Unmasking vulnerabilities in the age of COVID-19 (Review)

MOHD MUSTAFA[1], KASHIF ABBAS[2], RIZWAN AHMAD[1], WALEEM AHMAD[3], IRFAN QADIR TANTRY[4], SIDRA ISLAM[5], MOINUDDIN[1], MUDASSIR ALAM[2], MD IMTAIYAZ HASSAN[6], NAZURA USMANI[2] and SAFIA HABIB[1]

[1]Department of Biochemistry, J.N. Medical College, Faculty of Medicine, Aligarh Muslim University, Aligarh, Uttar Pradesh 202002, India; [2]Department of Zoology, Faculty of Life Sciences, Aligarh Muslim University, Aligarh, Uttar Pradesh 202001, India; [3]Department of Medicine, J.N. Medical College, Faculty of Medicine, Aligarh Muslim University, Aligarh, Uttar Pradesh 202001, India; [4]Department of Biochemistry, School of Biological Sciences, University of Kashmir, Srinagar, Kashmir 190006, India; [5]Department of Inflammation and Immunity, Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44196, USA; [6]Structural Biology Laboratory, Center for Interdisciplinary Research in Basic Sciences, Jamia Millia Islamia, New Delhi 110025, India

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Abstract. The coronavirus disease 2019 (COVID-19) pandemic, driven by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (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 present review navigates through the complexities of COVID-19. Beyond mild respiratory symptoms, the clinical spectrum includes severe conditions, such as multi-organ failure, pneumonia and acute respiratory distress syndrome. The 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. As regards the therapeutic domain, the present review discusses treatments, such as antivirals, immunomodulatory therapies and repurposed pharmaceuticals, with an emphasis on vaccine development for epidemic containment and herd immunity. Despite progress being made, global healthcare systems face formidable challenges, including equitable vaccine distribution, combatting disinformation, 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 present review aimed to provide profound insight into the diverse nature of COVID-19, fostering a more in-depth understanding, and guiding future research and public health initiatives.

Correspondence to: Dr Safia Habib, Department of Biochemistry, J.N. Medical College, Faculty of Medicine, Aligarh Muslim University, Medical Road, Aligarh, Uttar Pradesh 202002, India
E-mail: saf_h75@yahoo.co.in; safia.bh@amu.ac.in

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ARDS, acute respiratory distress syndrome; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; MERS-CoV, Middle East respiratory syndrome coronavirus; WHO, World Health Organization; RNA, ribonucleic acid; RBD, receptor-binding domain; S glycoprotein, spike glycoprotein; COG-UK, COVID-19 Genomics UK Consortium; TMPRSS2, transmembrane protease serine 2; ACE2, angiotensin-converting enzyme 2; SP, serine protease; FDA, US Food and Drug Administration

Key words: COVID-19, zoonotic spillover, pandemic, emerging variants, SARS-CoV-2, vaccine, clinical manifestations

Contents

1. Introduction

Severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2), which belongs to the coronaviridae family is the source of the current coronavirus disease 2019 (COVID-19) pandemic, which continues to affect humanity. The real-time observation of ongoing evolutionary processes has provided a marked understanding of SARS-CoV-2 diversification. Numerous variations have emerged as a result of this diversification, each set apart by unique traits, such as 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 ribonucleic acid (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 critical factor in viral evolution (2). Natural selection also helps to fix favorable mutations and improve transmissibility (3). However, viral evolution becomes complex 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). The present review aimed to provide insight into the evolutionary dynamics of SARS-CoV-2 across various scales. This encompasses examining the stages of the COVID-19 pandemic, identifying crucial factors influencing the evolution of the virus, exploring hypotheses surrounding the emergence of statistically significant variants, and contemplating potential evolutionary pathways that could affect public health in the future. Considering the substantial role of SARS-CoV-2 in triggering the COVID-19 pandemic, a comprehensive investigation into the infection and its repercussions for public health is essential. The present review also delves into the transmission of SARS-CoV-2 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.

In addition, the present review highlights the 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 herein. Given the considerable amount of studies on COVID-19 and the available literature, it appears difficult to address each element. The present review aimed to provide a comprehensive discussion 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 association between pre-existing comorbidities and COVID-19-associated mortality. Furthermore, the present review 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, such as human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), Ebola and historical influenza strains. SARS-CoV-2 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

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 Middle East respiratory syndrome (MERS) (7). The Huanan Seafood Wholesale Market, a wet market in downtown Wuhan known for selling seafood and live animals, including poultry and wildlife, was linked to the majority of the initial cases (8). On December 8, 2019, the earliest case was recorded (9).

The 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 betacoronavirus 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 individuals traveling and spreading the virus to additional Hubei Province cities, and ultimately to other regions of China (11). The escalation in severity led the WHO to declare the COVID-19 outbreak as a public health emergency of international concern on January 30, 2020 (12). The WHO officially designated the illness as COVID-19 on February, 11 2020 (13). A schematic diagram of the timeline of these events is presented in Fig. 1. China imposed strict public health measures, such as a city-wide lockdown of Wuhan on January 23, 2020 with travel and transportation restrictions, to contain the outbreak (14). The high transmissibility of the virus and global travel contributed to large clusters of infections being reported in numerous countries. Consequently, on March 11, 2020, the WHO formally declared the COVID-19 outbreak to be a pandemic (15,16). China was able to contain the virus relatively well; however, the number of cases in the USA and Europe increased rapidly (17).

As of August 20, 2024, the USA is experiencing a high prevalence of the SARS-CoV-2 Omicron variants KP.2, KP.2.3, KP.3, KP.3.1.1 and LB.1. The Center for Disease Control and Prevention indicate that KP.3.1.1 is expected to comprise ~37% of new COVID-19 cases in the USA. The estimated percentage of illnesses caused by KP.2.3 remains at 14.4%, similar to the previous 2-week period, and the estimated rate of diseases caused by LB.1 also remains at 14.1%. JN.1 has been reported by 115 countries, rendering it the most reported VOI, representing 90.3% of sequences in week 9, up from 89.4% in week 6. The parent lineage of JN.1, BA.2.86, decreased and was responsible for 2.2% of sequences in week 9, down from 3.0% in week 6 (https://covid.cdc.gov/covid-data-tracker/#variant-summary; https://www.who.int/publications/m/item/covid-19-epidemiological-update-15-march-2024).

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 SARS virus. Both infections have the potential to manifest as rapidly progressing pneumonia. It appears that the primary mode of transmission for both is infectious respiratory droplets

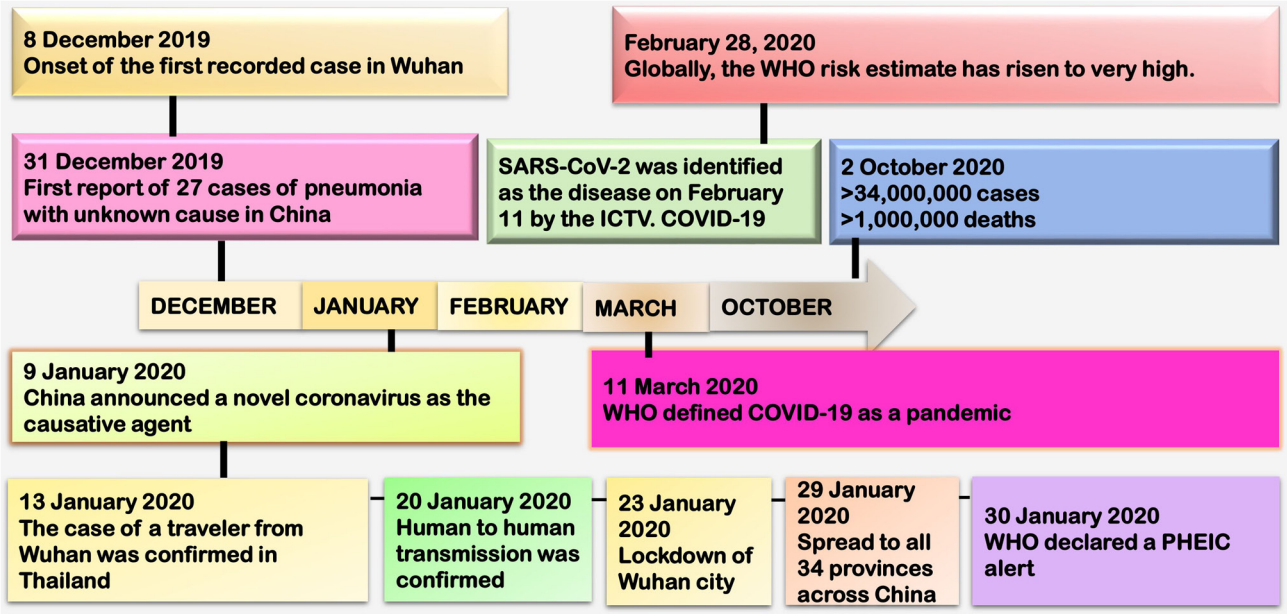

Figure 1. Schematic representation of the sequence of COVID-19 events recorded. SARS-CoV-2 has been identified as the causative agent of COVID-19 by the ICTV. The WHO declared it a PHEIC. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ICTV, International Committee on Taxonomy of Viruses; WHO, World Health Organization; PHEIC, public health emergency of international concern.

that are released from mucosal membranes (Table I). The viruses exhibit comparable stability and degradation in aerosols and on various surfaces (18). According to researchers, both viruses can live for up to 2 days on stainless steel and 3 days on plastic, and their viral titers on both surfaces exhibit comparable decay patterns (19-21). Both SARS and COVID-19 appear 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 research, the typical period of COVID-19 virus shedding is ~20 days, with some survivors shedding for as long as 37 days (25). By contrast, viral RNA remains detectable in non-survivors until mortality. Patients with severe COVID-19 infection may suffer viral shedding for a median of 31 days after the disease begins (26).

Betacoronaviruses and alphacoronaviruses have 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 >90% of their genome's sequence, including the variable spike glycoprotein (S glycoprotein) and open reading frame (ORF)8 regions, is particularly notable (28). Their close association 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). Notably, 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 have revealed that the genetic diversity observed in SARS-CoV-2 and its related bat coronaviruses stems from over 20 years of sequence evolution (31,32). 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 (33). These pangolin viruses are from two distinct sub-lineages and were independently traced in the provinces, of Guangxi and Guangdong (34-37). 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 display 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).

Table I. SARS and COVID-19 comparisons.

Parameter	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	*>8,000*	*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 the central nervous system and brain	**Yes**	

Bold font highlights similarities, text in italics highlights differences from COVID-19, and underlined text highlights features specific to COVID-19.

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-coronavirus (MERS-CoV), respectively (40). The viruses harbored by these hosts share a genome sequence identity of >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 marked 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 emergence of the virus. The animal source of SARS-CoV-2 is presently poorly understood, with limited knowledge available on this aspect. The reservoir hosts of the virus have yet not been identified, nor it has been determined if an intermediate host was involved in the transmission of the virus to humans. Significantly, the discovery of pangolin coronaviruses, RaTG13, and RmYN02 implies that SARS-CoV-2-like coronaviruses are prevalent in animals (43-45).

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 (46). Conversely, dogs, pigs, chickens and ducks have exhibited immunity to the virus (47). 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 (48). Although devoid of symptoms, two dogs in Hong Kong tested positive for spontaneous SARS-CoV-2 infection through serological and virological tests (49). Similarly, the analysis of blood samples from cats in Wuhan revealed the presence of neutralizing antibodies against SARS-CoV-2, confirming the infection in cat populations. However, the possibility of transmission from cats to humans remains uncertain (50). 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 insight 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 (51). Coronaviruses (CoVs) are categorized into four genera: α, β, γ and δ-CoV (52). 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 (53). Infections caused by HCoV-229E, HCoV-NL63, HCoV-HKU1 and HCoV-OC43 typically result in mild respiratory symptoms. By contrast, SARS-CoV and MERS-CoV can lead to severe respiratory disease, occasionally resulting in death due to multiple organ failure (54). SARS-CoV-2 shares notable similarities (>85%) with bat-derived SARS-like coronaviruses identified as bat-SL-CoVZC45 and bat-SL-CoVZXC21 (55). Compared to SARS-CoV and MERS-CoV, it demonstrates ~79 and 50% homology, respectively (56). This evidence and phylogenetic research strongly indicate that SARS-CoV-2 originated in bats and potentially transmitted to humans through an unidentified intermediate host species. The genomic structure, encoded structural and non-structural proteins, and the primary host of SARS-CoV-2 are illustrated in Fig. 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)

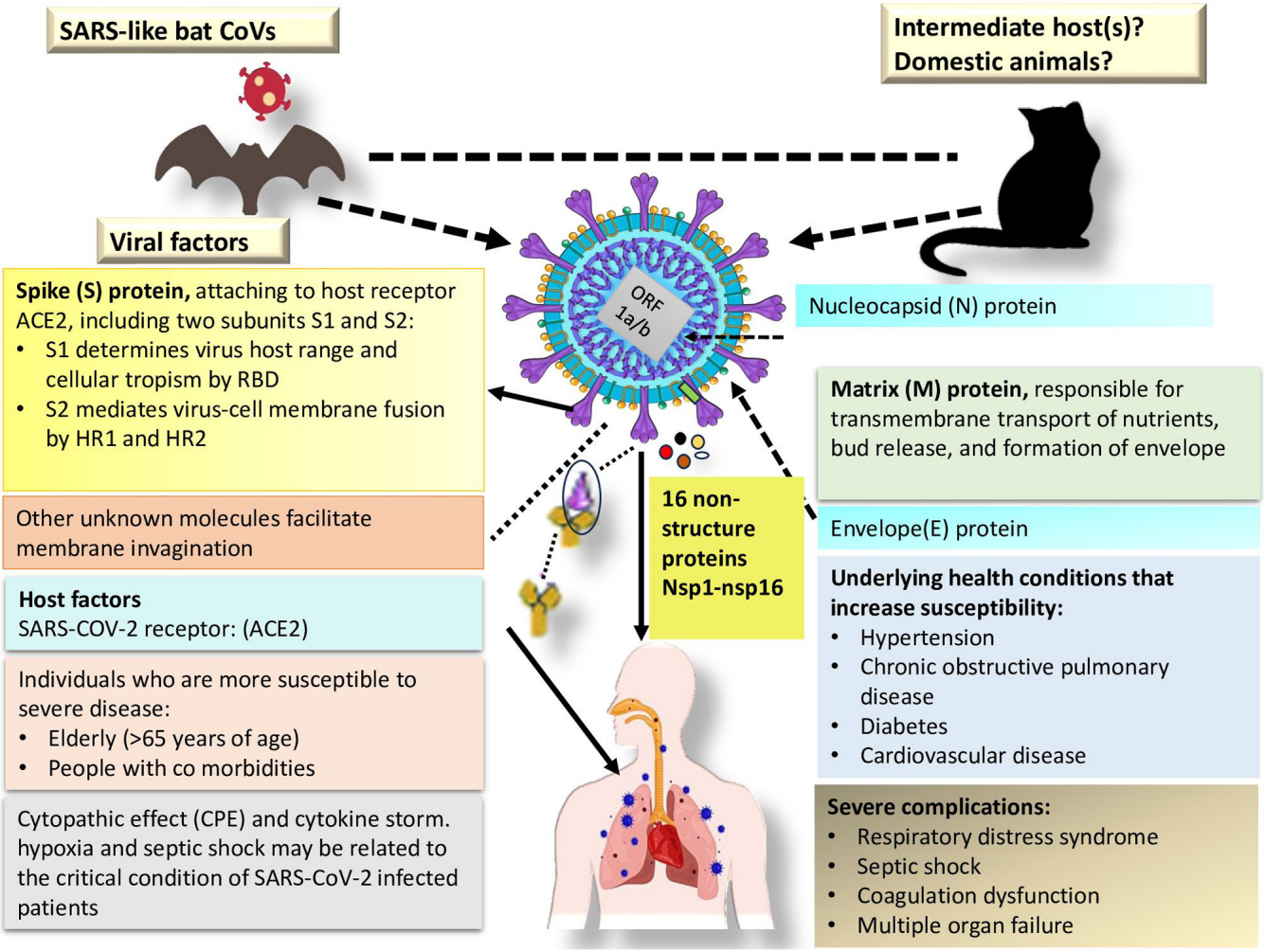

Figure 2. Schematic representation of the structural and genetic characteristics of SARS-CoV-2. There are numerous structural proteins, including the S glycoprotein (S), envelope (E), matrix (M) and nucleocapsid protein (N). The genetic segment ORF1ab encodes several non-structural proteins (nsp 1-16) 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. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin-converting enzyme 2.

dedicated to an ORF (ORF 1a/b), encoding 16 non-structural proteins crucial for replication. The remaining section of the genome encodes essential structural proteins (S 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 (57,58). Overall, the findings from several investigations demonstrate that SARS-CoV-2 is extremely infectious, with viral shedding commencing before symptoms develop and the virus spreading through many channels (15-17,59). Controlling the spread of the disease is a main concern for public health initiatives.

Although SARS-CoV-2 is less severe in terms of morbidity and mortality than MERS and SARS, 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 (59). Numerous studies have demonstrated the critical role symptomatic individuals play in COVID-19 transmission, mainly through respiratory droplet expulsion from actions, such as coughing or sneezing. On the other hand, nosocomial transmission was primarily responsible for the spread of MERS-CoV and SARS-CoV among healthcare personnel (60). 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 (61).

The SARS-CoV-2 virus changes in a variety of ways as it grows and spreads among the population. 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 SARS-CoV-2 in 2019, thousands of mutations have already manifested in its genome (62). 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 UK, particularly in South East England (63). 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 (64). Although viral mutations are normal, preliminary studies have indicated 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 (65). 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.

5. Role of ACE2 receptor, an angiotensin-converting enzyme

SARS-CoV-2 gains entry into the human host through receptor-mediated endocytosis, a mechanism through which viruses bind to specific receptors on the cell surface of the host, facilitating entry. The RBD of the virus establishes a connection with the appropriate receptor on the host cell, enabling entry. Both SARS-CoV and SARS-CoV-2 utilize the ACE2 receptor to infect cells. Previous research has shown that the S protein of SARS-CoV exhibits a strong affinity for the ACE2 receptor, serving as the entry point for the virus into host cells (66). A schematic diagram depicting the fusion of the virus with the host receptor is presented in Fig. 3.

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 ACE2 receptor and TMPRSS2 is essential for the efficient entry of SARS-CoV-2 into the host environment. It is noteworthy that TMPRSS2 exhibits a higher expression and broader distribution compared to ACE2 receptors, suggesting that ACE2 may function 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 (67). Studies involving human HeLa cells and animals with and without ACE2 expression support the involvement of ACE2 receptors in the cellular entry of the SARS-CoV-2 virus, particularly the Wuhan strain (68,69). Research on the SARS-CoV-2 infection of BHK21 cells has indicated higher infection rates when transfected with human and bat ACE2 receptors compared to BHK21 cells lacking ACE2 expression (70,71). Biophysical and structural data suggest that the ACE2 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 (72). This difference is considered to contribute to the variance in contagiousness between SARS-CoV-2 and SARS-CoV. Although the ACE2 and ACE-1 receptors share similarities, the ACE2 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 (73).

Furthermore, there is no evidence to suggest that angiotensin receptor blockers (ARBs), such as losartan, disrupt the activity of ACE2. 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 (74). 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 (75).

While TMPRSS2 has been recognized for its involvement in prostate cancer and viral infections, such as influenza, SARS and MERS (76), 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 (77,78).

6. Diagnostic and therapeutic approaches, and strategies to inhibit viral entry

The molecular detection of SARS-CoV-2 nucleic acid is the most accurate diagnostic approach (79). Various commercially available kits for viral nucleic acid detection target different genes, including ORF1ab (containing RdRp), N, E or S (80). 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 viral load is notably higher in samples from the lower respiratory tract (81). Viral nucleic acid has also been detected in intestinal 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 (81). 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

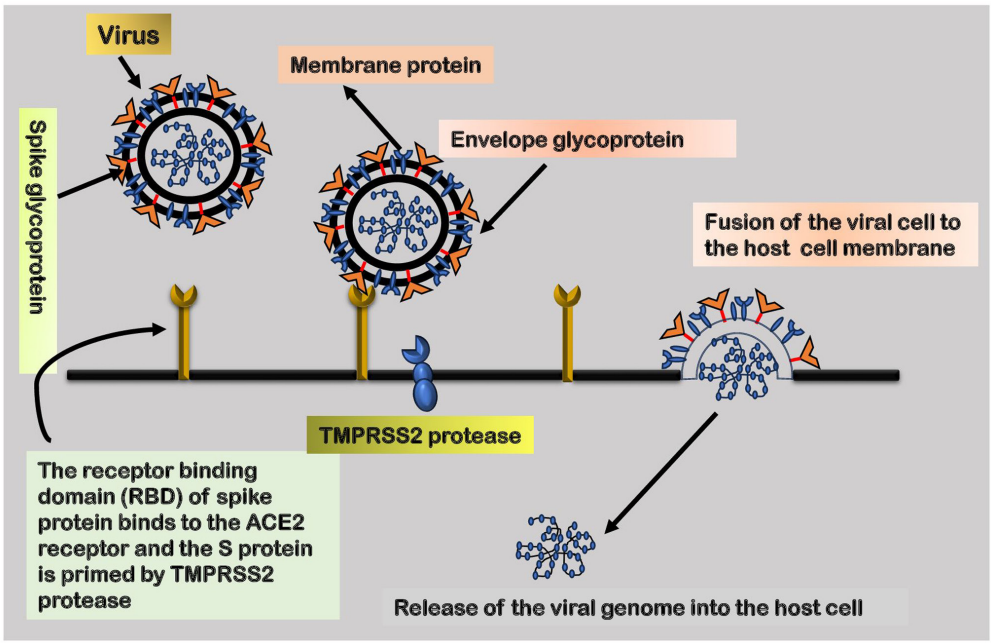

Figure 3. Entry of the viral genome. Schematic representation of the severe acute respiratory syndrome coronavirus 2 Spike protein with the host receptor and the subsequent fusion of the viral cell with the host cell membrane. ACE2, angiotensin-converting enzyme 2; TMPRSS2, transmembrane protease serine 2.

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 (76,82,83). The magnitude and duration of immunological responses are still unknown, and the sensitivity and specificity of existing serological assays vary. When selecting and interpreting serological testing, all these factors should be taken into consideration, possibly even extending to future assays for T-cell responses (84).

Currently, 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.

The pharmaceutical interventions available for COVID-19 therapy can be divided into several groups: Immunotherapy, cellular therapy, antiviral and other drugs. Immunotherapy mainly includes; immunoglobulins, interferons, convalescent plasma, and monoclonal therapy. Human immunoglobulin is tested in patients with pneumonia with COVID-19 and there are 478 clinical trials concerning immunoglobulins; 18 of these trials have been completed (https://www.clinicaltrials.gov/search?term=immunoglobulin&cond=Covid19&viewType=Table).

There are 87 clinical trials underway about interferons against COVID-19; of these, six clinical trials have been completed (https://www.clinicaltrials.gov/search?term=interferon&cond=Covid19&viewType=Table). In addition, 140 clinical trials examining the efficacy and safety of convalescent plasma for COVID-19 and, of these, nine trials have been completed (https://www.clinicaltrials.gov/search?term=convalescent%20plasma&cond=Covid19&viewType=Table).

Currently, 47 clinical trials are being conducted for monoclonal antibodies; none of have been completed (https://www.clinicaltrials.gov/search?term=monoclonal%20antibody&cond=Covid19&viewType=Table).

Cellular therapy primarily focuses on mesenchymal stem cells (MSCs) and natural killer (NK) cells. MSCs are potent anti-inflammatory and immunomodulatory tools of the immune system. MSCs can reduce the burden of lung injury and respiratory distress by preventing leakage of immune cells and proinflammatory cytokines to the pulmonary tissue. Of note, there are 55 ongoing clinical trials and two trials have been completed (https://www.clinicaltrials.gov/search?term=mesenchymal%20stem%20cell&cond=Covid19&viewType=Table).

As regards NK cells, they can identify the infected cells, mediate antibody-dependent cytotoxicity and maintain immunological homeostasis. A total of 28 clinical trials are underway on NK cells (https://www.clinicaltrials.gov/search?term=natural%20killer%20cell&cond=Covid19&viewType=Table). There are also ~84 clinical trials conducted with other drugs, and of these, 9 trials have been completed (https://clinicaltrials.gov/search?term=chloroquine&cond=Covid19&viewType=Table).

Potential antiviral targets for the treatment of COVID-19 are depicted in Fig. 3. A crucial strategy in combatting SARS-CoV-2 infection is to hinder viral entry. ACE2 exists in membrane-bound ACE2 (mACE2), located in the gallbladder, heart, intestines, kidneys and testes (85). 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 (86). *In vitro* studies have demonstrated its efficacy against SARS-CoV-2;

clinical data suggest that it may present a more effective treatment for COVID-19 when compared to lopinavir and ritonavir (87-91).

One notable drug that shows promise is camostat mesylate, which is licensed in Japan for the treatment of post-operative reflux esophagitis and pancreatitis (92). Previous studies have demonstrated the ability of camostat mesylate to inhibit TMPRSS2 activity and protect mice from fatal SARS-CoV infection (93). 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 (92-95).

Other drugs used to treat autoimmune diseases and prevent malaria, such as chloroquine and hydroxychloroquine, may also influence SARS-CoV-2 entry. They function by preventing membrane fusion by raising endosomal pH, interfering with the interaction between virus and host receptor, and inhibiting the glycosylation of cellular receptors (87). As regards 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 (96,97). 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 (98).

Another therapeutic approach involves the use of soluble recombinant human ACE2 (hACE2), specific monoclonal antibodies, or fusion inhibitors targeting the SARS-CoV-2 S protein to prevent its binding to the ACE2 receptor (99). 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. Potential antiviral targets for COVID-19 treatment are illustrated in Fig. 4. However, further clinical research is required to evaluate the effectiveness and safety of these approaches.

Novel diagnostic approaches are currently aimed at detecting COVID-19. Developing accessible point-of-care diagnostic devices customized for low-resource settings remains an urgent need. This can be accomplished through workflows that do not require cell lysis, bioassays that are increasingly sensitive and robust, improved methods for sample collection and processing that minimize risks to healthcare workers, and kits that are ready-to-use and do not require technical expertise, among other potential innovations. RT-LAMP and CRISPR/Cas-based methods, such as Specific High-Sensitivity Enzymatic Reporter UnLOCKing (SHERLOCK) and DNA Endonuclease-Targeted CRISPR Trans Reporter (DETECTR) are significant advancements that could be considered as promising alternatives (100,101). As regards portable diagnostic devices, few technologies hold as much promise as paper-based microfluidics (102). Natural remedies, such as *Withania somnifera* and *Tinospora cordifolia* have been tested on experiment models of COVID-19; research has shown their potency to limit the deterioration of the health of patients by reducing inflammation (99). Furthermore, the researchers are investigating the repurposing of drugs, such as procaine, which is an antiviral agent. It has demonstrated the *in vitro* inhibition of SARS-CoV-2, facilitating novel approaches for the treatment of the disease (103).

The implementation of these strategies requires vast capital investment. In light of concerns about a potential economic downturn and financial breakdown, resilient and effective leadership needs to emerge in healthcare, business, government, and at the community level. There is a need for immediate relief measures that should be adapted to assist the socioeconomically weaker, who may be left behind.

7. Current management approaches for COVID-19

Avoiding transmission should be the primary objective of COVID-19 treatment, particularly 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 (104). Corticosteroids may, however, be taken into consideration in situations when there are other signs, such as severe chronic obstructive pulmonary disease. Inhalers are used over nebulized medicines, which produce aerosols, to reduce the danger of airborne viral dissemination (105). Non-steroidal anti-inflammatory drugs (NSAIDs) have generated controversy die to their ability to affect epithelial cell ACE2 receptor levels and perhaps worsen viral infection (106). The specific effects of NSAID usage in COVID-19 remain uncertain. Some suggest that NSAIDs may elevate the risk of developing acute respiratory distress syndrome (ARDS) by triggering leukotriene release and bronchoconstriction (107). However, the application of NSAIDs for symptom management should be tailored to each individual. Presently, the European Medicines Agency (EMA) and the WHO do not advise against the use of NSAIDs (108). In hospital settings, acetaminophen is often preferred over NSAIDs to minimize the risk of bleeding and kidney damage (109).

Controversy has arisen regarding the use of ARBs 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 (110). The selection of antiviral and anti-inflammatory therapies should be personalized according to each the condition of each patient, 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 (111). Non-invasive and invasive mechanical ventilation are commonly required in situations of acute respiratory failure. Positive airway pressure is an aerosol-generating treatment; hence healthcare professionals have and must use a greater degree of personal protective equipment (112). Unless there are particular contraindications, pharmaceutical prophylaxis is used for these events and should be made available to hospitalized patients with COVID-19 due to the elevated risk of venous thromboembolism.

The PREDICT initiative by the US Agency for International Development (USAID) has significantly improved the local workforce and laboratories to identify emerging zoonotic virus

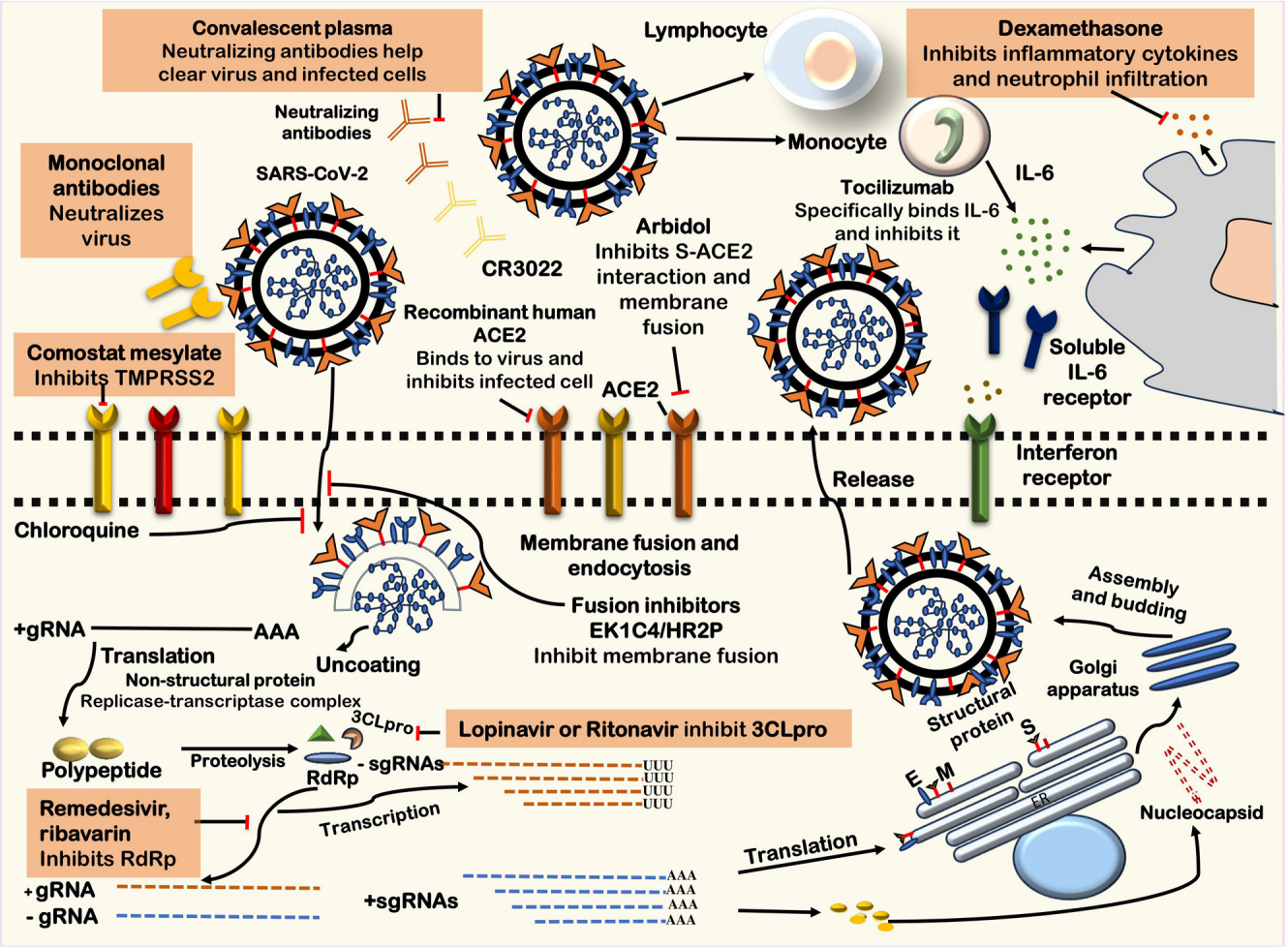

Figure 4. Potential antiviral interventions against SARS-CoV-2. In addition to antiviral agents immunomodulatory and immunoglobulin-based medications are potential treatments. Key molecular targets implicated in the viral replication cycle and potential treatments include ACE2, crucial for the initial interaction of the virus during receptor binding; 3CLpro, 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, a critical component of the viral replication process; HR2P, peptides considered for their potential in inhibiting viral fusion; interferon-stimulated gene, targeted by immunomodulatory agents to modulate the host immune response; M (membrane protein), a potential target for disrupting viral replication; RdRp, the key enzyme in the viral replication process targeted by antiviral agents such as remdesivir, favilavir, and ribavirin; sgRNA, involved in various stages of the replication cycle; S, a major target for therapeutic intervention considering its role in receptor binding and viral entry; and TMPRSS2, facilitating viral entry into host cells and a potential target for antiviral strategies. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; 3CLpro, 3C-like protease; gRNA genomic RNA; HR2P, SARS-CoV-2 spike protein derived peptides, heptad repeat 2; RdRp, RNA-dependent RNA polymerase; sgRNA, subgenomic RNA; S, Spike protein; TMPRSS2, transmembrane protease serine protease 2.

risks. Investment in spillover prevention in priority countries remains a focus for USAID, with ongoing projects aimed at building a 'One Health Workforce' in Asia and Africa and creating interventions to halt spillover at critical high-risk human-animal interfaces (113).

8. Preventing COVID-19: Progress in vaccine advancements

Research has been conducted to evaluate a range of innovative and repurposed medicines in the battle against COVID-19 (114). 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.

Technological approaches employed in the development of COVID-19 vaccines. Numerous technologies are employed by scientists and researchers globally in their endeavors 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 (115).

Vaccines based on protein subunits. Protein subunit vaccines, frequently administered through sophisticated systems, such as liposomes, virosomes, or polymeric nanoparticles, harness components of the pathogen to stimulate the immune system of the host (116). Liposomes and virosomes, serve as effective

adjuvants and carriers for antigens and are commonly employed in the development of vaccines against SARS-CoV-2 (117). For instance, research has reflected 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 DNA (118). The inclusion of cationic elements such as 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) enhances the interaction of the liposome with antigen-presenting cells (115). This liposome vaccine demonstrated improved T-cell immunity, activating $CD4^+$ and $CD8^+$ cells and promoting IgA synthesis for potential mucosal defense (119).

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 (120). 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 RBD, likely combined with alum or glucopyranosyl lipid A (GLA), a synthetic TLR4 agonist (121).

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 (NCT04611802; https://fdaaa.trialstracker.net/trial/NCT04611802/). This vaccine incorporates a recombinant S protein, demonstrating minimal reactogenicity and eliciting a T-helper 1 response without severe side-effects in the majority of individuals (122). Clover Biopharmaceuticals is also working on a highly pure S-trimer vaccine using their Trimer-Tag technology, previously employed in subunit vaccines for HIV, respiratory syncytial virus and influenza. In collaboration with GlaxoSmithKline (GSK) and Dynavax Technologies, Clover Biopharmaceuticals has completed enrollment in a phase 1 study (NCT04487210), employing the CpG 1018 adjuvant, a TLR9 agonist known to activate $CD4^+$ and $CD8^+$ T-cells with a favorable safety profile (123).

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 do not 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 rendered 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 (124). 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 (125). 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 (126). All participants in the phase 1/2 clinical trials developed antibodies in response to the vaccination, with few negative side-effects (125).

The most typical adverse effects, such as discomfort at the injection site and fever, were modest and self-limiting. Phase 3 studies are currently being conducted to assess the effectiveness and long-term safety of the vaccine. Sinovac Biotech Ltd. in China is involved in developing CoronaVac (formerly PiCoVacc), another inactivated vaccine. This vaccination places 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 (NCT04456595; https://covid19.trackvaccines.org/vaccines/7/), involving a participant pool of 8,870 individuals (127). In a distinct development, the University of Wisconsin, Madison, USA, 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 (128,129). This non-invasive nasal immunization approach exhibits potential in eliciting robust mucosal and systemic immune responses to combat respiratory virus infections, providing an alternative to traditional invasive parenteral vaccination methods.

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 (130). 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 (131). 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 (132). Phase 2 clinical trials for CanSino Biologics' Ad5-nCoV vaccine are presently underway (NCT04526990; NCT04540419), and the results are promising (133). 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 (134). 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 (135,136).

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 is probable that individuals 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 long COVID.

Nucleic acid-based vaccines. DNA vaccines or mRNA vaccines promise to be more effective than conventional immunizations. The direct administration of DNA plasmids that encode particular target antigens results in potent B- and T-cell responses with increased safety (137). These vaccinations are safe for those with impaired immune systems since they do not include any infectious organisms. Synthetic DNA vaccines facilitate the development process by enabling scalable manufacture, rapid 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, a gene-based vaccine is being developed 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 currently in phase 2 clinical trials (NCT04447781; NCT04336410). It is administered intradermally and then electroporated (138). 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, they are less stable due to their heat lability and susceptibility to hydrolysis by circulating ribonucleases (139). 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 (140). Despite the advancements, there are still difficulties in the global production, distribution and administration of COVID-19 vaccines.

Drugs approved for the treatment of COVID-19. Ongoing extensive clinical trials are underway to evaluate the potential effectiveness of several medications in the treatment of patients with COVID-19. 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 entry of the virus 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 (Table II).

Remdesivir, developed by Gilead Sciences, has received FDA approval for the treatment of patients ≥12 of age with COVID-19 requiring hospitalization. Remdesivir functions by inhibiting the RNA-dependent RNA polymerase, disrupting its interaction with the RNA of SARS-CoV-2 and thereby halting further replication (141). In a previous study, after receiving remdesivir intravenously, 36 out of 53 patients with COVID-19 exhibited an improvement, indicating positive clinical outcomes (142). Although lopinavir and ritonavir-based antiretroviral therapy have been investigated, it has not been 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 due to its potential to inhibit the S protein/ACE2 interaction (143).

Research indicates that favipiravir, which inhibits RNA polymerase and is approved for use against influenza in Japan, leads to an improved clinical outcome in mild cases of COVID-19 than umifenovir (144). In small-scale clinical trials conducted in China, chloroquine has demonstrated potential in attenuating the progression of pneumonia and viral replication in patients with COVID-19 (145,146). For patients with COVID-19, the combined use of statins and ARBs holds promise for the prevention of ARDS (147). Ongoing studies are exploring the potential benefits of these combined treatments in managing the severe consequences of the illness (Fig. 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. To make the most of these medications pharmacokinetically successful, it is important to understand the mechanisms of action and to keep in mind the safety profiles of the drug.

Remdesivir, initially developed for Ebola, has been repurposed as an antiviral for COVID-19. Its mechanism of action involves inhibiting the viral RNA polymerase, thereby disrupting viral replication (148). Lopinavir/ritonavir, FDA-approved for the treatment of HIV, is being explored for its ability to inhibit the 3CLpro enzyme in SARS-CoV-2, disrupting viral replication (149). 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 patients critically ill with COVID-19, potentially reducing mortality rates (150). 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 (151). 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 (152). 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 (153).

9. Challenges and future prospects

One major challenge is the ongoing emergence of new SARS-CoV-2 variants. These variants may acquire increased

Table II. COVID-19 vaccines[a], their mechanisms of action, advantages and disadvantages.

Form of vaccine	Vaccine and developer	Platform	Route of administration	Advantages/disadvantages and immune action	Stage/trial phase
Ribonucleic acid-based vaccine	mRNA-1273, Moderna/NIAID[b]	mRNA encapsulated in lipid nanoparticles	Intramuscular	Neutralizing antibodies and responses $CD4/8^+$ T-cell	Emergency use authorization by the FDA
	BNT-162, BioNTech/ Fosun Pharma/Pfizer	Lipid nanoparticle formulation encapsulated mRNA		Neutralizing antibody, and $CD4/8^+$ T-cell activation	
	ARCoV, People's Liberation Army, Academy of Military Sciences/Walvax Biotech[c]	mRNA (expressing S protein)		Neutralizing antibodies in primates	Phase 1 ChiCTR2000034112/ ChiCTR2000039212
Deoxyribonucleic acid-based vaccine	INO-4800, Inovio Pharmaceuticals	Electroporation-based Plasmid vaccine	Intradermal	High immune response	Phase 1/2 NCT04447781; NCT04336410
	ZyCoV-D/Zydus Cadila[c]	DNA plasmid (expressing S protein)		Significant immune responses in animal species	Phase 1/2 CTRI/2020/07/026352
	COVID-19 Vaccine/ Takara Bio, Osaka University	DNA plasmid (expressing S protein + adjuvant)	Intramuscular	Not applicable	Phase 1/2 NCT04463472; NCT04527081
Non-replicating viral vector	Ad5-nCoV, CanSino Biological Inc[d].	Adenovirus serotype 5 expressing Spike protein		Immunogenicity not maintained	Phase 2/3 NCT04526990; NCT04540419
	Ad26 Cov S1, Janssen Pharmaceutical	Adenovirus serotype 26 expressing Spike protein		Weakly immunogenic.	Phase 3 NCT04505722; NCT04614948
	Gam-COVID-Vac Lyo/Gamaleya Research Institute	rAd26 + rAd5 expressing Spike protein		Neutralizing and antibody, and $CD4/8^+$ T-cells	Phase 3 NCT04530396
Replicating virus	Institute Pasteur/Themis/ Univ. of Pittsburgh Xiamen University	Measles vector based		Not applicable	Phase 1 NCT04497298
Inactivated virus	PiCoVacc/Sinovac	whole virus particles + adjuvant		Neutralizing antibodies	Phase 3 NCT04456595, 669/UN6. KEP/EC/2020, NCT04582344, NCT04617483
	BBIBP-CorV Sinopharm/ Wuhan Institute of Biological Products	Inactivated SARS-CoV-2		High antibody titers	Phase 3 ChiCTR2000034780, ChiCTR2000039000, NCT04612972
	Institute of Medical Biology, Chinese Academy of Science	Inactivated SARS-CoV-2		Not applicable	Phase 1/2 NCT04470609

Table II. Continued.

Form of vaccine	Vaccine and developer	Platform	Route of administration	Advantages/disadvantages and immune action	Stage/trial phase
Protein subunit	Sanofi Pasteur/GSK	S protein (Baculovirus production)			Phase 1/2 NCT04473690
	SCB-2019/Clover Biopharmaceuticals In	Trimeric subunit spike protein		Neutralizing antibodies in animal models	Phase 1/2 NCT04530357
	Medigen Vaccine Corporation/NIAID/ Dynavax	S-2P protein + CpG 1018		Not applicable	Phase 1 NCT04487210

[a]Please see the previous study by Chung *et al* (166). [b]Repeated doses are required to stimulate immunity; [c]antibody response detected in non-human primates; [d]immune response declines even with booster doses.

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 (154,155). Healthcare systems in numerous 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 the 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 (156). 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 (157). 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, such as COVID-19.

Numerous outbreaks of zoonotic origin have been reported over the past century, most of which have presented with severe illnesses and fatalities. One example is the aforementioned SARS-CoV-2, the cause of COVID-19. Apart from the aforementioned aspects, it is equally important to understand the preparedness beyond COVID-19 and the implications of evolving zoonotic spillovers. Vaccines are pivotal for reducing pandemic, and post-pandemic consequences. The development of vaccines requires in-depth research, large investments, and an integrated and coordinated team of diverse scientists and clinicians. Viral targets can be located and identified for their potential outbreaks and candidates for vaccine design before any adverse event. Another possibility is to lessen the emergence, by vaccinating wild animals. This will reduce zoonotic spillovers, virus evolution and amplified transmission. For example, the study by Keusch *et al* (158) reported that 'vaccinating poultry or swine for emerging animal influenza

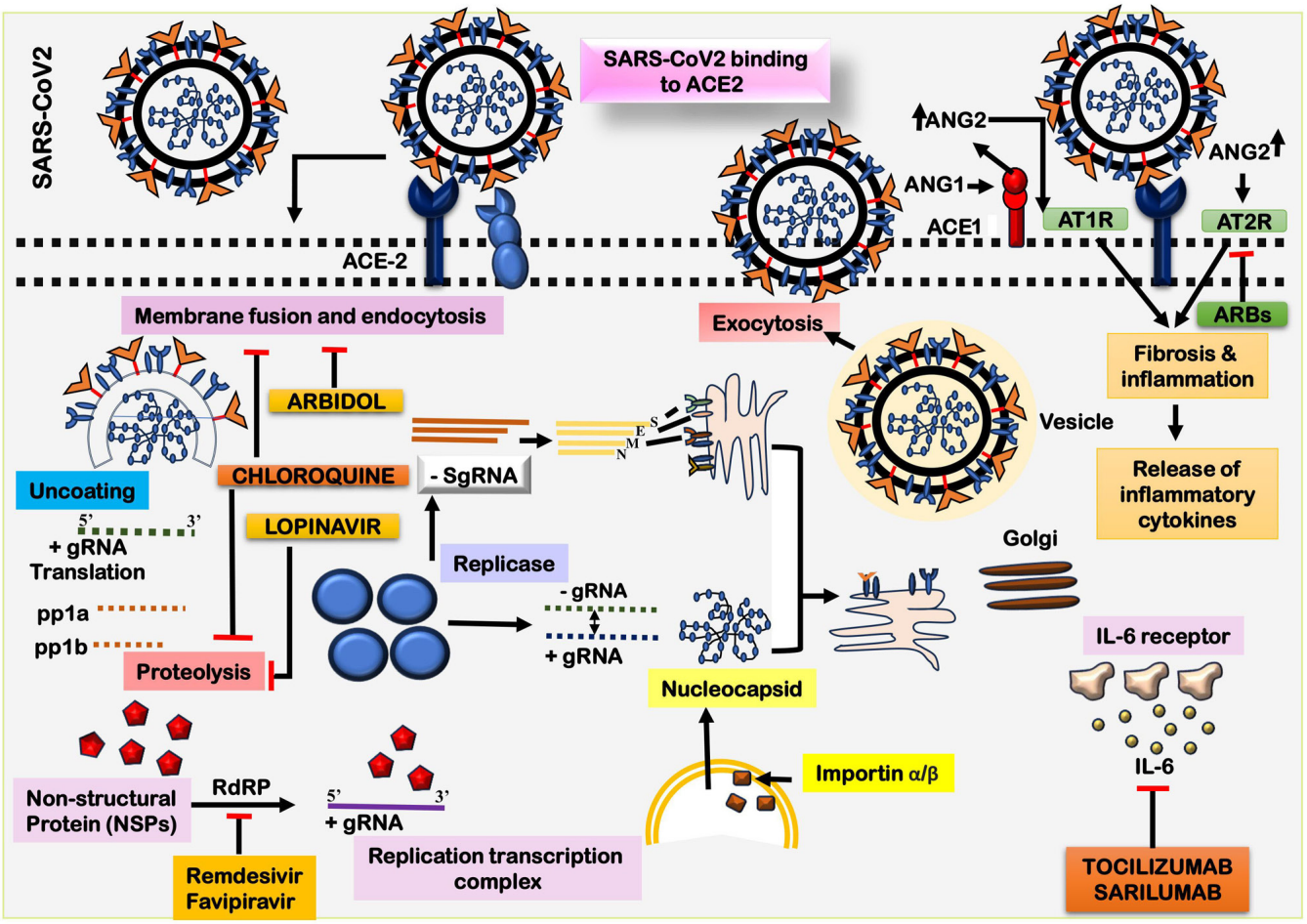

Figure 5. The illustration outlines the potential steps involved in the entry and replication of SARS-CoV-2. The sequence initiates with the conformational change of the viral S protein, triggered by its binding to the cellular ACE2 receptor. This interaction facilitates the fusion of the viral envelope 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. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin-converting enzyme 2; ARBs, angiotensin receptor blockers.

A strains or camels for MERS-CoV in endemic countries'. In addition, identifying and vaccinating potential hosts may reduce the threat in endemic countries. Creating awareness among the masses, clarifying misinformation, and providing recent research updates to health workers at every level in the developed and developing world will prepare them for COVID-19 and beyond (158).

Pandemic prevention can also be managed by reducing the spillover risk by monitoring live markets, wildlife and livestock trading. The expansion of these activities is associated with the socio-economic status of the country. Some practices are a part of traditional cultural events, and hence need to be tackled mildly and judiciously. Still, these activities require strict surveillance as they are the hotspots of infectious diseases. At times trading activities link the geographical distributions, further spreading the disease and connecting and increasing the hotspots. The policy changes introduced should be evidence-based and collaborative efforts and partnerships and should be economically compatible and likely for the benefit of mankind (159,160).

Socioeconomic status, public opinion, outreach activities and communication strategies play a crucial role in preventing and preparing for COVID-19, mainly due to political polarization, variable public opinion and the associated risk specifically in the low economic strata (161). The study by AlShurman *et al* (162) reported that fake news associated with exaggerated risk can increase susceptibility to misinformation, and make vaccination less accepted among the masses. Parents were reported to be hesitant to regarding the vaccination of their children. Older individuals were also of the belief that vaccination may enhance their morbid status. The same study also mentioned that with proper counseling and knowledge, individuals from different beliefs and low socioeconomic distribution agreed to get vaccinated, although the number remained lower than expected (162).

Along with the importance of identifying the intersection between COVID-19 and socio-economic factors and taking appropriate measures on them, it is equally important to spread knowledge about the alternative methods or cutting-edge diagnostic approaches that are being developed or currently in use.

RT-PCR is the primary method for detecting infection during the acute phase of COVID-19. The WHO and the National Health Commission of China have given the case definitions for COVID-19, which include a positive serology test even when RT-PCR is negative. The RT-PCR amplification is usually completed in a short timeframe; still the protocol includes, extraction, running time, sample processing and data management that in total requires up to 48 h. A large sample testing area where samples are transported requires even more time. RT-PCR is the gold standard for microbiological confirmation of COVID-19. Some antigen-based rapid kits are arising, such as: i) The novel Coronavirus (2019-nCov) Antigen Detection kit; ii) CLMSRDL, Sichuan Mass Spectrometry Biotechnology Co., Ltd.; iii) DIAQUICK COVID-19 Ag Cassette. These could provide rapid, point-of-care antigen tests for diagnosis of SARS-CoV-2 infection (163,164).

Infectious diseases are tackled differently, employing different approaches depending on the geographical distribution. To curb the infections some common legal measures are adopted. These measures primarily focus on the view that the need for protection is natural and necessary. Such interventions include compulsory vaccination, screening, examination, isolation and quarantines. Some studies and experts present a view that making vaccination and other measures obligatory appears to violate the patient's rights. Certain researchers are of the view, specifically in the context of COVID-19, that enforcing vaccination is unethical and does not take into consideration the ethical and religious beliefs of patients. Individuals resist undergoing vaccination due to diverse reasons, such as misinformation circulated by mass media, a lack of communication between health providers and the community, and individuals not being clear about the pros and cons of vaccination protocols. The vaccine is the only hope for this lethal infectious disease; however, it continues to face a number of ethical challenges. The study by Jalilian *et al* (165) and others have reported that the ethical considerations of COVID-19 fall under five categories as follows: i) Autonomy and accountability; ii) the supply of vaccines specifically to socio-economically weaker places; iii) post-vaccination safety issues; iv) the use of standard vaccine; v) fairness of reporting any adverse issues (164-166).

In principle, the equitable distribution of vaccines may not be possible due to controlled approval and limited production. Requirements, population density, policies and the capacity of low/middle-income countries vary compared to the high-income countries. To overcome these hurdles, COVAX prioritized the vaccine-receiving population and included healthcare workers and the elderly in vulnerable groups (167).

10. Conclusion and limitations

In conclusion, COVID-19 presents a range of challenges; however, 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 present comprehensive review provides an in-depth and enlightening examination of the COVID-19. Millions of individuals have been affected by the SARS-CoV-2 pandemic, which has created previously unheard-of challenges for global health. The present review elaborates on several aspects of the illness, starting with its zoonotic origin and moving on to person-to-person transmission and a map of its geographic distribution across continents. An key subject included herein is the clinical manifestations COVID-19, which may vary from modest respiratory symptoms to severe instances, leading to pneumonia, ARDS and multi-organ failure. By discussing the impact of the disease on different age groups and vulnerable populations, the present review highlights the need for specialist healthcare strategies to protect those who are most susceptible. The present review also discusses several COVID-19 diagnostic methods, including molecular tests, such as PCR and antigen assays, as well as serological testing for detecting antibodies. These tests are necessary for controlling illnesses, tracking down contacts and establishing containment procedures. Effective therapies mainly include repurposed drugs, immunotherapy, cellular therapy, antiviral and other drugs. The development and administration of vaccines are observed as crucial strategies for halting the pandemic and promoting herd immunity. The present review acknowledges that significant advancements have beebn made in the comprehension and management of COVID-19; however, challenges and hurdles remain for the global healthcare systems. The challenges include handling viral alterations understanding novel varieties, combating false information and vaccination resistance and preparing for impending outbreaks. The present 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.

In the era of long-COVID-19 presented by the silent persistence of the COVID-19 pandemic, there were a large number of studies or research in progress or in the press that could not be included or mentioned in the present review. However, the authors tried to minimize this limitation by including studies close to the discussed topic. Another limitation of the present study is that there appears to be no standardized fixed formula to cover or minimize the risk factors. Every government should accordingly make judicious decisions for the benefit of mankind. The policies adopted could not be discussed herein, as they may be circumstantial. To prevent failures in policy making and implementation, a collaborative effort among the stakeholders is necessary. The COVID-19 crisis and mandatory vaccination have become controversial.

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Authors' contributions

MM was involved in the conceptualization of the study, in the curation and investigation of data from the literature, as well as in the writing and preparation of the original draft of the manuscript. KA and RA were involved in the study design, and in the writing and editing of the manuscript. RA was involved in the curation and manuscript preparation. WA was involved in study supervision, and in the curation and investigation of data from the literature. SI was involved in the writing, review and editing of the manuscript. IQT was involved in writing, reviewing and in providing literature resources. M was involved in study supervision, in the conceptualization of the study, and in the writing, review and editing of the manuscript. MIH was involved in; study supervision and designing and image preparation. MA, NU and SH were involved in the conceptualization of the study, provision of literature and software resources, study supervision, and in the writing, review and editing of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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