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CORONA/COVID-19- Vaccines Current Scenario

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ABSTRACT

The pandemic COVID -19 caused by novel coronavirus, SARSCoV-2, has infected more than 125 million individuals and resulted in over 2,756,768 deaths globally spread over 219 countries and territories. There has been an intensive search for an effective drug against the virus and the resultant disease. However, till now no single effective drug could be found against SARS-CoV-2. Hence, all research efforts to contain the epidemic are being focussed on effective vaccine development. Here, we review the current scenario of vaccines being developed all over the world and also India to restrict the COVID-19. Advances in genetic sequencing and other technological developments have speeded up the establishment of a variety of vaccine platforms. Most of the platforms mainly based upon the viral spike protein due to its vital role in viral infectivity. Accordingly, numerous vaccines are under various stages of development. Some vaccines like Astra-Geneca, Moderna, Covaxine, and Pfizer are already released for vaccination to general public. Principles, advantages and disadvantages of different vaccine platforms are discussed. Notwithstanding the tall claims made by manufacturers, concerns are expressed especially over the rush, at which the vaccines are developed, and their efficacy and safety. In India, two vaccines viz, covaxin and covishield are released even before finishing the mandatory phase III trials on conditional trial basis. Salient features and differences between these two vaccines are discussed.

Keywords : Corona virus, SARSCoV-2, COID-19, Vaccines, Vaccine platforms, Covaxin, Covishield

I. INTRODUCTION

Measures such as surveillance, quarantine and social distancing taken work efficiently to prevent and control a pandemic, and thus to flatten the curve, albeit at a major cost to the economy. However, the development and deployment of effective tests, drugs, and vaccines to protect lives and limit disease spread are still urgent need. Emergency Use Authorizations (EUA) speeded up the availability of drugs to prevent serious or life-threatening conditions when adequate, approved alternatives are not available. For many drugs that are already marketed for other disease conditions, off-label use can increase access for patients who need them. Currently, thousands of clinical trials are ongoing to test clinical efficiency of drugs. Some candidate drugs targeting different such as cell membrane fusion, RNA-dependent RNA polymerase, viral protease inhibitor, interleukin 6 blocker, and convalescent plasma may improve the clinical outcomes of critical COVID-19 patients. Still, other supportive care measures for critical patients are necessary. Non availability of drugs that can specifically cure the COVID-19 is a major drawback for tackling the pandemic and there is no hope of getting an efficient drug in near future. Intensive clinical trials are necessary to confirm or refute the usefulness of several candidate drugs. Similar to several other viral pandemics of the past, vaccines hold promise to this pandemic also. Numerous research laboratories around the world supported by government and private organisations are competing to produce an effective vaccine against SARS-CoV-2 at the earliest possible, in order to be able to stop the spread of the new coronavirus.

Vaccines

The conventional medicines are oriented towards the treatment of a disease whose symptoms have manifested. But vaccines are primarily intended for use in persons not yet exhibiting disease symptoms, in order to prevent the occurrence and spread of diseases. Vaccines alert the immune system with the necessary instructions for recognizing and mobilizing lines of defense against the pathogenic microorganisms, such as bacteria or viruses. Traditional vaccines although proved to be extremely effective in combating highly contagious diseases such as measles, require large amounts of viruses or bacteria, which can last for months. Those microorganisms then become the key element in a vaccine, the so-called antigen that alerts and warns the human immune system. In classical vaccines, antigens are introduced into the body, originating from inactivated or half active bacteria or attenuated viruses. These antigens are capable of causing a mild disease, but are still capable of activating the immune system. If a vaccinated person comes in contact with the native pathogen, the immune system with existing antibodies effectively fight the pathogen.

Outlines of vaccine development

The development of a vaccine is a complex and time-consuming process. In several respects, it differs from the development of conventional medicines. The stipulated guidelines for vaccine development are much more stringent than those meant for drug development. The reasons are obvious: the vaccines are for global use, administered to different sections of vulnerable healthy populations such as children, elderly, and pregnant mothers, and thus have enormous potential for production and marketing. The process of vaccine development follows a unique stepwise pattern and is broadly divided into: Exploratory, Preclinical, Clinical, and Post-marketing stages. The clinical stage in turn is divided into 3 phases, viz, phases I, II and III. Further, two regulatory permissions are 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. Under normal situations, the period of development of a vaccine is 12-15 years (Han, 2015)

The safety and efficacy of the vaccine is initially assessed in laboratory studies with experimental animals like mice or rabbits. If the animals do not show signs of disease after receiving the vaccine, then the tests begin in humans (DeStefano *et al.,* 2015). The procedure of the clinical trial for a classical vaccine (after preclinical stage -.*in vitro* and *in vivo* tests) is as follows (Pronker *et al.,* 2013; Guerra Mendoza *et al.,* 2019): In phase I, also called the first human test, the vaccine is given to a small group of healthy volunteers (10 to 100). Here, the objective is not to test whether the vaccine protects against the disease, but to assess whether it is safe or whether it induces any severe side effects. In phase II, the candidate vaccine is administered to a larger group of subjects (100-1,000), and in phase III, to an even larger group (1,000-100,000). To assess whether a vaccine prevents the disease among those likely to be exposed to the infection, it should be tested in phase III studies, in a setting where the infection is actively prevalent. During a pandemic, because of demand urgency, these sequential studies may be shortened and partially overlapped; nevertheless, it is mandatory that thousands of vaccinated people are followed for several months before the release for mass vaccination programs.

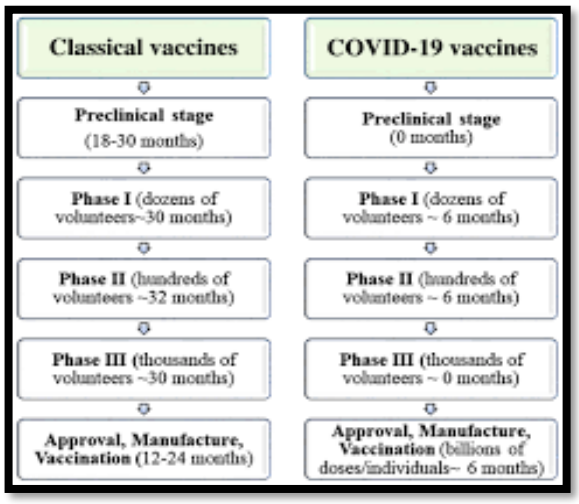

Fig. 1. Stages of clinical trial for classical vaccine compared with COVID- 19 vaccines.

In order to meet the pandemic demand, tens or hundreds of millions of doses of vaccine are needed. This production process takes at least six months, if the production line already available. Any novel vaccine involves a new production process that involves several quality control steps.

The manufacturer must ensure that each vaccine produced is of consistent quality and requires quality control at every step. Before initiating each stage of the human testing process, the developer must provide evidence that the vaccine has early indications of protection and is safe among those who have been tested. Research ethics committees review clinical trial plans, and authorities such as the European Medicines Agency (EMA) and Food and Drug Administration (FDA) oversee the entire vaccine development process before approving it for general use. These assessments usually take several weeks or months. Although such approvals could be shortened in the event of a pandemic, many potential COVID- 19 vaccines use new technologies, so regulators will not be able to rely on the experience of similar vaccines to speed up the process. Developers of the COVID- 19 vaccine were given a target to produce a vaccine in 12-18 months, while historically; vaccines took 15-20 years to develop. For efficient application of SARS-CoV-2 vaccines, not only the production procedure needs to be developed, but also requires a large-scale production followed by vaccination program targeting multimillion population of different regions. The manufacturer must ensure that each vaccine produced is of consistent high quality. Given the fact that vaccine manufacturing is a biological process, inevitably, some batches of vaccines will fail in quality control tests, the reasons are not always clear, which can further delay production. There are quite a few manufacturers in the world that can produce vaccines on a large enough scale to meet the demand of a pandemic (Calina *et al.,* 2020)

Current pandemic of COVID-19, caused by SARS-CoV-2, is an unprecedented global

epidemiological problem, the solution of which will require establishment of large-scale production of the vaccine. Given the experience of previous coronavirus outbreaks, showing a high variability of the virus, it is necessary to develop a vaccine production platform that provides the scalability, technological flexibility, and versatility. These vaccines must provide high efficacy, safety, and tolerability. Many 'candidate' vaccines, which initially look promising, are likely to fail during the subsequent testing processes.

Vaccine production platforms

The technology underlying the development of vaccines in R&D has been witnessing a tremendous transformation in the recent past. Over the years, the so called candidate vaccines were reduced through traditional methods. As a result, making of a prototype vaccine took 2 - 5 years and was confined to a few types of vaccines. It needed the availability of sophisticated research facilities in order to work with the infectious agent and such type of facilities were available only in few laboratories over the globe. Recently, platform technologies have been employed in developing candidate vaccines (Wadman, 2020; US FDA, 2020). Platform technologies are systems build upon a platform architecture that distributes the system out into different levels of abstraction. Platform technologies offer several advantages in the development of vaccines which include automation, speed, cost-effectiveness and ability to develop several prototype vaccines from the single system.

As of December 2020, just eleven months after the working out the details of the SARS-CoV-2 genome, there are over 150 official vaccine projects in the field (WHO, 2020; Akst, 2020. About fifty of them have already reached human experimentation and a few of these are currently administered to some sections of the general population. Making use of different technologies, these anti-SARS-CoV-2 candidate vaccines are targeting the whole SARS-CoV-2, molecules or fragments of molecules expressed on virus surface. These different candidate vaccines can be grouped based on the technological platform exploited to induce a protective immune response. However, almost every vaccine project has its peculiarities that make it unique and different from others. A large amount of available basic research data on the mechanisms of SARS-CoV-2 infection has convinced most developers of innovative vaccine to concentrate their efforts on inducing an immune response against the spike protein (Fig. 2). The new data emerging from Phase III studies show that vaccines based on nucleic acids (DNA, RNA) coding for the Spike protein, carried by vectors like liposomes or adenoviruses, can elicit an effective protective response.

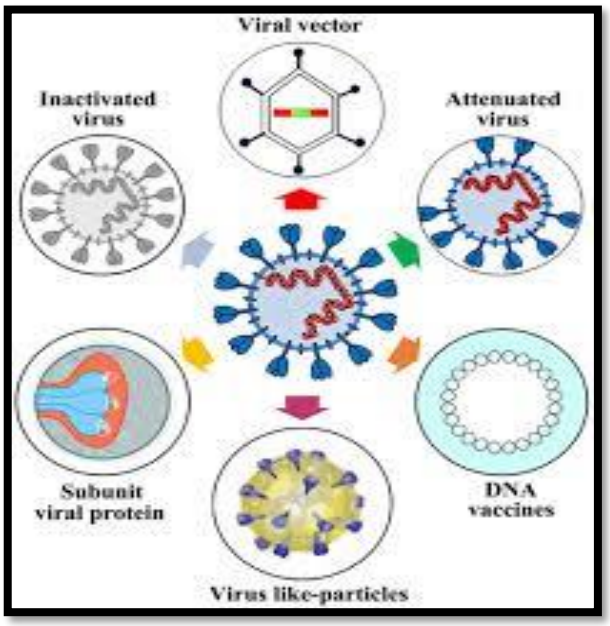

Fig. 2: Strategies of different vaccine producing platforms to produce COVID-19 vaccine

The various platforms being considered for the development of COVID-19 vaccines include

1. Vaccines based on attenuated SARS-CoV-2 viruses
2. Vaccines based on the inactivated SARS-CoV-2 viruses
3. Vaccines based on SARS-CoV-2 proteins
4. Naked DNA-based vaccines
5. mRNA-based vaccines
6. Vaccines based on viral vectors
7. A few other technological platforms

1. Vaccines based on attenuated SARS-CoV-2 viruses

The history of vaccination begins with vaccines based on a live microbe that has been

weakened so that it cannot cause disease. Since attenuated microbes retain the ability to replicate *in vivo* inciting a limited disease, they are very effective in stimulating the immune system and inducing a strong and persistent immune memory that is effective in preventing infection. Hundreds of millions of people all over the world have been protected from disabling and fatal diseases by using attenuated vaccines (Forni *et al.*, 2020).

Principle: This is the most traditional technology exploited in the development of vaccines. Live attenuated vaccines are obtained by growing the virus in unfavourable conditions or by generating a genetically weakened version of the virus. However, the attenuation of large quantities of viruses is complex, laborious and delicate and often associated with major biosafety risks. Once produced, their storage and handling require careful monitoring procedures.

Mechanism: Live attenuated vaccines induce the production of CD8+ cytotoxic T lymphocytes and T-dependent antibody responses. A vaccine is only effective for as long as the body maintains a population of these cells. Live attenuated vaccines can induce long-term, possibly lifelong, immunity without requiring multiple vaccine doses. Live attenuated vaccines can also induce cellular immune responses, which do not rely solely on antibodies but also involve immune cells such as cytotoxic T cells or macrophages (Cohen, 2020)

Safety: Live-attenuated vaccines stimulate a strong and effective immune response that is long-lasting. Given pathogens are attenuated, it is extremely rare for pathogens to revert to their pathogenic form and subsequently cause disease. (Pollard, 2020) Additionally, within the five WHO-recommended live attenuated vaccines (tuberculosis, oral polio, measles, rotavirus, and yellow fever) severe adverse reactions are rarely reported. However, similar to any medication or procedure, no vaccine can be 100% safe or effective. Individuals with compromised immune systems (e.g., HIV-infection, chemotherapy, combined immunodeficiencies) typically should not receive live-attenuated vaccines as they may not induce an adequate and safe immune response.

Advantages

- Accurately imitate natural infections.
- Are effective at evoking both strong antibody and cell-mediated immune reactions.
- Can elicit long-lasting or life-long immunity. Often only one or two doses are sufficient.
- Quick immunity onset.
- Cost-effective (compared to some other health interventions).

Disadvantages

- In rare cases, particularly when there is inadequate vaccination of the population, natural mutations can cause an attenuated virus to revert to its wild-type form or mutate to a new strain, potentially resulting in the new virus of infectious or pathogenic nature.
- Often not recommended for immuno-compromised patients due to the risk of potentially severe complications.
- Live strains typically require advanced maintenance, such as refrigeration and fresh media, transport to remote areas is difficult and costly.
- Attenuated viral vaccines that are currently in use are: Live attenuated influenza vaccine (LAIV), Japanese encephalitis vaccine, Measles vaccine, MR vaccine, MMR vaccine, MMRV vaccine, Polio vaccine, Rotavirus vaccine, Rubella vaccine, Yellow fever vaccine, Zoster/Shingles vaccine Manufacturers
- Only three projects of attenuated SARS-CoV-2 vaccines are in active preclinical development at the following institutions:
- ● The Serum Institute of India, India, in collaboration with Codagenix, a New York private biotech

- Indian Immunologicals Ltd, India, in collaboration with the Griffith University, Australia
- Mehmet al., i Aydunar Univ, Turkey
- None of these vaccine projects have yet reached the stage of clinical trials.

2. Vaccines based on the inactivated SARS-CoV-2 viruses

Vaccines based on killed microorganisms (inactivated vaccines) belong to a very traditional technological platform that has led to development of numerous successful vaccines. The vaccines produced using this method are more stable than live attenuated vaccines but their limit is mainly related to the short duration of immune memory which demands inoculation of higher amounts of vaccine or supplementing the inactivated microorganism with an adjuvant. The immune response elicited is directed not only against the Spike protein but also against many other SARS-CoV-2 antigens. The induced response is generally weaker but the vaccine is more easily handled, less expensive, and much safer.

Principle: The SARS-CoV-2 virus is inactivated through different physical chemical techniques. The virus is killed using a method such as heat or formaldehyde. All these candidate vaccines are injected intramuscularly.

Mechanism: The pathogen particles are destroyed and cannot divide, but the pathogens still maintain some of their integrity to be recognized by the immune system and evoke an adaptive immune response. When manufactured correctly, the vaccine is not infectious, but improper inactivation can result in intact and infectious particles. Because the killed pathogens in a properly produced vaccine do not reproduce, booster shots are required periodically to reinforce the immune response.

Advantages: More stable, can be lyophilized for easy transport, cheaper, and can be used in immune-compromised people

Disadvantages: Often requires booster shots, must ensure proper inactivation, not all viruses are immunogenic after inactivation.

Attenuated viral vaccines that are currently in use are: Poliovirus, hepatitis A virus, rabies (human), Japanese encephalitis virus, seasonal influenza (purified subunit).

Maufacturers

Seven vaccine candidates based on variously inactivated SARS-CoV-2 virions are in clinical trials, four of which in Phase III trials and already approved for limited use. Results of phase II trials suggest that the vaccine is safe and induces a high titer of antibodies.

- Sinovac Biotech, China, this vaccine called CoronaVac, has already been approved for limited use among the general population
- Sinopharm, China, two of its distinct projects are approved for limited use in the general population
- Wuhan Inst Biol Products, China, this vaccine has been approved for limited use in the general population
- Chinese Acad Med Sci, China
- Bharat Biotech, India, this vaccine, called Covaxin, has been approved for limited use in the general population
- RIBSP, Kazakhstan.

3. Vaccines based on SARS-CoV-2 proteins

As on today, there are several human vaccines based on proteins present on the surface of microbes. In the past, these proteins were purified from the microbes but today, in most of the cases, they are produced *in vitro* employing the recombinant DNA technology.

Principle: The large trimeric aggregates of the Spike protein that protrude from virion surface play a crucial role in the attachment of the SARS-CoV-2 to human cells. Hence, the Spike protein or its fragments are the targets of all these vaccines. However, in few cases other SARS-CoV-2 proteins -

mostly the nucleoproteins (NP) are also targeted. To activate a robust immune response, often these vaccines supplemented with adjuvants, either of bacterial or synthetic origin.

Mechanism: The subunit vaccine, however, exhibits low immunogenicity and requires auxiliary support of an adjuvant to potentiate the vaccine-induced immune responses. An adjuvant may enhance the biological half-life of the antigenic material, or it may ameliorate the immune-modulatory cytokine response. The addition of an adjuvant, therefore, helps in overcoming the shortcomings of the protein subunit vaccines. More recently, it has been observed that SARS-CoV S elicited polyclonal antibody responses, and vigorously neutralized SARS-CoV-2 S-mediated entry into cells.

Advantages: Spike protein based vaccines do not have any live component of the viral particle. Thus, they are safe with fewer side-effects. These vaccines can be created for viruses that do not propagate well in the laboratory. There is no chance of live virus reversion. Induce an immune response.

Disadvantages: Requires specialized expertise to create; they are not as immunogenic as whole virus preparations, expensive, more difficult to produce. Memory for future responses is doubtful.

Subunit or protein based viral vaccines that are in currently use are: Human papilloma virus and Hepatitis B virus

Manufacturers

There are very numerous vaccine projects based on SARS CoV- 2 proteins, their fragments, or their fragments combination. At least sixteen candidate vaccines are already in human trials and two in Phase II trial

a. Spike protein or its fragments plus adjuvant: Adimmune, Taiwan; Bektop, Russia; biotechnology Vector, Russia; Clover Biopharmarm plus GSK adjuvant, China-Italy; CoVaxx, US; Inst Finlay de Vacuna Vaccine, Cuba plus adjuvant; Medigen, Taiwan-US, plus CpG adjuvant; Sanofi plus GSK adjuvant, France - Italy; The Univ of Queensland, Australia; Univ Tubingen, Germany; Vaxine, Australia, plus adjuvant; West China Hosp Sichuan Univ., China; ZFSW Anhui Zhifei Longcom, China, plus adjuvant.

b. Proteins carried by nanoparticles : Novavax, US, US, Australia, and South Africa, plus adjuvant .

c. Oral tablet containing Spike protein fragments: Vaxart, US.

d. Microneedle skin patch delivering Spike proteins: Univ Queensland, Australia

e. Spike protein or its fragments inserted in virus-like particles (VLP): SpyBiotech/Serum Institute of India, India.

f. Tobacco plant-produced proteins: Kentucky Bio Processing, US.

4. mRNA-based vaccines

mRNA vaccines were reported to be effective for direct gene transfer for the first time by Woff *et al.,*1998. Currently, two forms of mRNA vaccines have been developed: conventional mRNA vaccines and self-amplifying mRNA vaccines, which are derived from positive strand RNA viruses. Although mRNA vaccines were first tested in the early 1990s, these vaccines were not initially extensively utilized due to concerns about their loss of integrity caused by ribonucleases and small-scale production.

Principle: Several vaccine projects are trying to exploit this technology for the creation of SARS-CoV-2 vaccines. Unlike DNA, RNA must be delivered in various ways to enter the human cell. The mRNA coding the full-length spike protein is delivered by some vectors like encapsulated in microliposomes. Upon successful entry, the mRNA vaccine temporarily induces the cell to produce the antigen protein coded by the mRNA.

Mechanism: mRNA-based vaccines comprise mRNA that encodes a protein antigen. mRNA employed in vaccines encode the antigen of interest that contains 50 and 30 untranslated regions, whereas the virally derived, self-amplifying RNAs encode not only the antigen but also the viral replication machinery that enables intracellular RNA amplification and abundant

protein expression. Recent mRNA vaccine designs have improved the stability and protein translation efficiency for enhanced innate and adaptive immunogenicity. Delivery of the mRNA vaccine has been optimized by use of lipid nanoparticles (liposomes) for intramuscular or intradermal administration. These vaccine preparations need to be stored at –30 to –80 °C.

Advantages: mRNA vaccines are non infectious and non-integrating; egg and cell culture free, rapid and scalable production, stimulation of innate immune response, induction of T and B cell immune response

Disadvantages: Two major concerns are instability and low immunogenicity

Manufacturers

There are many vaccine projects based on mRNA and its variants coding the Spike protein. Two of those have already finished the Phase III trials. The mRNA vaccine may be carried by:

a. Lipid vesicles (Liposomes)

Abogn, China; CureVac, Germany; Moderna, US ; Pfizer, US - BioNTech, Univ Oxford, UK

b. Nanoparticles

Arcturus Ther, Singapore

5. Naked DNA-based vaccines

The DNA platforms offer great flexibility in terms of manipulation of the coded antigen and great potential for speed. Currently, there are no DNA vaccines registered for human use; however, DNA vaccines are commonly used in veterinary medicine. These vaccines are stable and can easily be produced in large amounts in host bacteria.

Principle: DNA vaccines consist of plasmid-DNA encoding one or several antigens that will be expressed in host cells. DNA vaccines can be produced rapidly and at low cost. DNA vaccines encoding the S protein of the SARS-CoV and MERS-CoV have been shown to elicit T cell and neutralizing antibody responses, as well as protective immunity in mouse model and human studies. However, the need for specific delivery systems to achieve good immunogenicity and possible genomic integration and persistence in host cells is still a problem that needs to be resolved.

Mechanism: Once injected into the muscle or skin, DNA plasmids enter human cells, and their ability to enter may be enhanced by a very short local electrical pulse (electroporation). Once entered, plasmid DNA induces the cell to produce temporarily the target protein. In this way, DNA vaccination stimulates the production of antibodies and the activation of killer T cells.

Advantages: Non-infectious, stimulation of innate immune response; egg and cell culture free, stable, rapid and scalable production; induction of T and B cell immune response.

Disadvantages: Potential integration into human genome, poor immunogenicity

Manufacturers

Six DNA vaccine projects are entering human trials. All of them code the Spike protein or its fragments.

a. Naked DNA plasmids :Zydus Cadila, India; AnGes, Japan; Takis, Italy.

b. Naked DNA plasmids plus electroporation: Inovio, US; Genexine, Korea; Karolinska Inst, Sweden + Inovio, Italy.

At present, human trials are underway with several different DNA vaccines, including those for malaria, AIDS, influenza, and herpesvirus.

6. Vaccines based on viral vectors

Virus-based vectors are powerful tools for vaccination. Their effectiveness stems from the fact that their ability to infect cells. It allows them to be highly efficient, specific, and able to trigger strong immune responses. Viral vector vaccines use a modified version of a different virus (the vector) to deliver important instructions to our cells. For COVID-19 viral vector vaccines, the vector (not the virus that causes COVID-19, but a different, harmless virus) will enter a cell in our body and then use the cell's machinery to produce a harmless piece of the virus that causes COVID-19. This piece is often a spike protein and it is only found on the surface of the virus that causes COVID-19.

Principle: The virus inside which the DNA is inserted may lose its ability to replicate. Since a pre-existing immunity against the virus vector may affect vaccine efficacy, primate viruses (from chimpanzee, gorilla monkeys etc) are often exploited as vectors. In other cases, the DNA is inserted into replication active virus vectors: as these viruses can propagate to some extent, they may induce a more robust immune response (Krammer, 2020). Also in these vaccine projects, the target antigen coded by the DNA is mostly, if not only, the Spike protein, its variants, or its fragments. Commonly, these virus-based vaccines are injected intramuscularly.

Mechanism: Since the vector viruses carry the genetic material that code for spike protein. The immune-response is similar to viral sub unit protein.

Advantages: High-efficiency gene transduction; Specific delivery of genes to target cells; Induction of robust immune responses; Increased cellular immunity

Disadvantages: Low titre production; May induce antivector immunity; Generation of replication competent virus, which can induce tumorigenesis.

At present there are numerous vaccine projects based on viral vectors that are already in advanced clinical trials. Four of those are currently in Phase III trial or approved for limited use. The DNA vaccines differ with respect to DNA inserted inside:

A. Engineered non-replicating virus vectors

1. Chimpanzee adenovirus: AstraZeneca, Univ. Oxford, Sweden-UK-Italy, that is also testing a vaccine inhaled form not yet in Phase III trial

2. Gorilla adenovirus: v ReiThera, Italy.

3. Human adenoviruses: CanSino, China; Johnson & Johnson, US; Acad Mil Med Sci, China, Gamaleya Res Inst, Russia: this vaccine based on two human adenoviruses injected one after the other has been approved for limited use.

4. Adenoviruses specifically modified for nasal spray: Beijing Wantai Biol Pharm Enterprise, China; Acad Mil Sci, China, two projects; Bharat Biotech-Washington Univ, India-US; AstraZeneca, Sweden-UK; Altimmune, US.

5. Other viruses

B. Engineered replicating virus vectors

1. Injected intramuscularly: Measles virus, Merck, US; Vesicular Stomatitis Virus.

2. Influenza virus administered by nasal spray: Influenza virus: Univ Hong Kong; Valavax-Abogn, China; Beijin Vantal Biol Pharm, China.

In addition to above discussed platforms, some other technological platforms are also are trying to develop new type of vaccines and they are at various stages of clinical trials.

1. Immunomonitor, Canada: Phase I/II human trial are underway with heat-inactivated plasma from donors with COVID-19.

2. Symvivo, Canada: Phase I human trial is underway with orally administered Bifidobacterium probiotic, engineered to carry the DNA encoding the Spike protein.

3. Shenzhen Geno-Immune Medical, China: Phase I human trial is underway with dendritic cells engineered to express SARS-CoV-2 proteins.

4. Aivita Biomedical, US: Phase I/II human trial are underway with the patient's dendritic cells modified to express SARS-CoV-2 antigens.

Corona - COVID Vaccines- Challenges and Concerns

During the past few months, several companies all over the world have been expediting their vaccine production programs. Traditionally, vaccine development takes 10–15 years. However, to circumvent this, a period to only 15 months targeted has its own drawbacks and challenges, and some concerns have been ventilated (Sharma *et al.,* 2020)

Accelerating vaccine development by overlapping some phases involves trials being done on smaller groups. This is a significant concern because when the vaccine is released for public use globally, unknown side-effects may appear in the larger population which were not previously observed within targeted smaller groups. In addition, if all sections of people (elderly and young) and those with co-morbidities are

not included in the design of the clinical trials, there is a chance that unwarranted side-effects may be observed in those groups (Span *et al.,* 2020).

• Platforms based on nucleic acids such as DNA and RNA is new technological innovations. So far, they have not resulted in a successful vaccine for human diseases and hence it is yet to be seen how mRNA vaccines will be successful for the reason the vectors lipid nanoparticles are temperature-sensitive and this may be a major road block for scaling up production (Corey *et al.,* 2020). Furthermore, for DNA vaccines, its dependence on electroporation or an injector delivery device for vaccine administration is a challenge.

• Pre-existing immunity to vector viruses such as adenoviruses is a concern, particularly for those vaccine candidates utilizing human adenoviruses which may result in a reduced immune response to the vaccine (Zhu *et al.,* 2020; Sumner, 2020). To overcome this, AstraZeneca/Oxford's AZD1222 is using a genetically modified chimpanzee derived adenovirus (Folegatti *et al.,* 2020).

• Rapid large-scale manufacturing of vaccines still remains a challenge with lots of uncertainty to meet the demand of a pandemic.

• Political/governmental pressure is another concern which demands to rush the development and approval processes for a vaccine. It may result in an ineffective vaccine being released for public use. Public becomes hesitant to accept such type of vaccines.

•With regard to pandemics, Global Vaccine Summit has called for an equal allocation of vaccines whenever a vaccine is released, but there is still an apprehension that some countries reserve the vaccine for their citizens. A recent example is stockpiling of the drug, remdesivir by USA for the treatment of patients with COVID-19 (Global Vaccine Summit, 2020).

• Phase 3 trials require over a large number of volunteers (30,000) and mostly these trials are performed during the later stages of development. Hence, there is a high chance that at that stage there will be fewer cases of COVID-19 and hence, HCTs may be required. Although HCTs have been done in the past, they may pose more risk for COVID-19 given how there is very little known about the pathogenesis and the availability of an effective treatment for COVID-19 (Deming *et al.,* 2020).

• Mutations are very frequent in viruses. Mutations of the virus can result in vaccines having limited effectiveness against it (Makhoul, 2020 Morris, 2020). There is also risk of vaccine-enhanced disease for inactivated vaccine candidates; this should be kept in mind when developing vaccines against COVID-19 (Morris, 2020).

However, given the crucial need for the availability of a COVID-19 vaccine globally, being concerned and assessing such risks should not prevent the release of otherwise safe and effective vaccines to the public (Garber, 2020).

Corona - COVID Vaccines – Indian scenario

India is expected to become the world's second largest covid vaccine maker, and the country has the capacity to produce for both its domestic use and to other developing countries. Most of the world's vaccines have historically come from India. Even before Covid-19, it produced up to about 60% of the world's vaccines, and that too at a relatively low cost. Given the track record it should therefore be a strategic partner in the global inoculation against COVID-19.

On 5 January, 2021 Sunday, India approved the emergency authorisation of two vaccines against novel coronavirus: Covaxin by Bharat Biotech, Hyderabad and Covishield by Serum Institute of India, Pune. Mass vaccination campaign was initiated on 16th January 2021 and both the manufacturers released the fact sheets about their products before the release of their vaccines.

Covaxin

Covaxin has been developed by Hyderabad-based Bharat Biotech in collaboration with the

Indian Council for Medical Research (ICMR) and the National Institute of Virology. Bharat Biotech is an Indian Biotechnology company, headquartered in Hyderabad, India. The company was founded by Indian scientist, Krishna Ella in 1996. Bharat Biotech has one of the largest pharmaceutical manufacturing plants of its kind in Asia-Pacific. The company has the reputation for developing an eco-friendly recombinant and a naturally attenuated strain derived Rotavirus vaccine called ROTAVAC. They were one of the first to develop vaccines for viral diseases like Chikungunya and Zika. The company also produces vaccines for Japanese Encephalitis.

In May 2020, Indian Council of Medical Research's (ICMR's) National Institute of Virology approved and provided the virus strains for developing a fully indigenous COVID-19 vaccine. On June 29, 2020, the company got permission to conduct Phase 1 and Phase 2 clinical trials in India for a developmental COVID-19 vaccine named Covaxin, from the DCGI, Government of India. The Drugs Controller General of India (DCGI) has clearly mentioned that its approval is Emergency Use Approval (EUA) only. Covaxin is a whole-virion inactivated SARS-CoV-2 (Strain: NIV-2020-770), and the other inactive ingredients such as aluminium hydroxide gel (250 µg), TLR 7/8 agonist (imidazoquinolinone) 15 µg, 2-phenoxyethanol 2.5 mg, and phosphate buffer saline up to 0.5 ml. The vaccine (COVAXIN™) thus has been developed by using inactivated/killed virus along with the aforementioned chemicals. The vaccine is developed using Vero Cell derived platform technology. Inactivated vaccines do not replicate and are therefore unlikely to revert and cause pathological effects. They contain dead virus, incapable of infecting people but still be able to instruct the immune system to mount a defensive reaction against an infection. This indigenous, inactivated vaccine is developed and manufactured in Bharat Biotech's BSL-3 (Bio-Safety Level 3) high containment facility.

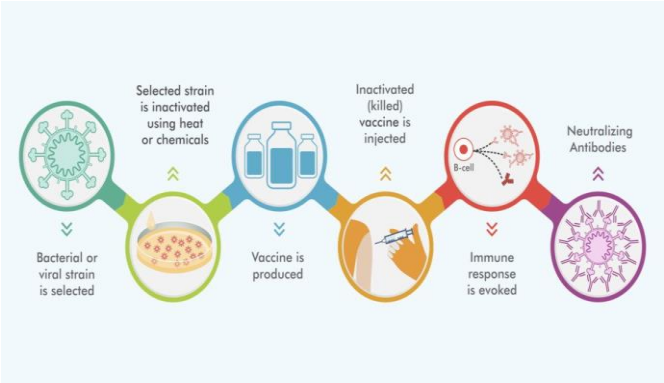

Fig. 3 : Outlines of protocol adapted by Bharat Biotech to produce COVAXIN™

Why it has selected Inactivated Vaccine?

Conventionally, inactivated vaccines have been used for decades. Numerous vaccines for diseases such as Seasonal Influenza, Polio, Pertussis, Rabies, and Japanese Encephalitis use the same technology to develop inactivated vaccines with a safe track record of more than 300 million doses of supplies to date. It is the well-established and time-tested platform in the world of vaccine technology.

Salient features of Covaxin

- COVAXIN™ has been granted approval for emergency restricted use in India by Drugs Controller General of India (DCGI) on Jan 03, 2021.
- COVAXIN® is included along with immune-potentiators, also known as vaccine adjuvants, which are added to the vaccine to increase and boost its immunogenicity.
- It is a 2-dose vaccination regimen given 28 days apart.
- It is a vaccine with no sub-zero storage, no reconstitution requirement, and ready to use liquid presentation in multi-dose vials, stable at 2-8°C.
- Pre-clinical studies demonstrated strong immunogenicity and protective efficacy in animal challenge studies conducted in hamsters & non-human primates.

- A total of 375 subjects have been enrolled in the Phase 1 study and generated excellent safety data without any reactogenicity. Vaccine-induced neutralizing antibody titers were observed with two divergent SARS-CoV-2 strains. Percentage of all the side-effects combined was only 15% in vaccine recipients.
- Phase 2 studies led to tolerable safety outcomes and enhanced humoral and cell-mediated immune responses.
- Efficacy is estimated by the incidence of COVID-19 cases accrual between the vaccine and the placebo group, which will commence two weeks after the second dose.
- The interim efficacy estimated to be 81% as declared on 5th March 2021

All India Institute of Medical Sciences (AIIMS) said that Bharat Biotech's Covid-19 vaccine, Covaxin, may provide immunity against the disease for nine to 12 months, as per the mathematical calculations. Data from Phase I and Phase II trials, and the ongoing Phase III trials, suggest that it is safe and effective, and by March-end tentatively, the data from Phase III trials will be available to establish its efficacy. In between, in phase III the vaccine is being administered to lakhs of people, and there are hardly any serious side-effects. No death has been reported so far. Covaxin satisfies the guidelines of drug regulator that for approval the efficacy of the drug should be more than 50%.

At present, Covaxin is being used by India in its vaccination campaign, which has already covered over 9 million health workers, and aims to cover 300 million people by August. Bharat Biotech has supplied 5.5 million doses to the government and will sell an additional 4.5 million doses.

Global Acceptance of COVAXIN™

Bharat biotech has been approached by several countries across the world for the procurement of COVAXIN. Clinical trials in other countries will commence soon. Supplies from government to government in the following countries would take place: Mongolia, Myanmar, Sri Lanka, Philippines, Bahrain, Oman, Maldives and Mauritius.

Covishield

Covishield is manufactured by Pune based Serum Institute of India, the world's largest vaccine manufacturer by volume. Originally, it was developed by British-Swedish pharma giant AstraZeneca and Oxford University. Earlier, Britain and Argentina had approved the emergency marker use of coronavirus vaccine developed by the University of Oxford and AstraZeneca. Serum Institute of India has joined hands with British-Swedish drugmaker to produce 1 billion doses of its COVID-19 vaccine. In June last year, AstraZeneca had reached a licensing agreement with Serum to supply one billion doses for low-and-middle-income countries, with a commitment to provide 400 million before the end of 2020.The local version of Oxford-AstraZeneca COVID-19 vaccine (ChAdOx1) will be known as Covishield.

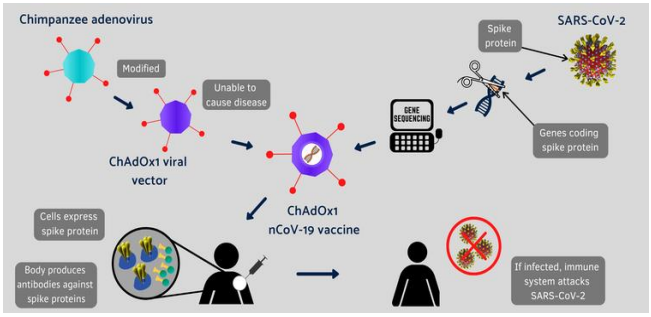

Fig. 4: Outlines of protocol adapted by Serum Institute of India to produce COVISHIELD™

Covishield is made from a weakened version of a common cold virus (known as an adenovirus) from chimpanzees. This Oxford vaccine packs the DNA that code for the spike protein in the shell of a genetically altered chimpanzee virus. The original adenovirus causes common cold in chimpanzees and it rarely, if ever, infects humans. The virus is further modified to ensure that this chimp virus cannot grow in people. The AstraZeneca vaccine uses the modified replication-deficient virus as a vehicle to deliver the COVID-19-causing spike or S-protein of the SARS-CoV-2 virus. It is produced in genetically modified human embryonic kidney (HEK) 293 cells.

On the whole, it has been modified to look more like coronavirus - although it can't cause illness. When the vaccine is injected into a patient, it prompts the immune system to start making antibodies and primes it to attack any coronavirus infection. The jab is administered in two doses given between four and 12 weeks apart. It can be safely stored at temperatures of 2^0C to 8^0C, about the same as a domestic refrigerator, and can be delivered in existing health care settings such as doctors' surgeries.

It has received emergency approval by WHO and DCGI to be used in India's mass inoculation campaign which aims to vaccinate some 300 million people in the first phase, most of them frontline workers and those above 50 or in high-risk groups.

Covishield is less expensive compared to some of the other vaccines being used — such as the ones from Pfizer-BioNTech and Moderna. It also doesn't need to be stored in ultra-low temperatures, which makes it suitable for use in many developing countries that lack necessary storage infrastructure. In view of its efficiency, affordability and storage, the demand for Covishield is also growing among many countries.

How effective is Covishield?

International clinical trials of the Oxford-AstraZeneca vaccine showed that when people were given a half dose and then a full dose, effectiveness hit 90%. But there was not enough clear data to approve the half-dose, full-dose idea. However, unpublished data suggests that leaving a longer gap between the first and second doses increases the overall effectiveness of the jab. In a sub-group given the vaccine this way it was found to be 70% effective after the first dose.

A comparison between Covishield and Covaxin

India has approved two vaccines — Covishield and Covaxin — for emergency use to fight Covid-19 pandemic in the country. The mass vaccination drive has begun on 16 January 2021. Covishield is the same vaccine that is being used in other countries including the UK. India's approval for Covaxin is conditional as it is still "in the clinical trial mode". Here is a comparison between the two Covid-19 vaccines approved in India:

Makers

- Covishield has been developed by the Oxford University scientists in collaboration with the pharmaceutical company AstraZeneca. In India, its trial was undertaken by the Serum Institute of India (SII), which is also manufacturing the Covishield vaccine for the mass vaccination drive.
- Covaxin has been developed by the indigenous vaccine developer Bharat Biotech in collaboration with the Indian Council for Medical Research (ICMR). Its hase III trial is in the final stage. The ICMR director, Dr Balram Bhargava said the full trial will be over in a week and by the time mass vaccination begins, the final set of data will be available.

How they were made

- Covishield vaccine has been developed by using the virus — adenovirus — that causes common cold infections among chimpanzees. Its genetic material is same as that of the spike protein of SARS-CoV-2 coronavirus. Spike protein is the part of SARS-CoV-2 using which the virus enters a human body cell. Covishield vaccine has been developed by using a weakened version of the adenovirus.
- Covaxin vaccine has been developed using dead coronavirus-called "inactivated" vaccine in medical parlance. Under inactivated state, the virus is not capable of infecting people or replicating on its own inside the body of a person after being injected. But a shot of the vaccine prepares the immunity system to recognise the actual virus and fight it if and when infection happens.

Efficacy

- While Covaxin is still in the final stage of clinical trial and no efficacy rate has been made public for this Covid-19 vaccine. However, the interim efficacy estimated to be 81% as declared on 5th March 2021. The efficiency of Covishield has been pegged at over 70 per cent. This efficacy rate is far below than the vaccines developed by Pfizer-NBiotech and Moderna, but it is above the qualifying efficacy benchmark of 50 per cent set by several countries.

Dosage

- Both Covishield and Covaxin are two-dose Covid-19 vaccines. But in an interesting development that was considered as inadvertent error, the Covishield vaccine was found to show over 90 per cent efficacy if one and a half doses are given to the recipient. However, in India, the SII conducted trials using full two-shot doses during testing.
- The two shots of the Covishield vaccine need to be spaced by six weeks. In the case of Covaxin, the interval between the two shots has not been yet prescribed by the Drug Controller General of India (DCGI) but its developer Bharat Biotech had earlier said the second shot would be given after 14 days.

Storage

- Both Covishield and Covaxin vaccines are easy to store as they require to be kept at 2-8 degree Celsius. Most vaccines commonly used in India are kept at this temperature range. This makes transport and local storage of both Covid-19 vaccines safe and easy for all parts of the country.

Pricing

- Though currently the government is controlling the vaccination drive against Covid-19, and it is free. Different reports have cited different prices for both the vaccines. The Covishield vaccine is reported to cost the government around Rs. 400-450 or Rs. 200-225 per dose.
- The pricing of indigenously developed Covaxin is not clear yet. However, some reports say the Bharat Biotech has priced its Covid-19 vaccine at Rs. 350.

Safety

- In the backdrop of reports questioning safety of the vaccines, the DCGI has said both Covishield and Covaxin are safe Covid-19 vaccines. DCGI VG Somani categorically said, "[Both] vaccines are 110 per cent safe. Some side effects like mild fever, pain and allergy are common for every vaccine.""We will never approve anything if there is slightest of safety concerns," Somani said.

The vaccination plan

- The government aims to vaccinate 30 crore people by July defining them as "priority population". They include frontline health workers, essential duty personnel and vulnerable sections of population. The first batch of 3 crore people will be given the shots of Covid-19 vaccines by March. Vaccination will be done through registration on Co-WIN, the digital platform developed by the government agencies to facilitate and monitor the drive against Covid-19 pandemic.

The other candidate vaccines which are in different stages of trials in India to test safety and efficacy include:

- **ZyCov-Di**, being developed by Ahmedabad-based Zydus-Cadila. Drugs Controller General of India (DCGI) has approved conducting phase III trials of the country's first DNA vaccine candidate against Covid-19 being developed by Zydus Cadila, the Department of Biotechnology said. The vaccine candidate has been supported by the National Biopharma Mission (NBM) under the aegis of

Biotechnology Industry Research Assistance Council (BIRAC), a PSU under the DBT.

- A vaccine being developed by Hyderabad-based Biological E, the first Indian private vaccine-making company, in collaboration with US-based Dynavax and Baylor College of Medicine.
- HGCO19, India's first mRNA vaccine made by Pune-based Genova in collaboration with Seattle-based HDT Biotech Corporation, using bits of genetic code to cause an immune response
- A nasal vaccine by Bharat BioTech
- The Sputnik V vaccine candidate developed by Dr Reddy's Lab and Gamaleya National Centre in Russia
- A second vaccine being developed by Serum Institute of India and American vaccine development company Novavax.

Conclusions

Scientists began working on coronavirus vaccines ever since the outbreaks of SARS and MERS, however, they could not succeed because of a myriad of difficulties. The current coronavirus pandemic, COVID- 19, appears much broader than SARS and MERS. Emergence of new variants intensifies the problem. Many research groups and companies are undertaking R & D programs to develop an effective vaccine against SARS-C oV-2 all over the world. A recent trend of vaccine research and development for SARS-C OV-2 is availability of varied range of evaluated technological platforms.

A close scrutiny of coronavirus vaccines revealed several safety concerns associated with the use of coronavirus S-based vaccines, including inflammatory and immunopathological effects. Assuming that the vaccine will generate an effective immune response the time frame of vaccine protection in vaccinated individuals is questionable. It is necessary to check the post-vaccination persistence of anti-COVID antibodies. Both safety and efficacy are significantly dependent on the type of vaccine, i.e. the technology or platform used. Some technologies are very new and therefore require more careful testing. Another aspect is not only the ability of a company to develop the technology, but also its large-scale production capacity so that it is quickly accessible globally. New production lines, capable of generating billions of doses in a few months, must be considered (Calina *et al.,* 2020). Applying short cuts in the development of vaccines can lead to errors with disastrous consequences. Relaxation of regulatory principles based on political pressure and goodwill needs to be resisted. Finally, vaccine development is a risky process, and one critical issue in the COVID-19 vaccine would be the occurrence of ADE which may be disastrous for those receiving the vaccine.

Vaccines are based on the principle of DNA and RNA requires insertion of these nucleic acids in to cells of people to be vaccinated. Although some recent data seem encouraging, these concepts have questionable efficiency in humans. The attenuated viruses would be variants of SARS-C oV-2 made less or not at all pathogenic by genetic engineering. They are by far the most immunogenic, but there is a risk that they will become pathogenic after mutations. Inactivated viruses, viral fragments, and synthetic peptides are all relatively weakly immunogenic. Considering all these, it is doubtful whether there ever will be a successful SARS-CoV-2 vaccine.

In India, two vaccines, covaxin and covishield are released for mass immunization on conditional basis. Many scientific organizations criticize that a vaccine released on such conditions cannot be released for vaccination of general public. Vaccination is taken up phase-wise. Frontline workers are targeted first. The manufacturers and government assure their effectiveness. But both of them did not indicate the time frame for immunoprotection. It is interesting to note that a number of countries halted use of the AstraZeneca vaccine (basis for covishield) because a small number of people developed blood clots. In light of onset of

second wave of pandemic, it needs to be seen the effectiveness of these vaccines.

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