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Feature Article

COVID-19 Vaccines: Current Status and Future Prospects

Kaushik Bharati†

Abstract

Vaccines against coronavirus disease 2019 (COVID-19) have been developed in record time – the fastest in medical history! Many types of vaccines, using both traditional platforms, as well as newer ones using novel technologies, have been developed. Many of these vaccines have already been deployed in global COVID-19 vaccination campaigns. Many more are still undergoing preclinical and clinical development, which will help to strengthen and replenish the vaccine pipeline. All the vaccines that are currently being used for mass vaccination are extremely safe and highly efficacious. These are capable of generating robust humoral and cell-mediated immune responses. However, with the emergence of variants, the efficacy of some of these vaccines have started to wane. The present review explores the current status of COVID-19 vaccines, as well as the future prospects for these life-saving tools, given that variants are now a stark reality.

Key Words: COVID-19, Vaccine, Status, Prospect.

Introduction

Coronavirus disease 2019 (COVID-19) has its origins from a cluster of atypical pneumonia cases of unknown etiology from the city of Wuhan in Hubei Province, China. These cases were reported to the World Health Organization (WHO) on 31st December 2019. The next day – New Year's Day 2020 – WHO immediately activated its emergency response team. This was to be the start of an unprecedented health catastrophe that only comes once in a century. This unanticipated global pandemic is still ongoing and shows no signs of abating.

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This novel virus belongs to the Family *Coronaviridae* and Sub-family *Betacoronavirus*. SARS-CoV-2 infects various types of animals, including mice, bats, dogs, cats, minks, cattle, and pangolins, among others. It generally circulates within this animal reservoir. But this is the first time it has jumped the species barrier and infected humans. As of 19th October 2021, the virus was responsible for 242 million cases and 4.9 million deaths across 221 countries and territories worldwide.[1]

Ever since the pandemic began, scientists were unanimous in their opinion that vaccines would be the answer to halting the disease. But developing vaccines against a brand-new

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†PhD, MIPHA, FRSPH (London), Health Policy Consultant – UNESCO, New Delhi
e-mail: dr.kaushik.bharati@gmail.com
ORCID: Kaushik Bharati: https://orcid.org/0000-0003-3764-0186

pathogen wasn't easy. There were too many unknowns. For example, it wasn't clear what type of immune responses would be generated and what the immune correlates of protection would be. Importantly, COVID-19 vaccine development efforts relied heavily on the knowledge gained from the previous severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) epidemics, which occurred in 2002 and 2012, respectively. The experience gained from these previous vaccine development efforts went a long way in designing the new vaccines against SARS-CoV-2. Given that vaccines are the best way to end the pandemic, there has been a concerted global effort to develop these life-saving tools.

History of Vaccines and Vaccination

A vaccine is a biological formulation derived from a particular pathogen that stimulates the immune system to generate humoral and cell-mediated immune responses, which confer protection against the pathogen. The process of delivering the vaccine into animals or humans is known as vaccination, which is often used interchangeably with the term immunization. It should be noted that vaccines harness the power of the immune system to kill harmful microbes.

The dawn of the vaccination era is said to begin with Edward Jenner. He was a simple country doctor who lived and practiced in a small village named Berkeley in the county of Gloucestershire in Southwest England. The idea of a vaccine originated from Jenner's observation of the hands of a milkmaid named Sarah Nelmes, who came in close contact with cows due to her occupation. At that time in England, smallpox was very rampant and spared no one. However, Jenner observed that when Sarah was infected with the smallpox virus, she didn't develop the disease. She merely developed some pustules on her hands and arms which healed by themselves. Jenner, being very sharp-minded, immediately deduced that there must be an agent in the cow milk (with which Sarah came into contact every day while milking the cows) that inactivated the smallpox virus that infected the milkmaid. He further realized that this agent must be present in the pustules on Sarah's hands. He scraped off the surface of these pustules and used it to inoculate a child named James Phipps, who was also miraculously saved from smallpox. This was a landmark achievement in medical science! Since the inoculum was derived from cows, which is known as *"Vacca"* in Latin, Jenner named it "vaccine". Thus, the field of Vaccinology was born. He carried out this very first vaccination at his home in the year 1796.

Figure 1: Dr. Edward Jenner FRCP, FRS

Approximately one hundred years later, in the year 1885, the celebrated French microbiologist, Louis Pasteur, first developed the rabies and anthrax vaccines. He successfully immunized a boy named Joseph Meister with his rabies vaccine, who was protected against rabies and didn't suffer any complications. In fact, the credit for developing vaccines along scientific lines goes to Pasteur. Yet another hundred years later, in 1980, smallpox was totally eradicated from the face of the Earth. This was also another landmark achievement, as it was the first infectious pathogen to be eradicated from the world.

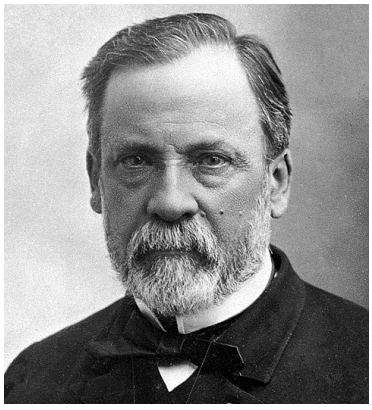

Figure 2: Prof. Louis Pasteur FRS

Types of Immune Responses Generated by Vaccines

The immune system protects us against

pathogens, just like an umbrella protects us against raindrops. The immune system is under constant attack from various microorganisms 24x7. The key components of this body system are a subset of the white blood cells (WBCs), termed lymphocytes, which usually circulate through the lymphatic vessels, but can also enter the blood circulation. These lymphocytes are processed either in the thymus or in the bone marrow. Accordingly, they are termed T-cells and B-cells, respectively. These two classes of cells act as the "soldiers" of the immune system. The T-cells generate cell-mediated immune responses, whereas the B-cells produce antibodies, which are the active components of the humoral immune response. Hence, these are the two types of immune responses that protect the body against infectious disease-causing pathogens. These humoral and cell-mediated immune responses are depicted in Figure 3.

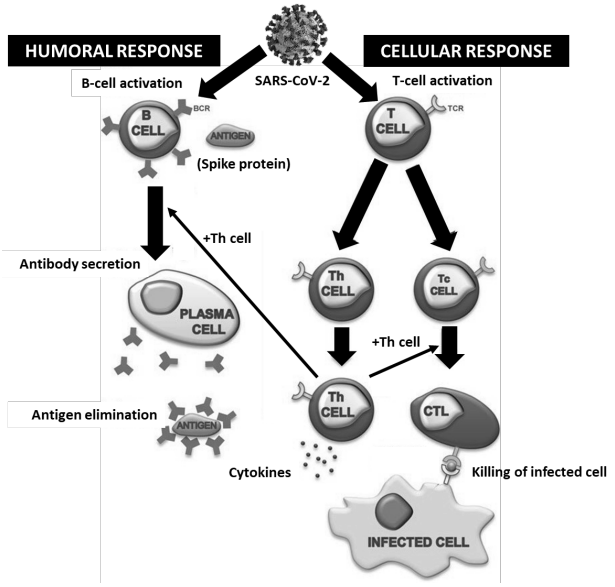

Figure 3: Humoral and cellular immune responses against SARS-CoV-2

Factors Influencing the Immune Response to Vaccination

Many factors influence the immune response elicited by vaccines. The most obvious and major factor is the vaccine itself. This includes the vaccine type, the pathogen used in the formulation, the type of adjuvant (immune-boosting agents), and the dose of the vaccine used for immunization. The vaccination schedule, as well as the route and site of vaccine delivery also play a crucial role. There are also several host factors that have an impact on the immunogenicity of the vaccine. These include age, gender, genetic aspects, as well as the presence of comorbidities, most notably, diabetes, hypertension, cardiovascular diseases, and cancer. Additionally, certain behavioral factors, such as smoking and alcohol consumption also have a significant impact on the magnitude and intensity of the immune response.

SARS-CoV-2 Spike Protein: The Target Antigen for COVID-19 Vaccines

The etiologic agent of COVID-19, namely, SARS-CoV-2 is a single-stranded, positive-sense ribonucleic acid (RNA) virus, having a genome size of approximately 29.9 kb. [2] SARS-CoV-2 has four structural proteins, namely, spike (S), envelope (E), membrane (M), and nucleocapsid (N). The first three are present on the surface, while the fourth one is present inside the virus, and is bound to the RNA, thereby protecting it from degradation. [3] The S protein is of vital importance in eliciting the immune response. The S protein binds to the angiotensin-converting enzyme 2 (ACE2) receptor on the cell surface, which facilitates the fusion of the virus and subsequent entry into the cell. It has two subunits – S1 and S2 that mediate receptor binding and fusion, respectively. The S1 subunit contains the receptor-binding domain (RBD), which actually binds to the ACE2 receptor. [4] Hence, scientists mainly focused on designing vaccines that specifically target the RBD, thereby preventing infection much more effectively (Figure 4).

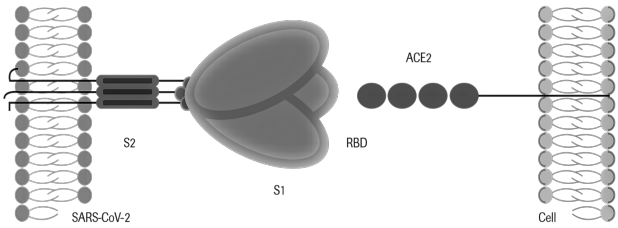

Figure 4: Structure of the SARS-CoV-2 spike protein

Immunodominant Epitopes: Vital for Optimization of Vaccine Design

Immunodominant epitopes are specific surface projections on the virus that are capable of stimulating the immune system more effectively

than other surface structures. Hence, if vaccines are optimally designed so that these immunodominant epitopes are concentrated on the virus surface, then a very specific and robust immune response would be generated. Moreover, excluding unnecessary and non-immunogenic surface structures will ensure that harmful side effects are minimized. Hence, the search for immunodominant B- and T-cell epitopes was a rigorous exercise during the initial stages of vaccine development. An intensive search yielded more than 50 such immunodominant epitopes. It was encouraging to see that these epitopes were safe since they didn't elicit any allergic reaction or exhibit toxicity. Moreover, they didn't give rise to autoimmunity either. Hence, these were chosen as possible candidates for designing vaccines. [5]

Types of COVID-19 Vaccine Platforms

As of 27th September 2021, there were 315 vaccines under development, including 121 in clinical trials and 194 in pre-clinical development in various animal models. There are several types of vaccine platforms, including traditional vaccine platforms (killed / inactivated and live-attenuated), recombinant protein vaccine platforms (protein subunit and VLP), viral vector vaccines (replicating and non-replicating), as well as more advanced ones, such as nucleic acid or genetic vaccine platforms (DNA and RNA), to name a few (Figure 5). [6] Many of these vaccines have already been approved and are currently being used globally for mass vaccination campaigns. Several of these vaccines have also received WHO's Emergency Use Listing (EUL), which is a stamp of quality that assures that the approved vaccine is absolutely safe and effective. [7]

These COVID-19 vaccines were developed in record-breaking time – the fastest in medical history! Much of the groundwork for the lightning speed at which the vaccines were developed, was laid by the Coalition for Epidemic Preparedness Innovations (CEPI), a global partnership that was launched in 2017 with the sole purpose of developing vaccine platforms so that they would be ready for use if a deadly pathogen suddenly emerged. We should be thankful that such dedicated efforts have paid-off when SARS-CoV-2 emerged in 2019. Hence, these concerted and sustained global collaborative efforts were responsible for the rapid development of these life-saving tools. The magnitude and intensity of these collaborations have never been witnessed before in the history of scientific research.

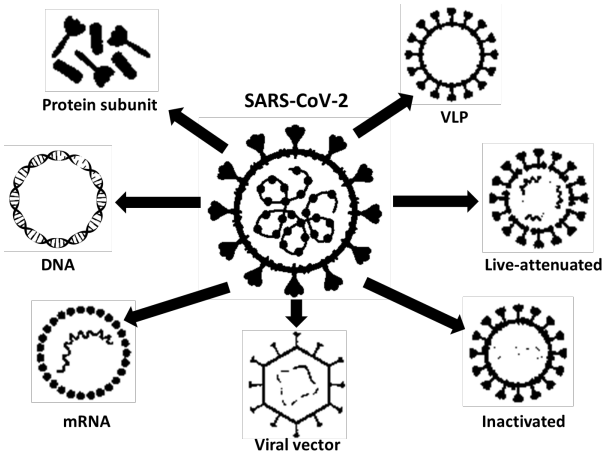

Figure 5: Major types of COVID-19 vaccine platforms

COVID-19 VACCINES: GLOBAL SCENARIO

There are a total of 315 vaccine candidates under different stages of development, of which 121 are undergoing clinical trials. Of the various types of vaccine candidates, the protein subunit vaccines are the front-runners, with a total of 43 candidates in clinical trials. Others include mRNA (21 candidates), non-replicating viral vector (18 candidates), inactivated virus (16 candidates), and DNA (11 candidates), among several others. The top 8 front-runners are presented in Figure 6.

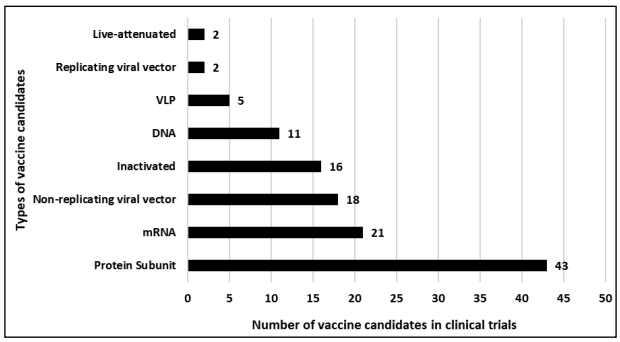

Figure 6: COVID-19 vaccines in clinical trials
(Source of data: WHO [6])

Protein Subunit Vaccines

This type of vaccine utilizes a small fragment (subunit) of protein instead of the whole virus. In the case of SARS-CoV-2, the protein subunit is the S protein. This vaccine has the largest number of candidates, the most advanced of which is the Novavax vaccine.

Novavax Vaccine: This vaccine has been developed by Novavax, a pharmaceutical company based in Maryland, USA. It is a two-dose vaccine that is administered 21 days apart. This vaccine is formulated with the so-called Matrix-M™ adjuvant, which boosts its potency. This vaccine was recently evaluated in a Phase 3 clinical trial and was found to be safe and showed an efficacy of 86.3% against the Alpha variant (B.1.1.7) and 96.4% against non-alpha variants (Beta, Gamma, and Delta variants). Its side effects are negligible, relatively mild, and transient.[8]

mRNA Vaccines

The so-called messenger RNA technology is used in the mRNA vaccines. These, along with the DNA vaccines, are collectively known as nucleic acid or genetic vaccines. The Pfizer/BioNTech and Moderna vaccines are the most advanced mRNA vaccines that have received WHO's EUL approval and are currently being widely used in vaccination campaigns across the globe.

Pfizer/BioNTech Vaccine: This is a two-dose vaccine that is delivered 21 days apart. Since the mRNA molecule is very labile and unstable, in this vaccine formulation, it is encased in a lipid nanoparticle (LNP), which protects the mRNA from degradation. Pfizer/BioNTech initially developed two vaccine constructs, which they termed BNT162b1 and BNT162b2. Both of them were almost identical, except for some minor differences at the molecular level. In a Phase 1 clinical trial in the US, the two vaccine constructs were tested head-to-head. It was seen that the BNT162b2 construct exhibited much lesser side effects, compared to BNT162b1. Since the side effects were much milder in the case of BNT162b2, it was taken forward for further clinical development. It should be noted that this was the first published clinical trial of an mRNA vaccine. [9] In a subsequent Phase 3 clinical trial in over 44,000 participants, BNT162b2 showed a staggering efficacy of 91.3% against COVID-19, even 6 months after the second dose.[10]

Moderna Vaccine: Much like the Pfizer/BioNTech vaccine, this is also an LNP-encapsulated mRNA vaccine, termed mRNA-1273. It is a two-dose vaccine that is administered 28 days apart. A large-scale Phase 3 clinical trial was conducted at 99 centers across the US, involving over 30,000 individuals. The vaccine showed an efficacy of 94.1% after the second dose across all categories of individuals, including those infected with SARS-CoV-2 and those above 65 years of age. The side effects were moderate and transient, and serious adverse events following immunization (AEFI) were rare. Therefore, the vaccine was capable of preventing severe COVID-19 illness, hospitalization, and death.[11]

DNA Vaccines

These are the second type of nucleic acid / genetic vaccines that are being developed against COVID-19. DNA vaccines are composed of double-stranded DNA molecules, whereas mRNA vaccines are composed of single-stranded mRNA molecules. This double-helical structure makes DNA much more stable than mRNA. This is a huge advantage as these vaccines are very stable, even in hot climates, without the need for a cold chain. This attribute is immensely attractive from a logistical standpoint during vaccine deployment in hard-to-reach geographical areas, where maintenance of a stringent cold chain is indeed very difficult.[12]

Zydus Cadila Vaccine: This DNA vaccine is termed ZyCoV-D and has been developed by Zydus Cadila. It is the world's first DNA vaccine to be granted emergency use authorization, which is a matter of great pride for India. The Drugs Controller General of India (DCGI) approved this vaccine on 20th August 2021. ZyCoV-D is a three-dose vaccine that is administered intradermally through a needle-free device in the form of a liquid jet. This needle-free delivery system, termed PharmaJet Tropis®, has been developed by PharmaJet, an American company based in Colorado. This mode of vaccine delivery is expected to become highly popular, mainly because it's absolutely painless, as opposed to needle injection. [13]

ZyCoV-D has been successfully tested in 30,000 individuals in all three phases of clinical trials. Importantly, it is the first Indian vaccine to be tested in 12 to 18-year-old children and adolescents and was found to be well-tolerated, safe, and immunogenic. The vaccine conferred 100% protection against moderate COVID-19 illness and exhibited an overall efficacy of 66.6%.

Inovio Vaccine: Besides ZyCoV-D, another DNA vaccine candidate, termed INO-4800, has been developed by Inovio Pharmaceuticals, which is based in Pennsylvania, USA. It utilizes mammalian expression plasmids, encoding the S protein gene, which are strongly expressed in humans and other mammals. INO-4800 generated both humoral and cell-mediated immune responses in mice and guinea pigs. Following the pre-clinical studies, it was successfully evaluated in Phase 1 clinical trials, where it was shown to be safe and immunogenic. It is currently being further evaluated in Phase 2/3 clinical trials.[14]

Viral Vector Vaccines

Viral vector vaccines use a non-infectious virus, such as adenovirus to carry the transgene encoding the S protein and deliver it into the cell. This approach is very similar to the Trojan horse strategy used by the Greeks to conquer the city of Troy during the Trojan War in pre-biblical times. As of 27th September 2021, there were 20 viral vector vaccine candidates (18 non-replicating and 2 replicating) in different stages of clinical trials. Adenovirus-based vaccines are capable of eliciting robust humoral and cell-mediated immune responses, even after the administration of a single dose. However, with regard to safety and efficacy, these vaccines appear to be slightly inferior to the mRNA and protein subunit vaccines. The major viral vector vaccines are discussed below.

Oxford University / AstraZeneca Vaccine: This vaccine was initially developed at the University of Oxford and subsequently taken forward by AstraZeneca for large-scale production. This vaccine is being manufactured in India by the Serum Institute of India in Pune and has been named Covishield. This vaccine is based on a chimpanzee-derived adenovirus and hence, technically termed as ChAdOx1nCoV-19 (Ch: chimpanzee; Ad: adenovirus; Ox: Oxford University; nCoV-19: novel coronavirus 2019). This adenovirus is non-replicating and thus doesn't interfere with the expression of the transgene, encoding the S protein.[15]

A Phase 1/2 clinical trial at five trial sites in the UK, established that the vaccine was safe and antibody levels were significantly elevated after the second dose. Three more clinical trials were conducted in the UK, Brazil, and South Africa, which confirmed the high degree of safety and efficacy of the vaccine against symptomatic COVID-19 disease.[16]

Sputnik V Vaccine: This non-replicating viral vector vaccine has been developed by the Gamaleya Research Institute of Epidemiology and Microbiology in Russia. Sputnik V is named after the series of famous Russian satellites launched into space during the late 1950s and 60s. This is a two-dose vaccine, administered 21 days apart. Although Sputnik V also uses an adenovirus vector, it is different from that used in the Oxford University / AstraZeneca vaccine. Unlike the chimp adenovirus used by the Oxford University / AstraZeneca vaccine, Sputnik V uses human adenoviruses – Ad26 for the first dose and Ad5 for the second dose, which expresses the S protein of SARS-CoV-2. In two Phase 1/2 clinical trials, Sputnik V induced strong humoral and cellular immune responses and was also shown to be safe. A subsequent Phase 3 clinical trial conducted at 25 healthcare facilities in Moscow, showed that Sputnik V exhibited an efficacy of 91.6% following the second dose. [17]

The recently developed Sputnik Light vaccine is a variation of Sputnik V. It is a single-dose vaccine and is essentially the first dose (Ad26) of Sputnik V. In a Phase 1/2 clinical trial in Russia, Sputnik Light exhibited an efficacy of 79.4%.

Janssen Vaccine: This is the world's first single-dose COVID-19 vaccine. It has been developed by Janssen Pharmaceuticals, which is wholly owned by the American pharmaceutical giant, Johnson & Johnson. As of 29th September 2021, it was the only single-dose vaccine to have received EUL approval by WHO.[7] It is a non-replicating viral vector vaccine that uses the Ad26 vector to carry the transgene, which encodes the full-length S protein of SARS-CoV-2. For this reason, it is technically termed Ad26.COV2.S. In Phase 3 trials, it exhibited an efficacy of 67%. [18]

Inactivated Vaccines

Inactivated vaccines are also called killed vaccines because the viral particles are killed using chemical treatments. The inactivated vaccines currently being developed, all use β-propiolactone for inactivating the viral particles. Consequently,

since the virus is dead, these vaccines don't pose any threat of infection or reversion of infectivity. Inactivated vaccines, together with live-attenuated vaccines (LAV) are known as traditional vaccines. This is because these vaccines are developed using traditional, time-tested methods that have been in existence for over a century. As of 27th September 2021, there were 16 inactivated vaccine candidates in clinical trials. The two major inactivated vaccines have been discussed below.

Sinovac Vaccine: This inactivated vaccine is named CoronaVac and has been developed by Sinovac Biotech, which is based in China. It is a two-dose vaccine that is administered 14-28 days apart. It is produced by culturing SARS-CoV-2 in cell culture media using African green monkey kidney cells, commonly known as the Vero cell line. Subsequently, the cultured viral particles are inactivated with ß-propiolactone and then purified. The vaccine is formulated with the adjuvant aluminum hydroxide, which boosts the immune response. [19] CoronaVac has been evaluated in several large-scale clinical trials in Turkey, Brazil, and Indonesia, but has shown varying levels of efficacy, ranging from 50% to over 80%. Hence, a big question-mark exists about the efficacy of this vaccine as it has performed differently in clinical trials conducted in different countries. [20, 21]

Sinopharm Vaccine: Similar to CoronaVac, this is also a two-dose vaccine and is produced using the same technique. It has been named BBIBP-CorV and is administered 21 days apart. A Phase 1/2 clinical trial was conducted with BBIBP-CorV, which showed that the vaccine was safe and well-tolerated by all the vaccinated individuals. [22] A Phase 3 clinical trial of BBIBP-CorV conducted in 31,000 individuals in Dubai showed that the vaccine had an efficacy of 86%. Moreover, the vaccine was absolutely safe and 100% effective in preventing moderate to severe disease. [23]

Live-attenuated Vaccines

Unlike inactivated vaccines, in the case of live-attenuated vaccines (LAV), the virus is not completely killed but is weakened by chemical treatments. During attenuation, a fine balance needs to be struck, with regard to the extent of weakening. The virus should be weakened to such an extent that it loses its virulence or infectivity, but retains its immunogenicity so that it can still stimulate the immune system to generate an immune response.

Only two LAV candidates are currently in clinical trials. These have been developed by Codagenix and Meissa. While Codagenix's vaccine candidate is in Phase 1/2 clinical trials, Meissa's candidate is still in Phase 1. Codagenix's COVI-VAC vaccine is discussed below.

Codagenix Vaccine: This is an intranasal vaccine that can be administered as nasal drops. It can be used as a single-dose or two-dose regimen and is administered 28 days apart. The vaccine has been found to be safe and effective in animal models and generates robust humoral and cell-mediated immune responses in humans. [24]

A Phase 1 clinical trial of COVI-VAC is currently ongoing and is scheduled to be completed in May 2022. This trial is evaluating the safety and immunogenicity of the vaccine in 48 individuals aged 18-30 years. [25] A Phase 1/2 clinical trial of the vaccine is currently being conducted in Vietnam. This trial aims to evaluate the safety and immunogenicity of the vaccine in 420 individuals aged 18-75 years and is scheduled to be completed on 30th September 2022. [26]

Virus-like Particle Vaccines

A virus-like particle (VLP) is like a virus but is not exactly the same. While viruses have genetic material (DNA or RNA), VLPs don't, which makes them non-infectious and therefore, very safe. VLPs essentially resemble a ball, which has a shell, but nothing inside. Hence, the surface proteins of VLPs remain intact. Therefore, the three surface proteins of SARS-CoV-2 (S, E, and M) remain unaltered in a VLP. Consequently, the VLP retains the ability to stimulate the immune system, without causing any infection. These structural proteins are usually expressed in bacteria, such as *E. coli*, following which, they self-assemble, thereby giving shape and imparting structural integrity to the VLP. [27] Currently, five VLP-based vaccine candidates are in clinical trials, which have been found to be highly immunogenic and capable of generating robust humoral and cell-mediated immune responses. [6]

Intranasal Vaccine – A Novel Technology that Generates Mucosal Immunity

Besides Codagenix's intranasal vaccine, COVI-VAC, which belongs to the LAV category, there is another intranasal vaccine currently under development, which is an adenoviral-vectored vaccine. A Phase 1 clinical trial was recently conducted in Wuhan, China, where this vaccine was delivered intranasally. This is a very simple and painless way to deliver vaccines, unlike conventional needle injections. This vaccine was well-tolerated and generated a robust immune response and will soon proceed to Phase 2/3 clinical trials. [28] An Indian intranasal vaccine is also under development. This live-attenuated vaccine, technically termed BBV154, is being developed by Bharat Biotech International Limited, which is a multinational biotechnology company headquartered in Hyderabad. This vaccine is currently undergoing animal trials.

Intranasal vaccines are advantageous over other vaccines because they can produce IgA antibodies that are capable of eliciting mucosal immunity. Since the nasal cavity is the major portal of entry of SARS-CoV-2, stimulation of the nasal mucosa to produce IgA antibodies would neutralize the virus and prevent it from entering the lungs and subsequently into the blood circulation. There is solid scientific evidence that has shown IgA molecules in the nasal washings of convalescent patients, which neutralized SARS-CoV-2. [29]

COVID-19 VACCINES: INDIAN SCENARIO

India currently has two vaccines in its armamentarium. These are Covishield and Covaxin, with several others in the pipeline. As of 11th October 2021, India had administered over 951 million doses of these two vaccines, including both the 1st and 2nd doses. [30]

Covishield: This vaccine was developed by the University of Oxford, UK, and is being manufactured by AstraZeneca. In India, it is being manufactured by the Serum Institute of India, Pune, which is the world's largest vaccine manufacturer in terms of the volume of vaccines produced. Besides these, other companies in South Korea, Japan, and Australia are also manufacturing this vaccine. Covishield is a non-replicating viral vector vaccine that uses an adenovirus derived from chimpanzees. It is a two-dose vaccine that is administered 12-16 weeks apart (1st dose: day 0; 2nd dose: 12-16 weeks). It is administered intramuscularly (IM) by conventional needle injection. Following the successful completion of Phase 3 clinical trials, it is currently being used for mass vaccination in India. In Phase 3 clinical trials, it showed an efficacy of 70.4% against severe disease and death. This vaccine can be stored in a normal refrigerator at 2-8°C, making it easy for transportation and storage in a cost-effective manner.

Covaxin: This vaccine was developed by the National Institute of Virology, Pune, which is a constituent institute of the Indian Council of Medical Research (ICMR), New Delhi. It is manufactured by Bharat Biotech, Hyderabad. Covaxin is technically termed BBV152 and like Covishield, is a two-dose vaccine, which is given 28 days apart. It is an inactivated (killed) vaccine, where SARS-CoV-2 is cultured in Vero cells, inactivated with ß-propiolactone, and adsorbed onto aluminum hydroxide, which acts as an adjuvant. Additionally, in this formulation, an imidazoquinoline molecule (TLR7/TLR8 agonist) was also mixed with the aluminum hydroxide to enhance the adjuvanticity. [31] In Phase 3 clinical trials, it showed an efficacy of 78% against symptomatic infection after 2 doses. [32] It also generated strong humoral and cell-mediated immune responses. [33, 31]

The side effects and contraindications of Covishield and Covaxin are presented in Table 1 and Table 2, respectively.

Table 1: Side effects of Covishield and Covaxin

Common Side Effects	Uncommon Side Effects
Injection Site: Pain, warmth, swelling, redness, itching, bruising	Nausea and vomiting
Fatigue, weakness, malaise, body ache	Joint or muscle pain
Fever	Abdominal pain
Headache	Loss of appetite
Rashes	

Table 2: Contraindications for Covishield and Covaxin

Covishield	Covaxin
Severe allergic reaction after a previous dose of the vaccine	History of allergies
Severe allergic reaction to any ingredient of the vaccine	Fever
	Bleeding disorder or use of blood thinners
	Immunocompromised individuals or use of immunosuppressants
	Prior immunization with a different COVID-19 vaccine

New Vaccines in the Pipeline in India

There are primarily five Indian vaccines that are in the pipeline. Three of these, namely, ZyCoV-D, Sputnik V, and Bharat Biotech's intranasal vaccine have already been discussed. Besides these, there are two others, which are highlighted below.

HGC019: This vaccine candidate is being developed by Gennova Biopharmaceuticals Limited, Pune in collaboration with HDT Biotech Corporation, Seattle, USA. This is India's very own mRNA vaccine candidate, which uses the so-called self-amplifying RNA technology. This vaccine candidate is currently in pre-clinical development. Its dose and route of administration have not been disclosed so far.

Corbevax: This is a protein subunit vaccine that is being jointly developed by Biological E Limited, Hyderabad, and CEPI, Oslo, Norway. It is a two-dose vaccine that is administered 28 days apart via the IM route. This vaccine candidate is currently in Phase 3 clinical trials.

Vaccines are not "Silver Bullets"

It should be remembered that vaccines are not "silver bullets". If you think vaccines are the answer to all your woes, you are wrong! They are a part of the solution, but not the whole solution. This is because vaccinated individuals can still get infected, as well as transmit the infection. The antibodies generated by all the currently available vaccines are a mixture of IgG and IgM, both of which are present in the blood circulation. It follows that only when SARS-CoV-2 enters the blood, it can get neutralized by these antibodies. However, it is well established that this virus primarily enters through the nasopharynx, where these antibodies are absent. Hence, in order to prevent virus transmission, vaccinated individuals will still need to follow COVID-appropriate behavior, such as masking, physical distancing, handwashing, among others (Figure 7). Only when intranasal vaccines become available, transmission could be blocked as these vaccines generate IgA antibodies in the nasal mucosa, which would be capable of neutralizing the virus at the portal of entry. But until then, all the public health measures will still need to be strictly adhered to.

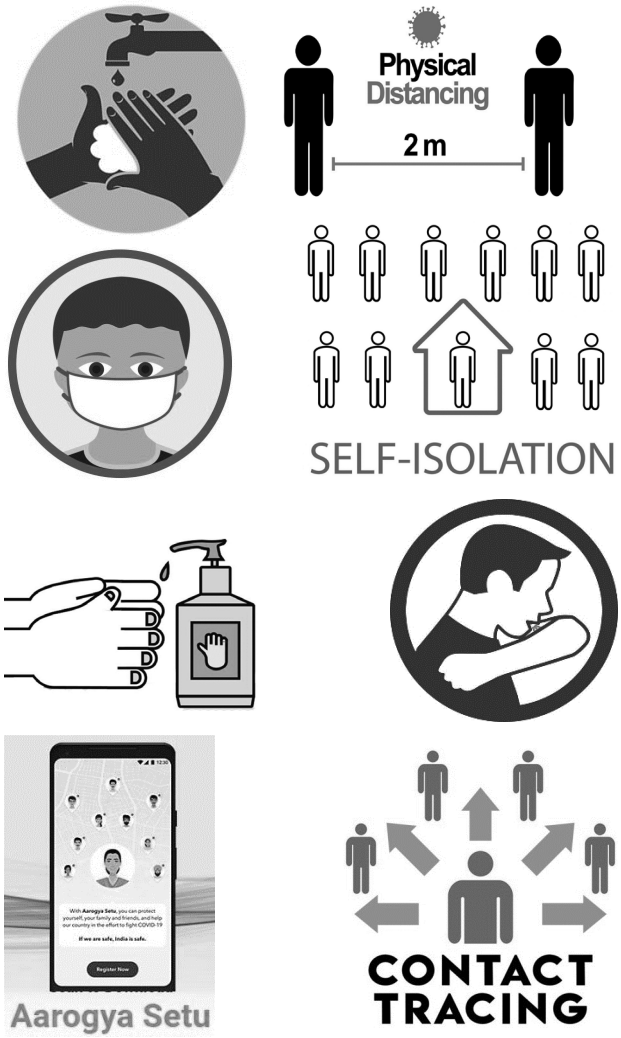

Figure 7: Public health measures for checking virus transmission

Emergence of Variants: A Major Challenge for Vaccination Campaigns

The emergence of variants occurs as a result of mutations in the parental strains, which make the new strains much fitter for survival. Variants exhibit several cardinal features, including an increase in transmissibility, severity, and viral load, as well as exhibiting immune escape. The phenomenon of immune escape essentially means that the new variant strain is capable of escaping the antibody response generated by the immune system as a result of vaccination. Although the first variant was D614G, which emerged in August 2020, it has largely been replaced by four other variants of concern (VOC), namely, Alpha, Beta, Gamma, and Delta. The Delta variant, which originated in India, is currently the dominant VOC that is circulating in over 185 countries worldwide. Importantly, it was this variant that wreaked havoc in India during the second wave. The major problem being faced by vaccinologists due to the Delta variant is the decrease in efficacy of the vaccines. For example, the efficacy of the Pfizer/BioNTech vaccine before the emergence of the Delta variant was 88%, whereas afterward, it fell to 74%. Likewise, the efficacy of Covishield was initially 70.4%, whereas, after the emergence of the Delta variant, it fell to 67%. This trend is quite worrisome and could seriously hamper the vaccination campaigns globally.

Future Prospects

Unprecedented progress has been made on the vaccine front in the past one year ten months. Much has been learned about the immune effector mechanisms, such as B-cell and T-cell immune responses against SARS-CoV-2. Unfortunately, it is increasingly being observed that the immunity is waning, largely because the antibody titers are falling over time. On top of this, the emergence of variants is making things even more worse by further reducing immunity. Hence, it is being debated whether booster shots might be required in the future. In fact, the US and some European countries have already started giving booster shots to their populations. In the long run, booster shots will likely be required for everyone in order to maintain adequate immunity.

It is encouraging to note that globally, the disease is showing signs of slowing down and could decrease in intensity over time and eventually become endemic. Sustaining the vaccination efforts will be of paramount importance for keeping the virus under pressure so that it doesn't mutate and give rise to new variants. In this regard, equitable access to vaccines is urgently required so that herd immunity can be attained sooner than later. However, attaining this will be an uphill task, which may be likened to conquering Mount Everest. So far, we've climbed just 6% by way of vaccination coverage at the global level. So, there is a long way to go before we reach the summit of achieving 100% vaccination coverage. However, it is heartening to know that we can now see the light at the end of the tunnel and we could soon conquer the pandemic and emerge victorious!

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