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Efficacy of mRNA, adenoviral vector, and perfusion protein COVID-19 vaccines

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ABSTRACT

Coronavirus disease 2019 (COVID-19) has a devastating impact on global populations triggered by a highly infectious viral sickness, produced by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The third major cause of mortality in the United States, following heart disease and cancer in 2020, was undoubtedly COVID-19. The centers for disease control and prevention (CDC) and the world health organization (WHO) separately developed a categorization system for differentiating new strains of SARS-CoV-2 into variants of concern (VoCs) and variants of interest (VoIs) with the continuing development of various strains SARS-CoV-2. By December 2021, five of the SARS-CoV-2 VoCs were discovered from the onset of the pandemic depending on the latest epidemiologic report by the WHO: Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529). Mutations in the receptor-binding domain (RBD) and n-terminal domain (NTD) have been found throughout all five identified VoCs. All strains other than the delta mutant are often found with the N501Y mutation situated on the RBD, resulting in higher binding between the spike protein and angiotensin-converting enzyme 2 (ACE2) receptors, enhanced viral adhesion, and following the entrance to host cells. The introduction of these new strains of SRAS-CoV-2 is likely to overcome the remarkable achievements gained in restricting this viral disease to the point where it is presented with remarkable vaccine developments against COVID-19 and strong worldwide mass immunization initiatives. Throughout this literature review, the effectiveness of current COVID-19 vaccines for managing and prohibiting SARS-CoV-2 strains is thoroughly described.

1. Introduction

The extremely infectious viral sickness produced by severe acute respiratory coronavirus syndrome 2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19), has a devastating influence on global demography [1]. Because their envelopes have spike glycoproteins, coronaviruses (CoVs) are positively-sense single-stranded RNA viruses (+ssRNA) with a morphologic similarity to the crown during an electron microscopic evaluation [2]. From a classification perspective, there are four strains of CoVs in the Orthocoronavirinae subfamily belonging to the Coronaviridae family (order Nidovirales), including Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV) [3].

There are five sub-genera or ancestries within the BetaCoV genus [4]. Bats and rodents are the most likely origins of alphaCoVs and betaCoVs, according to genomic analysis. In contrast, the gene pools of deltaCoV and gammaCoV appear to be species of birds [5]. CoVs have established themselves as the predominant pathogens in developing respiratory illness occurrences [6]. Among various animals, such as camels, cattle, cats, and bats, members of the larger family may induce pulmonary, intestinal, hepatic, or neurological illnesses [7]. Such viruses can transcend species boundaries and cause sickness throughout individuals

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varying from the rheum to more serious illnesses, including the middle east respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), for factors that remain to be described [8]. There have been seven human CoVs (HCoVs) discovered so far that are capable of infecting individuals. Although a few HCoVs were discovered throughout the mid-1960s, others were not discovered until the new millenary reports suggest that approximately 10% of the population is asymptomatic bearers of CoVs and that such viruses are accounting for roughly 5–10% of acute respiratory illnesses throughout the general community [9]. Following touring Wuhan, the genome of the novel HCoV, which was extracted from an uncommon pneumonia group, showed 89% nucleotide similarities to SARS-like COVZXC21 among bats and 82% with humans SARS-CoV [10]. The scientists from the international committee on taxonomy of virus (ICTV) have thus called it SARS-CoV-2. SARS-CoV-2 has 29891 nucleotides throughout the single-stranded RNA genome, which encodes 9860 amino acids [11].

Despite the fact that the source of SARS-CoV-2 is still undetermined, it is generally assumed to have started from an animal, indicating a possible zoonotic spread of the virus [12]. SARS-CoV-2 originated from a variant identified among bats, according to the findings of genomic research. In fact, there has been a considerable homology (96%) of SARS-CoV-2 and betaCoV RaTG13 of bats (Rhinolophus affinis) in a genomic analysis among humans SARS-CoV-2 and known animal CoVs (ACoVs) [13]. It was believed that SARS-CoV-2 was moved from bats to intermediate host groups, including the pangolins and minks and finally to people, comparable to SARS and MERS [14]. The WHO recently published study on the potential beginnings of SARS-CoV-2 was ambiguous since it did not identify the virus's origination [15]. Although it has been claimed that the spread of SARS-CoV-2 began as primary as December 2019, it is unclear when this happened. Some potential theories about the virus's genesis were investigated in this study, including the possibility that the virus originated from an animal [16]. The virus was transferred to intermediate host cells, and the virus then found its way to people. The objective of this review paper is to discuss the effectiveness assessment of existing vaccines for COVID-19 throughout the therapy and prohibition of SARS-CoV-2 strains in detail.

2. SARS-CoV-2 variants

The SARS-CoV-2 virus is susceptible to evolutionary processes, which may lead to a large number of strains with distinct features compared to their ancestral variants. A regular genome sequence is essential for viral specimens, particularly in the global context of a pandemic, since it aids to identify any emerging SARS-CoV-2 genetic strains, most importantly, with the development of the worldwide prevalence of D614G strain, which was linked with enhanced disease transmission however could not produce severe disease, the genetic transition was negligible at first [17]. Yet another strain has been discovered among individuals, which has been linked to the introduction of the virus into Denmark's farmed mink herd. This strain was not related to enhanced rates of infection [18]. Given their capability to induce increased infectivity or pathogenicity, decreased neutralization through antibodies acquired via usual infection or vaccination, the possibility to escape tracing, or a reduction of therapeutic strategies or vaccination efficiency, ever since, different strains of SARS-CoV-2 have been characterized, with a few of them regarded VoCs. The CDC and the WHO separately have developed a categorization framework to differentiate new SARS-CoV-2 strains into VoCs and VoIs [19,20], with the continuing development of numerous strains (Table 1).

3. SARS-CoV-2 variants of concern (VoCs)

3.1. Alpha (B.1.1.7 ancestry)

According to whole-genome sequencing of specimens taken from patients whose test is positive for SARS-CoV-2 in the United Kingdom at the end of December 2020, a novel SARS-CoV-2 variant of concern, B.1.1.7 ancestry, commonly known as Alpha strain or GRY (already known as GR/501Y.V1), has been identified [21]. The B.1.1.7 strain was discovered in a commercially available experiment, which was distinguished by the disappearance of S gene polymerase chain reaction (PCR) specimens (S-gene target failure, SGTF) and discovered via genome sequencing [22]. There are 17 mutations in the viral genome of the B.1.1.7 strain. Eight of these mutations are in the spike protein (S), including 69/70/144 deletion, N501Y, A570D, P681H, T716I, S982A, D1118H [23]. Higher selectivity of the spike protein for ACE2 receptors is shown in N501Y, resulting in improved viral adhesion and the following entrance into host cells [24].

Depending on distinct experimental measurements, this concern variant was already propagating in the UK in September 2020 [25]. The transmitted SARS-CoV-2 strains were estimated in Britain to be 43–82% higher, exceeding the previous ones [25]. At the termination of December 2020, the strain B.1.1.7 was detected throughout the U.S [26]. When comparing the B.1.1.7 ancestry to other known strains, a preliminary paired case-control study found no statistically significant variation in the danger of hospitalization or related death [27]. The incidence of illness in individuals infected with the B.1.1.7 ancestry was shown to be higher than in those contaminated with other transmitted types of viral strains, according to later research [28].

The death risk ratio of the B.1.1.7 ancestry was found to be 1.64 individuals with formerly disseminated variants, according to a comprehensive matched cohort research conducted in the UK (95% confidence interval 1.32–2.04, $P < 0.0001$) [29]. The strain of B 1.1.7, as compared with the other SARS-CoV-2 strains, was attributed to an elevated death rate (HR= 1.61, 95% CI 1.42–1.82) [29]. Participants with verified B.1.1.7 variants of concern had a higher mortality risk than those with non-1.1.7 SARS-CoV-2 (adjusted hazard ratio 1.67, 95% CI

Table 1
SARS-CoV-2 variants of concern (VoCs) and variants of interest (VoIs).

VoCs		VoIs	
Types of variant	Mutations of the spike protein	Types of variant	Mutations of the spike protein
Alpha (B.1.1.7)	69/70/144del, N501Y, A570D, P681H, T716I, S982A, D1118H	Epsilon (B.1.427)	L452R, D614G
Beta (B.1.351)	L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, A701V	Epsilon (B.1.429)	S13I, W152C, L452R, D614G
Gamma (P.1)	L18F, T20N, P26S, D138Y, R190S, H655Y, T1027I, D614G, K417T, E484K, N501Y	Zeta (P.2)	L18F, T20N, P26S, F157L, E484K, D614G, S929I, V1176F
Delta (B.1.617.2)	T19R, G142D, 156/157del, R158G, L452R, T478K, D614G, P681R, D950N	Eta (B.1.525) Iota (B.1.526)	A67V, 69/70/144del, E484K, D614G, Q677H, F888LL5F, T95I, D253G, S477N, E484K, D614G, A701V
Omicron (B.1.1.529)	69–70/142–144/211del A67V, T95I, Y145D, L212I, ins214EPE, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F	Theta (P.3) Kappa (B.1.617.1)	141/142/143del, E484K, N501Y, P681HT95I, G142D, E154K, L452R, E484Q, D614G, P681R, and Q1071H

1.34–2.09) [29]. The B.1.1.7 variant of SARS-CoV-2 has appeared as one of the most prevalent viruses propagating throughout the United States [30].

3.2. Beta (B.1.351 ancestry)

B.1.351 is another SARS-CoV-2 strain, commonly known as the Beta strain or GH501Y. The secondary peak of COVID-19 outbreaks was first identified throughout South Africa in October 2020 [31]. Strain B.1.351 contains nine mutations within spike protein, including the L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, and A701V [31]. The binding affinity for the ACE2 receptors is increased by three mutations of K417N, E484K, and N501Y situated within RBD [32]. At the termination of January 2021, SARS-SoV-2 501Y.V2 (B.1.351 ancestry) was detected in the United States. The higher danger of outbreak and neutralization process conducted by monoclonal antibody treatment, convalescent sera, and post-vaccination sera is documented about this strain [33].

3.3. Gamma (P.1 ancestry)

In December 2020 in Brazil, the third variant of concern, the p.1 strain, also recognized as the Gamma strain or GR/501Y.V3, was initially discovered in the US in January 2021 [34]. In the spike protein of the B.1.1.28 strain, there are eleven mutations, including L18F, T20N, P26S, D138Y, R190S, H655Y, T1027I, D614G, K417T, E484K, and N501Y [35]. There are three mutations throughout the RBD that are comparable to the B.1.351 strain: L18F, K417N, and E484K [36]. This strain, in particular, has the potential to decrease the neutralizing process by monoclonal antibody treatments, convalescent sera, and post-vaccination sera [37].

3.4. Delta (B.1.617.2 ancestry)

It was first discovered in December 2020 in India that the fourth variant of concern, B.1.617.2, also known as the Delta strain, was accountable for the catastrophic secondary peak of COVID-19 outbreaks that occurred on April 2021 throughout India [38]. This strain was primarily discovered in the U.S in March 2021. Initially, the Delta strain was deemed as a variant of interest. Meanwhile, this strain disseminates quickly across the globe, leading the WHO to categorize it as a VoC after May 2021 [39]. Consequently, ten mutations in the spike protein of B.1.617.2 strain, including T19R, (G142D*), 156/157del, R158G, L452R, T478K, D614G, P681R, and D950N were identified [40]. The B.1.617.2, which are the most prevalent SARS-CoV-2 variants throughout the United States over the next weeks, was anticipated by the investigators [30,41].

4. SARS-CoV-2 variants of interest (VoIs)

The VoI is characterized as strains that contain specific biomarkers linked with modifications that could induce elevated propagation or pathogenicity, lowering the antibiotic neutralization caused by natural infection or vaccination, the desire to prevent identification or reduction in curative or vaccine efficacy [42]. Epsilon (B.1.427 and B.1.429); Zeta (P.2); Eta (B.1.525); Theta (P.3); Iota (B.1.526); Kappa (B.1.617.1) and Lambda (C.37) where the total of seven VoIs documented in a WHO weekly epidemiological report published on June 22, 2021 [42].

The variations of Epsilon, also termed CAL 0.20 C/L452R, were found around June 2020 in the US. From 1 September 2020–29 January 2021, they rose from 0 to > 50% among sequenced instances [43]. The transmission rate of the wild-type distributed variants is increased by 18.6–24%. Particular mutations of these strains include B.1.427: L452R, D614G; B.1.429: S13I, W152C, L452R, D614G. The CDC has categorized this variant as a variant of concern throughout the USA because of its enhanced outbreak [43].

Among the major spike mutations found in Zeta (P.2) are the following: L18F; T20N; P26S; F157L; E484K; D614G; S929I, and V1176F [44]. It was originally discovered in Brazil in April 2020. The WHO and the CDC categorized this strain as a VoI because of the possible decrease in antibody neutralization and vaccination sera [44].

Strains of B.1.525 and B.1.526 have some critical spike mutations, including A67V, 69/70/144del, E484K, D614G, Q677H, F888L; and L5F*, T95I, D253G, S477N*, E484K*, D614G, A701V*, respectively [45]. Due to their possible reductions in antibody neutralization and vaccination sera, the CDC and WHO categorized these strains as a variant of interest [45].

Theta (P.3) strain, commonly known as GR/1092 K.V1, has major spike mutations, including 141/142/143del, E484K, N501Y, and P681H [45]. In February 2021, it was first identified in the Philippines and Japan and was categorized by WHO as a variant of interest [44].

Kappa (B.1.617.1) was first identified in India in October 2020 and contained important mutations, including T95I, G142D, E154K, L452R, E484Q, D614G, P681R, and Q1071H [36,46]. In addition, the WHO and the CDC have been categorized as a variant of interest Lambda (C.37) strain was initially found in Peru and, owing to an increased prevalence in South American, was established as VoI on June 2021 WHO [36].

The CDC has determined the Epsilon (B.1.427 and B.1.429) strains as VoCs and Eta (B.1.525); Iota (B.1.526); Kappa (B.1.617.1); Zeta (P.2); B.1.526.1; B.1.617, and B.1.617.3 as VOIs [47].

5. Epidemiology

The development of viral illnesses poses a significant danger to public health, according to the WHO [48]. Numerous virus-induced pandemics have been reported over the last 20 decades, including the SARS-CoVs from 2002 to 2003, H1N1 influenza in 2009, and MERS-CoVs in 2012, which had a substantial effect on world healthcare [48]. In addition, SARS-CoV-2, accountable for COVID-19 designated a worldwide pandemic by the WHO, has disseminated to 223 nations with more than 265 million diagnosed instances and over 5,2 million fatalities recorded worldwide [49].

As of 2020, COVID-19 was the third most common cause of death in the United States, behind only heart disease and cancer. Nearly 375,000 deaths were recorded from the virus [50]. According to the WHO's weekly epidemiological statement, the Alpha (B.1.1.7) strain has expanded to 170 countries, the Beta (B.1.351) strain has been recorded throughout 119 countries, the Gamma (P.1) strain has been identified throughout 71 nations, and the Delta strain (B.1.617.2) has expanded to 85 nations [51]. The estimated worldwide mortalities for COVID-19, according to the WHO, is 2.2%. Although age, underlying medical illnesses, and the severity of sickness all influence mortality, it differs considerably across nations.

6. Pathogenesis of SARS-CoV-2

SARS-CoV-2 resembles SARS-CoV and MERS-CoV both architecturally and phylogenetically and consists of four major constructional proteins, including spike (S), envelope (E), nucleocapsid (N), membrane (M) protein, along with 16 nonstructural proteins, and 5–8 accessory proteins [52]. Situated on the outside of the virion, the surface spike (S) glycoprotein, which mimics a crest, is cleaved into an amino N-terminal S1 subunit, which aids the virus entry into its host cell [52]. During virus-cell membrane fusing, a carboxyl C-terminal S2 subunit comprising a fusion peptide, a transmembrane region, and a cytoplasmic domain are involved [52]. The S1 subunit is additionally subdivided into a RBD and NTD that promotes viral entrance into the host cell and may be targeted by antisera or antibodies from vaccines [52]. As a binding location for the human ACE2 (HACE2) receptors, the RBD is a critical peptide domain in the development of contamination. The earlier predicted suppression of the renin-angiotensin-aldosterone pathway did not enhance the probability of admission for COVID-19 and serious infection

[53].

SARS-CoV-2 enters host cells by attaching to the SARS-CoV-2 spike or S-protein (S1) of the ACE2 receptors, prevalent on respiratory epithelial cells, including type II alveolar epithelial cells [54]. Other organs like the upper esophagus, ileum enterocytes, cardiac cells, renal cells located in proximal tubular, and urothelial bladder cells expressed the ACE2 receptors and pulmonary epithelial [55]. The mechanism of the viral adhesion is accompanied by the host transmembrane serine protease 2 (TMPRSS2), which triggers spike protein S2 subunit to facilitate cell enterprise and successive endocytosis of virus reproduction [52].

In brief, the RBD spike enables the alveoli and other organs to the ACE2 receptor. In addition, the effective digestion of an amino acid location (polybasic site) by the human enzyme furin (protease) is enabled by the presence of a spike protein there. Because of this mechanism, the fusion sequences may be accessible, and, as a result, the viral and cell membranes can fuse, creating a passageway for the virus to penetrate the cell.

7. Principles of novel SARS-CoV-2 variants on the pathogenesis of COVID-19

Genetic diversity in the SARS-CoV-2 genomes may have consequences for the virus's pathogenesis, particularly if it affects the RBD, promoting viral entrance into host cells and is a critical goal for monoclonal antibodies produced by vaccination serum [56]. Those five VoCs described in this study exhibit RBD and NTD mutation, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) [46]. The N501Y mutation, situated on the RBD and in all variations except for Delta, leads to enhanced sensitivity of the spike protein to ACE2 receptors, thus increasing the viral adhesion and the following entrance into the host cells [56]. RBD, in conjunction with nucleotide-binding domain (NBD), acts as the main neutralization goal and aids in the development of antibodies in reaction to antisera or vaccinations [57]. A single mutation of N501Y enhances interaction among RBD and ACE2 around ten times as much as the ancestral variant (N501-RBD) has been documented throughout two previous preprint investigations (not peer-reviewed) [58]. It is noteworthy that the B1.351 and P.1 strain bindings were much less than those of N501Y-RBD and ACE2 with N417/K848/Y501-RBD and ACE2 mutations [45].

8. COVID-19 prohibition

In addition to the significance of imposed public health and infection control actions to prevent or reduce SARS-CoV-2 dissemination, vaccinations to combat SARS-CoV-2 illness among countries worldwide are the most crucial approach in controlling this universal pandemic [59]. The discovery of new SARS-CoV-2 vaccines at an unparalleled pace has contributed to tremendous attempts by global clinical investigators during this pandemic to control this viral disease that devastated societies [60]. The SARS-CoV-2 vaccine stimulates the immune system, resulting in the development of neutralizing antibodies against the virus [61]. Over 2.4 billion dosages of the CoVs vaccine have been given as of June 22, 2021, according to the WHO's CoVs dashboard, with about 22% of the world's inhabitants were administered at least single-dose [62]. The most commonly vaccine platforms for COVID-19 such as mRNA, viral vector, inactivated, and perfusion are shown in Fig. 1.

8.1. BNT162b2 vaccine

People aged 16 and older who received two doses of the trial vaccine BNT162b2 (mRNA-based, BioNTech/Pfizer), given 21 days apart, were shown to have 95% protection against COVID-19, according to the findings of an ongoing international, placebo-controlled, observer-blinded, pivotal effectiveness study. The safety characteristics of this vaccine were found to be comparable to that of previous viral vaccines [63]. On 11 December 2020, the food and drug administration (FDA) afforded the an emergency use authorization (EUA) to administer the BNT162b2 vaccination to combat COVID 19, based on this vaccine effectiveness analysis findings.

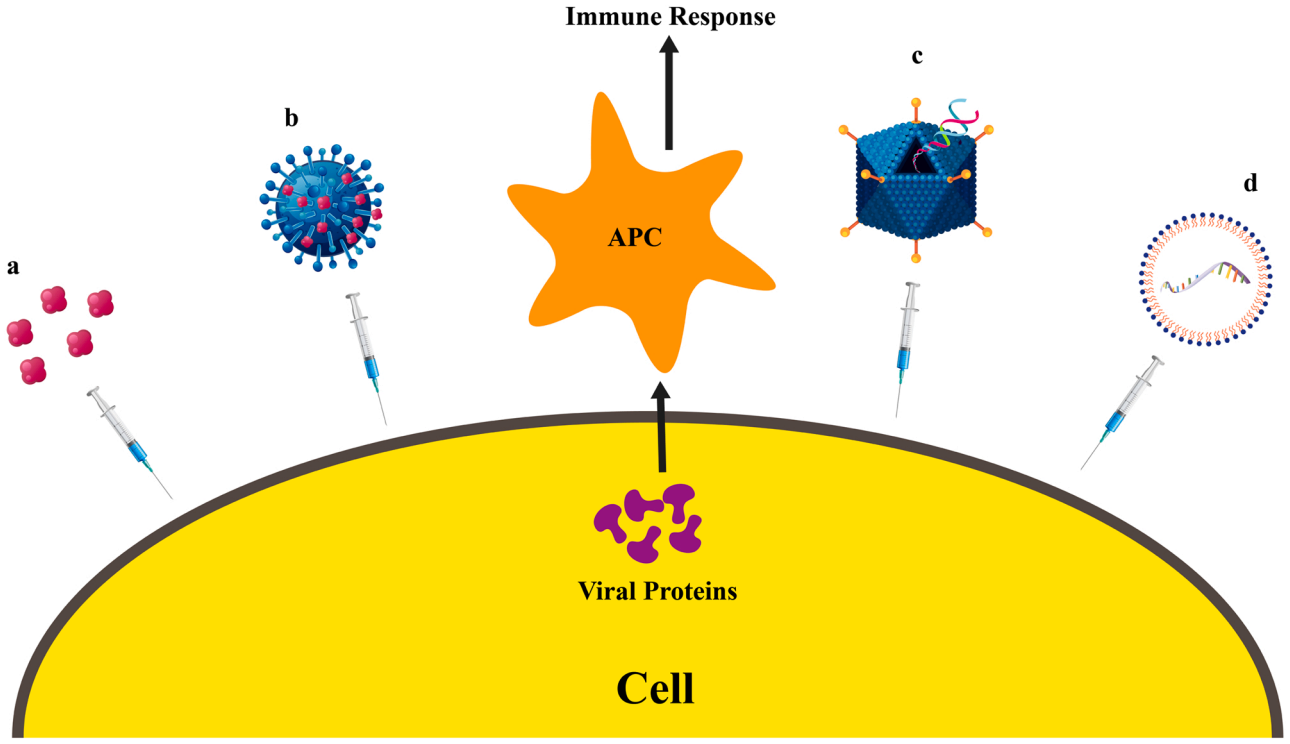

Fig. 1. The most commonly platforms for COVID-19 vaccination. a) Per-fusion viral protein subunits. b) Inactivated based vaccine. c) Adenovirus based vector vaccine. d) Lipid nanoparticle encapsulated mRNA.

8.2. mRNA-1273 vaccine

Participants who were randomized to take two dosages of mRNA-1273 (mRNA based, Moderna) vaccination administered 28 days intervals during another multicenter, Phase 3, randomized, observer-blinded, placebo-controlled trial exhibited 94.1% effectiveness in avoiding COVID-19 disease, and no safety issues were observed apart from transitory topical and systemic responses [64,65]. On 18 December 2020, the FDA afforded a EUA to approve the mRNA-1273 vaccine to prevent COVID-19, focusing on findings from this vaccination effectiveness experiment.

8.3. Ad26.COV2.S vaccine

According to the findings of an international multicenter, randomized, placebo-controlled multicenter, phase 3 study, a single dose of Ad26. COV2. S vaccine for the prophylaxis of COVID-19 provided 73.1% effectiveness in prohibiting COVID-19 throughout adult volunteers who were randomized to take the vaccine on February 27, 2021 [66].

8.4. ChAdOx1 nCoV-19 vaccine

The temporary analyzes of the continuing randomized control multicenter test showed a satisfactory safety and clinical effectiveness of 70.4% after two-dose administration and 64% for COVID-19 safekeeping following at least a normal single dosage [67]. In several countries throughout the globe, ChAdOx1 nCoV-19 has been authorized or permitted for an urgent prescription to combat COVID-19. Still, it has not acquired a EUA or FDA certification for consumption in the United States.

8.5. NVX-CoV2373 vaccine

The first findings of a randomized, observer-blinded, placebo-controlled phase II study in South Africa assessing the effectiveness and safety of NVX-CoV2373 (Novavax), a genetically engineered recombinant SARS-CoV-2 nanoparticle vaccine, indicated that the vaccine was effective in suppressing COVID-19 [68]. When this study was performed, the nation was suffering a secondary peak of illness owing to the Beta (B.1.351) strain, indicating that the drug was effective against this strain of the virus. Initial findings from a phase 3 clinical study in the United Kingdom assessed the NVX-CoV2373 vaccine have shown that the vaccination is effective in 89.3% of participants (not released yet).

Other vaccines, particularly protein-based and attenuated vaccines, have been formulated and tested in India (Covaxin), Russia (Sputnik V), and China (CoronaVac). Several of these vaccines have been authorized or given emergency use permission to combat COVID-19 in several countries across the globe, in addition to the ones listed above.

Few days following immunization with the ChADOx1 nCoV-19 and Ad26. COV2. S vaccines in early 2021, a novel, clinical thrombocytopenic condition (cerebral venous sinus thrombosis/splanchnic venous thrombosis) was found in several individuals. This new clinical condition showed remarkable parallels to thrombocytopenia caused by heparin (HIT); however, vaccine-induced thrombiotic thrombocytopenia (VITT) was called without previous heparin administration. VITT, on the other hand, is handled in a manner comparable to HIT [69].

9. Efficacy of available vaccines for COVID-19 in prohibition of SARS-CoV-2 variants of concern

To address SARS-CoV-2 spike protein, in which these strains have acquired mutations, the four novel vaccines, including BNT162b2, mRNA-1273, Ad26COV2S, and ChAdOx1 nCoV-19, have established a focus that raises questions about their effectiveness towards the emerging strain.

9.1. BNT162b2 vaccine

In the Qatari inhabitants, the effectiveness of BNT162b2 against the Alpha strain (B.1.1.7) was 87% (95% CI 81.8–90.7) and 75.0% (95% CI, 70.5–78.9) against the Beta (B.1.351) strain [70]. All the SARS-CoV-2 variants were effectively neutralized during in vitro examination of 20 blood specimens from 15 patients from the clinical effectiveness study of BNT162b2. The B.1.1.7 and P.1 strains were neutralized in an approximately comparable manner. B.1.351 was strongly neutralized, although less than the SARS-CoV-2 B.1.1.7 variant [71]. Clinical studies of the BNT162b2 vaccination against these four SARS-CoV-2 VoCs are underway, with results expected soon.

9.2. mRNA-1273 vaccine

It is not determined how effective the mRNA-1273 vaccination is against SARS-CoV-2 mutations. In vitro examination of serum specimens acquired from individuals who obtained the mRNA-1273 vaccination in clinical effectiveness study revealed that the mutations influencing the RBD of the B.1.1.7 strain demonstrated no significant impact on neutralization by sera collected from people who got the mRNA-1273 vaccine. The research revealed that the titers of neutralizing antibodies against B.1.1.7 +E484K, B.1.351, P.1, and B.1.427/B.1.429 also decreased. The B.1.351 variation had a much smaller decrease in neutralizing titers than the other strains [72].

9.3. Ad26.COV2.S vaccine

A single dose of this vaccine provides continuous immunity against COVID-19 throughout a wide range of nations, namely Brazil, which has a high prevalence of variants from the P.2 ancestry, and South Africa, which has a high prevalence of variants from the B.1.135 ancestry. It should be noted that the effectiveness of the vaccination in the US was 1.3 greater than that of South Africa (72% vs. 57%) [73].

9.4. ChAdOx1 nCoV-19 vaccine

According to findings from a multicenter, double-blind, randomized control study 33725432, a double-dosage strategy using the ChAdOx1 nCoV-19 vaccine has shown no immunity against mild to modest COVID-19 SARS-CoV-2 B.1.350 strain. Findings from another randomized ChAdOx1 nCoV-19 control study indicated that the effectiveness of neutralization against B.1.1.7 strain in laboratory settings was decreased relative to non-B.1.1.7 strain and the therapeutic performance of B.1.1.7 was 70.4% compared to 81.5% in non-B.1.1.7 [74].

10. Booster strategy for COVID-19 vaccines

Despite the development of vaccines versus SARS-CoV-2, we are still witnessing the prevalence of VoCs, and consequently the effectiveness of vaccines has been challenged. Therefore, two important categories (1) decrease the serum antibody titer of vaccinated individuals after 4–6 months and (2) the ability of VoCs to neutralize the immunogenicity of vaccines encourages communities to increase booster doses [75].

Evidence suggests that serum antibody levels are reduced in people who have been vaccinated versus SARS-CoV-2 with a variety of platforms and strategies. For example, immunogenicity of people vaccinated with BNT162b2 and mRNA-1273 after a second doses has been reported to be approximately 90% [76]. Choi et al. reported that booster doses under the mRNA platform was able to increase the titer of neutralizing antibodies [77]. Elderly and immunocompromised patients are among the first candidates for booster doses against the SARS-CoV-2 VoCs. Immune senescence and one or more co-morbidities, especially in the elderly, even with complete vaccination, reduce the titer of neutralizing antibodies against SARS-CoV-2 VoCs [76,78].

In another study, the third dose (booster) of the BNT162b2 vaccine

was given to the elderly and showed results in a ten-fold reduction in breakthrough infections [79]. In general, the quality and extent of humoral and cellular immune responses produced by various vaccine-boosting platforms against VoCs need further investigation.

11. Mix-and-match strategy for COVID-19 vaccines

Vaccination rates are rising worldwide. So far, more than 30% of the world's population has received the first and/or second doses [49,80], a significant percentage of which are allocated to developed and rich countries [79,81]. Hence, rich countries are injecting booster doses, while poorer countries have not yet received the first dose of vaccination [79,81]. However, low-income countries will have to inject any vaccine with any platform to increase vaccination rates in their communities [81]. On the other hand, several countries have decided to use another platform in the second dose due to reports of side effects of the AstraZeneca vaccine [82,83]. These challenges have led some countries to follow a mixed vaccination strategy. So far, several studies have been performed on mixed COVID-19 vaccines in mice. One of these studies showed that Sputnik V and AstraZeneca vaccines in mice were associated with higher immune responses [84]. The results of Spencer et al. showed that heterologous (self-amplifying RNA and an adenoviral vectored) vaccination in mice had a higher antibody response than its homologous form [85]. The results of the first preclinical study of heterologous vaccination proved that ChAdOx1-S vaccine in the first dose and BNT162b2 vaccine in the second dose were able to induce humoral and cellular immune responses well. In addition, no severe side effects were reported with this vaccination [86]. Another study showed that heterologous vaccination of ChAdOx1 nCoV-19/BNT162b2 increased antibody responses to anti-spike by approximately 11-fold compared to their homologous form [87].

12. Antiviral pills and vaccination as a novel combination therapy to combat COVID-19

Today, we need combination therapies to combat COVID-19. In this section, we intend to discuss one of the combination therapies, including oral antiviral drugs in addition to COVID-19 vaccination. The SARS-CoV-2 pandemic revolutionized the vaccine industry, with oral antiviral compounds being no exception. Recently, two antiviral pills called Molnupiravir and Paxlovid were developed by two companies, Merck and Pfizer, respectively. Interim results of the phase II/III trial indicate that the use of these drugs can significantly reduce the risk of hospitalization and even its duration in patients with Covid-19. Vaccinated susceptible groups may not have adequate immunogenicity and may have many problems if they become infected. Therefore, oral administration of these antiviral compounds can help in the recovery process of these people. Their advantage over other antiviral compounds is that they are given at home. Molnupiravir prevents its replication by causing multiple mutations in the SARS-CoV-2 genome. Paxlovid, on the other hand, disrupts the processing proteins of the virus, thereby inhibiting it. Until now, the administration of these compounds has been tolerable in COVID-19 patients [88–90]. However, more studies are needed to investigate their possible side effects. Overall, the equal distribution of vaccines and the administration of oral antiviral drugs at the onset of infection can be effective in reduction of virus transmission, hospitalization rates, and mortality.

13. Conclusion

In addition to causing more than 3.8 million fatalities globally, COVID-19, an extremely infectious viral disease produced by the SARS-CoV-2 virus, has had a devastating impact on the world's demography, arising as the most significant global health catastrophe since the influenza pandemic in 1918. In the termination of December 2019, when first cases in Wuhan, Hubei Province, China, this primarily respiratory virus were recorded, the SARS-CoV-2 spread quickly across the globe, prompting the WHO on 11 December 2020 to designate it a worldwide pandemic. With COVID-19 designated a global pandemic, several nations globally have been devastated and numerous health systems overburdened.

In the course of this pandemic, numerous strains of the SARS-CoV-2 were discovered, among which, considering their effect on global public health, only a handful are deemed VoCs by the WHO. However, following the latest epidemiological report by the WHO on 26 December 2021, five SARS-CoV-2 VoCs, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) have been discovered since the commencement of the pandemic.

Eighty-seven percent of the patients in a multicenter examination of the pulmonary tissue from autopsy in individuals who screened for COVID-19 showed usual alveolar diffuse destruction. Furthermore, type II pneumocyte hyperplasia, bronchial inflammation, and hyaline membranes existence across alveolar domains were shown to be common in the study population. Among 84% of participants, 42% reported massive vascular thrombin, platelet (CD61 positive), and fibrin microthrombi.

Severe hypoxic damage was observed in all cerebral and cerebellar patients in the single-center histopathological examination of brain tissues collected from 18 patients who deceased during COVID-19. Remarkably, there were no encephalitis characteristics or any other particular neurological abnormalities. Moreover, there is no cytoplasmic viral staining from immunohistochemistry examination of neural tissues.

It was discovered that the SARS-CoV-2 viral genome was present in the myocardium of 39 autopsy samples involving individuals whose tests are positive for SARS-CoV-2.

Evaluation of histopathological renal samples taken from 26 autopsy patients with COVID-19 revealed indications of widespread tubular proximal damage, including brush border disintegration, non-isometric vacuolar degradation, and necrotic reactions. Furthermore, the groups of coronavirus-like molecules with spikes throughout the tubular epithelium and podocytes were observed by electron microscopy.

Inside the cytoplasmic compartment of the gastric, duodenal, and rectal epithelium, endoscopic samples showed positive staining for the viral nucleocapsid protein. Throughout the lamina of the stomach, duodenum, and rectum, many infiltrating plasma cells and interstitial edema lymphocytes were identified.

According to results from a prospective single-center clinicopathologic case series research, including the postmortem histological examination of the central systems of eleven dead participants with COVID-19, all experienced hepatic steatosis. 73% of individuals had chronic congestion in their hepatic biopsies. Among four cases, various types of hepatocyte necrosis and 70% nodular proliferation have been reported.

The advent of these novel SARS-CoV-2 strains challenges the considerable achievements to restrict the transmission of this viral disease, despite the vaccine's extraordinary pace of advancement against the progression of COVID-19 and intense worldwide endeavors for massive immunization.

Recently, a new variant of SARS-CoV-2 was identified in South Africa, which the WHO categorized as VoCs and named it (B.1.1.529) Amicron. Many countries are currently tussle with the Delta variant, which the Amicron variant has caused a great deal of concern around the world. The recent prevalence of Delta and Amicron variants in South Africa indicates a very low vaccination rate, leading to a high mutation rate in SARS-CoV-2. We mentioned that rich and developed countries are injecting booster doses to their citizens, while many poor countries have not received the first dose of the vaccine.

Developed countries should make significant efforts to change their vaccination policies to reduce the emergence of VoCs in low-income countries. Another mechanism is the use of combination vaccines. Few studies in mice and humans have shown that heterologous vaccines have produced a significant increase in cellular and humoral immune

responses compared to homologous vaccines.

However, widespread use of this type of vaccination regimen requires further studies in terms of long-term immune responses, possible side effects, and decreasing or increasing the titer of neutralizing antibodies against emerging SARS-CoV-2 variants. These strategies can be a solution to compensate for vaccine shortages, reduction of mutations and emergence of VoCs, equitable vaccination allocation, especially in poor areas, and improve the effectiveness of vaccines.

Finally, combination therapies such as oral antiviral drugs and vaccination in high-risk groups can improve immunization, especially against the emergence of VoCs. We hope that in the near future, with a rapid change in vaccination policies as well as the use of these strategies, COVID-19 can be controlled.

Conflict of interest statement

The authors declare that they have no conflict of interests.

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