Exploratory Research and Hypothesis in Medicine **2023** vol. 8(2) | 157–170
DOI: 10.14218/ERHM.2022.00084

Review Article

Emergence of the SARS-CoV-2 Omicron Variant: Current Treatments and Vaccines for COVID-19

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Received: July 04, 2022 | **Revised:** July 12, 2022 | **Accepted:** July 19, 2022 | **Published online:** August 01, 2022

Abstract

The world is now in the third year of the COVID-19 pandemic. As such, enormous volumes of virological, immunological, and epidemiological knowledge pertaining to the SARS-CoV-2 infection have been obtained during these years. The SARS-CoV-2 Omicron variant is currently causing the latest wave of infection globally presumably due to its ability to transmit with ease among individuals and to escape from the existing neutralizing antibodies. Fortunately, numerous treatment agents as well as prophylactic vaccines are now available, thus providing people with a better chance to control this infectious disease. This review will discuss the Omicron variant of concern as well as the available treatments and vaccines for COVID-19.

Introduction

The Coronavirus Disease 2019 (COVID-19) still remains a pandemic in 2022. Furthermore, the presence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern (VOC) has contributed to the majority of the COVID-19 incidences. On November 26, 2021, the World Health Organization (WHO) declared a novel SARS-CoV-2 VOC named Omicron (Pango Lineage B.1.1.529).[1] Whole-genome sequencing results of the Omicron variant revealed approximately 50 mutations; many of which occurred in the spike glycoprotein, particularly in its receptor-binding domain (RBD).[1,2] The spike glycoprotein is an essential component of SARS-CoV-2 because it facilitates the viral entry into the host cells and serves as the primary target of neutralizing antibodies. Hence, changes in the spike glycoprotein raise a serious concern on whether the existing immunity, either due to natural infection or vaccination, could still protect the population from the Omicron variant.[3] This review was thus written to discuss the Omicron variant and its sublineages and to analyze the effectiveness of current COVID-19 vaccines and treatments to protect individuals against SARS-CoV-2 infection and severe COVID-19, respectively.

Keywords: COVID-19 pandemic; SARS-CoV-2; Omicron variant; Therapeutic agents; Prophylactic vaccines.

Abbreviations: ACE2, angiotensin-converting enzyme 2; ACTT, adaptive COVID-19 treatment trial; Ad, Adenovirus; BEVS, baculovirus expression system; COVID-19, coronavirus disease 2019; EUL, emergency use listing; LNP, lipid-nanoparticle; mAbs, monoclonal antibodies; NGS, next-generation sequencing; NHC, N-hydroxycytidine; PCR, polymerase chain reaction; PRINCIPLE, platform randomised trial of treatments in the community for epidemic and pandemic illnesses; RBD, receptor-binding domain; RECOVERY, randomized evaluation of COVID-19 therapy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGTF, spike gene target failure; TMPRSS2, transmembrane serine protease 2; VOC, variant of concern; WHO, World Health Organization.

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How to cite this article: Vidian V, Dikson , Litanto V, Christy SNA, Jo J. Emergence of the SARS-CoV-2 Omicron Variant: Current Treatments and Vaccines for COVID-19. *Explor Res Hypothesis Med* 2023;8(2):157–170. doi: 10.14218/ERHM.2022.00084.

The emergence and hallmarks of the Omicron variant

The SARS-CoV-2 Omicron variant has driven the latest infection wave worldwide to date. This VOC was initially detected in Gauteng province, South Africa, on November 8, 2021, and Gaborone, Botswana on November 11, 2021. In mid-November 2021, Gauteng province experienced a surge of SARS-CoV-2 infection cases accompanied by increased spike gene target failure (SGTF) during amplification with the polymerase chain reaction (PCR). The subsequent whole-genome sequencing revealed a highly mutated spike glycoprotein, including Δ69–70 deletion (previously detected in the Alpha variant) that caused the SGTF. The variant's existence was reported to the WHO on November 24, 2021, which prompted the WHO to declare the Omicron as a novel VOC on November 26, 2021.[4,5]

A substantial increase of Omicron's infectivity is attributed to numerous mutations, which occurred primarily on its spike gly-

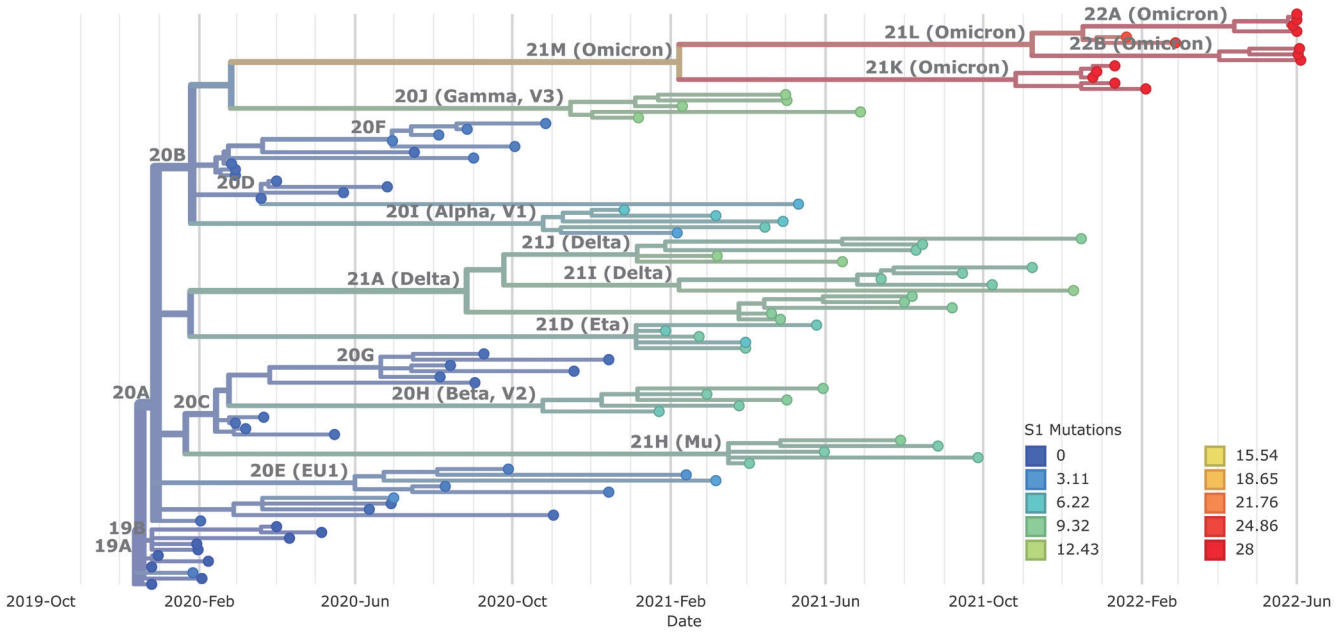

Fig. 1. The Nextstrain tree of the SARS-CoV-2 genome sequences. The numbers of accumulated mutations in the spike subunit 1 glycoprotein are shown with color codes. The Nextstrain tree indicates that the Omicron variant (21M) originated from the Nextstrain Clade 20B, and that it was not derived from the previous variants of concern (*i.e.*, Alpha, Beta, Gamma, and Delta variants). The figure was generated using the Nextstrain software with a built-in SARS-CoV-2 workflow and visualized using Auspice software.[20]

coprotein, consequently conferring a higher affinity to the human Angiotensin-converting enzyme 2 (ACE2), as well as a higher evasion from existing monoclonal antibodies and vaccine generated neutralizing antibodies.[6] An increased affinity of the Omicron spike glycoprotein to bind to the ACE2 orthologs of animal origin was hypothesized in order to grant a zoonotic potential to infect animals, such as rodents and poultry.[7,8] Collectively, these would enable the Omicron variant to reinfect convalescent and vaccinated individuals, in addition to infecting infection-naïve, unvaccinated individuals.[9–11]

Unlike other SARS-CoV-2 VOCs, the Omicron variant prefers to infect cells via the Cathepsin-dependent endosomal route and replicates in the upper respiratory tract due to its hindered capabilities of utilizing transmembrane serine protease 2 (TMPRSS2), mainly found in the lungs, as an entry route. This impedes the Omicron variant's abilities to infect lung tissue and to form syncytia, which might result in less severe clinical symptoms among Omicron-infected individuals.[8,12–16] Several reports indicated that mutations in the Omicron spike glycoprotein noticeably altered the viral behavior upon infection.[16–18] The N764K and/or N856K mutations introduced a spike glycoprotein cleavage site (cleaved by the SKI-1/S1P protease found in the upper respiratory tract but not the lungs) that could hamper the viral membrane fusion and syncytia formation, hence localizing the viral replication in the upper respiratory tract.[19] As a consequence, the N969K mutation affirmed the Omicron variant's preference of using the Cathepsin-dependent endosomal entry route rather than the TMPRSS2-mediated cell surface fusion route.[8] The reduced syncytia formation and localized viral replication in the upper respiratory tract could result in milder clinical symptoms and less severity upon the Omicron infection in exchange for immune evasion and increased transmissibility.

As shown in Figure 1, phylogenetic studies using the Nextstrain[20] tree schema of the SARS-CoV-2 genome sequences indicated that the Omicron variant (Nextstrain Clades 21K-22C) originated from Nextstrain Clade 20B. However, it could not explain the sudden increase of accumulated mutations, particularly on the spike glycoprotein as well as its originating hosts. The Omicron variant was hypothesized to emerge independently from a collection of unaccounted hosts, such as animals and chronically-infected individuals, which for an unknown amount of time were under little surveillance.[21] Over time, it had accumulated numerous mutations until it was detected in South Africa and Botswana in November 2021. In comparison to the original SARS-CoV-2 sampled in Wuhan, China in 2019 (*i.e.*, the ancestral strain), approximately 30 novel mutations were found in the spike glycoprotein of the Omicron variant.[19] A mutation of D614G was proposed to confer a better spike glycoprotein stability with reduced S1 shedding and therefore greater transmission efficiency.[22] Mutations of Δ142-144, Y145D, S371L, K417N, N440K, G446S, E484A, Q493R, and N501Y were suggested to confer an increased antibody evasion, which hampered therapeutic antibodies and existing vaccine effectiveness.[23] Mutations of S477N, T478K, Q493R, G496S, Q498R, N501Y, and Y505H were postulated to confer an increased binding affinity of the spike glycoprotein to ACE2, in which the Q498R and N501Y mutations strengthened the spike glycoprotein's binding with ACE2 of murine origin.[24–28] Mutations of P681H, H655Y, and N679K were postulated to confer an increase in the rate of cleavage of the spike glycoprotein by the Furin enzyme.[14] The mutations of N764K and/or N856K were suggested to introduce a cleavage site on the spike glycoprotein for the SKI-1/S1P protease, which was normally found in the upper respiratory tract but not in the lungs. Therefore, the cleavage of the spike glycoprotein in this manner might hinder the Omicron variant's membrane fusion and syncytia formation.[19] Collectively, these would confer increased infectivity and transmission, antibody evasion, as well as altered infection behavior of the Omicron variant.

As of early June 2022, two Omicron sublineages, referred to as Pango Lineages BA.4 and BA.5 (Nextstrain Clades 22A and 22B,

respectively), emerged and began to spread worldwide at an alarming rate.[29] Tuekprakhon *et al*.[30] suggested that two new mutations observed in BA.4 and BA.5 (*i.e.,* L452R and F486V) conferred a greater ability of antibody evasion than its ancestor, Nextstrain Clade 21L. The fact that BA.4 and BA.5 appeared to cause lower hospitalization and mortality rates as compared to the ones by the pre-Omicron variants and previous Omicron sublineages was of interest to public health globally, as this could reflect the population-level immunity against SARS-CoV-2.[29] A comparison of mutational maps among the Omicron sublineages is displayed in Figure 2.[31,32]

Of note, the COVID-19 diagnosis was confirmed by the reverse transcription-quantitative polymerase chain reaction (RT-qPCR),[33,34] and various modifications of this assay could be used to predict an infection by the Omicron variant, particularly in low- to middle-income countries that lacked next-generation sequencing (NGS) facilities. One of those modified assays was the RT-qPCR-based SGTF assay because a Δ69–70 deletion in most sublineages of the Omicron (*i.e.*, BA.1, BA.1.1, BA.3, BA.4, and BA.5) would hinder a detection of the spike gene but not of other genes.[35,36] However, this assay would not be able to differentiate between those sublineages of Omicron;[35] hence, the NGS facility was required to confirm the diagnosis.

Current treatments for COVID-19

Although the signs and symptoms of the Omicron infection are generally mild, the disease needs to be treated adequately, particularly among at-risk populations who contract severe COVID-19.[37] When COVID-19 emerged in late 2019, no suitable medication was initially available. Therefore, drug repurposing became an effective and rapid way to identify existing drugs with well-established safety profiles in order to treat COVID-19.[38] Several drugs with known benefits for treating COVID-19 patients evaluated by trustworthy clinical trial study groups (*i.e.*, the RECOVERY, Solidarity, ACTT, and PRINCIPLE clinical trials), are shown in Table 1.[39-47] Of note, drugs with no benefit are not shown. Briefly, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) was one of the largest international clinical trials on COVID-19 treatment coordinated by the University of Oxford, UK.[48] The Solidarity clinical trial was also an unprecedented, international collaboration, which was conducted by the WHO, to identify life-saving treatments for COVID-19 involving a large number of patients (~12,000 patients) from more than ~30 countries.[49] Likewise, the Adaptive COVID-19 Treatment Trial (ACTT) was an adaptive, randomized, double-blind, placebo-controlled trial conducted by the National Institute of Allergy and Infectious Diseases (NIAID) to evaluate the safety and effectiveness of novel therapeutic agents in hospitalized adults diagnosed with COVID-19 in the United States of America.[50] The Platform Randomised Trial of Treatments in the Community for Epidemic and Pandemic Illnesses (PRINCIPLE) was a multicenter, open-label, multi-arm, randomized, controlled, adaptive, United Kingdom-wide clinical study from the University of Oxford to discover COVID-19 treatments for recovery at home.[51] Moreover, two novel oral antiviral medications were recently approved by several countries to treat adults with mild-to-moderate COVID-19 who were at risk of developing severe illness.[52] The first of these was Molnupiravir by Merck Sharp and Dohme with the brand name of Lagevrio®,[52,53] which was a small-molecule ribonucleoside prodrug of N-hydroxycytidine (NHC) that underwent phosphorylation within the cells, thus becoming NHC triphosphate.[52,54] This phosphorylated agent became incorporated by viral RdRp into its genome by accumulating deleterious errors throughout the viral genome that rendered the virus non-infectious and unable to replicate.[52,54] The current prescribed dosage is 800 mg of molnupiravir every 12 hours for five days within five days of symptom onset.[53] It was reported that early treatment with molnupiravir was safe and could reduce the risk of hospitalization or death by approximately 30% in at-risk, unvaccinated adults with COVID-19.[54] The second one was a combination of 150 mg Nirmatrelvir and 100 mg Ritonavir by Pfizer with the brand name of Paxlovid™.[52] Nirmatrelvir was an orally administered antiviral agent targeting the SARS-CoV-2 3-chymotrypsin–like cysteine protease enzyme (Mpro) that was essential for viral replication.[55] Simultaneously, ritonavir inhibited cytochrome P450 that metabolized nirmatrelvir, consequently resulting in increased concentrations of nirmatrelvir within the blood plasma.[52] Additionally, it was reported that administration of nirmatrelvir plus ritonavir was safe and could lower the risk of progression to severe COVID-19 by approximately 89%.[52,55]

Next, the knowledge related to the interaction between the viral spike glycoprotein and ACE2 was translated to create anti-SARS-CoV-2 monoclonal antibodies (mAbs) that could inhibit the spike glycoprotein. As this treatment was functioned to block the viral entry/spread, it should be administered immediately after the diagnosis has been confirmed and within seven days of symptom onset.[56] Several therapeutic anti-SARS-CoV-2 mAbs have received emergency use authorizations by the Food and Drug Administration, USA to date: (i) bamlanivimab plus etesevimab, (ii) casirivimab plus imdevimab, (iii) sotrovimab, (iv) bebtelovimab, and (v) tixagevimab plus cilgavimab. The first four products could be administered intravenously to treat mild to moderate COVID-19 patients who were at high risk of contracting severe illness, while the last product could be administered intravenously for uninfected individuals who were at risk of eliciting an inadequate immune response to a COVID-19 vaccination or who had a history of severe adverse reactions to a COVID-19 vaccine or any of its components.[56] Of note, the effectiveness of the anti-SARS-CoV-2 mAbs depended on the circulating SARS-CoV-2 variant. Pertaining to the Omicron infection, sotrovimab, in contrast to bamlanivimab plus etesevimab as well as casirivimab plus imdevimab, was observed to be still effective against BA.1 or BA.1.1 *in vitro* and *in vivo*.[56,57] The antiviral activity of sotrovimab, however, decreased significantly against BA.2; hence, only bebtelovimab was recommended for Omicron-infected patients as bebtelovimab still retained sufficient *in vitro* activity against the current Omicron sublineages.[56,58]

Prophylactic vaccines for COVID-19

The proverb 'prevention is better than cure' could not be more relevant amidst the COVID-19 pandemic. The world has witnessed the rapid development and deployment of various COVID-19 prophylactic vaccines, which have the potential to generate specific immune responses as a protection against SARS-CoV-2 infection. As of June 21, 2022, there were 38 approved vaccines, of which 11 vaccines (from four different types) were granted emergency use listing (EUL) by the WHO (Table 2[59]). Different technologies were used in developing those four types of vaccines. The inactivated viral vaccine was arguably the simplest, but the most common, technology to develop a prophylactic vaccine. After culturing and collecting viral particles from a certain cell culture, the viral particles were inactivated through exposure to physical or chemical agents, such as formalin or β-propiolactone, to destroy the viral infectivity while retaining the immunogenicity.[60] Briefly, the

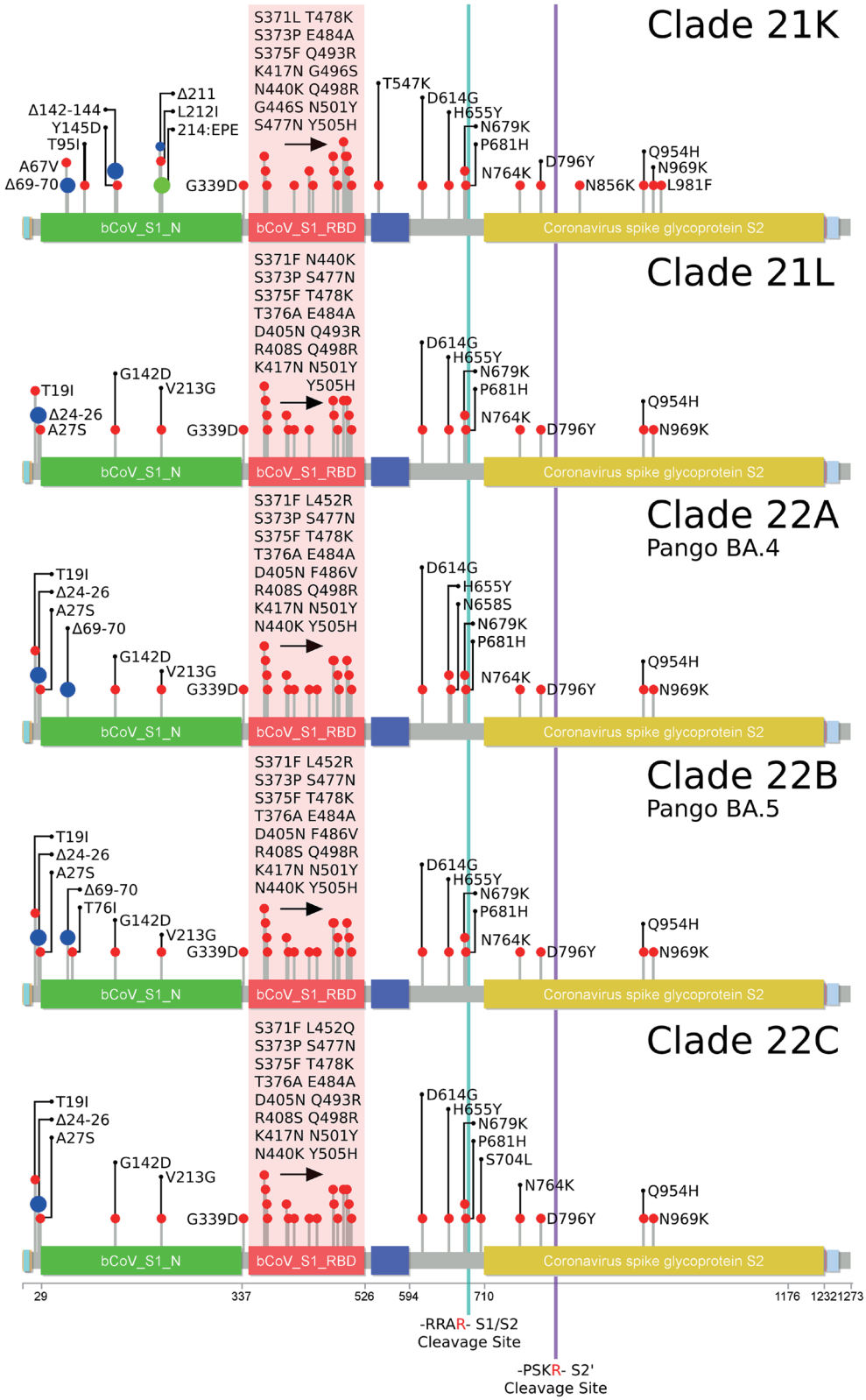

Fig. 2. Mutation map of the SARS-CoV-2 Omicron Variant. Spike glycoprotein mutation maps of the Omicron variant sublineages (*i.e.*, Nextstrain Clade 21K-21L-22A-22B-22C) are compared. The three domains of the spike glycoprotein (S1-N Terminal Domain, RBD, and S2) are displayed. The image was generated using the Nextclade software[31] and visualized using the Lollipops software[32] with UniProt sequence P0DTC2 as reference. RBD, receptor-binding domain.

Table 1. A summary on current COVID-19 treatments

Drug	Classification	Clinical Trial Results		
		RECOVERY	Solidarity	Other Trials
Remdesivir	RdRp inhibitor		Remdesivir had no significant effect on COVID-19 patients who were ventilated. Among other hospitalized patients, it had a small effect on death or progression to ventilation (or both).[39]	ACTT-1 revealed that Remdesivir shortened the recovery time in hospitalized COVID-19 adult patients as compared to hospitalized COVID-19 patients who received a placebo.[40] ACTT-3 revealed that Remdesivir alone was not inferior to a combination of Remdesivir plus Interferon beta-1a among hospitalized patients with COVID-19 pneumonia.[41]
Dexamethasone	Corticosteroid	Dexamethasone resulted in a lower 28-day mortality among the hospitalized patients who received either invasive mechanical ventilation or oxygen alone, but not among those who received no respiratory support.[42]		
Tocilizumab	Anti-IL-6 receptor monoclonal antibody	Tocilizumab improved the survival and other clinical outcomes in hospitalized patients with hypoxia and systemic inflammation.[43]		
Baricitinib	JAK inhibitors	Baricitinib significantly reduced the risk of death in hospitalized patients, but the benefit was smaller than those suggested by previous trials. Baricitinib reduced mortality in hospitalized patients by one-fifth.[44]		
Baricitinib with Remdesivir	JAK inhibitors (Baricitinib); RdRp inhibitor (Remdesivir)			ACTT-2 revealed that a combination of Baricitinib plus Remdesivir demonstrated a better therapeutic outcome for hospitalized patients compared to Remdesivir alone.[45] ACTT-4 revealed that among the hospitalized COVID-19 patients requiring supplemental oxygen, a combination of Barictinib plus Remdesivir resulted in similar mechanical ventilation-free survival by Day 29 when compared to a combination of Dexamethasone plus Remdesivir.[46]
Budesonide	Corticosteroids			PRINCIPLE Trial revealed that inhaled Budesonide improved the recovery time in infected people in the community setting who were at a higher risk of contracting complications.[47]

ACTT, adaptive COVID-19 treatment trial; COVID-19, coronavirus disease 2019; IL-6, interleukin 6; JAK inhibitor, janus kinase inhibitor; PRINCIPLE, platform randomized trial of treatments in the community for epidemic and pandemic illnesses; RdRp, RNA-dependent RNA polymerase; RECOVERY, randomized evaluation of COVID-19 therapy.

Table 2. Vaccines granted Emergency Use Listing by the WHO[59]

Vaccine Type	Manufacturer	Research Name	Trade Name	Date Granted EUL by the WHO
Protein subunit	Novavax#	NVX-CoV2373	Nuvaxovid	December 20, 2021
	Serum Institute of India#	NVX-CoV2373	Covovax	December 17, 2021
mRNA	Moderna	mRNA-1273	Spikevax	April 30, 2021
	Pfizer/BioNTech	BNT162b2	Comirnaty	December 31, 2020
Non- replicating viral vector	CanSino	Ad5.COV2.S	Convidecia	May 19, 2022
	Janssen (Johnson & Johnson)	Ad26.COV2.S/JNJ-78436735	Jcovden	March 12, 2021
	Oxford/AstraZeneca*	ChAdOx1-S	Vaxzevria	February 15, 2021
	Serum Institute of India*	ChAdOx1-S	Covishield	February 15, 2021
Inactivated virus	Bharat biotech	BBV152	Covaxin	November 3, 2021
	Sinopharm	BBIBP-CorV	Covilo	May 7, 2021
	Sinovac	CoronaVac	CoronaVac	June 1, 2021

#Both Nuvaxovid and Covovax use the same formulation (the Novovax formulation). *Both Vaxzevria and Covishield use the same formulation (the Oxford/AstraZeneca formulation). mRNA, messenger RNA; WHO, World Health Organization.

BBV152 vaccine was created from a whole SARS-CoV-2 virion (strain NIV-2020-770) with the D614G mutation of the spike protein. The viral particles were cultured in the African green monkey kidney cell line (Vero) and inactivated by β-propiolactone. This inactivated viral vaccine was formulated with a toll-like receptor 7/8 agonist (imidazoquinoline) adsorbed to alum; hence, it became the first alum-imidazoquinoline-adjuvanted vaccine that was authorized for public use.[61–63] The BBIP-CorV vaccine was created from a whole SARS-CoV-2 HB02 strain (cultured in the Vero cell line), inactivated by β-propiolactone, and formulated with an aluminum-based adjuvant.[64,65] Similarly, the CoronaVac vaccine was created from a whole SARS-CoV-2 CZ02 strain (cultured in the Vero cell line), inactivated by β-propiolactone, and adjuvanted with aluminum hydroxide.[66]

The protein subunit vaccine contained purified antigen fragments of the pathogen to activate host immune responses against it. The chosen antigens ranged from toxoids, subcellular components, to surface molecules. It could be produced by utilizing conventional biochemical or recombinant DNA technology.[67] The NVX-CoV2373 vaccine was developed from the SARS-CoV-2 recombinant spike protein with a Matrix-M adjuvant coupled with several inactive ingredients. The recombinant spike protein was constructed *in silico* based on the full length of the spike glycoprotein from the wild-type SARS-CoV-2 (*i.e.*, the Wuhan-Hu-1 isolate) documented in GenBank (the sequence MN908947; nucleotides 21563-25384). Subsequently, the recombinant spike protein was produced by using DNA technology with the baculovirus expression system (BEVS). Of note, this system utilized baculovirus, which was an insect virus, to infect a cell line that was derived from Sf9 cells of the fall armyworm, *Spodoptera frugiperda*. The BEVS-produced spike protein was subsequently used for the vaccine.[68] In addition, the Matrix-M adjuvant comprised saponin, cholesterol, and phospholipid, which this adjuvant was known to induce greater humoral and cellular immune responses.[69]

A non-replicating viral vector vaccine deployed viral particles that have lost their replicating ability to deliver a vaccine antigen into the host cells. Several viral vectors, including adenovirus, adeno-associated virus, alphavirus and herpesvirus, were designed primarily to be replication-defective vectors.[70] In order to modify the adenovirus as a viral vector, the E1 and/or E3 genes of the adenovirus (essential for viral replication) were deleted or replaced with a gene of interest (*i.e.*, target antigen). Of note, multiple studies on adenoviral vectors focused on human adenovirus serotype 5 (Ad5), thus allowing it to be the best studied adenoviral vector.[71] The Ad5.COV2.S vaccine utilized this vector to carry a full-length SARS-CoV-2 spike gene.[72] The majority of the human population, however, has been discovered to have pre-existing immunity against Ad5 presumably due to natural infection.[73,74] As a result, this raised a need to use a less prevalent adenovirus as the viral vector. The human Ad26 was observed to be less prevalent and less immunogenic than Ad5, but could still be an effective vector for COVID-19 vaccine.[71] Similar to Ad5.COV2.S, the Ad26.COV2.S vaccine used Ad26 as a vector to encode a full-length SARS-CoV-2 spike glycoprotein.[75] Another creative innovation for circumventing pre-existing immunity against human adenoviral vectors was by using the chimpanzee adenovirus (ChAd). The ChAdOx1 was isolated from the fecal sample of a chimpanzee and was edited by deleting its E1/E3 gene and modifying its E4 gene. The ChAdOx1-S vaccine was subsequently developed by using ChAdOx1 to carry the SARS-CoV-2 spike gene.[71]

The messenger RNA (mRNA) vaccine was arguably the newest and most advanced technology to develop vaccines. This technology inserted mRNA containing the viral genetic information into the cells, which would be translated into specific antigens and could induce specific immune responses. There has been vast interest in using mRNA-based technology to develop COVID-19 vaccines due to its presumably safe administration and high potency, capacity for rapid development, as well as potential for low-cost manufacturing.[71,76,77] The mRNA-1273 vaccine was an mRNA vaccine encapsulated by a lipid-nanoparticle (LNP) that expressed a prefusion-stabilized spike glycoprotein.[78,79] The BNT162b2 vaccine was an mRNA vaccine encapsulated by LNP that encoded the P2 mutant spike protein, in which it was formulated as an RNA-lipid nanoparticle of nucleoside-modified mRNA.[80]

Performances of the approved COVID-19 vaccines

The above-mentioned vaccines have been shown to generate host immune responses that may have variable levels of immunity and

Table 3. Strength and weakness of COVID-19 vaccines granted EUL by the WHO

Vaccine Type	Strengths	Weakness
Protein subunit	Safe for immunocompromised people; can induce a cellular and humoral immune response.	Less immunogenic.
mRNA	Strong cellular and humoral immune response.	Difficult storage condition; rare but serious adverse events.
Non-replicating viral vector	Strong cellular and humoral immune response.	Anti-vector immunity; rare but serious adverse events.
Inactivated virus	Mild adverse events; sufficient humoral immunity response.	Less immunogenic; protection wanes quickly.

COVID-19, coronavirus disease 2019; EUL, emergency use listing; mRNA, messenger RNA; WHO, World Health Organization.

different immune-inducing processes between them. Two types of immunities which may be induced by vaccination are cellular and humoral immunities. The activated cellular immunity is known to increase the $CD4^+$ and $CD8^+$ T cell-mediated immune responses in order to protect the vaccinated hosts. The activated humoral immunity involves the production of neutralizing antibodies by the plasma cells. The humoral and cellular immune responses induced by the mRNA-1273, BNT162b2, Ad26.COV2.S, and NVX-CoV2373 vaccines were also researched by Zhang *et al.*[81]

The advantages and disadvantages of each type of vaccine are shown in Table 3.[82] Three inactivated SARS-CoV-2 vaccines that received EUL from the WHO were BBV152, BBIBP-CorV, and Coronavac.[59] The inactivated viral vaccine was one of the most common types of vaccines because this technology was well-established and had a higher safety profile than the live attenuated viral vaccine.[83] The inactivated viral vaccine was less immunogenic than the live attenuated viral vaccine, thus requiring a strong adjuvant formulation and/or administration of multiple doses.[83] All three inactivated vaccines induced humoral immunity and provided an adequate protection from severe COVID-19 and death (but not mild/moderate illness) after completing two doses of vaccination.[84–89] The effectiveness of two doses of CoronaVac vaccination in Hong Kong in terms of protection against severe illness and death among younger adults of 20–59 and >60 years old were 91.7% and 71.1%, respectively.[90] The common adverse events were mostly mild to moderate, including pain at the injection site, fatigue, fever, headache and swelling.[62,91,92] It was observed that the immune responses induced by all COVID-19 vaccines waned over time, in which a substantial reduction was observed among individuals receiving inactivated SARS-CoV-2 vaccines.[93,94] This raised the importance of a heterologous prime boost strategy after two doses of primary vaccination with an inactivated viral vaccine in order to generate stronger and longer immunity.[84,95,96] The current protein subunit COVID-19 vaccine that has received EUL from the WHO was NVX-CoV2373 (under the brands of Nuvaxovid and Covovax).[59] Although less immunogenic than the live attenuated viral vaccine, the protein subunit vaccine with a strong adjuvant formulation or improved vaccine carrier could still generate sufficient humoral and cellular immune responses.[81,97,98] Several studies have reported that this protein subunit vaccine offered ±90% protection against the SARS-CoV-2 Alpha infection and a reduction in the rate of hospitalization. However, its effectiveness toward other variants was reduced, *i.e.*, between ±50% to ±90%.[99–102] The adverse events were primarily mild, including headache, myalgia, fatigue, and malaise.[99,100] Furthermore, this type of vaccine would be an ideal choice for administering to individuals with immunosuppression.[99]

The current non-replicating viral vector COVID-19 vaccines that received EUL from the WHO were Ad5.COV2.S, Ad26.COV2.S, and ChAdOx1-S.[59] The Ad5.COV2.S and Ad26.COV2.S vaccines utilized human adenovirus serotype 5 (Ad5) and 26 (Ad26), respectively to carry the gene of the spike protein. The ChAdOx1-S (under the brands of Vaxzevria and Covishield) in contrast used chimpanzee adenovirus to carry the gene of the SARS-CoV-2 spike protein. Additionally, the non-replicating viral vectors were known for their ability to drive a high degree of expression of the target antigen, thus being able to induce strong cellular and humoral immune responses. Nevertheless, the induced immune responses by the non-replicating viral vector COVID-19 vaccines are relatively lower in comparison to the mRNA-based vaccines.[81,103] As mentioned, a pre-existing immunity toward the Ad5 vector would reduce the vaccine's ability to generate a specific immune response.[73,74] On the contrary, the Ad26 vector is known to be less immunogenic than Ad5, but it is still an effective vector for immunization.[71] Ad5.COV2.S, Ad26.COV2.S, and ChAdOx1-S reduced the overall COVID-19-related symptoms by 65.7%, 66%, and 64.1%, respectively after a single vaccine dose. The common adverse events were pain at the injection site, swelling, headache, fatigue, muscle ache, malaise, and fever. However, a rare and serious adverse event upon the administration of the Ad26.COV2.S or ChAdOx1-S vaccines had been reported, *i.e.*, thrombosis with thrombocytopenia syndrome.[104–107] This syndrome was presumed to have occurred due to the production of autoantibodies against platelet factor 4 after vaccination.[104–107] In addition, the Ad26.COV2.S administration was associated with an elevated incidence of Guillain-Barré syndrome.[108] Of note, Ad26.COV2.S and ChAdOx1-S were contraindicated for individuals with a history of severe anaphylactic reactions.[109]

The mRNA COVID-19 vaccines granted EUL by the WHO were mRNA-1273 and BNT162b2.[59] The mRNA-based vaccines induced robust cellular and humoral immunities, respectively. During the period of the pre-Delta variants, the effectiveness of both mRNA vaccines in protecting adults against symptomatic infection was excellent, *i.e.*, around 89–95%.[78,110,111] Similar to Ad26.COV2.S and most likely other available vaccines, a reduction in the effectiveness of both mRNA vaccines against COVID-19 illness was observed during the wave of the Delta variant.[111,112] Both mRNA vaccines had relatively favorable safety profiles with common adverse events, such as soreness at the injection site, fever, fatigue, chills, and headache.[113] Nonetheless, rare and serious adverse events were also reported following administration of the mRNA vaccines, including myopericarditis, acute myocardial infarction, and anaphylaxis.[113] Of note, a technical limitation of the mRNA vaccines was that they needed to be kept at a very low temperature; hence, this hindered a worldwide deployment of the mRNA COVID-19 vaccines, particularly in under-resourced countries.[81,101,114,115]

Booster vaccination against SARS-CoV-2 infection

As mentioned, all COVID-19 vaccines that had been administered as the primary vaccination would experience a waning in their respective protective abilities over time, especially against newer SARS-CoV-2 variants. Thus, the reduction in a vaccine's effectiveness highlighted the importance of administering a booster vaccine. Two types of booster vaccinations are currently available: homologous and heterologous prime-boost vaccination. While the homologous prime-boost vaccination is a booster that is administered by using the same vaccine used in the primary vaccination, the heterologous prime-boost vaccination is a booster that is administered by using a vaccine that differs from the one used in the primary vaccination.[95,116]

Briefly, homologous and heterologous booster vaccinations were safe and immunogenic among adults who had completed the primary vaccination of COVID-19 at least 12 weeks earlier.[117] The homologous booster appeared to have more optimum effects in individuals who had received a primary vaccination of the mRNA COVID-19 vaccines, as the booster restored titers of neutralizing antibodies.[90,117] In light of this, certain populations/countries would prefer to receive a homologous booster with a lesser immunogenic vaccine (*e.g.*, inactivated viral vaccine), for example due to a concern of adverse events, which might be associated with a stronger immunogenic vaccine. Encouraging evidence from Hong Kong also suggested that three doses of CoronaVac provided better protection than two doses of CoronaVac against severe COVID-19 or death,[90] consequently indicating that boosters with any type of approved COVID-19 vaccine could provide protection against severe illness. Next, heterologous boosters appeared to have optimum effects in individuals who had received primary vaccination with either inactivated viral or non-replicating viral vector vaccine (*i.e.*, arguably less immunogenic than the mRNA vaccine) and subsequently received a booster with an mRNA vaccine due to the substantial elevation in the levels of neutralizing antibodies post booster administration.[96,116,117] This finding was supported by another finding, which reported that a heterologous booster among CoronaVac-vaccinated individuals with the Ad5.COV2.S vaccine induced greater cellular and humoral immune responses, as compared to the results observed upon a homologous vaccination with CoronaVac.[118] Taken together, the booster vaccination was safe and effective in protecting individuals against SARS-CoV-2 infection.

Effectiveness of the COVID-19 vaccination against the Omicron variant

The SARS-CoV-2 Omicron variant has swiftly replaced the Delta variant to cause the latest wave of infection globally. This variant has approximately 30 mutations in its spike protein; 15 of which are clustered within the RBD of SARS-CoV-2 Omicron.[119] As currently available COVID-19 vaccines concentrate on generating immune responses toward the viral spike protein, these mutations have raised some concern regarding the effectiveness of the available COVID-19 vaccines against Omicron infection.

Various studies have been performed in order to assess the effectiveness of the current vaccines against the SARS-CoV-2 Omicron variant. It has been reported that the effectiveness of two doses of mRNA-1273 vaccination against the Omicron variant declined after six months.[120,121] As mentioned, a way to restore immunity and protection against the Omicron variant is by administering a booster (third dose) of the mRNA-1273 vaccine.[122] Similarly, an *in vitro* study indicated that two doses of BNT162b2 were likely to be insufficient to neutralize the Omicron variant, and that a third dose of BNT162b2 was required to neutralize the Omicron variant effectively.[90,123] A study conducted in the UK reported that two doses of BNT162b2 or ChAdOx1-S provided limited protection against symptoms of the Omicron infection and that a booster vaccination with BNT162b2 or mRNA-1273 would substantially increase the level of protection.[116] Likewise, results from a study in South Africa supported this observation, which showed that a minimum of two doses of BNT162b2 or Ad26.COV2.S were required to provide protection against Omicron.[124] However, it was reported that the fourth dose of BBIBP-CorV did not significantly increase the neutralizing antibody titers against the Omicron variant as compared to the ones observed after the third dose, thus suggesting that the inactivated viral COVID-19 vaccine was less immunogenic and that the homologous booster of this vaccine did not provide an optimum level of protection.[125] Additionally, a study in the Dominican Republic reported that two doses of CoronaVac were not effective against the Omicron infection, but a heterologous booster with BNT162b2 could enhance the neutralization activity against the Omicron variant.[126] This result was also supported by our study, which reported that a majority of healthcare workers who had received a primary vaccination with CoronaVac and a heterologous booster with 100 mg of mRNA-1273 vaccine could be protected from the Omicron infection and the severity of the COVID-19 illness (manuscript in submission).

Collectively, the humoral immunity generated by the abovementioned vaccines could wane over time and could be insufficient in neutralizing novel Omicron sublineages. Therefore, it is worth mentioning that the concern of losing vaccination-induced protection against COVID-19 was primarily based on the assessment of humoral immune responses (*i.e.*, the titers and functionalities of the neutralizing antibodies). When the assessment was focused on cellular immune responses, it was reported that vaccine-induced T-cell responses were stable over time and cross-recognized numerous variants (including the Omicron variant), thus contributing to protection against severe COVID-19.[127,128] In addition, it is obvious that long-term studies that assess humoral and cellular immune responses after COVID-19 vaccination, as well as the clinical protection against SARS-CoV-2 infection or COVID-19 illness, are needed in order to draw a definite conclusion on the waning of vaccine-induced immune responses over time.

In order to ensure that COVID-19 vaccines will continue to provide an adequate level of protection, another strategy, besides providing a booster vaccination, would be to modify particular antigens of the COVID-19 vaccines.[129] Modification of the COVID-19 vaccines could be (i) a novel monovalent vaccine by targeting a particular antigen of the circulating VOC, (ii) multivalent vaccine containing antigens from different VOCs, or (iii) a pan vaccine that would be effective for all strains of SARS-CoV-2 virus or even sarbecovirus (*i.e.*, the subgenus of SARS-CoV-1 and SARS-CoV-2).[129,130] Table 4 displays the introduced modifications in the approved COVID-19 vaccines to create novel monovalent and bivalent vaccines.

Moderna is in the process of developing a bivalent booster vaccine covering specific mutations on the spike glycoprotein that were observed in the ancestral and Beta variants; namely, the mRNA-1273.211. The primary aim of the bivalent booster would be to retain sufficient titers of neutralizing antibodies and to broaden the immunity levels against numerous VOCs. Moderna recently compared 50 mg of the existing mRNA-1273 booster to 50 mg of mRNA-1273.211 booster among individuals who had received a primary vaccination with the mRNA-1273 vaccine. It was reported that a booster of mRNA-1273.211 generated greater antibody response and immunogenicity when compared to the mRNA-1273 booster

Table 4. Modified COVID-19 vaccines currently tested in clinical trials

Vaccine Type	Manufacturer	Research Name	Modification
mRNA	Moderna	mRNA-1273	Bivalent COVID-19 booster (mRNA-1273.211and mRNA-1273.214); Omicron-targeted monovalent booster (mRNA-1273.529).
	Pfizer/BioNTech	BNT162b2	Omicron-adapted monovalent booster; bivalent COVID-19 booster.
Inactivated virus	Sinopharm	BBIBP-CorV (Vero Cells)	Inactivated Omicron variant.

COVID-19, coronavirus disease 2019; mRNA, messenger RNA.

against the ancestral SARS-CoV-2, Beta, and Omicron variants, and that both mRNA-1273 and mRNA-1273.211 displayed similar safety and reactogenicity profiles.[131] Another bivalent booster vaccine being developed by Moderna is the mRNA-1273.214, which comprises the spike gene mRNA from both the ancestral and Omicron variants.[132] It was reported that administration of 50 mg of a bivalent Omicron booster among subjects with a primary vaccination with mRNA-1273 was safe and generated a similar level of neutralizing antibody titers against the ancestral strain, as well as a stronger level of neutralizing antibody titers against the Omicron variant, including BA.4 and BA.5.[132] In addition, Moderna is developing another booster vaccine that would be matched to the spike glycoprotein of the Omicron variant and is named mRNA-1273.529. In contrast to the results obtained from the bivalent booster, the administration of the mRNA-1273.529 booster in mRNA-1273-vaccinated non-human primates did not provide a better protection than the mRNA-1273 booster.[122] This suggested that a bivalent/multivalent vaccine would be a more reasonable approach in providing protection against SARS-CoV-2 infection in the near future.

A similar approach is also being pursued by Pfizer/BioNTech by creating Omicron-adapted monovalent and bivalent booster vaccines. Of note, the bivalent vaccine comprises the spike glycoprotein from the ancestral and Omicron BA.1 variants. In an ongoing study, in which the booster vaccines were used as the fourth dose (at 30 mg and 60 mg doses) in 1,234 participants of 56 years of age and older, both the Omicron-adapted monovalent and bivalent booster vaccines were well-tolerated and were able to neutralize the BA.1.[133] These Omicron-adapted booster vaccines were able to neutralize BA.4 and BA.5 as well, but at threefold lower than BA.1.[133] Of note, Sanofi/GSK is in the process of testing a new booster (*i.e.*, SARS-CoV-2 adjuvanted recombinant protein MV monovalent B.1.351/Beta vaccine), which would be used among individuals who have received a primary vaccination with BNT162b2.[134] Its preliminary result indicated that this booster was safe and generated high levels of neutralizing antibodies against the ancestral, Beta, Delta, and BA.1 variants.[134]

Sinopharm is currently developing a new inactivated viral vaccine targeting the Omicron variant as well. The Omicron-specific vaccine is currently being tested in a non-randomized, open-label, and externally controlled study with the aim to assess the immunogenicity and safety of the inactivated Omicron COVID-19 vaccine in a group of adults aged 18–60 years who had never received the COVID-19 vaccine.[135] This study would determine the usefulness of developing inactivated viral vaccines for new circulating VOCs.

Taken together, the fast-evolving SARS-CoV-2, particularly if COVID-19 becomes an endemic disease, would eventually require an updated version of the current COVID-19 vaccines. Matching the target antigens of an updated COVID-19 vaccine to the ones of currently circulating VOC could be a reasonable strategy although it would not be a straightforward solution due to the constantly emerging variants and the difficulty in predicting the efficacy levels of the induced immune responses.[136] A thorough learning of SARS-CoV-2 behavior as well as the magnitude and duration of the host immune responses upon vaccination would be required to create a more effective vaccine against SARS-CoV-2 in the near future.[129] Furthermore, the NIAID is currently conducting a phase 2 study named the COVID-19 Variant Immunologic Landscape (COVAIL) study in adults who have already received a primary COVID-19 vaccination and a booster in order to compare the immunogenicity of combinations of vaccines based on the ancestral, Beta, Delta, and Omicron variants (*i.e.*, mRNA vaccines and experimental protein-based booster by Sanofi/GSK).[129,136] The result of this trial could provide a guideline for modifying the COVID-19 vaccines.

Potential mucosal vaccines for COVID-19

An important fact to be aware of is that SARS-CoV-2 infects nasal and/or oral mucosal surfaces to enter the human body.[137,138] It is of interest therefore to develop a mucosal vaccine for COVID-19 in order to generate robust immune responses that could protect relevant mucosal tissues against the Omicron infection.[139] A mucosal vaccine is a promising strategy as the vaccine-generated protective immune responses at mucosal sites could prevent the viral infection from occurring in the first place.[139] Therefore, innovative adjuvant techniques and delivery strategies may be required to develop effective mucosal vaccines against SARS-CoV-2 infection.[139] As such, a variety of devices could be used for delivering the mucosal vaccines among which spray devices would be an ideal choice due to their being more precise than conventional pipettes.[140]

Pertaining to a potential nasal vaccine for COVID-19, it was reported that an intranasal administration of ChAdOx1-S from Oxford/AstraZeneca in preclinical models resulted in a reduced viral load in nasal swabs, bronchoalveolar lavage, and lower respiratory tract tissue.[141] An open-label clinical trial of intranasal administration of ChAdOx1-S among healthy human volunteers is currently underway.[142] Similarly, Bharat Biotech, Hyderabad, India has developed an intranasal vaccine by using a chimpanzee adenoviral vector (replication-incompetent) that encodes the stabilized spike glycoprotein of SARS-CoV-2, *i.e.*, ChAd-SARS-CoV-2-S.[143] A study conducted by Bharat Biotech demonstrated that an intranasal administration of one dosage of ChAd-SARS-CoV-2-S could induce neutralizing antibodies and T-cell responses and inhibit viral infection in nasal swabs, bronchoalveolar lavage fluid, and lungs in rhesus macaques.[143] Of note was the fact that the intranasal immunization might boost IFN γ-secreting tissue-resident memory $CD8^+$ T cells in the lungs and induce long-term immunity for at least nine months, as indicated by an expansion of long-lived plasma cells within the bone marrow.[140,143]

An oral vaccine candidate for COVID-19 is being tested as well. VXA-CoV2-1 is an oral recombinant COVID-19 vaccine candidate that would deploy a non-replicating recombinant adenovirus 5 vector containing a full-length SARS-CoV-2 spike gene under the control of the cytomegalovirus promoter and full-length SARS-CoV-2 nucleocapsid genes under the control of the human beta-actin promoter.[144,145] This vaccine would aim to generate

three types of immune responses: mucosal immune responses, strong serum neutralizing antibodies to the spike glycoprotein, as well as T-cell responses to the spike glycoprotein and nucleoprotein. In the preclinical studies, oral administration of VXA-CoV2-1 produced high titers of neutralizing antibodies, activated polyfunctional $CD4^+$ and $CD8^+$ T cells, as well as induced protection against SARS-CoV-2 infection in a Syrian hamster challenge model.[144] The safety and immunogenicity of an oral VXA-CoV2-1 are currently being tested among healthy adults.[146]

Future directions

The continuously evolving SARS-CoV-2 could result in the repeated emergence of highly infectious variants, as currently demonstrated by the Omicron variant. Therefore, further studies would be required to improve the virological and immunological understandings on the impacts of various viral mutations, particularly in escaping from the generated immune responses, either through past exposure, vaccination, or provision of recombinant anti-SARS-CoV-2 monoclonal antibodies. In terms of generating prophylactic protection, more data would be needed to understand the waning of vaccine-induced immune responses in various subpopulations, including the elderly, children, and adults with comorbidities, in which this information would be useful to determine the optimum frequency and interval of administering current COVID-19 vaccines and boosters to generate adequate, long-lasting protection against SARS-CoV-2 infection. Upcoming research in comparing the current and the modified COVID-19 vaccines would also be useful in deciding whether COVID-19 vaccines would require regular modification of their target antigens. Research on inducing specific mucosal immunity against SARS-CoV-2 would be very relevant as well. Therefore, the development of a universal vaccine would be, arguably, the holy grail in activating immune responses against all variants of SARS-CoV-2. In terms of providing treatment, development of novel antiviral medications that would be safe and more effective, as well as new recombinant anti-SARS-CoV-2 monoclonal antibodies that would not be affected by mutations in the viral RBD would improve the chances to control or even reduce the impact of this pandemic.

Conclusions

SARS-CoV-2 is continuously evolving, in which the currently circulating Omicron variant of concern is a somber reminder that another wave of infection could still occur globally. Various therapeutic agents are currently available for patients with COVID-19 ranging from repurposed drugs, novel antiviral agents, to anti-SARS-CoV-2 monoclonal antibodies. Furthermore, several COVID-19 prophylactic vaccines have been developed and deployed worldwide. Due to the accumulated mutations within the genome, particularly in the spike gene of the Omicron variant, there is a concern that currently approved vaccines might be inadequate in protecting individuals against upcoming SARS-CoV-2 infection. Hence, various strategies are being currently utilized, including homologous and heterologous booster vaccinations as well as vaccine modification. There are potentially two pressing issues of concern that have not been discussed in this review; namely, the need to ensure equal access for all populations to receive approved COVID-19 vaccines and the need to convince everyone to be fully vaccinated. It would be worth noting that it is the act of vaccination, not merely the vaccine, that protects people from COVID-19.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/ERHM.2022.00084.

Supplementary Table 1. SARS-CoV-2 genome sequences used in this study.

Acknowledgments

We thank Mr. Sumeet Bal, M. Biotech. (Protein Characterisation Division, CSIRO, Melbourne, Australia) for the critical reading of the manuscript. We also thank the authors from the originating laboratories and submitting laboratories who contributed SARS-CoV-2 genome sequences to the GISAID database utilized in this review (Supplementary Table 1). We sincerely apologize to those whose works could not be discussed due to space limitations.

Funding

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Conflict of interest

JJ has been an editorial board member of *Exploratory Research and Hypothesis in Medicine* since April 2022. The authors have no other conflict of interest related to this publication.

Author contributions

VV, D, VL, and SNAC wrote the initial draft of the manuscript. JJ critically reviewed and completed the manuscript. All authors made a significant contribution to this study and approved the final manuscript.

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