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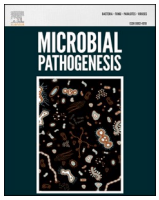

Novel coronavirus mutations: Vaccine development and challenges

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ABSTRACT

The ongoing global pandemic of novel coronavirus pneumonia (COVID-19) caused by the SARS-CoV-2 has a significant impact on global health and economy system. In this context, there have been some landmark advances in vaccine development. Over 100 new coronavirus vaccine candidates have been approved for clinical trials, with ten WHO-approved vaccines including four inactivated virus vaccines, two mRNA vaccines, three recombinant viral vectored vaccines and one protein subunit vaccine on the "Emergency Use Listing". Although the SARS-CoV-2 has an internal proofreading mechanism, there have been a number of mutations emerged in the pandemic affecting its transmissibility, pathogenicity and immunogenicity. Of these, mutations in the spike (S) protein and the resultant mutant variants have posed new challenges for vaccine development and application. In this review article, we present an overview of vaccine development, the prevalence of new coronavirus variants and their impact on protective efficacy of existing vaccines and possible immunization strategies coping with the viral mutation and diversity.

1. Introduction

There are seven known coronaviruses that infect humans, namely, HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV (severe acute respiratory symptom coronavirus), MERS-CoV (Middle Eastern respiratory syndrome-related coronavirus), and SARS-CoV-2. The most recent SARS-CoV-2 is the pathogen of Corona Virus Disease 2019 (COVID-19), leading to ongoing global pandemic [1,2], has resulted in a significant impact on global health and economy system. Since the outbreak of COVID-19 in the late December 2019, over 543 million confirmed cases of COVID-19, including nearly 6.4 million deaths, have been reported to the World Health Organization (WHO) by late June 2022.

SARS-CoV-2 has a diameter between 70 and 120 nm and contain segmented single-stranded RNA of 26–32 kb [3,4], encoding four structural proteins: envelope (E) protein, membrane (M) protein, nucleocapsid (N) protein and spike glycoprotein (S protein) [4–6]. The S protein binds to angiotensin converting enzyme 2 (ACE2) [7], the host cell surface receptor, and mediates viral entry through virus-cell membrane fusion [8]. The S protein is a homotrimeric glycoprotein consisting of two subunits, S1 and S2 [9]. The S1 subunit contains four structural domains: a N-terminal domain (NTD), a receptor binding domain (RBD) and two C-terminal domains (CTD1 and CTD2). The RBD in the S1 subunit is responsible for recognizing and binding ACE2, and has two different conformational states, "open" and "closed" [10]. Only in the "open" state, the receptor binding motif (RBM) of RBD can be protruded out of the glycan shield and bind to the ACE2 receptor [11–13]. S protein has been identified as key immunogenic proteins that can be used for vaccine design. As of June 26, 2022, a total of 11.9 billion doses of vaccines were administered globally [14]. In China, the domestic epidemic was under control, but the imported cases from abroad still pose a continuous challenge to China. Given the complex situation at home and abroad, over 3 billion doses of vaccines were used in China [15]. According to a large-scale cohort study by the Chinese Center for Disease Control and Prevention, more than 19% of patients with confirmed COVID-19 infection will develop severe or critical illness [16]. Although the global epidemic of COVID-19 has been largely curbed due to wide use of vaccines, with the mutation of SARS-CoV-2, the outbreak and spread of new SARS-CoV-2 mutants pose a major threat in some countries [17]. The new mutant strains will also lead to investment in the technology essential for vaccines innovation.

2. Overview of vaccine development

As of the end of December 2021, the total number of SARS-CoV-2 vaccine R&D announced by WHO is 365, including 167 in clinical trials and 198 in pre-clinical trials [18]. There are seven types of SARS-CoV-2 vaccine candidates: protein subunit (PS), viral vector (VV), DNA vaccine, inactivated virus (IV), RNA vaccine, virus like particle (VLP), live attenuated vaccine (LAV) and bacterial antigen-spore expression vector (BacAg-SpV). According to the data published by WHO, the number and proportion of these vaccine types are shown in Fig. 1. Recombinant protein vaccines account for the highest proportion by 36%, including protein subunit vaccines (32%) and virus-like particle

Abbreviations: IL-6, interleukin-6; PD-1, programmed cell death-1; TIM-3, T cell immunoglobulin domain and mucin domain-3.

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Abbreviations

COVID-19 coronavirusdisease 2019
SARS-CoV severe acute respiratory symptom coronavirus
MERS-CoV Middle Eastern respiratory syndrome-related coronavirus
SARS-CoV-2 severe acute respiratory syndrome coronavirus 2
WHO World Health Organization
ACE2 angiotensin converting enzyme inhibitor 2
NTD N-terminal domain
RBD receptor binding domain
CTD C-terminal domains
RBM receptor binding motif
R&D research and development
PS protein subunit
VV viral vector
IV inactivated virus
VLP virus like particle
LAV live attenuated vaccine
BacAg-SpV bacterial antigen-spore expression vector
Ad5 adenovirus type-5
VOC Variants of Concern
VOI Variants of Interest
VE vaccine efficacy
TLR toll-like receptor
PAPE Particulate alum via Pickering emulsion
LNPs lipid nanoparticles
BCR B-cell receptor
AAVP adeno-associated virus phage
Th2 T helper type 2
Th17 T helper type 17
IL-17 interleukin-17
GM-CSF granulocyte-macrophage colony-stimulating factor
HIV human immunodeficiency virus

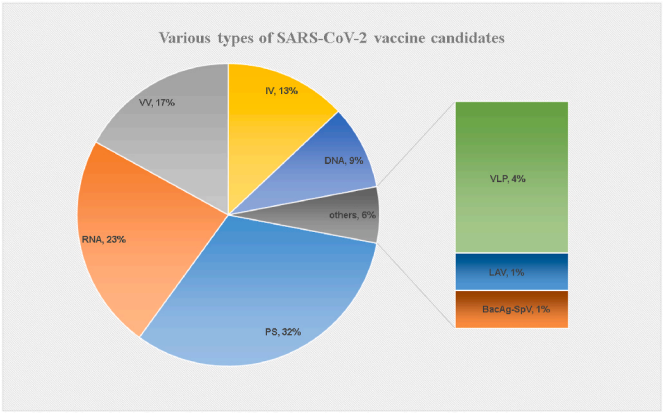

Fig. 1. Percentage of various types of SARS-CoV-2 vaccine candidates. According to the data published by WHO, the number and proportion of these vaccine types are summarized. Recombinant protein vaccines account for the highest proportion by 36%, including protein subunit vaccines (32%) and virus-like particle vaccines (4%), followed by RNA vaccines (23%), viral vector vaccines (17%) and inactivated virus vaccines (13%), DNA vaccines (9%), LAV (1%) and BacAg-SpV (1%).
Abbreviation: WHO: World Health Organization; PS: protein subunit; VV: viral vector; IV: inactivated virus; VLP: virus like particle; LAV: live attenuated vaccine; BacAg-SpV: bacterial antigen-spore expression vector.

vaccines (4%), followed by RNA vaccines (23%), viral vector vaccines (17%), and inactivated virus vaccines (13%) [19]. Inactivated vaccines are usually made from highly immunogenic pathogens that are cultured in large scale and inactivated by physicochemical methods [20], while live attenuated vaccines are made from attenuated viruses. Researchers hope to identify cross-protective strains of animal coronaviruses that are not pathogenic to human for subsequent development of novel coronavirus vaccines [21]. Recombinant protein vaccines are made by construction of viral target antigen gene expressing vector and transformation in bacterial, yeast, insect and mammalian expression systems [22,23]. The principle of viral vector vaccines is introducing the S protein coding gene into an non-replicative adenovirus, which is then used to infect host cells to express the S protein and elicit immune responses [24]. RNA vaccines are based on the introduction of the messenger RNA of the S protein and subsequent expression in the host cell [25–27]. Subunit protein vaccines utilize purified viral protein to train the immune system, instead of injecting inactivated whole pathogens to trigger an immune response. These fragments are incapable of replicating and causing viral diseases, thus the corresponding vaccines considered very safe. RNA and viral vector vaccines are not only faster to develop than other types of vaccines in the past, but are also easier to be modified to fight against new viral variants [28].

As of August 11, 2022, ten COVID-19 vaccines have been included in the WHO-certified “Emergency Use Listing”, namely four inactivated vaccines (Sinopharm BIBP, Sinovac-CoronaVac, Bharat BBV152 and the Valneva VLA2001 vaccine) , two mRNA vaccines (Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273), three viral vector vaccines (COVID-19 Vaccine ChAdOx1-S, Janssen Ad26.COV2–S and Cansino Ad5-nCoV-S) and one protein subunit vaccines (Novavax NVX-CoV2373) [29,30]. These COVID-19 vaccines are shown in Table 1.

Table 1
Global use of COVID-19 vaccines.

Type	Name	Manufacturer or Developers	Doses & Route	schedule	Date of approval
Inactivated vaccine	Sinopharm vaccine	Beijing Institute of Biological Products Co., Ltd	2, i.m[a]	Day0+21/28	May 07, 2021
	Sinovac-CoronaVac vaccine	Sinovac Research and Development Co., Ltd	2, i.m	Day0+14/28	June 01, 2021
	Bharat BBV152 Covaxin vaccine	Bharat Biotech International Limited	2, i.m	Day 0 + 14	November 03, 2021
	Valneva VLA2001 vaccine	Valneva Austria GmbH	2, i.m	Day 0 + 28	August 11, 2022
mRNA	BNT162b2 vaccine	Pfize/BioNTech Fosun Pharma	2, i.m	Day0+21-28	December 31, 2020
	Moderna mRNA-1273 vaccine	Moderna/National Institute of Allergy and Infectious Diseases	2, i.m	Day0+28	April 30, 2021
Viral Vector	ChAdOx1-S [recombinant] vaccine	AstraZeneca、University of Oxford	2, i.m	Day0+56-84	April 16, 2021
	Janssen Ad26.COV2.S vaccine	Janssen Pharmaceutical Johnson & Johnson	2, i.m	Day0	March 12, 2021
	Cansino Ad5-nCoV-S vaccine	CanSino Biological Inc. /Beijing Institute of Biotechnology	2, i.m	Day0	May 19, 2022
Protein subunit	NVX-CoV2373 vaccine	Novavax Serum Institute of India	2, i.m	Day 0 + 21	December 20, 2021

[a] Intramuscular.

3. The mutation and prevalence of new coronavirus strains

SARS-CoV-2 as a RNA virus can evolve at a very rapid rate by mutation and recombination. Furthermore, the same evolutionary forces as all organisms affects the genomic mutation rate by random genetic drift and natural selection [31]. Since the outbreak of the global pandemic of novel coronavirus pneumonia disease, several circulating mutant strains have emerged with altered viral transmissibility, pathogenicity and immunogenicity [32]. Due to the possible immune escape of some viral mutations, vaccine breakthrough by new SARS-CoV-2 variants poses a great threat to the effort at the control of the pandemic. In order to effectively monitor the viral mutants, the variants of SARS-CoV-2 have been classified into two types including Variants Of Concern (VOC) and Variants Of Interest (VOI) [33]. The International Committee on Taxonomy of Viruses (ICTV) has now approved and ratified a binomial genus-species naming system for virus species. This approval came in March 2021 after the meeting of ICTV Executive Committee in October 2020 [34]. At the end of Feb. 2021, the WHO proposed a formal definition for VOC: increased transmissibility or detrimental changes in COVID-19 epidemiology; or increased virulence or changes in clinical disease manifestations; or decreased effectiveness of public health and social measures or available diagnostic tools, vaccines, and treatments. A VOI is defined as a change in the phenotype of an isolate compared to a reference isolate or a mutation in the genome of an isolate that results in an amino acid change associated with a certain or suspected phenotypic effect and cause community transmission/multiple COVID-19 cases/clusters, being detected in multiple countries. So far, Omicron has been only one globally recognized VOCs, Including BA.1, BA.2, BA.3, BA.4, BA.5 and descendent lineages. There have been four previously circulating VOCs including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2). There is no currently circulating VOIs. The basic information about the major SARS-CoV-2 variants worldwide is shown in Table 2.

The relatively rapid mutation rate in the RNA structure of the SARS-CoV-2 virus can alter the binding affinity to ACE2. Compared with the other three VOCs (Alpha, Beta, Gamma), Delta variant has two unique L452R and T478K mutations. The L452R mutation is situated in the receptor-binding motif (RBM) region of RBD region, containing residues that bind to ACE2 [35–37]. Compared to D614G alone , the L452R mutation had a higher entry efficiency into host cells in 293T cells and in human airway lung organoids [35]. Delta variant carrying T478K has a higher possibility to undergo secondary mutation in a low titer antibody

Table 2
The basic information of major SARS-CoV-2 variants.

Category	WHO label	Pango lineages	Earliest documentation	Mutations on spike gene
Previously circulating VOCs	Alpha	B.1.1.7	United Kingdom Sep-2020	H69del,V70del,Y144del,N501Y,A570D, D614G,P681H, T716,S982A, D1118H
	Beta	B.1.351	South Africa May-2020	D80A,D215G,L241del,L242del,A243del,K417 N,E484K,N501Y,D614G, A701V
	Gamma	P.1	Brazil Nov-2020	L18F,T20 N,P26S,D138Y,R190S,K417T, E484K,N501Y,D614G,H655Y,T10271,V1176
	Delta	B.1.617.2	India Oct-2020	T19R,E156del,F157del,R158G,L452R,T478K,D614G, P681R,D95ON
Currently circulating VOCs	Omicron	B.1.1.529/ BA.1	South Africa Nov-2021	A67V,H69del,V7Odel,T95I,G142del,V143del,Y144del,Y145D,N211del,L2121, G339D,S371L, S373P,S375F,K417 N,N440K,G446S,S477 N,T478K,E484A,Q493R,G496S,Q498R,N501Y,Y505H, T547K,D614G,H655Y,N679K, P681H,N764K,D796Y,N856K,Q954H, N969K. L981
		BA.2	United Kingdom February 2022	Eight unique mutation (T19I, L24del (deletion), P25del, P26del, A27S, V213G, T376A, R408S
		BA.2.12.1	United States of America Dec-2021	BA.2 + S:L452Q, S:S704F
		BA.2.75	India, May-2022	BA.2 + S:K147E, S:W152R, S:F157L, S:I210V, S:G257S, S:D339H, S:G446S, S:N460K, S:Q493R reversion
		BA.4	South Africa Jan-2022	BA.2-like constellation in the spike protein + S:del69/70, S:L452R, S:F486V, S:Q493R reversion
		BA.5	South Africa Jan-2022	BA.2-like constellation in the spike protein + S:del69/70, S:L452R, S:F486V, S:Q493R reversion

environment [38]. The two mutations could enhance the binding affinity of RBD to ACE2. Omicron variant has at least one RBD mutation in common with the other 4 VOCs. Omicron variant is the first variant carrying N501Y, E484K and S477 N together, the mutations are likely to increase ACE2 affinity by 37-fold. Indeed, K417 N, T478K, G496S, Y505H and the triple S371L, S373P, S375F reduce affinity to ACE2, while driving immune evasion [39].

The D614G mutant became dominant worldwide for a short period of time. The D614G mutation is shared by all the mutant variants declared as VOIs/previous VOIs by the WHO and CDC. The D614G mutation does not significantly impact the immune escape [40]. The D614G mutation G614 variant had an altered conformation of the RBD region, which makes it highly efficient in cleaving the furin site [41]. The glycine mutation at the 614th position disrupts the formation of a salt bridge between D614 and lysine residue (K854), which leaves RBD in an open state in the G614 variant. The open-up conformation of the RBD enables the virus to infect the host [42]. The alteration and interaction of spike protein with antibodies suggest that the D614G mutation may elevate, drop, or bring no change in the neutralization effect as it is entirely controlled by the nature of the neutralizing antibody [43].

The N501Y mutation may also contribute to the spike protein maintenance in an open state, promoting greater efficiency in viral entry, contributing to greater the agent infectivity [44]. However, the N501Y mutation alone would not be sufficient to give the virus a different fitness from that observed in the wild-type virus [45]. Although its presence reduces the neutralizing activity of *anti*-RBD antibodies from convalescent sera [46].

The E484K mutation is the most threatening mutation to immune evasion, shared by both Beta (B.1.351) and Gamma (P.1) variants. The E484K mutation is a matter of great concern to public health since it favors the virus spread, impairs the neutralizing activity of therapeutic monoclonal antibodies [47] and also gives the virus an ability to evade immunity induced by natural infection and by vaccination [48]. The E484K mutation in the SARS-CoV-2 spike protein reduces neutralization of the USA-WA1/2020 virus or a recombinant (r)SARS-CoV-2 virus. Human sera with high neutralization titers against the USA-WA1/2020 strain were still able to neutralize the E484K rSARS-CoV-2 [49].When associated with the N501Y mutation, the E484K rSARS-CoV-2 shows rapid spread and high infectivity [50], and also show a significant decrease in neutralization was observed in polyclonal neutralization assays [51]. Another mutation at the same position (E484Q) has been reported in some variants, the L452R residue mutation usually occurs coincident with E484Q and contributes to the interaction with water molecules and overall re-stabilization of the complex, maintaining high binding activity [51,52]. Although this mutation occurs simultaneously with L452R, the two mutations do not appear to have a synergistic effect on the ability of anti-RBD antibodies to neutralize this variant [53].

4. *Efficacy of existing vaccines against various SARS-CoV-2 variants*

SARS-CoV-2 undergoes rapid evolution, which is a big concern for COVID-19 vaccine development, as the evolved variants may increase viral infectivity, disease severity, re-infection risk, or antigenicity alteration, resulting in reduction of vaccine efficacy. Before November 2021 the Delta variant may pose the highest risk of all the variants currently circulating worldwide, with increased transmissibility over Alpha variant and possible vaccine breakthrough. Since it was discovered in samples from South Africa and other places in early November, Omicron has spread rapidly across the world, replaced other coronavirus strains to be currently the dominant strain circulating globally. A related study of the Delta and Omicron variants found that the Omicron variant had a significant number of mutations in the SARS-CoV-2 RBD [54]. It means the Omicron variant had a higher affinity for human ACE2 indicating a higher potential for transmission. With the spread of these variants, it is necessary to assess the protective effect conferred by current vaccines [14].

4.1. *Inactivated vaccine*

Sinopharm vaccine Both inactivated vaccines against COVID-19 (designed by Wuhan Institute of Biological Products Co., Ltd, and Beijing Institute of Biological Products Co., Ltd) have been shown to be generally safe and stimulate vaccine specific antibody production in adults in phase I/II trials [55,56]. In a Phase II trial among adults without known history of COVID-19 in the United Arab Emirates and Bahrain, these 2 vaccines provided 72.8% and 78.1% protection between symptomatic COVID-19 cases, respectively [57,58]. Baoying Huang et al. evaluated the neutralization activities of two vaccines (One is designed by Beijing Institute of Biological Products Co., Ltd, and the other one is recombinant protein vaccine from Chongqing Zhifei Biological Products Co., Ltd) against 501Y.V2. and found that the neutralizing titers largely remained constant after using these two vaccines (with slightly reduction in months) against authentic virus. Meanwhile, these two vaccines had similar efficacy against wild type and D614G mutant virus [59]. WHO currently recommends the use of Sinopharm vaccine in China even if different variants (e.g. Delta) are present in the country, but encouraging to monitor vaccine effectiveness and potential breakthrough infections [60]. Xiaoqi Yu et al.found that diminished neutralization potency against multiple variants in vaccine-elicited sera, indicating the potential need for additional boost vaccinations [61].

CoronaVac An interim analysis in Turkey indicated that, in a population aged 18–59 years, CoronaVac had high efficacy preventing symptomatic COVID-19 (83·5% relative to placebo) and COVID-19-related hospitalization (100%) at least 14 days after the second dose [62]. Data from Phase III clinical trial in Brazil for the same vaccine showed that it had the efficacy of 51% against symptomatic SARS-CoV-2 infection, 100% against severe COVID-19 and 100% against hospitalization 14 days after receiving the second dose [63,64].While there were two reported cases of breakthrough infection with the P1 variant in patients vaccinated with CoronaVac, Estofolete CF et al. suggested that the vaccination could relieve the severity of the disease and highlighted the potential risk of post-vaccination and subsequent infection with the P1 variant, as well as the lasting protection against infection in vaccinated individuals [65].

BBV152 For the phase 3 trial of the BBV152 vaccine which conducted in India, the BBV152 vaccine provided an overall estimated vaccine efficacy of 78% (95% CI: 65–86) after the second dose. Vaccine efficacy was 79% (95% CI: 66–88) in younger participants (aged < 60 years) compared to 66% (33–84)in those aged ≥60 years [66]. In other study, estimation of effectiveness against reinfection among Health Care Workers in New Delhi was conducted in the same way [67]. Nevertheless, it is necessary to confirm this preliminary efficacy against the delta variant and other VOCs. Data from the phase 3 clinical trial included individuals infected with the Delta (B.1.617.2) variant show that the efficacy of 65·2% (95% CI 33·1–83·0) against Delta, the neutralization activity induced against the delta variant was 2·7-times lower than that against the Asp614Gly variant by BBV152 [66,68]. Pragya D Yadav et al. assessed the neutralization of sera from COVID-19 recovered cases and BBV152 vaccines against Beta and Delta variants, meanwhile they found that BBV152 confer significant protection [69]. One dose of BBV152 boosted antibody titers against the Delta and the Omicron variants, but the antibody levels against the Omicron variant remained low [70].

VLA2001 The COVID-19 Valneva vaccine is a highly purified, inactivated, and adjuvanted whole virus SARS-CoV-2 vaccine. In a randomized, dose escalation, double-blind phase 1/2 clinical trial among healthy adults, the highest dose group showed statistically significantly stronger immunogenicity with similar tolerability and safety [71]. VLA2001 has a favourable tolerability profile and met superiority criteria for neutralizing antibodies and non-inferiority criterion for seroconversion rates compared with ChAdOx1-S in an interim analysis of the immunobridging phase 3 trial in the UK [72].

4.2. COVID-19 mRNA vaccine

BNT162b2 The BNT162b2 vaccine strategy involves an accelerated two-dose vaccination regimen administered 21 days apart, which has been demonstrated a 95% efficacy in persons 16 years or older [73,74]. A large study about vaccine efficacy in Israel (596,618 vaccine recipients matched to unvaccinated controls) showed that during follow-up starting 7 days after the second vaccination, vaccine protective efficacy for recorded infections was 92%, for symptomatic COVID-19 was 94%, for hospitalization was 87%, and for severe COVID-19 was 92% [75]. Gidari A et al. confirmed the low neutralization efficiency with the serum from the convalescent patients infected with B.1.1.7 and P.1 (appeared in January 2021 during the third wave) against the early strain, i.e. the clade 20A.EU1 (lineage B.1) strain I appeared in May 2020 from a symptomatic infection during the first wave of infections in Italy. Human sera induced by BNT162b2 vaccine had an equivalent neutralization effect on B.1.1.7 variant and wild-typed virus, but lower neutralization effect on P.1 variant [76]. Lustig Y et al. performed a micro-neutralization assay with sera obtained from 36 healthcare workers (31 female) after inoculation with BNT162b2 and showed that the neutralization titer against Gamma (P.1) 2.3, Beta (B.1.351) 10.4, Delta 2.1 and 2.6 variants was significantly lower when compared with the original virus [77]. During the proxy Omicron period in South Africa, Shirley Collie et al. discovered a maintenance of effectiveness of the BNT162b2 vaccine against hospital admission for Covid-19 compared with the rate associated with the delta variant earlier in 2021 [78].

Moderna mRNA-1273 In a randomized clinical trial, Baden LR et al. reported that the efficacy of mRNA-1273 (Moderna) vaccine was 94.1% in preventing symptomatic COVID-19 caused by wild-type virus [79,80]. Chemaitelly H et al. reported that the mRNA-1273 vaccine in the population of Qatar is highly effective against symptomatic or asymptomatic infection, and against COVID-19 hospitalization and death caused by B.1.1.7 and B.1.351, [81,82]. Sera from participants immunized on a prime-boost schedule with the mRNA-1273 were tested for neutralizing activity against several SARS-CoV-2 variants, compared to neutralization of the wild-type virus (designated as D614G) [83]. It showed minimal, statistically non-significant effects on neutralization titers against the B.1.1.7 variant; other VOCs such as B.1.351, P.1, and B.1.617.2, showed significantly decreased neutralization titers ranging from 2.1-fold to 8.4-fold reductions, although all remained susceptible to mRNA-1273-elicited serum neutralization. While the serum neutralization elicited by mRNA-1273 against most variants tested was reduced compared with the wild-type virus, they are still expected to be protective.

4.3. Viral vector vaccine

ChAdOx1-S According to the median follow-up of 80 days post-vaccination in clinical trials in the UK, Brazil and South Africa, the protective efficacy of participants receiving the full series of vaccines (2 doses) was 61%, with a higher tendency when prolonged the vaccination interval [84]. More recent data from the interim analyses of the trial in the USA showed an efficacy of 76% against symptomatic SARS-CoV-2 infection [85,86].Emary KRW et al. showed that the ChAdOx1 vaccine could provide protection against symptomatic infection by the lineage B.1.1.7 [87]. Studies of antibodies elicited by immunization with ChAdOx1-S showed lower neutralizing activity against B.1.351, P.1 and B.1.617 variants than the ancestral strains [88–90]. However, current evidence does indicate that higher antibody titres are associated with greater protection against severe disease [91]. It has also been shown that neutralization of some VOCs requires higher antibody levels [92].

Ad26.CoV2–S The Ad26.CoV2–S vaccine expressed a stabilized S protein from the WA1/2020 strain of SARS-CoV-2, and recently proved its protective efficacy against symptomatic COVID-19 in several geographical regions [93,94]. In clinical trials of participants receiving a single dose of Janssen vaccine, the effectiveness was 66.9% against symptomatic SARS-CoV-2 infection, 76.7% and 85.4% against severe COVID-19 14 and 28 days post-vaccination, respectively, and 93.1% against hospitalizations [95–97]. A recent Phase III efficacy trial has shown that Ad26.COV2–S provided 86%, 88% and 82% protection against severe COVID-19 disease by 28 days post-vaccination in the USA, Brazil and South Africa, respectively [98,99]. It was also shown that 69% of the sequenced COVID-19 cases in Brazil were infected with P.2 variant, and 95% cases in South Africa were B.1.351 variant [100,101]. These findings imply that the Ad26.COV2–S vaccine could provide protection against SARS-CoV-2 VOCs.

Ad5-nCoV The phase III study of this vaccine has just been reported; 28 days after vaccination, efficacy against PCR-confirmed COVID-19 was found to be 57.5% and 91.7% protective against severe COVID-19 [102]. An international, placebo-controlled, randomised phase 3 clinical trial showed that Ad5-nCoV was well tolerated and produced high levels of anti-RBD antibodies and high levels of neutralizing antibodies. It means that a single dose of the Ad5-nCoV vaccine protected against laboratory-confirmed, symptomatic COVID-19 and was highly effective against severe disease [103].

4.4. Protein subunit vaccine

NVX-CoV2373 In the phase 2a/b randomized placebo-controlled trial in South Africa , VE against mild, moderate, or severe COVID-19 was 49% (95% CI: 28–63) during a period in which Beta was predominant [104]. A phase 2 trial conducted in Australia and the United States showed that geometric mean titers (GMTs) for IgG anti-spike protein were higher than wild-type virus neutralizing antibody in the 2-dose regimen of NVX-CoV2373 [105]. In a phase 3 study conducted in the United Kingdom during a period in which the SARS-CoV-2 Alpha variant was predominant, the NVX-CoV2373 vaccine administered to adult participants conferred 89.7% protection against SARS-CoV-2 infection, and the post hoc analysis showed an efficacy of 86.3% (95% CI, 71.3 to 93.5) against Alpha [106]. A phase 3 study in Mexico and the USA during a period in which multiple variants were in circulation, showed that VE against COVID-19 was 90% (95% CI: 83–95), with a median follow-up of 64 days after the second dose [107].

4.5. Bivalent COVID-19 vaccine

The U.S. Food and Drug Administration amended the emergency use authorizations (EUAs) of the Moderna and the Pfizer-BioNTech COVID-19 Vaccine in August 31, 2022. The bivalent formulations of the Moderna and the Pfizer-BioNTech vaccine are authorized for use as a single booster dose at least two months after primary or booster vaccination, and include an mRNA component of the original strain and an mRNA component in common between the omicron variant BA.4 and BA.5 lineages [108].

FDA analyzed immune response data among approximately 600 individuals 18 years of age and their analysis indicates that the immune response against BA.1 of the participants who received the Moderna COVID-19 Vaccine, Bivalent was better than the immune response of those who had received the monovalent one [109]. The mRNA-1273.211 vaccine (50-μg) elicited robust and persistent antibody responses against multiple variants of concern, even when some of these variants were not contained in the vaccine [110]. The bivalent omicron-containing vaccine mRNA-1273.214 elicited neutralizing antibody responses against omicron that were superior to those with mRNA-1273 [111].

Analysis of research data related to the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) shows that the immune response against BA.1 of the participants who received the bivalent vaccine was better than those who had received the monovalent vaccine [112]. Pre-clinical data showed a booster dose of the BA.4/BA.5-adapted bivalent vaccine generated a strong neutralizing

antibody response against the Omicron BA.1, BA.2, BA.4 and BA.5 subvariants, as well as the original virus [113].

It can be foreseen that the emergence of the new highly pathogenic mutant strains might be a challenge to the existing level of vaccine protection. So continuously monitoring of SARS-CoV-2 genomic evolution and antigenic changes were necessary. Although the evolution of SARS-CoV-2 has a negative impact on vaccination effect, the advantages of vaccination outweigh the disadvantages for people without contraindications, as long as the effectiveness and safety of vaccine are verified by clinical double-blind experiments. Homologous or heterologous booster vaccination led to an increase in levels of S-specific binding antibodies, neutralizing antibodies and T-cell responses, but these increases were highest in individuals who received heterologous regimens with mRNA vaccines [114]. Both the Moderna (50 μg) and Pfizer-BioNTech (30 μg) vaccines have been shown that antibody levels substantially increase when offered as a booster dose [115]. Among individuals with previous COVID-19 disease, one dose of BNT162b2 or two doses of CoronaVac could induce detectable serum Omicron NAb [116]. It is necessary to carry out a booster vaccination strategy which protects against emerging variants of concern. The bivalent formulations of COVID-19 vaccines deserve further optimization studies and comprehensive evaluation, so that provide broad protection against COVID-19 and better protection against the Omicron variant. In summary, optimization of immune strategies and vaccine R & D programs should continue as an important prevention strategy against the epidemic.

5. Effective vaccination strategies against future SARS-CoV-2 variants

Several current vaccines have obvious shortcomings against the COVID-19 pandemic. Firstly, inactivated vaccines generally require multiple boosters with low efficiency in inducing mucosal T cell responses. In addition, much more restrictive management is necessary for the large-scale mass production of such vaccines. RNA vaccine fragments are unstable and high cost. Its safety needs to be assessed in more large-scale clinical trials. Viral vector vaccines use conventional viral vector systems, but it inherits an inevitable problem, as some vaccines might be exposed to the same virus before and have developed immunity against the viral vector. Another concern for this type of vaccine is its potential carcinogenesis. Subunit vaccine is currently one of the safest vaccines, but due to its low immunogenicity, it needs to be combined with adjuvants to enhance its protective immune responses. Therefore, it is necessary to improve these vaccine development process and further evaluate the safety and effectiveness of them.

5.1. The impact of mass vaccination against COVID-19

According to the prediction of domestic and foreign experts, COVID-19 is very likely to coexist with humans for a long time, and will show seasonal or irregular recurrence. Therefore, the establishment of human herd immunity against the COVID-19 pandemic is a key and fundamental defense measure. Herd immunity can be established by both mass vaccination and worldwide infection with SARS- COV-2, the latter of which has disastrous consequences. It is safe to obtain herd immunity through mass vaccination, and herd immunity can protect those who cannot be vaccinated or have a weak immune system, but herd immunity protectiveness diminishes with time. It has been reported that the levels of specific antibodies in COVID-19 patients decrease over time [117,118]. Long QX et al. raised some caveats regarding COVID-19 vaccination based on previous studies: (1) two doses of COVID-19 vaccines per individual; (2) world travel is inevitable even though COVID-19 is now a pandemic; and (3) revaccination might be necessary, as the antibody levels often decline over time [119]. Vaccination only helps prevent COVID-19 or reduce the disease severity, while other control measures could also reduce the spread of the virus. In order to curb the virus spreading during the vaccination period, maintaining social distancing, wearing a mask, and washing hands frequently are still important prevention measures and should be continuously implemented.

Mass deployment of highly effective vaccines may quickly exert selection pressure on the SARS-CoV-2 virus. In view of the current situation of widespread mutant strains, escaping the vaccine-induced immune responses is cause for concern. By analyzing a simple model of various sensibility and contact rates between two populations, Gog JR et al. state main insights as follows: (i) vaccination aimed at reducing prevalence could be more effective at reducing disease than directly vaccinating the vulnerable; (ii) the highest risk of vaccine escape is likely to occur at intermediate vaccination levels [120]. A retrospective cohort study in the United Kingdom found that the risk of infection with SARS-CoV-2 and/or hospitalization was very low among the vaccinated population, and provided evidence that a single dose of Pfizer/BioNTech vaccine or Oxford/AstraZeneca vaccine could effectively reduce the risk of COVID-19 infection up to 60 days post-vaccination across all age groups, ethnic groups and risk categories in the UK urban population [121].

5.2. Improve immunogenicity of existing vaccines

New adjuvants: Adjuvants can help a vaccine induce stronger and longer-lasting immune responses, thus often being used as a key component for subunit vaccines and certain inactivated vaccines. In the past coronavirus vaccines usually used aluminum salts, emulsions [122], and TLR agonists [123,124] as adjuvants. One recent research showed that filling alum in the squalene/water intermediate phase to form a stabilized PAPE emulsion could be used as a safe adjuvant formulation to enhance the effectiveness of COVID-19 vaccination [125]. Due to the size advantage of nanoparticles, the development of nanoparticle-based vaccines with adjuvant properties is very promising [126]. Six nanoparticle-based vaccines are currently under development: lipid nanoparticles (LNPs) [74,127], virus-like particles (VLPs) [128,129], protein nanoparticles [130,131], polymer nanoparticles [132], liposomes [133], and micelles [134]. These vaccines can have antigens such as SARS-COV-2 virus nucleic acids or S proteins wrapped inside the particles, or they can have S or RBD protein antigens loaded on the particle surface, the latter can attract antigen-presenting cells and/or effectively promote B-cell receptor (BCR) cross-linking, thereby stimulating an immune response. Currently, at least 26 nanoparticle-based vaccine candidates are in human clinical trials and another 60 candidates are in various stages of preclinical development [135].

Phage-based vaccine: Staquicini, D.I. et al. developed phage particles displaying short SARS-CoV-2 S protein epitope short peptides and AAVP particles carrying the entire S protein gene to immunize mice, where they elicited systemic and specific immune responses. The vaccines based on engineered targeted phage and adeno-associated virus/phage particles usually possess inherent immunogenicity, genetic plasticity, stability, and flexibility. The cost-effectiveness of large-scale production and the proven safety in humans make the targeted vaccine an effective candidate for the development of COVID-19 vaccine prototypes to deal with the emergence of the different mutant strains [136].

T cell immunity: Th2 and Th17 were found to be responsible for pneumonia and edema resulting from COVID-19 infection. IL-17 and macrophage colony-stimulating factor (GM-CSF) could aggravate viral immunopathology by inhibiting Treg cells, enhancing neutrophil migration, and inducing Th2 response in the lungs [137]. It has been demonstrated that IL-6-mediated Th17 differentiation could promote lung pathology during SARS infection [138]. In mouse models, vaccination against SARS-CoV could result in Th2-type immunopathology and eosinophil infiltration [139]. However, no confirmatory studies have been conducted on the IL-6-mediated Th17 response during SARS-CoV-2 infection [140]. These latest studies confirmed the

feasibility of T cell immunity in developing therapeutic interventions. However, In COVID-19 patients, the expression levels of PD-1 and TIM-3 in Th cells and cytotoxic T cells are significantly elevated [141,142], indicating a exhausted state of T-cell function. Reliance on T-cell immunity to enhance immunogenicity requires a complete reconstitution process.

Boost vaccination: The T and B cell immune response diminishes over time with vaccination in individuals [143,144], Clinical trial data show breakthrough infections in early vaccination individuals [145,146]. Boost vaccination may be beneficial [147], but controversial. There is concern that continued vaccination could lead to the development of "Original Antigenic Sin" [148,149] in SARS-CoV-2, as in the case of influenza viruses, and that those who have been vaccinated against influenza had a lower protective antibody response than those who have not been vaccinated [150]. Stimulating with a similar antigen enhances the antibody response to the original strain and does not provide specific antibodies to the new variant. Studies are still underway to explore the impact of heterologous booster vaccination on immunity [151].

5.3. New strategies for vaccine development

As SARS-CoV-2 continues to evolve and circulate like the Influenza virus, a similar strategy for vaccine development might be employed. For example, the influenza vaccines currently in use target-specific influenza strains, thus when the vaccine strain matches the epidemic influenza virus, specific neutralizing antibodies can be elicited and provide effective protection; otherwise, it might not be able to do so. The influenza vaccine strains must be constantly adjusted according to regular track of the virus evolution [152,153]. Since the influenza vaccine has poor cross-protection between different subtypes, the development of universal influenza vaccines that can induce broad-spectrum and long-term immune responses is becoming the main focus of influenza vaccine development. Current research and development strategies of universal influenza vaccines are designed to protect against a wide range of pathogens [154,155]. Universal influenza vaccine is mainly based on cross-protective T cell response [156,157], and its adjuvants and vaccination methods [158] have also been studied. All of these strategies could be explored for COVID-19 vaccine development Neutralizing antibodies induced by vaccines are not the only mechanism of protection. Vaccines can also trigger cross-protective B- and T-cell responses [159] that can recognize different SARS-CoV-2 variants [160]. T cells play a major role in the control of SARS-CoV-2 infection [161].As the main goal of the future COVID-19 vaccines is to elicit a protective immune response against a series of SARS-CoV-2 variants, it is important to focus on the induction of broadly neutralizing antibodies, as well as T cell responses through innovative vaccine design and/or vaccination strategies [162].

6. Conclusion

The SARS-CoV-2 is a novel coronavirus infecting human being after the SARS-CoV outbreak in 2003 and MERS-CoV in 2012. Advances in studies on SARS-CoV and MERS-CoV have accelerated our understanding of the epidemiology and pathogenesis of SARS-CoV-2 and the development of interventions preventing viral infection [163]. Four types of SARS-CoV-2 vaccine have been quickly developed since the outbreak, including inactivated vaccine, recombinant protein, virus vector and RNA vaccine. However, new SARS-CoV-2 variants are constantly being updated, changing the transmissibility, pathogenicity and immunogenicity of the virus. Mutations in the S protein receptor binding domain of mutant strains are prone to cause immune escape of the virus. Therefore, it also has some negative impact on the effectiveness of commercially available vaccines. There is an urgency to develop a more effective vaccine against continuously emerging SARS-CoV-2 variants. Some new and feasible ideas for adapting vaccine development and vaccination efforts are summarized, such as: expanding herd immunization, improving vaccine development processes, and learning from influenza and HIV vaccine development ideas. Further development of the vaccine and the speedy control of the epidemic still require the efforts of global institutional organisations. There is still a long way to go.

Declaration of competing interest

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CRediT authorship contribution statement

Wan-Rong Luo: Writing – review & editing, Writing – original draft, Conceptualization. **Xiao-Min Wu:** Writing – review & editing, Data curation. **Wei Wang:** Writing – review & editing, Visualization, Formal analysis. **Jun-Ling Yu:** Visualization, Data curation. **Qing-Qing Chen:** Validation, Resources. **Xue Zhou:** Writing – original draft, Data curation. **Xin'er Huang:** Investigation, Formal analysis. **Hai-Feng Pan:** Writing – review & editing. **Zhi-Rong Liu:** Writing – review & editing, Conceptualization. **Yong Gao:** Writing – review & editing, Formal analysis, Conceptualization. **Jun He:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Data curation.

Data availability

Data will be made available on request.

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