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Review

Unmasking Vulnerabilities in the Age of COVID-19: A Comprehensive Review

Mohd Mustafa[1], Kashif Abbas[2], Waleem Ahmad[3], Rizwan Ahmad[1], Sidra Islam[4], Irfan Qadir Tantri[5], Moinuddin[1], Md. Imtaiyaz Hassan[6], Mudassir Alam[2], Nazura Usmani[2] and Safia Habib[1]*

[1]Department of Biochemistry, J.N. Medical College, Faculty of Medicine, Aligarh Muslim University, Aligarh, India

[2]Department of Zoology, Faculty of Life Sciences, Aligarh Muslim University, Aligarh, India

[3]Department of Medicine, J.N. Medical College, Faculty of Medicine, Aligarh Muslim University, Aligarh, India

[4]Department of Inflammation & Immunity, Lerner Research Institute, Cleveland, Clinic, Cleveland

[5]Department of Biochemistry, School of Biological Sciences, University of Kashmir, Srinagar, India

[6]Structural Biology Laboratory, Center for Interdisciplinary Research in Basic Sciences, Jamia Millia Islamia, New Delhi, India

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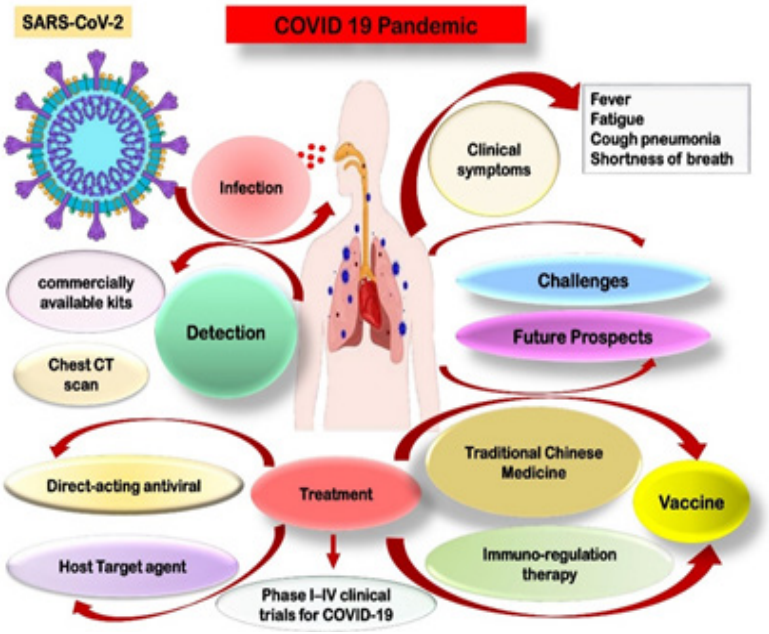
***Corresponding author:** Dr. Safia Habib, Department of Biochemistry, J.N. Medical College, Aligarh Muslim University, Aligarh 202002, India, E-mail: saf_h75@yahoo.co.in

Graphical Abstract



ABSTRACT

The COVID-19 pandemic, driven by the novel coronavirus SARS-CoV-2, has evolved into an unprecedented global health crisis, encompassing zoonotic origins, a shift in human-to-human transmission dynamics and global dissemination, The review navigates through the complexities of COVID-19. Beyond mild respiratory symptoms, the clinical spectrum includes severe conditions like multi-organ failure, pneumonia and acute respiratory distress syndrome (ARDS). Critical evaluation of COVID-19 diagnostic techniques, including PCR, antigen tests and serological assays, emphasizes their pivotal role in disease detection, management, contact tracing and containment. In the therapeutic domain, the review explores treatments such as antivirals, immunomodulatory therapies and repurposed pharmaceuticals, with a spotlight on vaccine development for epidemic containment and herd immunity. Despite progress, global healthcare systems face formidable challenges, including equitable vaccine distribution, disinformation combat, viral mutation management and strategic planning for future outbreaks. A comparative analysis of SARS highlights the need to distinguish between these diseases for effective epidemic management. The study aims to provide profound insights into the diverse nature of COVID-19, fostering a deeper understanding and guiding future research and public health initiatives.

Keywords: COVID-19, Zoonotic spillover, Pandemic, Emerging variants, SARS-CoV-2, Vaccine, Clinical manifestations

1. Introduction

The SARS-CoV-2 virus, which caused the SARS epidemic in 2002–2004, is the source of the current pandemic, which is still lurking. Real-time observation of ongoing evolutionary processes has provided a significant understanding of SARS-CoV-2 diversification. Numerous variations have emerged as a result of this diversification, each set apart by unique traits like immunological evasion, severity and transmissibility. Changes in immune profiles, human migration and infected individuals are all part of the complex evolutionary path that is intimately connected to ecological dynamics and the events of transmission[1]. Among the 180 identified species of RNA viruses capable of infecting humans, an average of two new species emerge each year. RNA viruses have extensively spread among humans, other mammals and occasionally birds, across both epidemiological and evolutionary timelines. Notably, 89% of human-infective species are zoonotic and a considerable proportion of the remaining species trace their origins back to zoonotic sources. The pace at which mutations are created and propagated across populations is the most important factor in viral evolution[2]. Natural selection also helps to fix favourable mutations and improve transmissibility[3]. However, viral evolution becomes complicated when viruses reproduce and develop inside humans while adapting to effective human-to-human transmission. As viral lineages evolve, antigenically distinct strains may emerge at higher organizational levels[4]. This article aims to explore the evolutionary dynamics of SARS-CoV-2 across various scales. This encompasses examining the stages of the COVID-19 (coronavirus disease 2019) pandemic, identifying crucial factors influencing the virus's evolution, exploring hypotheses surrounding the emergence of statistically significant variants and contemplating potential evolutionary pathways that could impact public health in the future. Considering the substantial role of the SARS-CoV-2 virus in triggering the COVID-19 pandemic, a comprehensive investigation into the infection and its repercussions for public health is essential. The review also delves into the transmission of the SARS-CoV-2 virus from patient to host, the utilization of mathematical models for predicting the risk of viral aerosol/droplet transmission, potential pathways for viral entry into the human host and the cellular mechanisms underlying these processes.

Also, highlights COVID-19 clinical symptoms and available diagnostic approaches for detecting the virus. The requirement for effective treatment techniques, such as vaccine development and medication repurposing, is emphasized here. Given the considerable study on COVID-19 and the available literature, it appears difficult to address every element. The article offers a comprehensive examination of diverse facets concerning the COVID-19 outbreak. It covers a wide range of topics, such as preventative measures against the virus, clinical characteristics of symptomatic and asymptomatic individuals, estimations of the infection and incubation periods, the immune responses that the virus elicits in humans and the relationship between pre-existing comorbidities and COVID-19 mortality. Furthermore, the article provides a historical framework for understanding pandemics, tracing their evolution from confined outbreaks to global epidemics, starting in the 16th and 19th centuries. It delves into zoonotic origins, elucidating the transmission of zoonoses from animals to humans, with illustrative examples like HIV/AIDS, Ebola and historical influenza strains. The SARS-CoV-2 virus exhibits significant genetic similarities to pangolin coronaviruses and bat betacoronaviruses, indicating that the ongoing COVID-19 pandemic has its origins in an animal reservoir[5]. As the battle against COVID-19 continues, the acquisition of knowledge and understanding remains indispensable in formulating efficacious strategies to safeguard global public health.

2. Emergence and spread of COVID-19 (coronavirus disease 2019)

Several pneumonia cases with an unclear cause emerged in late December 2019, in Wuhan, Hubei Province, China[6]. The afflicted individuals exhibited clinical signs of fever, cough, dyspnea, chest pain and bilateral lung infiltration, symptoms of viral pneumonia, which were comparable to those in SARS and MERS[7]. The Huanan Seafood Wholesale Market, a wet market in Wuhan's downtown known for selling seafood and live animals, including poultry and wildlife **(Figure 1)**, was linked to the majority of the initial cases[8]. On December 8, 2019, the earliest case was recorded[9].

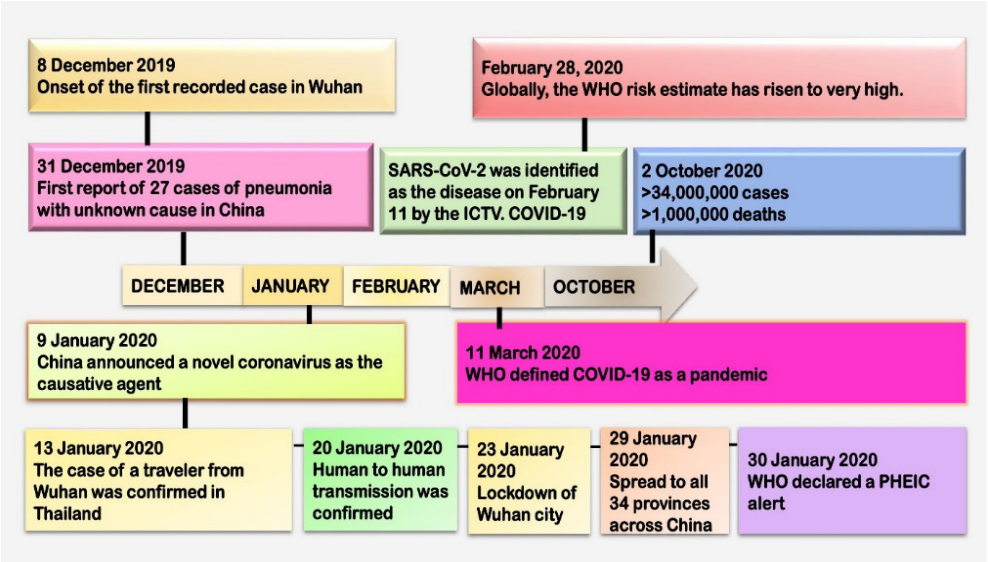


Figure 1: The figure represents the sequence of COVID-19 events recorded. The severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, has been identified as the causative agent of COVID-19 by the International Committee on Taxonomy of Viruses (ICTV). The World Health Organization (WHO) declared it a public health emergency of international concern (PHEIC).

World Health Organization (WHO) was formally notified that the Wuhan Municipal Health Commission reported an unknown pneumonia outbreak on December 31. Independent Chinese scientific teams revealed a novel beta coronavirus as the cause of this newly discovered disease[10]. The first genome sequence of the novel coronavirus was made available on January 10. The outbreak coincided with the Lunar New Year celebrations, which led to more people traveling and spreading the virus to additional Hubei province cities and ultimately to other regions of China[11]. The escalation in severity led the World Health Organization (WHO) to declare the COVID-19 outbreak as a public health emergency of international concern on January 30[12]. WHO officially designated the illness as COVID-19 on February 11[13]. **(Figure 1)** shows the timelines of these events. China imposed strict public health measures, such as a city-wide lockdown of Wuhan on January 23 with travel and transportation restrictions, to contain the outbreak[14]. The virus's high transmissibility and global travel contributed to large clusters of infections being reported in numerous countries. Consequently, on March 11, 2020, the World Health Organization (WHO) formally declared the COVID-19 outbreak to be a pandemic[15,16]. China was able to contain the virus quite well, but cases in the USA and Europe increased drastically[17].

3. SARS and COVID-19: Similarities and differences

There are notable similarities between the clinical manifestations and modes of transmission of the 2019 COVID-19 and the SARS (severe acute respiratory syndrome) virus. Both infections have the potential to manifest as rapidly progressing pneumonia. It seems that the primary mode of transmission for both is infectious respiratory droplets that are released from mucosal membranes **(Table 1)**. The viruses show comparable stability and degradation in aerosols and on various surfaces[18]. According to researchers, both viruses can live for up to two days on stainless steel and three days on plastic and their viral titers on both surfaces show comparable decay patterns[19-21]. Both SARS and COVID-19 seem to have a median incubation period of 4 to 7 days from first exposure to the start of symptoms. Furthermore, according to research, the maximum incubation time for both might be up to 14 days[22-24]. This longer incubation time adds to the difficulty of preventing the spread of these illnesses. Despite these similarities, it is important to emphasize that SARS and COVID-19 are caused by different viruses and are members of separate coronavirus subfamilies. In summary, whereas SARS and COVID-19 share clinical signs and transmission characteristics, they are caused by separate viruses and have distinct characteristics that distinguish them as distinct causative agents. Understanding these similarities and differences appears critical for successful epidemic management and prevention measures. The incubation time and length of viral shedding are critical for determining the risk of transmission, adopting isolation and quarantine measures and developing effective antiviral therapies for patients. According to recent epidemiological studies, the typical period of COVID-19 virus shedding is around 20 days, with some survivors shedding for as long as 37 days[25]. In contrast, viral RNA remained detectable in non-survivors until death. Severe COVID-19 patients may suffer viral shedding for a median of 31 days after the disease starts[26].

Table 1: SARS and COVID-19 comparisons: green highlights similarities, yellow highlights differences from COVID-19 and orange highlights feature specific to COVID-19.

SARS COVID-19		
Pre-transmissibility	NO	YES
Mild case transmissibility	NO	YES
Reproduction Number	1.7-1.9 (WHO)	2.0-2.5 (WHO)
Number of reported cases	More than 8000	692.52 million (July 31, 2023)
Number of reported deaths	774	6,903,467 (July 31, 2023)
Mortality rate	9%	3.1%

The primary mode of transmission	Infectious respiratory droplets dispersed from mucous
Ability to survive on surfaces	YES
Median incubation period	4-7 days
Maximum incubation period	14 days
Potential to cause severe respiratory infection	YES
Potential to infect CNS and brain	YES

Betacoronaviruses and alphacoronaviruses have important natural hosts in bats. RaTG13, a bat coronavirus isolated from Rhinolophus affinis in Yunnan province, China, is the closest known match to SARS-CoV-2 to date[27]. RaTG13 and SARS-CoV-2 share 96.2% of the full-length genome sequence, demonstrating a strong genetic similarity[28,29]. The fact that SARS-CoV-2 and RaTG13 share over 90% of their genome's sequence, including the variable S and ORF8 regions, is especially remarkable[28]. Their close relationship is highlighted by phylogenetic analysis, which lends credence to the theory that bats are the original host of SARS-CoV-2. SARS-CoV-2 and "RmYN02," a recently discovered coronavirus found in a Yunnan Rhinolophus malayanus bat, share 93.3% of their genome[29]. Interestingly, it shares a longer 1ab gene with SARS-CoV-2 with 97.2% identity, higher than RaTG13[30]. Furthermore, ZC45 and ZXC21, two additional bat coronaviruses that were previously discovered in eastern Chinese Rhinolophus pusillus bats, are members of the SARS-CoV-2 lineage within the Sarbecovirus subgenus[31]. These findings highlight the wide range of bat coronaviruses that are strongly associated with SARS-CoV-2, indicating that bats may be the virus's possible hosts. Recent investigations reveal that the genetic diversity observed in SARS-CoV-2 and its related bat coronaviruses stems from over 20 years of sequence evolution. Consequently, it is incorrect to categorize these bat coronaviruses as the immediate progenitors of SARS-CoV-2, despite being likely evolutionary ancestors.

Pangolins are another possible animal host connected to SARS-CoV-2. Between 2017 and 2019, several viruses related to SARS-CoV-2 were discovered in the tissues of pangolins[32]. These pangolin viruses are from two distinct sub-lineages and were independently traced in the provinces, of Guangxi and Guangdong[33-37]. Pangolins linked to various smuggling incidents have been found to have SARS-CoV-2-related coronavirus infections, suggesting that these animals may serve as hosts for the viruses[38]. Pangolins infected with coronaviruses displayed clinical symptoms and histological changes such as multiple organ infiltration of inflammatory cells and interstitial pneumonia, in contrast to bats, which typically carry the virus without obvious damage[39].

Emerging coronaviruses that are derived from bats require an intermediate host to proliferate. For example, dromedary camels and palm civets served as intermediary hosts for SARS-CoV and MERS-CoV, respectively[40]. The viruses harboured by these hosts share a genome sequence identity of over 99% with the corresponding viruses in humans[41]. The role of an intermediary host in the transmission of the SARS-CoV-2 virus, which is accountable for the COVID-19 pandemic, is under scrutiny and remains unclear. Pangolin coronaviruses exhibit only a 92% genomic identity with SARS-CoV-2, despite displaying a remarkably similar receptor-binding domain (RBD)[42]. Consequently, it is challenging to definitively ascertain whether pangolins acted as the intermediate host for SARS-CoV-2 or if they were directly implicated in the virus's emergence. The animal source of SARS-CoV-2 is presently poorly understood, with limited knowledge available on this aspect. The virus's reservoir hosts have not been identified, nor it has been determined if an intermediate host was involved in the virus's transmission to humans. Significantly, the discovery of pangolin coronaviruses, RaTG13 and RmYN02 implies that SARS-CoV-2-like coronaviruses are prevalent in animals[43-44].

In addition to wildlife, research has explored the susceptibility of domesticated and laboratory animals to SARS-CoV-2 infection. Experimental findings have demonstrated that SARS-CoV-2 can effectively replicate in cats and ferrets, particularly in the upper respiratory tract. Conversely, dogs, pigs, chickens and ducks have exhibited immunity to the virus[45]. Notably, minks have been observed to contract SARS-CoV-2, as evidenced by an outbreak on mink farms in the Netherlands, leading to severe cases of respiratory distress and interstitial pneumonia[46]. Although devoid of symptoms, two dogs in Hong Kong tested positive for spontaneous SARS-CoV-2 infection through serological and virological tests[47]. Similarly, blood samples from cats in Wuhan showed the presence of neutralizing antibodies against SARS-CoV-2, confirming the infection in cat populations. However, the possibility of transmission from cats to humans is still uncertain[48]. Ongoing comprehensive research and surveillance on animal susceptibility aim to provide a deeper understanding of potential hosts and transmission dynamics of the virus.

4. Comparative insights into SARS-CoV-2: Infectiousness, transmission and evolution

The virus accountable for acute respiratory illness, SARS-CoV-2, belongs to the coronavirus family and carries a non-segmented genome composed of positive-sense, single-stranded RNA enveloped by the viral capsid[49]. Coronaviruses (CoVs) are categorized into four genera: α, β, γ and δ-CoV[50]. While α- and β-CoV predominantly infect mammals, they can also affect birds. Human-infecting coronaviruses include HCoV-229E, SARS-CoV, HCoV-OC43, HCoV-NL63, MERS-CoV and HCoV-HKU1[51]. Infections caused by HCoV-229E, HCoV-NL63, HCoV-HKU1 and HCoV-OC43 typically result in mild respiratory symptoms, whereas SARS-CoV and MERS-CoV can lead to severe respiratory disease, occasionally resulting in death due to multiple organ failure[52]. SARS-CoV-2 shares notable similarities (over 85%) with bat-derived SARS-like coronaviruses identified as bat-SL-CoVZC45 and bat-SL-CoVZXC21[53]. In comparison to SARS-CoV and MERS-CoV, it demonstrates approximately 79% and 50% homology, respectively[54]. This evidence, combined with phylogenetic research, strongly indicates that SARS-CoV-2 originated in bats and potentially transmitted to humans through an unidentified intermediate host species. **(Figure 2)** illustrates the genomic structure, encoded structural and non-structural proteins and the primary host of SARS-CoV-2.

The pathogenesis of SARS-CoV-2 involves a complex interplay of viral and host factors. As an enveloped positive-sense single-stranded RNA virus, the genomic structure of SARS-CoV-2 comprises a significant portion (two-thirds) dedicated to an open reading frame (ORF 1a/b), encoding 16 non-structural proteins (NSPs) crucial for replication. The remaining section of the genome encodes essential structural proteins (Spike glycoprotein, Small Envelope protein, Matrix protein and Nucleocapsid protein) and accessory proteins with functions still under investigation. The S glycoprotein, essential for host cell entry, binds to the angiotensin-converting enzyme 2 (ACE2) receptor. However, the precise mechanism of membrane invagination for SARS-CoV-2 endocytosis remains unclear. Host factors, particularly ACE2 expression, influence viral tropism. The elderly and individuals with underlying health conditions are more susceptible to severe infections, partly due to age-related immune system changes and comorbidities. Host immune responses, both innate and adaptive, play a crucial role and dysregulated responses can contribute to disease severity. Additionally, genetic factors contribute to interindividual variability in susceptibility and disease outcomes. A comprehensive understanding of these viral and host elements is crucial for developing effective therapeutic interventions and vaccines against SARS-CoV-2. Ongoing research continues to unveil additional details about the intricate virus-host interactions shaping the pathogenesis of COVID-19. Without a doubt, expressive experimentation has shown that the virus infects people by attaching itself to respiratory system-expressed ACE2 receptors[55,56]. Overall, findings from several investigations show that SARS-CoV-2 is extremely infectious, with viral shedding commencing before symptoms develop and the virus spreading through many channels. Controlling the disease's spread is a key problem for public health initiatives.

SARS-CoV-2 is less severe in terms of morbidity and mortality than MERS and SARS, but it is more contagious. COVID-19 has a much lower mortality rate of 3.4% compared to 9.6% and 35% for SARS and MERS, respectively. COVID-19 primarily spreads through person-to-person contact, particularly between close friends and family members[57]. Numerous studies demonstrate the critical role symptomatic individuals play in COVID-19, mainly through respiratory droplet expulsion from actions like coughing or sneezing. On the other hand, nosocomial transmission was primarily responsible for the spread of MERS-CoV and SARS-CoV among healthcare personnel[58]. In MERS-CoV outbreaks, medical staff was responsible for 62%-79% of cases, whereas in the SARS case, they accounted for 33%-42% of cases. The most likely ways for a virus to spread are through direct contact with the host or interactions with an unidentified intermediate carrier[59].

The SARS-CoV-2 virus changes in a variety of ways as it grows and spreads among people. In December 2020, a noteworthy variant, VUI-202012/01, was examined due to 17 distinct alterations or mutations in its DNA. Since the discovery of the SARS-CoV-2 virus in 2019, thousands of mutations have already manifested in its genome[60]. As the pandemic continues, the continual mutation process in the population may result in the production of immunologically relevant mutations, thereby affecting vaccination effectiveness. These mutations are resulting in novel viral combinations. The COVID-19 genomics UK consortium (COG-UK) has conducted extensive epidemiological and virological investigations in response to the significant surge in COVID-19 cases recently observed in the United Kingdom (UK), particularly in South East England[61]. A novel variant was identified in viral genome sequences, forming a distinct phylogenetic grouping. This variant is distinguished by multiple spike protein mutations (deletion 69-70, deletion 144, N501Y, A570D, D614G, P681H, T716I, S982A and D1118H), accompanied by alterations in other genomic regions[62]. Although viral mutations are normal, preliminary studies show that this variant in the UK may be critical for increased transmissibility and is projected to possibly raise the reproductive number by 0.4 or more[63]. Notably, this new variety evolved during a period of increased family and social gatherings. However, there is no indication that it causes more severe infections than other variations.

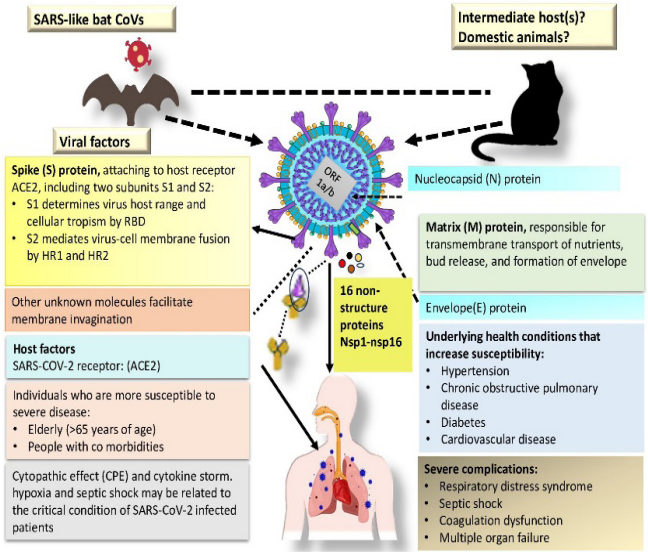


Figure 2: The figure represents the structural and genetic characteristics of SARS-CoV-2. Numerous structural proteins, including the spike glycoprotein (S), envelope (E), matrix (M) and nucleocapsid protein (N). The genetic segment ORF1ab encodes several non-structural proteins (nsp 1–16) concurrently. The host-related variables that can affect an individual's susceptibility to and the severity of a SARS-CoV-2 infection are listed in the lower section.

5. Role of ACE-2 Receptor, an Angiotensin-Converting Enzyme

SARS-CoV-2 gains entry into the human host through receptor-mediated endocytosis, a mechanism where viruses bind to specific receptors on the host cell's surface, facilitating entry. The virus's receptor-binding domain establishes a connection with the appropriate receptor on the host cell, enabling entry. Both SARS-CoV and SARS-CoV-2 utilize the angiotensin-converting enzyme-2 (ACE-2) receptor to infect cells. Earlier studies have shown that the S-protein of SARS-CoV exhibits a strong affinity for the ACE-2 receptor, serving as the entry point for the virus into host cells[64]. Figure 3 depicts the fusion of the virus with the host receptor.

The entry of SARS-CoV-2 into host cells is also mediated by S-protein priming by transmembrane protease serine-2 (TMPRSS2). This priming event is crucial for the fusion of the viral envelope with the host cell membrane, enabling subsequent viral entry. Therefore, the coordinated interplay between the ACE-2 receptor and TMPRSS2 is essential for the efficient entry of SARS-CoV-2 into the host environment. It is noteworthy that

TMPRSS2 exhibits higher expression and broader distribution compared to ACE-2 receptors, suggesting that ACE-2 may act as a limiting factor during the initial infection phase. While TMPRSS2 is a key component for viral entry, alternate proteases, such as cathepsin B/L, may act as substitutes for TMPRSS2. Hence, the simultaneous inhibition of these proteases becomes crucial in preventing cellular entry.

The structural characteristics of the S-proteins of SARS-CoV and SARS-CoV-2 facilitate the entry of the latter into cells[65]. Studies involving human HeLa cells and animals with and without ACE-2 expression support the involvement of ACE-2 receptors in the cellular entry of the SARS-CoV-2 virus, particularly the Wuhan strain[66]. Research on SARS-CoV-2 infection of BHK21 cells indicated higher infection rates when transfected with human and bat ACE-2 receptors compared to BHK21 cells lacking ACE-2 expression[67-69]. Biophysical and structural data suggest that the ACE-2 binding affinity of the SARS-CoV-2 S-protein ectodomain is significantly greater than that of the SARS-CoV S-protein by a ratio of 10:20[70]. This difference is believed to contribute to the variance in contagiousness between SARS-CoV-2 and SARS-CoV. Although the ACE-2 and ACE-1 receptors share similarities, the ACE-2 receptor has a smaller active site and a smaller binding pocket with different amino acids, making it resistant to typical ACE inhibitors such as lisinopril, enalapril and ramipril[71].

Furthermore, there is no evidence suggesting that angiotensin receptor blockers (ARBs), like losartan, disrupt the activity of ACE-2. TMPRSS2, identified as a type II transmembrane protease, consists of distinct domains, including an intracellular N-terminal domain, a transmembrane domain, an extracellularly extending stem region and a C-terminal domain facilitating its serine protease (SP) function[72]. The serine protease activity relies on a catalytic triad, comprised of His296, Asp345 and Ser441, responsible for cleaving basic amino acid residues, particularly lysine or arginine residues, aligning with its role in cleaving the S1/S2 site in SARS-CoV-2[73].

While TMPRSS2 has been recognized for its involvement in prostate cancer and viral infections such as influenza, SARS and MERS, it has recently gained attention from drug developers. Multiple studies are underway to uncover strategies aimed at reducing TMPRSS2 expression or blocking its activity in host cell membranes, with the ultimate goal of inhibiting SARS-CoV-2 entry into host cells[74,75].

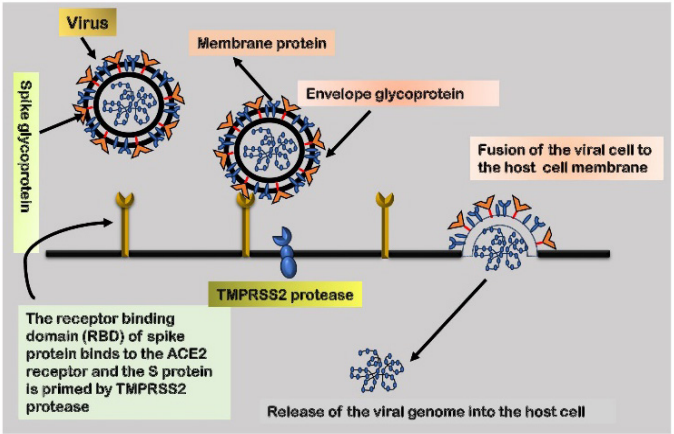


Figure 3: A representation of the SARS-CoV-2 spike protein with the host receptor and the subsequent fusion of the viral cell with the host cell membrane.

6. Diagnostic, Therapeutic Approaches and Strategies to Inhibit Viral Entry

Molecular detection of SARS-CoV-2 nucleic acid is the most accurate diagnostic approach[72]. Various commercially available kits for viral nucleic acid detection target different genes, including ORF1ab (containing RdRp), N, E or S[73]. The detection time may vary from a few minutes to several hours depending on the technology utilized. Although SARS-CoV-2 has been detected in throat swabs, posterior oropharyngeal saliva, nasopharyngeal swabs, sputum and bronchial fluid, the virus load is notably higher in samples from the lower respiratory tract[74]. Viral nucleic acid has also been detected in intestine and blood samples, even in cases where respiratory tests yielded negative results. The viral load may decrease from its peak at the onset of the illness, potentially leading to false negatives when using oral swabs[75]. It is advisable to employ multiple detection techniques to confirm a COVID-19 diagnosis.

To address the issue of false negatives, alternative detection approaches have been utilized. Therefore, for individuals with a robust clinical suspicion of COVID-19 despite an initial negative nucleic acid screening, a combination of CT scans and repeated swab testing has been recommended. Serological assays that identify antibodies to the N or S protein of SARS-CoV-2 could complement molecular diagnosis, particularly in the latter stages of the illness or for retrospective research[76,77]. The magnitude and duration of immunological responses are still unknown and the sensitivity and specificity of existing serological assays vary. When choosing and interpreting serological testing, all of these factors should be taken into consideration, possibly even extending to future assays for T-cell responses.

As of right now, neither COVID-19 nor specific antivirals that target SARS-CoV-2 have the potential to combat the disease. However, several treatments have shown some promise. Manufacturers and researchers are undertaking large clinical studies to examine new COVID-19 therapy options. As of October 2, 2020, over 405 therapeutic medicines were being developed for COVID-19, with almost 318 of them undergoing human clinical trials[78]. Potential antiviral target for the treatment of COVID-19 is depicted in **(Figure 3)**.

A crucial strategy in combatting SARS-CoV-2 infection is to hinder viral entry. Angiotensin-converting enzyme 2 (ACE2) exists in membrane-bound ACE2 (mACE2), located in the gallbladder, heart, intestines, kidneys and testes[79]. The virus uses human proteases as entry activators to break through host cells through membrane fusion and it uses ACE2 as a receptor. Treatments aimed at this entry mechanism have the potential for treating COVID-19. Umifenovir, also known as arbidol, is a drug approved for treating respiratory viral infections and influenza in China and Russia. Its mechanism of action involves preventing membrane fusion by interfering with the interaction between the S protein and ACE2[79]. In vitro studies have demonstrated its efficacy against SARS-CoV-2, Clinical data suggests that it may present a more effective treatment for COVID-19 when compared to lopinavir and ritonavir[80-84].

One notable drug that shows promise is camostat mesylate, which is licensed in Japan to treat postoperative reflux esophagitis and pancreatitis[85]. Previous studies have demonstrated the ability of camostat mesylate to inhibit TMPRSS2 activity and protect mice from fatal SARS-CoV infection[86,87]. Recent studies

have further indicated that camostat mesylate can inhibit the entry of SARS-CoV-2 into human lung cells[88]. This suggests potential utility as an antiviral drug against SARS-CoV-2 in the future, although further clinical data is required to confirm its effectiveness.

Other drugs used to treat autoimmune diseases and prevent malaria, such as chloroquine and hydroxychloroquine, may also influence SARS-CoV-2 entry. They work by preventing membrane fusion by raising endosomal pH, interfering with the interaction between virus and host receptor and inhibiting the glycosylation of cellular receptors[89-91]. Regarding their effectiveness in treating COVID-19, there remains a lack of scientific consensus. Despite concerns about an increased risk of cardiac arrest in treated patients, two clinical investigations found no correlation between these medications and patient mortality rates[92,93]. On June 15, 2020, due to documented adverse events, the US Food and Drug Administration (FDA) revoked the emergency use authorization for chloroquine and hydroxychloroquine in COVID-19 therapy[94].

Another therapeutic approach involves the use of soluble recombinant hACE2, specific monoclonal antibodies or fusion inhibitors targeting the SARS-CoV-2 S protein to prevent its binding to the ACE-2 receptor[95]. Examples of replication inhibitors include remdesivir (GS-5734), favilavir (T-705), ribavirin, lopinavir and ritonavir. The remaining three agents act on RdRp, except for lopinavir and ritonavir, which inhibit 3CLpro. **(Figure 4)** illustrates potential antiviral targets for COVID-19 treatment. However, further clinical research is necessary to evaluate the effectiveness and safety of these approaches.

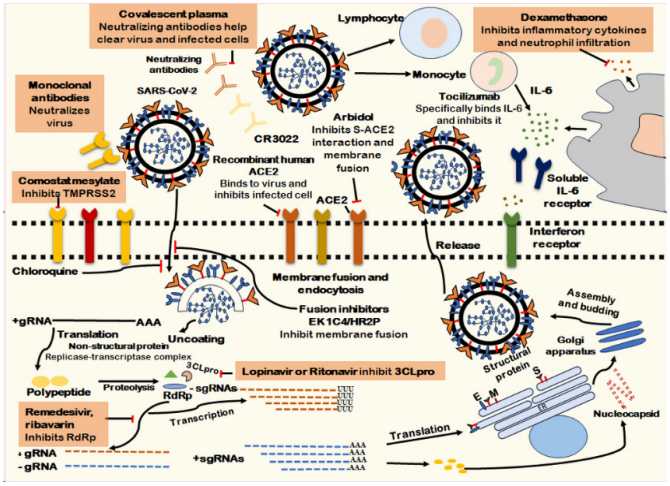


Figure 4: Potential antiviral interventions against the SARS-CoV-2.

In addition to antiviral agents immunomodulatory and immunoglobulin-based medications are potential treatments. Key molecular targets implicated in the viral replication cycle and potential treatments include ACE2 (Angiotensin-Converting Enzyme 2), crucial for the virus's initial interaction during receptor binding; 3CLpro (3C-Like Protease), a protease inhibited by lopinavir and ritonavir; CR3022, a human monoclonal antibody targeting the SARS-CoV virus; Envelope Protein (E), a potential target for disrupting viral replication; Endoplasmic Reticulum (ER), involved in various stages of viral replication and a potential therapeutic target; gRNA (Genomic RNA), a critical component of the viral replication process; HR2P (SARS-CoV-2 Spike Protein Derived Peptides, Hepatod Repeat 2), peptides considered for their potential in inhibiting viral fusion; ISG (Interferon-Stimulated Gene), targeted by immunomodulatory agents to modulate the host immune response; M (Membrane Protein), a potential target for disrupting viral replication; RNA-Dependent RNA Polymerase or RdRp, the key enzyme in the viral replication process targeted by antiviral agents such as remdesivir, favilavir and ribavirin; sgRNA (subgenomic RNA), involved in various stages of the replication cycle; S (Spike Protein), a major target for therapeutic intervention considering its role in receptor binding and viral entry; and TMPRSS2 (Transmembrane Protease Serine Protease 2), facilitating viral entry into host cells and a potential target for antiviral strategies.

7. Current Management approaches for COVID-19

Avoiding transmission should be the primary objective of COVID-19 treatment, especially in those with moderate symptoms, given the uncertainty surrounding the effectiveness of currently available antiviral medications. Individuals receiving at-home care must be closely monitored and if their health worsens, therapy must be escalated right away. Studies on the advantages of corticosteroids, weighing anti-inflammatory effects with possible hazards of viral replication, have shown conflicting findings[96]. Corticosteroids may, however, be taken into consideration in situations when there are other signs, such as severe COPD. Inhalers are used over nebulized medicines, which produce aerosols, to reduce the danger of airborne viral dissemination[97]. Nonsteroidal anti-inflammatory drugs (NSAIDs) have generated controversy because of their ability to affect epithelial cell ACE2 receptor levels and perhaps worsen viral infection[98]. The specific effects of NSAID usage in COVID-19 remain uncertain. Some suggest that NSAIDs might elevate the risk of acute respiratory distress syndrome (ARDS) by triggering leukotriene release and bronchoconstriction[99]. However, the application of NSAIDs for symptom management should be tailored to each individual. Presently, the European Medicines Agency (EMA) and the World Health Organization (WHO) do not advise against the use of NSAIDs[100]. In hospital settings, acetaminophen is often preferred over NSAIDs to minimize the risk of bleeding and kidney damage[101].

Controversy has arisen regarding the use of angiotensin receptor blockers and ACE inhibitors in COVID-19. Nonetheless, the American Society of Cardiology and the European Society of Cardiology presently do not recommend initiating or discontinuing these drugs[102]. The choice of antiviral and anti-inflammatory therapies should be personalized according to each patient's situation, guided by infectious disease experts and conducted within the context of a clinical trial or registry. Oxygen therapy, encompassing methods such as nasal cannula and high-flow oxygen, is often beneficial for individuals with mild to severe COVID-19[103]. Non-invasive and invasive mechanical ventilation are commonly needed in situations of acute respiratory failure. Positive airway pressure (PAP) is an aerosol-generating treatment; hence healthcare professionals had and must use a greater degree of personal protective equipment (PPE)[104]. Unless there are particular contraindications, pharmaceutical prophylaxis was used for these events and should be made available to hospitalized COVID-19 patients due to the elevated risk of venous thromboembolism.

8. Preventing COVID-19: Progress in vaccine advancements

Nearly 200 clinical studies were conducted to evaluate a range of innovative and repurposed medicines in the battle against COVID-19[105]. Among these programs, vaccinations hold promise since they could stop the spread of illness to a larger population. Before they may be used widely, the safety and efficacy of these immunizations must first be properly confirmed. It is impossible to overstate the importance of this stage since subpar immunizations run the danger of doing more damage than good via mechanisms including antibody-dependent augmentation. Therefore, meticulous testing and verification are crucial before the widespread adoption of any COVID-19 immunizations.

8.1. Technological approaches employed in the development of COVID-19 vaccines

Numerous technologies, were employed by scientists and researchers globally in their endeavours to create a secure and efficient vaccine for SARS-CoV-2. Among these technologies, gene vaccines, inactivated vaccines, viral vector vaccines and protein subunit vaccines stand out as the most promising candidates.

8.2. Vaccines based on protein subunits

Protein subunit vaccines, frequently administered through sophisticated systems like liposomes, virosomes or polymeric nanoparticles, harness components of the pathogen to stimulate the host's immune system[105]. Liposomes and virosomes, serve as effective adjuvants and carriers for antigens and are commonly employed in the development of vaccines against SARS-CoV-2[106]. For instance, a study reflects upon a cationic liposome protein subunit vaccine that incorporates the S1 component of the SARS-CoV-2 virus. This vaccine also includes two adjuvants: monophosphoryl lipid A (MPLA), acting as a TLR4 and TLR9 agonist and CpG ODN[107]. The inclusion of cationic elements such as 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) enhances the interaction of the liposome with antigen-presenting cells[108]. This liposome vaccine demonstrated improved T cell immunity, activating $CD4^+$ and $CD8^+$ cells and promoting IgA synthesis for potential mucosal defense[109].

Virosomes, lipid vesicles containing viral proteins, are preferred over liposomes as adjuvants due to their ability to shield pharmaceutically active compounds from degradation in endosomes until they reach the cytoplasm[110]. Virosomes have previously been utilized in the delivery of vaccines for SARS-CoV and MERS-CoV. The Centre for Vaccine Development at Texas Children's Hospital, Baylor College of Medicine, is working on a subunit vaccine against SARS-CoV-2. This vaccine employs a recombinant S-protein receptor-binding domain (RBD), likely combined with alum or glucopyranosyl lipid A (GLA), a synthetic TLR4 agonist[111].

The Australia University of Queensland and Novavax collaborated on the development of an immunogenic virus-like nanoparticle vaccine, NVX-CoV2373, currently in phase 3 trials. This vaccine incorporates a recombinant S-protein, demonstrating minimal reactogenicity and eliciting a T helper 1 response without significant side effects in most individuals[112]. Clover Biopharmaceuticals is also working on a highly pure S-trimer vaccine using their Trimer-Tag technology, previously employed in subunit vaccines for HIV, RSV and Influenza. In collaboration with GlaxoSmithKline (GSK) and Dynavax Technologies, Clover Biopharmaceuticals has completed enrolment in a phase 1 study, employing the CpG 1018 adjuvant, a TLR9 agonist known to activate $CD4^+$ and $CD8^+$ T cells with a favorable safety profile[113,114].

8.3. Vaccines with inactivated viruses

Weakened bacterial or viral pathogens used in inactivated vaccinations stimulate the immune system without actually infecting the recipient. Although these vaccinations don't provide lifelong protection, booster injections are often required to provide a long-term shielding effect. Large numbers of viral particles are propagated, condensed and then made inactive using chemical and/or physical techniques to make inactivated viral vaccines. Various techniques, such as the application of ascorbic acid, binary ethylenimine, gamma irradiation and high-temperature treatment, are commonly employed to render viral particles inactive[115]. The efficacy of these approaches relies on ensuring complete deactivation of the specific virus. The Wuhan Institute of Biological Products, affiliated with the China National Pharmaceutical Group (Sinopharm), actively worked on one of the initial inactivated COVID-19 vaccines[116,117]. In the development of this vaccine, the virus undergoes growth in the Vero cell line, followed by inactivation using formalin or β-propiolactone, with alum incorporated as an adjuvant[118]. All participants in the phase 1/2 clinical trials developed antibodies in response to the vaccination, with few negative side effects[119].

The most typical adverse effects, such as discomfort at the injection site and fever, were modest and self-limiting. Phase 3 studies are now being conducted to assess the vaccine's effectiveness and long-term safety. Sinovac Biotech Ltd. in China is involved in developing CoronaVac (formerly PiCoVacc), another inactivated vaccine. This vaccination puts genetic stability first, using the SARS-CoV-2 CN2 strain that was isolated from bronchoalveolar lavage fluid samples of hospitalized patients. The vaccine is presently in the midst of phase 3 clinical trials, involving a participant pool of 8,870 individuals[120,121]. In a distinct development, the University of Wisconsin, Madison, has collaborated with vaccine companies FluGen and Bharat Biotech to create an inactivated vaccine named CoroFlu, designed for intranasal delivery. Derived from FluGen's M2SR influenza vaccine, CoroFlu leverages the immune response targeting influenza. The M2SR vaccine has been adapted to incorporate the S-protein gene sequences of SARS-CoV-2, to elicit an immune response against the virus[122]. This non-invasive nasal immunization approach shows potential in eliciting robust mucosal and systemic immune responses to combat respiratory virus infections, providing an alternative to traditional invasive parenteral vaccination methods.

8.4. Adenovirus-based COVID-19 vaccines

Adenoviruses, with their icosahedral capsid and double-stranded linear DNA, are essential for initiating both innate and adaptive immunity in mammals. By increasing cytotoxic T lymphocytes and releasing pro-inflammatory cytokines, they aid in the immune response. These lymphocytes are in charge of identifying and getting rid of virus-infected cells[123]. Building on this method, adenoviral vectors have been extensively employed to combat a variety of illnesses, including influenza, Ebola, SARS, HIV and recently COVID-19[124]. Renowned

academic institutions and pharmaceutical companies including the Jenner Institute at Oxford University, CanSino Biologics and Johnson & Johnson have led the development of COVID-19 vaccines utilizing adenoviral vectors[125]. Phase 2 clinical trials for CanSino Biologics' Ad5-nCoV vaccine are presently underway and the results are promising[126]. This vaccine carries the genetic code for the S-protein of the SARS-CoV-2 virus and employs the non-replicating chimpanzee adenoviral vaccine vector, AZD1222. Noteworthy is its suitability for vulnerable populations such as children, the elderly and individuals with pre-existing medical conditions, as it necessitates only a single dose and triggers a substantial immune response without causing illness[127]. AstraZeneca and the University of Oxford have conducted phase 1 and phase 2 studies on AZD1222, demonstrating a promising safety profile and the successful generation of neutralizing antibodies against SARS-CoV-2[128,129].

Adenoviral vectors are still in the early stages of development and have not yet been approved for use in the treatment of infectious diseases in humans, even though they exhibit great promise for COVID-19 vaccines. Concerns have been raised about possible inflammatory responses as reported in AstraZeneca studies. Additionally, it's probable that people already have some amount of resistance to adenoviral vectors owing to their frequent exposure to them. While research and clinical trials continue, the scientific community is dedicated to developing safe and effective medicines to combat the COVID-19 pandemic and the long COVID.

8.5. Nucleic acid-based vaccines

DNA vaccines or mRNA vaccines, promise to be more effective than conventional immunizations. Direct administration of DNA plasmids that encode particular target antigens results in potent B and T cell responses with increased safety[130]. These vaccinations are safe for those with impaired immune systems since they don't include any infectious organisms. Synthetic DNA vaccines quicken the development process by enabling scalable manufacture, fast design and preclinical testing of several candidates and simpler regulatory approval for clinical use. Their stability at different temperatures also guarantees a longer shelf life. Currently being developed is a gene-based vaccine that specifically targets the S-protein of SARS-CoV-2. The vaccine candidate from Inovio Pharmaceuticals uses DNA-plasmid pGX9501, which was developed using MERS-CoV vaccine constructions from the past. The vaccine is now in phase 2 clinical trials. It is given intradermally and then electroporated[131]. Gene vaccines also use mRNA, which operates in the cytoplasm without having to cross the nuclear membrane, in addition to DNA. mRNA vaccines are less dose-intensive than DNA vaccinations and produce strong immune system memory. However, because of their heat lability and susceptibility to hydrolysis by circulating ribonucleases, they are less stable[132]. This is addressed by the formulation of mRNA vaccines as lipid nanoparticles, which improve stability and host distribution. Examples include the SARS-CoV-2-targeting drugs mRNA-1273 from Moderna and BNT162b1 from Pfizer, both of which are in advanced clinical moderation[133]. Despite the advancements, there are still difficulties in the global production, distribution and administration of COVID-19 vaccines.

8.6. Drugs approved for the COVID-19 treatment

Ongoing extensive clinical trials are underway to evaluate the potential effectiveness of several medications in treating COVID-19 patients. The selection of these medications is based on the hypothesis that they may hinder the virus from entering the host and replicating. Various compounds, including some that have undergone human clinical trials, are currently under assessment in clinical trials as potential COVID-19 treatments. Researchers are investigating the ability of experimental drugs to impede the virus's entry into the host and subsequent replication. While certain medications have been previously employed in treating SAR-CoV infections, others are being utilized for the first time in the context of SARS-CoV-2 infections.

Remdesivir, developed by Gilead Sciences, has received FDA approval for treating COVID-19 in patients aged 12 and above requiring hospitalization. Remdesivir works by inhibiting the RNA-dependent RNA polymerase, disrupting its interaction with the RNA of SARS-CoV-2 and thereby halting further replication[134]. After receiving remdesivir intravenously, 36 out of 53 COVID-19 patients showed improvement, indicating positive clinical outcomes[135]. Although lopinavir and ritonavir-based antiretroviral therapy have been investigated, it has not proven to be any more effective than standard care. Umifenovir, which has been licensed for influenza prevention in China and Russia, is used for the treatment of COVID-19 because of its potential to inhibit the S-protein/ACE2 interaction[136].

Research indicates that favipiravir, which inhibits RNA polymerase and is approved for use against influenza in Japan, has a better clinical outcome in mild cases of COVID-19 than umifenovir[137]. In small-scale clinical trials conducted in China, chloroquine has demonstrated potential in slowing pneumonia progression and viral replication in COVID-19 patients[138-139]. For COVID-19 patients, there is promise in the combination of statins and angiotensin receptor blockers (ARBs) to prevent acute respiratory distress syndrome (ARDS)[140]. Ongoing studies are exploring the potential benefits of these combined treatments in managing the severe consequences of the illness **(Figure 5)**. The strategy of employing existing, approved drugs for COVID-19 treatment capitalizes on the current pharmacopeia to swiftly address the urgent global health crisis. This tactic comprises repurposing well-known pharmaceuticals that were first authorized for a range of medical conditions to target particular aspects of the SARS-CoV-2 virus or the host immune system. Making the most of these medications' well-established pharmacokinetics, mechanisms of action and safety profiles is the main goal.

Remdesivir, initially developed for Ebola, is repurposed as an antiviral for COVID-19. Its mechanism of action involves inhibiting the viral RNA polymerase, thereby disrupting viral replication[141]. Lopinavir/Ritonavir, FDA-approved for treating HIV, is being explored for its ability to inhibit the 3CLpro enzyme in SARS-CoV-2, disrupting viral replication[142]. Agents with anti-inflammatory and immunomodulatory properties, such as dexamethasone-a potent corticosteroid with strong anti-inflammatory effects-are being repurposed to alleviate the severe inflammatory responses observed in critically ill COVID-19 patients, potentially reducing mortality[143]. The anti-inflammatory characteristics of azithromycin, an antibiotic, are currently under investigation for their ability to regulate the immune system and mitigate inflammation in individuals with COVID-19[144]. Monoclonal antibodies, designed to specifically

target SARS-CoV-2, are hypothesized to neutralize the virus, offering targeted therapeutic intervention.

Convalescent plasma, derived from individuals who have successfully recovered from COVID-19, contains antibodies that may neutralize the virus in infected patients, thereby enhancing the host's immune response[145]. Antibiotics and antiparasitic agents, including ivermectin, known for their well-established safety profile, are undergoing examination for potential antiviral effects against SARS-CoV-2. Additionally, azithromycin, an antibiotic, is explored for its potential synergy with other treatments in COVID-19 cases[146].

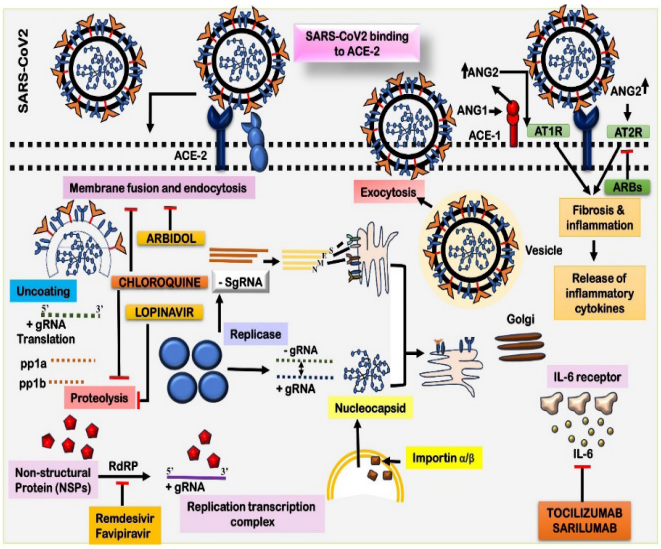


Figure 5: The illustration outlines the potential steps involved in the entry and replication of SARS-CoV-2.

The sequence initiates with the conformational change of the viral S protein, triggered by its binding to the cellular ACE2 receptor. This interaction facilitates the fusion of the viral envelope with the cell membrane through the endosome pathway. The genomic RNA undergoes translation, leading to the synthesis of the viral replicase polyproteins pp1a and 1ab. Viral proteases then cleave these polyproteins, generating smaller functional products. Following this, the viral polymerase transcribes irregularly, resulting in the production of subgenomic mRNAs. These subgenomic mRNAs, in turn, contribute to the translation of different viral proteins. During the assembly phase, viral proteins and genomic RNA combine to form virions within the endoplasmic reticulum (ER) and Golgi apparatus. The ER-Golgi intermediate compartment (ERGIC) plays a pivotal role in the maturation and transportation of virions. Ultimately, assembled virions are encapsulated into vesicles and released from the host cells.

9. Challenges and prospects

One major challenge is the ongoing emergence of new SARS-CoV-2 virus variants. These variants may acquire increased transmissibility, be resistant to immunity from previous infections or vaccines and may lead to more severe disease. Monitoring and adapting to these variants will be an ongoing challenge. Ensuring equitable and efficient distribution of COVID-19 vaccines in itself remains one of the major challenges. Disparities in access to vaccines can exacerbate the global health crisis and hinder efforts to achieve herd immunity. Vaccine hesitancy and misinformation continue to impede vaccination efforts. Promoting vaccine education and addressing concerns is crucial to achieving widespread vaccination and ending the pandemic. The long-term health effects of COVID-19, also referred to as "long COVID," are still difficult to understand. Some individuals experience persistent symptoms and complications long after recovering from the acute phase of the disease[147,148]. Healthcare systems in many regions around the globe are still grappling with the strain of the pandemic. Treating severe cases of COVID-19 can overwhelm hospitals and lead to delays in providing care for other serious medical conditions. The pandemic has caused severe economic and social unrest, Global cooperation and coordination are necessary to combat the pandemic effectively.

Research and development of booster shots and updated vaccines will likely continue to address emerging variants and provide longer-lasting immunity. The development of effective antiviral drugs to treat COVID-19 may improve outcomes for those infected and reduce the severity of the disease. Achieving herd immunity through vaccination remains a key goal for ending the pandemic. Encouraging vaccination in underserved communities and improving vaccine access are essential components of this effort[149]. The experience with COVID-19 underscores the need for improved pandemic preparedness, early warning systems and global response mechanisms to mitigate the impact of future infectious disease outbreaks. The pandemic has accelerated the adoption of telemedicine and digital healthcare solutions[150]. These innovations may continue to transform healthcare delivery and improve access to medical care. Addressing the mental health challenges arising from the pandemic will be a long-term prospect. Investing in mental health services and support systems is crucial for recovery. Promoting good hygiene habits and raising public health awareness can be very effective in stopping the transmission of contagious illnesses like COVID-19.

10. Conclusion

In conclusion, COVID-19 presents a range of challenges, but there is also hope for the future. Effective vaccination, treatments, global cooperation and preparedness efforts can contribute to bringing the pandemic under control and better preparing the world to respond to future health crises. The comprehensive review provides an in-depth and enlightening examination of the COVID-19 pandemic through September 2021. Millions of people have been affected by the SARS-CoV-2 pandemic, which has created previously unheard-of challenges for global health. The review article elaborates on several aspects of the illness, starting with its zoonotic origin and moving on to person-to-person transmission, as well as a map of its geographic distribution across continents. An important subject included in this research is COVID-19's clinical manifestations, which may vary from modest respiratory symptoms to severe instances leading to pneumonia, ARDS and multi-organ failure. Examining the disease's impact on different age groups and vulnerable populations, the article highlights the need for specialist healthcare strategies to protect those who are most susceptible. The report also discusses several COVID-19 diagnostic methods, including molecular tests like PCR and antigen assays and serological testing for detecting antibodies. These tests are necessary for controlling illnesses, tracking contacts and establishing containment procedures. Investigated in the search for effective therapies include repurposed drugs, immunomodulatory therapy and antiviral

drugs. The development and administration of vaccines are seen as crucial strategies for halting the pandemic and promoting herd immunity. The article acknowledges that COVID-19 comprehension and management have advanced significantly, but challenges and hurdles still wait for the global healthcare systems. The challenges include handling viral alterations understanding novel varieties, combating false information and vaccination resistance and becoming ready for impending outbreaks. The review provides a basis for further research and information for public health activities and scientists working at the molecular level, helping to decrease the consequences of the epidemic and prepare for any future health crises.

11. Abbreviations

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; ARDS: Acute Respiratory Distress Syndrome; PCR: Polymerase Chain Reaction; HIV/AIDS: Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; ICTV: International Committee on Taxonomy of Viruses; WHO: World Health Organization; PHEIC: Public Health Emergency of International Concern; RNA: Ribonucleic Acid; CNS: Central Nervous System; RBD: Receptor-binding Domain; RBM: Receptor-binding Motif; S: Spike Glycoprotein; E: Envelope; M: Matrix; N: Nucleocapsid Protein; ORF1ab: Open Reading Frame 1ab; nsp: Non-structural Protein; DNA: Deoxyribonucleic Acid; COG-UK: COVID-19 Genomics UK Consortium; TMPRSS2: Transmembrane Protease Serine 2; ACE-2: Angiotensin-converting Enzyme 2; SP: Serine Protease; S1/S2 site: Spike Protein Cleavage site; RdRp: RNA-dependent RNA polymerase; CT: Computed Tomography; ACE2: Angiotensin-converting Enzyme 2; T-cell: T-lymphocyte; SP: Serine Protease; FDA: U.S. Food and Drug Administration; hACE2: Human Angiotensin-converting Enzyme 2

12. Conflict of Interest

The authors declare that they have no discernible competing financial interests or personal connections that could be interpreted as influencing the conclusions made in this work.

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15. CRediT authorship contribution statement

Mohd Mustafa: Conceptualization, Data Curation, Investigation, Writing - Original Draft Preparation; Kashif Abbas: Methodology, Data Curation, Formal Analysis; Waleem Ahmad: Supervision, Data Curation, Investigation; Rizwan Ahmad: Data Curation, Investigation; Sidra Islam: Methodology, Writing-Review & Editing; Irfan Qadir Tantry: Funding Acquisition, Resources; Moinuddin: Supervision, Conceptualization, Writing-Review & Editing; Md. Imtaiyaz Hassan: Funding Acquisition, Supervision, Visualization; Mudassir Alam: Data Curation, Formal Analysis; Nazura Usmani: Funding Acquisition, Supervision, Formal Analysis; Safia Habib: Conceptualization, Funding Acquisition, Resources, Supervision, Writing-Review & Editing.

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