

# COVID-19 Vaccination Strategies and Challenges - A Literature Review

Dr Vidit Majmudar<sup>1</sup>, Dr Purva Shah<sup>2</sup>

<sup>1</sup>Intern doctor, BJ Medical College and Civil Hospital Ahmedabad, Gujarat, India

<sup>2</sup>Intern doctor, Baroda Medical College and SSG Hospital, Vadodara, India

**Abstract:** *The novel coronavirus disease, now popularly known as COVID-19, was first described in China in 2019. COVID-19 is caused by the SARS-CoV-2 which shares multiple genetic similarities with Middle East respiratory syndrome virus (MERS-CoV) and Severe Acute Respiratory Syndrome virus (SARS-CoV). The World Health Organization (WHO) declared COVID-19 a pandemic in March, 2020 due to rapid community transmission occurring worldwide. The emerging public health concerns pose challenges to health care systems world-wide and have left the medical community in a race against time for providing answers to this viral zoonotic disease now showing human to human transmission. Antiviral and immunomodulatory drugs have not yet given a clear edge over this fatal disease hence, focusing all the burden and hope on a potential vaccine that might help us overcome this pandemic. This literature review focuses on describing various approaches being used by pharmaceutical companies for developing a potential lifesaving vaccine. Apart from that this article focuses on the mechanism of various vaccine candidates while also providing a basic outline on the Coronavirus family. Finally, the review also talks about unrealised challenges and ethical issues that are or will be faced in the process of developing this potential vaccine.*

**Keywords:** Coronavirus, Vaccination, COVID-19, SARS-CoV-2

## 1. Introduction and Background

### *History of the disease*

Viral diseases have always been an ongoing health care concern in this world. A lower respiratory tract infection of unknown aetiology was reported in Wuhan, the largest area of Hubei province in China. The Chinese Centre of Disease Control investigated to find the pathogen responsible for this pneumonia of unknown origin. Further investigations resulted in finding this pathogen which the world now knows as SARS-COV-2. The first official reported case in WHO traces back to 31<sup>st</sup> December but literature shows that cases were reported in the beginning of December.<sup>68(1)</sup> The new virus was found to be highly contagious and similar to the SARS and the MERS. The International Committee of Taxonomy of Viruses named this virus as SARS-CoV-2. On March 11, 2020, cases of COVID-19 increased up to 13 times outside China following which it became a major public health concern and WHO declared this disease as a pandemic.<sup>1, 2(2,3)</sup>

### *Transmission:*

First few COVID-19 cases emerged from the sea food market of Wuhan in China showing that SARS-COV-2 is transmitted from animals to humans. The rapidly increasing number of cases worldwide showed that human to human transmission is also possible via aerosols or by direct contact. Life cycle of this disease is believed to have started from Bats as the main primary reservoir, pangolins are suspected to be intermediary hosts followed by animal to human transmission which ultimately lead to community human to human transmission.<sup>72,73(4,5)</sup> According to studies, similar to other respiratory viral pathogens like influenza virus or rhinovirus, corona virus can be transmitted from asymptomatic individuals.

WHO and Centre of Disease Control (CDC) have released guidelines indicating that adequate social distancing and

avoiding close contact is a key way to avoid getting infected by this virus.

Corona virus can survive up to 4 hours on copper, 24 hours on cardboard and up to 72 hours on plastic and stainless steel.<sup>2(3)</sup>

The most important strategy for the general population is to frequently wash their hands and use a portable hand sanitiser in addition to avoiding touching their face and mouth after coming in contact with a possibly contaminated surface. Healthcare workers caring for infected individuals should utilise contact and airborne precautions and utilise personal protective equipment (PPE) including N95 masks, eye protection, gowns, and gloves to prevent transmission of the pathogen.<sup>74(6)</sup>

### *Pathophysiology*

After entering the upper respiratory tract of humans, SARS-CoV-2 gets attached to epithelial cells in the respiratory tract as viral spike proteins have a special affinity for these cells. Further molecular studies have shown that these spike proteins on the surface of coronavirus have a high affinity for Angiotensin Converting Enzyme receptor-2 (ACE-R2). ACE-R2 protein has been located in arterial and venous endothelial cells and arterial smooth muscle cells in various human organs like oral and nasal mucosa, nasopharynx, lungs, gastrointestinal tract, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain. However, the most significant finding was the expression of ACE-R2 protein on the surface of pulmonary alveolar epithelial cells and enterocytes of small intestine.<sup>3-6</sup>

ACE-2 receptors have been a subject of intense research in order to find ways to prevent the entry of coronavirus. The reason for clinical manifestations like fever, cough with or without expectoration, dyspnea, diarrhoea and so on are believed to be due to cytokines and chemokines. COVID-19

Volume 9 Issue 11, November 2020

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patients reported high blood levels of certain cytokines and chemokines including interleukins (IL1- $\beta$ , IL1RA, IL7, IL8, IL9, IL10), basic fibroblast growth factor (FGF2), colony stimulating factors (GCSF, GMCSF), interferons (IFN $\gamma$ ), platelet derived growth factor-beta (PDGFB), tissue necrosis factor-alpha (TNF $\alpha$ ), and vascular endothelial growth factor (VEGFA).<sup>7,8,75</sup> Laboratory findings that are commonly noticed are high lymphocyte count, increased D-dimer levels, increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

## 2. Review and Discussion

### *Virus structure and function*

The name corona is derived from the Latin term “*Coronam*” which means crown-like. We can visualise this virus under electron microscope where spike proteins around the envelope give it its crown-like structure. These viruses belong to a family of *Coronaviridae*, subfamily *Orthocoronaviridae* and are divided into 4 genera -

- 1) *Alphacoronavirus*
- 2) *Betacoronavirus*
- 3) *Deltacoronavirus*
- 4) *Gammacoronavirus*.

Molecular genetic studies show that bats and rodents are reservoirs of alpha and beta coronaviruses while avian species are suspected to be the source for the other two genera.

Coronaviruses or CoVs are single stranded positive sense RNA viruses. They are enveloped viruses consisting of spike and envelope proteins. SARS-CoV-2 belongs to *Betacoronavirus* genus.<sup>69,70</sup> It is round or elliptical in shape and is of approximately 60-140 nm in size. Since it is an enveloped virus consisting of glycoproteins, it can be killed by lipid solvents including ether (75%), ethanol, chlorine-containing disinfectants, peroxyacetic acid, and chloroform but not by chlorhexidine. The efficacy of heat or ultraviolet rays in killing this virus is debatable.<sup>71</sup>

### *Vaccine preparation and its mechanism of action*

Antigen specific response mediated by antibody production by plasma cells and cell mediated immune response involving T cells form the cornerstone to development of efficacious and long lasting immune response mediated by the approved vaccines so far.<sup>8,9</sup> The use of next-generation sequencing and reverse genetics may lead to promising outcomes. Ideally, an effective vaccine is one that induces and maintains significant concentrations of virus-specific antibodies in serum and at local points of viral entry (e.g., mucosal surfaces), as well as development of virus-specific T-cell immunity. A strong neutralising antibody (NAb) response and a specific mucosal antibody response are desirable.<sup>10</sup>

Four approaches for vaccine preparation currently in use are as follows: (Figure 1)

- 1) Whole virus itself : May be inactivated or weakened
- 2) Viral vector: could be replicating or non-replicating
- 3) Nucleic acid: using DNA or RNA
- 4) Protein based: protein subunit or virus-like particle

1) The whole virus vaccine approach:

- a) Weakened virus is created by conventionally passing it through several cultures and subcultures in human and animal cells until it finally mutates itself to a nonvirulent form. Codagenix is working with Serum institute of India using this method to prepare the vaccine.<sup>15</sup>
- b) Inactivated virus approach uses chemicals like formaldehyde or heat to inactivate the virus. The Chinese giant Sinovac Biotech has used this method and claims to show promising antibody titres in its human trials.

2) The viral vector vaccine approach:

Recombinant viral vectors duplicate the cellular response involving uptake of a pathogenic molecule by host cells which in-turn is processed by class-I major histocompatibility complex (MHC) molecule inside cells. Then, it is presented on the cell surface for cluster of differentiation (CD8) cells to recognise and produce an innate immune response which is later followed by a cell mediated immune response to the foreign molecule.<sup>9</sup> Adenoviral vectors are capable of inducing a potent cell mediated as well as a humoral response in the body. *Replication deficient Ad-5* is the most commonly used viral serotype of adenovirus in which gene domains E1 and E3 responsible for replication are deleted and a foreign gene is inserted into the empty space that ensues.<sup>10</sup> The ability of adenovirus to target epithelial cells and produce strong interferon-gamma (IFN- $\gamma$ ) secretion along with cell mediated response and humoral response is one of the main reasons as to why these strains are used for development of vaccines.<sup>11,12</sup> However extensive use of Ad-5 viral vector and its repeated administration in humans showed development of immune response to the vector itself leading to ineffective therapeutic levels of the targeted gene.<sup>13</sup>

- a) Replicating viral vectors: Weakened measles and vesicular stomatitis virus are examples of viral vectors that have replicating capacity which can be used to introduce them into host cells. However, there are certain pitfalls to this preparation like prior immunity to the vector can prevent an immunogenic response in our body and rarely vesicular stomatitis virus could be neurovirulent.
- b) Non replicating viral vectors: Adenoviruses are heavily exploited in this field due to certain desirable characteristics like ability to infect both replicating and non-replicating cells, genomic stability, capacity to produce high titres in-vitro and lack of integration into the host genome. Jenner institute in Oxford University along with Astrazeneca Biopharmaceutical Company have used recombinant adenovirus infected chimpanzees for vaccine preparation. Certain pitfalls in this preparation include the requirement of multiple booster shots and prior immunity to the strain. Adenovirus vector technology like that used for Ebola, HIV, Zika induced a strong neutralizing antibody response as well as N-specific T-cell response in vaccinated rhesus macaques; however, subsequent virus challenge was not performed.<sup>15</sup> Johnson and Johnson are using this method for development of vaccines. CanSino Biological Inc. has used adenovirus type 5 and is among the frontrunners in producing the vaccine and is currently in phase-II trials

## 3) The nucleic acid vaccine approach:

a) DNA Vaccine: DNA vaccine candidates also elicit both CD4 and CD8 responses and they function by entering the cells which are recognised by receptors of the innate immune system. Stimulator of Interferon Genes (STING)/TANK-binding kinase 1 (TBK1)/ Interferon Regulatory Factors (IRF3) pathways and the Absent In Melanoma 2 (AIM2) inflammasome pathway along with other molecules are hypothesised to play a role in the mode of response of DNA vaccine.<sup>14,15</sup> Spike protein gene is integrated into a DNA vector following which it is inserted into human cells by creating pores in the cell membrane by the process of electroporation. This leads to the production of only immunogenic viral spike proteins that are released into the circulation. INO-4800 is currently a DNA based vaccine that is being developed by Inovio against SARS-CoV2.

b) RNA Vaccine: RNA based vaccines have a peculiar mechanism of producing a response in mammalian cells. Upon entry inside the cells they are recognised by two pathways i.e. endosomal and cytoplasmic. Pattern recognition receptors, also known as Toll-like Receptors (TLR) like TLR3, TLR7 and TLR8 are present on endosomes while retinoic acid-Inducible Gene I (RIG1), Melanoma Differentiation-Associated protein 5 (MDA-5), and Protein Kinase R (PKR) are located in the cytoplasm to sense foreign RNA. The interaction between receptors and RNA molecules is responsible for producing a strong response of cytokines and chemokines involving IL-12 and TNF of the innate immune system which ultimately leads to an effective immune response against the foreign molecule. Intradermal injections of the mRNA vaccines produce high levels of Chemokines - CXCL9, CXCL10, CXCL11 that recruit dendritic cells and macrophages to the site of injection culminating in a chain of reactions that provides a long lasting immunity.<sup>16,17</sup> The spike protein sequence material in RNA is enclosed into a lipid coat which facilitates its entry into human host cells. This leads to the translation of pathogenic proteins resulting in their recognition and subsequent production of an immunogenic response. Moderna and Stermima therapeutics of Shanghai East Hospital, have used mRNA coding for spike (S) glycoprotein covered by a lipid nanoparticles.<sup>11,12</sup> Moderna has successfully completed their PHASE-II trials and will move on to PHASE-III in July.

## 4) The protein based vaccine approach:

a) Protein subunit vaccine: Subunit vaccines consisting of soluble baculovirus-expressed N-terminal fragments of S protein were highly effective in protection against subsequent intranasal challenge with SARS-CoV.<sup>13</sup> These vaccines mainly utilise the Receptor Binding Domain (RBD) of S protein which has multiple conformational epitopes and is also responsible for providing a strong CD8 T-cell response.<sup>18-20</sup> The promising results of production of humoral and cell mediated response to these domains in SARS-CoV have led to a potential belief that the same could be true for SARS-CoV2 due to the similarity in epitopes of the Receptor Binding Domains (RBD) of S protein present in both viruses. S protein has been the epicentre around

which immune responses develop in the human body. Due to its structure and role in viral infectivity, it has emerged as a key molecule for vaccine design.<sup>21</sup> Apart from the potential use of spike protein as a target to develop antibodies, discussions continue whether to use the whole protein sequence as a target or just the receptor-binding domain.<sup>14</sup> Antigen targets in S protein include the full S protein, S1 subunit, S2 subunit and Receptor Binding Domain unit.<sup>21,22</sup> Whole S protein and S1 subunits have shown to develop massive immunological response in animal bodies by producing high levels of neutralizing antibodies. However, the non-neutralizing epitopes in these proteins are responsible for producing inflammatory response and Antibody Dependent Enhancement (ADE).<sup>23</sup> ADE is a process in which enhanced infection develops in the body following development of non-neutralizing antibodies.<sup>24-26</sup> An approach to bypass the ADE response is to develop the immune response that targets only the beneficial epitopes thereby mitigating unwanted responses.<sup>27</sup> RBD is a hotspot for vaccine development due to development of only neutralizing antibodies and no epitopes responsible for development of non-neutralizing antibodies. However, it is worth noting that multiple doses and adjuvants are required to maintain the desired level of antibody concentration due to its poor immunogenicity.<sup>28-30</sup> Multiple pharmaceutical giants are in the race of preparation of this vaccine that uses viral spike protein or its receptor binding domain. The downfall of this approach is that it will require multiple shots and booster doses for development of immunogenic response.

b) Virus-like Particles: An interesting approach that is used by a few companies is the use of a particle that mimics the structure of coronavirus but does not contain any genetic material that is originally present in the infective virus. These particles are difficult to manufacture and the process is very costly.<sup>45,46</sup> Geovax and BravoVax are developing modified vaccine using virus-like particles<sup>16</sup>

*Challenges faced*

Development of an RNA vaccine has always been tedious and without much success.<sup>47</sup> Secondly, the experience with the trials of SARS and MERS was not exactly promising. The immune system that was triggered by these vaccines leads to an exaggerated response leading to further lung parenchymal damage.<sup>48</sup> Animal models needed to replicate human immune responses to vaccines are difficult to find as their pathophysiology differs from the latter. Longevity of immunity provided by vaccines has not been specified. Also, whether one dose would be enough to confer immunity remains a grey area. The development of inactivated vaccines is a potential health care challenge as it requires high viral titres which in turn, necessitates biosafety-3 laboratory features.<sup>49</sup> Live attenuated vaccines targeting respiratory viruses like influenza and adenovirus resulted in the shedding of infectious viral particles in feces hence, raising concerns that a live attenuated SARS-CoV vaccine strain has the potential to spread to unvaccinated individuals.<sup>50</sup> Another concern is the risk of recombination of a live attenuated vaccine virus with wild-type CoV. The endpoints of vaccine effectiveness are considered to be based on two criteria mainly. The first one includes



laboratory seroconversion and the second one includes decrease in symptomatic cases worldwide and amelioration of severe cases that require reduction of hospitalization. Hence, reaching these primary endpoints depends on a lot of factors including epidemiologic and genetic factors.<sup>76</sup> COVID-19 vaccine will face 3 major challenges worldwide according to Coalition of Epidemic Preparedness Innovations (CEPI) - The speed of vaccine development, manufacture and deployment in a large scale, and global access.<sup>77</sup> Challenge studies for vaccine preparation were earlier used for smallpox, malaria, yellow fever and more recently, for typhoid, cholera, and influenza. Intentionally introducing a new pathogen about which we know very little of into a healthy adult comes with a vast array of ethical issues. Only after carefully weighing the pros and cons, can we commence these ethically controversial yet much needed challenge studies.<sup>51</sup> (Table 1)

### 3. Conclusion

The COVID-19 virus has affected almost every country and is here to stay for a long time. According to statements made by WHO, the worst is yet to come.<sup>52,53</sup> This literature review focuses on the mechanisms and approaches of vaccine development. It also brushes on the ethical issues and pitfalls that we might face in the race of developing a successful vaccine. Pharmaceutical companies are in a race against time for developing an effective vaccine. The primary focus of these companies has been on S protein and its RBD that have shown effective immune responses in clinical trials.<sup>54,55</sup> Also, nucleic acid based vaccines are in the race of developing an efficacious vaccine. These DNA and RNA based vaccines have a unique way of entering mammalian cells and have an equally complex immunologic mechanism of producing the required immunologic response.<sup>56,57</sup> The viral vector based approach has been on the rise since the time of HIV vaccination programs. A similar approach has been adopted by Jenner institute of Oxford university which is using chimpanzee-adenoviral vector and is in Phase-III clinical trials. However, the Chinese company, SINOVA Biotech and MODERNA are not far behind and have shown equally promising results. The race to developing this vaccine has almost reached its final stage. Which company develops the first vaccine against this virus does not really matter as there are several issues that will be faced even after it enters the markets worldwide. The production of a billion vaccines, cost of vaccine production, duration of an antibody response, mutagenic potential of the virus and adverse effects that may develop following vaccination are all a matter of concern which will become a primary issue to be dealt with in the future. Co-ordination and sharing of information along with adequate communication between countries and WHO will be a key determinant of the rapidity with which this giant coronavirus will be slayed.<sup>58</sup>

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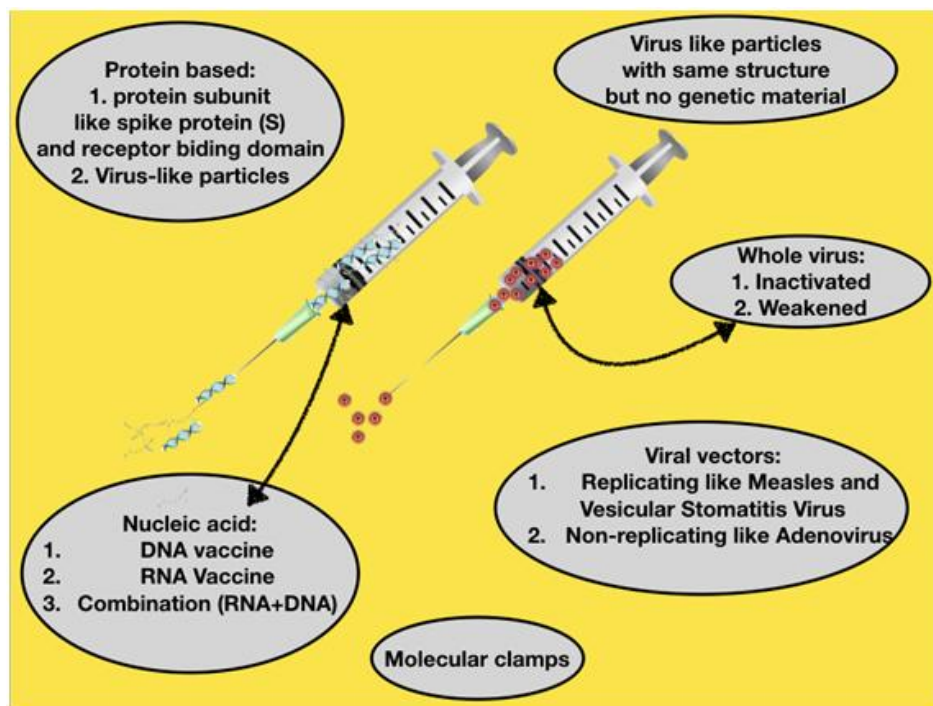
**Author Profile**

**Dr. Vidit Majmundar** is an intern doctor at BJ Medical College, Ahmedabad, India having passed medical school among the top 3 in his class and also an intern at StatPearlsWebsite.

**Dr. Purva Shah** is an intern doctor at Baroda Medical College and SSG Hospital, Vadodara, India having passed medical school being one of the toppers of her class and also a recipient of Indian Council of Medical Research- Short Term Studentship (ICMR-STs), 2019-20.

**Table 1**

Population	Advantage	Risk	Risk management strategies
Participants	Immunity induced from experimental vaccine or virus injected	Serious illness or even death due to virus introduction	Selection of low-risk participants
		Adverse Events Following Immunisation (AEFI)	Careful titration of viral dose to prevent severe illness
		Mental health issues due to long term isolation	reducing the number of participants to as low as reasonably acceptable
			compensation for study-related harm
Society	Early vaccine availability will have a positive impact on number of lives saved	Erosion of trust of the people challenge studies may pose a problem for vaccine development for future illnesses	psychological assessment form time to time
	Global economy will be revived faster		Educating the people about research design
	livelihood of people will return to normal		Engaging them in research activitie



**Figure 1**