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REVIEW

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Covid-19 vaccines and variants of concern: A review

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Abstract

Since the outbreak of coronavirus disease 2019 (Covid-19) in December 2019, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the number of confirmed infections has risen to more than 242 million worldwide, with nearly 5 million deaths. Currently, nine Covid-19 vaccine candidates based on the original Wuhan-Hu-1 strain are at the forefront of vaccine research. All nine had an efficacy over 50% against symptomatic Covid-19 disease: NVX-CoV2373 (~96%), BNT162b2 (~95%), mRNA-1273 (~94%), Sputnik V (~92%), AZD1222 (~81%), BBIBP-CorV (~79%), Covaxin (~78%), Ad26.CoV.S (~66%) and CoronaVac (~51%). However, vaccine efficacy (VE) can be jeopardised by the rapid emergence and spread of SARS-CoV-2 variants of concern (VOCs) that could escape from neutralising antibodies and/or cell-mediated immunity. Rare adverse events have also been reported soon after administration of viral vector and mRNA vaccines. Although many Covid-19 vaccines have been developed, additional effective vaccines are still needed to meet the global demand. Promising Covid-19 vaccines such as WIBP-CorV, AD5-nCOV, ZyCoV-D, CVnCoV, EpiVacCorona and ZF2001 have advanced to clinical studies. This review describes the most relevant mutations in the SARS-CoV-2 spike protein, discusses VE against VOCs, presents rare adverse events after Covid-19 vaccination and introduces some promising Covid-19 vaccine candidates.

KEYWORDS
Covid-19 vaccines, rare adverse events, SARS-CoV-2, vaccine efficacy, variants of concern

1 | INTRODUCTION

At the end of December 2019, a number of cases of pneumonia of unknown aetiology were detected in Wuhan, Hubei Province of China. A few days later, the Chinese authorities identified a novel coronavirus as the etiological agent of the disease.[1] As soon as the complete genome sequence of the 'Wuhan virus' was published online, the structures of various viral proteins were determined.[2] Based on the phylogenetic and taxonomic analysis of the causative agent, the International Committee on Taxonomy of Viruses designated the new virus as 'severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)'.[3] Subsequently, the World Health Organization (WHO) proposed 'Covid-19' as an abbreviation of coronavirus disease 2019.[4]

Abbreviations: ACE2, angiotensin-converting enzyme 2; Ad, adenovirus; CEPI, Coalition for Epidemic Preparedness Innovations; Covid-19, coronavirus disease 19; E, envelope protein; FP, fusion peptide; GBS, Guillain–Barré syndrome; HR1, heptapeptide repeat sequence 1; HR2, heptapeptide repeat sequence 2; ICTV, International Committee on Taxonomy of Viruses; LNP, lipid nanoparticles; M, membrane protein; MERS-CoV, middle east respiratory syndrome coronavirus; MHRA, Medicines and Healthcare products Regulatory Agency; MPER, membrane-proximal external region; N, nucleocapsid protein; nAb, neutralising antibody; NIAID, National Institute of Allergy and Infectious Diseases; NTD, N-terminal domain; ORF, open reading frame; PF4, platelet factor 4; PR, pityriasis rosea; RBD, receptor-binding domain; S, spike protein; S1, subunit 1; S2, subunit 2; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TM, transmembrane domain; TMPRSS2, transmembrane serine protease 2; TTS, thrombosis and thrombocytopenia syndrome; VE, vaccine efficacy; VOCs, variants of concern; WHO, World Health Organization; WT, wild-type.

Non-pharmaceutical measures including physical distancing, proper use of masks, teleworking, isolations and quarantines have been imposed to delay the spread of Covid-19.[5,6] However, these behavioural measures have unwanted effects, such as a negative psychological impact, major depressions and mental health consequences.[7] Developing a safe and efficient vaccine has been the only promising goal for the successful fight against Covid-19. WHO declared the global pandemic in March 2020.[8] In 22 October 2021, there were 322 vaccine candidates in development, according to information provided by the WHO. Around 40% were in clinical development (128 vaccine candidates), while 194 were in preclinical development.[9] The nine leading vaccines – manufactured by Pfizer-BioNTech, Moderna, Gamaleya, Novavax, Oxford-AstraZeneca, Sinopharm, Bharat Biotech, Johnson & Johnson and Sinovac – have been developed based on the use as antigen of the viral S glycoprotein of the wild-type (WT) strain. The emergence of four SARS-CoV-2 variants has raised concerns related to reduced effectiveness of neutralising antibodies and/or cell-mediated immunity elicited by currently available vaccines. According to the WHO, these variants are denoted as Alpha, Beta, Gamma and Delta.[10]

Rare adverse events have also been described following the immunisation with CoronaVac, AZD1222, Ad26.COV2.S, BNT162b2 and mRNA-1273.[11-18] However, causal links between Covid-19 vaccines and rare adverse events have not been established.

This review describes spike mutations of interest, discusses vaccine efficacy (VE) against variants of concern (VOCs) and reports on rare adverse events occurring after Covid-19 vaccination. It also serves as an introduction to some promising Covid-19 vaccine candidates. To the best of my knowledge, this is the first paper reviewing the VE of nine different vaccine candidates against VOC, outlining severe adverse events following the immunisation with five Covid-19 vaccines and presenting some potential good vaccines in the pipeline.

2 | NOVEL SARS-CoV-2

2.1 | Structure and genomic characteristics

SARS-CoV-2 is a spherical or pleomorphic enveloped virus with a diameter in the range of 70–110 nm containing a large unsegmented single-stranded positive-sense RNA (Figure 1a).[19] The genome size of SARS-CoV-2 is about 29.9 kb, which is between the genome sizes of severe acute respiratory syndrome coronavirus (SARS-CoV) (~29.7 kb) and middle east respiratory syndrome coronavirus (~30.1 kb).[20,21] It is composed of a 5′-leader-UTRs-replicase-S-E-M-N-3′ UTR-poly-A tail sequence and is characterised by the presence of a variable number (6–12) of open reading frames (ORFs) between conserved genes (ORF1ab, S, E, M and N).[1] S, M, E and N genes located at the ORFs 10 and 11 encode the four structural proteins: a spike protein (S), a membrane protein (M), an envelope protein (E) and a nucleocapsid protein (N), that are responsible for viral replication and propagation (Figure 1b).[22]

In the viral envelope, the S proteins form a crown-like structure that justifies the name given to this type of viruses ('corona'). The S protein is the most immunogenic component of the virus, and therefore the most potent target of neutralising antibodies that inhibit virus infection.[20] The M protein is the largest and the most abundant structural protein, which defines the shape of the virion and plays a crucial function in the budding process of viral particles from their host cells. The E protein is essential for virus infection and replication.[20] The assembly of S, E and M proteins forms the viral coat (Figure 1a). The N protein is associated with the genomic RNA and maintains the genetic material inside the envelope. It is an essential protein for viral replication. During self-assembly of viral particles, the M viral protein cooperates with other structural proteins to form the complete virion.[23]

2.2 | The spike protein and its role in the pathogenesis of SARS-CoV-2

The SARS-CoV-2 S protein (Mr 180,000–200,000) is made of 1273 aa.[24] It is composed of two subunits (S1 and S2) (Figure 1c). S1 contains an N-terminal domain and the receptor-binding domain (RBD). The 'S1 head' is responsible for receptor binding. S2 includes an internal membrane fusion peptide, two heptapeptide repeat sequences (HR1 and HR2), a membrane-proximal external region, and a transmembrane domain (TM) (Figure 1d).[23,25] The 'S2 filament' facilitates the entry of the genome into host cells by fusing the host and viral membranes.[26]

The trimeric S protein is the main surface glycoprotein,[27] which binds to the human angiotensin-converting enzyme 2 (ACE2) for viral entry and the serine host-cell protease 2 for S protein priming.[28] Therefore, SARS-CoV-2 S glycoprotein is the most relevant source of antigens for vaccine development.[23]

2.3 | Important mutations in the spike protein that appear in emerging SARS-CoV-2 variants

Current Covid-19 vaccines have been developed by including the S protein found in the original Wuhan-hu-1 strain. However, SARS-CoV-2 is throwing out notable missense mutations within the trimeric S protein (Figure 2). SARS-CoV-2 VOCs have acquired some of the potential spike protein mutations (Table 1) that may increase their transmissibility and/or virulence with a possible reduction of vaccine effectiveness.[29-31]

Non-synonymous mutations of particular interest that may be promoting the spread of SARS-CoV-2 include the following.

2.3.1 | Amino acid substitutions affecting K417

Lys417 is located in the RBD of the S glycoprotein, whichinteracts with the human ACE2 receptor protein. A non-synonymous mutation

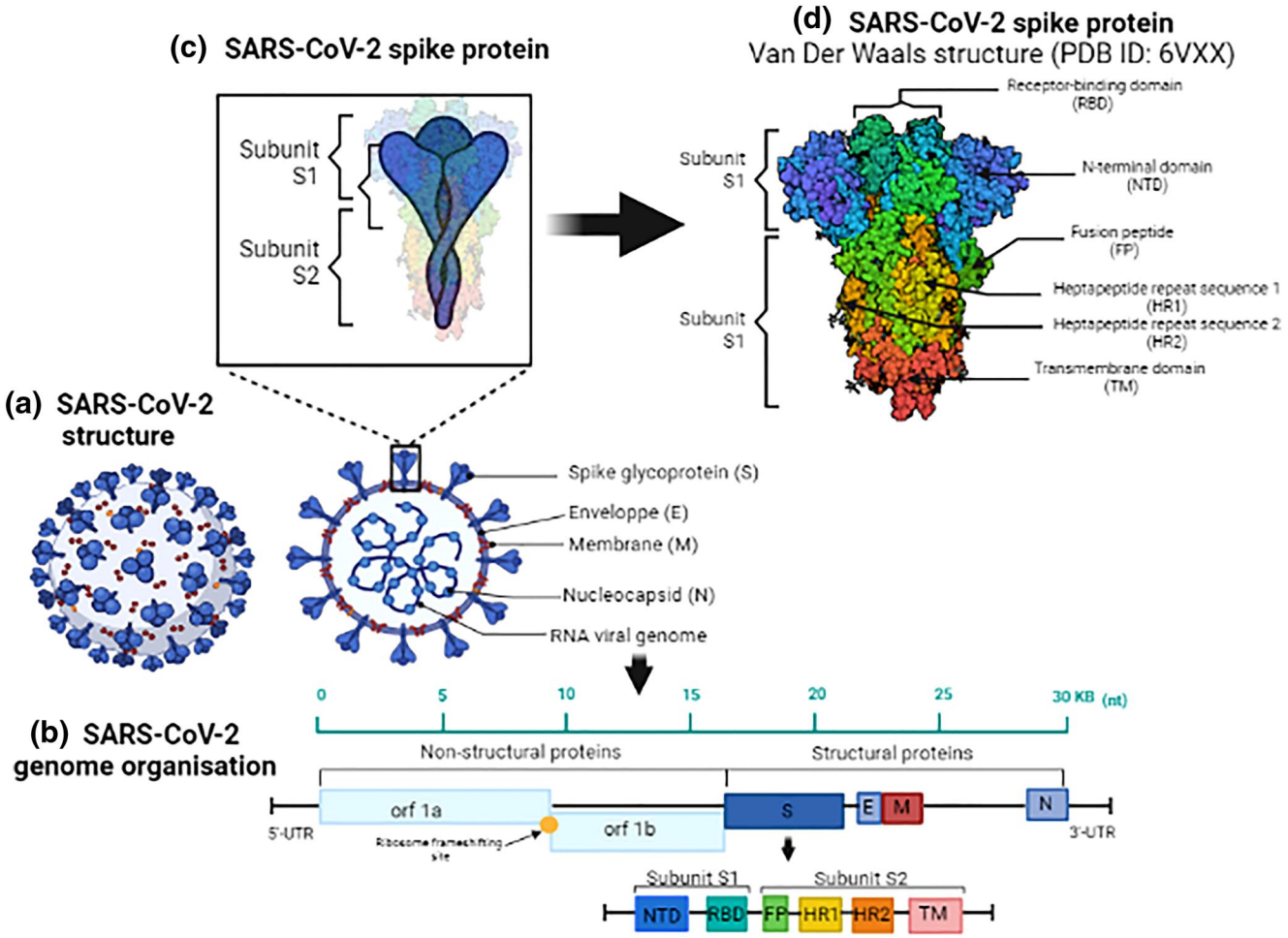

FIGURE 1 Structure and genomic characteristics of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). (a) Schematic representation of the SARS-CoV-2 structure showing the exterior envelope (E), membrane (M), spike glycoprotein (S), nucleocapsid (N) and RNA viral genome. (b) Schematic representation of the SARS-CoV-2 genome organisation (~30 kb) showing the two large open reading frames ORF1a and ORF1b, which encode the non-structural proteins, separated by the ribosome frameshift site. Genes encoding the structural proteins are as follows: spike (S), envelope (E), membrane (M) and nucleocapsid (N). The S glycoprotein consists of two subunits. Subunit S1 contains an N-terminal domain (NTD) and the receptor-binding domain (RBD). Subunit S2 includes an internal membrane fusion peptide (FP), two heptapeptide repeat sequences (HR1 and HR2), a membrane-proximal external region and a transmembrane domain (TM). (c) Schematic representation of SARS-CoV-2 spike protein showing the two subunits: S1 and S2. (d) Crystallographic structure of the SARS-CoV-2 spike protein (PDB ID:6VXX). Figure generated with BioRender

at this position (K417N) appears in the Beta variant (Figure 2b), while K417T appears in Gamma (Figure 2c).[32,33] Both mutations are associated with increased transmissibility and reduced sensitivity to neutralising antibodies.[33,34]

2.3.2 | Amino acid substitution L452R

L452R is found in the Delta variant and refers to the amino acid change from leucine (L) to arginine (R) (Figure 2d). This RBD mutation appears to enhance ACE2 receptor binding affinity and can diminish the interaction with vaccine-elicited antibodies.[35] Moreover, it could provide resistance to T cells, which are essential to target and destroy virus-infected cells.[36]

2.3.3 | Amino acid substitution E484K

The amino acid substitution E484K, also known as Eeek, indicates a change from glutamic acid (E) to lysine (K) at position 484. This missense mutation is shared by Beta and Gamma VOCs.[37] Eeek could improve the capability to escape the immune system by affecting antibody recognition. As a consequence, it could alter the effectiveness of current vaccines.[38]

2.3.4 | Amino acid substitution N501Y

The amino acid substitution N501Y, nicknamed Nelly, is shared by Alpha (Figure 2a), Beta and Gamma VOCs. The change from

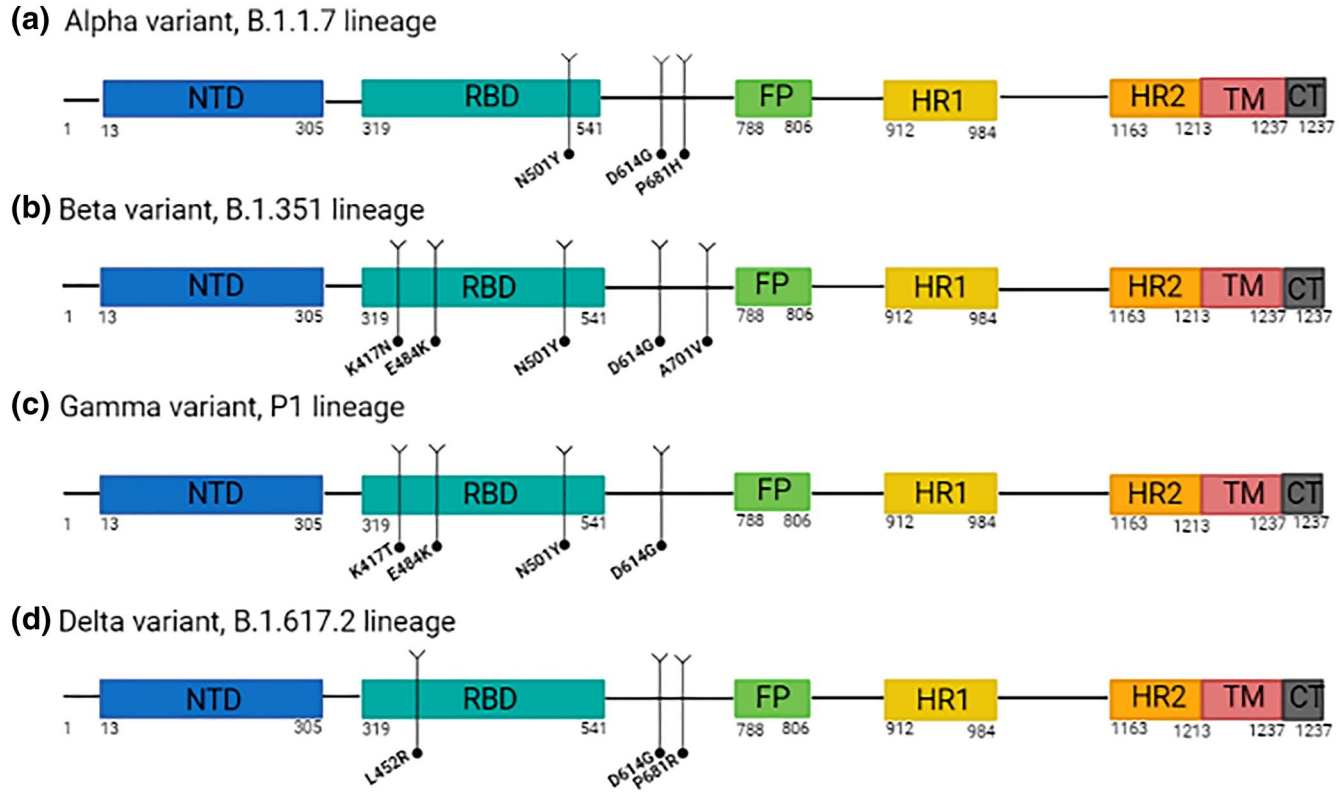

FIGURE 2 Important amino acid mutations in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein rendering variants of concern shown on an SARS-CoV-2 genome representation, and focused on the spike protein. (a) Important amino acid substitutions in the spike glycoprotein of the Alpha variant, B.1.1.7 lineage. (b) Notable spike mutations of the SARS-CoV-2 Beta variant, B.1.351 lineage. (c) Relevant amino acid substitutions in the spike of the SARS-CoV-2 Gamma variant, P.1 lineage. (d) Relevant amino acid substitutions in the spike of the SARS-CoV-2 Delta variant, B.1.617.2 lineage. Figure generated with BioRender. FP, fusion peptide; NTD, N-terminal domain; RBD, receptor-binding domain; TM, transmembrane domain

TABLE 1 Current variants of concern and spike mutations of interest

WHO name	Lineage + additional mutations	Name	Key spike protein mutations	Month and year of first detection	Country of first detection	Date of designation	Concern
Alpha	B.1.1.7	VOC-202012/01	N501Y D614G P681H	Sep 2020	United Kingdom	18 Dec 2020	- Increased transmissibility - Increased severity - Increased transmissibility
Beta	B.1.351	501 Y.V2	K417N E484K N501Y D614G	Oct 2020	South Africa	18 Dec 2020	- Increased transmissibility - Increased severity - Possible reduction of vaccine effectiveness
Gamma	P.1	VOC-202101/02	K417T E484K N501Y D614G	Jan 2021	Brazil	11 Jan 2021	- Increased transmissibility - Possible increased severity - Possible reduction of vaccine effectiveness
Delta	B.1.617.2	VOC-21APR-02	L452R D614G P681R	Dec 2020	India	11 May 2021	- Highly transmissible - Highly severe - Possible reduction of vaccine effectiveness

Abbreviations: VOC, variant of concern; WHO, World Health Organization.

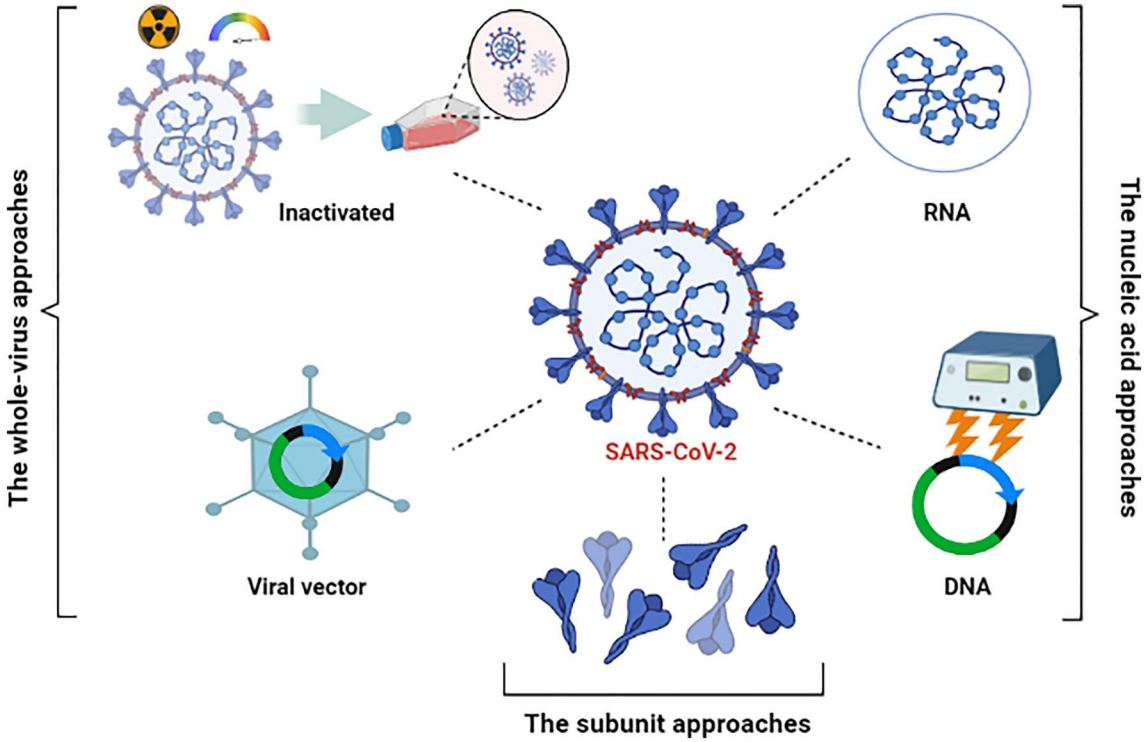

FIGURE 3 Major vaccine technology platforms are exploited for designing Covid-19 vaccines. Inactivated Covid-19 vaccines involve severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strains inactivated by radiation or high temperatures. Viral vector Covid-19 vaccines utilise an adenovirus that incorporate genetic material of the target virus. RNA-based Covid-19 vaccines are made of RNA encoding the target antigen and encapsulated within lipid nanoparticles. DNA-based Covid-19 vaccines are made of a DNA plasmid encoding the target antigen and generally administered by electroporation. The subunit Covid-19 vaccines contain purified antigens of SARS-CoV-2 that stimulate the immune system. Figure generated with BioRender

asparagine (N) to tyrosine (Y) at position 501 is believed to boost binding affinity to human ACE2.[38-40] This mutation induces higher concentrations in the pharynx and the nasal cavities, and therefore, increases its transmission rate.[41]

2.3.5 | Amino acid substitution D614G

The missense mutation D614G, also known as Doug, denotes a change from aspartic acid (D) to glycine (G) at position 614. D614G mutation is shared by all VOCs. Studies reported that it increases the transmission rate[42,43] and leads to higher infectivity of the olfactory epithelium, therefore, induces anosmia.[44]

2.3.6 | Amino acid substitutions affecting P681

P681H and P681R substitutions have been detected in Alpha and Delta, respectively. Worldwide, the prevalence of P681H has increased exponentially.[34,45] P681R is located at the furin cleavage site and increases viral fusogenicity[46] and may be associated with a higher pathogenicity.[47] Moreover, the P681R Delta spike mutation exhibits resistance to the neutralising antibodies elicited by immunisation.[48]

3 | VACCINE TECHNOLOGY PLATFORMS

Three major vaccine technology platforms are currently exploited to design safe and effective Covid-19 vaccines. These platforms are illustrated in Figure 3 and are summarised in Table 2.

3.1 | The whole-virus approach

3.1.1 | Inactivated vaccines

An inactivated vaccine contains complete viruses that have been killed by chemicals, radiation, or heat. The development of this type of vaccine requires special laboratory facilities to grow the virus safely, through a long-time production process, and requires two or three doses for effective delivery. Currently available flu and polio vaccines are examples of this type of vaccines.[49,50]

3.1.2 | Viral vector vaccines

A viral vector vaccine uses a safe virus, either replicating or non-replicating, that delivers specific components of the disease-causing virus that can stimulate the immune system while remaining

TABLE 2 Summary of SARS-CoV-2 vaccine technology platforms

Platform	Type of vaccine candidate	Immune response	Benefits	Drawbacks
Inactivated	Inactivated disease-causing virus either by chemicals, radiation or high temperature	Mostly humoral	- Well established technology - No live components - Relatively simple to manufacture	- Risk of vaccine-enhanced disease - Booster shots may be required
Viral vector	A safe virus transfers the instructions for making antigens from the disease-causing virus into cells	Humoral and cellular	- Well established technology - Safety - Large-scale production - Strong immunogenicity	- Pre-existing immunity to the vector could reduce the immune response - Relatively complex to manufacture
RNA	Lipid nanoparticle encapsulated mRNA of a disease-causing virus	Humoral and cellular	- Relatively simple to manufacture - Fast development - No live components, so no risk of the vaccine triggering disease	- Lipid nanoparticles require ultra-cold storage - Never been licensed in humans
DNA	DNA of the disease-causing virus delivered by electroporation	Humoral and cellular	- Relatively simple to manufacture - Electroporation generates a robust immune response - No live components, so no risk of the vaccine triggering disease	- Electroporation may be complicated - Different distribution systems may be required - Never been licensed in humans
Subunit	One or more antigens of the disease-causing virus	Humoral and cellular	- Well established technology - No live components, so no risk of the vaccine triggering disease - Relatively stable	- Relatively complex to manufacture - Adjuvants may be required - Determining the best antigen combination takes time

harmless. The virus vector carries target viral proteins into the human body in order to enhance the immune response. For example, the Ebola vaccine (Ad26.ZEBOV) consists of a human non-replicating adenovirus 26 vector, containing the Ebola virus Mayinga variant glycoprotein.[51,52]

3.2 | The nucleic acid approaches

The nucleic acid platform uses genetic information, either DNA or mRNA, to provide instructions to cells to produce specific proteins, not the entire virus.[53] No gene-based vaccines had been approved before the Covid-19 outbreak.[54]

3.3 | The subunit approaches

A subunit vaccine uses one or more purified antigens that can trigger the immune system.[55] It does not introduce the whole pathogen and does not require a safe viral vector. The Heplisav-B vaccine is an example of an approved subunit vaccine produced by yeast cells. It is based on the expression of the hepatitis B virus surface protein.[56]

4 | LEADING COVID-19 VACCINE CANDIDATES

Nine vaccine candidates based on the Wuhan-Hu-1 strain have led the Covid-19 vaccine quest. They showed over 50% effectiveness against symptomatic cases and good efficacy against VOCs. However, some rare side effects have been reported after vaccination (Table 3).

4.1 | Covid-19 vaccines based on attenuated SARS-CoV-2 virus

4.1.1 | Sinopharm BBIBP-CorV Covid-19 vaccine

Sinopharm BBIBP-CorV is an inactivated vaccine candidate produced by the Sinopharm's Beijing Institute of Biological Products (China). A sample of the WT virus (HB02 strain) was cultivated in Vero cells, chemically inactivated by β-propiolactone, then mixed with an aluminium-based adjuvant.[72] An interim analysis of the phase 3 study demonstrated that the vaccine was 78.1% effective against symptomatic Covid-19 cases.[57] A research study carried out with 282 individuals from Sri Lanka who received the vaccine preparation showed a 10-fold reduction in neutralising antibody (nAb) titres against Beta and 1.38-fold reduction against Delta, as compared with reference strain.[88]

TABLE 3 Characteristics of leading Covid-19 vaccines

	BBIBP-CorV	CoronaVac	Covaxin	AZD1222	Ad26.COV2.S	Sputnik V	mRNA-1273	BNT162b2	NVX-CoV-2373
Developer	Sinopharm	Sinovac Biotech	Bharat Biotech	University of Oxford and AstraZeneca	Janssen and Johnson & Johnson	Gamaleya	Moderna and NIAD	Pfizer and BioNTech	Novavax and CEPI
Type of vaccine	Inactivated virus	Inactivated virus	Inactivated virus	Chimpanzee adenoviral vector	Human adenoviral vector	Human adenoviral vectors (two serotypes)	mRNA	mRNA	Protein subunit
Target antigen	Whole virus	Whole virus	Whole virus	S protein	S protein	S protein	S protein	S protein	S protein
Storage	2–8°C[57]	2–8°C[58]	2–8°C[59]	2–8°C (6 months)[60]	2–8°C (3 months)[61]	−18°C (frozen)	−75°C (long period)	−80°C to −60°C[62]	2–8°C[63]
						2–8°C (lyophilised)[64]	−25°C (1 month)[65]		
Dose	4 μg in 0.5 mL[66]	3 μg in 0.5 mL[67]	6 μg[59]	0.5 mL[68]	0.5 mL (5×10^{10} virus particle)	0.5 mL (frozen)1.0 mL (lyophilised)[64]	0.5 mL (100 μg of mRNA)[69]	0.3 mL (30 μg of mRNA)[70]	5 μg of the recombinant vaccine + 50 μg of matrix-M1 adjuvant[71]
Dosage number	Two 21 days apart[57]	Two 14 days apart[58]	Two 28 days apart[59]	Two 12 weeks apart[a,60,68]	One[61]	Two 21 days apart[64]	Two 28 days apart[69]	Two 21 days apart[70]	Two 21 days apart[63]
Preclinical animal testing	Rats, mice, rabbits, guinea pigs, monkeys[72]	Mice, Wistar rats, monkey[73]	Hamsters, monkeys, mice, rats, rabbits[74,75]	Monkeys, guinea pigs[76,77]	Monkeys, hamsters[78,79]	Monkeys, ferrets[80]	Monkeys[81]	Monkeys, mice[82]	Monkeys, mice, baboon[83,84]
Subject age	≥18 years	≥18 years	≥18 years	≥18 years	≥18 years	≥18 years	≥18 years	≥16 years	≥18 years
Efficacy against symptomatic Covid-19	78.1%	50.7%	77·8%	81.3%[a]	66%	91.6%	94.1%	95%	96.4%
Efficacy against alpha[b]	N.R	N.R	N.R	74.5%	N.R	N.R	100% (Qatar study)	93.7%	86.3%
Efficacy against Beta[b]	N.R	N.R	N.R	10.4%	N.R	N.R	96.4% (Qatar study)	75%	51%
Efficacy against gamma[b]	N.R	N.R	N.R	77.9%	N.R	N.R	N.R	-	N.R
Efficacy against delta[b]	N.R	59.0%	65.2%	67%	N.R	90%	N.R	88%	N.R
Most common side effects	Injection site pain, fever, headache, fatigue[66]	Injection site pain, headache, fatigue[85]	Injection site pain, headache, fatigue, fever[59]	Injection site pain, fever, headache[60]	Injection site pain, headache, fatigue, muscle pain, nausea[86]	Injection site pain, hyperthermia, headache, asthenia, muscle and joint pain[80]	Local injection-site reactions, fever, fatigue, headache[87]	Local post-injection pain, fatigue, headache[62]	Injection site pain and tenderness, fatigue, headache, muscle pain[63]
Safety concern	N.R	PR, ReA	N.R	TTS	Anaphylaxis, TTS, CVST, GBS, myocarditis	N.R	Anaphylaxis, myocarditis	Anaphylaxis, myocarditis	N.R

Abbreviations: CEPI, Coalition for Epidemic Preparedness Innovations; CVST, cerebral venous sinus thrombosis; GBS, Guillain–Barré syndrome; N.R, not reported; PR, Pityriasis rosea; ReA, reactive arthritis; TTS, thrombosis and thrombocytopenia syndrome; VE, vaccine efficacy.

[a]When prime-boost doses injected at +12 weeks.

[b]VE against symptomatic infection.

4.1.2 | SinoVac CoronaVac Covid-19 vaccine

CoronaVac is an inactivated vaccine candidate manufactured by the biopharmaceutical company SinoVac (Beijing, China). Isolated SARS-CoV-2 virus (CN2 strain) was cultured in Vero cells, chemically inactivated using β-propiolactone, and mixed with alum adjuvant.[73] Phase 3 trial conducted in Brazil showed that VE to prevent symptomatic Covid-19 was 50.7%.[85] Lab studies revealed that the vaccine had a vaccinee serum less effective in neutralising B.1.1.7. However, nAb activity was significantly reduced for B.1.351 and P1 by a factor of 5.27 and 3.92, respectively.[89,90] Other data confirmed the reduced nAb activity against P1 lineage, compared with WT lineage.[91] Another lab study demonstrated that CoronaVac has an estimated VE of 59% against Delta.[92]

Akdas et al.[16] described a case report of pityriasis rosea (PR) in a 45-year-old woman with no history of allergies. PR was developed 4 days after receiving the first dose. Skin rashes were also reactivated 4 days after receiving the second dose and faded within 7 days. Reactive arthritis (ReA) was also described in a 23-year-old female who had a painful left knee for 18 days after CoronaVac immunisation. Her health condition was back to normal within 4 weeks of follow-up.[17]

4.1.3 | Bharat Biotech BBV152/Covaxin Covid-19 vaccine

BBV152, also known as Covaxin, is a Vero cell-based whole-virion inactivated SARS-CoV-2 vaccine developed by Bharat Biotech (India). It is formulated with a toll-like receptor 7/8 agonist molecule (IMDG) chemisorbed on aluminium hydroxide gel.[93]

Phase 3 trial in India showed that BBV152 is 77.8% effective against symptomatic cases and confers 65.2% protection against Delta variant.[94] De Souza et al.[95] reported that the convalescent sera of recipients of BBV152 failed to efficiently neutralise P.1 lineage. Further studies demonstrated that BBV152 has equivalent nAb titres to Alpha,[96] a threefold reduction in neutralisation activity against Beta variant and promising effect in neutralising the Delta VOC.[97]

4.2 | Covid-19 vaccines based on adenoviral vectors

4.2.1 | Oxford-AstraZeneca AZD1222 Covid-19 vaccine

AZD1222, known as ChAdOx1 nCoV-19, is a chimpanzee-based nonreplicating adenovirus vaccine vector (ChAdOx1). It contains the full-length S protein with an adjuvant sequence (tissue plasminogen activator).[76,98] AZD1222 was developed by Oxford University and the Sweden-based pharmaceutical company AstraZeneca.[60] Analysis in the United Kingdom, Brazil, and South Africa indicated that the AZD1222 vaccine was 81.3% effective at preventing symptomatic Covid-19 in participants who received two doses spaced within ≥12 weeks.[68] A study in the UK showed that ChAdOx1 nCoV-19 confers 74.5% protection against Alpha and 67.0% protection against Delta.[99] It is also 77.9% effective against Gamma[100]: however, it is only 10.4% effective against Beta.[101]

In mid-March, AZD1222 was suspended in 18 European and Asian countries following cases of thrombosis and thrombocytopenia syndrome (TTS) and deaths in some immunised people after exposure to the vaccine.[102] Two weeks later, the Medicines and Healthcare products Regulatory Agency reported 30 cases, including seven deaths, of blood clot events among 18.1 million doses of the AZD1222 vaccine.[103] Schultz et al.[11] and Tiede et al.[104] reported 10 cases of venous thrombosis and thrombocytopenia that occurred 5 to 11 days after prime vaccination in patients aged between 34 and 67 years old. All the cases had noticeably high levels of auto-antibodies to platelet factor 4 (PF4), although without previous exposure to heparin.[11,104]

4.2.2 | Janssen AD26.CoV2.S Covid-19 vaccine

Ad26.COV2.S was manufactured by Janssen Vaccines of Johnson & Johnson. It is composed of a non-replicating adenoviral vaccine (adenovirus serotype 26, Ad26) encoding a prefusion-stabilised SARS-CoV-2 S glycoprotein, which contains a mutation at the furin cleavage site and two proline stabilising mutations.[78] An interim analysis of the phase 3 trial showed that VE was 66% against symptomatic disease.[61] VE remained high even in South Africa and Brazil where new variants predominate.[61] A research study revealed a fivefold reduction in nAb activity against the Beta strain and a 3.3-fold reduction against the Gamma strain, as compared with the original strain. nAb titres were stable against Alpha, but a modest 1.6 fold reduction in neutralising activity was seen against Delta as compared with the B.1 lineage (the first variant of SARS CoV-2, D614G).[105]

Cases of TTS were reported in women aged between 18 and 49 years old at a rate of about 1 per 7 million.[106] For men of all ages and older women, TTS is even rarer. Sadoff et al.[107] described a case report of extensive thrombosis associated with severe thrombocytopenia and disseminated intravascular coagulation in a 25-year-old man who had received the Ad26.COV2.S vaccine 14 days before the appearance of symptoms. From 1 March to 21 April 2021, 12 US participants were reported with cerebral venous sinus thrombosis and thrombocytopenia.[12] All cases were women aged from 18 to younger than 60 years, and 25% of them died. During the same period, four cases of anaphylaxis were also reported, but none of them resulted in death.[14] In late June 2021, 108 cases of Guillain–Barré syndrome (GBS) were also reported, and one of them resulted in death.[15] Lately, Nassar et al. reported one case of a myocarditis-related death in a 70-year-old woman, 2 days after receiving the vaccine.[108]

4.2.3 | Gamaleya Sputnik V Covid-19 vaccine

Sputnik V was manufactured by the Gamaleya Research Institute of Epidemiology and Microbiology (Russia). It is an adenovirus-based vaccine composed of two adenoviral vectors (Ad26 and Ad5) carrying the gene coding for full-length S protein.[64]

Interim analysis of the phase 3 study showed that the VE of Sputnik V was 91.6% against symptomatic Covid-19.[80] In Argentina, 12 serum samples were collected from recipients of the vaccine to characterise its neutralisation activity.[109] Results showed that it efficiently neutralised the S protein of the B.1.1.7 variant and the B.1 lineage. However, the same sera had moderately reduced activity against the S protein of the Gamma variant carrying the E484K mutation alone, and a markedly reduced neutralising activity against the S protein of the Beta strain.[109] At the end of June 2021, Sputnik V developers announced that the vaccine was around 90% effective against the Delta variant.[110]

4.3 | Covid-19 vaccines based on RNA

4.3.1 | Moderna mRNA-1273 Covid-19 vaccine

The mRNA-1273 vaccine was developed by Moderna and the National Institute of Allergy and Infectious Diseases. The mRNA is encapsulated in lipid nanoparticles (LNPs) and encodes the full-length S antigen, with a transmembrane anchor and an S1-S2 cleavage site. Two proline subunits were included in the S2 to stabilise the S protein in its prefusion conformation, and therefore improve its immunogenicity.[69]

An interim analysis of the phase 3 clinical trial showed that the vaccine had 94.1% efficacy in preventing symptomatic infections[111] The RBD mutations found in the UK, South Africa, and Brazil variants decrease the VE by a small, but significant margin.[112] Shen et al.[113] further confirmed that Alpha remains sensitive to neutralisation by serum samples from recipients of mRNA-1273. Another study from Qatar indicated that the vaccine is highly effective against Alpha and Beta infections. Two weeks after the boost dose, mRNA-1273 was 100% effective against Alpha and 96.4% effective against Beta.[114] The neutralising activity against VOCs was further evaluated by Choi et al.[115] Studies indicated minimal effects on neutralising Alpha, whereas nAb activity against Beta, Gamma, and Delta variants decreased from 2.1-fold to 8.4-fold, as compared with the original virus.

Between 21 December 2020, and January 2021, over 4 million doses of mRNA-1237 were delivered. At the same period, 10 cases of anaphylaxis were reported after administration of the first dose.[116] No anaphylaxis-related deaths were reported. Since April 2021, cases of myocarditis have been reported within several days after the immunisation with mRNA Covid-19 vaccination, including Moderna and Pfizer vaccines. Described cases have occurred mainly in male adolescents and young adults after the boost dose.[18]

4.3.2 | BioNTech – Pfizer BNT162b2 Covid-19 vaccine

BNT162b2 was prepared by BioNTech with support from the pharmaceutical company Pfizer.[62] The mRNA is packaged in LNP and encodes the entire spike protein, modified after including two prolines in one of the subunits to stabilise the prefusion conformation and increase its immunogenicity.[117] The preliminary data from phase 2/3 clinical trials demonstrated that BNT162b2 had 95% efficacy in preventing symptomatic SARS-CoV-2 infections.[62]

The quick spread of UK and South Africa variants (both encoding the N501Y substitution) is of particular concern due to their location in the RBD of the S glycoprotein.[118] Reported data showed that the neutralising activity against the novel substitution was not reduced compared to the virus carrying the original Asn501.[118] Six volunteers who received two doses of the vaccine were recruited to test the effect of BNT162b2 against VOCs encoding E484K-, N501Y- or K417N/E484K/N501-mutant S proteins.[112] Data revealed that RBD mutations found in Alpha, Beta, and Gamma variants can decrease the efficacy of the vaccine by a small, but significant margin.[112] Tauzin et al.[119] further showed that a single dose of the vaccine boosts strong nAb capable to neutralise different spike mutations – including E484K, S477N, N501Y, and N501S. Later, Lopez Bernal et al.[99] revealed that VE was 93.7% and 88.0% against the Alpha and Delta variants, respectively. Moreover, BNT162b2 is 75% effective against Beta[120] and retains broad efficacy against the Gamma in people aged 80–96 years of age.[121]

Anaphylaxis was reported in a small number of people who received the Pfizer-BioNTech vaccine.[13] However, it was safe for recipients without previous allergic susceptibility to vaccine's components. A pooled analysis showed that myocarditis mainly occurs following the administration of the boost dose of BNT162b2 in males over the age of 16. All affected individuals recovered quickly.[122]

4.4 | Covid-19 vaccines based on subunit particles

4.4.1 | Novavax NVX-CoV2373 Covid-19 vaccine

NVX-CoV2373 was co-developed by the American biotechnology Novavax and the Coalition for Epidemic Preparedness Innovations foundation. The recombinant subunit vaccine was produced in the baculovirus- Sf9 insect cell expression system. It contains the full-length S glycoprotein stabilised in the prefusion conformation with a saponin-based Matrix-M™ adjuvant.[83,84] During predominant transmission of B.1.351 in South Africa, the phase 2a-b clinical trials indicated that NVX-CoV2373 confers cross-protection against Beta variants.[123] In fact, the recombinant vaccine is 51% effective against B.1.351 in HIV-negative volunteers. Phase 3 clinical trials showed that Novavax provided 96.4% protection against symptomatic Covid-19 and 86.3% against the Alpha variant.[71]

5 | PROMISING COVID-19 VACCINE CANDIDATES

Although many Covid-19 vaccines have been developed so far, additional effective vaccines are still needed to fight Covid-19. Promising Covid-19 vaccines with different mechanisms of action have demonstrated excellent safety and clinical efficacy profiles in clinical trials (Table 4).

5.1 | Covid-19 vaccines based on attenuated SARS-CoV-2 virus

5.1.1 | Sinopharm WIBP-CorV Covid-19 vaccine

WIBP-CorV is an inactivated SARS-CoV-2 vaccine candidate produced by the Chinese Sinopharm's Wuhan Institute of Biological Products and Wuhan Institute of Virology. An isolated SARS-CoV-2 strain (WIV-04) was cultivated in Vero cells, chemically inactivated by β-propiolactone, then mixed with an aluminium-based adjuvant.[129,130] Phase 1 and 2 trials revealed that WIBP-CorV had a low rate of side effects and good immunogenicity.[129] The interim analysis of phase 3 clinical trials showed that the vaccine is 72.8% effective against symptomatic Covid-19 cases and 100% against severe disease.[57]

5.2 | Covid-19 vaccines based on adenoviral vectors

5.2.1 | CanSino Bio Convidecia/AD5-nCOV Covid-19 vaccine

AD5-nCOV, also known as Convidecia, was developed by CanSino Biologics in cooperation with the Academy of Military Medical Sciences. It is an adenovirus-based vaccine composed of a replication-defective adenovirus type 5 vector (Ad5) incorporating the full-length gene coding for the S protein.[124] A phase 1 clinical trial demonstrated that Convidecia is safe, tolerable, and can induce humoral and cellular responses.[124] The phase 2 study showed that AD5-nCOV induced specific nAb and T cell responses.[139] In February 2021, the Pakistan subset trial indicated that AD5-nCOV is 65.7% effective at preventing symptomatic cases and 100% effective at preventing severe disease.[140]

5.3 | Covid-19 vaccines based on DNA

5.3.1 | Zydus Cadila ZyCoV-D Covid-19 vaccine

ZyCoV-D, the world's first plasmid DNA vaccine for human use, was prepared by Zydus Cadila, India. It comprises a DNA plasmid vector pVAX1 carrying the gene encoding the S glycoprotein plus the sequence encoding for the IgE signal peptide. The DNA plasmid construct was transformed into *Escherichia coli* DH5-alpha™ chemically competent cells.[131,132,137] ZyCoV-D is the first Covid-19 vaccine approved for young adults older than 12 years.[125] The phase 1 part of the phase 1/2 clinical trial found the DNA vaccine candidate safe and tolerable.[137] Moreover, ZyCoV-D induces antibody responses against S glycoprotein and nAb against WT virus strain. Interim data from the phase 3 clinical trial reported an efficacy of 66.6% against symptomatic cases.[141]

5.4 | Covid-19 vaccines based on RNA

5.4.1 | CureVac N.V. CureVac/CVnCoV Covid-19 vaccine

CVnCoV was developed by the biopharmaceutical company CureVac N.V. Unlike its competitors (Pfizer-BioNTech and Moderna vaccine candidates), it uses a natural RNA. CureVac is an LNPs encapsulated mRNA vaccine that encodes the full-length S glycoprotein.[128]

Interim data from phase 1 clinical trials showed that CVnCoV was safe and tolerable in all participants.[138] Furthermore, the mRNA vaccine induces strong nAb responses even at the lowest doses tested.[138] The primary data of the phase 2b/3 clinical trials indicated that the non-chemically modified mRNA is 48.2% effective against symptomatic Covid-19 cases, 70.7% against moderate-to-severe disease, and 100% against hospitalisation and death.[142] However, only 3% of the sequenced Covid-19 cases were WT SARS-CoV-2.

5.5 | Covid-19 vaccines based on subunit particles

5.5.1 | VECTOR Institute EpiVacCorona Covid-19 vaccine

EpiVacCorona is Russia's second Covid-19 vaccine candidate. This subunit vaccine candidate was prepared by the VECTOR Institute based on three chemically synthesised peptides of the S glycoprotein, expressed as a chimeric protein (with *E. coli* maltose-binding protein).[126] The phase 1/2 clinical trials showed that EpiVacCorona is safe and immunogenic. All the recipients of the peptide-base vaccine developed specific nAb against SARS-CoV-2 antigens 42 days following the first vaccination.[126]

5.5.2 | Anhui Zhifei ZF2001 Covid-19 vaccine

ZF2001 was co-developed by the Chinese Anhui Zhifei Longcom and the Academy of Military Medical Sciences. The recombinant subunit vaccine contains the dimeric form of the RBD of the S protein and a conventional alum adjuvant.[127] Phase 1 and 2 trials

TABLE 4 Characteristics of promising Covid-19 vaccines

	WIBP-CorV	Convidecia	ZyCoV-D	CVnCoV	EpiVacCorona	ZF2001
Developer	Sinopharm	CanSino Biologics	Zydus Cadila	CureVac N.V.	Vector institute	Anhui Zhifei Longcom
Type of vaccine	Inactivated virus	Human adenoviral vector	DNA	mRNA	Protein subunit	Protein subunit
Target antigen	Whole virus	S protein	S protein	S protein	S protein	S protein
Storage	2–8°C[57]	2–8°C[124]	2–8°C[125]	5°C	2–8°C (2 years)[126]	2–8°C[127]
				2–8°C (3 months)[128]		
Dose	5 μg in 0.5 mL[129]	(5×10^{10} virus particle)[124]	2 mg in 0.2 mL[125]	12 μg[128]	N.R	25 μg[127]
Dosage number	Two 21 days apart[57]	One[124]	Three 28 days apart[125]	Two 28 days apart[128]	Two 21 days apart[126]	Three 4 weeks apart[127]
Preclinical animal testing	Mice, rats, guinea pigs, rabbits, monkeys[130]	N.R	Mice, rats, guinea pigs, rabbits, monkeys[131,132]	Monkeys, rodents[133-135]	Hamsters, ferrets, monkeys[126]	Monkeys, mice, hamsters, ferrets[136]
Subject age	≥18 years of age	≥18 years of age	≥12 years of age	≥18 years of age	≥18 years of age	≥18 years of age
Full authorisation	China	China	None	N.R	Turkmenistan	None
Emergency authorisation	North Macdonia, Peru, Philippines, United Arab Emirates, Venezuela	Argentina, Chile, Ecuador, Hungary, Malaysia, Mexico, Indonesia, Moldova, Pakistan	India	N.R	Russia, Belarus	China, Indonesia, Uzbekistan
Efficacy against symptomatic infection	72.8%	65.7%	66.6%	48.2%	O.U	0.U
Most common side effects	Injection site pain, fever[129]	Pain at the injection site, fever, fatigue, headache, muscle pain[124]	Tenderness at the site of injection[137]	Injection site pain, headache and fatigue followed by myalgia and chills[138]	Short-term pain at the injection site[126]	Injection site pain, fever[127]
Safety concern	N.R	N.R	N.R	N.R	N.R	N.R

demonstrated that the RBD-vaccine induced high nAb titres and cytokines associated with T-helper 1 and T-helper 2 cells.[127] Recent data showed that RBD-vaccine retained neutralising effects against Beta and Gamma variants and preserved its neutralising activity against Delta strain.[143]

6 | CONCLUSIONS AND FUTURE PERSPECTIVES

The first generation of Covid-19 vaccines focusing on the spike glycoprotein has shown promise in diminishing the spread of Covid-19. However, the VE of current vaccines was affected by locally circulating variants. This review article suggests that frontrunners Covid-19 vaccines have good neutralising activity against the Alpha strain, an intermediate impact on Gamma and Delta strains, and a reduced effect on the Beta strain. Nevertheless, long-term evaluation of neutralising activity is needed to evaluate the persistence of protective antibodies against novel variants.

Rare adverse events have also been reported following Covid-19 immunisation – including TTS, anaphylaxis, myocarditis, and GBS. Although Ad26.CoV.S vaccine alleviates all these rare side effects, anaphylaxis and myocarditis mainly occur after immunisation with mRNA-Based vaccines, and thrombosis thrombocytopenia syndrome is associated with adenoviral vector-based vaccines. More research is needed to fully understand the link between Covid-19 vaccines and rare side effects and long-term investigation is further required to assess delayed reactions to immunisation.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The author confirms sole responsibility for the following: study conception and design, data collection and processing, analysis and interpretation of results, and manuscript preparation.

DATA AVAILABILITY STATEMENT

All data used are available in this review.

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