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A Review: COVID-19 Vaccine Development

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ABSTRACT:

At the time of writing, the SARS-CoV-2 virus has infected more than 49 million people causing more than 1.2 million deaths worldwide since its emergence from Wuhan, China in December 2019. Vaccine development against SARSCoV-2 has drawn the global attention in order to stop the spread of the virus, with more than 10 vaccines being tested in phase III clinical trials, as of November 2020. However, critical to vaccine development is consideration of the immunological response elicited as well as biological features of the vaccine and both need to be evaluated thoroughly. Tuberculosis is also a major infectious respiratory disease of worldwide prevalence and the vaccine development for tuberculosis has been ongoing for decades. In this review, we highlight some of the common features, challenges and complications in tuberculosis vaccine development, which may also be relevant for, and inform, COVID-19 vaccine development.

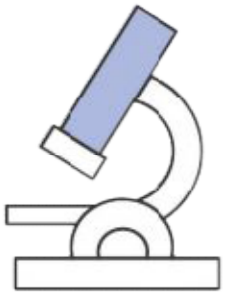
Keywords: COVID-19, SARS-CoV-2, Tuberculosis, Vaccine

Introduction

COVID-19 mechanism of transmission and pathogenesis Respiratory droplets (containing SARS-CoV-2) and contact transmission are the main routes of infection for COVID-19. It is also known that infected individuals can spread the virus to other humans with viruscontaining body fluids such as sputum and saliva through the oral and nasal cavities and possibly other mucous membranes (e.g. the eyes) . However, it is still unclear whether asymptomatic infected individu like (S) glycoprotein of the virus to its receptor, angiotensin converting enzyme 2 (ACE2), and initiates viral entry into type II pneumocytes. The S protein includes two domains: the S1 domain mediates binding to ACE2, and the S2 domain promotes fusion to host cell membrane [6]. The higher transmission rate of SARS-CoV-2 in comparison to other coronaviruses, such as SARCoV and MERS-CoV, (3–10 fold) is believed to be a result of four amino acid changes in the S1 domain [7]. Upon virus entry and infection of pneumocytes, viral pathogen-associated molecular patterns (PAMPs) are recognized by the host pattern recognition receptors (PRRs) which leads to local inflammatory responses and cytokine secretion such as transforming growth factor-β1 (TGF-β1), tumor necrotic factor-α (TNF-α), interleukins 1β and 6 (IL-1β and IL-6) . In severe COVID-19 cases, a cytokine storm, defined as dysregulated and excessive immune responses, is associated with acute respiratory distress syndrome (ARDS) and multiple organ failure . Elevated levels of IL-2, IL-6, IL-7, IL-10, IL-12, interferon-γ (IFN-γ), interferon induced protein-10 (IP-10) and TNF-α, and lymphopenia are associated with the severity of the disease and fatal outcomes . Humoral immunity plays a key role in the protection against the virus . The production of neutralizing antibodies can be detected as early as four days after the infection . Specific-IgM antibodies peak on the ninth day post-infection, while specific-IgG antibodies are detected after 3 weeks . Cell-mediated immunity also plays an important role in mediating the immune response to SARSCoV-2 . Antigen-specific T cells such as regulatory CD4+ T cells and CD8+ T cells, balance the battle against the virus and suppress the overproduction of cytokines that lead to aggressive inflammation . In addition, CD4+ helper T cells activate T-dependent B cells and increase the production of neutralizing antibodies; while cytotoxic CD8+ T cells kill virus infected cells to release the virus for neutralization by antibodies .

The Vaccine Process: From the Lab to You

Initial Development



New vaccines are first developed in laboratories. Scientists have been working for many years to develop vaccines against coronaviruses, such as those that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). SARS-CoV-2, the virus that causes COVID-19, is related to these other coronaviruses. The knowledge that was gained through past research on coronavirus vaccines helped speed up the initial development of the current COVID-19 vaccines.

Clinical Trials

After initial development, vaccines go through three phases of clinical trials to make sure they are safe and effective. For other vaccines routinely used in the United States, the three phases of clinical trials are performed one at a time. During the development of COVID-19 vaccines, these phases overlapped to speed up the process so the vaccines could be used as quickly as possible to control the pandemic. No trial phases have been skipped.

The clinical trials for COVID-19 vaccines have involved tens of thousands of volunteers of different ages, races, and ethnicities. Clinical trials for vaccines compare outcomes (such as how many people get sick) between people who are vaccinated and people who are not. Because COVID-19 continues to be widespread, the vaccine clinical trials have been conducted more quickly than if the disease were less common. Results from these trials have shown that COVID-19 vaccines are effective, especially against severe illness, hospitalization, and death.

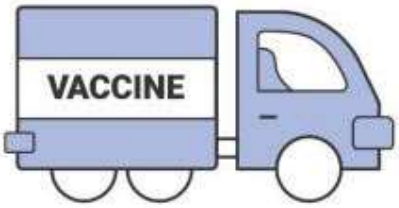
The clinical trials showed no serious safety concerns within 8 weeks following vaccination. This is an important milestone, as it is unusual for adverse effects caused by vaccines to appear after this amount of time. Now that COVID-19 vaccines are available to the public, CDC and FDA continue to monitor their safety and alert the public about health problems that are reported after vaccination.

Authorization or Approval

Before vaccines are made available to people in real-world settings, FDA assesses the findings from clinical trials. Initially, they determined that three COVID-19 vaccines met FDA's safety and effectiveness standards and granted those vaccines Emergency Use Authorizations (EUAs)external icon. The EUAs allowed the vaccines to be quickly distributed for use while maintaining the same high safety standards required for all vaccines. Learn more in this video about EUAs.

FDA has now granted full approval for Pfizer-BioNTech (COMIRNATY) COVID-19 Vaccineexternal icon for people ages 16 years and older and for Moderna (Spikevax) COVID-19 Vaccine for people ages 18 years and older. Before granting approval, FDA reviewed evidence that built on the data and information submitted to support the EUA. This included preclinical and clinical trial data and information, as well as details of the manufacturing process, vaccine testing results to ensure vaccine quality, and inspections of the sites where the vaccine is made. These vaccines were found to meet the high standards for safety, effectiveness, and manufacturing quality FDA requires of an approved product. Learn more about the process for FDA approvalexternal icon.

Manufacturing and Distribution



The U.S. government has invested substantial resources for both manufacturing and distribution of COVID-19 vaccines. This allowed manufacturing to begin when the vaccines were still in the third phase of clinical trials so that distribution could begin as soon as FDA authorized each vaccine.

Tracking Safety Using Vaccine Monitoring Systems

As vaccines are distributed outside of clinical trials, several monitoring systems continue to track them to ensure their safety. Hundreds of millions of people in the United States have received COVID-19 vaccines under the most intense safety monitoring in U.S. history. Some people have no side effects. Many people have reported common side effects after COVID-19 vaccination, like pain or swelling at the injection site, a headache, chills, or fever. These reactions are common and are normal signs that your body is building protection.

Reports of serious adverse events after vaccination are rare.

CDC and FDA continue to closely monitor several reporting systems, like the Vaccine Adverse Event Reporting System (VAERS), Vaccine Safety Datalink (VSD), and v-safe, which help look for safety issues now that the vaccines are being given to patients in real-world settings across the country. CDC provides timely updates on selected serious adverse events reported after COVID-19 vaccination.

COVID-19 vaccines under clinical trials

Some of the potential CVCs that are in Phase 3 clinical trials and might get EUA approval are described below. The other CVCs that are in clinical trials.

JNJ-78436735 by Johnson & Johnson

Johnson & Johnson (J&J) is developing JNJ-78436735 (Previously as Ad26.COV2.S), using their AdVac and PERC6 systems, also used to develop the Ebola vaccine. In partnership with BARDA, J&J has promised to invest more than $1 billion in vaccine research and development. JNJ-78436735 is currently funded by Janssen, BARD, NAID and the Operation Warp Speed .

A randomized, double blind, placebo-controlled, Phase 1/2 study of recombinant JNJ-78436735 in 1045 healthy subjects, 18–55 years of age, and in adults 65 years or older is ongoing. Study sites are selected in the US and Belgium (NCT04436276). The Phase 3 ENSEMBLE trial will enroll up to 60,000 subjects in the US and other countries (NCT04505722). The study protocol for the Phase 3 ENSEMBLE trial was released by J&J on September 23, 2020. Results from the Phase 1/2 study showed that a single dose of the vaccine was safe and immunogenic . The results of the preclinical study showed that a single injection of JNJ-78436735 produced a strong neutralizing antibody response and offered complete or near-complete protection in bronchoalveolar lavage and nasal swabs after SARS-CoV-2 administration in *Rhesus macaques* . Another preclinical study in hamsters indicated that the vaccine protected against severe disease when tested.

On June 10, 2020, J&J announced it is fast-tracking the Phase 1/2 trials. The ENSEMBLE trial was on hold pending a review of an adverse event, but J&J has been cleared to resume the trial in the US and Brazil after clearance from the Independent Data Safety and Monitoring Board. J&J also plan to start testing its vaccine in adolescents as soon as possible . This vaccine candidate requires storage at 2–8 °C .

Ad5-nCoV by CanSino Biologics

China's CanSino Biologics has developed a recombinant novel coronavirus vaccine that incorporates the adenovirus type 5 vector (Ad5) called Ad5-nCoV. A Phase 1 clinical trial in China involving 108 participants, 18–60 years old, is active, but not recruiting. In this trial the participants will receive

low, medium, and high doses of Ad5-nCoV (NCT04313127). A Phase 1 trial in China is also assessing intramuscular as well as mucosal vaccination of Ad5-nCoV across two doses (NCT04552366).

A Phase 1/2 trial involving 696 participants in Canada is registered and not yet recruiting (NCT04398147). A Phase 2 double-blind, placebo-controlled trial with 508 participants in China (NCT04341389) is active but not recruiting. A phase 2b trial in China is evaluating the safety and immunogenicity of Ad5-nCoV in participants who are 6 years of age and older (NCT04566770). A Phase 3 trial in Russia with 500 participants across multiple study centers is ongoing (NCT04540419). A Phase 3 trial involving 40,000 participants in countries including Pakistan, Saudi Arabia and Mexico is also ongoing (NCT04526990). A single dose of Ad5-nCoV vaccine protects against upper respiratory infection of SARSCoV-2 in ferrets. Results from the Phase 1 trial showed a humoral and immunogenic response to the vaccine. Adverse reactions such as pain (54%), fever (46%), fatigue (44%), headache (39%), and muscle pain (17%) were reported in 83% of the patients in the low and medium dose groups and in 75% of the patients in the high dose group. Results from the Phase 2 trial showed neutralizing antibodies and specific interferon γ enzyme-linked immunosorbent assay, at all dose levels for most of the participants. On June 25, 2020, China's Central Military Commission announced that Ad5-nCoV can be used in the military for a period of 1 year.

NVX-CoV2373 by Novavax

In March 2020, Novavax announced that it has manufactured a stable, prefusion protein nanoparticle vaccine candidate for COVID-19. A Phase 1/2 trial evaluating NVX-CoV2373 commenced on May 25, 2020 .

A randomized, observer-blinded, placebo-controlled trial involving 130 healthy participants, 18–59 years of age, is ongoing at two sites in Australia. In this trial, patients will receive a two-dose regimen of 5 µg or 25 µg of NVX-CoV2373 with or without Novavax's Matrix-M adjuvant (NCT04368988). A Phase 2b trial is also ongoing in South Africa, with two cohorts, group of 2,665 healthy adults and group of 240 HIV positive adults (NCT04533399). Phase 1 trial participants who received the vaccine developed an antibody response at multiple doses. NVX-CoV2373 was also reported to be safe .

Novavax received the Fast Track Designation from the FDA for NVX-CoV2373 . On May 11, 2020, CEPI announced that they had provided Novavax with $384 million for the development and manufacturing of NVX-CoV2373. Novavax plans to produce 1 billion doses of NVX-CoV2373 by 2021 as part of their latest acquisition of Praha Vaccines. Novavax was also awarded a $60 million US Department of Defense contract towards manufacturing NVX-CoV2373, and another $1.6 billion from Operation Warp Speed, if the candidate will be proved effective in clinical trials . A Phase 3 trial has also begun in the United Kingdom, which will evaluate the vaccine in 10,000 participants. Novavax provided an update on October 27, 2020, of its Phase 3 trial of NVX-CoV2373 in North America, stating that the trial would commence at the end of November, roughly one month later than expected .

Progress in the development of vaccines against COVID-19

Table 2 Pipeline of major COVID-19 vaccines in clinical trials

Vaccine name	Vaccine type	Clinical phase	Description
INO-4800	DNA	I/II	Synthetic DNA vaccine targeting SARS-CoV S protein [55]
RBD-dimer	Recombinant subunit	II	Beta-CoV vaccine against beta coronaviruses [56]
CTII-nCoV	Adenovirus-vector	II	Adenovirus vector encodes for full-length S protein [58]
BNT162	mRNA	III	Four vaccine candidates include: BNT62a1 and BNT62b1: contain nucleoside modified RNA, BNT162b2: uridine containing mRNA, and BNT162c2: using self-amplifying mRNA. Each is composed of S protein and combined with a lipid nanoparticle formulation [57]
mRNA-1273	mRNA	III	Lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine encoding full length S protein [59]
Ad26COVS1	Adenovirus-vector	III	Replication deficient adenovirus type 5 vector expressing S protein [60]
AZD1222	Adenovirus-vector	III	Chimpanzee adenovirus vector expressing S glycoprotein [61]
CoronaVac	Inactivated virus	III	Adsorbed COVID-19 (inactivated) vaccine [62]
BBIBP-CorV	Inactivated virus	III	Inactivated SARS-CoV-2 HB02 strain [63]

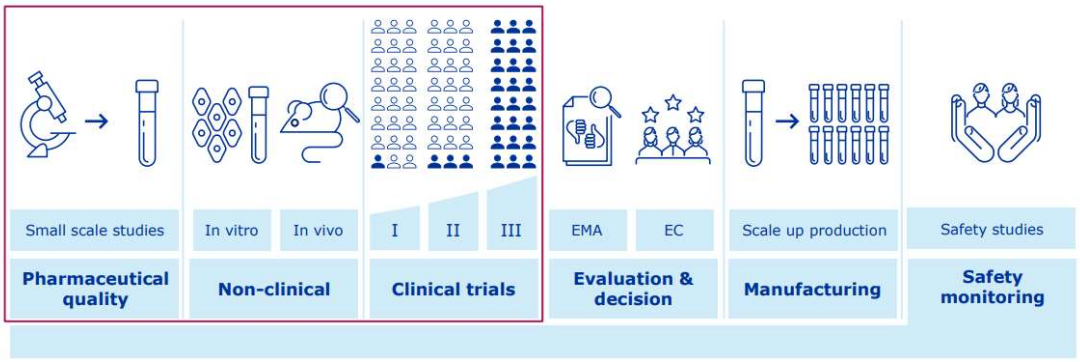
To date, more than 230 COVID-19 vaccines are being developed using various technologies [55–63], some of which are "traditional" such as inactivated , viral-vector vaccines [58, 60, 61] and adjuvanted subunit vaccines [56]. Other vaccine technologies being developed have not been used in licensed vaccines before e.g. mRNA and DNA vaccines Te leading vaccines in clinical trials are viral-vectored expressing the S protein of the SARS-CoV-2 mRNA vaccines [57, 59], inactivated and adjuvanted vaccines .Te aim of these vaccines is to protect from the infection and/or prevent clinical symptomatic disease and therefore reduce disease severity. At the time of writing Pfzer have reported in the mediapromising Phase III results for their mRNA based vaccine, but the data is not yet available.

Possible complications of COVID-19 vaccines

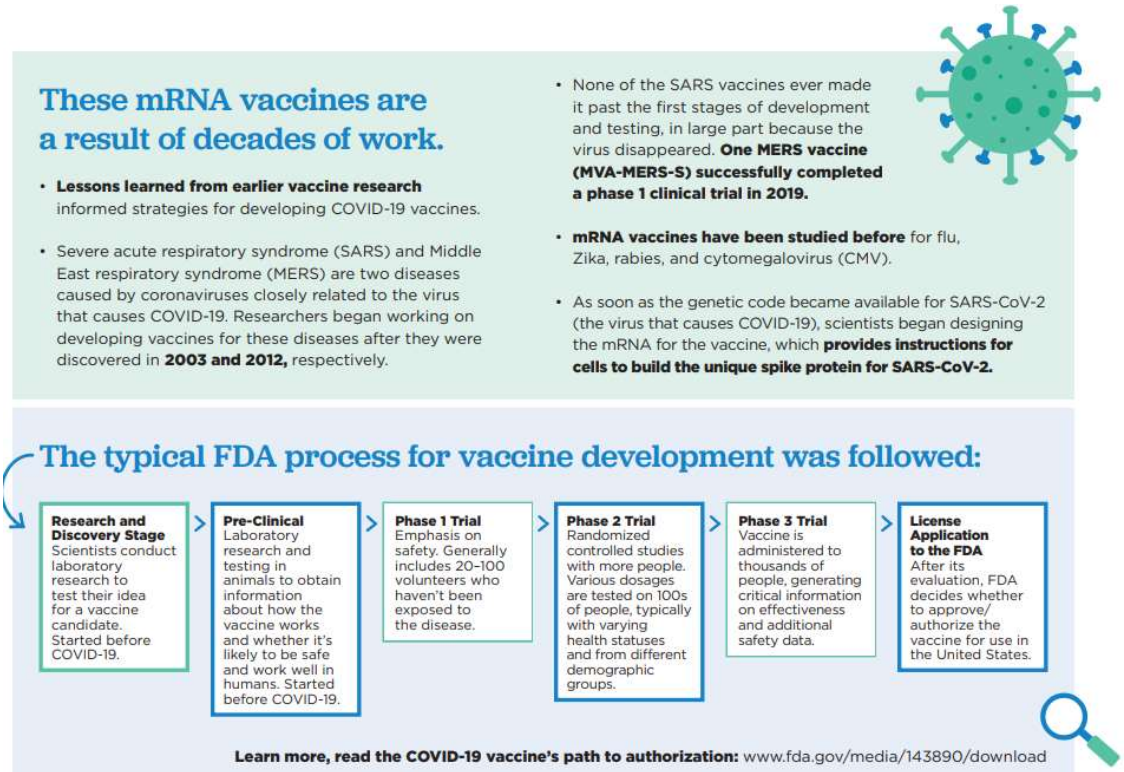
Vaccine safety is crucial in the vaccine development process. A number of health and safety issues can arise from vaccination that can vary from mild fever to death. Even though live attenuated vaccines mount a natural infection and can induce a primary immune response better than inactivated whole-cell and adjuvanted vaccines, there are safety concerns when vaccinating with live attenuated pathogens. Tis is illustrated by immunization of children with BCG which may lead to various complications such as BCG lymphadenitis, injection site complications, and disseminated BCG disease. In addition, BCG vaccination can cause disseminated BCGosis in immunocompromised individuals, e.g. HIV infected children, and therefore BCG is not approved as a vaccine for HIV exposed neonates in numerous countries . Te impaired T-cell responses in HIV-infected children, low BCG-induced CD8 T cell responses, IFN-γ, TNF-α and IL-2 cytokines secretion, and expression of "low quality" T cell responses, may explain the low protection provided by BCG and the dissemination of BCGosis. Viral-vectored vaccines expressing bacterial/virus specifc antigens are considered safer than live

attenuated vaccines. However, preexisting antibodies to the viral vector and inadequate human immune response in response to the vectored vaccines are the main limitations. In phase I clinical trials of TB vaccination, the immune response to the TB Ad5 Ag85A vaccine candidate was correlated with preexistinganti-adenovirus antibodies . Tis limitation may be resolved by changing the route of immunization. Satti and colleagues reported that aerosol administration of TB vaccine candidate MVA85A in humans overcame preexisting antibodies against the vaccine vector, whereas serum antibodies for the viral vector were detected after intradermal administration [78]. In addition, development of modifed adenovirus vaccines, such as chimpanzee adenovirus-vectors that can induce cellular and humoral cell responses may be another option [79]. Inadequate immune responses generated by inactivated viral vaccines and/or viralvectored vaccines can cause an adverse reaction known as antibody-dependent enhancement (ADE) . In ADE, viral entry into host cells is enhanced by efciency of virus-antibody complex to FcR bearing cells. Tis is often noticed when the vaccine-induced antibody fails to neutralize the virus because of diluted antibody levels or inaccurate specifcity [80]. Tis can lead to macrophage activation and infammatory cytokine secretion and subsequently tissue damage . showed that human macrophages were infected by SARS-CoV as a succeeding Ig-G mediated ADE . Additionally, vaccinating with SARS-CoV vaccine candidate expressing spike protein induced the infection human B cells in vitro . Te mechanism required to develop a vaccine that mimics the natural infection and induces adequate immune responses remains an ambitious immunological approach. Te immunological and serological specifcations that can explain the correlation of protection against SARS-CoV-2 infection, especially neutralizing antibody titer, need to be explored.

Covid-19 vaccine development, evaluation, approval and monitoring

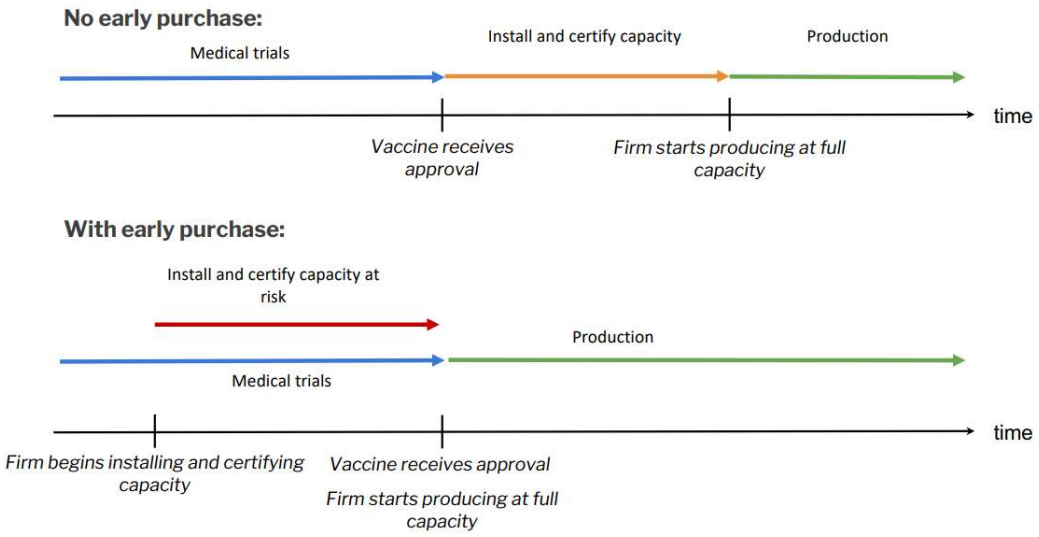


How Did the COVID-19 Vaccine Get Developed So Quickly?



Financing Vaccine Development

Against a backdrop of missteps in responding to emerging infectious disease threats, the Coalition for Epidemic Preparedness Innovations (CEPI) was launched and funded by public, private, philanthropic, and civil society organizations in 2017 to accelerate development of vaccines against emerging infectious diseases and enable equitable access to vaccines during outbreaks. “We’re not safe unless everybody is safe, and so we’ve got to talk about vaccines for the world, not just for the U.S., and we have to talk about vaccines for high-, middle- and low-income countries,” the preparedness expert said. Other than China and the United States, CEPI is the most prominent global funder of COVID-19 vaccine efforts. Along with the vaccine alliance known as Gavi and the World Health Organization, CEPI is leading the COVAX Facility,7 which is the vaccines arm of the Access to COVID-19 Tools Accelerator, a global collaboration of almost 200 countries working to accelerate the development, production, and equitable access to COVID-19 tests, treatments, and vaccines (see About the COVAX Facility for more information). COVAX currently has the world’s largest and most diverse COVID-19 vaccine portfolio, including nine candidate vaccines, with another nine candidates under evaluation.8 By supporting a diversified COVID-19 vaccine research portfolio, pooling negotiations with manufacturers, and investing in preinstalled vaccine production capacity, the COVAX Facility aims to deliver 2 billion vaccine doses by the end of 2021. Participating higher-income countries will self-finance, while lowerincome countries will be funded through donations to an advance market commitment for COVID-19 vaccines. Some COVAX participating higher-income countries are hedging their bets on having access to an effective vaccine by also contracting directly with manufacturers. The United States has declined to join the COVAX effort,9 preferring instead to go it alone with Operation Warp Speed, which aims to deliver 300 million doses of a safe, effective vaccine for COVID-19 by January 2021.



Ensuring Vaccine Manufacturing Capacity

Given the perilous path of vaccine development and manufacturing, where every step of the process must be tested and certified, many experts believe pursuing as many vaccine candidates as possible is the best guarantee of success. As of early September 2020, more than 100 coronavirus vaccine candidates were under investigation worldwide, with 37 already in clinical trials on humans.10 If and when coronavirus vaccines receive regulatory approval, the next challenge will be manufacturing and distributing the vaccines at a scale never before attempted—potentially billions of doses. "People outside the field don't fully appreciate how different it is to manufacture vaccines versus produce a pill," according to an economist presenting at the meeting. Understanding the global supply chain will be critical to quickly ramping up production and distribution of successful vaccine candidates. Along with the complicated manufacturing process of vaccines, each of those billions of doses will need a glass storage vial and a syringe to administer the vaccine. "Having lived through thelast few months, none of us would like to bet our lives on the supply chain working properly…If we can't make masks, how are we going to be sure we can make other things?" the economist said. Typically, manufacturers wait until a vaccine completes successful clinical trials before installing production capacity—or the infrastructure to make the vaccine—which can take months to bring online. Instead, many leading economists believe the best way to quickly scale up vaccine research and development and production is through a combination of so-called push and pull financing approaches. An example of a push approach would be direct subsidies of research to identify vaccine candidates, while a pull approach helps guarantee a market for a successful vaccine by lining up buyers before a vaccine even exists. An example of a pull approach is an advance market commitment, which guarantees vaccine manufacturers sales at a fixed price in return for an effective vaccine.11 The approach essentially pays manufacturers to preinstall and certify capacity to produce a vaccine once it clears regulatory hurdles, with payment for the actual vaccine close to marginal cost. If the vaccine candidate fails, buyers do not pay production costs. Such an approach avoids the lag between waiting until vaccines receive approval and then "letting the market figure it out," which could be a recipe for shortages and higher prices, the economist said.

Allocating Access to Vaccines

Once effective vaccines are available, the global health ideal is to distribute vaccines by countries' health needs, independent of their wealth, according to another economist who studies approaches to equitably allocating vaccines both across and within countries. In practice, however, allocation is much trickier in a global collaboration that brings together high-, middle- and low-income countries, where to some degree wealthier countries subsidize poorer countries. Unless high-income countries receive enough value for participating, they may opt out, so linking their vaccine allocations to their investments and offering portfolio flexibility are important. Gaining participation of high-income countries is critical because they bring bargaining power and investments in capacity that will remain available to produce more vaccine doses. "So even if the high-income countries get some of the first doses off the line or a proportional share relative to their investment, you still produce doses faster, which means you can distribute them more broadly faster," the economist said. For low-income countries funded through the advance market commitment, there is more discretion to set allocation rules, perhaps, conditioning allocation on countries taking basic precautionary measures and monitoring disease spread and severity. Moreover, inherent risk and health outcomes vary both across and within countries, so there is a need for a transparent allocation formula managed by a scientific board that can parse emerging evidence on transmission and mortality rates and consider a number of factors in making allocations, including each country's intrinsic.

COVID-19 vaccines approved through Emergency Use Authorization

Vaccines traditionally used are live attenuated viruses, inactivated viruses, protein or polysaccharide conjugated subunit vaccines and virus-like particles. Also, recently included vaccines are nucleic acids, DNA and RNA and viral vectors and recombinant proteins.SARS-CoV-2 induces a strong adaptive immune response of both T and B cell. Additionally, antibodies IgG and IgM appear about 10 days post-infection. The majority of the patients are able to seroconvert in 3 weeks. The antibodies are created against internal nucleoprotein (N) and spike protein (S) of the virion and possess

neutralizing activity. Antibodies which bind to the spike protein, particularly to its receptor-binding domain (RBD), inhibit its attachment to the host cell and counteract the virus . few vaccine candidates approved through EUA that reached up to or completed Phase 3 trials.

BNT162 vaccine by Pfizer and BioNTech

On December 2, 2020, UK became the first country to approve COVID-19 vaccine BNT162 developed by Pfizer and BioNTech via EUA. On December 11, 2020 US FDA issued first EUA for BNT162 having demonstrated 95% efficacy in preventing disease in phase III clinical trial results . Later Canada and Mexico also approved BNT162 via respective EUA pathways. On December 31, 2020, WHO approved first vaccine candidate, BNT162, for emergency use thereby making it easier to manufacture and distribute this vaccine globally . Initially, four candidates were developed of which two were nucleoside modified mRNA, modRNA; one was uridine containing mRNA, uRNA; and other was self-amplifying mRNA, saRNA. In the preclinical study, modRNA BNT162b2 showed protective antiviral effects in *Rhesus macaques* with concurrent elevated neutralizing antibody titers and a Th-1 biased cellular response in *Rhesus macaques*, as well as in mice. Therefore, BNT162b2 was selected for Phase 2/3 clinical trials .

In Phase 1/2 trial of two hundred participants aged 18–55 years with a vaccine dose range of 1–100 µg is currently recruiting (NCT04380701) as is a Phase 2/3 trial of about 32,000 participants (NCT04368728) and a Phase 1/2 trial of 160 participants between age 20–85 (NCT04588480) .On November 9, 2020, Pfizer and BioNTech declared interim results of 94 participants of Phase 3 trial claiming > 90% efficacy of BNT162b2 against SARS-Cov-2 infection at 7 days after the administration of second dose . Phase 1 trial data showed similar immunogenicity between BNT162b1 and BNT162b2, while BNT162b2 was associated with a lower incidence and severity of systemic reactions than BNT162b1 .

Another study of Phase 1/2 data for BNT162b1 (NCT04368728) showed robust immunogenicity at all three doses of 10 µg, 30 µg and 100 µg among 45 participants, 18–55 years of age. Adverse reactions were high at the maximum dose and therefore, participants were not given a second dose. Participants who were given two doses between 1 and 50 µg of BNT162b1 had vigorous receptor-binding domain (RBD)-specific IgG antibody, T-cell and favorable cytokine responses .

Both BNT162b1 and BNT162b2 received the FDA Fast Track designation. But BNT162b2 was preferred over BNT162b1 for Phase 2/3 safety study, based on preclinical and clinical study results. The developers have asked the FDA to consider an expanded protocol for the Phase 3 trial to include up to 44,000 participants. Europeans Medicines Agency (EMA) has initiated a rolling review of BNT162b2 which helped to accelerate its approval . One drawback with this vaccine is that it requires storage at − 80° to − 60 °C, a fact that could pose logistic problems .

mRNA-1273 vaccine by Moderna

Moderna's mRNA-1273 becomes the second CVC to be approved by FDA under EUA. It is developed on the basis of available data of coronaviruses causing severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS). A Phase 3 trial of 30,000 participants at higher risk for COVID-19 is ongoing. Participants will be given 100 µg dose of mRNA-1273 or placebo and then be followed for up to 24 months (COVE trial; NCT04470427). After successful completion of Phase 1 trial (NCT04283461) of 105 participants, Phase 2 trial of 600 participants evaluating 25 µg, 100 µg and 250 µg dose levels of the vaccine was carried out (NCT04405076). Then, Phase 3 results of 95 participants after an interim analysis revealed 94.5% efficiency of the vaccine with no significant safety concerns .

The mRNA-1273 effectively produced neutralizing antibody titers in 8 participants of Phase 1 trial after receiving 25 µg or 100 µg doses. Neutralizing antibody titers of these participants were similar to the convalescent sera from COVID-19 recuperated patients . Higher age adults subjects who received two doses of either 25 µg or 100 µg of the mRNA-1273 demonstrated safety and suffered mild or moderate effects including, fatigue, chills, headache, myalgia, and pain at the injection site . In a preclinical study, mRNA-1273 prevented viral replication in the lungs and produced neutralized titers similar to subjects receiving 25 µg or 100 µg doses of the vaccine . Another preclinical study consisting of nonhuman primates challenged with SARS-CoV-2 showed neutralizing activity and reduced inflammation and lung activity post administration of mRNA-1273 .

The mRNA-1273 also got the Fast Track designation from the US FDA. A Phase 3 trial of the vaccine is currently underway and is funded by the Operation Warp Speed . One potential issue for this vaccine could be the storage temperature requirement of − 25° to − 15 °C is required .

AZD1222 by AstraZeneca and University of Oxford

On December 30, 2020, UK and on January 2, 2021, India approved AZD1222 COVID-19 vaccine developed by AstraZeneca and the Oxford Vaccine Group at the University of Oxford. It was previously called as ChAdOx1, a chimpanzee adenovirus vaccine . This group has previously developed a MERS vaccine. In India, this vaccine is jointly developed by Serum Institute of India and AstraZeneca and is branded as Covishield. A preclinical study showed significantly reduced viral load and humoral and cellular immune response . Another preclinical study demonstrated an immune response inboth mice and pigs . ChAdOx1, a replication-deficient simian adenoviral vector expressing the full-length SARS-CoV-2 spike (S) protein, was commenced in April 2020 following preclinical studies involving non-human primates using a single dose. When one vs two doses of ChAdOx1 in both mice and pigs were compared, a single dose induced antigen-specific antibody and T cells responses, and a second booster dose enhanced antibody responses, particularly in pigs, with a significant increase in the level of SARS-CoV-2 neutralizing titers.

A Phase 1/2 (NCT04324606) study involving 1077 healthy adult participants aged 18–55 years, assessed the safety, reactogenicity, and immunogenicity of a viral vectored coronavirus vaccine, expressing the spike protein of SARS-CoV-2. The results demonstrated an acceptable safety profile for ChAdOx1 nCoV19 and increased antibody response by homologous boosting . A Phase 3 trial (NCT04516746) is ongoing and has enrolled more than 40,000 subjects. Preliminary results have demonstrated that the safety profile of the vaccine candidate is acceptable, with most patients demonstrating an antibody response after one dose and all patients showing a response after two doses . A Phase 3 trial in Brazil reported one death, which was confirmed by the Brazilian National Health Surveillance Agency (ANVISA). AstraZeneca stated that the results from the Phase 3 trial demonstrate immunogenicity, but have not yet publicly released any data . An inhaled version of the vaccine candidate is also being tested in a small trial involving 30 participants.

The trials by AstraZeneca are funded by BARDA and Operation Warp Speed. IQVIA also announced they are partnering with AstraZeneca to advance clinical trials for this vaccine. Phase 3 trials are being conducted in the United States and India but were put on hold following reporting of a serious

adverse event. Trials have since restarted. Additionally, EMAs human medicines committee (CHMP) and Health Canada have initiated a rolling review of AZD1222 to reduce the decision-making time related to safety and efficacy. The Australian Therapeutic Good Administration (TGA) granted AZD1222 provisional determination, the first step in the approval process. In Britain, the Medicines and Healthcare products Regulatory Agency (MHRA) has also started an accelerated review of AZD1222 . This vaccine requires refrigeration (2–8 °C), which can potentially be problematic for use in low-income countries .

CoronaVac by Sinovac

CoronaVac (formerly PiCoVacc) is approved by China through EUA. CoronaVac is a formalin-inactivated and alum adjuvanted vaccine candidate developed by Sinovac Biotech, China . Results from preclinical studies showed partial or complete protection in non-human primates exposed to SARS-CoV-2 [33].

A Phase 1/2 trial of 743 healthy participants (18–59 years old) who received two different dosages of the vaccine or placebo is active but not recruiting (NCT04551547). A Phase 1 trial of 143 participants (NCT04352608) and Phase 2 trial of 600 participants (NCT04383574) are both active but not recruiting. Phase 3 trial is underway (NCT04456595) to have 9000 participants. Trials are also ongoing in Turkey (NCT04582344) and in Indonesia (NCT04508075). Phase 1/2 trials revealed that the vaccine has good safety and immunogenicity with seroconversion occurring in 92.4% of participants after the 3 µg dose given on a 0–14 day schedule and 97.4% of participants with the same dose on a 0–28 day interval .

Preliminary results from the InstitutoButantan trial, declared by the Sinovac, showed CoronaVac is safe with no reported serious adverse events. However, the trial in Brazil was briefly suspended due to patient death, though the trial has resumed later .

COVID-19 vaccine by Sinopharm and the Wuhan Institute of Virology, China

China approved this vaccine via EUA. Sinopharm and Wuhan Institute of Virology under the Chinese Academy of Sciences have developed an inactivated CVC. A Phase 1/2 clinical trial (ChiCTR2000031809) involving healthy subjects is ongoing. According to a release from China National Biotec Group, this vaccine has demonstrated a strong neutralizing antibody response. Phase 1 and Phase 2 trials data also showed immunogenicity . A Phase 3 trial is in progress in Peru, Morocco, and United Arab Emirates.

Sputnik V by the Gamaleya Research Institute, Russia

Russia has approved first CVC as Sputnik V (previously as Gam-COVID-Vac). The Gamaleya Research Institute in Russia and Health Ministry of the Russian Federation are assessing their non-replicating viral vector vaccine, Sputnik V, in a Phase 3 trial. However, there is no trial data available to date. This led to criticism as even there is a lack of data on safety and efficacy, the vaccine is approved.

Two Phase 1/2 trials with 38 subjects each were conducted (NCT04436471, NCT04437875). Sputnik V is additionally being evaluated in a small Phase 2 trial with 110 subjects older than 60 years (NCT04587219). A Phase 3 trial with about 40,000 participants is also in progress (NCT04530396). Aside from Russia, Sputnik V is also being evaluated in Belarus (NCT04564716) and the United Arab Emirates. The results from the Phase 1/2 trials demonstrated the safety and immunogenicity of the vaccine . The Russian Direct Investment Fund also announced that Sputnik V is 92% effective based on the interim trial results from 20 participants. A preliminary pre-submission of the vaccine has also been proposed in Brazil [39].

BBIBP-CorV by Sinopharm and Beijing Institute of Biological Products, China

BBIBP-CorV is inactivated CVC developed by Sinopharm in association with Beijing Institute of Biological Products, China. Firstly China and later on United Arab Emirates (UAE) approved the vaccine through EUA .

BBIBP-CorV is currently being assessed in Phase 2 (CHiCTR2000032459) and Phase 3 trial in China (ChiCTR2000034780) as well as Phase 3 trial in Argentina (NCT04560881). BBIBP-CorV is shown to be highly effective in preventing disease against SARS-CoV-2 in *Rhesus macaques* [40]. Phase 1 results showed that BBIBP-CorV was safe and tolerated at all dose levels, with all participants showing a humoral response to the vaccine after 42 days. The UAE announced that the vaccine is 86% effective [41].

EpiVacCorona by Federal Budgetary Research Institution State Research Center of Virology and Biotechnology, Russia

Russia also granted regulatory approval to EpiVacCorona, a peptide vaccine candidate for COVID-19, developed by Federal Budgetary Research Institution State Research Center of Virology and Biotechnology .

A Phase 1/2 trial in Russia is assessing the effectiveness of the vaccine (NCT04527575). A Phase II clinical trial of the vaccine was completed recently. Head of the zoonotic diseases and flu department with the State Research Center of Virology and Biotechnology has said “participants have developed immunity a month after the first vaccination”, but there is no data available in the public domain.

Covaxin by Bharat Biotech and National Institute of Virology, India

On January 2, 2021, India approved an inactivated vaccine called Covaxin, developed by Bharat Biotech and India’s National Institute of Virology. A Phase 1/2 trial of about 1100 healthy subjects is ongoing after obtaining permission from the Drug Controller General of India. The Indian Council of Medical Research (ICMR) reported that Covaxin has entered Phase 2 clinical trials. On October 27, 2020, the ICMR approved Covaxin for Phase 3 trial. Results of a two-dose regimen study administered to *Rhesus macaques* demonstrated an increase in SARS-CoV-2 specific IgG and neutralizing antibodies as well as diminished viral replication in the nasal cavity, throat, and lungs . According to the trial principal investigator, initial results from the first fifty participants who received the vaccine seem to be promising. In addition, according to Bharat Biotech, the first two phases of the trial did not demonstrate any major adverse events. The proposed distribution for this vaccine is February 2021, according to an ICMR scientist who spoke with Reuters.

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