

Review Article

The Covid-19 Vaccine

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A B S T R A C T

To achieve the required level of herd immunity against SARS CoV-2, widespread deployment of COVID-19 vaccine is the best intervention to safeguard against the high mortality, economic disruption, and the major adjustments to our way of life.

Vaccine development and its roll out in the market typically goes through various phases viz. the exploratory phase, the preclinical study, human clinical trials, review and approval, manufacturing, and post-marketing surveillance. There are various COVID-19 vaccine platforms broadly classified as gene-based vaccines and the protein-based vaccines. As per WHO the efficacy of 50% is sufficient for a vaccine whereas an efficacy of less than 60% may fail to achieve herd immunity. Several international organizations are working in collaboration to ensure sufficient financing and fair distribution of the vaccine supply throughout the world. In India there are two vaccines which have been rolled out for public use viz. Covishield vaccine developed by Astra Zeneca in collaboration with Oxford University, UK and manufactured by the Serum Institute of India; and the Covaxin manufactured by the Bharat Biotech a local manufacturing company in collaboration with the Indian Institute of Medical Research (ICMR), India. Currently there are 242 candidate vaccines worldwide and 11 are licensed for public use in various countries. The speed with which the virus will be eliminated from the communities thus would depend not only on the presence of an efficient vaccine but also on the efforts to remove vaccine hesitancy, training of health workers and adequate vaccine coverage.

Keywords: COVID-19 Vaccine, Herd Immunity, Vaccine Hesitancy

Introduction

The COVID-19 pandemic due to the SARS COV-2 virus was first identified in Wuhan, the capital of China's Hubei province, on 31st December 2019 and has led to a global calamity affecting the global population immensely with its huge toll of morbidity, mortality and economic loss. The World Health Organization declared the outbreak as a Public Health Emergency of International Concern (PHEIC) on 30 January 2020 and a pandemic on 11 March 2020. The underprivileged countries experienced graver situation,

although it affected all the countries of the world equally. It is also speculated that the survivors of the disease would experience serious post COVID-19 complications.¹ With its high infection rate, long incubation period, along with mild-to-moderate symptoms COVID-19 has a potential to become a seasonal disease.² Herd immunity has a major role in slowing or halting the spread of the disease in communities. It has been well evidenced that the vaccines confer greater efficacy against severe disease than milder disease as seen earlier in case of pertussis, influenza, dengue, varicella,

pneumococcal bacteraemia and rotavirus.³ Thus, to achieve the required level of herd immunity against SARS CoV-2, widespread deployment of COVID-19 vaccine is the best intervention to safeguard against the high mortality, economic disruption and the major adjustments to our way of life.⁴ As per the earlier experiences with other infectious diseases it is well inferred that any vaccine against COVID-19 which is acting either against the infection, the disease or its transmission is capable of contributing to the disease control.⁵ Moreover, it has been proven that a vaccine can save a considerable number of lives, hospitalizations, and costs even if it does not prevent or halt an epidemic.⁶ An ideal vaccine candidate needs to be characterized by the robust induction of humoral and cell-mediated immunity, as well as the stimulation of the innate immune system.⁷

Vaccine Development and its Roll out in the Market

Typically, a vaccine development process includes the actual product development, its testing through clinical trials for its safety & effectiveness and roll out of the vaccine in the market. Usually this can take around 10 to 20 years of time.⁸ The vaccine for mumps is the fastest developed and approved vaccine in the history, which took approximately 5 years. Various phases in vaccine development involve exploratory phase, pre-clinical phase, clinical trial phase, review & approval and manufacturing & post-marketing surveillance.⁹

The Exploratory Phase: In this phase identification of antigens to be used in the vaccine with the help of basic laboratory research and computational modeling is done.

The Preclinical Study: The safety, efficacy and immunogenicity of the candidate vaccine on animal model is assessed in this phase. After a satisfactory level of these is observed then the trial is advanced to the human clinical trials.

Human Clinical Trials - Phase 1 (safety): Vaccine is given to a small number of healthy immune-competent people to examine immune response and safety. If this goes well then trial moves to **Phase 2 (expanded safety level)** - where the vaccine is given to hundreds of people split into different groups by demographics (example: elderly vs. young). Safety, appropriate dosage, and interval between doses are determined in this phase along with the immune response conferred by the vaccine. Then in the **Phase 3 trial** after clearance from earlier phase the vaccine in the prescribed doses is given to thousands of people to evaluate its efficacy. Vaccine Efficacy (VE) is defined as the percentage by which the rate of disease incidence is reduced in vaccinated groups as compared to placebo.

Review and Approval: A review of the results from clinical trials is done by the regulatory body of the state to decide

if the vaccine is fit to be approved. This process can take around 1 to 2 years. However, the regulatory authority may approve vaccines for emergency use in an expediting manner in a pandemic.

Manufacturing and Post-Marketing Surveillance: In this phase after the approval of the regulatory authority, the vaccine is marketed for public use and monitored for its general effectiveness, adverse effects within the population.⁹

There has been a huge change in the conventional pathway of vaccine development, and just within a year of the declaration of the COVID-19 pandemic various vaccines have been rolled out for public use. This has been possible with the extremely surprising and commendable efforts by researchers across the globe as far as the speed and the scale of vaccine development is concerned. The speedier development and production of the vaccine as well as the improvement of vaccines' potency has been possible with the remarkable scientific and technological advancements in terms of computational technologies enabling scientists with the possibility of accelerated and massive sequencing of complete genomes coupled with the recombinant DNA technology. The genome and structural information of SARS-CoV-2 was made available in record time.¹⁰ In addition to this the advances in nanotechnology helped to establish innovative vaccine technologies e.g. mRNA vaccine; and its expedited manufacturing.²

There are 3 types of antigens in the SARS-CoV-2 virus the membrane protein (M), the nucleo-protein (N) and the spike protein (S), which is localized on the virus surface and engages through the host cell angiotensin-converting enzyme 2 (ACE2) receptors. The S protein is crucial in inducing neutralizing antibodies to protect from re-infection. Studies have shown that when challenged with the virus animals developed protective humoral and cellular immune responses; and the neutralizing antibody titres were at levels like those seen in patients recovered from SARS-CoV-2 infection. The fact that viral S protein elicits an antibody response is the basis for the development of a vaccine to protect against SARS-CoV-2 infection through generating a strong neutralizing antibody response.⁷

It has been pointed out by many studies that, T cell response to the virus help them recover from the virus. T cells recognised not only spike protein but also the other proteins on SARS-CoV-2. Thus, T cells do play a role in eliminating SARS-CoV-2. Accordingly, it is important to see that a vaccine is eliciting not only a sufficient Neutralizing Antibody (NAb) response but also a good T cell response to ensure long lasting and effective immunity against SARS-CoV-2.⁹ It is imperative that, it is beneficial to include all these proteins in vaccine designs rather than only S as done in several current vaccines.¹¹

Various COVID-19 Vaccine Platforms

COVID 19 vaccine platforms can be classified as:

Gene based Vaccines: These deliver gene sequences that encode protein antigens that are produced by host cells. These include attenuated live virus vaccines, recombinant vaccine vectors, or nucleic acid vaccines.

Protein-based Vaccines: These include whole-inactivated virus, individual viral proteins or sub-domains, or viral proteins assembled as particles (virus like particles -VLP), all of which are manufactured in vitro.^{4,7}

Each method has different strengths and weaknesses.

The main method of vaccination for decades has been to use the live attenuated or inactivated whole virions as it often produces long-lasting immunity. The new and promising vaccine approaches are Nucleic acid-based vaccines e.g. the mRNA vaccines encoding the SARS-CoV-2 spike protein, or DNA vaccines also expressing the S protein fall under this category and are being pursued in the context of the COVID-19 pandemic although no such vaccines have developed on these platforms earlier.¹² A particular advantage of these vaccines is that in addition to antibody and CD4+ T cell responses, these can elicit CD8+ cytotoxic T cell responses, which plays a key role for virus eradication. The additional advantage of these platforms is the speed at which a candidate vaccine can be created allowing for the vaccine development process to be fast tracked in the event of a pandemic. Emerging nanotechnologies such as mRNA vaccines delivered by lipid nano particles and viral vector vaccines have already reached Phase II and III clinical trials.² These are also able to generate a robust immune response. The disadvantage of DNA-based vaccines is that it requires an electroporation or an injector delivery device for each dose creating an additional logistic challenge in order to ensure availability of these in sufficient number.¹²

The recombinant non-replicating viral vector (adenovirus, poxvirus, measles, para-influenza, etc.) vaccines have shown to be safe and effective immunologically as seen earlier with an Ebola vaccine candidate.⁷ The observed disadvantage for the adenovirus based vaccines, is the pre-existing immunity to it which can attack the vector, leading to a weaker-than-expected antibody response.⁹ Administering the vaccines as nasal sprays or pills may help in circumventing preexisting immunity to adenovirus in the bloodstream as per some experts.¹²

Inactivated virus technology-based vaccines usually do not generate as strong of an immune response unless used alongside, as an example, an aluminum adjuvant. One of the concerns for this type of vaccine is the phenomenon of ADE (antibody dependent enhancement) of COVID-19 disease. ADE as experienced with dengue, measles, influenza, and

respiratory syncytial virus vaccines occurs when antibodies bind to the virus and the resulting antibody-virus complex facilitates viral entry by host macrophages instead of neutralizing the virus, which might also trigger the cytokine storm in case the person is infected by the virus in future, after the vaccination.

Another matter of concern with these vaccines is the risk as they can cause VAERD (Vaccine Associated Enhanced Respiratory Disease) as has been seen in the past with measles and Respiratory Syncytial Virus (RSV) in humans and with SARS-CoV in animal models. VAERD is due to the presence of increased number of antibodies that do not neutralize the virus when a high viral load is present. This consequently can lead to severe respiratory disease.^{9,13}

The virus like particles, subunits, provide newer universal vaccine platforms. Evidences show that these agents infect the host cells or induce antigenic proteins to generate both T cell immune responses and antibodies.¹³

There are some peculiar COVID-19 immunity related findings observed in the population. As observed in a cohort study few study participants had circulating immunoglobulin G (IgG) antibodies that could cross-react with the S2 subunit of the SARS-CoV-2 spike protein. These antibodies were present in a higher proportion of SARS-CoV-2 - uninfected children and adolescents compared with other age groups.⁷

There is a startling observation that countries with universal BCG vaccinations, such as Japan and South Korea, have infection and disease rates of COVID-19 as much as 100-fold lower than countries without universal vaccination policies, such as Italy, the Netherlands, and the United States.¹²

Recently, a mutational change in the original Wuhan strain is found primarily in Europe and has been shown to have increased transmissibility and a higher viral load. As the mutation is not located in the RBD (receptor binding domain) of the spike S protein but rather in between the individual spike protomers to provide stability through hydrogen bonding it may have an impact on the infectivity of the virus; and should not drastically affect the effectiveness of the vaccines targeted towards S protein.⁹

The priority for COVID-19 vaccination would logically be for those at highest risk of infection, such as healthcare workers, and those at highest risk of severe disease, such as older adults. Vaccination of children to induce herd immunity has proven effective than vaccination of elderly people in preventing the spread of many infectious diseases such as influenza, pneumococcal disease, rotavirus and many others. It is important to accrue substantial safety data among adults before initiating pediatrics studies.¹⁴

International co-operation

Several international organizations are working in

collaboration to ensure sufficient financing and fair distribution of the vaccine supply throughout the world. GAVI, the Vaccine Alliance is a global public-private partnership organization is committed to ensure access to immunization for individuals from resource poor countries. It is also part of the recent Global Vaccine Summit, which allocated funding for COVID-19 vaccine development, health systems and towards adequate supply for developing countries. In addition, Bill and Melinda Gates Foundation (BMGF) is also supporting for the development of vaccines and the health care systems of resource poor countries. Coalition for Epidemic Preparedness Innovations (CEPI) is a foundation that is involved in financing vaccine development and directing efforts for equal access of COVID-19 vaccines for countries through COVID-19 Vaccine Global Access Facility (COVAX) initiated by the foundation. Similarly, the WHO is very much involved in various aspects of COVID-19 pandemic including ensuring vital equipment e.g. Personal Protective Equipment (PPE), research for COVID-19 vaccines and providing accurate information.⁷ In India, the Indian Council of Medical Research (ICMR) is the main advisory institution for the Government of India on various aspects of COVID-19 pandemic guidelines including development and roll out of the vaccine for public use in the country.

Safety & Efficacy of the Vaccines

Evaluation of humoral, cellular, and functional immune responses is needed to validate a candidate vaccine.¹²

In the efficacy trials if the infection is kept as a secondary endpoint the indirect evidence of protection from a vaccine can be deduced. To distinguish between an infection induced antibody response from a vaccine-induced antibody response a specialized assay is needed to be performed.⁷ The true efficacy could be determined via challenge infections; however, the ethics of this process have been questioned in the absence of a cure.¹²

Alternatively, the endpoint of COVID-19 symptomatic disease has been considered as a primary endpoint and has been selected as such for many phase 3 trials of COVID-19 vaccine candidates.³ Most quantitative RT-PCR assays do not distinguish between RNA from live, transmissible virus and non-infectious RNA persisting post-infection. Hence, both symptoms and PCR positivity are recommended as a primary outcome by the Coalition for Epidemic Preparedness Innovations.⁵ The most important efficacy endpoint is the ability of a vaccine to protect against severe disease and mortality, as the greatest burden would be on health-care systems with high rate of hospital and critical-care admissions.⁶

Various other factors may determine vaccine's efficacy like genetics, age, obesity, health status, immune competence, environmental factors and additionally, viral mutations

which may affect the susceptibility to infection, severity of the disease, and response to a vaccine. As per WHO the efficacy of 50% is sufficient for a vaccine whereas an efficacy of less than 60% may fail to achieve herd immunity.⁷ Bartsch SM, et al. (2020) found that the vaccine has to have an efficacy of at least 70% with a coverage of at least 80% to halt an epidemic without any other measures (e.g., use of masks, social distancing).⁶ Long-term safety, the duration of vaccine protection, the vaccine's level of protection against severe infection and death and the potential for the virus to evolve to escape vaccine induced immunity are some of the other major concerns about the rapidly developed COVID-19 vaccines.¹⁵ Even if COVID-19 vaccines have acceptable effectiveness in reducing morbidity and mortality in high-risk groups, they would have an important role, irrespective of the impact on transmission and population immunity.^{15,16} As far as the immunological memory to the COVID infection is concerned the spike IgG titres show a modest decline in 6 to 8 months. Whereas the SARS-CoV-2-specific CD4+ T cells and CD8+ T cells decline with a half-life of 3-5 months.⁷

It is recommended that follow-up of study participants should continue ideally for at least 1-2 years, to assess the duration of protection and potential for Vaccine-Associated Enhanced Respiratory Disease (VAERD) as the immune response to the vaccine wanes.^{15,17} Children should be included in the clinical trials in parallel to ongoing adult phase 3 clinical trials in a manner that is careful, methodical and transparent to establish safety and immunogenicity results.¹⁸

Vaccines in India

A country wide roll out of the COVID-19 vaccine has been initiated on 16th January 2021 in India. There are two vaccines available viz. Covishield and Covaxin. These vaccines have been initiated for the public use after the Emergency Use Authorization (EUA) from the Drugs Controller General of India (DCGI). The Government of India plans to vaccinate 300 million Indians by August 2021. Initially vaccine is to be given to the people more than 18 years of age. After ensuring a favourable post marketing surveillance result of the vaccine it will then be extended to the paediatric age group and pregnant & lactating women.

Covishield vaccine - It is developed by Astra Zeneca in collaboration with Oxford University, UK and manufactured by the Serum Institute of India. It is a recombinant technology based non replicating viral vector AZD1222 or ChAdOx1 vaccine that use an adenovirus from chimpanzees to deliver the gene for the spike protein of SARS-CoV-2 to trigger a robust immune response.⁷ The use of adenovirus from the non-human host (Chimpanzee) is to effectively address the concern about pre-existing immunity and thereby averting the lowering of immune response generated to

the vaccine.⁹ As per an interim analysis blending two trials of the vaccine in which people received different doses, the efficacy ranges from 62% to 90%. It is cheaper (about Rs. 250 per dose) as compared to other vaccines, and only needs refrigeration temperatures for storage. The vaccine is given in the dose of 0.5 ml, intramuscular in two doses 4 weeks apart. As per the recent phase III clinical trial report, the time duration of the booster if kept more than 8 weeks then the antibody production was found to be enhanced as compared to the 4 week regime.^{7,19}

Covaxin- It is manufactured by the Bharat Biotech a local manufacturing company in collaboration with the Indian Institute of Medical Research (ICMR), India. It is an inactivated whole-virion corona virus vaccine. It is expected to be 60% efficacious, the vaccine can be stored at temperatures between 2°C and 8°C, economical at a projected cost (About Rs. 500-600) per dose. The vaccine is given in the dose of 0.5 ml, intramuscular in two doses 4 weeks apart. The vaccine has been allowed for public use by the DCGI just after the Phase II trials in the public interest under EUA license.⁷

The adverse events to these vaccines have been notified as minor side effects such as vaccine site tenderness and pain, headache, myalgia, nausea, fatigue, etc.²⁰

ZyCov-Di vaccine- It is the next awaited vaccine which is being developed by Ahmedabad-based Zydus-Cadila and its acquired facility - Etna Biotech in Italy. This is an indigenous DNA based vaccine. This vaccine has entered phase III trials and the company is expecting to launch it by March 2021. ZyCov-D vaccine is proposed to be advantageous as compared to other nucleic acid based vaccines that use mRNA to induce an immune response e.g. CureVac, Moderna and BioNTech, and Pfizer since all of these typically need to be transported along cold chains at -70 degree Celsius. This vaccine can be stored at temperatures between two degrees Celsius and eight degrees Celsius. The vaccine dose is 0.1 ml to be given intra-dermal over the arm on days 0, 28 and 56.¹

The other candidates which are in different stages of trials in India include:

- The Sputnik V vaccine -an adenovirus vector-based vaccine developed by Dr Reddy's Lab and Gamaleya National Centre in Russia
- A subunit vaccine is being developed by Hyderabad-based Biological Ein collaboration with US-based Dynavax and Baylor College of Medicine
- HGCO19- mRNA vaccine made by Pune-based Genova in collaboration with US-based HDT Biotech Corporation
- BBV154 - A novel adenovirus vectored, intranasal vaccine for COVID-19 by Bharat BioTech
- NVX-CoV2373 recombinant nano-particle technology-

based vaccine is being developed by Serum Institute of India, Pune with Novavax, US.²¹

The current situation of COVID vaccination by states in India can be accessed at the Harvard University developed -"LIVE COVID-19 Vaccine Rollout Dashboard".²²

Various other Candidate Vaccines

Currently there are 242 candidate vaccines worldwide out of which 66 are in phase 3 clinical trial and 11 are licensed for public use in various countries.^{23,24}

The vaccines that are considered to be front-runners in the last phase of clinical trials include the following:

Sino Biotech's CoronaVac, which is an inactivated virus vaccine; Moderna's mRNA1273, which is an mRNA candidate; Pfizer's BNT162b2, which is an mRNA-based vaccine; Johnson & Johnson's JNJ-78436735, which is an adenovirus-based vaccine; the University of Oxford's candidate ChAdOx1 nCoV-19, which is an adenovirus-based vaccine; Sinovac's SARS-CoV-2 vaccine, which is an inactivated candidate; CanSino's Ad5-nCoV, which is a viral vector vaccine; Russian Gamaleya Institute's Sputnik V, which is an adenovirus-based vaccine; and Inovio's INO4800, which is a DNA plasmid vaccine.

Vaccine Hesitancy

A major obstacle to vaccination programs is the "vaccine hesitancy" which in turn dampens the achievable herd immunity required to safe guard the vulnerable populations.²⁵

Wide variation among the population of various countries regarding willingness to accept COVID 19 vaccine has been observed. This may potentially delay global control of the pandemic. One of the poll showed that only 49% of Americans were willing to take a COVID-19 vaccine when one becomes available.²⁶

Vaccine opponents (anti-vaxxers) and their false theories and influence, paved the way for the worst measles outbreak in the United States in 2019; and experts fear similar consequences for COVID-19.⁹ The most unfavourable part played by some politicians to question the vaccine's safety have been incompatible with science and risk further eroding vaccine confidence among the general public.¹⁶

Educational campaigns and the endorsement of community leaders, and healthcare professionals may address the issue to build up confidence towards vaccination before the mass campaigns are initiated. Timely communication efforts; well informed health care workers and rendering the vaccine soon after favourable safety and efficacy results are proven, are important measures for rapid vaccine uptake by the masses.²⁵

The way forward

It would be highly unethical to achieve protective level of the herd immunity against COVID-19 through natural infections. Thus, vaccine is the most important preventive intervention to achieve the same. But, it is again not the immunity of the herd but community action and public health measures to protect vulnerable people along with the development of efficient medical systems is necessary.²⁷ Furthermore, only having the effective vaccine will not be the end point of this emergency but when an adequate vaccination policy to reach out to people is in place in order to have fairly high coverage. Moreover, it will be important to manage the expectations of the public who may believe that no more social distancing, hand hygiene and masking will be needed as soon as a vaccine becomes available.^{6,28}

As the vaccine has been rolled out for the individuals more than 18 years, initially for the high risk groups and then for the whole population, it will also be important that robust, ongoing pharmaco-vigilance is in place post licensure to assess the long term safety. Additionally, it is necessary to include paediatric age group along with the adults in the post market surveillance for assessment of safety and efficacy of the given vaccine.^{5,28} It will be a continuous challenge to intervene for building confidence and reducing vaccine hesitancy in different contexts that would require particular awareness of and attention to existing public perceptions and felt needs. Engaging formal and informal opinion leaders within communities would fetch promising results.²⁶

The speed with which the virus will be eliminated from the communities thus would depend not only on the presence of an efficient vaccine but also on the efforts to remove vaccine hesitancy, training of health workers and vaccine coverage.

Conflicts of Interest: None

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