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Effectiveness of Coronavirus Vaccines against Syndrome Coronavirus 2 (SARS-CoV-2) and Its New Variants

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ABSTRACT

The widespread outbreak of coronavirus disease 2019 in late 2019 caused many people worldwide to die or suffer from certain clinical complications even after the recovery. The virus has many social and economic adverse effects. Studies on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have specified that spike, surface glycoprotein antigen, is considered as a major target to stimulate the immune system. This glycoprotein binds to the angiotensin-converting enzyme 2 on the surface of human cells especially lung epithelial cells and facilitates the virus entry. Therefore, the immune response stimulated by vaccination targeting this antigen may cause immunity against the whole virus. Currently, many companies are working on SARS-CoV-2 vaccines. They include 'traditional' vaccines like attenuated or inactivated virus platforms as well as the brand-new generations of vaccines such as viral vector-based, subunit, nucleic acid-based, and virus-like particle vaccines. Certainly, each vaccine platform presents several advantages and disadvantages affecting its efficacy and safety which is the main topic of this paper.

Keywords: COVID-19; COVID-19 vaccines; SARS-CoV-2; SARS-CoV-2 spike protein; SARS-CoV-2 variants

INTRODUCTION

Alpha (*α*), beta (*β*), gamma (*γ*), and delta (*δ*) coronaviruses constitute the subgroups of the coronavirus family. Until the outbreak of SARS-CoV in Guangdong, China, these viruses were thought to infect only animals.[1] To date, seven of these viruses have been identified in humans. HcoV-229E and HcoV-NL63 belong to α-coronaviruses, while HcoV-OC43, HcoV-HKU1, MERS-CoV (Middle East respiratory syndrome coronavirus), SARS-CoV (severe acute respiratory syndrome coronavirus), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belong to β-coronaviruses. However, SARS-CoV-2, unlike other beta coronaviruses, has exhibited

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dramatically higher numbers of person-to-person spread.

Almost two decades later, after the first detection of beta coronavirus infection in China, another pathogenic coronavirus outbreak has been identified in Wuhan, China. In December 2019, a kind of pneumonia was diagnosed, which was caused by an unknown pathogen.[2] Following the whole genome sequencing of that virus and the similarity of its genome to the SARS-CoV, it was named SARS-CoV-2.[3] Also, the disease caused by SARS-CoV-2 was called coronavirus disease 2019 (COVID-19). COVID-19 is known as a "thousand faces disease", because of the different symptoms of patients affected by COVID-19.[4] Ghazanfari et al in 2021 reported different biomarkers such as age, sex, underlying diseases, blood oxygen pressure, complete blood count along with C-reactive protein, lactic dehydrogenase, procalcitonin, D-dimer, and interleukin-6 evaluation, which are associate with severity and mortality of COVID-19.[5]

Response to the SARS-CoV-2 takes a different amount of time depending on the type of response. Immunoglobulin (Ig) M and IgA are the short-lived antibody responses against SARS-CoV, while IgG is a response against SARS-CoV that lasts a bit longer (less than six months and approximately twelve months, respectively).[6] Memory T cells against SARS-CoV can cause the long-term protective response to the SARS-CoV.[7] Although there is a similarity between the spike protein of SARS-CoV and SARS-CoV-2, neutralizing antibodies against the SARS-CoV spike protein cannot bind to the SARS-CoV-2 spike protein,[8] which means immunity against SARS-CoV cannot produce protective immunity against SARS-CoV-2.

There are two types of vaccines against SARS-CoV, including DNA vaccines (Spike gene) and inactivated vaccines which are in phase I clinical trials, and four vaccines against MERS-CoV, including DNA vaccines (Spike gene), and viral vector-based vaccines, which are in phase I clinical trial[9] and also there are some more vaccines in preclinical phases. However, those vaccines have not elicited a specific, long-term, and adequate immune response and protectivity against those viruses. Based on the similarity between these viruses and SARS-CoV-2, the results of those vaccines have been used for developing SARS-CoV-2 vaccines. As we discuss later in this article, based on the published information, spike protein has been used as an antigen in developing SARS-CoV-2 vaccines.

The newer generation of vaccines, such as the viral vector-based vaccines, nucleic acid-based vaccines, and virus-like particles (VLPs) vaccines, have a chance to prove themselves in SARS-CoV-2 outbreak, as most of them have not been licensed for human use.[7] To pass the tough quarantine conditions and return to previous patterns of working, schooling, and socializing, the traditional vaccines along with the new generation vaccines should effectively control the COVID-19 pandemic.

SARS-CoV-2 Genome

SARS-CoV-2 has a single-stranded positive-senseRNA genome with 29891 nucleotides (GenBank no. MN908947) in length which codes 9860 amino acids. Polyprotein 1a/1ab (pp1a/pp1ab) is directly transcribed from the genomic RNA between ORF1a and ORF1b (open reading frames) and encodes nonstructural proteins (nsps). Open reading frames (ORFs) on one□third of the genome near the 3'terminus are translated to a single long polyprotein. This polyprotein consists of at least four main structural proteins: the spike (S), envelope I, membrane (M), and nucleocapsid (N) proteins, and accessory proteins (involved in immune evasion).[10] The SARS-CoV-2 sequence has a homology of 77.5% and 50% with SARS-CoV, and MERS-CoV, respectively.[11] The error rate of the SARS-CoV-2 replication was estimated to be between 10^{-6} to 10^{-7} errors per nucleotide,[12] and several nucleotide deletions and variations at different positions throughout the entire genome of SARS-CoV-2 were detected.[13]

Spike Protein

Spike consists of a glycosylated protein expressed in large numbers on the surface of SARS-CoV-2, thus giving it the characteristic 'crown' appearance. This protein has a role in binding the virus to the host cell receptor named angiotensin-converting enzyme 2 (ACE2). Attaching spike to ACE2 initiates the entrance of the virus to the host cells,[14] then TM protease serine 2 (TMPRSS2) activates S protein and promotes the entrance of the virus into the host cell where the viral RNA replicate, and also translates to polyproteins.[15] Although there is considerable similarity, the spike protein of SARS-CoV-2 binds to ACE2 with a higher affinity than the spike protein of SARS-CoV.[16]

Spike protein has three main domains consisting of an extracellular N-terminus domain (NTD), a transmembrane I domain, and a short intracellular C-terminal domain (C-domain) with 180–200 kDa overall size and 1273 amino acids.[17] The first 13 amino acids of the S protein are signal peptides located at the N-terminus. The S1 (14–685 residues) and S2 subunits (686–1273 residues) follow the signal sequence. These two subunits are involved in virus binding attachment and entry into the host cells.[18] The receptor-binding domain (RBD) is placed in the S1 subunit and binds to the ACE2.[19] Fusion peptide (FP) region and two heptads repeat regions, HR1 and HR2, are placed in the S2 subunit.[20] Moreover, there is a unique furin-like cleavage site (FCS) in the S protein of SARS-CoV-2 (682 – 685, with RRAR sequence) located between S1 and S2 subunits, which is absent in the other lineage βCoVs.[21] Serine proteases of target cells are activated immediately after binding of RBD to ACE2, then cleavage of S protein into S1 and S2 subunits happens.[22] This cleavage mediates S protein activation, membrane fusion, and releasing the viral package into the host cytoplasm.

Theoretically, based on the central role of spike protein to enter into host cells, it seems that it has to be conserved, and natural mutations may not change it. Therefore, the companies that produce vaccines apply the whole S protein or partial S protein as an antigen to trigger an immune response against the SARS-CoV-2. Analyzing the recovered COVID-19 patients' blood showed neutralizing antibodies (nAb) against the SARS-CoV-2 target RBD.[23] Along with nAb, T cells, especially $CD4^+$ and $CD8^+$, also respond to the S protein. Recently, scientists reported that there are isolated antibodies from human blood that targets non-RBD epitopes[24] such as NTD[25] and S2.[26] Except for RBD, the whole surface of the S protein is covered by glycans, which reduce the immunogenicity of S protein. RBD is the only subunit of S protein that has no glycan cover; therefore, the immune system can respond to that epitope appropriately[27] which means humoral[28] and cellular[29] immune systems respond to the RBD effectively.

Antibodies against NTD cannot neutralize the virus completely, inhibit viral fusion, and virus infection.[26] Due to this fact, NTD-based vaccines have weaker protective efficacy than RBD-based vaccines.[30] Antibodies that target the S2 subunit can neutralize the virus and prevent infection.[31] However because of glycans coverage on subunits,[32] the accessibility of these epitopes for the immune system is reduced which means S2-based vaccines produce a lower immune response than RBD.

The N protein and the M protein can generate the total T cell response.[33] Due to small ectodomains for immune system recognition and small molecular sizes of M and E proteins, they are less immunogenic than S proteins and do not produce a protective immune response against the virus.[34] Unlike M and E proteins, N protein is highly immunogenic,[35] but N protein-based vaccines do not produce adequate immune response against SARS-CoV[36] nor SARS-CoV-2.[34]

S1 has several desired properties including metastability of the recombinant S1 protein, amenability to transform from pre-fusion to a post-fusion conformation, accessibility for immune recognition system, and last but not least neutralizing properties by targeting it, which make it the immunodominant antigen for the immune system.[37] Although, this subunit has many advantages that make it an excellent target for the immune system, its properties need to be improved. Two proline substitutions (2P), substitution at the cleavage sites, and change RRAR to SRAG or QQAQ are examples of those improvements.[37] S-2P and SRAG or QQAQ are used in the Janssen vaccine[38] and the Novavax vaccine,[39] respectively, to stabilize the S protein in its pre-fusion conformation.

SARS-CoV-2 Immune Response

The first line of response to the SARS-CoV-2, following the detection of SARS-CoV-2 components in the body, is innate immune systems. These responses recruit macrophages and monocytes, which start the nonspecific defense mechanisms. These cells release cytokines and trigger adaptive immune cells. Subsequently, the adaptive immune system, *i.e.,* B and T cells, initiate a specific response to virus antigens.

Innate Immunity

The innate immune response to SARS-CoV-2 infection starts with recognizing RNA or other molecular structures of the virus by immune cells. Viral RNA is detected by pathogen-associated molecular patterns (PAMPs), Toll-like receptor 8 (*TLR8)*, *TLR7*, and *retinoid-inducible gene* (*RIG*)/ *melanoma differentiation-associated 5* genes (*MDA5*). Moreover, the damage-associated molecular patterns (DAMPs) are in charge of detecting the virus ATP, DNA, and ASC gligomers.[21] Subsequently, several signaling pathways and, ultimately, transcription factors will be activated.

During SARS-CoV-2 infection, secretion of pro-inflammatory cytokines and chemokines, including IL-1β, IL-6, IFNγ, MCP1, and IP-10, into the blood are elevated.[40] Then, immune cells absorb the site of cytokines and chemokines secretion.[41] SARS-CoV-2 needs to induce aberrant inflammatory responses to protect itself. Multiple viral structural and nonstructural proteins of SARS-CoV-2 prevent the onset of interferon responses by blocking the interferon signaling pathway, which subverts the body’s innate antiviral cytokine responses.[42]

Adaptive Immunity

Both T and B cells can be detected in the COVID-19 patient’s blood after seven days of the onset of symptoms. Two types of T cells are essential in adaptive immune responses to viral infections. $CD8^+$ T cells destroy the viruses inside the host cells, and $CD4^+$ T cells produce cytokines to induce $CD8^+$ T cells and B cells to respond.[41]

In blood samples of COVID-19 patients, the number of $CD8^+$ T cells was more remarkable than $CD4^+$ T cells.[21] Due to the critical roles of T cells in preventing the reinfection with SARS-CoV-2, a sufficient number of memory T-cells is essential.[43] Zhang, F et al have demonstrated that specific memory T-cell responses can be induced and reactivated by several peptides derived from SARS-CoV-2, including S and M proteins, in most COVID-19 patients. Therefore, these peptides are among the potential targets for vaccine development.[44] However, activating the IFN-mediated pathways of T cells can be an alternative way to deal with the virus.

IgM, IgA, and IgG responses were also determined in most patients with COVID-19, suggesting that antibodies act in the generation production of protective immune responses against SARS-CoV-2.[45] Neutralizing antibodies are the primary humoral immune responses against SARS-CoV-2.[46] Since the high concentration of neutralizing antibodies correlate with mild COVID-19 symptoms, triggering the humoral immune responses might be a good strategy for providing future protection against SARS-CoV-2 reinfection.[47] However, some studies demonstrated a correlation between COVID-19 severity and SARS-CoV-2-specific T cells, which raises an important question regarding vaccine protection in humans.[48,49]

Immune Respond to SARS-CoV-2

SARS-CoV-2 can trigger the immune system in two ways. One of the ways is virus's phagocytosis by antigen-presenting cells (APCs) and T-cell activation via presenting virus antigens on major histocompatibility complex (MHC) class II. The other way is through the synthesis of virus proteins in infected cells. In this case, these proteins might be presented to $CD8^+$ cells using MHC class I or released from the cells and phagocytosed by APCs and presented on MHC class II. Dead vaccines and inactivated vaccines trigger the immune system similar to the native virus. However, viral vector-based vaccines and nucleic acid-based vaccines cannot directly stimulate the immune system. They must enter the cells. Then, specific SARS-CoV-2 related peptides are released and presented on the cell surface by MHC class I. Moreover, APCs phagocyte peptides which be released from the cell and present it on MHC class II. Subunit vaccines and VLPs vaccines can stimulate the immune system as well, through APCs. Presented antigens on MHC class I would activate $CD8^+$ T cells and $CD4^+$ T cells. $CD8^+$ T cells can destroy or damage infected cells directly. $CD4^+$ T cells respond to SARS-CoV-2 indirectly by activating both B and $CD8^+$ T cells. T and B memory cells play crucial roles in immune system response, and as long as they exist, resulting immune system can remain (Figure 1).

SARS-CoV-2 Suggested Vaccines

Utilizing an effective vaccine would be a good idea to achieve herd immunity against SARS-CoV-2 in the population.[50] The specific roles of antibodies and T cells in protection against SARS-CoV-2 infection in humans are yet unknown. Howbeit, neutralizing antibodies have shown a protective role in rhesus macaques.[51] Various candidate vaccines, including nucleic acid vaccines, inactivated virus vaccines, live attenuated vaccines, protein or peptide subunit vaccines, and viral-vectored vaccines, are being developed. Vaccines must have high safety and efficacy, which means that the side effects of vaccines should not outweigh the severity of natural diseases, and they should effectively stimulate the immune responses, respectively. Moreover, given the number of detected mutations in the SARS-CoV-2 virus,[52] vaccines should be designed in such a way that provides immunity not only against SARS-CoV-2 wild-type virus but also SARS-CoV-2 new variants. Table 1 summarizes different vaccines and demonstrates examples of approved vaccines for human use in each vaccine type.

Candidate vaccines are being tested in preclinical and clinical trials to determine their safety and efficacy. The preclinical trial has two stages, and in each one, the toxicity and teratogenicity of vaccines are tested. In the first stage, vaccines are tested on non-primate animals; if the result is acceptable, vaccines enter the second stage and are tested on non-human primates. Subsequently, the next step is studying the drugs in clinical trials. Clinical trials consist of four phases and in each phase, different aspects of vaccines are tested on volunteers. In the phase I trial, vaccines are tested on a limited number of healthy human volunteers. In this phase, the appropriate dose and the possible side effects of vaccines are determined. In the phase II trial, the vaccines' efficacy is tested on a small number of human volunteers who are naturally exposed to the pathogen or are challenged with the pathogen deliberately. Finally, in the phase III trial, vaccines are tested on many healthy volunteers who live in an endemic area or are challenged intentionally with pathogens.

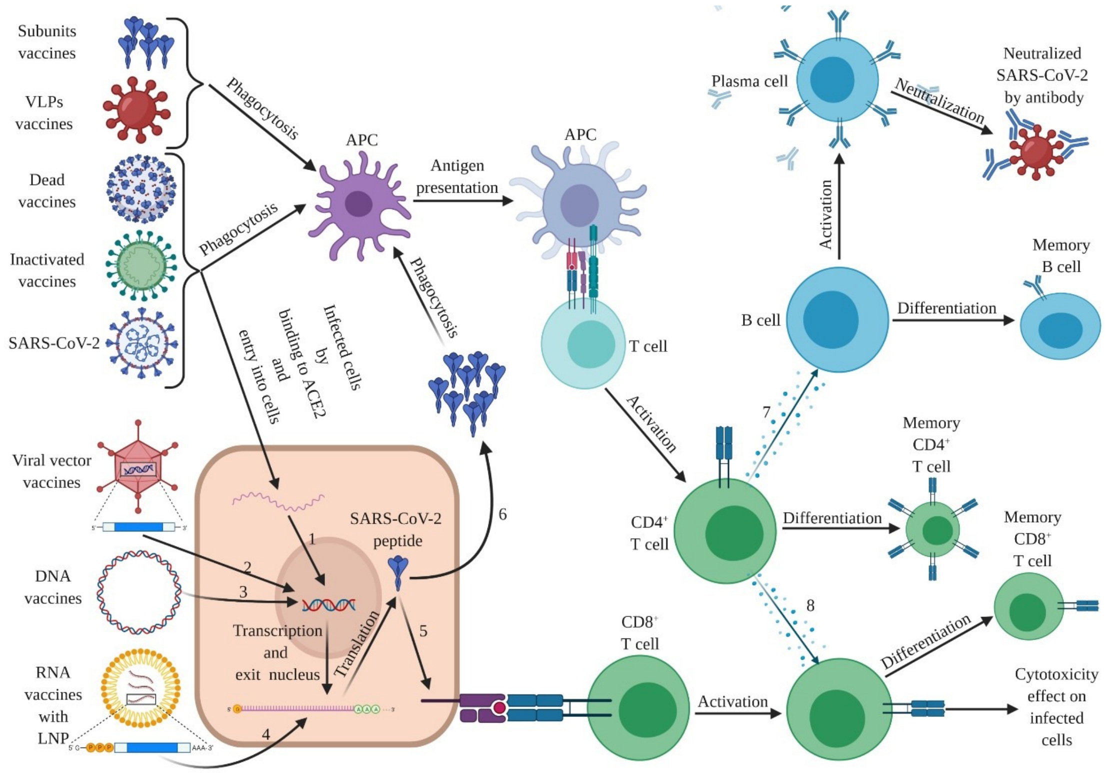

Figure 1. Downstream pathways as a result of immune system stimulation through each type of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines and also result of native SARS-CoV-2 infections. (1. SARS-CoV-2 genome will reverse transcribed to DNA following cell infection and entry to the nucleus. 2. Viral vector-based vaccines deliver DNA encoding specific SARS-CoV-2 peptides to vaccines cells. 3. DNA vaccines not only must cross the cell membrane but also, they should enter the nucleus. 4. mRNA vaccines that encode the specific SARS-CoV-2 peptides cross the cell membrane, and subsequently, the peptide translates into the cytoplasm. 5. SARS-CoV-2 peptide is processed in the infected cell and subsequently present on the MHC class I. (In nucleic acid base vaccines and viral vector-based vaccines, vaccinees cells present only one type of SARS-CoV-2 peptide, but in a native infection or whole vaccine, all the virus peptides present on the cell surface.) 6. CD4$^+$ T cells release cytokines to activate CD8$^+$ cells. 7. CD4$^+$ T cell release cytokines to activate B cells.). Antigen presentation on MHC class II results in CD4$^+$ T cell activation, which stimulates CD8$^+$ T and B cells. Three different types of memory cells will be produced, triggering the immune system in reinfection or natural infections. Figure created with Bio Render (https://biorender.com).

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Table 1. Some examples of different types of approved vaccines before the COVID-19 outbreak.

Types of Vaccines	Description	Some examples of previously approved vaccines
Live attenuated vaccines	Decrease pathogenicity but still immunogenic; may still replicate.	**Viral**: measles, mumps, rubella, vaccinia, varicella, zoster, yellow fever, rotavirus, intranasal influenza (LAIV), oral polio **Bacterial**: BCG, oral typhoid
Inactivated (dead) vaccines	Block replication by killing or inactivation of the pathogen but still immunogenic.	**Viral**: polio, hepatitis A, rabies, **Bacterial**: pertussis, typhoid, cholera, plague
Nucleic acid-based vaccines	Naked DNA or mRNA containing special sequences of the pathogen can stimulate an immunogenic response to the whole pathogen.	N/A
Viral vector-based vaccines	A virus-based vector containing recombinant DNA of pathogen antigen which infected vaccinees' cells and replicates transcribed and translated continually in there.	rVSV-ZEBOV Dengvaxia
Subunit vaccines	Synthesized or purified pathogen protein, peptides or polysaccharides.	hepatitis B, influenza, acellular pertussis, human papillomavirus, anthrax
Viral-like particles vaccines	Purified from natural sources or synthesized using recombinant DNA methods.	HBV, Gardasil, Cervarix

COVID-19: coronavirus disease 2019; BCG: Bacillus Calmette–Guérin (BCG); HBV: Hepatitis B vaccine

In each trial phase, if the results indicate unsafe or unacceptable efficacy of the vaccines, the trial will be stopped, and the vaccines will be discarded. If the vaccine successfully passes all these three phases of the trial, it will be licensed and distributed for human use. However, in phase IV, the safety and efficacy of vaccines are determined in the real world for rare adverse events. Therefore, if consequences of vaccines occur in real-life licenses of them can be dismissed.[53]

By May 2021, multiple phases of 3 clinical trials for SARS-CoV-2 vaccines are being performed in different parts of the world. According to the food and drug administration (FDA), at least 50% of vaccinated people must be immune against SARS-CoV-2 to consider SARS-CoV-2 vaccine as efficacious.[54] According to the world health organization (WHO), twenty-three SARS-CoV-2 candidate vaccines will be in phase 3 clinical trial or would pass this stage successfully, up to June 24th 2021.[55] Each approach has its own advantages and disadvantages, which will be discussed here.

SARS-CoV-2 Vaccine Targets

Vaccines must stimulate immune responses that generate long-lasting B and T memory cells against the related pathogen. Vaccines contain immunogenic but not pathogenic epitopes of pathogens. Therefore, they can induce immune responses without infecting the hosts.[56] The higher affinity of SARS-CoV-2' S protein to ACE2 compared to other coronaviruses is the reason for increased the infection rate of SARS-CoV-2. Several vaccines were developed by using the surface antigen that can stimulate immune response sufficiently.[57,58] Human-neutralizing antibodies against S protein have a crucial role in protecting against SARS-CoV.[59] S2 subunit is structurally conserved and has 88% sequence homology with the S2 domain of SARS-CoV.[60] The same result was detected following the analysis of neutralized antibodies against SARS-CoV-2 S protein.[61] Therefore, using the whole S glycoprotein, or a part of it, has increasingly gained attention for the vaccination purpose.

Different Type of Vaccines

Currently, there are several methods to develop a vaccine. Previously, design of vaccines was based on using live, attenuated, inactivated organisms or pathogenic products (toxoids). With recent advancements in biotechnology, new types of vaccines, namely subunit vaccines which purified from the natural organism, or synthesized *in vitro*, have been introduced. Lately, DNA and RNA vaccines, together with VLPs vaccines, have also been presented. DNA vaccines can be either recombinant vectors or naked DNA vaccines.[62] Each vaccine type has its advantages and disadvantages (Table 2). Therefore, to get the best immunity against the pathogen, the method used to construct vaccines is of great importance.

The “front runner candidates” are provided by companies or research institutes in China, Russia, Germany, the United Kingdom, and the United States. In the following sections, vaccines that are in phase 3 of clinical trials or have already passed this phase at the time of writing this article will be reviewed (Table 3).

Table 2. Advantages and disadvantages of different types of severe acute respiratory syndrome coronavirus 2 vaccines

Type of vaccine	Advantages	Disadvantages
Live attenuated vaccines	Immunogenicity similar to natural infection (extensive immunity with both humoral and cellular respond)[63] A single dose without a booster often is enough[64] Cost-effective [65] Present multiple viral proteins [66] Epitopes with correct conformation [66]	The potential transmissibility of the live attenuated vaccine[67] Less storage stability and necessity of cold chain transport[68] Revert to the virulent forms [69] Possibility of contamination during preparations [70]
Inactivated (dead) vaccines	Possibility of reversion close to zero[71] Immunogenicity similar to natural infection (extensive immunity with both humoral and cellular respond)[72] Stable and no need for cold chain[73] Virus contamination close to zero[71]	Minor immune system stimulation[74] Booster and several doses are needed[75] Less effective against intracellular pathogens[76]
Nucleic acid-based vaccines (DNA)	Adjuvant rule of bacterial sequences in plasmids[77] Almost stable in the body [78] Immunogenicity similar to natural infection (extensive immunity with all humoral, cellular, and innate respond)[79] Easy to manipulate and modify[80] Ready platform[81]	Lower efficacy of cytotoxic T lymphocytes (CTLs) response[82] Lower titer, avidity, and longevity of antibody[83] Possibility of integration and stimulate tumorigenic[84] Need nuclear delivery[84] Need promoter [84] Present just one antigen of pathogens[78] Wrong post-translational modifications[78]
Nucleic acid-based vaccines (mRNA)	Cost-effective [85] Fast production [85] No infection in the vaccine [78] No integration to the genome[78] Simple production [86] Immunogen with 94–95% efficacy [87.88] Ready platform [81] Room temperature storage [89]	Present just one antigen of pathogens [78] Wrong post-translational modification [78] Toxicity [90] Autoimmunity response [90] Low-temperature storage requirements [91]
Viral vector-based vaccines	High-efficiency gene transduction [92] Specific delivery of genes to target cells [92] Both humoral and cellular respond [93] Robust immune responses [92] Increased cellular immunity [92] Do not have the ultracold storage temperature requirements [91]	Pre-existing antiviral vector immunity [94] Hepatotoxicity [95] Lower efficacy than mRNA vaccines (92-70%) [96, 97]
Subunit vaccines	No possibility of infections [98] Stimulate T and B responses by modifying recombinant peptides [99] Stable and easy to transport [100]	Expensive [101] Tough to purify [101] Lower immunogenicity [102] Delivery system and adjuvant are needed[103-105]
Viral-like particles vaccines	No possibility of infections [106] Ease of production [107] Both humoral and cellular immune responses [108] More immunogenic than linear peptides [107] Self-adjuvating properties [109]	Expensive[110]

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Table 3. Different types of SARS-CoV-2 vaccines which are in phase 3 or 2/3 clinical trial or past these phases

Type of vaccine	Commercial Name	Generic Name	Name of Manufacturer	Address of Manufacturer	Doses	Explanations	Reference
Inactivated vaccine	CoronaVac	Sinovac	Sinovac Life Sciences Co., Ltd.	China	2	Inactivate with aluminum hydroxide	111
	BBIBP-CorV	Sinopharm	Wuhan Institute of biological products and Beijing Institute of biological products	China	2		112
	Covaxin (BBV152)	Bharat	Bharat biotech in collaboration with the Indian council of medical research.	India	2		55
	QazVac	QazCovid	Research institute for Biological safety problems	Kazakhstan	2		55
	-	Inactivated SARS-CoV-2 vaccine	Chinese Academy of Medical Sciences	China	2	Inactivated in Vero cells	55
	-	Minhai	Beijing Minhai Biotechnology Co	China	1,2 or 3	Inactivated in Vero cells	55
	-	Shenzhen Kangtai Biological Products Co	Shenzhen Kangtai biological products Co	China	2	Inactivated in Vero cells	55
	-	Valneva	Valneva	France	2		55
DNA vaccines	-	Zydus Cadila	Zydus Cadila	India	3	Full-length spike (S) protein	113
RNA vaccines	Moderna	Moderna, TAK-919 and mRNA-1273	Moderna, the United States national institute of allergy and infectious diseases (NIAID), and the biomedical advanced research and development authority (BARDA).	United States	2	LNP- mRNA-nano encoded full-length S protein	114
	Comirnaty	Pfizer	BioNTech, Fosun Pharma/Pfizer	Germany	2	LNP-mRNAs-nano encoded full-length S protein	115
	-	CVnCoV	CureVac AG	Germany	2	mRNA-LNP encoding the full-length S protein	55
	ARCoV	Walvax	Academy of Military Science (AMS), Walvax Biotechnology and Suzhou sbogen biosciences	Mexico	2	mRNA-LNP encoding the receptor-binding domain (RBD)	116

Viral vector vaccines	Vaxzevria, Covishield	nCoV-19, ChAdOx1-S, AstraZeneca	Oxford University and AstraZeneca	England	2	ChAdOx1-S expressing the full-length S protein	117
	-	CanSino	CanSino Biological Inc./ Beijing institute of biotechnology	China	2	Ad-5 Vector expressing the full-length S protein	118
	Sputnik V	Gam-COVID-Vac	Gamaleya research institute	Russian	2	rAd26-S+rAd5-S both expressing the full-length S protein	119
	Janssen	Ad26.COV2.S and Johnson & Johnson	Janssen vaccines in Leiden, Netherlands, and its Belgian parent company Janssen Pharmaceuticals, subsidiary of American company Johnson & Johnson	Netherlands, Belgian, United States	2	Ad-26 vector expressing the full-length S protein	120
Subunit vaccines	Covovax, TAK-019	NVX-CoV2373	Novavax and the coalition for epidemic preparedness innovations (CEPI)	United States	2	Full-length S protein vaccine adjuvanted with matrix M	121
	ZIFIVAX	ZF2001	Anhui Zhifei Longcom biopharmaceutical/institute of microbiology, Chinese Academy of Sciences	China	3	The adjuvanted recombinant protein (RBD-dimer) expressed in CHO cells	55
	CIGB-66	ABDALA	Center for genetic engineering and biotechnology (CIGB)	Cuba	3	RBD + aluminum hydroxide	55
	-	EpiVacCorona	Federal budgetary research institution state research center of virology and biotechnology (Vector)	Russian	2	Fragments of S protein	55
	FINLAY-FR-2	SOBERANA 02	Instituto Finlay de Vacunas	Cuba	2	RBD chemically conjugated to tetanus toxoid plus adjuvant	55
	-	Sanofi–GSK	Sanofi Pasteur and GlaxoSmithKline company (GSK)	France and England	2		55
VLPs vaccines	-	CoVLP	Medicago Inc	Canada	2	Plant-derived VLP adjuvanted with AS03	122

Live Attenuated Vaccines

Attenuated vaccines take advantage of using a live infectious agent while it has been attenuated. Live attenuated vaccines mimic natural infection and provoke humoral and cell-mediated immune responses, which provide immunity to prevent infections.[63] Highly replicating pathogens in cells (for viruses) or culture media (for bacteria) is one way to prepare attenuated vaccines.[123] Through this method, although microorganisms lose their virulence, they can replicate sufficiently. Attenuation is not stable, and the virulent form of the virus may return.[69]

Moreover, to prevent the microorganism from partial or total death, attenuated vaccines must be stored at low temperatures.[68] Multiple antigens with correct conformational structure can be presented by this type of vaccine to the immune system, which helps the immune system to respond better.[66] Pathogens in attenuated vaccines can still replicate. Therefore, only one dose[64] or small amounts of the virus is needed for vaccinations, which reduces vaccination costs.[65]

There is a concern that, live attenuated vaccines can transmit between healthcare workers and/or family members of immunocompromised patients. Therefore, both immunocompromised patients and/or persons receiving immunosuppressive therapy are at risk of being infected by the live attenuated vaccine.[67] An example was the occurrence risk of vaccine-associated paralytic poliomyelitis (VAPP) in the vaccinees or people in contact with the vaccine back in the 1990s in the United States, while the incidence of polio declined.[124] Moreover, as the pathogens are alive in this type of vaccine and no critical practice has been done during the vaccine preparation, contamination in vaccines with organisms is possible.[70] Live attenuated influenzas and vaccinia vaccines are among the other examples of this type of vaccine.[125,126] However, live attenuated Varicella, Measles, Mumps, and Rubella vaccines are still being used as no transmission cases have been reported.[127] Due to the possibility of causing severe conditions, live attenuated vaccines against chronic diseases such as HIV, or HCV, have not been developed.

Attenuated coronavirus vaccines stimulate immune responses similar to natural infection; however, reversion to wild type and causing severe infections are also possible. The live attenuated coronavirus vaccines have the advantage of presenting all the coronavirus antigens to the host immune system. As none of these vaccines have entered the phase 3 clinical trial study up to writing this article, information about these types of vaccines is limited. Natural SARS-CoV-2 infection does not provide proper and long-lasting immunity in the infected persons. Therefore, using this type of vaccine requires more research to prevail coronavirus infection. If both the transmissibility and the possibility of reversion to the virulent type would be omitted, one single dose should be enough to provide proper immunity. Attenuated vaccines typically have mounted both humoral and cell-mediated responses. Covi-Vac is one of the potential live attenuated vaccines that has entered into the clinical trial phases till the last revise of this article. This vaccine has developed in collaboration with Codagenix and the serum institute of India. Covi-Vac applies in a single-dose format and the virus was attenuated by codon de-optimization, which stimulates the immune system against all SARS-CoV-2 proteins.[128] BBIBP-CorV and PiCoVacc are two other examples of potential live attenuated SARS-CoV-2 vaccines that have been passaged many times and deactivated by β-propiolactone.[129,130]

Inactivated (dead) Vaccines

In dead vaccines, the whole microorganism becomes inactivated using a physical, γ-irradiation, or chemical method. Pathogens in inactivated vaccines have lost their ability for replication which reduces the possibility of transmission and reversion to an infectious form. However, inactivated vaccines induce immune responses to a lesser extent compared to attenuated vaccines.[131] Polio (Salk vaccine), Rabies, influenza, and Japanese B encephalitis are examples of inactivated viral vaccines.[132]

These vaccines are more stable, conservative, and safer than attenuated vaccines. However, the stimulation of the immune system by the dead virus is lower than the attenuated vaccines,[74] which means not only a large number of dead pathogens is required, but also several doses are needed to trigger the immune responses. These amounts can increase the risk of an allergic response and vaccination costs.[75] The main limitation of dead vaccines is that they stimulate the immune system less, as the dead pathogens cannot actively penetrate host cells and present their antigens on MHC class I.[133] Dead vaccines are stable; therefore, the cold chain transition can be omitted.[73] They are also safe as the vaccine preparation process dramatically reduces the risk of contamination with other live organisms.[71]

Sinovac, Wuhan Institute of Biological Products, Beijing Institute of Biological Products, Bharat Biotech, Research Institute for Biological Safety Problems, Rep of Kazakhstan, Beijing Minhai biotechnology Co, Shenzhen Kangtai Biological Products Co, Valneva, and Chinese Academy of Medical Sciences in collaboration with the Chinese Academy of Medical Sciences, have introduced inactivated vaccine candidates against SARS-CoV-2. Results in mice, rats, non-human primates, and 3 phases of clinical trials have shown the excellent immunogenicity of vaccines, while the number of adverse reactions was lower compared with viral-vectored vaccines, DNA, or RNA vaccines. [134] The Vero cell lines are continuous cell lines (CCLs) used to produce inactivated vaccines for many years.[135] This platform is in use by several developers to inactivate SARS-CoV-2 viruses and produce Vaccines too.

Nucleic Acid-based Vaccines

Instead of using the whole pathogens or part of them, the nucleic acid sequence of the immunogenic protein can be used in nucleic acid-based vaccines. Following the vaccination, cells uptake the nucleic acid and synthesize immunogens. Synthetized immunogens are then processed through the endogenous pathway, presented on cells, and activate cell-mediated responses.[136] Both DNA and RNA can be used in nucleic acid-based vaccines. Choosing the desired protein for encoding through nucleic acid vaccines is of high importance. A DNA vaccine is a plasmid that encodes the interested protein.[137] DNA is more stable and can express immunogens for a more extended period, but there is also a risk of integration into the genome.[138, 139]

Moreover, the produced antibody response to DNA vaccines has a lower titer, avidity, longevity, and CTL response than natural infections.[82,83] Special elements, which are needed for DNA vaccines, increase the cost and size of DNA vaccines.[84] However, only a microgram of this construct can trigger an immune response.[140] Besides, unlike the mRNA vaccines, toxicity and autoimmune responses have not been detected in DNA vaccines.[90,141,142] Bacterial sequences in plasmids can be manipulated to act as an adjuvant.[77] Also, the sequences of antigens can be easily modified for Special goals.[80]

RNA vaccines consist of messenger RNA (mRNA) molecules with pathogen-specific antigen sequences producing antigenic peptides or proteins *in situ* after entry into vaccinees cells. Following antigen presentation, the immune system will be triggered.[143] RNA vaccines only need to enter the cells and do not need a carrier to lead them to the nucleus.[86] Therefore using RNA vaccines needs fewer co-particles.[78] Also, the production of mRNA vaccines is more comfortable than other vaccines and more cost-effective.[85]

Moreover, some synthetic RNA sequences like CpG can stimulate an immune response.[144] New lipid nanoparticles (LNP)-encapsulated mRNA vaccines named ARCoV, increase the stability of mRNA, which could be stored at room temperature. This stability reduces the difficulty of transportation and decreases the cost of storage.[89] RNA vaccines are safer than DNA vaccines since RNA vaccines are generated in cell-free conditions.[145] Despite the reduced risk of integration, according to the high sensitivity of RNA, synthesis and delivery of this type of vaccine is very challenging.[78] However, in the case of the previous infection of vaccinees by a retrovirus, the required proteins for integrating mRNA into the genome are exist in cells.[146]

Nucleic acid vaccines are free of any living organisms, completely excluding the risk of using live organisms. The nucleic acid sequences can be modified and optimized to stimulate immune responses better.[147] Nucleic acid-based vaccines efficiently stimulate both humoral and cell-mediated responses together with innate immune responses.[79] It is of note that nucleic acid vaccines can only be used for mimicking the “one or a few” “peptide” antigens of the whole pathogen.[78] Human cells possess different post-translational modifications compared to most of the pathogens, affecting the immune response of encoded protein.[81]

Moderna, BioNTech, ARCoV, and CureVac have developed mRNA vaccines against SARS-CoV-2. Moderna and BioNTech groups have used lipid nanoparticles (LNPs) for the non-viral delivery of mRNA and protect mRNA from destruction. The formulation of LNPs is vital in terms of preventing RNA degradation. Also, triggering the immune responses with these particles has been shown in several studies.[148] Both of these vaccines have finished phase 3 clinical trials with high efficacy (approximately

95%) against SARS-CoV-2 infection.[87,88] CureVac's CvnCoV is an mRNA vaccine candidate that utilizes nucleotides without chemical modifications in the mRNA. The mRNA encodes the full-length spike protein of SARS-CoV-2 and is formulated with lipid nanoparticles. ARCoV is an mRNA-LNP vaccine that encoded RBD and can elicit robust neutralizing antibodies and cellular responses against SARS-CoV-2. One of the more critical advantages of ARCoV is storage at room temperature for at least one week.[116] The only type of DNA vaccine in phase 3 against SARS-CoV-2 was developed by Zydus Cadila and named that nCov vaccine.

Viral Vector-based Vaccines

Vector-base vaccines are composed of a carrier virus unrelated to the pathogen of interest, such as *Adeno* or *Vaccinia* viruses. These viruses become attenuated and modified to carry a gene of the pathogen.[149,150] The encoded gene by this viral vector will express in recipient cells, and consequently, the immune system will respond to the expressed protein which presents on MHC I. Although viral vector vaccines trigger both humoral and cell-mediated immune cell responses efficiently, the CTL activation may cause side effects.[92,93] Furthermore, these vaccines can be directed to specific issues for stimulating the immune response more sufficiently. Therefore, only a lower dose of vaccines can trigger an appropriate immune response.

Viral vector-based vaccines do not have any of the pathogens' genes except the gene which encodes the antigen. However, the possibility of viral vector reversion is not eliminated. The immune system response to the viral vector is another limitation of viral vector-based vaccines, which can neutralize the vector completely.[94] Serotypes with lesser exposure in humans can be used as a viral vector to prevent the neutralization of viral-based vectors. In this regard, chimpanzee adenovirus serotypeY25 (ChAdY25), is one of the most suitable serotypes of adenoviruses since it triggers no or a weak immune response in the human body. Besides, other chimpanzee adenovirus serotypes such as ChAd63 and ChAd3 and also human adenovirus serotype-5 (HadV-5), HadV-6, HadV-35 can be good candidates for as application in viral vectors.[151] Many biotech companies have explored several vector-based vaccine structures to develop new vaccines.[152,153] Before the COVID-19 outbreak and up to 2019, two viral vector-based vaccines (rVSV-ZEBOV and Dengvaxia) got the license for human use.

Among human adenovirus serotypes, Ad serotype 5 (Had5) has been mainly used as a viral vector in human vaccines. This vector has several advantages, such as high transduction efficiency, a high level of transgene expression, and a broad range of viral tropism. However, due to the high number of CARs on the hepatocyte surface, using Had5-based vectors may lead to the entrance of many viruses into the liver, which causes hepatotoxicity.[95]

Beijing Institute of biotechnology, University of Oxford, Gamaleya research institute, and Janssen pharmaceutical companies have introduced viral-based vaccines against SARS-CoV-2 which used ChAdOx1-S, Ad5, rAd26-S+rAd5-S, and Ad26 vector, respectively. Russian vaccine induced strong humoral and cellular immune responses against SARS-CoV-2,[54] which provide 92% protection.[97] These results for the Russian vaccine can be due to the use of two different viral vectors in each dose, which is new to the immune system at each injection, and there is no previous response to it in the recipient's body. The Oxford vaccine was reported to provide both humoral and cellular immune responses against SARS-CoV-2 with 70% protection [96] and no serious adverse events related to ChAdOx1.[155]

Subunit Vaccines

Any components of pathogens with the ability to trigger immune system responses can be used as a vaccine. These components can be generated through purification or by applying recombinant DNA technology.[156] These vaccines can consist of whole macromolecules, large fragments of macromolecules, polysaccharide chains, or polypeptide fragments of pathogens.[157]

Hepatitis B surface antigen (HbsAg), the first viral subunit vaccine, is an example of a vaccine with the whole macromolecules (of Hepatitis B).[158] In subunit vaccines, the possibility of contamination and reversion is excluded,[98] and despite the low immunogenicity,[102] modified subunit vaccines can trigger humoral and cellular immune responses.[99] Due to the stability of these vaccines, no special care is needed during transport.[100] Since even tiny changes in subunit vaccines may stimulate an inappropriate immune response, conformation and post-translational modification of components is extremely important.[159]

The half-life of subunit vaccines in the body is too short to be detected by the immune system; therefore, adjuvants and delivery vehicles seem necessary to protect them from degradation, or more doses are needed, which increases costs.[103-105] Moreover, it is critical to purify this type of vaccine.[101]

Currently, Novavax, center for genetic engineering and biotechnology (CIGB), Federal budgetary research institution state research center of virology and biotechnology, institute Finlay de vacunas, Sanofi Pasteur in collaborating with GlaxoSmithKline company (GSK), and Anhui Zhifei Longcom biopharmaceutical have developed the SARS-CoV-2 subunit vaccine, which reached to phase3 clinical trial successfully. Novavax has a full-length recombinant Spike glycoprotein nanoparticle vaccine adjuvanted with matrix M.[160] Matrix-M™ adjuvant in Novavax includes two 40-nm particles with different saponin fractions. Matrix-A and -C particles are produced from the leaves of the tree *Quillaja Brasiliensis* with cholesterol and phospholipid.[161] The role of this adjuvant in stimulating antigen-specific humoral and cellular immune responses was proven.[162]

In contrast, Anhui Zhifei Longcom Biopharmaceutical used the RBD, which is produced in the Chinese hamster ovary (CHO) cells. CIGB-66 and EpiVac vaccines have an RBD domain and fragments of a spike protein in an aluminum-containing adjuvant (aluminum hydroxide), respectively. FINLAY-FR-2 vaccine has an RBD domain produced in Chinese hamster ovary (CHO) cells conjugated chemically to tetanus toxoid. It seems that, in case of sufficient induction of humoral and cellular immune response against SARS-CoV-2 this type of vaccine, will provide a safer method without special adverse events and concerns in humans.

Virus-like Particles (VLPs)

Virus-like particles (VLPs) include self-assembled viral protein(s) in virus-shaped particles. These proteins mainly belong to the envelope; however, they sometimes contain viral core proteins like hepatitis B virus core proteins.[163]

Due to the absence of viral proteins encoding nucleic acids, VLPs cannot replicate independently. Therefore, the risk of replication and infection in the vaccinees body would be omitted.[106] VLPs are more immunogenic than subunit Vaccines and can induce both humoral and cellular arms of the immune system.[108] Epitope display on VLPs are similar to the native virus that can induce a potent antibody response as the epitope's conformation is correct. Moreover, VLPs size is suitable for uptake by dendritic cells (DCs).[164] VLPs can act as an adjuvant for their carrier epitopes, so unlike the subunit vaccines, there is no need for adjuvants to stimulate the immune system.[109] Besides, the preparation of VLPs is easier than viral vector-based vaccines, and unlike viral vector-based vaccine preparation, there is no need for human cells to produce VLPs vaccines. Preparation of VLPs vaccine is too laborious[110] which increases the vaccine price.[165]

There is just one VLP vaccine against SARS-CoV-2 currently in phase 2/3 clinical trial. In this regard, Medicago has developed self-assembling VLPs having SARS-CoV-2's spike protein on its surface and AS03 as the adjuvant. The spike protein is transiently expressed in *Nicotiana benthamiana*, a close relative of tobacco. Medicago's VLP has a similar shape and size to SARS-CoV-2. This vaccine can elicit both humoral and cellular responses and establish protective immunity in vaccinees. Medicago's platform has been previously applied to produce Vaccines for avian and seasonal influenza.[122] AS03 adjuvant is an oil-in-water emulsion, consisting of α-tocopherol, squalene, and polysorbate 80. AS03 has already been investigated in several nonclinical and clinical studies.[166]

Adverse Reactions of Some Vaccines

The most common side effects of vaccines are pain at the injection site, fever, myalgia, fatigue, and headache. One of the most significant adverse reactions of vaccination is anaphylactic reactions which can lead to death. Activation of mast cells followed by releasing mediators from them can cause anaphylactic reactions.[167] The possibility of anaphylactic reactions is higher in a person with a history of allergies to any food, drug, or vaccine. For most known vaccines, anaphylactic reactions occur one case per million injections.[168] Based on the published clinical trial data of SAR-CoV-2 vaccines, there were mild to moderate adverse reactions with few severe reactions in vaccinees.[169] Duo to no previous licensed viral vector-based, DNA, and mRNA vaccines; some populations may be at higher risk for adverse reactions related to a component of these vaccines.

Several cases of anaphylaxis (some of them had allergies history, but some others had no known allergies) associated with the Pfizer mRNA vaccine have been reported in the United States and UK.[167] After that, persons who have an allergy history have been excluded from vaccination programs. Several reports indicate Moderna vaccine adverse reactions are more frequently reported compared with the Pfizer vaccine. The clinical trial data of the Sinopharm, which is a whole virus vaccine, indicated that the occurrence of four severe adverse events was not related to the vaccination.[112] In ChAdOx1 nCoV-19 (AZD1222) vaccine, hemolytic anemia, transverse myelitis, fever higher than 40°C were reported as adverse events. There was one non-COVID-19 death in the experimental vaccine group, but these were considered unrelated to the vaccine.[170] Sputnik vaccine adverse events were mild, and most of the adverse reactions occurred after the second vaccination.[171] Clinical trials data of the Janssen vaccine demonstrated five serious adverse events (SAE), including hypotension, bilateral nephrolithiasis, legionella pneumonia, worsening of multiple sclerosis, and fever leading to hospitalization. Except for the last one, all these SAE were deemed unrelated to the vaccine.[172] There are no severe adverse reactions for the Novarax vaccine [173] and Covaxin vaccine[174] based on their clinical trials.

The New Variation of SARS-CoV-2

Due to the higher rate of mutation in the RNA virus, new variants of SARS-CoV-2 are expected to occur over time worldwide. By recognition of a new variant of SARS-CoV-2, its ability to spread, illness severity, symptoms, and also vaccine efficacy against it should be examined. SARS-CoV-2 interagency group (SIG) classified variants into three groups and named variants of interest (VOI), variants of concern (VOC), variants of high consequence (VOHC).[175] Based on SIG information, five variants of SARS-CoV-2 circulating in the United States (The B.1.1.7, B.1.351, P.1, B.1.427, and B.1.429 are among VOI variants) are classified as VOI..

B.1.1.7 (the United Kingdom or 501Y.V1) is the name of the variant which initially detected in the UK. It has 23 mutations with 17 amino acid changes.[176] Transmission[177] and case fatality[178] of this variant are more than the first identified SARS-CoV-2. Mutations in B.1.1.7 have no impact on treatment[179] and have little impact on vaccine efficacy,[180] which can be ignored. The variant was initially detected in South Africa in December 2020 named B.1.351 (501Y.V2 or South Africa), with 23 mutations with 17 amino acid changes.[176] This variant treatment strategy was changed duo to decrease in susceptibility to antibodies.[179] P.1 (Brazil, B.1.1.28.1, or 501Y.V3) with approximately 35 mutations and 17 amino acid changes was initially identified in travelers from Brazil, who were tested during routine screening at an airport in Japan in early January. An alternative treatment strategy was needed for this variant[179] and also vaccines efficacy was reduced against this variant.[180]

SIG also classified P.2, B.1.525, B.1.526.1, and B.1.526 in the VOI group. B.1.526.1 and B.1.526 were initially detected in the United States. B.1.525 and P.2 were initially detected in United Kingdom/Nigeria and Brazil, respectively. All these variants also have different treatment strategies and vaccine efficacy, but the transmission rate did not change significantly.[182] Several variants are not classified by SIG. B.1.617 (India) with several spike mutations is one of those variants. It was initially reported in India in early 2021 with a higher transmission rate than the first identified SARS-CoV-2.[183] B.1.427 and B.1.429 were first identified in California in February 2021 and were classified as VOCs in March 2021. These variants also have different transmission rate, treatment strategies, and vaccine efficacy.[181] Still, there is no variant in the VOHC group. Several mutations of significant SARS-CoV-2 variants were shown in Table 4.

There are a few published studies that analyzed the efficacy of the vaccine in patients with different SARS-CoV-2 variants. Ono of those studies confirmed AstraZeneca ChAdOx1 vaccine has 75% protection against B.1.1.7.[195] However, protection of this vaccine against the B.1.351 variant was just 10%.[196] Another study showed that the AstraZeneca ChAdOx1 vaccine has 74% and 22% efficacy against B.1.1.7[96] and the B.1.351[197] variants, respectively. In comparison, Johnson & Johnson's vaccine showed 64% protection against the B.1.351 variant.[120] The Novavax vaccine demonstrated 50% and 86% protection against B.1.351 and B.1.1.7 variants, respectively[195] which almost was confirmed by Wadman et al.[198] The CoronaVac/Sinovac vaccine efficacy against the P.1 variant was estimated to be about 50%.[199] Moderna vaccine has lower efficacy against B.1.1.7, B.1.351, and P.1 too.[176] Although some vaccines still have enough protection against some of the new variants, formulating new vaccines may be necessary to control some new SARS-CoV-2 variants.

Table 4. Several mutations of each variant of SARS-CoV-2 with its position and effect.

Variant	Mutations	Position	Effect	Reference
B.1.1.7	L18F	N-terminal domain (NTD)	Reduced sensitivity to neutralizing antibodies	184
	69–70del		Impact on immune escape	185
	144del			
	E484K	Receptor-binding site (RBS)	Escape from neutralizing antibodies	186
	N501Y	RBD	Improve the interaction between spike protein and angiotensin-converting enzyme 2 (ACE2)	187
	D614G	near the RBD	Increased transmissibility for viruses	
	P681H	near the furin cleavage site		188
	T716I			
	S982A	heptad repeat 1 (HR1)		
	D1118H	near the heptad repeat 2 (HR 2)		
B.1.351	L18F	NTD	Impair the efficacy of the current vaccine	189
	D80A			
	D215G			
	242–244del			
	R246I			
	K417N	RBD	Enhancement of the binding of RBD to ACE2	190
	E484K		Escape from neutralizing antibodies	
	N501Y		Improve the interaction between spike protein and ACE2	191
	A701V	near the furin cleavage site		
P.1	L18F	NTD	Reduced sensitivity to neutralizing antibodies	192
	T20N			
	P26S			
	D138Y			
	R190S			
	K417N	RBD	Enhancement of the binding of RBD to ACE2	
	E484K		Escape from neutralizing antibodies	
	K417T	RBD		
	N501Y		Improve the interaction between spike protein and ACE2	
	H655Y	near the RBD		
	T1027I	near the HR1		
B.1.617 (183)	G142D	NTD		193
	E154K			
	L452R	RBD	Improve the interaction between spike protein and ACE2	
	E484Q			
	D614G	near the RBD	Increased transmissibility for viruses	
	P681R	near the RBD		194
	Q1071H	near the HR2		

DISCUSSION

Based on vaccine efficiency, almost 67% of the population must be vaccinated to reach herd immunity for COVID-19.[200] This percent may be variable for different types of vaccines with various efficiencies. Although the vaccination does not mean the end of COVID-19, it can stop the disease's high prevalence. Based on what has been discussed, the safest vaccines with the most negligible long-term side effects are subunit vaccines. These vaccines, along with VLPs have a history of usage in humans, and due to the lack of certain harmful substances in these vaccines, they may not cause long-term side effects. A large number of subunit vaccines are being tested for SARS-CoV-2.[55] In addition to the lower risk, there is considerable focus on subunit vaccines due to their efficiency against other pathogens. However, it is of note that none of the subunit vaccines have provided a protective immune response against other RNA viruses, such as HIV and influenza. Viral vector-based vaccines and nucleic acid vaccines are placed in the following ranks of vaccine testing for SARS-CoV-2.[55] Due to the shorter lifespan of mRNA vaccines,[78] they seem to be more acceptable among the new generation of vaccines. However, for all vaccine types, longer-term follow-ups are needed. Vaccines against SARS-CoV-2 have shown up to 95% efficacy;[87] however, in order to have protection against new variants of SARS-CoV-2, it seems that several changes and improvements in vaccines may be needed.

Due to the requirement of vaccinating a large population and the unspecificity of the immunization period in vaccinated people, and the possible need for booster doses, the vaccine price is of high importance. Viral vector-based vaccines have been the most cost-effective type of vaccine, and each dose of this vaccine seems to be purchased for almost 3-10 dollars compared to $19.50 for Pfizer and $32-37 for Moderna. Another critical issue to note, is that whether the vaccine completely prevents infection or just reduces the symptoms. Since if reducing the symptoms is the case, the virus carriers will increase, contributing to the further spread of it. Another concern is how to distribute the vaccine properly. Delay to reach herd immunization in many countries, showed the importance of a precise and detailed planning to identify susceptible individuals who need to be vaccinated immediately. In case of new pandemic in the future, it would be a good idea to consider plans of successful countries all around the world.

In conclusion, SARS-CoV-2 vaccines have been developed faster than any other vaccines in history (the previous fastest production for vaccines belongs to the mumps vaccine, with a period of approximately four years). The reason for that may be the increasing number of companies and institutes working on the vaccines and more funds are assigned to this research area. Developing SARS-CoV-2 vaccines may affect the speed of the preparation process for other vaccines such as HIV and influenza.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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