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REVIEW ARTICLE **OPEN ACCESS**

Different strategies of treatment of Corona virus

Vikrant Verma[1]*,Parkhi Rastogi[2], Smita Singh[3] ,Pranjal Kumar Singh[3]
[1]Department of Pharmaceutical chemistry, KharvelSubharti College of Pharmacy, Swami VivekanandSubharti University Meerut,250005, Uttar Pradesh, India
[2]Department of Pharmacology, KharvelSubharti College of Pharmacy, Swami VivekanandSubharti University Meerut,250005, Uttar Pradesh, India
[3]SRM Modinagar College of Pharmacy, SRM Institute of Science and Technology,Delhi NCR Campus, Delhi Meerut Road, Modinagar, Ghaziabad, UP, India
*Corresponding author's e-mail:vijeetsingh84@rediffmail.com

ABSTRACT
With a special effort by the science community during the eleven months after the unearthing of the SARS-CoV-2 and its genome, over 300 vaccine proposals have been evolved. There are already more than 40 clinical assessments, of which 10 are in Phase III clinical trials, three with good findings in Phase III. Several of these novel emergency vaccinations are authorised. Existing findings lead to conclusion that novel vaccine candidates can play a prominent part in the protection and reduction of pandemic propagation. Because the conceptual and technological platforms used are so diverse, certain vaccinations are likely to be better suited to different segments of the human population. Furthermore, it is unclear whether and to what extent the capability of the vaccines under consideration and unrelated vaccines are related.Immunological fitness can be improved with vaccines like BCG, which educate innate immunity to SARS-CoV-2 and provide pathogen agnostic protection. These vaccines will be popular due to their fast development period and the uniqueness of the technology used.Launched with a number of outstanding issues that will only be fixed with the passage of time. In the long run, we believe that more than one vaccine will be required to enable equitable global access, protection of a wide range of patients, and immunisation against viral variations. Technical issues relating to the production of billions of doses, as well as ethical issues relating to the availability of these vaccinations in even the poorest countries, are looming concerns.
Keywords *SARS-CoV-2, B-cell,Vaccine, Immunisation*

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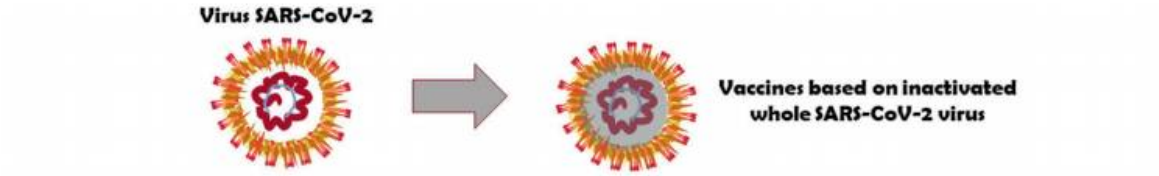
INTRODUCTION

The novel beta-coronavirus SARS-CoV-2 is believed to have emerged last year in 2019 in Wuhan from Bats. Crossing the species barrier it entered human beings with furtherance of infection through human to human transmission. The beta-coronaviruses have jumped between the species and have caused three zoonotic outbreaks namely, SARS CoV (2002-03), MERS-CoV (2012), and SARS-CoV-2 (2019- till date) in the last 2 decades. The existence of a myriad of coronaviruses in bats, including many SARS-related CoV (Severe Acute Respiratory Syndrome related Coronaviruses) and the sporadic crossing over of the species barriers of the coronaviruses to humans, suggest that the future occurrences of zoonotic transmission events may sustain. Since its emergence in Nov 2019, it 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 .As of 2 July 2020, 10,533,779 cases have been reported globally with 512,842 deaths. There has been a monumental increase in the number of infected patients, with a 7-day moving average of 210,209 cases per day, as of 2 July 2020[1-2].

Many efforts have been directed towards the development of the vaccines against COVID-19, to avert the pandemic and most of the developing vaccine candidates have been using the S-protein of SARSCoV-2. As of July 2, 2020, the worldwide SARS-CoV-2 vaccine landscape includes 158 vaccine candidates, out of which 135 are in the preclinical or the exploratory stage of their development. Currently, mRNA-1273 (Moderna), Ad5-nCoV (CanSino Biologicals), INO-4800 (Inovio, Inc.), LV-SMENP-DC, Pathogen-specific aAPC (ShinzenGeno-Immune Medical Institute), and ChAdOx1 (University of Oxford) have entered the phase I/II clinical trials.

The vaccines which are in the conduit are based upon inactivated or live attenuated viruses, protein sub-unit, virus-like particles (VLP), viral vector (replicating and non- replicating), DNA, RNA, nanoparticles, etc. with each exhibiting unique advantages and hindarances. COVID-19 vaccine landscape with percentage share of different types of vaccine is represented in Fig. 1. To enhance the immunogenicity, various adjuvant technologies like AS03 (GSK), MF-59 (Novartis), CpG 1018 (Dynavax), etc. are now accessible to the researchers for the vaccine development (Le et al., 2020). The immuno-informatics approach is also used for the epitope identification for the SARS-CoV-2 vaccine candidates. It can be used to identify the significant cytotoxic T cell and B-cell epitopes in the viral proteins [3-4].



Company and country	Vaccine name	Number of doses	Approval and registration
Sinovac Biotech, China	---	2	Ahead of Phase II trial it is offered to essential workers and other high-risk people of the Chinese town of Jiaxing for about 30 €/dose
Beijing Institute of Biological Products and Sinopharm, China	BBIBP-CorV	2	Limited approval for Chinese health care workers and ahead of Phase III trial. This vaccine has been approved by United Arab Emirates on the basis of preliminary data showing that it is 86% effective.
Wuhan Institute of Biological Products, and Sinopharm, China	---	2	Limited approval for Chinese health care workers and soldiers ahead of Phase III trial.
Bharat Biotech, India	COVAXIN	2	The Phase III trial with 26 000 volunteers is expected to close in February 2021.

Fig. 1 Twelve candidate vaccines currently in Phase III trial. COVID-19 vaccines based on the whole inactivated SARSCoV-2.

VACCINES BASED ON ATTENUATED SARS-COV-2 VIRUSES

The history of vaccination begins with vaccines based on a living microbe that has been weakened so it can not cause disease. Since attenuated microbes retain the ability to replicate in vivo giving rise to a limited disease, they are very effective in stimulating the immune system and inducing a strong and persistent immune memory that is efficacious in preventing infection. Hundreds of millions of people have been protected from disabling and fatal diseases by using attenuated vaccines. This is the most traditional technology exploited in the construction of vaccines. Live attenuated vaccines can be obtained by growing the virus in unfavorable conditions or by generating a genetically weakened version of the virus. However, the attenuation of trillions of viruses is complex and delicate and can be associated with major biosafety risks. Once produced, their storage and handling require carefully observed procedures. Only three projects of attenuated SARS-CoV-2 vaccines are in active preclinical development at the following institutions. The Serum Inst of India, India, in collaboration with Codagenix, a New York private biotech, Indian Immunologicals Ltd, India, in collaboration with the Griffith University, Australia; Mehmet Ali AydunarUniv, Turkey [5].

Ad5-nCoV

It is a recombinant, replication defective adenovirus type-5 vector (Ad5) expressing the recombinant spike protein of SARS-CoV-2. It was prepared by cloning an optimized full-length gene of the S Protein along with the plasminogen activator signal peptide gene in the Ad5 vector devoid of E1 and E3 genes. The vaccine was constructed using the Admax system from the MicrobixBiosystem. The phase I clinical trials have established a positive antibody response or seroconversion. A four-fold increase in the RBD and S protein-specific neutralizing antibodies was noted within 14 days of immunization and peaked at day 28, post-vaccination. Furthermore, the CD4 + T cells and CD8 + T cells response peaked at day 14 post-vaccination. However, the pre-existing anti-Ad5 immunity partly limited both the antibody and the T cell responses (Zhu et al., 2020). The study will further evaluate antibody response in the recipients who are between the age of 18 and 60, and received one of three study doses, with follow-up taking place at 3- and 6-months post-vaccination [6-7] .

Inactivated SARS-CoV-2 viruses based vaccines

Vaccines based on killed microorganisms (inactivated vaccines) belong to a very traditional technological platform that has led to numerous 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 the association of 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. While the induced response is generally weaker concerning that induced by attenuated viruses, the vaccine is more easily handled, less expensive, and much safer.

The SARS-CoV-2 is inactivated by exploiting different chemical techniques. All these candidate vaccines are injected intramuscularly. Seven vaccine candidates based on variously inactivated SARS-CoV-2 virions are in clinical trials, four of which inphase III trials and already approved for limited use . When available, reports from Phase II trials suggest that the vaccine is safe and induces a high titer of antibodies. The seven clinical trials are run by Sinovac Biotech, China, this vaccine called CoronaVac is in late-stage Phase III trial and interim results are expected in late November. Meanwhile, 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 InstBiol 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, is in late stage Phase III trial; RIBSP, Kazakhstan [8].

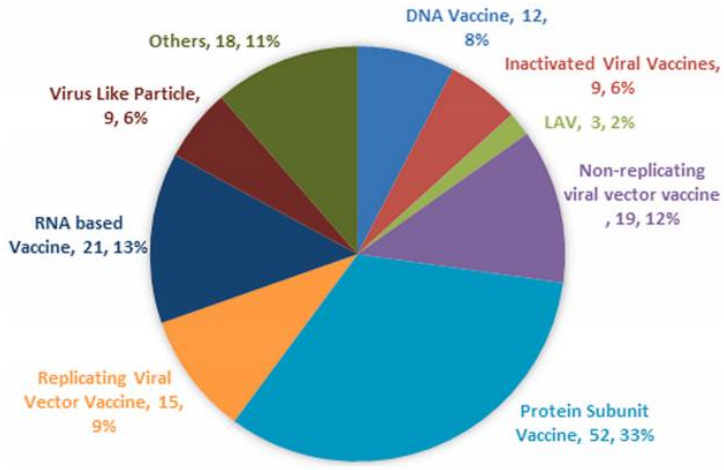


Fig. 2. Pie Chart showing the different categories of SARS-CoV-2 vaccines under research

Protein Sub-unit vaccine

A subunit vaccine is the one which is based on the synthetic peptides or recombinant antigenic proteins, which are necessary for invigorating long-lasting protective and/or therapeutic immune response . 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 immunomodulatory cytokine response. The addition of an adjuvant, therefore, helps in overcoming the shortcomings of the protein subunit vaccines . The S protein of the SARS-CoV-2 is the most suitable antigen to induce the neutralizing antibodies against the pathogen. The S Protein consists of two subunits. The S1 subunit has the NTD, RBD, and RBM domains while the S2 subunit comprises of FP, HR 1, &2 . The virus enters into the cell via endocytosis by utilizing the S-Protein mediated binding to the hACE2 receptor. Therefore, the S-Protein and its antigenic fragments are the prime targets for the institution of the subunit vaccine . The S glycoprotein is a dynamic protein, possessing two conformational states i.e. pre-fusion and post-fusion state. Therefore, the antigen must maintain its surface chemistry and profile of the original pre-fusion spike protein to preserve the epitopes for igniting good quality antibody responses . Moreover, means to target the masked RBM as an antigen will enhance the neutralizing antibody response and improve the overall efficacy of the vaccine [9-12].

mRNA Vaccine

mRNA is an emerging, non-infectious, and a non-integrating platform with almost no potential risk of insertional mutagenesis. Currently, the non-replicating RNA and the virus derived self-replicating RNAs are being studied. The immunogenicity of the mRNA can be minimized, and alterations can be made to increase the stability of these vaccines. Furthermore, the anti-vector immunity is also avoided as the mRNA is the minimally immunogenic genetic vector, allowing repeated administration of the vaccine

.This platform has empowered the rapid vaccine development program due to its flexibility and ability to mimic the antigen structure and expression as seen in the course of a natural infection [13-14].

PittCoVacc

It is a Micro-Needle Array (MNA) based recombinant SARS-CoV-2 vaccine which involves the administration of rSARS-CoV-2 S1 and rSARS-CoV-2-S1fRS09 (recombinant immunogens). A substantial increase in the antigen specific antibodies with a statistical significance was observed in the pre-clinical trials at the end of two weeks in the mice models. Furthermore, the immunogenicity of the vaccine was maintained even after the sterilization using gamma radiation. The statistically significant titers of antibodies at the early stages and also before boosting, support the feasibility of the MNA-SARS-CoV-2 vaccine [15]**.**

Triple Antigen Vaccine

It is a multi-antigenic VLP vaccine prototype wherein the recombinant spike, membrane, and envelope protein of SARS-CoV-2 have been co-expressed in an engineered *Saccharomyces cerevisiae* expression platform (D-Crypt™). The proteins then undergo self-assembly as the VLP. The TEM and allied analytical data simultaneously furnished the biophysical characterization of the VLP. This prototype has the potential to enter the pre-clinical trials as a vaccine candidate after further research and development. Furthermore, it is thought to be safe and easy to manufacture on a mass scale, in a cost-effective manner [16].

Vaccines based on viral vectors

The DNA coding for the Spike protein can be conveyed into the cells by viral vectors. By inserting the DNA in a virus, it is possible to exploit the virus's great ability to infect and deliver the mRNA into the human cells. The virus inside which the DNA is inserted may lose its ability to replicate. Since a preexisting immunity against the virus vector may affect vaccine efficacy, primate viruses (from chimpanzee, gorilla…) 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 There are very 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 vaccine DNA is inserted inside: Engineered non-replicating virus vectors .Chimpanzee adenovirus: AstraZeneca, Univ. Oxford, Sweden-UK-Italy (Fig. 5), that is also testing a vaccine inhaled form not yet in Phase III trial; 2. Gorilla adenovirus:vReiThera, Italy [17].

CONCLUSION

SARS-CoV-2 has been the matter of the moment from the date it was declared as a pandemic, it has led to the termination of economic activities universally. Scientists across the continents are joining hands for the innovative tie-ups with both the pharmaceutical giants and the medical start-ups to repurpose drugs, develop vaccines, and devices to impede the progress of this overwhelming pandemic. A large number of COVID-19 vaccine candidates based upon various platforms have already been identified. Despite the undergoing efforts, a definitive answer does not exist. The process of vaccine development is quite laborious with various stages, including the pre-clinical stage, and clinical development which is a three-phase process. However, if sufficient data is already available, it has been recommended to skip a few stages, to accelerate the attainment of a vaccine faster with a quick regulatory review, approval, manufacturing, and quality control. This novel Coronavirus has therefore forced the scientific community to use unconventional approaches to accelerate the process of vaccine development. The use of novel technologies for vaccine development requires extensive testing for the safety and efficacy of a vaccine. The scientific community needs to construct various processes and capacities for the large-scale manufacturing and administration of the coronavirus vaccines.

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