

Vaccines Developed against COVID-19: a narrative review

Laura Faustino Gonçalves¹ , Janaina Viana Stolz² , Patrícia Haas^{1*} 

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic calls for a quick evaluation of the multiple competence approaches to obtain protective immunity and safety, thus diminishing the undesired immune potentiation, which plays an important role in the pathogenesis of the virus^{1,2}.

The clinical manifestations change the disease from mild to serious, possibly leading to death. Other symptoms include rhinorrhea, productive expectoration, headache, and sore throat. Also, some people can have rare symptoms, such as gastrointestinal ones, including diarrhea and vomit. Other symptoms may also manifest themselves, such as hyposmia (impaired smelling capacity) and hypogeusia (impaired taste capacity)³.

Hence, pharmaceutical companies and research institutions have been competing to develop severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines—from conventional viral ones, based on proteins, to the most advanced, based on the DNA and mRNA¹. Each current vaccine strategy has different advantages and disadvantages. Therefore, it is essential to quickly advance various strategies and then evaluate their safety and effectiveness. One of the main obstacles in the initial development of the coronavirus vaccine against SARS was the discovery that whole-virus or protein vaccines increased infectiousness⁴.

Given the above, the main and guiding objective of this research was to verify the possible compositions of the vaccines being developed and produced against COVID-19, aiming to answer the following research question: What are the possible vaccine compositions being produced against COVID-19?

METHODS

Protocol and registry

This narrative review complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations⁵, aiming at the most rigorous scientific evidence protocol criteria. Two independent researchers searched for the scientific articles in the MEDLINE (PubMed), LILACS, SciELO, Scopus, Web of Science, and BIREME databases, without restriction of language and place of publication, encompassing the period from 2015–2020. The research was structured and organized in the PICOS framework, an acronym that stands for target population of interest or health problem (P) correspond to humans of both sexes with no age restriction; intervention (I): vaccine; comparison (C), composition; outcome (O): COVID-19; cross-sectional studies (S), observational studies, case reports, case-control studies, controlled clinical trials, and randomized controlled (Table 1).

Research strategy

The descriptors were chosen from the dictionary in Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH). The search in the other databases was adjusted based on the descriptors. At first, the following Boolean operators were proposed for the search: (((COVID* vaccine* hesitancy[Title/Abstract]) OR (COVID* vaccine acceptance[Title/Abstract])) OR (COVID* vaccin* hesitanc*[Title/Abstract])) OR (COVID* intention to vaccin* [Title/Abstract]) OR (COVID* vaccin* accept*[Title/Abstract]) AND (2020:2020[pdat]). The

¹Universidade Federal de Santa Catarina – Florianópolis (SC), Brazil.

²Universidade Federal de Pelotas – Pelotas (RS), Brazil.

*Corresponding author: patricia.haas@ufsc.br

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search was concentrated in January 2021. To complement it and avoid the risk of bias, the gray literature was searched in Google Scholar.

Eligibility criteria

The studies were included with no restriction of language, date, and place of publication. The inclusion and exclusion criteria, developed specifically for this research, are shown in Table 2. The study scored 12 in the modified protocol by Pithon et al.⁶, which evaluates their quality.

Risk of bias

The quality of the methods used in this study was independently evaluated by the reviewer (PH), following the PRISMA recommendation⁵. The evaluation gave priority to the clearly described information. In this stage, the review was blind, masking the names of authors and journals to avoid any potential bias and conflict of interest.

Exclusion criteria

Studies published as letters to the editor, guidelines, literature reviews, systematic reviews, meta-analyses, and abstracts were excluded. Studies with absent or unclear descriptions or not fully available were also excluded (Table 2).

Data analysis

The data were extracted for the study eligibility process using an appropriate spreadsheet for narrative reviews, developed by two researchers in Excel[®]. The extracted data were entered in the spreadsheet by one of the researchers and then checked by another one. The studies were selected at first by their title; then, the abstracts were analyzed, and only the potentially eligible ones were selected. Based on their abstracts, the articles were selected to be fully read.

Study selection process

Those whose title was within the context, but the abstract was unavailable, were also retrieved and analyzed in full. Studies not within the context, case reports, letters to the editor and/or editorials, literature reviews, indexes, abstracts, and studies on animals, were excluded.

Collected data

After the screening, the text of the selected article was reviewed, and its data were extracted in a standard manner by an author (LFG) supervised by PH. The year of publication, place of the research, language of publication, type of study, sample, method, result, and conclusion of the study were identified.

Clinical result

The clinical result of interest consisted of investigating possible compositions of the vaccines against COVID-19 that are being developed and produced. Those that did not follow the predefined approach were not included in the sample of the narrative review.

Table 1. Description of the PICOS components.

Acronym	Definition
P	Humans of both sexes without age restriction
I	Vaccine
C	Composition
O	COVID-19
S	Cross-sectional study Observational study Case reports Case-control studies Clinical trials Cohort studies

Source: Developed by the authors.

Table 2. Summary of the inclusion/exclusion criteria.

Inclusion criteria	
Design	Case reports Case and control studies Controlled clinical trials Cohort studies Screening studies Observational studies
Place	No restriction
Language	No restriction
Exclusion criteria	
Design	Letters to the editor Guidelines Literature reviews Systematic reviews Meta-analyses
Studies	Unclear, poorly described, or inadequate studies
Form of publication	Abstract alone

Source: Developed by the authors.

RESULTS

Initially, 56 articles were selected, narrowed down to 53 after excluding the repeated ones; then, the titles and abstracts were analyzed, and 51 papers were excluded for not being in the scope proposed for the research. Hence, two articles^{7,8} were included in the final analysis of the present research (Figure 1). The selected article was designed as a randomized controlled study.

The databases were consulted based on the selected descriptors, obtaining the results presented in Table 3.

The main characteristics of the research selected for this study—such as the number of recruited patients, methods, results, and conclusion—are shown in Table 4^{7,8}.

Study design

The first study⁷ was carried out between April 23 and November 4, 2020, with 23,848 recruited participants vaccinated— $n=1,077$ in COV001 (the United Kingdom), $n=10,673$ in COV002 (the United Kingdom), $n=10,002$ in COV003 (Brazil), and $n=2,096$ in COV005 (South Africa). Approximately, 11,636 participants in COV002 and COV003 met the inclusion criteria for the primary analysis, of whom 5,807 received two doses of ChAdOx1 nCoV-19 and 5,829 received two doses of the control product. Most of the participants in COV002 and COV003 included in the primary effectiveness analysis were 18–55 years old [$n=6,542$ (86.7%) of the 7,548 in the United Kingdom and 3,676 (89.9%) of the 4,088 in Brazil]. Participants 56 years old or more were recruited later and contributed with 12.2% of the total in the current analysis [$n=1,006$ (13.3%) in the United Kingdom and 412 (10.1%) in Brazil].

In the second research⁸, conducted from April 23 to May 21, 2020, approximately, 1,077 participants were included and vaccinated with either ChAdOx1 nCoV-19 ($n=543$) or MenACWY ($n=534$). The mean age of the participants was 35 years.

Vaccine and effectiveness

One participant had an asymptomatic infection 3 weeks after the first dose of ChAdOx1 nCoV-19. Another two participants in the control group had symptomatic infections 8 weeks and 21 weeks, respectively, after the initial sample collection. There were 131 symptomatic cases of COVID-19 eligible to be included in the primary effectiveness analysis more than 14 days after the second dose of the vaccine⁷.

There were 30 (0.5%) cases out of the 5,807 participants in the vaccine group and 101 (1.7%) cases out of the 5,829 participants in the control group, resulting in a 70.4% vaccine effectiveness. In participants who received two doses, the vaccine

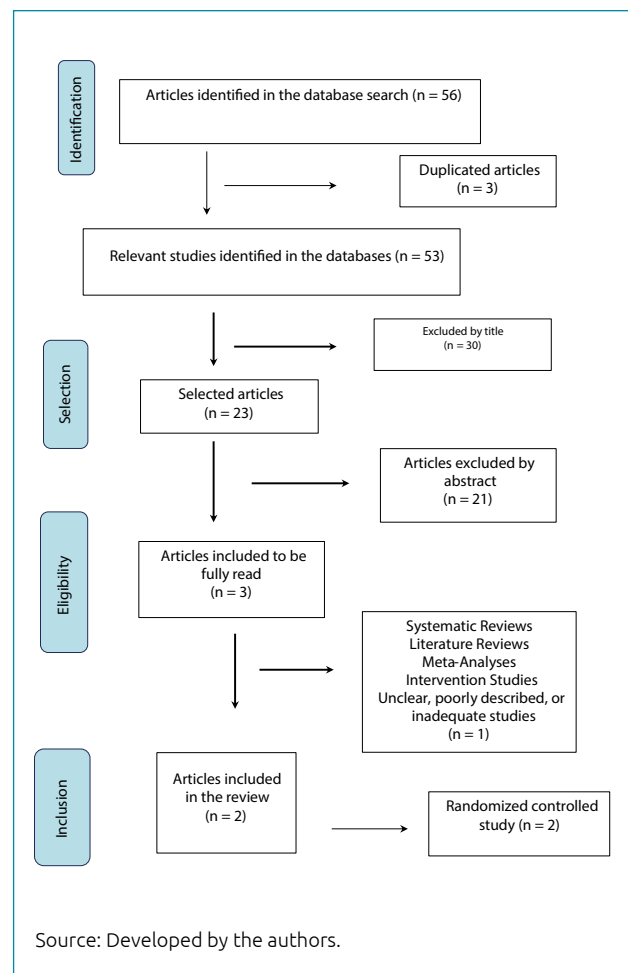


Figure 1. Flowchart of the search for and analysis of articles.

effectiveness was 62.1%; whereas, in those who received the first dose with a decreased amount of the vaccine and later a standard dose, the effectiveness was 90%⁷.

Two doses of the vaccine are obtained from the United Kingdom and Brazil, and the vaccine effectiveness was similar when analyzed in subgroups according to the duration between vaccines—53.4% in participants with an interval shorter than 6 weeks between the doses and 65.4% in participants with an interval of at least 6 weeks. For the secondary analysis of cases that occurred more than 21 days after the first standard dose in participants who received only standard doses, 192 cases were included with a 64.1% vaccine effectiveness⁷.

Vaccine and adverse events

More than 21 days after the first dose, 10 participants were hospitalized due to COVID-19, two of them with severe COVID-19, one of which was fatal. All these 10 cases were in the control group. Severe adverse events occurred in

Table 3. Classification of the references obtained from the PubMed, SciELO, LILACS, Web of Science, and Scopus databases.

Descriptors	Total number of articles	Number of excluded references	Reason for excluding	Number of selected articles	Database
(covid-19) and (SARS-CoV-2) and (vaccines) and (CITE-seq) and (immune response) and (infection) and (multi-omics) and (proteomics) or (single-cell RNA-seq) or (single-cell TCR-seq) or (single-cell) or (secretome)	0	–	–	–	SciELO
(covid-19) and (SARS-CoV-2) and (vaccines) and (CITE-seq) and (immune response) and (infection) and (multi-omics) and (proteomics) or (single-cell RNA-seq) or (single-cell TCR-seq) or (single-cell) or (secretome)	0	–	–	–	LILACS
(covid-19) and (SARS-CoV-2) and (vaccines) and (CITE-seq) and (immune response) and (infection) and (multi-omics) and (proteomics) or (single-cell RNA-seq) or (single-cell TCR-seq) or (single-cell) or (secretome)	0	–	–	–	Web of Science
(covid-19) and (SARS-CoV-2) and (vaccines) and (CITE-seq) and (immune response) and (infection) and (multi-omics) and (proteomics) or (single-cell RNA-seq) or (single-cell TCR-seq) or (single-cell) or (secretome)	0	–	–	–	Scopus
(covid-19) and (SARS-CoV-2) and (vaccines) and (CITE-seq) and (immune response) and (infection) and (multi-omics) and (proteomics) or (single-cell RNA-seq) or (single-cell TCR-seq) or (single-cell) or (secretome)	0	–	–	–	BIREME
(covid-19) and (SARS-CoV-2) and (vaccines) and (CITE-seq) and (immune response) and (infection) and (multi-omics) and (proteomics) or (single-cell RNA-seq) or (single-cell TCR-seq) or (single-cell) or (secretome)	56	53	Excluded by title (30); excluded by abstract (21); duplicated (3)	3	PubMed
Total	56	54		2	PubMed

Source: Developed by the authors.

168 participants, of which 79 received ChAdOx1 nCoV-19, while 89 received MenACWY. There were 175 events (84 in the ChAdOx1 nCoV-19 group and 91 in the control group), of which 3 were considered possibly related to the experimental or control vaccine⁷. Unsolicited adverse events in the 28 days after the vaccination considered possibly, probably, or definitely related to the ChAdOx1 nCoV-19 were predominantly mild and moderate and solved during follow-up⁸.

Vaccine and post-vaccination effects

Approximately 56 participants in the ChAdOx1 nCoV-19 group and 57 in the MenACWY group received prophylactic paracetamol. Of those who did not receive prophylactic paracetamol, 328 (67%) out of the 487 participants in the ChAdOx1 nCoV-19 group and 180 (38%) out of the 477 participants in the MenACWY group reported pain after the vaccination,

mostly in mild-to-moderate intensity. With the prophylactic paracetamol, the pain was reported in fewer participants—28 (50%) in the ChAdOx1 nCoV-19 group and 18 (32%) in the MenACWY group⁸.

Fatigue and headache were the most reported systemic reactions. Fatigue was reported in the ChAdOx1 nCoV-19 group by 340 (70%) participants without paracetamol and 40 (71%) with paracetamol, and in the MenACWY group by 227 (48%) participants without paracetamol and 26 (46%) with paracetamol. Headaches were reported in the ChAdOx1 nCoV-19 group by 331 (68%) participants without paracetamol and 34 (61%) with paracetamol, and in the MenACWY group by 195 (41%) participants without paracetamol and 21 (37%) participants with paracetamol. Other systemic adverse reactions were common in the ChAdOx1 nCoV-19 group, such as muscle pain [294 (60%) participants without paracetamol and 27 (48%) with paracetamol], malaise [296 (61%) and 27

Table 4. Summary of the included articles

Author/ year/ place of publication	Objective	n	Method	Results	Conclusion
Voysey et al., 2020 ⁷	To evaluate the safety and effectiveness of vaccine ChAdOx1 nCoV-19 in a combined interim analysis of four trials.	11,636	This analysis includes data of four ongoing blind randomized controlled studies, conducted in the United Kingdom, Brazil, and South Africa. The participants in the ChAdOx1 nCoV-19 group received two doses containing 5×10^{10} viral particles (standard dose); a subgroup in the United Kingdom study received half a dose as the first one, with a decreased amount, and a standard dose as the second one. The participants were analyzed according to the treatment received. The data cutoff date was November 4, 2020.	In participants that received two standard doses, the vaccine effectiveness was 62.1% in the ChAdOx1 nCoV-19 group, and in participants that received a decreased dose followed by a standard dose, the effectiveness was 90.0%. The general vaccine effectiveness in both groups was 70.4%. Twenty-one days after the first dose, there were 10 cases of hospitalization due to COVID-19—two classified as severe COVID-19, one of whom died. Three events were classified as possibly related to a vaccine.	The ChAdOx1 nCoV-19 has an acceptable safety profile and was considered effective against symptomatic COVID-19 in this provisional analysis of ongoing clinical trials.
Falegatti et al., 2020 ⁸	To evaluate the safety, reactogenicity, and immunogenicity of a vector coronavirus vaccine expressing the spike protein of SARS-CoV-2.	1,077	The co-primary outcomes evaluate its effectiveness (measured by virologically confirmed symptomatic COVID-19 cases) and safety (measured by the occurrence of severe adverse events). The analyses were conducted with group allocation in participants that received the vaccine. The safety was evaluated throughout 28 days after the vaccination.	Local and systemic reactions were more common in the ChAdOx1 nCoV-19 group (including pain, feverishness, chills, muscle pain, headaches, and malaise), many of which were diminished with prophylactic paracetamol. There were no severe adverse events related to the ChAdOx1 nCoV-19. After one booster dose, all the participants had neutralizing activity.	The ChAdOx1 nCoV-19 revealed an acceptable safety profile and antibody response. These results, along with the induced humoral and cellular immune responses, support the large-scale evaluation of this candidate vaccine in an ongoing phase 3 program.

(48%), chills [272 (56%) and 15 (27%)]; and feverishness [250 (51%) and 20 (36%)]⁸.

In the ChAdOx1 nCoV-19 group, 87 (18%) participants without paracetamol and 9 (16%) with paracetamol reported a temperature of at least 38°C, while 8 (2%) patients without paracetamol had a temperature of at least 39°C. The severity and intensity of local and systemic reactions were greater in the first post-vaccination day. The adjusted analysis of the effects of prophylactic paracetamol on the adverse reactions of any severity on the first two days of

post-vaccination with ChAdOx1 nCoV-19 revealed a significant decrease in pain, feverishness, chills, muscle pain, headache, and malaise⁸.

DISCUSSION

Due to the quick worldwide dissemination of SARS-CoV-2 infection and the high mortality rate, the development of a vaccine is an urgent commitment of public health, as the vaccination can restrain the propagation of COVID-19 and

reduce mortality. Intense research and vaccine development are currently underway, especially in China, Russia, the United Kingdom, the United States, besides other participating countries⁹.

Collaborative efforts are taking place to ensure unprecedented large-scale and quick production, which is necessary to immunize billions of people. It is also essential that the implementation be equitable all over the world. The different types of vaccines employ a variety of strategies (vector, DNA, mRNA, inactivated, and so on). Currently, the objective is to prove that they are safe and immunogenic in humans (studies in phases 1/2), advancing to phases 2 and 3 to demonstrate their effectiveness and collect comprehensive data on safety¹⁰. The first stage in vaccine development is the preclinical one, to establish its safety profile. The last phase in pharmacovigilance monitors the adverse event of the vaccine. This phase involves strict monitoring of the vaccines to detect, analyze, understand, prevent, and communicate any adverse events after immunization, or any other aspects related to the vaccination or immunization¹¹.

In one of the studies⁸, severe adverse events occurred in 168 participants, of which 79 had received ChAdOx1 nCoV-19 and 89 had received MenACWY. In the other study⁷, there were 175 events (84 in the ChAdOx1 nCoV-19 group and 91 in the control group), 3 of which were considered possibly related to the experimental or control vaccine. Unsolicited adverse events in the 28 days after the vaccination considered possibly, probably, or definitely related to the ChAdOx1 nCoV-19 were predominantly mild, moderate, and solved during follow-up. Other adverse systemic reactions were common in the ChAdOx1 nCoV-19 group, such as muscle pain, malaise, chills, and feverishness⁸.

There are still many unanswered questions that need to be clarified regarding SARS-CoV-2 to elucidate how the presence of antibodies will affect the clinical course and

severity of the disease. It needs to be found whether the infection will protect from future ones, and if so, for how long the protection will last and what are the correlations of this protection³. The authors of this study⁷ point out approximately 30 (0.5%) cases out of the 5,807 participants in the vaccine group and 101 (1.7%) cases out of the 5,829 participants in the control group, resulting in a 70.4% vaccine effectiveness. In participants who received two doses, the vaccine effectiveness was 62.1%, while in those who received the first dose with a decreased amount of the vaccine and later a standard dose, the effectiveness was 90%. However, the usefulness of the COVID-19 vaccination campaigns does not depend only on the vaccine effectiveness and safety¹².

CONCLUSIONS

Such a need is grounded on scientific knowledge, which makes it easier to develop an ideal COVID-19 vaccine in a short time, using new ways to facilitate its development, testing, and large-scale production. However, the challenge to researchers and health professionals consists of validating, confirming, and increasing the effectiveness of the vaccine. It will be essential to identify the vaccine components that induce protective immunity to protect the vulnerable population. Hence, the studies included in this review demonstrate that the developed and applied vaccines had significant results regarding their effectiveness and protection against COVID-19.

AUTHORS' CONTRIBUTIONS

LFG: Formal analysis, Investigation, Methodology. **PH:** Conceptualization, Data curation, Resources, Supervision. **JVS:** Validation, Visualization.

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