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A REVIEW ON THE NOVEL COVID-19 VACCINE: TYPES OF VACCINE PLATFORMS

Ruthika Ratnaveni Marri[1], Mamatha Tirunagari[1]*, Prasanthi Raghavarapu[1], Nida Tahreen[1], Siva Jyothi Buggana[1]

[1]Department of Pharmaceutical Quality Assurance, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Tarnaka, Secunderabad, Telangana State, India.

***Corresponding Author: Mamatha Tirunagari**
Department of Pharmaceutical Quality Assurance, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Tarnaka, Secunderabad, Telangana state, India.

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ABSTRACT
The mishap of the peculiar severe acute respiratory syndrome by coronavirus, SARS-CoV-2 is still a worldwide human setback. So far, no particular antiviral drug or therapy has been capable to break the extensive SARS-CoV-2. During this span, a phenomenal effort by the scientific coterie has led to the evolution of over 300 vaccine projects. Out of which 40 vaccines are subjected to the clinical evaluation and around 10 vaccines are going through phase 3 clinical trials also three vaccines have winded up the phase 3 clinical trials with effective results. In addition to these a couple of vaccines were consented for emergency use. It has been basically presumed that reviving protective immunity through the universal vaccination is a discrete strategy to survive this pandemic. To ease the consequence of the virus on the world's population and the international wealth vaccines were rapidly evolved. In not more than a year corresponding to usual clinical development rules, many vaccines were released on the market and many vaccine drives were brought into action. To develop a vaccine, it is necessary to know the patient's well-being associated behaviours and perceptions to manage the public health vaccination policy. It also involves attention towards the immunological and non-immunological perspective.

KEYWORDS: SARS-CoV-2 vaccinations, Technological problems, Vaccine drives, Clinical Trials, Efficacy, Types of vaccines, Perceptions, Immunological and non-immunological.

INTRODUCTION
In view of the fact that SARS-CoV-2 has led to the novel CoViD-19 pandemic since the early February of 2020, several scientists across the globe have been working on different types of vaccines. With the help of today's technological platforms our scientists came up with over 200 vaccine programmes in which almost 10 vaccines have ended phase 3 trials with positive results and a few vaccines like Covishield and Covaxin were approved for emergency cases. Since the pandemic won't stop spreading it is becoming difficult for the pharmaceutical industry to produce mass number of vaccinations at once. SARS-CoV-2 is a single stranded RNA virus belonging to the family Coronaviridae.[1] Since the virus being RNA virus, it undergoes high-rate mutations giving rise to various virus mutants which are stronger and even more resistant to the medications. To design and develop a vaccine one should know about the immunological and non-immunological standpoints of the patient. The already healed person contains higher range of antibodies that neutralize the SARS-CoV-2 virus. Also it is important to know the efficacy and potency of the vaccines. There is a lot of pressure from the media and also the global public health for the development of the vaccines. This article is going to be about the types of vaccines produced or under production or undergoing clinical trials, about the efficacy and the availability of the vaccine, technological platforms involved in the development of the vaccine, about the role of pharmacovigilance and pharmacoepidemiology in the safety guidance of the vaccines, also the predictions and perceptions of the vaccines in the long run and last but not the least alternative medications involved in the treatment of the Covid-19 virus.[2-4]

A brief explanation on the structure of the virus
The SARS-CoV-2 is basically a large enveloped, single stranded, positive sense RNA virus. Their membrane looks like a crown in shape as there are spike proteins present on the structure. The structural proteins are: a) Spike Glycoproteins(S), b) Small envelop proteins(E), c) Membrane or matrix proteins(M) and d) Nucleocapsid proteins(N).

The mechanism of action of sars-cov2
The SARS-CoV-2 acts by binding to the ACE2 receptors that is Angiotensin Converting Enzyme 2 receptors. These receptors are generally observed in the main organs like heart, kidneys and the intestine. To go into further more depth, the Spike(S) proteins is further

divided into two subunits S1 and S2. According to the data collected the S1 subunit binds to the ACE2 receptors and S2 subunit is associated with the transmembrane proteases' serine. As a combination of the earlier mentioned reactions the virus gets endocytosed and its RNA genome is released into the host cytoplasm. The newly integrated proteins subsequently traded from the ER and the Golgi apparatus, following the congregation of the new virions in the growing Golgi vesicles.[5]

Types of covid-19 vaccines

After the declaration of SARS-CoV-2 caused Covid-19, which was identified in Wuhan, China, as the pandemic there were almost of 150 vaccines officially undergoing the clinical evaluation among which around fifty of the vaccines were in the Phase 3 trials and a few of them at present are administered in few divisions of the world's general population.[6]

Vaccines are designed and developed based on certain targets like spike proteins and its fragments, nucleic acids, live microbes, killed or inactivated virus cells, viral vectors, antibodies, etc. As of February 9th 2021, over 63 vaccines against SARS-Cov-2 infection have entered clinical trials, while 179 vaccines were going through preclinical modifications.[7]

Table 1: This table contents about a few vaccines which have passed the Phase-3 trials and were administered to the people on approval by different regulatory bodies like FDA, CDSCO, etc all over the world.

S. No	Name of the Vaccine	Manufacturing Company	Chemical Name of the Vaccine	Type of the Vaccine	Number of Doses
1	Covaxin	Bharath Biotech, India	BBV152	Attenuated Vaccine	2
2	Covilo	Beijing Institute of Biological products and Sinopharm, China	BBIBP-CorV	Attenuated Vaccine	2
3	CoronaVac	Sinovac Biotech, China		Attenuated Vaccine	2
4	Covovax	Novavax, US	NVX-CoV2373	Spike protein-based vaccine	2
5	Covifenz	Medicago, Canada and GSK, Italy	Co-VLP	Spike protein-based vaccine	2
6	Comirnaty	Pfizer, US and BioNTech, Germany	BNT162b2	mRNA based Vaccine	2
7	Moderna, SpikeVax	Moderna, USA and US Government	mRNA-1273	mRNA based Vaccine	2
8	Covishield	AstraZeneca, Sweden-UK and Univ, Oxford, UK	ChAdOx1 nCov-19	DNA based vaccine	2
9	Sputnik V	Gamaleya Res Int, Russia	rAd26	DNA based vaccine	2
10	Convidecia	CanSino Biologicals, China	Ad5-nCoV	DNA based vaccine	1

Vaccines generated based on attenuated sars-cov2 virus

Attenuated vaccines are the vaccines that are prepared based on the live virus which is probably weakened in order to not cause the disease. The attenuated viruses have the capacity to replicate in vivo that brings about limited disease.[8] In the development of this vaccine a virulence gene is either deleted or mutated due to which the virus can reproduce to a restricted range in the live host without leading to serious infection. Many structural and non-structural genes which are hardly into the viral reproduction were put forward to generate attenuated forms of zoonotic coronavirus. Protein E is a particular structural protein that was deleted to design the attenuated coronaviruses. The distribution of these vaccines has a need for cold storage that controls the utilization over longer distances. Around the globe only three research institutes that include a) Indian Immunologicals ltd and Griffith University of Australia. b) Turkish Mehmet Ali Aydiniar University and c) Codagenix, a biotechnological company based in New York and Serum Institute of India. COVI-VAC has been generated by Codagenix's synthetic attenuated virus engineering (SAVE) technique that works on synthetic biology to recode the genes of viruses into secure and steady vaccines.[9]

Vaccines produced on the basis of inactivated sars-cov virus

Inactivated here means killed. These are the vaccines formulated on the basis of killed viruses. This technique is a very old technique that has helped in creating several vaccines. The vaccines manufactured based on this technique have greater stability when compared to live attenuated vaccines but these types of vaccines have shorter duration of immune memory which requests the inoculation of greater number of vaccine or the interdependence of the inactivated virus with an adjuvant. The immune response obtained is not only resistant towards the spike proteins but also is resistant to various other SARS-CoV-2 antigens. The persuaded response is basically weaker concerning that persuaded by the attenuated viruses, the vaccine is easy to handle, less expensive and even safer. In the current period, about nine cumulative clinical trials as well as 12 more inactivated SARS-CoV-2 vaccines in the preclinical stage are yet to be investigated. CoronaVac is the other inactivated vaccine developed by the Chinese Sinovac Biotech Ltd., which also is an alum-based vaccine and is the foremost vaccine to undergo phase-3 clinical trials in Indonesia.[10]

There is another vaccine which is formulated and manufactured by the Bharat Biotech, India. This vaccine is named, COVAXIN, which is in the last stage of the Phase-3 clinical trials. This vaccine has been formulated utilizing the Whole- Virion Inactivated Vero cells obtained from the platform mechanization. Inactivated vaccines do not mutate and are henceforth cannot go back to their original form and cause pathological effects. Though this vaccine is not having the capacity to infect people it can still build the immunity to ascend a reaction resistant to the infection. Covaxin constitutes of immune boosters that are included to boost the immunity. The research or the laboratory name of Covaxin is BBV152. The efficacy of Covaxin is said to be around 60%-91%, which is more effective than any other vaccine in the country. But this vaccine still needs to get an approval from WHO for international purposes.[11-12]

Vaccines formulated on the basis of Sars-Cov2 proteins

Many human vaccines based on the proteins present on the surface of the virus have been developed in the previous years. In the current situation present several vaccines are being formulated utilizing the recombinant DNA technology. There is a huge trimeric cluster of the spike protein that project out of the virion have an important role in the anchoring of SARS-CoV-2 to the human cells. The Spike proteins and its fragments are the major targets for such vaccines and in a few cases Nucleoproteins(N) which is one of the spike proteins is also a target. To create a strong and stable immune response, these vaccines use different adjuvants which are basically of bacterial or synthetic origin. Around 20 vaccines in this category are in the human trials and two of them are in Phase-2 clinical trials. There vaccines are developed based on various aspects of the virus proteins, such as: Vaccines developed based on the Spike proteins and its fragments:

These types of vaccines are developed by

i. Adimmune, Taiwan
ii. Biotechnology vector, Russia
iii. Clover Biopharmarm plus GSK adjuvant, China-Italy
iv. CoVaxx, US
v. Inst Finlay de Vacuna Vaccine, Cuba
vi. Medigen plus CpG adjuvant, Taiwan-US
vii. Sanofi Plus GSK adjuvant, France-Italy
viii. The University of Queensland, Australia.
ix. University Tubingen, Germany
x. Vaccine plus adjuvant, Australia
xi. ZFSW Anhui Zhifei Longcom plus adjuvant, China

- Vaccines developed based on the proteins carried by nanoparticles:

i. Novavax, US

- Oral tablet containing Spike Protein fragments-Vaxart, US
- Microneedle skin patch producing Spike proteins-University of Queensland, Australia
- Vaccines developed on the basis of the Spike proteins or its fragments inserted into virus like particles by Spy Biotech/Serum Institute of India.
- Vaccine based on the Tobacco plant proteins by Kentucky Bio Processing, US
- Vaccines developed based on the tobacco plant proteins inserted into the virus like particles-Medicago plus GSK adjuvant, US-Italy.

Virus like particles (VLP) are a couple of synthetic and spontaneous non-infectious virus like structures which consist of distinguished viral proteins without genetic materials. The same mechanization is still utilized to design and develop a vaccine against the HBV and HPV. In case of coronavirus these VLPs are produced in the infected eukaryotic cells along with active germination and have E, M, S and also the N proteins in which the encoding RNA genome is absent. VLPs surface the path for mass production and good manufacturing practice needs accession of the emerging coronavirus VLP vaccines. Two vaccines that are CoVLP by Medicago biotechnology company and RBD SARS CoV2 HBsAg VLP vaccine by Serum Institute of India are undergoing clinical trials while the rest are still in the preclinical phases.[13-14]

Vaccines formulated based on the Nucleic acids (RNA & DNA based)

The genetic engineering technology is the new and emerging platform that has provided the utilization of nucleic acids in the development of the vaccines. DNA-based vaccines are designed by the insertion of the encoding gene of an external antigen into the plasmid DNA. RNA based vaccines are made up of mRNA manifesting a viral antigen in Lipid Nanoparticle coating.[15]

Vaccines developed on the basis of DNA

The DNA and RNA based platforms show malleability towards the working of the coded antigen and has a great pace. However, there are no DNA vaccines manufactured for the human use. The DNA vaccines are generally stable and can be manufactured in larger amounts in a bacterium. In case of the current CoVid-19 situation, there is a novel approach towards the DNA vaccines. In general, the DNA vaccines are designed by altering the microbial antigens. In the production of DNA Vaccines, the DNA plasmids play vital role. The DNA plasmids are basic engineering platforms used in the vaccine development that stimulate both humoral and cell mediated responses. The capability of this vaccine to stimulate well balanced antibody and cellular immune responses has created a pathway towards the application of this technique for the therapeutic and preventive purpose.[16]

Vaccines formulated on the basis of RNA

Currently, there are many vaccine projects that use the technology of *messenger RNA* (mRNA) for the development of SARs-CoV-2 vaccine. RNA cannot be directly injected into the human cell like the DNA it requires different ways to get into the cell. Once, the mRNA gets inside, it accelerates the cell to give the antigen protein loaded by the mRNA. Generally, there are two main classes of mRNA vaccines- (a) *Conventional mRNA* (b) *Advanced Self-replicating and Transcribing RNA vaccines.* The RNA vaccines propagate the transcript of the viral antigen many times for a prolonged period and acquired robust elicitation of innate and adaptive immune responses. In addition to live attenuated vaccines, the dose sparing appearance is traceable after injection of this kind of RNA vaccine. Pfizer was approved to be one of the emergency vaccines in the UK and USA. *Arcturus Therapeutics, Singapore*, discloses a novel Covid Vaccine, ***ARCT-021***, which has been prepared based on the nanoparticles and has shown great outcomes with a single shot in lab animals. Mice vaccination with a single dose of ARCT-021 brought about substantial neutralizing antibody responses, which eventually elevated after two months. Apart from that, vigorous anti-spike specific $CD8^+$ T cell and Th1 responses were produced and human ACE2 transgenic mice were massively immunized against SARS-CoV2 challenge after ARCT-021 vaccination. ***LNP-nCoVsaRNA***, another self-amplifying RNA Vaccine was developed by *Imperial College of London*, which is no longer in progression. The mechanism of this vaccine is, it encodes the spike protein of SARS-CoV 2 and when administered intramuscularly in mice, it provoked particular IgG antibody and Th1 responses dose-dependently.[17-21]

Vaccines developed on the basis of viral vectors

Engineered vectors are the innovative creation of vaccines that adduce the recombinant DNA technology to introduce the encoding gene of pathogen antigens into the genome bacterial or viral vectors. The recombinant vector sometimes proliferates in the host body and persuades the potent B and T cell immune responses by expression and processing of pathogen antigens. Viral vectors depending on their ability to multiply in the host cells are divided into two main groups i.e., Replicating vectors and non-replicating vectors. The non-replicating vectors do not show the reproductive ability has a certain part of the genome is removed but they contract the capacity of expressing a target gene. These render for large share of vaccine manufacturing and are essentially designed based on adenovirus as well as adeno-associated virus (AVA). As of April 2021, 41 viral vector candidates against COVID-19 were undergoing preclinical trials and 16 candidates were undergoing clinical trials, while only 3 vaccines based on **ChAdOx1** (Chimpanzee Adenovirus; Covishield) and **Ad26** viral vectors were chosen for public private Operation Warp Speed (OWS) partnership of the US. As we are talking about the Serum Institute of India, there is another vaccine that has been manufactured by this institution and that is COVISHIELD. **Covishield** has been manufactured by **AstraZeneca**, a pharmaceutical company based in the United Kingdom, in association with **Oxford university**. The Covishield vaccine is said to be 63% effective against the CoVid-19 virus. It is a 2-dose vaccine and it is being proven that the longer gap between the two doses can be more effective and so the duration to take the second dose has been increased from 4-6 weeks to 4-8 weeks. There are many side effects recorded, the most common side effect is tenderness, pain, fever like, itchiness, fatigue chills, headache, nausea, muscle ache while common to rare side effects are vomiting, sore throat, running nose, cough to feeling dizzy, reduced appetite, enlarged lymph nodes. In a few cases serious and unpredicted side effects may also be seen.[22-24]

CONCLUSION

From the above discussion made we can conclude this by noting that the process of selection, preparation or formulation, evaluation and approval of the vaccine was done as early as possible to protect people from the COVID-19 infection. It was also stated that various vaccine platforms like mRNA vaccines, Adenoviral Vectored Vaccines were selected for the primary formulation of the current utilized vaccines. The efficacy and safety of the vaccines were demonstrated by the data collected from the clinical trials of the various Covid-19 vaccines.

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