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Review on the Severe Acute Respiratory Syndrome Corona Virus-2 (Sars Cov-2) and Covid -19 Different Potential Vaccines with Their Immunological Aspects

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Summary
On 31 December 2019, the outbreak of novel coronavirus causes cough, fever, and dyspnoea with ARDS on the peoples lived in the Wuhan city of Hubei Province in china. Later it spread across the world and affects not only the livelihood but affect economically, and also socially relentlessly. Scientist from different continents involved in discovering of its vaccine and many vaccines were produced. Therefore the objective of this work is to review the severe acute respiratory syndrome corona virus-2 and corona virus disease -19's different potential vaccines with their immunological aspects. A 2019-Novel Corona virus later renamed as severe acute respiratory syndrome coronavirus-2. By its nature this virus is positive-sense single-stranded RNA virus that contains spiral or circular genome inside of their crown like structure. Among the viruses structural protein, Spike protein play great role for entrance of virus into host cell. Following entry, the virus replicated in the cell, this leads to over-responsiveness of immune system that can caused gradual failures of organs and system. Although first coronavirus outbreak occurred two decades ago, no effective vaccine was developed. But after the outbreak of this virus, great number of scientists, clinicians and researchers were mobilized and develop vaccines in unprecedented timeline. Owing to urgent need, some vaccines licensed with minor side effects. Therefore, vaccine safety and efficacy should be assured prior to approval for the emergency use. Since vaccine development and sustainability have faced virus mutation, regular virus genome sequencing and analysing should be recommended to combat the upcoming viral infection.
Keywords: china, COVID-19, SARS CoV-2, mRNA, protein subunit, vaccine
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INTRODUCTION

At the end of December 2019, a novel coronavirus was recognized as the reason of presentation of patients with cough, fever, and dyspnoea with acute respiratory distress syndrome (ARDS) of unidentified aetiology in Wuhan city, from Huanan Seafood Wholesale Market, in the Hubei Province of China (http://en.nhc.gov.cn/2020-01/23/c_76004.htm). On 7 January 2020, the etiological agent of the pneumonia was officially announced as a novel coronavirus (Zhou, *et al*., 2020; Zhu, *et al.,* 2020) and abbreviated as 2019-nCoV by WHO, (Hui, *et al*., 2020). This pathogen was later renamed as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the International Committee of Taxonomy of Viruses (ICTV) and the disease was named coronavirus disease 2019 (COVID-19) by the WHO (Gorbalenya, *et al.,* 2020a). The Chinese Center for Disease Control and Prevention quickly identified the pathogen as a new type of coronavirus and deposited the first viral sequence into GenBank (LR757995, LR757998) on 30 January (Wang, *et al.,* 2021).

The virus belongs to the Nidovirales order that consists of families, namely, Roniviridae, Arteriviridae, and Coronaviridae (Hassan, *et al.,* 2020; Singhal, 2020). At the same time, the Coronaviridae family is divided into two, which include Torovirinae and Coronavirinae. Further, the Coronavirinae subfamily is classified as into alpha-, beta-, gamma-, and delta- COVs (Hassan*, et al., 2020*). Coronaviruses are large, enveloped, single-stranded RNA viruses found in humans and other mammals, such as dogs, cats, chicken, cattle, pigs, and birds. Coronaviruses cause respiratory, gastrointestinal, and neurological disease. The Coronavirus is a zoonotic virus that cause respiratory infections, which were first isolated in 1937 and designated as coronaviruses, because they have a crown-like appearance under microscopy, in 1965(Zhu, *et al*., 2020).

The types of coronavirus known to date are SARS-CoV, which causes severe acute respiratory syndrome (SARS) that originated in the china between 2002-2004; MERS-CoV, which causes Middle East respiratory syndrome (MERS) that originated in the Arabian Peninsula in 2012; and SARS-CoV-2, which causes the disease known as coronavirus disease 2019 (COVID-19). It has a diameter of 60 nm to 140 nm and distinctive spikes giving the virions the appearance of a solar corona (Goldsmith, *et al.,* 2004). Through genetic recombination and variation, coronaviruses can adapt to and infect new hosts. Bats are thought to be a natural reservoir for SARS-CoV-2, but it has been suggested that humans became infected with SARSCoV-2 via an intermediate host, such as the pangolin (Lu, *et al.,* 2019; Lam, *et al*., 2020).

The clinical manifestation of COVID-19 can vary from asymptomatic and mild flu-like symptoms to ARDS and death. Long-term pulmonary, cardiological, and neurological complications have also been reported in

COVID-19 cases (DelRio, *et al.,* 2020). Compared with SARSCoV and MERS-CoV, SARS-CoV-2 is highly contagious (Li, *et al.,* 2020). It was realized that vaccines could play an essential role in increasing the immunity of the population, preventing severe conditions caused by COVID-19 infection, reducing the burden on healthcare systems, and minimizing economic losses (Jeon, 2020). Traditionally, vaccines require 10–15 years of research, development, and testing before their clinical usage can begin (Dai, *et al.,* 2020). However, in early 2020, scientists embarked on attempts to produce safe and effective SARS-CoV-2 vaccines at record speed (Lee, *et al.*, 2021).

More than 250 vaccine projects were initiated worldwide in 2020 and according to a recent WHO report, 97 vaccines are in clinical trials from phases 1 to 3, and 182 are in their preclinical development stages. Different technologies have been applied in vaccine preparation, some conventional and some newly developed and applied for the first time in humans. (Grun, 2021; Forni and Mantovani, 2021). The vaccines can initiate adaptive immune response, particularly B- and T-cell, by introducing antigens. Although there are a lot of vaccine candidates under different phase of clinical trial, only a few numbers of vaccines has been approved for the usage. The safety, efficacy and immunogenicity of these vaccines are varies. Among vaccines licensed some of them require optimum temperature and others need ultra-cold storage temperature that imposed problem on vaccines usage in Poor County. In case of its safety, some vaccine has minor side effects and other vaccines safety remained unknown. Considering the rapid spread, serious public health crisis and high mortality of COVID-19, an effective, safe and stable vaccine is urgently needed to control this pandemic. Therefore the aims of current work are:

- To review severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and
- To update the recent development of COVID-19 vaccine and their immunogenicity

LITERATURE REVIEW

Virology

SARS-CoV-2 is an enveloped and positive-sense single-stranded RNA (+ssRNA) virus that can be categorized in the family Coronaviridae and order Nidovirales. The family consists of two subfamilies, Coronavirinae and Torovirinae and members of the subfamily Coronavirinae are subdivided into four genera: (a) Alpha coronavirus contains the human coronavirus HCoV-229E and HCoV-NL63, (b) Beta coronavirus includes HCoV-OC43, Severe Acute Respiratory Syndrome human coronavirus (SARS-HCoV), HCoV-HKU1, and Middle Eastern respiratory syndrome coronavirus (MERS-CoV), (c) Gamma coronavirus includes viruses of whales and birds and; (d) Delta coronavirus includes viruses isolated from pigs and birds (Burrell, *et al*., 2016). SARS-CoV-2 belongs to Beta-coronavirus together with two highly pathogenic viruses, SARS-CoV and MERS-CoV. (Kramer, *et al.,* 2006)

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Genomic features of SARS-CoV-2

Coronaviruses form enveloped, spherical particles and it has a cloverleaf structure such as glycoproteins and proteins on the virus's surface have created a crown-like structure on it. These viruses are called coronaviruses because of their crown structure. A nucleo-capsid is made of capsid-coated proteins that contain the virus's genetic material (Figure 1) (Mittal, *et al.,* 2020). The coronavirus genetic material is seen as a spiral or circular in the nucleocapsid. The genome of SARS-CoV-2 is around ~ 30 kb that starts with a 5'-cap structure and ends with a 3'-poly-A tail (Masters, 2006).

The virus genome consists of two terminal untranslated regions (5' and 3'- UTRs) and twelve putative functional open reading frames (ORFs) (Figure 2). The 5′-terminus of the CoV genome contains two overlapping ORF, ORF 1a and ORF 1b, that spanning over two thirds of the genome and encode the large replicase polyproteins (pp1a and pp1ab), which are post-translationally cleaved into 16 putative non-structural proteins (nsps) involving proteases, RNA polymerase, helicase, and other proteins involved in the transcription of viral genome, replication of SARS-CoV-2 and subgenomic mRNA synthesis (Enjuanes, *et al.,* 2016;–Chen, *et al*., 2020). The SARS-CoV-2 virus is composed four structural proteins, including S protein, envelope (E), membrane (M), and nucleocapsid (N) which are encoded by 3′-terminus of the CoV genome (Masters, P.S., 2006; Wang, N., *et al.,* 2020).

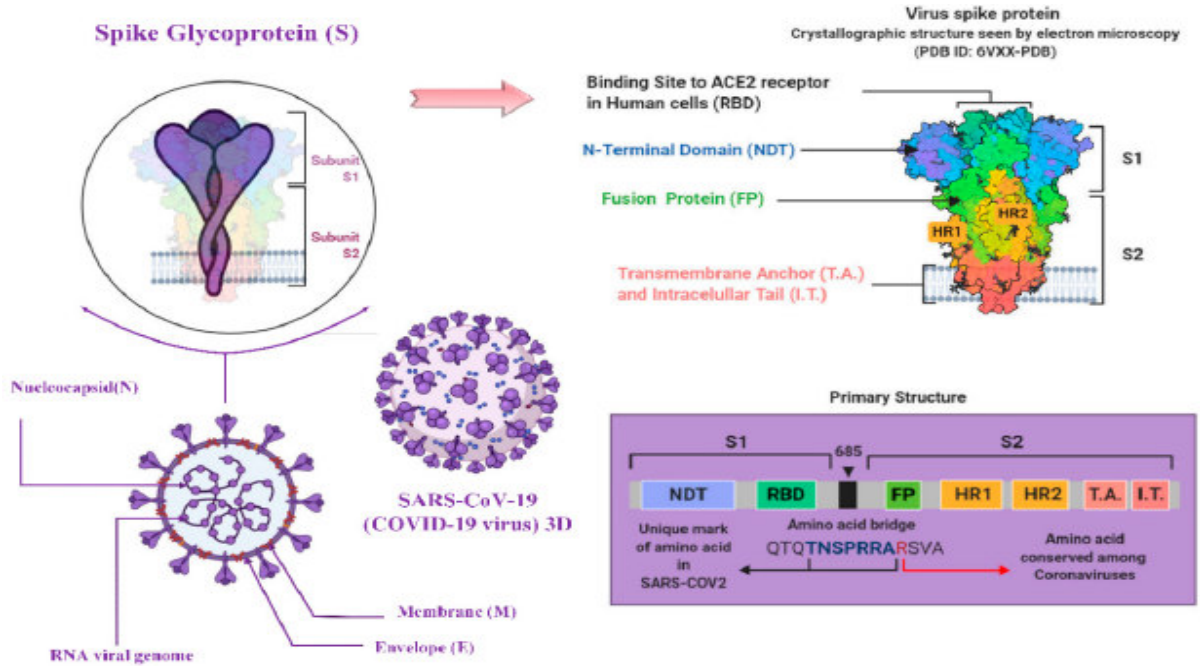

Figure 1. The SARS-CoV-2 Spike (https://app.biorender.com/biorendertemplates/figure)

S protein is responsible for the initial attachment of virion on the host cell surface. It has two subunits, S1 (specific receptor binding domain known as RBD) and S2 (CoV S2 glycoprotein). S protein, through its specific RBD, binds to its receptor on the host cell (Beniac, *et al.,* 2006). M protein has three transmembrane domains and plays a vital role in introducing the virus into the body and forming envelopes, whereas E protein is responsible for proliferation, germination, envelope formation, assembly and release of viral particles from the cell. It is also involved in viral pathogenesis (DeDiego, *et al.,* 2007). N protein has two domains, both of which can attach to the viral RNA in order to assist replication, and it also acts as a repressor of the RNAi system of the host cell, hence supporting the viral replication (Cui, *et al.,* 2015).

Pathogenesis of COVID-19

Coronavirus entry and replication

Coronavirus S protein is determinant of virus entry into host cells. First, S protein binds to cellular receptors through its receptor-binding domain (RBD), and the receptor-virus complex is subsequently translocated to endosomes (Du, *et al*., 2009). Both SARS-CoV and SARS-CoV-2 bind to angiotensin- converting enzyme 2 (ACE2), while MERS-CoV S protein attach to dipeptidyl peptidase-4 (DPP4) of cellular receptor (Wang, *et al*., 2020). At the endosome, S protein is further cleaved into S1 (RBD-containing) and S2 (non-RBD-containing) subunits, and the S2 subunit mediates fusion between the viral envelope and the host cell membrane (Du, *et al*., 2009).

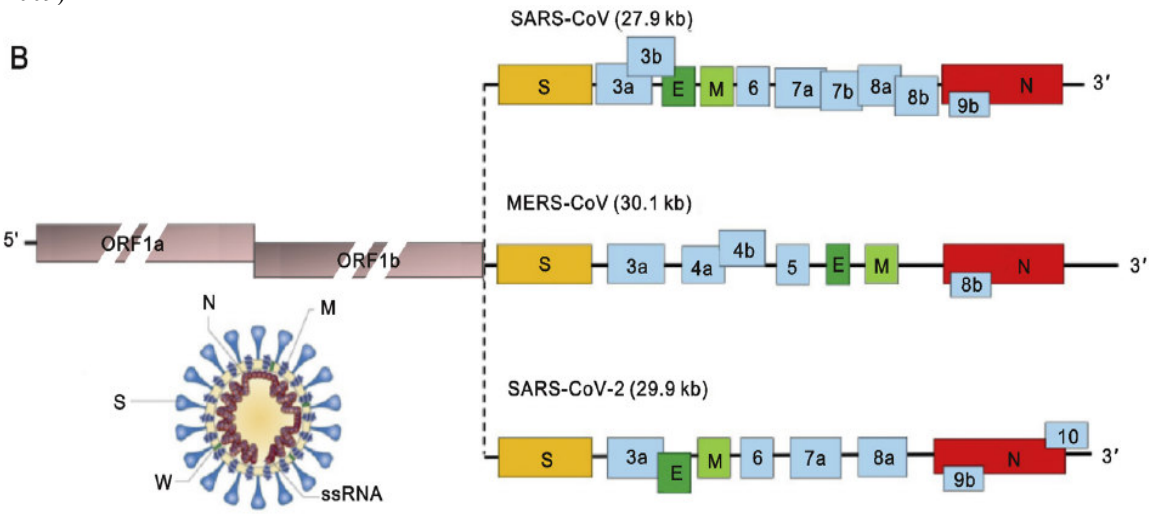

Figure 2. Spherical particles and the genome of SARS-CoV-2 virus.

After entering the cell, several Nsps, particularly RNA-dependent RNA polymerase (Nsp12) and helicase

(Nsp13), mediate the replication of the CoV genome and the transcription of CoV mRNA (Snijder, *et al.,* 2016). The CoV mRNA is further translated into different nonstructural and structural proteins. The N proteins bind to CoV genomic RNA to form viral nucleocapsids, and S, E, M proteins form the envelope of CoV. Then, viral particles assembled in the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). After assembly vesicles contain viral particles bud and exit the by exocytosis (Figure 3) (Du, *et al*., 2009).

Humoral and cellular immunity

The presentation SARS Cov-2 Antigen subsequently stimulates the body's humoral and cellular immunity, which are mediated by virus-specific B and T cells. The SARS-specific IgM antibodies disappear at the end of week 12, while the IgG antibody can last for a long time, which indicates IgG antibody may mainly play a protective role (Li, *et al*., 2003), and the SARS-specific IgG antibodies primarily are S-specific and N-specific antibodies. The latest report shows the number of CD4+ and CD8+ T cells in the peripheral blood of SARS-CoV-2-infected patients significantly is reduced. The acute phase response in patients with SARS-CoV is associated with severe decrease of CD4+ T and CD8+ T cells. Even if there is no antigen, CD4+ and CD8+ memory T cells can persist for four years in a part of SARS-CoV recovered individuals and can perform T cell proliferation, DTH response and production of IFN-g (Fan *et al.,* 2009).

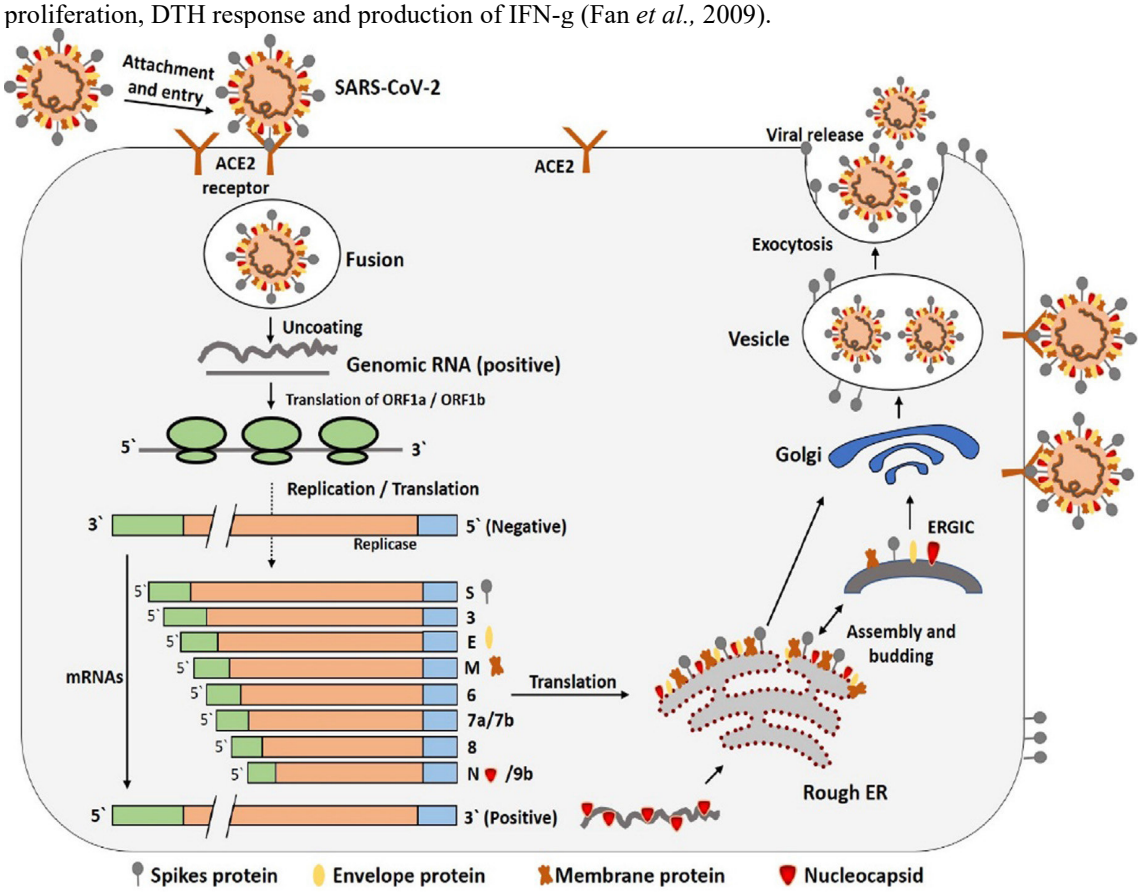

Figure 3. The life cycle of SARS-CoV-2 in host cells

Cytokine storm in COVID-19

After entering into the lungs, CoVs reaches the lower respiratory tract where alveoli are present and start to replicate there (Mehta, *et al.,* 2020). During this, the body produces large amounts of cytokines (IFN-a, IFN-g, IL-1b, IL-6, IL-12, IL-18, IL-33, TNF-a, etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) causing violent attack by the immune system to the body, referred to as cytokine storm syndrome (Williams, and Chambers, 2014; Channappanavar, and Perlman, 2017). The cytokine storm causes, alveoli destruction by the immune system that leads to secondary bacterial pneumonia and suppression of the lungs function, the thickening of the lung lining, due to infiltration of immune cell, that leads to shortness of breath and malfunctioning of lungs that leads to deprivation of oxygen for brain, kidney, and liver. Generally, the cytokine cause ARDS and multiple organ failure, and finally lead to death in severe cases of SARS-CoV-2 infection, just like what occurs in SARS-CoV and MERSCoV infection (Xu, *et al.,* 2020).

Host response to SARS-CoV-2

Epithelial cells, alveolar macrophages and dendritic cells (DCs) are three main components for innate immunity in the airway fight against viruses till adaptive immunity is involved. DCs reside underneath the epithelium. Macrophages are located at the apical side of the epithelium. (Yoshikawa, *et al*., 2009). T cell responses are initiated by antigen presentation via DCs and macrophages. DCs and macrophages can phagocytize apoptotic cells infected by virus (Fujimoto, *et al.,* 2000). Or DCs and macrophages may be infected with virus primarily. The expression of ACE2 on (splenic) dendritic cells and alveolar macrophages is present but limited. SARS-CoV can also bind to dendritic-cell specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) and DC-SIGN-related protein (DC-SIGNR, L-SIGN) in addition to ACE2 (Jeffers, *et al.,* 2004; Marzi, *et al*., 2004). DC-SIGN is highly expressed on dendritic cells and macrophages. It can help the virus to directly infect DCs and alveolar macrophages. The antigen presenting cells move to the draining lymph nodes to present viral antigens to T cells. CD4+ T cells activate B cells to promote the production of virus-specific antibody, while CD8+ T cells can kill viral infected cells (Yang, *et al.,* 2004).

POTENTIAL CANDIDATE VACCINE AGAINST SARS COV-2

A vaccine is a biological product that produces an acquired active immunity against a specific microbial disease (Baxter, 2007). Vaccines are very vital to save the lives of millions of people every year. The primary function of vaccines is to train and prepare the immune system to identify and fight the target pathogen. Vaccines has a common components like Active ingredients of pathogen antigens that directly stimulate the immune system, Adjuvants, Antibiotics, Stabilizers Sugar/gelatin, Preservatives and trace components. The research and development of COVID-19 vaccines is going on with a very high speed; and the entire vaccine development process including the required clinical trials has been amazingly shortened to 15–18 months instead of 10–15 years. As a result, simultaneous marketing of several vaccines has been started from the beginning of 2021 (Noor, 2021; Dutta, 2020).

Diversity of COVID-19 vaccine technology platforms

Notably, the technology platforms used on COVID-19 vaccines were abundant and each of the platforms has some advantages and disadvantages, as listed in table 1. The most common technology platforms, in descending order of frequency, were protein subunit (PS), RNA, viral vector non-replicating (VVNR), inactivated virus (IV), DNA, virus-like particle (VLP), viral vector replicating (VVR), VVR combined with antigen presenting cell (APC), live attenuated virus (LAV), dendritic cell vaccine (DCV) and T cell-based vaccine (TCV) (Huang, H.Y., *et al.,* 2021). Among all vaccine being evaluated in trials, vaccine types such as nucleic acid, viral vector, virus, and protein subunits (figure 4) are more frequently used (Mellet, J. and Pepper, M.S. 2021).

In the perspective of research and development of vaccine process, vaccine types including TCV, LAV, DCV, VVR+APC, were still in its initial phase that few products were designed for each type, and no product has been confirmed with adequate safety up to this date. Notwithstanding no effectiveness confirmed on status quo, VVR, VLP and DNA have more products arranged and part of involved products have already entered efficacy confirmatory phase. It is gratifying that there were two RNA vaccines, two PS vaccines, four VVNR vaccines and seven IV vaccines authorized for emergency use (table 2) (Huang, *et al.,* 2021).

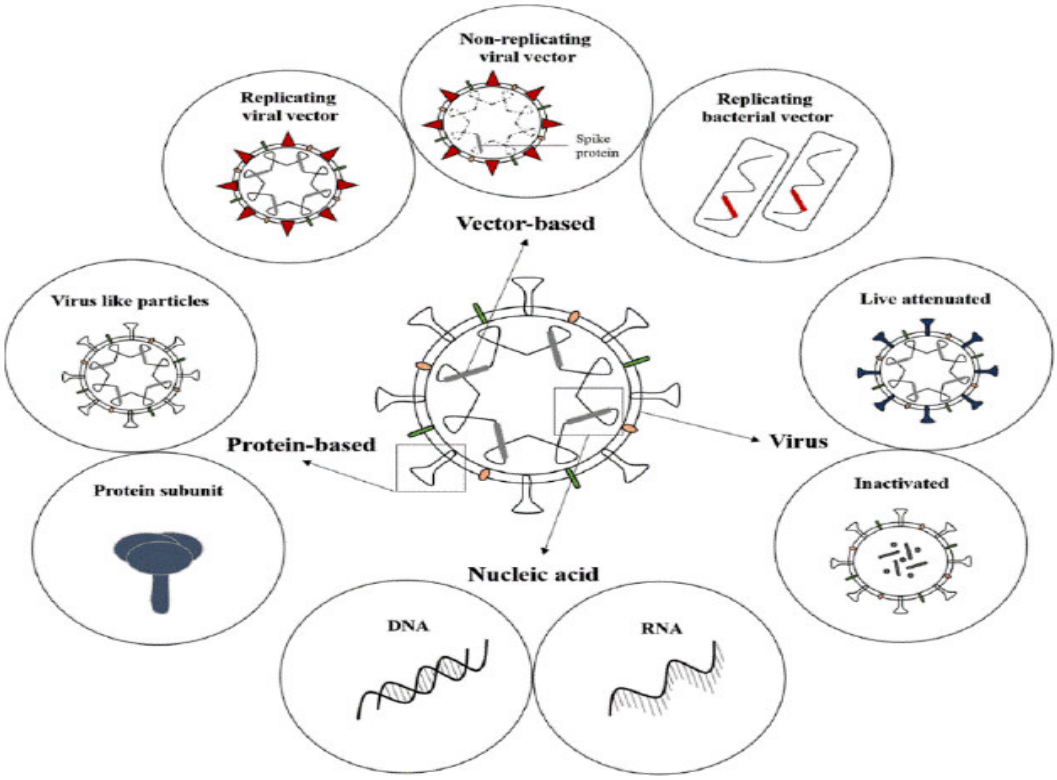

Figure 4. SARS-CoV-2 vaccine types

Inactivated Coronavirus Vaccines

Whole inactivated vaccines are composed of chemically or radiationally inactivated virions. They contain a full repertoire of immunogenic components of the original virus, and compared with attenuated viruses, they carry no risk of viral reactivation if properly inactivated. Although safer than live attenuated vaccines, the immunogenic epitopes of inactivated viruses may be structurally deformed during the inactivation process, which can undermine the protection they may provide. Moreover, both SARS-CoV and MERS-CoV whole inactivated vaccines have been reported to induce eosinophil-related lung pathology (Bolles, *et al.,* 2011; Tseng, *et al.*, 2012). These disadvantages make whole inactivated vaccines a less attractive strategy for coronavirus vaccine development.

Table 1: Advantage and Disadvantage of various vaccine platforms used for development of vaccine candidates against viral infections (Syeda and Shrivastava, 2021)

Vaccine platforms	**Advantage**	**Disadvantage**
Inactivated Virus	● Stable and safe ● Can be used together with adjuvant to increase the immunogenicity ● Immunocompromised individuals can also be vaccinated	● Require multiple boosters ● Low titre production
RNA-based	● Low cost and rapid manufacturing ● Good safety profile ● No risk of viral genome integration into host genome	● Show instability and thus low immunogenicity ● May be requiring multiple doses
Viral Vector	● Highly specific for gene delivery in target cells ● May induce robust immune response ● Increases cellular immunity	● Immunity against vector may reduce the efficacy ● Probability of integration of viral genome into the host genome that may lead to tumorigenesis ● Induces low titre production
Protein Subunit	● Good safety profile ● Immunocompromised individuals can also be immunised	● Low immunogenicity

DNA-based	● Stable ● Low cost manufacturing ● Good safety profile ● Infectious viral particles are not involved	● Low titre production ● May get integrated into host Genome
Virus-like particles	● Can be used with adjuvant to increase the immunogenicity	● May require multiple boosters ● Low titre production
Live-attenuated Virus	● High potency with low cost manufacturing ● Intrinsic ability to stimulate innate immune response	● Viral nucleotide substitution may occur leading to production of recombinant strain ● Not suitable for Immunocompromised individuals.

Inactivated vaccines are produced by formaldehyde inactivation, UV and gamma irradiation, or by growing SARS-CoV-2 in cell culture, usually on Vero cells 9 (monkey kidney cells) and grow in bioreactor tanks, followed by chemical inactivation of the virus (Wang, *et al*. 2020; Gao, *et al.* 2020). Dousing with a chemical called beta-propiolactone could disable the viruses by binding to their genes and thus preventing their replication; however, their proteins, including the spike (S) protein, remained intact (Liu, *et al*., 2020). The productivity of the virus in cell culture and the requirement for production facilities at biosafety level 3 are the common bottleneck for vaccine production. These vaccines are usually administered intramuscularly and can contain alum or other adjuvants to boost the immune response against the inactivated vaccine (Li and Zhu, 2021).

Four inactivated vaccines have been given authorization for use. The inactivated vaccines express a wide range of native viral antigens (Ganneru, *et al.,* 2020). Such multiple antigens can induce a TH2 response and lung eosinophilia, which may be worse in aged hosts (Simon, *et al.,* 2020). This broad-spectrum immune stimulation may result in a special condition in the post vaccination period called the vaccine-related enhancement of disease (VRED) Munoz, *et al.,* 2021). Therefore, TH1-skewing modified alum or other types of adjuvants such as CpG are recommended to be added to vaccine as alternatives to avoid VRED (Klasse, P.J et al 2021).

Covaxin Vaccine (COV; Bharat Biotech Vaccine, BBV152)

It was manufactured by collaboration of the Indian Bharat Biotechnology Company, Indian Council of Medical Research and National Institute of Virology (Ganneru, *et al* 2020). The COV has been granted permission in India for restricted use in emergency situations despite being in phase 3 of clinical trials (Ella, *et al.,* 2021a; Thiagarajan, 2021). This vaccine is used in a two-dose regimen with the doses given 4 weeks apart, and its efficacy is reported to be 81% (Ella, *et al.,* 2021b), although 82.8 to 91.9% of the vaccinated people generated antibodies (seroconverted) with robust immune responses (Ella, *et al.,* 2021b). It can be stored for one week at room temperature, which makes it suitable for usage in tropical and subtropical countries (Ella, *et al*., 2021a).

Table 1. Overview of authorized COVID-19 vaccines worldwide (Huang, *et al.,* 2021).

Vaccine	**Sponsor**	**Vaccine Type**	**Storage**	**Dosage**	**Efficacy**
Gam-COVID-Vac Lyo	Gamaleya Research Institute	VVNR	stable at 2–8°C	2 doses, 0/21days	92%
BBIBP-CorV*	Sinopharm	IV	stable at 2–8°C	2 doses, 0/21days	78.1%
EpiVacCorona	Federal Budgetary Research Institution	PS	Unclarified	2 doses, 0/21-28day	/
BNT162b2	Pfizer/BioNtech/ Fosun Pharma	RNA	Stable at −80 ~ −60°C; 2 ~ 8°C for 1 month	2 doses, 0/21	95%
mRNA-1273	Moderna/NIAID	RNA for 24 hours	Stable at −50 ~ −15°C; 2 ~ 8°C for 30 d; 8 ~ 25°C	2 doses, 0/28day	94%
AZD-1222	Oxford Universty/ AstraZeneca	VVNR	stable at 2–8°C	2 doses, 0/4-12 w	70%
COVAXIN	Bharat Biotech	IV	stable at 2–8°C	2 doses, 0/28d	81%
CoronaVac*	Sinovac	IV	stable at 2–8°C	2 doses, 0/14d	/
QAZCOVID-IN	Unclarified	IV	Unclarified	Unclarified	/
CoviVac	Russian Academy of Sciences	IV	Unclarified	Unclarified	51%
Unclarified*	Sinopharm	IV	stable at 2–8°C	2 doses, 0/21d	72.8%
Ad5-nCoV*	CanSino-BIO	VVNR	stable at 2–8°C	1 dose	/

Vaccine	Sponsor	Vaccine Type	Storage	Dosage	Efficacy
Ad26.COV2.S	Janssen	VVNR	Stable at −20°C; 2 ~ 8°C for 3 months	1 dose	/
ZF2001	Zhifei/Chinese Academy of Sciences	PS	stable at 2–8°C	3 doses, 0/30/60d	/
KCONVAC	Beijing Minhai Biotechnology Co	IV	Unclarified	2 doses, 0/28d	/

Viral vector non-replicating (VVNR); Inactivated virus (IV); Protein subunit (PS)

Sinopharm Vaccine (SV; BBIBP-CorV)

The Sinopharm vaccine is manufactured by Chinese company, Sinopharm Group, and is marketed with the cooperation of the UAE. This vaccine used a HB02 strain rather than WIV04 strain (Wang, *et al*., 2020). It is administered in a two-dose regimen, with the doses given 3 weeks apart by intramuscular injection. It showed an efficacy of 79.34% in China and 86% in the UAE, besides being 100% effective in preventing moderate and severe COVID-19 cases. The developers did not report any serious side effects during its phase III clinical trial or after its authorization for use. (Klasse, *et al.*, 2021)

Sinopharm-Wuhan Vaccine (SWV)

The Sinopharm-Wuhan Vaccine was prepared by the Chinese Wuhan Institute of Biological Products. It is effective in preventing COVID-19 in 72.5% of vaccinees (https://www.reuters.com/article/us-health-coronavirus-vaccine-sinopharm). It shows comparable side effects to the Sinopharm vaccine and is also in its phase III clinical trial (Kyriakidis, *et al*., 2021). The Wuhan vaccine utilizes the WIV-04 strain, which was isolated and cultivated in a Vero cell line for propagation. Then, the supernatant of the infected cells was inactivated. This vaccine is given in two doses 3–4 weeks apart. A third dose is recommended for those individuals who show weak immune responses (Kyriakidis, *et al.,* 2021).

CoronaVac Vaccine (CV; Formerly PiCoVacc)

CoronaVac Vaccine is manufactured by SinoVac Biotech, a private Beijing-based Biopharmaceutical Company, in collaboration with the Brazilian research center, Butantan. It is a beta-propiolactone inactivated, Vero cell line propagated whole virus vaccine originated from a patient-derived CN-2 SARS-CoV-2 virus strain. The vaccine is given in two doses (3 µg per 0.5ml dose by intramuscular injection) for individuals aged 18 years and older with the interval of 14 to 28 days apart between doses (Gao, *et al.,* 2020).

Moreover, it was reported that this vaccine generates a moderate immune response with lower antibody levels in comparison with levels in patients who have recovered from COVID-19 (Zhang, *et al*., 2021). Therefore, this vaccine requires an adjuvant, such as alum, to boost the immune response, but this requirement in turn makes the vaccine unsuitable for respiratory administration. CoronaVac vaccine showed no serious side effects and can be stored at the temperature of (2–8 °c), that making it suitable for worldwide distribution (Kyriakidis, *et al.,* 2021).

mRNA vaccines

mRNA vaccines are characterized by robust immunogenicity, intrinsic adjuvant properties, low costs for production, favourable safety profiles, quick production, special storage and delivery systems. This vaccine preparation has been investigated over the last 20 years for different viruses, such as rabies, influenza, and Zika (Mullard, 2020). The main advantage of this technology is that it allows the body's cells to produce S proteins rather than injecting them as in vaccines. This reduces the time required for building the vaccine and hence requires less time compared to that required for classical vaccines (Wang, *et al.,* 2020). The conventional mRNA vaccines utilize manufactured nucleoside-modified, single-stranded messenger RNA (see figure 5) to deliver genetic instructions to human cells for building up the coronavirus protein known as the spike protein (S) (Alfagih, *et al.,* 2020).

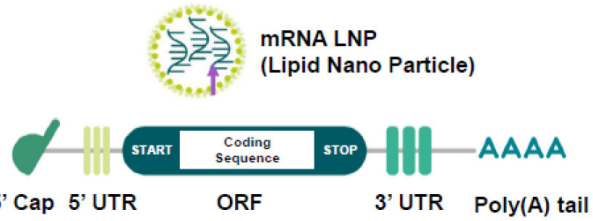

Figure 5. Structure of Conventional mRNA Vaccine (Jackson., *et al*., 2020)

Some intrinsic features of mRNA molecules demand special strategies to guarantee the stability, efficacy

and safety of mRNA vaccines. First, mRNA is intrinsically unstable and prone to degradation due to the omnipresence of RNases in the serum and plasma (Houseley, and Tollervey, 2009). Second, the cellular machinery recognizes exogenous RNA molecules as immunological mimic of viral infection, which results in an immediate immune response (Seth, *et al*., 2006). Thus, it is a prerequisite for the design of mRNA vaccines to maximize the stability of mRNA and translation efficiency and avoid the innate immune response by host cells (Zhang, *et al*., 2019; Pardi, *et al*., 2018).

The design achieved by 5'-capping of mRNA vaccine which is critical for protecting mRNA from exonuclease activity, facilitating pre-mRNA splicing, and serving as the binding site for eIF4F, the heterodimeric translation initiation complex (Gao, *et al.,* 2000; Izaurralde, *et al.,* 1994), Optimization of 5'- and 3'-UTR and the length of polyadenylation tail that is closely associated with the translation efficiency (Park, *et al*., 2016). Modification of the nucleosides in mRNA molecules by incorporating pseudouridine into mRNA molecules in the place of uridine, in order to supress the activation of TLR and to avoid the degradation of RNA by RNase L (Kariko, *et al.,* 2005; Anderson, *et al*., 2011).

The mRNA enters the human cells encapsulated by lipid nanoparticles (LNP) that prevent the cells of the body from degrading it and give stability to the mRNA, which is a fragile molecule. After mRNA has passed its instructions to the protein-making machinery in the cytoplasm of the body's cells, enzymes called ribonucleases (RNases) degrade the mRNA (Alfagih, *et al.,* 2020). Therefore, it is impossible for the mRNA to integrate with the DNA in the nucleus of the vaccinated cells, posing no risk of inducing genetic changes. After the S protein is produced by the cells of the body, the immune response is initiated with its two arms, i.e., humoral and the T-cell mediated immunity. The neutralizing antibodies can stop the spike protein. The killer T cells (CD8+) in vaccinated individuals recognize and destroy any coronavirus-infected cells that display the spike protein fragments on their surfaces (Abdulla, *et al*., 2021).

Moderna Vaccine (MV)

mRNA-1273 was developed by Moderna and consists of mRNA encoding the spike protein stabilized in the prefusion conformation, or SARS-CoV-2 S(2P), formulated in lipid nanoparticles (Corbett, *et al.,* 2020a). This vaccine has an advantage over Pfizer vaccine, in that it can be stored at temperatures equivalent to a standard freezer (-20 °c), making it easier to ship to remote and rural areas and it has an efficacy of 94.1%. It requires two shots four weeks apart (Baden, *et al.,* 2021). When mRNA-1273 was tested in nonhuman primates, the vaccine induced neutralizing antibodies at levels higher than human convalescent-phase serum (figure 6). There was a dose-dependent increase in Th1-biased responses with low or undetectable Th2 or CD8 T-cell responses 4 weeks after the second dose. Vaccinated animals did not have evidence of viral replication or virus RNA identified in broncho-alveolar lavage fluid or nasal samples. There was also limited lung inflammation on day 2 post exposures to SARS-CoV-2 virus in the vaccinated group (Corbett, *et al.,* 2020b).

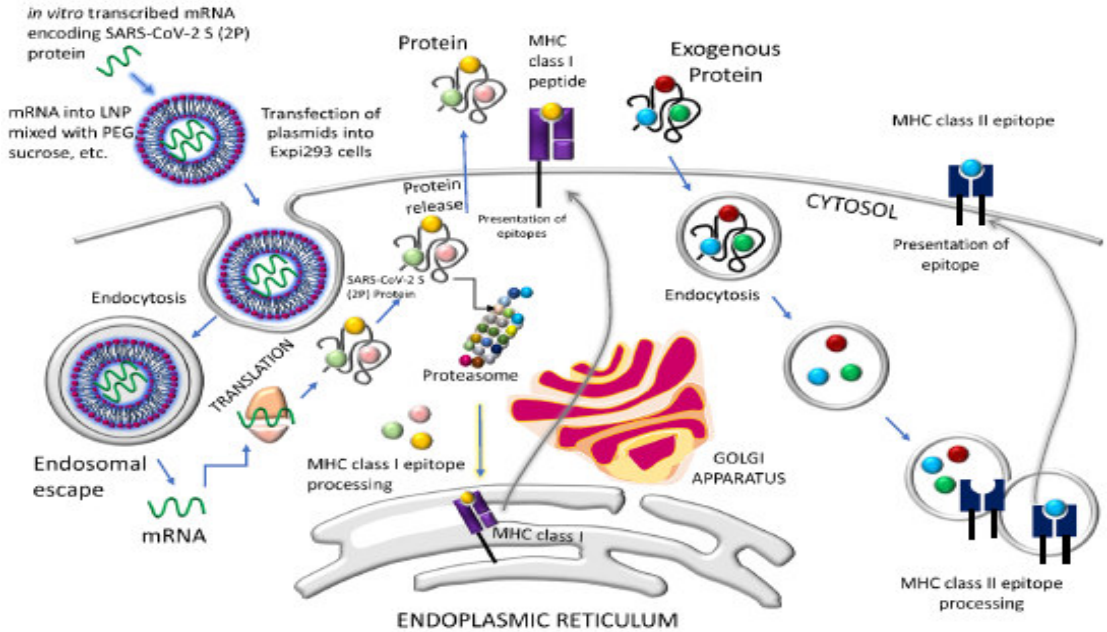

Figure 6. The mechanisms of action of the mRNA-1273 vaccine. Following endocytosis, the mRNA is translated to SARS-CoV-2 S protein, which is released and also undergoes the MHC class I processing for the antigenic presentation on the host cell surface. The exogenous protein undergoes endocytosis followed by processing by MHC class II (Jackson, *et al.,* 2020)

Pfizer–BioNTech Vaccine (PBV)

After the onset of the pandemic, Pfizer and german BioNTech collaborated and compared four mRNA-based vaccines to select a potential candidate against SARS-CoV-2 infections. Based on the trial results vaccine candidate options were narrowed down to two : BNT162b1 encoding receptor-binding domain, trimerized by adding a T4 fibritin foldon domain and BNT162b2 encoding full length S protein modified by two proline mutations (Vogel, *et al.*, 2020). The PBV is given in two doses 3 weeks apart (Seladi-Schulman and Goodwin, 2021). It is also recommended that vaccinated individuals receive a booster shot, or a third dose, within 12 months of being fully vaccinated and then annually thereafter. The vaccine is 95% efficacious in protection (Seladi-Schulman and Goodwin, 2021).

PBV offers strong protection against COVID-19 within 10 to 14 days of the first dose regardless of the recipient's race, weight, or age (Amit, *et al*., 2021). It can produce strong antibody and T-cell immune responses. This vaccine does not cause any serious side effects but frequently causes short-lived symptoms such as pain at the site of injection, mild fever, fatigue, and muscle pain (Polack, *et al*., 2020). It is interesting to note that BTN162b vaccines are suggested to be shipped and stored at ultra-cold temperature of (-80˚C) which imposes difficulties on its usage in certain countries (Vogel, *et al*., 2021).

CVnCoV Vaccine of CureVac (CVV)

It is produced by Tübingen's CureVac biotech firm in partnership with the Bayer Company and is currently in its combined phase 2b/3 clinical trial. This vaccine is considered a rival to the leading mRNA vaccines of PBT and MV (Abdulla, *et al.,* 2021). The CVV is, unlike the PBT and MV; it utilizes a natural, non-chemically modified, synthetic mRNA coding the prefusion-stabilized full-length spike protein of SARS-CoV-2. The CVV is administered intramuscularly in two-dose regimen, with the interval of four weeks. This vaccine requires lower doses (12 µg) than the 30 µg for PBV and the 100 µg for MV (https://www.curevac.com/en/covid-19/). The manufacturers claimed that it showed an efficacy of 95%. The vaccine remains stable for at least three months when it is stored at 5 ºc as suggested by its manufacturer. Moreover, it can be stored at room temperature as a ready-to-use the vaccine for up to 24 hours which makes it suitable for usage in poorer countries (Abdulla, *et al.,* 2021).

Non-replicating and Replicating Viral Vector-Based Vaccines

These types of vaccines utilize replication-deficient or attenuated replication-competent (bioengineered) viral vectors (Lundstorm, 2020; Zhu, *et al.,* 2020a). It can effectively introduce genes encoding viral antigens into host cells. The infected cells produce and release immunogenic antigens after certain period of vaccination (Enjuanes, *et al.,* 2016). Many viral vector platforms that have been tested in SARS-CoV and MERS-CoV are being explored in COVID-19 vaccines, including adenovirus (both human and non-human primates), measles virus, modified vaccinia virus Ankara (MVA), parainfluenza virus, rabies virus and vesicular stomatitis virus (VSV) (WHO, 2020). The most common replication-incompetent viral vectors currently in use are human Ad5 and Ad26 adenoviruses and a modified version of the chimpanzee adenovirus ChAdOx1. This vector carries and deliver double-stranded DNA segment of the RNA of SARS-CoV-2 that codes the S-protein antigen of the virus (Abdulla, *et al*., 2021).

After injection, genetic material escapes from the vectors and travels to the nucleus, where the DNA is stored but does not integrate with the body's DNA (Lundstorm, 2020; Zhu, *et al*., 2020a). Afterwards, it is transcribed into mRNA that leaves the nucleus to be read and "translated" into spike proteins; these proteins begin to be assembled on the surfaces of infected cells. Once the S proteins or their fragments are recognized by the immune system, it starts to send warning signals and generate specific neutralizing antibodies and activated T cells (CD4+ and CD8+), as well as memory cells of the B- and T-cell types. The protection generated from these vaccines ranges between 62 and 90% (average at 70%) (Kyriakidis, *et al.*, 2021; Peng, *et al.,* 2020). The vectors used with these vaccines have a tough protein coat that helps in protecting the genetic material inside them. For this reason, the vaccine does not have to stay frozen and can be stored for at least 6 months at refrigerator temperatures (2–8 ºc) (Peng, *et al.,* 2020).

Oxford–AstraZeneca Vaccine (OAV; AZD 1222; Vaxzevria)

AZD 1222 was developed by Oxford University and Jenner institute (AstraZeneca). It was one of the first to begin clinical trials and the only one using a debilitated chimpanzee adenovirus (ChAdOx1). AZD1222 vaccine expresses SARS-CoV-2 spike protein (Folegatti, *et al.,* 2020). The AZD1222 vaccine team published their phase I/II trial interim report in July 2020 and showed that AZD1222 can elicit S protein-specific antibody and T-cell response and induce neutralizing antibody in all participants after the prime-boost regimen (Folegatti, *et al*., 2020).

It has an acceptable safety profile and is efficacious in combating symptomatic COVID-19. In addition, this vaccine is effective against the new and more contagious U.K. SARS-CoV-2 variant B.1.1.7, and partially (10%

efficacy) against the South African B.1.351 variant (Wise, 2021). The OAV was reported to have an efficacy ranging from 62 to 90%, according to the two-dosage protocol of SD/SD or LD/SD, respectively (Voysey, *et al.,* 2021; Knoll and Wonodi, 2021). Furthermore, this vaccine can be kept at refrigerator temperatures, 2–8 ºc) for at least six months, which makes it easy to store, transport, and distribute globally (Voysey, *et al*., 2021; Knoll and Wonodi, 2021). The OAV triggers strong humoral and cellular immune responses. Again, this vaccine produces minor side effects, such as fatigue and headache (Knoll and Wonodi, 2021).

Sputnik-V Vaccine (SVV)/ Gam-COVID-Vac

SVV vaccine was developed by Gamaleya Research Institute of Russia and named in memory of the Soviet-era satellite program. This vaccine utilizes a combination of two adenoviruses that are not recognized by the human immune system as foreign (Jones and Roy, 2021; Logunov, *et al*., 2021). The first dose contains HAdV-26 vectored vaccine. The booster dose, given after 21 days, is composed of HAdV-5 vectored vaccine. It can be stored at a standard freezer temperature of -20°C. The vaccine is safe and well tolerated and there were no unexpected severe adverse effects. Cellular immunity, neutralizing antibodies, and RBD specific IgG were detected in all participants being vaccinated. The phase 3 trial results showed that, the vaccine had an efficacy of 91.4% on Day 28 after the first dose and efficiency above 95% on Day 42 after the first dose (Shim, *et al.,* 2012)

Johnson and Johnson Vaccine (J&J V; JNJ-78436735)

JNJ is developed by Janssen Pharmaceutical Companies of Johnson & Johnson. Their candidate is a replicating-defective adenovirus 26 based vector expressing the stabilized pre-fusion S protein of SARS-CoV-2. Their main difference from the CanSino vaccine candidate is the adenovirus serotype. As opposed to the ubiquitous Ad5 serotype, very few people have been exposed to the rare Ad26 serotype; therefore, pre-existing immunity against the vector reducing this candidate's immunogenicity is not expected to be a major concern. The second advantage of this candidate is that the dosing schedule involves a single immunization (Kyriakidis, *et al.,* 2021). In the phase I/II clinical trial, the vaccine JNJ-78436735 induced robust humoral and cellular immune responses in middle-age adults and the elderly (Sadoff, *et al.,* 2020).

JNJ-78436735 was administered at either dose levels of 0.5 × 1011 or 1 × 1011 viral particles per vaccination in participants. The reactogenicity of the vaccine was mild, mainly causing injection site pain, fever, headache, and myalgia. It can produce a neutralizing antibody response in 90% of vaccinated people after four weeks and in all recipients after two months. The JJV shows an efficacy of 66% globally and 72% in the United States. It is also capable of protecting against the SARS-CoV-2 variant of the B.I.351 lineage observed in South Africa. It can be stored for up to 3 months at refrigerator temperatures (2–8ºc) and for two years at (-20 ºc). It showed 66% effectiveness in preventing infection after a single dose and was capable of preventing 85% of severe COVID-19 cases 28 days after vaccination (Kyriakidis, *et al*., 2021).

AD5-nCoV (Convidecia) Vaccine

The AD5-nCoV vaccine is prepared by the Chinese CanSino Biologics Company in cooperation with the Academy of Military Medical Sciences. The Convidecia vaccine is based on using human adenovirus serotype 5 vectors (Ad5) to deliver the information that codifies for SARS-CoV-2 full-length S protein into host cells (Kyriakidis, *et al.,* 2021). It is currently in phase 3 clinical trials, and the Chinese government has already approved it for military use, for a period of one year. The efficacy of the vaccine after a one-shot dosage is 65.7%. It has the advantage of being suitable for storage at refrigerator temperatures (2–8°C). No serious adverse reactions after vaccination have been reported (Zhu, *et al*., 2020b).

Recombinant Protein Subunit Vaccines

These types of vaccines utilize no genetic materials but use whole or fragments of viral proteins packed in nanoparticles (Pollet, *et al.,* 2021; Arunachalam, *et al.,* 2021). This type of vaccine is considered very safe and incapable of causing disease. Five vaccines of this type are in preclinical trials utilizing different protein (peptide) subunits (Tan, *et al*., 2021). Since these subunits are poorly immunogenic, they require adjuvants and repeated administrations (Arunachalam, *et al.,* 2021). They can primarily induce reasonable CD4+ T-cell activation and specific neutralizing-antibody responses, but they show poorer stimulation of CD8+ T cells. Three types of recombinant protein subunit vaccines are described in the subsections below; they are in the late stages of phase 3 clinical trials or have received authorization in some countries (Wadman, 2021).

Novavax (NVX-CoV2373) Vaccine

The NVX vaccine is manufactured by a Maryland-based company, Novavax, in collaboration with GSK and Sanofi, two companies in the United Kingdom and France, respectively. It is a recombinant protein nanoparticle vaccine composed of trimeric spike glycoproteins and a potent Matrix-M1 adjuvant. Attaching viral proteins onto a nanoparticle carrier is used to aid efficient delivery and uptake by body cells (Keech, *et al.,* 2020). The

vaccine is administered in two doses three weeks apart by intramuscular injection. It can produce a strong antibody response, as well as T-cell activation (Wadman, 2020). It is stable at refrigerator temperatures and has an efficacy of 89.3%, reaching up to 96% in a U.K. clinical trial (Wadman, 2021).

ZF 2001 (RBD Dimer) Vaccine

The latest subunit vaccine candidate to enter Phase 3 clinical studies is the adjuvanted RBD-dimeric antigen designed by Anhui Zhifei Longcom Biopharmaceutical and the Chinese Academy of Medical Sciences. Phase 3 clinical study was launched on December 2020 (http://en.nhc. gov.cn/2020-11/20/c_82209.htm). The ZF 2001 vaccine is administered in a three-dose course with the doses given 4 weeks apart by intramuscular injection. The efficacy of this vaccine is officially unknown, as it is in a phase 3 clinical trial, but it has been approved for emergency use in Uzbekistan and China (Dai, *et al*., 2020).

EpiVacCorona Vaccine (EVCV)

The EVCV vaccine is manufactured by the Vector Institute, a Russian biological research center. It is based on using fragments of synthetic viral peptides reflecting SARSCoV- 2 antigens. It is given in two doses three weeks apart by intramuscular injection to people over 18 years of age as well as older people >60 years of age (Abdulla, et al., 2021). The developers claimed that it is stable during storage at refrigerator temperatures for up to two years. Its efficacy is officially unknown, and it is awaiting regulatory approval. However, all the volunteers who were administered the EVCV developed specific antibodies against its antigens (Abdulla, et al., 2021).

DNA vaccine

Nucleic acid vaccines are genetic vaccines consisting only of DNA or RNA, which are taken up and translated into protein by host cells and elicit immune responses. Because they contain no viral coat, naked nucleic acids are not generally subject to pre-existing immunity that can hamper the clinical efficacy of recombinant virus vaccines. In terms of higher safety and lower cost of production, nucleic acid vaccines have some major advantages over other types. Post-translational modifications under natural conditions are reproduced by the plasmid encoded protein, retaining immunogenicity (Sardesai and Weiner, 2011) and humoral and cellular immune-stimulating capabilities, simultaneously (Liu, 2011). Although there have been concerns about the safety of DNA vaccines in these early stages of development (Nichols, *et al.,* 1995), it appears that viral genes integration into host genes through plasmid vectors is extremely rare (Sheets, *et al.,* 2006).

DNA vaccines are routinely constructed from plasmid DNA molecules that encode one or more antigens. Once delivered, the plasmid DNA vaccine is internalized by host cells at the immunization site or by migrating antigen-presenting cells (APCs), where in order to induce an adaptive immune response; the DNA must enter the cell nucleus (Porgador, *et al.* 1998). Finally, the target gene is expressed and translated into protein (Leitner, et al., 1999). DNA vaccines are, to some extent stable as compared to mRNA-based vaccines. Plasmid DNA technology allows simple production of large quantities of vaccines with the possibility of conferring long-term immunity. An advantage of this kind of vaccine is the stimulation of both humoral and cellular immunity (Rauch, *et al.,* 2018). However, the disadvantages looming over DNA vaccines are due to their limitation of processing protein immunogen and the risk of vector chromosomal integration and mutations in the host genome (Kutzler, *et al*., 2008).

ZyCoV-D vaccine

ZyCoV-D has developed by Zydus Cadila health care limited in India. It is world's first plasmid DNA vaccine for covid-19 ever approved for mankind (Teijaro and Farber, 2021). This vaccine encodes the Spike protein-induced neutralizing antibody responses and T-helper-1 pro-inflammatory interferon-gamma responses in mice, guinea pigs and rabbits (Dey, *et al.,* 2021). The pVAX-1 vector is used in conjunction with a specific order encoding S-protein from the Wuhan strain of SARS-CoV-2. Phase 3 clinical trial shows promising results against the delta variant of SARS-CoV-2. During trial the vaccine was found to be safe and effective. The preliminary analysis in symptomatic RT-PCR positive cases revealed that ZyCoV-D had a primary efficacy of approximately 66.6%. The third dose of the vaccine proved to be 100% effective against moderate disease (Teijaro and Farber, 2021).

INO-4800 vaccine

One of the DNA vaccine candidate developed by US-Inovio Pharmaceuticals company. It can be delivered to cells intradermally. Administration of this vaccine requires the use of an electroporation device called CELLECTRA, to make the human cells more permeable and thus enables proper entry and incorporation of the DNA molecule into the cell. This candidate consists of plasmid DNA that, upon administration, prompts human cells to produce the antigenic SARS-CoV-2 spike protein. While DNA vaccines carry certain advantages, including optimal development speeds and thermostability, past trials have shown that producing sufficient

immunogenicity can be a challenge (Tregoning and Kinnear, 2014). Additionally, administration can often require larger volumes of DNA vaccine compared to more traditional vaccine types, and it requires the use of an electroporation device, which can be inconvenient (Tregoning and Kinnear, 2014).

bacTRL-spike vaccine/ live Bifidobacterium vaccine

It is developed by Symvivo Corporation in Canada. This vaccine is constituted by *Bifidobacterium longum* engineered to deliver synthetic DNA encoding the spike protein from SARS-CoV-2 contained in a plasmid vector. Now days it is under phase 1 clinical trial to analyze the safety and immunogenicity profiles of bacTRL-spike vaccine against SARS-CoV-2 (NCT04334980). The vaccine is orally administered, and the gut colonization by B. longum should provide continuous delivery and expression of SARS-CoV-2S protein encoding plasmids. A mucosal, systemic humoral and cell-mediated immune response is foreseen as a result of the translation of this plasmid within the gastrointestinal lymphoid tissues (Galdiero, *et al*., 2021).

GX-19 vaccine

GX-19 vaccine has developed by Biotech firm Genexine Inc. of South Korea. The vaccine constitutes a synthetic soluble spike DNA-based candidate. The ectodomain of the S gene has been codon optimized for increased antigen expression in mammalian cells and sub cloned into the plasmid pGX27 vector. Preliminary studies have shown that electroporation- enhanced GX-19 induced robust antibody and T cell responses. Furthermore, vaccination of GX-19 was shown to confer effective protection against SARS-CoV-2 challenge at 10 weeks following the last vaccination in immunized non-human primates supporting further expectations for GX-19 as a vaccine candidate against SARS CoV-2 in ongoing human clinical trials (Seo, *et al*., 2021).

Virus like particle vaccine

Virus-like particles (VLPs) are self-assembled viral structural proteins that mimic the conformation of native viruses but lack the viral genome. The VLP displays multiple copies of the target antigen on its surface and has a size that enhance recognition and subsequent uptake from antigen presenting cells, therefore promoting its efficient phagocytosis, processing, and presentation by dendritic cells, and inducing strong and broad humoral and cellular immune responses (Kyriakidis, *et al.* 2021). VLPs are unable to replicate or reverse mutate, suggesting better safety, especially for viruses that cause high morbidity and mortality. Up to now, VLP vaccines have been commercialized for the protection against human papillomavirus and hepatitis B virus (Lan, *et al.,* 2014).

VLPs are generally produced by encoding the viral structural proteins and expressing them in heterologous systems, such as recombinant vaccinia virus, mammalian cells (293T, CHO), baculovirus, yeast expression systems and plant expression vectors (Mohsen, *et al*., 2017). In practice, VLPs-based vaccines are similar to whole inactivated virus vaccines, but the antigenic proteins may be better preserved and exposed to the immune system since no inactivation step is performed. Therefore, it is less likely to affect the immunogenicity of viral proteins due to surface epitopes destruction. Moreover, since no live virus is used in any steps for the production, VLPs are conveniently accomplished in low-containment manufacture settings (Kushnir, *et al.,* 2012).

None of the VLP vaccines have yet been approved for use, but there are three promising VLP vaccines under development. Firstly, the Canadian company Medicago has genetically engineered plants. it uses the virus-transfected plant Nicotiana benthamiana to express the prefusion trimeric subunit form of the SARS-CoV-2 S-protein and assemble it on the surface of VLPs which are harvested and used for immunization (Kyriakidis, N.C., *et al.,* 2021). VLP vaccine is in phase 2/3 clinical trials and was recently granted Fast Track designation by the U.S. FDA (Abdulla. *et al*., 2021). Secondly, the ContiVir team at the Max Planck Institute for Dynamics of Complex Technical Systems (Magdeburg, Germany) has designed and produced a virus-like particle vaccine. Thirdly, a Georgia-based biotechnology company, GeoVax Atlanta, has used MVA (modified vaccinia virus ankara viral vectors to express VLPs (Jeyanathan, *et al.,* 2020).

Live attenuated vaccine

Live attenuated vaccines are live viruses weakened by deleting or mutating the pathogenic component of the viral genome. Similar to whole inactivated vaccines, they possess nearly the full immunogenic components of the original virus. Furthermore, they preserve the native conformation of viral antigens and present antigens to the immune system as in natural infections. Therefore, live attenuated vaccines are the most immunogenic kind of vaccine that does not require adjuvants to obtain an optimal response and have a long history of success in controlling a variety of infectious diseases (Minor, *et al*., 2015). However, live attenuated vaccines also carry a higher risk than other types of vaccines, including the possibility of reversion to a virulent state and the danger of persistent infection in immunocompromised patients (Li, *et al.*, 2020).

Historically, many human vaccines have been based on empirically attenuated strains of the actual pathogen, with deletion or mutation of virulence genes through a serial passage into animal models or tissue cultures. At

each “passage”, the selected viruses improve in infecting and replicating in the selected cell cultures but more and more their ability to enter and replicate in their original human host is lost. Attenuation can also be reached by growing microorganisms in suboptimal conditions (i.e., low temperature passages) allowing the selection of less virulent strains (Plotkin, 2014). This method selects viruses that replicate well in a colder environment but less well at body temperature, thus decreasing their pathogenicity in the human host, resulting in an attenuation of virulence while maintaining the ability to induce the immune response (Lauring, *et al*., 2010). Examples of live attenuated vaccines are: the measles vaccine, the BCG vaccine, the rabies vaccine, the yellow fever vaccine and the polio vaccine (Galdiero, *et al.* 2021). The virus strains are attenuated by mutating or eliminating virulence genes by means of genome engineering. The deletion of non-structural proteins, but also structural proteins such as protein E, has been proposed to design vaccine strains of various zoonotic and veterinary coronaviruses (Netland, *et al.,* 2010; Hou, *et al.,* 2019).

The envelope (E) protein, besides its structural roles, has a major role in inflammasome activation and is associated with exacerbated inflammation in the lung (Cao *et al.,* 2010). In addition, non- structural protein 16 (Nsp16) encodes ribose 2′-O-methyltransferase that is required for 5′ capping of viral RNA and it is viable target for the coronavirus vaccine (Qiu, *et al*., 2005). This methylation helps coronavirus avoid the activation of type I interferon-dependent innate immune response by viral RNA, and therefore deletion of E protein and nsp16 attenuates virulence of the virulence (Qiu, *et al*., 2005). SARS-CoV mutants lacking the E gene and nsp16 mutant vaccines have been reported to provide protection against challenge (Du, *et al.,* 2009; Wang, *et al*., 2020). Moreover, nsp14, which encodes exoribonuclease (ExoN) involved in RNA proofreading during replication, is also a useful target for live attenuated coronavirus vaccine (Tang, *et al*., 2014). The loss of ExoN will cause a profound decrease in replication fidelity, and lead to attenuation of coronavirus pathogenesis and reduce its virulence (Tang, *et al.,* 2014).

The new strategies of codon pair deoptimization method produces a chemically synthesized genome with the amino acid sequence identical to the original virus but containing a greater number of CpG and UpA RNA dinucleotides to upregulate host responses by swapping optimized and non-optimized codons (Coleman, *et al.,* 2008). So far, there are only three attenuated SARSCoV-2 vaccines generated by codon deoptimization in preclinical development, from Mehmet Ali Aydinlar University (Turkey), Codagenix and Serum Institute of India, and Indian Immunologicals Ltd and Griffith University (Brisbane, Australia) (Tang, *et al.,* 2014). Codagenix and the Serum Institute of India are involved in the development of a live attenuated SARS-CoV-2 vaccine, using codon deoptimization technology, following on their previous experience with vaccines against RSVand influenza using the same technology (Tregoning, *et al.,* 2020).

CONCLUSION AND RECOMMENDATIONS

Since the discovery of human coronaviruses, new types of coronaviruses have kept emerging and have gradually become a serious threat to global public health. Despite there have been almost two decades since the first coronavirus outbreak, the scientific community and other concerned body are not collaborated and well prepared with effective vaccine to tackle this virulent virus. Hence the emergence of SARS CoV-2 infection caused health crisis, psychological fear, economic loss and socio-politics turbulence across the world wide. Thereafter, a historically great number of scientists, clinicians, researchers and all government officials around the world were mobilized to work together in order to develop vaccines to mitigate this global disastrous. The global scientific community has investigating the virus origin, genome, pathogenesis, and so far developed many different vaccines which have virus immunogenicity in unprecedented timeline. Owing to urgent need of the vaccine, some vaccines get approval before it has fully developed for emergent use with minor side effects. In addition, the virus can mutate and become the bottle neck for the development vaccines and its sustainability. Lastly with the dedication of global scientific communities and all other stakeholders sooner or later the safer, efficient and multivalent vaccine will be developed.

Based on the above conclusions the following recommendations were forwarded:

1. Despite it is necessary to develop a vaccine quickly, assurance of vaccines safety and efficacy are essential and should get priority.
2. Although, there are a numbers of candidate vaccines licenced for urgent use, still safer and higher efficacy vaccines with no minor side effects should be developed.
3. Vaccines that can be stored and shipped at optimum temperature should be developed to make it suitable for the usage in poorer countries.
4. The virus genome needed to be regularly sequenced and analysed in order to advance vaccine development and to maintain vaccine sustainability.
5. The current vaccine’s S protein should be replaced with the renovated molecules with the required changes in the specific amino acid to effectively combat the upcoming SARS-CoV-2 infection
6. All responsible body should be committed to develop inestimable and pan-coronavirus vaccines that provide broad protection against more than one of these pathogenic viruses.

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