Review Article

A comprehensive insight on the COVID-19 vaccine candidates

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Abstract

The world is currently facing a pandemic triggered by the novel corona virus (SARS – CoV2), which causes a highly infectious infection that predominantly affects the lungs, resulting in a variety of clinical symptoms some cases may be asymptomatic while others may result in to severe respiratory disorder, if the infection is left unattended it may result in multi-organ failure and eventually death of the patient. The transmission of infection is by droplet and fomites of the infected person. The incubation period of virus is from 2 to 14 days. Most common symptoms resemble flu-like but later progress to pneumonia along with dyspnoea and worsening of oxygen saturation, thus requiring ventilator support. The diagnostic modalities include Reverse transcriptase real time PCR (Quantitative Reverse transcriptase polymerase chain reaction) which is recommended method used for diagnosis of the COVID-19 infection using oro-pharyngeal or nasopharyngeal swabs of the patients. Recently serological tests for antigen and antibody detection has been approved by ICMR. Till now, nine COVID-19 vaccines are granted emergency approval for prevention and for the management of infection symptomatic and supportive measures are being adopted. Globally major pharmaceutical firms are engrossed for development of a potent vaccine candidate. This review highlights on various vaccine candidates under clinical trials.

Keywords: Corona virus disease vaccine (COVID-19 vaccine), severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2)

Introduction

The novel Coronavirus causes a highly contagious viral infection known as corona virus disease or COVID 19. It is a RNA virus which bears an outer envelope with glycoprotein spokes protruding outwards that helps in attachment to the host receptor.[1,2]

First case of Coronavirus was reported in 1960 which was mild influenza like illness (ILI), after which sporadic cases were reported till 2002 and hence Coronaviruses were considered as non-fatal viruses. In the last two decades two outbreaks have occurred these were reported in China Guangdong province in the year 2002 while another outbreak was reported in Saudi Arabia in 2012 which came to be known as SARS-CoV-1 and MERS-CoV, respectively[3] SARS-CoV-2 first reported in Wuhan Hubai Province, China in December 2019 as a cluster of cases with pneumonia of unknown etiology which has now spread globally resulting in a pandemic. Cases of SARS-CoV-2 have increased exponentially world-wide from January 2020.[2,3] The World health Organization on 31st Jan 2020 declared it as a Public Health Emergency of International Concern and declared it officially as pandemic on March 7, 2020. At the time of this review (July 17, 2020) Total cases of Coronavirus world-wide are estimated to be about 13,961,697 with 593,016 deaths. In India cases of coronavirus are 10,03,832 with 25,602 deaths.[2] With Maharashtra state being worst affected.[2]

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Common symptoms of SARS-CoV-2 include influenza-like illness (ILI) comprising of fever, sore throat, cough, shortness of breath. Cases may range from being asymptomatic to those with severe pneumonia and multi-organ failure.[2,4] Infection spreads via droplet infection which are generated during talking, coughing or sneezing from an infected person to an healthy individual, and through fomites of infected person. Incubation period is about 2-14 days. Diagnostic modalities includes Reverse transcriptase real time PCR which is gold standard method for diagnosis of the infection. Recently ICMR (Indian Council of Medical Research) has also validated and approved kits for rapid antigen detection. Antibody detection is not for diagnosis rather it is restricted for use in containment zone, for epidemiological purposes and for COVID-19 frontline workers only.[2] As of now there is only supportive and symptomatic treatment for coronavirus cases. There is no approved prophylaxis for SARS-CoV-2. Therefore, adherence to simple measures like cleanliness of hand by regularly washing hands, maintaining distance of about six feet among each other and use of personal protective equipment (PPE) are the only resort to combat with this situation.

Appropriate drug therapy and vaccine for prophylaxis is the need of the hour. Although conventional clinical trials are different from ongoing trials but looking at the enormousity and magnitude of the problem and collateral damage it has incurred to global economies, potential vaccine candidates are explored for their safety and efficacy with unprecedented speed and scale therefore this review highlights on various vaccine candidates under clinical trials.

Since, healthcare providers are the frontline fighters in this global battle against COVID-19, it is important that they must be aware of the developments being made in the research regarding vaccine development for the pandemic. Thus, the present review is to provide them insight of the past experiences in vaccine development and the present progress being made to battle off pandemic and the challenges involved in the process.

Historical Milestones in Vaccine Development

For centuries, infectious diseases have been the center stage of medical practice and have been the prime cause for widespread mortality and morbidities in the people, especially during epidemics and pandemics. Starting from the first recorded evidence of vaccination 'Variolation'.[5] and several others in the pipeline.[6] The knowledge of immunology and microbiology has yielded in a sharp fall in cases per units of population of these diseases. Vaccines can be of several types such as live vaccines which are attenuated vaccines, killed vaccines, recombinant vaccines, toxin derived vaccines, conjugate vaccines, nucleic acid vaccines, and vector vaccines.[7] With disease prevention as the main goal in mind, vaccines are administered as either designed specifically for a particular disease keeping in mind the various strains of the pathogen and its structural characteristics as well as its interaction with host tissues.

There are several factors that need to be noted before-hand such as the population demographic (target population) and its socio-cultural factors, incidence of target disease, environmental factors, dose and route of administration, strategy for inducing herd immunity and regulation of vaccine administration as well as risk analysis of the target disease and the vaccine. The process itself typically takes up-to 12-15 years for a vaccine to be approved by regulatory authorities.[8] The effectiveness and safety of vaccines are the two main concerns making the process longer. The safety and efficacy of a vaccine is dependent on its ability to prevent development of the disease in the host on interaction with the native pathogen with minimum adverse effects such as ADE or antibody dependent enhancement producing aggravated form of the disease upon vaccination or presence of contamination in the vaccine (example- Rota virus vaccine found contaminated with Circo viruses). Vaccine safety is initially assessed in laboratory with studies on animals such as mice or rabbits. If they show promising results after receiving the vaccine, clinical trial on human volunteers is initiated. Like most other drug trials, vaccine development occurs in three phases in which the number of volunteers are progressively increased with continuous monitoring for any adverse effects such as severe inflammation or pain at injection site, immune malfunction or any delayed effects associated with the vaccine.

As the number of volunteer's increases in each phase there is a higher probability of a rare complication of the vaccine presenting itself that had been missed when the group was smaller. Other factors such as heterogeneity of immune response in different age brackets of the population also need to be tested separately during the three phases of vaccine development.[9]

Vaccine development being a biological process involving pathogens and the high risks of contamination or adverse reactions in the population that often have a delayed response require monitoring for long periods of time, making it a long and exhaustive process requiring good financial funding.

SARS (Severe Acute Respiratory Syndrome) Vaccine

SARS was n highly contagious viral infection caused by virus of Coronavirus family. This outbreak emerged in Guangdong province of China in 2002. There were several outbreaks of this disease in the early 2000s either from SARs-CoV-2 isolates from laboratories or from people coming in contact with animal hosts of the virus.[10]

Coronaviruses have been divided into antigenic three antigenic groups. SARS-CoV-2 does not belong to any of these antigenic groups, though there has been some resemblance of the virus to group 2 coronaviruses.[11] It is believed that SARS-CoV-2 may have originated in lower mammals but unlike humans did not result in disease. The virus is believed to have evolved under certain conditions to gain ability to transmit from animal host to humans and cause mild disease in them and then further evolve to have the potential to outbreaks with high mortality.[12]

For production of SARS vaccine there are three possible approaches-

1. The virus possesses various proteins which comprise of structural proteins like N, E, and S proteins where N is nuclear capsid, E is Outer envelope while S is spike glycoprotein. All of which can serve as antigens to induce production of neutralizing antibodies.[10] Formaldehyde, Ultra Violet light, and beta-propiolactone can be used to produce killed SARS-CoV-2 vaccine and has shown commendable results in animal models.[13,14] However, there are several safety concerns associated with this type of vaccine putting the production workers handling the vaccine at risk of infection as well as the vaccinated population in case of incomplete inactivation of the virus that has a potential for outbreaks of SARS. Viral proteins also have potential for inducing inflammatory responses or SARS like disease.[15]
2. SARS-CoV-2 has a transmembrane glycoprotein which is results in production of the neutralizing antibodies and which are responsible for attachment of virus to the host receptor, Virus fusion to host membrane and virus entry in to the host, these glycoproteins are known as S protein. It can thus be used in vaccine production. It is a single peptide containing three domains- these are trans membrane domain, intracellular domain and extracellular domain. The extracellular domain contains two parts -S1 and S2- of which S1 attaches to the host receptor which are ACE-2 receptors, found abundantly on various organs. The site on S1 binding to ACE-2 is known as the receptor binding domain (RBD) which results in virus and host receptor interaction. It then leads onto viral and host membrane fusion and viral entry.[16-18] Studies have demonstrated high level of titers of antibodies which are neutralizing in nature, in animal models which protected them when challenged with SARS-CoV-2. However there is a risk of enhancement of disease which is antibody dependent phenomenon known as ADE, on subsequent infection with the same virus.[19] Weingartl *et al.* demonstrated liver damage in ferrets if challenged by SARS-CoV-2 after vaccination with Modified Vaccinia Ankara-based Corona vaccine expressing Spike protein. These findings in animal models are responsible for concerns regarding the safety as well as efficacy of vaccines associated with S protein use. RBD fragment on S1 domain has been explored for vaccine development as it was observed that serum antibodies derived from the animals previously immunized with killed SARS-CoV-2 and SARS patients reacted strongly with the receptor binding domain.[14] The antibodies derived from serum of animals which were previously immunized were specific to receptor binding domain of the virus and had neutralizing potential.[20] Major hurdle in the development of vaccine for SARS is finding animal models which would be affected by SARS-CoV-2 in the same way humans would.

Components Which Can Be Used for Vaccines

The selection of pathogenic components used as vaccines need to be theoretically and clinically evaluated in terms of efficacy, safety and tolerance in the target population. These components should have the potential to stimulate an immunogenic reaction in the host without any severe adverse effects. Upon exposure of the host to the wild type pathogen in vivo, the vaccine should be able to prevent infection with the pathogen. This potential is often estimated with increased titers of neutralizing antibodies after vaccine administration, but is not an absolute indicator of successful vaccination. The various vaccines for COVID-19 in various phases are described in Table 1. The source for vaccines list is clinical trial.gov. Update on clinical development of vaccines can be taken from clinical trial.gov. The components which can be used in viral vaccine preparations are-

Live attenuated virus- These are early vaccines which employ microorganisms that have been cultured in suboptimal conditions or have undergone successive passage in cultures, thus attenuating their virulence while keeping their antigenicity intact.[21] These traditional vaccines are contraindicated in immunocompromised patients and have risks of mutation and virulence reversal. There are six vaccines in phase 3 and five vaccines in phase 4 of clinical trials.

Inactivated virus- These are whole virus preparations inactivated by chemical or physical methods such as formalin, ultraviolet light or beta propriolactone. There is just one vaccine in phase 1, one in phase 3 and six vaccines in phase 1 and 2 of clinical trials.

Viral vectors- This platform technology integrates the antigenic information of virus in the genome of another virus. The antigen is thus delivered by the other 'vector' virus. In the present time, the vaccines using viral vectors in phase 1 of clinical trials is one vaccine, in phase 2 is one vaccine and in phase 1 and 2 of clinical trials there are two vaccines.

Protein subunit-These subunit vaccines contain selected antigens of the pathogenic organisms, mainly surface fragments, that are obtained from either conventional cultures or recombinant DNA technology.[12,22] These fragments are often coupled with other protein carriers or aluminium salts due to possibility of loss of immunogenicity by antigen purifiers.[23] Currently one vaccine is undergoing phase one trial.

RNA vaccines- The mRNA coding for the S (spike) protein in SARS or some other surface antigen is used to create a laboratory like environment in cells of the host.[24] The immune cells process the mRNA in the lymph nodes and synthesize viral antigens which are then recognized by the other immune cells.[25] These antigens produced inside the host body thus induce immunogenic reaction similar to the viral pathogen. There is one vaccine in phase 1 and two vaccines in phase 1 and 2 of clinical trials.

DNA vaccines- With the advent of recombinant DNA technology, target immunogenic molecule/antigen can be encoded on plasmid and injected in the host with a promoter to initiate immunogenic protein synthesis.[26] They are limited to

Table 1: Potential Vaccine Candidate under Clinical Trials

Covid-19 vaccine developer/ manufacturer	Vaccine platform	Type of candidate vaccine	Route of adminstration	CLINICAL STAGE
Sinovac	Inactivated virus	SARS-CoV-2 vaccine (inactivated)	IM	PHASE 1/2: NCT04383574 NCT04352608 NCT04551547 PHASE 3: NCT04456595 669/UN6.KEP/Emergency approval granted/20200 NCT04508075 NCT04582344 NCT04617483
Wuhan Institute of Biological Products/Sinopharm	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell)	IM	PHASE 1/2: ChiCTR2000031809 PHASE 3: ChiCTR2000034780 ChiCTR2000039000 NCT04510207 Emergency approval granted
Beijing Institute of Biological Products/Sinopharm	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell)	IM	PHASE 1/2: ChiCTR2000032459 PHASE 3: ChiCTR2000034780 NCT04560881 Emergency approval granted
University of Oxford/ AstraZeneca	Non-Replicating Viral Vector	ChAdO×1-S - (AZD1222) (Covishield)	IM	PHASE 1/2: PACTR202006922165132 2020-001072-15 NCT04568031 PHASE 2: 020-001228-32 PHASE 3: ISRCTN89951424 NCT04516746 NCT04540393 NCT04536051 CTRI/2020/08/Emergency approval granted
CanSino Biological Inc./Beijing Institute of Biotechnology	Non-Replicating Viral Vector	Recombinant novel coronavirus vaccine (Adenovirus type 5 vector)	IM	PHASE 1: ChiCTR2000030906 NCT04568811 PHASE 2:ChiCTR2000031781 NCT04566770 PHASE 3: NCT04526990 NCT04540419
Gamaleya Research Institute	Non-Replicating Viral Vector	Gam-COVID-Vac Adeno-based (rAd26-S+rAd5-S)	IM	PHASE 1/2:NCT04436471 NCT04437875 PHASE 2:NCT04587219 PHASE 3:NCT04530396 NCT04564716; Emergency approval granted
Janssen Pharmaceutical Companies	Non-Replicating Viral Vector	Ad26.COV2.S	IM	PHASE 1/2: NCT04436276 PHASE 3: NCT04505722 NCT04614948
Novavax	Protein Subunit	SARS-CoV-2 rS/Matrix M1-Adjuvant (Full length recombinant SARS CoV-2 glycoprotein	IM	PHASE 1/2: NCT04368988 PHASE 2: NCT04533399 (phase 2b) PHASE 3: NCT04611802 EUCTR2020-004123-16-GB; NCT04583995
	RNA based vaccine	mRNA -1273	IM	PHASE 1: NCT04283461 PHASE 2: NCT04405076 PHASE 3: Emergency approval granted

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Table 1: Contd...

Covid-19 vaccine developer/ manufacturer	Vaccine platform	Type of candidate vaccine	Route of adminstration	CLINICAL STAGE
BioNTech/Fosun Pharma/Pfizer	RNA based vaccine	BNT162 (3 LNP-mRNAs)	IM	PHASE 1: NCT04368728 PHASE 1/2: 2020-001038-36 ChiCTR2000034825; NCT04537949 Emergency approval granted PHASE 3: NCT04368728
Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences	Protein Subunit	Recombinant SARS-CoV-2 vaccine (CHO Cell)	IM	PHASE 1: NCT04445194 PHASE 1/2: NCT04550351 PHASE 2: NCT04466085 PHASE 3: ChiCTR2000040153; NCT04646590
Curevac	RNA based vaccine	CVnCoV Vaccine	IM	PHASE 1: NCT04449276 PHASE 2: NCT04515147
Institute of Medical Biology, Chinese Academy of Medical Sciences	Inactivated virus	SARS-CoV-2 vaccine	IM	PHASE 1: NCT04412538 PHASE 1/2: NCT04470609
Research Institute for Biological Safety Problems, Rep of Kazakhstan	Inactivated virus	QazCovid-in® - COVID-19 inactivated vaccine	IM	PHASE 1/2: NCT04530357
Shenzhen Geno-Immune Medical Institute	Viral vector (Non-replicating) + APC	LV-SMENP-DC vaccine. Dendritic cells are modified with lentivirus vectors expressing Covid-19 minigene SMENP and immune modulatory genes. CTLs are activated by LV-DC presenting Covid-19 specific antigens.	SC & IV	PHASE 1/2: NCT04276896
Inovio Pharmaceuticals/ International Vaccine Institute	DNA based vaccine	INO-4800+electroporation	ID	PHASE 1/2: NCT04447781; NCT04336410 PHASE 2: ChiCTR2000040146 PHASE 2/3: NCT04642638
Osaka University/AnGes/Takara Bio	DNA based vaccine	AG0301-COVID19	IM	PHASE 1/2: NCT04463472; NCT04527081
Cadila Healthcare Limited	DNA based vaccine	nCov vaccine	ID	PHASE 1/2: CTRI/2020/07/026352
Genexine Consortium	DNA based vaccine	GX-19	IM	PHASE 1/2: NCT04445389
Bharat Biotech	Inactivated virus	Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152)	IM	PHASE 1/2: CTRI/2020/07/026300 CTRI/2020/09/027674 PHASE 3: Emergency approval granted; CTRI/2020/11/028976
Kentucky Bioprocessing, Inc	Protein Subunit	KBP-COVID-19 (RBD-based)	IM	PHASE 1/2: NCT04473690
Sanofi Pasteur/GSK	Protein Subunit	SARS-CoV-2 vaccine formulation 1 with adjuvant 1 (S protein (baculovirus production)	IM	PHASE 1/2: NCT04537208
Israel Institute for Biological Research/Weizmann Inst. of Science	Viral vector (Replicating)	rVSV-SARS-CoV-2-S Vaccine	IM	PHASE 1/2: NCT04608305
Arcturus/Duke-NUS	RNA based vaccine	ARCT-021	IM	PHASE 1/2: NCT04480957
Serum Institute of India/ Accelagen Pty	Virus like particle	RBD SARS-CoV-2 HBsAg VLP vaccine	IM	PHASE 1/2: ACTRN12620000817943
Symvivo	DNA based vaccine	bacTRL-Spike	Oral	PHASE 1: NCT04334980
ImmunityBio, Inc. & NantKwest Inc.	Viral vector (Non-replicating)	hAd5-S-Fusion+N-ETSD vaccine	SC	PHASE 1: NCT04591717
ReiThera/LEUKOCARE/ Univercells	Viral vector (Non-replicating)	GRAd-COV2 (Replication defective Simian Adenovirus (GRAd) encoding S)	IM	PHASE 1: NCT04528641
Adimmune Corporation	Protein subunit	AdimrSC-2f (recombinant RBD +/- Aluminium)	ND	PHASE 1: NCT04522089
Vaxart	Viral vector (Non-replicating)	VXA-CoV2-1 Ad5 adjuvanted Oral Vaccine platform	Oral	PHASE 1: NCT04563702

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Table 1: Contd...

Covid-19 vaccine developer/ manufacturer	Vaccine platform	Type of candidate vaccine	Route of adminstration	CLINICAL STAGE
Ludwig-Maximilians - University of Munich	Viral vector (Non-replicating)	MVA-SARS-2-S		PHASE 1: NCT04569383
Clover Biopharmaceuticals Inc./ GSK/Dynavax	Protein subunit	SCB-2019+AS03 or CpG 1018 adjuvant plus Alum adjuvant (Native like Trimeric subunit Spike Protein vaccine)	IM	PHASE 1: NCT04405908
Vaxine Pty Ltd/Medytox	Protein subunit	COVID19 vaccine	IM	PHASE 1: NCT04453852
University of Queensland/CSL/ Seqirus	Protein subunit	MF59 adjuvanted SARS-CoV-2 Sclamp vaccine	IM	PHASE 1: ACTRN12620000674932p ISRCTN51232965
Medigen Vaccine Biologics Corporation/NIAID/Dynavax	Protein subunit	MVC-COV1901 (S-2P protein+CpG 1018)	IM	PHASE 1: NCT04487210
Instituto Finlay de Vacunas, Cuba	Protein subunit	FINLAY-FR anti-SARS-CoV-2 Vaccine (RBD+adjuvant)	IM	PHASE 1: RPCEC00000338; RPCEC00000340 PHASE 1/2: RPCEC00000332
FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo	Protein subunit	EpiVacCorona (EpiVacCorona vaccine based on peptide antigens for the prevention of COVID-19)	IM	PHASE 1: Emergency approval granted
West China Hospital, Sichuan University	Protein subunit	RBD (baculovirus production expressed in Sf9 cells) Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	IM	PHASE 1: ChiCTR2000037518; NCT04530656 PHASE 2: ChiCTR2000039994; NCT04640402
University Hospital Tuebingen	Protein subunit	IMP CoVac-1 (SARS-CoV-2 HLA-DR peptides)	SC	PHASE 1: NCT04546841
COVAXX/United Biomedical Inc. Asia	Protein subunit	UB-612 (Multitope peptide based S1-RBD-protein based vaccine)	IM	PHASE 1: NCT04545749
Chulalongkorn University	RNA based vaccine	ChulaCov19 mRNA vaccine	IM	PHASE 1: NCT04566276
Institute Pasteur/Themis/Univ. of Pittsburg CVR/Merck Sharp & Dohme	Viral vector (Replicating)	V591-001 - Measles-vector based (TMV-o38)	IM	PHASE 1: NCT04497298 NCT04569786 PHASE 1/2: CT04498247
Jiangsu Provincial Center for Disease Prevention and Control	Viral vector (Replicating)	DelNS1-2019-nCoV-RBD-OPT1 (Intranasal flu-based-RBD)	IM	PHASE 1:ChiCTR2000037782 PHASE 2: ChiCTR2000039715
Imperial College London	RNA based vaccine	LNP-nCoVsaRNA	IM	PHASE 1: ISRCTN17072692
Shulan (Hangzhou) Hospital + Center for Disease Control and Prevention of Guangxi Zhuang Autonomous Region	RNA based vaccine	SARS-CoV-2 mRNA vaccine	IM	PHASE 1: ChiCTR2000034112 ChiCTR2000039212
Medicago Inc.	Virus like particle	Coronavirus-Like Particle COVID-19 (CoVLP)	IM	PHASE 1: NCT04450004 PHASE 1/2: NCT04636697
Entos Pharmaceuticals Inc.	DNA based vaccine	Covigenix VAX-001	IM	PHASE 1: NCT04591184
Shenzhen Kangtai Biological Products Co., Ltd.	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell)	IM	PHASE 1: ChiCTR2000038804 PHASE 2: ChiCTR2000039462
Shenzhen Geno-Immune Medical Institute	Viral vector (Replicating) + APC	Covid-19/aAPC vaccine. The Covid-19/aAPC vaccine is prepared by applying lentivirus modification with immune modulatory genes and the viral minigenes to the artificial antigen presenting cells (aAPCs).	SC	PHASE 1: NCT04299724
Jiangsu Provincial Center for Disease Prevention and Control	Viral vector (Replicating)	DelNS1-2019-nCoV-RBD-OPT1 (Intranasal flu-based-RBD)	IN	PHASE 2: ChiCTR2000037782
Providence Health & Services	DNA based vaccine	CORVax	ID	PHASE 1: NCT04627675
City of Hope Medical Center+National Cancer Institute	Viral vector (Non-replicating)	COH04S1 (MVA-SARS-2-S)	IM	PHASE 1: NCT04639466

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Table 1: Contd...

Covid-19 vaccine developer/ manufacturer	Vaccine platform	Type of candidate vaccine	Route of adminstration	CLINICAL STAGE
Aivita Biomedical, Inc. *	Viral vector (Replicating) + APC	Dendritic cell vaccine AV-COVID-19. A vaccine consisting of autologous dendritic cells loaded with antigens from SARS-CoV-2, with or without GM-CSF	IM	PHASE 1/2 : NCT04386252
Codagenix/Serum Institute of India	Live attenutaed virus	COVI-VAC	IN	PHASE 1: NCT04619628
Center for Genetic Engineering and Biotechnology (CIGB) *	Protein subunit	CIGB-669 (RBD+AgnHB)	IN	PHASE 1/2: RPCEC00000345
Center for Genetic Engineering and Biotechnology (CIGB) *	Protein subunit	CIGB-66 (RBD+aluminium hydroxide)	IM	PHASE 1/2: RPCEC00000346

protein immunogens but the immunity conferred by plasmids is long term and they are easy to manufacture. There are two vaccines in phase 1 and one vaccine in phase 1 and 2 of clinical trials.

Virion like Particles (VLPs)- These are complex vaccines with multiple protein in their structure which are designed to mimic native virus while lacking the viral genome making them safer vaccination options.[27]

Autologous dendritic cells loaded with SARS antigen- This technology of vaccine development uses serological testing of sera of volunteers who have not had previous contact with SARS. The peripheral blood monocytes are isolated from heparinized blood, during *in vitro* culture with cytokines like interleukin-4 and granulocyte monocyte colony stimulating factor these are differentiated into dendritic cells during. These dendritic cells along with SARS-CoV-2 antigen are incubated. There is one such vaccine in phase 1 and 2 of clinical trial.

Similar Viral Vaccines

The improvement in our understanding of viral behavior and its antigens, cell culture, molecular biology and newer antigen delivery systems there is a vast variety of viral vaccines that have been designed showing promising results, particularly in viral diseases with few or no interventions available. Vaccines of several viral diseases like small pox and polio has managed to nearly complete eradication of these diseases by arming the immune system of the population vaccinated as well as inducing herd immunity.[28] In India there are several viral vaccines available that have been integrated in several health programs to reduce disease load in the population.[29] These includes the following enlisted vaccines

Vaccines against Rotavirus diarrhea under the name of RotaTeq is a live vaccine which is pentavlent with human-bovine reassortant vaccine with G1, G2, G3, G4 and P1A[8] viruses and Rotarix which is live-attenuated monovalent human vaccine containing G1P[8] virus.

Vaccines against Rabies under the names of Rabivax, a beta-propiolactone (BPL) inactivated rabies virus cultured on human diploid cells; Abhayrab and Indirab which are beta Propriolactone inactivated rabies virus propagated on Vero cell lines; and VaxiRab, a purified duck embryo vaccine.

Vaccines against hepatitis (Hep-B) under the names of Gene Vac-B which uses *Hansenula polymorpha (Pichia angusta)* to express HBsAg and Enivac HB, Enivac HB safsy, Elovac-B, Elovac-B+ and Revac-Bmcf all of which express HBsAg in *Pichia pastoris*.

Vaccines against Cervical cancer under the names of Gardasil which contains a quadrivalent HPV (6,11,16,18) expressing L1 protein of HPV in *S. cerevisiae* and Cervarix which is a bivalent HPV (16,18) using baculovirus to express L1 protein of HPV. Strains of Human papilloma virus (HPV) are responsible for warts mainly in the genital area, carcinoma cervix and papilloma's in the respiratory tract.

Vaccine against Measles under the name of M-VAC, it is a live vaccine which has attenuated measles virus derived from Edmonston Zagreb strain cultivated on human diploid cell line.

Vaccine against Rubella under the name of R-VAC which is a live attenuated vaccine, Wistar RA 27/3 strain rubella virus grown on Human diploid cell line.

Another Vaccine Measles and Rubella vaccine Live U. S. P, against Measles and Rubella is an live attenuated vaccine which is made using common strains of measles and rubella these are Edmonston Zagreb strain and Wistar RA 27/3 strain respectively, both of them are cultivated on Human Diploid Cell line.

Vaccines against Measles, Mumps and Rubella (MMR) under the names of Tresivac and Abhay-Vac3, containing Edmonston Zagreb strain of measles virus and Wistar RA 27/3 strain of rubella virus propagated on HDC with L-Zagreb strain of measles virus propagated o chick embryo fibroblast cells.

Vaccine against the Pandemic H1N1 influenza under the name of Nasovac which is a live attenuated vaccine. H1N1 influenza virus causing pandemic is often cultivated on embryonated hen's egg.

Vaccines against Polio under the names of monovalent oral polio vaccine (mOPV) type 1 containing live attenuated Sabin strain of poliomyelitis type -1 virus which is propagated in monkey kidney cells; mOPV type-3 which contains live attenuated Sabin strain of poliomyelitis type-3 virus grown in monkey kidney cells; OPV and Biopolio which are live attenuated poliomyelitis types 1 and 3 viruses of Sabin strain grown in monkey kidney cells.

Vaccine against Japanese encephalitis which was derived from mouse and later inactivated by formalin was discontinued in 2008.[30] The vaccine currently used in India is imported from china which is SA 14-14-2, a live attenuated JE vaccine cultured in primary hamster kidney cell-culture. There are also several JE vaccines in advanced stages of development such as IMOJEV which is a chimeric vaccine using yellow fever virus 17-D and IXIARO which is a purified inactivated vaccine (PIV).[2,29,31] They have shown promising results in the pre-clinical and clinical stages of vaccine development. Intercell, the Austrian company developing IXIARO has a partner in India, Biological E, which will be responsible for the vaccine's production and marketing when it gets approved by the governing authorities.

Vaccine candidates against Dengue, Chikungunya and Chandipura virus have been undergoing active research for decades albeit without much success due to several efficacy and safety concerns as well as difficulties in vaccine production and delivery systems.[29]

There are several other viral diseases in the world which have effective vaccines available against the pathogen proving useful particularly in disease endemic areas. One such is the vaccine against yellow fever which acts as the single most important method of prevention of this disease, particularly for people travelling to endemic areas psych as Congo, Guinea, Uganda Brazil, Colombia, Peru etc., The yellow fever vaccine, 17D-204 YF, is a live attenuated freeze dried vaccine and is considered highly effective in preventing the disease.[32] HIV being an important disease responsible for widespread mortality and worsening of quality of life, there have been several attempts to develop a vaccine for HIV involving four concepts which are use of monomeric gp120 subunit which is a component of HIV-1 surface glycoprotein and adjuvant as alum. This concept did not help in disease prevention due to multiple reasons in the clinical trials, one of them being the disparities between the neutralizing potential of laboratory cultivated isolates of HIV-1 (easily neutralized) versus the primary isolates of the patients.[28] Use of recombinant poxvirus vector vaccine and other proteins that regulate important functions of virus. This was followed by boosting with recombinant subunit envelope to provide additional protection from potentially breakthrough infections. There were mixed opinions on the efficacy of this concept. Recombinant adenovirus serotype 5 (rAd5) vaccine contains important structural proteins like Gag, Pol, and Nef which would induce a response biased for CD8+ T-cells. This vaccine put to trial failed to prevent HIV infection, particularly due to absence of HIVsurface antigens.

Priming with DNA prior to boosting with rAd5, in addition to expressing Gag, Pol and Nef envelope proteins representing three major HIV-1 subtypes were expressed with the hopes of inducing antibodies which could neutralize HIV in vivo. The trials for this as well did not yield promising results to be continued. The unpredictability of efficacy of HIV vaccine in clinical trials and several disparities between theoretical concepts of inducing immune reactions against HIV infection and their outcome on trial subjects has been a major obstruction in the development of the vaccine.

Ebola being a highly devastating viral disease with the skyrocketing mortality of up to 90% made it an active area for vaccine research with at least 13 candidates being developed and tested in several parts of the world. Vaccine trials being a time exhaustive process. At present there is no vaccine that has received approval for management of Ebola cases. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6615805/There are a few candidates however, that went through clinical trials quickly and have been approved for emergency use (such as in an outbreak). They are the attenuated recombinant vesicular stomatitis virus vector vaccine (rVSVΔG-ZEBOV-GP), recombinant vesicular stomatitis virus-based (rVSV) plus human adenovirus type 5 vaccine (Ad5) prime boost (GamEvac-Combi) and recombinant adenovirus type 5 vector-based Ebola vaccine (Ad5-EBOV). The latter two have been licensed for emergency use in Russia and China.

Challenges in Vaccine Development

The global research and development efforts in response to the pandemic caused by Corona virus (SARS-CoV-2) are underway in a never seen before speed at a very large scale. Looking at the vast efforts put in globally there are chances that Coronavirus vaccine may be available in the first quarter of 2021. The traditional method of vaccine development requires about 10 years before being marketed. For development of Ebola vaccine it was accelerated as 5 years, but looking at the atrocities and collateral damage caused by COVID-19 globally, safe and efficacious vaccine development is the need of the hour. Currently there are seven main platforms explored for vaccine development. These platform include-1) Nucleic acids platform- DNA & RNA vaccines. 2) Subunit/Protein based vaccine. 3) and 4) viral vector vaccine, 5) Inactivated vaccine, 6) Live attenuated vaccine and 7) These include all other platforms that are currently explored like Virus like particle (VLP's), use of killed non –CoV-2 (killed rabies virus) or live modified horse pox virus and repurposed vaccines like BCG, MMR, OPV3.[3] But development of COVID-19 vaccine in such short span of time comes with many challenges.

1. Although many companies world-wide have started clinical trials of potential vaccine candidates and claim that vaccine will be marketed soon but reality seems like mirage as many factors have to be taken in consideration before manufacturing vaccine, safety and effectiveness of the vaccine candidate is of almost importance, along with the type of vaccine and platform used for vaccine development all needs

to be considered.[33] There are some new platforms used for vaccine development which need stringent testing and scrutiny while other platforms are previously known models which need to be modified for development of Coronavirus vaccine.[34]

2. The time constraint that we are facing presently and looking at the enormous magnitude of SARS-CoV-2 cases, there is a need of large scale production of vaccine, the time period required to manage the demand of vaccine is quite different from the reality.[22]
3. In pre-clinical trials of some vaccine candidates it is seen that anti-SARS and anti-MERS vaccine are effective in inducing immune response but they may result in severe form of disease when virus is subsequently inoculated. This needs further studies as can result in severe adverse effect in clinical trials. Also although Antibody dependent enhancement (ADE) phenomenon has not with reported in SARS-CoV-2 cases, but still should be under consideration while vaccine development as it is been seen in other viral infections like Dengue, Zika and influenza virus.[35]
4. Various parameters like age and co-morbidities are to be kept in mind while developing a vaccine, age being one of the important factors. Studies on influenza virus have shown that with ageing of immune system there is reduction in the effectiveness of vaccination.[36]
5. Most of the candidate vaccine under trial broadly induces antibodies against viral spike (S) protein. Spike proteins are responsible for uptake of virus via human ACE-2 receptors. Spike protein has 2 sub units S1 and S2. Among these two, S1 subunit is specific for SARS-CoV-2 and helps in differentiating between other corona viruses and thus makes it good target for vaccine development, while S2 sub unit shares epitopes with other SARS viruses. SARS-CoV-2 S1 subunit has undergone mutation with alteration in its component which has led to complete replacement from the ancesteral O subtype (seen in Wuhan) to A2a, which has made n-COV-2 more virulent. The virus spike protein is undergoing spontaneous alteration thus making it difficult as target for vaccine development.[36]
6. Last but not the least it is an essential question that needs to be answered the time frame till which vaccine will provide protection needs further evaluation.[37]

Conclusion

Novel coronavirus disease has become public health issue of international concern. The exponential rise in COVID-19 cases across world has forced authorities to take concrete steps in the form of government-imposed lock down, which has ceased all commercial activities and has given a harsh blow to global economy, we must be hopeful that given the speed and scale of research work, funding by Govt. as well as by non-government organizations (NGOs) and the efforts of major pharmaceutical companies, vaccine for SARS-COV-2 will be available to the general population. We primarily rely on symptomatic and supportive management (Corticosteroids, Remdesivir and Tocilizumab) and therefore prevention is important to avoid transmission of the infection.

It is learned from the past experiences that the vaccine development is a time and resources consuming process with many scientific and regulatory challenges. Despite of advancement of science, the scientists globally are struggling from many decades to discover vaccines against diseases like AIDS, malaria, tuberculosis etc., without any significant success so far. Major challenges involved in vaccine development are the continuous structural and functional mutations in microbes and variations in response due to geographical and ethnical differences. Thus, the strategy till the vaccine is available commercially for public use, is to control the spread of pandemic and the symptomatic and supportive treatment to reduce morbidity and mortality.

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Conflicts of interest

There are no conflicts of interest.

References

1. Li F. Structure, function, and evolution of coronavirus spike proteins. Annu Rev Virol 2016;3:237-61.
2. Appaiahgari MB, Vrati S. IMOJEV(®): A Yellow fever virus-based novel Japanese encephalitis vaccine. Expert Rev Vaccines 2010;9:1371-84.
3. Funk CD, Laferrière C, Ardakani A. A snapshot of the global race for vaccines targeting SARS-CoV-2 and the COVID-19 pandemic. Front Pharmacol 2020;11:937.
4. Chan-Yeung M, Xu RH. SARS: Epidemiology. Respirology 2003;8 Suppl (Suppl 1):S9-14.
5. Brimnes N. Variolation, vaccination and popular resistance in early colonial south India. Med Hist 2004;48:199-228.
6. Mathebula L, Ndwandwe DE, Pienaar E, Wiysonge CS. Effects of vaccines in protecting against Ebola virus disease: Protocol for a systematic review. BMJ Open 2019;9:e029617.
7. Clem AS. Fundamentals of vaccine immunology. J Glob Infect Dis 2011;3:73-8.
8. Han S. Clinical vaccine development. Clin Exp Vaccine Res 2015;4:46-53.
9. Franceschi C, Salvioli S, Garagnani P, de Eguileor M, Monti D, Capri M. Immunobiography and the heterogeneity of immune responses in the elderly: A focus on inflammaging and trained immunity. Front Immunol 2017;8:982.
10. Peiris JS, Guan Y, Yuen KY. Severe acute respiratory syndrome. Nat Med 2004;10 (12 Suppl):S88-97.
11. Snijder EJ, Bredenbeek PJ, Dobbe JC, Thiel V, Ziebuhr J, Poon LL, *et al.* Unique and conserved features of genome and proteome of SARS-coronavirus, an early split-off from the coronavirus group 2 lineage. J Mol Biol 2003;331:991-1004.
12. Zhang N, Tang J, Lu L, Jiang S, Du L. Receptor-binding domain-based subunit vaccines against MERS-CoV. Virus Res 2015;202:151-9.
13. Xiong S, Wang YF, Zhang MY, Liu XJ, Zhang CH, Liu SS, *et al.* Immunogenicity of SARS inactivated vaccine in BALB/c mice.

Immunol Lett 2004;95:139-43.

14. He Y, Zhou Y, Siddiqui P, Jiang S. Inactivated SARS-CoV vaccine elicits high titers of spike protein-specific antibodies that block receptor binding and virus entry. Biochem Biophys Res Commun 2004;325:445-52.
15. Jiang S, He Y, Liu S. SARS vaccine development. Emerg Infect Dis 2005;11:1016-20.
16. Bisht H, Roberts A, Vogel L, Subbarao K, Moss B. Neutralizing antibody and protective immunity to SARS coronavirus infection of mice induced by a soluble recombinant polypeptide containing an N-terminal segment of the spike glycoprotein. Virology 2005;334:160-5.
17. Bukreyev A, Lamirande EW, Buchholz UJ, Vogel LN, Elkins WR, St Claire M, *et al.* Mucosal immunisation of African green monkeys (Cercopithecus aethiops) with an attenuated parainfluenza virus expressing the SARS coronavirus spike protein for the prevention of SARS. Lancet 2004;363:2122-7.
18. Wang S, Chou TH, Sakhatskyy PV, Huang S, Lawrence JM, Cao H, *et al.* Identification of two neutralizing regions on the severe acute respiratory syndrome coronavirus spike glycoprotein produced from the mammalian expression system. J Virol 2005;79:1906-10.
19. Olsen CW, Corapi WV, Jacobson RH, Simkins RA, Saif LJ, Scott FW. Identification of antigenic sites mediating antibody-dependent enhancement of feline infectious peritonitis virus infectivity. J Gen Virol 1993;74:745-9.
20. Chen Z, Zhang L, Qin C, Ba L, Yi CE, Zhang F, *et al.* Recombinant modified vaccinia virus Ankara expressing the spike glycoprotein of severe acute respiratory syndrome coronavirus induces protective neutralizing antibodies primarily targeting the receptor binding region. J Virol 2005;79:2678-88.
21. Lauring AS, Jones JO, Andino R. Rationalizing the development of live attenuated virus vaccines. Nat Biotechnol 2010;28:573-9.
22. Calina D, Docea AO, Petrakis D, Egorov AM, Ishmukhametov AA, Gabibov AG, *et al.* Towards effective COVID-19 vaccines: Updates, perspectives and challenges (Review). Int J Mol Med 2020;46:3-16.
23. Wang M, Jiang S, Wang Y. Recent advances in the production of recombinant subunit vaccines in Pichia pastoris. Bioengineered 2016;7:155-65.
24. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines-A new era in vaccinology. Nat Rev Drug Discov 2018;17:261-79.
25. Maruggi G, Zhang C, Li J, Ulmer JB, Yu D. mRNA as a transformative technology for vaccine development to control infectious diseases. Mol Ther 2019;27:757-72.
26. Li L, Petrovsky N. Molecular mechanisms for enhanced DNA vaccine immunogenicity. Expert Rev Vaccines 2016;15:313-29.
27. Roldão A, Mellado MC, Castilho LR, Carrondo MJ, Alves PM. Virus-like particles in vaccine development. Expert Rev Vaccines 2010;9:1149-76.
28. Graham BS. Advances in antiviral vaccine development. Immunol Rev 2013;255:230-42.
29. Bharati K, Vrati S. Viral vaccines in India: An overview. Proc Natl Acad Sci India Sect B Biol Sci 2012;82:181-98.
30. McArthur MA, Holbrook MR. Japanese encephalitis vaccines. J Bioterror Biodef 2011;S1:002. doi: 10.4172/2157-2526.S1-002.
31. Eder S, Dubischar-Kastner K, Firbas C, Jelinek T, Jilma B, Kaltenboeck A, *et al.* Long term immunity following a booster dose of the inactivated Japanese Encephalitis vaccine IXIARO®, IC51. Vaccine 2011;29:2607-12.
32. Verma R, Khanna P, Chawla S. Yellow fever vaccine: An effective vaccine for travelers. Hum Vaccin Immunother 2014;10:126-8.
33. Thanh Le T, Andreadakis Z, Kumar A, Gómez Román R, Tollefsen S, Saville M, *et al.* The COVID-19 vaccine development landscape. Nat Rev Drug Discov 2020;19:305-6.
34. Wiedermann U, Garner-Spitzer E, Wagner A. Primary vaccine failure to routine vaccines: Why and what to do? Hum Vaccin Immunother 2016;12:239-43.
35. Tetro JA. Is COVID-19 receiving ADE from other coronaviruses? Microbes Infect 2020;22:72-3.
36. Lord JM. The effect of ageing of the immune system on vaccination responses. Hum Vaccin Immunother 2013;9:1364-7.
37. Boda D, Docea AO, Calina D, Ilie MA, Caruntu C, Zurac S, *et al.* Human papilloma virus: Apprehending the link with carcinogenesis and unveiling new research avenues (Review). Int J Oncol 2018;52:637-55.