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SARS-CoV-2 vaccines from A to Z: A review of the current challenges

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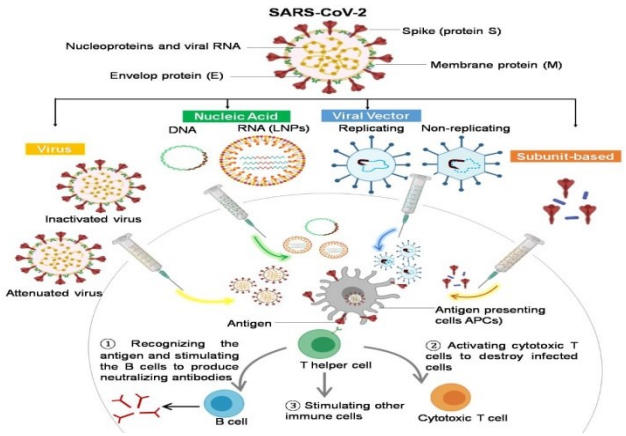
Graphical abstract



Abstract

COVID-19 pandemic is a major worldwide health disaster firstly reported in December 2019. The Food and Drug Administration (FDA) has offered the public hope of halting it, authorizing vaccinations for emergency use with more than 85% efficacy against serious acute respiratory syndrome (SARS-CoV-2). Recent outbreaks of SARS-CoV-2 variations including spike-protein mutations, the key vaccines viral target for immune response, have prompted a thorough investigation into the vaccine's long-term effectiveness. Consequently, this review assayed the details on SARS-CoV-2 infection mechanism and how to control the infection by different types of SARS-CoV-2 vaccines, and their effectiveness against other mutant strains. Additionally, the review summarized the different complaints which have been recorded after vaccination. In conclusion, these negative effects must be constantly weighed against the predicted advantages in terms of disease prevention. Although COVID-19 vaccination is recommended for everyone aged 5 years and older, SARS-CoV-2 is high likely to continue to be a pandemic infectious as a result of the broadcasting of variants of the virus.

Therefore, a booster vaccination, wearing a mask, and social distancing should be maintained.

Keywords: SARS-CoV-2 vaccines, COVID-19, neutralizing antibodies, Lambada mutation, delta mutation, mutant omicron

1. Introduction

Coronavirus disease 2019 (COVID-19) has spread rapidly worldwide since it was first reported in late December 2019 in Wuhan, China, and was formally asserted a pandemic by the World Health Organization (WHO) on March 11, 2020 (Kumar *et al*., 2021). COVID-19 pandemic is caused by SARS-CoV-2, it infected over 503,131,834 patients, causing more than 6,200,571 confirmed deaths worldwide (WHO, 2021b). The total vaccine doses of 11,324,243,310 have been administered by (Organization, 2021) on 18 April 2022. Several variants of SARS-CoV-2 have emerged, with the majority of mutations was related to the spike protein, such as B.1.1.7, B.1.351, B.1.427, P.1, B.1.526, B.1.429, and the recently detected Delta (B.1.617.2), Lambada (C.37), Delta plus, Mu and Omicron(B.1.1.529) variants (Wilhelm *et al*., 2021). Such mutations have been reported to alter the virus's infectivity, antigenicity, and transmissibility (Harvey *et al*., 2021; McCarthy *et al*., 2021), in addition to confer the virus's antibody neutralizing resistance. The existence of co-infection with influenza and respiratory pathogens was well documented (He *et al*., 2021). Similarly, co-infection with other pathogens, such as bacteria, viruses and fungi has been widely reported in patients with SARS-CoV-2 infections (Feldman & Anderson, 2021). These concurrent infections could result in a false diagnosis, worsening of the infection, and poor treatment outcomes.

The elderly and patients with co-morbidities such as cardiovascular disease, diabetes, chronic respiratory disease, and hypertension are more likely to have severe COVID-19 manifestations. In addition, compared with other coronaviruses, SARS-CoV-2 seems to undergo fast transmission (Hu, Guo, Zhou, & Shi, 2021), leading to urgent need for an effective vaccine for COVID-19 control and prevention. Based on WHO's a draft landscape of COVID-19 candidate vaccines (WHO, 2021c), there are about 153 candidate vaccines remain in the clinical evaluation stage, while around 196 candidate vaccines are still under development in the preclinical phase (WHO, 2021c). In clinical trials, candidate vaccines involve RNA, DNA plasmid, adenovirus-vectored, inactivated, protein subunit, and virus-like particle vaccines. Some of these candidates safety, efficacy, and immunogenicity have been presented in preclinical and clinical trials (Dey *et al*., 2022). An effective and safe vaccine against SARS-CoV-2 will be an important implement in controlling the pandemic (WHO, 2021a).

In addition to the mild side effects of all vaccines that targeted the immune system activation, some SARS-CoV-2 vaccines have been linked to severe post-vaccination symptoms, including heart problems with many participants with elevated levels of abnormal myocardial markers like troponin, lactose dehydrogenase (LDH), and ferritin (Cheng *et al*., 2021; VasanthiDharmalingam *et al*., 2021). Bilirubin, alanine transferase (ALT), aspartate transferase (AST), gamma-glutamyltransferase (GGT), and other liver enzymes were also high in some patients (Yu *et al*., 2021).

2. SARS-CoV-2 and its infection mechanism

Orthocoronavirinae can be categorized according to serological studies and genomic analysis into four genera: delta coronavirus, gamma coronavirus, beta coronavirus and alpha coronavirus. So far, six human coronaviruses (HCoV), called HCoV-HKU1, HCoV-229E, HCoV-NL63, HCoV-OC43, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV) were identified (Alekseev *et al*., 2008). SARS-COV-2 is a single-strand RNA virus coated by a nucleocapsid N-protein (McAndrews *et al*., 2020). Gene fragments are translated into structural and nonstructural proteins. The S, E, and M express structural proteins; glycoprotein spike (S-protein), the envelope protein (E-protein), and the membrane/matrix protein (M-protein), whereas 3-chymotrypsin-like protease, papain-like protease, and RNA-dependent RNA polymerase are nonstructural proteins (Clark, Green, Petit, & Dutch, 2021). S-protein that exists as a trimer consists of two subunits (S1 and S2 subunits), they play an important role in viral infection due to their recognition and attachment to the host cell receptor, mediation of cell-cell fusion, and neutralization antibodies (Suryadevara *et al*., 2021). SARS-CoV-2 receptor-binding domain (RBD) situates in the S1 subunit and binds to the angiotensin-converting enzyme-2 (ACE2) receptor, which is presented on the surface of host cells, and S2 which changes its conformation and inserts its fusion peptide into the target cell membrane, allowing viral entry into the host cell (Huang, Yang, Xu, Xu, & Liu, 2020).

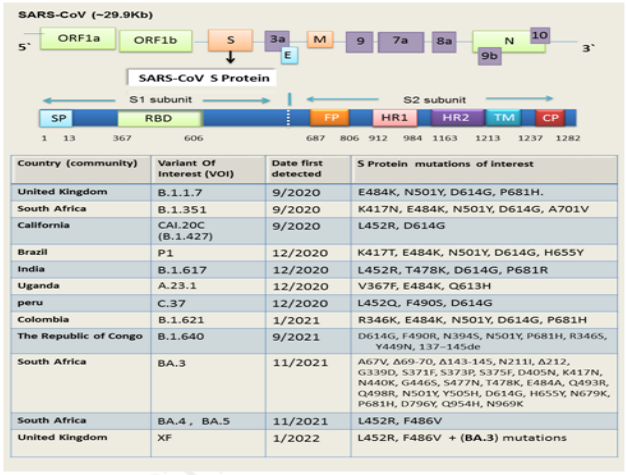
HCoVs pathogenic mechanisms are not yet fully elucidated. By studying the specific characteristics of each CoV, it is possible to differentiate between other HCoVs, including SARS-CoV, MERS-CoV, and SARS-COV-2(Song *et al*., 2004). Viral entry was done through the interaction between the target cell receptor and the viral S-protein in the sensitive host cell. Therefore, one of the S-subunits of S1 protein, including RBD, should be recognized and bounded by the target receptor. The second subunit, S2, is responsible for membrane fusion (Kirchdoerfer *et al*., 2016). Tissue affinity is primarily determined by the connection between the S-protein, the target receptacle, and the sensitive host organism (Yuan *et al*., 2017). Instead of the usual evidence-based receptors, HCoV uses a variety of biological receptors. HCoV-NL63, SARS-CoV-2, and SARS-CoV30 use the ACE2 receptor, which is one of these cellular receptors (Tipnis *et al*., 2000).

ACE2 is a secretory enzyme with a trans-membrane domain; it is the only efficient metalloprotease location, and a signal peptide (Wu, 2020). It is mainly present in the cell nucleus, vascular endothelium, gastrointestinal epithelium, alveolar macrophages, respiratory monocytes, trachea, bronchi, and alveolar epithelial cells. In contrast, ACE, which causes the pathogenesis of lung failure,

pulmonary edema, and lung damage (ALI), ACE2 protects against SARS (ALI). In a mouse model of acute respiratory distress syndrome (ARDS), the lack of ACE2 exacerbated symptoms of lung function, which could be recovered by recombinant ACE2. Blocking the renin-angiotensin system may help to prevent lung damage caused by SARS-CoV infection. Overall, ACE2 has the potential to become a new therapeutic target for most common respiratory diseases (Imai *et al*., 2005).

2.1. SARS-CoV-2 mutations

Viruses can acclimatize to a new host and/or escape their immune responses via genetic mutations. Generally, a mutation happens as a result of errors in the genome replication process, either in the viral DNA or RNA genomes. It resulted in changes in some components of the virus particles or rearrangement of the amino acids that, in turn, causes a partial or full conversion in the way of infection, adaptation, and transmission in addition to the rapidity of the viral spread. SARS-CoV-2 acquired significant genetic diversity due to the high transmission speed since its first detection in China in late-December 2019 (Zhu *et al*., 2020). SARS-CoV-2 mutations occurred in the virus particles; S ", E, M, and N proteins, chiefly S protein and its RBD domain. These mutations can explain the fast spread of SARS-CoV2 globally (Jakhmola *et al*., 2021).



Country (community)	Variant Of Interest (VOI)	Date first detected	S Protein mutations of interest
United Kingdom	B.1.1.7	9/2020	E484K, N501Y, D614G, P681H.
South Africa	B.1.351	9/2020	K417N, E484K, N501Y, D614G, A701V
California	CAI.20C (B.1.427)	9/2020	L452R, D614G
Brazil	P1	12/2020	K417T, E484K, N501Y, D614G, H655Y
India	B.1.617	12/2020	L452R, T478K, D614G, P681R
Uganda	A.23.1	12/2020	V367F, E484K, Q613H
peru	C.37	12/2020	L452Q, F490S, D614G
Colombia	B.1.621	1/2021	R346K, E484K, N501Y, D614G, P681H
The Republic of Congo	B.1.640	9/2021	D614G, F490R, N394S, N501Y, P681H, R346S, Y449N, 137–145de
South Africa	BA.3	11/2021	A67V, Δ69-70, Δ143-145, N211I, Δ212, G339D, S371F, S373P, S375F, D405N, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, D796Y, Q954H, N969K
South Africa	BA.4 , BA.5	11/2021	L452R, F486V
United Kingdom	XF	1/2022	L452R, F486V + (**BA.3**) mutations

Figure 1. Major mutations of SARS-CoV-2 around the world; this diagram shows the Covid-19 mutations around the world, such as B.1.621 and its mutations like E484K, N501Y, P681H, R346K, Y144T, Y145S, 46N that found in Colombia, CAI.20C(B.1.427/B.1 .429) and its mutations W152C, L452R that found in California, B.1.1.7 and its mutations N439K, S477N, S477R, N501T, N501Y, A570D, **Δ**H69/V70, **Δ**144/145, P681H, T716I, S982A, D1118H that found in The United Kingdom, B.1.617 and its mutations T19R, K27T, T95I, G142D, E154K, N440K, L452R, T478R, E484Q, D614G, P681R, D950N, Q1071H, H1101D, B.1.617.2.1 (AY.1/2), B.1.617.2 that found in India, P.1 and its mutations L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F that found in Brazil, B.1.351 and its mutations N501Y, E484K, K417N that found in South Africa, and Lambda (C.37) and its mutations Δ246-252, G75V, T76I, L452Q, F490S, D614G, T859N that found in Peru

D614G mutation (Aspartic acid "D" at 614 sites "wild type" to G614 Glycine "G" Mutant type) that occurred in S-protein has dominated since June 2020 among the numerous SARS-CoV-2 variants worldwide. It became ubiquitous and associated with increasing viral transmissibility during the early stages of the pandemic (Jakhmola *et al*., 2021). COVID-19 patients' sera and sera from vaccinated people were found to have a minor inhibitory effect on D614G (Weissman *et al*., 2021). New variants frequently appeared in many high-income countries, these lineages that affect viral virulence, immunogenicity, and transmission are divided into "variants of concern" (VOCs) and "variants of interest" (VOIs). They include B.1.1.49, which emerged in Denmark, B.1.525/VUI-202102/03, which emerged in the UK, and A.23.1, which was first detected in Uganda (Cherian *et al*., 2021) (Figure 1).

At the beginning of 2020, three global VOCs carrying several mutations, including the RBD of S-protein, emerged. The B.1.1.7 variant, first discovered in the United Kingdom (UK)(Chand *et al*., 2020), it has about 17 mutations, including the N501Y mutation that promotes fast transmission and more severe illness than the other circulating viruses (Leung *et al*., 2021). By the beginning of 2021, the B.1.1.7 variant became the main lineage in the UK and Europe, increasing the reported cases in the United States (US) (Washington *et al*., 2021). The presence of N501Y mutation in the RBD was associated with an increase in the virus's transmissibility (Leung *et al*., 2021). The second VOC is B.1.351 variant (501Y.V2), also known as the South Africa variant (Mwenda *et al*., 2021), and the third one is P.1 (501Y.V3), which was also known as the Brazil variant (Sabino *et al*., 2021). The S protein of these variants exhibits 9 and 11 mutations, respectively, including three mutations in the RBD domain; K417N/T, E484K, and N501Y (CDC). Antibody neutralization resistance was suggested, particularly with E484K mutation (Wang *et al*., 2021; Wibmer *et al*., 2021). Consequently, the efficacy of currently available vaccines could be decreased (Liu *et al*., 2021). According to the Global Initiative on Sharing All Influenza Data (GISAID), B.1.620 was the most common variant in many European countries and the US. It was characterized by its rapid transmission. This lineage was deemed to have plenty of mutations and deletions that affect antibody-mediated immunity (Dudas *et al*., 2021).

Entry of B.1.351, P.1, and B.1.1.7 variants to human cells can be blocked by soluble ACE2 (sACE2), inhibitors of Transmembrane Serine Protease 2 (TMPRSS2) protease activity, and the membrane fusion inhibitors. However, cell entry of P.1 and .1.351 variants via S-protein could not be completely inhibited by the monoclonal antibodies. Furthermore, sera from persons who had been immunized with Pfizer BNT162b2 and convalescent plasma had weaker inhibitory effects on these variations. These results pointed out those strategies depending on antibody-mediated inhibition of SARS-CoV-2 infection are at risk of the emergence of resistance (Hoffmann *et al*., 2020). A new variant with L452R mutation in RBD of S-protein was reported in California in January 2021 (Deng *et al*., 2021;

W. Zhang *et al*., 2021). The next strain nomenclature system was termed 20C/L452R (Githup), while the Pango system identified the new variant as B.1.427/B.1.429 (Rambaut *et al*., 2020). The variant frequency increased from 0% at the beginning of September 2020 to more than 50% by the end of January 2021, increasing the transmissibility of B.1.427/B.1.429, when compared with the non-B.1.427/B.1.429 lineages which only increased by 18.6- 24.2% (Deng *et al*., 2021). The investigators recognized two diverse lineages accompanied with the novel clade 20C: B.1.427 and B.1.429. B.1.427/B.1.429 variant has four new coding mutations; three of which are found in the S protein (W152C, S13I, and L452R), but not in the B.1.351, B.1.1.7, P.1 VOCs, or the other major spreading variants, one coding mutation in the orf1b (D1183Y), as well as two non-coding mutations. Four further mutations have been discovered, one of which is a coding mutation orf1a: I4205V related to B.1.429, and three of which are non-coding mutations related to B.1.427 (Deng *et al*., 2021). When compared to circulating wild strains, the viral transmissibility of the B.1.427/B.1.429 strain increased by 18.6–24%. Furthermore, they exhibited moderate resistance to the neutralizing antibodies elicited by the convalescent plasma (4.0 to 6.7-fold) or the sera of the vaccinated people (2-fold) (Zhang *et al*., 2021).

Data of 97.8% sequenced genomes in a study assessed by Baden *et al*.(Baden *et al*., 2021) indicated that the median PCR cycle threshold (Ct) value of infection caused by B.1.427/B.1.429 was significantly lower ($p=3.47x10^{-6}$) than that caused by the non-variant viruses. Additionally, B.1.427/B.1.429 contains the N/NP viral RNA higher than that present in non-variant viruses by two-fold in a swab sample (Drew, O'Donnell, LeBlanc, McMahon, & Natin, 2020). The viral infectivity by L452R may increase via stabilizing the S protein interaction with the ACE2 receptor (Teng, Sobitan, Rhoades, Liu, & Tang, 2021). Chand *et al*. (Chand *et al*., 2020)validated these findings, reporting that pseudoviruses loaded with L452R caused more lung organoids and 293T cells infection. Unlike N501, which changed to Y501 in B.1.351, P.1, and B.1.1.7 and was associated with increased transmissibility, the L452R variation did not directly bind with the ACE-2 receptor. Because L452 is located in the spike RBD hydrophobic patch, it produced structural changes in the domain that support the S-protein-ACE2 receptor connection (Xianding Deng *et al*., 2021).

L452R pseudo-viruses infectivity was greater than that of D614G by 6.7 - 22.5-fold in 293T cells and 5.8 - 14.7-fold in HAOs, but less than N501Y pseudo-virus, which had 23.5 to 37.8-fold in HAOs and 11.4 to 30.9-fold rise in 293T cells when compared with D614G (Hoffmann *et al*., 2020; Washington *et al*., 2021). Furthermore, when compared to D61497, the pseudo-viruses loaded with W152C showed a small increase in HAO and 293T cell infection (Xianding Deng *et al*., 2021). The effect of L452R on antibody binding was studied in Vero TMPRSS2 cells (Xianding Deng *et al*., 2021) using about 21 vaccine recipient' plasma (after the second dose by 4-28 days) and convalescent patients (18 to 71 days after the onset of symptoms) to compare the neutralization titers between B.1.429 and the USA-WA1/2020 as a control isolate. The study's results revealed that 88% of convalescent patients and 55% of vaccinated individuals with Pfizer BNT16b2 or Moderna mRNA-1273 had reduced PRNT50 titers plaque reduction neutralization of B.1.429 when compared with USA-WA1/2020, with median reductions of 6.7-fold ($p = 0.016$) and 2-fold ($p = 0.031$), respectively, with non-statistically significant difference between convalescent and post-vaccination plasma.

Additionally, about 90% of convalescent patients had lower TCID50 titers (Median tissue culture infectious dose at which half of the cultures displayed cytopathic effect), with median reductions of 5.3-fold and 4.0-fold for the USA-WA1/2020 and D614G, respectively. These findings backed up a previous study that found a reduced interaction between pseudo-viruses carrying the L452R mutation and antibodies from COVID-19 patients who had previously been infected. Escape from neutralization was seen in 75% of convalescent plasma samples (Zhuoming Liu *et al*., 2021).

The B.1.617 is the most frequent clade in India, and it is a new lineage with characteristic mutations G142D, D111D, E484Q, L452R, P681R, and D614G in the spike protein RBD. Otherworld variants have a mutation at 484, 452, and 681 positions. The structural analysis of E484Q, L452R, and P681R mutations in the furin cleavage site found that they increased ACE2 receptor binding and S1-S2 complex cleavage rate, resulting in increased transmissibility (Cherian *et al*., 2021). Certain monoclonal antibodies (mAbs) showed a poorer binding interaction with L452R and E484Q unique mutations than the wild-type strain, which may affect their neutralizing potential (Cherian *et al*., 2021; Y. Liu *et al*., 2021; Zhuoming Liu *et al*., 2021). These results were confirmed by Motozono *et al*, who verified that L452R mutation could evade the host's immune response, thus, increasing the viral infectivity and replication. Finally, E484Q has also been discovered in various sequences of GISAID, with the earliest strain being discovered in Denmark. P681H is among the B.1.1.7 (UK-variant) mutations, whereas P681R is a mutation in the VUI lineage A.23.1 (Cherian *et al*., 2021) (Figure 1).

In South America, a new SARS-CoV-2 lineage known as C.37 was identified. The Spike gene has a unique deletion (S:247-253, located in the N-terminal domain) and six nonsynonymous mutations (G75V, T76I, D614G, L452Q, F490S, T859N). The L452Q and F490S mutations corresponded to the RBD region of the S protein. The L452Q mutation was nearly completely similar to C.37 (Romero *et al*., 2021). The F490S has been linked with lower susceptibility to antibody neutralization in *vitro* (Z. Liu *et al*., 2021), while the T76I and L452Q mutations have been associated with the high infectivity of C.37 (Kimura *et al*., 2021). The ORF1a:3675–3677 deletion, which was seen in VOCs Alpha, Beta, and Gamma, was also present in C.37 (Sugden *et al*., 2021). This deletion was first reported in late December 2020 in Lima, Peru. By April 2021, it accounted for 97% of Peruvian public genomes. In addition to Chile and Argentina, this variant has been discovered in

Colombia, Ecuador, Mexico, The United States of America, Germany, and Israel (Romero *et al*., 2021). C.37 was classified as a VOI Lambda by WHO on June 15, 2021. Convalescent sera and vaccine-induced antibodies were used to assess the infectivity and sensitivity to neutralizing the Lambda mutant virus. It had increased infectivity and was neutralized with a titer fall of 2.3-3.3-times on average. The virus was neutralized by the regeneron therapeutic monoclonal antibody combination with no titer loss. According to the findings reported by (Tada *et al*., 2021); existing vaccines in addition to the monoclonal antibody therapy could protect against the lambda virus.

Delta plus variant was first discovered in India and has since spread to different countries such as the UK, US, Turkey, Russia, Canada, Switzerland, Portugal, Nepal, Japan, and Poland. The majority of reports have been collected mainly from the US, the UK, and Portugal. Delta with K417N mutation was the name given to this new variation. “AY.1” and “AY.2” are two Delta Plus variants that are steadily spreading worldwide. “AY.1” is widespread worldwide, whereas “AY.2” is perplexing in the United States, where it has been detected (Dasgupt, 2021).

Delta Plus versions are causing much concern. The mutant form is resistant to the monoclonal antibodies Casirivimab and Imdevimab, which were approved by the Central Drugs Standard Control Organization for use in the COVID-19 cocktail treatment (CDSCO). Until now, it has been impossible to anticipate the efficacy of all vaccines against Delta, as well as the effect of Delta infection on the lungs and other body organs, without doubting the vaccine's efficacy (Roy & Roy, 2021). Delta variant has small variations in breakthrough infection rates between Alpha and Delta forms, according to studies from India, where the population was still seeking mass immunization initiatives. In particular, the efficacy of BNT162b2 against symptomatic infection was documented to have decreased from 93.7 percent against Alpha to 88.0 percent against Delta. Furthermore, according to data from the United States, BNT162b2 vaccine efficacy towards infection with Delta variant decreased from 93% one month from vaccination to 53 % after four months, indicating that vaccine efficacy has waned over time (Evans *et al*., 2022).

Mu variant, also known as B.1.621, was a novel coronavirus strain that was discovered in Colombia (1) and has spread throughout the world, creating outbreaks (2). According to the World Health Organization, mutations may allow the new variety, mu, to attach to people's immunity built from previous infection or immunization (2). The immune system and existing vaccinations were both resistant to mutations (1). More research is needed to determine whether the mu variation is more deadly or resistant to existing vaccines and therapies, as well as to learn more about the new variant's features (Sarmiento, 2021).

They recently discovered that SARS-CoV-2 Mu variant is resistant to antibodies produced by natural SARS-CoV-2 infection and immunization. Nevertheless, it is still unknown which mutations explain SARS-CoV-2 Mu's resistance to antiviral sera. In addition, the mechanism by which SARS-CoV-2 Mu infection produces antiviral immunity is unknown. They show that the two mutations in the SARS-CoV-2 Mu spike protein, YY144-145TSN, and E484K, are responsible for COVID-19 convalescent and vaccination sera resistance in early 2020. Notably, SARS-CoV-2 Mu-infected people's convalescent sera are widely antiviral against Mu and other SARS-CoV-2 variants of concern/interest.(Keiya Uriu, 2022).

In the province of Botswana, South Africa, a new mutant of the COVID-19 virus called Omicron (B.1.1.529) was identified by the World Health Organization on November 26, 2021 as a worrying variant (WHO, 2021d). The researchers were able to determine the genetic sequence of this mutation in Botswana, and that it contains more than 30 changes in the Spike protein (Callaway, 2021). These changes increased its ability to infect and avoid antibodies. This increase the number of people infected with this mutation, and there is still an increase in numbers in Gauteng state (Graham, 2021).This new mutant is still under study to know more information about it, its side effects, and the ability of vaccines to resist it (Noorden, 2021).

The high numbers of mutations in the Omicron RBD and NTD, which are the principal targets of neutralizing antibodies, increases the danger that the variant will be resistant to neutralization by present EUA-approved vaccine-elicited antibodies, leading to reduced infection protection. They discovered that Omicron spike protein was particularly resistant to neutralization by serum antibodies in people who had received two Pfizer or Moderna mRNA vaccine vaccinations. A 6- to 8-fold rise in neutralizing antibody titers following homologous booster vaccination with an mRNA vaccine was projected to give a high level of protection. The Regeneron and Eli Lilly cocktail monoclonal antibodies failed to destroy the virus with the Omicron spike protein, whereas the efficacy of VIR-7183 (Sotrovimab) and the Evusheld monoclonal antibodies was severely reduced (Tada *et al*., 2022).

From 2021 new mutations arises; V-22APR-01 (XD), which has an Omicron S gene inserted into a Delta genome, is mostly found in France, but has yet to be discovered in the United Kingdom. Although the overall number of genomes is still modest, it has been identified based on data released in France that suggests it is physiologically different. V-22APR-02 (XE) is a BA.1/BA.2 recombination with most of its genome containing the BA.2 S gene. Although it is less than 1% of all sequenced samples, XE indicates signs of population transmission in England. In England, 1,125 cases of XE was already identified as of April 5th. The designation of XE was made based on community transmission and potential growth in England. V-22APR-03 (Omicron sub-lineage BA.4); on April 6, 2022, the VTG was categorized Omicron sub-lineage BA.4 as V-22APR-03. BA.4 was named after a spike mutation that had the potential to be biologically significant. Excluding the following mutations/deletions, V-22APR-03 (later referred to as BA.4) shares all mutations/deletions with the BA.2 lineage: S: 69/70 deletion, L452R, F486V, Q493 (WT); ORF 7b: L11F; N: P151S. NSP4: L438 (WT, wild type); S: 69/70 deletion, L452R, F486V, Q493 (WT); ORF 7b: L11F; N: P151S. The loss of the S gene 69/70 is linked to S gene target failure (SGTF).

Around 10 January 2022 and 30 March 2022, sequencing data from South Africa (45), Denmark (3), Botswana (2), Scotland (1), and England were discovered in GISAID (1). V-22APR-04 (Omicron sub-lineage BA.5); on April 6, 2022, the VTG categorized Omicron sub-lineage BA.5 as V-22APR-04.Except for the following mutations/deletions, V-22APR-04 (also known as BA.5) shares the same mutations/deletions as BA.4 (V-22APR-03): ORF 6: D61 (WT); ORF 7b: L11 (WT); N: P151 (WT); synonymous SNPs: A27038G and C27889T. M: D3N; ORF 6: D61 (WT); ORF 7b: L11 (WT); N: P151 (WT). On February 25 and March 25, 2022, all data submitted to GISAID were from South Africa (Agency, 2021).

2.2. SARS-CoV-2 vaccines

Inside the host cell, the virus starts to propagate, and in response, the innate immunity will be activated (Shang *et al*., 2020). However, in COVID-19 infections, the activity of dendritic cells (CDs) will be suppressed; furthermore, interferon type I and III production will be delayed (McAndrews *et al*., 2020; Remy *et al*., 2020). This alteration of interferon type I lead to massive damage and death of airway epithelia and parenchyma (Prompetchara, Ketloy, & Palaga, 2020). This hyper-innate inflammation could put the COVID-19 patients at high risk of severe conditions (Zhu *et al*., 2020). Adaptive immunity is considered a master key that protecting the human body against viruses invading. Firstly, the humeral immunity response is mediated by antibody (IgG and IgM) production against S-protein that helps in neutralizing the activity of SARS-Cov-2 (Dan *et al*., 2021). Then, the cellular immunity includes T-cells, CD4+, and CD8+ T-lymphocytes.

Moreover, helper T-cells stimulate the B-cells for antibody production and enhance the differentiation into memory cells (S. Kumar, Nyodu, Maurya, & Saxena, 2020). However, more recent studies on COVID-19 patients with acute respiratory syndrome demonstrated that their activity of $CD8^+$ was suppressed; leading to insufficient B-cell activity and delaying the clearance of virally infected cells (Yao *et al*., 2021). We can conclude that there is dis-regulation of both innate and adaptive immune responses in COVID-19 patients. Therefore, unproven technology-based vaccinations can greatly contribute to the containment of the pandemic, which has caused over 1,5 million fatalities so far by eliciting the immune response. This immune response builds immune memory, so our bodies can fight off SARS-CoV-2 in the future (Cohen, 2020).

There are many types of active immunization according to which part of the pathogen is introduced or the state of that antigen introduced to individuals (Figure 2). Adaptive immunity is considered a master key protecting the human body against virus invasion; humeral immunity response is mediated by antibody (IgG and IgM) production against S-protein that help in neutralizing the activity of SARS-Cov-2 (Dan *et al*., 2021), then, the cellular immunity including T-cells, CD4+, and CD8+ T-lymphocytes. However, McAndrews *et al*. (2020) and Remy *et al*. (2020) mentioned that the activity of dendritic cells (CDs) is suppressed, and production of interferon type I and III production are delayed during COVID-19 infections and this leads to massive damage and death of airway epithelia and parenchyma (Prompetchara *et al*., 2020). Nevertheless, more recent studies on COVID-19 patients with acute respiratory syndrome demonstrated that $CD8^+$ activity was suppressed leading to insufficient B-cell activity with delaying the clearance of virally infected cells (Yao *et al*., 2021). This hyper-innate inflammation could put the COVID-19 patients at high risk of severe conditions (Zhu *et al*., 2020). There are many types of active immunization according to which part of the pathogen is introduced or the state of that antigen introduced to individuals (Figure 2).

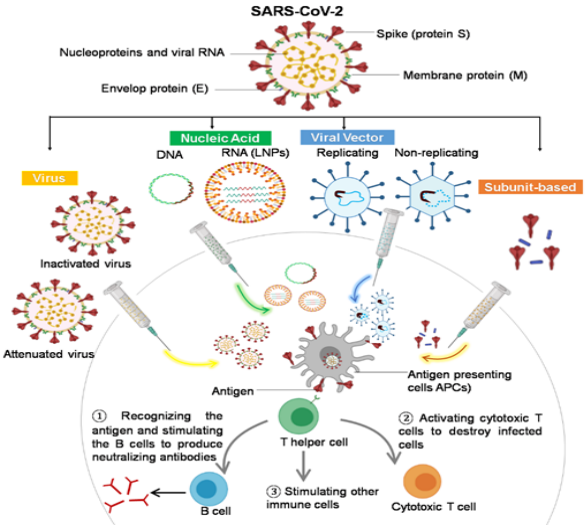


Figure 2.The immune response against different SARS-CoV-2 vaccines. Different SARS-CoV-2 safely deliver an immunogen (antigen able to elicit an immune response) to the immune system in order to train it to recognize the pathogen when it is encountered naturally by activating CD4+ helper T cells that in turn stimulate 1) B-cells to produce neutralizing antibodies specific to the virus, 2) CD8+ cytotoxic T cells to recognize and kill cells infected by the virus and/or 3) other immune cells and other pathways

Production of effective vaccines is considered the only way to create mass immunity. In this regard, many companies in different countries used advanced technologies to produce a variety of vaccines, including RNA, DNA, virus-like particles, and subunit vaccines by applying pre-clinical and clinical trials to thoroughly investigate any side effects of these vaccines.

Attenuated vaccines: attenuated vaccine, or live virus vaccine, causes a mild infection of a disease by using a weakened virus that starts an immune response without causing disease. The attenuated virus must replicate to elicit the desired immune response, which resembles the natural infection (Verch, Trausch, & Shank-Retzlaff, 2018). Since July 7, 2020, at least 160 vaccines across the world have been developed. However, only four live-attenuated SARS-CoV-2 developed vaccines remain in the clinical stage. The vaccines are 1-Codagenix/Serum Institute of India, 2-Indian Immunological Ltd./Griffith University, 3-Mehm*et al*i Aydinlar University/AcıbademLabmed Health Services AS,and 4-Meissa Vaccines (Sumirtanurdin & Barliana, 2021).

Inactivated vaccines; are obtained by replicating SARS-CoV-2 in cell culture, and then making the virus non-infectious either chemically or physically by heat. The coronaviruses in the inactivated vaccines are dead, so when injected into the human body with an adjuvant to boost immune response, they do not cause COVID-19 illness (Wang, Shang, Jiang, & Du, 2020). Inactivated vaccines (in advanced Phase III development) are being developed by BBIBP-CorV (Sinopharm + Beijing Institute of Biological Products) (Xia *et al*., 2020), CoronaVac (Sinovac Biotech) (Y. Zhang *et al*., 2020), and Covaxin (Bharat Biotech) (Ella *et al*., 2021) (Figure 3).

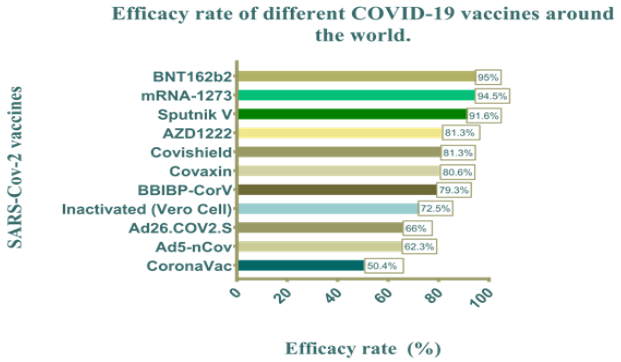


Figure 3: Efficacy rate of different SARS-CoV-2 vaccines around the world. The adenovirus-vectored and mRNA-based vaccines for COVID-19 had the greatest efficacy after the first and second doses, respectively. The mRNA-based vaccines, such as BNT162b2, mRNA-1273, and Sputnik V, showed greater efficacy. On the other side, vaccines such as Corona Vac have had the least amount of an impact

Protein subunit vaccines (Table 1); are those based on synthetic peptides or recombinant proteins. They contain unique viral antigenic fragments, specific parts that the immune system needs to recognize, without infectious virus components. Thus, the problems of live-attenuated/inactivated viral vaccines and viral vectored vaccines, such as incomplete inactivation of infectious components, virulence recovery, or pre-existing anti-vector immunity, are avoided in the subunit vaccines (Wang *et al*., 2020). Accordingly, Protein subunit vaccines are created by either synthesizing protein antigens using recombinant technology or cultivating large amounts of the pathogen *in vitro*, then isolating and purifying proteins (Kyriakidis *et al*., 2021). Adjuvants can be added to the protein subunit vaccines to overcome their limitation by enhancing their immunity, and their biological half-life (Ryzhikov *et al*., 2021). According to Wang *et al.* (Wang *et al*., 2020), many factors affect the immunogenicity of SARS-CoV-2 subunit vaccine candidates, for instance, protein length, amino acid mutations or deletions, immunization route, and adjuvant type. The ZF2001 Corona vaccine is based on chemically synthesized SARS-CoV-2 S-protein-peptide antigens conjugated to a carrier protein and adsorbed to aluminum hydroxide as an adjuvant, like the EpiVac vaccine (Ryzhikov *et al*., 2021). Although the EpiVac Corona vaccine is already approved for use, there are no available peer-reviewed articles about its efficacy or immunogenicity (Doroftei *et al*., 2021). Many subunit vaccines are also under active clinical trials, such as SCB-2019 (Richmond *et al*., 2021), Baculovirus/ Spodopterafrugiperda (SF9) (Yang *et al*., 2020), NVX-CoV2373 (Tian *et al*., 2021), Adjuvanted SARS-CoV-2Sclamp (Watterson *et al*., 2021), KBP-201(ClinicalTrials.gov., 2020), COVAX-19 (Das, A, Paul, & Ghosh, 2021), MVC-COV1901 (Kuo *et al*., 2020), SOBERANA 01 (FINLAY-FR-2) (Malik *et al*., 2021), etc.

There were 126 vaccines in clinical trials of which 43 vaccines (34%) were protein subunit vaccines. Different S-protein subunits including RBD-Fc, RBD, and the N-terminal domain of S-protein have shown different degrees of immune responses in several animal models (Adney *et al*., 2019). This made the synthetic-protein subunit vaccine one of the safest and most effective vaccines used to fight SARS-CoV-2. Recombinant spike protein is expressed in various cell lines such as the Spodoptera frugiperda (Sf9) insect cell expression system within the baculovirus, in addition to the Chinese hamster ovary (CHO) cell line (Johari *et al*., 2020) Since, peptides are often unstable; they were typically packaged into nanoparticles adsorbed onto specific adjuvant to increase their immunogenicity. Adjuvant type plays an important role in the effectiveness of the vaccine (Korber *et al*., 2020) Protein subunit vaccines are characterized by their safety profile because of the absence of handling with live virus particles; cost-effectiveness; consistent production with inducing strong cellular and humoral immune responses, however, the need for an effective adjuvant is essential to achieve higher immunogenicity.

The first group of the SARS-CoV-2 subunit vaccines uses the S protein as antigens. They include the SCB-2019 vaccine (Clover Biopharmaceuticals AUS Pty Ltd.), NVX-CoV2373 (Novavax), and Covax-19 (GeneCure Biotechnologies; Vaxine Pty Ltd.), the vaccine developed by the University of Queensland and MVC COV1901 (Medigen Vaccine Biologics Corp.). The second group is subunit vaccines employing the RBD domain of S protein as an antigen: KBP-COVID-19 (Kentucky BioProcessing, Inc.) and vaccine from Anhui Zhifei Longcom Biologic Pharmacy Co., Ltd. Vaccine NVX-CoV2373 (Novavax) is currently in phase 3, and others subunit vaccines against SARS-CoV-2 are in phase 1 or 2 of clinical trials (Table 1).

Naked DNA-based vaccines; are purified plasmid DNA that is not linked to lipids, protein, or any other protecting molecule and is released after the cell bursting (Pushparajah *et al*., 2021). Directly following the injection, plasmid DNA enters the cell and enforces it to produce the target protein. DNA-based vaccines boost antibody production and stimulate killer T-cells (Forni *et al*., 2021). Currently, no DNA vaccines are approved for human use in the case of COVID-19; however, six candidates are currently undergoing clinical trials. All the coding for the S protein or its fragments are either Naked DNA plasmids as ZydusCadila, India; Anges, Japan, and Takis, Italy or Naked DNA plasmids plus electroporation as Inovio, US; Genexine, Korea and KarolinskaInst, Sweden + Inovio, Italy (Forni *et al*., 2021).

MRNA–based vaccines (Table 2); in contrast to DNA, RNA must be carried to the human cells in various ways. When the mRNA vaccine enters, it temporarily stimulates the cells to produce the mRNA-coded antigenic protein (Forni *et al*., 2021). Furthermore, the target protein is mostly expressed by the S-protein, its variants, or its fragments. These vaccines have to be maintained at −30 to −80 °C (McAndrews *et al*., 2020). There are many mRNA–based vaccines under clinical trials, such as Pfizer BNT162b2 (Polack *et al*., 2020), Moderna mRNA-1273 (Baden *et al*., 2021), CVnCoV (CureVac) (Kremsner *et al*., 2020), ARCoV (Sagili Anthony, Sivakumar, Venugopal, Sriram, & George, 2021) (Academy of MilitaryMedical Sciences, Suzhou AbogenBiosciences and Walvax Biotechnology), and HGC019 (Genova/ HDT Biotech Corporation) (Sagili Anthony *et al*., 2021).

Viral vector vaccines (Table 3); are made by recombination of a part of SARS-CoV-2 genetic information (+ss RNA) with viral expression vectors (Lundstrom, 2020). The used genetic information is coding for the virus' spike proteins, while the vector used for delivery is a harmless virus. The infected host cells express and produce viral proteins forming an increased number of antigens that trigger the immune response (WHO, 2021a). The immune response involves antibody production of B-cells and T-cells; the latter identifies and destroys infected cells by recognizing the antigen's distinguished proteins' repertoire on the cell surface (Jeyanathan *et al*., 2020). Adenovirus-associated virus (AAV); Poxviruses, and Measles in mice, and Rhabdoviruses in hamsters were showed neutralizing antibody induction and functional memory T-cells responses (Zabaleta *et al*., 2021). The main viral vector to proceed to phase III was the non-replicating physically and genetically stable adenovirus (Ad) vector that targets mucosal inductive sites and dendritic cells (Shang *et al*., 2020). Interestingly, Oxford and AstraZeneca (ChAdOx1 nCoV-19) are approved to have a strong immune response with single delivery and a lack of pre-existing anti-vector immunity (Knoll & Wonodi, 2021) 18 Viral vector vaccines are still in the preclinical stage including Max-plank institute and Arizona university. 4 vaccines in Phase 1 and the MEDICAGO INC./ GLAXOSMITHKLINE vaccine Plant-based virus-like particle is currently in Phase 3 ((NACI), 2022; "Clinical Trial. Study of a Recombinant Coronavirus-Like Particle COVID-19 Vaccine in Adults.

3. Routes of vaccination

The most common route of administration of vaccines has been known to be the intramuscular route (Kyriakidis *et al*., 2021). It was revealed by clinical trials to be more immunogenic and cause fewer adverse effects than the subcutaneous route (Cook *et al*. 2006; Mark, 1999). However, the intradermal route was recommended by Schnyder *et al*. (2020) due to having a lower dose of the vaccine (Schnyder *et al*., 2020). Different routes of vaccination were found to exert their action by different mechanisms. In addition, the efficacy of the vaccination route could be related to its platform technology, such as DNA, mRNA, or adenoviral vector vaccine. Mucosal vaccinations have the potential to elicit strong protective immune responses in the areas where pathogen infection is most common. In theory, inducing adaptive immunity at mucosal locations through secretory antibody responses and tissue-resident T cells has the potential to prevent infection from occurring in the first place, rather than only curtailing infection and preventing the development of disease symptoms (Lavelle & Ward, 2022) Despite having more advantages than peripheral vaccination, mucosal vaccine development is challenging due to the lack of knowledge about mucosal immunity (Mestecky *et al*., 2007). Nasal vaccination strategy has been at the forefront of the alternative vaccine delivery routes being investigated. Immune response in the lower respiratory tract (LRT) is induced by intramuscular vaccination, but not in the upper respiratory tract (URT). Intranasal immunization, on the other hand, confers protection not just to the URT but also provides systemic immunity (Lijek *et al*., 2012; Lycke, 2012).

3.1. SARS-CoV-2 vaccines side effects

BLOOD CLOTTING DISORDER: The clots related to the AstraZeneca and Johnson &Johnson vaccines have distinct characteristics: they occur in odd body locations, including the brain or belly, and they are accompanied by reduced platelet numbers, which help blood coagulate (Ledford, 2021). Further data detected that heparin-induced thrombocytopenia (HIL) occurred in rare cases after taking the anticoagulant heparin (Muir *et al*., 2021). Notably, the HIT-like symptoms were detected with sputnik V, another vaccine based on the mRNA platform; therefore, the problem might be common to adenovirus vaccines (Gupta *et al*., 2021). However, there have been no published data on thrombosis or thrombocytopenia associated with Convidecia treatment (Trials, 2021). On the other hand, vaccines composed of mRNA encapsulated in lipid nanoparticles, such as Moderna and Pfizer-BioNTech, do not induce thrombosis and thrombocytopenia (Gupta *et al*., 2021). Recently, Moderna and Pfizer-BioNTech's possibility to trigger thrombocytopenia cannot be excluded, albeit very rarely (Lee *et al*., 2021) as cleared in Figure 4. There are also potential psychiatric and psychological consequences of vaccine-induced immune thrombotic thrombocytopenia, also known as vaccine-induced immune thrombocytopenia, and thrombosis, including depression and anxiety.

Skin manifestations: Some complications have been detected, such as "COVID ARM," a skin symptom that appeared coinciding with the start of taking the various SARS-CoV-2 vaccines, as a localized erythematous rash with redness and swelling surrounding the injection site (Baden *et al*., 2021; Bhopal *et al*., 2021; Rice at al., 2021). However, after the first and second doses of both Moderna and Pfizer-BioNTech vaccines, the injection site reactions were recorded after eight days(Fernandez‐Nieto *et al*., 2021), with mild pain to from the Pfizer vaccine, disappeared within 24 hours (Munavalli *et al*., 2021). Similarly, skin symptoms were recorded in November 2003 in the US; about 5 cases had an erythematous papule on the lower limbs for 12 hours after receiving the influenza vaccine (Jovanović at al., 2005). In addition, some cases of

dermatitis were reported after influenza vaccination (Gonnet *et al*., 2020). The published data about cutaneous adverse events from three major completed SARS-CoV-2 vaccine trials phases I, II, and III in the US, UK, Brazil, and South Africa demonstrated the development of rosacea flare, pruritus; cellulitis after ChAdOx1 nCoV-19, maculopapular rash, and transient urticaria on both legs five days after receiving the first dose of Moderna vaccine (Baden *et al*., 2021), as well as, 0.63% of hypersensitivity related to Pfizer-BioNTech vaccine (Munavalli *et al*., 2021). With filler injections (Sayan *et al*., 2021), a recent controversy overuse of COVID-19 vaccinations has been dea recent controversy over the use of COVID-19 vaccinations has been seen. FAD brief to Moderna vaccine reported reactions to dermal filler in different areas in three patients after vaccination, two of them had a facial swelling after six months of filler injection, and the other one had a lip swelling with unknown time of filler injection; however, there is no hereditary angioedema or positive SARS-CoV-2 (Rice *et al*., 2021).

On the other hand, since questions about the date of filler injection are not part of a standard assessment, no such reactions have been documented with the Pfizer vaccination. However, some cases with a slight eye swelling or inflammation in the filling areas were improved within 24 hours to four days (Munavalli *et al*., 2021). In comparison, Sinopharm and Sinovac caused only pain at the injection site in 14 cases (Bhopal *et al*., 2021). The reports of blood analysis for 46 samples that got the vaccination, both in dose including first and second revealed unexpected biochemical parameter values (Table 4). Following COVID-19 vaccination, a variety of cutaneous reaction patterns can develop, with many of these skin findings being of an immunological or autoimmunological nature (Gambichler *et al*., 2022) (Table 4). Following the COVID-19 vaccination, the most common type is an unspecific injection site reaction. Furthermore, numerous type I and type II hypersensitivity reactions, autoimmune-mediated skin abnormalities, functional angiopathies, and (re) activation of viral diseases have been linked to COVID-19 immunization.

Subacute thyroiditis: Subacute thyroiditis is more common in women than men, and the 30–50 age group is particularly susceptible. Recently, subacute thyroiditis following COVID-19 vaccination has been documented as well. Neck pain, fever, and other symptoms of thyrotoxicosis are common in subacute thyroiditis (Wightman *et al*., 2022).

Liver injury: Although, there are about 0.6% of patients with liver dysfunction received Pfizer and Moderna vaccines, data for them are very sparse. In contrast, the data showed the aberrant liver biochemistry was observed in just one of the 12021 participants who received ChAdOx1-nCoV-19. Notably, Hepatitis C virus (HCV) vaccines, known as ChAd vaccines, had previously been safely administered to a limited number of participants with non-cirrhotic chronic HCV infection (Kelly *et al*., 2016). Notably, cirrhotic patients (n=20) had a lower response rate to the adjuvanted trivalent influenza vaccine (75–85 % vs. 90 %) than healthy controls (n = 8) (Gaeta *et al*., 2002). Cirrhotic patients have impaired responses to currently available licensed vaccines, such as those for pneumococcus (McCashland at al., 2000). After examining a patient that received COVID-19 vaccine abdominal Ultrasound showed high echogenicity in the liver compatible with fatty spreading. Viral serologies for hepatitis A, B, and C and phytoprotein returned negative. Minimum pallor refers to scattered inflammatory cells (Rupinder Mann, 2021).

Vaccination of patients with decompensated cirrhosis should be prioritized due to the increased COVID-19-related mortality in this subgroup (Webb *et al*., 2020). Therefore, patients' education about the benefits of SARS-CoV-2 vaccination programs will also be critical to cirrhotic patients, especially vaccines that may frequently be suboptimal (Stroffolini *et al*., 2020). The ChAdOx1-nCoV-19 and other mRNA vaccines were recommended for liver transplantation, but the best time to administer those vaccines is unknown (Chong & Avery, 2017) as clear in Figure (4).

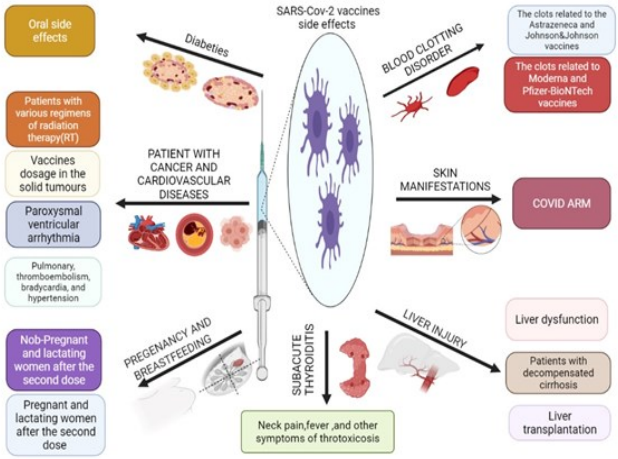


Figure 4: SARS-CoV-2 vaccines side effects. This figure showsSARS-CoV-2 vaccines side effects that include blood clotting disorder; skin manifestations such as COVID ARM, liver injury;in case of pregnancy and breastfeeding such as fever, headache, myalgia, and chills; cancer and cardiovascular diseases such as pulmonary thromboembolism, bradycardia, and hypertension; and diabetes such as oral side effects (blisters, halitosis, ulcers, bleeding gingiva, and white/red)

Table 1 Current protein subunit vaccines under clinical trials

Vaccine	Developer	Clinical trial stage	Immune response and Effectiveness against COVID-19	References
SCB-2019 (S-Trimer)	Clover Biopharmaceuticals, China	Phase 1: NCT0440590& Phase II/III NCT04672395	Induction of neutralizing antibodies and Th1 cellular immune response It has an efficacy of 67·2% (95·72% CI 54·3–76·8) against COVID-19 of any severity, 83·7% (97·86% CI 55·9–95·4) efficacy against moderate to-severe COVID-19, and 100% (97·86% CI 25·3–100·0) efficacy against severe COVID-19. The vaccine candidate is currently being evaluated in Phase 2/3 clinical trials	(Bravo *et al*., 2022)
West China Hospital COVID-19 vaccine (RBD – baculovirus expressed in SF19 cell)	West China Hospital, Sichuan University, China	Phase II: ChiCTR2000039994 NCT04640402 NCT04718467	Induction of IgG and neutralizing antibodies against RBD in mice and non-human primates (NHPs). Under investigation in Phase 3 clinical trials.	(R. Wang *et al*., 2021)
NVX-CoV2373	Novavax	Phase III NCT04611802	Induction of strong antibody response, as well as T-cell activation It has 96.4% efficacy against non-B.1.1.7 variants, 86.3% against B.1.1.7 variant, 60% against B.1.351 varian.	(Tian *et al*., 2021)
Adjuvanted SARS-CoV2 Sclamp (Spike glycoprotein clamp)	University of Queensland	Phase I NCT04495933	Induction of neutralizing antibodies and Th1/Th2 cellular immune response.Under investigation.	Watterson *et al*. (2021)
COVAX-19	Vaxine Pty Ltd	Phase I NCT04453852	COVAX-19 Removed to Phase 2 clinical trial after obtaining long-lasting protection with superior safety and tolerability results.	(Das *et al*., 2021)
MVC-COV1901	Medigen Vaccine Biologics Corporation/ NIAID/ Dynavax Technologies	Phase IINCT04695652	Induction of high titer of neutralizing antibodies against pseudotyped virus or live SARS-CoV-2Two doses correlate to approximately 90% vaccine efficacy against the prototype strain	(Cheng at al., 2021) (Feng *et al*., 2021) (Estrada *et al*., 2022)
FINLAY-FR-1A (Soberana Plus)	Instituto Finlay de Vacunas(IFV)	Phase I/II: RPCEC00000332	The vaccine elicited > 21 fold increase in IgG anti-RBD antibodies 28 days after vaccination, with an increase in RBD-specific T cells producing IFN-γ and TNF-α.It has more than 90% efficacy.	(Chang-Monteagudo *et al*., 2021)
SOBERANA 02 (FINLAY-FR-2)	Instituto Finlay de Vacunas.	Phase III: RPCEC00000354	Anti-SARS-CoV-2 Vaccine (RBD chemically conjugated to tetanus toxoid plus adjuvant).Phase 1 and 2 clinical trials proved its immunogenicity, promoting neutralizing IgG together with specific T-cell response. Two doses were safe and attained efficacy of 71.0% Incorporating SOBERANA Plus after the two doses of SOBERANA 02 increased the efficacy from 71.0 to 92.4% (Clinical Trials IFV/COR/09 number, RPCEC00000354).	(Malik *et al*., 2021) (Toledo-Romani *et al*., 2021)
CIGB-66 (Abdala)	Finlay Institute in Cuba	Phase I / II: RPCEC00000346 Phase III RPCEC00000359	The vaccine elicited IgG anti-RBD antibodies. t has 92.28% effecacy against symptomatic infection after three doses.	Reardon (2022)
EpiVacCorona Vaccine(EVCV)	Federal Budgetary Research Institution State Research Center of	Phase III: NCT04780035	Have three synthetic viral peptides (One Spike, One N protein and one bacterial peptide) that are conjugated to a large carrier protein. Efficacy is officially unknown, and it is awaiting regulatory approval.	(Dobrovidova, 2021)

	Virology and Biotechnology "Vector"		However, all the volunteers who were administered the EVCV developed specific antibodies against its antigens.	
ZifiVax (ZF2001) (RBD-Dimer)	Anhui Zhifei Longcom, China	phase II NCT04466085) Phase III	Recombinant protein subunit vaccine from China manufactured in the Chinese Hamster Ovary (CHO) cell lines, encoding a dimeric form of the receptor-binding domain of S proteinIn phase 1 and 2 clinical trials, the vaccine showed high efficacy with a low side effect profile. China authorized the emergency use of the vaccine on March 10, 2021. Currently the vaccine candidate is currently being evaluated in Phase 3 clinical trials	Yang *et al*. (2021).
VAT00002&8	Sanofi& Pasteur GSK	Phase II & Phase III: PACTR20201152310 1903	VAT02 showed strong rates of neutralizing antibody response with 95% to 100% efficacy after the second dose.VAT08 efficacy with the monovalent formulation was 57.9% (95% confidence interval [CI, 26.5, 76.7]) against any symptomatic COVID-19 disease in the seronegative population. 100% protection against severe disease and hospitalizations and 75% efficacy against moderate-to-severe disease.Early data indicate 77% efficacy against any delta variant-associated symptomatic COVID-19 disease[4].Phase 3 study is still ongoing for evaluating the efficacy of its bivalent formulation as primo-vaccination	

Table 2 Current mRNA-based vaccines under clinical trials

Vaccine	Developer	Clinical trial Stage	Immune response	Effectiveness against COVID-19	Effectiveness against B.1.1.7, B.1.351, and P.1 variants
BNT162b2 (tozinameran)(Polack *et al*., 2020)	BioNTech/Pfizer	Phase I/II/III in healthy individuals: NCT04368728 Phase 2/3 in healthy pregnant women: NCT04754594 Phase 1/2/3 in healthy children and young adults : NCT04816643	phase I/II trial in healthy adults: it perfectly triggers the immune response against SARS-CoV-2 to generate specific neutralizing antibodies, $CD4^+$ and $CD8^+$ T-cells, and cytokines like IFNγ. Phase II/III: still ongoing Phase 2/3 in healthy children: phases showed serum SARS-CoV-2 neutralization.	95% after two doses in healthy adults.90.7% after two 10ug doses in 5-11-year-old children.	It is effective against B.1.1.7 with a slight to no loss in neutralization. On the other hand, neutralizing activity against B.1.351 and P.1 is the lowest (Hoffmann, 2021)
	Moderna/NIAID	Phase III: NCT04470427	In early-stage clinical trial: mRNA-1273 could induce a neutralizing and binding antibody response, but without knowing the exact duration of the immune response (19), and CD4+ T cells. $CD8^+$-T-cells may be induced but with low levels.	94% after the second dose	The vaccine is highly effective against B.1.1.7 and B.1.351 variants with no vaccine-induced immune response evidence (Chemaitelly *et al*, 2021). A very recent study showed different neutralizing activities against all three variants after the second dose with the lowest activity against B.1.351 (Pegu *et al*, 2021).
CVnCoV(Kremsner *et al*., 2020)	CureVac	Phase IIb/III:NCT04652102	An obvious increase in immune responses and virus-neutralizing antibodies have been detected according to phase 1 (Kremsner *et al*, 2021a) and	48% after second dose (Fiolet at al., 2021)	A reported evidence showed similar efficacy of CVnCoV against both B.1.1.7 and P.q variants (Kremsner *et al*, 2021b).

			non-human primates model studies (Gebre *et al*, 2021).		No data reported about B.1.351 yet.
ARCoV(Sagili Anthony *et al*., 2021)	Academy of MilitaryMedical Sciences, Suzhou AbogenBiosciences and Walvax Biotechnology	Phase II: ChiCTR2100041855	A strong response against SARS-CoV-2 receptor binding domain with IgG antibodies detection in animals and non-human primate model trials. In ARCoV-treated mice, $CD4^+$, $CD8^+$ effector memory T-cells, IL-2, IF-2, IFN-γ, and TNF-α were detected with no change in IL-4 and IL-6 in this group or placebo group.	NR	NR
HGC019(Sagili Anthony *et al*., 2021)	Gennova/ HDT Biotech Corporation	Phase I/II had been approved by The Drugs Controller General of India (DCGI).	In rodent model studies, HGC019 showed good safety, immunogenicity, and antibody neutralization.	NR	NR

**NR: Not reported*

Table 3 Current Viral vector Vaccines under clinical trials

Vaccine	Developer	Clinical trial stage	Immune response	Effectiveness against COVID-19	Effectiveness against Alpha	Effectiveness againstDelta	Effectiveness againstGamma
Oxford and AstraZeneca: AZD1222(Forni *et al*., 2021)	Oxford University and *AstraZeneca*	Phase IIINCT04864561	Strong with single delivery and lack of pre-existing anti-vector immunity(V. M. Kumar, Pandi-Perumal, Trakht, & Thyagarajan, 2021)	82.4%	70.4%	low as 10%	
Sputnik V (Gam-COVID-Vac)(Logunov *et al*., 2021)	The Gamaleya National Center of Epidemiology and Microbiology	Phase III NCT04530396	Strong humoral immune response	91.6% (M. Rahman, Masum, Ullah, Wajed, & Talukder, 2022)	NR*	NR	
SPUTNIK LIGHT (Vanaparthy *et al*., n.d.)	The Gamaleya National Center of Epidemiology and Microbiology(Tukhvatulin *et al*., 2021)	Phase III NCT04741061	strong humoral and cellular immune response	79.4%	As per the Gamaleya center, this vaccine is effective against all new variants		
Convidecia AD5-nCOV)(Mahase, 2021a)	CanSino Biologics	Phase III NCT04526990	has a strong impact with a single delivery	65.28%	NR	NR	
		Phase III	has a strong impact with a single delivery	65.28%	NR	NR	
Johnson & Johnson(Johnson., 2021)	Janssen Pharmaceutical Companies of Johnson & Johnson	Phase III NCT04505722	triggers weak response	85%	70.4% (Fiolet, Kherabi, MacDonald, Ghosn, & Peiffer-Smadja, 2022)	85% (Johnson, 2021)	

65.28% Medicago Covifenz [9, 10]	Medicago Inc	Phase 3 NCT04636697	Th1-biased cellular *immune response*.	69.5%	100%	75%	88.6%

Table 4 Blood biochemical parameters influenced by different types of SARS-CoV-2 vaccines

Vaccine	Cases	Abnormal Value of Biochemical parameters	Vaccine dose	PCR-COVID-19	Description	References
Pfizer	Male (n=21; age range 14:60) Female (n=6; age range 24: 54)	Troponin I range (0.37: 103 ng\mL). Troponin T range (0.66 :232 ng\mL). CPK (2380 U\L); CK-MB (53.8 ng\ml,450 U\L); LDH (228 U\L); PTT range (22.3: 75.2 s). CRP rang (0.7: 29 mg\dL); ESR range (21:70 mm\hr); D-dimer (2.99 mg\L,1.52 Ug\mL) NT-proBNP (376 pg\ml,428 pg\ml); AST range (45:982 U\L); ALT range (56:2001 U\L); ALP (170 U\L); bilirubin (4.8 mg\dL); Platelet count (0 U\L); IgG ((+),n=3); PEG 2000 ((+),n=1); PEG 4000 ((+),n=1); PEG 6000((+),n=1); polysorbate 80 ((+),n=1)	Frist (n=9) Second (n=16) NR* (n=2)	Negative (n=18), including case, had a history of COVID-19 NR (n=2)	**Slight increase:** LDH, D-dimer, ALT, bilirubin **Moderate increase:** CK-MB, CRP, ESR, ALP, PTT **High increase:** Troponin I, Troponin T, CPK, NT-proBNP, AST, ALT **Slight decrease:** PTT **High decrease:** platelet count **Diagnosis:** Autoimmune phenomenon of (myocarditis, thrombocytopenia, hepatitis) **Medical history:** Not found except 3 cases had allergy **Risk factor:** Not found **Uncommon symptoms:** Not found	(Bril *et al*., 2021; Ishay *et al*., 2021; Marshall *et al*., 2021; Ortega *et al*., 2021; Pickert *et al*.,2021; Rosner *et al*., 2021; Sellaturay *et al*., 2021; Singh *et al*., 2021)
Moderna	Male (n=5; age range 24:80) Female (n=1; age 21)	Troponin I range (2.3:18.94 ng\ml); CK (764 U\L ,6546 U\L); CRP range (0.08:264 mg\dL) Ferritin (2400 ng\mL). AST (112 U\L,196 U\L). ALT (47 U\L,90 U\L); ALP (216 U\L); LDH (359 U\L, 381 U\L); ESR (7:52 mm\hr); D-dimer (640 ng\mL), IgG ((+),n=1)	Second (n=5) Frist (n=1)	Negative (n=6), including case, had a history ofCOVID-19	**Slight Increase:** ESR **Moderate Increase:** Troponin I, CRP, LDH, ALT, ALP **High Increase:** CK, Ferritin, AST, D-dimer **Slight Decrease:** CRP **Diagnosis:** myocarditis, except a case that had rhabdomyolysis **Medical history:** Not found; only 3 cases had hepatitis C, QT syndrome, diabetes mullites **Risk factor:** Not found, except a case have an active smoker **Uncommon symptoms**: Not found	(Mack *et al*., 2021; Malayala *et al*., 2021; Mansour *et al*., 2021; Rosner *et al*., 2021)
AstraZeneca	Male (n=4; age range 27:36) Female (n=4; age range 39:59)	Ferritin (12 ng\mL); LDH (337 U\L); GGT (136 U\L, 141 U\L); CRP (14 mg\L; D-dimer range (3.4:6050 mg\L); fibrinogen range (0.7:1.9 g\L) Bilirubin range (0.017 mmol\L,26 mmol\L); Platelet count range (18×10^9 :255×10^9 \L); ALT range (144:1774 U\L); APPT (33.2s);AST (633 u\L,1496 U\L); CK (1025600 u\L);Anti-PF4-ELISA ((+),n=2)	Frist (n=5) NR (n=3)	Negative (n=6) NR (n=2)	**Slight increase:** CRP, PTT **Moderate increase:** LDH, bilirubin **High increase:** D-dimer, GGT, ALT, AST, CK **Moderate Decrease:** Ferritin, Fibrinogen **High decrease:** platelet count	(Clayton-Chubb, *et al*., 2021; Greinacher *et al*., 2021; Guetl *et al*., 2021; Suresh & Petchey, 2021; Tan *et al*., 2021)

					Diagnosis: Autoimmune phenomenon of (thrombocytopenia, hepatitis) and the case had rhabdomyolysis **Medical history:** Not found except 3 cases had Iron deficiency anemia, fatty acid disorder (FAOD), hypersensitivity, plus eye disease. **Risk factor:** Not found **Uncommon symptoms**: -Right-side hemiparesis -Cerebral thrombosis -Subconjunctival hemorrhage -Blurred vision -Complication of kidney, respiratory and cardiovascular systems	
Johnson & Johnson/Janssen)	Male (n=1; age 28) Female (n=1; age 48)	Platelet count (13×10^9\L); Fibrinogen (89 mg\dL); PPT (41s); D-dimer (117.5 mg\L); troponin I (3.55 ng\mL)	NR	Negative	**Slight Increase:** PPT **Moderate Increase:** Fibrinogen **High increase:** D-dimer, Troponin I **High Decrease:** Platelet count **Diagnosis:**Thrombocytopenia, myocarditis like -illness **Medical history:** Not found **Risk factor:** heparin drug **Uncommon symptoms**: Cerebral thrombosis	(Muir, *et al*., 2021; Rosner *et al*., 2021)
Covishield	Male (n=1; age 63) Female (n=1; age 75)	CRP (59 mg\L); ESR (23mm\hr); LDL-C (126 mg%); platelet count ($235\times10^3mm^3$); CK-MB (>150 U\L); Troponin I (49.28 ng\mL); AST (184 U\L); LDH (1647 U\L)	First	Negative (n=1) NR (n=1)	**Slight increase:** ESR, LDL-C **Moderate increase:** CK-MB **High increase:** CRP, Troponin I, AST, LDH **High decrease**: platelet count **Diagnosis:** Thrombocytopenia **Medical history:** A case had acute coronary syndrome (Watterson *et al*.) **Risk factor:** psychological stress **Uncommon symptoms**: Not found	(Chatterjee *et al*., 2021; Srinivasan, Sathyamurthy, & Neelagandan, 2021)
Inactivated SARS-CoV-2 vaccine	Female (n=1; age 43)	Ferritin (8140.4 mg\L); triglyceride (2.43 mmol/L); fibrinogen (1.41 g/L); AST 254 U/L); LDH (1033 U/L); platelet (27×10^9/L)	Frist	Negative	**High increase:** Ferritin, AST, LDH **Moderate increase:** triglyceride **Slight decrease:** Fibrinogen **High decrease:** platelet count **Diagnosis:**HemophagocyticLymphohistiocytosis (HLH) **Medical history:** Epstein barr-virus infection **Uncommon symptoms**: Not found	(Tang & Hu, 2021)
Sinopharm	Male (n=1; age 62)	ALT: 722 U/L (normal range <37), AST: 435 U/L (normal range <41), ALP: 512 U/L (normal range: 80–306), total bilirubin: 8 mg/dl (normal range: 0.1–	Second	NR (n=1)	**High increase:** AST, ALT, Bilirubin, ALP **Moderate increase:** CK-MB **Slight decrease:** PPT **High decrease:** platelet count **Diagnosis**: autoimmune Hepatitis	(H. Ghorbani *et al*.,2022)

	1.2), direct bilirubin: 3.2 mg/dl (normal range < 0.3)	**Medical history:** hypertension and diabetes mellitus **Risk factor:** Not found **Uncommon symptoms**: Not found

**NR: Not reported*

pregnancy and breastfeeding: Fever was reported as a side effect after the second dose in pregnant, lactating, and non-pregnant and lactating women who received either Moderna or Drug company (Collier *et al*., 2021). Other studies reported that pregnant women experienced more injection-site discomfort than non-pregnant women, whereas headache, myalgia, chills, and fever were less commonly reported (Shimabukuro *et al*., 2021). The most recommended vaccines for pregnant and lactating women are Pfizer-BioNTech and Moderna (Gray *et al*., 2021; Mahase, 2021b). SARS-CoV-2 mRNA vaccines induced a favorable response by increasing non-neutral binding, neutral, and functional antibodies in addition to $CD4^+$ and $CD8^+$ T cells in these women (Collier *et al*., 2021).Even though all umbilical cord blood and breastmilk samples included vaccine-delivered antibodies, neutralizing antibody levels were higher in maternal sera thanin the umbilical cord. Also, only SARS-COV-2 IgG levels were higher in maternal blood and breastmilk after the second vaccine dose (boost dose), but not IgA. Durable humoral immunity was provided to pregnant and lactating women, by SARS-CoV-2 mRNA vaccines, with equivalent levels of immunogenicity and reactogenicity

Compared to non-pregnant women (Gray *et al*., 2021). According to a recent statement from the Academy of Breastfeeding Medicine, vaccine-induced antibodies and T-cells might be found in breast milk, thereby providing the infant with a strong immune system and protection against SARS-CoV-2 infection. Therefore, they do not recommend the intermission of breastfeeding in vaccinated individuals (Zipursky *et al*., 2021). If a pregnant or lactating woman is eligible and has no contraindications, the Society of Obstetricians and Gynecologists of Canada recommends that she should be offered the SARS-CoV-2 vaccine at any time (Chelsea at al., 2020). The vaccine significantly impacts injection site discomfort, an injection site reaction or rash, headaches, muscular aches, exhaustion, and fever or chills. Some participants also observed allergic reactions (Magon at al., 2022)

Patient with cancer & cardiovascular diseases: Administration of the Pfizer-BioNTechSARS-CoV-2 vaccine induced the recurrent respiratory papillomatosis (RRP) development in two patients with various regimens of radiation therapy (RT). Therefore, decisions on the immunization of RT patients should include reasonable reasons for the risk of RRP adverse events following vaccination (Soyfer *et al*., 2021). The improved permeation retention effect of mRNA lipid carrier vaccines is predicted to build up tiny liposomes in tumorous tissues; the vaccine dosage in solid tumors is unknown (Fanciullino at al., 2020). Live SARS-CoV-2 vaccines are not recommended for cancer patients (Hwang *et al*., 2021). Regarding cardiovascular diseases, the Pfizer-BioNTech vaccine caused some adverse events, including paroxysmal ventricular arrhythmia (Polack *et al*., 2020). Moreover, the Modernavaccine may cause cardiovascular alterations (with an incidence rate of less than 0.1%), such as pulmonary thromboembolism, bradycardia, and hypertension (Martins *et al*., 2021).

4. Patient with cardiovascular diseases

Symptoms such as headache, loss of consciousness (LOC), oxygen saturation of less than 93 percent, and the necessity for mechanical ventilation were significantly associated with the mortality rate of COVID-19 cardiovascular patients.

4.1. Patient with cancer

Compared to healthy controls, cancer patients treated with immunotherapy after receiving two doses of the Pfizer/BioNTech vaccine showed a significant improvement in survival. In a study of 134 patients, the most prevalent side effect was pain at the injection site (which occurred in 21 percent of patients after the first dose). Overall, the incidence of systemic adverse effects was low, with fatigue (4 percent), headache (3 percent), myalgia (2 percent), and chills being the most often reported (1 percent) (Re *et al*., 2022)

Diabetes: The Pfizer–BioNTech COVID-19 vaccine, oral side effects as blisters (Figure 4), which were the most prevalent oral adverse effect, halitosis, ulcers, bleeding gingiva, and white/red. Skin-related adverse effects were rashes and urticaria. The main place was the upper limb, the chest, and the trunk (Riad *et al*., 2021).

5. Conclusion

This review handles several aspects related to the SARS-CoV-2 and its vaccines. According to the collected data, the four SARS-CoV-2 viruses genera can use various forms of receptors instead of the typical receptors resulting in massive damage to human organs. Notably, the COVID-19 infection predisposes to microbial, bacterial, fungal, and viral co-infections due to human immune system damage throughout the disease. Although elucidating the causative mechanism, control of COVID-19 infection remains challenging. The unprecedented research efforts showed that SARS-CoV-2 mutations could be blamed for the spread of the pandemic.

Consequently, the whole world is in urgent need of vaccines. The major types of SARS-CoV-2 vaccines were highlighted in this review. Some of these vaccines were mRNA–based vaccines as BioNTech, Pfizer, and Moderna, NIAID vaccines which showed the highest efficacy rates (95% after two doses and 94% after the second dose respectively), followed by viral vector vaccines (Oxford – AstraZeneca) with about 82.4% efficacy and inactivated vaccines (Sinopharm-Beijing) with about 79% efficacy. Certain side effects were documented after SARS-CoV-2 vaccination, including blood clotting disorders, skin manifestations, and others. Despite these recorded side effects, vaccination is highly recommended because of its great importance in the containment of pandemics. However, we need more studies and continuous monitoring of the long-term effects of SARS-CoV-2 vaccines, which can help better contain the pandemic.

Abbreviations

ALI: Acute lung injury; PCR-CT: Polymerase chain reaction-cycle threshold test; HAOs: Human airway lung organoids; USA-WA1/2020: SARS-CoV-2 strain; IgG: Immunoglobulin G; IgM :Immunoglobulin M; COVAX-19: COVID-19 Vaccine Global Access; Th1:Type 1T helper cell ;Th2:Type 2 T helper cell; NIAID: National Institute of Allergy and Infectious Diseases; CD4+: Cluster differentiation 4; CD8+ : Cluster differentiation 8; IF-2: Interferon type II ;IFN-γ: Interferon-gamma; IL-2: Interleukin 2; IL-4: Interleukin 4; IL-6: Interleukin 6; TNF-α: Tumour Necrosis Factor alpha; CPK: Creatine phosphokinase; CK-MB: Creatinine kinase-MB;CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate ;NT-proBNP: N-terminal pro–B-type natriuretic peptide ; ALP: Alkaline phosphatase; APTT : Active partial thromboplastin time; Anti-PF4-ELISA: Anti-platelet Factor 4- Enzyme linked immunoassay; PTT :Partial thromboplastin time; PEG: Polyethylene glycol test; LDL-C: low density lipoprotein-cholesterol; HLH :Hemophagocytic Lymphohistiocytosis.

Author contributions

M.J.A. conceived of the presented idea. G.A.M., M.J.A., H.F.F., G.A.A., M.S.E.M.B., E.K.M.K., E.S.E., L.I.A., Z.I.A., S.S.A., and N.E.E. designed, and supervised the study. M.J.A., H.F.F., Z.I.A., A.S.N., A.A. E., S.A.M., F.M.A., M.A.M., H.M.B., S.S.A., and N.E.E. analyzed the data and prepared the tables and figures. G.A.A., M.S.E.M.B., E.K.M.K., E.S.E., L.I.A., Z.I.A., G.A.M., and N.E.E. commen-ted on the data and its interpretation and revised the content critically. All authors did the literature search, data extraction, data collection and the final manuscript approved by all authors.

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