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Progress in Biophysics and Molecular Biology 178 (2023) 32–49

Contents lists available at ScienceDirect

Progress in Biophysics and Molecular Biology

journal homepage: www.elsevier.com/locate/pbiomolbio

An overview of the vaccine platforms to combat COVID-19 with a focus on the subunit vaccines

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ARTICLE INFO

Keywords:
COVID-19
Omicron
Vaccine platforms
Subunit vaccine

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an emerging virus that has caused the recent coronavirus disease (COVID-19) global pandemic. The current approved COVID-19 vaccines have shown considerable efficiency against hospitalization and death. However, the continuation of the pandemic for more than two years and the likelihood of new strain emergence despite the global rollout of vaccination highlight the immediate need for the development and improvement of vaccines. mRNA, viral vector, and inactivated virus vaccine platforms were the first members of the worldwide approved vaccine list. Subunit vaccines. which are vaccines based on synthetic peptides or recombinant proteins, have been used in lower numbers and limited countries. The unavoidable advantages of this platform, including safety and precise immune targeting, make it a promising vaccine with wider global use in the near future. This review article summarizes the current knowledge on different vaccine platforms, focusing on the subunit vaccines and their clinical trial advancements against COVID-19.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the 7th known coronavirus capable of infecting humans; HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 are associated with mild symptoms, while Middle Eastern respiratory syndrome coronavirus (MERS-CoV), SARS-CoV, and SARS-CoV-2 can cause severe symptoms and severe respiratory syndromes (Ghasemlou et al., 2022; Ghassemlou et al., 2021; Rezaei et al., 2022a). The case fatality rates for SARS-CoV and MERS-CoV reached 15% (8096 cases and 774 deaths) and 37% (2494 cases and 858 deaths), respectively. Early reports of the death rate for SARS-CoV-2 were on average 2–4%, but according to the latest update from Johns Hopkins University (January 25, 2023), this rate has reached 18% in some countries and 673,732,242 cases and 6,749,705 deaths have been registered globally (Abdelghany et al., 2021; Cui et al., 2019; Güler et al., 2021). Although several vaccines against SARS-CoV and MERS-CoV were developed pre-clinically, no licensed vaccine was developed against coronavirus before the 2019 outbreak (Graham et al., 2013; Yong et al., 2019). The reason may be that those viral infections were self-restraint with limited geographical distribution (Nagy and Alhatlani, 2021). Despite the low priority of the previous coronaviruses for vaccine manufacturers, the obtained knowledge from the pre-clinically tested vaccines notably facilitates and accelerates the urgent vaccine development against the SARS-CoV-2 pandemic.

The standard vaccine development process usually needs several years to accomplish clinical trials, which takes, on average, over ten

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https://doi.org/10.1016/j.pbiomolbio.2023.02.004
Received 22 September 2022; Received in revised form 13 February 2023; Accepted 16 February 2023
Available online 18 February 2023

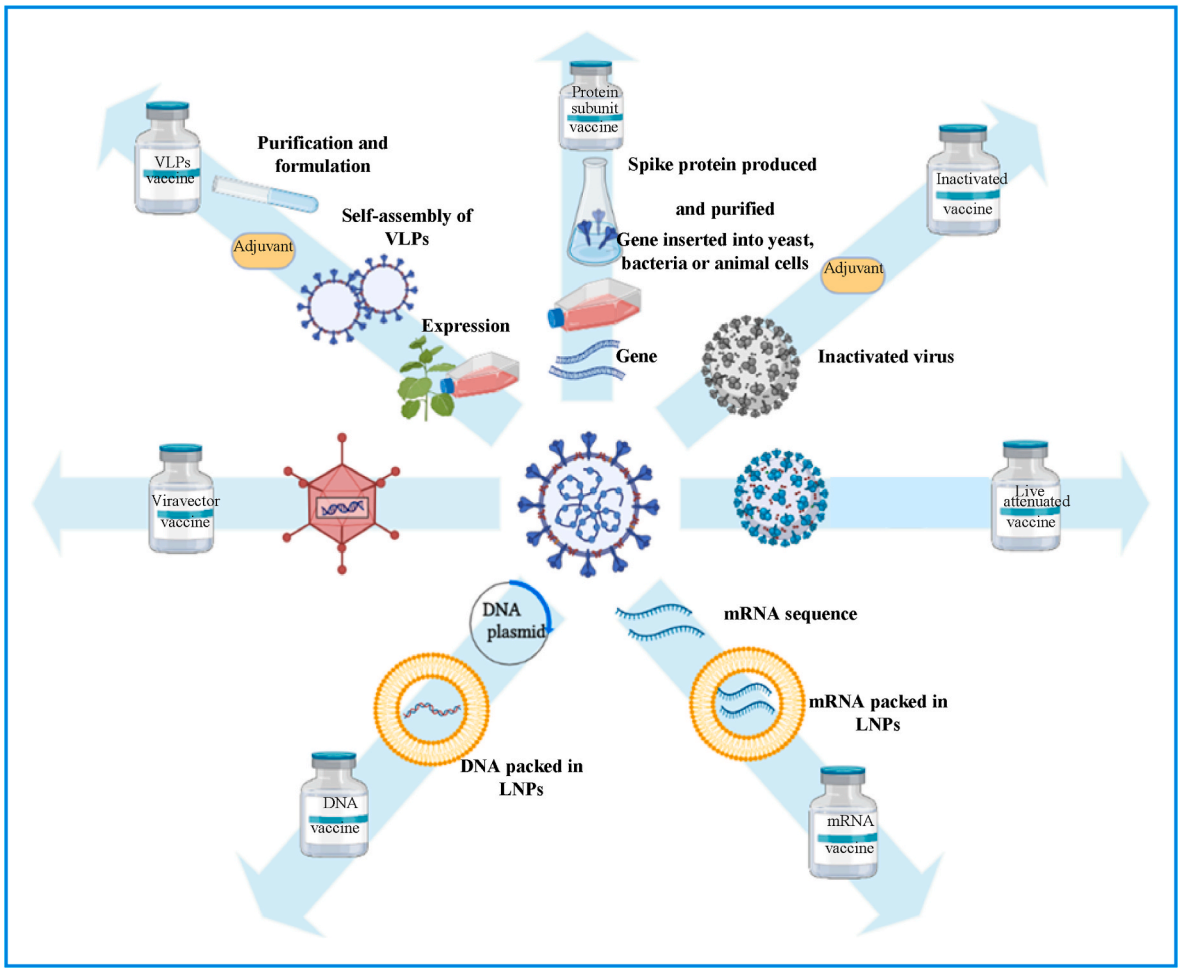

Fig. 1. Distinct vaccine platforms considered for vaccine development against SARS-CoV-2.

years. However, the detrimental effect of the SARS-CoV-2 pandemic on the global healthcare system and its serious socio-economic implications have necessitated an unprecedentedly fast response in global vaccine R&D efforts and a fundamental change in the traditional vaccine development pathway. In December 2020, one year after the first detected COVID-19 case in Wuhan, the first vaccine, the so-called Pfizer-BioNTech, received emergency authorization from the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). Shortly thereafter, key regulators granted the Moderna vaccine full approval (Thanh Le et al., 2020). Currently, there are multiple COVID-19 vaccines in development or use, utilizing different platforms. Some use traditional vaccine approaches, including killed/inactivated virus and protein-based vaccines. Others employ the newer and novel vaccine approaches comprising mRNA and DNA and viral-vector vaccines (H.-Z. Chen et al., 2020). One of the safest and most frequently used vaccines among vaccine platforms are protein subunit vaccines, which have been highly effective against various infectious diseases, such as hepatitis B, diphtheria, pertussis, tetanus, and shingles (Arunachalam et al., 2021). Protein subunit vaccines contain a segment or whole part of an antigenic protein in the target pathogen that elicit immune responses (Dong et al., 2020). Protein subunit vaccines mostly stimulate antibody-mediated immunity with a weak induction of T-cell response (Dai and Gao, 2021; Li et al., 2021). An immune-stimulatory agent is paired with adjuvants as essential ingredients of subunit vaccines that enhance the immune response quality and permanence as well as the vaccine efficacy (Awate et al., 2013). The subunit vaccines received lots of attention in controlling the COVID-19 pandemic, which is the main focus of the present review. Fig. 1 represents different available vaccine platforms used by vaccine developers against COVID-19.

2. Summary of different types of available vaccine platforms

2.1. Live attenuated vaccines

Live attenuated vaccines contain the whole viable pathogen with reduced virulence. The wild virus or bacteria are attenuated using the serial passaging protocol. The target pathogen is introduced into a species in which it cannot replicate well and is forced to be replicated repeatedly for a long time. Accumulation of mutations during their evolution to adapt to the new environment lead to a weaker strain with respect to its natural host. The immune system cannot distinguish between the infection with an attenuated viral or bacterial vaccine and a wild pathogen. Hence, the generated immune response due to attenuated vaccine is virtually identical to that produced by natural infection. After administration of one or two doses, live attenuated vaccines elicit strong cellular and humoral immunity that usually persists for a lifetime (Dong et al., 2020). Attenuated vaccines are unable to replicate sufficiently to cause disease in healthy recipients; however, sometimes, there is the risk of virulence reversion in the individuals with impaired immunity (Dong et al., 2020).

2.2. Inactivated vaccines

Vaccines that have been inactivated, also known as killed, are made of bacteria, virus particles, or other pathogens that have been grown in

culture before having had their genetic material physically (through heat or radiation) or chemically destroyed (formalin or phenol). They cannot reproduce as a result, but the immune system can still detect them. Compared to their attenuated counterpart, inactivated vaccines elicit the immune system (especially cellular immunity) response less efficiently and with lower persistency, and usually there is a need for multiple doses and immunologic adjuvants (Louten, 2016). This platform does not cause infectious diseases in immunocompromised patients (Clem, 2011). Both attenuated and inactivated vaccines require high biosafety level laboratories for cultivation, which is a considerable challenge for their production (Nagy and Alhatlani, 2021). Despite the liveness of attenuated vaccines, they usually do not need refrigeration. They can be easily stored and transported in a freeze-dried form, making this platform more affordable in developing countries (Louten, 2016).

2.3. Nucleic acid vaccines

Nucleic acid vaccines, which are a relatively newer technology than other vaccine platforms, contain genetic materials (DNA or mRNA) from the target pathogen. The genetic code of the antigen is delivered to the body cells and converted to a protein using the recipient cell transcription/translation machinery. The produced protein is processed and presented to immune cells by antigen-presenting cells (APCs) (Ingolotti et al., 2010). The induced immune system is exclusively against the desired protein(s).

2.3.1. DNA vaccines

DNA vaccines are made using bacterial plasmids and contain two main units: (1) the expression unit containing the mammalian promoters followed by the desired antigen encoding sequence and terminator, (2) the production unit consisting of required bacterial sequences for plasmid amplification and antibiotic resistance for selection. DNA vaccines are easily produced *in vitro*. The target antigen sequence is inserted into the plasmids using recombinant DNA technology, and the constructed recombinant plasmid is transformed into the bacterial host for propagation. Bacterial cells that receive the plasmids are screened based on antibiotic resistance and cultured in the appropriate medium containing the same antibiotic to maintain the selection pressure and avoid plasmid loss. After the purification of circular plasmids from other bacterial cell components, they are ready to be used as a vaccine (Liu, 2019).

DNA vaccines are stable at room temperature, facilitating prolonged shortage and easy transportation. Due to the possibility of easy manipulation in DNA sequence, the potency of this vaccine platform can be increased in a short time and has considerable potential for application in new and fast-emerging infectious diseases or adaptation to new mutations in existing pathogens (Farris et al., 2016; Liu, 2019).

According to animal studies, injection of DNA vaccine induces both cellular and humoral immune responses against the expressed protein and can be applied against different human infectious or noninfectious diseases in the near future (Liu, 2003). In contrast to viral vector vaccines, preexisting immunity to the vaccine backbone is not a problematic factor for DNA vaccines because there is little or no host immune response to plasmid DNA (Shafaati et al., 2022).

2.3.2. RNA vaccines

The mRNA vaccines consist of synthetic mRNA molecules that encode the antigen of interest, which will induce the immune response following *in vivo* translation (Sahin et al., 2014). With the emergence of the SARS-CoV-2 pandemic, the mRNA vaccine became the pioneering technology in the COVID-19 vaccine race. Currently, two major types of mRNA vaccines are utilized: non-replicating mRNA (NRM), and self-amplifying mRNA (SAM). Both types have five common elements, including 5' cap, 5' untranslated region (UTR), an open reading frame that encodes the antigen, 3' UTR, and a poly(A) tail. Besides these basic features, SAM contains a viral replicase gene that encodes an RNA-dependent RNA polymerase. This gene provides an mRNA vaccine with the ability to self-replicate within the host cells and produces larger amounts of antigen with reduced mRNA concentrations (Bhattacharya et al., 2022).

One of the most commonly applied mRNA vaccine delivery approaches is that of encapsulating mRNA molecules in lipid nanoparticles (LNP). Their high entrapment efficiency protects mRNA from degradation, while the ease of fusion of liposomes with recipient cells improves the efficiency of mRNA delivery (Zhan Zhang et al., 2022). The efficiency of using LNP as the delivery system for siRNA has been demonstrated since 2006; however, its application as the *in vivo* delivery tool for mRNA molecules has only been considered in recent years. Intradermal, intramuscular, and subcutaneous administration of mRNA-LNP complexes has been indicated to generate prolonged protein expression at the site of injection (Kanasty et al., 2013; Pardi et al., 2018).

After vaccination, mRNA-LNP is delivered to the cytosol of the host cell. Then the released mRNA is used as a template for the synthesis of protein antigens in a way that mimics the viral infection by using the host cells to translate mRNA into the antigen and trigger both cellular and humoral immune responses (Khalid et al., 2021).

2.4. Viral vector vaccines

This type of vaccine uses modified, unrelated viruses that encode one or more antigens. This technique uses replicating (live but often attenuated and harmless) or non-replicating vectors (Rauch et al., 2018). Replicating viral vector vaccines maintain their replication potential and produce new viral vectors in the infected cells. Once injected, these viral vector vaccines infect the body cells by inserting their genetic materials, which contain the antigen of interest, into the cell nuclei. The viral genes, including the incorporated antigen, are manufactured by the host cells' translational machinery and presented on the cell surface alongside several other proteins. The immune cells detect the foreign proteins and mount humoral and cellular responses. Compared to non-replicating viral vector vaccines, the replicating ones can promote longer and higher expression of immune cells even with lower immunization doses. However, due to the safety concerns over the use of the replicating vector, especially in immune-compromised individuals, non-replicating viral vaccines have been considered more extensively. In non-replicating viral vectors, the genes encoding the structural proteins are deleted from the viral genome to prevent the assembly of virions in the infected cells. So, the vaccine vector assembly requires a helper virus. Among the currently available viral vectors, adenoviruses are the most appealing and applicable delivery system (Li et al., 2021).

2.5. Protein subunit vaccines

The protein subunit vaccines are the most popular design for modern vaccines. Usually, they consist of immunogenic proteins of a pathogen produced using conventional biomedical methods or recombinant DNA technology (Clem, 2011). In the recombinant subunit vaccine, the coding sequence of one or more antigenic proteins of a pathogen (whole segment or part of them) is inserted into the prokaryotic or eukaryotic manufacturing cells (such as bacteria or yeast) (Wang et al., 2016). Compared to other platforms, such as live-attenuated or inactivated vaccines, the recombinant production of subunit vaccines facilitates rapid scale-up for industrial manufacturing (Wang et al., 2016). Peptide-based vaccines are another subset of subunit vaccines composed of minimal immunogenic epitopes of an antigen. They are easily synthesized in large-scale and pure form; however, they have greatly reduced immunogenicity. With the rapid development in bioinformatics and immunoinformatics tools for vaccine design, the coding sequence of various peptide epitopes can be combined to generate the multi-epitope vaccines with improved immunogenicity (Banerjee et al., 2020; Li et al., 2014).

Subunit vaccines are generally safe and alleviate the risks associated

Table 1
Advantages and disadvantages of vaccine platforms.

Vaccine platform	Advantages	Disadvantages	Ref.
Subunit	• Applicable to immunocompromised patients • Relatively safe with fewer chances of side effects • High neutralizing antibody titer compared to inactivated virus vaccines • Cold chain storage is not required for mass vaccination. • Favorable immunogenicity by heterologous or homologous booster dose with some subunit vaccines and efficacy similar to mRNA vaccines	• Less immunogenic than live attenuated vaccines, and need adjuvant for stimulating immune responses • The high immunogenic antigen(s) need to be identified for appropriate efficacy. • Multiple doses are required for long-lived immunity	(Lidder and Sonnino, 2012; Muik et al., 2022; Vartak and Sucheck, 2016)
Live attenuated	• The closest mimic of natural infection that provides a good teacher for the immune system • Usually confers lifelong immunity with strong induction of cellular and humoral immunity • One or few doses without adjuvant for immunization • Administration via intranasal spray and stimulates mucosal antibody immune responses	• The risk of virulence reversion due to the back-mutations • Require critical storage conditions to maintain potency (e.g., temperature) • Not appropriate to be administered in the immunocompromised patients	Yadav et al. (2014)
Killed/ Inactivated	• Safe for use in immunocompromised patients Compared to attenuated vaccines • Require less severe storage conditions	• Less immunogenic than live attenuated vaccines with the low capability to induce cellular responses, and need adjuvant to enhance the immunity • Require to use of large amounts of antigen and booster doses to achieve the desired immunity • Inactivation is a time-consuming and costly process, and not all viruses become immunogenic after inactivation	Kyriakidis et al. (2021)
DNA	• Ease of design and development, relatively inexpensive and scalable, relatively stable at room temperature for storage and shipping • Antigen presentation by both MHC I and II molecules and induce humoral and cellular immune responses	• The risk of integration into the host genome • The expression inside the host body may induce the immunological tolerance • Low efficiencies probability due to the rapidly degradation of naked DNA vaccines by nucleases and different biological barriers	Khan (2013)
RNA	• Antigens are produced by the host cells just like natural infection by an RNA virus • Less likelihood of biological changes during production in the vaccinated host • Degraded within a short time in the body and barely has a chance of changing the genome • The mRNA vaccines can elicit strong Th1 cell responses and GC B-cell responses, and also, they produce long-lived plasma cells and memory B cells that can consequently elicit SARS-CoV-2 neutralizing antibodies. • To simplify a timely update, the mRNA vaccines can be directly modified on the original sequence.	• The Low stability of RNA molecules in high temperatures makes global distribution difficult. • Complications from mRNA vaccinations, including myocarditis, can be occurred.	(Heymans and Cooper, 2022; Li et al., 2022; Verbeke et al., 2021; Zhang et al., 2019)
Viral-vector	• Has better safety profiles than many live attenuated virus vaccines and is more immunogenic than inactivated virus vaccines. The carrier has a good stimulating response to B cells and T cells and can boost immunity. • Present the desired antigens in the natural conformation to the immune system • Highly efficient viral vector transduction leads to higher amounts of antigen production *in vivo*, compared to DNA vaccine • In comparison to inactivated vaccines, the manufacturing process for viral vector vaccines is comparatively safe because no live SARS-CoV-2 is involved	• Risk of host genome integration Previous immunity to the vector due to previous virus exposure and production of neutralizing antibodies can reduce the effectiveness of the vaccine • Virus vector vaccinations based on adenovirus can trigger side effects, including thrombocytopenia.	(Holman et al., 2009; Li et al., 2022)
Virus like particle (VLP)	• Compared to the recombinant protein, VLPs show adaptive epitopes similar to native viruses, and induce immune responses more effectively. • Has self-adjuvant properties. • VLPs can be produced in a wide range of production systems, which makes them flexible in terms of production conditions. • VLPs vaccines aren't infectious since they are no viral genomes in them. • Oral delivery vaccines could be made from plant-based VLP vaccines.	• Difficult downstream processing and high production cost • The VLP vaccines are loaded with many proteins at the same time and the degree of immune response induced by it is not clearly known.	(Deng, 2018; Grgacic and Anderson, 2006; Li et al., 2022)

with pathogen handling, virulence recovery, and induction of harmful immune responses. However, these vaccines usually do not induce robust or long-lasting immune responses and require appropriate adjuvants and repeated doses. The vaccine delivery systems with self-adjuvanting properties have been introduced and applied in the newer approaches to boost the immune responses. These include different polymer-based vaccine delivery systems, for example, liposome, virosome, and virus-like particles (VLPs) that mimic the form and size of a virus particle lacking the viral genetic materials. These constructs can simulate the natural immune response by incorporating more viral components (Mohan et al., 2013).

Subunit vaccines have recently attracted growing interest. The vaccine against hepatitis B and papillomaviruses are examples of successfully licensed subunit vaccines. Furthermore, this platform is considered a promising candidate against many other infectious diseases, such as the Zika virus, malaria and Ebola, alongside the emerging SARS-CoV-2

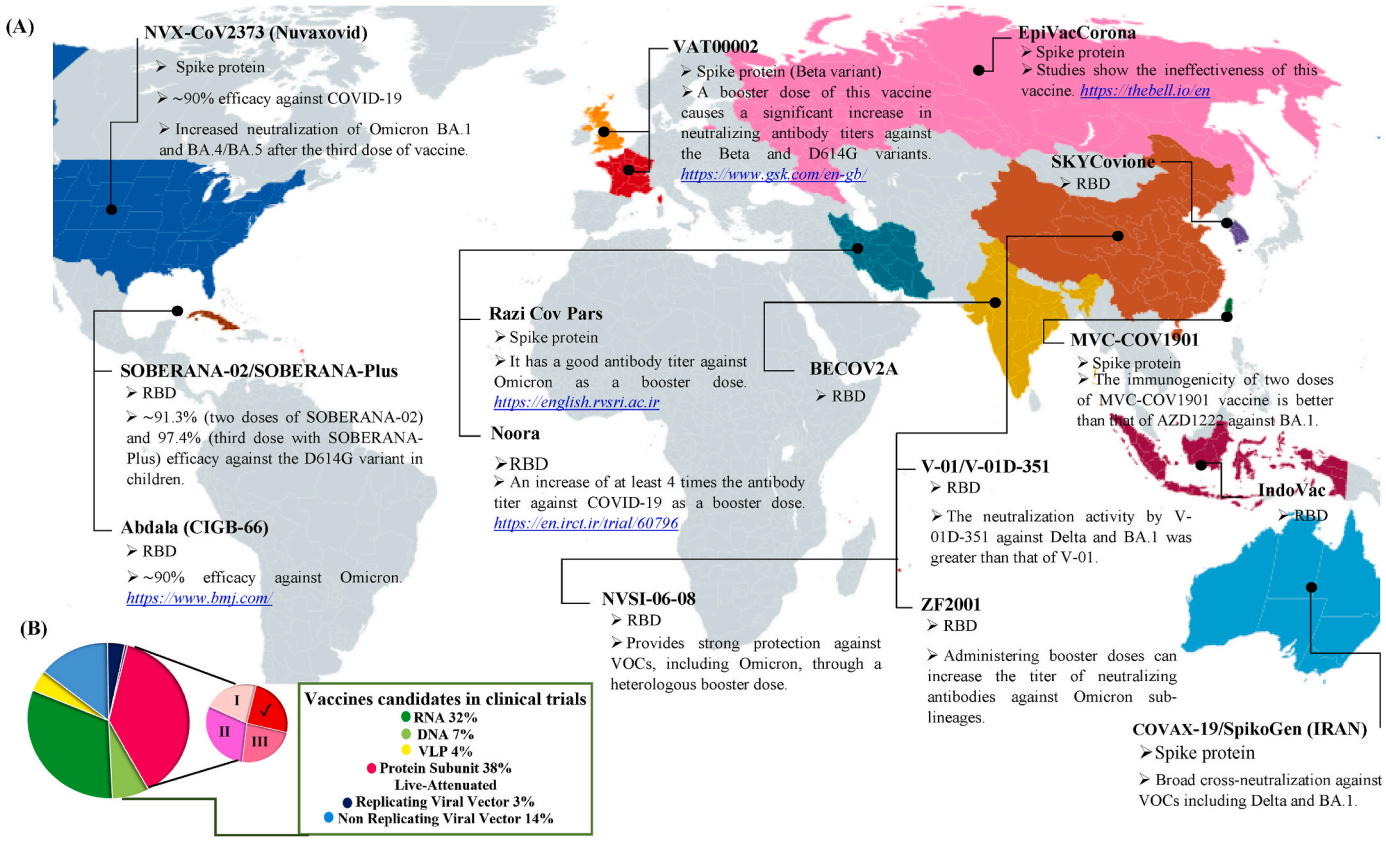

Fig. 2. (A) Approved protein subunit vaccines against COVID-19. **(B)** Statistics for COVID-19 vaccine candidates at various stages of clinical evaluation until December 2022 (https://covid19.trackvaccines.org/). The statistics for different clinical stages of subunit protein vaccines are presented in the figure (Phase I: 22%, Phase II: 30%, Phase III:23%, Approved or ✓:25%). Information on the approved protein subunit vaccines is collected in Table S1.

(Tai et al., 2019).

3. Advantages and disadvantages of the vaccine platforms

Each of the vaccine platforms has its strength and limitations that should be considered in the planning projects. Table 1 displays a summary of the main advantages and disadvantages of the vaccine platforms.

4. Protein subunit vaccine design for COVID-19

Different vaccine platforms have been considered in the fight against this pandemic from the beginning of the outbreak. Inactivated virus, mRNA-based, and viral vector platforms won the race and were the first generation of approved vaccines against SARS-CoV-2. However, the rapid emergence of SARS-CoV-2 variants led to the generation of variants of concern; some show different degrees of resistance to the available vaccines. Besides, the development of diverse platforms facilitates faster and more efficient worldwide vaccine coverage (Lazarevic et al., 2021; Winger and Caspari, 2021). There are several protein subunit vaccine candidates against SARS-CoV-2 in clinical trials or approved in some countries. Successfulness of such vaccines relies on the selected antigen and the choice of the expression system (Fig. 2).

4.1. Antigen selection for protein subunit vaccines against SARS-CoV-2

Among the four major structural proteins, the S protein is known as the principal target for vaccine development and one of the main immunogens widely used in developing serological assays. The S protein is the main inducer of neutralizing antibody and T-cell response and generates protective immunity. Furthermore, the S protein is involved in receptor recognition and virus entry to the host cell, and is considered a hotspot for mutations with high relevance to the virus virulence, transmissibility, and host immune escape. These traits represent the S protein (full-length, truncated, or its specific domains or epitopes) as an ideal target for vaccine development (Du et al., 2009; Khateeb et al., 2021).

4.1.1. S protein

The S protein is a homotrimeric protein composed of a large ectodomain, a transmembrane anchor, and a short cytoplasmic domain (CD). Each monomer is 1273 aa long and consists of two subunits: S1 and S2. The S1 subunit is located on the N-terminal of the S protein and divided into the N-terminal domain (NTD) and the RBD, also known as the C-terminal domain (CTD), which mediates receptor recognition and binding. S2 is involved in fusing virus and host cell membranes by forming a six-helical bundle via its two HR1 and HR2 domains (Jaimes et al., 2020; Rezaei et al., 2022b; Rezaei and Sefidbakht, 2021).

4.1.1.1. NVX-CoV2373 (Novavax). Novavax COVID-19 vaccine (NVX-CoV2373), sold under the trade names Nuvaxovid in Europe and Covovax in India, has been described as an adjuvanted recombinant protein nanoparticle vaccine. The vaccine is composed of trimeric full-length S protein and Matrix-M1 adjuvant. The S protein sequence in NVX-CoV2373 has been modified at two critical sites that stabilize the protein in the prefusion conformation: (1) the S1/S2 furin cleavage site has been modified from RRAR to QQAQ to prevent the proteolytic cleavage of S protein, (2) K986 and V987 residues at the C terminal of HR1 were replaced with proline amino acids to stabilize the S protein in the prefusion conformation (Tian et al., 2021). This stabilized prefusion confirmation is desirable for vaccine development because it stimulates the conformation found on infectious virions and exposes most

neutralizing epitopes that can be recognized by antibodies to block the virus entry. Besides increased immunogenicity, it has been reported that the recombinant production yield of S protein in perfused stabilized structure is higher than in the native structure, possibly due to the inhibition of protein misfolding (Bos et al., 2020; Hsieh et al., 2020). The related designed gene was codon-optimized according to the insect cells' expression system and is produced heterologously in the *Spodoptera frugiperda* (sf9) insect cells. The harvested S proteins are incorporated into a synthetic lipid nanoparticle delivery vehicle composed of phospholipid, cholesterol, and saponin. The S proteins are exposed in a micelle-attached structure that mimics the virus particle. The resulting prefusion stabilized trimeric S protein showed improved affinity (~2 fold) for binding to the human ACE2 compared to the wild-type counterpart (Tian et al., 2021; Zhang et al., 2021). In preclinical studies, the NVX-CoV2373 was administered with saponin-based Matrix-M adjuvant, and low doses of the vaccine elicited a high titer of anti-S IgG (that blocks S protein binding to human ACE2) and neutralizing antibodies and protected against SARS-CoV-2 challenge in mice and baboon animal models. The antibodies titer was increased significantly after a booster dose administration. Using adjuvant significantly increases the frequency of IFN-γ^+, TNF-α^+, and IL-2^+ cytokine-secreting $CD4^+$ and $CD8^+$ T cells, as well as multifunctional T cells. The Matrix-M adjuvant was also indicated to enhance the germinal center (GC) B cell and T follicular helper (Tfh) cell differentiation, which are central to the induction and maintenance of long-lived, high-affinity T cell-dependent B cell responses (Tian et al., 2021). Two main clinical trials were conducted for NVX-CoV2373, including over 45,000 people older than 18 years. In total, the results of both studies showed high vaccine efficiency (~90% reduction in the number of symptomatic COVID-19 cases) for NVX-CoV2373. The observed side effects were mild to moderate and disappeared within a few days. A recent study reported enhanced neutralization of Omicron BA.1 and BA.4/BA.5 following three doses of the NVX-CoV2373 vaccine, with responses similar to three doses of an mRNA vaccine. Evaluation of the vaccine's effectiveness against the Omicron variant is still ongoing (Bhiman et al., 2022; Vohra-Miller and Schwartz, 2022). Because of the low vaccination rates or the flow of misleading information about mRNA vaccines in some countries, and due to the use of manufacturing technology similar to what was used in pertussis and influenza vaccines, which have been used routinely in pregnancy, pregnant women may be more accepting of this vaccine (Parums, 2022).

The European Medicines Agency (EMA) recommended Nuvaxovid for authorization across the EU, and the European Commission granted conditional marketing authorization for Nuvaxovid on December 20, 2021. The Medicines and Healthcare Products Regulatory Agency (MHRA) granted this vaccine conditional marketing authorization (CMA) in Great Britain for use in individuals ≥18 years on February 3, 2022 (Parums, 2022).

4.1.1.2. MVC-COV1901. MVC-COV1901 (NCT04695652) vaccine candidate is based on a recombinant stabilized prefusion SARS-CoV-2 S protein (S–2P) vaccine adjuvanted with aluminum hydroxide (alum) and CpG 1018 developed by Medigen Vaccine Biologics Corp. This vaccine candidate obtained Taiwan's EUA approval on July 19th, 2021. CpG 1018, a TLR-9 agonist, binds to the DNA receptor on plasmacytoid dendritic cells (pDCs) and enhances immunogenicity by stimulating CD4+/CD8+ T lymphocytes. In preclinical studies, hamsters were immunized with two injections of 5 μg or 1 μg of the vaccine. Six days after the infection of vaccinated hamsters, there was a significantly decreased lung pathology and no infection-related weight loss. In addition, the viral load of the lungs was reduced to less than that of unvaccinated animals (Lien et al., 2021). Also, according to the study of the effectiveness of MVC-COV1901 against VOCs, the antibodies elicited after the third dose in rats effectively neutralized the Beta variant. In the clinical phase, although the neutralization with the Beta variant decreased, the neutralizing ability against D614G and Alpha variants was shown (Lien et al., 2022). In a recent study, the immunogenicity of two doses of MVC-COV1901 and AZD1222 vaccines was compared. The results showed high levels of IgG1 and IgG3 produced by both vaccines, but MVC-COV1901 induced more IgG subclasses (Torales et al., 2023). The immunogenicity of MVC-COV1901 was also evaluated against the Omicron (BA.1, and BA.4/5), showing a significant reduction in the geometric mean HI antibody titers (GMTs, which is a seroprotection rate defined as the proportion of participants with a serum antibody titer level of ≥1:40 postvaccination) compared to that of the Wuhan-hu-1 (Liu et al., 2022). However, data from the seropositive individuals indicated that neutralizing Omicron (BA.1) titers were higher in the MVC-COV1901-vaccinated individuals than in the patients vaccinated with AZD1222 (Torales et al., 2023).

4.1.1.3. COVAX-19®/SpikoGen®. COVAX-19® a vaccine candidate for COVID-19 that consists of the spike extracellular domain (ECD) expressed in baculovirus insect cell lines and formulated with Advax-CpG adjuvant (Tabynov et al., 2022). The design and production of COVAX-19 have distinct advantageous features. First off, since ECD contains two domains, RBD and NTD, it induces a broader repertoire of neutralizing antibodies. The second advantage is the difference in glycosylation in the insect expression system (paucimannose-type glycans) compared to the other expression systems (with high-mannose- and complex-type glycans). This difference could mean that protein expression by insect cells exposes more epitopes to the immune system (Tabarsi et al., 2022b). Preclinical studies of this vaccine in South Australia were conducted by Vaxine Pty Ltd. under the supervision of Nikolai Petrovsky in collaboration with the University of Georgia, U.S., based on the harmless insect cell protein expression on a ferret, mice, and monkey. The role of the SARS-CoV-2 S protein was identified and confirmed with the help of Etaluma LS620 Microscope, and the team also used High-Performance Computing based on Oracle Cloud and artificial intelligence (AI) to develop COVAX-19®. Petrovsky expects the vaccine immunity to last for at least two years and protect against the new SARS-CoV-2 mutants, including India (Delta variant), Brazil (Gamma variant), and South Africa (Beta variant). Independent the PARC clinical trial team, a Phase I trial (NCT04453852) was performed with the participation of 40 healthy individuals aged between 18 and 65 years at the Royal Adelaide Hospital. The candidate vaccine entered Phase II/III of clinical trials by CinnaGen Company, which is an Iran-based biotechnology company, under the brand name "SpikoGen®". The second Phase trial (NCT04944368) was conducted at the Espinas Palace Hotel in Tehran with 400 participants (18–65 years old). Phase III (NCT05005559) injections were performed in two doses at 21-day intervals in the non-dominant deltoid muscle with the participation of 16,876 adults (Chavda et al., 2021). In a recent study, results from a booster dose of SpikoGen® after the primary vaccination (with different types of the vaccine, including inactivated whole virus) showed broad cross-neutralization against VOCs including Delta and Omicron (BA.1) (Tabarsi et al., 2022a).

4.1.1.4. RAZI-COV PARS. The first recombinant protein-based Iranian-made COVID-19 vaccine, RAZI-COV PARS, is constructed out of recombinant SARS-CoV-2 spike protein in its monomeric (encompassing amino acid number of 1–674 for S1 and 685–1211 for S2 subunits) and trimeric forms (S-Trimer) formulated in the oil-in-water adjuvant system RAS-01 (Razi Adjuvant System-01). Compared to S1, S2 subunit of the spike protein is noticeably more conserved across coronaviruses, induces more cross-reactivity with CoV-specific antibodies, and has proven benefits in vaccine design (Banihashemi et al., 2022b). In the S2 subunit of SARS-CoV-2, certain fragments including residues 795–848 that correspond to the residues of fusion peptide (FP) and residues 1127–1177 (HR2) were shown to stimulate neutralizing antibodies against SARS-CoV-2, eliciting a longer-lasting and stronger memory

response, and reducing the likelihood of sequence-altering mutations which may reduce the efficacy of the vaccine (Banihashemi et al., 2022b; Zheng et al., 2020). Preclinical studies of this vaccine were conducted on four experimental animal species including Syrian hamster, BALB/c mice, Pirbright guinea pig, and New Zeeland white (NZW) rabbit. In contrast to the placebo and control groups, three doses of this candidate vaccine stimulated significant titers of neutralizing antibodies, S1, Receptor-Binding Domain (RBD), and N-terminal domain (NTD) specific IgG antibodies, and IgA antibodies. None of the vaccinated animals showed any changes in clinical observations. The results of the preclinical studies on the RAZI-COV PARS candidate vaccine showed high humoral and cellular immune responses in animal models. This vaccine is administered in three doses (two injections and one nasal spray) (Banihashemi et al., 2022a). Four clinical trials were conducted for RAZI-COV PARS. In the first phase of the human clinical test, 133 healthy volunteers with the age range of 18–55 participated, and this vaccine candidate showed to be safe and with mild associated complications.

4.1.1.5. Sanofi/GSK: VidPrevtyn Beta. VAT00002 Sanofi–GSK COVID-19 vaccine, developed by Sanofi Pasteur and GSK, is another recombinant protein subunit vaccine. VAT00002 vaccine contains the SARS-CoV-2 spike protein generated in insect cells using a baculovirus vector with AS03 adjuvant (CoV2 preS dTM-AS03). AS03 is an adjuvant system consisting of α-tocopherol, squalene, and polysorbate 80 in an oil-in-water emulsion (Garçon et al., 2012). In the Phase I study of this vaccine, which began in the US in September 2020 with 439 healthy participants aged 18 and above, the immunogenicity and safety of the VAT00001 vaccine were evaluated. Based on the results, neutralizing and binding antibodies after two doses of the vaccine were higher in adjuvanted vs. unadjuvanted groups, in high-dose vs. low-dose groups, and in younger vs. older adults. In February 2021, Sanofi-GSK launched a Phase II trial including 722 healthy adults aged 18 and above, in the United States and Honduras. This study evaluated the immunogenicity, safety, and reactogenicity of two injections administered 21 days apart at three antigen dosage levels of 5, 10, and 15 g (de Bruyn et al., 2022).

4.1.1.6. EpiVacCorona. EpiVacCorona vaccine is manufactured by the Vector Institute, a Russian biological research center. It is based on using fragments of synthetic viral peptides, including one Spike, one protein N, and one bacterial peptide that are conjugated to a large carrier protein reflecting SARSCoV-2 antigens and adjuvanted with aluminum hydroxide (Chavda et al., 2021; Dobrovidova, 2021). Protein N was suggested as a valuable component of subsequent SARS-CoV-2 vaccines (Dutta et al., 2020) and it was also found to induce T-cell immune responses. EpiVacCorona vaccine comprises protein N, which was chosen to be utilized as a carrier for peptide antigens owing to its high level of conservation and immunogenicity, as a valuable source of $CD4^+$ T-cell epitopes (A. B. Ryzhikov et al., 2021). The amino acid sequences of the three peptides of the EpiVacCorona vaccine are: CRLFRKSNLKPFERDISTEIYQAGS, CKEIDRLNEVAK NLNESLIDLQE, and CKNLNESLIDLQELGKYEQYIK (Aleksandr B. Ryzhikov et al., 2021). EpiVacCorona is administered in two doses 3 weeks apart by intramuscular injection to people over 18 years of age, as well as older people >60 years of age (Dobrovidova, 2021). It was found this vaccine induced virus-specific antibodies and neutralizing antibodies in 100% of volunteers, at levels demonstrated by preclinical studies (hamsters, ferrets, and primates), which could shorten the duration of infection by a 5–7days and prevent pneumonia. The peptide-based EpiVacCorona Vaccine has low reactogenicity and is a safe, immunogenic product. Phase I was a study of the vaccine safety, reactogenicity and immunological activity involving 14 volunteers aged 18–30 years and is publicly available. Phase II was a single-blind, comparative, randomized, placebo-controlled trial involving 86 volunteers aged 18–60 years. All local reactions following vaccination were mild, including short-term pain at the injection site. There were no signs of local or systemic adverse reactions. The two-dose vaccination program induced antibodies in 100% of the volunteers, which are specific for the antigens that make up the vaccine. 21 days after the second immunization, 100% of the volunteers reported seroconversion with a neutralizing antibody titer ≥1:20. (Pollet et al., 2021; A. B. Ryzhikov et al., 2021). However, based on recent analyses, EpiVacCorona has proven to be an ineffective vaccine and cannot protect against COVID-19 (Matveeva and Ershov, 2022).

4.1.2. The RBD

Similar to SARS-CoV, SARS-CoV-2 recognizes the ACE2 receptor on the host cells through the RBD domain (residues 331 to 524) of the S1 subunit in the S protein. The RBD transiently fluctuates between two conformations called “down” and “up” states, and only binds to the ACE2 in its up conformation, which is the exposed state (Yuan et al., 2021). Administration of recombinant RBD has been shown to induce neutralizing antibodies and long-term protective immunity in animal models and human studies. Furthermore, deletion of potential ADE-promoting S protein epitopes located outside of the RBD may make it a safer vaccine candidate. Potential manufacturing advantages of RBD-based vaccine, compared to full-length S protein, make this vaccine an appropriate choice at an affordable cost, especially for low- and middle-income countries. Different platforms of RBD-based immunogens with monomeric, dimeric, or multimeric forms of antigen display have been shown to induce anti-RBD neutralizing antibodies in animal models and humans. Hence, RBD is defined as the foremost likely target for developing therapeutic virus attachment inhibitors, inducing neutralizing antibodies, and vaccine design (Hotez et al., 2020; Kleanthous et al., 2021; Yuan et al., 2021).

4.1.2.1. Zifivax vaccine (ZF2001). Zifivax vaccine (ZF2001), developed by Anhui Zhifei Longcom Biopharmaceutical, is a three-dose dimeric RBD-based vaccine. ZF2001 is made from an RBD dimer protein (aa R319- K537 from SARS-CoV-2) produced in Chinese Hamster Ovary (CHO) cells with an aluminum hydroxide adjuvant (Martínez-Flores et al., 2021). A tandem repeat dimer was formed by attaching two copies of RBD. The RBD-dimer construct was transformed into clinical-grade CHO cell lines. In accordance with current Good Manufacturing Practices, cell lines with the best antigen yields were chosen for scaling-up the antigen synthesis. With the affinity similar to the RBD monomer, the CHO-generated RBD-dimer bound to hACE2 receptor, showing the proper exposure of the receptor-binding motif. A stock solution was then formulated with aluminum hydroxide as an adjuvant and placed into ZF2001 vaccination vials. In preclinical studies, immunogenicity and efficacy of the ZF2001 vaccine were evaluated in mice and non-human primates (NHPs) and the results demonstrated that ZF2001 induced a strong neutralizing antibody response and also considerable $CD4^+$ T cell responses in mice and NHPs (An et al., 2022). The ZF2001 vaccine was found to be safe, with an acceptable side-effect profile, and immunogenic in humans in Phase I and II clinical trials (Yang et al., 2021). A recent study showed that the antibody induced by this vaccine was able to recognize Alpha, Beta, Delta, and Omicron strains, despite a nearly 3- to 22-fold fall in nAb titer when compared to the prototype strain. Overall cross-reactivity to VOCs was induced in macaques and potential effective protection of ZF2001 for current VOCs (He et al., 2022). The six Phase III clinical trials were conducted in China and Uzbekistan, with Indonesia, Pakistan, and Ecuador following as study sites (Huang et al., 2021; Yang et al., 2021). Researchers conducted a randomized, double-blind, placebo-controlled, Phase III clinical trial involving adult participants (≥18 years of age) to evaluate the efficacy and confirm the safety of ZF2001. Based on the results, for at least six months following complete vaccination, ZF2001 vaccine was found to be safe and effective against symptomatic and severe-to-critical COVID-19 (Dai et al., 2022). In addition, based on the reports, ZF2001 vaccine could induce humoral immunity that is more tolerable to contemporary VOCs than inactivated

vaccines. Also, a clinical trial was conducted among healthcare professionals at Beijing Ditan Hospital who had received two doses of CoronaVac in a 28-day interval 4–8 months earlier to examine the impact of a heterologous third dose of ZF2001 and the results revealed that the third dose of ZF2001 vaccine exhibited a substantial increase in humoral immunogenicity and SARS-CoV-2 anti-spike IgG antibody titers were considerably high in participants who had been given ZF2001. GMTs were higher in all groups against the prototype strain than against the Gamma, Beta, and Delta variants. Indeed, the vaccine's efficacy against Delta, Alpha, and Kappa infections was found to be 77.54%, 92.93%, and 84.8%, respectively (Dai et al., 2022). The results of ZF2001's third-dose vaccination in individuals with primary vaccination of inactivated vaccines demonstrated that it could enhance the neutralization titers against the Omicron variant (He et al., 2022). Since the ZF2001 protein subunit vaccine consists of a fused antigen on the RBD, its using could induce increased titers of neutralizing antibodies against Omicron sub-lineages via the administration of multiple booster doses and immune-maturation methods. According to recent research, better protection against the immune escape of current sub-lineages (especially BA.4 and BA.5) requires the development of updated vaccines as boosters (Zhao et al., 2022).

4.1.2.2. SOBERANA-02 and SOBERANA-Plus. SOBERANA-02 (FINLAY-FR-2, recombinant RBD antigen chemically conjugated to the tetanus toxoid) and SOBERANA-Plus (FINLAY-FR-1A, RBD dimer) were produced at the Finlay Vaccine Institute and Center of Molecular Immunology in Cuba. The base sequence of RBD in both vaccines is the Arg319-Phe541 fragment of S protein, which is adsorbed on alumina, and genetically modified Chinese hamster ovary (CHO) cells were used to produce these vaccines (Puga-Gómez et al., 2023; Toledo-Romaní et al., 2023). A heterologous three-dose schedule (first two injections of SOBERANA-02 every 28 days, third dose or SOBERANA-Plus booster on day 56) elicited a mixed Th1/Th2 response by the balanced induction of IL-4 and IFN-γ from peripheral blood mononuclear cells (PBMC). The titer of the neutralizing antibodies was evaluated in 48 children. Two doses of SOBERANA-02 had 91.3% clinical efficacy against the D614G variant of SARS-CoV-2. After the third dose of SOBERANA-Plus in children, the clinical efficacy increased to 97.4%. Also, in people aged 19–80 years, the effectiveness of the vaccine in the two-dose and the three-dose plan was predicted to be 58%–87% and 81%–93%, respectively, against the D614G (Puga-Gómez et al., 2023). Studies have shown that the third heterologous dose increased the titer of neutralizing antibodies such that IgG antibodies against D614G and VOCs Alpha, Beta, Delta, and Omicron were present months after the third dose (Toledo-Romaní et al., 2023).

4.1.2.3. Recombinant SARS-CoV-2 Vaccine (CHO cell). The RBD spike glycoprotein of SARS-CoV-2 naturally exists in a trimeric form, which became an attractive target for the development of a COVID-19 vaccine. Yu Liang et al. used computational analyses to mimic native three-dimensional compounds in a natural protein S trimer, in which the three RBDs were connected end-to-end. It grafted from three different SARS-CoV-2 strains (multi tri-RBD, NVSI-06-08) or RBDs were all from the prototype strain (homo-tri-RBD, NVSI-06-07). Multi-tri-RBD generated extensive neutralizing activity against different types of SARS-CoV-2 compared to homo-tri-RBD due to harboring immune escape-associated mutations. However, immunization of both homo-tri-RBD and multi-tri-RBD with aluminum hydroxide adjuvant increased specific IgG levels and neutralizing antibodies against the prototype SARS-CoV-2 strain in mice (Liang et al., 2021). Using NVSI-06-08 and NVSI-06-07 as heterologous booster doses in BBIBP-CorV recipients can provide more robust protection against VOCs including Omicron than a third dose of BBIBP-CorV (Kaabi et al., 2022a, 2022b). NVSI-06-09 is a trimeric RBD vaccine (mosaic-type). The RBD of Omicron BA.1 type and two other variants include key mutations (K417N, L452R, T478K, F490S, and N501Y) and (E484K, S477N, and K417T), respectively. Immunogenicity analysis of the BBIBP-CorV/NVSI-06-09 heterologous booster was performed in individuals 18 years of age and older from the United Arab Emirates (UAE). nAb responses against BA.2, BA.4, and BA.5 variants were significantly higher than for those boosted by BBIBP-CorV (Kaabi et al., 2022a).

4.1.2.4. V-01 and V-01D-351. The active component of V-01 includes a fusion protein (IFN-PADRE-RBD-Fc dimer) as its antigen, which was expressed by Chinese Hamster Ovary (CHO) cells. COVID-19 vaccine (V-01) was jointly developed by Livzon Bio Inc. China, the Chinese Academy of Sciences, and the Institute of Biophysics. To enhance antigen-presenting and for the long-lasting effect with target and activate Dendritic cells (DCs) to migrate toward the local draining lymph nodes (DLNs), the N-terminal RBD is armed with interferon-α (IFNα) and the C-terminal is dimerized by human IgG1 Fc, which is eventually called (I-R-F). The low dose of I-R-F in the mouse model showed robust $CD8^+$ T cell response and produced strong antibody titers from the balanced IgG1 and IgG2a subtypes, which indicates strong I-R-F immunogenicity against the RBD monomer. In order to stimulate the T helper cell, the PADRE sequence or the pan HLA DR-binding epitope in I-R-F (I–P-R-F) was intended (Liao et al., 2021). With the emergence of Beta and Delta variants, the bivalent vaccine V-01D-351 containing neutralizing epitopes was developed. The immunogenicity of V-01 and V-01D-351 as heterologous boosters was evaluated after two doses of inactivated COVID-19 vaccine (ICV). Although the V-01 was not designed against new variants, the safety response against the BA.1 was satisfactory. Viral neutralization activity by V-01D-351 against Delta and BA.1 was 3.5- to 6-fold greater than V-01 (Zhiren Zhang et al., 2022), which is due to bearing in mind the important mutations of VOCs in the vaccine design (such as K417N, N501Y, E484, L452R and T478K). Therefore, V-01D-351 can be considered an effective treatment option against Omicron sub-lineages (BA.1, BA.4/5, XBB, BQ.1.1, etc.).

4.1.2.5. GBP510. The GBP510 (also known as SKYCovione) is a recombinant protein vaccine developed by the South Korean company SK Bioscience and the Institute for Protein Design (IPD) at the University of Washington with the use of GlaxoSmithKline's (GSK; a British multinational pharmaceutical company) adjuvant (AS03). GBP510 is a self-assembled nanoparticle vaccine that targets the RBD of the SARS-CoV-2 spike protein. Phase I/II trial was conducted for GBP510 adjuvanted with AS03 including healthy adults aged 19–85 years. In total, the GBP510 adjuvanted with AS03 was well-tolerated with an acceptable safety profile, and it was found highly immunogenic. The Phase I/II results showed a high level of neutralizing antibodies with a 100% seroconversion rate in participants given the adjuvanted GBP510 vaccine. Most adverse effects were mild and moderate in severity, and commonly include injection site pain, myalgia, fatigue, and headache (Kleanthous et al., 2021; Song et al., 2022). The Phase III trial (NCT05007951) was conducted for GBP510 adjuvanted with AS03 including approximately 4037 participants (from New Zealand, Philippines, Republic of Korea, Thailand, Ukraine, and Viet Nam) aged 18 years and over. The results showed a favorable safety profile compared to the control vaccine with mild or moderate adverse reactions (Heidary et al., 2022).

4.1.2.6. UB-612/COVAXX& United biomedical Inc. UB-612 is a SARS-CoV-2 S1-RBD-protein-based vaccine. It consists of a CHO cell–produced S1-RBD fused with a single-chain Fc protein (S1-RBD-sFc), 5 promiscuous designers Th cell and CTL epitope peptides from the N, M, and S2 proteins of sarbecovirus, which are known to bind to multiple class I and class II human leukocyte antigens (HLAs), and an extrinsic HLA class II epitope (UBITh1a) modified from a measles virus fusion (MVF) protein, which would act as a catalyst for T cell activation (He et al., 2022). Also, aluminum phosphate, a proprietary CpG TLR-9

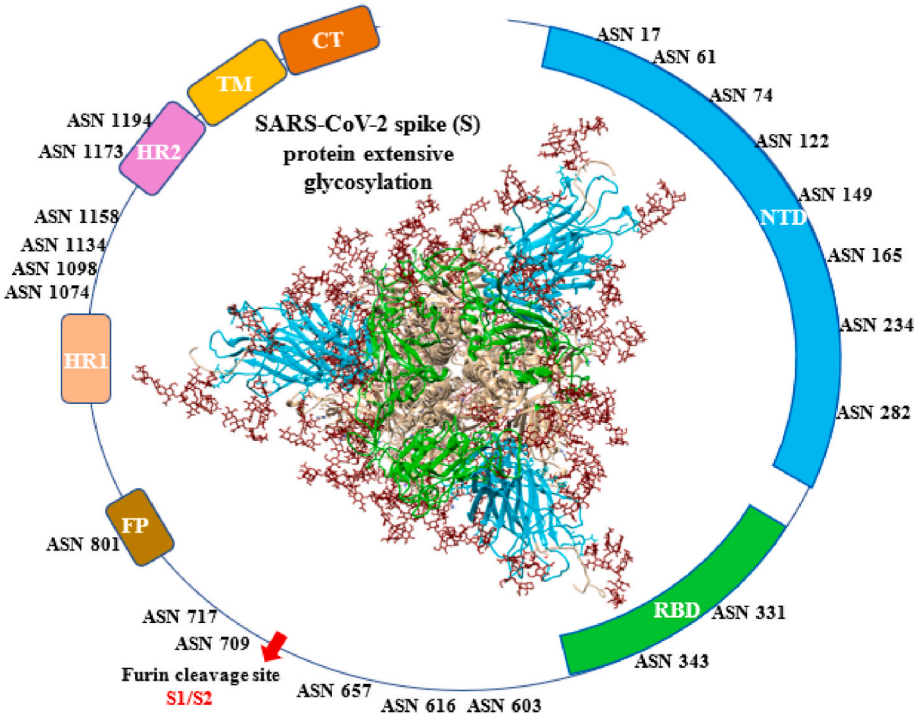

Fig. 3. Some specific features of the SARS-CoV-2 spike protein. A schematic view of SARS-CoV-2 S protein (PDB: 6VSB) extensive glycosylation, labeled on a single monomer. NTD, residues14-305, cyan, RBD, residues 319–541, green, Fusion Peptide (FP), residues 788–806, yellow, HR1, residues 912–984, sandy brown, HR2, residues 1163–1213, goldenrod. Transmembrane domain (TM), residues 1213–1237, yellow, and Cytoplasmic Tail (CT), residues 1238–1273, orange.

agonist, is used as an adjuvant. Vaccination with this vaccine creates a strong and specific T-cell immune response and helps to clear the virus before it causes serious symptoms. In preclinical trials and immunogenicity studies in guinea pigs and rats, high immunogenicity and robust antibody response were seen. In Phase I (with ~4000 participants) and Phase II clinical trials, UB-612 showed favorable safety and low reactogenicity after repeating doses (Guirakhoo et al., 2022b). Additionally, *in vitro* testing showed the antibody bound to the target spike protein antigen, blocking the binding of the hACE2 receptor and neutralizing the viral replication ability. Recent studies have indicated that UB-612 has induced a profound virus-neutralizing immune response against the Delta and Omicron variants. A third (booster dose) of UB-612 demonstrated increasing in neutralizing antibody titers against Omicron variant which constitutes a 61- and 73-fold higher GMT than those gained after two doses. The third (booster dose) of UB-612 stimulated robust IgG binding and neutralizing antibodies against current variants of SARS-CoV-2, including Omicron. Also, UB-612 immunization has been found to elicit T-cell responses against S, N, and M Th/CTL peptides and could provide long-lasting antibody responses. Investigation of the booster immunogenicity of UB-612 showed that UB-612 booster was safe and well tolerated without concerns of sevear adverse effects, and also it provided potent, broad, and long-lasting B-cell and T-cell memory immunity. Based on the results, the UB-612 booster induces high viral-neutralizing antibodies against Omicron BA.1/BA.2/and current BA.5 variants, offering a potential to be used as a universal vaccine to fend off Omicrons and new VOCs (Guirakhoo et al., 2022a; C.Y. Wang et al., 2022).

5. The roles of glycans in the SARS-CoV-2 S protein

It is important to consider all the strategies created by viruses to escape the host's immune response when it comes to vaccine design. In this context, many viruses use a glycan shield to cover immunogenic epitopes targeted by neutralizing antibodies (Bayani et al., 2022; Vassaux et al., 2021; Q. Wang et al., 2021). Glycosylation of viral proteins is a post-translational modification that plays a multitude of critical biological roles. Various enveloped proteins in well-known human viral pathogens such as HIV-1, influenza, Zika, dengue, Ebola, and SARS viruses are highly glycosylated. Actually, the pathogens modify their own proteins by using the host cell machinery for glycosylation. These surface-exposed glycans derive various structural and practical roles in the viral cell cycle and host immune responses to the infection. Glycosylation may facilitate the host immune system evasion and mediates binding to host cell receptors. On the other hand, it may enhance immune cell infection (Watanabe et al., 2019).

As explained previously, due to the high antigenicity and ability to elicit neutralizing antibodies in convalescent individuals, the S protein is considered an ideal candidate for vaccine development (Zhao et al., 2021). One of the S protein's key features is its extensive glycosylation (see Fig. 3), which depends on the host's glycosylation machinery.

Depending on the amino acid atom to which the sugar moiety is attached, glycosylation is divided into O-linked (sugars attached to the oxygen atom in the Threonine or Serine side chain) and N-linked (sugars attached to the nitrogen amide atom in the Asparagine side chain) (Casalino et al., 2020; Zhao et al., 2021). The analysis of the glycan structure of the S protein trimer produced recombinantly in the human embryonic kidney 293 (HEK293) indicated that 17% of its molecular weight belongs to glycans. These glycoforms shield approximately 40% of the protein surface (Grant et al., 2020). The S protein's glycan shield helps the virus evade the human immune response by providing a thick sugar-coated barrier against any antibody (Ghorbani et al., 2021). More specifically, the SARS-CoV-2 spike has 22 predicted N-glycosylation sites per protomer (Bogetti et al., 2021), and at least two predicted O-glycosylation sites (Q. Wang et al., 2021). The O-linked glycosylation pattern flanking the S1/S2 cleavage site is suggested to regulate the S protein activation during the viral infection (Andersen et al., 2020), (Sanda et al., 2020). Whereas 19 N-glycans essentially camouflage the spike head region, only three N-glycosylation sites (N1158, N1174, and N1194) are present on the stalk (Casalino et al., 2020). The glycosylation at the stalk fragment is highly conserved in coronavirus members

and is not considered a specific therapeutic target (Vassaux et al., 2021; Q. Wang et al., 2021). N-linked glycosylation begins with the synthesis of precursor oligosaccharides, is converted by glucosidases to high mannose forms, and is cleaved into complex shapes in the Golgi apparatus using glucosyltransferases. The signal transmission and other glycobiological functions depend on the precise stereochemistry of the glycans (Lee et al., 2015). Diverse functions have been suggested for S protein glycans, including immunological shielding, ACE2 receptor binding, and viral cell entry. Molecular dynamic simulations showed that the active conformation of RBD (up-state) is mostly exposed with few glycans at the receptor-binding interface. This lack of shielding renders RBD susceptible to being recognized by the host immune system, making it a prime target for vaccine development (Grant et al., 2020). The RBD in SARS-CoV-2 is contacted by N-glycans at residues N165 and N234 in the NTD fragment. A simulation study shows that deletion of these two glycans by mutation resulted in a conformational shift in RBD from up to down-state, which significantly reduces its binding to the ACE2 receptor (Casalino et al., 2020). Besides vaccine development, the possible strategy to control the conformational plasticity of the RBD may be harnessed to advantage in viral infection inhibition and therapeutic efforts (Casalino et al., 2020).

6. The variants of SARS-CoV-2

The emergence of new SARS-CoV-2 variants may be explained by one of the four following theories: (1) the virus starts circulating and mutating in a closed group of people, where it continuously mutates to become extremely different from the variants outside of that group, after which it is introduced to a broader population (Du et al., 2022); (2) the virus' long-term persistence in immune-compromised patients results in the virus' continued evolution and the emergence of variants with more mutations; (3) the virus may transmit back and forth between human and animal hosts leading to mutation amplification; (4) simultaneous infection with two coronaviruses may create the chance for recombination and the rise of new variants (Khandia et al., 2022; Mallapaty, 2022). Some of the most well-known variants are reviewed in the following sections.

6.1. Alpha/B.1.1.1.7/(also known as 201/501Y.V1)

This variant is the first identified major variant of concern. It was initially identified in the UK in the fall of 2020, and compared to the original SARS-CoV-2, spreads approximately 50% faster. The Alpha variant has nonsynonymous mutations, including: [T1001I, A1708D, and I2230T] in ORF1ab, [Q27stop, R52I, Y73C] in ORF8, [N501Y, P681H, A570D, T716I, S982A, D1118H] in the S protein, and [D3L, S235F] in the N protein. Synonymous mutations of that variant include: [T26801C] in the M gene, [C5986T, C913T, C14676T, T16176C, C15279T] in ORF1ab. The deletions include: [SGF 3675–3677 del] in ORF1ab, and [H69–V70 del and Y144 del] in the S protein. The N501Y mutation is an important contact residue in the RBD that increases the binding affinity of the virus for human ACE2 (Ali et al., 2021). The P681H mutation is directly adjacent to the furin cleavage site in spikes, a region known to be important for infection and transmission (Harvey et al., 2021). H69–V70 deletion mutation leads to a conformational change and increases viral infection through the S protein.

6.2. Beta/B.1.351/known as 20H/501Y.V2

The B.1.351 variant was first identified in Nelson Mandela Bay in South Africa in October 2020, which the Republic of South Africa reported on December 18, 2020 (Mohammadi et al., 2021). Its mutations include [D215G, L18F, D80A, D215G, LAL 242–244 del, R246I, K417N, E484K, N501Y, D614G, and A701V] in the S protein, [K1655N, T265I, K1655N, K3353R, H2799Y, S2900L, D4527Y, T5912I, P314L, SGF 3675–3677 del] in ORF1ab, [Q57H, S171L] in ORF3a, [T205I] in the N protein, and [P71L] in the E protein. Three substitutions (K417N, E484K, and N501Y) in RBD may have functional importance (Tegally et al., 2021). The significant feature of this variant is the higher transmission rate (P. Wang et al., 2021; Zhou et al., 2021). The NVX-CoV2373 vaccine was efficacious and induced notable cross-protection during a pandemic with a dominant circulation of the B.1.351 variant (Shinde et al., 2021).

6.3. Gamma/P.1 or B.1.1.28.1 variant/also known as 20J/501Y.V3

The B.1.1.28.1 (Gamma or P.1) variant was first detected by Japan's National Institute of Infectious Diseases on January 6, 2021, and was identified just outside of Tokyo at Haneda airport among four travelers from Amazonas, Brazil, on January 2, 2021 (Hoffmann et al., 2021; Rees-Spear et al., 2021). These variant mutations include: [L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, H655Y, D614G, T1027I and V1176F] in the S protein. K417N and K417T are present in B.1.351 and P.1, respectively, and are two of the key mutations related to increasing immune escape of VOC (Harvey et al., 2021). Sinovac Biotech clinical trials demonstrated that the CoronaVac vaccine is 50% effective in preventing infection with the P.1 variant in Brazil (Vasireddy et al., 2021). Five mutations are in the NTD of the S protein, of which L18F has been shown to interfere with the binding of neutralizing antibodies that target NTD (McCallum et al., 2021).

6.4. Delta/(B.1.617.2) variant/also known as 21A/S:478K

Delta (B.1.617.2) was first reported in India but rapidly spread globally (Singh et al., 2021). The lineage includes three main subtypes (B1.617.1, B.1.617.2, and B.1.617.3), which contain diverse mutations in the NTD and the RBD. The variant is characterized by the spike mutation L452R, which confers a higher affinity of the S protein for the ACE2 receptor and reduced recognition capability of the host immune system. The P681R is a substitution at position 681, which may boost cell-level infectivity of the variant (Kupferschmidt and Wadman, 2021). A recent sub-lineage of the Delta variant (B.1.617.2) named Delta Plus (Arora et al., 2021; Pedro E. Romero, Alejandra Dávila-Barclay, Luis Gonzáles, Guillermo Salvatierra, Diego Cuicapuza, Luis Solis, Pool Marcos, Janet Huancachoque, Dennis Carhuaricra, Raúl Rosadio, Luis Luna, Lenin Maturrano, 2021) has had a significant number of mutations which confer high prevalence (≥20%) and more transmissibility compared to the original Delta variant. K417N, V70F, and W258L spike mutations were exclusively present in the Delta Plus variant and T95I, A222V, G142D, R158G, K417N key mutations were significantly more prevalent in the Delta Plus variant. Another sub-lineage of the Delta variant, provisionally called Delta-V, was observed in Vietnam and contains mutations found in the S protein of the Alpha (B.1.1.7) variant (Arora et al., 2021).

6.5. Omicron

The Omicron (also known as B.1.1.529), the most recent SARS-CoV-2 variant, was initially detected in Botswana and South Africa in November 2021 (Khandia et al., 2022). Omicron is the only SARS-CoV-2 lineage with the insertional mutation (ins 214EPE). This insertion may have occurred due to template switching during SARS-CoV-2 virus co-infection in the same host cell (Khandia et al., 2022). The continuous evolution of Omicron has led to more than one hundred sub-lineages, such as BA.1, BA.1.1, BA.2, BA.2.12.1, BA.2.3, BA.2.9, BA.3, BA.4, and BA.54. Notably, mutations in the receptor-binding domain (RBD) of these sub-lineages converge on several hotspots, including R346, K356, K444, L452, N460K, and F486 (Cao et al., 2022). The deletion of two amino acids (69 and 70) in the S protein may serve as a proxy marker for Omicron presence verification. Three mutations, K417N, E484A, and Y505H, present the Omicron variant's capacity to escape from COVID-19 vaccine immunity and induce breakthrough infections which

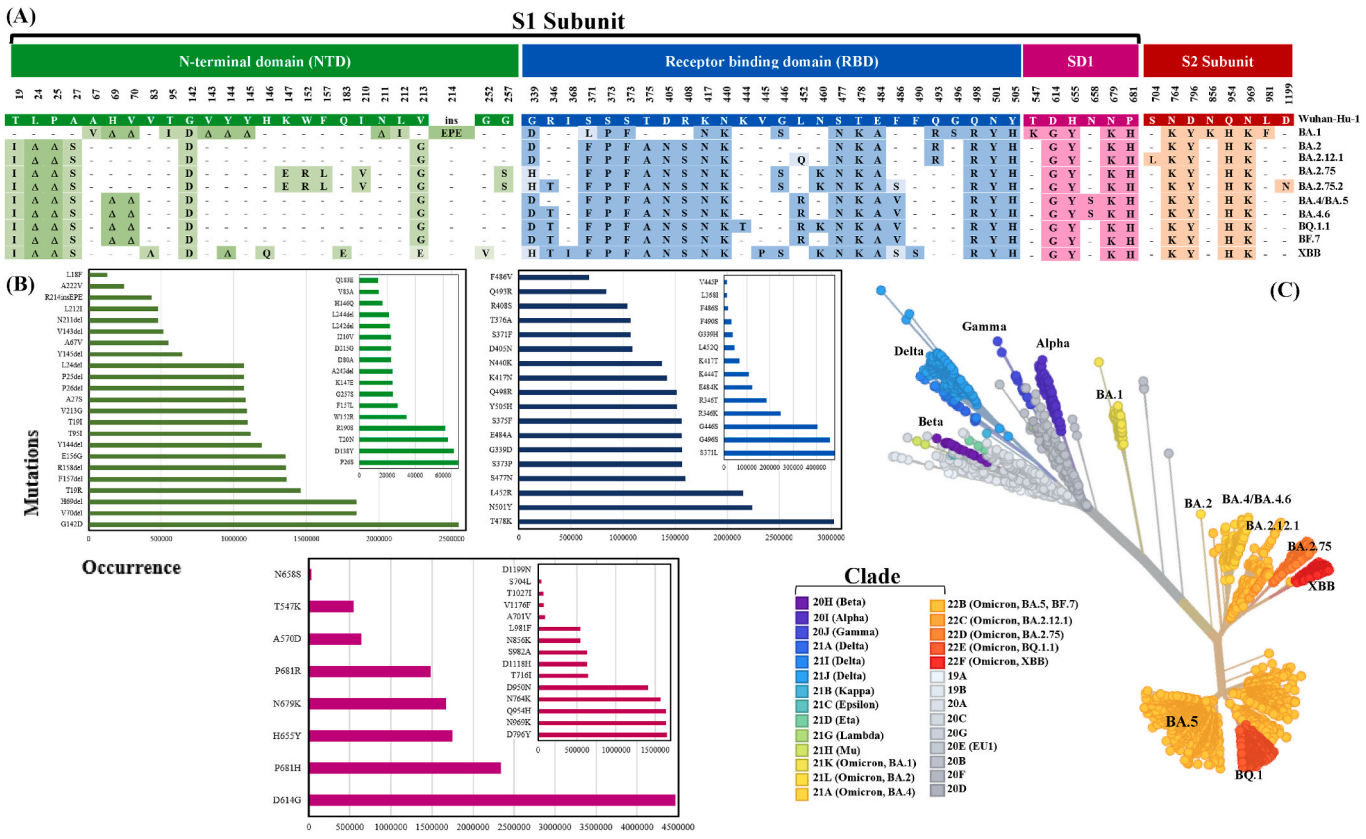

Fig. 4. (A) Details of mutations in Omicron sub-lineages compared to Wuhan-Hu-1 in the spike glycoprotein. (B) The graphic shows the occurrence of mutations collected from the beginning of 2019 to January 2023 in different geographical areas by the GISAID database. These mutations are located in the spike glycoprotein. (C) Unrooted phylogenic tree based on 2866 genomes sampled between December 2019 to January 2023; from GISAID (https://nextstrain.org/ncov/gisaid/global/6m).

are estimated to be higher than the Delta variants (Shrestha et al., 2022; Tegally et al., 2022). A great number of non-synonymous mutations were identified in the S protein and RBD H655Y, N679K, and P681H mutations in the S1–S2 furin cleavage site may be associated with greater transmissibility of Omicron. The Omicron variant's unique mutations in the receptor binding domain (RBD) enhanced the virus's transmissibility and its immune escape mechanisms. Except for the addition of the 69–70 deletion (found in the Alpha variant and the BA.1 lineage), L452R (found in the Delta variant), F486V, and the wild-type amino acid at Q493, the spike proteins of BA.4 and BA.5 are identical and similar to those of BA.2. In addition, BA.4 has additional mutations at ORF7b: L11F and N: P151S, as well as a triple amino acid deletion in NSP1: Δ141–143, while BA.5 has the M:D3N mutation (Shrestha et al., 2022; Tegally et al., 2022). Additional reversions at ORF6: D61 and nucleotide positions 26,858 and 27,259 occur in BA.5. Moreover, shared mutations in the RBD of these Omicron lineages, combined with unique substitution mutations, such as L452R and F486V mutations that occur in BA.4 or BA.2.12.1-specific L452Q mutations, play critical roles in immune evasion. Previous studies indicate that L452Q/R mutation could cause significant humoral immunity escape, and is also related to the cellular immunity evasion (Motozono et al., 2021; Xia et al., 2022). Deletions at L3674-, S3675-, and G3676- are suggested to contribute to innate immune evasion by compromising the cell's ability to destroy viral components. The envelope gene has the lowest mutation; only one at T9I (Khandia et al., 2022). According to recent research, Omicron has a distinct strategy for entering the host and is capable of penetrating cells without the help of the transmembrane serine protease 2 (TMPRSS2). In contrast to the Delta variant, Omicron utilizes the endocytic pathway for entry and viral replication, which may lead to differences in disease presentation (Arora et al., 2022). Furthermore, because of the "S gene target failure", the Omicron variant gives a false negative result in polymerase chain reaction (PCR) tests, paving the way for the virus to spread at a faster rate around the world (Araf et al., 2022). The latest Omicron variants and numerous sub-lineages have been shown to significantly alter the spike protein through mutation (Fig. 4), thus questioning the efficacy of vaccines and mAbs. Currently available data indicate that XBB and BQ.1 variants predominate in India and Singapore, and represent critical threats to the current COVID-19 vaccines. BQ.1 sub-lineage is related to BA.5, and is currently responsible for most cases in the UK, Germany, South Africa, the US, Australia, and South Korea (Cao et al., 2022). XBB, a hybrid/recombinant variant, potentially emerged from BA.2 (BA.2.10.1 and BA.2.75) sub-lineages, i.e., BJ1 and BM.1.1.1. and has spread to more than 15 countries. The XBB and BQ.1.1 show a strong resistance to mAbs that target RBD and increase ACE2-binding affinity. Based on the reports, CA.1, BR.2, BQ.1.1, BM.1.1.1, and XBB are the most antibody-evasive strains tested (Kurhade et al., 2022). In addition, recent data revealed that both XBB.1 (with G252V mutation) and XBB.3 sub-lineages were much more evasive to the immune system than BA.5.2 and the ancestral strain, and might be associated with a higher risk of reinfection (Xiaojuan Zhang et al., 2022). Nascent Omicron sub-lineages with similar spike mutations, such as BA.4.7 with R346S, BF.7 with R346T, have also been detected, and their spike mutations make them contagious by evading immunity (Q. Wang et al., 2022). Pfizer's vaccine efficacy decreased almost to half, from 86% to 43% from February to October, Moderna vaccine dropped from 89% to 58%, and Johnson & Johnson's Janssen vaccine from 86% to 13%. Wilhelm et al., reported a reduction in sera's neutralization capacity of individuals that have been vaccinated twice with Pfizer-BioNTech and Moderna BNT162b2, when used against Omicron (Mittal et al., 2022).

7. Safety of COVID-19 vaccine

Two major vaccine safety issues are antibody-dependent enhancement (ADE) and vaccine-associated enhanced disease (VAED). ADE is a phenomenon that occurs when the interaction of virus-antibody immunocomplexes with cells bearing complement or Fc receptors promotes internalization of the virus and increases infection (Kulkarni, 2020). ADE may account for some of the adverse effects of novel antiviral therapeutics and provide a considerable impediment in preventing viral infection by vaccination (Taylor et al., 2015). The ADEs have been observed in SARS-CoV, MERS, and certain other human respiratory viral infections such as RSV and measles, suggesting that ADEs may be a serious concern in SARS-CoV-2 vaccine development (Peng et al., 2021). Wand et al., have reported that the bivalent interaction of two neutralizing mAbs, MW01 or MW05, with SARS-CoV-2 S trimer could enhance the infection of SARS-CoV-2 pseudovirus on FcγRIIB-expressing B cells *in vitro* (S. Wang et al., 2022). VAED refers to a condition in which a vaccinated individual develops a more severe disease presentation than someone without prior vaccination (Tunjungputri et al., 2021). In recent studies, the interaction of the enhancing antibodies with the NTD of the spike protein has been mentioned. These antibodies increase the interaction of RBD with ACE2 and thus increase infection. Also, *in vitro*, the unknown mechanism of ADE and VAED responses dependent on the 597-LYQDVNC-603 amino acid sequence in the spike protein S2 subunit of SARS-CoV-1 has been pointed out. This sequence is also found in the spike of SARS-CoV-2. Therefore, RBD-based subunit vaccines can be beneficial both in terms of vaccine efficacy and safety. However, so far no evidence of ADE and VAED in the SARS-CoV-2 infection has been reported, especially in full-length spike protein-based subunit vaccines (Gartlan et al., 2022).

8. Personalized vaccines

Vaccination has been the most effective medical intervention, saving many lives and increasing human life expectancy worldwide. Developing safer and more effective vaccines with more sustainable delivery mechanisms is essential to prevent and control existing or emerging infectious diseases (de la Fuente and Contreras, 2021). In the current medical practice approaches, the vaccines are administered universally to everyone with pre-determined doses, assuming that everybody is at the same level of risk for every pathogen and reacts with a similar pattern of immunological responses (Poland et al., 2011). This approach provides easy widespread access to almost all the world's population to vaccines and has immensely helped prevent or control infectious diseases. However, this policy ignores the individual variability and host-related factors' effect on immune responses (Linnik and Egli, 2016). Amongst the main known factors likely affecting the heterogeneity of the adaptive and innate immune response, the following can be listed: gender, age, pregnancy, immunodeficiency diseases, genetic background, and the intestinal microbiome (Castiblanco and Anaya, 2015). Advances in biological sciences and exponential growth in high throughput technologies facilitated quick large-data analysis. These 'Big Data' obtained in a cost-effective and reasonable time paved the way to select the most effective therapeutic drug and appropriate doses for each individual; the strategy that is known as "personalized medicine". Scientists hope that personalized medicine will help to improve public health, use the existing resources more efficiently and reduce healthcare costs by helping with earlier diagnosis and selecting more efficient therapeutics. In the field of vaccinology, there is also a new tension to move from the traditional population-level toward the individual-level paradigm. Achieving this goal needs comprehensive recognition of physical aspects and molecular mechanisms underlying the heterogeneity of immune responses to vaccines (Haralambieva and Poland, 2010). Innate immunity, induced immediately after exposure to infectious agents, functions as the first line of defense. Natural killer cells, macrophages, neutrophils, dendritic cells, mast cells, eosinophils, and basophils are the main players of innate immunity, which exert their effect through the release of different cytokines, chemokines, and other immune-modulating mediators (Lacy, 2015). The long-term, pathogen-specific adaptive immune responses are initiated in the second line of defense, and lymphocytes undergo clonal expansion and massively proliferate. T-cells and B-cells, respectively are responsible for cell-mediated and antibody-mediated immunity. Successful activation and differentiation of naive T-cells occurs only in the presence of three signals: (1) interaction with the antigenic peptides that loaded on the HLA molecules and presented by the APC; (2) delivering of the second signals to T cell by the interaction between CD80 and CD86 on the APC surface with their ligand (CD28) on the T cell; and (3) secreting cytokines that regulate immune response (Thomas and Moridani, 2010). The reciprocal interaction between innate and adaptive immune responses is involved in immune homeostasis and highly impacts infectious diseases' outcomes (Maynard et al., 2012). Lots of genes are involved in innate and adaptive immune responses. So far, some genetic variations have been found to affect the clinical outcome after SARS-CoV-2 infection that may underpin vaccine efficiency (Dos Santos, 2021). Knowing these genetic variations will help predict the vaccine efficiency and potentially be used for more specific and personalized vaccine design against different strains of COVID-19 in the future.

One of the most important such examples is the highly polymorphic genomic loci of HLA (a gene complex located on chromosome 6) (Poland et al., 2008). The HLA locus is divided into three main regions: class I, II, and III. The HLA classes I (HLA-A, HLA-B, and HLA-C) and II (HLA-DRB1 and HLA-DQB1) proteins play a central role in the adaptive branch of immune responses. Both classes appear on the APCs surfaces and function to present the processed peptides to the T cells. While class I is expressed on almost all APC cells and recognized by $CD8^+$ T cells, class II is only presented on the surface of professional APCs and B lymphocytes and activates $CD4^+$ T cells. The class III region contains non-HLA-related immune genes (Couture et al., 2019).

Humans have various allelic versions of the HLA genes, and at these loci, certain variants and haplotypes encode for cell receptors that can bind less reliably to some viral peptides and blunt the immune system's normal defenses against viruses in susceptible patients. Significant differences between HLA alleles can define susceptibility to disease or vaccine effectiveness. In the Italian population, for instance, the two frequent HLA haplotypes (HLA-A*:01:01g-B*08:01 g-C*07:01g-DRB1*03:01g and HLA-A*02.01g-B*18.01g-C*07.01g-DRB1*11.04g) showed positive (susceptibility) and negative (protectivity) correlation with COVID-19 incidence and mortality (Pisanti et al., 2020). Nguyen et al., performed a comprehensive *in silico* analysis for SARS-CoV-2 peptides-HLA class I binding affinity. They found that HLA-B*46:01 genotype has the fewest predicted binding peptides for SARS-CoV-2, and individuals with this allele may be susceptible to COVID-19 infection. On the contrary, HLAB*15:03 has the greatest capacity to present highly conserved SARS-CoV-2 peptides shared among common human coronaviruses, and it could potentially induce cross-protective T-cell immunity (Nguyen et al., 2020). Association of many other susceptibility markers with SARS-CoV-2 infection like ABO blood antigens, ACE2 deletion/insertion (D/I) polymorphisms, a protective polymorphism (rs35705950-T) in Mucin 5B gene, and loss-of-function mutations in the X-chromosomal TLR7 gene, to name just a few, have been considered in many other studies (Adli et al., 2022; Delanghe et al., 2020; Hantschke, 1996). The diversity and heterogeneity of the immune response to vaccines is still a potential issue in providing vaccines to the public (Poland et al., 2007) . Public health vaccination policies can usually take the individual characteristics of age and disease comorbidity into account but rarely consider the genetic background (Valdés-Fernández et al., 2021). The advent of high-throughput sequencing technologies has allowed obtaining individual genomic information fast and accurately (Poland et al., 2007; Seib et al., 2009). Considering human genome diversity can provide the best recommendation for individual vaccination doses and timing. It is also critically

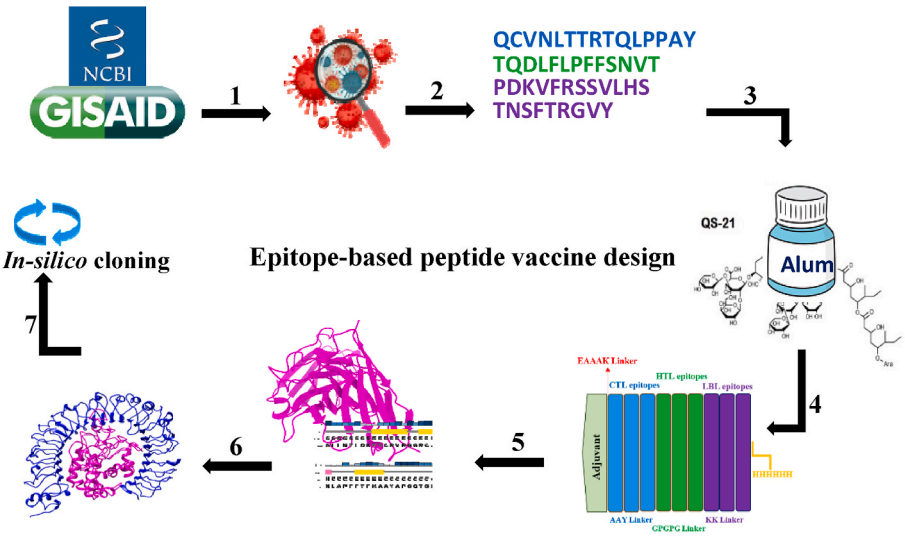

Fig. 5. Multi-epitope design. The step-by-step procedure of *in silico* analysis is depicted. **1)** Retrieval of protein sequences and antigen protein selection; **2)** prediction of B-cell and T-cell epitopes and evaluation of their validity; **3)** selection of appropriate adjuvants and linkers; **4)** vaccine structure design; **5)** prediction of secondary and tertiary structures and evaluation of the validity of the designed vaccine; **6)** molecular docking and molecular dynamics simulation of designed vaccine with a suitable receptor; **7)** *in-silico* cloning and immune simulation.

important for designing advanced recombinant or other platforms of vaccine and personalized vaccine formulations to set a new paradigm of personalized health care.

9. Immunoinformatics approaches for subunit vaccine design

Multi-epitope vaccines are a novel developed strategy with a unique design concept based on a series of overlapping antigenic epitopes. In a multi-epitope vaccine design, the immunogenic T-and B-cell epitopes are predicted using immunoinformatics tools and attached using proper linkers to make an epitope-rich peptide. In the first place, the designed constructs are evaluated for physicochemical, structural, and immunological characteristics using bioinformatics tools. The binding interaction and stability of the construct are simulated by molecular docking. After *in silico* verification, the designed multi-epitope peptide is expressed in the appropriate expression system (Bayani et al., 2023; Rezaei et al., 2021; Tahir Ul Qamar et al., 2020). To date, lots of studies have been conducted on the functional mapping of the cytotoxic T-lymphocyte (CTL), Th and B-cell epitopes on the SARS-CoV-2 proteins, especially S protein, using immunoinformatics and experimental research (W.-H. Chen et al., 2020; Chen et al., 2021). The results make this strategy a promising approach against SARS-CoV-2 (Zhang, 2018). UB-612 is one of the first developed multi-epitope vaccine designs incorporating the RBD, Fc domain of single-chain IgG1, and six highly conserved immunogenic peptide sequences from the S, N, and M of SARS-CoV-1 and SARS-CoV-2 that induce a strong T-cell response. Using immunostimulatory complexes and adjuvants such as CpG oligonucleotides and aluminum phosphate empowers the immune responses. The vaccine has been developed in CHO cells and is in Phase II/III of clinical trials (Martínez-Flores et al., 2021). MigVax-101 is another multi-epitope vaccine that is currently under development. Its designed construct is composed of RBD, two domains of N protein, and heat-labile enterotoxin B (LTB), which is a mucosal adjuvant. This chimeric protein is designed to generate mucosal, humoral, and cellular immunity simultaneously (Pitcovski et al., 2022). The schematic diagram of *in silico* multi-epitope vaccine design and testing is shown in Fig. 5. Tables S2 and S3 provide a list of epitope prediction servers, which have been used in studies related to SARS-CoV-2 epitope prediction.

10. Conclusions

Scientists are currently trying to find a definitive cure for COVID-19 despite the continuous mutations in the viral proteins and the corresponding evolution of SARS-CoV-2 to escape the immune system. Therefore, to maintain the high efficacy of the vaccines against variants of concern, such as Beta, Delta, and Omicron, it is necessary to update the vaccine composition. Using a high-throughput screening strategy and sequencing technologies through the immunoinformatics approach, a formulation with the highest immunogenicity and biosafety of subunit vaccines based on multiple epitopes can be found and administered to effectively stimulate the host immune response with minimal side effects. Since this virus is a global crisis and has had devastating effects on the health and business of countries, the production, storage, and transport of vaccines are of great importance. Subunit protein vaccines are more cost-effective than other platforms, such as mRNA, and studies have shown that heterologous booster doses with subunit vaccines are very effective in increasing antibody titers in people who received their initial dose from other vaccine platforms.

Author Contributions

Conceptualization, Y.S.; methodology, Y.S, V.N.U; software, F.B, S.A, N.S; validation, V.N.U, Y.S.; investigation, F.B, N.S, S.A, S.M.J and V.U.; resources, Y.S and V.N.U.; writing—original draft preparation, F.B.; N.S, S.A, S.R, V.U., V.N.U, and Y.S.; writing—review and editing, V.N.U, V.U, S.A, S.M.J, S.O.R.S and Y.S.; visualization, F.B, N.S, S.A, V.N.U, M.A, Y.S, S.M.J.,; supervision, V.N.U and Y.S.; project administration, V.N.U and Y.S.; All authors have read and agreed to the published version of the manuscript.

Declaration of Competing interest

There is no conflict of interest regarding this manuscript.

Data availability

Data will be made available on request.

Acknowledgments

This research has been conducted using the research credits of Shahid Beheshti University, Tehran, Iran (Grant number SAD/600/1846).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pbiomolbio.2023.02.004.

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