



Vaccines for COVID-19 - state of the art


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Abstract

Vaccine candidates against COVID-19 have diverse compositions, from traditional inactivated virus vaccines to various new-generation vaccines. Currently, approximately 175 research teams worldwide are studying various vaccine possibilities as the necessity to vaccinate the entire population against the SARS-CoV-2 virus is urgent. Although, the development of a safe and effective COVID-19 vaccine is not easy, the manufacturing, distribution, and administration of the vaccine can also face extraordinary challenges. In this review, we enhance some of the current knowledge regarding the clinical trial phases on different COVID-19 vaccine candidates, its potential strengths and disadvantages, and to discuss ethical aspects and their chances of success in large-scale applications.

Key words Vaccines, COVID-19, Pandemic



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Introdução

The COVID-19 pandemic has the most promising and eagerly awaited hope in vaccines.¹ An effective vaccine will be crucial in controlling the pandemic, which has already affected about thirty-one million individuals and killed one million people worldwide.² Ensuring immunity will allow us to be less concerned about social distancing and all its major socioeconomic implications.³

The genetic sequence of the virus released early on January 11, 2020 triggered intense global research activity to develop a vaccine against the disease.² The impact of the humanitarian and economic scale of the COVID-19 pandemic has driven the use of new platforms on vaccine technology to accelerate the research, and the first vaccine candidate entered the clinical trials for humans in mid-March 2020 at an unprecedented speed.⁴

The speed on research means that vaccines may be available in an emergency by early 2021. If this occurs, it will be the fastest vaccine development program ever seen in history. It will represent a fundamental shift in the traditional trajectory of vaccine release, which takes about ten years to implement.^{5,6} In addition, new paradigms will be needed, involving adaptations in the development phases, regulatory processes and large-scale of manufacturing capacity.⁴

The vaccine production process follows the phases of a clinical study, with pre-clinical steps, performed in laboratories, in general, in animal models, aiming to evaluate the dose and toxicity in this population. The clinical trials, in humans, are divided into three stages. Phase 1 studies aim to evaluate the safety of the product, while phase 2 studies evaluate safety, dose and frequency of administration, as well as its immunogenicity. Phase 3 trials have as main outcome evaluation on the efficacy of the product, through controlled and randomized clinical trials involving thousands of volunteers. After the scientific publication of these data, the vaccine candidate is submitted to evaluation by regulatory agencies for further production and distribution. Finally, phase 4 or post-licensing studies estimate the effects and adverse events after a large-scale use of the vaccine in the target population.⁷ Each step in this process lasts an average of several months to years.

Reducing the entire process to a period of 12 to 18 months is unprecedented. But is this all possible without damaging the effectiveness and safety?

About 175 research teams around the world are

studying various vaccine platforms. Vaccine development programs are continuously updated by the World Health Organization (WHO), with projects coming from public and private sources.

Several production of technologies are being evaluated, including nucleic acids (DNA and RNA), use of viral vectors (replicants and non-replicants), viral vaccines (attenuated or inactivated), and protein vaccines (recombinant or PLV - virus-like particles - technology used in HPV vaccine).⁸ Some of these platforms have never been used in currently licensed vaccines, but experience exists in areas such as oncology, and new opportunities for vaccine production are emerging with increased manufacturing speed.⁶ However, this process, like everything that is new and untested, requires caution to not offer false hope at such a difficult time for humanity.

Most vaccines studied for COVID-19 aim to induce neutralizing antibodies against the viral subunits, most of them targeting to the RBD region (Receptor Binding Domain) of the most conserved virus protein, Spike (S), thus preventing the capture of the virus by the human ACE2 receptor (converting enzyme of angiotensin 2).⁹ It is not clear how the S protein variants used in different vaccine candidates relate to each other or to the genomic epidemiology of the disease.⁶

Vaccines with viral vectors: Non-replicants Adenovirus have been the main viral vectors used in the development platforms for COVID vaccines. They can be human (Ad5 and Ad26) or apes (Chimpanzees ChAd).¹⁰

Aviral vector-based, ChAdOx1 nCoV-19 vaccine developed at Oxford University in England in partnership with the AstraZeneca laboratory induces a robust immune response, including cellular response, after the application of two doses. It uses, as a vector, a non-replicant chimpanzee adenovirus that expresses the SARS-CoV-2 S protein. Phase 1 and 2 studies involving a control group with meningococcal conjugate vaccine in healthy adults showed a specific T-cell response on day 14 after application, with neutralized antibodies detected between 91 and 100% of the patients presenting an acceptable and safety profile.¹¹ Currently, it is in phase 3 studies involving health professionals and high exposure groups from the United Kingdom and four other countries, including Brazil. The emergence of a serious and unexpected adverse event in a volunteer who presented with a transverse myelitis condition caused the laboratory to temporarily suspend phase 3 study at all the centers for further analysis of the case. After evaluation by the external

monitoring committee, a causal relationship between the vaccine and the adverse event was removed and the study continues worldwide.

The American laboratory Johnson & Johnson is also testing a vaccine based on viral vectors. The results of phase 1 and 2 tests were encouraging and phase 3 tests started in August on a global scale, including a research center in Brazil.¹²

Other viral vector-based vaccines are already released for restricted use in certain population groups in China and Russia. The Chinese laboratory CanSino has released phase 1 studies demonstrating promising results with a vaccine that uses Ad5 as a vector, but no phase 3 studies have been published and the vaccine is currently approved in that country for exclusive use for the Chinese military.¹³

Also with the technology of adenovirus use, vaccination of health professionals and teachers of the vaccine produced by the Gamaleya Institute in Moscow has been initiated. A recently published Phase 1/2 study tested 02 vaccine formulations based on 02 adenovirus subtypes and all the participants produced antibodies against the SARS-CoV-2 glycoprotein with a 100% seroconversion rate after 42 days of application. The cell response on day 28 was also evaluated, with the detection of CD4 and CD8 proliferation in all the studied population.¹⁴ The Russian vaccine uses Ad26 as a viral vector in the first and Ad5 in the second dose. There is a proposal to extend vaccination to all Russian citizens in October and the government of the state of Paraná, Brazil is negotiating access to the so-called *Sputnik V* vaccine.

Genetic vaccines: The messenger RNA vaccines have shown, in general, an excellent safety profile and with good cellular and humoral immune responses. It has the advantage of being produced on a larger scale, because they are synthetic products, and it has the disadvantage of being products that require freezing conservation. The RNA vaccine is wrapped in a lipidic layer, thus avoiding its degradation. So far, no DNA vaccine has reached phase 3 in the clinical trials.¹⁰

The American laboratory Modern, in partnership with the National Institutes of Health (NIH), initiated the clinical testing of its messenger RNA-based vaccine (mRNA-1273) only two months after the identification of the virus sequence and published in July its phase 1/2 study in human volunteers. The vaccine, which encodes the stabilized S protein, resulted in the production of a large amount of neutralized antibodies in all the participants studied, detected by two different methods, and with values

similar to serum samples from convalescent patients with self-limited adverse events.¹⁵ Phase 3 study was initiated in June and aims to prevent the symptomatic disease of COVID-19.¹⁶

Also based on the mRNA, the vaccine produced by the American laboratory Pfizer, in partnership with the German biotechnology company BioNTech, demonstrated good response in inducing humoral and cellular immunity in its phase 1 and 2 studies. The results showed titers of neutralized antibodies on average 1.8 to 2.8 times higher when compared to the panel of human serum convalescents of COVID-19.¹⁷ The study of phase 3 began in August and involves about 30,000 participants in countries such as Brazil, Argentina and Germany, in addition to the United States.

Viral vaccines: traditional technologies on vaccine production such as live attenuated and inactivated viruses have been used in several clinical trials. Concerns about the biosecurity of attenuated vaccines have made studies difficult with this platform, and some inactivated vaccines are already in Phase 3 testing.¹⁰

The Chinese laboratory Sinovac vaccine uses the classical inactivated virus platform, with cell culture of the virus in vero cells with subsequent inactivation. In Brazil, it has established a partnership with the government of the State of São Paulo, through the Butantan Institute, and is being tested on health professionals from 12 Brazilian centers. Published in early August, phase 1 and 2 study tested different schemes by varying doses and applying intervals, demonstrating seroconversion in 100% of those evaluated in phase 1 study and those receiving a second dose at 21 days in phase 2 studies.¹⁸ There were low rates of adverse effects and the vaccine was approved for emergency use by health professionals in China.

Two other inactivated vaccines from Sinopharm laboratory has also began their phase 3 studies.

Protein vaccines: the classic technology of using viral proteins (structural and non-structural) in vaccine manufacturing has also been tested for COVID. Sub-unit or virus-like particle (NPV) vaccines have already reached clinical phases.¹⁰

The Novavax laboratory vaccine uses a recombinant version of the S protein developed with the nanoparticle technology, associated with an adjuvant. Phase 1 and 2 trials demonstrated its safety and immunogenicity, authorizing the initiation of phase 3 studies.

In an unprecedented collaboration, two of the

world's largest vaccine producers, Sanofi Pasteur (France) and GlaxoSmithKline (GSK-UK), joined forces to produce an adjuvanted protein unit vaccine, starting phase 1 and 2 studies in September.

Previous exposure to other coronaviruses can play a protective role through some degree of cross-protection, and can be one of the factors related to the disproportionality with which children are more exposed to common colds caused by other coronaviruses, are less affected by severe forms of the disease.¹⁹

Vaccines such as BCG, oral polio, and triple viral polio may also, through modulation of the innate immune response, play some role in preventing severe forms of COVID-19, a phenomenon described as non-specific effects of vaccines; there are some studies seeking to evaluate this hypothesis.²⁰

To date, the best approach to demonstrate the effectiveness of a vaccine against COVID-19 is through clinical trials showing protection against the disease. Comparing this effectiveness between different vaccines will not be an easy task, as it will have to take into account differences in the population and study designs. Therefore, considering that only 10 of the vaccines in development have started their phase 3 studies, and many of these do not have a date for completion, we do not anticipate the availability of data that would allow us to answer at least in parts, “what is the ideal vaccine?”.²¹

Viruses can challenge vaccine manufacturers by quickly changing so that antibodies that act on one viral strain fail on another. The new coronavirus does not seem to undergo major changes, so a vaccine that proves to be effective should probably work in any country.²² This does not mean, however, that this risk is ruled out, and caution should be considered in this regard.

Scientists are increasingly optimistic that a vaccine can be produced in record time, but making and distributing it are other greater challenges. Another condition, which should not be neglected, are the possible barriers in reaching adequate vaccine coverage. Decreasing the number of cases when a vaccine is licensed, hesitation to receive a new product, and lack of confidence in political and health authorities in many countries can act as major barriers.²³

The World Health Organization (WHO) has made a proposal to the European Union recommending a voluntary pool of patents, which would put pressure on companies to give up their monopolies of the vaccines they have developed.²⁴ WHO initiative in partnership with GAVI Global Alliance

for Vaccines (COVAX) has united countries together in a vaccine delivery fund on an equitable basis for the countries that signed the agreement.

Oxfam, an international charity, has published an open letter to 140 world leaders and experts calling for a “people's vaccine” to be made available at “no cost to all people in all the countries”. Helen Clark, former Prime Minister of New Zealand, who also signed the letter, commented that “vaccines against COVID-19 must be a public good and we are not safe until everyone is safe”.²⁵

Vaccine researchers are concerned that amidst the desire to end the COVID-19 pandemic, vaccine producers have been overly enthusiastic about the chances of their products working.²³

Another key aspect is the vaccine developers' profile. Just over half of the vaccine candidates are being developed by private companies, while about 45% of the projects are led by universities, the public sector and other non-profit organizations, of which about 50% are still in the pre-clinical phase. In addition, while several developers are multinational companies with extensive vaccine experience, many of the major groups of COVID-19 vaccine are small and/or inexperienced in a large-scale of immunobiological manufacturing.⁶

About 33 countries are developing research to produce a vaccine against SARS-CoV-2.

Table 1 presents the vaccine candidates for COVID-19 that are in phase 3 with details of its platforms, laboratories and developing countries. Of these ten projects, four are North American, four Chinese, one English and one Russian. North America and Asia (excluding China) account for about 30% of the research, while China accounts for 10%. The United States is the country with the largest number of research in the area, totalizing around 20%, a value similar to all the studies in Europe. Currently, there is little involvement and resources allocated to the vaccine research in Africa and Latin America, which collectively account for about 6% of the research.

Ensuring vaccines are safe and effective requires much testing, careful planning and execution. All of us are vulnerable to the new coronavirus, except (probably) those who have already had the disease. In phase 3 vaccines currently under study, two doses are needed for better immunogenicity. Thus, more than 15 billion doses may be needed for the world to be protected from COVID-19.²⁶

Some gaps in knowledge, especially regarding the immune response to the virus, are still being filled out.²¹ The correlate protection against the disease, the exact role that cell immunity plays in

immune response, the duration of neutralizing antibodies induced by a vaccine, the immune response in different age groups, and the possibility of developing antibody-dependent enhancement (ADE) secondary to vaccine application are unknown.^{26,27}

Ethical aspects related to clinical research should also be considered in a pandemic scenario. Would it be possible to shorten the observation and follow-up time in a study? Is voluntary exposure to the virus after the administration of a vaccine candidate ethi-

cally acceptable? Does flexible licensing criteria impose any risk?²⁸

One of the largest health regulatory agencies, the U.S. Food and Drug Administration (FDA), stated in June that for a vaccine to be approved, there must be evidence of reduced occurrence and severity of disease in at least 50% of patients.²¹ Considering the average time to complete clinical trials and the urgent need for vaccine protection, there are strands that advocate that such approval should be based

Table 1

Vaccine Candidates for COVID-19 in phase 3 - Platforms, laboratories and developing countries. Recife, 2020

Vector viral	Genetic-RNA	Proteins	Inactivated Viral
AstraZeneca / Oxford (United Kingdom) Chimpanzee Adenovirus (ChAd)	Pfizer / BioNTech (Germany) messenger RNA	Novavax (United States) Subunits	Sinovac (China)
CanSino Biological (China) Human Adenovirus type 5 (Ad5)	Modern (United States) messenger RNA		Sinopharm Wuhan (China)
Gamaleya (Russia) Human Adenovirus types 5 and 26 (Ad5 and Ad26)			Sinopharm Beijing (China)
Jansen (United States) Human Adenovirus type 26 (Ad26)			

only on antibody levels or other biomarker and not on clinical data. However, additional knowledge of the immunology and vaccine response to SARS-CoV-2 that is reasonably related to the disease protection is still needed to consolidate such a proposal.^{21,29}

There are also popular and political movements that advocate that the population should have access to unapproved substances. Since this is a scheme of mass vaccination of a healthy population against a disease that sometimes manifests itself in a mild or asymptomatic manner, even if only a small number of patients evolve with severe reactions, anaphylaxis or ADE, the results could be catastrophic.³⁰

Therefore, we cannot underestimate the importance of safety studies, which involve thousands of patients in order to detect severe adverse reactions, even more when they involve production of technologies never used.²⁹

Appropriate communication with the population,

informing the real benefits of a vaccine, its limitations and the importance of individual and collective protection will be a great challenge to be faced, due to geopolitical issues involved. Confidence in the vaccines must be maintained at any cost, or we will put at risk all the achievements in control and elimination and diseases around the world.

Strong international coordination and cooperation among researchers, regulators, policymakers, financiers, public health agencies and governments will be needed to ensure that promising vaccines can be manufactured in sufficient quantities and supplied equitably to all affected areas, particularly in economically less advantaged countries.³

There are many scientific, ethical and political challenges to overcome. We do not yet know whether there will indeed be a successful vaccine against SARS-CoV-2, but we can be sure that the efforts involving its formulation and production are unprecedented.

Authors' contribution

Fonseca Lima EJ and Kfourri RA participated in the literature review, elaboration of the article and final review. Almeida AM participated in the literature review and preparation of the article. All authors approved the final version of the article.

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