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Review Article

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Review on Covid-19 vaccine and its immunological aspects

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Abstract

A virus has brought dangerous life-threatening situation hardly when the world deal with one strain of virus and other emerges. A similar situation happened when a new strain of SARS-COV-2 emerges which has not been previously known. SARS-COV-2 firstly emerges in china and was rapidly transmitted worldwide. Its outbreak and rapid transmission of COVID-19 have endangered global health and economy which also affect Ethiopia. This effect has called for an extensive mobilization of studies on COVID 19. Thus, the present review gives an update on COVID 19 vaccine and its immunological aspect. SARS-COV-2 belongs to the family of enveloped, single-strand RNA viruses known as Beta coronavirus in Coronaviridae, it has several non-structural proteins and four structural proteins. The virus uses its spike proteins for entering the host by interacting with a specific receptor called angiotensin-converting enzyme-2(ACE2). Currently, there is no approved medication for this virusalthough many scientists have published the treatment options against COVID-19. The devastating SARS-COV-2 infection rapid transmission across the world ignited extensive effort toward the development of COVID-19 vaccine that can be used globally for ending the pandemic and to meet the urgent need for the entire vaccine development process compressed amazingly to 15- 18 months. Various platforms for vaccine development are available including live attenuated virus, viral vectors, inactivated virus, subunit vaccines, recombinant DNA, and protein vaccines. Based upon these platforms potential COVID-19 vaccine candidates have been identified. They are designed using antigens from target pathogen that are generated by vaccine recipient and infection signal that alert and activates host immune system. As the result of vaccine development taken time; novel coronavirus has crippled the world in terms of economy, human health, and life. Even though currently effective commercial vaccines against COVID-19 is produced, further work should be done on vaccine production and distribution to vaccinate all people across the world or globe and since it is severe in infected people, it is recommended to do further on different measures which may be useful for future remedies.

Keywords: COVID-19, Ethiopia, Immunological aspects, SARS COV 2 and Vaccines.

Introduction

By the end of year 2019, Wuhan city of China had witnessed several cases of pneumonia like conditions, which later on found to be caused by 2019-novel coronavirus (2019-nCoV)(Lam *et al.*, 2020).World Health Organization(WHO) had declared the disease as a global health emergency on January 30(Lipsitch, 2020; WHO, 2020). The novel coronavirus was termed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the international virus classification commission on February 11, 2020 and the disease named COVID-19(CoronaVirus Disease-19) by WHO on the same day(Rawat *et al.*, 2020).As Xiaojun Li *et al.*(2020), wrote in March 2020, WHO announced that the infection was a pandemic.

Coronaviruses (CoVs) are important pathogens for human and vertebratesin which they affect respiratory, gastrointestinal, hepatic, and central nervous system of human, livestock, birds, bat, mouse, and many other wild animals (ChenandGuo, 2016).SARS-CoV-2 belongs to the family of enveloped, single-strand positive sense RNA viruses known as Beta coronavirus in Coronaviridae which have four structural proteins encoded by the genome: nucleocapsid (N), membrane (M), spike (S), and envelope (E)(Shereen *et al.*, 2020). The spike protein was the primary target antigen in the SARS-CoV-2 vaccine(Watanabe *et al.*, 2020).

The newly emerging SARS-CoV-2 has been circulating the world with over 33 million cases and 1,000,000 deaths reported worldwide within the span of nine months despite unprecedented control measures(Coudeville *et al.*, 2020).Furthermore, over 327,066 cases and 5,035 fatalities have been documented in Ethiopia, and only 0.5% of the population has been fully immunized through the middle of September 2021(MoH Ethiopia, 2021).

Currently, no potential drugs are available to treat COVID-19. So development of vaccines can be the most prominent approach to prevent the deadly virus to cause COVID-19 and hence will play a vital role in controlling the spread of the virus and reducing mortality (Rawat *et al.*, 2020). Nowadays, scientists are attempting to generate vaccines to fight against SARS-CoV-2 worldwide, with protein based vaccines becoming the most advanced types of the study(Jooband Wiwanitkit, 2020). Therefore, the present review gives a sneak peek of recent updates on the development of COVID-19 vaccine and its immunological aspect.

Features of COVID-19

Coronaviruses are belonging to the subfamily Coronavirinae in the family of Coronaviridae of the order Nidovirales. and this subfamily includes four genera: Alpha coronavirus, Beta coronavirus, Gamma coronavirus, and Deltacoronavirus(Chen *et al.*, 2020; Xiaowei*et al.*, 2020).These have been identified so far, with human coronaviruses (HCoVs) detected in the alpha coronavirus (HCoV-229E and NL63) and beta coronavirus (MERS-CoV, SARS-CoV, HCoV-OC43 and HCoV-HKU1) genera(Perlman and Netland, 2009). However, in the past two decades, three of the human coronavirus of zoonotic origin including SARS-CoV, MERS-CoV and SARS-CoV-2 have resulted in lethal endemics in 2002, 2012 and 2019 respectively(Ahmed *et al.*, 2020).

Structurally SARS-CoV-2 is pleomorphic, large, enveloped viruses with a characteristic fringe of projections composed of S protein on their surface. These viruses are equipped with a positive sense single stranded RNA genome (26-32 kb), which is complexed with the nucleocapsid (N) protein forming helical nucleocapsids. The genome is both capped and polyadenylated(Kaur and Gupta, 2020).Besides, the SARS-CoV-2 virus contains four structural proteins namely, spike (S), nucleocapsid (N), envelope (E), and membrane (M) proteins which are encoded by the 3'-end of the viral genome(WHO, 2020).

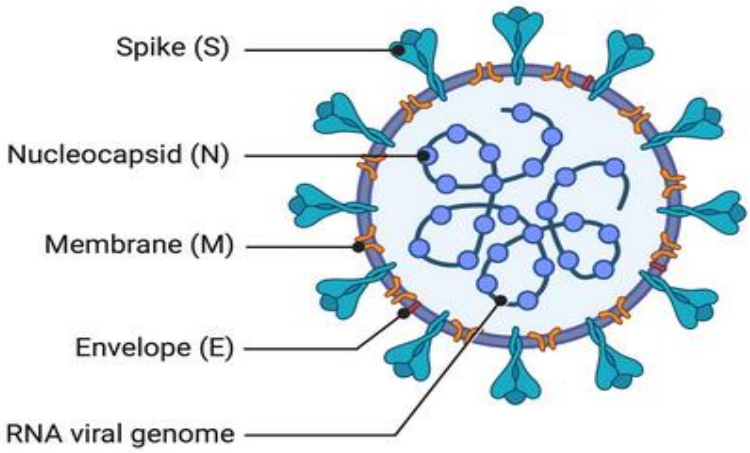

Figure 1: Corona virus structure. **Source**:Biophysical Society, 2020; NIH, 2020.

Protein S forms a glycoprotein (200–220 kDa) membrane with the shape of "spikes" emerging from the surface of the viral envelope giving crown like appearance to Electron Microscope. This S protein contains two subunits. The S1 subunit contains a fragment called the receptor-binding domain (RBD) that is able to bind ACE2 and induce neutralizing antibodies (NAbs) and T-cell immune responses. The S2 subunit is responsible for the fusion of viral and cellular membranes(Dong *et al.,* 2020; Fischer *et al.*, 1998).

The E protein that forms E channels (called the viroporins), and is involved in a myriad of functions in the viral replication cycle involving assembly, release, pathogenesis, etc. In addition, it

can be used as pharmacological target(Kaurand Gupta, 2020).

The M protein, the central organizer of CoV assembly, is most abundantly expressed in the virus particle. It functions crucially in the morphogenesis and assembly of the SARS-CoV-2 by interacting with the nucleocapsid(Yoshimoto, 2020).

Protein N is the most conserved structural protein in the coronavirus which is required for the encapsulation of the genomic RNA and its incorporation into the virion. It is also possible that this protein is involved in RNA replication(Risco *et al.,* 1996).

Most of the nonstructural proteins (NSP) of nsp116 have been reported for their specific roles in the replication of CoVs. The NSPs perform various functions like genome replication, inducing the cleavage of host mRNA, membrane rearrangement, generation of the autophagosome, cleavage of the NSP polyprotein, capping, tailing, methylation, unwinding of the RNA duplex which are essential for the viral life cycle(Chen*et al.*, 2020; Silva *et al.*, 2020).

Immunopathology of COVID-19

The immunopathology of COVID-19 explains the reaction of immune system against novel coronavirus infection. Immune defense against viral pathogens involves the coordination of immediate innate and later pathogen-specific adaptive responses that promote viral recognition, containment, clearance, and host immunological memory(Rouse and Mueller, 2019; Yang *et al.*, 2020).

The novel SARS-CoV-2 virus enters the host cell when the viral spike (S) glycoprotein on the surface of the virus binds to a complementary angiotensin-converting enzyme 2 (ACE2) receptor which is notably expressed on lung alveolar cells, enterocytes of the small intestine and is also present in vascular endothelia(Habas *et al.,* 2020). After binding, there is a membrane fusion between the virus and the host cell and a protease of the host cell cleaves and activates the receptor-bounded spike protein allowing the virus to enter the host cell through endocytosis(RothanandByrareddy, 2020).

While the virus facilitates the uncontrolled viral replication, its viral RNA recognizes by Toll-like receptor (TLR) followed by turning off interferon(IFN)production and turning on the intracellular inflammatory pathway to generate neutrophils, monocytes, macrophages, and dendritic cells (DCs) to the site of infection creating the state of cytokine storm, i.e., the level of interleukin (IL)-6, IL-8, and IL-12 and the tumor necrosis factor-α (TNF-α) increases(Noor, 2021a; Sikandar *et al.,* 2020).

After entry of virus in to cell a part of it as antigen is presented on the surface of antigen presentation cells (APC),especially by the DCs and macrophages through major histocompatibility complex(MHC) for T cell activation which is crucial for the body's immune response. Antigen presentation on B cells ultimately leads to the production of the typical pattern of immunoglobulin M(IgM) and immunoglobulin G(IgG) antibodies. Researchers have found that these IgM antibodies lasts untilweek 12, while the IgG antibodies remain long lasting and can provide prolonged protection(Li *et al.,* 2003). In general, T cells are the major immune cells those fight against viral infections in body either by production of virus specific antibodies (Cluster of differentiation 4+ (CD4+) helper type T cells mediated response) or by killing the virus-infected cells (CD8+ cytotoxic type T cells mediated response together with natural killer cell ending in apoptosis)(Mubarak *et al.,* 2019; Noor, 2021c).

However, there could be the several possible mechanisms involved in the depletion and dysfunctioning of T lymphocytes induced by SARS-CoV-2 such as SARS-CoV-2 can directly infect T cells and macrophages by binding to the surface markers (CD 26 and CD 147)García, (2020), or the ACE-2 receptors present on their surface Marcos-Jiménez *et al.*(2005), as well as SARS-CoV-2 induce spleen atrophy and lymph node necrosis thereby destroying lymphatic organs(Cao, 2020).

The other mechanism is cytokine storm induced by SARS-CoV-2, the increased level of cytokines like TNFα, IL-6, and IL-10 is inversely correlated with the decreased T cell population(Diao *et al.,* 2020).

COVID-19 vaccine platform

Even though the preventive measures suggested by the WHO to encounter the ongoing disastrous pandemic are being followed more or less all over the world, the situation appears as an irresistible state, and the suppression of the COVID-19 transmission seems to be possible only when the herd immunity (i.e., the resistance against the viral spread within a population and a sufficient population may trigger the protective immunity against SARS-CoV-2 thereby reducing the probability of transmission between both the infected and susceptible individuals) will develop(Chung *et al.,* 2020; Mulligan *et al.,* 2020).

Many efforts have been directed towards the development of the vaccines against COVID-19, to avert the pandemic and most of the developing vaccine candidates have been using the S-protein of SARS CoV-2(Dhama *et al.,* 2020).The entire vaccine development process including the required clinical trials has been amazingly shortened to 15–18 months instead of 10–15 year(Dutta, 2020). So far approximately 164 candidate vaccines are in the process of development of which 24 have been brought in

the advanced stages of vaccine development(Noor, 2021b).

Vaccine platforms are divided into six categories: live attenuated virus, recombinant viral-vectored vaccines that are bioengineered to express target pathogen antigens in vivo, inactivated or killed virus, protein subunit vaccines, virus-like particles (VLPs) and nucleic acid-based (Deoxyribo nucleic acid (DNA) or messenger RNA (mRNA)) vaccines*(*Shang *et al.*, 2020).

NUCLEIC ACID BASED VACCINES

b) a)mRNA vaccine

mRNA vaccines represent a promising alternative compared to conventional vaccines due to their high potency, ability for rapid development, and cost-efficient production(Pardi *et al.*, 2018).

The mRNA works based on the contentment ofmRNAas the active ingredient that encodes the viral spike glycoprotein (S) of SARS-CoV-2 (that meansRNA serves as the template to generate the specific protein that triggers the host immune response against the virus)complexed with a carrier such as lipid nanoparticles can be efficiently delivered in vivo into the cytoplasm of host cell(Societyand of Rheumatologists, 2020).

Currently, there are 6 COVID-19 vaccine candidates in clinical evaluation. Pfizer-BioNTech and Moderna appeared as the most successful in constructing vaccines using nanotechnology with the mRNA platform(Corbett*et al*., 2020)

However, despite such fast progress by Pfizer-BioNTech and Moderna, some adverse effects of the vaccination in the trial stage have been noticed as the onset of fatigue, headache, muscle and joint pains, chills, fever, and, in some cases of the participants, the lymphadenopathy(Noor, 2021c).

c) DNA vaccine

The DNA vaccine, which induces both humoral and cell mediated immunity, is made on the principle that the genetic material of the SARS-CoV-2 is trans located (the antigenpresenting cells or APCs receive the genetic material) to the host's cell nucleus so that the mammalian promoter present in the plasmid vector is activated, triggering the transcription and translation of the transfected gene(s) within the host(Silveira *et al.*, 2020).

Plasmid DNA that can be widely produced in bacteria usually contain mammalian expression stimuli and a gene encoding the spike protein, which is expressed in the vaccinated individual upon delivery. The major advantage of these techniques is the possibility of large-scale production of Escherichia coli, as well as the high stability of the plasmid DNA(Jbeliand Jelassi, 2021).

The resulting vaccine antigenic protein can then be presented to the APCs (mainly the DCs) through the MHC I signalingthe CD8+ T cell immunity is induced by the myocytes which in turn stimulates the excretion of interferon (IFN)-γ and the tumor necrosis factor (TNF)-α, and thus, the viral replication inside the host is hindered and CD4+ helper T cells are activated by macrophages (MHC II signaling), and the DCs (MHC II signaling) activate the CD8+ T cells by triggering the production of interleukin (IL)-10, IL12, and the tumor necrosis factor (TNF)-α, and the CD4+ helper T cells are activated by these DCs when they produce IL-4(Berry *et al.*, 2004; Duerr *et al.*, 2020).

Hence, DNA vaccines also have great therapeutic potential due to their ability to enhance T-cell induction and antibody production, the excellent biocompatibility of plasmid DNA, low-cost manufacturing, and their long shelf life(Hobernik and Bros, 2018).However, their disadvantage is that the DNA molecules must cross the nuclear membrane to be transcribed, and they generally have low immunogenicity(Yu *et al.*, 2020).

Currently, there are four plasmid DNA-based COVID-19 vaccines in clinical testing. INO-4800 is now under the phase I clinical trial (NCT04336410), has been prepared on the basis of the codon-optimized spike protein sequence to which an IgE leader sequence is attached, and the digested DNA is included into the expression plasmid pGX0001 resulting in the production of S protein reactive and the RBD-binding IgG as well as the required T cell responses(Noor, 2021c).

VIRAL VECTOR VACCINES

A vaccine based on viral vectors is a promising prophylactic solution against a pathogen. These vaccines are highly specific in delivering the genes to the target cells, highly efficient in the gene transduction, and efficiently induce the immune response(Ura *et al.*, 2014).

Typically, these vaccines rely on another virus such as adenovirus that is designed to express the spike protein but prevented from reproducing in vivo by deleting parts of its genome(Jbeli& Jelassi, 2021). The major advantage of this platform is the capability to induce both humoral and cellular immunity(Rollier *et al.*, 2011).
The adenoviral vector Ad5 being used for COVID-19 vaccine development is cost effective approach andalready been used for Ebola virus.However, it will be important to consider whether humans have pre-existing immunity against the viral backbone. Therefore an additional trial using chimpanzee derived adenoviruses (ChAd) is being conducted to combat preexisting immunity(Afkhami *et al.*, 2016; Rawat *et al.*, 2020).

Live attenuated vaccines (LAV)

The most common traditional method which involves manually weakened live pathogen which is no longer able to induce infection but able to induce immune response and hence mimic features of natural infection(Barría *et al.*, 2013).

It is possible to rationally design attenuated virus strains by mutating or deleting virulence genes. These deletion mutants can often replicate to a limited extent in host cells but lose the ability to cause disease in vivo. Coronaviruses have several genes that are not required for replication and that can be deleted, leading to attenuation in vivo. Deletion of various non-structural proteins, as well as of the structural E protein, has been used as a strategy to engineer vaccine strains of several zoonotic and veterinary coronaviruses(Almazán *et al.*, 2013; Hou *et al.*, 2019). Deletion of the 2′-O-methylase gene from the SARS-CoV genome removes the ability of the virus to (MDA5) (also known as IFIH1) and IFIT1, thereby inducing a robust antiviral response in vivo(Menachery *et al.*, 2014).

Another approach to viral attenuation is known as codon deoptimization, whereby the nucleic acid sequence is modified to use suboptimal codons to encode the wild-type amino acid sequence, which considerably slows the translation of the viral protein during infection(Mueller *et al.*, 2020).

An important advantage of these vaccines is that they can be administered intranasally, the main entry route for the virus, and thus stimulate mucosal immune responses (IgA) that can protect the upper respiratory tract and the drawbacks of these vaccines include safety concerns and the need for virus modification(Yang *et al.*, 2020).

So far, there are only three attenuated SARS-CoV-2 vaccines generated by codon deoptimization under preclinical development, by Mehmet Ali Aydinlar University in Turkey, Codagenix and Serum Institute of India,Zhang *et al.*(2020),and Indian Immunologicals Ltd and Griffith University(Koch *et al.*, 2021). In any case, several limitations might be represented during the LAV extensions to fight against SARS-CoV-2(Chen and Chen, 2020).

Inactivated viral vaccines

These are produced by completely inactivating or killing the pathogen, on injecting it to the host, they primarily induce protective antibodies against epitopes on hemagglutinin glycoprotein on surface of virus(Kumar *et al.*, 2018).

These vaccines are produced by promoting SARSCoV-2 in cell culture, usually in Vero cells, followed by chemical inactivation of the virus(Jbeli and Jelassi, 2021).

Usually, these vaccines are given by intramuscular injection and may contain aluminum hydroxide or other adjuvants. When the main virus is added to the immune system, not only the SARS-CoV-2 antigen but also the matrix, envelope, and nuclear proteins are likely to be targeted by immune response(Pandey *et al.*, 2020). Currently, there are 3 COVID-19 vaccine candidates in preclinical evaluation stage developed using this platform(COVID, 2020).

Virus like particles

These are protein multimers mimicking the structure of real virus but lacking genetic material and hence are non-infectious in nature(Roldão *et al.,* 2010). In the case of enveloped coronaviruses, VLPs form when the viral proteins S, M and E, with or without N, are co-expressed in eukaryotic producer cells(Lu *et al.,* 2007). This results in active budding from the producer cells of VLPs that are structurally identical to the infectious virus. The presence of S protein on the surface of VLPs enables them to bind and enter ACE2+ cells in the same manner as the parent virus(Naskalska *et al.*, 2018).

VLPs act by stimulating antigen presenting cells mediated activation of B- and T-cell immune responses. These are also involved in CD8+ cytotoxic T cell mediated killing of pathogenic cells. The immune system recognizes VLPs in the same way as it recognize original virus and thereby induce immune responses(Novak *et al.*, 2013).
VLPs also typically require an adjuvant and repeated administration(Donaldson *et al.,* 2018). Currently, there are two COVID-19 vaccine candidates developed as VLPs in clinical evaluation and 15 COVID-19 vaccine candidates in preclinical evaluation stage developed(Rawat *et al.*, 2020).

Protein Sub-Unit Vaccine

Subunit vaccines in which viral proteins are injected into the host have the potential to exhibit efficacy in protecting animals or human from viral infection(Enjuanes *et al.,* 2016). However, itexhibits low immunogenicity and requires auxiliary support of an adjuvant to potentiate the vaccine-induced immune responses. An adjuvant may enhance the biological half-life of the antigenic material, or it may ameliorate the immunomodulatory cytokine response(Kaur and Gupta, 2020).

Subunit vaccines primarily induce CD4+ T helper (Th) cell and antibody responses. Therefore, most of these vaccines contain full-length SARS-CoV-2 S protein or portions of it with the goal of inducing neutralizing antibodies(Zhou *et al.*, 2018).
Currently, there are seven COVID-19 subunit vaccines in clinical trials with 50 other candidates under preclinical development(Johansen and Nohynek, 2021).

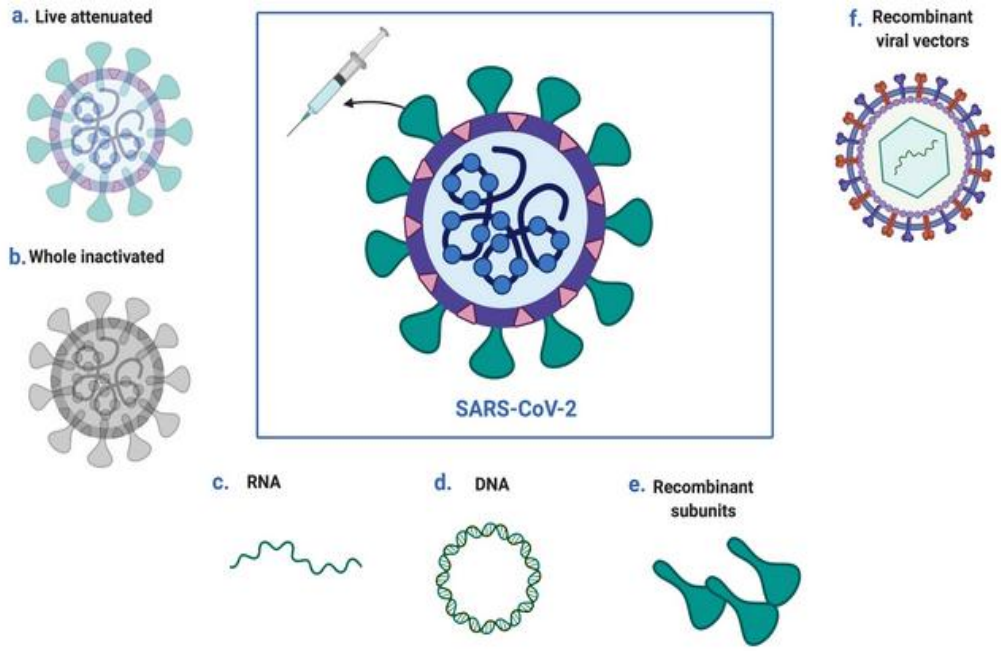

Figure 2: Approach of COVID-19 Vaccine development
Source:(Nidom*et al.,* 2020; Biophysical Society, 2020).

Potential Vaccine Candidates

The research and development of COVID-19 vaccines is going on with a very high speed in a way preclinical and clinical stages of vaccine development are compressed and move forwards in parallel(Dutta, 2020). As a result, simultaneous marketing of several vaccines has been started from the beginning of 2021(Noor, 2021c).

Conventionally, the safety, immunogenicity and protective efficacy of experimental vaccines are rigorously evaluated and established in animal models first before clinical trials are begun(Jeyanathan *et al.,* 2020). The promising candidates which can be commercially applied for the quick mitigation of the disease are listed below:

a)ChAdOx1 nCoV-19 vaccine

ChAdOx1 nCoV-19 (also known as AZD-1222), consists of non-replicating simian adenovirus is being developed by Oxford University, UK, and AstraZeneca, is the most clinically advanced COVID-19 vaccine.(van Doremalen et al., 2020).

Humans have low sero-prevalence for ChAd, hence its strong immunogenicity and utility for heterologous prime–boost COVID-19 vaccination(Colloca et al., 2012). The vaccine given intramuscular at a dose of 5 × 101viral particles is safe and tolerated with paracetamolthen thesecond dose of vaccine administered after 28 days of first dose to induce neutralizing antibodies in all the participants and showed 70.4% effectiveness after against symptomatic COVID-19(Voysey *et al.,* 2021).

b)mRNA-1273 vaccine

mRNA-1273, which is produced by Moderna, an American biotech company that has experience with mRNA-based MERS vaccines, encodes a perfusionstabilized SARS-CoV-2 S protein encapsulated in lipid nanoparticles. It entered clinical testing even before the release of preclinical data (Blumberg et al., 2021).

Medium doses of two repeated parenteral injections are generally safe and induce strong S protein-specific antibody responses and a primarily CD4+ T cell response(Jackson et al., 2020). Furthermore, it is considered to be relatively safe as it is neither made up of the inactivated pathogen nor the sub-units of the live pathogen(Tu *et al.*, 2020).

c)Gamaleya's Sputnik V (Gam-COVID-Vac)

This adenovirus vector-based vaccine was registered by the Russian Ministry of Health on August 11 and became the first registered COVID-19 vaccine on the market(Baraniuk, 2021).The vaccine uses a heterologous recombinant adenovirus approach using adenovirus 26 (Ad26) and adenovirus 5 (Ad5) as vectors for the expression of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein. The use of two varying serotypes, which are given 21 days apart, is intended to overcome any pre-existing adenovirus immunity in the population(Logunov *et al.*, 2021).

The vaccine induced strong antibody and cellular immune response and the effectiveness against COVID-19 has been announced to be 91.6%(Ghiasi *et al.*, 2021).

d)BNT162b1 RNA vaccine

BioNTech/Pfizer, another leading pharmaceutical company, developed the SARS-CoV-2 vaccine (namely, BNT162b1) as stated previously which is actually a lipidnanoparticle-formulated nucleoside-modified mRNA vaccine encoding the receptor-binding domain (RBD) of the S protein of the virus, who developed robust S protein-specific antibody and CD4+ and CD8+ T cell responses following two repeated parenteral injections(Mulligan *etal.*, 2020; Society & of Rheumatologists, 2020).

In general, the RNA based vaccine candidate BNT162b1 showed acceptable safety profile and also found to produce adequate antibody titer after booster dose(Zhu *et al.*, 2020).

e)CoronaVac (SinoVac)

This most advanced candidate vaccine is an inactivated whole SARS-CoV-2 virus vaccine developed by the Wuhan Institute of Biological Products and Sinopharm. It protects rhesus macaques against SARS-CoV-2, with reduced viral titers and immunopathology associated with adequate Nab antibodies to S protein and nucleocapsid(Wang *et al.*, 2020).
The trial was conducted using a middle dose of vaccine, i.e. 5 μg antigen protein content showed the vaccine candidate is acceptably safe and better immunogenic profile with no serious adverse event. However, it require the booster shots to maintain the immunity(Kaurn and Gupta, 2020).

f) JNJ-78436735/Ad26.COV2.S (Johnson & Johnson)

It is a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector vaccine which encodes and stabilizes SARS-CoV-2 spike protein(Tegally *et al.*, 2020). The vaccine has been found to elicit the required immune responses including the spike (S) protein-specific responsiveness of CD4+T cells, CD8+ cells, and the T helper cell 1 (Th1)(Noor, 2021b).

A single dose at 5×10^{10} viral particles is safe and induce durable protection(Mercado et al., 2020). It can be stored for up to 2 years in a standard freezer and up to 3 months at refrigerator temperatures, which simplifies transport, storage, and use in a pandemic(Sadoff *et al.*, 2021).

g) NVX-CoV2373

It is a recombinant severe acute respiratory syndrome coronavirus 2 (rSARS-CoV-2) nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 spike glycoproteins optimized for the baculovirus-*Spodopterafrugiperda* (Sf9) insect cell expression system(Bala *et al.*, 2020).

It demonstrated high immunogenicity in animal model with measuring anti spike antibodies, that prevent the attachment of the spike protein to the receptor, as well as wild-type virus neutralizing antibodies(Keech et al., 2020).

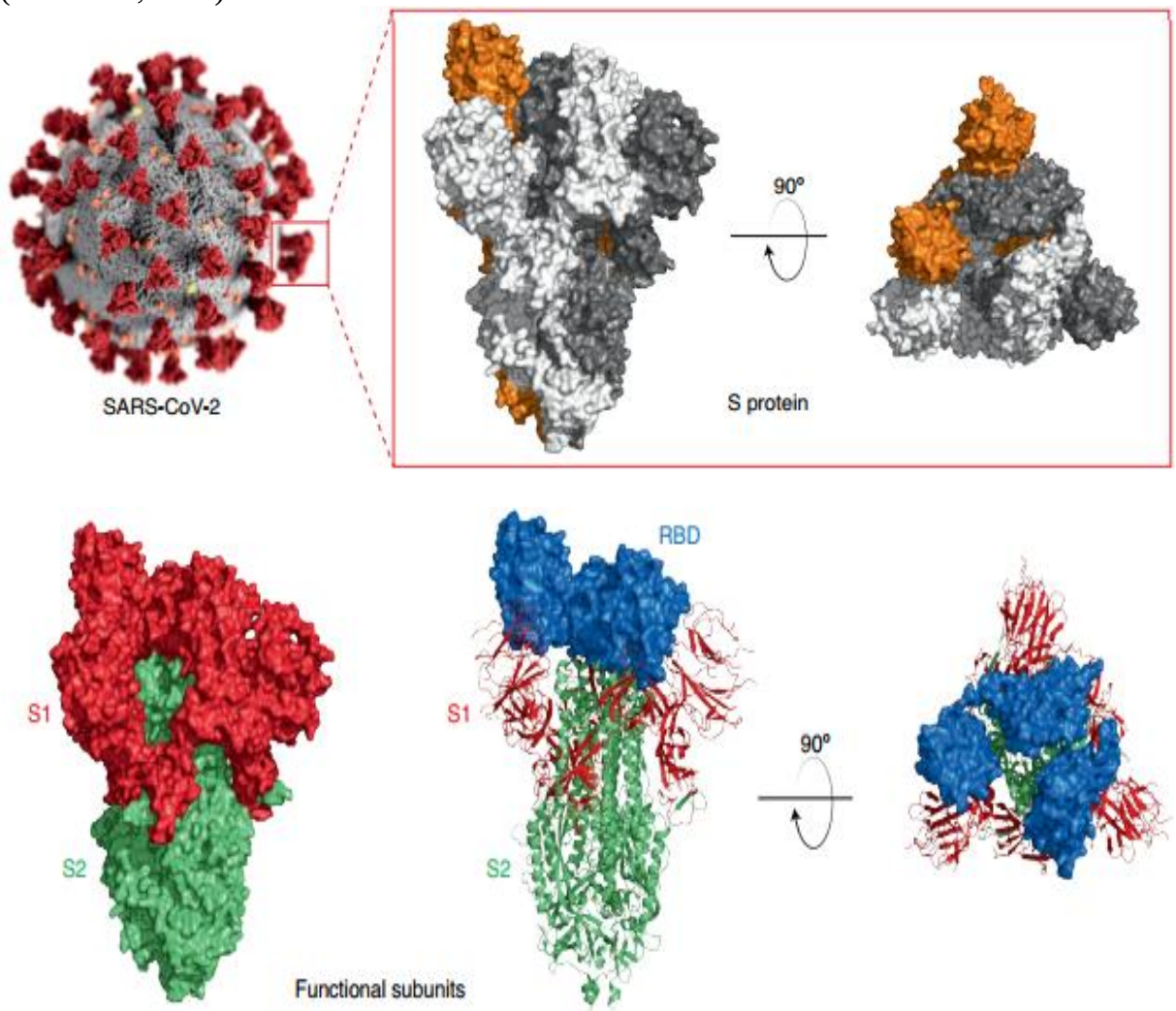

Figure 3: The spike protein (S protein) protruding from the coronavirus SARS-CoV-2 is the primary target for various ongoing vaccine development efforts.
Source:(Matthew *et al.*, 2020).

IMMUNE RESPONSE TOWARDS VACCINE ADMINISTRATION

The rapid transmission of SAR-CoV-2 infection across the world ignited extensive efforts toward the development of effective and safeCOVID-19 vaccine candidates that can be used globally for ending the pandemic (Prompetchara *et al.*, 2020). Some of these vaccine candidates are designed using different vaccine platforms which require two components: antigens from the target pathogen that are provided to or generated by the vaccine recipient; and an infection signal (such as a pathogen-associated molecular pattern)

that alerts and activates the host immune system(Xia *et al.,* 2020).Live attenuated vaccines can provide these two components which is capable of providing long-term memory to the immune system, whereas nonliving vaccines provide shorter-term protectionbut often requires artificial signals to activate the body's immune response, usually known as adjuvant forms(Jeyanathan *et al.,* 2020; Rauch *et al.,* 2018).

Most of the developing SARS-CoV-2 vaccine candidates involve at least part of the spike protein as in the case of SARS-CoVonly antibodies targeting protein S can neutralize the virushence is considered as most important vaccine target antigen(Buchholz *et al.,* 2004).

In viral-vectored recombinants were known to have a high level of safety and ability to induce a T cell response without the need for vaccine adjuvants and the opposite occurs with the inactivated viral vaccine and the protein subunit vaccine platforms, both of which have a weakness in inducing a CD8+ cytotoxic T cell response(Dhama *et al.,* 2020; Schaecher *et al.,* 2007).

Any stimulation of immune response to vaccines begins with the body's reaction to the first detection of the incoming agent, whether it is recognized as a threat or an immunization. Then, the innate immune system carries out any initiation stage. The process of initiation and detection begins when the immune system recognizes the epitope of antigen. The components of innate immune system will form opsonization or bind to antigens and help to be recognized by APCs such as macrophages or monocytes. APC will process and insert the antigen that has beenprocessed together with MHC class 1 protein onto the APC surface and carried to CD8+ cells which will then trigger the cell-mediated immune system. The activated APC correctly translates the nature of the threat, then transmits this information to secondary lymphoid organs, and promotes the relevant adaptive immune response(López-Sagaseta *et al.,* 2016).

The density of antigen protein and its distribution in a particle is key factor that determine the effectiveness of vaccine. The high density and orderly arrangement of antigens in a particle will make it easy to bond between the immunoglobulin on the surface of the host B cell and the particle, which is an important step in inducing an immune response(Li *et al.,* 2020).

Several factors inhibiting the induction of immune response through vaccines have become the main focus in developing SARS-CoV-2 vaccine candidates. Antibody dependent enhancement(ADE) has become a tipping point for vaccine development. In this case, defining the titers of neutralizing antibodies that are protective, ensuring that COVID-19 vaccines can achieve these titers and avoiding waning of antibodies to sub-neutralizing levels through frequent boosting will be important to minimize the possibility of ADE(Diamond and Pierson, 2020; Nidom *et al.,* 2020). Generally, in order for the vaccine to work effectively and on target, it is important to induce an immune response that produces a long-term memory(Walls *et al.,* 2020).

COVID-19 VACCINES IN ETHIOPIA

Ethiopia is one of the 213 countries that registered COVID-19 cases since 13th of March 2020(Geda et al., 2020). Since then, the number of new cases increase dramatically based on daily reports of the ministry of health in Ethiopia which is great concern for country(Emeto et al., 2021). Over 286,286 cases and 4,450 fatalities have been documented in Ethiopia in which only 2% of the population has been vaccinated by the middle of August 2021 (MoH Ethiopia, 2021).

The Government has strengthened its preparedness and response efforts to combat COVID-19 and has set up a well-organized national preparedness and response coordination mechanism through an Emergency Operation Center(Zikargae, 2020).

It has disseminated a regular briefing in the media campaign to address all citizens, Ethio-telecom has been using cell-phone ring tones to remind

and create awareness about the public health hygiene responses including frequent hand washing, maintaining a social distancing, and wearing of facemasks to fight COVID-19 and also declared a state of emergency. Further, the Ethiopian government has been implementing stringent contact tracing after the case report, isolation as well as care, obligatory quarantine, and treatment (Akalu*et al*., 2020).

Although various intervention measure to prevent the spread of virus has been taken vaccination is the most effective way of controlling infectious diseases(Prüβ, 2021). On March 7, 2021, Ethiopia received 2.184 million doses of Astra Zeneca COVID-19 vaccination through the COVAX Facility(Mesele, 2021). And on March 29, 2021, 300,000 dose of sinopharm COVID 19 Vaccines was donated from China's state-backed China National and Pharmaceutical Group (Reuters, 2021) and also on June 19, 2021 Ethiopia received 500,000 dose of Sinopharm vaccine donated by the Chinese Red Cross Society (Xinhua, 2021) Recently Ethiopia got 1,664,150 dose of J&J/Janssen vaccine by USA donation (COVAX roll-out, 2021).

It started primarily on health professionals, high risks, and communities that live in major cities (Dereje et al., 2021). Despite this, the population has hesitancy about the vaccine for religious or ethical, and safety reasons (Thorsteinsson et al., 2020).Only 2.1% of populations had received at least one dose of vaccine by the middle of September 2021, and only 0.5% of the Ethiopian population had been fully vaccinated (MoH, 2021; Our World in data, 2021).

Conclusion and Recommendations

COVID-19 pandemic has imposed a huge financial and social burden to the world. It remains a challenging task to restrict the transmission of infection among the population due to its continuously evolving nature. In order to cope with this emerging disease development of vaccines is the prominent approach.To date, multiple vaccine candidates havebeing developed, manufactured and authorized for use in under a year. These candidates vaccine against SARS-CoV-2 act against infection, disease, or transmission, and a vaccine capable of reducing any of these elements could contribute to disease control. But there is a lot more to explore about immunopathological basis of COVID-19so that its immune evasion mechanism can be targeted and it will also provide deeper insights into vaccine designing strategies.

Based on the above conclusive remarks, the following recommendations are given:

- ❖ Researchers should continue to develop new vaccines and optimize their safety, effectiveness, and quality.
- ❖ Vaccination should be encouraged to avert the transmission of virus by developing herd immunity.
- ❖ Gathering of important information like immunization route, finding more target antigen(s) apart from targeting Spike protein as antigen only, can be helpful in eradicating the infection.
- ❖ Information about tests should be transparent and accessible to reassure the public about safety.
- ❖ To enhance the willingness of COVID-19 vaccine, Ethiopian government with different stakeholders should strengthen public education using mass media about the advantage of getting COVID-19 vaccination.

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