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Review Article

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Therapeutic Modalities for Coronavirus SARS-CoV-2 (COVID-19)

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Abstract

The ongoing outbreak of coronavirus disease 2019 (COVID-19) that has accelerated in such short a period has spurred the investigation on existing and new therapeutic modalities. Therapeutic value of different classes of drugs have been tested including anti-parasites (Ivermectin), steroids (Dexamethasone), immune regulators (Tocilizumab), combination therapy MATH+ (Methylprednisolone, Ascorbic Acid, Thiamine), corticosteroid (Heparin), and antiviral medications (Molnupiravir or Paxlovid). Similarly, different types of vaccines, including mRNA-based vaccines, viral vector vaccines, and inactivated vaccines (requiring adjuvants) have also developed. Outbreaks of numerous COVID-19 variants, such as Omicron with rapid and frequent genomic mutations, have rendered vaccines less effectiveness against COVID-19. Due to short-term immune protection and treatment-induced adverse effects (e.g., vision problems, vertigo, diarrhea, nausea, allergic reaction, hypokalemia, hypertension, thrombosis with thrombocytopenia syndrome, Guillain-Bare syndrome, Bell's palsy) boosters or secondary treatment is needed. Although various vaccines and therapeutics have been developed, further testing is required to obtain higher efficacy across age, gender, and race ranges and to establish long-term immunity. This review summarizes current treatment options available against COVID-19, their mechanisms of action, undesired side effects, as well as safety and efficacy protocols.

Introduction

The COVID-19 pandemic characterized by the rapid and rampant spread of coronavirus disease, which is due to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The COVID-19 pandemic began as an epidemic in Wuhan, China, confirmed to have started on December 12, 2019. By January 26, 2020, there were 2,794 positive cases (confirmed by laboratory diagnostic testing) as well as 80 deaths resulting from infection [2]. COVID-19 disease varies in severity, with most severe complications resulting from alveolar damage and viral pneumonia [2]. The main symptoms characterized as dry cough, fever, and shortness of breath in addition to other symptoms like aches, fatigue, vomiting, and vertigo [3].

In terms of severity of clinical presentations and general disease progression, there are clear indicators that can be utilized to determine the extent of severity. Those who are of an older age (generally those 55 years of age or older) are more prone to more severe outcomes and have a higher mortality rate than younger individuals [4-6]. In addition, those who have pre-existing conditions like hypoxia, lung abnormalities such as chronic obstructive pulmonary disease (COPD), and those who have biomarkers indicative of end-organ dysfunction (elevated C-reactive protein, troponin, etc.) are also more likely to have severe cases of COVID-19 [4-6].

SARS-CoV-2 is of the B lineage of genus Betacoronavirus that is part of the larger Coronaviridae family and has 14 open reading frames (ORFs) and its genome encodes for 27 proteins [7-9]. It has a genome of around 30kb (kilobase), longer than most coronaviruses. As a coronavirus, SARS-CoV-2 spike proteins have two main regions: S1 (binding to host receptors) and S2 (membrane fusion role) [10]. In the 3'-terminus, there are the spike surface (S), small envelope (E) protein, nucleocapsid (N) protein, and matrix (M) protein, as well as the accessory proteins 3A, 3B, 6P, 7A, 7B, 8B, 9B, and orf14 proteins [10]. The N protein, which forms the nucleocapsid, is a common drug target studied for the

purpose of the development of antiviral therapeutics [11]. In the case of SARS-CoV-2, its N protein structure is very similar to that of SARS-CoV. There are three intrinsically disordered regions (IDRs): linker region (LKR), N-arm, and C-tail [11]. There are also two structural domains in the N protein, C-terminal domain (CTD) and N-terminal domain (NTD). Both domains bind RNA, while CTD is the main dimerization domain [11].

SARS-CoV-2 has about 80% genetic homology with SARS-CoV-1, the virus responsible for the 2002-2004 severe acute respiratory syndrome (SARS) epidemic [12]. As a coronavirus, SARS-CoV-2 is a positive-strand RNA virus, as with SARS-CoV [12]. As an RNA virus, it relies on an RNA-dependent RNA polymerase for genetic replication and the transcription process, the two processes that aid in subsequent production of viral progeny [13]. The RNA polymerase consists of non-structural protein (nsp) 12, nsp7, and nsp8. Because of the long genomic nature of SARS-CoV-2, nsp8 has helical extensions that extend along the exiting RNA material, which has been shown to allow processing of such long genomes in coronaviruses [14].

The COVID-19 pandemic is still highly active and is rapidly affecting the lives and health of growing affected populations, prompting progressive usage of existing therapies, as well as demand for newly developed drugs. Because there is a range of severity of COVID-19 disease, there is a resulting complexity in drug selection and usage on an individual patient basis [15]. There is a continuously developing understanding of the COVID-19 pandemic and its associated effects on health, drug development, vaccination monitoring, etc. Below, we will discuss the currently available treatment modalities (medications, mRNA-based vaccines, viral vector vaccines) against COVID-19. Summary of information pertinent to dosing, safety, efficacy of the various medications against COVID-19 can be found in Table 1.

Table 1: Safety and Efficacy of Current Covid-19 Treatment Modalities

Medication	Dosage	Side Effects	Route of Administration	Length of Observation	Rate of Mortality	Reference
Ivermectin	12 mg daily	Vision problems, vertigo, diarrhea, nausea	Oral	5 days	Significant reduction of 42% in severe cases	[16,17]
Dexamethasone	6mg daily	No other adverse reactions besides immune-insufficiency	Oral or Intravenous (IV)	10 days	Significant reduction of 11%	[18]
Tocilizumab	400-800 mg primary dose and secondary dose within 24 hours	gastrointestinal perforation	Intravenous (IV)	28 days	Significant reduction of 11%	[19]
Remdesivir	200mg first day, followed by 100mg daily	nausea, headache, hypokalemia	Intravenous (IV)	5 days	Significant reduction of 25%	[20]
MATH +	1.5 g Vitamin C daily, 100mg thiamine, 40mg heparin, 1 to 2 mg/kg methyl-prednisone daily	No significantly reported adverse reactions	Combined	Varied	Varied	[21]
Molnupiravir	1,600 mg daily	No significant reported adverse reactions	Oral	5 days	Significant reduction of 50% in initially milder cases	[15]
Paxlovid	300 mg nirmatrelvir and 100 mg ritonavir twice a day	hypertension, pain, and diarrhea	Oral	5 days	Significant reduction of 88%	[22]

Ivermectin

Ivermectin is an FDA-approved drug to treat patients with intestinal strongyloidiasis and onchocerciasis, two conditions caused by parasitic infections (worms). Additionally, some topical forms of ivermectin are approved for the treatment of external parasites like head lice, and skin conditions like rosacea [23]. In addition to its effects on parasites, ivermectin can effectively target RNA viruses such as the West Nile virus, Dengue virus, influenza virus, and Venezuelan equine encephalitis viruses [23]. Ivermectin has demonstrated anti-viral potency in *in-vitro* and clinical studies, thus, has recently become a popular investigative drug for the treatment of COVID-19. Ivermectin's efficacy in the control and treatment of RNA virus infections is credited to its nuclear import inhibitory effects. Specifically, ivermectin is an inhibitor of importin α/β heterodimer, inhibiting the nuclear protein import mechanism that is essential for such RNA viruses to infect and replicate. Importin α/β is important in regulating import of proteins into the nucleus, specifically targeting the import of proteins with nuclear signalization sequences. Because viruses depend on nuclear import ability, importin α/β is an important target [24]. Ivermectin is effective in targeting HIV replication through inhibition of importin α/β binding to HIV integrase [25,26]. Because importin α/β plays a role in nuclear import ability of SARS-CoV-2, ivermectin's mechanism of action is of interest for the treatment of COVID-19.

The clinical efficacy of ivermectin was evaluated in 72 hospitalized patients in a clinical investigation based in Dhaka, Bangladesh [16]. Three patient groups were assigned: ivermectin alone, ivermectin and doxycycline, and placebo. For the first group, 12 mg of ivermectin was orally administered once daily for a period of five days. For the second patient group, the first day consisted of 12 mg of ivermectin and 200 mg of doxycycline, while the following four days consisted of 100 mg doxycycline dosages in 12-hour intervals. The duration until viral clearance was achieved was utilized as a metric of drug protocol efficacy. The group that only received ivermectin over a 5-day course had an earlier achievement of viral clearance, at 9.7 days relative to the placebo patient group of 12.7 days ($p = 0.02$). The second group achieved viral clearance after 11.5 days ($p = 0.27$). Based on this clinical investigation, a 5-day course of oral ivermectin alone is an effective treatment protocol for hospitalized COVID-19 patients relative to the placebo and the ivermectin and doxycycline group.

Another study at the Broward Health hospitals in Florida further investigated the anti-viral efficacy of ivermectin in 280 hospitalized patients. Of these, 107 patients (38%) were treated with non-ivermectin protocols while 173 patients (62%) were treated with 200 ug/kg ivermectin for a 7-day period [17]. It was concluded that ivermectin reduced mortality risk in patients with severe cases of COVID-19; mortality rates of 80.7% in non-ivermectin patients and 38.8% in ivermectin-treated patients ($p = 0.001$) were observed. Although the rate of extubation was not significantly different between the two patient groups, ivermectin was effective in symptomatic patients. Noteworthy, all patients enrolled in this trial were treated with additional drugs (hydroxychloroquine and/or azithromycin), potentially having unintended effects on the observations of this clinical study. Such studies demonstrate that ivermectin can potentially be used as a therapy solely for severe COVID-19 cases that usually have significant pulmonary involvement, as opposed to wide-ranging manifestations of COVID-19 cases. Although ivermectin seems to be effective in reducing mortality risk, its effects on clinical symptoms and extubation rates are not as significant [16,17]. Ivermectin, as with many antiviral drugs, have potential side effects. In another hospital study investigating ivermectin use for COVID-19, it was found that usual side effects are vision problems, vertigo, diarrhea, and nausea. Other common adverse reactions are transaminase level elevation, an allergic reaction to ivermectin, and low leukocyte count. Ivermectin and its successful results of Covid-19 fatalities should be evaluated more thoroughly through broader experimental techniques, such as larger test cohorts, for further solidarity of immunogenic potential [27].

Dexamethasone

Dexamethasone is a corticosteroid that functions as an immunosuppressant [28]. Due to its relative prior effectiveness in MERS and SARS, dexamethasone has been considered as a potential drug for COVID-19 [28]. Substantial immune reactions to the pathogen, such as a cytokine storm, commonly seen in severe infections, can be a risk factor for mortality. Using an immunosuppressant drug can also help reduce such hyperactivity and its associated effects. A clinical study at the Fatima Memorial Hospital in Lahore, Pakistan compared the efficacy of dexamethasone patients relative to methylprednisolone (another corticosteroid) on 100 hospitalized COVID-19 patients [29]. Thirty-five patients were included in the dexamethasone group, while 65 patients were in the methylprednisolone group. 42.8% of dexamethasone-treated patients and 33.8% of the methylprednisolone group were admitted to the ICU. Clinical symptoms including body temperature, C-reactive protein (CRP) levels, and oxygen levels improved under both protocols by the fifth day of the trial. The mortality rates of the dexamethasone and methylprednisolone groups were 17.1% and 15.3%, respectively. Although there is no control patient group, the results of this study indicate that dexamethasone, relative to another common and standard corticosteroid, is also effective in improving clinical symptoms of COVID-19 [29].

In a larger study as part of the RECOVERY trial based in the U.K., 2104 patients were administered dexamethasone in addition to standard care and 4321 patients received standard care of non-dexamethasone treatment plans for a 10-day period. Mortality rate was lower in the dexamethasone group (22.9%) than in the standard care patient group (25.7%) after a 28-day period [18,19]. Mortality rate was 29.3% and 41.4% in the dexamethasone and standard care groups, respectively among patients who were under invasive ventilation. Among patients who were receiving oxygen (non-invasive), mortality rate was 23.3% and 26.2% in the dexamethasone and standard care groups, respectively [18,19]. Mortality rate was not significantly different among those who were not under any pulmonary support in the dexamethasone and standard

care groups (17.8% and 14.0%). In contrast to patients who did not receive any pulmonary support, dexamethasone was effective in reducing mortality rate among patients who were administered oxygen or invasive ventilation. Thus, one can conclude that dexamethasone is effective in lowering the risk of mortality in more severe COVID-19 cases compared to milder cases [30].

Despite its relative efficacy, dexamethasone remains an undecided-upon therapeutic for COVID-19 due to its immunosuppressive activity. Immunosuppression, although important for reducing mortality associated with exaggerated immune reactions, can cause decreased sensitivity to pathogenic invasion and overall compromised immunity [28]. Dexamethasone's effectiveness is due to its ability to target a hyperactive immune response that is triggered by SARS-CoV-2 infection, the main cause of the symptoms manifested by severe COVID-19 cases. Because corticosteroids are not highly recommended for routine use in the treatment for COVID-19 at present, medical and health care providers have to be mindful in evaluating individual patient's risk [31].

Tocilizumab

The anti-interleukin-6 (IL-6) receptor monoclonal antibody (anti-IL-6R mAb), tocilizumab, functions as an immunosuppressant like dexamethasone and other corticosteroids [32]. The proinflammatory cytokine, IL-6, stimulates the immune system, thereby playing a role in the development of inflammation-related COVID-19 symptoms, as seen in cytokine storm case [32]. Tocilizumab antagonizes the IL-6 receptor to reduce inflammatory reactions and alleviate disease-associated symptoms [32]. Tocilizumab is approved by the FDA for the treatment of a variety of diseases, such as rheumatoid arthritis and polyarticular juvenile idiopathic arthritis. Symptoms of acute respiratory distress syndrome are, in part, caused by cytokine-release syndrome, with IL-6 playing a major role in the inflammatory manifestations of the syndrome [32].

A clinical trial investigating the effectiveness of tocilizumab in COVID-19 pneumonia patients included 60 patients treated with tocilizumab and 66 with controlled standard care [33]. Progression of clinical symptoms were seen in 28.3% and 27.0% of the patients in the tocilizumab and standard care patient groups, respectively. Within 30 days, mortality rate was 2 and 1 in the tocilizumab and standard care patient groups, respectively, with 6 and 5 patients requiring intubation, respectively. This study demonstrated no significant differences in the efficacy of tocilizumab treatment versus controlled standard care patient groups. Small sample size was a limitation of this study, warranting enrollment of larger patient numbers in future trials.

As part of the RECOVERY trial, 2022 patients were treated with tocilizumab while 2094 were treated with standard care; 28-day mortality rate of 31% and 35%, respectively (p=0.0028) was observed [18,19]. For milder hospitalized cases, tocilizumab-treated patients had a lesser probability of needing mechanical ventilation or dying with 28 days (35% vs 42%, $p < 0.0001$). Patient discharge rate was higher in the tocilizumab group relative to the control group, at 57% and 50%, respectively ($p < 0.0001$). An increased chance of gastrointestinal (GI) perforation, via an unknown mechanism, occurred in tocilizumab-treated patients [34]. Prior history of diverticulitis is a risk factor for lower GI perforation [34]. Nevertheless, according to this study, tocilizumab was effective in the treatment of COVID-19, regardless of the severity of hospitalized cases and despite the dependence or invasiveness of respiratory support, unlike the previously discussed therapies. The discrepancies between these studies, hence differences in patient outcomes, can be explained by differences in the sample size and other potential confounding variables. The latter study had significantly larger sample size, representing conclusions that are more reliable. These studies warrant further investigation.

Remdesivir

Remdesivir is an FDA-approved antiviral drug used for diseases associated with infections with RNA viruses like Filoviridae, Pneumovirinae, and Orthocoronavirinae [35]. Because it is a nucleoside analog, its mechanism is dependent upon the inhibition of RNA-dependent RNA polymerases. Remdesivir is specifically an adenosine triphosphate analog, inhibiting endogenous adenosine triphosphate and terminating viral RNA replication [35]. Due to its effectiveness in treating diseases caused by RNA viral infections, remdesivir has been investigated for its efficacy for the treatment of hospitalized COVID-19 patients. An international study across 105 hospitals throughout Asia, Europe, and America studied evaluated remdesivir effectiveness in COVID-19 patients. 533 patients completed the trial, where it was concluded that in moderate COVID-19 cases, patients on a 5-day remdesivir treatment had a significant improvement of clinical status relative to those in the standard care and 10-day remdesivir protocols [20]. However, more frequent side effects (nausea, headache, hypokalemia) were observed in the 5-day remdesivir group. Another randomized, double blind, placebo-controlled trial throughout multiple hospitals in Hubei, China concluded that remdesivir therapy was not statistically significant in promoting clinical benefits [10]. However, remdesivir reduced the time required for clinical improvements in adults. This observation was confirmed in another randomized trial consisting of 1062 patients. The remdesivir-treated patient group recovered within a median of 10 days, relative to the placebo group with a recovery period of 15 days ($p<0.001$) [36]. The mortality rate by day 29 reduced, at 11.4% in the remdesivir group vs 15.2% in the placebo group. A reduction in time until clinical improvement or recovery was also noticed. However, additional large cohort studies needed to support remdesivir's efficacy in improving clinical symptoms.

Methylprednisolone, Ascorbic Acid, Thiamine, and Heparin (MATH+) Protocol

The MATH+ protocol consists of methylprednisolone, ascorbic acid, thiamine, and heparin, along with other components including vitamin D and zinc [37]. MATH+ deemed effective for use in sepsis cases prior to the COVID-19 pandemic, thus, peaking interest in its potential for the treatment of SARS-CoV-2 infection. Methylprednisolone is a steroid with anti-inflammatory effects,

which aids to reduce inflammation-related symptoms in more severe COVID-19 cases. Ascorbic acid or vitamin C is an anti-inflammatory coenzyme known for its positive impact on the function of immune system. Thiamine, or vitamin B1, is a coenzyme that is important in many metabolic processes in humans. Heparin, an anticoagulant, reduces the risk of formation of blot clot and thrombosis that has observed with COVID-19 disease progression [37].

Thiamine investigated for its efficacy in improving clinical outcomes and survival in COVID-19 cases. The study consisted of 166 patients; 83 patients (50%) received 100mg thiamine for an average duration of 7 days [38]. The mortality rate of thiamine-treated patients within 30 days and during hospital stay was significantly lower than non-thiamine-treated patients ($p = 0.009$ and $p = 0.008$, respectively). This is most likely due to the observation that thiamine also reduced risk of thrombosis during hospitalization ($p = 0.03$). An animal study demonstrated that thiamine potentiates the anti-inflammatory activity of corticosteroid in chronic inflammation cases [39]. In such animal models, thiamine increases the activity of corticosteroids that are already used in COVID-19 treatment plans like dexamethasone. Thus, thiamine might serve a potential role as a co-medication alongside corticosteroids for treatment of cytokine storms and inflammatory reactions related to COVID-19 [39]. These results suggest that thiamine potentially has a similar effect when used with methylprednisolone in the MATH+ protocol for COVID-19 [39].

Heparin reduces the risk of developing thrombosis and blot clots. Because heparin is an anticoagulant, it has a great ability in reducing clotting. This is rather important during severe infectious diseases cases due to the activation of clotting that sometimes co-occurs with the inflammation in the host as a result of infection [21]. An Italian multicenter study demonstrated that heparin use in COVID-19 patients reduced mortality rates [21]. This is mostly due to its effectiveness in reducing thrombosis and clotting associated with COVID-19 disease due to heparin's mechanism of action that targets clotting. Another study focused on the effectiveness of corticosteroids dexamethasone and methylprednisolone in COVID-19 patients [29]. Although dexamethasone was slightly more effective than methylprednisolone in reducing inflammation in COVID-19 patients, methylprednisolone was effective in improving symptoms such as fever and hypoxia and improving clinical outcomes.

Another component of the MATH+ protocol currently being extensively studied for COVID-19 is ascorbic acid (vitamin C). Sixty patients were recruited into an open-labeled, randomized, and controlled study in Tehran, Iran. Two groups (30 patients per group) were randomly assigned: one group receiving high dose intravenous vitamin C (HDIVC) (1.5 grams vitamin C every 6 hours for a period of 5 days) and a control group. Both groups also received primary treatment of lopinavir/ritonavir and hydroxychloroquine. Peripheral capillary oxygen saturation was higher in the vitamin C-receiving group ($p = 0.014$) and by the third day of hospitalization, body temperature was significantly reduced with vitamin C administration ($p = 0.001$). However, contrary to expectations, the length of hospital stay was longer in the experimental group (8.5 days) relative to the control (6.5 days) ($p = 0.028$). Nevertheless, clinical observations improved with HDIVC administration. However, these improvements may not be significant enough to justify using vitamin C alone (monotherapy) to treat COVID-19 patients. Another Chinese study investigated the effectiveness of Vitamin C for COVID-19 treatment. The experimental patient group received 12 g/50 mL IV vitamin C (12mL/hour) every 12 hours for a duration of 7 days. It was found that IL6 was lower in the experimental patient group receiving vitamin C relative to the control group. However, mortality rate and invasive mechanical ventilation dependence was not improved with vitamin C administration. Studies demonstrating the effectiveness of MATH+ protocols focus on their use as adjuvant therapies as opposed to primary therapies. MATH+ protocols are commonly used in conjunction with more intensive therapies for the treatment of infections, particularly COVID-19, making it a relatively suitable secondary treatment.

Molnupiravir

As a potent antiviral drug, molnupiravir considered as a potential therapy for COVID-19 disease. Molnupiravir targets the viral RNA-dependent RNA polymerase (RDRP) in SARS-CoV-2 and other viruses and induces mutagenesis in a wide range of viruses through a polymerase-dependent mechanism [40]. The viral RNA polymerase as a substitute of cytidine triphosphate utilizes Molnupiravir, also known as β-d-N4-hydroxycytidine (NHC) triphosphate, or uridine triphosphate, resulting in mutated RNA [40]. Because this process is observed in a broad range of viruses, molnupiravir is used in multiple viral infections.

Daily oral administration of 1600 mg of molnupiravir has been demonstrated to be effective in reducing the duration until viral clearance in milder COVID-19 cases ($p = 0.013$) [15]. In addition, molnupiravir also significantly reduced the risk of hospitalization or mortality related to COVID-19 by 50% in initially milder cases ($p = 0.0012$) [15]. Clinical trial investigating molnupiravir efficacy also noted no significant adverse reactions or effects and demonstrated its safety for COVID-19 treatment. Despite its efficacy in mild COVID-19 cases, molnupiravir is ineffective in treating hospitalized or severe cases of COVID-19 [15]. Unlike most other drugs that are more beneficial in severe cases, molnupiravir is better suited for patients with milder cases of COVID-19 that do not require hospital stay.

The efficacy of molnupiravir was evaluated on 202 outpatient participants, with a placebo and molnupiravir group (800 mg/day, twice/day). After treatment, virus was isolated from 1.9% of the molnupiravir-receiving group and 16.7% of the placebo patient group ($p = 0.02$) [41]. In addition, viral clearance was achieved significantly earlier in the molnupiravir group ($p = 0.01$), and no severe adverse effects were reported [41]. This study confirmed the efficacy of molnupiravir in outpatient and relatively milder COVID-19 cases does not support its use in hospitalized or severe cases of COVID-19.

Paxlovid

Pharmaceutical leader Pfizer has recently developed a novel therapy for COVID-19 disease. This therapy, also known as PAXLOVID, is a combination of two existing antiviral drugs nirmatrelvir and ritonavir [22]. Nirmatrelvir is a SARS-CoV-2 main protease inhibitor, while ritonavir is a CYP3A and HIV-1 protease inhibitor [42]. Ritonavir slows the metabolism of nirmatrelvir via cytochrome P450 enzyme inhibition [43]. This allows for greater antiviral potency against SARS-CoV-2 while the drug is active in the host. As of now, PAXLOVID has allowed for use in mild-to-moderate COVID-19 cases for up to five consecutive days [22].

In a study with 2246 non-hospitalized patients investigated the use of nirmatrelvir-ritonavir therapeutic combination, found that PAXLOVID reduced the risk of hospitalization or death due to COVID-19 by 88% [42]. Because the participants were in an outpatient setting and the study was monitoring risk of disease progression, the study confirms effectiveness in mild-to-moderate cases only. Due to its complicated mechanism of action involving two drugs, PAXLOVID has potential adverse reactions. The most noted side effects were issues with sense of taste, hypertension, pain, and diarrhea. It is also important to consider the extensive list of drug interactions and contraindications of PAXLOVID with other drugs such as amiodarone and rifampin [22,42]. As a newer Covid-19 treatment, data is still limited that would depict real world efficacy and long-term safety.

The Omicron Variant

Recently, a new variant of SARS-CoV-2, the Omicron variant, was originated in South Africa has since become a variant of significant health concern worldwide. The Omicron variant is due to 32 genetic changes or mutations mostly in the receptor-binding region and the N-terminal domain [44]. Because of such changes, the spike protein that is recognized by the immune system and targeted by antibodies is altered [44]. A South African study analyzed various aspects of COVID-19 cases caused by all SARS-CoV-2 variants. It was found disease caused by the Omicron is less severe than that caused by previous variants. This is possibly due to increased immunity to SARS-CoV-2 that has stemmed from immunizations and prior infection [45]. Preliminary studies suggest that the SARS-CoV-2 Omicron variant harbors mutations in the spike protein, thus, the efficacy of immunity previously elicited by recently administered COVID-19 delta variant-specific vaccinations are principally ineffective against omicron-induced infections. Because of the rapid mutation rate of SARS-CoV-2, assumed that variant-specific vaccines may be required for mounting effective and specific immunity [46]. Due to the development of clinical observations related to the new Omicron variant, more information expected that could aid in guiding the trajectory of COVID-19 pandemic.

Vaccine Booster

The long-term effects of COVID-19 vaccines/boosters are currently under investigation; however, some insight on the COVID-19 vaccine booster is becoming available. An Israel-based study investigated the effectiveness of the BNT162b2 (BioNTech-Pfizer RNA vaccine for COVID-19) booster in 1,137,804 people based on the Israeli Ministry of Health COVID-19 database [47]. All participants were fully vaccinated at least 5 months prior, and a booster and a non-booster group formed. The booster-receiving group had a reduced risk of infection by a factor of 11.3 and severe COVID-19 disease by a factor of 19.5 12 days after booster administration [47]. Another study focusing on vaccine boosters in adults under 60 years old indicated that a third dose of CoronaVac (inactivated virus Sinovac vaccine) significantly increased immunity and raised antibody levels against SARS-CoV-2 [48]. Booster use should also include consideration of more specific conditions such as local infection rates, supply of vaccines, etc. [48]. A UK-based clinical study analyzed the interval between the second and third booster dose and its role in increasing immunity against SARS-CoV-2 [49]. A longer interval between the second and third dose (a period of 3 months) was associated with higher efficacy compared to relatively shorter intervals [49]. More substantial information regarding the long-term effectiveness and possible side effects of the booster vaccine is needed; an area that is under intense research.

mRNA-Based Vaccines

The mRNA vaccines currently in use to prevent the SARS-CoV-2 virus have emerged as a convergence of new technologies and years of research. Although clinical trials are ongoing for safety and efficacy purposes, initial short-term findings of mRNA-1273 and BNT162b2 are encouraging in terms of safety and prevention of the SARS-Cov-2 virus that causes the disease Covid-19 [50,51].

mRNA vaccines have the potential to provide fewer risks to host cells, have the advantage of speedy development, and are flexible in high-volume manufacturing [52]. mRNA vaccines have lower risk potentials than live attenuated vaccines, as they do not require the handling of large batches of pathogenic materials in the process of growth or manufacturing [53]. Whole virus inactivated vaccines create less of an immune response and require adjuvants, whereas mRNA vaccines may be designed to be self-adjuvanting [52]. Notably safer when compared to DNA vaccines, mRNA vaccines act as a transporter of information into the cytoplasm, bypassing the risk of crossing the nuclear membrane and interacting with the host cell's genome. mRNA vaccines combine characteristics of several types of more established vaccines, offering safety and a strong immunogenic response. The encoded mRNA changed easily to produce proteins of any kind, rearranging the sequence while maintaining the general chemical structure. This allows mRNA vaccines great flexibility in the potential viruses and diseases they can address, while showing little need for large shifts in manufacturing and production once the infrastructure is established [52].

The unprecedented speed with which the mRNA vaccines synthesized, brought to clinical trial, and granted Emergency Use Authorization (EUA) was a coordinated effort that brought together decades of research in the field of mRNA as vaccine transport [53].

For the last three decades, mRNA has been recognized for its immunogenic potential. Research over the last 15 years has focused on coronavirus (SARS-CoV & MERS-CoV) and respiratory syncytial virus (RSV) mRNA vaccines, which helped lead to the creation of the mRNA-1273 and BNT162b2 vaccines [53]. Additionally, the mRNA vaccines were created and approved so quickly with the help of advances in lipid nanoparticle (LNP) technology [54]. In particular, the 2018 FDA approval of Patisiran, the first LNP short interfering RNA-based drug, put the lipid nanoparticle field through rigorous testing [54]. Gaining FDA approval paved the way for future innovative LNP technologies, including mRNA vaccines rely on LNPs for protection and transport across the host cell membrane into the cytoplasm [54].

Once in the cytoplasm, the mRNA vaccine is translated by the cell's ribosomes to build altered spike (S) proteins [55]. The S protein is the prominent crown-like ("corona") ectodomain of the SARS-CoV-2 virion, and acts as the viral-host connection site for viral entry and recognized as an antigen by the immune system [56]. The S protein was recognized and utilized in previous studies of MERS-CoV, SARS-CoV-1 and RSV as an appropriate target area for vaccine development because the protein induces an antibody response [56,57]. Structural shape changes in the S protein, between perfusion and fusion stages of viral-host contact, are dramatic, allow for membrane fusion, and host cell infection [58]. The vaccine encodes the altered S protein to stabilize it in its perfusion conformation using two proline substitutions (2P), creating SARS-CoV-2 S-2P [56]. Creating an altered S protein stabilized in the perfusion stage trains the immune system to respond to the antigen, it is exposed to the SARS-CoV-2 virus, before viral entry into the host cell takes place [59].

Although mRNA-1273 and BNT162b2 have proven to be highly effective in their protection against Covid-19, waning antibody levels approximately 6+ months after the second dose and highly transmissible variants of the virus that evade the immune system, have led to the CDC's recommendation that individuals receive a booster shot [60]. A full third dose of the vaccine recommended for individuals who are immunocompromised. Variants of concern (VOCs) are more transmissible and adaptive, presenting mutations and deletions on the spike protein and receptor-binding domain (RBD) [61]. In particular, the Omicron variant (B.1.1.529) shows more than 30 mutations on the spike protein and RBD, the target points of Covid-19 vaccines and the immune response [61]. Computer simulated models suggesting Omicron could be 10 times more transmissible than the original virus, coupled with the variants' ability to evade vaccination, has led to Omicron specific mRNA vaccine manufacturing and testing by Pfizer, Moderna and China's Academy of Military Medical Sciences [62,63]. With respect to data found about variants and overall vaccine effectiveness, some lawmakers urge for more evidence before making final decisions on which populations should receive vaccines [64].

A: MODERNA: mRNA-1273

The mRNA-1273 prophylactic vaccine was created with the intention to prevent severe disease and protect against the SARS-CoV-2 virus, which causes the coronavirus disease Covid-19 [50]. The vaccine was developed in mid-January of 2020 by biotech company Moderna, Inc. and the U.S. National Institute of Allergy and Infectious Diseases (NIAID) - National Institutes of Health (NIH), upon the public release of the SARS-CoV-2 genetic sequence by the Chinese Center for Disease Control and Prevention [50]. Phase 1 clinical trials for mRNA-1273 began in the United States on March 16, 2020 [57]. Phase 2 trials began May 29, 2020, phase 3 began July 27, 2020, and Emergency Use Authorization (EUA) was granted by the Food and Drug Administration (FDA) on December 18, 2020 [50,57,65]. The Phase 3 clinical trial for mRNA-1273 took place in 99 locations across the United States and enlisted 30,420 volunteers selected specifically for their potential high-risk exposure to SARS-CoV-2 based on "location and circumstances" [50]. In line with FDA trial criteria, each trial location enlisted individuals that better reflected the local community, addressing each specific population in terms of race, ethnicity, and risk [50]. All individuals were 18 years or older, considered in "medically stable" condition and had no knowledge of previous infection by SARS-CoV-2 [50]. The clinical trial was "randomized, stratified, observer-blinded, placebo-controlled" and had a vaccine to placebo 1:1 ratio [50]. Allocation of vaccine or placebo was stratified and randomized based on age and risk factors. Risk categories were as follows: 65 years or older, people 65 years or younger with higher risk of Covid-19, people 65 years or younger without higher risk. Individuals put into the higher risk category if any of the following were present: severe obesity, diabetes, cardiac disease, or chronic lung disease. Individual status of vaccine/placebo blinded from all trial staff apart from pharmacists administering shots and Moderna team members who were required to communicate with regulatory agencies for monitoring and safety protocols. Each trial participant was given two intramuscular injections in the deltoid of 100 μg of mRNA-1273 or saline placebo, administered 28 days apart, with 96% completing both doses. Doses were held at 2° to 8°C (35.6° to 46.4°F) for storage and remained stable and viable at room temperature for 8 hours before administration. Trial participants given a nasopharyngeal reverse-transcriptase-polymerase-chain-reaction (RT-PCR) swab test before each injection to determine current SARS-CoV-2 infection status. The primary end point of the clinical trial was the prevention of Covid-19 infection within 14 days after the second dose of vaccine/placebo, as exhibited by associated symptoms [50]. The target end point was said to be not met if trial individuals presented two or more of the "following symptoms: fever, chills, myalgia, headache, sore throat, new olfactory/taste disorder," one symptom of respiratory distress: "cough, shortness of breath, clinical or radiographic evidence of pneumonia," or a positive RT-PCR Covid-19 test. Secondary efficacy end points were defined as the prevention of severe Covid-19 infection as indicated by more extreme symptoms of cardiovascular and respiratory distress, admission to intensive care and death. In all symptomatic cases blood samples and RT-PCR tests were taken and individuals were monitored until symptoms terminated. Independent board with no knowledge of vaccine/placebo group status monitored all participants in the study [50].

Efficacy for the primary end point was expressed as a "percentage hazard reduction" of contraction of SARS-CoV-2 using the Cox proportional hazards model for analysis. The primary analysis, 2 months after the second dose was administered, provided results of 94.1% efficacy, with 11 cases in the mRNA-1273 group and 185 cases in the placebo group. Prevention of severe Covid-19 cases, the trial's secondary end investigation, gave results of vaccine efficacy of 100%, showing no cases of severe Covid-19 in the vaccine group. In contrast, the placebo group showed thirty cases of severe Covid-19 cases with one death associated with the virus. These numbers were consistent portraying efficacy across demographic groups of age, race, sex, ethnicity, and risk [50].

Safety protocols were adhered to and monitored by an independent safety board on a weekly basis. The mRNA-1273 vaccine did not produce unexpected physical reactions or patterns of concern, and remained consistent with reactogenicity of the phase I trial. There were reports of mild to moderate pain at the injection site after the initial dose and moderate-to-severe fatigue, arthralgia, fever, chills, headache, and myalgia occurring in more than 50% of participants after the second dose [50,56]. The mRNA-1273 group reported more adverse events (8.2%) than the placebo group (4.5%), with the most common being fatigue and headache. Adverse effects were not deemed age related and subsided within approximately 2 days in most trial members. Although the sample size was small in terms of evaluating rare instances of adverse effects, no acute hypersensitivity was reported. However, instances in "slight excess" of Bell's palsy were reported in the mRNA-1273 vaccine phase 3 trial and the BNT162b2 vaccine trial [50].

Context and clinical trial limitations should be noted. During the summer and fall of 2020 there was a rise in Covid-19 cases across much of the United States. This is reflected by the increased number of positive cases found in trial members, which occurred at a faster rate than anticipated. Mask wearing, social distancing, select business closures and school closures across the United States were ongoing through this clinical trial and may have had effects on results [50]. A correlate of protection was not determined during this trial and was expressed as a limitation for future studies. Pregnant women and children under 18 years of age were not included in this trial. This trial provided short-term results on efficacy, with the intention of ongoing evaluation of participants for 2 years after secondary dose completion [50].

As mentioned above, updated data has revealed waning levels of antibody response approximately 6 months after the second dose of vaccination [60]. This, in combination with novel variants of the SARS-CoV-2 virus, have led to the CDC recommending booster shots and third doses for immuno-compromised individuals [60]. The exclusion of pregnant women from initial mRNA vaccine clinical trials led to a deficit in safety and efficacy data regarding Covid-19 vaccinations in this population, and confusion in healthcare guidance during early vaccination rollout [66]. Prior to the availability of authorized Covid-19 vaccines, cohort studies suggested pregnant women were at greater risk for severe illness, hospitalization, and death from Covid-19 [66]. In addition, contracting Covid-19 while pregnant may increase the risk of preterm birth, stillbirth, or other complications during pregnancy [67]. Pregnant women and their physicians were guided by reproductive and developmental animal data provided by Moderna. The data, which suggested mRNA-1273 safety in primates, and the safety of mRNA vaccine technology [68]. Ongoing studies and passive data collected from 35,691 pregnant women post-mRNA vaccination using CDC vaccination monitoring systems ("v-safe after vaccination health checker", the v-safe pregnancy registry, and the Vaccine Adverse Event Reporting System (VAERS) between December 2020 – February 2021, suggest mRNA vaccination during pregnancy is safe, prevents severe illness, and offers protection against Covid-19 for mothers and infants [66,67]. The CDC, Advisory Committee on Immunization Practices (ACIP), American College of Obstetricians and Gynecologists and the American Academy of Pediatrics currently recommend all pregnant women, at any stage of pregnancy, receive an mRNA vaccine with a booster [66,67]. Clinical trials studying pregnant women inoculated with mRNA-1273 are ongoing.

Children and adolescents under the age of 18 were not included in any preauthorization clinical trials for mRNA-1273 [50]. Although most children who contract Covid-19 have milder symptoms than adults do, hospitalization and severe illness are possible [69]. An ongoing phase 2-3 clinical trial was initiated in December 2020 for adolescents aged 12-17-years-old. The trial was placebo-controlled and consisted of two intramuscular 100 µg injections (the same amount as the adult vaccine), administered 28 days apart [69]. The trial's preliminary conclusion suggested the mRNA-1273 vaccine met safety guidelines and immune response targets for adolescent's 12-17-years-of-age [69]. The Advisory Committee on Immunization Practices (ACIP) evaluated reports of myocarditis and myopericarditis, occurring post-vaccination in predominantly adolescent and young adult males [70]. The ACIP reviewed all available data and created a risk-benefit analysis in June 2021, concluding that the benefits of the mRNA Covid-19 vaccines outweighed the possible risks [70]. Emergency Use Authorization (EUA) was expanded to include 12-15-year-olds for Pfizer's BNT162b2; however, the FDA has not granted EUA for mRNA-1273's use for 12-17-year-olds [71]. Summary of information pertinent to dosing, safety, efficacy of the MODERNA vaccine can be found in Table 2.

Table 2: Safety and Efficacy of Current mRNA-Based Covid-19 Vaccines

Vaccination	Dosage	Side Effects	Route of Administration	Frequency of Dose	Rate of Mortality	Reference
Moderna	6-11 yrs: 50µg 12 yrs & older: 100µg Booster: 50µg	Possible pain at injection site, fatigue, arthralgia, fever, chills, headache, myalgia, rare instances of Bell's palsy, rare instances of myocarditis in adolescent males	Intramuscular injection (IM): deltoid	Primary: 2 doses 28 days apart Booster: 1 dose 5 mos after primary series Third full dose or 2nd booster if immune compromised	97.9% effectiveness against death from Covid-19	[50,56,60, 70,72]
Pfizer	5-11 yrs: 10µg 12 yrs & older: 30µg Booster: 30µg,	Possible pain at injection site, fever, headache, rare instances of Bell's palsy and lymphadeno-pathy	Intramuscular injection (IM): deltoid	Primary: 2 doses 21 days apart Booster: 1 dose 5 mos after primary series Third full dose or 2nd booster if immune compromised	96.7% effectiveness against death from Covid-19	[51,73,74]

B: Pfizer: BNT162b2

The BNT162b2 prophylactic vaccine was created with the intention to prevent and protect against the SARS-CoV-2 virus, which causes the coronavirus disease Covid-19. The phase I clinical trial began in the United States on April 29, 2020 and the Phase 2-3 clinical trial began in July 2020 in 152 study locations in the United States, Germany, Argentina, Brazil, South Africa and Turkey [51]. After review of safety and efficacy data from the ongoing phase 3 trail, the FDA granted Emergency Use Authorization (EUA) for the BNT162b2 vaccine on December 11, 2020 [65]. The phase 3 clinical trial for BNT162b2 recruited 43,548 volunteers for a multinational, placebo-controlled, observer-blinded, efficacy and safety study with a randomized 1:1 ratio of group selection for vaccine or placebo, with 99.7% receiving both injections [51]. Eligible participants were 16 years or older, healthy or considered in stable medical condition if a chronic disease existed (e.g. HIV, hepatitis B, hepatitis C). For data analysis, participants were evaluated as younger (ages 16-55) and older (>55 years old). Ineligibility factors included a previous positive Covid-19 diagnosis, use of immunosuppressant's, diagnosis of an immunocompromising condition and women who were pregnant or breastfeeding. Trial members were randomly placed in vaccine and placebo groups using a Web-based system. Participants were given two intramuscular injections in the deltoid of 30 µg of BNT162b2 vaccine or saline placebo, administered 21 days apart. Team members observing participants for acute adverse effects for 30 minutes after administration of the injections, were blinded from group status [51].

The primary end point of the clinical trial was the prevention of Covid-19 infection at least 7 days after the second dose of vaccine/placebo, as exhibited by a new onset of associated symptoms. The second primary end point was the efficacy of BNT162b2 against Covid-19 in individuals who had and had not exhibited prior infection [51]. Covid-19 diagnosis was made according to the FDA criteria of at least one of the following symptoms: "fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, or vomiting, combined with a respiratory specimen obtained during the symptomatic period or within 4 days before or after it that was positive for SARS-CoV-2 infection". The secondary end point was the prevention of severe Covid-19 infection with exhibited symptoms of respiratory failure, shock, acute renal, hepatic, or neurologic dysfunction, hospitalization/intensive care, or death [51].

Efficacy analysis for the primary end point of Covid-19 prevention was 95.0% when evaluating 36,523 participants with no previous SARS-CoV-2 infection. Of this group, eight positive cases were detected among the vaccine recipients, 162 positive cases were detected in the placebo group, and 7 days after the second dose was administered. The second primary end point of participants with/without evidence of prior SARS-CoV-2 infection yielded similar results with 94.6% vaccine efficacy. Vaccine efficacy amongst subgroups of age, sex, race, obesity, hypertension, and preexisting conditions proved consistent with the overall group analysis. Although the trial was not intended to evaluate a single-dose regi-

men, data showed 52% efficacy after the first dose of BNT162b2, offering protection as little as 12 days after the initial dose. Ten cases of severe Covid-19 were observed, one case in the vaccine group and nine cases in the placebo group, suggesting preliminary evidence of protect against severe infection [51].

An independent team reviewing unblended data to meet protocols throughout the trial monitored safety. Reactogenicity was monitored in a subset of 8,183 trial participants for 7 days after each injection. BNT162b2 recipients reported more complaints of mild-to-moderate pain at the site of injection than placebo group member did. Pain was rated in terms of interference with daily activities, with more pain reported by younger participants (< 55 years old) than older participants (> 55 years old) were. Instances of pains recorded after first and second doses with both age groups reporting more pain after the first injection (83% of younger participants, 71% of older participants). Less than 10% of each group reported redness or swelling at the injection site. The two most common systemic reactogenicity complaints made by the BNT162b2 group were fatigue (59%) and headache (52%) after the second dose [51]. Fever (≥100.4°F) was reported after the second dose in younger participants (16%) and older participants (11%) in the vaccine group. Pain, redness, and soreness were resolved in one or two days after injection; onset of fever reported within 1 or 2 days of injection with resolution shortly thereafter. Adverse event analyses were made with data from all 43,252 participants and reflect the data collected from the subgroup for reactogenicity, with more vaccine participants reporting adverse events than placebo group members [51]. Lymphadenopathy was reported in 0.3% of the BNT162b2 group and <0.1% of the placebo group. BNT162b2 group members reported four severe adverse events related to the vaccine: shoulder injury, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia. Six trial participants died (2 in the vaccine group, 4 in the placebo group); however, none of the deaths was attributed to BNT162b2 or the placebo upon investigation [51]. Four vaccine recipients reported Bell's palsy [75]. Although this number does not exceed the normal frequency found in the general population, it is noted in relation to Bell's palsy cases found in "slight excess" in the vaccine group of the mRNA-1273 trial as a point of further monitoring [50].

The clinical trial reports several limitations. Although the study was able to report more than 83% probability of detecting at least one adverse event, the number of participants was still too small to determine "less common" adverse events with confidence. Further, the study offers only short-term analysis of efficacy and safety (2 to 3.5 months of monitoring after the second dose), which limits the scope of the data [51]. This trial will continue to observe and monitor participants for long-term efficacy and safety (2 years after the second dose) however, it will be done without a placebo group, and it has been noted that withholding the approved vaccine from the placebo group for two years would be unethical. This trial did not address BNT162b2 as prevention of asymptomatic infection. A correlate of protection was not established [51]. Cold storage requirements for vaccine stability were a limitation of the Pfizer vaccine, however, updated FDA guidelines state that conventional pharmaceutical freezer temperatures are adequate, and if undiluted, BNT162b2 can be stored at normal refrigeration temperatures for up to one month [76]. New data and new mutations of the virus have revealed lower levels of antibody response approximately 6 months after the second dose of vaccination [60]. The CDC now recommends booster shots for anyone >12 years old, and a third full dose for individuals who are immunocompromised [60].

Pregnant women and breastfeeding women were not included in the initial phase 3 trial [51]. However, Pfizer began a global Phase 2/3 BNT162b2 study for safety and immunogenicity in healthy pregnant women 18 years and older in February 2021 [68]. The study is randomized, placebo-controlled and observer-blinded and will include 343 pregnant women to be monitored until August 2022 [68]. Studies in Israel have taken advantage of the real-world data provided by the "unprecedented vaccination campaign" in Israel that included pregnant women [77]. An observational cohort study in Israel comparing 10,861 vaccinated pregnant women to 10,861 non-vaccinated pregnant women with similar demographic and clinical distinctions, reported 96% efficacy of BNT162b2 vaccination in pregnant women; which is similar to the general population [78]. A study funded by the Israel Science Foundation and the Weizmann Institute Fondazione Henry Krenter conducted between April 2020 and March 2021, collected blood samples from 1094 pregnant mothers and fetuses [77]. Results of the study show that a BNT162b2-elicited immunoglobulin response in the mother is transferred to the fetus via the placenta, building fetal immunity two weeks after initial maternal vaccination [77]. While these studies are encouraging, more data is needed on the long-term safety and efficacy of mRNA Covid-19 vaccines in relation to mothers and infants [68]. Currently, the CDC, ACIP, American College of Obstetricians and Gynecologists and the American Academy of Pediatrics recommend all pregnant women, at any stage of pregnancy, receive an mRNA vaccine with a booster [66,67].

Children and adolescents under the age of 16 were not included in any preauthorization clinical trials for BNT162b2 [51]. Pfizer initiated clinical trials with adolescents 12-15-years-old in April 2020 [74]. The study included 2260 adolescents, was placebo-controlled, and observer-blinded. Participants received two intramuscular injections of 30 μg of BNT162b2 vaccine or placebo, 21 days apart. The study concluded that the BNT162b2 vaccine met safety guidelines and was 100% effective for protection against Covid-19 in adolescents 12-15-years-old. The FDA's Emergency Use Authorization (EUA) of Pfizer's BNT162b2 vaccine was expanded to include 12–15-year-olds on May 10, 2021 [74]. A phase 1 clinical trial to test safety, immunogenicity, and efficacy of BNT162b2 on 5-11-year-olds progressed cautiously to find an appropriate dose of vaccine, using the guideline of 30 μg that had been determined for 12-15-year-olds [73]. A two-dose regimen, each 10 μg administered 21 days apart, was selected based on immunogenicity and reactogenicity. The phase 2-3 clinical trial for 5-11-year-olds was placebo-controlled, observer-blinded, and included 2268 random-

ly selected children. Based on the data from this study, safety, immunogenicity, and efficacy targets were met [73]. On October 29, 2021, the FDA amended the EUA to include the new dose information for Covid-19 vaccine BNT162b2 for 5-11-year-olds [79]. Summary of information pertinent to dosing, safety, efficacy of the Pfizer vaccine can be found in Table 2.

Viral Vector Vaccines

Viral vector technology has been evolving since the 1970's and has not only been integral to the development of vaccines, but has also been vital to gene therapy, and cancer treatment. The use of recombinant viral vectors in vaccine development is reliant on the ability that viruses have to infect host cells [80]. These viral vectors work by spurring a host cell to produce antigens to promote a specific immune response needed to fight a target infectious agent [81]. Adenovirus (Ad) vectors specifically, are utilized due to specific advantages "high transduction efficiency, high level of transgene expression, and broad range of viral tropism." Conversely, a disadvantage of using Ad vectors is that preexisting immunity may already exist, due to the high probability that an individual has of having a past exposure to an Ad serotype [80]. Adenovirus vectors can be replicating and non-replicating. Replicating Ad vectors consist of viruses that can reproduce within the host cell, allowing it to continuously infect, and thus stimulate the cell to make more of the necessary vaccine antigen [81]. Non-replicating Ad vectors are characterized by "the deletion of the E1A and E1B viral gene region." [80]. The E1A region specifically plays a role in perpetuating viral replication during host cell infection [80]. Therefore, the deletion of this region almost always results in the inability for viral replication to occur [82]. The desirability of using non-replicating vectors lies in their increased safety profile, due to decreased virulence as the viral DNA does not proliferate and is cleared from the host body over time [80].

Janssen/Jenssen (J&J):

In March 2020, Janssen and Janssen announced their leading vaccine candidate in the fight against Covid-19. Janssen Biotech Inc., a Janssen Pharmaceutical Company of Johnson & Johnson began manufacturing Ad26.COV2.S in August 2020, after entering into an agreement with the U.S. government ensuring 100 million doses for wide scale delivery of the experimental vaccine, following full or emergency use authorization (EUA) by the US Food and Drug Administration (FDA). The FDA granted EUA of Ad26.COV2.S on February 27, 2021 in order to prevent moderate to severe disease from Covid-19 for individuals 18 years of age or older [83]. Ad26.COV2.S is a non-replicating vector-based Covid-19 vaccine that encodes for the viral surface "SARS-CoV-2 spike protein in a perfusion-stabilized conformation." [84]. Perfusion conformation of the S protein is stabilized by two proline substitutions [85]. This conformation has been shown to induce higher immunogenicity than its wild type. The spike protein of SARS-CoV-2 is central to the virus's successful rate of transmissibility, in that it fuses to the Angiotensin Converting Enzyme 2 (ACE2) receptor of the host cell allowing it to enter and infect [85]. Because of this integral role, the S protein has remained the primary target for vaccine candidates [86].

The ENSEMBLE international phase 3 trial for Ad26.COV2.S was initiated by a collaboration of efforts between Janssen Research and Development and the Operation Warp Speed Covid-19 Rapid Response team [85]. ENSEMBLE is a randomized, double blind, and placebo-controlled trial that has been implemented to assess safety and efficacy that Ad26.COV2.S at 5x1010 viral particles has in protecting against moderate to severe Covid-19 disease. Though the trial will be ongoing and will run over the course of 2 years, the initial analysis cutoff date was on January 22, 2021- 4 months after the beginning of trial enrollment on September 21, 2020 [85]. The trial conducted in a 1:1 ratio of participants receiving a single intramuscular dose of either Ad26.COV2.S or a saline placebo. The full analysis set of participant's totals 43,783, with 21,895 in the Ad26.COV2.S vaccine group and 21,888 in the placebo group. Qualifications for eligibility included an age range of ≥18 years old, with 29,111 (66.5%) individuals in the 18 to 59-year age range and 14,672 (33.5%) in the ≥60-year age range. Female participants make up 45% of the total distribution, 54.9% are male, and the rest are non-binary or unknown. Total participants with a BMI of ≥30 is 12,481 (28.5%). Total participants with ≥1 coexisting condition(s) is 17,858 (40.8%) [85].

A primary objective for this trial is the overall investigation of Ad26.COV2.S safety, efficacy, and immunogenicity post vaccine administration. A subpopulation of approximately 6000 participants was chosen to record data in an electronic diary outlining adverse effects experienced at 7 days post injection and at 28 days post injection [85]. At 7 days following injection administration, participants were asked to report local and systematic adverse events. The vaccine group ultimately reported more solicited adverse events. The most prevalent local reaction reported was injection site pain at 48.6%, while "the most common systemic reactions were headache (in 38.9%), fatigue (in 38.2%), myalgia (in 33.2%), and nausea (in 14.2%)." [85]. Serious adverse effects experienced by 0.4% of both vaccine group and placebo group. It was ultimately determined by investigators that 7 out of the 83 participants who reported serious adverse effects from the vaccine group were affected directly from Ad26.COV2.S. 3 deaths were reported in the vaccine group and 16 deaths were reported in the placebo group, none of which were attributed to the trial. However, the placebo group reported 5 Covid-19 related deaths. Furthermore, two serious adverse reactions to the vaccine were reported as 1 case of "transverse sinus thrombosis with cerebral hemorrhage" and 1 case of Guillain-Barré syndrome [85].

Overall efficacy of Ad26.COV2.S in establishing humoral and cellular immunity has also been a central objective in this phase 3 trial. A per-protocol population of 40,000 participants was used to determine efficacy. These individuals had received either Ad26.COV2.S or saline placebo, were negative for Covid-19 or had unknown status at time of injection, and "had no protocol deviations that were likely to affect vaccine efficacy." [85]. Those who were excluded were participants that tested positive by RT-PCR screen-

ing between 1- and 14-days or 1- and 28-days post administration, with symptom onset after 14 or after 28 days. The two primary endpoints used to analyze the vaccine efficacy of mitigating moderate to severe-critical disease from Covid-19 are prevention at onset of 14 days after administration and at 28 days after administration [85]. The cases that would be deemed severe-critical amongst seropositive participants would be those who presented with at least 3 symptoms. The null hypothesis that rejected assumed that vaccine efficacy would be no higher than 30% at each primary endpoint. At the first primary endpoint at onset ≥14 days, there were 464 moderate to severe cases reported among the total per-protocol population (116; vaccine group, 348; placebo group), indicating 66.9% efficacy. At the second primary endpoint at onset ≥28 days, there were 259 moderate to severe cases reported among the total per-protocol population (66; vaccine group, 193; placebo group), indicating 66.1% efficacy. Regarding severe-critical disease from Covid-19, the efficacy at the first primary endpoint was 76.7% and at the second primary endpoint was 85.4%. At day 42, the efficacy against severe-critical disease reached 92.4% [85]. Ad26.COV2.S showed protection against other variants as well. Protection against the effects of South African variant 20H/501Y. V2 was represented in the ENSEMBLE trial. At ≥14 days onset efficacy against moderate to severe-critical cases reached 52.0%, and at ≥28 days it reached 64.0%. Whereas efficacy against severe-critical cases reached 73.1% at ≥14 days, and 81.7% at ≥28 days. The placebo group also saw 6 hospitalizations and 5 deaths, compared to none for either outcome in the vaccine group [85]. Other data has shown that even after 8 months, Ad26.COV2.S has maintained significant "humoral and cellular responses with minimal decreases", with "increased neutralizing antibody responses to SARS-COV-2 variants over time".

Shortcomings of Ad26.COV2.S can be seen in some adverse reactions experienced amongst the population after vaccine rollout. As of April 13, 2021, 8 out of 7 million individuals who received the vaccine developed thrombosis with thrombocytopenia syndrome [TTS], resulting in 1 fatality [86]. Because of this, Janssen and Janssen delayed initial vaccine distribution in Europe and paused continued rollout in the US to investigate this rare blood clot incidence. It was shown that the primary risk group for this particular reaction has been women between 30-49 years old, 3 weeks post injection [87]. The rare blood clot usually was found in the brain or abdomen [86]. By July 8, 2021, 38 cases of TTS arose within 15 days of vaccination (8.8 cases per million doses). Another serious adverse reaction has been the development of Guillain-Barre syndrome (GBS), which is a rare neurological disorder that causes the immune system to degrade the body's nerves, resulting in muscle weakness and paralysis. Between February 27, 2021 and June 30, 2021, 100 cases of GBS has been reported, with onset at 21 days post vaccination [87]. Incidence of GBS cases reported has been greatest amongst "males aged 50-64 years." [87]. As of July 2021, there has been 1 fatality resulting from vaccine induced GBS. The Advisory Committee of Immunization and Practices (ACIP) ultimately concluded that the benefits of Ad26.COV2.S outweighed the risk of TTS and GS [87].

AstraZeneca

ChAdOx1 nCoV-19 (AZD1222) is a viral vector vaccine originating from a non-replicating chimpanzee adenoviral vector [88]. Chimpanzee adenovirus vectors are unique in that they are non-reactive to "pre-existing human adenovirus neutralizing antibodies" since chimpanzee adenovirus infection is not prevalent among the human population [89]. AZD1222 was developed at Oxford University, and like other Covid-19 viral vector vaccines, contains the viral DNA that codes for the SARS-CoV-2 spike protein [88]. The WHO recommended vaccine schedule consists of 2 separate intramuscular doses (0.5 ml each), 8-12 weeks apart for maximum efficacy [90]. An international phase 3, double-blind trial has been designed and implemented by AstraZeneca, the Department of Health and Human Services, and the National Institutes of health in an effort to determine latest safety and efficacy in producing humoral and cellular immune response to prevent moderate to severe-critical disease in those who contract Covid-19. This is an ongoing 2-year study that is taking place at 88 different sites in the US, Chile, and Peru. The primary analysis cutoff date was March 5, 2021. This trial was randomly assigned in a 2:1 ratio, with participants between ≥18 years old and 64 years old, and 25% of the participants at ≥65 years old. Participants received 2 intramuscular (IM) doses of either AZD1222 or a saline placebo 4 weeks apart. Ultimately, 21,635 participants received intramuscular AZD1222 and 10,816 participants received intramuscular saline placebo [90].

Safety analysis showed that among the participants, 8771 individuals in the vaccine group and 3201 individuals in the placebo group reported 23,538 total adverse events [90]. Within 28 days after either dose, serious adverse events were reported among 101 individuals in the vaccine group and 53 individuals in the placebo group. Local solicited adverse events were experienced by 74.1% of the vaccine group and 24.4% of the placebo group. Systematic solicited adverse effects were experienced by 71.6% of the vaccine group and 53.0% of the placebo group. There were 7 deaths in each group, none related to the vaccine or placebo. There were 2 deaths in the placebo group related to Covid-19 [90]. The primary endpoint for analysis of vaccine efficacy was SARS-COV2 incidence at ≥15 days after the administration of the second dose of either the vaccine or placebo [90]. These participants had no known history of Covid-19 at the time of recruitment. By the time of data analysis, a total of 203 symptomatic Covid-19 incidents occurred among both groups. 73 cases (0.4%) were counted among the vaccine group and 130 cases (1.5%) were counted in the placebo group. Estimated vaccine efficacy resulting from the data provided was 74.0%. The secondary endpoints for analysis included but were not limited to symptomatic Covid-19 incidence ≥15 days post second dose, severe Covid-19 illness, and Covid-19 illness resulting in emergency care. The study concluded that the "vaccine was significantly effective against all other key secondary efficacy end points". No severe cases were reported among the participants in the vaccine group, while 8 were reported in the placebo group [90].

Inactivated Virus Vaccines

The use of virus inactivation for vaccine development was first referenced in 1886 when Daniel Elmer Salmon and Theobald Smith used hog cholera that was inactivated with heat treatment to immunize pigeons [91]. However, large-scale production was only possible after the discovery of cell culture technology that allowed viral replication in vitro. During vaccine production, once viral propagation is achieved using continuous cell lines, the virus is purified and concentrated [91]. It must then become inactivated by using chemicals: β-propiolactone, formalin, or ethylenimine-heat, or radiation [92]. The goal of this method is to accomplish virus neutralization, while also stimulating the proper proliferation of antigens needed to combat the virus. Inactivated whole virion vaccine production is also characterized by the addition of adjuvants utilized to enhance the efficacy of the vaccine. Both WHO approved Chinese Covid-19 vaccines, Sinopharm and CoronaVac; use aluminum hydroxide as an adjuvant [93]. After inactivation, the virus purified further by using techniques such as, "ultrafiltration, size-exclusion chromatography (SEC), and sucrose gradient centrifugation" [92].

There are both advantages and disadvantages when utilizing inactivated whole virion vaccines to combat a pathogen. A desirable aspect of using this technology is that inactivated viral vaccines are safer and less reactogenic than live attenuated vaccines [91]. Once the virus is inactivated, it cannot return to its transmissible and replicative phenotype. Furthermore, production methods are desirable since manufacturers have the "ability to utilize existing equipment, reagents and disposables that are in routine use for treatment of blood products to produce an inactivated vaccine preparation when using purified viral stocks of the target virus" [92]. Conversely, drawbacks are also present. Since a large amount of antigen is needed to promote proper immune response, the schedule may require multiple injections in conjunction with possible booster shots to induce meaningful immunity [94]. Another disadvantage seen in utilizing inactivated whole virion vaccines is that rather than specifically targeting the spike protein, like other Covid-19 vaccines, inactivated whole virion vaccines elicit a response against several different viral proteins [95]. This would ultimately degrade immunogenicity through the lack of targeting specificity. Furthermore, the medium used to inactivate the virus can also cause changes to antigens that may affect robust immunogenicity [94]. However, β-propiolactone, which is used as the inactivating agent in CoronaVac and Sinopharm, does not damage the antigens in the same way [93]. Another disadvantage is that neutralizing antibodies necessary for fighting the virus wanes quickly in comparison to other vaccines [95]. Despite this, studies show that after time, T-cells and B-cells are detectable at the same levels as those found in mRNA Covid-19 vaccines [95]. Safety is also a concern. As has been also shown in the past, if the viruses are not properly inactivated, the virus that is thought to be non-replicating is in fact capable of replicating [91]. This has been seen in a notable instance in vaccine history known as The Cutter incident. In 1955, a polio vaccine that contained replication competent poliovirus was distributed to 40,000 children [91]. During the production process, the virus was improperly purified, which allowed the presence of cell debris to prevent formaldehyde inactivation [91]. As a result, the children who received the vaccine contracted polio; 51 children were paralyzed, and 5 children died [91].

Sino pharm

There have been two vaccines developed out of China that have been approved by the WHO for emergency use. Sino pharm has developed two vaccines, one out of Wuhan and the other out of Beijing. Sinovac has also developed the vaccine CoronaVac out of Beijing [96]. All three of the vaccines are inactivated whole virion vaccines stemming from inactivated SARS-COV-2. Specifically, Sino pharm isolated two SARS-COV-2 strains (WIV04 and HB02) from a patient in Jinyintan Hospital in Wuhan, China that were utilized for the development of the vaccines WIV04-CorV and HB02-CorV (BBIBP-CorV) [97]. WHO approved BBIBP-CorV for emergency use on May 7, 2021 and recommends it at a two-dose schedule, 4 weeks apart for individual's ≥18 years old. The WHO has not yet approved the WIV04-CorV Wuhan unit. Both vaccines underwent a phase 3 randomized clinical trial demonstrating its efficacy and safety when used to prevent symptomatic Covid-19. Published by JAMA on May 26, 2021, the study was conducted at multiple sites in the United Arab Emirates and Bahrain and administered in a 1:1:1 ratio of 40,382 participants receiving at least one dose of either SARS-CoV-2 WIV04 (5 μg/dose), BBIBP-CorV (4 μg/dose) both with an aluminum adjuvant or an aluminum hydroxide placebo [97]. 38,206 participants received both intramuscular doses indicated by the administration schedule, 21 days apart. Eligibility for trial participation included individual's ≥18 years old with no known history of SARS-COV-2 or MERS. The mean age of participants recruited for the study was 36.2 years old, 92% were <60 years old, and 84-85% were male. The trial's primary endpoint for efficacy was the prevention of symptomatic Covid-19 ≥14 days after second dose and the secondary endpoint for efficacy was prevention against severe Covid-19 and death ≥14 days after second dose [97]. Safety endpoints for the trial were solicited and unsolicited adverse reactions within 7 days of the first dose. Symptomatic Covid-19 2 weeks after the second dose was experienced by; 95 of 13,458 participants in the placebo group, 26 of 13,459 participants in the WIV04 group, and 21 of 13,456 participants in the BBIBP-CorV group [97]. The efficacy determined by data presented reached 72.8% prevention against symptomatic Covid-19 when given WIV04 and 78.1% when given BIBBP-CorV [97]. Severe Covid-19 reported within either of the vaccine groups, and two instances reported in the control [97]. According to Johns Hopkins, the study presents multiple drawbacks. These include; a limited number of individuals older than 60 years of age, lack of female participants, minimal data on comorbid conditions, limited variability of SARS-COV-2 transmission rates in the three regions the trial was conducted, and the lack of data on efficacy of prevention against newer, more transmissible variants [97].

On September 15, 2021, The Lancet released data pertaining to the safety and immunogenicity that BBIBP-CorV has when adminis-

tered to individuals between 13-17 years old [98]. Shangqui City Liang yuan District Center for Disease Control and Prevention held a phase 1 and phase 2 randomized, double blind, controlled study that was assigned in a 1:1:1:1 ratio of participants receiving 3 doses of either vaccine or control 28 days apart [98]. In phase 2, there were three separate groups of 180 participants that received 3 varying doses of the vaccine (2 µg/4 µg/9 µg) and one control group of 180 participants. Each group was separated into three age cohorts (3-5 years, 6-12 years, and 13-17 years). Adverse reactions to the vaccine ranged from mild to moderate [59]. Similarly shown in other Covid-19 vaccines, the most common local reaction for the vaccine group was injection site discomfort. The most common systematic reaction to the vaccine was fever [98]. After two doses, BBIBP-CorV was shown to be safe for healthy individuals between 3-17 years old in the effort to prevent symptomatic Covid-19 [98].

CoronaVac

CoronaVac is another inactivated whole virion vaccine to come out of China that has been approved by the WHO [99]. It is prepared with the CZ02 strain of Covid-19 that has been inactivated by β-propiolactone and uses aluminum hydroxide as the adjuvant. Despite still being in phase 3 clinical trials in other countries, interim results were published in July 2021 analyzing data from a randomized, double-blind, controlled phase 3 trial in Turkey. This trial was conducted to determine CoronaVac prevention against moderate to severe Covid-19. This study analyzed participants between the age of 18-59 years old who have received 2 intramuscular doses of either CoronaVac or an aluminum control, 4 weeks apart [99]. Date range for this particular analysis was September 15, 2020 - January 6, 2021 and took place across 24 study centers. A per protocol population of 10,029 participants (6,559 individuals in the vaccine group/3,470 individuals in the placebo group) was used to analyze the results. The median age of these individuals was 45 years old. Comorbidity rates among the per protocol population consisted of 15% of participants that were obese and 11.8% that were hypertensive [99]. Vaccine efficacy shown within the data set was determined to be 83.5%. Incidence of symptomatic Covid-19 at least 14 days post second dose was 9 individuals in the vaccine group and 32 individuals in the placebo group. The placebo group saw 6 hospitalizations and neither group experienced any fatalities resulting from Covid-19. 3845 total adverse events were reported, spread among 1259 participants in the vaccine group and 603 participants in the placebo group [99]. Solicited events made up most of the reports as they were reported among 1148 individuals in the vaccine group and 537 in the placebo group. Among the solicited events, the most common was injection site pain. The most reported systematic adverse effect was fatigue and seen primarily in the vaccine group. Both groups had a very low incidence of unsolicited events [99]. Serious adverse effects were reported among 6 individuals in the vaccine group and 5 individuals in the placebo group. However, the only incident that was determined to be causal upon investigation was a grade 3 allergic reaction that occurred after vaccine administration and resolved after 24 hours [99].

To determine the safety and tolerability of CoronaVac among individuals between 3-17 years of age, an ongoing phase 1 and 2 trial has been instigated at Hebei Provincial Center for Disease Control and Prevention in Zanhuang, China [100]. In phase 1, 72 participants assigned in a 3:1 ratio received CoronaVac in two blocks of either 1.5 µg or 3.0 µg, or an aluminum placebo. In phase 2, 480 participants between the ages of 3-17 years old assigned in a 2:2:1 ratio received CoronaVac in 2 blocks of either 1.5 µg or 3.0 µg, or an aluminum placebo [100]. The primary safety endpoint for the trial was the resulting incidence of adverse reactions within 28 days of the first dose amongst 550 participants (219 individuals receiving 1.5 g/217 receiving 3.0 g/114 receiving placebo) who had received at least one dose of vaccine or placebo [100]. The most common adverse effect reported was injection site pain, primarily found among those who received the vaccine. The most serious adverse reaction reported was pneumonia in the placebo group. However, the bout of pneumonia found to be unrelated to the trial. Ultimately, CoronaVac was determined to be safe and elicit the appropriate humoral response for individuals between 3-17 years old [100]. In June 2021, Tribune India announced that China authorized CoronaVac for use for individuals above 3 years old as a prophylactic measure against Covid-19. However, studies performed in Santiago, Chile concluded that subjects treated with CoronaVac had a decline in antibodies within the six-month trial period, in comparison to BNT162b2 vaccine, Pfizer, which showed a significant increase in human antibodies [101]. These findings suggest that further exploration into the vaccine's efficacy is essential in order to use the greater population. Summary of information pertinent to dosing, safety, efficacy of the non-mRNA based vaccines (viral vectors and inactivated virus vaccines) found in Table 3.

Table 3: Safety and efficacy of current non-mRNA-based COVID-19 vaccines (viral vectors, inactivated virus)

Vaccination	Dosage	Side Effects	Route of Administration	Frequency of Dose	Mortality	Reference
AstraZeneca	2 separate doses (0.5 ml each),	Local reactions, headache, fever, diarrhea, myalgia, nausea, - TTS	Intramuscular injection (IM): deltoid	8-12 weeks apart	Estimated 74.0% efficacy of protecting against severe-critical disease.	[90,102,103]
CoronaVac	2 doses (0.5 ml each)	Local reactions, fatigue, muscle pain, joine pain,	Intramuscular injection (IM): deltoid	4 weeks apart	Efficacy of protecting against death, 55.7%.	[99,104,105]
Sinopharm	2 doses (0.5 ml each)	Fatigue, dizziness, headache, fever, local reactions	Intramuscular injection (IM): deltoid	3-4 weeks apart	Efficacy of protecting against death, 97.0%	[59,97,106]
J&J	0.5 mL single dose	-GBS (7.8 per million cases) -TTS (47 cases) Common; -injection site swelling, erythema, fever, fatigue, myalgia, headache	Intramuscular injection (IM): deltoid	Single dose administered	After day 42, efficacy of protecting against severe-critical disease reached 92.4%	[85-87,103]

Discussion

Modalities such as medical drugs and mRNA vaccines, along with their respective boosters, have shown great prevalence among the numerous treatments used in response to the novel coronavirus, SARS-CoV-2. Therapeutic medications were used in treating both severe and mild Covid-19 infections due to their protease inhibitors allowing for SARS-CoV-2 metabolism to slow down providing greater antiviral potency, and their substantial anti-inflammatory effects that decrease inflammatory symptoms [32]. Prior drug-use experiments conducted in multiple test cohorts shared related outcomes such as decreased hospitalizations and greater stimulated immunity [33]. However, these examinations have also had similar opposing results including cytokine storms that decrease immunity and immunosuppressive abilities that trigger viral infections [28]. Following these results, future studies should be aimed at a subject's immune system itself as it may express specific target proteins that support an individual's immune health without triggering SARS-CoV-2. Further experiments regarding therapeutic drugs should also focus on the average age and social factors of an individual as the environmental conditions they face reflect their susceptibility to disease infection.

mRNA vaccines and their subsequent administered boosters were used to prevent SARS-CoV-2 infection by behaving as transporters of nucleic acid information into the cytoplasm allowing the host cell's genome to be left alone [52]. Prior studies have indicated that when mRNA vaccines are administered and nanoparticles have reached the cytoplasm, mRNA is translated to build an altered, chiral spike protein that allows the immune system to respond to future encounters with SARS-CoV-2 thereby eliciting antibodies. Studies have also proven that vaccines provide immunogenic potential that further assists in preventing infections or at least prevents fatalities. Inactivated vaccines, which were also studies in prior experiments, stimulate proliferation of antigens which enhances the efficacy of the vaccine. This technique for vaccine production infers certain drawbacks as it may require multiple injections to create immunity and thereby degrades target specificity for immunogenic potential [94]. Continuing studies that emerge from findings with respect to mRNA vaccines should consider the state restrictions taken place among specific test cohorts, including social distancing, facial coverings, and capacity restrictions. Further studies should also consider the emerging health conditions, such as Bell's Palsy, from test subjects who were administered respective vaccines, as it may imply future concerns for public health of different socioeconomic conditions.

The significance of therapeutic modalities, including medications and vaccines, greatly impact transmission and infection rates of Covid-19 by enhancing immune support. Proceeding studies should focus on lengthened evaluation periods with respect to an individual's social background. This may allow a variety of results that may apply to different populations rather than a specific subset of patients, so preceding approaches can understand why particular individuals are impacted from SARS-CoV-2 (either minor or severe disease). In addition, studies should aim to address rising concerns of rapid outbreak of various COVID-19 variants

that may need individual vaccines for a subject's immune health and asymptomatic infection that may be unsusceptible to current vaccine administration [107-114].

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