A Review on COVID-19 Vaccines

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The coronavirus disease 2019 (COVID-19) outbreak was first reported in Wuhan, China in late 2019. Since its emergence, COVID-19 has spread to 188 countries and 25 territories around the globe despite elaborate efforts by WHO and Governments to contain the infection, primarily owing to the highly infectious nature of this virus. To date, over 30.6 million COVID-19 cases and 950 000 deaths have been reported to WHO (1). It is widely believed that pre-pandemic normalcy will never return until a safe and effective vaccine strategy becomes available and a global vaccination program is implemented successfully. Efforts on COVID-19 vaccines started very early on at the initial outbreak of novel coronavirus and spread worldwide as the disease was declared a pandemic by WHO. However, we will not have an effective COVID-19 vaccine before 2021 as per very optimistic estimates. This is because a successful COVID-19 vaccine will require a cautious validation of its efficacy and adverse reactivity as the target population includes high-risk individuals over the age of 60, particularly those with chronic co-morbid conditions, frontline healthcare workers and those involved in essential industries.

Vaccine immunology-Adaptive Immune Response

A vaccine is medical preparation ranging from intact organisms (attenuated live or inactivated) to genetically engineered parts of the organisms (antigenic) that induce both arms of the adaptive immune system and stimulate a sufficient number of memory T cells and B lymphocytes (2). Vaccines should contain antigens necessary to mount the specific response without causing disease. Once challenged with the pathogen, memory cells yield effector T cells and antibody-producing B cells and fight the infection. The antibodies have to be the neutralizing type which binds to the virus and block infection (3). The virus coated with neutralizing antibodies either cannot interact with the receptor or may be unable to uncoat of the genome. Most currently licensed vaccines induce neutralizing antibody responses capable of mediating long-term protection against lytic viruses, such as influenza and smallpox. The T cell–based responses that recognize and kill infected cells also fight the infection (4). Following antigen processing in dendritic cells, the small peptides are displayed at the cell surface at the groove of major histocompatibility complex (MHC) class I and class II molecules. Cytotoxic T cells (CD8+) recognize MHC class I-peptide complexes and differentiate into cytotoxic effector cells capable of killing infected cells or pathogens. Helper T cells (CD4+) recognize MHC class II-peptide complexes and differentiate in effector cells that produce preferentially T helper 1 cells (Th1) or T helper cells 2 (Th2) cytokines (5) (Figure 1). Th1 support CD8+ T cell differentiation, which is in contrast inhibited by Th2-like cytokines.

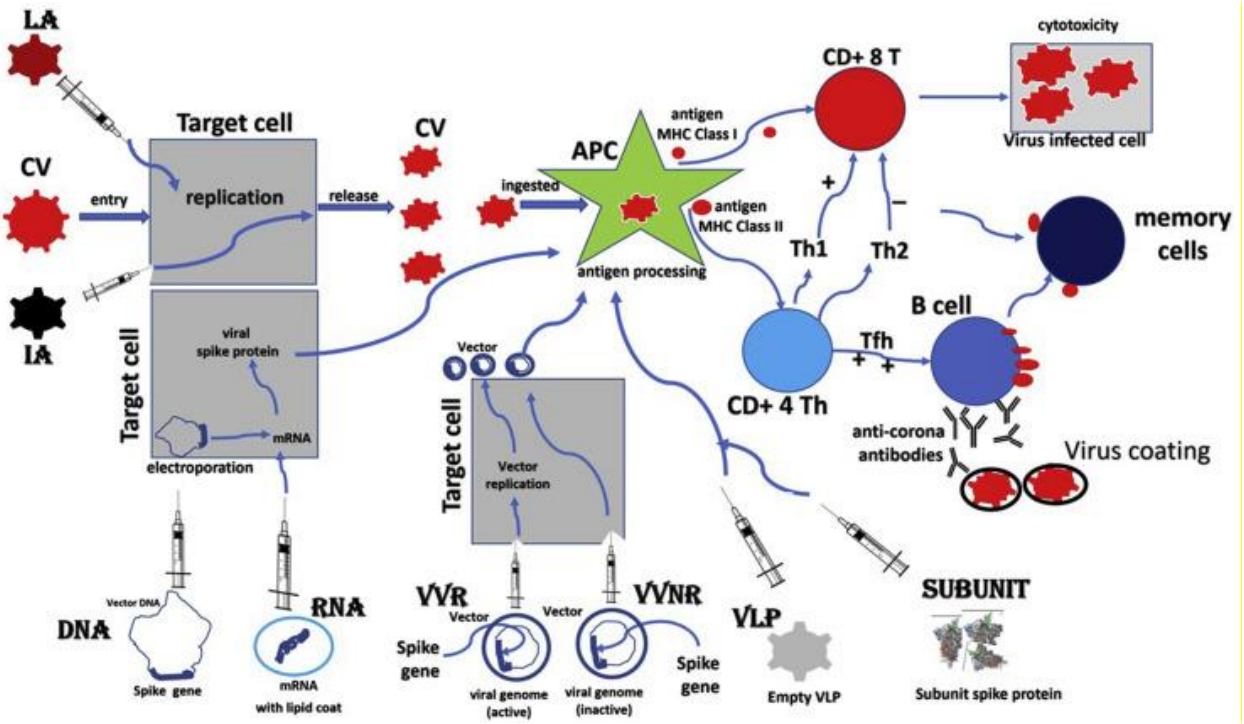


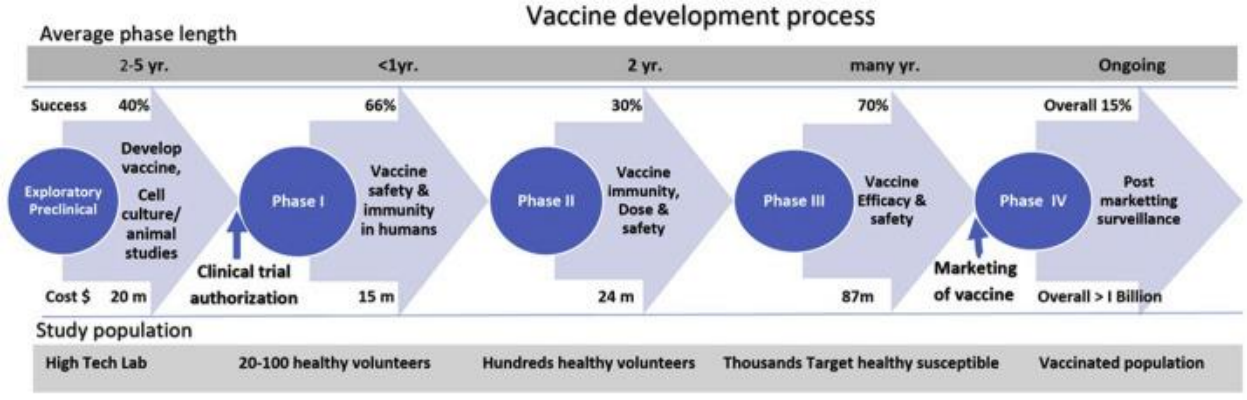
Figure 1

Schematic drawing of 8 platform strategies used for the development of COVID-19 vaccines, and the pathway each one follows to induce T cell and B cell immune response. The strategies include live-attenuated vaccine (LA), inactivated vaccine (IA), DNA vaccine (DNA), RNA vaccine (RNA), viral vector replicating vaccine (VVR), viral vector nonreplicating (VVNR), virus-like particles (VLP), and subunit vaccine (Subunit). CV, coronavirus; APC, antigen processing cell.

Developing a COVID-19 vaccine

Stages of Vaccine Development

Every new vaccine follows a stringent protocol in Research and Development (R&D) which has to be meticulously followed and completed before it is licensed to be marketed (5) (Figure 2). Regulatory authorities - namely WHO, U.S. Food and Drug Administration, the European Medicines Agency, and national authorities of many countries - have issued guidelines relevant to the clinical evaluation of vaccines (6) (7) (8). The guidelines for vaccine development are more stringent than those meant for drug development. The reason for this is obvious; these vaccines are for global use, have enormous potential for production and marketing, and are given to healthy populations including children, elderly, and pregnant mothers. Vaccine development follows a unique stepwise pattern and is broadly divided into Exploratory, Preclinical, Clinical, and Post marketing stages. The clinical stage is divided into 3 phases, namely phases I, II, and III. There are 2 regulatory permissions needed namely “Clinical Trial Authorization” before the clinical stage to allow “First-in-human” testing and “Biologic License Application/Approval” for the marketing of the vaccine after successful clinical trials



COVID-19 Vaccine Platform Technologies

Several vaccine designs by researchers are up for trial as candidate vaccines against COVID-19. Overall, 8 types of designs, under 4 broad groups, have been tried to develop candidate COVID-19 vaccines (5) (Table 1). Each vaccine design has a subtle structure, advantages, and disadvantages in immunogenicity, safety, ease of use, and effectiveness (5) (Figure 1)

Live-attenuated vaccines are developed by a process in which a live virus is passed through animal or human cells until genome mutates and is unable to cause disease. Such vaccines are good to attain herd immunity in the population and block transmission of disease. However, there is a small chance of mutation reversal to virulence and the occurrence of disease. Inactivated vaccines are treated with formaldehyde or heat, and as the virus is killed, such vaccines are safe and cannot cause disease. However, such vaccines do not replicate, cause a suboptimum immune response, and need repeated dosing and adjuvants to enhance immunity.

Nucleic acid vaccines are the new generation vaccines, made available by modern technology. A DNA vaccine is made by inserting DNA encoding the antigen from the pathogen into plasmid DNA. RNA vaccines employ lipid-coated mRNA of the SARS-CoV-2 which expresses Spike protein. The expressed proteins are presented by MHC class I to CD+ 8 T cells and inducing a strong T cell response. These vaccines are safe, easy to manufacture by the platform technology, and may be gamechangers in the future of vaccines. As of today, there are no nucleic acid vaccines in clinical practice.

Recombinant vector virus vaccines are produced through recombinant DNA technology. This involves inserting the DNA, encoding an antigen from the pathogen into bacteria or virus vectors, expressing the antigen in these cells, and then purifying it from them. During vaccination, the vector replicates, and along with it, the encoded DNA is expressed and processed, giving robust T cell and B cell immune response. Vectors may be bacteria such as *E. coli* or viruses such as Adenovirus or poxvirus.

Subunit vaccines are composed of purified antigen peptides of viruses like Spike protein of SARS-CoV-2 and are safe to use. Such an antigen is directly presented to MCH class II and often does not generate a robust cytotoxic T cell response (MHC class I dependent). Thus, such vaccines need repeated dosing and adjuvants to enhance immunity. Virus-like particles are made from empty virus particles without genetic material. Such vaccines are safe and immunogenic, however, are difficult to manufacture.

Table 1

Vaccine	Structure	Comments
Virus vaccines		
Attenuated	Virus is weakened by passing through animal or human cells, until genome mutates and unable to cause disease	Inexpensive, rapid production Live vaccine, small chance of disease, replicates Needs cold chain Induces strong long-lasting T cell & B cell immune response Good for attaining herd immunity in the community Vaccine in use: BCG, Smallpox, MMR, Chickenpox, Rotavirus, Yellow fever, Polio (OPV)
Inactivated	Virus inactivated with formaldehyde or heat	Noninfectious, cannot cause disease. Can be freeze dried, no cold chain needed Needs adjuvant for immune response Can cause T_H2 cell skewed response (ADE) Vaccines in use: Polio (IPV), HAV, Rabies. Hepatitis A, rabies, Flu. Candidate COVID-19 vaccine: PiCoVacc (Sinovac Biotech)
Nucleic acid vaccines		
DNA vaccine	Gene encoding antigenic components (Spike protein)	Safe, cannot cause disease. Yet unproven in practice. Can cause T_H2 cell skewed response (ADE) when used alone. Highly immunogenic, generate high titre neutralizing antibodies when given with inactivated vaccine. Electroporation device needed for delivery Candidate COVID-19 vaccine: INO-4800 (Inovio Pharma, CEPI, Korean Institute of Health, International Vaccine Institute)
RNA vaccine	mRNA vaccine for spike protein, with a lipid coat	Safe, cannot cause disease, Can cause T_H2 cell skewed response, Yet unproven in practice Candidate COVID-19 vaccine: mRNA-1273

Vaccine	Structure	Comments
		(Moderna/NIAID). BNT162 (a1, b1, b2, c2) (BioNTech/Fosun Pharma/Pfizer)
Viral vector vaccines		
Replicating	An unrelated virus like measles or adenovirus is genetically engineered to encode the gene of interest	Safe, Induces strong T cell and B cell response, Vaccines in use: Hepatitis B, pertussis, pneumonia caused by *S. pneumoniae*, HPV, Hib (*Haemophilus influenza*)
Nonreplicating	An unrelated virus like measles or adenovirus (with inactive gene) is genetically engineered to encode the gene of interest	Safe, Need booster shots to induce long-term immunity, No vaccine licensed yet Candidate COVID vaccine: Ad5-nCoV (CanSino Biological Inc./Beijing Institute of Biotechnology). ChAdOx1-nCoV-19 (University of Oxford)
Protein-based vaccines		
Subunit	Antigenic components (spike protein) are generated *in vitro* and harvested for vaccine	Safe, Need multiple dosing and adjuvants
Virus-like particles	Empty virus shells with no genetic material	Safe, Strong immune response, Difficult to manufacture

SARS-CoV-2 Structure

Coronaviruses are pleomorphic, enveloped viruses with a characteristic fringe of projections composed of S protein on their surface. The SARS-CoV-2 virus contains four structural proteins namely, spike (S), nucleocapsid (N), envelope (E), and membrane (M) proteins which are encoded by the 3'-end of the viral genome (10). Amongst the 4 structural proteins the S glycoprotein, being a large multi-functional trans-membrane protein, plays the vital role of viral attachment, fusion, and entry into the host cell (10). The S protein consists of S1 and S2 subunits, which are further split into different functional domains. The S1 subunit has two functional domains viz. N-terminal Domain (NTD) and Receptor Binding Domain (RBD) and the latter contains conserved receptor binding motif (RBM) (11). SARS-CoV-2 uses the human angiotensin-converting enzyme 2 (hACE2) receptor to seize the target cell through the spike

glycoprotein (S-Protein). It has been suggested that the coronaviruses exercise the use of conformational masking and glycan shielding of the spike protein to circumvent the host immune cells. The E protein that forms E channels (called the viroporins), and is involved in a myriad of functions in the viral replication cycle involving assembly, release, pathogenesis, etc (12). M protein, the central organizer of CoV assembly, is most abundantly expressed in the virus particle. It functions crucially in the morphogenesis and assembly of the SARS-CoV-2 by interacting with the essential structural proteins. The binding of the M and N protein stabilizes the N protein and RNA complex, and the internal core of the virus. In addition to stabilizing the ssRNA genome of the virus particle, the N protein is an antagonist of the antiviral RNAi. It is responsible for the inhibition of the cell cycle of the host cell as it can inhibit the entry of the cell into the S-phase (13).

A vaccine that elicits the production of S protein neutralizing antibodies in the vaccinated subjects is the primary aim of all the programs for COVID-19 vaccines (14).

Late Stage COVID-19 Vaccines

Here is a look at the prospective vaccines that have reached phase three and beyond, including a quick primer on how they work and where they stand (15) (Table 2).

Table 2

Name	Company	What	Status
JNJ-78436735	Johnson & Johnson	Johnson & Johnson is developing an adenovector vaccine, which introduces a piece of DNA from SARS-CoV-2 into the common cold-causing adenovirus that has been genetically changed so that it can't replicate in the body. This vaccine builds on the technology Johnson & Johnson used to develop an Ebola vaccine as well as vaccine candidates for Zika and HIV. In July, a study published in Nature showed that the vaccine elicited neutralizing antibodies in monkeys and provided "complete or near-complete" protection with just one dose.	On September 23, Johnson & Johnson announced the launch of a phase three ENSEMBLE trial that will evaluate the safety of the vaccine—and how well it works—among up to 60,000 adults from a variety of countries. The trial will include "significant representation" from older populations and will include those with underlying conditions that make them more susceptible to COVID-19.
Ad5-nCoV	CanSino Biologics	CanSino has also developed a viral vector vaccine, using a weakened version of the adenovirus as a vehicle for introducing the SARS-CoV-2 spike protein to the body. Preliminary results from phase two trials, published in The Lancet, have shown that the vaccine produces "significant immune responses in the majority of recipients after a single immunisation." There were no serious adverse reactions documented.	Though the company was still technically in phase two of its trial, on June 25, CanSino became the first company to receive limited approval to use its vaccine in people. The Chinese government has approved the vaccine for military use only, for a period of one year. On August 15, Russian biopharmaceutical company Petrovax announced it had launched the first phase three clinical trial of Ad5-nCoV**.**

mRNA-1273	Moderna Therapeutics	This vaccine candidate relies on injecting snippets of a virus's genetic material, in this case mRNA, into human cells. They create viral proteins that mimic the coronavirus, training the immune system to recognize its presence. This technology has never been licensed for any disease. If successful, it would be the first mRNA vaccine approved for human use. This vaccine requires two doses, four weeks apart.	On July 27, Moderna announced it had started the third phase of its clinical trials, even as it continues to monitor phase two results. Preliminary findings from phase one have shown that healthy subjects—including elderly patients—produced coronavirus antibodies and a reaction from T-cells, another arm of the human immune response. Phase three will test the vaccine in 30,000 U.S. participants; Moderna says it is on track to deliver at least 500 million doses per year beginning in 2021, thanks in part to the deal it has struck with Swiss manufacturer Lonza that will allow it to manufacture up to one billion doses a year. In September, however, Moderna's chief executive Stéphane Bancel told the New York Times that it was unlikely the vaccine would be widely available in the first half of 2021.
BNT162b2	Pfizer	Pfizer and BioNTech are also developing an mRNA vaccine based on the German company's earlier efforts to use the technology in experimental cancer vaccines. Pfizer has signed a nearly $2 billion contract with the U.S. government to provide 100 million doses by December 2020—an agreement that goes into effect if and when the drug is approved and delivered.	On July 27, Pfizer and BioNTech launched a trial that combines phase two and three by enrolling a diverse population in areas with significant SARS-CoV-2 transmission. It has expanded the trial to include 44,000 people across multiple countries. The project is aiming to seek regulatory review before the end of the year—and hopes to supply 1.3 billion doses by the end of 2021. Preliminary results of phase one/two data show the vaccine produces antibodies and T-cell responses specific to the SARS-CoV-2 protein.
ChAdOx1 nCoV-19	University of Oxford	Oxford's candidate is what's known as a viral vector vaccine, essentially a "Trojan horse" presented to the immune system. Oxford's research team has transferred the SARS-CoV-2 spike protein—which helps the coronavirus invade cells—into a weakened version of an adenovirus, which typically causes the common cold. When this adenovirus is injected into humans, the aim is for the spike protein	Preliminary results from this candidate's first two clinical trial phases revealed that the vaccine had triggered a strong immune response—including increased antibodies and responses from T-cells—with only minor side effects such as fatigue and headache. It is in phase three of clinical trials, aiming to recruit up to 50,000 volunteers in Brazil, the United Kingdom, the United

		to trigger an immune response. AstraZeneca and Oxford plan to produce a billion doses of vaccine that they've agreed to sell at cost.	States, and South Africa. On September 8, AstraZeneca paused the trials for a safety review due to an adverse reaction in one participant in the U.K. The details remain unclear, though the company has described the pause as a "routine action." After an investigation by independent regulators, the trials resumed in the U.K., Brazil, South Africa, and India but remained on hold in the U.S. as of September 23.
CoronaVac	Sinovac	CoronaVac is an inactivated vaccine, meaning it uses a non-infectious version of the coronavirus. While inactivated, pathogens can no longer produce disease but can still provoke an immune response, such as with the annual influenza vaccine.	On July 3, Brazil's regulatory agency granted this vaccine candidate approval to move ahead to phase three, as it continues to monitor the results of the phase two clinical trials. Preliminary results in macaque monkeys, published in Science, revealed that the vaccine produced antibodies that neutralized 10 strains of SARS-CoV-2. Sinovac has also released preprint results of its phase two human trial that likewise showed the vaccine produced antibodies with no severe adverse reactions. Phase three will recruit nearly 9,000 healthcare professionals in Brazil. Sinovac will also conduct phase three trials in Indonesia and Bangladesh.
BCG	Murdoch Children's Research Institute	For nearly a hundred years, the Bacillus Calmette-Guerin (BCG) vaccine has been used to prevent tuberculosis by exposing patients to a small dose of live bacteria. Evidence has emerged over the years that this vaccine may boost the immune system and help the body fight off other diseases as well. Researchers are investigating whether these benefits may also extend to SARS-CoV-2, and this trial has reached phase three in Australia. Though as of April 12, the World Health Organization says there is no evidence that the BCG vaccine protects people against infection with the coronavirus.	In April, researchers from the Murdoch Children's Research Institute began a series of randomized controlled trials that will test whether BCG might work on the coronavirus as well. They aim to recruit 10,000 healthcare workers in the study.
None	Sinopharm	Sinopharm is also using an inactivated SARS-CoV-2 vaccine that it hopes will reach the public by the end of 2020.	On August 22, Sinopharm revealed that it began to inoculate medical workers and other high-risk groups with the

		Preliminary findings from two randomized trials, published in JAMA, have shown the vaccine can trigger an antibody response with no serious adverse effects. The study did not measure T cell-mediated immune responses. These results are significant, though, as they are the first published data from human clinical trials for a COVID-19 vaccine that uses a whole, inactivated virus.	Sinopharm trial vaccines in July, making it the first experimental vaccine available to civilians beyond clinical volunteers. Also in July, Sinopharm launched its first phase three trial among 15,000 volunteers—aged 18 to 60, with no serious underlying conditions—in the United Arab Emirates. The company selected the UAE because it has a diverse population made up of approximately 200 nationalities, making it an ideal testing ground. Sinopharm will also undertake phase three trials in locations such as Peru and Bahrain.
Sputnik V	Gamaleya	Gamaleya has developed a viral vector vaccine that also uses a weakened version of the common cold-causing adenovirus to introduce the SARS-CoV-2 spike protein to the body. This vaccine uses two strains of adenovirus, and it requires a second injection after 21 days to boost the immune response. Russia has not published any data from its clinical trials, but officials with the institute state that they have completed phases one and two. The researchers also claim the vaccine produced strong antibody and cellular immune responses.	Despite the lack of published evidence, Russia has cleared the Sputnik V vaccine for widespread use and claimed it as the first registered COVID-19 vaccine on the market. Russia reports that it will start phase three clinical trials on August 12; the World Health Organization, however, lists the Sputnik V vaccine as being in phase one of clinical trials.

Outlook

More than 150 coronavirus vaccines are in development across the world and hopes are high to bring one to market in record time to ease the global crisis. Several efforts are underway to help make that possible, including the U.S. government's Operation Warp Speed initiative, which has pledged $10 billion and aims to develop and deliver 300 million doses of a safe, effective coronavirus vaccine by January 2021. The World Health Organization is also coordinating global efforts to develop a vaccine, with an eye toward delivering two billion doses by the end of 2021.

Although the leading COVID-19 vaccine candidates have progressed to advanced stages of clinical development at exceptional speed, many uncertainties remain given the lack of robust clinical data so far. Moreover, given the highly unusual circumstances associated with developing a vaccine during the evolution of a novel global pandemic, probability of success benchmarks for traditional vaccine development are likely to underrepresent the risks associated with delivering a licensed vaccine for COVID-19. The most advanced candidates are expected to begin reporting data from pivotal studies over the coming months, which if positive will be used to support accelerated licensure of the first COVID-19 vaccines. Such data will also provide valuable insights for the field and inform ongoing and future

development activities aimed not only at controlling the current global pandemic, but also for effective long-term immunization strategies against the disease.

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