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ORIGINAL ARTICLE

The effect of RNA and non-RNA vaccines in variants of Covid-19: A narrative review

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ABSTRACT

Coronaviruses are detected in humans and mammals; these are big-size and single-stranded RNA viruses with nucleocapsid. SARS-CoV-2 has included four structural proteins (S, E, M, and N); between these proteins, S protein makes attaching ability in the virus. This ability causes the virus to bind to angiotensin-converting enzyme 2(ACE2) and host cell membrane in targeted tissues. Currently, several mutations of SARS-CoV-2 were identified. On the other hand, these new mutations cause SARS-CoV-2 to have different variants with various severity, such as the South African variant (B.1.351) and the UK variant (B.1.1.7). Throughout the COVID-19 pandemic, diverse therapeutics routes and prevention assays have been applied, following that several drugs and therapy assays have been investigated. One of the most important routes in this pandemic is the vaccine. Currently, at least in all of the world, almost 13 vaccines have been accepted with different mechanisms against COVID-19. This review explored current mRNA and non-mRNA vaccines against SARS-CoV-2 and their immunogenicity, safety, and Efficacy. We substantially focused on emerging mutations, the glycoprotein of the spike, and variants of concern (VOCs). Due to recently published articles of selected data, there were no specific outcomes to distinguished and compared between complete Efficacy and safety of approved vaccines against COVID-19. However, it must be noticed that widespread vaccination against SARS-CoV-2 and its different variants is necessary. This review is a novel study in the duration of the pandemic of COVID-19, and it needs additional particular studies. Hence we desire other scientists and related researchers to continue assessing this topic.

Keywords: SARS-CoV-2, mRNA vaccines, non-mRNA vaccines, Efficacy of vaccine, COVID-19, Severe acute respiratory syndrome coronavirus 2, Mutation, Variant of coronavirus, public health

INTRODUCTION

As the SARS CoV2 virus spreads globally, researchers are now faced with a new challenge contradicting their strenuous efforts in producing a vaccine. The novel Coronavirus that first appeared in Wuhan, China, back in late December 2019, spread globally within weeks. The number of infected individuals rose from tens to hundreds to thousands and is currently at almost 150 million cases [1]. The SARS CoV2 virus, on the other hand, has been successfully able to mutate and structure itself to defend against various countermeasures across several countries. Variants such as the UK variant (B.1.1.7) and the South African variant (B.1.351) have emerged using a combination of mutations in their Receptor Binding Domain (RBD), Spike proteins, as well as other structural proteins [2,3]. What makes this unsegmented positive-sense single-stranded RNA virus which originates within the beta lineage of the Coronavirus genus unique, is its ability to mutate itself to defend against both mRNA and Live vaccines [4]. Mutations such as in the spike levels of N501Y, P681H, T716I, S982A, D1118H, and many more across various variants have occurred in response to global immunization efforts.

After infection from the virus, symptoms vary on a scale from mutant to mutant, including mild respiratory symptoms such as dry cough, fever, loss of taste, to chronic neurological symptoms such as cerebral hemorrhage, cerebral infarction, and instability in walking [5,6]. In addition, while many infected patients tend to suppress the viral infection and express limited symptoms, some, with weaker immune systems, tend to show more chronic severe symptoms such as Cardiac myopathies showing high levels of troponin I [7]. Finally, Pulmonary edema, pro-inflammatory concentrates, and an indication of early-phase acute respiratory distress syndrome (ARDS) were noted as well in COVID-19 patients' autopsy [6].

Treatments: Throughout the pandemic, numerous therapeutics have been employed, with various degrees of success. These treatments include but are not limited to corticosteroids, Lopinavir/Ritonavir (protease inhibitors), Oseltamivir, hydroxychloroquine, arbidol hydrochloride, and even convalescent plasma[8]. Like hydroxychloroquine & Lopinavir/Ritonavir, some of these treatments showed great promise and were used extensively during the pandemic onset, yet were later proven ineffective at reducing mortality even mechanical ventilation [9,10]. At the same time, other drugs like remdesivir were found to shorten recovery time in hospitalized covid-19 patients and thus are still prescribed frequently [11]. Unfortunately, most of these treatments leave much to be desired. However, the race to procure effective therapies is far from finished, as Pfizer plans on releasing a new protease inhibitor capable of combating covid-19 by the end of the year [12].

Vaccines: As of writing this article (4/23/2021), 13 vaccines have been approved in at least 1 part of the globe, while a further 60 are still in development, each incorporating a different mechanism to generate immunity [13]. Some like BNT162b2 and mRNA-1273 are mRNA-based, which are known for their high efficacy and low severity adverse effects[14], while others are inactivated vaccines (BBV152) or adenovirus vaccines (AZD1222).

This article investigates a handful of mRNA and non-mRNA vaccines' Efficacy, immunogenicity, and safety, especially concerning emerging mutations within the spike glycoprotein and variants of concern (VOCs).

Coronaviruses are enveloped, significant, single-stranded RNA viruses with nucleocapsid, discovered in mammals and humans. They cause gastrointestinal, respiratory, and neurological problems. 229E, OC43, HKU1, and NL63, are the most common coronaviruses that cause cold symptoms. The first coronavirus caused severe respiratory syndrome (SARS). This coronavirus was discovered in China in 2002- 2003. The second coronavirus found in Arabia Peninsula in 2012 caused Middle East respiratory syndrome (MERS). The third coronavirus is SARS-CoV-2 which caused severe global disease in humans in the last two decades [15]. SARS-CoV-2 is mainly spread from large respiratory droplets and can directly infect the cells of upper and lower respiratory tracts, particularly alveolar epithelial and nasal ciliated cells. It also can apply to other human tissues, like the heart, small intestine, thyroid, kidneys, testis, and adipose tissue [16]. This virus has 60 -140nm diameter and distinctive spikes(9-12nm) that make the solar Corona appearance [15]. SARS-CoV-2 has a +ssRNA (Positive-Sense Single-Stranded RNA) genome with almost 29.9kb in length (the giant RNA virus). This virus has four structural proteins: S (spike), E(envelope), M (membrane) (these three proteins make the viral envelope which has an essential role in the viral gathering, release, and promoting viral pathogenesis), and N (nucleocapsid) which holds the RNA genome. The S protein gives the virus the ability to attach to angiotensin-converting enzyme 2(ACE2) and join with the host's cell membrane [17]. Despite 72% equality in amino acid sequences of S protein in SARS-CoV-2 and SARS-CoV, SARS-CoV-2 has a higher affinity for the ACE2 receptor [16]. Then virus uses serin proteases TMPRSS2(transmembrane protease serine 2)for S protein priming, infecting the host cell. The S protein includes two subunits: the S1 receptor binding subunit and the S2 fusion subunit. The S cleavage site separates these two. The viral RNA steals the target cell’s machinery to begin genome replication and polypeptides synthesis and also creates the replication- transcription complex (RCT) (necessity to synthesize the subgenomic RNAs along with structural protein) [17]. By genetic variation and recombination, these viruses adapt quickly and infect new hosts. It was thought that bats were the natural supply of SARS-CoV-2; now, they suggested that this virus-infected humans by an intermediate host such as pangolin[15].

RESULTS

In this article, Elisabeth and Mahase investigated a study regarding the effectiveness of the Oxford- AstraZeneca vaccine against the south African variant (501Y.V2), which was conducted on 2000 young, HIV hostile adults with a mean age of 31, and it appears to have deemed the vaccine ineffective against mild to moderate disease. In the study, 1000 participants were categorized in a placebo group while the other half were administered the vaccine, yet Due to the nature of the research and the age group, correctly predicting the vaccine's effects on the severe disease was challenging. Nevertheless, this study, yet to be peer-reviewed as of writing this article, goes to show that vaccines have to be updated following mutations, and booster jabs may, and indeed already are, necessary [18].

Madhi and fellow authors masterminded a randomized, double-blinded case-control trial in South Africa. They divided 2026 HIV-negative individuals with no history of anaphylaxis, not suffering from morbid obesity and no previous Covid-19 infection into two groups during the study. The participants were between 18 and 65, and the doses contained 5X1010 particles. The first consisting of 1010 were given a placebo(0.9%NaCl), while the second group, consisting of 1011 individuals, received two doses of ChAdOx1-nCoV (the Oxford-AstraZeneca vaccine) within 21-35 days, 28 days on average. The study's primary objective was to determine the vaccine's Efficacy 14 days after the 2nd dose was administered against a NAAT (Nucleic Acid Amplification Test) confirmed Covid-19 case. However, the authors also determined secondary objectives such as safety analysis and VE (vaccine efficacy) against the B.1.351 variant. To assess the vaccine's safety, participants were observed for seven days post-vaccination in case of solicited reactogenicity and for 28 days in case of unsolicited adverse effects. The safety evaluation found it safe for use. During the study, the participants took NAATs routinely or when symptoms developed. Overall, 42 participants grew Covid-19, 23 were in the placebo arm, and 19 were in the vaccine arm. They concluded that two doses of the vaccine had an efficacy of 10% against the B.1.351 variant and, therefore, ineffective in preventing its spread [19].

Sapkal et al designed a research that Most Vaccine candidates were designed to be recombinant or target the original D614G spike protein sequence and subsequently might not be able to produce a reasonable immune response against VOC (variants of concern); the study mentioned earlier is an unfortunate example. Therefore they intended to determine the BBV152 (made in India) vaccine efficacy, an inactivated whole-virion vaccine, against the B1.1.7 (UK variant) strain. In phase II clinical trials conducted by Ella R et al., 38 individuals had received two doses of BBV152 with a 28-day interval. The first dose was 6 µg and the second dose was 3 µg. 4 weeks after the last dose, The authors conducted PRNT50 on sera from these 38 vaccine recipients, against the UK variant, as well as a PRNT50 on extracted serum from 20 vaccinated individuals against a heterologous strain with the L3606F substitution. The sera were serially diluted four times and were mixed with 50-60 plaque-forming units in 0.1ml. The result of the tests was similar Efficacy and plaque neutralization regarding both the UK variant and other heterologous strains in comparison to the homologous strain. This article found out that the BBV152 vaccine was effective against the UK variant and different heterologous

strains and further stated that the 501Y mutation evident in the south African variant would not be of concern [20].

Collier et al projected a research to evaluate the Efficacy of the Pfizer-BioNTech vaccine (BNT162b2) against the B.1.1.7 variant (UK variant) by measuring the immune response three weeks after the first dose was administered on 23 individuals with a mean age of 82. Serum antibody titers were inspected by a Luminex bead system utilizing flow cytometry. While conducting the study, They observed higher antibody titers among the vaccine recipients than the control group, which is a testament to its Efficacy. Still, large-scale variation was seen in antibody responses to spike and spike RBD. Lesser immunogenicity to spike was also evident in those above the age of 80. Utilizing lentiviral pseudotyping techniques, the authors also installed wild-type spike proteins onto enveloped virions and found that vaccine sera showed a wide range of inhibitory dilutions giving 50% neutralization (ID50). Eight of the participants also showed no notable neutralization against the wild-type virus. The effects of 3 concerning mutations evident within the B.1.1.7 VOC (a variant of concern), deletion 69/70, N501Y, A570D, were also calculated by comparing the mutant spike to the wild type serum neutralization test of the participants' sera. The result was similar neutralization of both. The authors also created a spike protein bearing all eight mutations seen within the B.1.1.7 variant and found that 10 out of 15 participants showed lowered Efficacy against it. Overall the authors found the vaccine effective against the B.1.1.7 variant, although to a lesser degree, and immunogenicity appears to drop the older the subject becomes [21].

Baray et al planed a study to describe a new mRNA-Lipid nanoparticle vaccine developed in Bangladesh, called BANCOVID. The mRNA used to create the vaccine contains sequences to fight against the D614G effectively, K986P, and V987P mutations and is encapsulated within a lipid nanoparticle. The vaccine's safety and effectiveness were assessed in a study on 30 Swiss albino mice (half male and half female), 6-8 weeks old, in which they were separated into five groups of 6. 3 of these groups received the vaccine, administered in different doses(0.1 µg- 10µg). In contrast, one was administered a placebo, and the last group was not injected with anything. No adverse effects were recorded among the mice. Immunogenicity in the three groups that received one dose of the vaccine was analyzed, and vaccine-generated antibodies were seen binding to SARS-CoV-2 spike proteins. IgG binding endpoint titers were observed both 7 and 14 days after administration, all of which contained balanced ratios of different antibodies. In addition, neutralization assays were taken against Adeno based pseudoviruses and retro-based pseudoviruses, both with SARS-CoV-2 spike proteins embedded on their surfaces. These assays clearly illustrated the vaccine's ability to prevent infection. The binding affinity of the antibodies was also measured utilizing surface plasmon resonance technology, which showed the antibodies targeting the entirety of the spike protein rather than a single domain. To sum up, BANCOVID appears to effectively neutralize the G614 variant of SARS-CoV-2 without the risk of adverse effects. The authors hope that the phase I clinical trials underway will further support their findings [22].

In this article Lubbe et al attempted to estimate the immunogenicity, safety, and dose regimen of the adenovirus serotype-26 vaccine with SARS-CoV-2 G614 Spike proteins on its surface. To do so, The vaccine was administered to male Syrian hamsters, aged 9-11 weeks, at doses of 109 or 1010 particles, and compared to 2 other prototype vaccines, one with wild-type spike proteins and the other with spike proteins that had a C-terminal fold on replacing its transmembrane domain. The hamsters were either vaccinated once or twice(with a four-week interval) to determine the dose regimen and consequently infected with the G614 virus variant intranasally four weeks after the last dose. They found that the Ad26.COV2.S was the most effective by comparison, generating the most significant immune response, and that a second dose increased neutralization titers. Another study was also conducted on Female New Zealand White rabbits, roughly four months old, in which a two-dose vaccine regimen with an 8-week interval was employed. The latter study supported the findings of the previous research. A dose-titration study was performed to assess the vaccine's safety, and no adverse effects were observed. Overall they found Ad26.COV2.S to be effective against the SARS-CoV-2 G614 spike variant virus, especially when a second dose is administered, and also validated its safety. It should be noted that the vaccine is still in clinical trials. The study showed the vaccine to be effective, and no adverse effects were observed in the study [23].

Lubbe et al investigate another study to assess 36 epitopes on the S protein were distinguished and analyzed for mutations; only 3 of them had some form of mutation, meaning that vaccines should focus on these 36 to create an effective multi-epitope vaccine. In this article, the authors intended to Evaluate the Efficacy of the Pfizer-BioNTech vaccine (BNT162b2) against the B.1.1.7 variant (UK variant) by measuring the immune response three weeks after the first dose was administered on 23 individuals with a mean age of 82. Serum antibody titers were inspected by a Luminex bead system utilizing flow cytometry. While conducting the study, They observed higher antibody titers among the vaccine recipients than the control group, which is a testament to its Efficacy. Still, large-scale variation was seen in antibody responses to spike and spike RBD. Lesser immunogenicity to spike was also evident in those above the age of 80. Utilizing lentiviral pseudotyping techniques, the authors also installed wild-type spike proteins onto enveloped virions and found that vaccine sera showed a wide range of inhibitory dilutions giving 50% neutralization (ID50). Eight of the participants also showed no notable neutralization against the wild-type virus. The effects of 3 concerning mutations evident within the B.1.1.7 VOC (a variant of concern), deletion 69/70, N501Y, A570D, were also calculated by comparing the mutant spike to the wild type serum neutralization test of the participants' sera. The result was similar neutralization of both. The authors also created a spike protein bearing all eight mutations seen within the B.1.1.7 variant and found that 10 out of 15 participants showed lowered Efficacy against it. Overall the authors found the vaccine effective against the B.1.1.7 variant, although to a lesser degree, and immunogenicity appears to drop the older the subject becomes [24].

Polack et al considered a research on BNT162b2 that is a nucleoside-modified lipid nanoparticle formulated RNA vaccine. They did a study in 2020 on 43488 people who were 16 years old or older. They assigned people randomly in two groups; One received a placebo (a substance or treatment which is designed to have no therapeutic value), and the other received BNT162b2. Both of them were in two doses. The second dose was received 21 days after the first dose. After at least seven days from the double dose, there were 8 cases of COVID-19 from BNT162b2 receivers and 162 cases of COVID- 19 among placebo receivers. Therefore this vaccine was 95% effective against covid-19. The side effects of this vaccine were short-term pain at the injection site, tiredness, and headache [27].

Voysey et al. tested the ChAdO×1 nCoV-19 vaccine (AZD1222)in UK, Brazil, and South Africa in 2020. There was four progress blinded, randomized, controlled trials. In this analysis, people who were 18 years old or older were divided randomly into three groups: two groups for ChAdO×1 nCoV-19 vaccine (one group received two standard doses, and the other group received Low dose in their first time and then standard dose as their second dose (in the UK trails)); and one control group. As a result, this vaccine was 70.4% safe and effective on COVID-19 [28].

Baden et al. studied on Efficacy and safety of the mRNA-1273 vaccine in 2021. This study assigned adult people randomly in two groups: 1- Placebo-controlled group 2- who received an intramuscular injection of mRNA-1273.Both of the groups received two doses 28 days apart. This study was in the United States. The first endpoint was the prevention of illness at least 14 days after receiving the second dose. As a result, 185 members of a placebo group and 11 receivers of mRNA-1273 had symptoms of COVID-19. Thus, the vaccine was 94.1% efficacy at preventing" even server" COVID-19 illness. About the side effects of this vaccine: the injection site events were pain and mainly grade 1 or 2 for 2-3 days. It had some reactions like erythema, Tenderness, and induration. Solicited adverse events happened more frequently in the receivers of mRNA-1273 than placebo receivers [29].

Hayashi et al. did a study on the effect of Y453F mutation in the spike glycoprotein of SARS-CoV-2. This mutation (the mutation of amino acid 453 of RBD (Tyrosin) to Phenylalanine) is from farmed mink and now is widespread among humans. The RBD mutation (Y453F) does not change the three-dimensional structure of the spike glycoprotein of conventional SARS-CoV2. They examined IgG (Immunoglobulin G) affinity in the serum of 21 covid-19 positive patients and ten covid-19 negative patients with RBD or RBD Y4453F mutation (analyzed by Enzyme-linked ImmunoSorbent Assay). They figured out that there is a strong attraction of IgG for RBD in 14 but no attraction for RBDY453F in 19 positive patients. Also no attraction for both RBD and RBDY453F in 10 negative patients. Thus this mutation has the repressive effect of the neutralizing antibody on binding between ACE2 (Angiotensin-converting enzyme 2) and RBD. So we should pay more attention to the mutations for designing vaccines [30].

Zaheer et al .studied all available genomes of SARS-CoV-2 (all were recovered in GISAID(Global initiative on sharing all influenza data) and NGDC(National Geophysical Data Center)) to find the best multi-epitope for designing a vaccine. First, they put them through CTLpred(Cytotoxic T lymphocyte prediction) (using for CD8 Tcell) and HLApred(human leukocyte antigen prediction). Then they tested CTL epitopes for antigenicity(using VaxiJen), immunogenicity, and Powerful binding attraction with HLA superfamily alleles. Furthermore, they tested HTL (Helper T lymphocyte) epitopes for antigenicity, overlapping B cell epitopes, interferon induction potential, powerful HLA DR (Human Leukocyte Antigen – DR isotype) binding potential. Appropriately they designed epitopes in two multi-epitopes orders: Cov-I-Vac (without adjuvant) and Cov-II-Vac (with β-defensin adjuvant). For comparing these two multi-epitopes, Cov-I-Vac presents better interaction with TLR8 (an endosomal receptor that recognizes single-stranded RNA (ssRNA)), and it needs more energy to disfigure the structure. This study is so helpful for future studies on the COVID-19 vaccine [31].

X.Chang et al .did a study on BNT162b2 vaccine recognition of mutants SARA-CoV-2. They provided SARS-CoV-2 mutants with one mutation in RBD (receptor binding domain) region (E484K, K417N, N501Y) or with all three mutations. (B.1.351 mutation in South Africa and P.1 mutation in Brazil). As a result, the vaccine recognized both wild-type and mutant RBDs. However, recognition of RBDN501Y and RBDK417N was 2.5-3 times reduced, while recognition of RBDE484K and the triple mutant was ten times reduced. They figured out that the E481K(mutation at position 484) is an obstacle to immune recognition. Thus they suggested that making a new vaccine is sanctioned [32].

Cohen et al researched about the Efficacy of the Astra Zeneca's Covid-19 vaccine has seen a significant drop in Efficacy in south Africa claiming a clinical trial of 4000 participants (avg. 30 years) in southern Africa of the Astra Zeneca vaccine has resulted in the Efficacy being even under 25%, a number that does not meet international standards [38]. This result has emerged due to the rising variant B.1.351 that can escape essential antibodies created by the vaccine. Other vaccines in the market, such as J&J (Human adenovirus) and Pfizer (mRNA virus), have also dropped in Efficacy, unlike anywhere else, but have managed to stay above international standards. The trial principal investigator Shabir Madhi was reasonably optimistic about the vaccine's defense mechanism against the B.1.351 variant and claimed that the vaccine could generate a strong T cell response and eliminate cells infected with the variant. Oxford, the producer of the vaccine, primarily conducted a trial that took place between June and November of 2020 and found that two weeks post full immunization, 19 participants who were vaccinated obtained mild or moderate symptoms of disease vs. the 23 in the placebo group resulting in an efficacy of 21.9%. Researchers linked the decreased Efficacy of the vaccine to the sudden widespread of the B.1.351 variant in South Africa. Subsequently, they quickly got to work finding a contribute that would identify the spike proteins of the variant. Although the decrease in Efficacy of the Astra Zeneca's Covid-19 vaccine can solely be attributed to the B.1.351 variant, it is unknown whether any other variant could affect the vaccine's Efficacy and whether it would sustain more robust variants [37].

Madhi et al. conducted similar research in South Africa and the Bill and Melinda Gates Foundation vaccine, the ChAdOx1(Adenoviral) [35]. The research team was able to carry out a successful multicenter, double-blinded, randomized controlled trial to test the Bill and Melinda Gates foundation's ChaAdOx1 nCoV-19 vaccine to whether it would positively respond in HIV hostile adults to the variant or not. 2026 HIV-negative participants (ages 18-65) were used in the controlled trial. Almost 50% of participants received 0.3-0.5 ml dosages of the vaccine, while 50% received a placebo of 0.9% Sodium Chloride. Regular follow-ups were carried out with nucleic acid amplification tests for the presence of SARS CoV2. Rigorous testing and continuous checkups resulted in 19 of 750 vaccine recipients and 23 of 717 placebo recipients virus acquiring the B.1.351 virus leading to the Efficacy of 21.9%, well below the international standard of 50% [38]. ChAdOx1 nCoV-19 thus proved to be incompetent to the SARS CoV2 B.1.351 variant. Although, as we saw, the Efficacy of the ChAdOx1 nCov-19 vaccine dropped to a similar efficacy of the Astra Zeneca vaccine (21.9%) in reaction to the variant while mRNA vaccines such as Pfizer withheld their Efficacy, the effects of Non-mRNA vaccines against the B.1.351 variant of the SARS CoV2 virus goes under question[37,39].

Conti et al. proposed arguments signifying that D614G mutations seen in European variants were incapable of neutralizing the vaccines' effects and could only lessen the Efficacy of the vaccines. Such mutations result in a higher viral growth rate and become undetectable by RT-PCR techniques. The SARS COV2 virus works by inducing Interleukin-1 (IL-1) in living organisms. The rise of levels of such cytokine other than its physiological amount leads to extreme inflammation. mRNA Vaccines stimulate CD4+ T Cells leading to the creation of IgG antibodies. These antibodies then work against the immune response of the body and suppress inflammation in the respiratory tract. Based on current knowledge, the data at hand does not suffice for believing that such mutations will impact the Efficacy of vaccines. However, there is potential for such to occur. Extreme variants may be able to, in certain hard-to-reach conditions, neutralize the vaccine. Thus, rigorous work is needed to understand the complexity of such variants. P. Conti et al. proposed arguments in this article to emphasize that mutations amongst the SARS CoV2 virus cannot neutralize vaccine effects [40].

In this research article, Edara et al. conducted a cohort study of 19 people with COVID-19 infection between 5-19 days after symptom onset. They were destined to determine whether the Receptor Binding Domain (RBD) of the South African variant (B.1.351) and the B.1 variant from Atlanta would impact IgG antibody and vaccine-induced antibody binding. Using electrochemiluminescence-based multiplex assay, 19 patients were chosen as a cohort with a symptom onset of 5-19 days. Results signified a decrease in RBD-IgG binding within the assays. Subsequently, the research team performed a longitudinal analysis of RBD binding and viral neutralization on a group of 30 convalescent SARS CoV2 infected patients. Observations were made as IgG binding to the B.1.351, and the B.1 variant decreased up to 4.8 folds in the 1–3-month time frame.

Similarly, 19 Adults aged >56 years were administered 100 µg dosage of mRNA-1273 vaccine and were bound to follow up as the cohort. It was noted that both B.1- and B.1.351-RBD binding had decreased. This showed that antibodies could attach to the B.1.351 and the B.1 variant's RBD; however, the mutations within the RBD such as K417N, E484K, and N501Y of the B.1.351 variant reduced the Efficacy of the vaccine. It was then concluded that all though the mRNA-1273 vaccine in vaccinated persons did eventually neutralize the threat, efficacy loss was noted to some extent. Thus, it is fair to say that neutralizing B.1.351 and B.1 variants via both induced and innate immunity did see some resistance [41].

Emary et al designed a randomized controlled trial (1:1) including volunteers (n=8534) aged 18 years and older being administered the ChAdOx1 vaccine ($5x10^{10}$ viral particles) or a meningococcal conjugate as control (Men ACWY) was carried out. to Test the Efficacy of the ChAdOx1 vaccine. Participants who showed symptoms of COVID-19 had samples taken and assessed using MHRA-derogated NAAT assays. Necessary precautions were taken to ensure all biases had been reduced to minimal effect. Viral genomes were put together while protruding various frequencies using shiver. Lineages were categorized by Pangolin version 2.1.7 and B.1.1.7, and Non-B.1.1.7 variant (Victoria) assays were compared and analyzed to signify neutralization in both. The study resulted in a 70.4% efficacy for B.1.1.7 infected assays and 81.5% for non-B.1.1.7 assays. Thus, it was concluded that the Efficacy of the ChAdOx1 did indeed drop in patients with the B.1.1.7 compared to patients with non-B.1.1.7 variant. To complete, the results speak for themselves, and as we saw, the ChAdOx1 vaccine created by the Bill and Melinda Gates Foundation did resist against the B.1.1.7 variant but did eventually sacrifice a small percentage of its Efficacy while doing so [42].

Collier et al conducted a assessments of antibody binding to B.1.1.7 variant of SARS CoV2 novel virus were made. Thirty-seven participants (Median age: 63.5 years) received the first dosage of BNT162b2 three weeks before blood serum analysis. Using flow cytometry, Serum IgG titers to N (Nucleocapsid) proteins, S protein, and S receptor binding domain was analyzed. A 100-fold variation of IgG titers to proteins S and RBD was observed in the assay. The viruses observed in the assay were of wild type bearing D614G and mutant B.1.1.7 S proteins. Out of 37 participants, 8 exhibited inconsistent neutralization. Subsequently, another batch of 29 participants was vaccinated with a single dose of the BNT162b2 mRNA vaccine. All eight mutations of the S protein present in the B.1.1.7 mutant were induced, including D614G. Twenty samples showed loss of Efficacy of antibodies against the B.1.1.7 mutant. The study resulted in proving the three mutations in S1, including (N501Y, A570D, ΔH69/V70) that did not affect neutralization in a pseudovirus assay. However, pseudoviruses containing S protein with all eight mutations present in the B.1.1.7 mutant (i.e., ΔH69/V70, Δ144, N501Y, A570D, P681H, T716I, S982A, D1118H) depicted a reduction in neutralization by vaccines. We can thus conclude; vaccine efficacy is not solely related to

mutation of SARS-CoV2 but the type of mutation and location of modification [43].

Zhou et al. tested the strains of SARS-CoV-2 that are emerging as B.1.1.7 (identified in the United Kingdom) and B.1.351 (identified in South Africa) and P.1 (which has been identified in Brazil) to evaluate the neutralization of B.1.351 (a mutation) by1) Convalescent blood plasma2) Vaccinated serum. 3) A large panel (the wide range) of monoclonal antibodies (mAbs).This issue requires more research, but the adequate neutralization titers against B.1.351 were, on average, 13.3 times lower. Second, they verify the effects of the Pfizer vaccine and the Oxford-AstraZeneca vaccine on neutralizing Victoria and B.1.351. Pfizer-BioNTech vaccine serum and BNT162b2 or Oxford-AstraZeneca vaccine neutralize Victoria higher than B.1.351. Significantly, the Pfizer-BioNTech vaccine serum showed higher neutralization titers against the Victoria strain than the Oxford-AstraZeneca vaccine. Finally, they utilize the 20 strangest monoclonal antibodies (mAbs) such as anti-RBD (the receptor-binding domain) and anti-NTD (N-terminal domain) to evaluate their Efficacy in neutralizing Victoria and B.1.351 strains. Nevertheless, the majority of them have serious consequences, and their experiences are inconclusive [44].

Furthermore, Coronaviruses can impair their proteins with dramatic effects; Over the past few months, the number of spike protein mutations have quickly increased in prevalence, such as B.1.1.7 and 501Y.V2, also known as B.1.351 and P.1. All of them include mutations in the ACE2 receptor binding imprint of the receptor-binding domain (RBD), 1 in B.1.1.7, 3 in 501Y.V2 and P.1. N501Y mutation is also a common mutation.

Researches show that these mutations enhance the affinity for ACE2 and disrupt the binding of neutralizing solid antibodies.

Supasa et al conducted a study To analyze the effects of the N501Y mutation on antibody binding. utilized their set of 377 mAbs generated from cases infected with SARS-CoV-2 in the first wave of the pandemic in the United Kingdom. They found that the 20 neutralizing solid antibodies confine the RBD, except mAb 159, which confines the NTD. Large numbers of mAbs still require more testing and investigation, but they found two sets of mAbs that reached late-phase clinical trials for SARS-CoV-2: Regeneron REGN10933 and REGN10987 and AstraZeneca AZD1061 and AZD8895 (mAbs names). The significant point is that these antibodies have only a moderate effect [45].

In addition, Zhang and colleagues developed a lipid nanoparticle-encapsulated mRNA (mRNA-LNP) coding for the RBD of SARS-CoV-2 as a vaccine applicant (known as ARCoV).

The RBD of SARS-CoV-2 was selected as the target antigen for the mRNA coding sequence and the RBD protein expressed through the mRNA; a range of mAbs against SARS-CoV-2 may identify this RBD protein.This research shows that intramuscular immunization of ARCoV mRNA-LNP resulted in solid neutralizing antibodies besides a Th1-biased cellular response in mice and other nonhuman cases. 2 doses of ARCoV vaccine offer comprehensive protection against the provocation of a strain adapted to SARS-CoV-2 in the mouse. ARCoV can be kept at room temperature for a minimum of one week and assessed in Phase 1 clinical trials [46].

Shinde et al managed a research on mRNA vaccines (BNT162b2 and mRNA-1273) to show the vaccine efficiency of 94% to 95%4,5 and vector-based vaccines reported 71% (pooled) vaccine efficacy for ChAdOx1-nCoV19, 92% for Gam-COVID-Vac and 66% for Ad26. The effectiveness of the post-hoc vaccine against B.1.351 was 51.0% (95% CI -0.6-76.2) in HIV-negative participants. NVX-CoV2373 effectively prevented COVID-19, which was mainly mild to moderate and was caused by variant B.1.351 [47].

Mahasa et al, investigated more about vaccines, the US biotechnology company does some experiments with 3 phases to check the Efficacy of the Novavax vaccine against the original and newer variants of SARS-CoV-2. In the first trial, two doses of the vaccine were administered three weeks apart, and 62 symptomatic cases of COVID-19 were reported who were divided into two groups, placebo and vaccinated.The A phase II trial is also in progress in South Africa with 4400 volunteers. A single-dose vaccine is 66% effective in the prevention of moderate to severe diseases 28 days post-vaccination. The Phase III trial took place on three continents with more participants. Fortunately, A single-dose vaccine, which can be readily stored and administered in the long term, offers complete protection from hospitalization and death, and it is 95.6% effective against the original variant of SARS-CoV-2; it also offers protection against newer variants B.1.1.7 (85.6%) and B.1.351 (a mutation) (60%) [48]. Finally, they found that Novavax (name a vaccine) works effectively to address COVID-19.The UK's medicines regulator approved the Oxford-AstraZeneca and Pfizer COVID-19 vaccines. For most patients, the various viruses are called B117.The Oxford vaccine was about 70% effective between the 22nd day following the first dose and the second dose; also, people should receive their second dose of Pfizer vaccine at least 21 days following the first dose. One crucial thing that has reduced all chances of transmission and spread of infections because that the virus is more susceptible to mutations and variation than many people ever thought [49].

In addition, Madhi and colleagues evaluated the safety and effectiveness of the ChAdOx1 nCoV-19 vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and new variants of SARS-CoV-2 of concern, including variant B.1.351 (or 501Y.V2).They studied 2026 HIV-negative adults (average age, 30 years), and 1010 and 1011 Participants received one or more doses of placebo or vaccine. The efficiency of the primary endpoint analysis is 21.9% (95% confidence interval [CI] from 49.9 to 59.8), and the effectiveness of the vaccine analyzed as a secondary endpoint was 10.4% (95% CI 76.8-54.8).The only dangerous side effect of the vaccine was a body temperature higher than 40°C after the first dose; Fever has been down for 24 hours.This study has shown that two doses of the ChAdOx1 nCoV-19 vaccine had no efficiency against the B.1.351 variant in preventing mild to moderate Covid-19 [50].

Diamond et al. used the animal immune serum, human serum from the recipient's vaccine of the PfizerBioNTech (BNT162b2) mRNA, human convalescent

serum, monoclonal antibodies (mAbs). This study reported the influence of antibody neutralization from authentic SARS-CoV-2 variants containing a strain of chimeric Washington with a spike gene of South African (Wash SA-B.1.351), a B.1.1.7 isolate, and recombinant variants (isogenic) with designed deletions or mutations at positions of the spike protein: 69-70, 417, 484, 501, and 614. Various extremely neutralizing mAbs appealing the N-terminal domain (NTD) or receptor-binding domain (RBD) lost inhibitory effects unto recombinant variants with a mutation in E484K spike or Wash SA-B.1.351. Based on their results, most virtually all mRNA vaccine-contained immune serum tested, and convalescent serum has shown remarkably reduced neutralizing activity versus recombinant viruses, including mutations (position 484 and 501) or strain of Wash SA-B.1.351. They also noted, for neutralization assays or development of virus stocks, selection of cell line used can affect the antibodies potency versus different SARS-CoV-2 variants; furthermore, that has implications for standardization and conformity of results among laboratories. Since lack-of-neutralization potency (in vitro) unto appearing variants in various antibodies binding particular regions of the NTD and RBD were shown. Hence, to arrest loss of protection (in vivo), targeting highly protected regions, updated cocktails of mAb, and arrangements to the sequences of spike or increment of mAb potency, vaccines may be required [51].

Scully et al. reported the findings of 23 patients with presented symptoms of thrombocytopenia and thrombosis between 6 -24 days after taking the ChAdOx1 nCoV-19 vaccine (AstraZeneca) for the first dose. In this study, based on clinical and laboratory outcomes of patients, they identified a newfound underlying mechanism that could have addressed the implications of therapeutics. In the absence of pretreatment medical conditions, the status of patients including 22 individuals with thrombosis and acute thrombocytopenia, mainly cerebral venous thrombosis, and one patient with isolated thrombocytopenia and a hemorrhagic phenotype. The antibody testing results from platelet factor 4 (PF4) were negative and 22 positive (with one equivocal). Due to the pathophysiological features observed in participants of this study, Marie Scully et al. recommended that platelet transfusions as a treatment beware and avoided because the risk of development in thrombotic symptoms was noted. For the first event of these symptoms, the administration of intravenous immune globulin and an anticoagulant agent (nonheparin) must be noticed. Eventually, SARS-CoV-2 vaccination for control of this world pandemic as a critical function has been noted. After vaccination with the ChAdOx1 nCoV-19 vaccine, the pathogenic PF4-dependent syndrome can have occurred, unlinked to the heparin therapy. However, due to the therapeutic implications of this rare syndrome, Rapid identification of this syndrome has been noted as necessary [52].

Nidom et al. investigated the mutation analysis of the full-length genome of 166 SARS-CoV-2 isolates of Indonesian as of Jan 12, 2021. In their study, all data of isolates were elicited from the GISAID (Global Initiative on Sharing All Influenza Data) EpiCoV database. Furthermore, Nidom et al. focused on the Indonesian SARS-CoV-2 isolates S protein of unlocking of mutation. As a virus source, according to CoVsurver, the default was used of WIV04 isolate, which was emanated from Wuhan, China. The results indicated that the mutation analysis for a full-length genome of Indonesian SARS-CoV-2 isolates (n=166) was successfully detected. Any mutation such as a single mutation was characterized in S protein and then imagined by employing BioRender besides, that it found D614G mutation emerged in Indonesian SARS-CoV-2 isolates (n=103) [53].

Emary et al. studied the Efficacy of the vaccine of adenoviral vector, ChAdOx1 nCoV-19 (AZD1222), in opposition to this variant. This study was a post-doc analysis. Participants were ≥ 18 years old. These UK's volunteers were randomized and have finished efficacy studies of Phase 2/3 vaccination. The randomized volunteers were selected to Meningococcal Conjugate Control Vaccine (MenACWY) or ChAdOx1 nCoV-19 (1:1). Using by nucleic acid amplification test (NAAT) for SARS-CoV-2, the swabs were examined. For detection of sequence from positive samples were used by the COVID-19 Genomics UK consortium. A microneutralization test of live virus counted responses of Neutralizing antibodies against the non-B.7 canonical line and B.7 line. Due to their methodology, the Efficacy of symptomatic COVID-19 in negative serum of participants with a positive swab of NAAT more than 14 days later than the second dose of vaccination, were evaluated. Based on results, volunteers between May 31-Nov 13, 2020 were enrolled, and booster doses were injected during Aug 3 -Dec 30, 2020, to participants. Of 8534(100%) volunteers in the early efficacy cohort, 78% were 18-55 years old, and the rate of the female participant was 59%. The during this study, throat swabs, and NAAT positive nose about (1466) from these volunteers were collected. Of 1466 volunteers, 401 swabs from 311 contributors were sequenced successfully. The neutralization activity of laboratory virus by antibodies from the vaccine was less versus the B.1.1.7 variant than opposed to the Victoria lineage. The rate of Efficacy of clinical vaccine against positive infection of symptomatic NAAT for B.1.1.7 was 70·4% and for non-B.1.1.7 lineages were noted 81·5%. Finally, ChAdOx1 nCoV-19 appeared decreased neutralization activity unto the B.1.1.7 variant compared with an in vitro non-B.1.1.7 variant. However, the vaccine against the B.1.1.7 variant of SARS-CoV-2 is revealed Efficacy [54].

Limitation: In this topic , Some of the articles are not written in English and limit our accessibility to a wide range of articles. Also, the lack of a sound English translation system made it impossible for us to read them in English. Another limitation of our study was that research on the types of vaccines and their performance, advantages, and disadvantages have not finished and there are much ambiguity about them.

Since that COVID-19 is a new issue globally, we offer a wide range of studies about it and the types of vaccines and their effects on COVID-19 prevention.

Moreover, we highly recommend that infectious disease specialists to study and research coronavirus structure , functions , mechanism of mutations and the effects of vaccines to know it more clearly.

CONCLUSION

In this review, we tried to assess different COVID-19 vaccines in various mutations of Coronavirus . However, additional researches are needed to find the best vaccine for different mutations .

Effects/Dosage	Results	References
Two months of follow-up 2199 participants used NVX-CoV2373 2188 used placebo 30% of participants were HIV-positive. 94% of seronegative participants were HIV-negative (18 to 84 years of ages), and 6% are PLWH (18 to 64 years of ages) Two doses, given 21 days apart.	Between 94% of those without HIV, the NVX-CoV2373 affected about 60.1% and effectively prevented Covid-19.	[56]
Oxford can be stored at 2 to 8°C in the refrigerator. The Pfizer vaccine's second dose is given after 21 days. The Oxford vaccine's second dose is given 22 days later.	Oxford vaccine was found to be 62.1% helpful in two doses (n=4440) and 90% useful for people with a low dose followed by a standard dose (n=1120).	[57]
This trial evaluated the effect of Novavax in two viral variants. Phase III was tested on more than 15,000 participants aged 18 to 84, including 27 percent over 65. The trial tested two doses of the vaccine every three weeks and used both placebo and variant vaccines in South Africa. A Phase II test involved 4,400 participants, where 29 of them were in the placebo group (a severe case) and 15 in the vaccinated group.	The Novavax vaccine has an 86% impact on the UK variant and 60% on the South African variant.	[58]
Use of mRNA-LNP ARCoV at 1 mg/kg, Evaluation of the Efficacy of one or two doses of ARCoV against a strain adapted to SARS-CoV-2.	Intramuscular vaccination has produced strong neutralizing antibodies to SARS-CoV-2 and partial Th1 cell response in mice and nonhuman primates. In addition, two doses of the ARCoV vaccine in mice provided complete protection from the challenge of a SARS-CoV-2-adapted strain.	[59]
The neutralization of B.1.351 (a mutation) was assessed using. 1) convalescent plasma patients were gathered from the first rise of UK SARS-CoV-2. 4-9 weeks follow-up in June 2020. 2) Vaccine serum Pfizer-BioNTech vaccine affected 25 health care workers. 4-17 days following up. 3 weeks later, the second dose was given. In the case of the Oxford-AstraZeneca vaccine, cases were collected between 14 and 28 days after the second dose. The Pfizer-BioNTech vaccine neutralizes 3.6 times more against the Victoria strain than the AstraZeneca vaccine ($p < 0.0001$) 3)mAbs 20 most potent mAbs (FRNT50 titers < 100 ng/mL, 19 anti-RBD and 1 anti-NTD) were selected. 14 of 20 antibodies were completely activity knockout. ARCoVmRNA-LNP	Both Oxford-AstraZeneca and Pfizer-BioNTech vaccine neutralize Victoria more than B.1.351.	[60]
It is about analysis in 20 most potent neutralizing antibodies (FRNT50 < 100 ng/mL), 19 anti-RBD, and one anti-NTD (N-terminal domain). to neutralization of the B.1.1.7 and Victoria strains using serum obtained from recipients of the Oxford-AstraZeneca and Pfizer vaccines For the AstraZeneca AZD1222 vaccine, serum was obtained at baseline and 14 and 28 days following the second dose. For the Pfizer vaccine, serum was obtained 7–17 days following the second dose of the vaccine, which was administered three weeks after the first dose.	That neutralizing responses against the Victoria virus are less effective against B.1.1.7.	[61]
Main details (Dosage, Duration, etc.)	Results	References
Both placebo and BNT162b2 vaccine candidates received two doses (30 µg per dose), 21 days apart.	After seven days from the second dose, there were 8 cases of COVID-19 in BNT162b2 vaccine candidates and 162 cases in placebo receivers. Therefore this vaccine is 95% effective.	[62]
They randomly assigned people to two groups: the control group (meningococcal group A, C, W, and Y conjugate vaccine or saline) and the ChAdOx1 nCoV-19 vaccine group. The vaccine members received two doses containing five × 1010 viral grains (standard dose; SD/SD cohort). In the UK trial, one subset received half of the normal dose in their first dose and the normal dose in their second dose (LD/SD cohort).	This vaccine was 62.1% effective in the group with two standard doses, while it was 90% effective in the UK subset with one low dose as their first dose and one standard dose as their second dose. As a result, this vaccine is 70.4% effective and has a good safety profile.	[63]
They assigned people with a high possibility of SARS-CoV-2 infection in two groups. One group received a placebo, and the other group received the mRNA-1273 vaccine (intermuscular injection). Both in two doses (100 µg), 28 days apart.	185 receivers of placebo and 11 receivers of the vaccine had symptoms of COVID-19, at least 28 days after receiving the second dose. So this vaccine is 94.1% effective.	[64]
Efficacy of RBDY453F SARS-CoV-2 mutation on affinity for this virus in IgG.	They figured out that this mutation caused less affinity between IgG (immunoglobulin) and mutant virus. Thus this mutation is considered an immune inhibitor.	[65]

They studied all SARS-CoV-2 genomes to find the best epitope for designing a vaccine.	Finally, they found two multi-epitopes: 1- Cov-I-Vac (without adjuvant), which presented better interaction with TLR8 and needed more energy to disfigure the structure. 2- Cov-II-Vac (with β-defensin adjuvant).	[66]
They studied the BNT162b2 vaccine recognition of SARS-CoV-2 mutations. So they made mutant viruses with just one mutation in one of the positions (E484K, K417N, N501Y) or with all three mutations.	As a result, recognition of RBDN501Y and RBDK417N was 2.5-3 times reduced, and recognition of RBDE484K and the triple mutant was 10 times reduced. They concluded that the E481K is an obstacle for immune recognition, making a new vaccine sanctioned.	[67]

Effects/Dosage	Results	References
-	Astra Zeneca's adenoviral SARS CoV2 vaccine resulted in an even lower than 25% efficacy in battle with the B.1.351 South African variant.	[68]
2026 HIV-negative participants (18-65), of which 50% were given 0.3-0.5 ml dosages of the vaccine. The other 50% control group was injected 0.9% Sodium Chloride. Vaccine succumbed to variant	The ChAdOx1 Adenoviral vaccine had its Efficacy drop from 89.3% to 21.9 % while fighting the B.1.351 variant	[69]
mRNA and Live vaccines both had positive effects until the introduction to D614G Mutations, where they lost efficacies.	D614G mutations seen in European variants of SARS CoV2 are incapable of entirely neutralizing mRNA and Live vaccines. However, decreased Efficacy was noted in both.	[70]
19 participants with Covid-19 infection with 5–19-day post-symptom onset given 100 μg of mRNA-1273 were seen to show decreased RBD-IgG binding.	Neutralizing B.1.351 and B.1 variants using mRNA-1273 vaccine witnessed resistance and reduction in Efficacy.	[71]
A Controlled randomized trial of 8534 participants administered $5x10^{10}$ viral particles of the ChAdOx1 vaccine resulted in a 70.4 % efficacy while exposed to B.1.1.7 variant compared to 81.5% efficacy in non-B.1.1.7 exposure.	ChAdOx1 vaccine successfully resisted the B.1.1.7 SARS CoV2 variant but showed a slight reduction in Efficacy in combating the variant.	[72]
37 participants aged 63.5 received the first dosage of BNT162b2 mRNA vaccine 3 weeks before blood serum analysis. 29 participants were then administered the same vaccine following blood serum analysis	Vaccine efficacy is not solely related to mutation of SARS CoV2 but, in fact, factors such as the type of mutation and location of mutation matter as well.	[73]

Main Details (Dosage, Duration, etc.)	Results	References
Participants between May 31-Nov 13, 2020, were registered, and during Aug 3 -Dec 30, 2020, booster doses were injected. Standard-dose of ChAdOx1 nCoV-19 vaccine: 5 × 1010 viral particles Control: A meningococcal group A, C, W, and Y conjugate vaccine (MenACWY)	ChAdOx1 nCoV-19 can decreased neutralization activity unto the B.1.1.7 variant compared with non-B.1.1.7 variant (an in vitro). The vaccine against the B.1.1.7 variant of SARS-CoV-2 has Efficacy.	[74]
Two doses of the vaccine: -placebo (0.9% NaCl) or -viral particles (5x1010) with a duration of 21- 35 days. ChAdOx1-nCoV19 or placebo: 0.33-0.5ml (lot dependent).	Due to the variant of B.1.351, a vaccination of ChAdOx1-nCoV19 including two-dose did not appear protective effect against mild-moderate Covid-19. VE for severe covid-19 is undefined.	[75]
Animal immune sera, monoclonal antibodies (mAbs), human convalescent sera, and human sera from recipients of the PzerBioNTech (BNT162b2) mRNA vaccine were used report the antibody neutralization effect on valid SARS-CoV-2 variants.	The lack-of-neutralization potency (in vitro) against appearing variants in various antibodies binding particular regions of the NTD and RBD was shown. Accordingly, vaccines may be needed: to arrest loss of protection (in vivo), targeting highly protected regions, updated cocktails of mAb, arrangements to the sequences of a spike, or increment of mAb potency.	[76]
In this study, to investigate doubted vaccine-induced thrombosis and thrombocytopenia, participants were recognized.	SARS-CoV-2 vaccination as a critical function has been mentioned for control of this world pandemic. However, the pathogenic PF4-dependent syndrome can have occurred after vaccination with the ChAdOx1 nCoV-19 vaccine, which is unlinked to the heparin therapy.	[77]
S protein of unlocking of mutation (Indonesian SARS-CoV-2 isolates).	The mutation analysis for a full-length genome of Indonesian SARS-CoV-2 isolates was successfully discovered. (n=166)	[78]

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REFERENCES

1. Nishiura, Hiroshi, et al. "The extent of transmission of novel coronavirus in Wuhan, China, 2020." (2020): 330.
2. Planas, Delphine, et al. "Sensitivity of infectious SARS-CoV-2 B. 1.1. 7 and B. 1.351 variants to neutralizing antibodies." Nature medicine 27.5 (2021): 917-924.
3. Kemp, Steven, et al. "Recurrent emergence and transmission of a SARS-CoV-2 Spike deletion ΔH69/V70." bioRxiv (2020).
4. Wang, Rui, et al. "Mutations on COVID-19 diagnostic targets." Genomics 112.6 (2020): 5204-5213.
5. Wang, Hai-Yang, et al. "Potential neurological symptoms of COVID-19." Therapeutic advances in neurological disorders 13 (2020): 1756286420917830.
6. Geier, Mark R., and David A. Geier. "Respiratory conditions in coronavirus disease 2019 (COVID-19): Important considerations regarding novel treatment strategies to reduce mortality." Medical hypotheses 140 (2020): 109760.
7. Zheng, Ying-Ying, et al. "COVID-19 and the cardiovascular system." Nature Reviews Cardiology 17.5 (2020): 259-260.
8. Tobaiqy, Mansour, et al. "Therapeutic management of COVID-19 patients: a systematic review." Infection Prevention in Practice (2020): 100061.
9. Cao, Bin, et al. "A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19." New England Journal of Medicine (2020).

10. Magagnoli, Joseph, et al. "Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19." Med 1.1 (2020): 114-127.
11. Beigel, John H., et al. "Remdesivir for the treatment of Covid-19." New England Journal of Medicine 383.19 (2020): 1813-1826.
12. zer Initiates Phase 1 Study of Novel Oral Antiviral Therapeutic Agent Against SARS-CoV-2 2021 March 123, 202]; Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-initiates-phase-1-study-novel-oral-antiviral
13. Craven, J. COVID-19 vaccine tracker. 2021 23 April 2021 29 April 2021]; Available from: https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker.
14. Xu, Shuqin, et al. "mRNA vaccine era—mechanisms, drug platform and clinical prospection." International Journal of Molecular Sciences 21.18 (2020): 6582.
15. Wiersinga, W. Joost, et al. "Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review." Jama 324.8 (2020): 782-793.
16. Bohn, Mary Kathryn, et al. "Pathophysiology of COVID-19: Mechanisms underlying disease severity and progression." Physiology 35.5 (2020): 288-301.
17. Kumar, Manoj, and Souhaila Al Khodor. "Pathophysiology and treatment strategies for COVID-19." Journal of translational medicine 18.1 (2020): 1-9.
18. Mahase, Elisabeth. "Covid-19: South Africa pauses use of Oxford vaccine after study casts doubt on efficacy against variant." (2021).
19. Madhi, Shabir A., et al. "Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B. 1.351 variant in South Africa." MedRxiv (2021).
20. Sapkal, Gajanan N., et al. "Inactivated COVID-19 vaccine BBV152/COVAXIN effectively neutralizes recently emerged B. 1.1. 7 variant of SARS-CoV-2." Journal of Travel Medicine (2021).
21. Collier, Dami, et al. "Impact of SARS-CoV-2 B. 1.1. 7 Spike variant on neutralisation potency of sera from individuals vaccinated with Pfizer vaccine BNT162b2." MedRxiv (2021).
22. Baray, Juwel Chandra, et al. "BANCOVID, the first D614G variant mRNA-based vaccine candidate against SARS-CoV-2 elicits neutralizing antibody and balanced cellular immune response." bioRxiv (2020).
23. van der Lubbe, Joan EM, et al. "Ad26. COV2. S-elicited immunity protects against G614 spike variant SARS-CoV-2 infection in Syrian hamsters and does not enhance respiratory disease in challenged animals with breakthrough infection after sub-optimal vaccine dosing." bioRxiv (2021).
24. van der Lubbe, Joan EM, et al. "Ad26. COV2. S-elicited immunity protects against G614 spike variant SARS-CoV-2 infection in Syrian hamsters and does not enhance respiratory disease in challenged animals with breakthrough infection after sub-optimal vaccine dosing." bioRxiv (2021).
25. Polack, Fernando P., et al. "Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine." New England Journal of Medicine 383.27 (2020): 2603-2615.
26. Voysey, Merryn, et al. "Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK." The Lancet 397.10269 (2021): 99-111.
27. Baden, Lindsey R., et al. "Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine." New England Journal of Medicine 384.5 (2021): 403-416.
28. Hayashi, Takuma, and Ikuo Konishi. "Effect of RBD (Y453F) in spike glycoprotein of SARS-CoV-2 variant on COVID-19 vaccine." (2021).
29. Zaheer, Tahreem, et al. "Anti-COVID-19 multi-epitope vaccine designs employing global viral genome sequences." PeerJ 8 (2020): e9541.
30. Chang, Xinyue, et al. "BNT162b2 mRNA COVID-19 vaccine induces antibodies of broader cross-reactivity than natural infection but recognition of mutant viruses is up to 10-fold reduced." bioRxiv (2021).
31. Planas, Delphine, et al. "Sensitivity of infectious SARS-CoV-2 B. 1.1. 7 and B. 1.351 variants to neutralizing antibodies." Nature medicine 27.5 (2021): 917-924.
32. Kemp, Steven, et al. "Recurrent emergence and transmission of a SARS-CoV-2 Spike deletion ΔH69/V70." bioRxiv (2020).
33. Tegally, Houriiyah, et al. "Sixteen novel lineages of SARS-CoV-2 in South Africa." Nature Medicine 27.3 (2021): 440-446.
34. Hoffmann, Markus, et al. "SARS-CoV-2 variants B. 1.351 and B. 1.1. 248: Escape from therapeutic antibodies and antibodies induced by infection and vaccination." BioRxiv (2021).
35. Cohen, Jon. "South Africa suspends use of AstraZeneca's COVID-19 vaccine after it fails to clearly stop virus variant." Science 10 (2021).
36. Weedon, A., Coronavirus vaccines only need to be 50 per cent efficacious according to the WHO - why?, in ABC news. 2021, ABC News: abc.net.au.
37. Madhi, Shabir A., et al. "Efficacy of the ChAdOx1 nCoV-19 Covid-19 vaccine against the B. 1.351 variant." New England Journal of Medicine (2021).
38. Conti, P., et al. "The British variant of the new coronavirus-19 (Sars-Cov-2) should not create a vaccine problem." J Biol Regul Homeost Agents 35.1 (2021): 1-4.
39. Edara, Venkata Viswanadh, et al. "Reduced binding and neutralization of infection-and vaccine-induced antibodies to the B. 1.351 (South African) SARS-CoV-2 variant." bioRxiv (2021).
40. Emary, Katherine RW, et al. "Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B. 1.1. 7): an exploratory analysis of a randomised controlled trial." The Lancet 397.10282 (2021): 1351-1362.
41. Collier, Dami A., et al. "SARS-CoV-2 B. 1.1. 7 sensitivity to mRNA vaccine-elicited, convalescent and monoclonal antibodies." medRxiv (2021).
42. Zhou, Daming, et al. "Evidence of escape of SARS-CoV-2 variant B. 1.351 from natural and vaccine-induced sera." Cell 184.9 (2021): 2348-2361.
43. Supasa, Piyada, et al. "Reduced neutralization of SARS-CoV-2 B. 1.1. 7 variant by convalescent and vaccine sera." Cell 184.8 (2021): 2201-2211.
44. Zhang, Na-Na, et al. "A thermostable mRNA vaccine against COVID-19." Cell 182.5 (2020): 1271-1283.
45. Shinde, Vivek, et al. "Preliminary efficacy of the NVX-CoV2373 Covid-19 vaccine against the B. 1.351 variant." MedRxiv (2021).
46. Mahase, Elisabeth. "Covid-19: Novavax vaccine efficacy is 86% against UK variant and 60% against South African variant." (2021).
47. Mahase, Elisabeth. "Covid-19: UK approves Oxford vaccine as cases of new variant surge." (2020).
48. Madhi, Shabir A., et al. "Efficacy of the ChAdOx1 nCoV-19 Covid-19 vaccine against the B. 1.351 variant." New England Journal of Medicine (2021).
49. Diamond, Michael, et al. "SARS-CoV-2 variants show resistance to neutralization by many monoclonal and serum-derived polyclonal antibodies." Research square (2021): rs-3.
50. Scully, Marie, et al. "Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination." New England Journal of Medicine (2021).
51. Nidom, Reviany V., et al. "An Updated Investigation Prior To COVID-19 Vaccination Program In Indonesia: Full-Length

Genome Mutation Analysis Of SARS-CoV-2." bioRxiv (2021).
52. Emary, Katherine RW, et al. "Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B. 1.1. 7): an exploratory analysis of a randomised controlled trial." The Lancet 397.10282 (2021): 1351-1362.
53. Madhi, Shabir A., et al. "Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B. 1.351 variant in South Africa." MedRxiv (2021).
54. Shinde, Vivek, et al. "Preliminary efficacy of the NVX-CoV2373 Covid-19 vaccine against
55. Mahase, Elisabeth. "Covid-19: UK approves Oxford vaccine as cases of new variant surge." (2020).
56. Mahase, Elisabeth. "Covid-19: Novavax vaccine efficacy is 86% against UK variant and 60% against South African variant." (2021).
57. Zhang, Na-Na, et al. "A thermostable mRNA vaccine against COVID-19." Cell 182.5 (2020): 1271-1283.
58. Zhou, Daming, et al. "Evidence of escape of SARS-CoV-2 variant B. 1.351 from natural and vaccine-induced sera." Cell 184.9 (2021): 2348-2361.
59. Supasa, Piyada, et al. "Reduced neutralization of SARS-CoV-2 B. 1.1. 7 variant by convalescent and vaccine sera." Cell 184.8 (2021): 2201-2211.
60. Polack, Fernando P., et al. "Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine." New England Journal of Medicine 383.27 (2020): 2603-2615.
61. Voysey, Merryn, et al. "Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK." The Lancet 397.10269 (2021): 99-111.
62. Baden, Lindsey R., et al. "Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine." New England Journal of Medicine 384.5 (2021): 403-416.
63. Hayashi, Takuma, and Ikuo Konishi. "Effect of RBD (Y453F) in spike glycoprotein of SARS-CoV-2 variant on COVID-19 vaccine." (2021).
64. Zaheer, Tahreem, et al. "Anti-COVID-19 multi-epitope vaccine designs employing global viral genome sequences." PeerJ 8 (2020): e9541.
65. Chang, Xinyue, et al. "BNT162b2 mRNA COVID-19 vaccine induces antibodies of broader cross-reactivity than natural infection but recognition of mutant viruses is up to 10-fold reduced." bioRxiv (2021).
66. Cohen, Jon. "South Africa suspends use of AstraZeneca's COVID-19 vaccine after it fails to clearly stop virus variant." Science 10 (2021).
67. Madhi, Shabir A., et al. "Efficacy of the ChAdOx1 nCoV-19 Covid-19 vaccine against the B. 1.351 variant." New England Journal of Medicine (2021).
68. Conti, P., et al. "The British variant of the new coronavirus-19 (Sars-Cov-2) should not create a vaccine problem." J Biol Regul Homeost Agents 35.1 (2021): 1-4.
69. Edara, Venkata Viswanadh, et al. "Reduced binding and neutralization of infection-and vaccine-induced antibodies to the B. 1.351 (South African) SARS-CoV-2 variant." bioRxiv (2021).
70. Emary, Katherine RW, et al. "Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B. 1.1. 7): an exploratory analysis of a randomised controlled trial." The Lancet 397.10282 (2021): 1351-1362.
71. Collier, Dami A., et al. "SARS-CoV-2 B. 1.1. 7 sensitivity to mRNA vaccine-elicited, convalescent and monoclonal antibodies." medRxiv (2021).
72. Emary, Katherine RW, et al. "Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B. 1.1. 7): an exploratory analysis of a randomised controlled trial." The Lancet 397.10282 (2021): 1351-1362.
73. Madhi, Shabir A., et al. "Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B. 1.351 variant in South Africa." MedRxiv (2021).
74. Diamond, Michael, et al. "SARS-CoV-2 variants show resistance to neutralization by many monoclonal and serum-derived polyclonal antibodies." Research square (2021): rs-3.
75. Scully, Marie, et al. "Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination." New England Journal of Medicine (2021).
76. Nidom, Reviany V., et al. "An Updated Investigation Prior To COVID-19 Vaccination Program In Indonesia: Full-Length Genome Mutation Analysis Of SARS-CoV-2." bioRxiv (2021).