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**A review of COVID-19 vaccines in development: 6 months into the pandemic**

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## Abstract

*The advent of the COVID-19 pandemic and the dynamics of its spread is unprecedented. Therefore, the need for a vaccine against the virus is huge. Researchers worldwide are working around the clock to find a vaccine. Experts estimate that a fast-tracked vaccine development process could speed a successful candidate to market in approximately 12-18 months. The objective of this review was to describe the coronavirus vaccines candidates in development and the important considerations. The review was conducted through a thematic analysis of the literature on COVID-19 vaccines in development. It only included data until the end of June 2020, 6*

*months after the emergence of the COVID-19. Different approaches are currently used to develop COVID-19 vaccines from traditional live-attenuated, inactivated, subunit vaccines, to more novel technologies such as DNA or mRNA vaccines. The race is on to find both medicines and vaccines for the COVID-19 pandemic. As with drugs, vaccine candidates go through pre-clinical testing first before they go through the three phases of clinical trials in humans. Of the over 130 vaccine candidates, 17 are in clinical trials while others are expected to move to clinical testing after the animal studies.*

## Introduction

Coronavirus is spreading around the world. As of July 12th, 2020, more than 12,552,736 cases of COVID-19 have been reported in over 216 countries and territories, resulting in 561,617 deaths [1, 2]. The virus spreads easily and most of the world's population is still vulnerable to it. It is therefore, of paramount importance to get a vaccine that can stop the spread of the virus. Researchers are working hard to control the pandemic. We are only over 6 months after the current outbreak was first reported from Wuhan, China yet the virus SARS-CoV-2 has been identified, sequenced, and shared to the whole world. This is unprecedented for a new disease. Rapidly advancing potential vaccines is critical to stemming the virus´s devastating impact on human health and the global economy. A vaccine would provide some protection by training people's immune systems to fight the virus so they should not become sick. Besides the anticipated health benefits from a coronavirus vaccine, there are several impacts on economic and social aspects. This would allow lockdowns to be lifted more safely, and social distancing to be relaxed. The objective of this review was to describe the coronavirus vaccines candidates in development and the important considerations.

## Methods

This review was conducted through a thematic analysis of the literature on COVID-19 vaccines in development. The review is conceptual and focuses on the WHO COVID-19 vaccines landscape, clinicaltrials.gov, media reports, and the respective websites of companies reported to be working on a COVID-19 vaccine. The review only included data until the end of June 2020, 6 months after the emergence of the novel coronavirus, SARS-CoV-2.

## Current status of knowledge

There are different types of vaccines in development for COVID-19. The pipeline includes over 130 candidates in development and as of end June 2020, 17 are already in various phases of clinical development, while the others are in preclinical development. Each of the different vaccine platforms available, traditional, or novel, is currently being explored. The World Health Organization (WHO) landscape of COVID-19 vaccine candidates (19 June 2020) lists 136 vaccine candidates [3]. Researchers striving to develop a coronavirus vaccine are working with different approaches, all with their respective advantages and disadvantages (Figure 1). Live attenuated vaccine [4, 5]; inactivated vaccine [5]; vector-based vaccine [6]; protein subunit vaccine [7]; DNA vaccine [6-11] and mRNA vaccines [6]. The sections below will discuss these different vaccine approaches. A summary of all the vaccine candidates currently in clinical trials is provided in Table 1.

**Live-attenuated vaccine:** live-attenuated vaccines use an altered version of SARS-CoV-2 so that it is less virulent (Table 2). These vaccines are very effective, and a single dose is often enough to induce long-lasting immunity. Serum Institute of India has partnered with US-based clinical-stage biotechnology company Codagenix to co-develop a live-attenuated vaccine against the coronavirus. Viruses will then be grown and tested in vivo by contracted laboratories suitable for containment,

prior to testing in clinical trials [12]. Griffith University is working with Indian Immunologicals Limited to develop a live attenuated vaccine using a codon de-optimization technology to change the virus´s genome and decrease the replication efficiency in human cells [13]. The German Center for Infection Research is working on an attenuated virus (MVA: modified vaccinia virus Ankara), which had previously been used in a smallpox eradication vaccination campaign [14].

**Inactivated vaccine:** inactivated (or killed) vaccines consist of pathogens inactivated through physical, chemical, or biological means (Table 2). Beijing-based vaccine manufacturer, Sinovac´s candidate vaccine-called CoronaVac-was tested in 743 healthy volunteers between 18 and 59 years old, including 143 participants in Phase 1 and 600 in Phase 2. The vaccine induced neutralizing antibodies in over 90% of volunteers after receiving two doses, two weeks apart. Phase 3 clinical trials are expected to be conducted both within China and in countries outside China [15]. Sinopharm´s vaccine candidate, called BBIBP-CorV, induced neutralizing antibodies against SARS-CoV-2 in rodents, rabbits, and monkeys [16]. China´s Institute of Medical Biology candidate is in Phase 1 while the rest are in pre-clinical [3].

**Viral vector vaccine:** a vector is another virus that is not harmful and acts as the delivery system to carry antigens to the immune system. Scientists design a vector to carry only a small part of the SARS-CoV-2 genetic material so that it cannot cause infection. Once inside the body, the genetic material is converted to protein (Table 3). The advantages of viral vectors are: 1) high efficiency gene transduction; 2) highly specific delivery of genes to target cells; 3) induction of robust immune responses and increased cellular immunity [17]. This technology uses either live (replicating but attenuated) or non-replicating vectors. A growing number of viruses have been used as platforms to make experimental vaccines and for SARS-CoV-2, replicating viral vectors used include: yellow fever, measles, horsepox, influenza, Vesicular Stomatitis Virus, and Newcastle Disease Virus. Non-replicating viral vectors include: adenovirus, Modified Vaccinia Ankara (MVA), influenza, parainfluenza, and rabies [3].

China´s CanSino Biologics was the first company in the world to begin a clinical study of a SARS-CoV-2 vaccine. Less than 10 weeks later, the company published the Phase 1 trial data. The vaccine candidate, using a genetically engineered adenovirus vector to deliver the gene that encodes the SARS-CoV-2 spike protein into human cells. CanSino measured neutralizing antibodies concentrations in subjects and found that 75% of people who received the high dose and 50% of those who received a medium or low dose developed levels of neutralizing antibodies considered high by the researchers [18]. AZD1222, developed by Oxford University´s Jenner Institute and the Oxford Vaccine Group, uses a replication-deficient chimpanzee viral vector based on an attenuated version of a common cold (adenovirus) virus that causes infections in chimpanzees and contains the genetic material of SARS-CoV-2 spike protein. The vaccine has gone through Phase 1 and is starting Phase 2/3 in England and Brazil [19].

**Protein subunit vaccine:** instead of the whole pathogen, subunit vaccines include only specific components or antigens that have been proven through pre-clinical studies to stimulate the immune system (Table 4) [20]. Including only certain antigens in the vaccine can minimize side effects but it usually requires the addition of adjuvants to elicit a stronger immune response because antigens alone are not sufficient to elicit adequate long-term immunity [21]. There are several protein-based vaccine candidates (similar to 50) [3]. The candidates furthest along in clinical trials are the one made by Shenzhen Geno-Immune Medical Institute (COVID-19 aAPC) and Novavax´s protein subunit vaccine (NVX CoV2373). COVID-19 aAPC vaccine uses a lentivirus to construct artificial antigen-presenting cells (APCs) to present structural and nonstructural SARS-CoV-2 antigens and is administered in three doses [22]. The Phase 1/2 clinical trial of the

Novavax, supported by the Coalition for Epidemic Preparedness Innovations (CEPI), is being conducted in two parts. Phase 1, conducted in Australia, is a randomized, observer-blinded, placebo-controlled trial designed to evaluate the immunogenicity and safety of both adjuvanted with Matrix M and unadjuvanted. The protocol´s two-dose trial regimen assesses two dose sizes (5 and 25 micrograms) with Matrix M and without. Phase 2, to be conducted in multiple countries, including the United States, will assess immunity, safety and COVID-19 disease reduction in a broader age range [23]. Most protein-based vaccine candidates are targeting the Spike (S) protein, while others are targeting the receptor binding domain (RBD). The candidate from the University of Queensland uses a peptide frozen into prefusion conformation via a molecular clamp. This potentially promotes a strong neutralizing antibody response, but earlier study on Respiratory syncytial virus (RSV) showed the technology induced an antibody response that was robust but not neutralizing [24].

**Vaccines based on virus-like particles (VLPs):** Virus-like particles (VLPs) are structures resulting from self-assembly of virus proteins without a nucleic acid genome or a lipid envelope (Table 5). VLPs have structural and antigenic similarity with the parental virus and some have proven to be successful as vaccines against virus infection [25]. The human immune system recognizes and interacts with VLPs on the basis of two major characteristics: size and surface geometry [26].

**DNA vaccines:** DNA vaccination involves the direct introduction into appropriate tissues of a plasmid containing the DNA sequence encoding the antigen or antigens for which an immune response is desired (Table 6) [27]. The DNA encoding the target molecule is introduced via a plasmid or viral vector or cell line, in which DNA is expressed and translated into protein. The injected DNA is a plasmid plus a promoter that provides immunogenic protein synthesis [28]. DNA vaccines can stimulate both humoral and cellular immunity and do not require maintenance under the usual conditions for traditional vaccine (+2°C to +8°C). In addition, unlike live attenuated vaccines, the risks arising from a potential inadequate attenuation are non-existent for DNA vaccines [29].

INO-4800 is being developed by Inovio Pharmaceuticals and its partner Beijing Advaccine Biotechnology, with the support of a Coalition for Epidemic Preparedness Innovations (CEPI) grant. INOVIO has extensive experience working with coronaviruses and has a Phase 2a vaccine for a related coronavirus that causes Middle East Respiratory Syndrome (MERS). INO-4800 is using CELLECTRA 3PSP, a portable, hand-held delivery device that delivers a short electrical pulse to open small pores int the cell, enabling the plasmid to enter. Once inside, the cell uses the plasmid to produced coded antigens, which trigger an immune response. INO-4800 entered Phase 1 in April 2020. Participants will receive two doses of INO-4800 every four weeks and initial safety and immune response data from the study are expected by 3rd quarter of 2020. Inovio has partnered with Advaccine and the International Vaccine Institute to advance Phase 2/3 clinical trials in China and South Korea, respectively [30].

**RNA vaccines:** there are over a dozen mRNA COVID-19 vaccine candidates and 2 are in clinical phase. mRNA-1273, from the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases NIAID and the biotech Moderna, is a novel lipid nanoparticle (LNP)-encapsulated mRNA vaccine against the COVID-19 encoding for a prefusion stabilized form of the Spike (S) protein (Table 6). Like the DNA vaccine, the mRNA technology injects snippets of genetic code into a person´s muscle so that the muscle cells, in theory, start producing the viral protein themselves. The Phase 1 open-label, dose-ranging trial study (NCT04283461)) evaluated the safety and immunogenicity of three dose levels of mRNA-1273 (25, 100, 250 µg) administered on a two-dose vaccination schedule, given 28 days apart. An analysis of the response in eight individuals showed that those who received a 100 microgram dose and people who received a 25 microgram

dose had levels of protective antibodies to fend of the virus that exceeded those found in the blood of people who recovered from COVID-19, the illness caused by the coronavirus [31]. mRNA-127 is currently in a Phase II clinical trial, which will enroll 600 healthy participants aged 18 and above. Phase 3 trials will begin in July and will primarily study the efficacy of the vaccine in preventing symptomatic COVID-19 disease and secondarily, the prevention of severe cases of COVID-19 which require hospitalization [32]. Pfizer and BioNTech´s COVID-19 mRNA vaccine program, BNT162, started Phase 1 clinical trials in May. The Phase 1/2 study is designed to determine the safety, immunogenicity, and optimal dose level of four mRNA vaccine candidates evaluated in a single, continuous study. The dose level escalation portion (Stage 1) of the Phase 1/2 trial in the U.S. will enroll up to 360 healthy subjects into two age cohorts (18-55 and 65-85 years of age [33].

**Existing live attenuated vaccines for other diseases:** an increasing body of evidence suggests that live vaccines can induce broader protection beyond the specific protection against the targeted pathogen. These non-specific effects (also called "heterologous effects" or "off-target effects") likely occur by inducing interferon and other innate immunity. Non-specific effects have been discussed in the past. In 2013, a working group organized by the WHO systematically evaluated the evidence for non-specific effects of Bacillus Calmette-Guérin (BCG), measles and DTP (diphtheria, pertussis, tetanus) vaccines. The following year, the WHO reviewed the evidence and concluded that the findings merit further research [34]. The stimulation of innate immunity by BCG or oral polio vaccine (OPV) could provide temporary protection against COVID-19. BCG is already being studied by several groups in different countries. For all live vaccines (BCG, oral polio vaccine, measles), the theory is that they induce protection against several infections (apart from the ones they are supposed to work against) by long-term boosting of innate immune responses (called “trained immunity”). When the immune systems of people who had the BCG vaccine were compared to those who have not, it´s been shown that the immune cells that first respond to disease in BCG vaccinated people are more alert and ready to act on a potential threat [35]. Researchers in The Netherlands and Greece [36] have started a clinical trial using BCG. Other live attenuated TB vaccines candidates in clinical trials [37] are VPM1002, [38] derived from BCG, or MTBVAC derived from *M. tuberculosis.* Like BCG, these could show non-specific effects and could be candidates to be studied for their protection against COVID-19. OPV has been shown to reduce infection-related hospitalization in developed countries by providing protection against unrelated pathogens. With a proven safety profile, there is enough scientific justification to evaluate OPV for anti-viral protection against SARS-CoV-2 [39]. An analysis of the effect of annual and biannual national OPV immunization campaigns showed that they reduced all-cause mortality by 19%, with each subsequent campaign adding a further 13% reduction [40] suggesting that repeated immunization could have additive protective effects.

**Expert commentary:** vaccines are preventive or therapeutic interventions that dramatically reduce morbidity and mortality caused by infectious diseases. They are clinically simple but immunologically complex. The pressure to develop a COVID-19 vaccine is huge. But its development without fully understanding the kinetics of immune responses involved in the disease and the safety risks of the vaccine could bring unwarranted setbacks-now and in the future. In addition, SARS-CoV-2 might mutate in ways that would make previously effective vaccines useless. A great many steps have to be taken in the development of any vaccine. With COVID-19, there are added complexities given that its severity appears be different across gender and age. There´s also evidence that it might be mutable and that it has different strains. Then there is the fact that it is very new, which means there´s still limited knowledge about immune responses to SARS-CoV-2. In addition, a multiplicity of disciplines must be involved. A safe and effective

vaccine will not be developed without detailed understanding of host-pathogen interaction. This is happening in the trials that are being currently run. What this adds up to is that a safe and efficient COVID-19 vaccine might not be realized soon. Most experts think a vaccine is likely to become widely available by mid-2021, about 12-18 months after the new virus, known officially as SARS-CoV-2, first emerged. That would be a huge scientific feat and there are no guarantees it will work. Four coronaviruses already circulate in human beings. They cause common cold symptoms and we do not have vaccines for any of them.

Coronaviruses display spicules (Spike protein or S protein) which they use to attach to receptors in human cells. Many of the vaccine candidates are targeting the S proteins as these are well recognized by the human immune system. This is true for all strains of coronavirus, including SARS-CoV-1, MERS-CoV, and SARS-CoV-2 responsible for COVID-19 [41]. The scientific community has learned a lot about COVID-19 considering that the virus and the disease only emerged in early 2020 but the immune mechanism is still not well understood particularly on how the immune system reacts to the virus although severity stems from inappropriate, excessive and/or inadequate immune responses. A major challenge of these vaccine candidates will be immune enhancement - discovered in the 1960s when a vaccine candidate for respiratory syncytial virus (RSV) was tested which showed that the disease worsened after vaccinated children were exposed to the virus, with 2 mortalities. Decades ago, animal vaccines developed against another coronavirus, feline infectious peritonitis virus, increased cats´ risk of developing the disease caused by the virus [42]. Similar phenomena have been seen in animal studies for other viruses, including the coronavirus that causes severe acute respiratory syndrome (SARS) [43]. The mechanism that causes this is not fully understood and is one of the difficulties of successful development of a coronavirus vaccine.

Scientific research landscape has a pattern where emergence of novel pathogens causing an outbreak leads to an increase in research investment but when the outbreak dies down, priorities change and interest in research stops. Funding for this kind of research should rest with governments and non-profits because for-profit pharmaceutical companies do not have interest to fund projects that will not have commercial potential. Progress was made in the West Africa Ebola outbreak that ended in 2016. It spurred the creation of the Coalition for Epidemic Preparedness Innovations (CEPI) [44], a private-public partnership based in Norway and funded in part by the Bill and Melinda Gates Foundation. Funding is one of the major factors for the unprecedented speed in the development of vaccines for COVID-19. The often mentioned “12-18 months” (i.e. in 2021) is the bare minimum amount of time needed to develop a vaccine-this is possible only if all the phases in the clinical trials are successful. The inactivated mumps vaccine, considered the fastest ever approved, took three years to develop from identification of the pathogen and collecting viral samples to licensing. Vaccine clinical trials involve testing healthy individuals and following up after a specific amount of time to check for safety and efficacy. Phase 1 for safety lasts between 1-2 years; Phase 2 to further demonstrate safety and some efficacy lasts between 2-3 years and Phase 3 for safety and efficacy in natural disease conditions lasts between 5-10 years. Regulators must continue to require vaccine developers to check for potentially harmful responses in animal studies. They must also carefully assess the volunteers for the presence of antibodies against any coronaviruses before enrolling them in safety trials.

Given the uncertainty in defining a correlate of protection, a vaccine candidate that generates both humoral and cellular immune responses is desirable, and this ideally should be shown by the vaccine candidates. It is also necessary to be clear on the objective of the vaccine. A vaccine capable of protecting against the complications of COVID-19 is already a good vaccine. Induction of

total immunity (called "sterilizing immunity") is a high bar for a vaccine. Inducing protective immune response in healthy volunteers is already a challenge but it is expected to be even more challenging in people with weakened immune system by old age, obesity, illness or medical treatments that slow down immune defences. Vaccines with effective adjuvants are often needed to protect these vulnerable populations. The U.S. Food and Drug Administration (FDA) has signalled that when responding to an urgent public health situation such as novel coronavirus, regulatory flexibility and accelerated testing schedules should be considered. One option to accelerate timeline for vaccine development is approval under the FDA´s Animal Rule [45] established to facilitate approval of new products for life-threatening conditions when traditional trials in humans are unethical or impractical. Vaccine developers are still required to conduct routine animal testing to make sure the vaccine itself is not toxic and induces protection from the virus. With anti-government sentiments and the anti-vaccine movement, the urgency of vaccines should be weighed carefully with safety risks. Rushing vaccines without fully understanding certain phenomena, such as immune enhancement, could result to unwarranted setbacks and further aggravate anti-science.

## Conclusion

The unprecedented morbidity and mortality from the current COVID-19 pandemic has challenged every aspect of our global ability to effectively detect, respond to, and control such a rapidly emerging infectious disease. In response to this urgent global health crisis, a massive effort is under way to develop vaccines for coronavirus within months and make it available to save lives. Several candidate vaccines strategies are being investigated in laboratories of universities and companies in many parts of the world. Of the over 130 vaccine candidates, 17 are already in clinical trials, while the others are in various stages of preclinical development. Each of the different vaccine platforms available, traditional or novel, is currently being explored. Some platforms, such as DNA and RNA vaccines, have not produced licensed vaccines but may prove to be the first one to reach the finish line. Three vaccine candidates, one each from the US, UK, and China, have completed Phase I. While vaccine efficacy of the candidates is still under evaluation, there have been few or no adverse reactions in humans. Not a single vaccine has been approved for any other coronavirus so far, and there is no guarantee that a successful SARS-CoV-2 vaccine will be available soon. Robust and well-designed trials in populations with ongoing outbreaks in multiple locations and international collaborations are necessary to develop safe and effective COVID-19 vaccines.

## Competing interests

The authors declare no competing interests.

## Authors' contributions

All authors have read and approved the final version of the manuscript.

## Tables and figure

**Table 1**: all COVID-19 vaccine candidates in clinical trials (as of 19 June 2020)
**Table 2**: live attenuated and inactivated COVID-19 vaccine candidates, WHO landscape (as of 09 June 2020)
**Table 3**: viral vector COVID-19 vaccine candidates, WHO landscape (as of 09 June 2020)
**Table 4**: protein subunit COVID-19 vaccine candidates, WHO landscape (as of 09 June 2020)
**Table 5**: VLP-based vaccine candidates, WHO landscape (as of 09 June 2020)
**Table 6**: DNA and RNA vaccine candidates, WHO landscape (as of 09 June 2020)
**Figure 1**: different vaccine approaches-their advantages and disadvantages

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| **Table 1:** all COVID-19 vaccine candidates in clinical trials (as of 19 June 2020) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Phase** | **Name** | **Type** | **N** | **Age (years)** | **Randomized** | **Design** | **Location** | **Start date** | **End date** | **Study Number** | **Status** |
| I | Cansino Ad5-nCoV | Non-replicating viral vector | 108 | 18-60 | No | Open-label, dose-finding | China | 16/03/2020 | 30/12/2020 | ChiCTR2000030906/ NCT04313127 | Active, not recruiting |
| I | Moderna mRNA-1273 | RNA | 155 | 18-55 | No | Open-label, dose-finding | USA | 16/03/2020 | 22/11/2021 | NCT04283461 | Recruiting |
| I | Inovio INO-4800 | DNA | 120 | ≥18 | No | Open-label, dose-finding | USA | 03/04/2020 | 31/07/2021 | NCT04336410 | Recruiting |
| I/II | WIBP vaccine | Inactivated | 1264 | ≥6 | Yes | Double-blind, dose-finding | China | 11/04/2020 | 10/11/2021 | ChiCTR2000031809 | Not yet recruiting |
| II | Cansino Ad5-nCoV | Non-replicating viral vector | 508 | 18-60 | Yes | Double-blind | China | 12/04/2020 | 31/01/2021 | NCT04341389 | Active, not recruiting |
| I/II | Sinovac vaccine | Inactivated | 744 | 18-59 | Yes | Double-blind, dose-finding | China | 16/04/2020 | 13/08/2020 | NCT04352608 | Recruiting |
| I/II | BioNTech BNT162 | RNA | 200 | 18-55 | No | Open-label, dose-finding | Germany | 23/04/2020 | 31/08/2020 | NCT04380701 | Recruiting |
| I/II | Oxford ChAdOx1 | Non-replicating viral vector | 1090 | 18-55 | Yes | Single-blind | UK | 23/04/2020 | 31/05/2021 | NCT04324606 | Active, not recruiting |
| I/II | BioNTech BNT162 | RNA | 7600 | 18-55 | Yes | Observer-blind, dose-finding | USA | 29/04/2020 | 28/06/2021 | NCT04368728 | Recruiting |
| I | Symvivo bacTRL-Spike | Other | 84 | 19-55 | Yes | Observer-blind, dose-finding | Canada | 30/04/2020 | 31/08/2021 | NCT04334980 | Not yet recruiting |
| I/II | Cansino Ad5-nCoV | Non-replicating viral vector | 696 | 18-84 | Yes | Double-blind, dose-finding | Canada | 01/05/2020 | 31/03/2021 | NCT04398147 | Not yet recruiting |
| II/III | Oxford ChAdOx1 | Non-replicating viral vector | 10260 | ≥5 | Yes | Single-blind | UK | 01/05/2020 | 31/08/2021 | NCT04400838 | Not yet recruiting |
| I/II | Sinovac vaccine | Inactivated | 422 | ≥60 | Yes | Double-blind, dose-finding | China | 20/05/2020 | 20/07/2020 | NCT04383574 | Not yet recruiting |
| I | Novavax SARS-CoV-2 rS | Protein subunit | 131 | 18-59 | Yes | Observer-blind, dose-finding | Australia | 25/05/2020 | 31/12/2020 | NCT04368988 | Recruiting |
| II | Moderna mRNA-1273 | RNA | 600 | ≥18 | Yes | Observer-blind, dose-finding | USA | 25/05/2020 | 31/03/2021 | NCT04405076 | Recruiting |
| I | Clover SCB-2019 | Protein subunit | 150 | ≥18 | Yes | Double-blind, dose-finding | Australia | 20/06/2020 | 20/10/2020 | NCT04405908 | Not yet recruiting |
| I/II | Chinese Academy of Medical Science vaccine | Inactivated | 942 | 18-59 | Yes | Double-blind, dose-finding | China | 15/05/2020 | 30/09/2020 | NCT04412538 | Recruiting |

| **Table 2:** live attenuated and inactivated COVID-19 vaccine candidates, WHO landscape (as of 09 June 2020) | | |
|---|---|---|
| **Live attenuated COVID-19 vaccine candidates** | | |
| **Vaccine type** | **Developer** | **Development Stage** |
| Deoptimized live-attenuated | Serum Institute of India; Codagenix | Pre-clinical |
| Deoptimized live-attenuated | Indian Immunologicals Ltd; Griffith University | Pre-clinical |
| Live-attenuated measles virus | DZIF – German Center for Infection Research | Pre-clinical |
| **Inactivated COVID-19 vaccine candidates** | | |
| Inactivated + alum | Sinovac/Dynavax | Phase 1 / 2 NCT04383574; NCT04352608 |
| Inactivated | Wuhan Institute of Biological Products; Sinopharm | Phase 1 / 2 ChiCTR2000031809 |
| Inactivated | Beijing Institute of Biological Products; Sinopharm | Phase 1 / 2 ChiCTR2000032459 |
| Inactivated | Institute of Medical Biology, Chinese Academy of Medical Sciences (CAMS) | Phase 1 NCT04412538 |
| Inactivated | Beijing Minhai Biotechnology Co., Ltd | Pre-clinical |
| Inactivated | Osaka University/ BIKEN/ NIBIOHN | Pre-clinical |
| Inactivated+CpG 1018 | Sinovac/Dynavax | Pre-clinical |
| Inactivated+CpG 1018 | Valneva/Dynavax | Pre-clinical |
| Inactivated | Research Institute for Biological Safety Problems, Kazakhstan | Pre-clinical |

| **Table 3:** viral vector COVID-19 vaccine candidates, WHO landscape (as of 09 June 2020) | | |
|---|---|---|
| **Vaccine candidate** | **Developer** | **Development Stage** |
| **Replicating viral vector COVID-19 vaccine candidates** | | |
| Replicating horsepox vector | Tonix Pharma/Southern Research | Phase 1 NCT04412538 |
| Replicating YF17D vector | KU Leuven; UZ Leuven | Pre-clinical |
| Replicating measles vector | Zydus Cadila | Pre-clinical |
| Replicating measles vector | Institut Pasteur / Themis / Pittsburg Center for Vaccine Research / Merck | Pre-clinical |
| Replicating measles vector | FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo | Pre-clinical |
| Attenuated influenza virus backbone (intranasal) | BiOCAD and IEM | Pre-clinical |
| Recombinant vaccine based on Influenza A virus | FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo | Pre-clinical |
| Influenza expressing an antigenic portion of S protein | Fundação Oswaldo Cruz and Instituto Buntantan | Pre-clinical |
| M2-deficient single replication (M2SR) influenza vector | UW–Madison / FluGen / Bharat Biotech | Pre-clinical |
| Influenza vector expressing RBD | University of Hong Kong | Pre-clinical |
| Replication-competent VSV chimeric virus technology (VSVΔG) | IAVI / Merck | Pre-clinical |
| Vesicular Stomatitis Virus | University of Western Ontario | Pre-clinical |
| Vesicular Stomatitis Virus | FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo | Pre-clinical |
| Newcastle disease virus vector | Intravacc / Wageningen Bioveterinary Research/Utrecht Univ | Pre-clinical |
| **Non-replicating viral vector COVID-19 vaccine candidates** | | |
| ChAdOx1-s | University of Oxford / Astra Zeneca | Phase 1 / 2 2020-001072-15 Phase 2b / 3 2020-011228-32 |
| Adenovirus Type 5 Vector | CanSino Biological Inc. / Beijing Institute of Biotechnology | Phase 1 ChiCTR2000030906 Phase 2 ChiCTR2000031781 |
| Adeno-associated virus vector (AAVCOVID) | Massachusetts Eye and Ear / Massachusetts Gen Hospital / AveXis | Pre-clinical |
| MVA encoded VLP | GeoVax/ BravoVax | Pre-clinical |
| AD26 (alone or with MVA boost) | Janssen Pharmaceutical Companies | Pre-clinical |
| Replication defective Simian Adenovirus (GRAd) | ReiThera / LEUKOCARE / Univercells | Pre-clinical |
| MVA-S encoded | DZIF – German Center for Infection Research | Pre-clinical |
| MVA-S encoded | IDIBAPS-Hospital Clinic, Spain | Pre-clinical |
| Adenovirus-based NasoVAX expressing S-protein | AltImmune | Pre-clinical |
| [E1-, E2-, E3-] hAd5-COVID19-Spike/Nucleocapsid | ImmunityBio, Inc.; NantKwest, Inc. | Pre-clinical |
| Ad 5 (GREVAX ™) platform | Greffex | Pre-clinical |
| Oral Ad 5 S | Stabilitech Biopharma Ltd | Pre-clinical |
| Adenovirus-based + HLA-matched peptides | Valo Therapeutics Ltd | Pre-clinical |
| Oral vaccine platform | Vaxart | Pre-clinical |
| MVA-S encoded | Centro Nacional Biotechnologia (CNB-CSIS), Spain | Pre-clinical |
| Dendritic cell based vaccine | University of Manitoba | Pre-clinical |
| Parainfluenza virus 5 (PIV5)-based vaccine expressing the S protein | University of Georgia; University of Iowa | Pre-clinical |
| Recombinant deactivated rabies virus containing S1 | Bharat Biotech; Thomas Jefferson University | Pre-clinical |
| Inactivated flu-based vaccine + adjuvant | National Center for Genetic Engineering & Biotechnology (BIOTEC) / GPO, Thailand | Pre-clinical |

| **Table 4:** protein subunit COVID-19 vaccine candidates, WHO landscape (as of 09 June 2020) | | |
|---|---|---|
| **Vaccine candidate** | **Developer** | **Development Stage** |
| COVID-19 artificial antigen-presenting cells (APCs) | Shenzhen Geno-Immune Medical Institute | Phase 1 |
| Native like Trimeric subunit Spike Protein vaccine | Clover Biopharmaceuticals Inc. / GSK / Dynavax | Phase 1 NCT04405908 |
| Full length recombinant SARS-CoV-2 glycoprotein nanoparticle + Matrix M adjuvant | Novavax | Phase 1 / 2 NCT04368988 |
| Adjuvanted microsphere peptide | VIDO-InterVac, University of Saskatchewan | Pre-clinical |
| Adjuvanted recombinant protein (RBD-Dimer) | Anhui Zhifei Longcom Biopharmaceutical / Institute of Microbiology, Chinese Academy of Sciences | Pre-clinical |
| Adjuvanted protein subunit (RBD) | Biological E Ltd | Pre-clinical |
| Capsid-like protein | AdaptVac (PREVENT-nCoV consortium) | Pre-clinical |
| COVID-19 XWG-03 truncated S (spike) proteins | Innovax / Xiamen University / GSK | Pre-clinical |
| Drosophila S2 insect cell expression system | ExpreS2ion | Pre-clinical |
| gp-96 backbone | Heat Biologics / University of Miami | Pre-clinical |
| Ii-Key peptide | Generex / EpiVax | Pre-clinical |
| Microneedle arrays S1 subunit | University of Pittsburgh | Pre-clinical |
| Molecular clamp stabilized Spike protein | University of Queensland / GSK / Dynavax | Pre-clinical |
| Nanoparticle vaccine | LakePharma, Inc. | Pre-clinical |
| OMV-based vaccine | Quadram Institute Biosciences; BiOMViS Srl / University of Trento | Pre-clinical |
| OMV-based subunit | Intravacc / Epivax | Pre-clinical |
| OMV-based peptide | Intravacc / Epivax | Pre-clinical |
| Oral E. coli-based protein expression system of S and N proteins | MIGAL Galilee Research Institute | Pre-clinical |
| Orally delivered, heat stable subunit | Applied Biotechnology Institute, Inc. | Pre-clinical |
| Peptide | Vaxil Bio; Flow Pharma Inc; FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo | Pre-clinical |
| Peptide antigens formulated in LNP | ImmunoVaccine Inc. | Pre-clinical |
| Peptides derived from Spike protein | Axon Neuroscience SE | Pre-clinical |
| Protein subunit | University of San Martin and CONICET, Argentina ; MOGAM Institute for Biomedical Research, GC Pharma | Pre-clinical |
| Protein Subunit EPV-CoV-19 | EpiVax | Pre-clinical |
| RBD-based | Neovii / Tel Aviv University; Kentucky Bioprocessing, Inc.; Baylor College of Medicine | Pre-clinical |
| Recombinant protein | Yisheng Biopharma | Pre-clinical |
| Recombinant S protein in IC-BEVS | Vabiotech | Pre-clinical |
| Recombinant protein, nanoparticles (based on S-protein and other epitopes) | St. Petersburg Research Institute of Vaccines & Serums | Pre-clinical |
| Recombinant spike protein with Advax™ adjuvant | Vaxine Pty Ltd / Medytox | Pre-clinical |
| Recombinant S1-Fc fusion protein | AnyGo Technology | Pre-clinical |
| RBD protein fused with Fc of IgG + adjuvant | Chulalongkorn University/GPO, Thailand | Pre-clinical |
| S protein | WRAIR / USAMRIID; AJ Vaccines; Sanofi Pasteur / GSK | Pre-clinical |
| S protein + adjuvant | National Institute of Infectious Disease, Japan | Pre-clinical |
| S peptide | EpiVax / University of Georgia | Pre-clinical |
| Subunit vaccine | FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo | Pre-clinical |
| Subunit protein, plant produced | iBio/ CC-Pharming | Pre-clinical |
| Synthetic Long Peptide Vaccine candidate for S and M proteins | OncoGen | Pre-clinical |
| Structurally modified spherical particles of the tobacco mosaic virus (TMV) | Lomonosov Moscow State University | Pre-clinical |
| Spike-based | University of Alberta | Pre-clinical |
| Spike-based (epitope screening) | ImmunoPrecise | Pre-clinical |
| S-2P protein + CpG 1018 | Medigen Vaccine Biologics Corp / NIAID / Dynavax | Pre-clinical |
| VLP-recombinant protein + adjuvant | Osaka University / BIKEN / National Institutes of Biomedical Innovation, Japan | Pre-clinical |

| **Table 5:** VLP-based vaccine candidates, WHO landscape (as of 09 June 2020) | | |
|---|---|---|
| **Vaccine type** | **Developer** | **Development Stage** |
| VLP + Adjuvant | Mahidol University/ The Government Pharmaceutical Organization (GPO) | Pre-clinical |
| VLP, lentivirus and baculovirus vehicles | Navarrabiomed, OncoImmunology group | Phase 1 NCT04412538 |
| Cucumber Mosaic Virus VLP | Saiba AG; AGC Biologics | Pre-clinical |
| Plant-derived VLP | Medicago Inc. | Pre-clinical |
| ADDomer™ multiepitope display | Imophoron Ltd; Bristol University's Max Planck Centre | Pre-clinical |
| VLP | Doherty Institute | Pre-clinical |
| VLP | OSIVAX | Pre-clinical |
| envelope virus like particles (eVLP) | ARTES Biotechnology | Pre-clinical |
| VLPs peptides / whole virus | University of Sao Paulo | Pre-clinical |
| Spike-based (epitope screening) | ImmunoPrecise | Pre-clinical |

| **Table 6:** DNA and RNA vaccine candidates, WHO landscape (as of 09 June 2020) | | |
|---|---|---|
| **Vaccine type** | **Developer** | **Development Stage** |
| **DNA vaccine candidates** | | |
| DNA plasmid vaccine with electroporation | Inovio Pharmaceuticals | Phase 1 NCT04336410 |
| bacTRL-Spike | Symvivo | Phase 1 NCT04334980 |
| DNA vaccine (GX-19) | Genexine Consortium | Pre-clinical |
| DNA plasmid vaccine with electroporation | Karolinska Institute / Cobra Biologics (OPENCORONA Project) | Pre-clinical |
| DNA plasmid vaccine | Osaka University / AnGes / Takara Bio | Pre-clinical |
| DNA vaccine | Takis / Applied DNA Science / Evvivax | Pre-clinical |
| DNA plasmid, needle-free delivery | Immunomic Therapeutics, Inc. / EpiVax, Inc. / PharmaJet | Pre-clinical |
| DNA plasmid vaccine | Zydus Cadila | Pre-clinical |
| DNA vaccine | BioNet Asia | Pre-clinical |
| DNA vaccine | Entos Pharmaceuticals | Pre-clinical |
| **RNA vaccine candidates** | | |
| LNP-encapsulated mRNA | Moderna / National Institute of Allergy and Infectious Diseases | Phase 1 NCT04283461; Phase 2 NCT04405076 |
| 3 LNP-encapsulated mRNAs | BioNTech / Fosun Pharma / Pfizer | Phase 1 / 2 2020-001038-36; NCT04368728 |
| LNP-mRNA | Translate Bio/Sanofi Pasteur CanSino Biologics / Precision NanoSystems | Pre-clinical |
| LNP-encapsulated mRNA cocktail encoding VLP | Fudan University / Shanghai Jiao Tong University / RNACure Biopharma | Pre-clinical |
| LNP-encapsulated mRNA encoding RBD | Fudan University / Shanghai Jia Tong University / RNACure Biopharma | Pre-clinical |
| Replicating defective SARS-CoV-2 derived RNA | Centro Nacional Biotecnologia (CNB-CSIC), Spain | Pre-clinical |
| LNP-encapsulated mRNA | University of Tokyo / Daiichi-Sankyo | Pre-clinical |
| Liposome-encapsulated mRNA | BIOCAD | Pre-clinical |
| Several mRNA candidates | RNAimmune, Inc. | Pre-clinical |
| mRNA | FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo | Pre-clinical |
| mRNA | China CDC / Tongji University / Stermina | Pre-clinical |
| mRNA | Arcturus / Duke-NUS Singapore | Pre-clinical |
| saRNA | Imperial College London | Pre-clinical |
| mRNA | CureVac | Pre-clinical |
| mRNA in an intranasal delivery system | eTheRNA | Pre-clinical |
| mRNA | Greenlight Biosciences | Pre-clinical |
| mRNA | Institut d'Investigacions Biomèdiques August Pi i Sunyer IDIBAPS-Hospital Clinic, Spain | Pre-clinical |

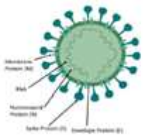
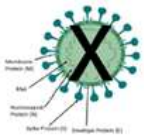
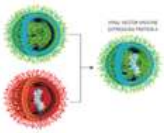
| | Live Attenuated Vaccine | Inactivated Vaccine | Vector-based Vaccine | Protein Subunit Vaccine | DNA Vaccine | mRNA Vaccine |
|---|---|---|---|---|---|---|
| |  |  |  |  |  |  |
| **PROS** | ▪ Single dose can provide long lasting and effective immunity<br>▪ Good immunity in oral dosing<br>▪ No adjuvants needed<br>▪ May have cross protection | ▪ Safer – no risk of recovering virulence and causing disease | ▪ Innate immune response stimulation, T & B cell response induction<br>▪ Versatility based on vector used | ▪ Safer<br>▪ Applicable to populations who are immuno-compromised / immunosenescent Long-term immunity | ▪ Stimulates both cellular & humoral immunity<br>▪ No risk for virulence<br>▪ Reversion<br>▪ Reduced vaccine-related side effects<br>▪ Temperature stable<br>▪ Generally more stable compared to RNA | ▪ Not infectious<br>▪ No risk for genome integration |
| **CONS** | ▪ May recover virulence and cause disease<br>▪ Horizontal spread of vaccine strain possible<br>▪ Cold-chain sensitive<br>▪ Transient immunosuppression | ▪ Short-lived immunity without adjuvants | ▪ Possibility of anti-vector immunity or pre-existing anti-vector immunity | ▪ Low immunogenicity<br>▪ Needs adjuvant<br>▪ Needs multiple dosing for long-term protection | ▪ Rare occurrences of activating oncogenes<br>▪ Risk of eliciting anti-DNA antibodies<br>▪ Need for adjuvants to induce high immunogenicity<br>▪ Need for multiple doses | ▪ Instability concern<br>▪ Low immunogenicity |

**Figure 1:** different vaccine approaches-their advantages and disadvantages