Review

Unravelling Insights into the Evolution and Management of SARS-CoV-2: A Comprehensive Review

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Unravelling Insights into the Evolution and Management of SARS-CoV-2: A Comprehensive Review

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Abstract: Worldwide, the COVID-19 pandemic, which was brought on by the brand-new coronavirus SARS-CoV-2, has claimed a sizable number of lives. Despite the urgency, COVID-19 does not have any particular antiviral treatments at this time. As a result, scientists are concentrating on repurposing already existing antiviral medications or creating brand-new ones. The SARS-CoV-2 main protease, which is necessary for viral replication, has been identified as a possible target for a family of medicines called main protease inhibitors (MPIs). Studies of the major proteases from SARS-CoV and MERS-CoV, which have remarkably similar structures and functions to SARS-CoV-2, have provided insight for the creation of MPIs. By analyzing the MPI trials for SARS-CoV and MERS-CoV, this review sheds light on the possible therapeutic uses of MPIs for COVID-19. The review talks about how MPIs work, how effective they are against SARS-CoV and MERS-CoV, and how safe they are. The paper also emphasizes current developments in the creation of MPIs for SARS-CoV-2, including as computational studies, in vitro and in vivo research, and clinical trials. According to the review, there is a lot of hope for MPIs in the treatment of COVID-19, and numerous medications are in the works. Although more research is needed to assess their safety and effectiveness in clinical settings, these medications may offer patients with COVID-19 a much-needed therapeutic option. The review also emphasizes the importance of ongoing research into the structure and function of the SARS-CoV-2 main protease, as this information will be critical for the development of effective MPIs and other antiviral drugs in the future.

Keywords: main protease inhibitors; SARS-CoV-2; COVID-19; mutations; vaccines; therapeutics; drug repurposing; management strategies

Introduction

The global pandemic that was caused by the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019 caused a considerable amount of illness and mortality globally (1,2). The coronavirus family, which also contains the viruses causing Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), includes SARS-CoV-2. SARS-CoV-2's fast spread and mutation have posed a serious challenge to the global public health and medical communities (3). Since its appearance, a lot of work has gone into figuring out how SARS-CoV-2 is transmitted, how it presents clinically, and how to treat it (4). Understanding the virus' evolution and epidemiology has laid the groundwork for the creation of solutions to stop its spread and lessen the pandemic's negative effects on public health and the global economy (5).

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The creation of efficient prevention and management plans is significantly hampered by the SARS-CoV-2 virus's continuing evolution (6). In order to provide efficient treatments and vaccines, scientists and researchers from all over the world have made enormous efforts to understand the mechanics of viral reproduction and mutation (7). A number of vaccines with high success rates against SARS-CoV-2 have been developed as a result of these efforts, and several clinical trials are ongoing to investigate additional therapeutic possibilities (8).

Due to the disease's variable clinical symptoms and uncertain course, SARS-CoV-2 care has proven difficult (9). Fever, coughing, and shortness of breath are the most typical signs of COVID-19, the illness brought on by SARS-CoV-2. However, the virus can also cause severe respiratory distress, pneumonia, and multi-organ failure (10,11). The management of COVID-19 requires a multidisciplinary approach, including supportive care, oxygen therapy, and antiviral treatments (12).

With severe morbidity and mortality, as well as extensive interruptions to everyday life and economic activities, SARS-CoV-2 has had an unprecedented worldwide impact (13). The pandemic has made it clear how crucial it is for nations to work together and have a coordinated public health response to face new infectious illnesses (14). A thorough knowledge of the virus's evolution, transmission, and clinical symptoms is necessary for the creation of efficient SARS-CoV-2 preventive and management measures.

We intend to offer a summary of the current knowledge about SARS-CoV-2, including its evolution, transmission, clinical manifestation, and management, in this in-depth review. We will review the most recent findings on the processes of viral replication, mutation, and transmission as well as the status of available therapies and vaccine research. Additionally, we will explore the global impact of the pandemic and the public health response to mitigate the spread of the virus.

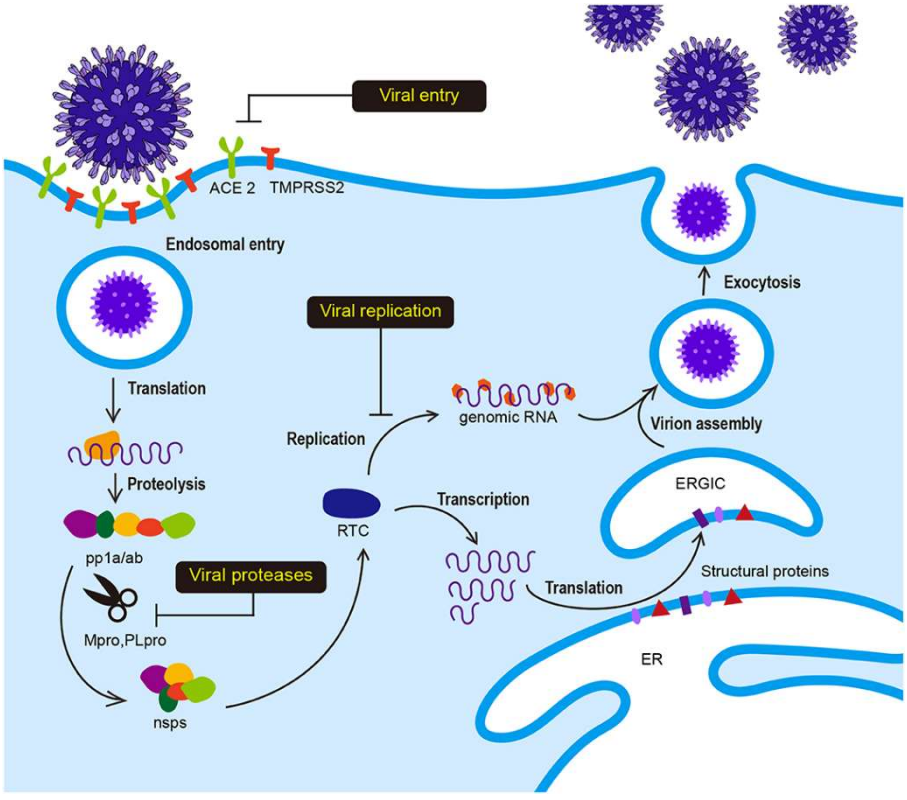

Figure 1. viral life cycle of SARS-CoV-2 (adapted from https://www.frontiersin.org/articles/10.3389/fmicb.2020.01723/full).

I. Clinical description of SARS-CoV-2

Despite containment efforts, the COVID-19 pandemic, which started in Wuhan, China in December 2019, spread fast throughout the world (15,16). The respiratory system is the primary target of COVID-19 symptoms, which very frequently include cough and respiratory discomfort.

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Fever is present in virtually all cases (17). As with its predecessors SARS-CoV and MERS-CoV, COVID-19 is brought on by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has caused a global health emergency and high rates of morbidity and mortality (18). As of March 27, 2020, COVID-19 had a mortality rate of 1% to 5% and had affected over 510,000 people in 199 countries and territories (19). The World Health Organization has classified COVID-19 as a Public Health Emergency of International Concern due to the pandemic's intensity (20).

Similar to the SARS and MERS outbreaks, respiratory symptoms are the most frequent COVID-19 clinical signs (21). Fever, cough, and respiratory distress are the most typical clinical manifestations of the virus, while some patients may also exhibit unusual symptoms such diarrhea, headaches, and myalgia (22). The condition can be mild or catastrophic in severity, and some patients will need mechanical breathing and intensive care (22,23). Additionally, secondary infections like bacterial pneumonia, which can worsen patient outcomes, can affect the clinical course of COVID-19 (24).

Understanding the clinical characteristics of the illness is essential for providing appropriate medical care and creating successful preventative and treatment plans as the COVID-19 pandemic spreads. Healthcare specialists throughout the world are working nonstop to contain the pandemic due to the severity of the illness and its potential for spread, which have made it a global health emergency. Critical elements in the fight against COVID-19 include quick diagnostic tests, sufficient personal protective equipment for healthcare workers, and the creation of efficient vaccinations and antiviral treatments. To guide public health policy and stop the spread of the disease, more study is needed into the clinical manifestation and pathogenesis of SARS-CoV-2.

II. SARS-CoV-2 prevalence and pathology

It is thought that coronaviruses like SARS-CoV, MERS-CoV, and SARS-CoV-2 were first discovered in bats and spread to humans via intermediate hosts like civet cats and camels (25). The first instances of human-to-animal transmission were recorded in Hong Kong in February 2020, but the COVID-19 pandemic has shown that companion animals like cats and dogs can also be susceptible to the virus (26). In addition, SARS-CoV-2 has been detected in monkeys, white-tailed deer, and minks, indicating a wider spectrum of possible hosts. Numerous animal species, including ferrets, hamsters, macaques, and baboons, have been shown to be susceptible to SARS-CoV or SARS-CoV-2 infection in experimental infection studies (27).

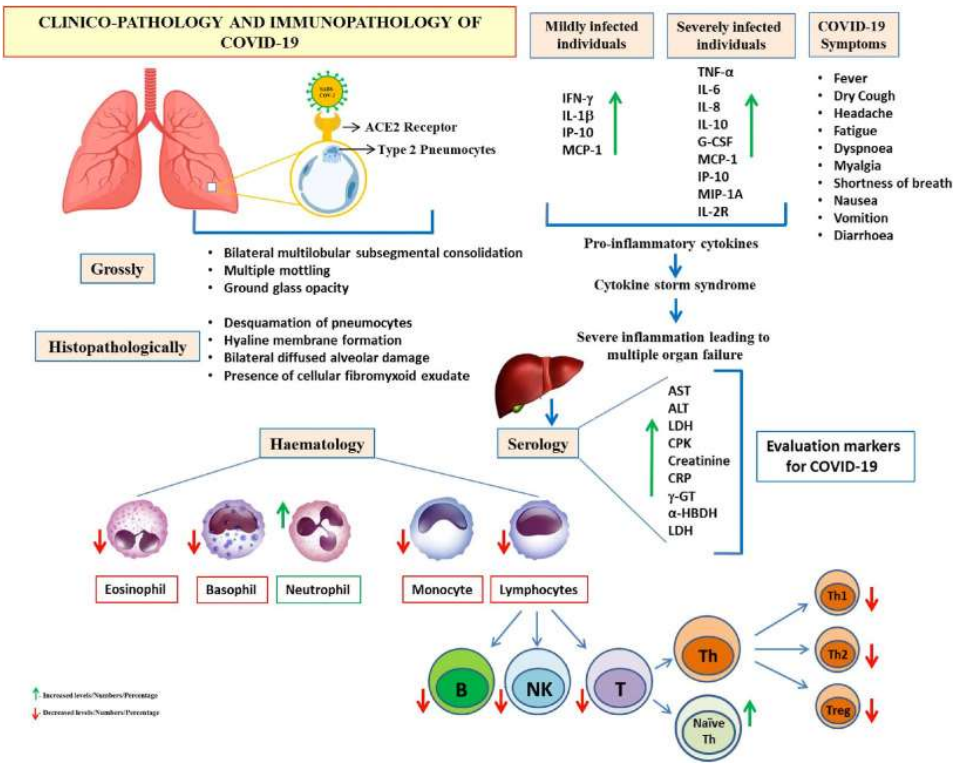

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Figure 2. An overview of COVID-19 clinical pathology, pathogenesis and immunopathology (adapted from https://www.sciencedirect.com/science/article/pii/S1477893920302349#fig2).

II.1. SARS-CoV-2 transmission, clinical presentation, and risk factors for severe disease and fatality

The signs and symptoms of COVID-19 can include pneumonia, acute respiratory distress, dry cough, tiredness, and fever. There have been reports of gastrointestinal involvement, and the discovery of viral RNA in fecal samples raises the possibility of fecal-oral transmission. Isolation and medical monitoring are essential preventative measures since asymptomatic carriers can unintentionally spread the infection to others A median hospital stay of 12 days is required for 20% of confirmed COVID-19 patients. 25% of patients in hospitals require acute critical care (30). Adults 55 and older have been the main demographic for severe COVID-19 cases. Mortality risk increases gradually with a mortality rate of 1.4–4.9% in the 55–74 age group, 4.3–10.5% in the 75–84 age group, and 10.4–27.3% in the 85–plus age group (31). People who have underlying medical conditions like cardiovascular disease, diabetes, liver, kidney, malignant tumors, or a suppressed immune system are more likely to develop a severe form of the illness and die from it (32).

According to the available data, SARS-CoV-2 is a naturally occurring virus that is mainly spread by inhaling cough droplets (33). Another important method of transmission occurs when hands that have come into contact with droplets-contaminated surfaces touch the face, eyes, or nose. Despite the lack of certainty regarding SARS-CoV-2's seasonality, mounting evidence points to a potential role for climate factors in the spread of the virus.

There are three stages of SARS-CoV-2 clinical pathology: mild, severe, and critical, with critical being the stage that results in mortality (34). Adults who are infected typically show no symptoms or just mild, temporary symptoms, whereas those who show symptoms are most contagious the day before symptoms appear (35,36).

With a typical incubation time of 4-6 days, COVID-19 clinical signs include respiratory and intestinal problems (37). It is difficult to detect transmission chains and conduct subsequent tracing since the clinical symptoms are less severe than those associated with SARS and MERS infections. Severe COVID-19 symptoms are more likely to develop in older, immune-compromised people with pre-existing diseases such cardiovascular disease, hypertension, asthma, and diabetes (27,38).

The signs and symptoms of COVID-19 can include pneumonia, acute respiratory distress, dry cough, tiredness, and fever (39). There have been reports of gastrointestinal involvement, and the discovery of viral RNA in fecal samples raises the possibility of fecal-oral transmission. Isolation and medical monitoring are essential preventative measures since asymptomatic carriers can unintentionally spread the infection to others (40). To stop the virus's cycle of spread, preventive measures have been put in place, including limiting population movements, preventing large gatherings, and closing educational institutions.

Most individuals who recovered from COVID-19 disease had severe lung damage by the tenth day after the onset of symptoms (41). In addition, pneumonia linked to SARS-CoV-2 infection was observed to include a significant portion of the lower respiratory tract (42).

II.2. Profile Characteristics and Prognostic Markers in COVID-19/SARS-CoV-2

Aspartate aminotransferase and hypersensitive troponin I levels are high in COVID-19 individuals, and they also exhibit unique blood laboratory profile traits such lymphopenia, leukopenia, thrombocytopenia, and RNAaemia (43). Procalcitonin levels start out normal but gradually rise as the disease progresses, suggesting the risk of secondary infections. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels have increased in COVID-19, whereas platelet count and procalcitonin levels are normally within range. Aspartate aminotransferase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), creatinine, and prothrombin time, which can be employed as diagnostic markers, are however associated with higher levels in severe instances (43,44).

Prognostic indicators for COVID-19 include lymphopenia, neutrophilia, increased levels of LDH, C-reactive protein, D-dimer, total bilirubin, hepatic transaminases, ferritin, and troponins (45).

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The number of T cells, B cells, and natural killer (NK) cells is also lowered in severe instances, as are the numbers of helper, regulatory, and memory T cells. Severe instances are marked by higher levels of proinflammatory cytokines and chemokines like IFN-, IL-1, IP-10, MCP-1, TNF-, G-CSF, IL-8, IL-10, and MIP-1A (44,45).

The release of pro-IL-1b and subsequent synthesis of mature IL-1b, which regulates fever, pulmonary inflammation, and fibrosis, are triggered by the interaction of SARS-CoV-2 with Toll-like receptors (TLR) (45). Therefore, IL-37 and IL-38 could be thought of as an appropriate therapeutic agent and may be highly beneficial in COVID-19 patients to reduce pulmonary inflammation by suppressing IL-1b and other proinflammatory IL-family members. The wide range of immunopathological effects caused by the 2019-nCoV novel human coronavirus in humans are influenced by different HLA types and different epitope binding affinities (46).

III. Discussion on postulated hypothesis on Covid-19 mutations

In an unprecedented effort to stop the COVID-19 epidemic, the scientific community from around the world has teamed up. Similar to other RNA viruses, Covid-19 exhibits a high mutation rate that can be brought on by copying errors during viral replication, recombination, or contact with agents that can neutralize the virus, like host antibodies (47,48) The transport and load of the virus to ACE2 target cells may be improved by molecular changes that lessen the damage to the viral capsid, which is crucial for safeguarding the viral genome and replications. This would increase infectivity without necessarily changing the virus' inherent pathogenicity or virulence. Mutations that increase the affinity of spike S-protein to receptors on ACE2 cells could also increase viral load and infectivity (49).

Although many SARS-CoV-2 mutations may not directly affect the virus's virulence, they may result in increased infectivity and transmissibility (50). For instance, the D614G mutation in the SARS-CoV-2 spike protein was discovered early in the epidemic and quickly took over as the predominant form everywhere (50,51). The virus's capacity to infect cells is improved by the mutation, which may also increase its transmissibility (51). Other changes to the spike protein could make the virus more resistant to antibodies produced by the host immune system or vaccines, decreasing their effectiveness (52). Therefore, it is essential to keep track of SARS-CoV-2 mutations in order to spot any potentially dangerous variants and create workable defenses.

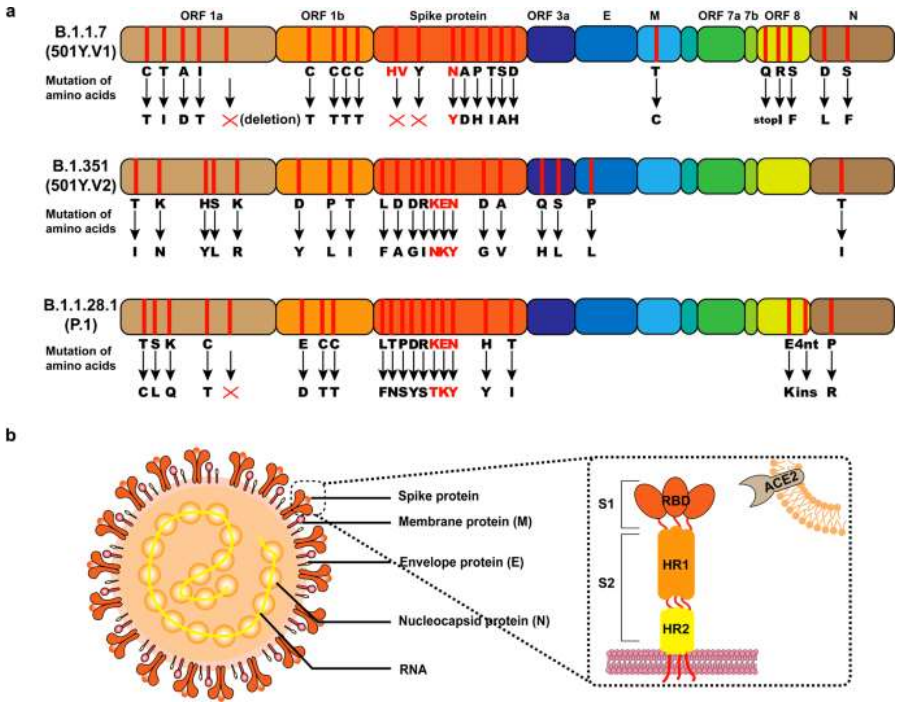

Figure 3. Information of fast-spreading SARS-CoV-2 variants and major SARS-CoV-2 structure (adapted from https://www.nature.com/articles/s41392-021-00644-x).

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Studying and comprehending the underlying principles of viral evolution is essential given the rapid evolution of SARS-CoV-2 and the high mutation rates seen (53). This information will be useful in creating efficient vaccinations and therapies that can be quickly modified to address newly discovered virus strains. The progress gained thus far emphasizes the need of ongoing multidisciplinary research and collaboration in containing the ongoing covid-19 pandemic (54). The scientific community has made tremendous progress in understanding the biology of SARS-CoV-2.

IV. Covid-19 therapies, vaccines, and other ongoing clinical trials therapies

Effective treatments and vaccines are urgently needed to combat the COVID-19 pandemic. While natural supplements like vitamin D and zinc are being looked into for their potential prophylactic benefits, supercomputers have been used to screen the library of already licensed medications for potential therapeutics against COVID-19 (55). Daily vitamin D supplements were found to protect against acute respiratory infections in a recent meta-analysis (56), whereas increased intracellular zinc concentrations have been demonstrated to hinder the reproduction of several RNA viruses (57). However, excessive intake of zinc can lead to undesirable sequelae, and it is not currently recommended to give elemental zinc supplementation above the recommended dietary allowance for the prevention of COVID-19 (57,58).

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Table 1. Table of current potential anti-SARS-CoV-2 agents.

Approved SARS-CoV-2 Vaccines						
Vaccine Name	Manufacturer	Type	Dosage	Efficacy	Target	Reference
Pfizer-BioNTech	Pfizer, BioNTech	mRNA	2 doses, 21 days apart	95%	Spike protein	Haas, Eric J., Frederick J. Angulo, John M. McLaughlin, Emilia Anis, Shepherd R. Singer, Farid Khan, Nati Brooks et al., 2021
Moderna	Moderna	mRNA	2 doses, 28 days apart	94.1%	Spike protein	Baden, L.R., El Sahly, H.M., Essink, B., et *al.*, 2021.
Johnson & Johnson	Johnson & Johnson	Viral vector	1 dose	72% (in the U.S.)	Spike protein	Creech, C.B., Walker, S.C. and Samuels, R.J., 2021.
AstraZeneca	AstraZeneca, University of Oxford	Viral vector	2 doses, 4-12 weeks apart	70.4% (average)	Spike protein	Keeling, M.J., Moore, S., Penman, B.S. and Hill, E.M., 2023.

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SARS-CoV-2 therapeutics						
Drug name	Manufacturer	Type	Target	Antiviral Agent	Status	References
Remdesivir	Gilead Sciences	Antiviral	RNA polymerase	Nucleotide analogue	FDA-approved for emergency use in hospitalized patients	Pruijssers, A.J., George, A.S., Schäfer, A., *et al.*, 2020.
Baricitinib	Eli Lilly and Company	Anti-inflammatory	AP-1	Janus kinase inhibitor	FDA-approved for emergency use in combination with remdesivir	Poduri, R., Joshi, G. and Jagadeesh, G., 2020.
Tocilizumab	Roche	Anti-inflammatory	IL-6	Monoclonal antibody	FDA-approved for emergency use in hospitalized patients	Fu, B., Xu, X. and Wei, H., 2020.
Sotrovimab	GlaxoSmithKline, Vir Biotechnology	Monoclonal antibody	Spike protein	Monoclonal antibody	FDA-approved for emergency use in high-risk individuals	Gupta, A., Gonzalez-Rojas, Y., Juarez, E., *et al.*, 2021.
Molnupiravir	Merck & Co.	Antiviral	RNA polymerase	Nucleotide analogue	Currently under review for emergency use authorization	Ashour, N.A., Abo Elmaaty, A., Sarhan, A.A., *et al.* 2022.

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Ongoing clinical trials for SARS-CoV-2						
Study name	Sponsor	Type	Phase	Target	Antiviral Agent	Status
ACTIV-6	NIH	Therapeutic	3	Various	Various	Ongoing Naggie, S., Boulware, D.R., Lindsell, C.J., et al., 2023.
COMET-ICE	NIAID, Lilly	Therapeutic	3	Various	Various	Ongoing Gupta, A., Gonzalez-Rojas, Y., et al,2021.
REGN-COV2	Regeneron	Therapeutic	3	Spike protein	Monoclonal antibody	Ongoing Baum, A., Ajithdoss, D., Copin, R., *et al.*, 2020.
COV-BOOST	University of Oxford	Vaccine	2/3	Spike protein	N/A	Ongoing Chavda, V.P. and Apostolopoulos, V., 2022.
COV-FLU	Novavax	Vaccine	2/3	Influenza virus	N/A	Ongoing

						Cao, K., Wang, X., Peng, H., Ding, *et al*., 2022.

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Current knowledge of viral genomes and transcriptomics is essential to addressing the global catastrophe brought on by the unique SARS-CoV-2 virus (59). This knowledge can enable the creation of therapeutic approaches, new drugs, and vaccines as well as insights into the pathogenicity, transmission, and epidemiology of viral infections (60). The review also offers a comprehensive list of sources that will enable researchers to access a wide range of databases concerning SARS-CoV-2 OMICs and therapeutic strategies pertaining to COVID-19 treatment.

In conclusion, there has been extensive multidisciplinary research conducted all around the world due to the urgent need for new treatments and vaccines against COVID-19 (61). The research of the prophylactic advantages of natural supplements, as well as the development of structure-based designs of decoy ligands that can disrupt important processes mediating infectivity, have showed promise in the fight against the virus (62). For gaining insights into viral pathogenicity, transmission, and epidemiology as well as the origins and global spread of the virus, up-to-date knowledge on viral genomes and transcriptomics is crucial (63). In the ongoing fight against COVID-19, this understanding will be crucial in developing methods for therapeutic interventions, medication discovery, and vaccine development.

V. Drug Repurposing for COVID-19

Drug repurposing has become a vital tactic in the pursuit of successful COVID-19 treatment. It is being looked at old antiviral medications and substances that are either approved or being researched for use against other viral infections (64). SOLIDARITY is a multinational clinical trial being conducted by the World Health Organization to look into the efficacy of repurposed medications in treating COVID-19 (65). Drugs like lopinavir-ritonavir, chloroquine, remdesivir, and favipiravir are among those being looked into. These medications' possible applications in the treatment of COVID-19 will be discussed in this article (66).

The FDA has approved the medication combination lopinavir-ritonavir for the treatment of HIV-1. Ritonavir boosts the efficacy of lopinavir by delaying the rate at which it is metabolized in the liver, whereas lopinavir is a protease inhibitor that prevents virus particle formation (67). The medication has shown some promise in treating COVID-19, but more clinical trial findings are needed to confirm its effectiveness (68).

An RNA-dependent RNA polymerase inhibitor called favipiravir has shown promise in combating influenza and other viral diseases (69). Initial clinical trials carried out in Shenzhen and Wuhan have demonstrated its efficacy against SARS-CoV-2 (70). Favipiravir-treated patients had a stronger therapeutic response, especially in terms of faster viral clearance and a higher rate of improvement in chest imaging (71). The National Medical Products Administration of China has approved favipiravir as the first anti-COVID-19 medication in the nation in light of these encouraging findings (70,71).

Cheap medications like chloroquine and hydroxychloroquine are used to treat autoimmune disorders and malaria. They are thought to reduce endosomal pH, which prevents virus replication (72). Recent research has demonstrated their effective antiviral activity against SARS-CoV-2. Chloroquine treatment for COVID-19 has been shown in clinical trials to be effective in reducing pneumonia exacerbations and to have a tolerable safety margin (73). An analog of chloroquine called hydroxychloroquine has been proven to hasten recovery and virus clearance in COVID-19 patients and has a better clinical safety profile (74).

Nucleotide analogue prodrug Remdesivir provides broad-spectrum antiviral action against a variety of RNA viruses (75). In contrast to protease inhibitors, which focus on the late steps of virus reproduction, it inhibits RNA-dependent RNA polymerase, preventing an early stage of viral replication (76). It has been utilized as an experimental medicine for the treatment of Ebola, MERS-CoV, and SARS-CoV-2 and has demonstrated to limit replication of SARS-CoV-2 in animal models (77). Clinical improvement was seen in 68% of patients treated with remdesivir in a sample of patients hospitalized for severe COVID-19 (78). Remdesivir has not yet received approval to treat COVID-19, and more studies are needed to determine its effectiveness (79).

To sum up, medication repurposing has been used in the effort to treat COVID-19. The effectiveness of repurposed medications such lopinavir-ritonavir, chloroquine, remdesivir, and

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favipiravir is currently being studied in the WHO SOLIDARITY trial (65). Although some patients with COVID-19 have responded favorably to these medications, more studies are required to confirm their efficacy and identify the most potent drug combinations (80).

V.1. Vaccine Development

One of the main areas of concentration for scientific study around the world is the development of a vaccine against SARS-CoV-2. Inactivated and attenuated vaccines, protein subunit and virus-like particle vaccines, viral vector-based vaccinations, and more recent DNA- and RNA-based vaccines are a few of the techniques to vaccine creation that are being studied (81). All approaches are being developed simultaneously to create an effective vaccine, and each has advantages and disadvantages of its own. Since it is present in all coronaviruses encountered and is exposed to the immune system of a person, the spike protein is thought to be the most vaccine-promising among the structured proteins of the virus because it allows the body to mount an immune response against it and retain it for future defense (82).

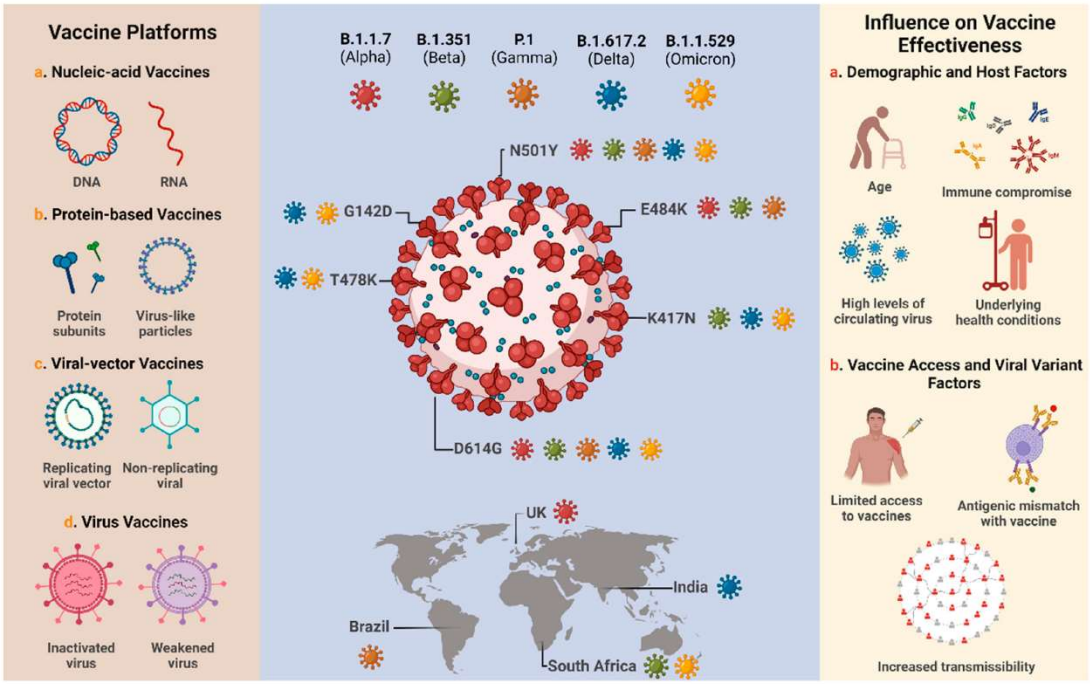

Figure 4. Overview of the major technology platforms used for COVID-19 vaccine development, the SARS-CoV-2 variants of concern and their respective spike protein mutations, and the factors that may influence the effectiveness of available vaccines. Adapted from Tregoning et al. [44] and Mistry et al. [94]. Created with BioRender.com (accessed on 17 February 2022). (adapted from https://www.mdpi.com/2076-393X/10/4/591).

The mRNA-1273 vaccine, a revolutionary RNA-based vaccine created by Moderna Therapeutics, is the first to start clinical testing (83). In order to inject the nanoparticles into the body, it exploits a portion of the spike protein genetic code (83,84). The first phase I clinical trial of this vaccine, which had shown promise in animal research, began on March 16, 2020, in partnership with the NIH, and involved 45 healthy people between the ages of 18 and 55 (83,84). Due to pipeline, capacity building, and regulatory challenges, even if the clinical trials are successful, it will be a while before the product can be made available to the general public. There are numerous additional mRNA-based vaccines in various phases of development (85).

To address viral infection, further cutting-edge vaccine strategies and treatment interventions are also being explored. For instance, Codagenix developed a live-attenuated vaccine employing a reverse technique by changing the viral sequences by substituting its optimized codons with non-optimized ones to weaken the virus (86), and Inovio Pharmaceuticals' INO-4800 is a DNA-based

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vaccination using the spike gene (87). The Milken Institute COVID-19 Treatment and Vaccine Tracker provides information on the several vaccinations that are currently being developed, along with their present progress (88). Numerous innovative initiatives are being supported by significant international vaccine funding organizations in an effort to select the most promising ones for future mass production.

V.2. Experimental Therapeutic Interventions

V.2.1. Convalescent Plasma (CP) Therapy

Since the start of the pandemic, there has been active research into experimental therapeutic interventions for COVID-19. Convalescent Plasma (CP) therapy, one of the conventional methods, has been used successfully for more than a century to treat infectious diseases like SARS, MERS, and H1N1 (89). In order to provide this treatment, neutralizing antibody-rich plasma from a recovered patient is extracted and given to the infected patient (90). Significant improvement has been seen in preliminary tests on patients with severe COVID-19, and further clinical trials are still being conducted. Researchers are also profiling specific antibodies from recovered patients in order to create functional antibodies as a COVID-19 treatment, in addition to CP therapy (91). More than 500 distinct antibodies were found in the serum of a recovering COVID-19 patient, and companies like AbCellera and Eli Lilly are collaborating to create medicines based only on human IgG1 mAbs (92).

In addition, cutting-edge methods for treating COVID-19, such as aerosolized siRNAs and nanoviricides, are being developed (93). A technique created by Alnylam Pharmaceuticals that delivers aerosolized siRNAs directly to the lungs is undergoing in vitro and in vivo testing (94). On the other hand, "virucidal nanomicelles" are being chemically attached to the S protein to form nanoviricides (95). Additionally, because complement factor 5a has been found to be the primary contributor to tissue damage in patients, InflaRx and Beijing Defengrei Biotechnology are developing human IgG1 mAbs against it (94,95). Such antibodies have already received Chinese government approval for clinical trials. These cutting-edge treatments may be able to effectively cure COVID-19 and help to contain the current pandemic (96).

V.2.2. Soluble Human Angiotensin-Converting Enzyme 2 (ACE2)

Due to its capacity to prevent SARS-CoV-2 replication, soluble human angiotensin-converting enzyme 2 (ACE2) has become recognized as a potential COVID-19 treatment option (97). The virus enters human cells through the cellular receptor ACE2, hence inhibiting this connection may be a useful therapeutic approach (98). Recent in vitro investigations have demonstrated the therapeutic potential of human recombinant soluble ACE2 (hrsACE2), which can considerably lower viral loads in Vero cells and block virus infection in constructed human blood arteries and kidney organoids (99,100). These results suggest that hrsACE2 could be used to protect patients from lung injury and SARS-CoV-2 infection by preventing viral entry into target cells (99).

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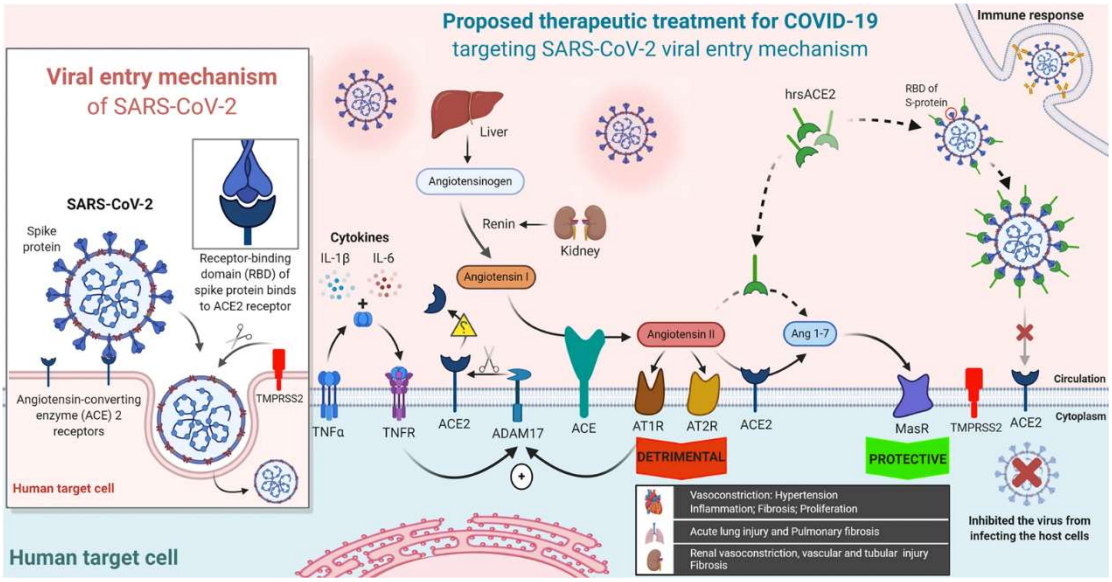

Figure 5. Schematic diagram of the renin-angiotensin system and the proposed therapeutic treatment for COVID-19 targeting SARS-CoV-2 viral entry mechanism (adapted from https://www.nature.com/articles/s41392-020-00374-6).

In the fight against COVID-19, using soluble ACE2 as a therapeutic intervention shows promise (101). hrsACE2 has the ability to prevent viral replication and lower viral loads by preventing the communication between the virus and its host receptor (102). Additionally, hrsACE2 has been demonstrated to be effective against SARS-CoV-2 in human blood vessels and kidney organoids, suggesting that it may be able to shield patients from the virus's severe lung damage (103). As a result, the therapy of COVID-19 patients may benefit from the use of soluble ACE2. However, more investigation is required to establish its security and effectiveness in clinical trials (104).

VI. Non-Pharmacological Interventions

To successfully stop the spread of SARS-CoV-2, neither vaccinations nor particular pharmaceutical treatments are yet available (105). Effective pharmaceutical treatments and vaccinations for COVID-19 are anticipated to take several months to a year to develop. Implementing non-pharmacological interventions (NPI) is therefore the most efficient public health response to the ongoing outbreak (63,106). NPIs include early case detection and isolation, in-depth contact tracing of suspected secondary cases, travel prohibitions, tight contact reductions, physical segregation, increased cleanliness, and routine hand washing (107). Closing non-essential public areas, services, and facilities is one of these strategies. Another is for educational institutions to switch to digital learning modalities, and for enterprises to implement self-isolation/work from home programs (63). According to modeling projections, integrated NPIs are anticipated to have the biggest and fastest impact on reducing the reproductive number and slowing the rate of viral transmission if they are adopted early in the outbreak (108). The creation of efficient treatment interventions and vaccines is made possible by the knowledge gained from these NPIs, which are interim measures while the effort to better understand viral genomes continues (63,107).

Despite the fact that there aren't any specific medications or vaccines for SARS-CoV-2 yet, applying NPIs can drastically reduce the virus's transmission (109). To reduce transmission, such measures include early detection of infected persons, seclusion, and tracking of their close connections. Travel restrictions, social withdrawal, enhanced hygiene, and consistent hand washing can also help stop the virus's spread. Schools may need to switch to digital learning, and non-essential public areas and services may need to be shut down in order to execute these measures (110). Work from home efforts and self-isolation may also be required for enterprises. NPIs have the ability to reduce viral reproduction and delay viral transmission if implemented early, which would lessen the

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impact of the outbreak. However, while NPIs are effective in the interim, efforts must continue to develop effective therapeutic interventions and vaccines to address the ongoing crisis (111).

VII. Future Directions for COVID-19 Research

Reduce infections, lower the strain on healthcare systems, and lessen the pandemic's social and economic effects are the three goals of efforts to limit the COVID-19 pandemic. Non-pharmacological therapies will continue to serve as the main line of protection while we wait for viable vaccinations. Therefore, projections and planning for anticipated healthcare capacity can be informed by accurate and current data on the daily number of new cases and the case characteristics (112). The BCG childhood vaccine as well as national immunization programs may have an impact on the pandemic's intensity. COVID-19 will undoubtedly have a large worldwide impact that could take a long time to reverse (113). To combat upcoming pandemics, healthcare systems must to think about including efficient regulatory mechanisms. The approach to the present pandemic has already been influenced by lessons learned from the earlier SARS-CoV outbreaks in Hong Kong, Singapore, and Taiwan (114,115). With regard to the pathogenicity, transmissibility, and therapeutic response of the viral isolates, genomic characterisation will also have effects on regional and global populations. Before an outbreak occurs, AI should be tested to predict and track infections. This could help us get ready for outbreaks in the future (63).

In conclusion, the international community must cooperate to make the greatest technology resources available in order to combat the current pandemic and maintain readiness for potential future epidemics (116). For the development of efficient vaccinations and the discovery of new drugs, it is essential to comprehend the genetic makeup of viral strains (117). Planning and predictions for expected healthcare capacity should be guided by data-driven initiatives (118). To combat upcoming pandemics, effective regulatory measures and national immunization strategies should be taken into consideration (63,119). To anticipate and track infections before the outbreak occurs, AI should be tested. The social, cultural, and economic infrastructures will be significantly impacted by the COVID-19 pandemic over the long term, thus it is crucial to draw lessons from this experience and improve readiness for breakouts in the future (120,121).

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