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IN QUEST OF A COVID-19 VACCINE: A RACE AGAINST TIME

KK Aggarwal [1] & NK Ganguly [2]

1 President Confederation of Medical Associations in Asia and Oceania & Heart Care Foundation of India; Past President Indian Medical Association

2 Former Director-General, Indian Council of Medical Research

emedinews@gmail.com

Abstract

Covid-19 or Coronavirus disease-2019, caused by the novel Coronavirus (SARS CoV-2), continues to be a major global public health crisis. There is no specific drug for its treatment and no immunity against the virus. Allowing herd immunity to develop naturally would add to the already high morbidity and mortality and it may take many years. But, the speed with which the virus is spreading leaves us with no choice but to have a vaccine, or at least an emergency-use vaccine ready for use, at the earliest. There are frantic efforts across the world to develop a vaccine. Different approaches such as inactivated and attenuated vaccines, viral vector-based vaccines and DNA- and RNA-based vaccines are being studied. Many vaccines have shown promise in preclinical studies; many have completed or are in phase 1 trials. A safe and effective vaccine against Covid-19 is eagerly awaited. But, even when a vaccine is available, public health measures such as personal hygiene, social distancing, will be equally important to reduce disease transmission. In this article, we give a brief overview of the types of vaccines and the various vaccine initiatives around the world.

Keywords

COVID-19, herd immunity, vaccine

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Full Text

Introduction

The world is eagerly awaiting a vaccine for Coronavirus disease (Covid-2019) to control a pandemic, which is showing no signs of stopping and continues to spread around the world. Covid-19 has caused considerable morbidity and taken a heavy toll of lives. The economic fallout of the disease too has been enormous. Globally, more than 5 million people have been affected and more than 3 lakh people have died due to Covid-19, as per the Worldometers website on 21st May.[1] According to data available from the Ministry of Health & Family Welfare, Govt. of India website on 21st May, 2020, India has 63624 active cases; 45299 have been cured / discharged; there have been 3435 deaths. Covid-19 is an infectious disease caused by a novel corona virus (nCoV), officially named as SARS-CoV-2. It is a rapidly evolving

disease, caused by a highly infectious and contagious virus. Although we are nearly five months into the outbreak (*at the time of writing this*), we do not know much about it. We are still learning about the disease. There is no specific proven antiviral drug for its treatment. Treatment is mainly directed towards managing symptoms of the patient and preventing development of complications.[2] Potential therapies are being explored. Existing medicines (hydroxychloroquine, azithromycin, lopinavir, ritonavir) are being repurposed.

COVID-19 is a new virus; hence, the population has no immunity against the virus. In such a situation, vaccines become the option. The need of the vaccine also arises when there are a large number of asymptomatic persons in the community. We now know this to be true for Covid-19. Asymptomatic transmission is playing a major role in the spread of the disease and has been described as the "Achilles' heel" of present approaches to control the infection.[3] The spread of any outbreak slows down when the population to develop natural "herd" immunity in due course of time. Young children, the elderly, pregnant women, immunocompromised individuals, people who lack access to immunization or those who do not opt for immunization, benefit from herd immunity.[4]

There are many ways to describe herd immunity. One, it is the percentage of individuals in a population, who have immunity against the infection. Secondly, it is the threshold specific percentage of individuals with immunity, which reduce the infection. Herd immunity is also referred to as the pattern of immunity that should protect a population from a new infection. [5] Smith in 1970 and Dietz in 1975 put forth the term "Herd Immunity Threshold" (HIT), which means that if immunity (i.e., successful vaccination) were delivered at random and if members of a population mixed at random, such that on average each individual contacted R_0 individuals in a manner sufficient to transmit the infection, then incidence of the infection would decline if the proportion immune exceeded $(R0 - 1)/R_0$, or $1 – 1/ R_0$.[5] Here, R_0 (R_{naught}) is the reproduction number and measures the contagiousness or transmissibility of the pathogen i.e. the number of persons infected by one infected person. The R_0 for Covid-19 it is 3-4.

Low R_0 values are associated with lower HITs, while higher R0 values lead to higher HITs.[5]

- If R_0 is 1, then 10% of population would need to get infected to develop herd immunity.
- If R_0 is 1.5, then 29% of population would need to get infected to develop herd immunity.
- If R_0 is 3, then 66% of population would need to get infected to develop herd immunity.

But, allowing natural immunity to develop through infection would result in high rate of serious illness and death, which would leave the health systems unable to cope. The more infectious a disease, the greater the population immunity needed to ensure herd immunity.[6] Herd immunity can be developed faster through vaccines. It may take at least 3 years or more to build up herd immunity of any substance for Covid-19. But, we still do not know if Covid-19 infection provides immunity to the affected individual. The WHO has also said that there is currently no evidence that people who have recovered from Covid-19 and have antibodies are protected from a second infection. [7] However, two studies in macaque monkeys, published May 20, 2020 in Science, have shown protective immunity against re-exposure to the Covid-19 virus acquired either due to natural infection or through vaccine. [8,9]

Types of vaccines

Live attenuated vaccine

Live attenuated vaccine is an established standard method, which uses a weakened (or attenuated) form of the disease-causing pathogens (virus or bacteria). Unlike the killed vaccines, they can emulate the

infection and produce a strong and long-lasting immune response after only a single immunization. [10] Live attenuated vaccines provide long-term protection without the need for a booster dose. [11]

To date, live attenuated vaccines for Covid-19 virus have not been evaluated. Systems have been developed to generate complementary DNAs (cDNAs) 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. This system has been used for genetic analysis of SARS-CoV protein functions and will enable researchers to engineer specific attenuating mutations or modifications into the genome of the virus to develop live attenuated vaccines. [12] The Covid-19 virus has been isolated from the foeces of Covid-19 patients. [13] This has raised concerns that a live attenuated SARS-CoV vaccine strain may also be shed in feces and be a potential source of infection to unimmunized persons. [12] There is also a concern that reassortants may sometimes be produced. The live attenuated strain combines with the circulating strain (wild-type CoV) and a new reassortant virus emerges, which either dies naturally or may establish itself. This has happened in HIV and polio.

Killed inactivated vaccines

Inactivated vaccines are prepared by treating the agent with a chemical (e.g. formalin) to denature the toxin or to kill the agent. [10] Inactivated whole-cell vaccines are safe as they do not contain live components. But, require several doses to produce adequate immune response. [14] The presence of contaminants in the culture filtrate may generate reactogenicity in some inactivated vaccines. [10] However, the 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. Additionally, incomplete inactivation of the vaccine virus presents a potential public health threat. Production workers are at risk for infection during handling of concentrated live SARS-CoV, incomplete virus inactivation may cause SARS outbreaks among the vaccinated populations, and some viral proteins may induce harmful immune or inflammatory responses, even causing SARS-like diseases. [12]

Genetically engineered vaccines

These vaccines use genetically engineered RNA or DNA that has instructions for making copies of the S protein, which produce an immune response to the virus. There is no handling of handling of infectious virus in these vaccines. [15]

DNA vaccines

DNA vaccines encoding the S, N, M, and E proteins of SARS-CoV have been evaluated in mice. These vaccines induce a strong immune response against the virus in animal models, mice in particular. But there is limited clinical data in humans. Both humoral and cellular immune responses are seen with DNA vaccines encoding for S-, M-, and N-proteins. [12]

Vector-based vaccines

In viral vector-based vaccines, an unrelated, modified virus is used as a vector (tool) to deliver the viral antigen (protein) in the host, in whom antigens are expressed and an immune response is produced against the target pathogen when delivered. Replicating (but often attenuated) or non-replicating viruses are used as vectors. [16]

Some of the viruses used as vectors are adenoviruses, paramyxoviruses (measles virus, Newcastle disease virus or human parainfluenza virus), parvoviruses (adeno-associated viruses, AAV), rhabdoviruses (vesicular stomatitis virus, VSV), and poxviruses (Modified vaccinia Ankara, MVA). [16] Chimeric parainfluenza virus, MVA, rabies virus, VSV and adenoviruses have been used as vectors for SARS-CoV proteins. Studies with vector-based vaccines further demonstrate that induction of S protein specific neutralizing antibodies is enough to confer protection. [12] Dengvaxia, a recombinant Dengue vaccine based on the yellow fever attenuated strain 17D, is the only viral vector based vaccine licensed for use in humans. [16]

Combination vaccines against Coronavirus

Combination vaccines have been evaluated for their ability to augment immune responses to SARS-CoV. 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 neutralizing antibody (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. [12]

The SARS-CoV vaccine strategies reported to date demonstrate that S protein-specific NAbs alone are enough to provide protection against viral challenge. While SARS-CoV has not yet re-emerged, its unknown reservoir leaves open the possibility that it, or a related virus, will again infect the human population. The development of vaccines targeting this virus will help, in the event of its re-emergence, 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. [12]

Monoclonal antibodies

Monoclonal antibodies (mAbs) against the infectious pathogens target the virus surface proteins and prevent the entry of the virus in the cells. Palivizumab approved for prevention of respiratory syncytial virus (RSV) infection is a monoclonal antibody against the RSV fusion (F) glycoprotein. Antiviral mAbs targeting the conserved hemagglutinin A stem of Haemophilus influenzae is undergoing investigation. [17] Some mAbs against bacteria can be both therapeutic and prophylactic, for example, by targeting the protective antigen domain of Bacillus anthracis or a Clostridioides difficile toxin). [17] The high costs and requirement for parenteral administration preclude the routine use of mAbs. But, they may be helpful for certain emerging infectious diseases, where treatment of active disease and/or targeted prophylaxis might be especially important in persons who have not been vaccinated against a pathogen, but need immediate protection. [17]

Vaccine initiatives around the world

Institutes and pharmaceuticals across the world are engaged in efforts to develop a vaccine to prevent the infection. Inactivated and attenuated vaccines, viral vector-based vaccines and DNA- and RNA-based vaccines are some of the types of vaccine being studied. [18] Of the four major structural proteins of the Covid-19 virus, it is the S protein, which induces an immune response in the host, neutralizing antibodies and/or protective immunity against the infection. Vaccine developed from the S protein could produce antibodies, which may block the binding and fusion of the virus or neutralize the infection. [19] Hence, most

vaccines are being developed using either the pre-fusion or full-length spike (S) protein. Here is brief review of the some of the vaccines being developed against Covid-19.

Moderna vaccine

The most promising vaccine is the LPN-RNA vaccine being developed by Moderna Therapeutics, a US-based biopharmaceutical company. The vaccine was developed using a genetic platform called mRNA (messenger RNA). It has completed Phase 1 trial of its two-dose vaccine mRNA-1273, with the help of Emory, and has started recruiting for Phase 2. The phase I clinical trial (6 weeks) was conducted in 45 healthy individuals aged 18–55 years. It was led by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH) and started on 16th March. Three different doses (25, 100, 250 µg) were used in phase 1. Study participants were administered two doses of the vaccine via intramuscular route in the upper arm at a gap of 28 days. In the second phase, Moderna will enroll 600 healthy volunteers, half of whom are 18-55 years old and the rest over 55 years old. On May 18, 2020, Moderna published interim clinical data from the phase 1 study, which are encouraging. The vaccine was generally safe and well tolerated. [20]

- Dose dependent increases in immunogenicity were seen across the three dose levels, and between prime and boost within the 25 µg and 100 µg dose levels.
- All participants ages 18-55 (n=15 per cohort) across all three dose levels seroconverted by day 15 after a single dose.
- At day 43, two weeks following the second dose, at the 25 µg dose level (n=15), levels of binding antibodies were at the levels seen in convalescent sera tested in the same assay.
- At day 43, at the 100 µg dose level (n=10), levels of binding antibodies significantly exceeded the levels seen in convalescent sera.

Novavax vaccine

The vaccine from Novavax is NVX-CoV2373; it is a stable, prefusion protein made using Novavax' proprietary nanoparticle technology. The vaccine has demonstrated high immunogenicity and stimulated high levels of neutralizing antibodies in animal models. High levels of spike protein-specific antibodies with ACE-2 human receptor binding domain blocking activity and SARS-CoV-2 wild-type virus neutralizing antibodies were observed after a single immunization. [21] It is also undergoing Phase-I trial in the United States (US) and Australia. The Phase 1 trial is a placebo-controlled observer blinded study of around 130 healthy adults. Besides safety and immunogenicity, the trial will also evaluate the dosage and number of vaccinations. The preliminary immunogenicity and safety results of the phase 1 clinical trial are expected to be available in July. [21] In partnership with Cadila Pharmaceuticals in India, the US-based Novavax is using the virus-like particles (VLP) platform, which has been previously used for the papilloma virus vaccine. Using this platform, the company has marketed seasonal influenza, H1N1 and rabies vaccines in India.

Oxford vaccine

Oxford University is using a chimp-adenovirus platform, infused with the genetic material of SARS-CoV-2 spike protein to develop a vaccine candidate "ChAdOx1 nCoV-19".

Data available May 13, 2020 on the preprint server *bioRxiv* from vaccine efficacy testing on the macaques at NIAID's Rocky Mountain Laboratories (RML) in Hamilton, Montana show that a single dose of ChAdOx1

nCoV-19 vaccine reduced replication of the virus in the lungs of rhesus macaques and protected them from COVID-19 pneumonia.[22] These findings are not yet peer-reviewed. The vaccine is in the Phase 1 trial stage to study safety and efficacy in healthy volunteers aged 18 to 55 years, across five trial centers in Southern England. It will be manufactured by AstraZeneca in Europe and Serum Institute in India.

INOVIO vaccine

INOVIO Pharmaceuticals has developed a DNA vaccine candidate "INO-4800", which has gone into Phase 1 open-label trial in the US in 40 healthy volunteers to investigate safety, tolerability and immunogenicity. The preliminary results are expected in June 2020. The vaccine may enter Phase 2/3 efficacy trials in the summer after regulatory approval. The two dose vaccine will be administered intradermally followed by electroporation. INO-4800 is also in phase 1 trial in South Korea.

Johnson & Johnson vaccine

The Johnson & Johnson vaccine is using Adeno-26 platform and pre-fusion spike protein, which has been successfully used by them in Ebola and RSV vaccine trials. This platform is not being used by any company in India. Adeno-26 is a rare adenovirus and is not present in the population, it does not have oncogenicity.

In India,

- **Gennova Pharmaceuticals** has developed and patented a messenger RNA vaccine that is used with a carrier lipid iron oxide (LION) and an adjuvant known as GLA-SE. Experiments in convalescent serum and mouse and monkey challenge studies have obtained very high neutralizing antibody titers.
- **Aurobindo** has bought a small startup from Pfizer in the US and is using a vesicular stomatitis virus platform for vaccine development, which is likely to be manufactured in their unit in Hyderabad.
- The other projects moving fast in India are the CSIR-funded CCMB-**Bharat Biotech** partnership using a killed-vaccine for which the strain was obtained from the National Institute of Virology, Pune.
- **Zydus-Cadila** in India is also in the fray with a measles virus platform.
- The **Serum Institute of India** has collaborated with **Codagenix**, an US biotech company to develop a live attenuated vaccine in which viral sequences have been changed by swapping its optimized codons with non-optimized ones to weaken the virus.

Johnson and Johnson (New Brunswick, NJ, USA) and Altimmune Inc. (Gaithersburg, MD, USA) are developing intranasal, recombinant adenovirus-based vaccines to stimulate the immune system.[18]

Immunoglobulins

Immunoglobulins against specific epitopes of Covid-19 antigens will come before vaccines only 1 is available from Israel and a cocktail of 3 are available in United States and are undergoing trials (These provide passive vaccination).

Coronavirus vaccine: A quick review

- **Coronaviruses:** Virus, spike protein; envelope, membrane, RNA, nucleocapsid
- **Difficulties/ limitations**: Virus causes immune inflammatory reaction, causes cytokine storm, causes thrombo-inflammatory reaction, brings down immunity (we do not know the exact method of

protection that the vaccine will afford and there is a fear of autoimmune reaction); Covid-19 also has latency like HIV (we do not know if the current vaccines under development will be able to tackle the virus within the cell); another challenge is that men and women respond differently to the infection as do children and the elderly.

- **Immunity:** Several unanswered questions - Short term or long term; multiple doses, booster doses, immunity lasting one year,
- **Herd immunity threshold:** R-1/R, protecting older people, disabled people, immunocompromised people.
- **Long development time**: Pre clinical studies 3 months, small phase I study for safety, medium size phase 2 study, formulation, dose, safety immunogenicity and reactogenicity, large phase 3 efficacy
- **People have no immunity to COVID-19.** Therefore, it is likely that two shots will be needed, 3 to 4 weeks apart. People would likely start to achieve immunity to COVID-19 one week after the first vaccination and a large boost after the second dose.
- There are 120 vaccine initiatives around the world.
- **Virus vaccines (Live attenuated or inactivated)**: At least seven teams are developing vaccines using the virus itself, in a weakened or inactivated form. Sinovac Biotech in Beijing has started to test an inactivated version of SARS-CoV-2 in humans. The inactivated version will also be developed in the Serum Institute.
- **Viral-vector vaccines** (Replicating or non-replicating): The following platforms are being used: Measles, Chimp adenovirus, Adenovirus 26, Pox virus vectors etc.
- **Nucleic-acid vaccines**: (in the form of DNA or RNA) for a coronavirus protein that prompts an immune response. The nucleic acid is inserted into human cells, which then churn out copies of the virus protein; most of these vaccines encode the spike protein of the virus.
- **Protein-based vaccines**: Many researchers want to inject coronavirus proteins directly into the body. Fragments of proteins or protein shells with adjuvants that mimic the outer coat of the coronavirus can also be used (virus subunit or virus like particle)

Conclusion

Pandemics are striking with greater frequency primarily because of deforestation, environmental degradation, rapid urbanisation, overpopulation, migration and growing animal and human conflict. There is no herd or population immunity against new pathogens such as the Sars-Cov-2 that causes the coronavirus disease (Covid-19), and till herd or population immunity crosses 70%, it will continue to spread. In these circumstances, public health interventions in combination with an effective vaccine may mitigate the situation.

The speed with which the Covid-19 pandemic is progressing leaves the world with no choice but to have an emergency-use vaccine ready within six to eight months. We cannot afford to wait for years. In the past, the Ebola vaccine has been rapidly made available. The world already has some experience with coronavirus vaccines against viruses that cause Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS). The platforms and proven adjuncts being used for vaccines development are established and have been used to deliver other vaccines. Since we are not starting from scratch, an early vaccine is possible.

There are 110-plus vaccine projects going on at the moment, with unprecedented approaches being adopted by developers. Emergency use of the vaccine is given as soon as they finish Phase-II and move to Phase-III, and mass manufacturing begins taking up the risk of failure in Phase-III. Countries in which they are situated often fund for risk reduction and provide market commitments. This has never happened before.

One of the challenges will be to determine who gets vaccinated first. There are several scenarios; one of them is to vaccinate frontline workers, doctors, health care, sanitation and delivery workers. Dentists and anesthetists are the most vulnerable population among the doctors. The second scenario is to give them to children, people with underlying comorbidities and old people with comorbidities and the last is to conduct ring vaccination around the hotspots to immunize all the contacts and the asymptomatics. The World Health Organization (WHO) will provide guidance in this matter.

Even when we have a vaccine, public health measures will be equally important, including avoiding risky behavior, keeping social distancing, working on nutrition and access to poor populations and creating a mechanism to avoid animal and human transmission. If trials fail and a vaccine is not available in time globally, the world will have to live with this disease for a very long time.

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