema, swelling, itch, and muscular weakness [9–11].
SERIOUS VACCINE-RELATED ADVERSE EVENT	Deaths, hospitalisation [12].

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, and APFC, will independently assess the risk of bias in the eligible studies using the Cochrane risk-of-bias tool [13]. The Risk of Bias 2 (RoB 2) tool [14] will be used to assess the risk of bias. Bias is assessed as a judgment (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and others).

Data synthesis and analysis

Data will be entered into the Review Manager software (RevMan5.2.3). 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 (I2≥50%), the random-effects model will be used to combine the studies to calculate the OR and 95% CI, using the DerSimonian–Laird algorithm in the meta for package, which provides functions for conducting meta-analyses in R.

Meta-bias

To grade the strength of evidence from the included data, we will use the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) [15] approach. The summary of the assessment will be incorporated into broader measurements to ensure the judgment 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 [16,17].

For all these reasons, scientists worldwide entered a real race time 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 each stage, and the researchers analyze the test results to ensure that a vaccine can be licensed [19-22]. As of December 2020, more than 200 vaccine candidates for COVID-19 have been developed. Of these, at least 52 vaccine candidates are being tested in humans [18]. In December 2020, some vaccine candidates against COVID-19 received authorization for emergency use in some countries. Comprehensive studies of several vaccine candidates have reported encouraging preliminary results. On December 31, 2020, the World Health Organization (WHO) listed the

mRNA vaccine against COVID-19 for emergency use, making this Pfizer/BioNTech immunizer the first to receive WHO emergency validation from the beginning outbreak [18].

The development and approval of several safe and effective vaccines less than a year after the virus was isolated and sequenced is an outstanding scientific achievement. However, it is essential to note that the first vaccine approval does not mean that the work is done, on contrary. More vaccines are on the way that should be evaluated to ensure that enough doses are available to vaccinate everyone. Other prevention approaches are likely to emerge in the coming months, including monoclonal antibodies, hyper-immune globulin, and convalescent titer. If proven effective, these approaches could be used in high-risk individuals, including health care workers, other essential workers, and older adults [23]. It is also 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.

In this context, in a previous search in the databases, we can see that there are few published studies on this topic, and the only systematic review [24] found is still in the pre-print format and presents limitations in current studies, such as the short follow-up time and small size of subjects. Furthermore, this pre-print [24] has some weaknesses, such as the lack of registration in Prospero; the small number of studies included a small number of patients involved, taking into account the beginning of the vaccine use and the speed at which the systematic review was written. Thus, it is expected that some questions will remain unclear.

For this reason, 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.

CONCLUSION

During the COVID-19 pandemic, humanity has experienced the most severe health crisis in recent years. So far, no vaccine has been considered safe and effective for use in the population. The study of the efficacy and safety of these vaccines is of utter importance to control this epidemic plaguing the entire world.

Contributors

KSM, ACS, and APFC contributed to the design of this review. KSM and ACS drafted the protocol manuscript, and APFC and AKG revised it. KSM, AKG, and APFC developed the search strategies, and KSM, CLF, and ACAS will implement them. KSM, CLF, ACS, and APFC will track potential studies, extract data, and assess quality. In cases of disagreement between the data extractors, AKG will advise on the methodology and will work as a referee. KSM will complete the data synthesis. All authors will approve the final version for publication.

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Competing interests

None declared.

Patient and public involvement statement

Patients were not involved in the development of this protocol.

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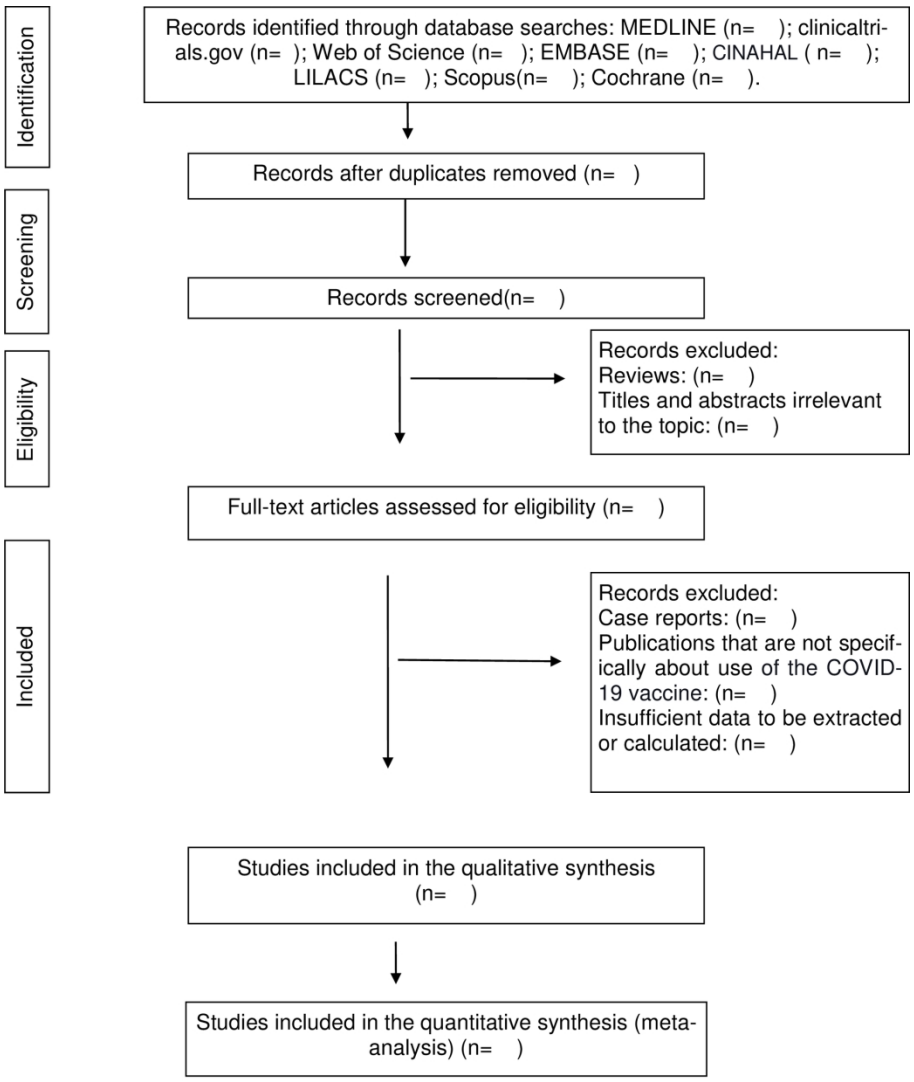

Figure 1 Flow diagram of the search for eligible studies on the side effects, safety, and toxicity of the COVID-19 vaccine: CENTRAL, Cochrane Central Register of Controlled Trials.

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168x222mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	X
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	X
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	X
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	X
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	X
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	X
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	X
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	X
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	X
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	X
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	X
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	X
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	X
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	X
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	X
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	X
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	X

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SIDE EFFECTS OF COVID-19 VACCINES: A SYSTEMATIC REVIEW/META-ANALYSIS PROTOCOL OF RANDOMIZED TRIALS

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ABSTRACT

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for a large number of global coronavirus disease 2019 (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 randomized controlled trial (RCT)-type studies that evaluate the side effects of the COVID-19 vaccine. PubMed, Web of Science, Embase, CINAHAL, 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 Evaluation (GRADE) 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.

Systematic review registration: CRD42021231101.

Keywords: COVID-19; SARS-Cov-2; COVID-19 vaccine; SARS-CoV-2 vaccine

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The results obtained in this systematic review will, through evidence-based medicine, indicate the rates of adverse reactions (local and systemic) of COVID-19 vaccines.
- Four authors, KSM, APFC, ACAS, and 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.
- Potential limitations include a great diversity of existing vaccines, still being tested, and heterogeneity of systemic and local adverse events.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for a large number of global coronavirus disease (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-CoV2 is an RNA virus with a high mutation rate, 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 Spike protein. Altogether more than 40 vaccines are now under clinical evaluation, ten of them are in Phase III clinical trials, three of them have closed Phase III with positive results. 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 scrutinized by leading medical agencies around the world, like the Centers for Disease Control and Prevention (CDC) and Food & Drug Administration (FDA). 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 Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines [8, 9]. This protocol is registered with the International Prospective Register of Systematic Reviews (CRD42021231101).

Eligibility criteria

The inclusion criteria involved (1) randomized 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: randomized controlled trials (RCT)

Information sources

The following databases will be searched: Medline/PubMed, Web of Science, Embase, CINAHAL, 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, application process during neither the analysis nor dissemination of results.

Search strategy

Our keyword search will be based on Medical Subject Headings (MeSH) 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.

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

Study records

Four researchers (KSM, APFC, ACAS, and 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 analyzed the selected texts to assess compliance with the inclusion criteria. A fifth reviewer, AKG, solves the discrepancies. The flowchart of this study is shown in Figure 1.

[Insert Figure 1]

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.

Data collection process and management

A standardized 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 (GI) symptoms, injection site-related adverse effects, and serious vaccine-related adverse events (Table 2). Furthermore, participant characteristics (e.g., mean age, gender), and results for immunogenicity will be collected.

Table 2 Adverse events of COVID-19 vaccines

Adverse Events	
Systemic events reactions (10, 11)	Fever or hyperthermia or feverish, headaches, fatigue, vomiting, diarrhea, muscle pain, joint pain, cough, nausea, dyspnea, appetite impaired, dizziness, mucosal anormality, pruritus [10, 11], hypersensitivity, syncope [10], asthenia, rhinorrhea, malaise, sore throat (throat irritation), pain in the oropharynx (pharyngalgia), hives, nasal congestion [12, 13].
Injection site adverse reactions (10-12)	Pain, induration, redness or erythema, swelling, itch, and muscular weakness [10-12].
Serious vaccine-related adverse event	Deaths, hospitalisation [13], Thrombotic complications [14, 15].

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 is data that is not clear in some articles, the corresponding author will be contacted for possible clarification.

Risk of bias in individual studies

Three authors, KSM, ACAS, and APFC, will independently assess the risk of bias in the eligible studies using the Cochrane risk-of-bias tool [16]. The Risk of Bias 2 (RoB 2) tool [17] will be used to assess the risk of bias. Bias is assessed as a judgment (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and others).

Data synthesis and analysis

Data will be entered into the Review Manager software (RevMan5.2.3). 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 (I2≥50%), the random-effects model will be used to combine the studies to calculate the OR and 95% CI, using the DerSimonian–Laird algorithm.

Meta-bias

To grade the strength of evidence from the included data, we will use the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) [18] approach. The summary of the assessment will be incorporated into broader measurements to ensure the judgment 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 [19,20].

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 each stage, and the researchers analyze the test results to ensure that a vaccine can be licensed [21-23].

One hundred seventy-three vaccines were in preclinical development and 64 in clinical trials until January 20th, 2021. On December 31, 2020, the World Health Organization (WHO) listed the mRNA vaccine against COVID-19 for emergency use, making this Pfizer/BioNTech immunizer 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 [19, 24].

With the starting vaccination, several studies were carried out to ascertain the safety of these vaccines, since they were produced in record time [25-27]. Currently, one systematic review about the thematic showed that of eleven published clinical trials of COVID-19 vaccines included in 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 were reported in four trials: COVID-19 Vaccine AstraZeneca (AZD1222)—168 SAE with only three related to the vaccine; Ad26.COV2.S- fou with none related to the testing vaccine; five with Comirnaty (BNT162b1) and one with Covaxin (BBV152) vaccine [24].

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 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 monoclonal antibodies, hyper-immune globulin, and convalescent titer. If proven effective, these approaches could be used in high-risk individuals, including health care workers, other essential workers, and older adults [28,29]. 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.

CONCLUSION

During the COVID-19 pandemic, humanity has experienced the most severe health crisis in recent years. It's important to remember that, although the COVID-19 vaccines are being widely used a lot places the world, the Emergency Use Approval is different from marketing approval, and although the clinical trials demonstrated good results until now, the study of the efficacy and safety of these vaccines, included safety data from larger sample size and of longer duration, the is extremely important for user security of COVID-19 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.

Contributors

KSM, ACAS, and APFC contributed to the design of this review. KSM and ACAS drafted the protocol manuscript, and APFC and AKG revised it. KSM, AKG, and APFC developed the search strategies, and KSM, CLF, and ACAS will implement them. KSM, CLF, ACAS, and APFC will track potential studies, extract data, and assess quality. In cases of disagreement between the data extractors, AKG will advise on the methodology and will work as a referee. KSM will complete the data synthesis. All authors will approve the final version for publication.

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Competing interests

None declared.

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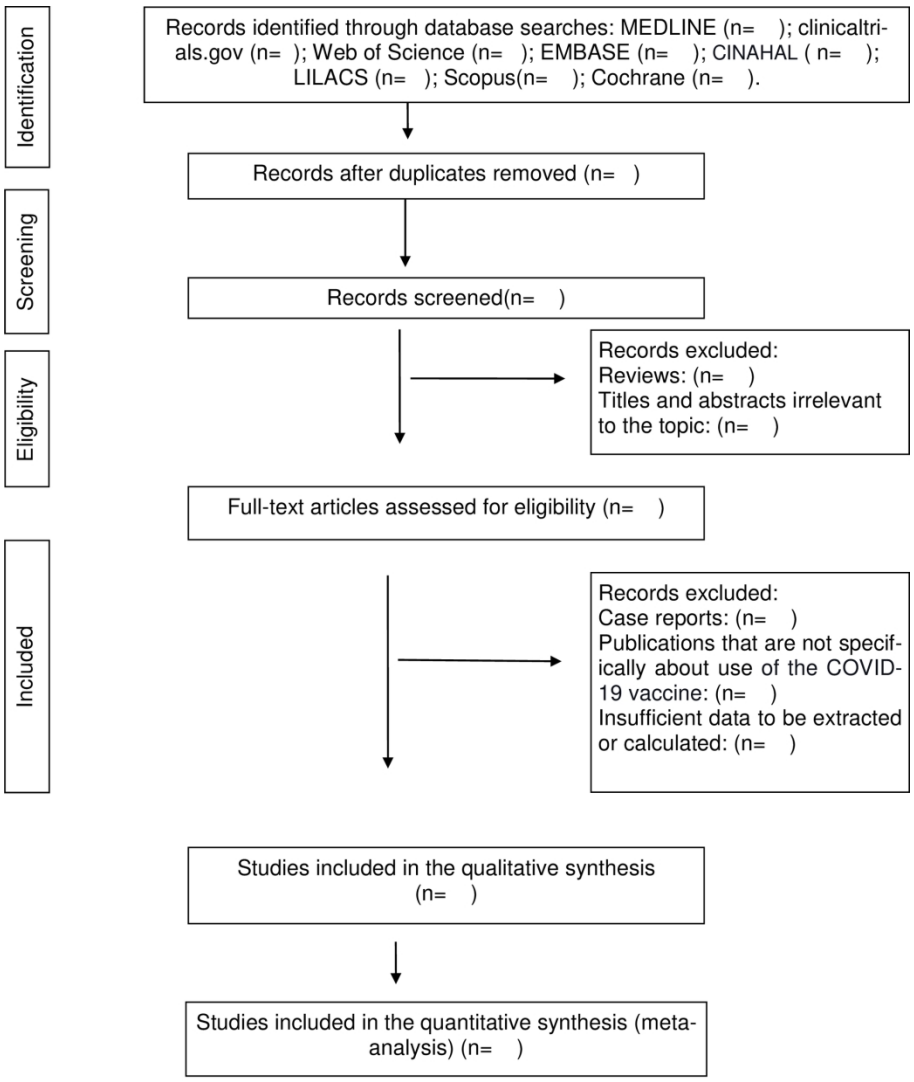

Figure 1 Flow diagram of the search for eligible studies on the side effects, safety, and toxicity of the COVID-19 vaccine: CENTRAL, Cochrane Central Register of Controlled Trials.

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.

168x222mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	01
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	02
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	01
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	01
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	x
Sponsor	5b	Provide name for the review funder and/or sponsor	x
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	03
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	04
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	05
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	05

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	06
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	08
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	08
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	09
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	09
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	09
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	09
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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SIDE EFFECTS OF COVID-19 VACCINES: A SYSTEMATIC REVIEW/META-ANALYSIS PROTOCOL OF RANDOMIZED TRIALS

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SIDE EFFECTS OF COVID-19 VACCINES: A SYSTEMATIC REVIEW/META-ANALYSIS PROTOCOL OF RANDOMIZED TRIALS

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ABSTRACT

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for a large number of global coronavirus disease 2019 (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 randomized controlled trial (RCT)-type studies that evaluate the side effects of the COVID-19 vaccine. PubMed, Web of Science, Embase, CINAHAL, 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 Evaluation (GRADE) 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.

Systematic review registration: CRD42021231101.

Keywords: COVID-19; SARS-Cov-2; COVID-19 vaccine; SARS-CoV-2 vaccine

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Four authors, KSM, APFC, ACAS, and 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 (1986) (DL) method may underestimate the true between-study variance, potentially producing overly narrow confidence intervals (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

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for a large number of global coronavirus disease (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-CoV2 is an RNA virus with a high mutation rate, 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 Spike 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 scrutinized by leading medical agencies around the world, like the Centers for Disease Control and Prevention (CDC) and Food & Drug Administration (FDA). 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 Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines [8, 9]. This protocol is registered with the International Prospective Register of Systematic Reviews (CRD42021231101).

Eligibility criteria

The inclusion criteria involved (1) randomized 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: randomized controlled trials (RCT)

Information sources

The following databases will be searched: Medline/PubMed, Web of Science, Embase, CINAHAL, 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, application process during neither the analysis nor dissemination of results.

Search strategy

Our keyword search will be based on Medical Subject Headings (MeSH) 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.

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

Study records

Four researchers (KSM, APFC, ACAS, and 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 analyzed the selected texts to assess compliance with the inclusion criteria. A fifth reviewer, AKG, solves the discrepancies. The flowchart of this study is shown in Figure 1.

[Insert Figure 1]

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.

Data collection process and management

A standardized 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 (GI) symptoms, injection site-related adverse effects, and serious vaccine-related adverse events (Table 2). Furthermore, participant characteristics (e.g., mean age, gender), and results for immunogenicity will be collected.

Table 2 Adverse events of COVID-19 vaccines

Adverse Events	
Systemic events reactions (10, 11)	Fever or hyperthermia or feverish, headaches, fatigue, vomiting, diarrhea, muscle pain, joint pain, cough, nausea, dyspnea, appetite impaired, dizziness, mucosal anormality, pruritus [10, 11], hypersensitivity, syncope [10], asthenia, rhinorrhea, malaise, sore throat (throat irritation), pain in the oropharynx (pharyngalgia), hives, nasal congestion [12, 13].
Injection site adverse reactions (10-12)	Pain, induration, redness or erythema, swelling, itch, and muscular weakness [10-12].
Serious vaccine-related adverse event	Deaths, hospitalisation [13], Thrombotic complications [14, 15].

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 is data that is not clear in some articles, the corresponding author will be contacted for possible clarification.

Risk of bias in individual studies

Three authors, KSM, ACAS, and APFC, will independently assess the risk of bias in the eligible studies using the Cochrane risk-of-bias tool [16]. The Risk of Bias 2 (RoB 2) tool [17] will be used to assess the risk of bias. Bias is assessed as a judgment (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and others).

Data synthesis and analysis

Data will be entered into the Review Manager software (RevMan5.2.3). 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 (I2≥50%), the random-effects model will be used to combine the studies to calculate the OR and 95% CI, using the DerSimonian–Laird algorithm.

Meta-bias

To grade the strength of evidence from the included data, we will use the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) [18] approach. The summary of the assessment will be incorporated into broader measurements to ensure the judgment 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 [19,20].

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 each stage, and the researchers analyze the test results to ensure that a vaccine can be licensed [21-23].

One hundred seventy-three vaccines were in preclinical development and 64 in clinical trials until January 20th, 2021. On December 31, 2020, the World Health Organization (WHO) listed the mRNA vaccine against COVID-19 for emergency use, making this Pfizer/BioNTech immunizer 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 [19, 24].

With the starting vaccination, several studies were carried out to ascertain the safety of these vaccines, since they were produced in record time [25-27]. Currently, one systematic review about the thematic showed that of eleven published clinical trials of COVID-19 vaccines included in 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 were reported in four trials: COVID-19 Vaccine AstraZeneca (AZD1222)— 168 SAE with only three related to the vaccine; Ad26.COV2.S- fou with none related to the testing vaccine; five with Comirnaty (BNT162b1) and one with Covaxin (BBV152) vaccine [24].

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 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 anti-viral agents, drugs may be to decrease disease progression, monoclonal antibodies, hyper-immune globulin, and convalescent titer If proven effective, these approaches could be used in high-risk individuals, including health care workers, other essential workers, and older adults [28 - 31]. 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.

Contributors

KSM, ACAS, and APFC contributed to the design of this review. KSM and ACAS drafted the protocol manuscript, and APFC and AKG revised it. KSM, AKG, and APFC developed the search strategies, and KSM, CLF, and ACAS will implement them. KSM, CLF, ACAS, and APFC will track potential studies, extract data, and assess quality. In cases of disagreement between the data extractors, AKG will advise on the methodology and will work as a referee. KSM will complete the data synthesis. All authors will approve the final version for publication.

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Competing interests

None declared.

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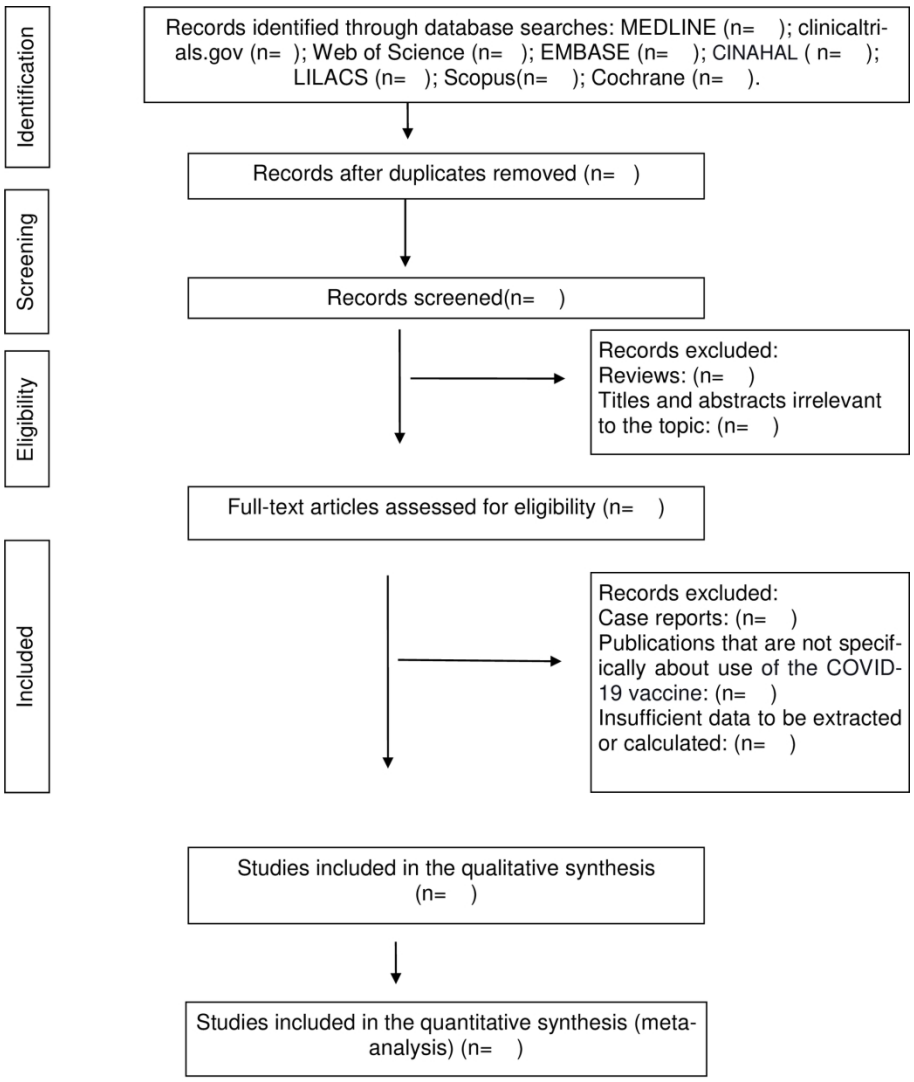

Figure 1 Flow diagram of the search for eligible studies on the side effects, safety, and toxicity of the COVID-19 vaccine: CENTRAL, Cochrane Central Register of Controlled Trials.

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.

168x222mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	01
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	02
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	01
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	01
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	x
Sponsor	5b	Provide name for the review funder and/or sponsor	x
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	-
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	03
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	04
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	05
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	05

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	06
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	08
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	08
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	09
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	09
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	09
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	09
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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