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Current Status of Vaccines Developed for SARS-CoV-2 Infection: A Review

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Abstract

COVID-19 is a respiratory disease caused by SARS-CoV-2 which at the beginning of 2020 started a global pandemic. During the pandemic, multiple medications have emerged to treat it, however, the best way to control this calamity is through the prevention giben y vaccines. This review has the aim of understanding the immune response triggered by SARS-CoV-2 and the strategies used by vaccines to fight it during the COVID-19 pandemic. The search was made in PubMed, Google Scholar, and Scopus using "SARS-CoV-2", "COVID-19", "vaccines", "immune response", and "infection" as keywords, then 120 articles were selected. The challenge posed by SARS-Cov-2 infection has been addressed with the development of effective vaccines in a short time, additionally, some of them are innovative such as RNA vaccines. However, phase 3 trials indicate variations by population group that have had to be adjusted for the vaccine to be effective in different parts of the world. The current challenge is imposed by effective immunization against the variants that have emerged and are more contagious. [*Bangladesh Journal of Infectious Diseases, April 2022;9(suppl_1):S40-S54*]

Keywords: Acute severe respiratory syndrome; SARS-CoV-2; COVID-19; vaccines; immune response

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Introduction

The current pandemic that began at the end of 2019 in the city of Wuhan in China, is caused by a coronavirus called SARS-CoV-2[1]. This virus has a positive-sense single-stranded RNA genome, which encodes for 16 non-structural proteins (Nsp) and four basic structural proteins: these are the spike glycoprotein (S, one of the most important), a small envelope protein (E), matrix protein (M) and

nucleocapsid protein (N)[2]. The spike protein (S) is the protein that gives the crown shape, this cleavage protein is capable of interacting with angiotensin-converting enzyme receptor 2 (ACE 2)[3].

The Nsp3 protein is encoded in the ORF1a/b as the large polyprotein 1a/b. It has different functions such as helping the polyprotein processing and assisting in viral replication by binding to the N protein and RNA. Additionally, it has demonstrated its pathogenic role in inhibiting the innate response[4]. Additionally, it interacts with the proteins Nsp4 and Nsp6 to allow the rearrangement of the endoplasmic reticulum membrane and assists in the recruitment of other non-structural proteins such as Nsp2, showing its direct relationship in the replication of viral RNA.[5] The Nsp6 protein also participates in the synthesis and expansion of autophagosomes[6].

Protein S is vitally important for a viral infection to take place. This protein contains two subunits called S1 and S2, of which S1 contains the transmembrane domain and S2 the extra-membrane domain, essential for fusion to the cell membrane[7]. The virus replication begins through the RBD (Receptor Binding Domain), the component of S1 responsible to recognize ACE2, key receptor for the entry of SARS-CoV and SARS-CoV-2 to the host cell. The virus uses S2 to fuse its viral membrane to the host membrane, causing structural changes in S2 and ACE2. Once the virus enters into the host, it exits from its vesicle and releases the viral genome into the cytoplasm, ORF1a and ORF1b are immediately translated into two polyproteins: pp1a and pp1b, which are cleaved by different proteases to produce 16 non-structural proteins. These proteins form the Replication and Transcription Complex (RTC) that translate the rest of the genome into structural and accessory proteins to later be packaged with subgenomic RNA forming a virion in the Golgi compartment and is finally released by exocytosis[8-10].

Once the virus interacts with the target cells of the respiratory tract, the infection takes place and can trigger the disease COVID-19[11-12]. Currently, there is no antiviral therapy, so the treatment of the infection is based on support therapy and the control of inflammation in critically ill patients[13]. For this reason, efforts are focused on containing the spread of the infection through maximum vaccination in all countries. Currently, there are a number of vaccines in phase 2 and 3 and some of them have been approved for application in the general community[14-15].

This review article describes immune response in COVID-19 and development of vaccines to contain the current pandemic caused by SARS-COV-2.

Immunopathology of SARS-CoV-2 Infection

The effective defense mechanism against SARS-CoV-2 infection is the first line of defense for innate immunity. The mechanical barrier that constitutes the ciliated epithelium of the respiratory mucosa, together with reflex mechanisms such as coughing and sneezing, eliminate most of the viral load that enters after contact. In addition, chemical factors such as mucus, pH, lysozyme, surfactant SP-1 secreted by type 2 pneumocytes, among others, constitute an important complement in the effective action against the virus in this first line of defense[16-17].

In viruses that infect the cell, their viral RNA is recognized as pathogen-associated repetitive molecular patterns (PAMPs) by cytoplasmic pattern recognition receptors (PRRs). Retinoic acid acid type receptors (RLR) and Toll-like receptors (LTR) (LTR-3, LTR-7 and LTR-8) are the most important in the recognition of the coronavirus genome, triggering a signal transduction cascade that leads to the activation of transcriptional factors: interferon inducing factor (IRF) and nuclear kappa-B (NF-κB) with the consequent expression of the genes encoding type I and III interferons (INF)[18-20]. During the initial stage of infection, the production of type I and III INF is the main mechanism in the antiviral response. Type I and III INF together with TNF-α, IL-1, IL-6 and IL-8 are released in order to increase the adaptive immune response[19-20]. The most critical complications occurring in COVID-19 suggest an important immunopathogenic role in the disease[21-25].

A higher level of helper T cells (CD3+, CD4+) and cytotoxic suppressor T cells (CD3+, CD8+) are present in asymptomatic patients[21], while severe patients show lower levels in peripheral blood, clarifying the important role of lymphocytes in the immune response and control of infection[22]. Some investigators suggest that the cause of lymphopenia may be related to increased levels of the interleukinsIL-6, IL-10 and tumor necrosis factor alpha (TNF-α). These cytokines are believed to induce the expression of lymphocyte-retaining adhesion molecules in lymphoid organs and binding to the endothelium[23-25]. This hypothesis is supported by increased lymphocyte counts in COVID-19 patients treated with tocilizumab, an IL-6 antagonist[24-25]. Interestingly, lymphopenia affects cytotoxic suppressor T cells more than helper T cells, with a consequent decrease in the ability to destroy

infected cells[21]. Additionally, secondary hemophagocytic lymphohistiocytosis (sHLH) has been reported in critically ill patients, inducing down-regulation of cytotoxic T and NK cells, thus increasing levels of inflammation[22].

However, high levels of type I IFN have been detected in patients with severe COVID-19, probably caused by its delayed production that triggers the dysregulated immune response observed in these patients.[23] On the other hand, it is suggested that there is an increase in prostaglandin D2 and phospholipase A2 (PLA2G2D) with advanced age. These molecules are associated with a defect in migration and the weak response of T cells[24]. Lymphocyte and macrophage infiltrations have been found in the lungs of postmortem COVID-19 patients[25]. The pulmonary infiltration of macrophages is probably caused by a delay in the production of type I IFN that causes dysregulation of the early control of the infection. As a consequence, massive activation of neutrophils and monocyte-macrophages is triggered with the consequent increase in the production of inflammatory cytokines and greater recruitment of myeloid cells causing lung injury[26-27]. The injured lung tissue elicits a response known as "Macrophage Activation Syndrome" (MAS), which increases the production of pro-inflammatory cytokines such as IL-6 and the recruitment of a greater number of macrophages and pro-inflammatory granulocytes[27].

Coronaviruses have mechanisms to evade immune recognition. In this sense, it has been shown that the viral protein Nsp15, which is an endonuclease, hydrolyzes the polyuridine junctions at the 5´ end of the viral genome, preventing the recognition of cytoplasmic PRRs[28]. SARS-CoV-1 and SARS-CoV-2 share similar mechanisms of immune response evasion. In the case of interaction with Mitochondrial Antiviral Signalling (MAVS), there is evidence that ORF9b sequence of SARS-CoV-2, interacts indirectly with the MAVS signalling adapter, similar to SARS-CoV-1. The Nsp13 of SARS-CoV-2 interacts with the intermediate signalling between TBK 1, while in SARS-CoV-1 it is the M protein that suppresses the TBK1 complex signaling[29]. These mechanisms allow the virus to elude the immune response and replicate more efficiently.

Immunological Target for SARS-CoV-2 Vaccines

The understanding of the mechanism of entry to the host is the main tool used to design the vaccine target, thereby the principal target used in vaccines is the RBD, the key protein that permits the first contact with ACE2.[3] Consequently, most vaccines have been designed to trigger antibodies against the RBD or the whole S protein. Interestingly, RBD was shown to be capable of producing neutralizing antibodies (NAb) and T cell responses[30]. The immunization with RBD in rodents, generated effective Nab[31]. On the other hand, the M, N and Nsps proteins also have potential, since they are associated with an unbalanced immune response in the host, because these interfere with different immunization chains[32]. In the peripheral blood of convalescent patients, high levels of helper T lymphocytes reactive to the S, N and M proteins and low levels against the Nsp3, Nsp4 and ORF8 proteins have been determined[33]. Also, a robust response cytotoxic suppressor T cells against M and S proteins and a notable response against Nsp6, ORF3a and N protein has been found[34]. However, the cellular immune response against protein S turns out to be the most immunogenic[35]. SARS-CoV infection triggers a humoral immune response that generates specific antibodies against the virus (immunoglobulin (Ig) G and IgM) that are detected approximately 2 weeks after infection and reach their maximum peak at 60 days, with levels remaining high for up to 180 days. High titers of neutralizing antibodies specific to SARS-CoV have also been reported in patients recovered from SARS[36]. These findings suggest that immune responses, both humoral and cellular, are crucial for the elimination of SARS-CoV2 infection. This is why the induction of antibodies such as the T cell response are necessary to generate an optimal long-term protective response.

Type of vaccines Developed against SARS-CoV-2

Several therapeutic strategies have been proposed to develop vaccines that stop the spread of SARS-CoV-2 infection. The main strategies used are summarized below.

Whole-Virus Vaccines: The vaccines with the oldest history of success, undoubtedly are the whole virus vaccines. This type of vaccine is characterized by the presentation of the whole virus to the immune system, which causes a response against every protein of the virus, and consequently one of the most immunological responses between different types of vaccines. The whole virus vaccines are divided into live-attenuated vaccines, inactivated vaccines, and pseudo viral particles. This type of vaccine commonly requires a strict cold chain for its preservation[35, 37].

Live-Attenuated-Virus Vaccine: The live-attenuated vaccine consists in a weakened version of

the virus, which can be recognized by the immune response and easily destroyed. This type of vaccine triggers a very effective immune response, but there is the possibility that the attenuated virus may become pathogenic in patients with immunodeficiency[38]. This type of vaccine is commonly injected intramuscularly, however it can be received intranasally in a procedure that doesn´t require pre-trained healthcare personnel. The creation of live-attenuated vaccines can be done in different ways, one of them is codon deoptimization, in which a rational modification of the virus genome is made in the genes responsible for counteracting the immune response[39-40]. On the other hand, the virus can be attenuated by adapting it to unfavorable situations such as temperature or growth in non-human cells[40]. As the virus is replicating inside the vaccinated individual, it generates immunity for both structural and non-structural proteins. In addition, it should be taken into account that if the vaccine can be inoculated intranasally, it could generate immunity of the respiratory mucosa, which can lead to protection of the upper airways[41]. As an example, it is known that the E protein plays a key role in the exaggerated pulmonary inflammation seen in ICU patients, so a deletion of this protein could have encouraging results for live-attenuated vaccines[39, 41].

The principal benefits of this type of vaccine are its high immunogenicity and its ability to induce TLRs[39]. Since a long time ago, has been demonstrated the production of TLR in response to different live attenuated vaccines, one of them is the yellow fever vaccine YF-17D in use since 1937[42]. This vaccine has shown to activate the intracellular receptors TLR3, TLR7, TLR8, TLR9, and the TLR2 transmembrane receptor on plasmacytoid and Dendritic cells (DCs)[43.] Probably, the multiple TLR activation could be one factor that allows the yellow fever vaccine to induce high affinity neutralizing antibody responses in mice along his entire lifespan[38]. In humans, the yellow fever vaccine has shown to be highly immunogenic and provide long term protection[42]. The disadvantages of this type of vaccine are the necessity of very specific conditions for the preservation, which is not feasible for countries with a deficient infrastructure, and the risk of a virus reactivation in patients with immunodeficiency[39].

Codagenix Inc. and the Serum Institute of India are the strongest candidates in the development of live-attenuated vaccines, showing their effectiveness and safety with previous trials done for influenza virus and respiratory syncytial virus. Their vaccine is a single dose, intranasal and live attenuated vaccine known as COVI-VAC, which in January 2021 began a phase 1 trial (NCT04619628). At the moment there is no report of other trials. They used Codavax technology by de-optimizing codons to attenuate the virus[44]. The codon deoptimization is a technique used to reduce the virus replication maintaining the antigenic identity, and consequently the immunogenicity. The process consists in rearranging the position of synonymous viral codons. This process doesn't change the encoded protein amino acid composition, but surprisingly affects the translation process, and therefore the replication.[41] The reason for the attenuation is not well understood yet, but has been hypothesized that it could be the high number of underrepresented codon pairs in the protein sequence that generate inadequate conditions for the translation and processing of the protein[39,41]. A benefit that differentiate this attenuation technique to others, is that the virus is not capable of reactivating in patients, thus the vaccines attenuated through codon deoptimization are safer than other attenuated vaccines[41].

Inactivated-Virus Vaccine: The inactivated virus vaccines have been used in many infectious diseases such as influenza, typhoid and HP. This type of vaccine is one of the most immunogenic types, however their effectiveness in vivo may be affected since it requires physical and chemical modifications in cell culture, which can alter the virus structure and turn it uneffective[45]. This type of vaccine is made by infecting a mammalian cell culture by a virus, then are added components that inactivate it, such as β-propiolactone or formaldehyde, resulting in a time-consuming but relatively easy process. However, it requires a biosafety level 3 laboratory and a good scale cultivation. An important benefit of these vaccines is that most of them can be conserved in a temperature between 2-8° C. Unlike Live-Attenuated-Virus vaccines, these do not have a risk of reactivation if the processes have been carried out fully[37].

Inactivated viruses have shown significant production of neutralizing antibodies. Unfortunately, it has been shown that in mice this type of vaccine produces poor protection at the time of presenting SARS-CoV.[46] In addition, it produces an eosinophilic inflammatory response and other pathologies associated with eosinophils in the lungs.[47] This immunopathology, caused by eosinophilia, has been related in some studies with the viral nucleocapsid[47]. The most sold vaccine of this type is developed by Sinovac Life Sciences and is called CoronaVac[48]. The BBIBP-CorV and an unnamed vaccine from China National Pharmaceutical Group, known as Sinopharm[49] and

Covaxin developed by Bharat Biotech, India, are the other licensed inactivated virus vaccines[50].

The CoronaVac vaccine, also known as PicoVacc, is made by the virus attenuation in a SARS-CoV-2 infected Vero cell culture, which is an African green monkey kidney cell culture[48]. The process of inactivation is gained by the use of β-propiolactone, once the virus is inactivated, it absorbed into aluminum hydroxide and diluted in a sodium chloride, phosphate buffered saline and water solution, prior to the sterilization and filtration, processes that finalize the vaccine manufacture[51]. The vaccine induced seroconversion in 92.0% of the adults and 98.0% of the 60 aged or older adults in the phase 1/2 interim analysis (ChiCTR2000031809) and demonstrated safety, although his effectiveness is in doubt due to preliminary results of phase 3 clinical trials in Brazil and Turkey that shows an efficacy of 50,4% and 83.5% respectively [52-53] and currently being assessed in Phase IV.

BBIBP-CorV vaccine is created from the SARS-CoV-2 WIV04 strain infected Vero cell culture that after its propagation is inactivated by the double addition of β-propiolactone. Then, the virus is exposed to aluminum hydroxide and absorbed by it, and ultimately is diluted in a phosphate buffered saline solution inside the syringe[49].

The phase 1/2 trials (ChiCTR2000032459) have demonstrated safety and seroconversion in all participants, indicating strong immunogenicity[49]. The World Health Organization (WHO) announced an estimate of the vaccine efficacy, using the clinical data derived from a multi-country phase 3 trial (NCT04510207), which resulted in 78,1% of efficacy[54]. In mid-March 2021, Phase IV clinical trials began. The vaccine without name, has demonstrated a strong immunogenicity among 320 patients in phases 1/2 clinical trials (ChiCTR2000031809), with a low rate of adverse reactions[45]. In the phase 1 trial, the low and high-dose groups, all participants presented seroconversion, while in the medium-dose group the seroconversion rate was 95.8%. In the phase 2 trial, the seroconversion rate was 97.6% demonstrating a high immunogenicity in both trials. Actually, a phase 3 trial (NCT04456595) that enrolled 12688 participants, is being carried out[46].

The BBV152 vaccine, also known as Covaxin, developed by Bharat Biotech, is produced by the NIV-2020-770 strain, which is characterized by its mutation in spike protein (Asp614Gly). The SARS-CoV-2 NIV-2020-770 strain infected Vero cell culture, and is then inactivated by β-propiolactone. Ultimately, the vaccine is administered with Algel-IMDG (toll-like receptors 7/8 agonist absorbed to aluminum hydroxide) as coadjuvant[50].

In the phase 1 trial (NCT04471519) showed a cellular response by the IFN-γ production from helper T cells and cytotoxic suppressor T cells in a subset of the Algel-IMDG groups[55]. In the phase 2 trial (NCT04471519), the seroconversion rate was 96.6% in the 6 μg dose with the Algel-IMDG group. There was an increase in $Th_{1/2}$ cytokines, like IFN-γ, TNF-α, IL-2, IL-5, IL-13 and IL-10, indicating a cellular response[56]. This vaccine has demonstrated a high seroconversion rate against the hCoV-19/India/2020Q111 strain, which shares all signature mutations with the UK variant[56]. Recently, Bharat Biotech announced a 78% vaccine efficacy according to a phase 3 trial interim analysis in which have been considered 25800 participants[57].

All the SARS-CoV-2 vaccines that will be presented below use protein S in its complete structure or its subunits (S1 and S2) as a target, since it generates the best humoral and cellular immunogenic response[17,19].

Pseudovirus Vaccine or Virus-like particle vaccine: A pseudovirus is a recombinant virus particle whose core and membrane proteins derive from other viruses. The main particularities of this type of virus are its proteins which have an altered structure compared to the original counterpart, nevertheless conserve a high similarity and are capable of enabling virus entry in the cell. Another particularity is its ability to replicate only one time since it entered the cell, which made it not pathogenic. Because of this particularity, this virus-like particle has been widely used in studies about cellular tropism, vaccines and many other processes related to the entry of the virus in the cell[58].

Pseudovirus vaccines have previously been used against Rift Valley fever virus (RVFV). This type of vaccine uses a recombinant vesicular stomatitis virus (VSV) infected cell culture.[59] The RVFV codon-optimized envelope glycoprotein sequences are incorporated in the recombinant DNA via pcDNA 3.1 expression vector, a plasmid. In mouse models, this vaccine showed neutralizing antibodies against glycoproteins, but not against other viral proteins[60]. Similar to this, a recombinant pseudovirus used against SARS-CoV-2 has been created. This vaccine consists of a VSV pseudovirus with the full length S protein on its membrane and contains the S protein gene from the Wuhan-Hu-1 strain, introduced in the genome by the eukaryotic expression plasmid pcDNA3.1.S2, used as a vector[61]. The isolation

process of the SARS-CoV-2 pseudovirus showed a high compatibility of the virus with human hepatoma cells7 (Huh7) cell cultures, which can be selected as the best substrate for SARS-CoV-2 pseudovirus replication. The presence of SARS-CoV-2 S protein on the pseudovirus membrane was confirmed by western blotting[61].

A pseudovirus system to create a vaccine against SARS-CoV-2 has not been used yet, in return the VSV pseudovirus system has been used in neutralization assays to test the efficacy of COVID-19 vaccines[58]. The main advantage is the mimicry of a structural virus with single cycle replication that can be manipulated in biosafety level 2 laboratories[59]. However, these types of vaccines are expensive to produce and require high doses for immunization[15, 16].

Viral-Protein-Based Vaccines: This type of vaccine contains only the most immunogenic viral proteins of the virus or the antigenic epitope. Therefore, it triggers a unique immune response against viral proteins, decreasing the side effects that other vaccines could cause[14-16]. Due to the small dimension of the antigen, this type of vaccine is generally administered with a protein adjuvant to facilitate immune recognition and enhance the immune response[62]. Furthermore, it is easy to manufacture at low cost and does not require a strict cold chain like nucleic acid vaccines or viral vectors[16].

Protein Subunit Vaccine or Recombinant Protein Vaccines: The protein subunit vaccine is based on the most immunogenic protein or one of its subunits. Thus, these vaccines use the whole S protein or uniquely a RBD epitope to generate a specific immune response[62]. These recombinant proteins can be produced by different types of cell culture, depending on the cell origin. The most used expression system in recombinant protein vaccines against SARS-CoV-2, is the insect cell culture which has been demonstrated to be a high density culture because of the high yield.[63-65] This system uses a baculovirus vector and an insect cell as host; it has an average cost, but its principal advantage is that it expresses well folded recombinant proteins that generally contain the desired post transcriptional modifications[63-65]. Another type of system widely used is based on mammalian cells, especially appreciated for its ability to express well folded glycoproteins in their native structures and with post transductional modifications, nevertheless this system has a high cost of production[66].

There are different recombinant protein vaccines against the SARS-CoV-2, the most promising are the NVX-CoV2373 developed by Novavax[67] and the ZF2001 developed by Anhui Zhifei Longcom Biopharmaceutical, the Institute of Microbiology and the Chinese Academy of Sciences[68]. The NVX-CoV2373 vaccine is based on a recombinant nanoparticle coated with the full length S protein, known as rSARS-CoV-2, it is administered with the Matrix M1 protein coadjuvant. The S protein used in rSARS-CoV-2, is derived from the wild type SARS-CoV-2, which have been produced in a baculovirus-Spodoptera frugiperda (Sf9) insect cell culture. With the aim of stabilize the S protein in a prefusion conformation have been realized two proline substitutions, one at the top of the heptad repeat 1 and the other in the S2 subunit, while another mutation has been realized at the furin cleavage site in the S1/S2 cleavage site to confer protease resistance[68].

The immune response against this vaccine, in the phase 1/2 trial (NCT04368988) has detected IL-2, IFN-γ, and TNF-α demonstrating a Th1 cellular response, while Th2 response was minimal[69]. The phase 3 trial (NCT04583995) carried out in the United Kingdom, showed a 96,4% efficacy[70]. In the case of the ZF2001 vaccine uses a RBD dimer administered with aluminum hydroxide as coadjuvant. The RBD dimer is produced by a CHOZN CHO K1 cell culture, that actually is a chinese hamster ovary cell culture. The phase 1/2 trials (NCT04445194; NCT04466085) suggested a higher safety and immunogenicity in a 25μg three dose regimen. The phase 2 trial showed a high seroconversion rate of neutralising antibodies 14 days after the third dose[68]. Actually, is ongoing a phase 3 trial (NCT04646590) that enrolled 29000 participants.

Both vaccines, the NVX-CoV2373 and the ZF2001 are injected intramuscularly and are stored at 2-8°C[67-68].

Peptide Vaccines: The peptide vaccines use the peptide that conforms the epitope recognized by the immune system. These vaccines are designed taking into account the advances in biotechnology, since for their manufacture design are used programs that allow the development of protein 3D models such as RaptorX, which permits to extract the epitope from them through biochemical processes, and tools such as VaxiJen, bioEdit and Prediction of T-Cell Epitopes[71]. This process is done in order to identify the epitopes that activate the cellular immune response from B cells and T cells, and synthesize them chemically. The B cell epitopes usually are

proteins, while the T cell epitopes are short peptide fragments[72].

The E protein is found within the host cell in the endoplasmic reticulum and the Golgi complex, it helps with the assembly, intracellular trafficking and budding of virions[73]. The E protein gene has been shown to have a higher probability to be immunogenic, so it has become one of the main targets for developing peptide vaccines[72-73]. Some advantages of this type of vaccine are its low allergic reactions occurrence, and its low probability of re-infection and serious autoimmune responses, especially in immunocompromised patients[73-74]. Furthermore, it confers significant flexibility regarding the integration of various epitopes in the same vaccine and consequently can cause an immune response against different antigens. The main disadvantage of this type of vaccine, is that the peptides used in it, can be easily degraded by enzymes, so they need modifications and a carrier protein to avoid it. They also need an adjuvant to improve the immune response[74].

Unfortunately, very few vaccines (15 specifically) reached phase 3 clinical trials, and only one has been used in Russia and China for early use[75]. The EpiVacCorona vaccine developed by the Vector Institute, is a peptide vaccine known to be the second choice vaccine in Russia[76]. This vaccine is composed of SARS-CoV-2 peptide antigens chemically synthesized in a laboratory. As previously mentioned, in this type of vaccine the peptides can be degraded by different enzymes, so it is conjugated with a carrier protein to avoid its degradation. Then the nanoparticle is absorbed on aluminum hydroxide, which acts as an adjuvant. Currently, is ongoing a phase 3 trial (NCT04780035) that enrolled 3000 participants[77].

Nucleic Acid Vaccines: This type of vaccine is relatively new compared to the others. It uses a DNA or mRNA strand to induce the production and migration of the antigenic protein from the nucleus to the host cell membrane surface, and thus generating an immune response. These vaccines use simple expression vectors such as plasmids, lipid nanoparticles and viral vectors, which facilitate their mass production. Additionally, have shown a robust antigenic expression and immunogenicity[78].

DNA vaccine

This type of vaccine uses a double stranded DNA (dsDNA) fragment which encodes a viral protein that acts as an antigen. The DNA is easy to degrade in extracellular space, thus lipid nanoparticles or viral vectors such as adenoviruses, measles virus, vesicular stomatitis virus and lentivirus are used to avoid its degradation[79-80]. The DNA can be delivered to the cell also through plasmids via electroporation, a low voltage electrical pulse that facilitates the entry of the plasmid to the host cell. In account of the dimensions of the vectors, an adjuvant is not required[80]. An important advantage is that the DNA can encode two or more antigens and is easy to manufacture[79]. However, this type of vaccine is associated with disadvantages related to the degree of purity, genomic integration and for some viral vectors, the preexisting immunity. A prototype of this type of vaccine has shown safety and good humoral and cellular immune responses represented by neutralizing antibodies, IFN-γ and helper and cytotoxic T cells cytokines production[80].

Plasmid-Based Vaccine

A plasmid-based vaccine is INO-4800 developed by Inovio Pharmaceuticals. This vaccine uses the pGX9501 plasmid that has been created using a genetic optimization algorithm known as "in silico" patented by Inovio. The production of the plasmid used in this vaccine consisted in the synthesis of an optimized S protein sequence and its digestion by Bam HI and XhoI. Then it has been cloned into the pGX0001 vector under promoter control of human cytomegalovirus and a bovine growth hormone. As a result, the plasmid pGX9501 that contains 3 paired S protein sequences and pGX9503 that contains an atypical S protein sequence were obtained[80].

The pGX9501 has been manufactured by the insertion of a whole optimized S protein sequence derived from the Wuhan strain, into the pGX0001 plasmid, then has been added a N-terminal IgE leader sequence. This vaccine is administered with electroporation, which eases the entry of the plasmid to the cells and triggers a higher immune response[81]. In the phase 1 trial (NCT04336410) has demonstrated safety, a high humoral response and a robust cellular response represented predominantly by cytotoxic T cells cytokines[80], and with the phase 2/3 trial (NCT04642638) a dose of 2.0 mg was established to be used in the phase 3 trial that is currently underway[82].

An interesting advantage of this vaccine is its temperature stability and that it is free from the cold chain, which permits it to be stable approximately for 1 year at 37° C.81

Viral Vector Vaccine: This type of vaccine consists of a recombinant viral vector which has inserted the target sequence of the vaccine, known as transgene, in its genome. Numerous viral vectors have been studied, such adenoviruses, poxviruses, lentiviruses, retroviruses, cytomegalovirus and adeno-associated viruses. From these viruses has been removed the sequence that permits the replication, hence these cannot replicate and thus be virulent. The task of the vector is to transport its genome containing the target sequence, to the host cell nucleus with the aim of synthesizing the antigens targets of the vaccine. Around the world, the most applied viral vectors vaccines use adenoviruses vectors, which have been selected for their high transgene expression, high transduction efficiency and the broad spectrum tropism[83-84].

The adenovirus species genome contains five early genes (E1a, E1b, E2, E3, E4) that encode for essential proteins related to replication and host immune evasion, and one late gene which encodes for structural proteins. During the adenovirus adaptation process to a safe vector, it is necessary to remove its E1a and E1b genes with the purpose of preventing the virus replication, hence the adenovirus vectors used in vaccines cannot replicate and be virulent.[83] Then, the transgene is inserted in the E1a and E1b place, although with the aim to place a larger transgene, the E3 gene can be replaced to give more space. Once the genes have been replaced, the adenovirus is cultured in a E1-complementing cell line which permits the adapted adenovirus vector replication[84].

The adenovirus vector vaccine is characterized to induce innate immune response and its ease to be produced in mass[83-84]. The main disadvantage of this vaccine is the preexisting immunity against the Human Adenovirus 5 serotype, the most used in adenovirus vaccines. The preexisting immunity consists in impeding the entry of a pathogen already recognized by the antibodies. To solve this can be used other serotypes or even non-human serotypes[84]. The most used viral vector vaccines are the ChAdOx1 nCoV-19, also called AZD1222, developed by Oxford and Astrazeneca[85,86] the Ad26.COV2.S developed by Johnson & Johnson's Janssen (J&J/Janssen),[87] the Gam-COVID-Vac developed by Gamaleya National Research Centre for Epidemiology and Microbiology (NRCEM),[88] and the Ad5-nCoV developed by Cansino Biologics and the Beijing Institute of Biotechnology[89]. All these vaccines use modified adenovirus vectors to transport the dsDNA encoding S protein to the nucleus and then express the viral proteins.

The vaccine developed by Oxford/Astrazeneca-AZD1222 (DB15656), uses the replication-deficient chimpanzee adenoviral vector ChAdOx1, which in its genome contains the whole S protein[85]. The phase 1/2 trial, classified as COV001 (NCT04324606) began in the United Kingdom (UK) with 1077 participants between 18 and 55 years old and demonstrated that a single dose is able to induce an immune response associated with IFN-γ, TNF-α, cytokines secretion by $CD4^+$T lymphocytes and production of monofunctional, polyfunctional and cytotoxic $CD8^+$T lymphocytes[85]. The vaccine showed a 64,1% efficacy in preventing the symptomatic disease after the first dose and 70,4% after the second dose.

The phase 2/3 trial, COV002 (NCT04400838), also carried out in the UK, has focused on people over 56 years old. Both studies showed safety and an immune response associated with IFN-γ and antibody generation. It should be noted that another phase 3 trial, COV003 (ISRCTN89951424), was conducted in Brazil and another phase 1/2 trial, COV005 (NCT04444674), in South Africa[86]. At the moment, is ongoing another phase 3 trial (NCT04516746) which is carried out in Argentina, Chile, Colombia, France, USA and Perú[90]. WHO stated that an efficacy between 60.0% and 80.0% would reduce the limitations of distancing, thus concluding that ChAdOx1 nCoV-19 could contribute to global immunization.

The European Medicines Agency identified a possible vaccine-related adverse effect due to embolic and thrombotic cases that have occurred in Europe at a low occurrence[91]. The J&J/Janssen COVID-19 vaccine, known as Ad26.COV2.S is a single dose vaccine. Is based on a replication deficient adenovirus type 26, which in its genome encodes the whole S protein derived from the Wuhan strain. The encoded protein probably will be locked in the native prefusion conformation once it is synthesized, due to mutations in the furin cleavage site and proline substitutions, added in the plasmid development[87]. The platform used for the creation of this vaccine, which uses the PER.C6 cell line, has previously been used in the research of a vaccine for Ebola[92].

In the phase 1/2a trial interim analysis (NCT04436276), the vaccine showed safety and cellular response by $CD4^+$and $CD8^+$ revealed by IFN-γ and IL-2 secretion. Additionally, showed neutralizing antibodies production in all participants after day 57 post-vaccination[93-94]. In a cohort of the same study (NCT04614948) RBD-binding

antibodies in 90.0% of the participants has been detected[95].

In its phase 3 trial (NCT04505722), the vaccine demonstrated a 66.1% efficacy in preventing the SARS-CoV-2 infection, and 85,4% efficacy in preventing severe disease[96]. The FDA and the CDC identified a possible vaccine-related adverse effect at very low occurrence. The possible adverse effects consist in thrombosis and thrombocytopenia with an onset of symptoms one to two weeks after the vaccination. It has been mostly associated with women between 18 and 49 years old. In addition, they open the possibility that the immune response induced by the vaccine may be diminished in people with immunodeficiencies[97].

The Gamaleya National Research Center of Epidemiology and Microbiology and the Russian Direct Investment Fund developed the vaccine called Gam-COVID-Vac or Sputnik V, which has the peculiarity to use a different vector for each dose[88]. In the first dose is administered an adenovirus type 26 as a vector, while for the second dose is used an adenovirus type 5[88]. Both vectors are replication deficient and their genome encodes the whole S protein. This vaccine showed safety in the phase 1/2 trials (NCT04436471; NCT04437875), and in an interim analysis of its phase 3 trial (NCT04530396) showed 73.1% efficacy after the first dose and 91.6% efficacy after the second dose. It also showed a 95.83% seroconversion rate and demonstrated to induce cellular response by IFN-γ secretion[92]. According to a nationwide data analysis made by the Russian Direct Investment Fund, the vaccine efficacy could be 97.6%[89].

The Cansino Biologics with the Beijing Institute of Biotechnology developed a recombinant adenovirus 5 vectored COVID-19 vaccine, known as Ad5-nCoV[90]. This vaccine uses a replication deficient adenovirus type 5 vector which in its genome encodes the whole S protein derived from the Wuhan strain. In the phase 2 trial (NCT04341389) the vaccine showed safety and a cellular response revealed by the IFN-γ secretion. Also demonstrated a 97.0% seroconversion rate against the RBD[90]. According to a phase 3 trial interim analysis (NCT04526990) made by the Independent Data Monitoring Committee, the vaccine efficacy could be 65.7% in preventing symptomatic cases and 90,98% in preventing severe disease[98]. The lower efficacy compared to other vaccines, could be in consequence of the preexisting immunity against the adenovirus type 5.

RNA vaccine: This novel type of vaccine can use dsRNA (double stranded RNA) or ssRNA (single stranded RNA) which encodes the target antigen. There are many delivery systems, however the one used in vaccines against SARS-CoV-2, consists in delivering the mRNA to the cell through a lipidic nanoparticle that coats it, and then gets endocytosed by the host cell. Unlike the DNA vaccines, once the mRNA enters the cell it can be translated directly into the cytoplasm, a characteristic which makes the antigen production more efficient[99]. Once the mRNA accomplishes his task, it is easily decomposed inside the cell. Notably, this type of vaccine despite its dimensions does not require adjuvants since the mRNA has self-adjuvant properties[99-100].

The mRNA vaccines against SARS-CoV-2 encode the S protein due to its high immunogenicity. Once the mRNA is carried to the ribosomes or to the nucleus, the encoded antigen is expressed and carried to the cell membrane. Then, it can be recognized by a variety of cells depending on the antigen presentation, and can trigger a seroconversion or a $CD4^+$and $CD8^+$T cells response. Both mRNA vaccines demonstrated humoral and cellular immunity[100-101].

Generally, the mRNA is produced by the use of a T3, T7 or Sp6 phage RNA polymerase on a DNA template, which can be derived from a linearized plasmid or produced via PCR[102]. Once the mRNA has been synthesized, it can be optimised with the aim to increase translation efficiency and mRNA stability. The RNA vaccines are easy to standardize, and can be produced rapidly because its manufacture doesn't need the purification step. However, usually mRNA must be transcribed by enzymes in vitro from an initial plasmid, an additional step compared to DNA vaccines[100].

This type of vaccine has a low cost of production and is very safe. Their safety is in account that the mRNA does not integrate in the genome, conversely it is degraded in the cytoplasm[101]. Additionally, taking in account the weak structure of the mRNA molecule, the antigen expression turns out to be transient, so it will not remain latent in the body, a characteristic that could improve the safety of the vaccine[100]. The main disadvantage of this type of vaccine is the strict maintenance of a cold chain, which needs to be at least at -94° F.

During this pandemic have been commercialized the two first mRNA vaccines, which are the BNT162b2 developed by Pfizer-BioNTech[102] and mRNA-1273 developed by Moderna Inc. and the National Institute

of Allergy and Infectious Diseases (NIAID) and the National Institutes of Health (NIH)[103].

The BNT162b2 vaccine is based on the use of a mRNA molecule encapsulated by a lipid nanoparticle. The mRNA encodes a whole S protein locked in the prefusion conformation by two proline mutations, making it more similar to the intact virus[102]. The phase 2/3 trial (NCT04368728) that enrolled 43,448 participants showed safety and a high efficacy rate, the 52.4% efficacy after the first dose and the 94,6% after the second dose[104]. A nationwide study developed in Israel, estimated the vaccine efficacy regarding mass vaccination. In this study the vaccine was demonstrated to prevent the symptomatic disease and the severe disease in 94.0% and 92.0% of cases respectively after the second dose. Further, the vaccine showed 72.0% efficacy in preventing death after the first dose[105]. This vaccine also demonstrated efficacy against the UK strain, since in a prospective cohort study developed in the UK, known as SIREN, the vaccine showed 70.0% effectiveness after the first dose and 85.0% effectiveness after the second dose in health-care workers[106].

The mRNA-1273 vaccine, similarly to BNT162b2 uses a mRNA molecule that encodes by whole S protein stabilized in the prefusion conformation by two proline mutations[103,107]. In the phase 1 trial, it showed safety and capacity to induce high levels of neutralizing antibodies and cellular response. However, these results occurred in a very small sample group[107]. In the phase 3 trial (NCT04470427), the vaccine showed safety and 94.1% efficacy in preventing symptomatic disease[108]. An interim estimate of mRNA vaccine effectiveness which used BNT162b2 and mRNA-1273 as model, revealed that mRNA vaccines have been shown to be 80% effective after the first dose and 90.0% effective 14 days after the second dose[109].

Table 1: Summary of SARS-CoV-2 Vaccines Developed

Vaccine name	Type of vaccine	Developer /manufacturer	Efficacy after Second dose	Registry Number
NVX-CoV2372	Recombinant protein	Novavax	96,4%	DB15810
BNT162b2	mRNA	Pfizer/BioNTech	94,6%	DB15696
mRNA-1273	mRNA	Moderna, NIAID, NIH/Moderna	94,1%	DB15654
Gam-COVID-Vac	Adenovirus vector	Gamaleya NRCEM	91,6%	DB15848
CoronaVac	Inactivated virus	Sinovac Life Sciences	83,5%	DB15806
BBIBP-CorV	Inactivated virus	Beijing Institute of Biological Products/Sinopharm	78,1%	DB15807
BBV152	Inactivated virus	Bharat Biotech	78%	DB15847
AZD1222	Adenovirus vector	Oxford University/AstraZeneca	70,4%	DB15656
Ad26.COV2.S	Adenovirus vector	Janssen	66,1%	DB15857
Ad5-nCoV	Adenovirus vector	Cansino Biologics, Beijing Institute of Biotechnology	65,7%	DB15655
COVI-VAC	Live attenuated	Serum Institute of India/Codagenix Inc.	-	-
ZF2001	Protein subunit	Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology, Chinese Academy of Sciences/Anhui Zhifei Longcom Biopharmaceutical	-	DB15893
EpiVacCorona	Peptide	Vector Institute	-	DB16439
INO-4800	Plasmid	Inovio Pharmaceuticals	-	DB15693

*The Ad26.COV2.S and Ad5-nCoV are single dose vaccines; **The efficacy reported to CoronaVac refers to Turkey trials

SARS-CoV-2 Variants and Vaccine Effectiveness

During the COVID-19 pandemic, genetic variants of SARS-CoV-2 that circulate throughout the world have been generated. The Centers for Disease Control and Prevention (CDC) classified these variants in three classes, Variants of Interest, Variants of Concern and Variants of High Consequence[110]. The variants of interest can be characterized by changes in the receptor binding, a partial resistance to antibodies, reduced efficacy of treatments, or the predisposition to mutate in a more contagious or pathogenic variant. The most known variants included in this group are the P.2 (Brazilian) variant and the B.1.617 (also known as Delta) variant[111].

SARS-CoV-2 genetic variants of concern can be characterized by evidence of increased transmissibility or disease severity, a partial resistance to antibodies, reduced efficacy of treatments, or diagnostic detection failures. The most known variants included in this group are Alpha variant belonging to the B.1.1.7 lineage, Beta variant (B.1.351 lineage), Gamma variant, (B.1.1.28.1 (P.1) lineage), and the Californian variant (B.1.429 lineage). The variants of high consequence can be characterized by its ability to reduce the effectiveness of the disease prevention measures and the medical countermeasures. A variant to be classified in this group, needs to demonstrate evidence of an increased diagnostic failure, evidence for a significantly diminished vaccine efficacy, and the ability to cause more severe disease and increase the hospitalizations. Currently, there are no variants classified in this group[111].

B.1.1.7 lineage originally reported in UK consists of 14 mutations, of which eight are located in the S protein[112]. A phase 2/3 trial exploratory analysis (NCT04400838) of AZD1222 vaccine, showed a 70,4% efficacy against this variant and a 81.5% efficacy against lineages different from it[113]. Also the BNT162b2 vaccine has been evaluated against the B.1.1.7 lineage in a pseudovirus essay, proving to be effective[68]. The most effective vaccine against this variant appears to be the NVX-CoV2373 vaccine, which in its phase 3 trial (NCT04583995) demonstrated 86.3% specificity against the UK strain[71].

The B.1.351 lineage, first described in the Republic of South Africa has demonstrated to be partially resistant to the antibodies produced during a natural infection or by BNT162b2 and ChAdOx1 vaccines[114]. In addition, the AZD1222 vaccine demonstrated a 10.4% efficacy against the Beta variant in its phase 1b/2 trial (NCT04444674) carried out in South Africa[115]. Furthermore, the NVX-CoV237 vaccine in its phase 2a/b trial (NCT04533399) performed in South Africa, showed 51% efficacy against this variant[116]. The mutations considered responsible for the antibodies resistance are the E484K and K417N, which could reduce the binding affinity to the antibody and thus the effectiveness of a humoral response[117].

B.1.1.28.1 lineage, identified in Brazil and Japan has 17 mutations, three of them in the RBD[118]. It shares the E484K mutation with the B.1.351 variant, conferring the ability to evade antibodies. Has been estimated that this variant could be from 1.2 to 2.2 times more transmissible and from 25% to 61% more likely to evade the immune response compared to other variants[114]. Also, this variant has demonstrated to be resistant to antibodies produced by a natural infection and those produced by the BNT162b2 vaccine[119]. Both the B.1.351 and B.1.1.28.1 are resistant to Casirivimab and Bamlanivimab, two antibodies used in the treatment for COVID-19[120].

Subsequently, the B.1.617 lineage was reported in October in India with 13 mutations in protein S. The E484Q mutation is very similar to the E484K mutation found in variants B.1.351 and B.1.1.28.1 and has been named the "escape mutation." An evaluation of sera from COVID-19 patients convalescing with the BBV152 vaccine in Maharashtra, India, demonstrated that the antibodies generated were able to neutralize this variant[57].

Conclusion

The emergence of new methodologies for creating vaccines has been on the rise over time and has accelerated due to the COVID-19 pandemic. Whole virus vaccines have been one of the first-hand options to face epidemics for decades, vaccines such as COVI-VAC or CoronaVac are still under study. Nucleic acid-based vaccines are the ones with the greatest impact today, since they are vaccines that use technologies such as recombinant DNA, mRNA and different vectors, which makes them important bidders for being safe and highly effective. Recombinant DNA vaccines, which usually use an adenoviral vector, showed good efficacy and safety. In relation to mRNA vaccines, shown in trials and different large population studies, have high efficacy and very high safety, these new vaccines could be an important advance in future pandemics or for other diseases. However, viral variants turn out to be a challenge that must be carefully monitored, due to the mutation generated in the target sites with the probable decrease in the affinity for neutralizing

antibodies caused by the action of the vaccines, possibly affecting their effectiveness. A plausible solution to this problem is the so-called "herd immunity", which helps to stop the transition and replication of the virus and thus reduce the mutation rate. It should be noted that mass immunization is still ongoing, so large-scale results could show new results.

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