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Review article

Towards novel nano-based vaccine platforms for SARS-CoV-2 and its variants of concern: Advances, challenges and limitations

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ABSTRACT

Vaccination is the most effective tool available for fighting the spread of COVID-19. Recently, emerging variants of SARS-CoV-2 have led to growing concerns about increased transmissibility and decreased vaccine effectiveness. Currently, many vaccines are approved for emergency use and more are under development. This review highlights the ongoing advances in the design and development of different nano-based vaccine platforms. The challenges, limitations, and ethical consideration imposed by these nanocarriers are also discussed. Further, the effectiveness of the leading vaccine candidates against all SARS-CoV-2 variants of concern are highlighted. The review also focuses on the possibility of using an alternative non-invasive routes of vaccine administration using micro and nanotechnologies to enhance vaccination compliance and coverage.

1. Introduction

Coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It belongs to Betacoronaviruses subfamily. Bats are believed to be its natural host [1]. The name coronavirus is related to the crown-like glycoprotein spikes on its surface. The first human infection by SARS-CoV-2 virus was reported in December 2019 in Wuhan, a city in the Hubei Province of China [2]. After a short period, the virus continued to spread around the world; resulting in a global pandemic [3]. About 588,103,191 active cases and 6,434,829 deaths have been reported worldwide up to August 6, 2022, according to WHO. The highest numbers of patients with COVID-19 were stated in the US (93,866,641), India (44,141,222), France (34,053,040), Brazil (33,994,470), Germany (31,228,314), UK (23,368,899), and Italy (21,286,771) [4].

The optimal way to fight this pandemic is the achievement of herd or community immunity [5]. The latter is achieved when a large part of the population within a community becomes either naturally or artificially immunized [5]. Accordingly, vaccination is the most effective strategy to ensure the production of strong and lasting immune responses against SARS-CoV-2 virus and its variants. Currently, there are hundreds COVID-19 vaccines under development or undergoing clinical evaluation and that number is still rising [6]. However, up to August 6, 2022, 85 vaccines are in Phase 3 clinical trials and only 11 vaccines are in post marketing surveillance trials (Phase 4 clinical trials) and granted emergency use listing (EUL) by WHO [8]. The WHO approved vaccines are Pfizer/BioNTech (BNT162b2), Moderna (mRNA-1273), Janssen (Ad26.COV2.S), Oxford/AstraZeneca (AZD1222), Covishield (AZD1222), CanSino (Convidecia),Novavax (NVX-CoV2373), COVOVAX (NVX-CoV2373), Bharat Biotech (Covaxin), Sinopharm (Beijing) BBIBP-CorV (Vero Cells), and Sinovac (CoronaVac).During a public health emergency, a vaccine may receive Emergency Use Authorization (EUA) before getting formal approval based on the regulations in each country [7]. Recently, only 33 vaccines have been granted EUA [8].

Different platforms are used to produce safe and effective vaccine against SARS-CoV-2 and its potential variants, using either manipulated viral particles or nano-based delivery systems. The use of nanocarriers is a new approach in vaccine design technology. They not only act as delivery vehicles for antigenic components but also can themselves act as adjuvants to induce the immunogenicity [9,10]. These nanocarriers have been employed in the development of infuenza, toxoplasmosis, Ebola, HIV, malaria, and toxoplasmosis vaccines [11]. Sekimukai et al., 2020 [12], reported that gold nanoparticle (NP)-adjuvanted Spike (S) protein of SAR-CoV stimulated a strong immune response against

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SAR-CoV-related infections [12]. Similarly, aluminium NPs were studied for their ability to deliver the antigenic components of MERS-CoV and SAR-CoV to the host cells [13]. However, the cellular toxicity of these nanocarriers and/or the need for an adjuvant may be considered as significant limitations of such nano-based vaccines [14,15].

Nanotechnology tools can play a pivotal role in advancing COVID-19 vaccine development. They possess unique physiochemical properties that enable them to be suitable candidates for vaccine delivery of SARS-CoV-2. Accordingly, rational designing of these vaccines is crucial for their clinical success. This review provides updated information on the nanotechnology approaches used in COVID-19 vaccines. The efficacy of different platforms against the new variants of SARS-CoV-2 are also discussed. Strategies related to the nanocarrier selection, limitations, challenges, ethical considerations, and risks of diverse types of SARS-CoV-2 vaccines are highlighted. The review also focuses on the possibility of using an alternative routes of vaccine administration using micro- and nano-technologies to enhance vaccination compliance and coverage.

2. SARS-CoV-2 structure and pathophysiology

SARS-CoV-2 is an enveloped virus with a single-stranded mRNA [2]. It has nearly 79% and 50% genetic similarity with SARS-CoV and MERS-CoV, respectively [16]. It can be transmitted directly via inhalation of respiratory droplets from an infected person and/or direct contact with a contaminated object or surface [16].

The SARS-CoV-2 genome encodes 4 major types of structural proteins: the spike (S) protein, membrane (M) protein, nucleocapsid (N) protein, and the envelope (E) protein. Fig. 1 represents how the SARS-CoV-2 infects human cell along with potential immune responses elicited. After respiratory tract exposure, the virus uses its S proteins to enter the human cell via binding to the angiotensin-converting enzyme 2 (ACE 2) receptors located on its surface. Then, the virus releases its stored RNA inside the infected cell to be translated into protein. Next, the virus is assembled in the cell's cytoplasm and is eventually released from the cell [3]. Once released, the Antigen-Presenting Cells (APCs) such as dendritic cells (DCs), macrophages, B cells, or Langerhans cells capture the virus or antigen on their surface [3]. A $CD4^+$ cells (helper T cells), bind to the viral peptide; leading to activation of the B cells to produce antibodies against the virus. Furthermore, the infected cells are killed by the activated cytotoxic T cells ($CD8^+$ cells) [3]. Most recovered patients have antibodies and T-cell responses against multiple SARS-CoV-2 proteins; however, vaccination may be necessary to prevent reinfection [10].

The reason for mortality due to SARS-CoV-2 infection could be due to the cytokine storm. The immune responses activated by this infection result in uncontrolled inflammatory responses and ultimately cause the cytokine storm [17]. Severely ill COVID-19 patients tend to have a high concentration of pro-inflammatory cytokines, especially interleukin (IL)-6 [17]. The cytokine storm can lead to apoptosis of epithelial and endothelial cells, vascular leakage and, finally, result in acute respiratory distress syndrome, multi-organ failure, other severe syndromes, and even death [17].

SARS-CoV-2 attacks not only the epithelial cells of the respiratory and gastrointestinal (GI) tracts but also the kidneys and blood vessels [18]. The level of the ACE 2 expression is higher in children below the age of 10–14 years than in adolescents and adults [19]. This may facilitate the infection but reduce the inflammation and limit the risk of serious disease because of the role of ACE 2 in the transformation of angiotensin II into angiotensin-(1–7). The latter has anti-fibrotic, antithrombotic, anti-inflammatory, and anti-oxidant effects [19]. This can potentially explain why SARS-CoV-2 infection is less severe in children than adults [19].

All the current SARS-CoV-2 vaccines consist of a key ingredient (antigen or genetic material) with or without an adjuvant, embedded in a carrier such as NP or a viral vector to deliver them into the host cell.

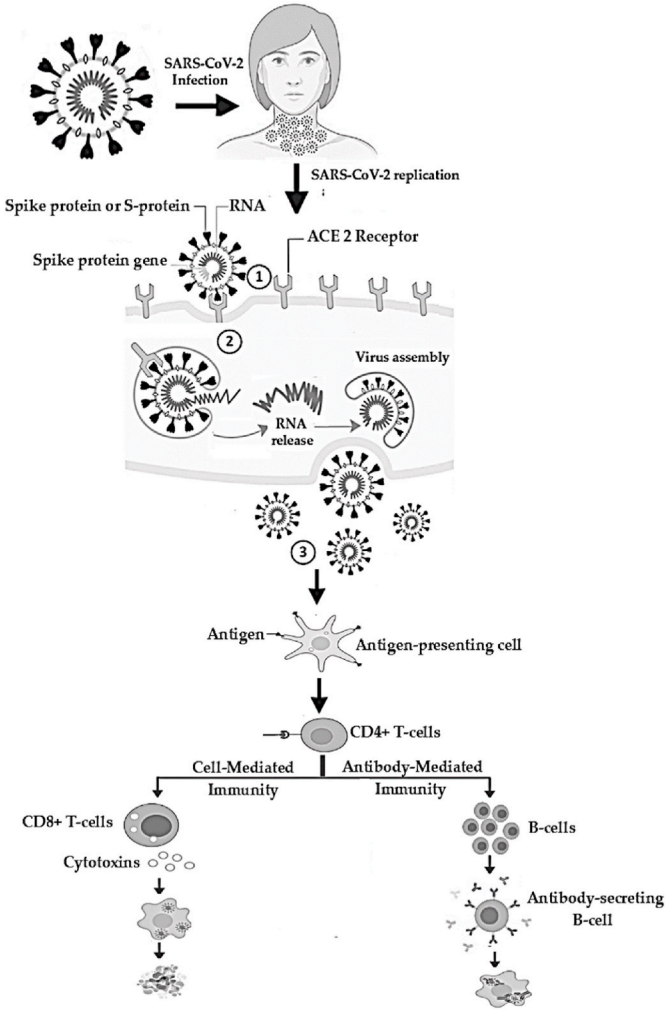

Fig. 1. How SARS-CoV-2 infects human cell along with potential immune responses elicited. (1) A spike protein binds to an ACE 2 receptor on the surface of the human cell; allowing it to pass into cell; (2) Viral replication inside the cell to release its RNA; and (3) Copies of virus are released from the infected cell.

The S protein is a major element in the design of SARS-CoV-2 vaccine [20]. The delivered S protein is intended to trigger specific neutralizing antibodies and antiviral T and B memory cells which provide an ongoing protection against SARS-CoV-2 infection [21]. However, even if we manage to develop an effective vaccine against SARS-CoV-2, the main question lies in how mutations of the SARS-CoV-2 strains will affect the vaccine effectiveness.

3. SARS-CoV-2 variants

The year 2020 was difficult, but the year 2021 was even more challenging due to the development of new diverse SARS-CoV-2 variants with different genetic instructions. This may influence the virus properties such as increased transmissibility, infection rate, severity of associated disease, and the vaccine effectiveness [22]. The ones considered most dangerous ones are announced as variants of concern (VOC) [6]. Despite the benefits of various COVID-19 vaccines, increasing the vaccination rates may carry some risks. This is because the other mutations which succeed in resisting the vaccine's protection, can easily infect people. The same phenomenon was previously shown in influenza virus which changes its antigenic structure over time, leading to generation of new major antigenic variants every 3–8 years [23].

During late 2020, Alpha (B.1.1.7; 20I/501Y.V1) and Beta (B.1.351; GH/501Y.V2) VOCs were detected in UK and South Africa, respectively,

followed by Gamma variant (P.1; GR/501Y.V3) in Brazil and Delta variant (G/478 K.V1; B.1.617.2) in India. The first three variants (Alpha, Beta, and Gamma) possess many genetic variations in the S protein in comparison with the original Wuhan virus [24]. These mutations impact the interaction with the human ACE2 receptor, resulting in higher mortality rate. The Alpha and Beta lineages were identified with 23 and 17 critical mutations in the original virus, respectively [22]. The Alpha variant was more contagious and severe (40–80%) than the original virus. It also spreads more easily spread among individuals [25,26]. The crucial mutations (K417 N, E484K, and N501Y) at RBD of the S protein of Beta and Gamma variants resulted in a higher transmission rate and better virus survival by avoiding neutralizing monoclonal antibodies [27,28].

On May 11, 2021, the Delta lineage was reported as VOC by the WHO. The Delta variant is nearly twice as contagious as earlier variants and causes more severe illness. It seems to be approximately 60% more transmissible than the Alpha variant [29–31]. It possesses many mutations (9–13) in the S protein [67]. The T478K, P681R and L452R are of the greatest concern. T478K mutation increases the viral infectivity (Di Giacomo et al., 2021). The P681R mutation avoids some monoclonal antibodies, thereby increasing the survival capability of the Delta variant [30,31]. Another notable mutation is L452R which increases transmissibility (18–24%) and induces a 20 fold reduction in the neutralizing titers from the vaccinated individual [32].

On November 24, 2021, the world watched with interest and growing concern the newly discovered variant, Omicron (B.1.1.529), as being more communicable than existing circulating variants across South Africa, including Delta. The Omicron lineage contains approximately 32 mutations in the S protein alone compared to other variants; resulting in increased transmissibility and decreased vaccine effectiveness [33,34]. Further, it can bypass the immunity generated by either natural infection or vaccination. The re-infection rate with Omicron in fully vaccinated or previously infected individuals is much higher than those reported during the earlier variants, Beta and Delta [33]. Accordingly, the emergence of variants is a major challenge in designing COVID-19 vaccines.

4. SARS-CoV-2 vaccine platforms

COVID-19 vaccine platforms can be classified into two categories: traditional whole-cell vaccine (live-attenuated or inactivated) and novel nano-based vaccines (protein- and gene-based vaccines). Protein-based vaccines are protein subunit and virus-like particles called “VLP” vaccines whereas, gene-based vaccines are DNA or RNA vaccines, and non-replicating viral vector vaccines [35]. Also, live attenuated, inactivated, and viral vector vaccines can be considered nanotechnologies [11]. Many vaccine platforms are at different stages of clinical trials. Currently, WHO approved some SARS-CoV-2 vaccines for emergency use, such as mRNA- and nanotechnology-based vaccines (e.g., Pfizer/BioNTech and Moderna), and adenoviruses-based vaccines using either a human adenovirus (e.g., Janssen vaccine by Johnson and Johnson”J&J″) or a chimpanzee adenovirus (e.g., Oxford/AstraZeneca vaccine) [36]. Some of the traditional and novel vaccine platforms are described below. Table 1 lists some of current SARS-CoV-2 vaccines which are approved for emergency use or currently being evaluated.

4.1. Whole-virus vaccines

Whole-virus vaccines belong to the traditional strategy for viral vaccinations which use a weakened (attenuated) or inactivated virus to trigger the immune response.

4.1.1. Live-attenuated vaccines

Live attenuated vaccine uses a living but weakened virus that can still replicate and is recognised by the immune system without causing a real infection. The advantages of these vaccines are rapid manufacturing without the need to add an adjuvant, strong immunogenicity, and toll-like receptor stimulation [104]. Additionally, they provide a continuous antigen source and a long-lasting immunity due to their slow reproduction in the body, as shown in smallpox, poliovirus and measles [104]. Therefore, such vaccines do not require a booster dose [104]. The major drawbacks of these vaccines are the handling of live virus particles during the production phase and the risk of virus reactivation allowing it to regain its virulence in the future [105]. Many live-attenuated vaccines against SARS-CoV-2 are under investigation such as COVI-VAC (Codagenix), MV-014–210 (Meissa Vaccines), and Bacillus Calmette-Guerin vaccine (BCG) (Murdoch Children’s Research Institute) (Table 1).

4.1.2. Inactivated vaccines

Inactivated vaccine contains a dead or inactivated virus in which the genetic material has been destroyed by radiation, chemicals, or heat, in order to stimulate the immune response without replication or cell infection. These vaccines are relatively safer than live attenuated vaccines. However, they are not strongly immunogenic and often need many vaccine doses to achieve robust and long-term immune memory [106]. Accordingly, an adjuvant is required to increase the immune response [106]. Despite the well-established development process, it requires long processing time and handling of the live virus [107].

Many inactivated vaccines have been developed to control the spread of SARS-CoV-2 (Table 1). Three vaccines were approved for emergency use by WHO due to good efficacy and their safety in human clinical trials [8]. These vaccines are CoronaVac (Sinovac Biotech, Beijing, China), BBIBP-CorV (Sinopharm-Beijing, China), and Covaxin (Bharat Biotech, India). These vaccines are well tolerated, with mild side effects compared with other vaccine groups [108]. Both CoronaVac and Sinopharm are adjuvanted with aluminum hydroxide, whereas, Covaxin is adjuvanted with Alhydroxiquim-II [109]. Aluminum salts are the most common adjuvants, utilised in nearly 80% of human adjuvanted vaccines. They are produced utilising Vero monkey cell lines. The protective effect of a BBIBP-CORV reached 91.25% protection in Brazil and Turkey [110]. Also, CoronaVac was found to be 65.3% effective against symptomatic COVID-19, 87.5% against hospitalisation, 90.3% against ICU admissions, and 86.3% against deaths [111,112]. Other inactivated SARS-CoV-2 vaccines which received EUA before getting formal approval are depicted in Table 1.

4.2. Nano-based SARS-CoV-2 vaccine platforms

The nano-based platforms may be protein-based or gene-based vaccines.

4.2.1. Protein-based vaccines

Protein-based platforms are classified as protein subunit and VLP vaccines. These platforms are potentially less expensive than mRNA based vaccines and may not require cold-chain process for storage or distribution. They are produced in vitro without handling of live viruses [113]. A schematic illustration of protein subunit and VLP vaccines is shown in Fig. 2.

4.2.1.1. Protein sub-unit vaccines. Protein subunit vaccines have been used previously in other vaccines such as hepatitis and shingles [114]. These platforms deliver protein fragments, made in the laboratory, along with an adjuvant to boost a strong immune response [113,114]. They don’t contain the whole virus or a viral vector. Protein based vaccines are stable, safe, and well tolerated, even in people with special needs such as the elderly or immunodeficient people [115]. Protein based vaccines use genetically engineered cells from mammals, insects, or microbes during the production process, rather than handling of live virus particles [114]. However, these vaccines are expensive and require a long production period [105].

Table 1
Some of the SARS-CoV2 vaccine candidates in market or clinical trials.

Vaccine Candidate	Company	Route	Production†	Lab Tests	Clinical Phase	Status	Efficacy on variants	Ref.
Live-attenuated vaccines								
Bacillus Calmette-Guerin (BCG)	Murdoch Children's Research Institute, Australia.	IM	NA	NA	Phase 3	Not yet approved	NA	[3,8]
COVI-VAC	Codagenix, Serum Institute of India.	IN	NA	NA	Phase 1	Not yet approved	NA	[8,37]
MV-014–210 (RSV + S protein).	Meissa Vaccines, Inc. USA.	IN	○ Vero monkey cells	NA	Phase 1	Not yet approved	NA	[8,11, 103]
Inactivated vaccines								
CoronaVac (+ Al OH_3 adjuvant)	Sinovac; Research and Development Co., Ltd, China.	IM	○ Vero monkey cells	●○protein test-HEK293 cells	Phase 4	53 Countries*	- 2-dose: Alpha (91%) & Delta (72.5%). - Gamma (↓ symptoms, admissions, and deaths). - Omicron (50% at 1 month after booster-dose).	[8, 38–41, 103]
Covilo (BBIBP-CorV) (+ Al OH_3 adjuvant)	Beijing institute of biological products/ Sinopharm, China.	IM	○ Vero monkey cells	○ Cytopathic test - Vero monkey cells	Phase 4	88 Countries*	- 2-dose: highly effective against Alpha, and moderate effective against Beta, Gamma & Delta.	[8,42, 43, 103]
Covaxin (BBV152) (+Algel-IMDG adjuvant)	Bharat biotech International Limited, India	IM	○ Vero monkey cells	○ Antibody ELISA Plaque reduction-Vero monkey cells	Phase 4	13 Countries*	- Neutralizing antibodies decline in the range of 3 to 10-fold in the order of Alpha > Delta > Beta, with no impact of Gamma and Kappa. - Omicron (90% after Booster).	[8,44, 45, 103]
WIBP-CorV (+ Al OH_3 adjuvant)	Wuhan institute of Biological products/ Sinopharm, China.	IM	○ Vero monkey cells	○ Vero monkey cells –Plaque reduction neutralization test.	Phase 3	EUA in China Philippines	NA	[3,8, 103]
TURKOVAC (ERUCOV-VAC)	Health Institutes of Turkey & Erciyes University.	IM	NA	NA	Phase 3	EUA in Turkey	NA	[8,46]
COVIran Barekat	Shifa Pharmed, Iran	IM	NA	NA	Phase 3	Iran	Delta.	[8,47]
FAKHRAVAC (MIVAC)	Organization of Defensive Innovation & Research, Iran.	IM	NA	NA	Phase 3	Iran	NA	[8,48]
KCONVAC (KconecaVac)	Minhai Biotech, China.	IM	○ Vero monkey cells	NA	Phase 3	China Indonesia	NA	[3,8, 103]
QazVac (QazCovid-in)	Research Institute for Biological Safety Problems, Kazakhstan.	IM	NA	NA	Phase 3	Kazakhstan Kyrgyzstan	NA	[8,49]
CoviVac	Chumakov Centre, Russia.	IM	NA	NA	Phase 3	EUA (Russia)	NA	[8,50]
VLA2001 (alum + CpG 1018 adjuvants)	Valneva, France & Austria.	IM	○Vero monkey cells	NA	Phase 3	Not yet approved	NA	[3,8, 103]
Protein-subunit vaccines								
Nuvaxovid **NVX-CoV2373** (NP containing S protein + Matrix-M adjuvant)	Novavax, Gaithersburg, Maryland, USA.	IM	○ Sf 9 insect cells	●○ Pseudovirus HEK293 cells	Phase 3	32 Countries*	- Alpha (92.6%), Beta (51%) after double dose. - Delta (booster dose provides 6-Fold antibodies). - 2-dose demonstrated immune responses against Omicron.	[8, 51–53, 103]
NanoCovax (rS protein + alum adjuvant)	Nanogen Biotechnology, Vietnam.	IM	NA	NA	Phase 3	Not yet approved	NA	[8,54]
COVOVAX (NVX-CoV2373) (Protein NPs)	Serum Institute of India.	IM	NA	NA	Phase 3	India Indonesia Philippines	NA	[8,55]
SpikoGen (COVAX-19)	Vaxine/CinnaGen, Australia.	IM	NA	NA	Phase 3	Iran	NA	[8,56]

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Table 1 (*continued*)

Vaccine Candidate	Company	Route	Production†	Lab Tests	Clinical Phase	Status	Efficacy on variants	Ref.
(rS protein + Advax-CpG adjuvant)								
Razi Cov Pars (rS protein)	Razi Vaccine and Serum Research Institute, Iran.	IM & IN	NA	NA	Phase 3	Iran	NA	[3,8]
MVC-COV1901 (rS protein + CpG 1018 + alum adjuvants)	Medigen Vaccine Biologics + Dynavax + NIAID	IM	NA	NA	Phase 3	Taiwan	NA	[8,57]
Soberana Plus (Finlay-FR-1) (dimeric RBD + alum adjuvant)	Instituto Finlay de Vacunas Cuba.	IM	○RBD produced in mammalian cells	NA	Phase 2	Not yet approved	NA	[8,58, 103]
Soberana 02 (Finlay -FR-2) (RBD bound tetanus toxoid + adjuvant)	Instituto Finlay de Vacunas Cuba.	IM	○RBD produced in mammalian cells	NA	Phase 3	4 Countries	NA	[8,58, 103]
CIGB-66 (Abdala) (RBD + Al OH_3 adjuvant)	Genetic Engineering & Biotechnology Center, Cuba.	IM	NA	NA	Phase 3	4 Countries	NA	[3,8]
EpiVacCorona (peptide antigens conjugated to a carrier protein + Al OH_3 adjuvant)	The Vektor State Research Center of Virology and Biotechnology in Russia.	IM	○ Chemically synthesized peptide antigens	NA	Phase 3	Russian Federation Tur kmenistan	NA	[8,59, 103]
ZF2001 (RBD-Dimer + alum adjuvant)	Anhui Zhifei Longcom + Institute of Microbiology at the Chinese Academy of Sciences.	IM	●HEK293T cells. ○ CHO hamster cells.	●Pseudovirus HEK293T cells	Phase 3	China Indonesia Uzbekistan	NA	[8,60, 103]
S protein20 (VAT00002) (Monovalent and bivalent S protein + AS03 adjuvant)	Sanofi and GSK, Protein Sciences, France, USA.	IM	○ r baculovirus - Sf9 insect cells	●○ Pseudovirus HEK293T cells	Phase 3	Not yet approved	NA	[8,61, 103]
SCB-2019(Trimeric S protein + CpG 1018 + Alum adjuvants)	Clover Biopharmaceuticals, Chengdu, China	IM	○ cDNA in expression vector; transfect CHO hamster cells - CHO hamster cells	●○Pseudovirus HEK293 cells- Cytopathic effect Vero monkey cells.	Phase 2/3	Not yet approved	NA	[8,62, 103]
KBP-201(Plant-expressed RBD)	Kentucky BioProcessing, Inc., USA.	IM	○ rDNA for RBD - Plant expression of RBD peptide.	NA	Phase 1/2	Not yet approved	NA	[8,63, 103]
Virus-like particle vaccines								
CoVLP (Plant-expressed S protein + CpG1018 or AS03 adjuvants)	Medicago, Quebec City, Canada; GSK; Dynavax	IM	○ rDNA in Agrobacterium, transformation of plant cells - Plant expression of protein and VLP.	●○ Pseudovirus HEK293 cells	Phase 2/3	Not yet approved	NA	[8,64, 103]
SpyCatcher003-mi3 (RBD SARS-CoV-2 HBsAg VLP)	SpyBiotech, Serum Institute of India.	IM	NA	NA	Phase 1/2	Not yet approved	NA	[8,65]
VBI-2902a (S glycoprotein + alum. phosphate adjuvant)	VBI Vaccines Inc., USA.	IM	NA	NA	Phase 1/2	Not yet approved	NA	[8,66]
Viral vector-based vaccines								
Vaxzevria (ChAdOx1 nCoV-19 or AZD1222) (Chimpanzee Ad5 expressing S protein)	AstraZeneca/University of Oxford, UK.	IM	●HEK293 cells	●HEK293 cells MRC-5 cells	Phase 4	137 Countries*	- Alpha (74.5%) after double dose. - 2-dose was 41.8% against Delta increased to 93.8% after a BNT162b2 booster. - A 2-dose did not show protection against Beta. - No effect against Omicron from 15 weeks after 2 doses.	[8, 67–72, 103]

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Table 1 (*continued*)

Vaccine Candidate	Company	Route	Production†	Lab Tests	Clinical Phase	Status	Efficacy on variants	Ref.
Ad26.COV2.S (Ad26 encoding full-length S protein)	Janssen Research & Development, Inc., (Johnson & Johnson), USA.	IM	●PER.C6 cells	NA	Phase 4	106 Countries*	- Neutralizing activity was reduced for Beta (3.6-fold), Gamma (3.4-fold), and Delta (1.6-fold) reduction. - Single-dose lacked detectable neutralizing activity against Omicron.	[8, 73–75, 103]
Covishield (AZD1222) (Oxford/ AstraZeneca formulation)	Serum Institute of India.	IM	NA	NA	Phase 4	47 Countries*	- Two doses are effective against Alpha & Gamma. - A 2-dose regimen did not show protection against Beta. - Low effect against Delta. - No or limited effect against Omicron.	[8,68, 69,76]
Sputnik V(Gam-COVID-Vac) (rAd26 & rAd5 encoding full-length S protein).	Gamaleya Research Institute, Russia.	IM	● HEK293 cells	NA	Phase 3	74 Countries*	- High effect against Alpha & Gamma. - Reduced neutralizing capacity against Beta and all variants with E484K substitution of S protein. - Delta (90% protection). - > 2 times higher titers of neutralizing antibodies to Omicron.	[8, 77–80, 103]
Sputnik Light (Ad26, booster)	Gamaleya Research Institute, Russia.	IM	NA	NA	Phase 3	24 Countries	- 88.61% against Delta. - Robust neutralizing antibody response to Omicron.	[8,81, 82]
BBV154 (Ad vectored S protein)	Bharat Biotech, USA.	IN	NA	NA	Phase 2/ 3	Not yet approved	NA	[3,8]
AdCOVID (Ad expressing RBD)	Altimmune, Inc., USA.	IN	●PER.C6 cells	NA	Phase 1	Not yet approved	NA	[3,83, 103]
hAd5-S-Fusion + N-ETSD vaccine (hAd5 encoding S + N antigens)	ImmunityBio, Inc. + NantKwest, Inc., USA.	SC, oral,	●E.C7 cells (derivative of HEK293 cells)	●Protein and antibody test HEK293T cells	Phase 1/ 2	Not yet approved	NA	[3,84, 103]
GRAd-COV2 (Gorilla Ad encoding S protein)	ReiThera + Leukocare + Univercells, Italy.	IM	●HEK293T cells	●HEK293T cells	Phase 2/ 3	Not yet approved	NA	[3,85, 103]
Convidicea (hAd5-nCoV expressing S protein)	CanSino Biologics, China	IM	● HEK293 cells	NA	Phase 3	10 Countries	NA	[3,86, 103]
LV-SMENP-DC (LV-SMENP-DC).	Shenzhen Geno-immune Medical Institute, China.	SC & IV	NA	NA	Phase 1/ 2	Not yet approved	NA	[3,87]
VXA-CoV2-1 (Ad vector expressing S & N protein + dsRNA adjuvant)	Vaxart, California, USA	Oral	●HEK293 cells	NA	Phase 2	Not yet approved	NA	[3,88, 103]
mRNA-based vaccines								
mRNA-1273 (Spikevax) (LNPs loading Full-length S protein + proline substitutions)	Moderna, Inc. with National Institutes of Health, USA.	IM	○No cells used.	●○ Protein test & pseudovirus HEK293 cells Plaque reduction neutralization Vero monkey cells	Phase 4	85 Countries*	- 1-dose: Alpha (88.1%), Beta (61.3%), and Delta (77.0%). - 2-dose: Alpha (98.4%), Beta (96.4%), Delta (86.7%), mu (90.4%), and Omicron (30.4%). - 3-dose: Delta (95.2%) and Omicron (62.5%).	[8, 89–91, 103]

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Table 1 (*continued*)

Vaccine Candidate	Company	Route	Production†	Lab Tests	Clinical Phase	Status	Efficacy on variants	Ref.
BNT162b2 (Comirnaty) (3 LNP-mRNAs) Full-length S protein + proline substitutions)	Pfzer/BioNTech, USA + Fosun Pharma, Germany.	IM	○No cells used.	●○ Protein test & pseudovirus HEK293 cells Neutralization assay Vero monkey cells	Phase 4	131 Countries*	- 1-dose: Alpha (48.7%) and Delta (30.7%). - 2-dose: Alpha (93.7%), Beta (75%), Delta (63.5%) and Omicron (88.0%). - 90% of boosted subjects showed neutralizing activity against Omicron.	[8,67, 71,92, 103]
ARCT-021 (S protein)	Arcturus Therapeutics, USA.	IM	○No cells used	●Protein test HEK293 Protein expression Hep3b cells Plaque reduction neutralization ○Vero monkey cells	Phase 2	Not yet approved	NA	[3,8, 103]
CVnCoV (LNP- encoding the full-length S protein)	CureVac AG, Germany.	IM	○No cells used.	○ Protein test Reticulocyte lysate, ●HeLa cells	Phase 3	Not yet approved	- 47% efficacy against currently circulating variants.	[8,93, 103]
DS-5670a	Daiichi Sankyo, Japan.	IM	NA	NA	Phase 1/ 2	Not yet approved	NA	[3,8]
EXG-5003	Elixirgen Therapeutics, Japan.	ID	NA	NA	Phase 1/ 2	Not yet approved	NA	[3,8]
TAK-919 (Moderna formulation)	Takeda, Japan.	IM	NA	NA	Phase 2	Japan	NA	[8,94]
RQ3013-VLP (LNPs encoding S, M, E proteins)	Zhongshan Hospital, Fudan University, Shanghai, China.	IM	NA	NA	Phase 1/ 2	Not yet approved	NA	[3,8]
LNP-nCoVsaRNA (S protein)	Imperial College London, UK.	IM	●Designed by HEK293 cells. ○No cells used in production.	○Pseudovirus ●HEK293T cells	Phase 1	Not yet approved	NA	[8,95, 103]
ARCoV or ARCoVax (LNP- encoding RBD)	Walvax Biotechnology, Suzhou Abogen Biosciences, & the PLA Academy of Military Science.	IM	NA	NA	Phase 3	Not yet approved	NA	[8,96]
MRT5500 (LNP encapsulated mRNA transcribed by RNA polymerase with a plasmid DNA)	Sanofi Pasteur, France and Translate Bio, USA.	IM	●Designed by HEK293T cells. ○No cells used in production.	●○protein test & pseudovirus HEK293 cells	Phase 1/ 2	Not yet approved	NA	[8,97, 103]
PTX-COVID19-B (LNP encapsulated mRNA transcribed by RNA polymerase with a plasmid DNA).	Providence Therapeutics, Canada.	IM	●Designed by HEK293T cells. ○No cells used in production.	●○Pseudovirus, serum neutralization HEK293T cells Vero monkey cells	Phase 1	Not yet approved	NA	[8,98, 103]
DNA-based vaccines								
ZyCoV-D (S protein + *E. coli* plasmid)	Zydus Cadila, headquartered, Ahmedabad, India.	ID	○No eukaryotic cells used *E. coli* < /em	○Expression analysis Plaque reduction Vero monkey cells	Phase 3	India	NA	[8,99, 103]
INO-4800 + electroporation (S1 & S2 subunits)	Inovio and partners, USA.	ID	○No cells used	●○ protein test& pseudovirus HEK293 cells	Phase 3	Not yet approved	NA	[8,100, 103]
GLS-5310 (S protein and a second antigenic target of SARS-CoV-2)	GeneOne Life Science, South Korea.	ID	NA	NA	Phase 1/ 2	Not yet approved	NA	[3,8]
CORVax12 (S protein ± electroporated IL-12p70 plasmid)	OncoSec + Providence Cancer, USA.	ID	NA	NA	Phase 1	Not yet approved	NA	[3,8]
GX-19N	Genexine Consortium, Korea.	IM	○ No cells used	○ No cells used	Phase 1/ 2	Not yet approved	NA	[8,101, 103]

(*continued on next page*)

Table 1 (*continued*)

Vaccine Candidate	Company	Route	Production†	Lab Tests	Clinical Phase	Status	Efficacy on variants	Ref.
(S protein + Electroporation)								
AG0302- & AG0301 (S protein + *E. coli* plasmid)	AnGes Inc, Japan.	IM	○No cells used *E. coli* < /em	○Virus neutralization Vero E6 monkey cells.	Phase 2/3	Not yet approved	NA	[8,102,103]
COVID-eVax (RBD of S protein)	Takis, Rottapharm Biotech, Italy.	IM	NA	NA	Phase 1/2	Not yet approved	NA	[3,8]
Covigenix VAX-001 (Full-length S protein)	Entos Pharmaceuticals, Canada.	IM	NA	NA	Phase 1/2	Not yet approved	NA	[3,8]
COVIGEN (S protein)	BioNet-Asia.	IM & ID	NA	NA	Phase 1	Not yet approved	NA	[3,8]
***BacTRL*-Spike™** (S protein; Genetically engineered *LAB*)	Symvivo Corporation, Canada.	Oral & IV	○No cells used	NA	Phase 1	Not yet approved	NA	[3,8,103]

IM, intramuscular; IN, intranasal; ID, intradermal; SC, subcutaneous; Ad., Adenovirus, LN, lentivirus; RSV, respiratory syncytial virus; EUA, Early use approval; DC, dendritic cell; CHO, Chinese hamster ovary; SMENP, SARS-CoV-2 spike, membrane, nucleocapsid, envelope and protease; LAB, lactic acid bacteria, and NA, Not applicable.

*Approved for emergency use by WHO (EUL).

○Does not use abortion-derived cell line.

● **Use abortion-derived cell line.**

○● **Some tests do not use abortion-derived cells, some do.**

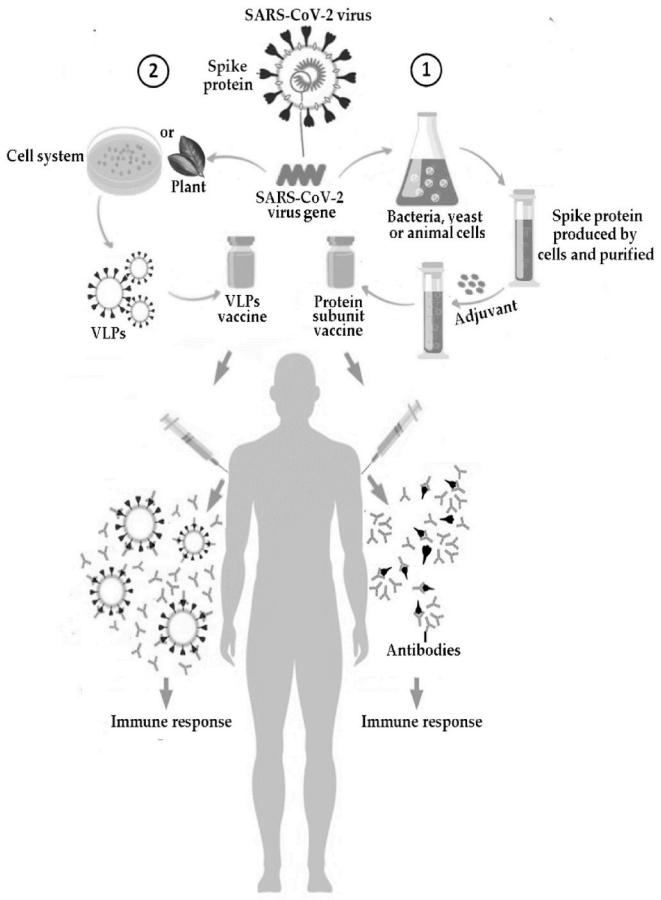

Fig. 2. Schematic illustration of (1)Protein subunit vaccines and (2) Virus-like particles (VLPs) vaccines.

Protein subunit COVID-19 vaccines can be prepared using free-floating protein or by tethering protein to a NP, along with an immunity-stimulating adjuvant [114]. Some COVID-19 subunit vaccines are recorded in Table 1. They use S protein or only a key part of a protein, the RBD, to trigger a strong immune response against SARS-CoV-2 [114]. The NVX-CoV2373 (Novavax, Maryland, USA) is the leading protein subunit vaccine. It is a NP-encapsulating S protein of SAR-CoV, adjuvanted with matrix-M [3]. It has been approved for emergency use by WHO due to high immunogenicity and tolerability in phase 3 human clinical trials [8]. ZF2001 (Anhui Zhifei Longcom in collaboration with the Institute of Microbiology at the Chinese Academy of Sciences) is another adjuvanted protein subunit vaccine with conditional approval in China (Table 1). Heterologous BBIBP-CorV/ZF2001 vaccination could boost and preserve a long-lasting recall of humoral immune responses against SARS-CoV-2 and its VOCs [116]. Other subunit SARS-CoV-2 vaccines granted EUA before receiving formal approval from WHO are shown in Table 1.

4.2.1.2. Virus-like particles vaccines (VLP). VLP is a self-assembled nanostructure which mimics the 3D configuration of the real virus. VLP vaccines lack the viral genome so, they are non-infectious and non-replicating [117]. They are safe, with powerful immunogenicity and adjuvant properties. VLPs are easily recognised by the immune system. They are edible vaccines produced in plant cells or cell systems, therefore, they are considered an ideal platform for oral delivery vaccines [117]. CoVLP vaccine, developed by Medicago, is one of the COVID-19 vaccines that recently entered phase 2/3 clinical trials (Table 1). CoVLP is a plant-expressed S protein particle adjuvanted with CpG1018 [64].

4.2.2. Gene-based vaccines

Gene-based vaccines are a new class of vaccines. Using a nanotechnology platform, they deliver the genetic sequence of specific viral proteins, or part of it, rather than the whole virus, to the host cells [115,118]. The efficacy of this type of vaccine in humans depends heavily on the delivery system carrying the target genes into cells [35]. The synthesis of the viral protein is initiated inside the host cells, resulting in a

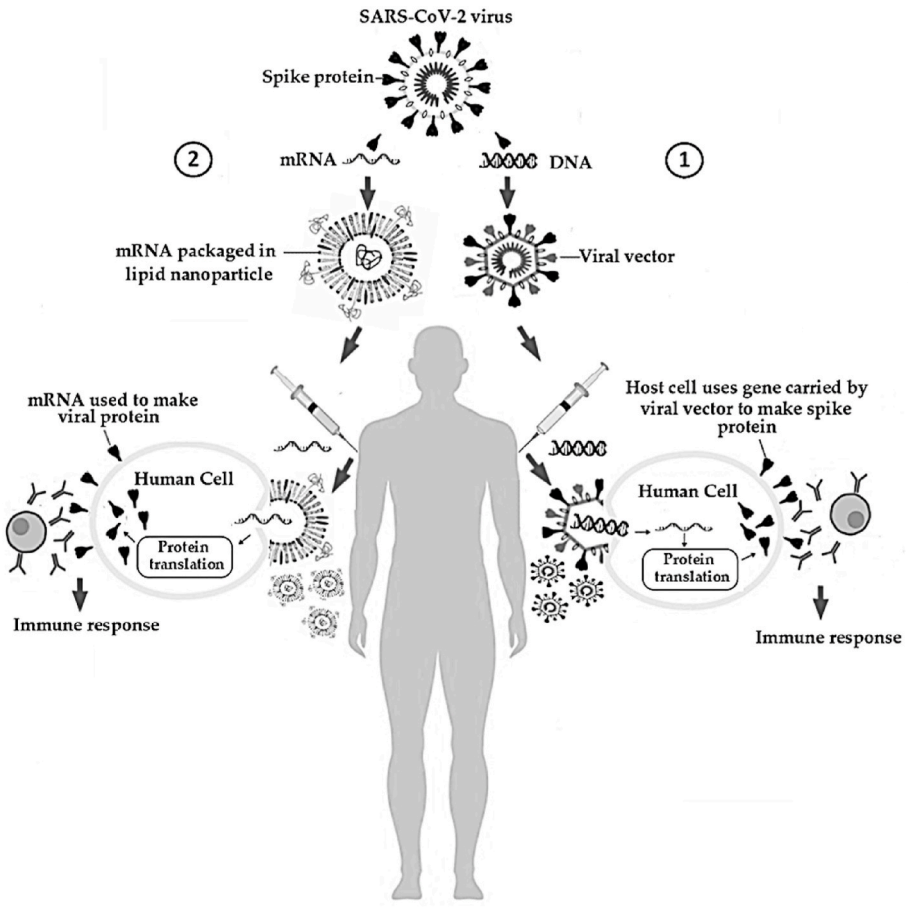

Fig. 3. Schematic representation of (1) viral vector DNA vaccines and (2) mRNA-based vaccines.

strong immune response. The advantages of gene-based vaccines over conventional vaccine platforms are: low production costs, rapid and easy production, better safety profile, specificity, and potent cell-mediated protective immunity [118]. However, the major concern about such vaccines is the fact that they have never been approved for use in humans before the COVID-19 pandemic. Moreover, they usually require an ultra-cold-chain process for storage and distribution. Despite the high protective efficacy of such vaccines, many side effects are also induced [3].

Based on the antigen carrier, the gene-based vaccines for SARS-CoV-2 can be classified into vector-based, mRNA, and plasmid DNA vaccines. Viral vector-based vaccines contain mRNA encoding the S protein of SARS-CoV-2, whereas mRNA-based vaccines are double-stranded DNA adenovirus-based vaccines encoding the same S protein. Some gene-based vaccine platforms are described below. A schematic illustration of viral vector-based and mRNA-based vaccines is shown in Fig. 3.

4.2.2.1. Vector-based vaccines. Vector-based vaccines may be bacterial vector- or viral vector-based vaccines. Some of the leading vaccine candidates are shown in Table 1.

Bacterial vector-based vaccines use a safe, non-pathogenic bacteria as a vector or gene delivery vehicle [3]. The Symvivo's COVID-19 vaccine, bacTRL-Spike, is an oral or intravenous DNA vaccine that uses a lactic acid bacteria (LAB) as a vector (Table 1). Currently, the vaccine is in phase 1 clinical trials [8]. The bacTRL-Spike technology can be lyophilized to enhance the stability of the vaccine [119].

Viral vector-based vaccine uses a viral vector to deliver genes that encode a specific antigen of the pathogen to the host cell. These are safe replication-defective platforms [120]. The vector is an infectious attenuated virus such as adenovirus (Ad), adeno-associated, measles, or pox virus, genetically modified to act as a carrier [121]. The viral vector mimics the real viral infection and uses the host cell to manufacture a non-harmful piece of SARS-CoV-2 such as S protein, to trigger robust cellular and humoral responses. Although these vaccines are immunogenic and well tolerated in healthy adults, they have many drawbacks, including; potential risk for inflammatory adverse reactions, risk of infection, pre-existing immunity against the vector, chromosomal integration, and oncogenesis [122].

Several non-replicating Ad vector-based vaccine platforms are being developed for COVID-19 (Table 1). The Ad type-5 (Ad5) vector was previously used in many vaccines such as Ebola vaccine (Ad5-EBO). However, in some cases, it may be unacceptable due to pre-existing immunity and intolerable high-dose immunisation [106]. Accordingly, the use of rare human Ad serotypes or nonhumans Ads, in combination with other vaccine platforms for immunisation, will be the typical solutions. Three viral vector-based vaccine are approved by WHO to date [8]. These Ad-based COVID-19 vaccines are a human Ad vaccine (Janssen vaccine by J&J) or a chimpanzee Ad vaccine (Oxford/AstraZeneca vaccine & Covishield) [36].

The University of Oxford and AstraZeneca jointly developed the first non-replicating chimpanzee Ad-based attenuated vaccine against COVID-19; the ChAdOx1nCoV-19 (AZD1222), which encodes the S-protein of the SARS-CoV2 (Table 1). The vaccine was commercially renamed as Vaxzevria and has been licensed in 137 countries [8]. Covishield (AZD1222) vaccine, developed by the Serum Institute of India, utilised the same formulation as Vaxzevria vaccine. Both vaccines are in phase 4 clinical trials. Scalability, acceptable safety profile, and natural adjuvant properties are all advantages of AZD1222 vaccine [9]. However, the adenoviral vector efficacy may be limited due to the pre-existing immunity of the pre-Ad-based vaccine in humans. The

effectiveness of a single dose of ChAdOx1nCoV-19 is 33.4%, 55.1%, and 61.8% against symptomatic Covid-19, hospitalisation, and death, respectively. The effectiveness of the 2-dose regimen is 77.9% against symptomatic COVID-19, 87.6% against hospitalisation, and 93.6% against death [76].

Other in-use SARS-CoV2 replication-defective human Ad vector vaccine platforms are J&J (Ad26.COV2.S) developed by Janssen Research & Development, Inc., USA, and Convidicea (Ad5-nCoV) developed by the CanSino Biologics, China [123,124] (Table 1). J&J's vaccine is an Ad26 vector encoding full-length S protein of SARS-CoV2. The vaccine is currently in phase 4 clinical trials and was approved for emergency use by WHO in February 2021 [8]. Ad26.CoV2.S is an effective and safe one-shot vaccine with mild to moderate reactogenicity [69]. A single dose provided 76.7% and 85.4% protection against severe–critical COVID-19 after 14 and 28 days following administration, respectively [125]. A booster shot of Ad26.COV2.S increased protection to 94% against moderate to severe disease. CanSino, J&J, and Oxford/AstraZeneca are utilising genetically engineered common cold viruses in the manufacturing of COVID-19 vaccines [126].

Sputnik V (Gam-COVID-Vac), developed by the Gamaleya, Russia, is the first non-replicating Ad-based SARS-CoV-2 vaccine utilising a heterogeneous boosting technique with 2 different Ad viral vectors (Ad26 and Ad5) for 2 vaccine shots (Table 1) [123]. The vaccine is currently in phase 3 clinical trials. It generated a stable humoral and cellular immune response without severe adverse effects [127]. The efficacy of the vaccine is 91.6% against SARS-CoV-2. The vaccine is approved for EUA in 74 Countries [77].

4.2.2.2. mRNA-based vaccines. The mRNA-based vaccine is a promising weapon against many viral diseases and cancer. The mRNA-based SARS-CoV-2 vaccines use the mRNA encoding the target antigen, instead of weakened or dead virus, to function as a platform for the generation of many S protein copies (Fig. 3). These vaccines have several advantages compared with other traditional approaches: such as rapid production, scalability, fully synthetic, robust and long-lasting humoral and cellular immune response, negligible risk of genetic integration, and an acceptable safety profile [106,128–130].

Naturally occurring mRNA is a negatively-charged hydrophilic molecule with low transfection efficacy [106]. For safe and efficient transportation into human cells without being degraded in the circulation, mRNA needs a nanocarrier such as liposomes or lipid nanoparticles (LNP) to improve the stability and enhance the mRNA transfection efficacy [128,129]. The negatively-charged mRNA is complexed with positively-charged lipids, forming a stable lipoplexes which are self-assembled virus-sized particles that can be administered via different routes [129]. The mRNA condensing lipids such as 1,2-dioleoyl-3- trimethylammonium-propane (DOTAP) and dilinoleylmethyl4-dimethylaminobutyrate (DLin-MC3-DMA) are the key components of this platform [131].

There are many mRNA-based CONID-18 vaccines currently undergoing clinical trials (Table 1). Some of them have been approved in many countries but only 2 vaccines have been granted a formal approval from WHO to date, Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) vaccines [8]. BNT162b2 and mRNA-1273 vaccines are the first PEGylated LNP-encapsulated mRNA-based vaccines allowed for use in humans (Table 1). The PEGylated LNPs are useful as molecule stabilizers [132]. Currently, both vaccines are in phase 4 clinical trials and showed about 95% protection against COVID-19. However, mRNA-1273 is more protective than BNT162b2. Pilishvili and his coworkers, 2021, found mRNA-1273 vaccine to be 96.3% effective in preventing symptomatic illness in health care workers, compared to 88.8% for Pfizer [133].

Both vaccines encode the full-length S protein of SARS-CoV2; inducing both humoral and Th1-mediated responses [106]. Despite the clear advantages of mRNA-based vaccines, they have many drawbacks such as risk of adverse reactions, high cost, instability under physiological conditions and they typically require an ultra-cold chain process for storage and distribution. Additionally, the mRNA molecule itself and/or the LNPs can both induce unwanted pro-inflammatory responses [128,134,135]. The compositions of the PEGylated LNPs are very similar for Pfizer/BioNTech and Moderna vaccines. They contain an ionisable cationic lipid, cholesterol, a polyethylene glycol (PEG) 2000, and the phospholipid distearoylphosphatidylcholine (DSPC) as a helper lipid [135]. However, Moderna vaccine contains tromethamine, which can potentially lead to immune hypersensitivity reactions [136].

4.2.2.3. DNA vaccines. DNA vaccines contain bacterial plasmid DNA that encodes one or more viral antigens [137]. Inside the nucleus of the host cell, they are converted into mRNA which translated into the S protein; eliciting both humoral and cell-mediated immunity. DNA vaccines also have some advantages, including easy production, safe handling, stability, no risk of infection, and long-term persistence of immunogens [138]. Additionally, the DNA molecules can be freeze-dried for long-term storage [3,107]. DNA vaccines may also be administered orally, intradermally, and subcutaneously (SC). However, the drawbacks of these platforms cannot be ignored, such as potential risk of genetic integration, poor immune responses in humans, and toxicity induced by repeated doses [138,139]. The major concern is the possibility of plasmid DNA NPs transfecting nontarget cells, such as brain cells, when administered by inhalation [138,139].

Different intradermal DNA plasmid vaccines for COVID-19 were developed such as INO-4800, ZyCoV-D, GLS-5310, CORVax12, and COVIGEN (Table 1). There is no DNA vaccine approved by WHO for human use to date. India approved the first 3-dose DNA plasmid vaccine to administer to humans, ZyCoV-D (Zydus Cadila, Ahmedabad) in August 2021 (Table 1). The vaccine uses DNA plasmid that encodes the S protein of SARS-CoV-2 to prime a strong immune system [140]. This needle-free vaccine is administered using the PharmaJet® technology. Currently, the vaccine is in phase 3 clinical trials [8]. ZyCoV-D vaccine is 67% protective against symptomatic COVID-19 [140].

Similarly, INO-4800 vaccine (Inovio and partners, USA) used CELLECTRA 2000® electroporation device for intradermal administration [107]. Interestingly, electroporation itself may perform as a physical adjuvant by stimulating the release of pro-inflammatory cytokines in the skin [141]. The vaccine is currently in Phase 3 clinical trials (Table 1). INO-4800 vaccine is safe, stable at room temperature for more than 1 year, immunogenic, and well tolerated [142]. Other DNA vaccines undergoing clinical trials are listed in Table 1.

5. New vaccine formulation strategies

Nano-sized particles may be natural, such as VLPs and viral vectors, or synthetic particles such as cationic liposomes and polymeric NPs [143]. Nanocarriers can be utilised as potential carriers for antigen, to protect it from degradation and enhance the intracellular uptake of nucleic acid by APCs [144]. Also, a nanocarrier itself may act as an immune stimulating adjuvant. Nanoscale delivery systems have the capability to simultaneously deliver antigens and adjuvants in a single particulate carrier. This improves the vaccine efficacy by inducing robust humoral and cellular responses [145]. Furthermore, these platforms can be formulated in different dosage forms administered via oral, intramuscular (IM), sublingual or buccal routes [3].

Nanotechnology tools can play an important role in advancing COVID-19 vaccine development. They have unique physiochemical properties which make them a suitable tools for vaccine delivery of SARS-CoV-2 such as; miniature particle size, high loading efficiency, low toxicity, site-specific delivery of antigens, higher surface-to-volume ratio, enhanced intracellular trafficking, high stability, reduction of adverse effects, and controlled release of incorporated drug molecules [3,145]. They include several types of nanotechnology platforms such as liposomes, polymeric NPs, LNPs, micro and nanospheres, nanoemulsion,

DCS, and polymeric micelles [3]. Some of these systems are illustrated below.

5.1. Nanoliposomes

Liposomes are nanoscale lipid vesicles which are considered as a good vehicle for both hydrophilic and lipophilic antigens [146]. They consist of one or more phospholipid bilayers enclosing an aqueous internal core. This unique structure of liposome allows the encapsulation of both lipophilic and hydrophilic antigens, respectively [146]. The composition of liposomes can be modified to stimulate the desired immune response and adjuvant characteristics. It can produce a sustained release of the encapsulated antigens and create a depot action to facilitate long-term retention [147]. The surface of the liposome can be modified to enhance mucosal adherence, lymphatic drainage, immune cell targeting capacity, stability, and encapsulation efficiency [146, 148]. The drawbacks of a liposomal vaccine delivery system include cost, inactivation of phospholipid membrane integrity, and poor stability in the GI tract [147]. The latter can be solved easily by the formulation of bilosomes via incorporation of biocompatible and biodegradable bile salts [146]. Oral bilosomes can elicit a mucosal IgA response not only at the site of induction, but also at various remote mucosal sites.

During the current COVID-19 pandemic, the creation of a PEGylated liposome-based mRNA vaccine was made possible. Numerous liposome-based vaccines are still in the preclinical stage or in clinical trials. Mabrouk et al., 2021, developed a successfully freeze-dried liposome-based liquid vaccine for probable use in SARS-CoV-2 vaccines [149]. Liu and his group, 2020, prepared cationic liposomes encoding the anionic S1 subunit of the SARS-CoV-2 virus, employing the thin film hydration technique and using amphiphilic monophosphoryl lipid A (MPLA) and CpG oligodeoxynucleotide (for TLR 9) as adjuvants [150].

5.2. Lipid nanoparticles

LNP is a liposome-like structure, which is suitable for encapsulation of nucleic acid cargos (DNA and RNA). The mRNA-LNPs are fully synthetic, biocompatible, and manufactured without handling of living cells [151,152]. Furthermore, the high production capacity of these vaccines is more appropriate for a pandemic than conventional vaccine production.

Moderna and Pfizer–BioNtech mRNA vaccines rely on LNPs platform to carry mRNA that encodes the S glycoprotein into the host cells. Both vaccines have shown good efficacy and safety in phase 4 clinical trials, and were approved for emergency use by WHO [21,153]. The long-term stability of LNPs elicited a strong immune response (95%) against the S glycoprotein of SARS-CoV-2 [106]. LNPs used in these vaccines are made of three components: (1) a PEGylated lipid to minimize opsonization in vivo, improve stability, and reduce clearance of LNPs from the blood, (2) cholesterol to support particle formation, and (3) phospholipid distearoylphosphatidylcholine (DSPC) [154]. The molecular weight of PEG is only 2000 [155]. Adjuvants are not required in these types of vaccines because both mRNA and LNPs possesses potent immunostimulatory properties [156]. Another two LNPs-based vaccines are developed by Novavax, Gaithersburg, Maryland and CureVac N.V, Germany which also encode the S protein (Table 1).

Novel LNPs vaccines encoding S protein of SARS-CoV-2, are in development. These novel platforms are LNP-nCoVsaRNA (Imperial College London, UK) which utilizes self-amplifying RNA to enhance antigen expression at lower doses and RQ3013-VLP (Zhongshan Hospital, Fudan University, Shanghai, China) which uses mRNA cocktails encoding 3 structural proteins of SARS-CoV-2 (S, M, and E) (Table 1).

5.3. Nanoemulsion

Nanoemulsion is a heterogeneous formulation of two different immiscible liquids (oil and water), stabilised by surface-active agents to produce droplets within the nano-range (20–200 nm) [157]. Both the oil in water (O/W) and water in oil (W/O) emulsions have been demonstrated to encapsulate vaccines for mucosal delivery [146]. They are ideal for lipophilic antigens [158]. Nanoemulsions are promising vaccine platforms for tackling viral outbreaks, such as COVID-19, due to their long-term stability, safety, compatibility, miniature size, antigen protection, slow release of antigen, prolonged blood circulation, low cost, and easy of storage and transportation [7,146,159]. Furthermore, pharmaceutical nanoemulsions can be administered by SC, IM, intravenous, and mucosal routes [7]. Nanoemulsion can be used as an adjuvant. The O/W nanoemulsion adjuvant vaccines produce immunity through multiple pathways. A nanoemulsion SARS-CoV-2 vaccine MF59C, developed by Seqirus, Australia, has recently entered clinical trials in Australia [160]. It contains an adjuvant (MF59) along with the SARS-CoV-2 Sclamp antigen. The new nanoemulsion vaccine triggers both neutralizing antibodies and T-cell responses [161]. The modern squalene-based nanoemulsion MF59® was used previously in influenza vaccine [159].

5.4. Polymeric nanoparticles

Polymeric NPs are nano-sized particles (1–1000 nm). They have shown a great potential for targeted delivery of drugs and antigens [162]. Polymeric NPs can be loaded with antigen entrapped within or surface-adsorbed onto their polymeric core. They can be administered via intravenous, oral, dermal, and intranasal routes. They are classified as pH sensitive NPs, specific ligand attached NPs and mucoadhesive NPs. The most commonly used polymers in vaccine delivery are polylactic co glycolic acid (PLGA), polylactic acid (PLA) and polyanhydrides [146, 163]. Despite versatile features such as biodegradability, biocompatibility, and low cytotoxicity, their use is limited due to high cost, scale-up difficulty, poor loading efficiency, and immediate burst release at acidic pH [162].

Chitosan, PLGA, or polyethylenimine have been previously used to develop NP vaccines for other coronaviruses (e.g. SARS-CoV, MERS-CoV, or hCoV) [164]. Chitosan is a natural bioadhesive polymer. Chitosan has the advantage of non-immunogenicity and high solubility. Cationic chitosan-containing NPs enhance the absorption of key ingredient through prolonging retention time and exposure to intestinal cells. The major drawback of chitosan NPs is the immediate burst release at acidic pH, which can be overcome by encapsulating antigen loaded chitosan NPs within liposomes or by electrostatic coating with anionic polysaccharide alginate [162].

The biomimetic pseudoviruses approach was used for the development of a rapid and efficient bionic NP COVID-19 vaccine. This approach uses PLA, PLGA, and polyhydroxyalkanoates (PHAs) to stabilise the spherical structure and achieve a long-lasting protective effect [106]. The bionic NP vaccine was decorated with antigen to form a spherical VLP structure through self-assembly. The vaccine is safe and stable however, the effectiveness of this approach in the COVID-19 vaccines is not yet confirmed.

5.5. Micelles

Micelles are another promising nanocarrier for SARS-CoV-2 vaccines. They are nanoscale, spherical self-assembled, amphiphilic structures that have a hydrophobic core and a hydrophilic shell. The hydrophilic shell allows for intravenous delivery. The hydrophobic core carries an antigen payload, thus protecting it from elimination and increasing its circulation time. The protein subunit vaccine, NVX-CoV2373 (Novavax, USA), is a NP containing full-length S protein of SARS-CoV2, along with Matrix-M adjuvant and polysorbate 80 detergent to induce self-assembly of micelles [165] (Table 1). Currently, it is in phase 3 clinical trials and approved for emergency use by WHO [8]. NVX-CoV2373 vaccine was reported to be 89.3% efficacious against

wild-type SARS-CoV-2 (https://ir.novavax.com/2021-01-28-Novavax-COVID-19-Vaccine-Demonstrates-89-3-Efficacy-in-UK-Phase-3-Trial).

6. The effectiveness of vaccines against variants

All SARS-CoV-2 vaccines encode the S protein of the original WA1/2020 strain. Therefore, any mutation in the S protein of the Wuhan-Hu-1 isolate (especially at the amino acids E484 and E417 of the RBD) will have a significant impact on the vaccine effectiveness and the variant can easily bypass the immune system [166,167]. The emergence of variants is a major challenge in designing SARS-CoV-2 vaccines. The effectiveness of the leading vaccines against VOCs are illustrated below (Table 1).

6.1. Alpha (B.1.1.7)

The leading vaccine candidates, Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2), are effective against symptomatic Alpha variant infections [168]. Their effectiveness was not changed in S447 N mutation, but decreased neutralization against E484K mutation [6,169]. mRNA-1273 vaccine showed decreased protection of 88.1% and 98.4% after a single and second dosage, respectively [90]. Two doses of the BNT162b2 vaccine are needed to reach the high level of expression of neutralizing antibody and cell-mediated immune response [170]. The effectiveness of two doses of BNT162b2 was 93.7% against the Alpha variant [67]. Additionally, based on real-world vaccinations, the BNT162b2 vaccine was more than 95% effective against severe disease or death from Alpha and Beta variants [67].

The J&J (Ad26.CoV2. S) vaccine single shot offers 74% protection against Alpha and Delta variants [171]. Similarly, Sputnik V vaccine effectively neutralised the Alpha variant [79]. AstraZeneca vaccine (ChAdOX ncov-19) was 48.7% and 74.5% against Alpha variant after one dose and two doses, respectively [67,172]. Novavax (NVX-CoV2373) vaccine showed decreased protection (92.6%) against the Alpha VOC after the second dose [53]. The RBD-specific antibodies and memory B cells induced by Covaxin (BBV152) vaccine declined in the range of 3- to 10-fold against the SARS-CoV-2 variants in the order of Alpha > Delta > Beta, with no observed impact of gamma (P.1) and kappa (B.1.617.1) variants [44].

6.2. Beta (B.1.351)

The majority of the SARS-CoV-2 vaccines showed decreased neutralization against Beta variant. The effectiveness of 2 doses of BNT162b2 showed only 75% efficacy against the Beta variant [67,92]. The mRNA-1273 vaccine was 61.3% and 96.4% effective against Beta variant after a one- and two-dose regimens, respectively [89–91]. Therefore, first generation mRNA-LNPs vaccines have been updated to fight the emergence of variants. Moderna has developed a Beta variant-specific vaccine (mRNA-1273.351) for booster immunization. The updated vaccine encodes the S protein from the Beta VOC [154]. Boosting with mRNA-1273.351 is more effective against Beta and Gamma variants in comparison with boosting with mRNA-1273 [173].

ChAdOX ncov-19 vaccine failed in preventing even mild and moderate infection due to Beta variant, where, it showed only 10% protection [68,174]. Also, the effectiveness of Ad26.CoV2. S vaccine against Beta variant was reduced (3.6-fold reduction) compared to Wuhan-Hu-1 strain [73–75], showing only 57% effectiveness against Beta VOC [172]. Similarly, Sputnik V produced only moderate neutralization of the E484K substitution such as Beta variant where the efficacy was markedly reduced (6.1-fold reduction) [78,79]. A two-dose regimen of NVX-CoV2373 also showed less protection (51%) against Beta variant [52]. The BBBP-CorV (Sinopharm) retained moderate neutralizing activity (1.6-fold reduction) against the Beta variant compared with the original virus [43,175].

A cocktail or mosaic of heterologous antigens loaded on a single NP may cover the range of variants recognised by neutralizing antibodies [176]. SpyCatcher003-mi3, a mosaic protein NP SARS-CoV-2 vaccine, displays 4 to 8 distinct RBDs of S protein on a synthetic VLP platform, using SpyTag/SpyCatcher technology (Table 1) [65]. The vaccine is currently in phase 1/2 clinical trials. A low dose of RBD-SpyVLP vaccine administered to mice produced a strong neutralizing antibody response in comparison with SARS-CoV-2-RBD NPs or COVID-19 convalescent human plasma [65]. Another approach is a subunit vaccine, RBD–NP. The vaccine consists of RBD of S protein displayed on I53-50 protein NP scaffold. It encodes RBDs from 4 sarbecoviruses: SARS-CoV-1, SARS-CoV-2 and 2 bat Coronaviruses WIV1 and RaTG13 [177]. The neutralizing activity of RBD–NP was studied in mice after administration as a mosaic (4 RBDs co-displayed on the same NP), or as a cocktail (4 NPs each expressing a single type of RBD). The results showed a broad neutralizing activity of the RBD–NP vaccine against SARS-CoV-2 and Beta variant [177].

6.3. Gamma (P.1)

mRNA-based vaccines (BNT162b2 and mRNA-1273) were less effective against the Gamma variant [37]. The effectiveness of Ad26. CoV2. S vaccine against Gamma variant was decreased (3.4-fold reduction) compared to the original WA1/2020 strain [73–75]. Two doses of the ChAdOX ncov-19 vaccine afford significantly increased protection against the Gamma variant [76]. Similarly, Sputnik V produced antibodies capable of neutralizing the Gamma variant [80]. A two-dose regimen of CoronaVac vaccine was associated with a reduction in symptoms, hospital admissions, and deaths in adults aged ≥70 years infected with the Gamma variant [39].

6.4. Delta (B.1.617.2)

A one dose regimen of all COVID-19 vaccines showed reduced neutralization in cases of the highly contagious Delta variant. The efficacy of both mRNA-1273 and BNT162b2 was decreased in Delta VOC. The effectiveness of one dose of mRNA-1273 and BNT162b2 vaccines was 77.0% and 30.7% whereas, two-dose protection of the same vaccines was 86.7% and 63.5% against Delta variant, respectively [67,71,90–92]. However, the protection induced by mRNA-1273 vaccine was nearly twice than that observed in case of BNT162b2 [178]. Concerning hospital admissions with the Delta variant, the effectiveness of both vaccines was 97.5% and 96% for mRNA-1273 and BNT162b2 vaccines, respectively [67]. A two-dose regimen of CoronaVac vaccine showed 72.5% protection against Delta [39–41]. In an attempt to increase the protection against SARS-CoV-2 and decrease the BNT162b2 vaccine-related side effects, Intapiboon and his coworkers, 2021, conducted a phase 1 clinical trials of an intradermal BNT162b2 booster, in healthy volunteers who were fully vaccinated with CoronaVac vaccine in Thailand [179]. They found that IM injection of the BNT162b2 vaccine was superior compared to the fractional intradermal boosting of BNT162b2 (one fifth) however, the neutralizing activity against the Delta variant seemed to be comparable between these two routes of vaccination.

CureVac mRNA-LNPs showed only 47% efficacy against VOCs, including Delta variant [180]. Also, ChAdOx1 nCoV-19 vaccine was 67% effective against Delta VOC, 2 weeks after the second dose [67,172]. In comparison, Ad26.COV2.S induced strong, persistent activity against Delta variant where only 1.6-fold reduction in neutralizing activity was observed for Delta variant [74]. Sputnik V vaccine demonstrated 90% protection against Delta variant [77–80). Sputnik Light booster was 88.61% effective against symptomatic Delta VOC infection [81,82].

6.5. Omicron (B.1.1.529)

All of COVID-19 vaccines have shown markedly reduced their

effectiveness against Omicron variant in comparison with the previously dominant Delta variant [30,31,38]. This may lead to a rise in breakthrough infections with the Omicron variant in previously infected or full vaccinated individuals. Interestingly, mRNA vaccines still provide partial protection and significantly decrease the severity of illness and the hospitalisation rate [181]. A substantial reduction in neutralization antibodies was observed after mRNA-1273 and BNT162b2 vaccines. However, they remain effective against severe disease, hospitalisation, and death. A 2-dose regimen of mRNA-1273 and BNT162b2 was only 30.4% and 62.5% against Omicron variant, respectively. A 3-dose course of mRNA-1273 was 62.5% against Omicron [67,71,90–92]. However, data from South Africa showed reports of breakthrough infections in people vaccinated with the BNT162b2 vaccine [33]. A booster vaccination with BNT162b2 and mRNA-1273 improved protection against severe disease caused by Omicron [71,182]. Moderna plans to develop an Omicron variant-specific vaccine and hopes to begin clinical trials soon [182].

Both WHO approved viral vector-based vaccines, Ad26.COV2.S and ChAdOx1 nCoV-19, lacked detectable neutralizing activity against Omicron [72–75]. Also, Omicron variant escapes neutralizing antibodies induced by a two-dose regimen of Covishield and Coronavac vaccines [38,68,69,76]. A booster vaccination of the BNT162b2 or mRNA-1273 vaccines is 60% effective against symptomatic disease caused by Omicron in fully immunized individuals with ChAdOx1 nCoV-19 vaccine. Ten weeks after dosing, the effect was decreased to 35% and 45% in case of BNT162b2 and mRNA-1273 vaccines, respectively. Sputnik Light booster following Sputnik V vaccination induced neutralizing antibodies against Omicron in all individuals [81,82].

Accordingly, the CDC has recommended that individuals fully immunized with mRNA-based vaccines (BNT162b2 and mRNA-1273) or adenoviral vaccine (J&J) should receive a booster vaccine 6 months after the second dose of mRNA vaccines or 2 months after J&J vaccine [183]. Tailored reformulation of the leading vaccine platforms to encode the Omicron S protein are crucial to combat the spread of the recently developed SARS-CoV-2 genetic mutations [172]. However, these tailored vaccines may fail to give protection against previous VOCs due to the antigenic distance of Omicron. Therefore, multivalent vaccine formulations should be considered to fight different VOCs [72].

7. Heterologous SARS-CoV-2 booster vaccinations

The “mix-and-match” or heterologous SARS-CoV-2 vaccine regimens are a combination of two or more current vaccine platforms [184]. This combination is highly effective in preventing infection; almost matching or even exceeding the performance of mRNA vaccines [184]. The heterologous prime-boost strategies have many advantages, such as: (1) allow potent immune responses, (2) offer greater flexibility of vaccination schedules, and (3) decrease the side effects generated by some vaccines e.g., adenoviral vaccine (ChAdOx1 nCoV-19) [185]. Mixed adenoviral and mRNA schedules provide safe, tolerable, and immunogenic alternatives to homologous schedules. One dose of ChAdOx1 nCoV-19 followed by another dose of mRNA-LNP vaccine (mRNA-1273 or BNT162b2) is more effective than 2 doses of ChAdOx1 nCoV-19 (68% *vs.* 50%) [186]. Similarly, boosting ChAdOx1 nCoV-19 vaccine primed subjects with one dose of BNT162b2 was 88% effective in preventing infection; similar to the effectiveness of 2 doses of BNT162b2 [184]. A BNT162b2/mRNA-1273 schedule induced higher antibody and T-cell responses than the standard 2-dose BNT162b2 schedule [187]. Boosting ChAdOx1 nCoV-19 vaccine primed subjects with a second dose of protein subunit vaccine (NVX-CoV2373) or mRNA-1273 vaccines, generated a robust immune response exceeding that of 2-dose ChAdOx1 nCoV-19 schedule [187]. BNT162b2/NVX-CoV2373 regimen induced higher antibodies than 2-dose ChAdOx1 nCoV-19 schedule but lower than a 2-dose BNT162b2 schedule [187]. However, the efficacy of heterologous SARS-CoV-2 vaccine regimens against the Beta and Delta VOCs had decreased, and this was a trend across the mixed schedules [187].

8. Challenges and limitations of current SARS-CoV-2 vaccines

COVID-19 vaccine platforms could potentially face many challenges related to safety, manufacturing, distribution, storage, administration, and acceptability, as well as ethical considerations. All these challenges and limitations are vaccine-dependent and are discussed below.

8.1. Adverse events

Some adverse events or risk of complications following COVID-19 vaccinations have been reported worldwide. Therefore, the potential risks and complications of different vaccine platforms should be identified and weighed against potential benefits. The most common adverse events experienced following vaccination include COVID arm (soreness at point of injection), redness, swelling, hair loss, menstrual cycle changes, tiredness, fatigue, headache, muscle pain, chills, fever, diarrhea, nausea, drowsiness, and rash. Other potentially severe but rare side effects include myocarditis, transverse myelitis, swollen lymph nodes, and blood clotting [114,188–190]. These rare but possible adverse events may raise serious concern among the public and probably lead to vaccination hesitancy or refusal. The differences in the intensity and pattern of adverse events could be attributed to the difference in the type of vaccine platform. The side effects detected from the inactivated vaccines were markedly lower than the adenoviral-based and mRNA-based vaccines [191,192]. Interestingly, females and younger individuals were more likely to report vaccine-related adverse events than older individuals [193].

The risk of blood clotting is experienced in women aged <50 years old, following vaccination of adenoviral (AstraZeneca and J&J) and mRNA (Moderna and Pfizer-BioNTech) vaccines [194,195]. Interestingly, the blood clots were detected in unusual parts in the body such as brain, eye, and abdomen. This very rare and possibly life-threatening condition is usually accompanied by low levels of platelets, which can be resolved by immediate intervention with non-heparin anticoagulants [196].

A few reports of rare neurological effects have been observed post-vaccination of AstraZeneca, Moderna and Pfizer-BioNTech. Inflammation of the spinal cord has been shown following AstraZeneca vaccine (Singh, 2020). Guillain–Barre Syndrome was reported post-vaccination with Pfizer-BioNTech, Moderna, J&J vaccines and [197].

Severe myocarditis and pericarditis have been observed post-vaccination of mRNA-LNPs in young adults (Moderna and Pfizer-BioNTech) [188]. This heart inflammation resolves without medical intervention in at least half of the patients. However, it may lead to dilated cardiomyopathy, heart transplantation, or death in up to a quarter of cases [198]. Some drugs such as beta-blockers, intravenous anti-inflammatory drugs, and corticosteroids may help to alleviate the symptoms of myocarditis [59,199]. Adverse events associated with the oral cavity and orofacial region were also detected in a few people post-vaccination of the same two Moderna and Pfizer vaccines [200].

The excipients used in vaccine formulations should be thoroughly investigated due to the likelihood that they may induce adverse reactions [201]. A life-threatening allergic reactions were reported following administration of LNPs vaccines [202,203]. These reactions are related to the PEGylated lipids of LNPs vaccines. The Pfizer-BioNTech and Moderna vaccines contain PEG 2000 which may cause anaphylaxis, especially in subjects with asthma, rhinitis, urticaria, or pre-existing anti-PEG antibodies [203–205]. This may raise questions concerning the use of other PEG derivatives, such as polysorbates which are present in Moderna, Novavax and AstraZeneca NPs vaccines [202,205]. Moderna vaccine also contains another potential cause for anaphylactic reactions; tromethamine/trometamol [136,206]. Therefore, inactivated vaccine may be a safe alternative in individuals who have experienced anaphylactic reactions with adenoviral or LNPs

vaccines [192]. Further studies are needed to identify the exact causes of severe reactions which may be related to any excipient used in the formulation of NPs vaccines.

8.2. Vaccine storage and handling

Lack of thermostability is a major challenge which may limit the global vaccine distribution especially mRNA-LNPs vaccines requiring an ultra-cold chain for storage and transportation [207]. For Pfizer BioNTech, the maximum shelf life is 9 months at −80 °C to −60 °C, protected from light [208]. For AstraZeneca vaccine, the maximum shelf life is 6 months at 2–8 °C without light exposure. Protein-based NPs vaccines may also face extensive challenges related to the rigorous specifications of GMP-grade cell-line development, combined with other complicated challenges such as purification, formulation, and stability issues [209]. Therefore, vaccine formulations such as lyophilized vaccines which do not require the cold-chain limitations would be most preferable worldwide, especially in developing countries. Recently, Moderna have developed mRNA-1283, the next generation of its vaccine for easier distribution. The refrigerator-stable vaccine (2–5 °C) does not require on-site dilution and recently entered a phase 2 clinical trials [8].

8.3. Ethical concerns

In various stages of vaccine production, some of the SARS-CoV-2 vaccines used immortal cells originally isolated from human fetuses aborted electively in the 1970s and 1980s. The cells included HEK-293 (kidney cell line) and PER.C6 (retinal cell line) [103,210]. They were also used in the confirmatory laboratory test to study the efficacy of some vaccines in human cells. These fetal cells were previously used in the development of rubella, chickenpox, hepatitis A, and rabies vaccines. The use of fetal cell lines may raise concerns within some faith communities about the ethics of using materials derived in this way. A list of COVID-19 vaccines which used the abortion-derived cell lines in development or confirmatory laboratory tests is listed in Table 1.

8.4. Refusal of vaccines

Acceptance of vaccines is influenced by public perception and knowledge about the contents, safety and effectiveness of vaccines [192,211–213]. Many claims, with no scientific evidence, are raised worldwide regarding the presence of toxic aluminum or graphene oxide, contamination of some vaccines with spores or other living microorganisms, fear of RNA-modifying transhumanism, and lipids used in the manufacturing of NPs [214]. Although aluminum has been used in some vaccines since the 1930s as an adjuvant, it is now used in a low concentration that can't be absorbed easily. There is no scientific evidence that the vaccines contain graphene oxide, microchips, or metals, especially since all vaccine manufacturers have shared their ingredients publicly.

Finally, vaccinations should not be made mandatory. Forced vaccine administration will undoubtedly violate human rights. Health care providers should raise community awareness by educational interventions via communication and media coverage concerning the important role of vaccines in fighting the COVID-19 pandemic [215]. It is crucial for everyone to have adequate information to make a fully informed decision regarding COVID-19 vaccination. Transparency, and accurate information about COVID-19 vaccines and their ingredients, must be available globally to eliminate any concerns about the safety of the vaccines [216].

8.5. Equitable distribution of vaccines

The majority of national vaccine distribution systems are not intended for large-scale adult vaccination programs, but rather for children to ensure that they receive their full immunization schedule. As more COVID-19 vaccines are developed and authorized for emergency use, governments should be ready for the identification of vulnerable populations to guarantee fair access and ensure that the right people receive the right vaccine at the right time. Additionally, governments should plan for the mass production and distribution of the billions of COVID-19 vaccine doses to their populations through implementation of creative solutions to scale-up the manufacturing capacity. Assuring equitable vaccine access worldwide, and producing enough quantities of these vaccines and sustaining supply chain capacity are two essential parts of supplying and delivering these vaccines around the globe [217].

The COVAX-WHO facility was established to hasten the research and production of COVID-19 vaccines and to ensure fair access to these vaccines in all countries. Further financial investments into COVAX should be made. However, the small middle-income countries may not benefit from the COVAX initiative. So, governments should be encouraged to work together and create a "distributive manufacturing model" to purchase vaccines in a coordinated manner [217]. This will become more crucial if regular COVID-19 booster/vaccination campaigns are required to combat emerging viral strains or declining vaccine effectiveness over time, as is the case with seasonal flu.

8.6. Route of administration

Route of vaccine administration plays a critical role in the vaccination outcome against the COVID-19 pandemic, especially among young adults [218]. Almost all the approved SARS-CoV-2 vaccines are administered via IM route which may influence the mass immunisation rate. Pain felt during IM vaccine administration is one of the most frequently reported causes of vaccine hesitancy. Therefore, a needle-free delivery system can enhance the vaccination rate and acceptance among populations.

9. Needle-free particulate delivery systems of COVID-19 vaccine

Needle-free mucosal vaccinations via intranasal, pulmonary, and oral routes may be preferable to parenteral vaccinations, especially in cases of respiratory viruses such as SARS-CoV-2 [3]. This is because parenteral vaccination can only stimulate systemic immunity while mucosal immunity is believed to be the first defense against airborne viruses. Particulate vaccine formulations can be administered by a mucosal route. Key innovations of different needle-free vaccination technologies are discussed in this section. Their potential to overcome common vaccination-related limitations and improve compliance are also highlighted.

9.1. Oral administration

The most patient-friendly route for vaccines is oral administration, which is pain-free, non-invasive, low cost, and easy to administer to the mass population [163]. Oral vaccines not only stimulate the mucosa-associated lymphoid tissue (MALT) located in the GI tract, but also can stimulate the gut-associated lymphoid tissue (GALT) [219]. The MALT is present in many submucosal membrane sites of the body, such as intestinal villi, salivary glands, tonsils, nasopharynx, lungs, thyroid, breasts, eyes, and skin [219]. GALT is a component of MALT. It includes immune cells such as B and T lymphocytes, macrophages, and APCs for protecting the body from pathogens invading the gut. Accordingly, oral administration of vaccines can elevate the mucosal immune response, which is a first line of protection against respiratory infections such as SARS-CoV-2 [146,163]. Oral SARS-CoV-2 vaccination may remove the limitations of the current IM vaccines.

Despite the clear benefits of oral vaccines, only a few have been successfully developed, such as polio vaccine [220]. Oral vaccines may face some challenges related to GI biology such as acidity, mucus, degradation due to proteolytic enzymes, and low intestinal permeability. In addition, poor immunogenicity of orally delivered antigens

could impact the success of stimulating effective immunity [146].

Oral particulate vaccine formulations may protect the antigen loaded into nanoparticles or microparticles from GI degradation [221,222]. Oral administration of nanoemulsion vaccines could be a therapeutic or protective tool against COVID-19. Oral tumor nanoemulsion vaccine encapsulating a melanoma-specific antigen was developed by Long et al., 2019 [223]. The new oral vaccine elicited mucosal immune responses and inhibited tumor growth *in vivo* [223]. Similarly, the effectiveness of mucosal immunisation of VLP-based HPV vaccine against anogenital cancer has been studied [224]. The results supported the possibility of mucosal immunisation following peroral administration of VLP-based HPV vaccine [224]. Accordingly, the current particulate IM mRNA vaccines of SARS-CoV-2, may be converted by the addition of some biodegradable and biocompatible polymers, charged particles, or ligands into microparticles and delivered via the oral route as an enteric coated tablet, solution, or suspension [3]. The use of polymers, such as pH-dependent polymers, could achieve site-specific delivery of antigens to the intestine particularly to the Peyer's patches, along with antigen protection [225]. The pH-dependent polymers are cellulose acetate trimellitate, cellulose acetate phthalate, shellac, or hydroxypropyl methylcellulose phthalate [226]. Upon administration, the oral particulate vaccine can elicit a local intestinal immune response as well as systemic immunity [3].

Several oral SARS-CoV-2 vaccines including bacTRL DNA plasmid vaccine (Symvivo Corporation), VXA-CoV2-1 Ad vector (Vaxart), and Ad vector hAd5-S-Fusion + N-ETSD (ImmunityBio, Inc) are currently under clinical development (Table 1). The oral enteric coated tablet COVID-19 vaccine, VXA-CoV2-1, encoded both the S protein and N protein of SARS -CoV-2 which is less prone to mutations than the S protein. Therefore, VOCs may be less likely to avoid vaccine effectiveness. VXA-CoV2-1 vaccine triggers broad systemic and mucosal protection in humans. The tableted vaccine employed VAAST™ (Vector-Adjuvant-Antigen Standardized Technology) delivery platform with an Ad5 as a vector and a Toll Like Receptor-3 (TLR-3) agonist as an adjuvant. The vaccine has several advantages such as simple production, storage and transportation. Furthermore, the unwanted anti-vector responses as expected with other Ad-vectored vaccines, such as AstraZeneca and J&J vaccines, can be avoided. The vaccine is currently in phase 2 clinical trials (Table 1) and provided a high level of protection against COVID-19 [88].

9.2. Sublingual and buccal administration

Sublingual and buccal routes allow medications to be absorbed via the sublingual and buccal mucosa, bypassing the GI tract barriers such as GI enzymatic degradation and hepatic first-pass effect [3]. The oral cavity and saliva are important sites for SARS-CoV-2 infection and transmission [227,228]. Buccal or sublingual vaccines may be effective for the induction of both systemic and local immunity [229]. Therefore, they could be a good alternative for mass protection during pandemic situations.

Orally dissolving films (ODFs) loaded with vaccine microparticles/nanoparticles are another form of noninvasive immunisation. ODFs can be manufactured and administered easily. They can be prepared employing a spray drying approach, solvent casting, or using a 3D bioprinter [230]. Biocompatible and biodegradable polymers can be utilised to develop OFDs, along with permeation enhancer and plasticiser [3]. Gala and coworkers, 2017, developed measles microparticles ODF vaccine using the spray drying technique [231]. The vaccine microparticles were prepared with bovine serum albumin polymer, then incorporated into an ODF. A significantly higher antibody titer was observed following administration of the buccal ODF vaccine to juvenile pigs, indicating the efficiency of the measles microparticles ODF vaccine formulation [231].

9.3. Intranasal administration

Vaccination via pulmonary route is another non-invasive technique that is easy to administer to the mass population with better patient compliance [232]. Millions of people have received the COVID-19 vaccine worldwide. In some people, the vaccine cannot resist the virus's invasion, but only reduce the symptoms of the disease produced. Intranasal vaccination provides better systemic and mucosal immune protection compared to SC route, especially in case of respiratory viruses like SARS-CoV-2 [233]. It can trigger continuous nasal IgA and serum IgG responses for up to 6 months [234]. The MERS-CoV and SARS-CoV-1 vaccines succeeded in inducing mucosal protection through induction of IgA at the site of the viral entry, hindering viral spreading to the lung [235]. The intranasal delivery may confer a stronger clinical immunity than oral delivery, as in the case of *Bordetella bronchiseptica* vaccine [236]. However, the main drawback of mucosal vaccines is the poor immunogenicity produced due to poor absorption and rapid removal of antigens from the nasal cavity [237].

A few nasal mucosal killed or live attenuated vaccines have been authorized for use in humans such as nasal influenza vaccine [232]. Many intranasal COVID-19 vaccines, MV-014-210 (Meissa Vaccines, Inc. USA), BBV154 (Bharat Biotech, USA), AdCOVID™ (Altimmune, Inc., USA), COVI-VAC (Codagenix, Serum Institute of India), and Razi Cov Pars(Razi Vaccine and Serum Research Institute, Iran), were developed and evaluated in clinical trials [8] (Table 1). AdCOVID™ vaccine is a promising vaccine candidate against COVID-19 [83]. It is a single-dose Ad5-vectored vaccine intranasal vaccine that was designed to elicit a broad and strong immune response against RBD of SARS-CoV-2, including both serum neutralizing IgG response and nasal IgA & T cells [83]. Currently, AdCOVID™ is in Phase 1 clinical trials. Similarly, BBV154 is another Ad vectored, intranasal vaccine for COVID-19 (Table 1). It is currently in Phase 2/3 clinical trials. It was shown to stimulate both serum and mucosal antibody immune responses.

Vaccination via the intranasal route has been investigated. VLP-based HPV vaccines showed a possibility for mucosal immunisation [224,238]. Bernstein and his colleagues, 2019, developed an intranasal nanoemulsion-adjuvanted herpes simplex virus subunit vaccine (Nano-Vax®) which activated both the mucosal and systemic immunity [239]. Recently, an intranasal mannosylated chitosan-based NPs encapsulating killed SwIAV antigen vaccine was developed by Renu et al., 2021 [240]. The intranasal immunisation of this vaccine induced a strong IgA and IgG antibody titers against influenza virus in pigs [240]. For the COVID-19 pandemic, Du and coworkers, 2021, generated an intranasal recombinant SARS-CoV-2 RBD-based subunit vaccine [241]. The vaccine induced mucosal immunity as well as a robust systemic humoral immunity. Similarly, the immunogenicity of the RBD of SARS-CoV-2 S glycoprotein loaded into N,N,N-trimethyl chitosan NPs was studied in mice [242]. The intranasal vaccine stimulated both local mucosal and systemic immunity [242]. Also, a modified intranasal porous silicon microparticle (mPSM)-adjuvanted SARS-CoV-2 RBD vaccine was developed [243]. Boost vaccinations with intranasal mPSM-RBD vaccine diminished lung inflammation and viral loads following Delta variant infection [243]. It stimulated SARS-CoV-2 specific IgA responses, lung resident memory T and B cells, along with potent systemic immunity [243].

Acknowledging this, the intranasal COVID-19 vaccine may be feasible. However, the need for a particular delivery device, such as nebuliser, may limit the use of a nasal or pulmonary vaccine. Additionally, the potential loss of virus titer cannot be ruled out, due to the use of a nebuliser [244]. So, it is not surprising that nearly all SARS-CoV-2 vaccine platforms are administered via injection (Table 1), although they may not be able to produce mucosal immunity [13].

Intranasal vaccines prepared as inactivated vaccines, live attenuated vaccines, or viral vector-based vaccinations can elicit potent mucosal and systemic immunity. However, the safety of these non-synthetic vectors is uncertain. Antibodies present in the mucosal layer may

neutralize protein subunit vaccines. Furthermore, the proteases found in the nose can also diminish their immunogenicity [245]. Novel vaccine delivery systems are necessary for nasal vaccination. NPs have greater controllability and safety as an alternative to biological vectors [245]. PLGA NPs, liposomes, and NP assemblies have the ability to stop the neutralization of antigens and improve cellular uptake. Nasal immunization with polysaccharide-based nanovaccines can elicit both mucosal and systemic immunity. The use of chitosan nanoparticles as an adjuvant and delivery system for SARS-CoV-2 nanovaccines is theoretically possible. The excellent adhesion of chitosan can decrease the nasal clearance of the vaccine, increase its retention time, and boost its effectiveness. A particulate adjuvant system, quil-A-loaded chitosan (QAC) nanovaccine, was developed by Chandrasekar et al., 2021 [246]. QAC-nanovaccine had the ability to trigger robust mucosal immune responses against respiratory SARS-CoV-2. Similarly, Bakkari et al., 2021 [247] created an intranasal nanovaccine prepared with inulin acetate, toll-like receptor-4 agonist, that successfully stimulated both systemic and mucosal immunity in mice.

The development of a vaccine platform based on protein assemblies is also a promising approach. Wuertz et al., 2021 [248] prepared a next-generation COVID-19 vaccine, SARS-CoV-2 spike ferritin self-assembled nasal NPs vaccine. The latter provided a defense against SARS-CoV-2-induced illness and viral replication following intranasal Alpha or Beta variants challenge. An inhalable nanovaccine with biomimetic coronavirus structure was designed by Zheng and his coworkers, 2021 [249]. For effective vaccination, NPs may be assembled with antigens to form a SARS-CoV-2-like molecule that simulates the process of viral infection. The nanovaccine that mimic virosome is composed of biomimetic pulmonary surfactant liposomes and poly(I:C). The authors reported that the inhalable nanovaccine with bionic VLP structure has a better mucosal protective effect than conventional IM and SC administration.

The intranasal or pulmonary vaccines can be formulated in different dosage forms such as aerosol, powder, or gel [250]. Nasal delivery of antigens, in the form of inhalable dry powder particles, may enhance the thermostability of vaccines, decrease the cost of vaccination, and eliminate the dependence on cold chains [251]. Such vaccine formulations not only elicit systemic and mucosal immune responses, but also have logistical advantages over injectable vaccines [251]. The dry powder-based inhalable vaccine formulations are prepared by different drying methods such as freeze-drying, spray-drying, or a mix of these [251]. Despite many advantages of dry powder-based nasal vaccine vaccines, they are not involved in the current race for SARS-CoV-2 vaccines. Such non-invasive vaccines should be developed for the future SARS-CoV-2 vaccine design.

10. Conclusion

COVID-19 vaccines offer the best hope for fighting the SARS-CoV-2 pandemic. However, the emergence of variants is a major challenge in developing COVID-19 vaccines. Only eleven vaccines with different traditional and nano-based platforms have been granted an emergency use authorization by WHO and more are still under development. The nano-based vaccine platforms are a promising and powerful weapon against many viral diseases, including SARS-CoV-2. However, the major concern of such vaccines is the fact that they were never approved for marketing before the COVID-19 pandemic. Despite favorable outcomes and promising results, the goal of global COVID-19 vaccination has not been achieved due to many challenges and limitations of the existing vaccines. It is important to make sure that potential safety risks are identified and weighed against potential benefits. Accordingly, further studies are required concerning the efficacy and safety of SARS-CoV-2 vaccines, especially nanotechnology-based vaccine platforms. As SARS-CoV-2 and its variants will likely circulate for many years to come, new thermostable non-invasive particulate vaccine platforms, which are easy to administer to the mass population, should be considered. Such particulate vaccines can elicit both mucosal and systemic immunity. Finally, vaccinations should not be made mandatory. Forced vaccine administration will certainly violate human rights. Proper health system programs are required to enhance public knowledge and awareness of the crucial value of vaccination. Transparency along with accurate and appropriate information about COVID-19 vaccines and their ingredients must be submitted globally to eliminate any suspicions regarding the safety of these vaccines.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Sally A. Helmy reports was provided by Damanhour University Faculty of Pharmacy. Sally A. Helmy reports a relationship with Damanhour University, Taibah University that includes: employment. Sally A. Helmy has patent pending to I don't know. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jddst.2022.103762.

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