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Ongoing Clinical and Immunization Trials for Novel Zoonotic Covid -19 Pandemic

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Abstract

Some of the contagious diseases have created history and also remains with us today. So it becomes utmost important to understand such infectious diseases and exploring their remedies. One such disease which has created havoc across the globe is COVID-19, caused by an agent SARS CoV-2 virus. The current threat of coronavirus is the human health and economy, which can be overcome by the development of a target vaccine at a specific level by blocking the entry of virus inside the host cell. This step not only will reduce the morbidity and mortality rate associated with this viral infection but will also improve upon the prevailing economy crisis. Hence, this review chapter aims at the ongoing clinical and immunization trials for novel zoonotic COVID-19 pandemic. Currently the clinical trials are happening throughout the world and all the trials are to be registered in publicly available domain which is recommended by ICMJE. Different phase of trials in various parts of the globe, includes Phase-I to Phase-III and insights of vaccine developers involved in the development of COVID vaccines are the focused areas in this review chapter.

Keywords: COVID-19; SARS CoV-2; Immunization; Clinical trial; Vaccines.

1. Introduction

Immunizations defines the process whereby people are given protection against deadly disease caused by infection with micro-organisms (formally called pathogens). The term vaccine refers to the material used for immunization, while vaccination refers to the act of giving a vaccine to a person to protect him/her from any kind of deadly disease.

A vaccine typically contains an agent resembling a disease-causing microorganism. When this biological preparation is injected into the body, the immune system will be stimulated, responds and recognizes the agent as a foreign substance and destroys it. However, the immune system remembers the agent (microbe, its toxins, or one of its surface proteins) and next time, when the actual microbe attacks, it safeguards the organism against the disease. These Vaccines are usually made from the toxins of the killed or weakened microorganism.

An extremely huge majority of health professionals, medical researchers, and professional medical organizations recommends immunization. Getting immunized is important for at least two reasons: to protect yourself and to protect others who are around you. Vaccines (vaccination) are the one of the best method to prevent infectious disease. A successful immunization program depends on the co-operation of each and every person.

- Vaccinations gives strength to the immune system to develop protection and prevents you or your child from getting diseases for which there are often no medical treatments. These illnesses can result in many serious complications and even it may lead to death.
- A very few people may be vulnerable to diseases, such as those with impaired immune systems. After vaccination few might not develop immunity apart from this many might not get vaccination. Individual protection against certain diseases might help for others to get vaccinated so the illnesses become less common.
- Community spread of disease might have low or high risk which can lead to pandemic until people develop immunity. If the immunization is done for large number of population, it results in herd immunity.

Increase in Personal hygiene, good sanitation, and people living conditions generally help develop healthier environment and reduce the risks of spreading diseases to many places. But the theatrical and long-term decrease of diseases is primarily because of the immunization awareness created throughout the population in community spread disease.

Many Infectious diseases are caused by pathogenic microorganisms, such as bacteria, viruses, parasites or fungi, and each year millions are affected by them. Many infectious diseases have minor complications on earlier diagnosed and treated appropriately. But if it is left untreated, others—including pneumonia, tuberculosis, HIV and meningitis—can be life-threatening.

Even today we have greater challenge for some infectious disease which posed deadly two decades ago.

- For example, New bacteria, viruses, fungi and parasites emerge and evolve each year.
- Densely populated regions and easy travel speed up the spread of infectious disease.

Globally antibiotic resistance bacteria, fungi, virus, is a major health concern. Globally more than 2 million develop drug-resistant infections each year.

1.1. Diagnosis of Every Infection at the Early Stages is Very Important and Crucial Because

- Diagnosis usually can improve the effectiveness of treatments and avoid many long-term complications for the infected patient.
- Undiagnosed patients surely can unknowingly transmit the disease to others. Early diagnosis always helps to prevent or stop an outbreak.
- Extensive overuse and misuse of antibiotics contribute to antibiotic resistance. To develop antibiotic or any treatment initial diagnostic is very important.

To address the tropical disease diagnostics and treatment in the developing countries, WHO (World Health Organization) along with UNICEF (United Nations Children's Fund), world bank and UNDP (United Nations Development Program) have come up with a special program TDR who arranged an expert advisory panel for designing and conducting of standard diagnostic evaluation. Another collaboration of WHO with FIND is working on policy making and implementation for testing and providing effective diagnostic techniques of infectious diseases to different countries based on their specific requirements.

Spread of disease from one person to other person have shaped human history and they remain with us today. As the new coronavirus spreads across mainland China and to other parts of globe, such infectious diseases are top of mind for many of us. Here's a look at some of the worst of these infections, from HIV, ebola and dengue to the more recent SARS, the new coronavirus and Zika virus.

Smallpox

About 3000 years ago smallpox appeared which causes skin lesions which swept india or Egypt before sweeping other parts of the globe. The Variola virus, which causes smallpox, took away as many as a third of those it infected and left others scarred and blinded, as per World Health Organization.

WHO declared the disease officially eradicated in 1980 after a decade-long vaccination campaign. The last remaining samples of the virus are being held in facilities in the United States and Russia.

2. Plague

This ancient killer is still with us. Caused by a bacterium carried by fleas, plague has been blamed for decimating societies including 14th-century Europe during the Black Death, when it wiped out roughly a third of the population, including in Basel, Switzerland, depicted in this painting from 1349. The disease comes in three forms, but the best known is bubonic plague, which is marked by buboes, or painfully swollen lymph nodes. Though antibiotics developed in the 1940s can treat the disease, in those who are left untreated, plague can have a fatality rate of 50% to 60% by WHO.

3. Malaria

Even though it is a preventable and curable malaria has devasted many parts of Africa which devasted about 20% of childhood deaths as per WHO. It is also found in other continents as well. A parasite carried by blood-sucking mosquitoes causes the disease, which is first characterized by fever, chills and flu-like symptoms before progressing on to more serious complications. By 1951, the disease was eliminated from the U.S. with the help of the pesticide DDT. A subsequent WHO campaign to eradicate malaria was successful only in some places, and the goal was downgraded to reducing transmission of disease, according to the U.S. Centers for Disease Control and Prevention.

4. HIV/AIDS

At the end of 2018, about 37.9 million people were living with a Human Immunodeficiency Virus (HIV) infection worldwide, with 25.7 million of those individuals in Africa. About 770,000 people worldwide died from HIV/AIDS in 2018; 49,000 of those deaths were in the Americas, according to the WHO.

HIV the 19th century disease which has a long standing relationship with humans. HIV's decimating effect on certain immune system cells was first documented in 1981. By destroying part of the immune system, HIV leaves its victims vulnerable to all sorts of opportunistic diseases. It is believed to have emerged from Simian Immunodeficiency Virus (SIV), which infects apes and monkeys.

5. Ebola

Ebola virus disease (EVD) though rare is an often fatal infection caused by five strains of the Ebola virus. This virus spreads very rapidly, as per our own body immune system responses and which causing fever, muscle pain, headaches, weakness, diarrhea, vomiting and abdominal pain. Some who contract Ebola also bleed from the nose and mouth in the late stages of the disease — a condition known as hemorrhagic syndrome.

The Ebola virus is spread from person to person through bodily fluids, and a healthy person can contract the virus by coming into contact with an infected person's blood or secretions or by touching surfaces (like clothing or bedding) containing these fluids.

Past two years in west Africa approximately 11,300 people have died in this outbreak from 2014-2016. In August 2018, the Democratic Republic of Congo announced an outbreak of Ebola in its northern province of Kivu. That outbreak, which has infected 3,428 people and killed 2,246 as of February 2020, is still ongoing. A vaccination for close contacts of Ebola patients, called rVSV-ZEBOV, was approved in 2019.

6. Influenza

A seasonal, respiratory infection, flu is responsible for about 3 million to 5 million cases of severe illness, and about 250,000 to 500,000 deaths a year across the globe, according to the World Health Organization.

Some viral infection becomes devasting as decade passes. A pandemic in 1918 killed about 50 million people worldwide. That compared to it became from "swine flu" and "bird flu" scares in recent years, some influenza viruses can jump between species.

7. Middle East Respiratory Syndrome (MERS)

As if bat-borne diseases like Ebola and Marburg weren't enough, it turns out the flying mammals are also host to another deadly disease: Middle East respiratory syndrome, or MERS, a viral respiratory disease that was first identified in 2012 in Saudi Arabia. However, though MERs originated in bats, its major reservoir in the Middle East is likely dromedary camels, according to the WHO.

The MERS coronavirus (MERS-CoV) is closely related to SARS and the 2019-ncOv coronavirus currently spreading in China. Many contract MERS who develop severe breathing problems like respiratory illness, fever, cough and shortness of breath. As of 2020, 2,494 cases of the illness had been reported, mostly in Saudi Arabia. As many as 30-34% contracted this illness have died as per WHO.

8. SARS

SARS have spread to people by bats much like Ebola viruses it’s an severe acute respiratory syndrome which behind the 2002 -2003pandemic which killed not more than 750 people worldwide. SARS is spread to people by bats, much like Ebola viruses, Marburg virus and MERS. The SARS virus likely originated in horseshoe bats in China, according to the National Institutes of Health. These symptoms have high fever, dry cough, breathing shortness, pneumonia as per WHO.

8.1. SARS Coronavirus

A single-stranded positive-sense RNA viruses which belongs to subfamily coronavirinae. Which also known as SARS-CoV which causes severe acute respiratory syndrome (SARS). There are seven human coronaviruses: HCoV-229E, HCoV-OC43, HCoV-229E, HCoV-OC43, SARS-CoV, HCoV-NL63 and HCoV-HKU1, other novel human coronaviruses have also been discovered in recent years. The range of symptoms this virus causes is from mild symptoms to common cold and leads to other serious respiratory illness. For animals the primary symptoms is respiratory and enteric diseases. Coronavirus symptoms include rhinorrhea, sneezing, cough, nasal obstruction, bronchitis and so on. There are 3 main groups of coronaviruses: alpha, beta, and gamma. In 2012 a novel coronavirus identified as the causative agent of a rapidly progressive acute respiratory infection in 2 men from middleeast. .

SARS-CoV causes an atypical pneumonia that spread rapidly throughout parts of Asia, North America, and Europe during 2002-2003. SARS-CoV infection can cause bronchial epithelial cell peeling, cilia damage, the formation of multinucleated giant cells, squamous cell aplasia, alveolar interstitial fiber cell hyperplasia, and fibrotic lung disease.

SARS-Coronavirus has the same structure proteins as three known groups of coronaviruses: spike glycoprotein (S), membrane protein (M), envelope protein (E) and nucleocapsid protein (N). Coronavirus N protein is required for coronavirus RNA synthesis, and has RNA chaperone activity that may be involved in template switch.

Structure of compiling an glycoprotein of 1255 amino acid which is lower than other coronavirus of about 20-27percent. Its carboxyl terminus (C-terminus) is comprised of the transmembrane region and the cytoplasmic tail. The extracellular domain of the SARS-CoV spike glycoprotein is comprised of two heptad repeat regions which are known as heptad repeat region 1 (HR1) and heptad repeat region 2. SARS-CoV spike glycoprotein has two functional domains: S1 and S2. S1 is responsible for the binding with its receptor angiotensin-converting enzyme 2 (ACE2) on host cells and defines the host range of the virus. S2 is the transmembrane subunit that facilitates viral and cellular membrane fusion. Membrane fusion occurs when there is a conformational change in the HRs to form a fusion core. The HRs of the protein fold into coiled-coil structure-called the fusogenic state-causing the HR domains of the S protein to fold into a hairpin-like formation. This hairpin structure results in the cellular and viral membranes being pulled together and ultimately fusing.

8.2. Vaccines for Corona Virus

Vaccine a key armor for the prevention of viral infection to control widespread reduction of morbidity and mortality linked to many viral infections. In this pandemic the threat of avian influenza of the human population and the potential of this reemergence of many severe acute respiratory syndrome (SARS) which is associated to coronavirus. The necessity for the development of therapeutic and preventive strategies to combat viral infection.

8.3. Different Types of Vaccines for Corona Virus

Development of Coronavirus vaccines may be inactivated form of coronavirus, live attenuated coronavirus, or S protein-based. Apart, known types there are still vectored vaccines, DNA vaccines, and combination vaccines against coronaviruses. In current situation Vaccines are targeting several animal CoVs have been developed, and some have been demonstrated to be efficacious in preventing viral infection.

However, a phenomenon of enhanced disease following vaccination has been observed in cats upon infection with feline infectious peritonitis virus following previous infection, vaccination, or passive transfer of antibody.

Complete process is not known yet the studies continues to be believed that enhanced uptake and spread of virus through binding of virus-antibody immune complexes towards Fc receptors on the surface of macrophages.

Antibodies directed towards s protein are the mainly responsible even though antibody enhancement appears to be limited to feline infectious peritonitis virus among CoVs. This type of combination concerns have been raised with SARS-CoV. Continuation of the previous studies many infected mice and hamsters were protected by subsequent infection with SARS-CoV in the absence of enhanced disease.

Vaccine studies and passive immunoprophylaxis performed with mice and hamsters suggest that previous exposure and the presence of Nabs provide protection.

8.4. Inactivated Coronavirus Vaccine

Development of inactivated vaccines requires the propagation of high titers of infectious virus which in the case of SARS-CoV requires biosafety level 3-enhanced precautions and is a safety concern for production staffs. Between these the immunogenicity or the efficacy of inactivated SARS-Cov vaccines have been established and experimented to animals and clinical trails are been evaluated.

Inactivated vaccines which are incomplete inactivation of the vaccine virus present and the potential public health threat is a big concern. Many production workers are at a high risk during handling of live virus which may cause again an outbreak among vaccinated population which can reverse the action of some viral proteins that leads to harmful immune or inflammatory responses.

8.5. Live Attenuated Coronavirus Vaccine

An old process of live attenuated vaccine is not yet developed for SARS-CoV many systems have to be developed to generate cDNA encoding the genomes of CoVs including SARS-CoV. The panel of cDNAs spanning the entire CoV genome can be systematically and directionally assembled by in vitro ligation into a genome-length cDNA from which recombinant virus can be rescued.

An vaccine targeting respiratory virus, including influenza virus and influenza virus and adenovirus the approved for use in humans, observation of this infectious virus is shed in the feces of many SARS-CoV infected individuals can raise concerns of live attenuated SARS-CoV vaccine strains that might also shed in feces with potential to spread to unvaccinated individuals.

Risk factor increases with live attenuated vaccines virus with wild type of CoV there may be many ways to engineer the genome of the vaccine virus to minimize the risk, these system has been used for genetic analysis of virus protein functions and will enable many researches to engineer specific attenuating mutations or modifications of the genome of the virus to develop live attenuated vaccines.

8.6. S Protein-based Coronavirus Vaccine

Virus main protein are the binding receptor and fusion membrane section. S protein which induce antibodies to block virus binding and fusion on the membrane to neutralize the virus infection. S protein an main structure in the antigenic component that is responsible for inducing host immune response and neutralizing antibodies or protect immune against virus infection. S protein has therefore been selected as an important target for vaccine and anti-viral development.

Although full-length S protein-based SARS vaccines can induce neutralizing antibody responses against SARS-CoV infection, they may also induce harmful immune responses that cause liver damage of the vaccinated animals or enhanced infection after challenge with homologous SARS-CoV, raising concerns about the safety and ultimate protective efficacy of vaccines that contain the full-length SARS-CoV S protein.

8.7. Vectored Vaccines Against Coronavirus

Several groups have reported preclinical evaluation of vaccines utilizing other viruses as vectors for SARS-CoV proteins, including a chimeric parainfluenza virus, MVA, rabies virus, vesicular stomatitis virus (VSV), and adenovirus.

A live attenuated parainfluenza vaccine from chimeric bovine or human parainfluenza virus 3 were utilized as a vector for SARS CoV structural proteins which includes S,N, matrix (M), and the envelope protein (E) alone or in combination with vector vaccines further demonstrate that induction of S protein-specific Nabs is sufficient to confer protection to vaccinated or non-vaccinated groups of preclinical sections.

8.8. DNA Vaccines Against Coronavirus

Clinical data for DNA vaccines shows strong induction of immune response to viral pathogens in animals majorly in mice but clinical data on humans are comparatively less. Mice data shows vaccines encoding the S, N, M, and E protein of SARS-CoV from DNA vaccines. Humoral and cellular immune response were induced with DNA vaccination with S, M, N- which has some variation in the relative levels of induction.

8.9. Combined Vaccines Against Coronavirus

SARS-CoV shows some immune responses towards combined vaccines. Administration of two doses of a DNA vaccine encoding the S protein, followed by immunization with inactivated whole virus, was shown to be more immunogenic in mice than either vaccine type alone. The combination vaccine induced both high humoral and cell-mediated immune responses. High NAb titers were also observed in mice vaccinated with a combination of S DNA vaccines and S peptide generated in Escherichia coli. Combination vaccines may enhance the efficacy of DNA vaccine candidates.

SARS-CoV has not yet emerged for S protein-specific Nabs its still unknown reservoir which leaves open the possibility that it or to its related virus will again infect the human population. S-Protein-specific Nabs are an sufficient to provide protection against viral challenge. The development of vaccines targeting this virus will help, in the event of its reemergence, to potentially stop its spread before it wreaks the social and economic havoc caused by the previous outbreak. Furthermore, lessons learned from the generation of these vaccines may aid in the development of future vaccines against known and newly identified coronaviruses

8.10. Clinical and Ongoing Trials

Over the past two decades, three novel pathogenic human coronaviruses have emerged from animal reservoirs. These are Middle East respiratory syndrome-related coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), and, most recently, severe acute respiratory syndrome coronavirus 2 (referred to as COVID-19, SARS-CoV-2, or 2019-nCoV). All three have led to global health emergencies, with significant morbidity and mortality [1]. Before 2020, the largest outbreak was of SARS-CoV in 2003, which affected over 8000 individuals globally and was associated with 774 deaths (case fatality rate of 9.6%)i . The overall cost to the global economy of SARS-CoV was estimated to be between US$30 billion and US$100 billion.

Following the first identification in patients with severe pneumonia in Wuhan province, China in November 2019, COVID-19 has spread rapidly and now affects all permanently inhabited continents. This is the greatest pandemic of modern times and has been declared a Public Health Emergency of International Concern by the WHO Director-Generalii. As of 27 March 2020 (date of submission), COVID-19 was affecting 199 countries and territories, with >510 000 confirmed cases globallyiii. It is associated with an estimated mortality of between 1% and 5%iii. Furthermore, human-to-human transmission has continued apace, despite escalating public health measures. Current estimates of the impact on the worldwide economy are US$1 trillion and risingiv.

Currently, there are no approved therapies for either the treatment or prevention of COVID-19. With the predicted number of cases set to rise significantly, this represents a prodigious acute unmet medical need. Several national and international research groups are working collaboratively on a variety of preventative and therapeutic interventions. Potential avenues being explored include vaccine development, convalescent plasma, interferon-based therapies, small-molecule drugs, cell-based therapies, and monoclonal antibodies (mAbs) [2]. However, drug therapy development is a costly and timely process with a high attrition rate [3]. A normal drug is developed in such a speed which is not acceptable in the context of the global emergency. Therefore, there has been considerable interest in repurposing existing drugs and expediting developmental antiviral treatments, such as those for influenza, hepatitis B (HBV), hepatitis C (HCV), and filoviruses, to allow more rapid development [2]. The swift genomic sequencing of COVID-19 has facilitated this process, allowing comparison with MERS-CoV, SARS-CoV, and other morbific viruses [4]. This strategy has identified several genomic regions of interest for therapeutic modulation, specifically the identification of highly conserved regions involving viral enzymes between different pathogenic coronaviruses.

Since 2005, it has been recommended by the International Committee of Medical Journal Editors (ICMJE) that all clinical trials should be registered in publicly available domains before they may be considered for publication [5]. The introduction of this requirement and other initiatives to increase clinical trial transparency has contributed to an increasing number of trials being recorded in online registries, such as Clinical Trials. govv and the International Clinical Trials Registry Platform (ICTRP)vi of the WHO. The logging of trials on registries has vastly facilitated the dissemination of information across several domains, including intervention, methodology, patient group, and outcome measures. Furthermore, in the event of the nonpublication of results, it means that trial information remains freely available for analysis.

8.11. Novel Coronavirus Vaccine Has Been Approved Trails In Humans Just To Stop the Spread of Virus from Various Countries

As of now, the new coronavirus, which causes the respiratory disease COVID-19, has infected over 2.5 million people across the globe, as well as causing at least 179,725 deaths, according to a tracker provided by Johns Hopkins University.

Germany, Russia, United States, China became the most recent country to approve COVID-19 vaccine trials in humans. The Paul Ehrlich Institute, German's regulatory authority for vaccines, authorized human trials for a vaccine developed by a local firm BioNTech and the U.S. pharma company Pfizer.

Considering the serious consequences of the COVID-19 pandemic, this is a significant step toward developing an efficacious and safe COVID-19 vaccine available in Germany and making it available worldwide as soon as possible a statement for Paul Ehrlich Institute.

Oxford university has developed a human vaccine and trails have also been approved by United Kingdom health secretary Matt Hancock, another vaccine developed by imperial college is set to begin recruiting volunteers by June. Vaccine of this college is a liquid which carries the necessary genetic material to the bloodstream.

Oxford University announced they will use a common cold virus from chimpanzees to develop their vaccine, with the hopes it will boost the immune system of those undergoing the trial. Both vaccines are aiming to recreate part of the novel coronavirus, so that the human body can learn how to fight it.

Earlier in April, a vaccine, funded by the Bill and Melinda Gates Foundation, was approved by the Food and Drug Administration (FDA), which began trials with volunteers who received their first dose.

8.12. Vaccine Candidates

CEPI had classified development stages for the vaccines as "exploratory" (planning and designing for a candidate, having no evaluation in vivo), "preclinical" (in vivo evaluation with preparation for manufacturing a compound to test in human beings), or initiation of phase I safety studies in healthy subjects.

As of mid-July, around 205 total vaccine candidates are in early stages of development confirmed as either active projects or in "exploratory" or "preclinical" development.

In a few dozens of healthy subject, Phase I trials test primarily for safety and also preliminary dosing. While phase II trials – following the success in phase I – evaluate immunogenicity, dose levels (efficacy based on biomarkers) and adverse effects of the candidate vaccine, typically in hundreds of people. A phase I–II trial combined consists of preliminary safety and immunogenicity testing, while determining more precise, effective doses is typically randomized, placebo-controlled, and at multiple sites. Phase III trials typically involve more participants, including a control group, and test effectiveness of the vaccine to prevent the disease (an "interventional" trial), while monitoring for adverse effects at the optimal dose.

Clinical trials started in 2020
COVID-19: candidate vaccines in phase I–III trials

Table-1.1

Vaccine Developers	Technology	Current phase	Completed phase, Immune repose, Adverse effect	Location	Duration
Ad5-nCoV CanSinoBIO, Beijing Institute of Biotechnology of the Academy of Military Medical Sciences	Recombinant adenovirus type 5 vector	**Phase II** (508) Interventional trial for dosing and side effects	**Phase II** (508) Neutralizing antibody and T cell responses. **Adverse effects**: moderate over 7 days: 74% had fever, pain, fatigue	wuhan	Mar–Dec 2020
AG0301-COVID19 AnGes Inc AMED	DNA plasmid	**Phase I-II** (30) Non-randomized, single-center, two doses	-	Osaka	Jun 2020 – Jul 2021
ZD1222 AstraZeneca	Modified chimp adenovirus vector (ChAdOx1)	**Phase II-III** (10,260) Interventional; randomized, placebo-controlled study for efficacy, safety, and immunogenicity	**Phase I-II** (543) Spike-specific antibodies at day 28; neutralizing antibodies after a booster dose at day 56. **Adverse effects**: pain at the injection site, headache, fever, chills, muscle ache, malaise in more than 60% of participants; paracetamol allowed for some participants to increase tolerability	20 in the UK, São Paulo	May 2020 – Aug 2021
BNT162 a1, b1, b2, c2 BioNTech, Fosun Pharma, Pfizer	mRNA	**Phase II-III** (30,000) Randomized, placebo-controlled, dose-finding, vaccine candidate-selection	**Phase I-II** (60) Preprint. Strong RBD-binding IgG and neutralizing antibody response peaked 7 days after a booster dose, robust CD4+ and CD8+ T cell responses, undetermined durability. **Adverse effects**: dose-dependent	62 in the US, Germany	Apr 2020 – May 2021

			and moderate including pain at the injection site, fatigue, headache, chills, muscle and join pain, fever		
CoronaVac Sinovac, Institut o Butantan	Inactivated SA RS-CoV-2	**Phase I-II** (1,166) Randomized, double-blinded, single-center, placebo-controlled in Xuzhou (744); Renqiu (422)	Pending phase I report	2 in China, 12 in Brazil	• Apr–Dec 2020 in Xuzhou • May–Jul 2020 in Renqiu • Jul 2020 – Oct 2021 in Brazil
COVAX-19 Vaxine Pty Ltd	Recombinant p rotein	**Phase I** (40)		Adelaide	Jun 2020 – Jul 2021
COVID-19/aAPC] Shenzhen Genoimmune Medical Institute	Lentiviral vector with mi nigene modifyi ng aAPCs	**Phase I** (100)		Shenzhen	Mar 2020 – 2023
CVnCoV CureVac, CEPI	mRNA	**Phase I** (168)		Ghent, 3 in Germany	Jun 2020 – Aug 2021
Gam-COVID-Vac Lyo Gamaleya Research Institute of Epidemiology and Microbiology	Non-replicating vira l vector	**Phase I** (38)		Moscow	Jun 2020 – Aug 2020
GX-19 Genexine consortium,[107] I nternational Vaccine Institute	DNA	**Phase I** (40)		Seoul	Jun 2020 – Jun 2022
INO-4800 Inovio, CEPI, Ko rea National Institute of Health, Internati onal Vaccine Institute	DNA plasmid deliver ed by electroporat ion	**Phase I-II** (40)	Pending phase I report	3 in the US, Seoul	Apr–Nov 2020
LNP-nCoVsaRNA MRC clinical trials unit at Imperial College London	mRNA	**Phase I** (105) Randomized trial, with dose escalation study (15) and expanded safety study (at least 200)		4 in the UK	Jun 2020 – Jul 2021
LV-SMENP-DC Shenzhen Genoimmune Medical Institute	Lentiviral vector with mi nigene modifyi ng DCs	**Phase I** (100)		Shenzhen	Mar 2020 – 2023
mRNA-1273 Moderna, NIAID , BARDA	Lipid nanoparti cle dispersion containing mR NA	**Phase III** (30,000) Interventional; randomized, placebo-controlled study for efficacy, safety, and immunogenicity	**Phase I** (45) Dose-dependent neutralizing antibody response on two-dose schedule; undetermined durability. **Adverse effects**: fever, fatigue, headache, muscle ache, and pain at the injection	89 in the US	Jul 2020 – Oct 2022

			site		
NVX-CoV2373 Novavax	SARS-CoV-2 recombinant spike protein nanoparticle with adjuvant	**Phase I** (131)	**Phase I** (131) Preprint. Strong IgG nad neutralizing antibody response with adjuvant after booster dose, and CD4+ T cell response. **Adverse effects**: short-duration and low grade including local tenderness and pain, headache, fatigue, myalgia, rarely severe or long-lasting	2 in Australia	May 2020 – Jul 2021

8.13. COVID-19 Vaccine: Most Recent Updates

By 2021, public health experts are expecting one or several vaccines for COVID-19 will be ready. Around 200 vaccines are under study, and many candidates have reached to phase III human studies. Before it can get FDA approval it's the final step to prove if the vaccine is safe and effective.

To help in accelerating the process of the development and funding of the trials, the U.S. has set up Operation Warp Speed, which is a partnership with the Department of Health and Human Services, the FDA and other federal agencies. The ultimate goal is to supple 300 million doses of effective, safe vaccines by January 2021.

The companies included in the program are as follows: AstraZeneca, Janssen (Johnson & Johnson), Moderna, Novavax, Pfizer and etc.

8.14. Vaccine Developers

For any vaccine to be approved, it needs to prevent infection or decrease its severity in at least 50% of the people vaccinated according to the The FDA report. The goal of any vaccination, is to inject abundant people with the vaccination program so that immunity extents through a community, even if not everybody gets the vaccine which is known as "herd immunity." For this coronavirus, some experts say about 60% to 70% of the population would need to develop antibodies, whether from a vaccine or getting and recovering from COVID-19, to create herd immunity.

If not enough people get vaccinated with the vaccine and as soon as once one or several are approved, it may show difficulty to reach herd immunity.

At first, vaccine manufacturers must also show that it's safe.

The FDA also had mentioned that it could issue an emergency use authorization (EUA) for a COVID-19 vaccine, as it would be decided on a case-by-case basis.

8.15. Vaccines Which Are in Phase III Trials

As a results from earlier trials, Phase III trial confirms and expand on safety and effectiveness. As of Aug these COVID vaccines are in Phase III:

AstraZeneca & University of Oxford. Scientists from University of Oxford in partnership with AstraZeneca to develop a COVID-19 vaccine which is made from a weakened version of the common cold virus, the adenovirus, which is taken from chimpanzees. It cannot reproduce itself, as the adenovirus is genetically altered. The vaccine in combination with the genes of the spike protein trigger production of antibodies against it, which allows the immune system to destroy the SARS-CoV-2 virus.

BioNtech, Pfizer & Fosun Pharma. Four vaccines are being tested by the companies, each using messenger RNA in different combinations to targeted antigens (in order to produce antibodies) which is called BNT162b2, and the the vaccine is being tested in phase II/III trials which was launched on July 27 in the U.S., and is expected to include upto 30,000 participants between ages 18 to 85 at about 120 sites all over the world.

Volunteers in Germany and the U.S. received the vaccine in a phase I/II clinical trial previously. The trial evaluated its safety, ability to give immunity, and the best dose out of the four candidates.

The testing of the vaccine was done in people between 18 to 55 initially. Of all the 24 people, one of the four candidates who received both the lower and the higher dose of the vaccine had developed neutralizing antibodies that can halt the virus as of the early results which were shown. Of people recovering from COVID-19, the antibodies were produced at or above levels found in the blood. Side effects, such as low-grade fever, were more common after the second dose than the first, but generally were mild and temporary.

9. Moderna

On July 27, Moderna in partnership with the National Institutes of Health, launched phase III trial of its vaccine and expecting to enroll 30,000 adult volunteers. Moderna announced that every person who received its vaccine, mRNA-1273, developed an immune response to the virus earlier in July. Researchers also reported some side effects in the 45 people in the phase I study, but no significant safety issues as such. Enrollment in the phase II study was completed by July 8 and the trial is still in progress.

Moderna's vaccine uses mRNA (messenger RNA). It carries instructions for making the spike protein, a key protein on the surface of the virus that allows it to enter cells when a person is infected. After it's injected, it goes to the immune cells and instructs the cells to make copies of the spike protein, acting as the cells have been infected with the actual coronavirus allowing other immune cells to develop immunity.

Sinopharm. Phase III clinical trial in the United Arab Emirates had started during mid-July by Sinopharm. In 15,000 volunteers between ages 18-60, for 3 to 6 months, the study will assess two forms of the vaccine. From the Sinopharm Wuhan Biological Products Research Institute in China the vaccine was tested previously in 1,120 people ages 18-59 in phase I/II clinical trials and the vacicine had produced a strong neutralizing antibody response of 97.6% to 100%, which depends on the timing and dosing of the injections. Iinactivated version of the virus has been used in the vaccine.

Sinovac Biotech., an inactivated version of the virus had been used by Sinovac Biotech's vaccine, CoronaVac. To launch a phase III trial, Sinovac had partnered with Instituto Butantan in Brazil. In 90% of people who received it early results of a Phase II clinical trial released in June show that the vaccine induced antibodies to neutralize the virus after 14 days. According to the company, the vaccine requires two injections, given 2 weeks apart. In 743 healthy volunteers, no serious side effects have been reported in either phase I or II trials. Based in Beijing, Sinovac Biotech, had mentioned it will develop the vaccine for global use.

Other Candidates

Inovio. In phase I clinical trials, with 40 volunteers, Inovio's vaccine, INO-4800, is a DNA vaccine. As designed to produce a specific immune response, the technology uses DNA. To open small pores in the skin in order to deliver the vaccine a handheld smart device uses a brief electrical pulse. Once the DNA is inside a cell, it instructs it to make many copies of the artificial DNA, which stimulates the body's natural immune response.

Johnson & Johnson. In U.S. and Belgium, the company had launched the phase I/IIa study in July with 1,000 volunteers. The vaccine consists of genes from the coronavirus with a modified adenovirus. It is known as Ad26.CoV2. S. If FDA approves the vaccine, the U.S. government had agreed to pay Johnson & Johnson $1 billion for 100 million doses.

Merck. To develop a COVID-19 vaccin, Merck is partnering with the International AIDS Vaccine initiative (IAVI) and had acquired an Australian company.

Novavax. In 131 healthy adults which were tested, the company said **r**esults from the phase I part of a phase I/II trial showed that Novavax's vaccine, NVX-CoV2373, is well-tolerated and triggered strong antibody responses. Tenderness and pain were the most common side effects. After a single dose all volunteers developed antibodies and after the second dose all developed neutralizing antibodies (which decrease the strength of the virus). The U.S.-based company developed the vaccine which used technology that generated antigens (that stimulated the immune system) derived from the coronavirus spike protein. Two different doses of the two-dose regimen are being tested. First one includes an adjuvant designed to boost the immune response.

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