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Review Article

Microbiology Section

A Sneak Peek into COVID-19 Vaccines-Present Status

SWATHI GURAJALA

ABSTRACT

The Coronavirus Disease 2019 (COVID-19) pandemic has taken a toll on all of us for one year with more than 1.94 million deaths. Despite many educational interventions and precautionary measures, there is increasing number of cases with rising mortality. The only ray of hope in this uncertain situation is the development of "vaccines" against the disease. Several pharmaceutical companies across the world have started vaccine production which are in different phases of clinical trials. Till date only four vaccines, Pfizer/BioNTech, Moderna, Oxford-AstraZeneca and Gamaleya Sputnik V, have completed the Phase 3 trials, received Emergency Use Authorisation (EUA) and two Indian vaccines-COVISHIELD and COVAXIN™ have received restricted use approval and are ready to be given according to the priority list given by the Centers for Disease Control and Prevention (CDC). Several countries have started the process of vaccination to their high risk population above the age of 16. In this review, authors have listed the various vaccine options available till the time this article is written, their route of administration, dosage with few concerns related to the storage and safety of the vaccine. Let's hope that atleast one of the vaccines in the pipeline will give promising results and help us to overcome the pandemic.

Keywords: Genetic vaccines, Inactivated vaccines, Subunit vaccines, Vaccination risks, Viral vector vaccines

INTRODUCTION

COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has made the world come to a standstill since December 2019. There has been implementation of precautionary measures at the individual level, such as hand hygiene, wearing face masks, physical distancing, and practicing respiratory etiquette. At the national level, precautionary measures, such as lockdowns, prevention of mass gatherings, and travel restrictions, have been implemented. But still, the infection could not be limited. As of January 11, 2021, about 90,980,141 cases and 1,948,083 deaths have been reported due to the COVID-19 pandemic [1]. Almost every sector of the population is in wait for the availability of an effective vaccine against this deadly pandemic with the hope that normal life will be restored. With this interest, literature search was conducted in the internet by using the keywords "COVID-19 vaccines", "latest update about the COVID-19 vaccines". Relevant information with the latest updates were found in the authenticated public databases like the US Food and Drug Administration (FDA), CDC, World Health Organisation (WHO), Johns Hopkins Coronavirus Resource Centre and few newspaper articles. Thorough study of the available information was done and finally in this review, Authors have tried to give a sneak peek into the latest advancements in vaccine development against COVID-19 and few concerns regarding the use of these vaccines.

THE PIPELINE: CLINICAL TRIALS

Vaccine development moves through established pipelines that require rigorous safety and efficacy testing before public availability [2]. After identification of a vaccine candidate, preclinical studies in cultured cells and animals ensure the vaccine elicits an effective immune response without being toxic before clinical trials begin in humans. At this point, the FDA recognises the vaccine as an Investigational New Drug (IND) [3].

- The Phase 1 Clinical Trial assesses risk factors or adverse effects, what dose is required, whether this dose is the same for different individuals, and if the vaccine promotes healthy immune systems to make antibodies [4].
- If there are no risk factors or adverse effects in Phase 1 trials, Phase 2 and Phase 3 trials expand to more volunteers, increasing statistical power. Each phase has built-in objectives and endpoints and volunteers are monitored for months. After Phase 3, the vaccine must receive FDA approval before licensing and distribution [4].
- Then, Phase 4 Clinical Trials is the last and includes ongoing studies of risk and side effects after the vaccine is distributed [5].

Characteristics of the Desired Vaccine [6]

The ideal SARS-CoV-2 vaccine should be:

- Safe and with only mild, transient side effects
- Provide long term protection in >80% of vaccine recipients
- Protect against disease and prevent transmission of the virus to others
- Given as a single dose
- Easy to manufacture
- Can be stored easily
- Can be easily transported
- Can be easily administered

Types of Available COVID-19 Vaccines [7]

- Genetic vaccines- Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) vaccines
- Viral vector vaccines
- Viral subunit vaccines
- Live attenuated vaccines
- Inactivated virus vaccines

The complete list of the vaccines till date in preclinical development, Phase 1, Phase 2, and Phase 3 clinical trials is shown in [Table/Fig-1] [7].

Type of vaccines	Name of the vaccine	Company	Country	Doses (days)	Route*	Trials	Status
Nucleic acid vaccines	DNA vaccines	Inovio	USA	2 (0,28)	ID	Phase 2	
		Zydus cadila	India	3 (0,28,56)	ID	Phase 2	
		Osaka University/AnGes/Takara Bio	Japan	2 (0,14)	IM	Phase 2	
		Genexine consortium	Korea	2 (0,28)	IM	Phase 2	
		Entos pharmaceuticals	Canada	2 (0,14)	IM	Phase 1	
		Symvivo	Canada	1 (0)	Oral	Phase 1	
		OncoSec immunotherapies	USA	-	-	Phase 1	
		Providence health and services		2 (0,28)	ID	Phase 1	
		Many DNA vaccines in preclinical development - Sanofi, Applied DNA Sciences, EvviVax and Takis Biotech; DIOSynVax; Elixirgen Therapeutics; ETheRNA; HDT Bio; Infectious Disease Research Institute and Amyris; Mediphage Bioceuticals; the OPENCORONA Consortia; Scancell; the Spanish National Center for Biotechnology and the Spanish National Research Council.					
	RNA vaccines	Pfizer/BioNTech	USA/Germany	2 (0,28)	IM	Phase 3	**Complete**
		Moderna	USA	2 (0,28)	IM	Phase 3	**Complete**
		Curevac	Germany	2 (0,28)	IM	Phase 2	
		Imperial college london	UK	2	IM	Phase 2	
		Arcturus therapeutics and Duke-NUS medical school	USA/Singapore		IM	Phase 1/2	
		Academy of military medical sciences, suzhou abogen biosciences and walvax biotechnology	China	2	IM	Phase 1	
		Chulalongkorn university	Thailand	2 (0,21)	IM	Phase 1	
	Viral vector vaccines	Oxford-AztraZeneca	UK	2 (0,28)	IM	Phase 3	**Complete**
		CanSino biologics	China	2 (0,28)	IM	Phase 3	
		Janssen	USA	2 (0,56)	IM	Phase 3	
		Gamaleya-Sputnik V	Russia	2 (0,21)	IM	Phase 3	**Complete**
		ReiThera	Italy	1	IM	Phase 1	
		Vaxart	USA	2 (0,28)	Oral	Phase 1	
		Merck Sharp & Dohme/IAVI	USA	1	IM	Phase 1	
		Institute Pasteur/Themis/Univ. of Pittsburgh CVR/Merck Sharp & Dohme	USA/France	1 or 2 (0,28)	IM	Phase 1	
		University of Hong Kong and Xiamen University	Hongkong	1	Nasal spray	Phase 1	
		German center for infection research	Germany			Phase 1	
		Immunity bio & nantkwest inc	USA	2 (0,21)	SC	Phase 1	
		Israel institute for biological research	Israel	1	IM	Phase 2	
		City of hope	USA	2 (0,28)	IM	Phase 1	
		Ludwig-Maximillian's-University of Munich	Germany	2 (0,28)	IM	Phase 1	
		Other viral vector vaccines in active preclinical development include vaccines from: NOVARTIS, Altimmune; Icahn School of Medicine at Mount Sinai; Intravacc; KU Leuven; Meissa Vaccines; the Spanish National Center for Biotechnology and the Spanish National Research Council; Thomas Jefferson University and Bharat Biotech; Tonix Pharmaceuticals; University of Pittsburgh; Vivaldi Biosciences; Washington University.					
Protein vaccines	Viral subunit vaccines	Novavax	USA	2 (0,21)	IM	Phase 3	
		Clover Pharmaceuticals Inc./GSK/Dynavax	China	2 (0,21)	IM	Phase 1	
		Medicago (Plant based vaccine)	Canada	2 (0,21)	IM	Phase 2/3	
		Anhui Zhifei Longcom and the Chinese Academy of Medical Sciences	China	3 (0,28,56)	IM	Phase 3	
		Finlay vaccine institute	Cuba	2 (0,28)	IM	Phase 2	
		Vector Institute	Russia	-	-	Phase 2/3	
		Sanofi	France	2 (0,21)	IM	Phase 2/3	
		SpyBiotech/Serum institute of India	UK	2 (0,28)	IM	Phase 1/2	
		West China Hospital of Sichuan University	China	2 (0,28) or 3 (0,14,28)	IM	Phase 2	
		University of Queensland	Australia	2 (0,28)	IM	Phase 1	
		Vaxine Pty Ltd/Medytox	Australia	1	IM	Phase 1	
		Kentucky Bioprocessing (Plant based vaccine)	USA	2 (0,21)	IM	Phase 1	
		Medigen	Taiwan	2 (0,28)	IM	Phase1	
		Ad immune	Taiwan			Phase 1	
		COVAXX, a subsidiary of United Biomedical	USA	2 (0,28)	IM	Phase 1	
		University of Tübingen	Germany	1	SC	Phase 1	
		Center for Genetic Engineering and Biotechnology of Cuba	Cuba	3 (0,14,28 or 0,28,56)	Nasal spray	Phase 1	

		Center for Genetic Engineering and Biotechnology of Cuba	Cuba	3 (0,14,28 or 0,28,56)	IM	Phase 1	
		SK Bioscience	South Korea	2 (0,28)	IM	Phase 1	
		Other protein-based vaccines in active preclinical development include vaccines from: University of Pittsburgh, Adaptive Phage Therapeutics; AdaptVac and Bavarian Nordic; Applied Biotechnology Institute; Artes Biotech; Axon Neuroscience; BiOMVis and University of Trento; City College of New York and TechnoVax; EpiVax; GeoVax; Heat Biologics; IBio and CC-Pharming; Icosavax and University of Washington; ImmunoPrecise Antibodies; IMV; Instituto Butantan; Intravacc; IrsiCaixa; Izmir Biomedicine and Genome Center; National Autonomous University of Mexico; Navarrabiomed; NidoVax; OncoGen; Oragenics; OSE Immunotherapeutics; Osivax; PDS Biotechnology; Pontifical Catholic University of Chile; Saiba; SK Bioscience; University of Alberta; University of Amsterdam; University of Georgia and EpiVax; University of Saskatchewan and VIDO-InterVac; University of Virginia; UNSAM-CONICET; Vaxform; Vaxil-Bio; VBI Vaccines; Verndari; VIDO-InterVac; Voltron Therapeutics; Walter Reed Army Institute of Research; Wyss Institute and Harvard University; Yisheng Biopharma.					
Viral vaccines	Live attenuated virus	Codagenix	New York	1 (0) or 2 (0,28)	IN	Phase 1	
		Indian Immunologicals	India	-	-	-	
		Griffith University	USA	-	-	-	
	Inactivated vaccines	SinoVac	China	2 (0,14)	IM	Phase 3	
		SinoPharm	China	2 (0,21)	IM	Phase 3	
		Bharat Biotech	India	2 (0,28)	IM	Phase 3	
		Institute of Medical Biology at the Chinese Academy of Medical Sciences	China	2 (0,28)	IM	Phase 2	
		Chumakov Center at the Russian Academy of Sciences	Russia			Phase 2	
		Research Institute for Biological Safety Problems	Kazakhstan	2 (0,21)	IM	Phase 1	
		Shenzhen Kangtai biological products	China	2	IM	Phase 1	
		Erciyes University	Turkey			Phase 1	
		Other inactivated or attenuated coronavirus vaccines in active preclinical development include vaccines from: Valneva; Vivaldi Biosciences; Washington University; Western University.					

[Table/Fig-1]: Types of COVID-19 vaccines in the pipeline and status [7].
*IM: Intramuscular; IN: Intranasal; SC: Subcutaneous

Why Multiple Vaccines?

Different types of vaccines for COVID-19 are in the pipeline around the world. According to WHO as of December, 2020, there are 58 vaccines in Clinical Trials and 164 candidate vaccines in preclinical evaluations. These vaccines stimulate the host immune response to produce immune cells to eliminate the virus [7].

As this is a new disease with evolving knowledge about the virus mutations, pathogenesis, different clinical symptomatology, several vaccines are in different phases of clinical trials as every preparation has its advantages and disadvantages. Also, the average success rate of a vaccine is only around 10% (starting from discovery stage to actual vaccination). Hence, in this current scenario, if one type of preparation fails or is unsafe, different types can be tried which will help control the pandemic.

Why Multiple Doses?

When the person is infected with the SARS-CoV-2 for the first time or has taken the 1st dose of the vaccine, the initial immune response is slow and takes days to a couple of weeks for the generation of antibodies and T-cells to kill the virus. Few B and T-cells generate immune memory, the memory cells that "remember" SARS-CoV-2 [8].

When the person is exposed to the virus for the booster doses, the body responds much quicker and produces a stronger secondary immune response. The memory B-cells now produces higher antibody concentrations and T-cells, to eliminate the virus at a faster rate, reducing the complications of the infection. Further, many memory B and T-cells are produced which strengthen the immune memory against the virus [8].

DIFFERENT KINDS OF VACCINES EXPLAINED

DNA Vaccines

Deoxyribonucleic acid vaccines are made up of small strands of DNA, a gene, encoding the antigen of interest (in this case Spike Protein or S-Protein of SARS-CoV-2). The gene is attached to a plasmid for delivery into the body. The plasmid is used so that the body does not degrade the foreign gene before it can evoke an immune response. The vaccine once given, the DNA is taken up by the host cells and these cells will then express the S-Protein antigen on their cell surface, thus stimulating the host immune response [6].

- Inovio Pharma (USA) - DNA vaccine is in Phase 2 clinical trials [7].
- Zydus Cadila (India) - DNA-based vaccine which can be delivered by a skin patch is in Phase 2 clinical trials [7].
- Symvivo (Canada) has prepared a DNA vaccine using a non-pathogenic bacterium as a vector and had administered this orally. The bacteria when it reaches the gut will induce IgA antibodies [7].
- OncoSec Immunotherapies has prepared CORVax12 vaccine, which consists of DNA that encodes for both the spike protein and Interleukin (IL)-12, causing the body to make extra IL-12, which could potentially enhance the immune system's ability to make antibodies to the spike protein [7].

mRNA Vaccines

Ribonucleic acid vaccines consist of an mRNA encoding the antigen of interest- the SARS-CoV-2 Spike protein or S-Protein. This is placed in a Lipid Nanoparticle (LNP) vehicle. The LNP prevent the mRNA degradation by the host until it is taken up by the cell. When the vaccine is given, the host cells take up the mRNA. The intracellular lipases degrade the LNP exposing the mRNA. The mRNA is then translated into the S-protein and is expressed on its cell surface, resulting in an immune response [9].

- Boston based company; Moderna has developed the RNA vaccine-mRNA-1273 encapsulated in LNP. The RNA used is the viral RNA, isolated, and spliced to give the exact gene. On November 30, 2020, the researchers estimated that the vaccine had 94.1% efficacy. They found that the vaccinated people who developed COVID-19 did not develop severe disease [7].
- New York-based Pfizer and German-based BioNTech have developed a mRNA vaccine that is genetically engineered in the laboratory from the sequenced viral genome. This vaccine is approved for emergency use in the UK. This vaccine claims a 90% efficacy rate [7].

Concerns

a. The genetic material may be quickly degraded outside the cells, may not produce an effective immune response [10].

b. Safety issue- The vaccine DNA /RNA can incorporate into the host's genome resulting in mutations, and the development of tumour cells or malignancies [10].

c. Storage issues- The Moderna vaccine has to be stored at -25°C and -15°C (-13°F and 5°F) and the Pfizer/BioNTech vaccine at -70°C (-94°F) [10]. Curevac vaccine prepared by German scientists could be kept at 41° [7].

Vector Vaccines

Viral vector vaccines use a harmless virus or an attenuated virus known as a vector to carry a foreign gene, for example, the Spike Protein of SARS-CoV-2. When the vector virus enters the host cell, they transfer the gene into the cell which is then transcribed and translated to produce the antigen, which is displayed on the surface of the cell to induce a host immune response. The vector virus can also replicate inside the infected cell, allowing more cells to get infected and display the antigen on their surface. This results in immune cell activation, resulting in stronger response and memory [6].

- The Oxford/AstraZeneca, Gamaleya-Sputnik V, and the Janssen vaccines are all vector vaccines [7].
- AZD1222, developed by Oxford University, in partnership with AstraZeneca contains a non-replicating chimpanzee adenovirus as a vector carrying the gene for the whole S protein [7].
- Gam COVID Vac (Sputnik V) vaccine uses two different recombinant human adenoviruses as vectors to carry the gene for the whole S protein. This vaccine is approved for early use in Russia [7].
- The American company Merck, is employing an attenuated measles virus that carries a gene for the coronavirus spike protein [7].
- Israel Institute for Biological Research has developed a vector vaccine employing vesicular stomatitis virus [7].
- ReiThera, an Italian biotechnology company, has developed the GRAd-COV2 vaccine, using adenovirus as a vector [8].
- German Center for Infection Research and the City of Hope, USA made a Modified Vaccinia Ankara (MVA)-based vaccine for SARS-CoV-2 [8].

Concerns

a. Cannot be used in the population who are immunocompromised or immunosuppressed [6].

b. Maybe less effective in people with pre-existing antibodies against the viral vector [6].

c. These vectors are considered as a Genetically Modified Organism (GMO) and may carry a potential threat to the environment, and maybe subjected to strict environmental regulation and risk management [6].

Live Attenuated Vaccines

Live attenuated vaccines contain a live but less infective/attenuated/weakened form of the pathogen. This vaccine can generate a strong and long-lasting immune response as it has all the antigenic properties of the virus. There are currently three COVID-19 live attenuated vaccines produced by Codagenix, Indian Immunologicals and Griffith University with only Codagenix entering clinical trials in the US [9].

Concerns

a. Requires specialised biosafety laboratories [6].

b. Strict maintenance of cold chain [6].

c. Not to be used in immunocompromised or immunosuppressed patients [6].

d. Attenuated SARS-CoV-2 can revert to its original form due to mutations [6].

Inactivated Vaccines

Inactivated vaccines contain a whole pathogen that is killed or inactivated by chemical, heat, or radiation. These vaccines are comparatively safer, can be stored at room temperature, allowing easy transportation to even the remote areas of the world [9].

SinoVac, SinoPharm and Bharat Biotech inactivated vaccines are in Phase 3 trials [7,8].

Concerns

a. Requires booster doses to develop a stronger immune response [6].

b. The shape of the antigens may be altered during the inactivation of the pathogen [6].

Viral Subunit Vaccines

As the name indicates, the subunits of the pathogen are used in vaccine preparation. These vaccines can produce strong antibody responses and are simpler, cheaper, and safe to administer as the whole pathogen is not injected, so it will not cause infection [6].

Repurposed Vaccines

The Bacillus Calmette-Guerin (BCG) vaccine used against tuberculosis is thought to protect children against COVID-19. The Murdoch Children's Research Institute, Australia is conducting a clinical trial called BRACE, to see if the vaccine partly protects against the coronavirus [8].

The risks, immune response, and ease of production of the different types of vaccines are summarised in [Table/Fig-2].

Type of vaccine	Risks	Immune response	Ease of production
DNA vaccine	Risk of integration/ Mutation	Medium	Require special facility
RNA vaccine	Safe	Strong	Easy
Viral vector vaccine	Risk of integration/ Mutation	Strong	Easy
Live attenuated vaccine	Risk of infection	Robust response	Easy
Inactivated vaccine	Safe	Strong	Require special facility
Subunit vaccine	Safe	Strong	Easy

[Table/Fig-2]: Risks, immune response and ease of production of the vaccines.

DISTRIBUTION OF VACCINES

- Once available, vaccine distribution follows guidelines recommended by the CDC's Advisory Committee on Immunisation Practices (ACIP).
- The CDC recommends vaccinating the highest risk populations first. A priority list is phased out recently on December 1, 2020.
  - **Phase 1a-** Healthcare personnel and Long-Term Care Facility (LTCF) residents.
  - **Phase 1b-** Essential workers (examples: Education Sector, Food and Agriculture, Utilities, Police, Firefighters, Corrections Officers, Transportation).
  - **Phase 1c-** Adults with high risk medical conditions, adults with age of more than 65 years [11].
- Before a vaccine is widely available, Compassionate Use Authorisations (CUA), EUAs, and the strategic national stockpiles are designed to streamline responses during a crisis and mitigate the most severe cases [12].

CURRENT SCENARIO

The Pfizer/BioNTech, Moderna, Oxford-AstraZeneca and the Gamaleya Sputnik V, which have completed the Phase 3 trials have received EUA from the USFDA and few countries have started using them to vaccinate the individuals 16 years of age and older since mid-December, 2020 [13].

However, as with any other vaccines, few side effects have been documented after administration of the COVID-19 vaccines. The most common side effects among participants in both the Pfizer-BioNTech and Moderna Phase 3 clinical trials as per the FDA are injection site pain, fatigue, headache, muscle pain, chills, joint pain, fever, swollen lymph nodes and very rarely severe allergic reactions [13]. Four people who received Pfizer's vaccine and three who received Moderna's developed Bell's palsy [13].

In India, two COVID-19 vaccines have received approval on January 3, 2021 for restricted emergency use from the Drugs Controller General of India (DCGI). One is the COVISHIELD Vaccine developed by Serum Institute of India (SSI) in collaboration with AstraZeneca and Oxford University and the other is COVAXIN™, by Bharat Biotech developed in collaboration with the Indian Council of Medical Research (ICMR)- National Institute of Virology (NIV) [14-16]. Concerns have been raised regarding the sudden approval of COVAXIN™ by the DCGI without peer reviewed Phase 1 and 2 trial results and incomplete Phase 3 trial. The vaccine company claims that there is 100% protection in animal trials and Phase 3 trial results will be available by March, 2021 [17]. The Phase 3 efficacy trial was initiated in India on 25,800 volunteers and till date, approximately 22,500 participants have been vaccinated across the country and COVAXIN™ has been found to be safe as per the data available till date [18].

However, after so many questions about the approval of COVAXIN™, the heads of prestigious institutes in India, who are a part of the National COVID-19 Task Force have reiterated that unlike COVISHIELD vaccine, COVAXIN™ will be used only in 'clinical trial mode', where consent will be taken and side effects monitored and will be used as a "back-up", only if the country needs extra doses to vaccinate a large number of people, particularly given the possibility of a surge triggered by the UK variant [19].

CONCLUSION(S)

Despite the availability of many different types of vaccines, only few vaccines have been approved for use. Moderna, AstraZeneca, Pfizer, and Gamaleya Sputnik V vaccines have completed Phase 3 clinical trials and have received the EUA. The COVISHIELD and COVAXIN™, in India have received restricted approval in public interest. Even though many vaccines are being approved, many are concerned about the efficacy and safety issues of these approved vaccines. Let's hope that atleast one of the vaccines in the pipeline will give promising results and help us to overcome the pandemic.

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PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Respiratory Care, College of Applied Medical Sciences, Jubail, Imamabdul Rahman Bin Faisal University Jubail, Eastern Province, Saudi Arabia.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Swathi Gurajala,
Assistant Professor, Department of Respiratory Care, College of Applied Medical Sciences, Jubail, Imam Abdul Rahman Bin Faisal University,
Jubail, Eastern Province, Saudi Arabia.
E-mail: drswathi.gurajala@gmail.com

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