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Coronavirus Disease-19: Vaccine Production and Development

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Abstract

The coronavirus disease (COVID-19) pandemic, which emerged in Wuhan, China, in late December 2019, is now rampantly spreading worldwide. There is a serious need for ultimate treatment of the disease, to stop the spread of the virus globally. In these unprecedented times, vaccines can play a pivotal role in strengthening the immunity of the community. Many drugs are being prescribed in hospital setups to treat the disease caused by the virus. Most of these drugs act as tools for symptomatic relief and palliative care in individuals. A noteworthy drug, favipiravir is being used in some countries like India, for COVID-19 positive patients, who have been hospitalized, in a debilitated state. However, drugs provide a cure at an individual level, but to control such a massive pandemic, a safe and efficacious vaccine is needed. Vaccines are the tools that have a huge impact on "herd immunity." Not only the researchers but also the general public are eagerly anticipating the development of the vaccine so that they can be relieved of the multiple lockdowns and can rest assured. Unless a safe and efficacious vaccine against SARS-CoV-2 is developed, there is always a risk of new outbreaks of the disease. This article highlights some important points that help us feed the curiosities, with information on, what is a vaccine? Why do we need a vaccine for COVID-19? How will the vaccine develop?

Keywords: Coronavirus disease-19; SARS-CoV-2; vaccine; herd immunity; vaccine development

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Introduction

Many people across the globe are suffering from this devastating disease that has either disturbed the life of people or taken lives. A proper solution to combat this disease is by vaccination, and that is why nearly 150 countries have taken up the challenge of developing a vaccine and nearly 200 prophylactic vaccines are currently in development against coronavirus disease (COVID-19), at an accelerated pace.[1,2]

To produce an effective vaccine, it is important to know the structure of the virus.

COVID-19 is caused and spread by an infectious virus, SARS-CoV-2 that belongs to the family of Coronaviridae. Coronaviridae is a family of enveloped, positive-sense single-stranded RNA viruses that carry petal or club-shaped peplomers (Spikes).[3]

Like alternative coronaviruses, SARS-CoV-2 particles are spherical in shape and have proteins known as "spikes" jutting from their surface. A new modality like cryoelectron microscopy is done to take detailed pictures of the structure of the spike protein (S-protein).[4]

The spikes latch onto the ACE-2 receptor on human cells then, they undergo structural modification that enables the infectious agent membrane to fuse with the plasma membrane, and this is known as membrane fusion. Before entering the host cell, the virus particle is uncoated and the Ribonucleic acid is deposited into the cytoplasm.

Some researchers found that the SARS-CoV-2 spike has 10–20 times more affinity to bind ACE2 receptors on human cells than the SARS -2002 virus spikes. This makes SARS-Cov-2 more infectious than the earlier virus.[3,4]

The virus has many serotypes that are very fastidious which makes it a difficult process to grow in cell cultures. Most human coronaviruses come under either of the serotypes: OC43-like, 229E-like; other serotypes are SARS-CoV, NL63, HKU-1, and MERS-CoV.[4]

The researchers are currently engaged in developing vaccine candidates that target the SARS-CoV-2 S-protein. They additionally hope to use the spike protein to isolate antibodies from those who have recovered from the infection. If created in massive quantities; such antibodies might probably be useful in treating new infections before a vaccine is obtained.[5]

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What is a Vaccine?

A vaccine is a biological preparation that is used to stimulate the production of antibodies and provide immunity against one or many diseases. It provides artificially acquired active immunity to a particular infectious disease.

It is usually made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins.[3]

In the case of SARS-CoV-2, there is more research going on the S-Protein that could act as a potential antigen to create antibodies against the virus.

Why Do We Need a Vaccine for COVID-19?

The main process by which anyone can fight the disease is by strengthening one's immunity against the disease. This can be achieved in two ways, either by getting infected and developing

antibodies (natural immunity) or by vaccination (artificial immunity).

The immune system of our body is capable of protecting us from invading pathogens by producing immunoglobulins. If the immune system is not fast enough, the pathogens invade and we fall sick. Vaccines mimic the actual pathogen and provide a balanced and controlled exposure of pathogens.

It is more important for the whole community to acquire immunity and that can be achieved by herd immunity.

Herd immunity is the overall level of immunity in a community/population. When an outsized proportion of people in a community are immune to a microorganism, the herd immunity to the microorganism is considered satisfactory. Eradication of communicable diseases depends on the development of high levels of herd immunity.[3]

Herd immunity concept is used in the production of vaccines that have successfully controlled deadly contagious diseases such as smallpox, polio, diphtheria, and rubella.[5]

Often, a proportion of the population should be capable of obtaining a disease so as for it to spread. This is known as a threshold proportion. If the proportion of the population that is immune against the disease is more than this threshold, the spread of the disease can decline. This is called the herd immunity threshold.[6]

The herd immunity threshold of SARS-Cov-2 is 29–80%, on an average 60%, that is, at least 60% of people in a community should be vaccinated to stop the spread.[7]

Some health-care professionals contradict the idea that attaining herd immunity through natural exposure to the pathogen. "This pandemic cannot be overcome by thinking that tomorrow we will have herd immunity. Herd immunity has failed in the UK. There is no point in saying that India has developed herd immunity. We have tried to contain the virus through the lockdown" as said by a professor at All India Institute of Medical Sciences.[8]

How are COVID-19 Vaccines Produced?

An ideal SARS vaccine should have three features as follows:

1. It should be able to elicit highly potent neutralizing antibodies against a broad spectrum of viral strains
2. Induce protection against infection and transmission
3. Should be safe by not inducing any infection-enhancing antibodies or harmful immune or inflammatory responses.[9]

All the vaccines have to undergo a series of clinical trials that include the phases shown in Table 1.[10]

To respond faster to the COVID-19 pandemic, a broad range of candidate COVID-19 vaccines are being investigated using various technologies and platforms including viral-vectored, protein subunit, nucleic acid (deoxyribonucleic acid [DNA], and RNA), live attenuated, and inactivated vaccines, of which some have entered clinical trials.[11]

Before we deal with the vaccines against COVID-19, it is essential to know, what the types of vaccines are.

Live Attenuated Vaccines

Live attenuated vaccines contain live microbes that are rendered avirulent. Live vaccines induce a wide range of antibodies to many viral antigens. This vaccine tends to be more effective, provides immunity that lasts longer than the killed ones. One dose is usually sufficient. However, they pose a risk of reversion to virulence, but this is a rare drawback. These vaccines should be used cautiously or are contraindicated in immune-suppressed individuals

Inactivated/Killed Vaccines

It consists of microbes killed by heat or chemicals. They require a series of injections before prior immunization. The immunity is comparatively short-lasting and might require multiple doses. Subunit vaccines pose less adverse reactions, as the virus is split by detergents and other chemicals, and only required antigens are incorporated in the vaccine.

These vaccines induce cell-mediated immunity.[3,10]

Many pharmaceutical company firms are pioneering in using innovative technologies in producing effective vaccines.

AstraZeneca's AZD-1222 and Moderna's mRNA-1273 are presently the foremost promising vaccine candidates, each using novel technologies that include delivering and manufacturing the COVID-19 (S-protein) into the body to mount a reaction. This mechanism is anticipated to supply a long-lasting immunity by altering the binding of the S-proteins of the coronavirus to stop the infection.[2]

Moderna's - mRNA-1273 vaccine candidate inserts a messenger ribonucleic acid (mRNA) sequence into the body that encodes for the S-protein, leading to the production of the 2019-nCoV S-protein, which induces the host cells to mount an immune response against the S-protein. This vaccine is expected to enter the phase-3 trial by July 27, 2020.[2]

While Moderna was working on mRNA based vaccine, AstraZeneca collaborated with the University of Oxford in the development of a recombinant adenoviral vaccine, AZD-1222.

AZD-1222 uses genetically altered adenovirus to prevent replication and consists of a replication-deficient chimpanzee adenovirus vector (ChAdOx1), which delivers the S-protein. Moreover, the Oxford University claims that the vaccine under development can provide "double protection" by inducing antibody production as well as the Killer-T-lymphocytes that kill the virus-infected cells.[2,12]

CureVac is another mRNA based vaccine that is currently in phase-1 of the clinical trial.

Sinovac Biotech is developing CoronaVaC, an inactivated vaccine that is currently in Phase I/II trial. The preliminary results have shown the vaccine to exhibit a favorable safety profile.[2,13]

Table 1: Various phases a vaccine goes through

Preclinical studies	*Phase-1*	*Phase-2*	*Phase-3*	*FDA review*	*Phase-4*
Exploratory studies of synthesized vaccine	Human pharmacology safety and dosing of vaccine	Therapeutic exploration and effectiveness	Therapeutic confirmation and comparison	To confirm the safety and effectiveness of the drug	Post marketing surveillance/Data gathering studies
Tested on animals to explore the pharmacological profile	Total 20–80 human subjects	100–500 human subjects	500–3000 human subjects		1000+ human subjects

Inovio INO-4800 utilizes innovative DNA immunogen technology composed of changed plasmids to supply associate degree response targeting the S-protein. Inovio had declared that the preliminary clinical test results showed INO-4800 to be safe and tolerable.[2]

Covaxin is India's 1st candidate against SARS-CoV-2 infection. Covaxin is an inactivated vaccine. The vaccine has been developed by a pharmaceutical company, Bharat Biotech in collaboration with the National Institute of Virology and Indian Council of Medical Research (ICMR). The Drug Controller General of India (DCGI) earlier approved the biotech company to initiate Phases I and II human clinical trials.

As the number of cases are exploding across the planet, vaccines are being developed at an accelerated pace. ICMR has once again said that there is nothing wrong with the ambitious vaccine timeline and even went on to say that India will have a "big role" to play in vaccine development globally.[12]

Various pharmaceutical companies and biotech firms are developing intramuscular vaccines that are under different phases of clinical trials while some firms in different countries are developing a nasal/mucosal route of administration of vaccines.

Intranasal vaccines are sprayed through nose/orally to the respiratory tract. It target he nearby B-lymphocytes that produce immunoglobulin-A that provides local immunity and helps in healing the mucosal surface and also the B-lymphocytes induce the T-lymphocytes that provide systemic immunity. A mucosal vaccination is beneficial as it triggers local, as well as systemic immunity whereas intramuscular vaccination mainly induces an antibody response.

Moreover, the nasal spray particles are aerosolized and can get lodged in the lungs, intestines, and hence provide immunity.[12,13]

At present, many firms of different countries are developing various intranasal vaccines, some of them are:

Coroflu

The vaccine development firm, FluGen has collaborated with the University of Wisconsin-Madison to produce the vaccine called Coroflu. Coroflu is developed on the basis of the M2SR flu vaccine, which is a self-limiting version of the influenza virus that induces an immune response against the flu.[13,14]

Canadian Vaccine

This vaccine candidate is a DNA-based vaccine that can be given through a nasal route. The University of Waterloo in Canada is developing the vaccine. The scientists are using a novel approach based on bacteriophages.[13]

Intravacc

This is a Dutch research and development vaccine institute established in the Netherlands. Intravacc has collaborated with Wageningen Bioveterinary Research and Utrecht University to develop an intranasal Covid-19 vaccine. The vaccine will contain a Newcastle disease virus, that acts as a vector, which expresses the SARS-CoV-2's immunogenic spike (S) protein, the main target for neutralizing antibodies, it demonstrated safety for intranasal or intratracheal delivery in mammals.[13,15]. Other intranasal vaccines AdCOVID and Finland nasal spray are still in preclinical trials.[13] The time at which the vaccines will be available is highly variable. Many scientists and researchers are slogging harder and working faster to create viable protection for mankind against COVID-19.

Conclusion

COVID-19 is a highly infectious disease caused by SARS-CoV-2. The disease has become a pandemic, that caused a huge economical imbalance due to restrictions in trade and lockdowns in the market. Across the globe, people are living a "socially-compromised life" like staying at homes, restricted movement due to the quarantine of contacts and isolation of cases. Many individuals are looking forward to the work of many pharmaceutical companies and vaccine development firms. These companies have invested billions of dollars in vaccine development. Multiple clinical trials are being conducted in various countries to produce a vaccine. But, until then individuals should follow all the guidelines given by the governing bodies in order to stop the spread of the infection. The responsibility to reduce the infection lies in the hands of both community and the healthcare professionals. Hence, the citizens of the community and the healthcare system should be united in order to live a healthy life.

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