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# In Search of a COVID-19 Vaccine

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***Abstract:*** *The Novel Coronavirus SARS-CoV-2, has spread around the world in the past four months, has infected more than four million people worldwide and is causing a pandemic which is killing several lakhs of people. COVID-19 caused by SARS-CoV-2 has also completely paralyzed the global economy, with the threat of bringing the world economy to a standstill. Following detection of a novel coronavirus SARS-CoV-2 in Wuhan, in December 2019, the genetic sequence of SARS-CoV-2 was published on 11 January 2020, and this started a race globally, to be prepared for the outbreak and speed up the development of a preventive vaccine. There is no previously available vaccine for preventing a coronavirus infection. A vaccine for preventing an infectious disease has historically taken a few to several years to develop. However with worldwide efforts, and also studying previous research to develop coronavirus vaccines, a potential COVID-19 vaccine could be developed at a much faster rate. A single research institution does not have the capacity nor has all the prerequisites to develop a vaccine individually. There are various stages in the process of development and production of a successful vaccine, which takes considerable amount of time, before it can be given to the masses. Although no vaccine has completed the phase trials, for the COVID-19 vaccine, there are several attempts in the search for and in the race to develop a COVID-19 vaccine. Nearly 123 vaccine candidates are in current research and testing, globally and at least 8 vaccines have entered the human clinical trial stages. A potential COVID-19 vaccine is likely to be ready for mass use before the end of 2020. Six Indian companies are working on a COVID-19 vaccine, and have joined the global efforts, to contain and stop the spread of the Novel Coronavirus SARS-CoV-2.*

***Keywords****: COVID-19 – Novel Coronavirus – SARS-CoV-2 – Search of COVID-19 vaccines – Vaccine candidates – Pandemic – Phase trials – COVID-19 vaccines in India*

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## I. Introduction

The Coronaviruses are a large family of viruses that that circulate among animals and some of them are also known to infect humans. Coronaviruses are zoonotic pathogens. Corona viruses causing human infection were first identified in the mid 1960s. Initially they were considered as mild pathogens for humans and causative agents of the common cold. Coronaviruses (CoV) are non-segmented positive sense RNA viruses that are large, enveloped, spherical shaped, 80-160 nm in size and belong to the family Coronaviridae. These viruses characteristically contain peplomers which are arranged in a crown shape, and are hence named Corona, meaning crown.

On Dec 8, 2019, a series of cases of pneumonia of unknown etiological cause started emerging in Wuhan, Hubei province, China. This problem has been the focus of worldwide interest due to its clinical presentations. This new Corona virus has been named the Novel Corona virus (SARS-CoV-2). The disease caused by this virus is called (COVID-19) or Corona Viral Disease 2019.The disease has rapidly spread from China to cause epidemics in a number of countries. COVID-19 was declared a Public Health Emergency of International Concern, on January 30, 2020 and was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. As of May 15, 2020, the virus has spread to over 213 countries, affecting more than 4.5 million people and has caused more than 303,880 deaths worldwide [1].

Human-to-human transmission occurs through close contact. The virus seems to be transmitted mainly by respiratory droplets that infected persons sneeze, cough or exhale. The virus can also survive for several hours on surfaces such as steel and plastic. There is high risk to the general public from these outbreaks because of how highly contagious the virus is and how quickly it spreads between people. The severity of the disease varies from mild common cold like illness to severe acute respiratory syndrome. Common symptoms include fever, cough, and shortness of breath. A majority of cases result in mild symptoms, some cases progress to pneumonia and multi-organ failure. The virus spreads 2–4times as rapidly as the flu and is highly contagious; it has a long incubation period of up to 14 days and can be transmitted by

people with mild or sometimes no symptoms. It can survive on contaminated surfaces for several hours to days. This makes it very difficult to contain the virus and control spread of infection among the population [2, 3].

Currently with no specific vaccines or medications to treat the illness, COVID-19 is creating panic among the public. There is an urgent need to prevent the rapid spread of this disease. The governments of various countries are conducting awareness programmes about Covid-19, to educate the public, and have employed lockdown programmes to contain and control the spread of the virus [1]. The Indian government went into a National Lockdown from March 24, 2020. There outbreak of COVID in India started in 30 January 2020. As India is the world's second most populous country, there is a high risk of transmission and the virus has rapidly spread to several parts of the country. As of May 15, 2020, nearly 90,000 confirmed cases of COVID - 19 and 2649 deaths have been reported in India [4].

**WHAT IS A VACCINE?**

A vaccine is a biological preparation that provides active acquired immunity to a particular infectious disease. A vaccine is usually made from weakened or killed microorganisms, the toxins produced by the microorganism, or from its surface proteins [5]. The most effective way to prevent a disease is by vaccination. The human body is protected from disease causing microbes by vaccines which activate the immune system of the human body, to recognize microbes like bacteria and viruses and to effectively destroy them. There are 4 main types of traditional vaccines: Live-attenuated vaccines, inactivated vaccines, Subunit, recombinant, polysaccharide, and conjugate vaccines.

**WHY IS THERE A DELAY IN THE DEVELOPMENT OF A VACCINE FOR COVID-19?**

The pre clinical trials for a vaccine candidate usually involve testing in small and large animals. The most important step before a vaccine is granted regulatory approval is Clinical trials. Generally clinical trials take place in three phases. All experimental vaccines pass through these three phases. Human trials are done on different populations in various geographical areas and needs to generate a huge data in the 3 phases of human trials, for regulatory sanctions [6]

PHASE I: The vaccine is first given as a single dose to a few dozen healthy volunteers, this is actually for safety testing and monitoring adverse effects of the vaccine.

PHASE II: In the second phase, the vaccine is given to several hundred people, usually people from areas severely affected by the disease. This phase tests the effectiveness of the vaccine.

PHASE III: In the third phase, the vaccine is given to several thousand people. This involves testing in the field. This is the final phase which decides whether the vaccine can be given to the general public.

Scientists then wait until enough people become naturally infected with the virus, to see whether the vaccinated persons are truly protected, before the vaccine is declared as a safe and effective vaccine for the public.

However in case of emergencies like the COVID -19 pandemic situation, fast tracking of the vaccine candidates is possible. Still the experimental vaccines have to go through various trials, before finally being introduced in the market. Human challenge studies are an alternative approach in case of emergencies. Around 100 healthy volunteers, preferably between 20-45 years old, are vaccinated with a potential vaccine for SARS CoV2, and then purposely exposed to the virus. The ability of the vaccine to protect the volunteers from getting infected is monitored. This drastically shortens the time required for trials and the efficacy and safety of the vaccine can be studied. In Challenge studies the volunteers have to remain isolated during the study period. In the past human challenge studies have been done for other infections like dengue, malaria, influenza, cholera and typhoid [7].

The SARS-CoV-2 is an animal virus, which has mutated as it adapted to infect other animals and then to infect humans. There are several reports stating that it is continuing to mutate. The mutation of the virus may also vary in different geographical regions and in different parts of the world. Will a vaccine be an effective preventive measure in if the virus continues to mutate? To overcome this challenge, while preparing a COVID-19 vaccine, only the recent mutants or current versions of the virus should be used [8]. Only then the chances of the vaccine to succeed in effectively preventing the infection are high.

Nearly a 123 vaccine candidates vaccine candidates are in the pre-clinical and clinical trial stages. Experts believe it will take 12 to 18 months before a vaccine is available [9].

**THE URGENT NEED AND SPEED IN DEVELOPMENT FOR A COVID-19 VACCINE**

With no effective drugs and no specific vaccines, countries around the world have resorted to containment strategies, which seem to have only slowed the spread of the respiratory disease, Covid-19. Even though it may take time there is a race for development of a successful vaccine to prevent Covid-19, as a vaccine is the only way to prevent people from falling sick and best method to control and finally end the

pandemic. The need to rapidly develop a vaccine against SARS-CoV-2 has come at a time of expansion of scientific technology, especially in areas such as genomics and structural biology, which is supporting a completely new chapter in vaccine development. In the recent past, researchers and the vaccine industry have been asked to urgently prepare vaccines in response to epidemics due to H1N1 influenza, Ebola and Zika.

Within a few weeks of the epidemic in China, China sequenced the genetic material of Sars-CoV-2, and shared the sequence on 11 January, 2020 by publishing the entire genome of SARS-CoV-2, so research groups around the world could grow the virus and study how it invades human cells to cause disease COVID-19 and probable death. [10]. Data is being shared internationally using online tools by scientists, especially statistical data on real time. The various modes of social media available makes the sharing of data extremely fast, when compared to previous pandemics, where data sharing used to take several days to months. Due to this there is an unparalled speed in the development of a vaccine world over, which has never been seen in earlier pandemics. As a result laboratories around the world are able to track this particular strain of Corona virus as it is spreading around the world. Therefore scientists are actually monitoring the real-time evolution of the virus. Five hundred clinical studies worldwide, across all stages of development on vaccine and therapeutic candidates for COVID-19, are registered with the World Health Organization Clinical Trial Registry, as of March 2020 [10, 11]

## VACCINE CANDIDATES IN CURRENT RESEARCH AND CLINICAL TRIALS

Traditional vaccines were prepared by using live, weakened forms of the virus, or part or the virus, after being treated and inactivated by chemicals or by heating. A few of the Covid-19 vaccine projects are using traditional methods, but several projects are using newer technologies [12]. Several modern and latest technologies are being experimented in the vaccine development landscape for COVID-19, which includes using viral nucleic acid (DNA and RNA), virus-like particle, peptide, viral vector (replicating and non-replicating), recombinant protein, live attenuated viruses and inactivated viruses for vaccine preparation[13].

**Table I** : The most advanced and promising vaccine candidates that have recently moved into Human phase clinical trials:

| Vaccine | Country | Company | Type | Stage |
|---|---|---|---|---|
| **Ad5-nCoV** | China | CanSino Bio, Institute of Biotechnology of the Academy of Military Medical Sciences | Non-replicating viral vector, | Phase II |
| **Ad5-nCoV** | China | CanSino Bio, Institute of Biotechnology of the Academy of Military Medical Sciences | Recombinant Adenovirus type 5 vector | Phase II |
| **Covid-19/aAPC** | China | Shenzhen Geno-Immune Medical Institute | Lentiviral Vector | Phase II |
| **mRNA-1273** | USA | Moderna Therapeutics | RNA | Phase II |
| **ChAdOx1 nCoV-19** | UK | University of Oxford | Non-replicating viral vector | Phase I/II |
| **BNT162 (a1,b1,b2, c2)** | Germany | BioNTech Pfizer | RNA | Phase I/II |
| **INO-4800** | US South Korea | Invivo pharmaceuticals, CEPI, Korea NIH | DNA plasmid vaccine | Phase I/II |
| **PiCoVacc** | China | Sinovac Biotech | Inactivated SARS-CoV-2 virus | Phase I/II |

[5, 9]

Most COVID-19 vaccine development activity is in North America, with (46%) developers of the confirmed active vaccine candidates compared with (18%) in China, (18%) in other Asian countries and Australia, and (18%) in Europe. There may be differences in the epidemiology of COVID-19 in different geographical areas, so to effectively control the pandemic, there must be large scale involvement and participation of the other countries in the southern hemisphere, in research and development for producing an

effective COVID-19 vaccine. The Coalition for Epidemic Preparedness Innovations (CEPI) is working with global health authorities and vaccine developers to support the development of vaccines against COVID-19 [12, 13].

China may have a head start on the development of a covid-19 vaccine, as China was the first to map out the genome sequence of the novel coronavirus, immediately after the epidemic caused by SARS CoV 2 in Wuhan in December 2019[14]. China has begun the Phase 2 clinical trials for a COVID-19 vaccine, with 3 vaccine candidates, with volunteers from the city of Wuhan. China's CanSino Bio and its collaborators at the Academy of Military Medical Sciences Institute of Biotechnology have become the first among COVID-19 vaccine developers to enter into phase 2 trials, this is just after three weeks after the phase 1 study.

**Ad5-nCoV**

A large number of vaccine developing companies are dependent on time-tested, older more traditional methods and techniques. A vaccine jointly developed by CanSino Biological Inc and Beijing Institute of Biotechnology, called Ad5-nCoV, is in Phase 2 trial. The Sinovac Biotech SARS-CoV-2 vaccine is made by chemically inactivating whole viral particles and alum is added as an immune booster. Sinovac has already used the same methods for a SARS vaccine which had entered a phase I clinical trial 16 years ago. The advantage of inactivated virus is that it can be developed easily by many countries, which are already familiar with traditional vaccine development methods. CanSino is currently testing a vaccine which uses a non -replicating version of Adenovirus type 5 (Ad5). The Adenovirus type 5 which also causes the common cold, is used as a "vector", to carry in the gene for the coronavirus spike protein. Sinovac claims its new vaccine candidate has produced strong immune responses in animal models and that it is also highly safe [15].

**Ad5-nCoV**

A Chinese research firm under the Chinese military has become the first organisation to enter the Phase 2 trial studies, in the race by all countries of the world, to develop a vaccine for the novel coronavirus. The vaccine is also an adenovirus vector vaccine, developed by a research team led by Major General Chen Wei of the Institute of Biotechnology, under the Academy of Military Medical Sciences of the People's Liberation Army of China. It is the first COVID-19 vaccine in the world that has entered the second phase of clinical trial .The first phase of the clinical trial was completed at the end of March, with 108 volunteers. All of them reportedly have been released from medical observation and are in good health. The second phase started on April 12 [16].

**PiCoVacc**

The Beijing-based Sinovac Biotech's, Purified inactivated novel coronavirus vaccine(PiCoVacc) vaccine was able to induce formation of specific neutralizing antibodies in three animal models. PiCoVacc was tested on mice, rats and rhesus macaques monkeys. PiCoVacc was found to give partial to complete protection in rhesus macaques according to the dosage given which was 3 microgram or 6 microgram per dose, used for testing. The neutralizing antibodies formed could act on 10 representative SARS-CoV-2 strains. Therefore the vaccine shows a broader range of neutralizing capacity, aganist the SARS-CoV-2 strains. PiCoVacc was also found to be a safe and effective vaccine candidate, which did not enhance antibody dependant enhancement of infection in the animal models [9, 17].

**Covid19/aAPC**

A synthetic minigene has been engineered in Shenzhen Genoimmune Medical Institute. The binding of the Spike protein of the SARS- CoV-2 to the ACEII receptor initiates the infection of Covid-19. The replication of the virus depends on the molecular mechanisms of these viral proteins. The objective of this study is to develop an universal vaccine and to test innovative Covid-19 minigenes engineered based on multiple viral genes. This is by use of a lentiviral vector system (NHP/TYF) to express viral proteins and immune modulatory genes to modify artificial antigen presenting cells (aAPC). The T cells will be activated by this vaccine [18, 19].

**ChAdOx1**

WHO health experts initially predicted that a possible covid-19 vaccine was would take at least 18 months to come to the market after completion of successful trials.

Production of the vaccine is being scaled up and is ready for larger trials. Researchers at Oxford University say that this vaccine However, researchers from Jenner Institute, Oxford University have said that they will be able to come up with a vaccine for the SARS-CoV-2 by September 2020. Lead researcher of the vaccine development programme, Prof Sarah Gilbert and her team has said that they can make make one million vaccine doses available by September 2020.

The ChAdOx1 is the fourth COVID-19 vaccine candidate in the world which has entered the human phase trials of vaccine development. ChAdOx1 is special because of potential delivery of mass quantities of the vaccine in a much shorter period than other vaccine candidates, and is being called a 'super fast vaccine'. ChAdOx1 is a chimpanzee adenovirus vaccine vector, it is not a replicating virus, so it is very safe as it cannot cause infection after vaccination and is also safe enough to be given to children and the elderly who are immunosuppressed. It can potentially generate a strong immune response from one dose. The Oxford vaccine contains the genetic sequence of the surface spike proteins of the SARS CoV2. After vaccination, the surface spike protein of the coronavirus is produced, which sensitizes the immune system from an attack by SARS CoV 2. Researchers have enrolled over 500 healthy volunteers to test their vaccine. The first clinical trials for this vaccine began on April 22, 2020.will be available as early as September 2020, and if proven effective [20]. The Indian Council of Medical Research (ICMR) also pitched for the Oxford vaccine, saying 'ChAdOX1' is the frontrunner in the race to take on the deadly COVID-19 virus.

**BNT162 (a1, b1, b2, c2)**

The Paul-Ehrlich-Institut in Germany approved a vaccine BNT162 for a Phase 1/2 trial. Pfizer and BioNtech have announced an agreement to collaborate on developing four COVID-19 vaccine candidates originally developed by BioNTech, Germany. Two candidates are nucleoside modified mRNA-based (modRNA), one is uridine containing mRNA-based (uRNA), and the fourth candidate is self-amplifying mRNA-based (saRNA). BioNTech says that a vaccine could become available by September 2020 for emergency use [21]. Pfizer and BioNTech began the Phase I/II human trials in US on May 5, 2020. The trial consists of 360 volunteers from US, and the first sets of vounteers have already received the vaccine injections. Around 200 patients have been enrolled from Germany also as part of the trials [22].

**INO-4800**

Inovio Pharmaceuticals, CEPI, Korea National Institute of Health, International Vaccine Institute, is developing a DNA plasmid delivered by electroporation , DNA Covid-19 vaccine. Joseph Kim, CEO of Inovio Pharmaceuticals, says a response by T cells which can clear infected cells, proved a better correlate of immunity with the DNA vaccine, in monkey studies. He suggests that a balance of antibody and T cell responses is the best approach to fight COVID-19[23].

**mRNA-1273**

RNA LNP encapsulated mRNA Moderna/NIAID

One of the first vaccines that entered the first phase of trials is from the US-based biotech firm Moderna and the National Institute of Allergy and Infectious Diseases (NIAID) . Moderna, has prepared a COVID-19 vaccine using messenger RNA. The Moderna vaccine is a lipid nanoparticle (LNP) encapsulated mRNA candidate vaccine. The vaccine uses a RNA platform with multiple candidates. The genetic information of the virus is de-coded from the DNA to make proteins mRNA, or messenger RNA. This acts as an intermediary between the genetic information in DNA and the amino acid sequence of proteins, and gives cells the command to make certain proteins that can inhibit the viruses. Moderna's mRNA-based SARS-CoV-2 candidate entered a phase 1 clinical trial on March 16, less than 10 weeks after the first genetic sequences were released. The first dose of phase 1 trial of the vaccine was given to a volunteer, Jennifer Haller of Seattle on 16 March.—she became the first person (outside of China) to receive an experimental vaccine against the SARS-CoV-2 virus, at the Kaiser Permanente Washington Health Research Institute. Haller has had no serious side effects from the mRNA injected into her arm so far. Moderna says that they can be sure of the efficacy and safety of the vaccine by January 2021 [24]. Moderna's COVID-19 vaccine, has got 'fast track approval' from the US Food and Drug Administration(FDA), to conduct Phase II trials, on 6 May 2020. Phase II trials, will involve enrollment of 600 healthy volunteers, who will be given two vaccine doses of the mRNA-1273, and the second dose is to be given 28 days after administration of the first dose[9].

**PittCoVacc**

Researchers at the University of Pittsburgh's School of Medicine, after successful animal tests—have announced a potential vaccine, against SARS-CoV-2. The vaccine called "PittCoVacc" (short for Pittsburgh CoronaVirus Vaccine) uses lab-made pieces of viral protein to build immunity. When tested in mice, PittCoVacc generated a surge of antibodies specific to SARS-CoV-2, within two weeks of a micro-needle prick, at quantities thought to be sufficient enough, for neutralizing the SARS-CoV-2. The researchers are using a new method to deliver the vaccine, called a micro-needle array. In this method, a fingertip-sized patch of 400 tiny needles is administered, which delivers the spike protein pieces of the virus into the skin, as this is where the

immune reaction is the strongest. The micro needles are made entirely of sugar and the protein pieces .The patch is placed on the skin of a volunteer, similar to a Band-Aid, where the needles will later dissolve into the skin According to researchers, the vaccine will still take around 12 months to be marketed, if the trials are successful. It is the first study to be published that describes a candidate vaccine for COVID-19 [25].

**NVX-CoV2373**

Protein Subunit VL Precombinant protein nanoparticle vaccine + Matrix M Novavax. Two other epidemics that were caused by Corona viruses in recent years are ; the severe acute respiratory syndrome (Sars) in China in 2002-04, and Middle East respiratory syndrome (Mers), in Saudi Arabia in 2012. Research work for production of vaccines for both the Sars and Mers viruses were initiated urgently, but were later aborted and shelved when these epidemics were controlled, Novavax is based in Maryand, USA. The Novavax is construcing a recombinant vaccine. This involves extracting the genetic code for the protein spike on the surface of Sars-CoV-2, which is the antigenic part which can trigger an immune response in humans. This genetic code is incorporated into the genome of a bacterium or yeast and they are made to produce, huge quantities of the required protein. Novavax has received a funding of $384-million from the Coalition for Epidemic Preparedness Innovations (CEPI), and will soon be starting human phase trials with its NVX-CoV2373 vaccine. Novavax has enrolled 130 volunteers from Australia for its phase trials [9,12].

**COVID-19 XWG-03**

GlaxoSmithKline has announced plans to collaborate with China's Xiamen Innovex on a potential vaccine to treat COVID-19. The vaccine known as COVID-19 XWG-03 is a recombinant protein based vaccine aganist corona virus, which is being developed by Innovax with Xiamen University. The vaccine uses a version of the spike proteins present on the surface of the SARS-Cov-2 to activate the immune system. Glaxo Smith Kline says that, the use of an adjuvant in their vaccine incresases the immune response to the vaccine and reduces the amount of antigen [26].

**Curevac**

Curevac is a German company which has developed a mRNA vaccine. According to the scientists of the German company CureVac, even though no mRNA vaccine has been approved or entered a phase III clinical trial, the production of huge numbers of doses may be easier for mRNA vaccines than for traditional vaccines. The experimental Rabies vaccine developed by CureVac induced a good immune response with a single microgram of mRNA, therefore they conclude that 1 gram of mRNA could vaccinate 1 million people. So, according to the developers of Curevac, the production of around a hundred of grams, can be sufficient to vaccinate large populations [12].

**Takis vaccine**

An Itaian Biotech company Takis, has developed a DNA vaccine for the Corona virus. The tests are being conducted at the Lazzaro Spallanzani National Institute for Infectious Diseases in Rome, Italy. Takis is doing research studies on four different DNA vaccines, for COVID-19. A DNA vaccine is a vaccine which contains the genetic code for specific parts of the virus, such as the spikes, which can induce our immune system to produce antibodies to act against it. Of the four vaccines at Takis, one reportedly comprises the gene coding for the spike protein of SARS-COV-2, the causative agent of COVID-19. The spike is what determines the binding of the virus to healthy cells. The other three vaccines are DNA sequences corresponding to specific epitopes on the surface of the virus; they have been modified, so that they work properly as a vaccine when introduced into human cells. Takis researcher's experiments on mice resulted in the mice developing antibodies that could block the SARS-CoV-2, and prevent infection. Researchers state that the five vaccine candidates generated a large number of antibodies, and can protect human cells also [27]. Researchers at Takis also claim that the vaccine candidates could adapt to any evolution of SARS-COV-2 and its possible mutations.

**Bacillus Calmette-Guerin (BCG) live attenuated vaccine for COVID-19**

The BCG is a live attenuated bacterial vaccine, given to people to protect against Tuberculosis. Recent research indicates that in countries where BGC vaccine is a mandatory paediatric vaccine, the number of positive cases and the mortality rate for COVID-19 is low, when compared to countries which do not need the BCG vaccine. Several countries are conducting phase 2/3 trials of the BCG vaccine to test its effectiveness, as a preventive vaccine for humans, to be protected against COVID-19. The University of Melbourne and Murdoch Children's Research Institute, Australia is involved in a randomized, controlled, Phase 3 BRACE trial and the Radboud University Medical Center of the Netherlands is also involved in a randomized, parallel assignment Phase 3 BCG CORONA trial [9].

**COVID-19 VACCINE DEVELOPMENT IN INDIA**

Currently in India around 30 different companies and institutions have given proposals to develop vaccines. Six vaccine companies from India are in the frontline, in the COVID -19 vaccine race and are working on the production and development of a Covid-19 vaccine.

**The Serum institute of India**, Pune is the world's largest manufacturer of vaccines by the number of doses produced and sold. The Serum Institute of Pune India has entered into a partnership with the Oxford University ChAdOx1 vaccine project, as one of the seven global institutions behind manufacturing the vaccine. Adar Poonawala the CEO of Serum institute has said that human trials for Covid-19 vaccine will begin by the end of 2020. The Oxford University is already conducting Phase I human trials for the ChAdOx1 nCoV-19 vaccine after successful animal trials conducted in Rhesus monkeys. The Serum institute will begin mass production of the vaccine in May 2020, for global distribution. The first set of doses will be available by September 2020. Serum institute has geared up to manufacture 4 to 5 million doses per month , and if the trials for the ChAdOx1 nCoV-19 vaccine are successful, it may scale upto 10 million doses per month for distribution in India and world wide[3, 28]. The Serum institute is also in collaboration with Codagenix, an American Biotech company, for the production of a live attenuated vaccine for Covid-19. The vaccines are to be manufactured at Pune.
**Bharat Biotech,** a Hyderabad-based biotech company is developing and testing a nasal vaccine for Covid-19. This is in collaboration with the vaccine companies FluGen, and virologists from the University of Wisconsin, Madison, USA, together with Bharat Biotech. The name of the vaccine is CoroFlu. FluGen's flu vaccine candidate known as M2SR, which a self-limiting version of the influenza virus that induces an immune response against the flu, is the backbone for development of Coroflu. Selected gene sequences from SARS-CoV-2, will be inserted by virologists into M2SR so that the new Coroflu vaccine will also induce an immune response against Covid-19. The manufacture of the vaccine, conduction of clinical trials, production of nearly 300 million doses of the vaccine will be done by Bharat Biotech, Hyderabad, India for global distribution. FluGen is to transfer its existing manufacturing processes to Bharat Biotech. Production scale-up to do safety testing and vaccine efficacy testing in humans will also be done by Bharat Biotech. Coroflu is expected to be in human trials by the end of 2020 [3, 28]
**Zydus Cadilla** which has one of the best vaccine development infrastructures in India, situated in Ahmedabad, is developing a DNA DNA vaccine for the Novel Corona virus from February 2020.
**Indian Immunologicals limited(IIL)**, which is a Hyderabad based company is in collaboration with the Griffith University of Australia, is to conduct experimental research and studies for a COVID -19 vaccine.
**Biological E Limited** which is also a Hyderabad based company is also involved in the development of a COVID -19 vaccine.
**Mynvax Private Limited** is a Bengaluru based company, is reportedly testing the vaccine candidates of The Indian Institute of Sciences (IISc), which is involved in an effort to produce a successful vaccine for COVID-19 [28].

**CHALLENGES TO BE FACED AFTER DEVELOPMENT OF A SUCCESSFUL VACCINE**

A number of additional challenges will present itself, once a successful COVID-19 vaccine has been approved. Even after a vaccine is made available after successful completion of human trials, the exact duration of immunity provided by the vaccine will still be unknown, and whether the vaccine will give lifelong immunity or longer duration of immunity with naturally acquired infection can be seen only much later. Similarly, whether single-dose vaccines or added booster doses can provide adequate immunity will remain uncertain until further serum research studies and clinical studies are done in the vaccinated populations [29].

In a pandemic situation, once vaccine candidates are proved safe and effective, doses must be manufactured in large quantities. In heavily populated countries like India, at least a billion people have to be vaccinated, to reach the herd immunity level for COVID-19.

Currently there is no particular global entity responsible for financing or production of mass vaccine manufacture. A few countries can afford to finance the development, production and manufacture for only their own country's population. During pandemics there will always be a global demand for vaccines from all directions around the world. But for providing a globally fair vaccine allocation and distributing system, vaccines should be first provided to the populations which is at the highest risk from Covid-19 [30]. This can be

confirmed by only further clinical research and serologic studies, of the vaccinated population. The problem is, making sure the vaccine gets to all those who need it. Even within countries, during a pandemic, the population which is at highest risk such as healthcare workers, social care workers, the elderly and whoever is at highest medical risk should be vaccinated first.

## II. Conclusions

Manufacturing has been scaled up for vaccines which are in phase 2 trials, and this is costing millions of dollars. In vaccine candidates with novel platform technologies, most of which are unlicensed, usually large scale manufacturing is never done. But in the case of the pandemic due to COVID -19, technologies are being transferred, and manufacturing process have been adapted, by collaboration projects between, the research centres or Universities developing the vaccine and large scale manufacturing pharmaceutical companies of different countries. This is being done even without knowing the complete success rate of the vaccine [29, 30].

There is a chance for the COVID-19 pandemic to suddenly end even before a vaccine is fully approved and ready. Still, as a precautionary measure against a second wave of the pandemic, seasonal outbreaks of COVID-19 or if the virus becomes endemic, and to better face future pandemics by SARS- CoV- 2, we should be prepared. So, the most promising vaccine candidates must be further developed, stocked and kept ready for use in case of outbreaks or emergency situations. A safe and effective vaccine against COVID-19 is the only means to save millions of human lives, and is the only definite exit strategy from the pandemic.

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