Review Article

Novel SARS-CoV-2 Vaccine Candidates: A Review

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ABSTRACT

The novel COVID-19 emerged from Wuhan and has spread worldwide. Globally, there are about 16.3 million confirmed cases including 650,805 deaths and still counting, during which the USA, Brazil, India, Russia, and South Africa are the most affected countries as of July 28, 2020. Considering the potential spread of the disease and precipitously increasing the number of cases, the demand for rapid development of therapies and vaccines is increased. Vaccines are amongst the essential tools to manage SARS-CoV-2, several institutions, and firms worldwide running tough for the development of vaccines towards coronavirus. Several vaccine candidates, using different technologies, especially towards spike proteins because of it's important characteristics in viral infection. Based on the prevailing outbreak right here we focus on modern-day updates on the development of vaccine candidates against SARS-CoV-2.

Keywords: SARS-COV-2, COVID-19, vaccine candidates, spike proteins.

INTRODUCTION

The outbreak of the current pandemic novel coronavirus was first identified in Wuhan, Hubei of China in December 2019[1]. It was declared as a public health emergency of international concern by WHO on 30th January[2]. On February 11, WHO termed 2019-CoV as COVID-19 (coronavirus infectious disease - 2019)[3], International Committee on Taxonomy of Viruses (ICTV) named the virus as severe acute respiratory syndrome corona virus-2 (SARS-CoV-2)[1]. SARS-CoV-2 belongs to the family *Coronaviridae*[4].

SARS-CoV-2 is a positive-sense, single-stranded RNA virus that's relatively large and encapsulated within a membrane protein envelope that's surrounded via membrane glycoprotein spikes due to which it gives the virus crownlike appearance (Figure 1) its hosts ACE2 membrane-bound receptor which is the binding site for S-protein. Additionally, the SARS-CoV-2 encodes few non-structural proteins essentially including RNA-dependent RNA polymerase (RdRp), coronavirus main protease (3CLpro), and papain-like protease (PLpro). The serine protease TMPRSS211 synthesized via the host cell facilitates S-protein priming necessary for the invasion process[5]. After invading within the host cells, the single-stranded positive RNA (viral genome) is released, through utilizing protein translation machinery of the host cell is translated into viral polyproteins, which besides split into effector proteins through viral proteinases 3CLpro and PLpro. Besides, PLpro may undergo the deubiquitination of certain host cell proteins, including interferon factor 3 and NF-κB, thus leading to suppression of the immune system in COVID-19 affected patients[6].

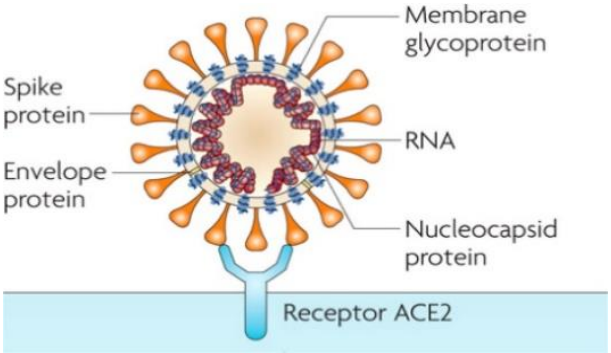


Figure 1: Illustration of the SARS-CoV-2 structure and receptor ACE2 on the host cell surface[5].

The SARS-CoV-2 accountable for causing respiratory tract infection called COVID-19, with a mean incubation phase of 5 days[7]. In 80% of cases, moderate intensity of respiratory symptoms like cough, dyspnoea, pyrexia is characterized predominantly, however, a few cases may have intense manifestations (bilateral interstitial pneumonia), with development to acute respiratory distress, respiratory failure, the preeminent reason of mortality. Some of the early symptoms had been disclosed in a few patients (particularly in the younger ones) hyposmia/anosmia and hypo/dysgeusia. There are also a few instances experiencing gastrointestinal manifestations[8].

VACCINES FOR COVID-19

Due to the rapid increase in COVID-19, efforts are made by different countries for the development of safe and effective vaccines to cope with its spread and recurrence. The experimental vaccine consists of both traditional and innovative technologies which range from virus vectors

and nucleic acids to recombinant proteins combined with adjuvants[9].

Based on phylogenetic analysis and full-length genome it had been perceived that SARS CoV2 is close to SARS-CoV[10,11]. As the SARS-CoV-2 virus has significant sequence homologies like other coronaviruses, SARS, and MERS, the vaccines developed for SARS and MERS viruses may potentially ease the layout of vaccines against SARS-CoV-2[5]. SARS-CoV and SARS-CoV-2 both bind the identical ACE2 host cell receptor and may share limited cross-neutralizing antibodies and similar disease pathogen[12].

Higher neutralizing antibody titers and more protection were produced by an S subunit of the virus, compared to full-length S-protein, DNA based S-protein, and live attenuated protein vaccines in SARS-CoV[13]. The target site in SARS/MERS was preferred to be S-protein/gene for the development of the vaccine. Potentially the identical strategy is beneficial in developing the SARS-CoV-2 vaccine[5].

Multiple vaccine candidates proposed are in varied phases of development. Different strategies are employed for the development of vaccine candidates, including inactivated viral vaccines, live attenuated vaccines, RNA-based vaccines, DNA-based vaccines, viral vector-based, and protein-based vaccines (Figure 2). The foremost advanced candidates have recently moved into clinical trials. A couple of other vaccines are yet in the animal studies (Graph 1) and the bulk of candidate vaccines intend to set off neutralizing antibodies, to counteract the viral S-protein, preventing its uptake through the human ACE2 receptor[12].

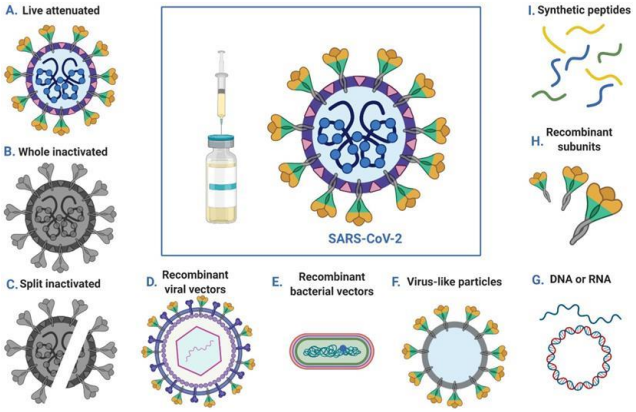


Figure 2: Approaches for devising the COVID-19 vaccine[23].

Types of vaccines against SARS-CoV-2

1. RNA based vaccine

A new genetic method is employed for the development of the mRNA vaccine against SARS-CoV-2, which doesn't require the growth of the virus in the laboratory. As the virus is immediately given within the human frame it transforms the human frame right into a dwelling laboratory[14].

Spike protein (S) encoding mRNA is crucial for host cell infection and membrane fusion[15]. Membrane fusion is an important step when an encapsulated virus enters the cell. Double lipid layer fusion calls for catalysis to overcome a high kinetic barrier, and additionally, the viral fusion proteins are retailers that perform this catalytic function[16].

The advantage of mRNA for the approach of prophylactic vaccines may include its ability to mimic natural infections to indicate more potent immune responses and its ability to combine multiple mRNAs into a single vaccine[5].

2. DNA based vaccine

Another type of nucleic acid-based vaccine is a DNA vaccine that contains DNA-plasmid encoding one or several antigens that will be expressed in the host cell[17].

Based on the information provided, WHO announced M protein, Spike glycoprotein, NK protein, Li key peptide, and gp-96 protein-based DNA vaccines are under development[18].

DNA based vaccines act by targeting the S-protein of SARS-CoV-2. The target molecule encoding DNA is inserted into the target microorganism through the plasmid or viral vector in which DNA is translated to protein. Through the purification or by extraction process the product is recuperated[19].

3. Protein subunit vaccine

Subunit vaccines carry only antigenic parts of the microorganisms that are required to produce protective immune responses. An antigen is presented to the immune system by the protein subunit vaccine without a viral particle using an isolated protein of pathogen. Acquired by either recombinant DNA technology or conventional cultivation processes[20, 21].

Protein-based vaccines are built based on molecular clamp technology which copies the protein conformation on the live virus creating a strong immune reaction. The S-protein of the virus which is present on the surface of SARS-CoV-2 is injected[18].

4. **Viral vector-based vaccine**

In this viral vector vaccines, a different harmless virus is used as a vehicle, it is genetically modified so that the surface imitates the typical structure of the targeted pathogen. When the virus disguised in this way is administered the immune system forms antibodies that would fight against the target pathogen. Adenovirus serotype (Ad5) can be easily produced and have a broad range of viral tropism and have a high level of transgene expression so it is one of the most used vectors. Ad5 enhances the mucosal immunity by targeting the gut and upper respiratory tract epithelial cells which are the main sites expressing high levels of ACE2 receptor for SARS-CoV-2[12].

This type of vaccine contains the whole microorganism but it is rendered uninfectious using chemicals such as formaldehyde or heat. It is the quickest means of approach for vaccine development following a new outbreak. This

technique is used for the successful development of vaccines for Influenza and enterovirus 71[22].

5. Live attenuated virus-based vaccine

These are derived from disease-causing organisms both virus or bacteria, that have been weekend under laboratory conditions. These provide antigenic stimulation leading to the production of memory cells. These vaccines are acquired by cultivating the microorganisms under suboptimal conditions or by successively passing in the cultures, the techniques determining the attenuation of virulence while maintaining its capacity to produce the immune responses. Though these types of vaccines are very effective. The disadvantage, it may have mutations and can be reverted to original form thus causing harm to immunocompromised patients[21].

STATUS OF CURRENT COVID-19 VACCINE CANDIDATES

As of July 28, 2020, more than 135 vaccines are at preclinical evaluation and 25 vaccines have already in clinical evaluation out of which six vaccine candidates entered phase 3, two in phase 2, nine in phase 1/2, and eight in phase I (Table 1).

Table 1: Candidate vaccines at different phases of development[24, 25, 26].

S.no	Candidate	Type of candidate vaccine	Sponsor	Current trial phase	Institute	Mechanism of the vaccine candidate
1.	AZD1222	[Nonreplicating Viral Vector] ChAdOx1-S [Chimpanzee adeno virus]	University of Oxford/ AstraZeneca	Phase 3	The University of Oxford, the Jenner institute	A virus encoding the similar to proteins on the surface of coronavirus is engineered that produces an immune response against SARS-CoV-2.
Related Coverage: A single-blinded randomized efficacy, safety, and immunogenicity study. Preclinical Data – remarkably reduced viral load in rhesus monkeys after a single vaccination, also immune response shown in mice and pigs. A Phase III trial of AZD1222 is being conducted in Brazil and South Africa. July-2 – Oxford published phase 1/2 data demonstrating an immunologic response with mild to moderate side effects. May deliver emergency vaccines by October, total manufacturing capacity stands 2 billion doses.						
2.	CoronaVac	[Inactivated] Formalin inactivated + Alum adjuvanted	Sinovac	Phase 3	Sinovac Research and Development Co., Ltd	An inactivated virus is induced and the immune response is generated.
Related Coverage: A double-blinded, randomized, placebo-controlled study. May 6 – Announced that in preclinical studies CoronaVac completely protected macaques. June 14 – Stated that no serious side effects were found, neutralizing antibodies were found after 14 days of vaccination in 90% of participants. July – Launched phase III trials in brazil at Instituto Butantan. Building facility to manufacture annually up to 100 million doses.						
3.	Inactivated	[Inactivated vaccine]	Wuhan Institute of Biological Products/Sinopharm	Phase 3	Henan Provincial Centre for Disease Control and Prevention	An inactivated virus is induced and the immunologic response is generated.
Related Coverage: A randomized, double-blind, placebo parallel-controlled. Phase 1/2 trials vaccine has shown a strong neutralizing antibody response. An agreement was made with the United Arab Emirates to test its efficacy in the Gulf state.						
4.	BBIBP-CorV	Inactivated	Beijing Institute of Biological Products/Sinopharm	Phase 3	Henan Provincial Centre for Disease Control and Prevention	An inactivated virus is injected resulting in activation of the immune system.
Related Coverage: A randomized, double-blind, placebo-controlled study. Preclinical studies – Showed "highly efficient protection" against SARS-CoV-2 in rhesus macaques who underwent challenge against the virus. Stated that by end of 2020 vaccines will be entered into the market.						
5.	mRNA-1273	[RNA] LNP-encapsulated mRNA	Moderna Therapeutics /NIAID	Phase 3	Kaiser Permanente Washington Health Research Institute	mRNA-1273 encodes the protein found on the surface of SARS-CoV2 which stimulates an immune response against it.
Related Coverage: A randomized, stratified, observer-blind, placebo-controlled study. May 18 – Discloses interim Phase 1 data, in which eight participants developed neutralizing antibody titers, same as preclinical data in which vaccine prevented viral replication in lungs and neutralizing titers in a mouse model. Safe and well-tolerated. July-14 – Phase 1 results showing consistent immune response with mild to moderate side effects. Expecting to have vaccine doses ready by early 2021.						

6.	BNT162	RNA 3 LNP-mRNAs	BioNTech/Fosun Pharma/Pfizer	Phase 3	Multiple study sites in Europe and North America	The Company uses strands of mRNA to generate protective antibodies.

Related Coverage:

A randomized, placebo-control study.

April 29 – An initiated clinical trial in Germany.

May 5 – Started clinical test study in the U.S.

July 1 – Announced Phase 1/2 trial produced antibodies against SARS-CoV-2 at three doses; while some experienced moderate side effects, such as sleep disturbances and sore arms at high levels so from next vaccination they reduced the dose.

A well-tolerated and immunogenic dose level of the BNT162b1 may be between 10 µg and 30 µg, according to the researchers.

Shanghai's Fosun Pharma signed a deal to market BioNTech's vaccine in China if it's eventually approved.

On 30 May CEO of Pfizer Albert Bourla stated that they may deliver vaccines in October; providing hundreds of millions of doses by the end of 2020 and then up to billion by the end of 2021.

7.	Ad5-nCoV	[Nonreplicating Viral Vector] Adenovirus Type 5 Vector	CanSino Biological Inc./Beijing Institute of Biotechnology	Phase 1/2	Tongji Hospital; Wuhan, China	A snippet of coronavirus ordering and entwining it with a harmless virus, thereby exposing healthy volunteers to the novel infection and spurring the assembly of antibodies.

Related Coverage:

A randomized, double-blinded, placebo-controlled.

May 22 – Phase 1 of the trial has shown humoral and immunogenic responses to the vaccine in volunteers.

- June 25 – Chinese regulators provisionally approved CanSino's vaccine for military used for 1 year [LIMITED APPROVAL].

Adverse reactions such as pain (54%), fever (46%), fatigue (44%), headache (39%), and muscle pain (17%) occurred in 83% of patients in the low and medium dose groups and 75% of patients in the high dose group.

July-20 – publishes interim phase 2 data showing consistent immunogenicity, but seemed to be diminished in older subjects.

8.	Protein Subunit	Adjuvanted recombinant protein (RBD-Dimer)	Anhui Zhifei Longcom Biopharmaceutical/ Institute of Microbiology, Chinese Academy of Sciences	Phase 1/2	Institute of Microbiology, Chinese Academy of Sciences	It is a combination of viral proteins and an adjuvant that evokes an adaptive immune reaction.

Related Coverage:

A multi-centered, double-blinded, randomized, placebo parallel controlled study.

The company is part of Chongqing Zhifei Biological Products and has collaborated with the Chinese Academy of Medical Sciences.

9.	Inactivated	Inactivated	Institute of Medical Biology, Chinese Academy of Medical Sciences	Phase 1/2	Institute of Medical Biology	The viral particle is inactivated, maintaining some of its integrity for immune activation.

Related Coverage:

A randomized, double-blind, placebo-controlled study.

The phase II trial started in June.

10.	INO-4800	[DNA] DNA plasmid vaccine with electroporation	Inovio Pharmaceuticals/ International Vaccine Institute	Phase 1/2	Center for Pharmaceutical Research, Kansas City. Mo.; University of Pennsylvania, Philadelphia	Electroporation enhances the uptake of nucleic acids associated with DNA vaccination greatly stimulates immune responses.

Related Coverage:

A randomized, open-label (part A) double-blinded (part B) study.

April 6 – Initiated Phase 1 trial.

Preclinical data – Vaccine in mice and guinea pigs resulted in neutralizing antibodies as well as humoral and T cell responses. In guinea pigs, researchers observed protein-binding antibody titers and blocking of angiotensin-converting enzyme 2 (ACE2)/SARS-CoV-2 S-proteins.

April 16 – Started working with the Korea Institute of Health (KNIH) to conduct a phase 1/2 clinical trial in South Korea.

June 30: Stated that its vaccine led to an immune response in 94% of patients with no serious adverse effects.

11.	DNA	DNA plasmid vaccine + Adjuvant	Osaka University/ AnGes/ Takara Bio	Phase 1/2	Osaka City University Hospital	DNA encoded pathogen with adjuvant when injected boosts the immunogenicity.

Related Coverage:

A non-randomized, open-label, non-controlled study.

June 30 – Japanese biotechnology announced that they have started safety trails on DNA.

12.	DNA	DNA plasmid vaccine	Zydus Cadila/ Cadila Healthcare Limited	Phase 1/2	Various	Direct inoculation of naked plasmid DNA persuades robust immune responses.

Related Coverage:

A prospective, randomized, adaptive, multicentric study.

July 3 – Approved for starting human trails.

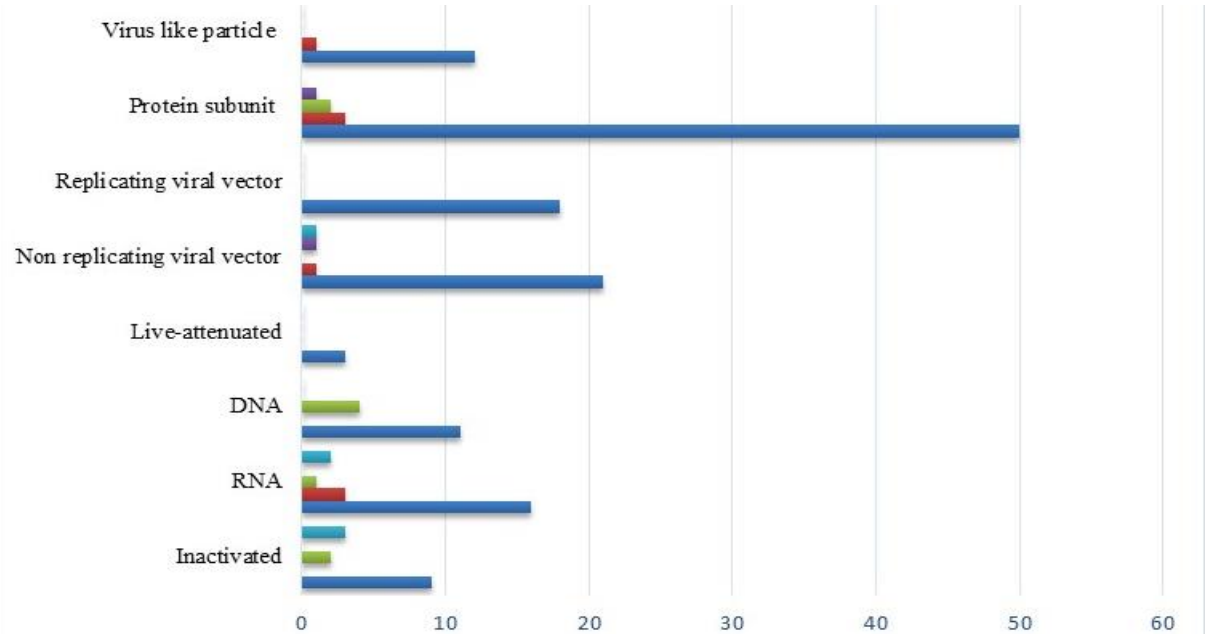
July 9 – Stated that they have finished animal trials.

About to start phase 1/2 trial enrolling over 1000 subjects at multiples clinical sites in India.

13.	GX-19	DNA	Genexine Consortium	Phase 1/2	Genexine	Genetically engineered DNA encodes the target pathogen producing resistance to viral antigen.
Related Coverage: A randomized double-blinded placebo control study, 190 healthy volunteers. The company aims to complete Phase 1 in 3 months before moving to a multinational Phase 2 trial.						
14.	Covaxin	Inactivated	Bharat Biotech	Phase 1/2	Various	A strain of novel coronavirus is inactivated and introduced to produce immunogenicity.
Related Coverage: A randomized double-blinded multi-center study. July – Phase 1/2 started.						
15.	NVX-CoV2373	[Protein Subunit] Full-length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	Novavax	Phase 1/2	Novavax	Novavax has isolated the spike protein found on the surface of the novel coronavirus and injected to supply a protective immune response.
Related Coverage: A 2-part, phase 1/2, randomized, observer-blinded study. Novavax plans to manufacture 1 billion doses of NVX-CoV2373 by 2021 as a part of its recent acquisition of Praha Vaccines.						
16.	Protein subunit	RBD-based	Kentucky Bioprocessing, Inc	Phase 1/2	Various	A cloned portion of the COVID-19 genetic sequence extracted led to the generation of potential antigen which was introduced into Nicotiana benthamiana (the herbaceous plant used to create recombinant proteins for vaccines in use) for reproduction. On repercussions, the antigen was purified and used.
Related Coverage: A randomized, placebo-controlled, parallel study. Vaccine candidates resulted in a positive immune response in preclinical studies.						
17.	LUNAR-COV19	mRNA-based	Arcturus Therapeutics, Inc.	Phase 1/2	Arcturus/Duke-NUS	Self-replicating mRNA encoding pre-fused spike protein of SARS-CoV-2.
Related Coverage: A randomized, parallel, double-blinded, placebo-controlled study. Preclinical studies have shown favorable findings also stated that a single dose may be sufficient to produce a potential and durable immune response. The company notified that they are working further to increase its production capacity anticipating to manufacture millions of doses across 2020 and 2021.						
18.	Gam-COVID-Vac	Nonreplicating Viral Vector Adeno-based	Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation	Phase 1	Various	Enhances immunity by using a combination of Ad5 and Ad26 both engineered with virus genes.
Related Coverage: A non- randomized, open-label study. June – Launched phase I trial.						
19.	SCB-2019	[Protein Subunit] Native like Trimeric subunit Spike Protein vaccine	Clover Biopharmaceuticals Inc./GSK/Dynavax	Phase 1	Linear Clinical Research (Australia)	S-trimer subunit vaccine that resembles native trimeric viral spike via rapid mammalian cell culture.
Related Coverage: A randomized, double-blinded, placebo-control study. June 19 – Initiated clinical trails. A Phase I trial of 150 healthy volunteers who will receive the SCB-2019 vaccine candidate alone, with the AS03 adjuvant, or with the CpG 1018 adjuvant with potassium aluminum sulphate (Alum).						
20.	COVAX-19	[Protein Subunit] Monovalent Recombinant spike protein with Addax™ adjuvant	Vaxine Pty Ltd/Medytox	Phase 1	Royal Adelaide Hospital	Acts by generating the neutralizing antibodies and T-cells against spike proteins of SARS-CoV-2.
Related Coverage: A randomized, triple blinded, parallel controlled study. July – Started phase I clinical trials.						
21.	Protein Subunit	Molecular clamp stabilized Spike protein with MF59 adjuvant	University of Queensland/CSL/Seqirus	Phase 1	Queensland hospitals	It stabilizes the pre-fusion sort of viral fusion proteins to mimic the protein conformation found on the live virus.

Related Coverage: Randomized, double-blinded, placebo-controlled single centered study. July 14 – Started testing on human volunteers.						
22.	LNP-nCoVsaRNA	[RNA] Self-amplifying RNA vaccine	Imperial College London	Phase 1	Imperial College London	The test vaccine is loaded with mRNA which encodes the new coronavirus proteins then injected into the body.
Related Coverage: On June 7th Imperial College London announced its partnership with Morning side ventures to ascertain VacEquity Global Health, an initiative that may help keep costs down for their COVID-19 vaccines for citizens within the UK and internationally.						
23.	RNA	mRNA based	CureVac	Phase 1	CureVac	Activates the immune system by non-chemically modified mRNA nucleotides.
Related Coverage: A randomized, partially blinded, placebo-controlled study. May 14 – Announced preclinical data that it has shown neutralizing titers and T-cell responses to the vaccine candidate. June 17 – Announced that it had received regulatory approval to initiate phase I trials. The company said its German facility can make hundreds of millions of vaccine doses a year.						
24.	ARCoV	RNA mRNA	People's Liberation Army (PLA) Academy of Military Sciences/ Walvax Biotech.	Phase 1	Institute of military medicine	mRNA encoded pathogen introduced to trigger immunity.
Related Coverage: A parallel study design. Stated that earlier studies on monkeys shown protective effects.						
25.	CoVLP	Plant-derived VLP	Medicago Inc./ University Laval	Phase 1	Medicago	Genes are injected into plant leaves, which mimics the viruses by creating the protein shell.
Related Coverage: A randomized, partially-blinded, dose-ranging study. Medicago and GSK drug maker announced a partnership in Phase 1 clinical trial on July 7 using a plant-based vaccine with GSK's adjuvant. Positive antibody response was obtained after 10 days of trial on mice. Phase 2 trials are expected by the end of the year 2020.						

LNP = lipid nanoparticle; RBD = receptor-binding domain; mRNA = messenger RNA; VLP = virus-like particle



	Inactivated	RNA	DNA	Live-attenuated	Non replicating viral vector	Replicating viral vector	Protein subunit	Virus like particle
Phase III	3	2	0	0	1	0	0	0
Phase II	0	0	0	0	1	0	1	0
Phase I/II	2	1	4	0	0	0	2	0
Phase I	0	3	0	0	1	0	3	1
Preclinical	9	16	11	3	21	18	50	12

Graph 1: Representation of vaccine candidates©.

CONCLUSION

Until safety is not provided in the clinical trial phases, the product is not yet a vaccine it is merely a candidate. The entire world is watching various countries' health care preparedness and COVID-19 vaccine development and deployment of the volunteers for the various phases of the clinical trials. we are cautiously optimistic that by the end the year or beginning of the year 2021 we may have one or more than one vaccine available but it's quite clear that no single manufacturer could meet the world's vaccine needs, global demand could only be met if several companies are producing in parallel. An overall brief is research can't be rushed. Diktat will not work for science.

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