CHAPTER 2

Introduction and Review of Literature

Introduction and Review of Literature

Following the emergence of SARS-CoV and MERS-CoV, both caused by coronaviruses, a novel coronavirus known as SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) led to an outbreak of viral pneumonia. This disease, named Coronavirus Disease (COVID-19), originated in Wuhan, China, in late 2019 and has since posed a significant threat to global public health and society [1, 2].

This introduction aims to provide a comprehensive overview of COVID-19 and SARS-CoV-2, detailing its clinical manifestations, underlying pathophysiology, and the evolution of its various variants. Additionally, it discusses the main protease, its inhibitors, the spike protein, and key biomolecules such as receptors that facilitate the entry of virus into the host cells.

2.1. COVID-19 and SARS-CoV-2

The novel coronavirus disease, commonly referred to as COVID-19, is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This virus was first identified in Wuhan, China, in December 2019. The unique genomic structure of SARS-CoV-2 enables it to induce viral pneumonia and facilitates rapid human-to-human transmission [3]. The delayed implementation of preventive measures in many countries contributed to a sharp rise in cases globally. Additionally, due to its high transmissibility, COVID-19 rapidly spread across continents, surpassing previous coronavirus outbreaks such as SARS in 2002 and MERS in 2012 in terms of both infection rates and geographical distribution [4,5]. The COVID-19 pandemic has posed an unprecedented challenge to global public health [6,7]. As of March 14, 2024, the virus has affected 229 countries, infected over 704,235,761 individuals and resulted in 7,006,139 fatalities, while 675,108,072 people have recovered [8,9]. However, the actual number of infections is likely underestimated, as mild cases often resolve without being officially recorded.

The causative agent of COVID-19, SARS-CoV-2, belongs to the Coronaviridae family within the order Nidovirales and is classified under the subfamily Coronavirinae. This subfamily comprises four genera: Alphacoronavirus (α), Betacoronavirus (β), Gammacoronavirus (γ), and Deltacoronavirus (δ) [10]. SARS-CoV-2 is a Betacoronavirus characterized by a positive-sense, single-stranded RNA genome [11]. It is an enveloped virion with a diameter ranging from 60 to 140 nm and exhibits an oval to round morphology, often displaying polymorphic features **(Figure 2.1)** [12].

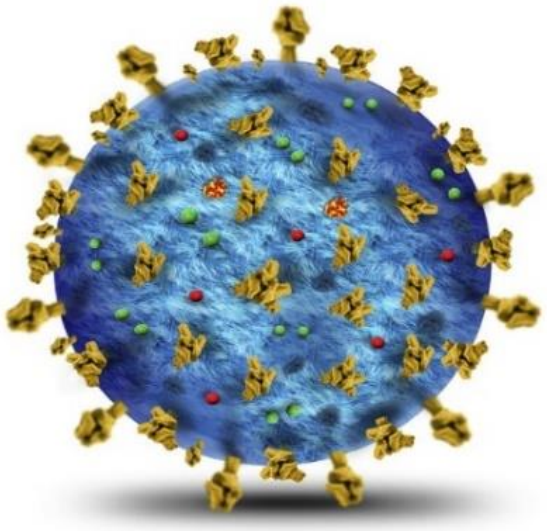

***Figure 2.1**. A three-dimensional (3-D) structure of the novel coronavirus (COVID-19). (Taken from [12])*

The genome of SARS-CoV-2 consists of a large, positive-sense, single-stranded RNA that is non-segmented, with an approximate length of 30 kb. Among the 29 proteins encoded by the viral genome, there are 25 putative non-structural and accessory proteins, along with four structural proteins [13,14]. Approximately one-third of the viral genome is responsible for encoding structural proteins, including the spike glycoprotein (S), membrane (M), envelope (E), nucleocapsid (N), and several accessory proteins [15,16]. The remaining two-thirds of the genome encodes non-structural proteins (NSPs) [15,16].

The SARS-CoV-2 spike (S) protein consists of 1,273 amino acids, making it longer than the spike proteins of SARS-CoV (1,255 amino acids) and known bat SARS-related coronaviruses (1,245–1,269 amino acids) [17]. These viruses, which exhibit either a spherical or pleomorphic morphology, are enclosed within an envelope containing a helical nucleocapsid composed of nucleoproteins (N) that associate with the viral RNA genome. Embedded within this envelope is the spike glycoprotein (S), which plays a critical role in host cell receptor binding. Additionally, the envelope contains integral membrane (M) and envelope (E) proteins [18], as depicted in **Figure 2.2.**

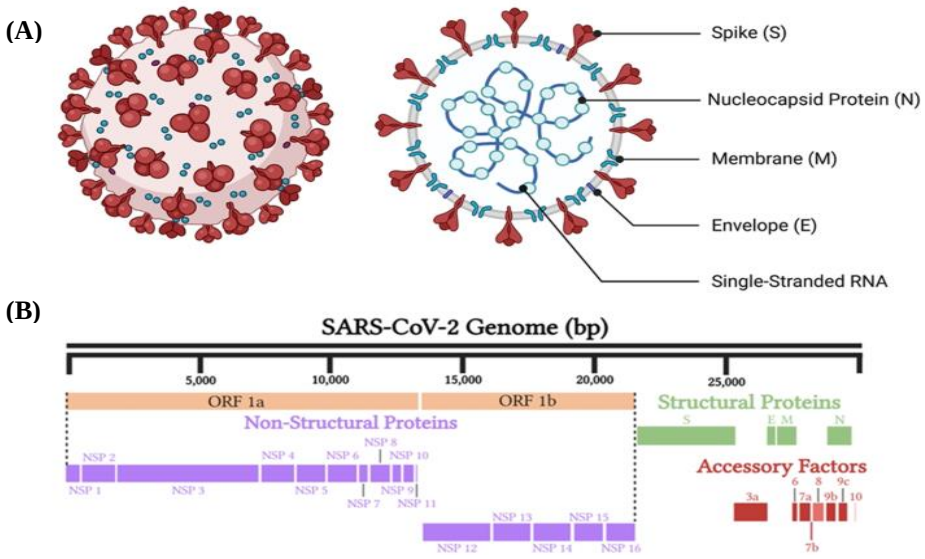

Figure 2.2. (A) *The structural elements of the virus, including the spike protein, envelope, membrane, and internal components such as the viral single-stranded RNA and nucleocapsid proteins.* ***(B)*** *SARS-CoV-2 genome components (Taken from [19])*

Viral entry into the host cell is primarily mediated by the S protein, which extends from the viral surface and possesses receptor-binding and fusogenic properties. Angiotensin-converting enzyme 2 (ACE2) has been identified as the functional receptor responsible for SARS-CoV-2 infection [20]. The high genomic and structural similarity between the S proteins of SARS-CoV and SARS-CoV-2, with a 76% amino acid sequence identity, supports ACE2 as the primary cell-surface receptor for viral entry [21-24]. The S protein binds to ACE2 receptors on the surface of permissive host cells, where it undergoes cleavage by a host serine protease, such as TMPRSS2, which is expressed in nasal epithelial cells. This cleavage transitions the S protein into a fusion-permissive state, enabling viral entry via the plasma membrane. Alternatively, SARS-CoV-2 can enter the host cell through endosomal uptake, where intracellular vesicles facilitate fusion [25].

Following membrane fusion, the nucleocapsid is released into the host cytoplasm, where uncoating of the viral genome occurs. The genomic RNA undergoes translation of open reading frames ORF1a and ORF1b, producing two polyproteins, pp1a and pp1b. These polyproteins are subsequently co-translationally and post-translationally processed into individual non-structural proteins (NSPs), which are integral to viral replication and transcription. Once translation is completed, the synthesized structural proteins are translocated to the endoplasmic reticulum (ER) membranes and then transported through the ER-to-Golgi intermediate compartment (ERGIC). At this stage, newly synthesized genomic RNA interacts with N-encapsidated proteins, facilitating viral assembly and budding into the

lumen of secretory vesicles. The mature virions are ultimately released from the infected cell through exocytosis [26]. The detailed pictorial representation of the life cycle of SARS-CoV-2 is shown in **Figure 2.3**.

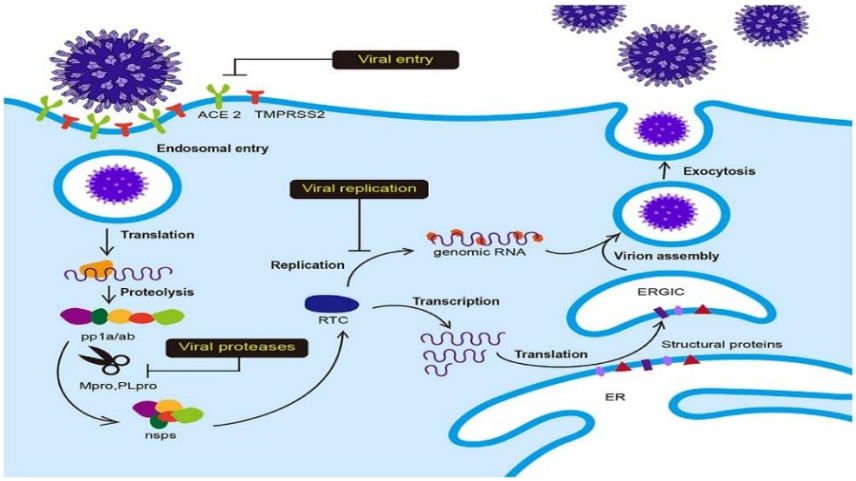

Figure 2.3. *Viral life cycle of SARS-CoV-2. Interaction between the S protein of SARS-CoV-2 and hACE2 initiates SARS-CoV-2 infection. Following receptor binding, the virus enters the cell by acid-dependent proteolytic cleavage of the S protein by TMPRSS2 or other proteases. Upon fusion of the viral and host cell membranes, viral genomic RNA is released in the cytoplasm. The viral RNA initiates translation of co-terminal polyproteins (pp1a/ab) by−1 frameshifting. These polyproteins are subsequently cleaved into nonstructural proteins (nsps) by Mpro and PLpro. Several nsp proteins interact with nsp12 (RdRp) to form the replicase-transcriptase complex (RTC), which is responsible for the synthesis of full-length viral genome (replication) and sub-genomic RNAs (transcription). The viral structural proteins are expressed and translocated into the endoplasmic reticulum (ER). The nucleocapsid (N) protein-encapsidated genomic RNA translocates with the structural proteins into the ER-Golgi intermediate compartment (ERGIC) for virion assembly. The newly synthesized virions are budded through the cell membrane and exocytosed. (Taken from [27])*

2.2. History of coronaviruses

Based on existing literature, seven human coronaviruses have been identified to date. Among them, HCoV-229E and HCoV-NL63 belong to the alphacoronavirus group, while HCoV-OC43, HCoV-HKU1, MERS-CoV, SARS-CoV, and SARS-CoV-2 fall under the betacoronaviruses category and have been detected at different times of the year in various regions across the globe [28-31]. Human coronaviruses (HCoVs), such as HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1, are typically associated with mild respiratory symptoms resembling the common cold. In contrast, SARS-CoV and MERS-CoV have emerged as highly lethal pathogens over the past two decades, causing significant mortality and economic disruptions.

HCoV-229E and HCoV-OC43 have been known for over 50 years, whereas HCoV-NL63 and HCoV-HKU1 were identified following the SARS-CoV outbreak. These coronaviruses spread primarily through direct human-to-human transmission while in contrary, SARS-CoV and MERS-CoV, are believed to originate from an animal reservoir. Nonetheless, there is considerable genetic variability among human coronaviruses. Although these viruses are present worldwide, their prevalence varies depending on time and location [32].

The first recorded SARS-CoV cases were reported in Foshan, Guangdong province, China, in November 2002 [33]. This later led to a SARS outbreak that affected 28 countries, resulting in 8,096 confirmed infections and 774 fatalities [33]. Subsequent research identified masked civet cats and raccoon dogs as the initial hosts of the SARS-CoV virus. Moreover, distinct CoVs related to SARS-CoV have been found in Chinese rhinolophid bats (Rhinolophus spp.), indicating that these bats might serve as natural hosts for the virus [34,35].

Similarly, the first MERS-CoV infection in humans was detected in Jeddah, Saudi Arabia, in June 2012 [33]. By November 2019, a total of 2,494 MERS-CoV cases had been reported across 27 countries, leading to 858 deaths (WHO, 2020). Initially, bats were considered the primary source of MERS-CoV. However, researchers later discovered a significant presence of MERS-CoV-neutralizing antibodies in camels from Oman and the Canary Islands [36,37]. Serological studies suggest that MERS-CoV-like viruses were circulating among dromedary camels in regions such as East Africa, North Africa, and the Middle East as early as 1983. Furthermore, dromedary camels in Saudi Arabia have been found to carry multiple viral genetic lineages [38], facilitating cross-species transmission and human outbreaks. Collectively, these findings strongly indicate that dromedary camels act as a crucial reservoir for MERS-CoV. Laboratory evidence suggests that viruses originating from bats may have been transmitted to dromedary camels more than three decades ago **(Figure 2.4)** [39].

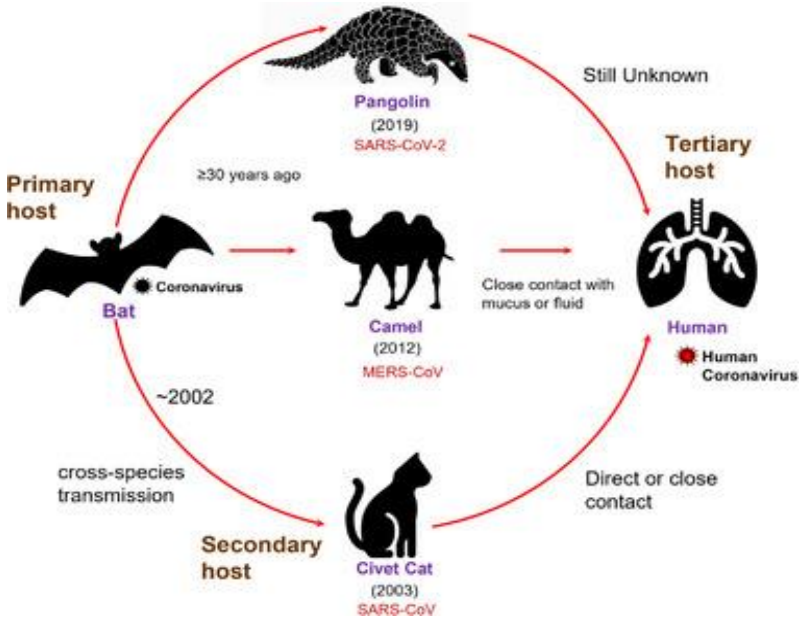

Figure 2.4. *Schematic diagram of the transmission process of three HCoVs. Humans acquired SARS-CoV and MERS-CoV from bats through civet cats and dromedary camels, respectively. It is unclear how SARS-CoV-2 spread to humans. (Taken from [40])*

Among the seven coronaviruses identified to infect humans [41], SARS-CoV-2 is the third to have recently emerged, following SARS-CoV [42] and MERS-CoV [43], both of which have caused severe outbreaks. SARS-CoV-2 belongs to the Betacoronavirus genus and has a zoonotic origin [44], sharing approximately 79% genetic similarity with SARS-CoV [45-48].

Epidemiological research indicates that the Huanan Seafood Market in Wuhan was the initial and primary epicenter of the SARS-CoV-2 outbreak. Two of the first three documented cases of COVID-19 were directly linked to the market's wildlife trade, and 28% of all cases reported in December 2019 had direct connections to the market [49]. During that month, around 55% of cases were associated with other markets in Wuhan, with a higher concentration of cases occurring in the first half of December [49]. An analysis of case locations showed that early infections were primarily clustered around the Huanan Market, supporting its identification as the outbreak's origin. Additionally, these areas experienced an excess of pneumonia-related deaths in January 2020, a metric less influenced by reporting bias [50].

Some of the earliest cases appeared to have no direct connection to the market, which could be attributed to undetected transmission chains and asymptomatic spread. A similar pattern was observed in the initial SARS-CoV outbreak [51]. **Figure 2.5** illustrates the timeline for the emergence of human coronaviruses.

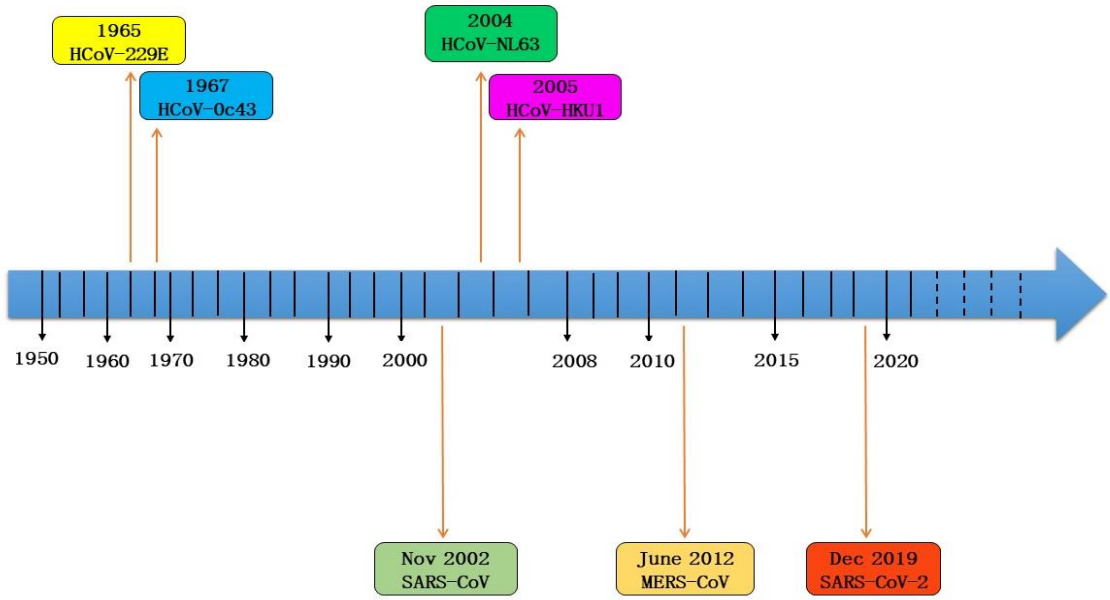

Figure 2.5. Timeline for the emergence of human coronaviruses **(***Based on data from [52] and the image was self-created using Canva)*

2.3. Symptoms and signs

Coronaviruses are a group of pathogens capable of infecting the lower respiratory tract in humans, leading to a spectrum of illnesses ranging from the common cold to severe infections with mortality rates reaching up to 50% [53]. COVID-19, caused by the SARS-CoV-2 virus, is an exceptionally transmissible infectious disease, with each infected individual potentially spreading the virus to an average of three others [54]. This reproductive rate surpasses that of SARS (1.7–1.9) and MERS (<1), indicating a higher propensity for widespread outbreaks. The increased transmissibility of COVID-19 compared to SARS and MERS is largely attributed to its relatively milder clinical presentation, allowing undiagnosed individuals to contribute to community transmission [55].

Although the majority of COVID-19 cases present with mild symptoms, a subset of patients may develop severe complications, including respiratory failure, arrhythmias, septic shock, renal impairment, cardiovascular injury, and hepatic dysfunction, particularly those with pre-existing health conditions [56,57]. The case fatality rate (CFR) of COVID-19 has been estimated at approximately 3.8%, though this figure varies among individuals with multiple comorbidities [58]. The predominant symptoms include fever, cough, and myalgia or fatigue [59]. Individuals presenting with fever and upper respiratory tract symptoms, in conjunction with lymphopenia or leukopenia, should be considered as potential cases [59]. Some patients may experience

diarrhoea prior to the onset of fever, and a minority may report headaches [60]. Notably, diarrhoea is a more frequently observed symptom in SARS cases [55].

Beyond its primary respiratory manifestations, which can progress to pneumonia, sepsis, or acute lung injury, emerging evidence suggests that COVID-19 may exert systemic effects, impacting multiple organ systems [61]. The observation that nearly 50% of affected individuals experience gastrointestinal symptoms, including diarrhoea and vomiting, raises the possibility of viral involvement in the gastrointestinal tract. **Figure 2.6** illustrates some common, uncommon, and severe symptoms in patients with COVID-19.

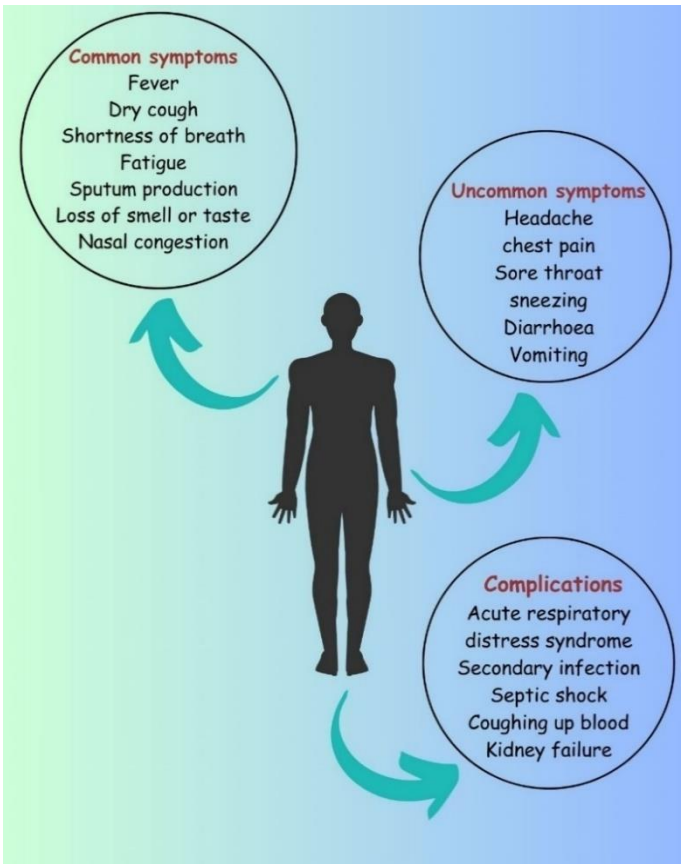

Figure 2.6. *The common, uncommon, and severe symptoms in patients with COVID-19 (Based on data from [62,63] and the image was self-created using Canva)*

Several studies suggest that 2019-nCoV infection, like certain other viral infections, may be associated with cardiac injury [62]. Severe inflammation of the heart muscle can lead to arrhythmias and compromise the heart's ability to pump blood effectively [64]. Consequently, individuals with pre-existing cardiovascular conditions and hypertension face a significantly higher risk of mortality compared to those without such conditions. Additionally, hospitalized

COVID-19 patients often exhibit abnormalities in blood clotting and an increased likelihood of venous thromboembolism, making anticoagulant therapy or thromboprophylaxis necessary in many cases [65]. Emerging evidence also indicates that COVID-19 may have a severe impact on the central nervous system (CNS). Some reported neurological symptoms include loss of smell, taste, or vision, along with reduced alertness [66].

In the early stages, COVID-19 symptoms may appear mild but can rapidly progress to severe complications. Monitoring the progression of symptoms is crucial, as many individuals do not exhibit signs of infection immediately after exposure. Symptoms may take up to 14 days to manifest, while some individuals remain asymptomatic throughout the course of infection. Initially, nasal congestion, sore throat, and cough are among the most common symptoms. Around three to five days after symptom onset, patients are more likely to experience fever, muscle pain, and headaches, with symptoms typically peaking during this period [67].

2.4. Pathophysiology

The pathogenic phases of COVID-19 remain incompletely understood but previous studies have proposed that SARS-CoV-2 may consist of the following phases:

A. Transmission of infection

Although relatively uncommon, coronaviruses have the potential to be transmitted from animals to humans [68]. The outbreak of the major coronaviruses in the past in humans suggested that bats act as reservoirs for these viruses that crossed the species barrier and infected humans as well as other domestic and wild mammals [69]. While the exact origin of SARS-CoV-2 remains uncertain, there is a clear possibility that the virus may have been transmitted from infected animals such as civet cats, snakes, or other species to humans at the Huanan seafood market [70]. Furthermore, various domestic animals, including ferrets, cats, and dogs, have been found to be susceptible to SARS-CoV-2, reinforcing the need to consider animal-to-human transmission as a potential pathway for viral spread [71]. Current scientific evidence suggests that human-to-human transmission remains the primary mode of SARS-CoV-2 dissemination [68]. Generally, individuals with symptoms of COVID-19 are more likely to transmit the virus to those in close proximity [72,73]. However, asymptomatic carriers also play a significant role in viral transmission, as they can unknowingly spread the infection [74-76]. This silent transmission mechanism has contributed to the rapid and widespread increase in COVID-19 cases, particularly in communities that have not strictly adhered to isolation and social distancing protocols, as well

as within households where asymptomatic individuals unknowingly infect family members [77-79].

SARS-CoV-2 can be transmitted through both direct and indirect means. Direct transmission occurs via respiratory droplets expelled during coughing, sneezing, or even talking, particularly when individuals are within one meter of an infected person [80-82]. Indirect transmission, on the other hand, involves contact with contaminated surfaces. If a person touches a surface carrying viral particles and subsequently makes contact with their eyes, nose, or mouth, infection may occur [82]. The role of faeces in the transmission of COVID-19 is unclear and considered to be an area of ongoing investigation. The presence of viral RNA in the faeces of infected individuals suggests the possibility of a faecal-oral transmission route [83,84]. There have been suggestions that the gastrointestinal system is a critical route for the spread of this virus [85]. The COVID-19 virus infects cells via the surface receptor, ACE2. The high expressions of ACE2 in gastric glandular, colon and ileum absorptive enterocytes, duodenal and rectal cells suggests that the virus spread via the faecal-oral route [86-88]. Environmental sampling has detected SARS-CoV-2 on surfaces such as toilet bowls, sinks, and door handles in restrooms used by COVID-19-positive individuals. Hence, poorly maintained public restrooms could pose a potential risk for viral transmission through contact exposure [89].

In summary, although human-to-human transmission remains the primary mode of SARS-CoV-2 spread, the possibility of zoonotic transmission and other pathways, including fecal-oral transmission should not remain unnoticed [89,90]. A schematic representation of SARS-CoV-2 Transmission Routes is shown in **Figure 2.7.**

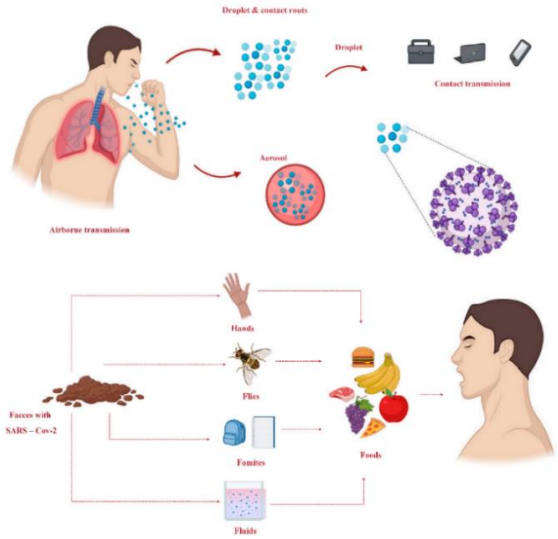

Figure 2.7. *Schematic representation of SARS-CoV-2 Transmission Routes (Taken from [91])*

B. Pathogenesis mechanisms

The pathogenesis of COVID-19 begins with the viral invasion of host cells via specific receptor interactions [92]. SARS-CoV-2 comprises four primary structural glycoproteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N). The S protein, which is critical for viral entry, consists of two subunits, S1 and S2. The S1 subunit specifically binds to the ACE2 receptor, facilitating viral attachment, while the S2 subunit undergoes proteolytic cleavage by transmembrane serine protease 2 (TMPRSS2), promoting membrane fusion between the virus and the host cell [93]. Following receptor binding, the fusion of viral and cellular membranes enables the internalization of the virus, initiating the infection process [94].

C. Body systems and organs affected

(i) Pulmonary effects

Pulmonary sequelae following SARS-CoV-2 infection exhibit significant heterogeneity and are classified as a post-COVID-19 condition, commonly referred to as long COVID and develop symptoms that persist for more than 3 months after SARS-CoV-2 infection. Among the notable pulmonary sequelae are pulmonary fibrosis and thromboembolic disease, though breathlessness remains the most frequently reported symptom, adversely impacting multiple biological systems [95].

Approximately 80% of individuals infected with COVID-19 experience mild to moderate symptoms, which may include a dry cough or sore throat. In some cases, the infection progresses to pneumonia, characterized by inflamed alveoli within the lungs [96]. Also, an average of 14% of severe illnesses requiring hospitalization and oxygen support [97]. In critical COVID-19 in about 5% of total cases the infection can damage the walls and linings of the air sacs in your lungs. As the immune system responds, inflammation intensifies, leading to fluid accumulation in the lungs making it harder for them to swap oxygen and carbon dioxide [96]. Severe COVID-19 has been associated with life-threatening complications, including acute respiratory distress syndrome (ARDS), sepsis, septic shock, acute kidney injury, and heart failure [98]. Old age and chronic diseases have been reported as risk factors for mortality. Among the elderly, the number of people in need of hospitalization and respiratory support has sharply increased [99]. In many cases, lung tissue damage resulting from the infection leads to varying degrees of long-term pulmonary abnormalities in affected individuals [100].

(ii) Cardiac effects

Cardiovascular complications, including myocardial injury, may manifest during COVID-19 infection. Myocardial injury, characterized by the death of cardiac muscle cells, can occur without noticeable symptoms in some individuals, while others may experience clinical manifestations such as chest pain, dyspnea, or lower extremity swelling [101]. Additionally, SARS-CoV-2 has been linked to an increased risk of myocardial infarction and cerebrovascular events due to its ability to infect arterial wall tissues, including associated macrophages. This infection triggers inflammation within atherosclerotic plaques, potentially leading to acute cardiovascular events such as heart attacks or strokes [102].

The body's immune response to the virus typically involves inflammation as a defense mechanism. However, in certain individuals with COVID-19, this inflammatory response becomes excessive, leading to further cardiac damage. Excessive inflammation can disrupt the electrical signaling of the heart, impair its pumping efficiency, and lead to abnormal heart rhythms, called arrhythmia, or make an existing arrhythmia worse [103]. In children and teenagers, an exaggerated inflammatory response known as multisystem inflammatory syndrome in children has been observed, with significant implications for cardiac function. Furthermore, severe cases of COVID-19 can induce widespread microvascular thrombosis, including within the myocardium, potentially contributing to long-term cardiovascular damage [103]. Cardiovascular sequelae may persist long after viral clearance and clinical recovery. Chronic inflammation can continue undetected, leading to long-term complications such as dyslipidemia, pulmonary fibrosis, and avascular necrosis, all of which have been reported among COVID-19 survivors [104].

(iii) Effects on brain

Coronaviruses not only affect the respiratory and circulatory systems but also exert significant impact on the central nervous system (CNS). Neurological manifestations associated with viral infections can be broadly categorized into those affecting the CNS and the peripheral nervous system (PNS) [105]. Common CNS manifestations include headache, altered consciousness, paresthesia, dizziness, ataxia, changes in sensorium, encephalitis, stroke, and seizures. In contrast, PNS involvement primarily manifests as skeletal muscle injury and peripheral neuropathies, including hyposmia and hypogeusia [105,106]. Headache is frequently reported among CNS symptoms during viral infections and usually remains associated with fever.

Additionally, impaired consciousness has been reported, particularly in critically ill patients [105].

Certain individuals develop meningitis and encephalitis, indicating direct viral invasion of the CNS. This invasion can lead to the suppression of brainstem reflexes, including those responsible for detecting oxygen deprivation. Neurological manifestations are more common in people with more severe disease and altered oxygen and carbon dioxide levels including dizziness, headache, impaired consciousness including confusion, delirium, and inability to rouse have been observed in such cases. Among these, delirium is a common occurrence and has been associated with long-term cognitive impairments, including memory deficits [107-110].

(iv) Effects on eyes

The ocular surface is a potential entry point for SARS-CoV-2, with exposure occurring through aerosolized droplets or direct hand-eye contact. Additionally, the ocular surface may act as a viral reservoir, contributing to the transmission of infection to others [111]. During the SARS epidemic, healthcare workers who had ocular exposure to infectious fluids were found to have an increased risk of contracting SARS-CoV-2 [112,113]. ACE2 receptor functions as the primary cell surface receptor facilitating SARS-CoV-2 entry into host cells [114-117]. The TMPRSS2 protease is also crucial for viral entry, as it mediates the cleavage of the viral spike protein following its attachment to ACE2 [114,118]. Studies have demonstrated the presence of ACE2 receptors in the conjunctiva, limbus, and cornea, particularly in the superficial epithelium and substantia propria. Furthermore, research confirms that all eye and conjunctival specimens express TMPRSS2, reinforcing the susceptibility of eyes to viral infection [111]. The presence of ACE2 receptors on the ocular surface, makes the eyes a potential target for SARS-CoV-2 leading to symptoms such as conjunctival congestion, excessive tearing, eyelid edema, itching, and photophobia. These symptoms are more commonly observed in individuals with severe systemic disease but, in rare cases, may also be the initial manifestation of COVID-19 [119]. To date, according to the American Academy of Ophthalmology, most reported cases of conjunctivitis associated with SARS-CoV-2 have been mild, bilateral, and follicular in nature, with minimal corneal involvement. While conjunctivitis is the most frequently observed ocular symptom in COVID-19, the virus may also contribute to other ocular conditions, including chronic dry eye, corneal nerve damage, uveitis, and retinal abnormalities [120].

(v) Gastrointestinal effect

Apart from the respiratory, cardiac and circulatory effects however, some COVID-19 patients also have gastrointestinal (GI) manifestations, such as diarrhea, nausea, vomiting and abdominal pain [121-123]. The involvement of the GI tract in SARS-CoV-2 infection is primarily attributed to the role of ACE2 receptors. Research indicates that ACE2 is abundantly expressed in the gastrointestinal system, particularly within the small and large intestines [124,125]. This suggests that the virus gains entry into host enteric cells through receptor-mediated mechanisms and furthermore provide a basis for its possible transmission route through the feces.

SARS-CoV-2 infection in the gastrointestinal tract has been linked to inflammation and, in some cases, gastrointestinal bleeding which have an impact on the intestinal immune system and further influence the immune system of the whole body thus worsening the severity of COVID-19 in the lungs and other organs [126, 127]. Additionally, SARS-CoV-2 infection disrupts the balance of gut microbiota, which may further impact overall immune homeostasis and disease progression [128]. The body systems and organs affected during COVID-19 has been depicted in **Figure 2.8.**

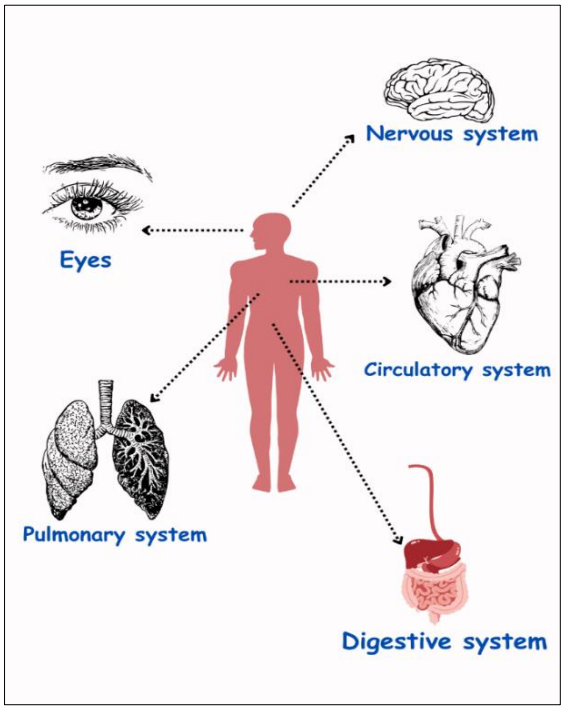

Figure 2.8. *Showing the body systems and organs affected during COVID-19 (The image was self-created using Canva.)*

2.5. Occurrence of covid-19 and SARS-CoV-2 variants

The COVID-19 pandemic has left a lasting impact on the world, claiming millions of lives, overwhelming healthcare systems, and disrupting societies and economies on an unprecedented scale. The first officially reported case dates back to December 31, 2019, when the World Health Organization (WHO) was alerted to a cluster of pneumonia cases in Wuhan City, Hubei Province, China, with no known cause at the time [129,130]. As the number of infections surged rapidly, the WHO officially declared COVID-19 a global pandemic on March 11, 2020. The disease, caused by the novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread at an alarming rate, leading to multiple waves of outbreaks.

The first wave primarily affected countries in early 2020, overwhelming hospitals and resulting in widespread lockdowns to curb transmission. The second wave, which struck in late 2020 and early 2021, was even deadlier in many regions due to the emergence of more transmissible variants, causing severe strain on healthcare resources and leading to high mortality rates [131]. While the first and second waves caused devastating consequences worldwide, the number of confirmed cases gradually began to slow down from February 2022 onward, eventually stabilizing, as reported by Worldometer. A timeline summarizing the major events for the occurrence of covid-19 is shown in **Figure 2.9**.

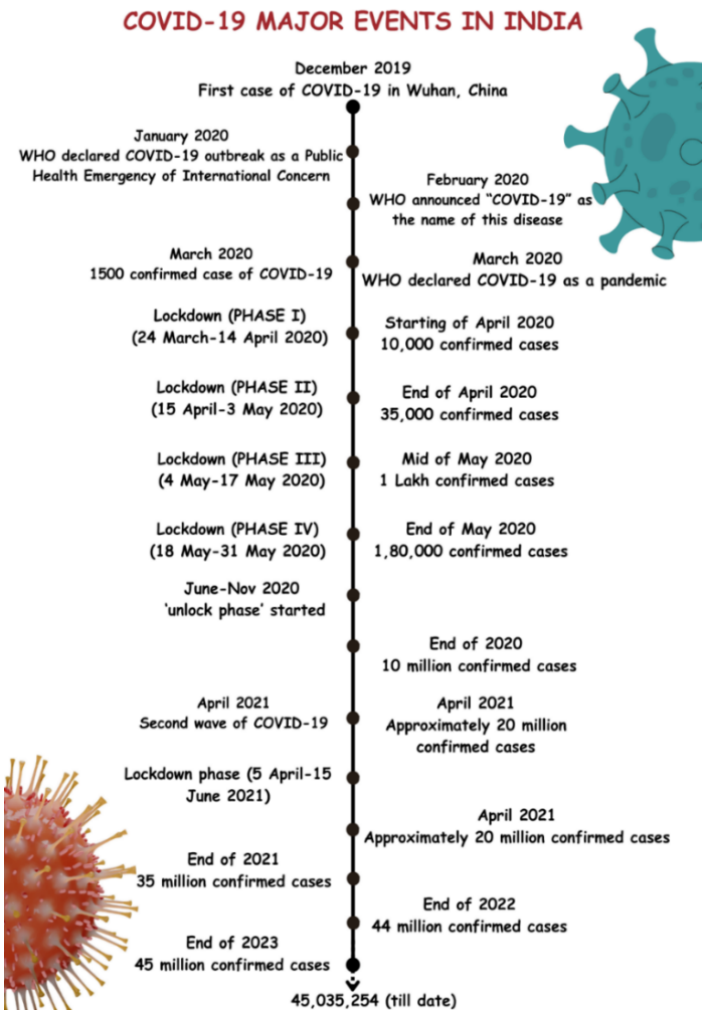

Figure 2.9. *Showing the COVID-19 major events in India (Based on data from [132-135] and the image was self-created using Canva.)*

The rise in COVID-19 cases throughout the pandemic was largely driven by the emergence of various SARS-CoV-2 variants. These new variants often had increased virulence, making them more infectious and leading to rapid transmission. To categorize these variants, different classification systems have been used, including GISAID, Nextstrain, and Pango, which group them based on genetic lineages. For easier public communication, the WHO recommended using Greek letters to name significant variants, especially for non-scientific audiences—for example, the Delta variant (lineage B.1.617.2) [136,137].

One of the most critical factors in studying SARS-CoV-2 variants is the spike protein. Mutations in this protein can significantly impact how easily the virus spreads, the severity of illness it causes, and even the effectiveness of vaccines designed to combat it [137-139]. Since the original Wuhan strain, several notable variants have emerged, including Alpha

(B.1.1.7), Beta (B.1.351), Epsilon (B.1.427 and B.1.429), Delta (B.1.617.2), Gamma (P.1), as well as the more recent XBB and JN.1 variants.

1. **Wuhan strain:** The novel coronavirus was first detected in December 2019 during an outbreak in Wuhan, the capital of Hubei province in China. Initially, the virus was largely confined to Wuhan and nearby regions in Asia, but by early 2020, it had rapidly spread across the globe. During the early days of the outbreak, the virus and disease were commonly referred to as "coronavirus," "Wuhan coronavirus [129-131]," "the coronavirus outbreak," and the "Wuhan coronavirus outbreak" [140]. The original strain of SARS-CoV-2, known as the Wuhan strain, was the first documented variant responsible for the initial wave of infections. It exhibited high transmissibility and primarily spread through respiratory droplets. Research suggests that the original Wuhan strain has undergone multiple mutations as it spread among populations, leading to the emergence of several new variants. These variants have appeared in different regions worldwide, with some becoming more dominant due to increased transmissibility. Among the most widespread SARS-CoV-2 variants are Alpha, Beta, Epsilon, Gamma, Delta, Kappa, and Omicron [141].
2. **Epsilon variant:** The Epsilon variant, also referred to as CAL.20C, is a strain of SARS-CoV-2, the virus responsible for COVID-19. It was first identified in California, USA, in July 2020 [142]. This variant includes two related lineages, B.1.427 and B.1.429, both carrying the same mutations in the receptor-binding domain (RBD) of the spike protein [143]. The rapid increase in cases linked to these lineages was largely associated with the L452R mutation in the spike protein, which may have enhanced the virus's ability to infect human cells. Due to its increased transmissibility, the U.S. Centers for Disease Control and Prevention (CDC) classified the Epsilon variant as a Variant of Concern (VOC) [144,145].
3. **Alpha variant:** The Alpha variant (B.1.1.7) was one of the first major VOC of SARS-CoV-2, first detected in Kent, UK, in September 2020. By December 2020, it had rapidly spread across multiple countries, becoming the dominant strain in several regions [146]. With 40–80% higher transmissibility than the original strain, it significantly contributed to the surge in COVID-19 cases worldwide [147]. The Alpha variant's increased contagiousness was linked to mutations in the S protein, particularly N501Y, which improved the ability of the virus to bind to the ACE2 receptor [148,149]. Research also

indicated greater disease severity, leading to higher hospitalization and mortality rates [150]. Although the variant did not fully evade vaccine-induced immunity, some studies reported a mild reduction in vaccine effectiveness, but vaccines still provided strong protection against severe illness [151]. The Alpha variant spread to over 100 countries but declined by late 2021 due to the emergence of more transmissible variants, including Beta, Delta, and Omicron [152].

4. **Beta variant:** Following the emergence of the Alpha variant, the Beta variant (B.1.351) [146] of SARS-CoV-2 was identified. It was first reported in Nelson Mandela Bay, Eastern Cape, South Africa, in October 2020 [153]. This variant quickly became the dominant lineage in South Africa and was later detected in 115 countries worldwide [154]. The Beta variant is characterized by 21 mutations, including nine mutations in the spike protein [153. Studies suggest that it may be more transmissible than earlier SARS-CoV-2 strains, with data indicating that the Beta variant was responsible for approximately 40% of new SARS-CoV-2 infections, compared to just 20% for the Alpha variant [154,155].
5. **Delta variant:** The Delta variant (B.1.617.2) of SARS-CoV-2 was first detected in Maharashtra, India, in October 2020 and quickly gained recognition as a variant of concern (VOC) due to its high transmissibility and widespread impact on COVID-19 cases worldwide [156]. Research suggests that Delta was 40–60% more transmissible than the Alpha variant (B.1.1.7), spreading 1.37–2.63 times faster, with an estimated 63%–167% increase in transmission rates [157]. This variant carries key spike protein mutations, including L452R and T478K, which strengthen its ability to bind to ACE2 receptors, thereby increasing infectivity [158]. Although vaccines continued to provide protection against severe illness, some studies indicated a decline in effectiveness against symptomatic infection caused by the Delta variant [159,160].

   Following the Delta variant, another similar lineage with greater virulence called Delta plus has been reported in Maharashtra, India during the late 2020. The Delta Plus variant contains additional mutation (K417N) in S-protein compared to the Delta variant [158,161]. Therefore, since October 2020 two variants i.e. Delta and Delta plus became a cause for concern.
6. **Kappa variant:** The Kappa variant (B.1.617.1) of SARS-CoV-2 was initially identified in India during December 2020. By April 1, 2021, Public Health England had classified it as a Variant Under Investigation (VUI-21APR-01). This variant encompasses several notable mutations in the spike protein, including E154K in the N-terminal domain (NTD), L452R

and E484Q in the receptor-binding domain (RBD), and P681R near the furin cleavage site [162]. Due to its possession of these critical spike protein mutations also found in the Delta variant, the Kappa variant is considered a precursor to the highly transmissible Delta variant, which significantly contributed to the severity of the second COVID-19 wave in India [163,164].

7. **Gamma variant**: The Gamma variant (P.1) is a significant variant of SARS-CoV-2 which classified under lineage P.1, carries 17 amino acid substitutions, with ten occurring in the spike protein [146]. Among these mutations, N501Y, E484K, and K417T are particularly concerning due to their impact on viral behavior [165]. The variant was first identified by the National Institute of Infectious Diseases (NIID) in Japan on January 6, 2021, in four individuals who had traveled from Amazonas, Brazil, to Tokyo just four days earlier [166,167]. The emergence of the P.1 variant significantly altered the epidemiological landscape of COVID-19 due to its increased transmissibility and ability to partially evade immune responses [168]. The presence of the N501Y mutation enhances the variant's binding affinity to the ACE2 receptor, contributing to its higher infectivity. Studies have shown that the transmissibility of the Gamma variant is approximately 1.4 to 2.2 times greater than the original strain of SARS-CoV-2 [169-171].
8. **Omicron variant:** The Omicron variant has impacted countries across the globe, including India, playing a major role in the course of the pandemic. Just as the world anticipated the end of COVID-19, Omicron unexpectedly emerged, spreading rapidly due to its high transmission rate and affecting a vast population [172]. The World Health Organization (WHO) first identified and classified Omicron (B.1.1.529) as a variant of concern in November 2021 [172-174], with initial cases detected in Botswana and South Africa [175]. The Indian SARS-CoV-2 Genomics Consortium (INSACOG) reported in its January 2022 bulletin that Omicron had entered community transmission in India, leading to a sharp rise in new infections [174,176]. Omicron was notable for its extensive mutations, particularly in the spike protein, where it exhibited approximately 15 mutations, significantly increasing its potential impact on disease spread and immune escape [177]. Compared to previous variants like Delta and Beta, Omicron demonstrated greater transmissibility, allowing it to spread more rapidly than earlier SARS-CoV-2 variants [178]. Following the emergence of the original B.1.1.529 lineage, genetic mutations led to the development of multiple subvariants, including BA.1 (B.1.1.529.1), BA.2 (B.1.1.529.2), BA.3 (B.1.1.529.3), BA.4 (B.1.1.529.4), and BA.5 (B.1.1.529.5) [172]. These subvariants exhibited distinct S protein

mutations, particularly in the N-terminal domain and receptor-binding regions, contributing to variations in transmissibility and immune evasion [172,179].

Beyond the primary Omicron subvariants (BA.1, BA.2, BA.3, BA.4, and BA.5), further mutations gave rise to additional sub-lineages that significantly influenced the pandemic on a global scale. These include BA.2.12 (B.1.1.529.2.12) and BA.2.12.1 (B.1.1.529.2.12.1), BA.2.75 and BA.2.75.2, as well as XBB and XBB.1, among others [180].

9. **XBB omicron:** The SARS-CoV-2 Omicron variant has continued to evolve, giving rise to new subvariants such as XBB and its derivatives, including XBB.1.5 and XBB.1.16. These emerging subvariants have drawn considerable attention due to their increased transmissibility and strong immune evasion capabilities [181,182]. The XBB lineage, identified in late 2022, is a recombinant strain that originated from the genetic recombination of two distinct Omicron subvariants. Structural studies suggest that the S proteins of XBB subvariants have reinforced conformations, allowing them to effectively evade neutralizing antibodies. This adaptation enhances their ability to spread rapidly and increases the risk of breakthrough infections [183].

Among these subvariants, XBB.1.5 has gained prominence due to its rapid transmission across multiple regions. Clinical data suggests that XBB.1.5 infections tend to be mild, with most cases being asymptomatic or presenting with mild symptoms, and severe hospitalizations remaining relatively rare in specific populations. The widespread detection of XBB.1.5 in various countries highlights its global impact [184-187].

Similarly, the XBB.1.16 subvariant has demonstrated a growth advantage over earlier strains. Despite showing slightly lower binding affinity to the ACE2 receptor compared to XBB.1.5, it retains a similar level of infectivity [188]. Overall, the emergence and spread of XBB and its subvariants underscore the continuous evolution of SARS-CoV-2 and the necessity for ongoing genomic surveillance and adaptation of public health strategies.

10. **JN.1:** The COVID-19 pandemic continues to evolve globally, driven by the emergence of new SARS-CoV-2 variants that necessitate intensive surveillance and monitoring [189]. One such recent variant, JN.1, was first identified in the United States in September 2023 and has since become dominant in several countries, including the United Kingdom, Iceland, and Portugal (WHO, 2023) [189]. JN.1 is a descendant of the BA.2.86

lineage and is characterized by multiple mutations in the spike gene, which introduce new challenges in understanding its transmissibility and immune evasion mechanisms [189]. Among these mutations, the Leu455Ser spike protein mutation is a key distinguishing feature of JN.1, significantly enhancing its ability to spread more efficiently and evade immune responses compared to its parental variant [190]. A timeline showing the emergence of different SARS-CoV-2 variant is shown in **Figure 2.10**.

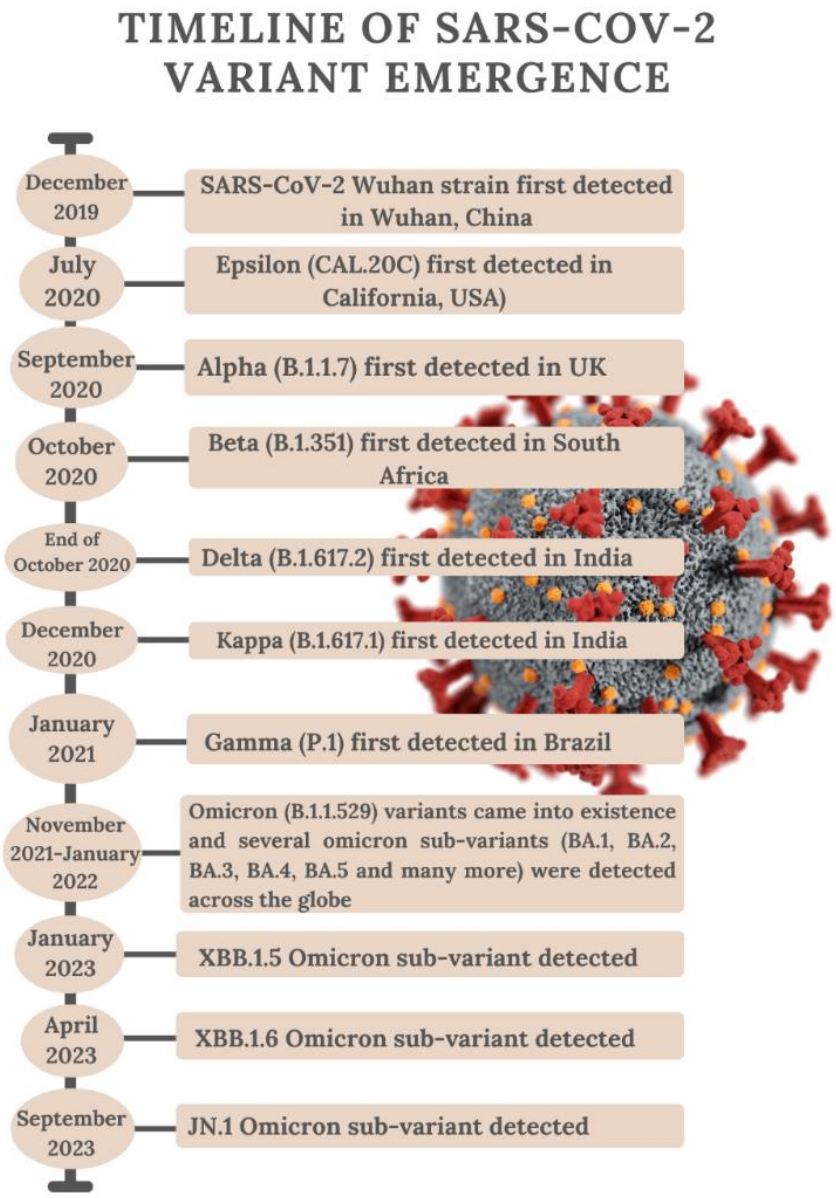

***Figure 2.10**. Timeline of SARS-CoV-2 variant emergence (Based on data from [191,192] and the image was self-created using Canva.)*

2.6. Diagnosis and treatment

Diagnosis for COVID-19:

A patient's history of exposure or close contact with suspected or confirmed COVID-19 cases serves as essential diagnostic evidence. However, in instances where such a history is unknown, clinical manifestations and imaging findings can indicate a possible COVID-19 infection. To confirm the diagnosis, a real-time reverse-transcription polymerase chain reaction (RT-PCR) test should be conducted as the reference standard [193,194]. Nonetheless, due to the potential for false-negative results in SARS-CoV-2 PCR testing using nasal swabs, clinical, laboratory, and imaging findings may also support a presumptive diagnosis [195].

As per the diagnostic guidelines issued by the National Health Commission (NHC) of China, the criteria include: (1) a history of exposure to individuals with respiratory symptoms from Wuhan or other affected cities within two weeks before symptom onset, (2) clinical indicators such as fever, a normal or decreased white blood cell (WBC) count, a reduced lymphocyte count, and/or imaging evidence of pneumonia, and (3) a positive RT-PCR test for COVID-19. A confirmed case of COVID-19 pneumonia requires hospitalization and isolation for appropriate treatment [194,196].

Based on the WHO recommendations for SARS and MERS, the NHC of China proposed criteria for diagnosis and treatment of COVID-19 pneumonia. A person with two clinical conditions and one contact history is regarded as a suspected patient. Without any clear contact history, suspected cases should have three clinical features [193,194].

Treatment for COVID-19:

As stated by the National Institutes of Health (NIH), the pathogenesis of COVID-19 is primarily driven by two key processes: the replication of the virus during the initial stage of infection and a dysregulated immune or inflammatory response to SARS-CoV-2 in the later phase, which results in widespread tissue damage. Consequently, the treatment strategy focuses on the use of antiviral medications to inhibit viral replication during the early phase of the illness, while immunomodulators are employed in the later stage to manage the inflammatory response [197].

Several drugs have received approval or emergency use authorization (EUA) for the treatment of COVID-19 and the approval status varies by country and regulatory agency. Below are some of the key drugs that have been used for COVID-19 treatment:

Remdesivir, originally formulated to target Ebola virus infections, was later repurposed for the treatment of COVID-19 due to its broad-spectrum antiviral capabilities. It was the first antiviral medication to get fully approved from the U.S. Food and Drug Administration (FDA) for COVID-19 treatment. [198,199]. Remdesivir is a nucleotide analog prodrug that is metabolized intracellularly into its active form, GS-441524. This metabolite inhibits RNA-dependent RNA polymerase (RdRp), a crucial enzyme for viral replication, by causing premature termination of RNA synthesis. This mechanism grants Remdesivir efficacy against coronaviruses, including SARS-CoV-2 [200]. Studies have shown that Remdesivir reduces hospitalization duration in COVID-19 patients and decreases the likelihood of disease progression to severe stages. It is mainly administered to hospitalized individuals with moderate to severe COVID-19 who need supplemental oxygen but are not reliant on mechanical ventilation [201].

Favipiravir is an antiviral medication that selectively targets and inhibits viral RNA polymerase, exhibiting effectiveness against various RNA viruses [202,203]. Clinical research has shown that early administration of oral favipiravir, alongside standard supportive care, significantly reduces recovery time in patients with mild-to-moderate COVID-19 compared to supportive care alone [204]. This drug functions as a substrate for the RNA-dependent RNA polymerase (RdRp) enzyme, which misidentifies it as a purine nucleotide, thereby disrupting enzyme activity and halting viral protein synthesis [205,206].

Protease plays a crucial role in the processing of coronavirus polyproteins, making it a significant target for COVID-19 treatment. In recent years, extensive research has been conducted on protease inhibitors for managing the disease. Lopinavir, a viral protease inhibitor, is primarily used in the treatment of human immunodeficiency virus (HIV). Ritonavir enhances the serum concentration of lopinavir by inhibiting its CYP3A-mediated metabolism in vivo [207,208]. As a result, lopinavir and ritonavir are formulated as a combination therapy.

Molnupiravir, a ribonucleoside prodrug of N-hydroxycytidine, exhibits antiviral activity against SARS-CoV-2 and other coronaviruses [208,209]. Clinical trials demonstrated that it reduced the risk of hospitalization or death by nearly 50% in nonhospitalized adults with mild-to-moderate COVID-19 who were at risk for severe outcomes [208,210]. A phase 3 clinical trial further confirmed its effectiveness in reducing hospitalization and mortality rates

when administered early [208, 211]. Additionally, studies indicate that molnupiravir is active against major SARS-CoV-2 variants, including delta, gamma, and mu, with a moderate antiviral effect [208, 212, 213]. Given its efficacy, the UK Medicines Regulator and the US FDA have authorized its emergency use for treating mild-to-moderate COVID-19 in adults.

2.7. SARS-CoV-2 Viral proteins

2.7.1. Introduction to Spike protein – Structure and function

SARS-CoV-2, the virus responsible for severe acute respiratory syndrome coronavirus [214], is an enveloped virus with a positive-sense single-stranded RNA genome approximately 30 Kb in length [214,215]. This viral genome contains 14 open reading frames (ORFs) that encode 16 nonstructural proteins (nsp1–16), 9 accessory proteins (ORFs), and 4 structural proteins, each playing a distinct role in viral infectivity and transmission [216-218]. The virus's structural proteins include the spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins, collectively referred to as surface glycoproteins **(Figure 2.11)** [216-219]. These proteins are essential for maintaining the architecture of SARS-CoV-2, with the S protein being a key therapeutic target due to its role in viral entry. Since the virus's emergence, significant advancements in understanding the structural biology of the SARS-CoV-2 S protein have greatly enhanced knowledge of its entry mechanisms [220,221].

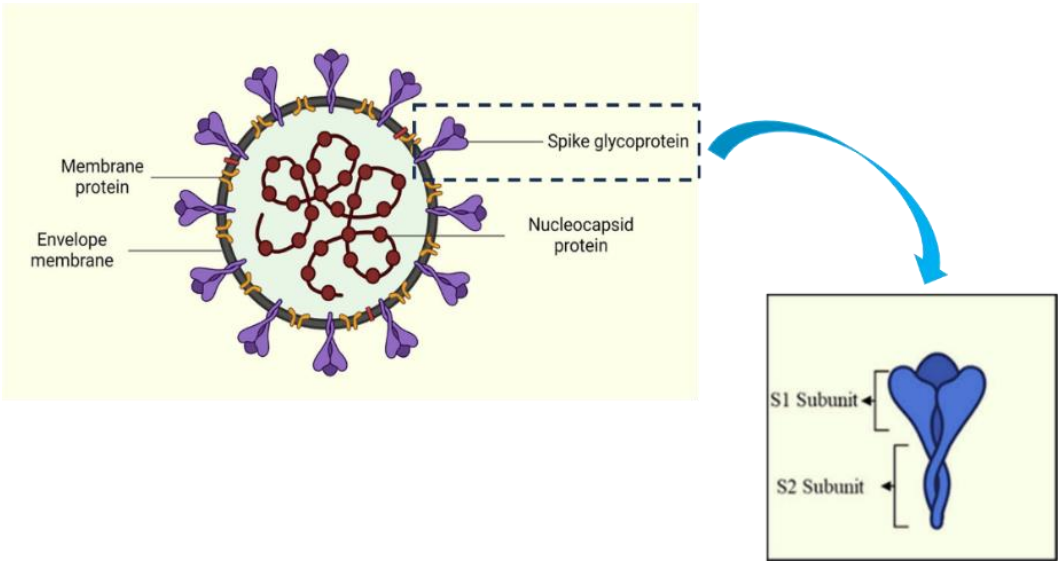

Figure 2.11. *SARS-CoV-2 virus depicting the location of the nucleocapsid (N), membrane (M), envelope (E), and spike (S) protein and zooming out the S protein (Based on data from [5] and the image was self-created using Canva).*

The S protein, a glycoprotein of approximately 180 kD, protrudes from the viral surface and plays a critical role in viral attachment and entry into host cells. The initial stage of the infection cycle in enveloped viruses involves interaction with cellular receptors followed by fusion with the host cell membrane, a process facilitated by the spike protein [222]. Structurally, the S protein comprises an extracellular N-terminal region, a transmembrane (TM) domain embedded in the viral membrane, and a short intracellular C-terminal segment [223]. It is composed of a signal peptide (amino acids 1–13) at the N-terminus, along with two key subunits: S1 (residues 14–685), which is responsible for receptor binding, and S2 (residues 686–1273), which mediates membrane fusion. Within the S1 subunit, there is an N-terminal domain (14–305 residues) and a RBD (319–541 residues). Meanwhile, the S2 subunit contains functional regions essential for viral fusion, including the fusion peptide (FP) (788–806 residues), heptapeptide repeat sequence 1 (HR1) (912–984 residues), HR2 (1163–1213 residues), TM domain (1213–1237 residues), and cytoplasmic domain (1237–1273 residues) **(Figure 2.12)** [224].

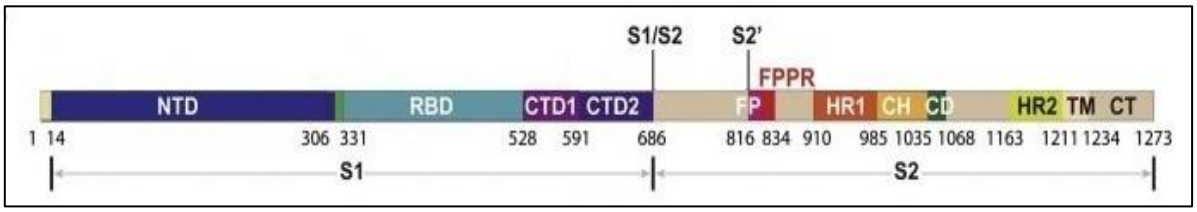

Figure 2.12. *Schematic representation of the SARS-CoV-2 spike protein organization. Segments of S1 and S2 include: NTD, N-terminal domain; RBD, receptor-binding domain; CTD1, C-terminal domain 1; CTD2, C-terminal domain 2; S1/S2, S1/S2 cleavage site; S2', S2' cleavage site; FP, fusion peptide; FPPR, fusion peptide proximal region; HR1, heptad repeat 1; CH, central helix region; CD, connector domain; HR2, heptad repeat 2; TM, transmembrane anchor; CT, cytoplasmic tail (Taken from [224]).*

The infection process begins when viral particles bind to specific cell receptors on the host cell surface, making receptor recognition a crucial factor in viral entry and a key target for drug development. Within the S1 subunit, the RBD interacts with the ACE2 receptor on host cells. The RBD consists of a core subdomain and a receptor-binding motif, which directly engages with ACE2 [225,226]. This domain has been widely utilized as a target in the development of antiviral drugs and vaccines against SARS-CoV. The S1 region also contains the NTD and CTD. Notably, the SARS-CoV-2 S CTD possesses more residues (21) that interact with ACE2 compared to the SARS-CoV RBD (17), leading to a larger buried surface area when complexed

with ACE2 [227-229]. While the primary role of the S1 domain is receptor binding, the S2 domain is responsible for facilitating membrane fusion [230-232].

2.7.2. Receptor of spike: ACE2 and S protein-ACE2 interaction

The entry of coronaviruses into host cells marks the beginning of infection, facilitated by the spike glycoprotein on the viral envelope, which interacts with specific receptors on the host cell membrane. Research has identified ACE2 as the primary functional receptor for SARS-CoV [233]. Zhou et al. confirmed that SARS-CoV-2 can successfully infect cells expressing ACE2, whereas cells lacking this receptor remain resistant to infection, establishing ACE2 as the key entry receptor for SARS-CoV-2 [234]. ACE2 is an enzyme that plays a crucial role in counteracting the renin–angiotensin–aldosterone system (RAAS) and functions as a receptor for SARS viruses [233–235]. Once the RBD of the spike glycoprotein attaches to subdomain I of ACE2, membrane fusion between the virus and the host cell is triggered, allowing viral RNA to enter the cytoplasm and initiate infection [236,237]. In SARS-CoV infection, both the intact ACE2 receptor and its transmembrane domain are internalized along with the virus [238].

ACE2 is expressed at varying levels in most human organs, with the highest concentration found in type II alveolar epithelial cells. It is weakly expressed in epithelial cells of the oral and nasal mucosa, as well as the nasopharynx, indicating that the lungs are the primary target of SARS-CoV-2 [239,240]. Additionally, ACE2 is highly expressed in myocardial cells, proximal tubule cells of the kidney, and bladder urothelial cells. It is particularly abundant in enterocytes of the small intestine, especially in the ileum [239–241]. **Figure 2.13** illustrates the ACE2 expression throughout the body.

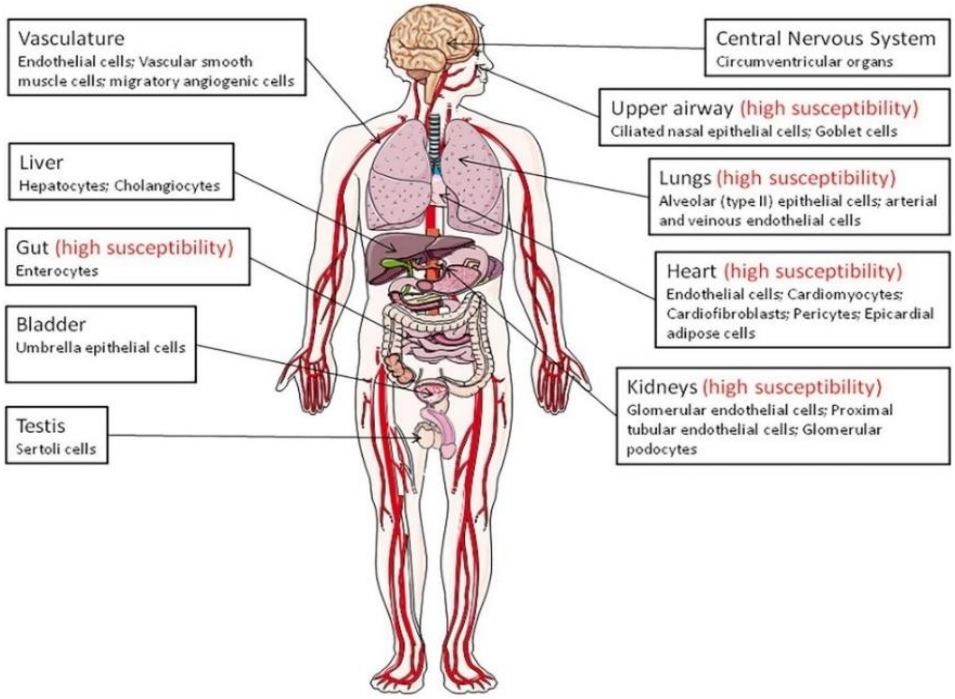

***Figure 2.13**. Angiotensin-converting enzyme 2 (ACE2) expression throughout the body. The organs vulnerability to SARS-CoV-2 infection is also indicated (high susceptibility) (Taken from [242]).*

Spike-ACE2 interaction:

The SARS-CoV-2 S protein relies on human ACE2 as its entry receptor to infect target cells. Therefore, the interaction between the S protein and ACE2 is essential for membrane fusion, contributing to viral transmission and disease progression [243]. The recognition of the ACE2 receptor by the spike glycoprotein is a key factor in determining the infectivity, pathogenicity, and host range of SARS-CoV-2. The spike protein exists in two structural states: a closed form, where the RBDs shield the S2 core, preventing ACE2 interaction, and an open form, where one S1 subunit shifts to expose the RBD, enabling ACE2 binding [244–248]. **(Figure 2.14).**

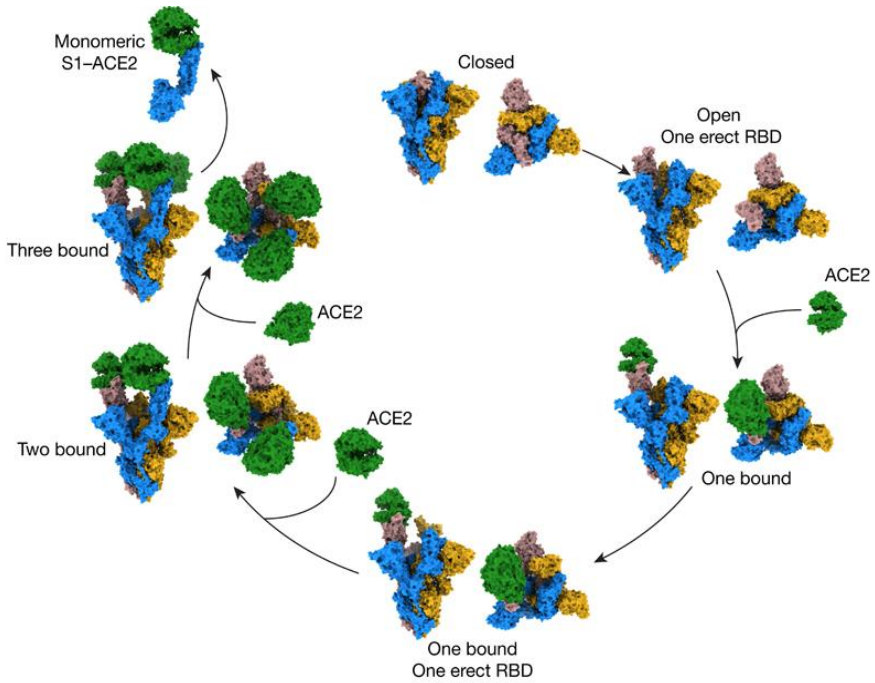

Figure 2.14. *Surface representation of the spike, with monomers coloured in blue, rosy brown and gold, and ACE2 coloured in green. Each step shows two views of the spike complexes: a trimer axis vertical view (left) and an orthogonal top-down view along the axis (right). Clockwise from the top, we show structures for closed, open but unbound RBD, followed by sequential ACE2-binding events until reaching the fully open, three-ACE2-bound spike protein state. From this final trimeric species, we show dissociation into monomeric S1–ACE2, which may also occur for the one- or two-ACE2-bound species (Taken from [248]).*

The RBD of the SARS-CoV-2 S protein interacts with ACE2 through an extended receptor-binding motif (RBM) that aligns with the N-terminal helix of ACE2, creating a concave binding interface [249–251]. This interaction involves 20 ACE2 residues and 17 RBD residues, forming a network of hydrophilic side-chain interactions. Mutations in these interacting residues [252–257] may enhance receptor binding or contribute to antibody resistance. The overall ACE2 binding mechanism remains largely similar between SARS-CoV and SARS-CoV-2 RBDs [249–251,258], with the key difference being an additional residue in SARS-CoV-2, Lys417, which forms a salt bridge with Asp30 of ACE2.

2.7.3. Alternative receptors of Spike

Although ACE2 is a significant and considered to be the primary receptor for SARS-CoV-2 infection, the pathology caused by SARS-CoV-2 cannot be characterised by its distribution. Apart from ACE2 receptors, certain human cells possess ACE2-dependent accessory receptors or co-receptors that may facilitate viral entry by interacting with SARS-CoV-2 spike proteins

[259,260]. Even though cells that express ACE2 facilitate strong SARS-CoV-2 viral replication [261], ACE2 expression levels are not entirely correlated with immunological responses or clinical manifestations [259,261,262]. For instance, ACE2 expression in the lung is low and limited to ciliated cells and type II alveolar cells [263], yet lung pathology is not limited to these cells and are the most affected organ during COVID-19. The inference is that SARS-CoV-2 infected organs or cells that do not express ACE2 to the extent of its infectivity suggesting the involvement of alternative receptors for SARS-CoV-2 [260,264-267]. Furthermore, highly transmissible SARS-CoV-2 variants have evolved to be less reliant on the host protease TMPRSS2, resulting in altered entry mechanisms, shifts in cell tropism, and changes in disease progression [268–271]. This suggests that alternative receptors may contribute to viral evolution and immune evasion. Gaining a deeper understanding of these alternative receptors is essential for the development of targeted antiviral therapies and strategies to reduce virus-induced immune responses and clinical complications.

According to literature, CAT, AGTR2, L-SIGN, and DC-SIGN are some possible co-receptors or alternative receptors for SARS-CoV-2. Not only did they express themselves specifically in the lung and other organs affected by COVID-19, but also had higher binding affinities with S protein than ACE2 [272].

Catalase (CAT), a key antioxidant enzyme [273], is predominantly expressed in the lungs, kidneys, intestines, and other tissues affected by COVID-19. Elevated CAT expression has been linked to hypertension prevention, reduced renal oxidative stress, and a potential correlation with ACE2 expression [274]. Notably, ACE2 deficiency has been shown to enhance NADPH-mediated oxidative stress in the kidneys, suggesting a possible connection with CAT [275]. Additionally, protein-protein interaction studies indicate that CAT may exhibit a stronger binding affinity to the SARS-CoV-2 spike protein compared to ACE2 [272].

AGTR2, a member of the G protein-coupled receptor 1 family, serves as an angiotensin II receptor and interacts with ACE2. It exhibits high tissue specificity, with significant expression in the lungs. Consistently, research has indicated that AGTR2 demonstrates a stronger binding affinity to the SARS-CoV-2 spike protein compared to ACE2 [276]. Consequently, both CAT and AGTR2 are considered potential ACE2 co-receptors, playing a role in stabilizing the interaction between ACE2 and the spike protein, thereby facilitating viral entry into host cells [272].

Previous studies have indicated that L-SIGN and DC-SIGN may interact with the SARS-CoV spike protein, facilitating viral infection [277]. Furthermore, both DC-SIGN and L-SIGN

exhibit higher binding affinities to the S protein compared to ACE2, suggesting their potential roles as alternative receptors that function independently of ACE2 [272]. Notably, unlike ACE2, which is expressed at relatively low levels in the lungs and other organs, DC-SIGN is abundantly present in lung tissue. Additionally, L-SIGN is widely expressed in the lungs, colon, and cerebral cortex, implying its potential role as a broad-spectrum receptor across multiple organ systems.

2.7.4. Introduction to Mpro – Function and Structure

The main protease (Mpro), also referred to as 3-chymotrypsin-like protease (3CLpro), is a highly conserved cysteine hydrolase found in β-coronaviruses and represents a crucial target for antiviral drug development [278,279]. SARS-CoV-2 Mpro plays a fundamental role in processing viral polyproteins into their functional forms, which are essential for viral RNA synthesis [280]. Following proteolytic cleavage by Mpro, nonstructural proteins (nsps) contribute to the formation of the viral replication-transcription complex, facilitating RNA synthesis [281,282]. Additionally, Mpro is vital in encoding two polyproteins, pp1b and pp1ab, which undergo self-cleavage. It also mediates the cleavage of 11 other sites, leading to the production of 16 nonstructural proteins necessary for viral replication [283]. Given its indispensable role in viral gene expression and replication, Mpro is a key target for therapeutic intervention. Since 3CLpro is crucial for CoV replication, particularly in the SARS-CoV and SARS-CoV-2 outbreaks, it has been identified as a promising target for developing broad-spectrum antiviral agents [284-288]. Furthermore, the absence of a human homolog of 3CLpro allows for the design of highly selective inhibitors that exhibit minimal effects on human proteases, thereby reducing potential side effects.

Structure

The Mpro is a homodimeric protein, with each monomer arranged perpendicularly to the other. Each monomer consists of 306 amino acids and is structured into three distinct domains: domain I (residues 8–101), which contains four α-helices and seven β-strands; domain II (residues 102–184), composed of seven β-strands; and domain III (residues 201–303), which includes five α-helices [289-292] **(Figure 2.15).** The catalytic site of 3CLpro is situated at the interface between domains I and II, while domain III plays a crucial role in homodimerization, a process essential for the enzyme's catalytic function [293,294].

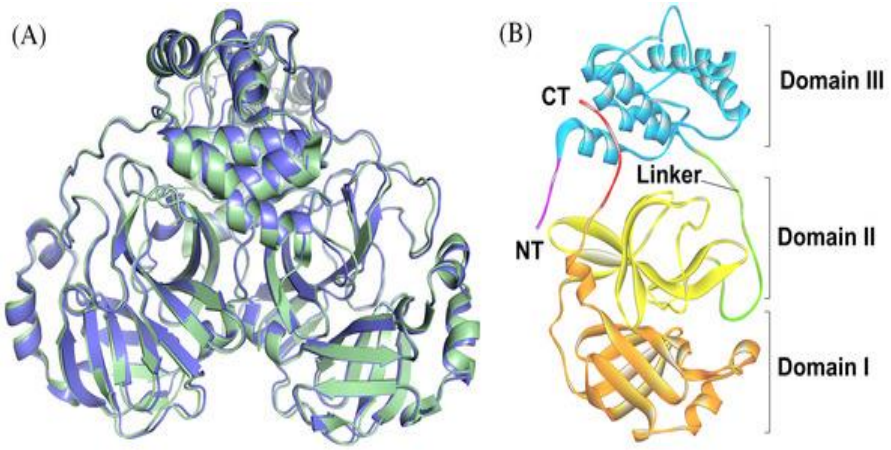

Figure 2.15. (A) *The 3D structure of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 3CLpro (pale green, PDB: 6XHU) and severe acute respiratory syndrome coronavirus (SARS-CoV) 3CLpro (slate, PDB: 1UJ1).* ***(B)*** *Three structural domains (domain I: orange, domain II: yellow, domain III: blue) of SARS-CoV-2 3CLpro monomer (Taken from [278]).*

Unlike conventional chymotrypsin-like enzymes and numerous serine (Ser) or cysteine (Cys) hydrolases, the Mpro of SARS-CoV-2 features an unusual cysteine-based catalytic mechanism. It comprises a Cys-His catalytic dyad, specifically Cys145 and His41, which plays a crucial role in enzymatic activity **(Figure 2.16)** [295-299]. In this catalytic dyad, Cys145 acts as a nucleophile in the proteolytic process, while the imidazole side chain of His41 functions as a general base [300]. The active sites of Mpro exhibit a high degree of conservation, and its binding pocket predominantly consists of hydrophilic residues [300]. Sequence alignment revealed that the 3CLpro-CoV-2 shares 96% similarity with SARS, which is highly conservable among CoVs [301]. Meanwhile, the structure of these proteins (in apo forms) was also found to be very similar as indicated by the low RMSD. value (0.459 Å) from the structural superimposition. In addition, none of the mutation effected the overall structure of 3CLpro-CoV-2.

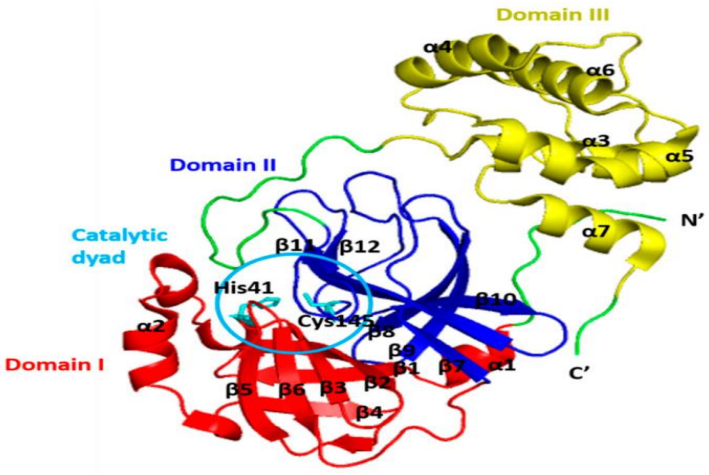

Figure 2.16. *Domain organization of the monomeric structure of the SARS-CoV-2 3CLpro. Domain I (residues 8–101) is colored in red, domain II (residues 102–184) is colored in blue and domain III (residues 201–303) is colored in yellow. The catalytic dyad (His14 and Cys145) of 3CLpro is shown in stick (indicated by circles) (Taken from [295]).*

2.7.5. Inhibition of Mpro

Proteases have been a primary target in the development of antiviral drugs designed to combat viral infections [302]. However, the identification of effective Mpro inhibitors for COVID-19 treatment remains limited. Many computational studies have investigated the potential of existing antiviral drugs that target viral replication as possible therapeutic options for COVID-19 [303-307].

In recent years, computer-aided drug discovery (CADD) has become a vital tool in drug development, significantly enhancing the identification of protein inhibitors and the analysis of protein-drug and protein-protein interactions. Given the substantial time and financial investment required for drug development, computational approaches such as virtual screening, molecular docking, molecular dynamics (MD) simulations, and binding free energy calculations offer efficient strategies for identifying potential drug candidates from extensive compound libraries.

Small-molecule inhibitors provide notable advantages in drug development, including favorable oral bioavailability and the feasibility of rational design [308]. In contrast, despite having a strong affinity and specificity for their target proteins, peptides were frequently overlooked as possible targets for drug development. Compared to proteins, they are smaller and can be produced synthetically using reliable and affordable techniques [309]. As of now, over 11.8 billion vaccine doses have been administered worldwide [310, 311]. Several antiviral drugs have

been granted emergency use authorization to combat SARS-CoV-2 infection and replication, including Remdesivir, Dexamethasone, Favipiravir, Lopinavir/Ritonavir, Nirmatrelvir/Ritonavir (a main protease inhibitor), and Darunavir [312-317]. Additionally, the Chinese National Medical Products Administration has approved three antivirals: Azvudine, Renmindevir, and Xiannuoxin (a combination of Simnotrelvir and Ritonavir) [16]. Among these, Remdesivir [318], Molnupiravir [319], Renmindevir [320], and Azvudine [321] inhibit SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), while Nirmatrelvir [312], Ensitrelvir [322], and Simnotrelvir [317] target the main protease (Mpro). However, they have several shortcomings as a consequence of the pandemic emergency response, such as inadequate potency, toxicity, or pharmacokinetic characteristics, such as low oral drug exposure, poor oral bioavailability, and intermediate stability in human liver microsomes [318-320, 323].

Medicinal plants yielding biologically active compounds have always been of great interest to scientists as they play an essential role in preventing human diseases. India, in particular, has been widely recognized for its traditional use of spices as medicinal agents. Numerous active pharmaceutical ingredients with diverse physiological and pharmacological properties have been identified and extracted from these natural sources [324]. In addition to approved antiviral drugs, extensive research has been conducted to explore the therapeutic potential of Indian spices in the search for bioactive compounds capable of inhibiting SARS-CoV-2 Mpro. According to existing literature, certain small chemical molecules, including Carnosol, Arjunglucoside-I, and Rosmanol, derived from Indian spices, have been identified as potential inhibitors of SARS-CoV-2 Mpro, indicating their possible antiviral properties against the novel coronavirus [325]. Moreover, these compounds have also demonstrated anti-carcinogenic activities [326-328]. However, further investigations are required to establish their efficacy before clinical trials can be pursued.

2.8. Scope of thesis

1. As discussed earlier both the S protein and Mpro has gained outmost importance during COVID-19 because of their vital role in the viral entry into the host cell and viral replication respectively. Hence, before going into the depth analysis of these target proteins, a detailed analysis on the structural insights of both the proteins are quite necessary. In **Chapter 4** of the thesis the salient structural features on the Mpro and the S protein were investigated. **Chapter 4** also involves the study on the conformational accessibility analysis on the S protein with its ACE2 receptor. The S protein can be receptor accessible as well as inaccessible depending on

the state of S protein. Therefore, in the second part of this chapter, a computational study was designed to analyze the conformational accessibility of SARS-CoV-2 S-protein with the ACE2 receptor using three different states (open, closed and Intermediate) of the Spike and checked the extent of accessibility and inaccessibility of ACE2 receptor to different states of S protein.

2. Mpro has been validated as a promising target for developing broad-spectrum anti-CoV agents because of its vital role in the viral gene expression and replication. Despite its potential, the search for Mpro inhibitors that could be used to treat COVID-19 has been a limitation throughout the pandemic. Researcher through virtual screening method has identified few small chemical molecules from Indian spices that have the capacity to inhibit SARS-CoV-2 Mpro and may have antiviral properties against nCoV. Therefore, in **Chapter 5** of the thesis a computational study has been designed to analyze the structural dynamics and characteristic features of binding of three small molecules (Carnosol, Arjunglucoside-I, and Rosmanol) to the Mpro and to validate the inhibition property of these small molecules.

3. Apart from the small molecules, despite having a strong affinity and specificity for their target proteins, peptides were frequently overlooked as possible targets for drug development. Compared to proteins, they are smaller and can be produced synthetically using reliable and affordable techniques. Even though a huge number of inhibitors or drugs has been developed since the onset of the pandemic but it remains a strategic priority to develop new drug candidates with minimal side effects. Hence, **Chapter 6** of the thesis involves the designing of the peptides which will bind to the active site of the Mpro with greater affinity and may inhibit its functioning, thus diminishing the effect of COVID-19.

4. Both **Chapter 5** and **Chapter 6** focuses on the development of therapeutics in order to diminish the effect of the disease. Apart from these another important thing is the study of the variants emerging over time during the pandemic. The interaction and binding profiles of different variants could provide information about how different mutations can have an impact on its extent of virulence. Therefore, **Chapter 7** of the thesis demonstrates the effect of mutations in the S protein on its interaction with ACE2 receptor taking into consideration the variants having a serious impact on the global health throughout the pandemic. **Chapter 7** consists of five sections and each section consists of different SARS-CoV-2 variants examined over time.

5. It has been observed that the expression profiles of the primary receptor, ACE2 are not completely associated with infection patterns, immune responses, and clinical manifestations. Large-scale clinical studies show that the lung, where ACE2 expression is least, is the major site of infection for COVID-19, suggesting that additional factors may be involved in viral entry. So, in **Chapter 8** of the thesis we have carried out the analysis of the interaction profile of RBD of S protein with few other alternative/co-receptors of SARS-CoV-2 in order to check the Efficiency of those alternative receptors for S Protein thereby facilitating the viral entry into the host cell.

2.9. Main Objectives of the Thesis

1. Structural insights into the SARS-CoV-2 viral proteins

1.1. Salient structural features of SARS-CoV-2 Main protease (Mpro)

1.2. Salient structural features and conformational accessibility of SARS-CoV-2 Spike protein (S-protein)

2. Interaction of small bioactive compounds with SARS-CoV-2 main protease

2.1. Natural compounds or peptide that target the Mpro

3. Interaction of biomolecules with SARS-CoV-2 spike protein

3.1. Interaction of RBD of SARS-CoV-2 spike protein with ACE2 and other receptors

3.2. Effect of mutations in the Spike protein on its interaction with ACE2 receptor

2.10. Bibliography:

[1]. Mahase, E. COVID-19: WHO declares pandemic because of "alarming levels" of spread, severity, and inaction. *BMJ (Clinical research ed.)*, 368, m1036, 2020. http://dx.doi.org/10.1136/bmj.m1036.

[2]. Lv, M., Luo, X., Estill, J., Liu, Y., Ren, M., Wan, J., Wang, Q., Zhao, S., Wang, X., Yang, S., Feng, X., Li, W., Liu, E., Zhang, X., Wang, L., Zhou, Q., Meng, W., Qi, X., Xun, Y., Yu, X., and Chen, Y. COVID-19 evidence and recommendations working group. Coronavirus disease (COVID-19): a scoping review. *Eurosurveillance*, 25(15): 20001252020, 2020. http://dx.doi.org/10.2807/1560-7917.

[3]. Rafieepour, A., Masoumi, G., and Dehghani, A. Health responses during the COVID-19 pandemic: An international strategy and experience. *Health in Emergencies and Disasters Quarterly*, 6(3): 147–160, 2021. http://dx.doi.org/10.32598/hdq.6.3.310.1

[4]. Wu, J.T., Leung, K., and Leung, G. M. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. *The Lancet*, 395(10225): 689–697, 2020. https://doi.org/10.1016/S0140-6736(20)30260-9.

[5]. Hui, D.S., I Azhar, E., Madani, T.A., Ntoumi, F., Kock, R., Dar, O., Ippolito, G., Mchugh, T.D., Memish, Z.A., Drosten, C., Zumla, A., and Petersen, E. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. *International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases*, 91: 264–266, 2020. https://doi.org/10.1016/j.ijid.2020.01.009.

[6]. Deng, S.Q., and Peng, H.J. Characteristics of and Public Health Responses to the Coronavirus Disease 2019 Outbreak in China. *Journal of clinical medicine*, 9(2): 575, 2020. https://doi.org/10.3390/jcm9020575.

[7]. Han, Q., Lin, Q., Jin, S., and You, L. Coronavirus 2019-nCoV: A brief perspective from the front line. *The Journal of infection*, 80(4): 373–377, 2020. https://doi.org/10.1016/j.jinf.2020.02.010.

[8]. Wang, W., Tang, J. and Wei, F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. *Journal of Medical Virology*, 92: 441-447, 2020. https://doi.org/10.1002/jmv.25689

[9]. Wu, Y.C., Chen, C.S., and Chan, Y.J. The outbreak of COVID-19: An overview. *Journal of the Chinese Medical Association: JCMA*, 83(3): 217–220, 2020. https://doi.org/10.1097/JCMA.0000000000000270.

[10]. Chen, Y., Liu, Q., and Guo, D. Emerging coronaviruses: genome structure, replication, and pathogenesis. *Journal of Medical Virology*, 92(3): 418–423, 2020. https://doi.org/10.1002/jmv.25681

[11]. Ahmed, S.F., Quadeer, A.A., and McKay, M.R. Preliminary identification of potential vaccine targets for the COVID-19 coronavirus (SARS-CoV-2) based on SARS-CoV immunological studies.

Viruses, 12(3): 254, 2020.https://doi.org/10.3390/v12030254

[12]. Abbasi-Oshaghi, E., Mirzaei, F., Farahani, F., Khodadadi, I., and Tayebinia, H. Diagnosis and treatment of coronavirus disease 2019 (COVID-19): Laboratory, PCR, and chest CT imaging findings. *International Journal of Surgery*, 79: 143–153, 2020. https://doi.org/10.1016/j.ijsu.2020.05.018

[13]. Zhou, P., Yang, X.L., Wang, X.G., Hu, B., Zhang, L., Zhang, W., Si, H.R., Zhu, Y., Li, B., Huang, C.L., Chen, H.D., Chen, J., Luo, Y., Guo, H., Jiang, R.D., Liu, M.Q., Chen, Y., Shen, X.R., Wang, X., Zheng, X.S., Zhao, K., Chen, Q.J., Deng, F., Liu, L.L., Yan. B., Zhan. F.X., Wang. Y.Y., Xiao, G.F., and Shi, Z.L. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 579:270–273,2020. https://doi.org/10.1038/s41586-020-2012-7

[14]. Wu, C. R., Yin, W. C., Jiang, Y., and Xu, H. E. Structure genomics of SARS-CoV-2 and its Omicron variant: drug design templates for COVID-19. *Acta pharmacologica Sinica*, 43(12): 3021–3033, 2022. https://doi.org/10.1038/s41401-021-00851-w

[15]. Poran, A., Harjanto, D., Malloy, M., Arieta, C. M., Rothenberg, D. A., Lenkala, D., van Buuren, M. M., Addona, T. A., Rooney, M. S., Srinivasan, L., and Gaynor, R. B. Sequence-based prediction of SARS-CoV-2 vaccine targets using a mass spectrometry-based bioinformatics predictor identifies immunogenic T cell epitopes. *Genome medicine*, 12(1): 70, 2020. https://doi.org/10.1186/s13073-020-00767-w

[16]. Lowery, S. A., Sariol, A., and Perlman, S. Innate immune and inflammatory responses to SARS-CoV-2: Implications for COVID-19. *Cell host & microbe*, 29(7): 1052–1062, 2021. https://doi.org/10.1016/j.chom.2021.05.004

[17]. Hu, B., Guo, H., Zhou, P., and Shi, Z. L. Characteristics of SARS-CoV-2 and COVID-19. *Nature reviews. Microbiology*, 19(3): 141–154, 2021. https://doi.org/10.1038/s41579-020-00459-7

[18]. Agarwal, K.M., Mohapatra, S., Sharma, P., Sharma, S., Bhatia, D., and Mishra, A. Study and overview of the novel corona virus disease (COVID-19). *Sensors international*, 1: 100037, 2020. https://doi.org/10.1016/j.sintl.2020.100037

[19]. Jamison, D. A., Jr, Anand Narayanan, S., Trovão, N.S., Guarnieri, J.W., Topper, M.J., Moraes-Vieira, P.M., Zaksas, V., Singh, K.K., Wurtele, E.S., and Beheshti, A.A comprehensive SARS-CoV-2 and COVID-19 review, Part 1: Intracellular overdrive for SARS-CoV-2 infection. *European Journal of Human Genetics*, 30: 889–898, 2022. https://doi.org/10.1038/s41431-022-01108-8

[20]. Li, W., Moore, M. J., Vasilieva, N., Sui, J., Wong, S. K., Berne, M. A., Somasundaran, M., Sullivan, J. L., Luzuriaga, K., Greenough, T. C., Choe, H., and Farzan, M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*, 426(6965): 450–454, 2003. https://doi.org/10.1038/nature02145

[21]. Letko, M., Marzi, A., and Munster, V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nature microbiology*, 5(4): 562–569, 2020. https://doi.org/10.1038/s41564-020-0688-y

[22]. Zhou, P., Yang, X.L., Wang, X.G., Hu, B., Zhang, L., Zhang, W., Si, H.R., Zhu, Y., Li, B., Huang, C.L., Chen, H.D., Chen, J., Luo, Y., Guo, H., Jiang, R.D., Liu, M.Q., Chen, Y., Shen, X.R., Wang, X., Zheng, X.S., Zhao, K., Chen, Q.J., Deng, F., Liu, L.L., Yan, B., Zhan, F.X., Wang, Y.Y., Xiao, G.F., Shi, Z.L. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 579(7798): 270-273, 2020. https://doi.org/10.1038/s41586-020-2012-7.

[23]. Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N. H., Nitsche, A., Müller, M. A., Drosten, C., & Pöhlmann, S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 181(2):271–280, 2020. https://doi.org/10.1016/j.cell.2020.02.052

[24]. Walls, A.C., Park, Y.J., Tortorici, M.A., Wall, A., McGuire, A.T., and Veesler, D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell*, 181(2): 281–292.e6, 2020. https://doi.org/10.1016/j.cell.2020.02.058

[25]. Jackson, C.B., Farzan, M., Chen, B., and Choe, H. Mechanisms of SARS-CoV-2 entry into cells. *Nature reviews. Molecular cell biology*, 23(1): 3–20, 2022. https://doi.org/10.1038/s41580-021-00418-x.

[26]. V'kovski, P., Kratzel, A., Steiner, S., Stalder, H., and Thiel, V. Coronavirus biology and replication: implications for SARS-CoV-2. *Nature Reviews Microbiology*, 19(3): 155–170, 2021. https://doi.org/10.1038/s41579-020-00468-6.

[27]. Jeong, G.U., Song, H., Yoon, G.Y., Kim, D., and Kwon, Y.C. Therapeutic Strategies Against COVID-19 and Structural Characterization of SARS-CoV-2: A Review. *Frontiers in microbiology*, 11: 1723, 2020. https://doi.org/10.3389/fmicb.2020.01723

[28]. Van Der Hoek, L., Pyrc, K., and Berkhout, B. Human coronavirus NL63, a new respiratory virus. *FEMS Microbiology Reviews*, 30(5): 760–773, 2006. https://doi.org/10.1111/j.1574-6976.2006.00032.x

[29]. Esper, F., Weibel, C., Ferguson, D., Landry, M.L., and Kahn, J.S. Coronavirus HKU1 infection in the United States. *Emerging Infectious Diseases*, 12(5): 775–779, 2006. https://doi.org/10.3201/eid1205.051316

[30]. Gerna, G., Percivalle, E., Sarasini, A., Campanini, G., Piralla, A., Rovida, F., Genini, E., Marchi, A., and Baldanti, F. Human respiratory coronavirus HKU1 versus other coronavirus infections in Italian hospitalised patients. *Journal of Clinical Virology*, 38(3): 244–250, 2007. https://doi.org/10.1016/j.jcv.2006.12.008

[31]. Kaye, H.S., Marsh, H.B., and Dowdle, W.R. Seroepidemiologic survey of coronavirus (Strain OC 43) related infections in a children's population. *American Journal of Epidemiology*, 94(1): 43–49, 1971.https://doi.org/10.1093/oxfordjournals.aje.a121293

[32]. Long, S. S., Pickering, L. K., and Prober, C. G. *Principles and practice of pediatric infectious diseases*. Elsevier Health Sciences, 6th Edition, 2003.

[33]. Hu, B., Ge, X., Wang, L.F., and Shi, Z. Bat origin of human coronaviruses. *Virology Journal*, 12(1): 221, 2015. https://doi.org/10.1186/s12985-015-0422-1

[34]. Lau, S.K., Woo, P.C., Li, K.S., Huang, Y., Tsoi, H.W., Wong, B.H., Wong, S.S., Leung, S. Y., Chan, K.H., and Yuen, K.Y. Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. *Proceedings of the National Academy of Sciences*, 102(39): 14040–14045, 2005. https://doi.org/10.1073/pnas.0506735102

[35]. Li, W., Shi, Z., Yu, M., Ren, W., Smith, C., Epstein, J.H., Wang, H., Crameri, G., Hu, Z., Zhang, H., Zhang, J., McEachern, J., Field, H., Daszak, P., Eaton, B.T., Zhang, S., and Wang, L. F. Bats are natural reservoirs of SARS-like coronaviruses. *Science*, 310(5748): 676–679, 2005. https://doi.org/10.1126/science.1118391

[36]. Kirtipal, N., Bharadwaj, S., and Kang, S.G. From SARS to SARS-CoV-2, insights on structure, pathogenicity and immunity aspects of pandemic human coronaviruses. *Infection, Genetics and Evolution*, 85: 104502, 2020.https://doi.org/10.1016/j.meegid.2020.104502

[37]. Reusken, C.B., Haagmans, B.L., Müller, M.A., Gutierrez, C., Godeke, G.J., Meyer, B., Muth, D., Raj, V.S., Smits-De Vries, L., Corman, V.M., Drexler, J.F., Smits, S.L., El Tahir, Y.E., De Sousa, R., van Beek, J., Nowotny, N., van Maanen, K., Hidalgo-Hermoso, E., Bosch, B.J., Rottier, P., Osterhaus, A., Gortázar-Schmidt, C., Drosten, C., and Koopmans, M.P. Middle East respiratory syndrome coronavirus neutralising serum antibodies in dromedary camels: A comparative serological study. *The Lancet Infectious Diseases*, 13(10): 859–866, 2013. https://doi.org/10.1016/s1473-3099(13)70164-6

[38]. Sabir, J.S., Lam, T.T., Ahmed, M. M., Li, L., Shen, Y., Abo-Aba, S.E., Qureshi, M.I., Abu-Zeid, M., Zhang, Y., Khiyami, M.A., Alharbi, N.S., Hajrah, N.H., Sabir, M.J., Mutwakil, M.H., Kabli, S.A., Alsulaimany, F.A., Obaid, A.Y., Zhou, B., Smith, D.K., Holmes, E.C., Zhu, H., and Guan, Y. Co-circulation of three camel coronavirus species and recombination of MERS-CoVs in Saudi Arabia. *Science (New York, N.Y.)*, 351(6268): 81–84, 2016. https://doi.org/10.1126/science.aac8608

[39]. Müller, M.A., Corman, V.M., Jores, J., Meyer, B., Younan, M., Liljander, A., Bosch, B.J., Lattwein, E., Hilali, M., Musa, B.E., Bornstein, S., and Drosten, C. MERS coronavirus neutralizing antibodies in camels, Eastern Africa, 1983-1997. Emerging Infectious Diseases, 20(12), 2093-2095, 2014. https://doi.org/10.3201/eid2012.141026

[40]. Hao, Y.J., Wang, Y.L., Wang, M.Y., Zhou, L., Shi, J.Y., Cao, J.M., and Wang, D.P. The origins of COVID-19 pandemic: A brief overview. *Transboundary and Emerging Diseases*, 69(6): 3181–3197, 2022. https://doi.org/10.1111/tbed.14732

[41]. Su, S., Wong, G., Shi, W., Liu, J., Lai, A.C.K., Zhou, J., Liu, W., Bi, Y., and Gao, G.F. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends in Microbiology*, 24(6): 490–502, 2016. https://doi.org/10.1016/j.tim.2016.03.003

[42]. Ksiazek, T.G., Erdman, D., Goldsmith, C.S., Zaki, S.R., Peret, T., Emery, S., Tong, S., Urbani, C., Comer, J.A., Lim, W., Rollin, P.E., Dowell, S.F., Ling, A.E., Humphrey, C.D., Shieh, W.J., Guarner, J., Paddock, C.D., Rota, P., Fields, B., DeRisi, J., Yang, J. Y., Cox, N., Hughes, J. M. , LeDuc, J.W., Bellini, W.J., Anderson, L.J., and SARS Working Group (2003). A novel coronavirus associated with severe acute respiratory syndrome. *New England Journal of Medicine*, 348(20): 1953–1966, 2003. https://doi.org/10.1056/nejmoa030781

[43]. Zaki, A.M., van Boheemen, S., Bestebroer, T.M., Osterhaus, A.D.M.E., and Fouchier, R.A.M. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *New England Journal of Medicine*, 367(19): 1814–1820, 2012. https://doi.org/10.1056/nejmoa1211721

[44]. Sabir, J. S., Lam, T. T., Ahmed, M. M., Li, L., Shen, Y., Abo-Aba, S. E., Qureshi, M. I., Abu-Zeid, M., Zhang, Y., Khiyami, M. A., Alharbi, N. S., Hajrah, N. H., Sabir, M. J., Mutwakil, M. H., Kabli, S. A., Alsulaimany, F. A., Obaid, A. Y., Zhou, B., Smith, D. K., Holmes, E. C., Zhu, H., Guan, Y. Co-circulation of three camel coronavirus species and recombination of MERS-CoVs in Saudi Arabia. *Science*, 351(6268), 81–84, 2016. https://doi.org/10.1126/science.aac8608

[45]. Zhang, Y.Z., and Holmes, E.C. A genomic perspective on the origin and emergence of SARS-CoV-2. *Cell*, 181(2): 223–227, 2020. https://doi.org/10.1016/j.cell.2020.03.035

[46]. Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N., Bi, Y., Ma, X., Zhan, F., Wang, L., Hu, T., Zhou, H., Hu, Z., Zhou, W., Zhao, L., Chen, J., Meng, Y., Wang, J., Lin, Y., Yuan, J., Xie, Z., Ma, J., Liu, W.J., Wang, D., Xu, W., Holmes, E.C., Gao, G.F., Wu, G., Chen, W., Shi, W., and Tan, W. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet*, 395(10224): 565–574, 2020. https://doi.org/10.1016/s0140-6736(20)30251-8

[47]. Wu, F., Zhao, S., Yu, B., Chen, Y.M., Wang, W., Song, Z.G., Hu, Y., Tao, Z.W., Tian, J.H., Pei, Y.Y., Yuan, M.L., Zhang, Y.L., Dai, F.H., Liu, Y., Wang, Q.M., Zheng, J.J., Xu, L., Holmes, E. C., and Zhang, Y.Z. A new coronavirus associated with human respiratory disease in China. *Nature*, 579(7798): 265–269, 2020. https://doi.org/10.1038/s41586-020-2008-3

[48]. Zhou, P., Yang, X.L., Wang, X.G., Hu, B., Zhang, L., Zhang, W., Si, H. R., Zhu, Y., Li, B., Huang, C. L., Chen, H.D., Chen, J., Luo, Y., Guo, H., Jiang, R. D., Liu, M. Q., Chen, Y., Shen, X.R., Wang, X., Zheng, X.S., Zhao, K., Chen, Q.J., Deng, F., Liu, L.L., Yan, B., Zhan, F.X., Wang, Y.Y.,

Xiao, G.F., and Shi, Z. L. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 579(7798): 270–273, 2020. https://doi.org/10.1038/s41586-020-2012-7

[49]. Andersen, K.G, Rambaut, A., Lipkin, W.I, Holmes, E.C., and Garry, R.F. The proximal origin of SARS-CoV-2. *Nature Medicine*, 26:450-452, 2020. https://doi.org/10.1038/s41591-020-0820-9

[50]. Holmes, E.C., Goldstein, S.A., Rasmussen, A. L., Robertson, D.L., Crits-Christoph, A., Wertheim, J.O., Anthony, S.J., Barclay, W.S., Boni, M.F., Doherty, P.C., Farrar, J., Geoghegan, J. L., Jiang, X., Leibowitz, J.L., Neil, S.JD., Skern, T., Weiss, S.R., Worobey, M., Andersen, K.G., Garry, R.F., and Rambaut, A. The origins of SARS-CoV-2: A critical review. *Cell*, 184(19): 4848–4856, 2021. https://doi.org/10.1016/j.cell.2021.08.017

[51]. Xu, R.H., He, J.F., Evans, M.R., Peng, G.W., Field, H.E., Yu, D.W., Lee, C.K., Luo, H.M., Lin, W.S., Lin, P., Li, L.H., Liang, W.J., Lin, J.Y., and Schnur, A. Epidemiologic clues to SARS origin in China. *Emerging Infectious Diseases*, 10(6): 1030–1037, 2004. https://doi.org/10.3201/eid1006.030852

[52]. Zhao, X., Ding, Y., Du, J., and Fan, Y. 2020 update on human coronaviruses: One health, one world. *Medicine in Novel Technology and Devices*, 8: 100043, 2020. https://doi.org/10.1016/j.medntd.2020.100043.

[53]. Drosten, C., Günther, S., Preiser, W., van der Werf, S., Brodt, H.R., Becker, S., Rabenau, H., Panning, M., Kolesnikova, L., Fouchier, R.A., Berger, A., Burguière, A.M., Cinatl, J., Eickmann, M., Escriou, N., Grywna, K., Kramme, S., Manuguerra, J.C., Müller, S., Rickerts, V., Stürmer, M., Vieth, S., Klenk, H.D., Osterhaus, A.D., Schmitz, H., and Doerr, H.W. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *New England Journal of Medicine*, 348(20):1967–1976, 2003. https://doi.org/10.1056/nejmoa030747

[54]. Alimohamadi, Y., Taghdir, M., and Sepandi, M. The estimate of the basic reproduction number for novel coronavirus disease (COVID-19): a systematic review and meta-analysis. *Journal of Preventive Medicine and Public Health*, 53(3): 151–157, 2020. https://doi.org/10.3961/jpmph.20.076 10.3961/jpmph.20.076

[55]. Petrosillo, N., Viceconte, G., Ergonul, O., Ippolito, G., and Petersen, E. COVID-19, SARS and MERS: are they closely related? *Clinical Microbiology and Infection*, 26(6): 729–734, 2020. https://doi.org/10.1016/j.cmi.2020.03.026 10.1016/j.cmi.2020.03.0264

[56]. Anderson, R.M., Heesterbeek, H., Klinkenberg, D., and Hollingsworth, T.D. How will country-based mitigation measures influence the course of the COVID-19 epidemic? *The Lancet*, 395(10228): 931–934, 2020. https://doi.org/10.1016/S0140-6736(20)30567-5

[57]. Guo, Y.R., Cao, Q.D., Hong, Z.S., Tan, Y.Y., Chen, S.D., Jin, H.J., Tan, K.S., Wang, D.Y., and Yan, Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. *Military Medical Research*, 7(1): 1–10, 2020.

https://doi.org/10.1186/s40779-020-00240-0

[58]. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). *Geneva: World Health Organization*, 2020.

[59]. Zu, Z.Y., Jiang, M.D., Xu, P.P., Chen, W., Ni, Q. Q., Lu, G.M., and Zhang, L.J. Coronavirus disease 2019 (COVID-19): a perspective from China. *Radiology*, 296(2): E15–E25, 2020. https://doi.org/10.1148/radiol.2020200490

[60]. Guan, W.J., Ni, Z.Y., Hu, Y., Liang, W.H., Ou, C.Q., He, J.X., Liu, L., Shan, H., Lei, C.L., Hui, D.S., and China Medical Treatment Expert Group for COVID-19. Clinical characteristics of 2019 novel coronavirus infection in China. *medRxiv*, 2020.02.06.20020974. https://doi.org/10.1056/NEJMoa2002032

[61]. Zaim, S., Chong, J. H., Sankaranarayanan, V., and Harky, A. COVID-19 and multi-organ response. *Current Problems in Cardiology*, 45(10): 100618, 2020. https://doi.org/10.1016/j.cpcardiol.2020.100618

[62]. Esakandari, H., Nabi-Afjadi, M., Fakkari-Afjadi, J., Farahmandian, N., Miresmaeili, S.M., and Bahreini, E. A comprehensive review of COVID-19 characteristics. *Biological Procedures Online*, 22: 19, 2020. https://doi.org/10.1186/s12575-020-00128-2

[63]. Hussain, A., Kaler, J., Tabrez, E., Tabrez, S., & Tabrez, S. Novel COVID-19: A comprehensive review of transmission, manifestation, and pathogenesis. *Cureus*, 12(7): e8184, 2020. https://doi.org/10.7759/cureus.8184

[64]. Zhu, H., Rhee, J.W., Cheng, P., Waliany, S., Chang, A., Witteles, R.M., Maecker, H., Davis, M.M., Nguyen, P.K., and Wu, S.M. Cardiovascular complications in patients with COVID-19: consequences of viral toxicities and host immune response. *Current Cardiology Reports*, 22(5), 32, 2020. https://doi.org/10.1007/s11886-020-01292-3

[65]. Kollias, A., Kyriakoulis, K.G., Dimakakos, E., Poulakou, G., Stergiou, G.S., and Syrigos, K. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. *British Journal of Haematology*, 189(5): 846–847, 2020. https://doi.org/10.1111/bjh.16727

[66]. Wu, Y., Xu, X., Chen, Z., Duan, J., Hashimoto, K., Yang, L., Liu, C., and Yang, C. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain, behavior, and immunity*, 87: 18–22, 2020. https://doi.org/10.1016/j.bbi.2020.03.031

[67]. Baj, J., Karakuła-Juchnowicz, H., Teresiński, G., Buszewicz, G., Ciesielka, M., Sitarz, R., Forma, A., Karakuła, K., Flieger, W., Portincasa, P., and Maciejewski, R. COVID-19: Specific and Non-Specific Clinical Manifestations and Symptoms: The Current State of Knowledge. *Journal of clinical medicine*, *9*(6): 1753, 2020. https://doi.org/10.3390/jcm9061753

[68]. Singla, R., Mishra, A., Joshi, R., Jha, S., Sharma, A. R., Upadhyay, S., Sarma, P., Prakash, A., and Medhi, B. Human animal interface of SARS-CoV-2 (COVID-19) transmission: a critical

appraisal of scientific evidence. *Veterinary research communications*, 44(3-4): 119–130, 2020. https://doi.org/10.1007/s11259-020-09781-0.

[69]. Malik, Y. S., Sircar, S., Bhat, S., OR, V., Tiwari, R., Sah, R., Ali, A., Rodriguez-Morales, A. J., and Dhama, K. Emerging coronavirus disease (COVID-19), a pandemic public health emergency with animal linkages: Current status update, *The Indian Journal of Animal Sciences*, 90(3): 303-317, 2020. https://doi.org/10.56093/ijans.v90i3.102316

[70]. Peeri, N. C., Shrestha, N., Rahman, M. S., Zaki, R., Tan, Z., and Bibi, S. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? *International Journal of Epidemiology*, 49(3): 717-726, 2020. https://doi:10.1093/ije/dyaa033

[71]. Shi, J., Wen, Z., Zhong, G., Yang, H., Wang, C., and Huang, B. Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS–coronavirus 2. *Science*, 368: 1016-1020, 2020. https://doi.org/10.1126/science.abb7015

[72]. She, J., Jiang, J., Ye, L., Hu, L., Bai, C., and Song, Y. Novel coronavirus of pneumonia in Wuhan, China: emerging attack and management strategies, *Clinical and Translational Medicine*, 9(1): 1-7, 2020. https://doi.org/10.1186/s40169-020-00271-z

[73]. Boldog, P., Tekeli, T., Vizi, Z., Dénes, A., Bartha, F. A., and Röst, G. Risk assessment of novel coronavirus COVID-19 outbreaks outside China. *Journal of Clinical Medicine*, 9(2): 571, 2020. https://doi.org/10.3390/jcm9020571

[74]. Rothe, C., Schunk, M., Sothmann, P., Bretzel, G., Froeschl, G., Wallrauch, C., Zimmer, T., Thiel, V., Janke, C., Guggemos, W., Seilmaier, M., Drosten, C., Vollmar, P., Zwirglmaier, K., Zange, S., Wölfel, R., and Hoelscher, M. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *The New England Journal of Medicine, 382*(10): 970–971, 2020. https://doi.org/10.1056/NEJMc2001468

[75]. C. Zhou. Evaluating new evidence in the early dynamics of the novel coronavirus COVID-19 outbreak in Wuhan, China with real time domestic traffic and potential asymptomatic transmissions. *medRxiv*, 2020. https://doi:10.1101/2020.02.15.20023440

[76]. Hu, Z., Song, C., Xu, C., Jin, G., Chen, Y., Xu, X., Ma, H., Chen, W., Lin, Y., Zheng, Y., Wang, J., Hu, Z., Yi1, Y., and Shen H. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China, *Science China Life Sciences*, 63(5): 706–711, 2020. https://doi.org/10.1007/s11427-020-1661-4

[77]. Riou, J., and Althaus, C.L. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020, *Euro Surveill*, 25(4): 2000058, 2020. https://doi:10.2807/1560-7917.ES.2020.25.4.2000058

[78]. Phan, L.T., Nguyen, T.V., Luong, Q.C., Nguyen, T.V., Nguyen, H.T., Le, H.Q., Nguyen, T.T., Cao, T.M., and Pham, Q.D. Importation and human-to-human transmission of a novel coronavirus in Vietnam. *New England Journal of Medicine*, 382 (9): 872-874, 2020. https://doi:10.1056/NEJMc2001272

[79]. Zhonghua Jie He He Hu Xi Za Zhi. Respiratory Care Committee of Chinese Thoracic Society *Chinese journal of tuberculosis and respiratory diseases*, *43*(4): 288–296, 2020. https://doi.org/10.3760/cma.j.cn112147-20200304-00239

[80]. Azer, S.A. COVID-19. Pathophysiology, diagnosis, complications and investigational therapeutics, *New Microbes and New Infections*, 37: 100738, 2020. https://doi.org/10.1016/j.nmni.2020.100738.

[81]. Lotfi, M., Hamblin, M. R., and Rezaei, N. COVID-19. Transmission, prevention, and potential therapeutic opportunities. *Clinica chimica acta; international journal of clinical chemistry*, *508*: 254–266, 2020. https://doi.org/10.1016/j.cca.2020.05.044

[82]. McIntosh, K., Hirsch, M. S., and Bloom, A. *Coronavirus disease 2019 (COVID-19).* In M. S. Hirsch & A. Bloom (Eds.), UpToDate, 5(1), 873, 2020.

[83]. Tang, A., Tong, Z., Wang, H., Dai, Y., Li, K., Liu, J, Wu, W.J., Yuan, C., Yu, M., Li, P., and Yan, J. Detection of novel coronavirus by RT-PCR in stool specimen from asymptomatic child, China. *Emerging Infectious Diseases*, 26(6): 1337–1339, 2020. https://doi.org/10.3201/eid2606.200301

[84]. Zhou, J. Q., Liu, G. X., Huang, X. L., and Gan, H. T. The importance of fecal nucleic acid detection in patients with coronavirus disease (COVID-19): a systematic review and meta-analysis. *Journal of Medical Virology*, 94(6): 2317-2330, 2022. https://doi.org/10.1002/jmv.27652

[85]. Dong, X., Cao, Y., Lu, X. X., Zhang, J.J., Du, H., Yan, Y. Q., Akdis, C. A., and Gao, Y. D. Eleven faces of Coronavirus disease 2019. *Allergy*, 75: 1699–1709, 2019. https://doi.org/10.1111/all.14289

[86]. Yeo, C., Kaushal, S., and Yeo, D. Enteric involvement of coronaviruses: is faecal–oral transmission of SARS-CoV-2 possible? *Lancet Gastroenterol Hepatol*, 5(4): 335–337, 2020. https://doi.org/10.1016/S2468-1253(20)30048-0

[87]. Lake, M. A. What we know so far: COVID-19 current clinical knowledge and research. *Clinical Medicine*, 20(2): 124–127, 2020. https://doi.org/10.7861/clinmed.2019-coron

[88]. Zhang, H., Kang, Z., Gong, H., Xu, D., Wang, J., Li, Z., Cui, X., Xiao, J., Meng, T., Zhou, W., Liu, J., and Xu, H. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. *BioRxiv*, 2020. https://doi.org/10.1101/2020.01.30.927806

[89]. Lau, S. K. P., Li, K. S. M., Huang, Y., Shek, C. T ., Tse, H., Wang, M., Choi, G. K. Y., Xu, H., Lam, C. S. F., Guo, R., Chan, K. H., Zheng, B. J., Woo, P. C. Y, and Yuen, K. Y. Ecoepidemiology and complete genome comparison of different strains of severe acute respiratory syndrome-related Rhinolophus bat coronavirus in China reveal bats as a reservoir for acute, self-limiting infection that allows recombination events. *Journal of Virology*, 84(6): 2808–2819, 2010. https://doi.org/10.1128/jvi.02219-09

[90]. Danchin, A., Ng, T. W., and Turinici, G. A new transmission route for the propagation of the SARS-CoV-2 Coronavirus. *Biology*, 10(1): 10, *2020*. https://doi.org/10.3390/biology10010010

[91]. Salahshoori, I., Mobaraki-Asl, N., Seyfaee, A., Nasirabad, N. M., Dehghan, Z., Faraji, M., Ganjkhani, M., Babapoor, A., Shadmehr, and Hamrang, A. Overview of COVID-19 Disease: Virology, Epidemiology, Prevention Diagnosis, Treatment, and Vaccines. *Biologics*, 1(1): 2-40, 2021. https://doi.org/10.3390/biologics1010002

[92]. Bohn, M. K., Hall, A., Sepiashvili, L., Jung, B., Steele, S., and Adeli, K. Pathophysiology of COVID-19: Mechanisms Underlying Disease Severity and Progression. *Physiology*, 35(5): 288–301, 2020. https://doi.org/10.1152/physiol.00019.2020

[93]. Borczuk, A. C., and Yantiss, R. K. The pathogenesis of coronavirus-19 disease. *Journal of Biomedical Science*, 29(1): 87, 2022. https://doi.org/10.1186/s12929-022-00872-5

[94]. Masters, P. S. The molecular biology of coronaviruses. *Advances in Virus Research*, 66: 193–292, 2006. https://doi.org/10.1016/S0065-3527(06)66005-3

[95]. Oliveira, R. K. F., Nyasulu, P. S., Iqbal, A. A., Hamdan Gul, M., Ferreira, E. V. M., Leclair, J. W., Htun, Z. M., Howard, L. S., Mocumbi, A. O., Bryant, A. J., Tamuzi, J. L., Avdeev, S., Petrosillo, N., Hassan, A., Butrous, G., and de Jesus Perez, V. Cardiopulmonary disease as sequelae of long-term COVID-19: Current perspectives and challenges. *Frontiers in medicine*, *9*: 1041236, 2022. https://doi.org/10.3389/fmed.2022.1041236

[96]. Surveillances V. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—China, 2020. *China CDC Weekly*, 2(8): 113–22, 2020.

[97]. Wu, F., Zhao, S., Yu, B., Chen, Y. M., Wang, W., Song, Z. G., Hu, Y., Tao, Z. W., Tian, J. H., Pei, Y. Y., Yuan, M. L., Zhang, Y. L., Dai, F. H., Liu, Y., Wang, Q. M., Zheng, J. J., Xu, L., Holmes, E. C., and Zhang, Y. Z. A new coronavirus associated with human respiratory disease in China. *Nature*, 579: 265–269, 2020. https://doi.org/10.1038/s41586-020-2008-3

[98]. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Q., Wang, J., and Cao, B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, 395(10223): 497–506, 2020. https://doi.org/10.1038/s41586-020-2008-3

[99]. Lee, J. Y., Kim, H. A., Huh, K., Hyun, M., Rhee, J. Y., Jang, S., Kim, J. Y., Peck, K. R., and Chang, H. H. Risk Factors for Mortality and Respiratory Support in Elderly Patients Hospitalized with COVID-19 in Korea. *Journal of Korean medical science*, 35(23): e223, 2020. https://doi.org/10.3346/jkms.2020.35.e223

[100]. Kanne, J. P., Little, B. P., Schulte, J. J., Haramati, A., and Haramati, L. B. Long-term Lung Abnormalities Associated with COVID-19 Pneumonia. *Radiology*, 306(2): e221806, 2023. https://doi.org/10.1148/radiol.221806

[101]. Eberhardt, N., Noval, M. G., Kaur, R., Amadori, L., Gildea, M., Sajja, S., Das, D., Cilhoroz, B., Stewart, O. J., Fernandez, D. M., Shamailova, R., Guillen, A. V., Jangra, S., Schotsaert, M., Newman, J. D., Faries, P., Maldonado, T., Rockman, C., Rapkiewicz, A., Stapleford, K. A., Narula, N., Moore, K. J., and Giannarelli, C. SARS-CoV-2 infection triggers pro-atherogenic inflammatory responses in human coronary vessels. *Nature cardiovascular research*, 2(10): 899-916, 2023. https://doi.org/10.1038/s44161-023-00336-5

[102]. Eberhardt, N., Noval, M. G., Kaur, R., Amadori, L., Gildea, M., Sajja, S., Das, D., Cilhoroz, B., Stewart, O. J., Fernandez, D. M., Shamailova, R., Guillen, A. V., Jangra, S., Schotsaert, M., Newman, J. D., Faries, P., Maldonado, T., Rockman, C., Rapkiewicz, A., Stapleford, K. A., Narula, N., Moore, K. J., and Giannarelli, C. SARS-CoV-2 infection triggers pro-atherogenic inflammatory responses in human coronary vessels. *Nature Cardiovascular Research*, *2*(10): 899–916, 2023. https://doi.org/10.1038/s44161-023-00336-5

[103]. Jain, U. Effect of COVID-19 on the Organs. *Cureus*, 12(8): e9540, 2020. https://doi.org/10.7759/cureus.9540

[104]. Mao, L., Wang, M. D., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., Li, Y., Jin, H., Hu, B. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. *MedRxiv*, 2020. https://doi.org/10.1101/2020.02.22.20026500

[105]. Wu, Y., Xu, X., Chen, Z., Duan, J., Hashimoto, K., Yang, L., Liu, C., and Yang, C. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain, Behavior, and Immunity*, 87: 18-22, 2020. https://doi.org/10.1016/j.bbi.2020.03.031.

[106]. Nath, A. Neurologic complications of coronavirus infections. *Neurology*, 94(19): 809-810, 2020. https://doi.org/10.1212/WNL.0000000000009455

[107]. Lahiri, D., and Ardila, A. COVID-19 pandemic: a neurological perspective. *Cureus*, 12(4): e7889, 2020. https://doi.org/10.7759/cureus.7889

[108]. Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., Miao, X., and Li, Y. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurology*, 77(6): 683-690, 2020. https://doi.org/10.1001/jamaneurol.2020.1127

[109]. Solomon, I. H., Normandin, E., Bhattacharyya, S., Mukerjee, S. S., Keller, K., Ali, A. S., Adams, G., Hornick, J. L., Padera, R. F., and Sabeti, P. Neuropathological features of Covid-19. *The New England Journal of Med*icine, 383(10): 989-992, 2020. https://doi.org/10.1056/NEJMc2019373

[110]. Oxley, T. J., Mocco, J., Majidi, S., Kellner, C. P., Shoirah, H., Singh, I. P., De Leacy, R. A., Shigematsu, T., Ladner, T. R., Yeager, K. A., Skliut, M., Weinberger, J., Dangayanch, N. S., Bederson, J. B., Tuhrim, S., Fifti, J. T. Large-vessel stroke as a presenting feature of Covid-19 in the young. *The New England Journal of Medicine*, 382(20): e60, 2020. https://doi.org/10.1056/NEJMc2009787

[111]. Seah, I., and Agrawal, R. Can the coronavirus disease 2019 (COVID-19) affect the eyes? A review of coronaviruses and ocular implications in humans and animals. *Ocular Immunology and Inflammation*, 28(3): 391-395, 2020. https://doi.org/10.1080/09273948.2020.1738501

[112]. Lu, C. W., Liu, X. F., and Jia, Z. F. 2019-nCoV transmission through the ocular surface must not be ignored. *Lancet*, 395(10224): e39, 2020. https://doi.org/10.1016/S0140-6736(20)30313-5

[113]. Hoffmann, M., Kleine-Weber, H., Schroeder, S., Kruger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N. H., Nitsche, A., Muller, M. A., Drosten, C., and Pohlman, S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*, 181(2): 271-280, 2020. https://doi.org/10.1016/j.cell.2020.02.052

[114]. Walls, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T., and Veesler, D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell*, 181(2): 281-292, 2020. https://doi.org/10.1016/j.cell.2020.02.058

[115]. Yan, R., Zhang, Y., Li, Y., Xia, L., Guo, Y., and Zhou, Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science*, 367(6485): 1444-1448, 2020. https://doi.org/10.1126/science.abb2762

[116]. Lan, J., Ge, J., Yu, J., Shan, S., Zhou, H., Fan, S., Zhang, Q., Shi, X., Wang, Q., Zhang, L., and Wang, X. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature*, 581(7807): 215-220, 2020. https://doi.org/10.1038/s41586-020-2180-5

[117]. Matsuyama, S., Nao, N., Shirato, K., Kawase, M., Saito, S., Takayama, I., Nagata, N., Sekizuka, T., Katoh, H., Kato, F., Sakata, M., Tahara, M., Kutsuna, S., Ohmagari, N., Kuroda, M., Suzuki, T., Kageyema, T., and Takeda, M. Enhanced isolation of SARSCoV-2 by TMPRSS2-expressing cells. *Proceedings of the National Academy of Sciences*, 117(13): 7001-7003, 2020. https://doi.org/10.1073/pnas.2002589117

[118]. Alrawashdeh, H. M., Zubi, K. A., Abdulmannan, D. M., Al-Habahbeh, O., and Abu-Ismail, L. Conjunctivitis as the only sign and symptom of COVID-19: A case report and review of literature. *Qatar medical journal*, 2021(2): 31, 2021. https://doi.org/10.5339/qmj.2021.31

[119]. Chen, L., Deng, C., Chen, X., Zhang, X., Chen, B., Yu, H., Qin, Y., Xiao, K., Zhang, H., and Sun, X. Ocular manifestations and clinical characteristics of 534 cases of COVID-19 in China: A cross-sectional study. *Acta ophthalmologica*, 98(8): e951–e959, 2020. https://doi.org/10.1111/aos.14472

[120]. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Xiang, R., Gao, Z., Jin, Q., Wang, J., and Cao, B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, 395(10223): 497–506, 2020. https://doi.org/10.1016/S0140-6736(20)30183-5

[121]. Yi, Y., Lagniton, P. N. P., Ye, S., Li, E., and Xu, R. H. COVID-19: what has been learned and to be learned about the novel coronavirus disease. *International Journal of Biological Sciences*, 16(10): 1753–1766, 2020. https://doi.org/10.7150/ijbs.45134

[122]. Cheng, J. L., Huang, C., Zhang, G. J., Liu, D. W., Li, P., Lu, C. Y., and Li, J. Epidemiological characteristics of novel coronavirus pneumonia in Henan. *Zhonghua Jie He He Hu Xi Za Zhi= Chinese Journal of Tuberculosis and Respiratory Diseases*, 43(4): 327–331, 2020. https://doi.org/10.3760/cma.j.cn112147-20200222-00148

[123]. Hamming, I., Timens, W., Bulthuis, M. L. C., Lely, A. T., Navis, G. J., van Goor, H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *The Journal of Pathology*, 203(2): 631–637, 2004. https://doi.org/10.1002/path.1570

[124]. Wrapp, D., Wang, N., Corbett, K. S., Goldsmith, J. A., Hsieh, C. L., Abiona, O., Graham, B. S., and Mclellan, J. S. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*, 367(6483): 1260–1263, 2020. https://doi.org/10.1126/science.abb2507

[125]. Lin, L., Jiang, X., Zhang, Z., Huang, S., Zhang, Z., Fang, Z., Gu, Z., Gao, L., Shi, H., Mai, L., Liu, Y., Lin, X., Lai, R., Yan, Z., Li, X., and Shan, H. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. *Gut*, 69(6): 997-1001, 2020. https://doi.org/10.1136/gutjnl-2020-321013

[126]. Effenberger, M., Grabherr, F., Mayr, L., Schwaerzler, J., Nairz, M., Seifert, M., Hilbe, R., Seiwald, S., Scholl-Buergi, S., Fritsche, G., Bellman-Weiler, R., Weiss, G., Muller, T., Adolf, T. E., and Tilg, H. Faecal calprotectin indicates intestinal inflammation in COVID-19. *Gut*, 69(8): 1543-1544, 2020. https://doi.org/10.1136/gutjnl-2020-321388

[127]. Xu, K., Cai, H., Shen, Y., Ni, Q., Chen, Y., Hu, S., Li, J., Wang, H., Yu, L., Huang, H., Qiu, Y., Wei, G., Fang, Q., Zhou, J., Sheng, J., Liang, T., and Li, L. Management of COVID-19: the Zhejiang experience. *Journal of Zhejiang University, MedicalSciences*, 49(2): 147-157, 2020. https://doi.org/10.3785/j.issn.1008-9292.2020.02.02

[128]. Gou, W., Fu, Y., Yue, L., Chen, G. D., Cai, X., Shuai, M., Xu, F., Yi, X., Chen, H., Zhu, Y., Xiao, M., Jiang, Z., Miao, Z., Xiao, C., Shen, B., Wu, X., Zhao, H., Ling, W., Wang, J., Chen, Y., Guo, T., and Zheng, J. S. Gut microbiota may underlie the predisposition of healthy individuals to COVID-19. *MedRxiv*, 2020-04, 2020. https://doi.org/10.1101/2020.04.22.20076091

[129]. Vijaykumar, S., Raamkumar, A. S., and Zhao, N. COVID-19, coronavirus, Wuhan virus, or China virus? Understanding how to "do no harm" when naming an infectious disease. *Frontiers in Psychology*, 11: 561270, 2020. https://doi.org/10.3389/fpsyg.2020.561270

[130]. Zhao, N., Zhou, G., and Li, L. Analysis of COVID-19 name varieties in Chinese mass and social media. *International Journal of Environmental Research and Public Health*, 18(18): 9850, 2021. https://doi.org/10.3390/ijerph18189850.

[131]. Bhatia, R., Singh, H. K., Kaur, M., Sharma, A., and Singh, P. A retrospective study on mortality during the first and second waves of COVID-19 in India. *Journal of Public Health Research*, *12*(4): 1234-1245, 2023. https://pubmed.ncbi.nlm.nih.gov/37829991/

[132]. Mathews, M., Ramesan, K., Kumar, A., Kurian, S., and Divakaran, B. Descriptive Epidemiology of COVID-19 Deaths in the First, Second, and Third Pandemic Waves: A Comparative Study from Southern India. *Asian Journal of Medical Sciences*, 13(7), 1–7, 2022. https://doi.org/10.3126/ajms.v13i7.45249

[133]. Baber, H., Shaik, M., and Gupta, H. An Analysis of the Indian Economy during the Three COVID-19 Pandemic Waves. *Technological and Economic Development of Economy*, 31(1), 169–183, 2025. https://doi.org/10.3846/tede.2024.21872

[134]. Sharma, S., Zhang, M., Gao, J., Zhang, H., Kota, S. H., and Saxena, P. Effects of COVID-19 Lockdown Phases in India: An Atmospheric Perspective. *Environmental Science and Pollution Research International*, 28(43), 60651–60661, 2021. https://doi.org/10.1007/s11356-021-15047-6

[135]. Kumari, A., and Ranjan, P. An Interrupted Time Series Analysis of the Lockdown Policies in India: A National-Level Analysis of COVID-19 Incidence. *International Journal of Epidemiology*, 50(4), 1219–1227, 2021. https://doi.org/10.1093/ije/dyab140

[136]. Oude Munnink, B. B., Worp, N., Nieuwenhuijse, D. F., Sikkema, R. S., Haagmans, B., Fouchier, R. A. M., and Koopmans, M. The next Phase of SARS-CoV-2 Surveillance: Real-Time Molecular Epidemiology. *Nature Medicine*, 27(9): 1518–1524, 2021. https://doi.org/10.1038/s41591-021-01472-w

[137]. Parra-Lucares, A., Segura, P., Rojas, V., Pumarino, C., Saint-Pierre, G., and Toro, L. Emergence of SARS-CoV-2 Variants in the World: How Could This Happen? *Life*, 12(2): 194, 2022. https://doi.org/10.3390/life12020194

[138]. Kyriakidis, N. C., López-Cortés, A., González, E. V., Grimaldos, A. B., and Prado, E. O. SARS-CoV-2 Vaccines Strategies: A Comprehensive Review of Phase 3 Candidates. *Nature Partner*

Journals Vaccines, 6(1): 28, 2021. https://doi.org/10.1038/s41541-021-00292-w

[139]. Flanagan, K. L., Best, E., Crawford, N. W., Giles, M., Koirala, A., Macartney, K., Russell, F., Teh, B. W., and Wen, S. C. Progress and Pitfalls in the Quest for Effective SARS-CoV-2 (COVID-19) Vaccines. *Frontiers in Immunology*, 11: 579250, 2020. https://doi.org/10.3389/fimmu.2020.579250

[140]. Zhu, H., Wei, L., and Niu, P. (2 March 2020). The novel coronavirus outbreak in Wuhan, China. *Global Health Research and Policy*. 5(1): 6, 2020. https://doi.org/10.1186/s41256-020-00135-6

[141]. Das, C., Hazarika, P. J., Deb, A., Joshi, P., Das, D., and Mattaparthi, V. S. K. Effect of Double Mutation (L452R and E484Q) in RBD of Spike Protein on its Interaction with ACE2 Receptor Protein. *Biointerface Research in Applied* Chemistry, 13(1): 97, 2023. https://doi.org/10.33263/BRIAC131.097

[142]. Zhang, W., Davis, B. D., Chen, S. S., Martinez, J. M. S., Plummer, J. T., and Vail, E. Emergence of a novel SARS-CoV-2 variant in Southern California. *JAMA*, 325(13): 1324–1326, 2021. https://doi.org/10.1001/jama.2021.1612

[143]. Rambaut, A., Holmes, E. C., O'Toole, Á., Hill, V., McCrone, J. T., Ruis, C., du Plessis, L. and Pybus, O. G. A dynamic nomenclature proposal for SARS-CoV-2 lineages to assist genomic epidemiology. *Nature Microbiology*, 5(11): 1403-1407, 2020. https://doi.org/10.1038/s41564-020-0770-5

[144]. McCallum, M., Bassi, J., De Marco, A., Chen, A., Walls, A. C., Di Iulio, J., Tortorici, M. A., Navarro, M. J., Silacci-Fregni, C., Saliba, C., Sprouse, K. R., Agostini, M., Pinto, D., Culap, K., Bianchi, S., Jaconi, S., Cameroni, E., Bowen, J. E., Tilles, S. W., Pizzuto, M. S., Guastalla, S. B., Bona, G., Pellanda, A. F., Garzoni, C., Van Voorhis, W. C., Rosen, L. E., Snell, G., Telenti, A., Virgin, H. W., Piccoli, L., Corti, D., and Veesler, D. SARS-CoV-2 immune evasion by the B.1.427/B.1.429 variant of concern. *Science (New York, N.Y.)*, 373(6555): 648-654, 2021. https://doi.org/10.1126/science.abi7994

[145]. Tchesnokova, V., Kulakesara, H., Larson, L., Bowers, V., Rechkina, E., Kisiela, D., Sledneva, Y., Choudhury, D., Maslova, I., Deng, K., Kutumbaka, K., Geng, H., Fowler, C., Greene, D., Ralston, J., Samadpour, M., and Sokurenko, E. Acquisition of the L452R mutation in the ACE2-binding interface of Spike protein triggers recent massive expansion of SARS-Cov-2 variants. *bioRxiv* 2021, https://doi.org/10.1101/2021.02.22.432189.

[146]. Duong D. Alpha, Beta, Delta, Gamma: What's important to know about SARS-CoV-2 variants of concern? *CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne*, 193(27): E1059–E1060, 2021. https://doi.org/10.1503/cmaj.1095949

[147]. Volz, E., Mishra, S., Chand, M., Barrett, J. C., Johnson, R., Geidelberg, L., and Ferguson, N. M. Assessing transmissibility of SARS-CoV-2 lineage B.1.1.7 in England. *Nature*, *593*(7858), 266-269, 2021. https://doi.org/10.1038/s41586-021-03470-x

[148]. Davies, N. G., Abbott, S., Barnard, R. C., Jarvis, C. I., Kucharski, A. J., Munday, J. D., and Edmunds, W. J. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. *Science*, *372*(6538), 2021. https://doi.org/10.1126/science.abg3055

[149]. Galloway, S. E., Paul, P., MacCannell, D. R., Johansson, M. A., Brooks, J. T., MacNeil, A., and Tamin, A. Emergence of SARS-CoV-2 B.1.1.7 lineage—United States, December 29, 2020–January 12, 2021. *Morbidity and Mortality Weekly Report*, 70(3): 95, 2021. https://doi.org/10.15585/mmwr.mm7003e2

[150]. Challen, R., Brooks-Pollock, E., Read, J. M., Dyson, L., Tsaneva-Atanasova, K., and Danon, L. Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: matched cohort study. *BMJ*, 372: n579, 2021. https://doi.org/10.1136/bmj.n579

[151]. Bernal, J. L., Andrews, N., Gower, C., Stowe, J., Robertson, C., Tessier, E., and Ramsay, M. Effectiveness of COVID-19 vaccines against the B.1.1.7 variant. *New England Journal of Medicine*, *385*(7): 585-594, 2021. https://doi.org/10.1056/NEJMoa2108891

[152]. WHO. Tracking SARS-CoV-2 variants. *World Health Organization*, 2021. Retrieved from https://www.who.int/en/activities/tracking-SARS-CoV-2-variants

[153]. Tegally, H., Wilkinson, E., Giovanetti, M., Iranzadeh, A., Fonseca, V., Giandhari, J., Doolabh, D., Pillay, S., San, E. J., Msomi, N., Makhanini, M., Lessells, R. J., Mlisana, K., Bhiman, J. N., Williamson, C., and de Oliveira, T. Emergence of a SARS-CoV-2 variant of concern with mutations in spike glycoprotein. *Nature*, 592(7854): 438-443, 2021. https://doi.org/10.1038/s41586-021-03402-9

[154]. Pearson, C. A. B., Russell, T. W., Davies, N. G., Kucharski, A. J., and Edmunds, W. J. Estimates of severity and transmissibility of novel SARS-CoV-2 variant 501Y.V2 in South Africa. *The Lancet Global Health*, 9(4), e470-e471, 2021. https://doi.org/10.1016/S2214-109X(21)00021-6

[155]. Yadav, P. D., Sarkale, P., Razdan, A., Gupta, N., Nyayanit, D. A., Sahay, R. R., Potdar, V., Patil, D. Y., Baradkar, S., Kumar, A., Aggarwal, N., Shete, A. M., Kaur, H., and Mohandas, S. Isolation and characterization of SARS-CoV-2 Beta variant from UAE travelers. *Journal of Infection and Public Health*, 15(2): 182–186, 2022. https://doi.org/10.1016/j.jiph.2021.12.011

[156]. Dhar, M. S., Marwal, R., Radhakrishnan, V. S., Ponnusamy, K., Jolly, B., Bhoyar, R. C., and Gupta, V. (2021). Genomic characterization and epidemiology of an emerging SARS-CoV-2 variant in India. *Science*, *374*(6573), 995-999. https://doi.org/10.1126/science.abj9932

[157]. Liu, Y., Rocklöv, J. (2021). The reproductive number of the Delta variant of SARS-CoV-2 is far higher compared to the Alpha variant. *Journal of Travel Medicine*, *28*(7), taab124.

https://doi.org/10.1093/jtm/taab124

[158]. Dhawan, M., Sharma, A., Priyanka, Thakur, N., Rajkhowa, T. K., and Choudhary, O. P. Delta variant (B.1.617.2) of SARS-CoV-2: Mutations, impact, challenges and possible solutions. *Human Vaccines and Immunotherapeutics*, 18(5): 2068883, 2022. https://doi.org/10.1080/21645515.2022.2068883

[159]. Planas, D., Veyer, D., Baidaliuk, A., Staropoli, I., Guivel-Benhassine, F., Rajah, M. M., and Schwartz, O. (2021). Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. *Nature*, 596(7871), 276-280. https://doi.org/10.1038/s41586-021-03777-9

[160]. Lopez Bernal, J., Andrews, N., Gower, C., Robertson, C., Stowe, J., Tessier, E., and Ramsay, M. (2021). Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) variant. *New England Journal of Medicine*, 385, 585-594. https://doi.org/10.1056/NEJMoa2108891

[161]. Kannan, S. R., Spratt, A. N., Cohen, A. R., Naqvi, S. H., Chand, H. S., Quinn, T. P., Lorson, C. L., Byrareddy, S. N., and Singh, K. (2021). Evolutionary analysis of the Delta and Delta Plus variants of the SARS-CoV-2 viruses. *Journal of Autoimmunity*, 124, 102715. https://doi.org/10.1016/j.jaut.2021.10271

[162]. Cherian, S., Potdar, V., Jadhav, S., Yadav, P., Gupta, N., Das, M., Rakshit, P., Singh, S., Bhargava, B., and Panda, S. (2021). Convergent evolution of SARS-CoV-2 spike mutations, L452R, E484Q, and P681R, in the second wave of COVID-19 in Maharashtra, India. *Journal of Virology*, 95(17), e01102-21. https://doi.org/10.1128/JVI.01102-21

[163]. Ferreira, I. A., Kemp, S. A., Datir, R., Saito, A., Meng, B., Rakshit, P., Takaori-Kondo, A., Kosugi, Y., Uriu, K., Kimura, I., Shirakawa, K., Tokunaga, K., Sato, K., and Gupta, R. K. (2021). SARS-CoV-2 B.1.617 emergence and sensitivity to vaccine-elicited antibodies. *Nature*, 597(7878), 273-277. https://doi.org/10.1038/s41586-021-03996-2

[164]. Singh, J., Malhotra, A. G., Biswas, D., Shankar, P., Lokhande, L., Yadav, A. K., Raghuvanshi, A., Kale, D., Nema, S., Saigal, S., and Singh, S. Relative Consolidation of the Kappa Variant Pre-Dates the Massive Second Wave of COVID-19 in India. *Genes*, 12(11): 1803, 2021. https://doi.org/10.3390/genes12111803

[165]. Faria, N. R., Claro, I. M., Candido, D., Franco, L. A. M., Andrade, P. S., Coletti, T. M., Silva,C. A. M., Sales, F. C., Manuli, E. R., Aguiar, R. S., Gaburo, N., Camilo, C. C., Fraiji, N. A., Crispim, M. A. E., Carvalho, M. P. S. S., Rambaut, A., Loman, N., Pybus, O. G., Sabino, E. C., on behalf of CADDE Genomic Network. "Genomic characterisation of an emergent SARS-CoV-2 lineage in Manaus: preliminary findings". *Virological*, 372 (2021): 815-821, 2021.

[166]. Fujino, T., Nomoto, H., Kutsuna, S., Ujiie, M., Suzuki, T., Sato, R., Kuroda, M., and Ohmagari, N. Novel SARS-CoV-2 variant in travelers from Brazil to Japan. *Emerging Infectious Diseases*, 27(4): 1243–1245, 2021.https://doi.org/10.3201/eid2704.210138

[167]. National Institute of Infectious Diseases, Japan. *Brief report: New variant strain of SARS-CoV-2 identified in travelers from Brazil*, 2021. https://www.niid.go.jp/niid/en/2019-ncov-e/10108-covid19-33-en.html

[168]. Banho, C.A., Sacchetto, L., Campos, G. R. F., Bittar, C., Possebon, F. S., Ullmann, L. S., Marques, B. C., da Silva, G. C. D., Moraes, M. M., Parra, M. C. P., Negri, A. F., Boldrin, A. C., Barcelos, M. D., Dos Santos, T. M. I. L., Milhim, B. H. G. A., Rocha, L. C., Dourado, F. S., Dos Santos, A. L., Ciconi, V. B., Patuto, C., Versiani, A. F., da Silva, R. A., de Oliveira Lobl, E. E., Hernandes, V. M., Zini, N., Pacca, C. C., Estofolete, C. F., Ferreira, H. L., Rahal, P., Araújo, J. P. Jr., Cohen, J. A., Kerr, C. C., Althouse, B. M., Vasilakis, N., and Nogueira, M. L. Impact of SARS-CoV-2 Gamma lineage introduction and COVID-19 vaccination on the epidemiological landscape of a Brazilian city. *Communications Medicine*, 2: 41, 2022. https://doi.org/10.1038/s43856-022-00108-5

[169]. Wang, Z., Schmidt. F., Weisblum, Y., Muecksch, F., Barnes, C. O., Finkin, S., Schaefer-Babajew, D., Cipolla, M., Gaebler, C., Lieberman, J. A., Oliveira, T. Y., Yang, Z., Abernathy, M. E., Huey-Tubman, K. E., Hurley, A., Turroja, M., West, K. A., Gordonm K., Millard, K. G., Ramos, V., Da Silva, J., Xu, J., Colbert, R. A., Patel, R., Dizon, J., Unson-O'Brien, C., Shimeliovich, I., Gazumyan, A., Caskey, M., Bjorkman, P. J., Casellas, R., Hatziioannou, T., Bieniasz, P. D., and Nussenzweig, M. C. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. *Nature*, 592(7855): 616–622 https://doi.org/10.1038/s41586-021-03324-6 (2021).

[170]. Liu, H., Zhang, Q., Wei, P., Chen, Z., Aviszus, K., Yang, J., Downing, W., Jiang, C., Liang, B., Reynoso, L., Downey, G. P., Frankel, S. K., Kappler, J., Marrack, P., and Zhang, G. The basis of a more contagious 501Y.V1 variant of SARS-CoV-2. *Cell Research*, 31: 720–722, 2021. https://doi.org/10.1038/s41422-021-00496-8

[171]. Faria, N. R., Mellan, T. A., Whittaker, C., Claro, I. M., Candido, D. D. S., Mishra, S., Crispim, M. A. E., Sales, F. C. S., Hawryluk, I., McCrone, J. T., Hulswit, R. J. G., Franco, L. A. M., Ramundo, M. S., de Jesus, J. G., Andrade, P. S., Coletti, T. M., Ferreira, G. M., Silva, C. A. M., Manuli, E. R., Pereira, R. H. M., Peixoto, P. S., Kraemer, M. U. G., Gaburo, N. Jr., Camilo, C. D. C., Hoeltgebaum, H., Souza, W. M., Rocha, E. C., de Souza, L. M., de Pinho, M. C., Araujo, L. J. T., Malta, F. S. V., de Lima, A. B., Silva, J. D. P., Zauli, D. A. G., Ferreira, A. C. S., Schnekenberg, R. P., Laydon, D. J., Walker, P. G. T., Schlüter, H. M., Dos Santos, A. L. P., Vidal, M. S., Del Caro, V. S., Filho, R. M. F., Dos Santos, H. M., Aguiar, R. S., Proença-Modena, J. L., Nelson, B., Hay, J. A., Monod, M., Miscouridou, X., Coupland, H., Sonabend, R., Vollmer, M., Gandy, A., Prete, C. A. Jr., Nascimento, V. H., Suchard, M. A., Bowden, T. A., Pond, S. L. K., Wu, C. H., Ratmann, O., Ferguson, N. M., Dye, C., Loman, N. J., Lemey, P., Rambaut, A., Fraiji, N. A., Carvalho, M. D. P. S. S., Pybus, O. G., Flaxman, S., Bhatt, S., and Sabino, E. C. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. *Science*, 372(6544): 815–821, 2021. https://doi.org/10.1126/science.abh2644

[172]. Chavda, V. P., Balar, P., Vaghela, D., Solanki, H. K., Vaishnav, A., Hala, V., and Vora, L. Omicron Variant of SARS-CoV-2: An Indian Perspective of Vaccination and Management. *Vaccines*, 11(1): 160, 2023. https://doi.org/10.3390/vaccines11010160

[173]. Kandeel, M., Mohamed, M. E. M., Abd El-Lateef, H. M., Venugopala, K. N., and El-Beltagi, H. S. Omicron variant genome evolution and phylogenetics. *Journal of Medical Virology*, 94(4), 1627–1632, 2022. https://doi.org/10.1002/jmv.27515

[174]. Gao, S.-J., Guo, H., and Luo, G. Omicron variant (B.1.1.529) of SARS-CoV-2, a global urgent public health alert! *Journal of Medical Virology*, 94(4): 1255–1256, 2022. https://doi.org/10.1002/jmv.27491

[175]. Karim, S. S. A., and Karim, Q. A. Omicron SARS-CoV-2 variant: a new chapter in the COVID-19 pandemic. *The Lancet*, 398(10317), 2126–2128, 2021. https://doi.org/10.1016/S0140-6736(21)02758-6

[176]. Kannan, S., Shaik Syed Ali, P., and Sheeza, A. Omicron (B.1.1.529) – variant of concern – molecular profile and epidemiology: a mini review. *European Review for Medical and Pharmacological Sciences*, 25(24): 8019–8022, 2021. https://doi.org/10.26355/eurrev_202112_27653

[177]. Ou, J., Lan, W., Wu, X., Zhao, T., Duan, B., Yang, P., Ren, Y., Quan, L., Zhao, W., Seto, D., Chodosh, J., Luo, Z., Wu, J., and Zhang, Q. Tracking SARS-CoV-2 Omicron Diverse Spike Gene Mutations Identifies Multiple Inter-Variant Recombination Events. *Signal Transduction and Targeted Therapy*, 7(1): 138, 2022. https://doi.org/10.1038/s41392-022-00992-2

[178]. He, X., Hong, W., Pan, X., Lu, G., and Wei, X. SARS-CoV-2 Omicron Variant: Characteristics and Prevention. *Medical Communications*, 2(4): 838–845, 2021. https://doi.org/10.1002/mco2.110

[179]. Yao, L., Zhu, K. L., Jiang, X. L., Wang, X. J., Zhan, B. D., Gao, H. X., Geng, X. Y., Duan, L. J., Dai, E. H., and Ma, M. J. Omicron subvariants escape antibodies elicited by vaccination and BA.2.2 infection. *The Lancet Infectious Diseases*, 22 (8): 1116–1117, 2022. https://doi.org/10.1016/S1473-3099(22)00410-8

[180]. Mohandas, S., Shete, A., Kumar, A., Wakchaure, K., Rai, V., Mote, C., Dighe, H., Sarkale, P., Gawande, P., Yemul, J., Suryawanshi, A., Joshi, Y., and Yadav, P. D. Comparative pathogenicity of BA.2.12, BA.5.2, and XBB.1 with the Delta variant in Syrian hamsters. *Frontiers in Microbiology*, 14: 1183763, 2023.https://doi.org/10.3389/fmicb.2023.1183763

[181]. Tamura, T., Ito, J., Uriu, K., Zahradnik, J., Kida, I,. Anraku, Y., Nasser, H., Shofa, M., Oda, Y., Lytras, S., Nao, N., Itakura, Y., Deguchi, S., Suzuki, R., Wang, L., Begum, M. M., Kita, S., Yajima, H., Sasaki, J., Sasaki-Tabata, K., Shimizu, R., Tsuda, M., Kosugi, Y., Fujita, S., Pan, L., Sauter, D., Yoshimatsu, K., Suzuki, S., Asakura, H., Nagashima, M., Sadamasu, K., Yoshimura, K., Yamamoto, Y., Nagamoto, T., Schreiber, G., Maenaka, K., Genotype to Phenotype Japan (G2P-

Japan) Consortium, Hashiguchi, T., Ikeda, T., Fukuhara, T., Saito, A., Tanaka, S., Matsuno, K., Takayama, K., and Sato K. Virological characteristics of the SARS-CoV-2 XBB variant derived from recombination of two Omicron subvariants. *Nature Communications*, 14(1): 2800, 2023. https://doi.org/10.1038/s41467-023-38435-3

[182]. Davis-Gardner, M. E., Lai, L., Wali, B., Samaha, H., Solis, D., Lee, M., Porter-Morrison, A., Hentenaar, I. T., Yamamoto, F., Godbole, S., Liu, Y., Douek, D. C., Lee, F. E., Rouphael, N., Moreno, A., Pinsky, B. A., and Suthar, M. S. Neutralization against BA.2.75.2, BQ.1.1, and XBB from mRNA bivalent booster. *The New England Journal of Medicine*, 388(2): 183–5, 2023. https://doi.org/10.1056/NEJMc2214293

[183]. Huang, B., Dai, L., Wang, H., Hu, Z., Yang, X., Tan, W., and Gao, G. F. Structural basis of XBB.1.5 escape from neutralizing antibodies. *Nature Structural & Molecular Biology*, 30(5), 431-439, 2023. https://pubmed.ncbi.nlm.nih.gov/39059371/

[184]. Chen, C., Nadeau, S., Yared, M., Voinov, P., Xie, N., Severyn, C. J., and Stadler, T. The evolution and global spread of XBB.1.5. *Frontiers in Virology*, 3, 1158703, 2023. https://www.frontiersin.org/articles/10.3389/fviro.2023.1158703/full

[185]. Channabasappa, N. K., Niranjan, A. K., and Emran, T. B. SARS-CoV-2 variant omicron XBB.1.5: challenges and prospects - correspondence. *International Journal of Surgery (London, England)*, 109(4): 1054–1055, 2023. https://doi.org/10.1097/JS9.0000000000000276

[186]. Samal, J., Bhugra, A., Suroliya, V., Gautam, P., Agarwal, R., Bihari, C., and Gupta, E. The emergence of the Omicron XBB.1.5 variant in India: a brief report on clinical presentation of a few cases. *Frontiers in Virology*, 3: 1158703, 2023. https://doi.org/10.3389/fviro.2023.1158703

[187]. Yue, C., Song, W., Wang, L., Jian, F., Chen, X., Gao, F., Shen, Z., Wang, Y., Wang, X., and Cao, Y. Enhanced transmissibility of XBB.1.5 is contributed by both strong ACE2 binding and antibody evasion. *bioRxiv* 18(3): 278–80, 2023. https://doi.org/10.1101/2023.01.03.522427

[188]. Tamura, K., Fukui, M., Toba, S., Miyazaki, M., and Saito, K. Comparative infectivity and immune evasion of emerging XBB subvariants of SARS-CoV-2. *The Lancet Infectious Diseases*, 23(5), 278-285, 2023. https://www.thelancet.com/article/S1473-3099(23)00278-5/fulltext

[189]. Idris, I., and Adesola, R. O. Emergence and spread of JN.1 COVID-19 variant. *Bulletin of the National Research Centre*, 48: 27, 2024. https://doi.org/10.1186/s42269-024-01183-5

[190]. Kosugi, Y., Plianchaisuk, A., Putri, O., Uriu, K., Kaku, Y., Hinay, A. A. Jr., Chen, L., Kuramochi, J., Sadamasu, K., Yoshimura, K., Asakura, H., Nagashima, M., Ito, J., Genotype to Phenotype Japan (G2P-Japan) Consortium, and Sato, K. Virological characteristics of the SARS-CoV-2 omicron HK.3 variant harboring the “FLip” substitution. *BioRxiv*, 2023-11, 2023. (preprint) https://doi.org/10.1101/2023.11.14.566985

[191]. Flores-Vega, V. R., Monroy-Molina, J. V., Jiménez-Hernández, L. E., Torres, A. G., Santos-Preciado, J. I., and Rosales-Reyes, R. SARS-CoV-2: Evolution and Emergence of New Viral Variants. *Viruses*, 14(4): 653, 2022. https://doi.org/10.3390/v14040653

[192]. Ghafari, M., Liu, Q., Dhillon, A., Katzourakis, A., and Weissman, D. B. Investigating the Evolutionary Origins of the First Three SARS-CoV-2 Variants of Concern. *Frontiers in Virology*, 2: 942555, 2022. https://doi.org/10.3389/fviro.2022.942555

[193]. Zu, Z. Y., Jiang, M. D., Xu, P. P., Chen, W., Ni, Q. Q., Lu, G. M., and Zhang, L. J. Coronavirus disease 2019 (COVID-19): a perspective from China. *Radiology*, 296(2): E15-E25, 2020. https://doi.org/10.1148/radiol.2020200490

[194]. Abbasi-Oshaghi, E., Mirzaei, F., Farahani, F., Khodadadi, I., and Tayebinia, H. Diagnosis and treatment of coronavirus disease 2019 (COVID-19): Laboratory, PCR, and chest CT imaging findings. *International journal of surgery*, 79: 143–153, 2020. https://doi.org/10.1016/j.ijsu.2020.05.018

[195]. Wiersinga, W. J., Rhodes, A., Cheng, A. C., Peacock, S. J., and Prescott, H. C. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*, 324(8): 782–793, 2020. https://doi.org/10.1001/jama.2020.12839

[196]. Pan, F., Ye, T., Sun, P., Gui, S., Liang, B., Li, L., Zheng, D., Wang, J., Hesketh, R. L., Yang, L., and Zheng, C. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. *Radiology*, 200370, 2020. https://doi.org/10.1148/radiol.2020200370

[197]. Stebbing, J., Phelan, A., Griffin, I., Tucker, C., Oechsle, O., Smith, D., and Richardson, P. COVID-19: Combining antiviral and anti-inflammatory treatments. *The Lancet Infectious Diseases*, 20(4): 400–402, 2020. https://doi.org/10.1016/S1473-3099(20)30132-8

[198]. Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W., and Xiao, G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research*, 30(3): 269–271, 2020. https://doi.org/10.1038/s41422-020-0282-0

[199]. Williamson, B. N., Feldmann, F., Schwarz, B., Meade-White, K., Porter, D. P., Schulz, J., Doremalen, N. V., Leighton, I., Yinda, C. K., Perez-Perez, L., Okumura, A., Lovaglio, J., Hanley, P. W., Saturday, G., Bosio, C. M., Anzick, S., Barbian, K., Cihlar, T., Martens, C., Scott, D. P., Munster, V. J., and Wit, E. D. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. *Nature*, 585(7824): 273–276, 2020. https://doi.org/10.1038/s41586-020-2423-5

[200]. Gordon, C. J., Tchesnokov, E. P., Feng, J. Y., et al. (2020). Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. *Journal of Biological Chemistry*, 295(20), 6785–6797. https://doi.org/10.1074/jbc.RA120.013679

[201]. Beigel, J. H., Tomashek, K. M., Dodd, L. E., et al. (2020). Remdesivir for the treatment of Covid-19 — Final report. *New England Journal of Medicine*, 383(19), 1813–1826. https://doi.org/10.1056/NEJMoa2007764

[202]. Delang, L., Abdelnabi, R., and Neyts, J. Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. *Antiviral Research,* 153: 85–94, 2018. https://doi.org/10.1016/j.antiviral.2018.03.003

[203]. Furuta, Y., Gowen, B. B., Takahashi, K., Shiraki, K., Smee, D. F., and Barnard, D. L. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. *Antiviral Research,* 100(2): 446–454, 2013. https://doi.org/10.1016/j.antiviral.2013.09.015

[204]. Udwadia, Z. F., Singh, P., Barkate, H., Patil, S., Rangwala, S., Pendse, A., Kadam, J., Wu, W., Caracta, C. F., and Tandon, M. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: A randomized, comparative, open-label, multicenter, phase 3 clinical trial. *International Journal of Infectious Diseases,* 103: 62–71, 2021. https://doi.org/10.1016/j.ijid.2020.11.142

[205]. Furuta, Y., Gowen, B. B., Takahashi, K., Shiraki, K., Smee, D. F., and Barnard, D. L. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. *Antiviral Research,* 100(2): 446–454, 2013. https://doi.org/10.1016/j.antiviral.2013.09.015

[206]. Agrawal, U., Raju, R., and Udwadia, Z. F. Favipiravir: A new and emerging antiviral option in COVID-19. *Medical journal Armed Forces India*, 76(4): 370–376, 2020. https://doi.org/10.1016/j.mjafi.2020.08.004

[207]. Yao, T. T., Qian, J. D., Zhu, W. Y., Wang, Y., and Wang, G. Q. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-a possible reference for coronavirus disease-19 treatment option. *Journal of Medical Virology*, 92(6): 556–563, 2020. https://doi.org/10.1002/jmv.25729

[208]. Yuan, Y., Jiao, B., Qu, L., Yang, D., and Liu, R. The development of COVID-19 treatment. *Frontiers in immunology*, 14: 1125246, 2023. https://doi.org/10.3389/fimmu.2023.1125246

[209]. Wahl, A., Gralinski, L. E., Johnson, C. E., Yao, W., Kovarova, M., Dinnon III, K. H., Liu, H., Madden, V. J., Krzystek, H. M., De, C., White, K. K., Gully, K., Schafer, A., Zaman, T., Leist, S. R., Grant, P. O., Bluemling, G. R., Kolykhalov, A. A., Natchus, M. G., Askin, F. B., Painter, G., Browne, E. P., Jones, C. D., Pickles, R. J., Baric, R. S., and Garcia, J. V. SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801. *Nature*, 591(7850): 451–457, 2021. https://doi.org/10.1038/s41586-021-03312-w

[210]. Mahase, E. Covid-19: Molnupiravir reduces risk of hospital admission or death by 50% in patients at risk, MSD reports. *BMJ*, 375: n2422, 2021. https://doi.org/10.1136/bmj.n2422

[211]. Bernal, A. J., Gomes da Silva, M. M., Musungaie, D. B., Kovalchuk, E., Gonzalez, A., Reyes, V. D., Martin-Quiros, A., Caraco, Y., William-Diaz, A., Brown, M. L., Du, J., Pedley, A., Assaid, C., Strizki, J., Grobler, J. A., Shamsuddin, H. H., Tipping, R., Wan, H., Paschke, A., Butterton, J. R., Johnson, M. G., and Anda, C. D. Molnupiravir for oral treatment of covid-19 in nonhospitalized patients. *The New England Journal of Medicine*, 386(6): 509–520, 2021. https://doi.org/10.1056/NEJMoa2116044

[212]. Sticher, Z. M., Lu, P., House, R., Barrett, K. T., Tang, J., Ding, L., Rao, R., VanBlargan, L. A., Zhang, Y., Bopp, N. E., Binshtein, E., Case, J. B., Mackin, S., Hume, A. J., Chong, Z., Seiler, C., Bixler, S. L., Metzger, C. M. J. A., Threeton, B., and Pruijssers, A. J. Molnupiravir maintains antiviral activity against SARS-CoV-2 variants and exhibits a high barrier to the development of resistance. *Antimicrobial Agents and Chemotherapy*, 67(10): e00953-23, 2023. https://doi.org/10.1128/aac.00953-23

[213]. Whitley, R. Molnupiravir - a step toward orally bioavailable therapies for covid-19. *The New England Journal of Medicine*, 386(6): 592–593, 2021. https://doi.org/10.1056/NEJMe2117814

[214]. Naqvi, A. A. T., Fatima, K., Mohammad, T., Fatima, U., Singh, I. K., Singh, A., Atif, S. M., Hariprasad, G., Hasan, G. M., and Hassan, M. I. Insights into SARS-CoV-2 genome, structure, evolution, pathogenesis and therapies: Structural genomics approach. *Biochimica et Biophysica Acta Molecular Basis of Disease*. 1866: 165878–165878, 2020. https://doi.org/10.1016/j.bbadis.2020.165878

[215]. Duan, L., Zheng, Q., Zhang, H., Niu, Y., Lou, Y., and Wang, H. The SARS-CoV-2 spike glycoprotein biosynthesis, structure, function, and antigenicity: implications for the design of spike-based vaccine immunogens. *Frontiers in Immunology*, 11: 576622: 2020. https://doi.org/10.3389/fimmu.2020.576622

[216]. Durmaz, B., Abdulmajed, O., and Durmaz, R. Mutations observed in the SARS-CoV-2 spike glycoprotein and their effects in the interaction of virus with ACE-2 receptor. *Medeniyet Medical Journal*, 35: 253–60. 2020. https://doi.org/10.5222/mmj.2020.98048

[217]. Mittal, A., Manjunath, K., Ranjan, R. K., Kaushik, S., Kumar, S., Verma, V. COVID-19 pandemic: insights into structure, function, and hACE2 receptor recognition by SARS-CoV-2. *PLoS Pathogens*, 16(8): 1008762, 2020. https://doi.org/10.1371/journal.ppat.1008762

[218]. Navhaya, L. T., Blessing, D. M., Yamkela, M., Godlo, S. and Makhoba, X. H. A comprehensive review of the interaction between COVID-19 spike proteins with mammalian small and major heat shock proteins. *Biomolecular Concepts*, 15(1): 2022-0027, 2024. https://doi.org/10.1515/bmc-2022-0027

[219]. Ramasamy, S., and Subbian, S. Critical determinants of cytokine storm and type I interferon response in COVID-19 pathogenesis. *Clinical Microbiology Reviews*. 34(3): e00299-20, 2021.

https://doi.org/10.1128/CMR.00299-20

[220]. Zhang, J., Xiao, T., Cai, Y., and Chen, B. Structure of SARS-CoV-2 spike protein. *Current Opinion in Virology*, 50: 173-182, 2021. https://doi.org/10.1016/j.coviro.2021.08.010.

[221]. Barcena, M., Barnes, C. O., Beck, M., Bjorkman, P. J., Canard, B., Gao, G. F., Gao, F., Hilgenfeld, R., Hummer, G., Patwardhan, A., Santoni, G., Saphire, E. O., Schaffitzel, C., Schendel, S. L., Smith, J. L., Thorn, A., Veesler, D., Zhang, P., and Zhou, Q. Structural biology in the fight against COVID-19, *Nature Structural & Molecular Biology*, 28(1): 2-7, 2021. https://doi.org/10.1038/s41594-020-00544-8

[222]. Wu, X. D., Shang, B., Yang, R. F., Yu, H., Ma, Z. H., Shen, X., Ji, Y. Y., Lin, Y., Wu, Y. D., Lin, G. M., Tian, L., Gan, X. Q., Yang, S., Jiang, W. H., Dai, E. H., Wang, X. Y., Jiang, H. L., Xie, Y. H., Zhu, X. L., Pei, G., Li, L., Wu, J. R., and Sun, B. The spike protein of severe acute respiratory syndrome (SARS) is cleaved in virus infected Vero-E6 cells. *Cell research*, 14(5): 400–406, 2004. https://doi.org/10.1038/sj.cr.7290240

[223]. Bosch, B. J., van der Zee, R., de Haan, C. A., and Rottier, P.J. The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. *Journal of Virology*, 77(16): 8801–11, 2003. https://doi.org/10.1128/jvi.77.16.8801-8811.2003

[224]. Xia, S., Zhu, Y., Liu, M., Lan, Q., Xu, W., Wu, Y., Ying, T., Liu, S., Shi, Z., Jiang, S., and Lu, L. Fusion mechanism of 2019-nCoV and fusion inhibitors targeting HR1 domain in spike protein. *Cellular and Molecular Immunology*. 17(7): 765–767, 2020. https://doi.org/10.1038/s41423-020-0374-2

[225]. Li, F., Li, W., Farzan, M., and Harrison, S.C. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Science*, 309(5742):1864–1868, 2005. https://doi.org/10.1126/science.1116480

[226]. Xia, X. Domains and Functions of Spike Protein in Sars-Cov-2 in the Context of Vaccine Design. *Viruses*, 13(1):109. 2021. https://doi.org/10.3390/v13010109

[227]. Wrapp, D., Wang, N., Corbett, K. S., Goldsmith, J. A., Hsieh, C. L., Abiona, O., Graham, B. S., and McLellan, J. S. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*, 367(6483): 1260–1263, 2020. https://doi.org/10.1126/science.abb2507

[228]. Lan, J., Ge, J., Yu, J., Shan, S., Zhou, H., Fan, S., Zhang, Q., Shi, X., Wang, Q., Zhang, L., and Wang, X. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor, *Nature*, 581(7807): 215–220, 2020. https://doi.org/10.1038/s41586-020-2180-5

[229]. Huang, Y., Yang, C., Xu, X. F., Xu, W., and Liu, S. W. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. *Acta Pharmacologica Sinica*, 41(9): 1141–1149, 2020. https://doi.org/10.1038/s41401-020-0485-4

[230]. Lai, M. M., and Cavanagh, D. The molecular biology of coronaviruses. *Advances in Virus*

Research, 48: 1–100, 1997. https://doi.org/10.1016/S0065-3527(08)60286-9

[231]. Poh, W. P., Narasaraju, T., Pereira, N. A., Zhong, F., Phoon, M. C., Macary, P.A., Wong, S. H., Lu, J., Koh, D. R., and Chow, V.T. Characterization of cytotoxic T-lymphocyte epitopes and immune responses to SARS coronavirus spike DNA vaccine expressing the RGD-integrin-binding motif. *Journal of Medical Virology*, 81(7): 1131–1139, 2009. https://doi.org/10.1002/jmv.21571

[232]. Zhang, J., Xiao, T., Cai, Y., and Chen, B. Structure of SARS-CoV-2 spike protein. *Current opinion in virology*, 50: 173–182, 2021. https://doi.org/10.1016/j.coviro.2021.08.010

[233]. Li, W., Moore, M.J., Vasilieva, N., Sui, J., Wong, S.K., Berne, M.A., Somasundaran, M., Sullivan, J.L., Luzuriaga, K., Greenough, T.C., Choe, H., and Farzan, M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*, 426: 450–454, 2003. https://doi.org/10.1038/nature02145

[234]. Zhou, P., Yang, X.L., Wang, X.G., Hu, B., Zhang, L., Zhang, W., Si, H.R., Zhu, Y., Li, B., Huang, C.L., Chen, H.D., Chen, J., Luo, Y., Guo, H., Jiang, R.D., Liu, M.Q., Chen, Y., Shen, X.R., Wang, X., Zheng, X.S., Zhao, K., Chen, Q.J., Deng, F., Liu, L.L., Yan, B., Zhan, F.X., Wang, Y.Y., Xiao, G.F., and Shi, Z.L. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 579: 270–273, 2020. https://doi.org/10.1038/s41586-020-2012-7

[235]. Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T.S., Herrler, G., Wu, N.H., Nitsche, A., Müller, M.A., Drosten, C., and Pöhlmann, S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 181(2):271–280, 2020. https://doi.org/10.1016/j.cell.2020.02.052

[236]. Song, W., Gui, M., Wang, X., and Xiang, Y. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. *PLOS Pathogens*, 14(10): e1007236, 2018. https://doi.org/10.1371/journal.ppat.1007236

[237]. Li, F., Li, W., Farzan, M., and Harrison, S. C. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Science*, 309(5742): 1864–1868, 2005. https://doi.org/10.1126/science.1116480

[238]. Kuba, K., Imai, Y., Penninger, J. M., and Ohto-Nakanishi, T. Trilogy of ACE2: a peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. *Pharmacology & Therapeutics*, 128(1): 119–128, 2010. https://doi.org/10.1016/j.pharmthera.2010.06.003

[239]. Hamming, I., Timens, W., Bulthuis, M.L.C., Lely, A.T., Navis, G.J., and Goor, V.H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *Journal of Pathology*, 203(5): 631–637, 2004. https://doi.org/10.1002/path.1570

[240]. Zou, X., Chen, K., Zou, J., Han, P., Hao, J., and Han, Z. Single-cell RNA sequencing data

analysis reveals ACE2 expression and the potential risk of different human organs vulnerable to 2019-nCoV infection. *Frontiers of Medicine*, 14(2): 185–192, 2020. https://doi.org/10.1007/s11684-020-0754-0

[241]. Zhang, H., Li, H. B., Lyu, J. R., Lei, X. M., Li, W., Wu, G., Lyu, J., and Dai, Z.M. Specific ACE2 expression in small intestinal enterocytes may cause gastrointestinal symptoms and injury after 2019-nCoV infection. *International Journal of Infectious Diseases*, 96: 19–24, 2020. https://doi.org/10.1016/j.ijid.2020.04.027

[242]. Devaux, C. A. An update on angiotensin-converting enzyme 2 structure/functions, polymorphism, and duplicitous nature in the pathophysiology of coronavirus disease 2019: Implications for vascular and coagulation disease associated with severe acute respiratory syndrome coronavirus infection. *Frontiers in Microbiology*, 13: 1042200, 2022. https://doi.org/10.3389/fmicb.2022.1042200

[243]. Borkotoky, S., Dey, D., and Hazarika, Z. Interactions of angiotensin-converting enzyme-2 (ACE2) and SARS-CoV-2 spike receptor-binding domain (RBD): a structural perspective. *Molecular Biology Reports*, 50(3): 2713–2721, 2023. https://doi.org/10.1007/s11033-022-08193-4

[244]. Walls, A.C., Park, Y.J., Tortorici, M.A., Wall, A., McGuire, A.T., and Veesler, D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell*, 181(2): 281–292, 2020. https://doi.org/10.1016/j.cell.2020.02.058

[245]. Wrapp, D., Wang, N., Corbett, K. S., Goldsmith, J.A., Hsieh, C.L., Abiona, O., Graham, B.S., and McLellan, J.S. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*, 367(6483): 1260–1263, 2020. https://doi.org/10.1126/science.abb2507

[246]. Yuan, Y., Cao, D., Zhang, Y., Ma, J., Qi, J., Wang, Q., Lu, G., Wu, Y., Yan, J., Shi, Y., Zhang, X., and Gao, G.F. Cryo-EM structures of MERS-CoV and SARS-CoV spike glycoproteins reveal the dynamic receptor binding domains. *Nature Communications*, 8: 15092, 2017. https://doi.org/10.1038/ncomms15092

[247]. Gui, M., Song, W., Zhou, H., Xu, J., Chen, S., Xiang, Y., and Wang, X. Cryo-electron microscopy structures of the SARS-CoV spike glycoprotein reveal a prerequisite conformational state for receptor binding. *Cell Research*, 27(1): 119–129, 2017. https://doi.org/10.1038/cr.2016.152

[248]. Benton, D. J., Wrobel, A.G., Xu, P., Roustan, C., Martin, S.R., Rosenthal, P.B., Skehel, J.J., and Gamblin, S. J. Receptor binding and priming of the spike protein of SARS-CoV-2 for membrane fusion. *Nature*, 588(7837): 327–330, 2020. https://doi.org/10.1038/s41586-020-2772-0

[249]. Shang, J., Ye, G., Shi, K., Wan, Y., Luo, C., Aihara, H., Geng, Q., Auerbach, A., and Li, F. Structural basis of receptor recognition by SARS-CoV-2. *Nature*, 581(7807): 221–224, 2020. https://doi.org/10.1038/s41586-020-2179-y

[250]. Lan, J., Ge, J., Yu, J., Shan, S., Zhou, H., Fan, S., Zhang, Q., Shi, X., Wang, Q., Zhang, L., and

Wang, X. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature*, 581(7807): 215–220, 2020. https://doi.org/10.1038/s41586-020-2180-5

[251]. Jackson, C.B., Farzan, M., Chen, B., and Choe, H. Mechanisms of SARS-CoV-2 entry into cells. *Nature Reviews Molecular Cell Biology*, 23(1): 3–20, 2022. https://doi.org/10.1038/s41580-021-00418-x

[252]. Planas, D., Veyer, D., Baidaliuk, A., Staropoli, I., Guivel-Benhassine, F., Rajah, M.M., Planchais, C., Porrot, F., Robillard, N., Puech, J., Prot, M., Gallais, F., Gantner, P., Velay, A., Le Guen, J., Kassis-Chikhani, N., Edriss, D., Belec, L., Seve, A., Courtellemont, L., Péré, H., Hocqueloux, L., Fafi-Kremer, S., Prazuck, T., Mouquet, H., Bruel, T., Simon-Lorière, E., Rey, F.A., and Schwartz, O. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. *Nature*, 596(7871): 276–280, 2021. https://doi.org/10.1038/s41586-021-03777-9

[253]. Sheikh, A., McMenamin, J., Taylor, B., Robertson, C., and Public Health Scotland and the EAVE II Collaborators. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *The Lancet*, 397(10293): 2461–2462, 2021. https://doi.org/10.1016/s0140-6736(21)01358-1

[254]. Grabowski, F., Preibisch, G., Gizinski, S., Kochanczyk, M., and Lipniacki, T. SARS-CoV-2 variant of concern 202012/01 has about twofold replicative advantage and acquires concerning mutations. *Viruses*, 13(3): 392, 2021. https://doi.org/10.3390/v13030392

[255]. Tegally, H., Wilkinson, E., Giovanetti, M., Iranzadeh, A., Fonseca, V., Giandhari, J., Doolabh, D., Pillay, S., San, E. J., Msomi, N., Mlisana, K., von Gottberg, A., Walaza, S., Allam, M., Ismail, A., Mohale, T., Glass, A. J., Engelbrecht, S., Van Zyl, G., Preiser, W., Petruccione, F., Sigal, A., Hardie, D., Marais, G., Hsiao, N.Y., Korsman, S., Davies, M.A., Tyers, L., Mudau, I., York, D., Maslo, C., Goedhals, D., Abrahams, S., Laguda-Akingba. O., Alisoltani-Dehkordi, A., Godzik, A., Wibmer, C.K., Sewell, B.T., Lourenço, J., Alcantara, L.C.J., Kosakovsky, P. Ond, S.L., Weaver, S., Martin, D., Lessells, R.J., Bhiman, J.N., Williamson, C., and de Oliveira, T. Detection of a SARS-CoV-2 variant of concern in South Africa. *Nature*, 592(7854): 438–443, 2021. https://doi.org/10.1038/s41586-021-03402-9

[256]. Voloch, C.M., da Silva Francisco, R., Jr, de Almeida, L.G.P., Cardoso, C.C., Brustolini, O.J., Gerber, A. L., Guimarães, A.P.C., Mariani, D., da Costa, R.M., Ferreira, O.C., Jr, Covid19-UFRJ Workgroup, LNCC Workgroup, Adriana Cony Cavalcanti, Frauches, T.S., de Mello, C.M.B., Leitão, I.C., Galliez, R.M., Faffe, D. S., Castiñeiras, T.M.P.P., Tanuri, A., and de Vasconcelos, A.T.R. Genomic characterization of a novel SARS-CoV-2 lineage from Rio de Janeiro, Brazil. *Journal of Virology*, 95(10): e00119-21, 2021. https://doi.org/10.1128/JVI.00119-21

[257]. Tada, T., Zhou, H., Dcosta, B.M., Samanovic, M.I., Mulligan, M.J., and Landau, N.R. SARS-CoV-2 lambda variant remains susceptible to neutralization by mRNA vaccine-elicited antibodies

and convalescent serum. *bioRxiv*, 2021.07.02.450959, 2021. https://doi.org/10.1101/2021.07.02.450959

[258]. Li, F., Li, W., Farzan, M., and Harrison, S. C. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Science*, 309(5742): 1864–1868, 2005. https://doi.org/10.1126/science.1116480

[259]. Lim, S., Zhang, M., and Chang, T. L. ACE2-Independent Alternative Receptors for SARS-CoV-2. *Viruses*, 14(11): 2535, 2022. https://doi.org/10.3390/v14112535

[260]. Masre, S. F., Jufri, N. F., Ibrahim, F. W., and Abdul Raub, S. H. Classical and alternative receptors for SARS-CoV-2 therapeutic strategy. *Reviews in Medical Virology*, 31(5): 1-9, 2021. https://doi.org/10.1002/rmv.2207

[261]. Sun, G., Cui, Q., Garcia, G. Jr., Wang, C., Zhang, M., Arumugaswami, V., Riggs, A. D., and Shi Y. Comparative transcriptomic analysis of SARS-CoV-2 infected cell model systems reveals differential innate immune responses. *Scientific Reports*, 11(1): 17146, 2021. https://doi.org/10.1038/s41598-021-96462-w

[262]. Blanco-Melo, D., Nilsson-Payant, B. E., Liu, W. C., Uhl, S., Hoagland, D., Møller, R., Jordan, T. X., Oishi, K., Panis, M., Sachs, D., Wang, T. T., *Schwartz, R. E., Lim, J. K., Albrecht R. A., and tenOever, B. R.* Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. *Cell*, 181(5): 1036–1045.e1039, 2020. https://doi.org/10.1016/j.cell.2020.04.026

[263*]*. Hikmet, F., Méar, L., Edvinsson, Å., Micke, P., Uhlén, M., and Lindskog, C. The protein expression profile of ACE2 in human tissues. *Molecular Systems Biology*, 16(7): e9610, 2020. https://doi.org/10.15252/msb.20209610

[264]. Singh, M., Bansal, V., and Feschotte, C. A Single-Cell RNA Expression Map of Human Coronavirus Entry Factors. *Cell Reports*, 32(12): 108175, 2020. https://doi.org/10.1016/j.celrep.2020.108175

[265]. Xu, C., Wang, A., Geng, K., Honnen, W., Wang, X., Bruiners, N., Singh, S., Ferrara, F., D'Angelo, S., Bradbury, A. R. M., Gennaro, M. L., Liu, D., Pinter, A., and Chang, T. L. Human Immunodeficiency Viruses Pseudotyped with SARS-CoV-2 Spike Proteins Infect a Broad Spectrum of Human Cell Lines through Multiple Entry Mechanisms. *Viruses*, 13(6): 953, 2021. https://doi.org/10.3390/v13060953

[266]. Hoffmann, M., Sidarovich, A., Arora, P., Krüger, N., Nehlmeier, I., Kempf, A., Graichen, L., Winkler, M. S., Niemeyer, D., Goffinet, C., Drosten, C., Schulz, S., *Jäck, H. M., and Pöhlmann, S.* Evidence for an ACE2-Independent Entry Pathway That Can Protect from Neutralization by an Antibody Used for COVID-19 Therapy. *American Society for Microbiology*, 13(3): e0036422, 2022. https://doi.org/10.1128/mbio.00364-22

[267]. Beyerstedt, S., Casaro, E. B., and Rangel, É. B. COVID-19: Angiotensin-converting enzyme, 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. *European Journal of Clinical Microbiology & Infectious Diseases*, 40(5): 905–919, 2021. https://doi.org/10.1007/s10096-020-04138-6

[268]. Meng, B., Abdullahi, A., Ferreira, I., Goonawardane, N., Saito, A., Kimura I., Yamasoba, D., Gerber P. P., Fatihi, S., Rathore S., Zepeda, S. K., Papa, G., Kemp, S. A., Ikeda, T., Toyoda, M., Tan, T. S., Kuramochi, J., Mitsunaga, S., Ueno, T., Shirakawa, K., Takaori-Kondo, A., Brevini, T., Mallery, D. L., Charles, O. J., CITIID-NIHR BioResource COVID-19 Collaboration, Genotype to Phenotype Japan (G2P-Japan) Consortium, Ecuador-COVID19 Consortium, Bowen, J. E., Joshi, A., Walls, A. C., Jackson, L., Martin, D., Smith, K. G. C., Bradley, J., Briggs, J. A. G., Choi, J., Madissoon, E., Meyer, K. B., Mlcochova, P., Ceron-Gutierrez, L., Doffinger, R., Teichmann, S. A., Fisher, A. J., Pizzuto, M. S., de Marco, A., Corti, D., Hosmillo, M., Lee, J. H., James, L. C., Thukral, L., Veesler, D., Sigal, A., Sampaziotis, F., Goodfellow, I. G., Matheson, N. J., Sato, K., and Gupta, R. K. Altered TMPRSS2 usage by SARS-CoV-2 Omicron impacts infectivity and fusogenicity. *Nature*, 603(7902): 706–714, 2022. https://doi.org/10.1038/s41586-022-04474-x

[269]. Willett, B. J., Grove, J., MacLean, O. A., Wilkie, C., De Lorenzo, G., Furnon, W., Cantoni, D., Scott, S., Logan, N., Ashraf, S., Manali, M., Szemiel, A., Cowton, V., Vink, E., Harvey, W. T., Davis, C., Asamaphan, P., Smollett, K., Tong, L., Orton, R., Hughes, J., Holland, P., Silva, V., Pascall, D. J., Puxty, K., da Silva Filipe, A., Yebra, G., Shaaban, S., Holden, M. T. G., Pinto, R. M., Gunson, R., Templeton, K., Murcia, P. R., Patel, A. H., Klenerman, P., Dunachie, S., PITCH Consortium, COVID-19 Genomics UK (COG-UK) Consortium, Haughney, J., Robertson, D. L., Palmarini, M., Ray, S., and Thomson, E. C. SARS-CoV-2 Omicron is an immune escape variant with an altered cell entry pathway. *Nature Microbiology*, 7(8): 1161–1179, 2022. https://doi.org/10.1038/s41564-022-01143-7

[270]. Pia L., and Rowland-Jones, S. Omicron entry route. *Nature Reviews Immunology*, 22(3): 144, 2022. https://doi.org/10.1038/s41577-022-00681-9

[271]. Peacock, T. P., Brown, J. C., Zhou, J., Thakur, N., Sukhova, K., Newman, J., Kugathasan, R., Yan, A. W. C., Furnon, W., De Lorenzo, G., Cowton, V. M., Reuss, D., Moshe, M., Quantrill, J. L., Platt, O. K., Kaforou, M., Patel, A. H., Palmarini, M., Bailey, D., and Barclay, W., S. The altered entry pathway and antigenic distance of the SARS-CoV-2 Omicron variant map to separate domains of spike protein. *BioRxiv, 15: e0241955, 2022.* https://doi.org/10.1101/2021.12.31.474653

[272]. Guo, D., Guo, R., Li, Z., Zhang, Y., Zheng, W., Huang, X., Aziz, T., Zhang, Y., and Liu, L. Cat, AGTR2, L-sign and DC-sign are potential receptors for the entry of SARS-COV-2 into human cells. *BioRxiv*, 2021: 451411, 2021. https://doi.org/10.1101/2021.07.07.451411

[273]. Goyal, M. M., and Basak, A. Human catalase: looking for complete identity. *Protein & Cell*, 1(10): 888–97, 2010. https://doi.org/10.1007/s13238-010-0113-z

[274]. Shi, Y., Lo, C. S., Chenier, I., Maachi, H., Filep, J. G., Ingelfinger, J. R., Zhang, S. L., and Chan, J. S. D. Overexpression of catalase prevents hypertension and tubulointerstitial fibrosis and normalization of renal angiotensin-converting enzyme-2 expression in Akita mice. *American Journal of Physiology-Renal Physiology*, 304(11): F1335–46, 2013. https://doi.org/10.1152/ajprenal.00405.2012

[275]. Wysocki, J., Ortiz-Melo, D. I., Mattocks, N. K., Xu, K., Prescott, J., Evora, K., Ye, M., Sparks, M. A., Haque, S. K., Batlle, D., and Gurley, S. B. ACE2 deficiency increases NADPH-mediated oxidative stress in the kidney. *Physiological Reports*, 2(3): p. e00264, 2014. https://doi.org/10.1002/phy2.264

[276]. Cui, C., Huang, C., Zhou, W., Ji, X., Zhang, F., Wang, L., Zhou, Y., and Cui, Q. AGTR2, one possible novel key gene for the entry of SARS-CoV-2 into human cells. *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, 18(4): 1230-1233, 2020. https://doi.org/10.1109/TCBB.2020.300909

[277]. Han, D. P., Lohani, M., and Cho, M. W. Specific asparagine-linked glycosylation sites are critical for DC-SIGN- and L-SIGN-mediated severe acute respiratory syndrome coronavirus entry. *Journal of Virology*, 81(21): 12029–39, 2007. https://doi.org/10.1128/JVI.00315-07

[278]. Hu, Q., Xiong, Y., Zhu, G. H., Zhang, Y. N., Zhang, Y. W., Huang, P., and Ge, G. B. The SARS-CoV-2 main protease (M^{pro}): Structure, function, and emerging therapies for COVID-19. *MedComm*, 3(3): e151, 2022. https://doi.org/10.1002/mco2.151

[279]. Qiao, J., Li, Y. S., Zeng, R., Liu, F. L., Luo, R. H., Huang, C., Wang, Y. F., Zhang, J., Quan, B., Shen, C., Mao, X., Liu, X., Sun, W., Yang, W., Ni, X., Wang, K., Xu, L., Duan, Z. L., Zou, Q. C., Zhang, H. L., Qu, W., Long, Y. H. P., Li, M. H., Yang, R. C., Liu, X., You, J., Zhou, Y., Yao, R., Li, W. P., Liu, J. M., Chen, P., Liu, Y., Lin, G. F., Yang, X., Zou, J., Li, L., Hu, Y., Lu, G. W., Li, W. M., Wei, Y. Q., Zheng, Y. T., Lei, J., and Yang, S. SARS-CoV-2 M^{pro} inhibitors with antiviral activity in a transgenic mouse model. *Science*, 371(6536): 1374-1378, 2021. https://doi.org/10.1126/science.abf1611

[280]. Zhang, L., Lin, D., Sun, X., Curth, U., Drosten, C., Sauerhering, L., Becker, S., Rox, K., and Hilgenfeld, R. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. *Science*, 368(6489): 409–412, 2020. https://doi.org/10.1126/science.abb3405.

[281]. Jin, Z., Du, X., Xu, Y., Deng, Y., Liu, M., Zhao, Y., Zhang, B., Li, X., Zhang, L., Peng, C., Duan, Y., Yu, J., Wang, L., Yang, K., Liu, F., Jiang, R., Yang, X., You, T., Liu, X., Yang, X., Bai, F., Liu, H., Liu, X., Guddat, L. W., Xu, W., Xiao, G., Qin, C., Shi, Z., Jiang, H., Rao, Z., and Yang,

H. Structure of M^{pro} from SARS-CoV-2 and discovery of its inhibitors. *Nature*, 582(7811): 289–293, 2020. https://doi.org/10.1038/s41586-020-2223-y

[282]. Grottesi, A., Besker, N., Emerson, A., Manelfi, C., Beccari, A. R., Frigerio, F., Lindahl, E., Cerchia, C., and Talarico, C. Computational studies of SARS-CoV-2 3CLpro: Insights from MD simulations. *International Journal of Molecular Sciences*, 21(15): 5346, 2020. https://doi.org/10.3390/ijms21155346

[283]. Samrat, S. K., Xu, J., Xie, X., Gianti, E., Chen, H., Zou, J., Pattis, J. G., Elokely, K., Lee, H., Li, Z., Klein, M. L., Shi, P. Y., Zhou, J., and Li, H. Allosteric inhibitors of the main protease of SARS-CoV-2. *Antiviral Research*, 205: 105381, 2022. https://doi.org/10.1016/j.antiviral.2022.105381

[284]. Anand, K., Palm, G. J., Mesters, J. R., Siddell, S. G., Zeibuhr, J., and Hilgenfeld, R. Structure of coronavirus main proteinase reveals combination of a chymotrypsin fold with an extra alpha-helical domain. *The EMBO Journal*, 21(13): 3213-3224, 2002. https://doi.org/10.1093/emboj/cdf327

[285]. He, J., Hu, L., Huang, X., Wang, C., Zhang, Z., Wang, Y., Zhang, D., and Ye, W. Potential of coronavirus 3C-like protease inhibitors for the development of new anti-SARS-CoV-2 drugs: insights from structures of protease and inhibitors. *International Journal of Antimicrobial Agents*, 56(2): 106055, 2020. https://doi.org/10.1016/j.ijantimicag.2020.106055

[286]. Pillaiyar, T., Manickam, M., Namasivayam, V., Hayashi, Y., and Jung, S. H. An overview of severe acute respiratory syndrome-coronavirus (SARS-CoV) 3CL protease inhibitors: peptidomimetics and small molecule chemotherapy. *Journal of Medicinal Chemistry*, 59(14): 6595-6628, 2016. https://doi.org/10.1021/acs.jmedchem.5b01461

[287]. Zhang, L., Lin, D., Sun, X., Curth, U., Drosten, C., Sauerhering, L., Becker, S., Rox, K., and Hilgenfeld, R. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved alpha-ketoamide inhibitors. *Science*, 368(6489): 409-412, 2020. https://doi.org/10.1126/science.abb3405

[288]. Ziebuhr, J., Snijder, E. J., and Gorbalenya, A. E. Virus-encoded proteinases and proteolytic processing in the Nidovirales. *Journal of General Virology*, 81(4): 853-879, 2000. https://doi.org/10.1099/0022-1317-81-4-853

[289]. Li, X., and Song, Y. Structure and function of SARS-CoV and SARS-CoV-2 main proteases and their inhibition: A comprehensive review. *European Journal of Medicinal Chemistry*, 260: 115772, 2023. https://doi.org/10.1016/j.ejmech.2023.115772

[290]. Denesyuk, A. I., Permyakov, E. A., Johnson, M. S., Permyakov, S. E., Denessiouk, K., and Uversky, V. N. Structural and functional significance of the amino acid differences Val35Thr, Ser46Ala, Asn65Ser, and Ala94Ser in 3C-like proteinases from SARS-CoV-2 and SARS-CoV. *International Journal of Biological Macromolecules*, 193(B): 2113-2120, 2021. https://doi.org/10.1016/j.ijbiomac.2021.11.043

[291]. Feng, J., Li, D., Zhang, J., Yin, X., and Li, J. Crystal structure of SARS-CoV 3C-like protease with baicalein. *Biochemical and Biophysical Research Communications*, 611: 190-194, 2022. https://doi.org/10.1016/j.bbrc.2022.04.086

[292]. Kneller, D. W., Phillips, G., O'Neill, H. M., Jedrzejczak, R., Stols, L., Langan, P., Joachimiak, A., Coates, L., and Kovalevsky, A. Structural plasticity of SARS-CoV-2 3CL Mpro active site cavity revealed by room temperature X-ray crystallography. *Nature Communications*, 11(1): 3202, 2020. https://doi.org/10.1038/s41467-020-16954-7

[293]. Pozzi, C., Vanet, A., Francesconi, V., Tagliazucchi, L., Tassone, G., Venturelli, A., Spyrakis, F., Mazzorana, M., Costi, M. P., and Tonelli, M. Antitarget, anti-SARS-CoV-2 leads, drugs, and the drug discovery–genetics alliance perspective. *Journal of Medicinal Chemistry*, 66(6): 3664-3702, 2023. https://doi.org/10.1021/acs.jmedchem.2c01229

[294]. Zhang, L., Lin, D., Sun, X., Curth, U., Drosten, C., Sauerhering, L., Becker, S., Rox, K., and Hilgenfeld, R. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. *Science*, 368(6489): 409-412, 2020. https://doi.org/10.1126/science.abb3405

[295]. Razali, R., Asis, H., and Budiman, C. Structure-Function Characteristics of SARS-CoV-2 Proteases and Their Potential Inhibitors from Microbial Sources. *Microorganisms*, 9(12): 2481, 2021. https://doi.org/10.3390/microorganisms9122481

[296]. Kneller, D. W., Phillips, G., O'neill, H. M., Jedrzejczak, R., Stols, L., Langan, P., Joachimiak, A., Coates, L., and Kovalevsky, A. Structural plasticity of SARS-CoV-2 3CL Mpro active site cavity revealed by room temperature X-ray crystallography. *Nature Communications*, 11(1): 3202, 2020. https://doi.org/10.1038/s41467-020-16954-7

[297]. Xue, X., Yu, H., Yang, H., Xue, F., Wu, Z., Shen, W., Li, J., Zhou, Z., Ding, Y., Zhao, Q., Zhang, X. C., Liao, M., Bartlam, M., and Rao, Z. Structures of two coronavirus main proteases: Implications for substrate binding and antiviral drug design. *Journal of Virology*, 82(5): 2515–2527, 2008. https://doi.org/10.1128/jvi.02114-07.

[298]. Zhao, Q., Li, S., Xue, F., Zou, Y., Chen, C., Bartlam, M., and Rao, Z. Structure of the main protease from a global infectious human coronavirus, HCoV-HKU1. *Journal of Virology*, 82(17): 8647–8655, 2008. https://doi.org/10.1128/jvi.00298-08

[299]. Anand, K., Ziebuhr, J., Wadhwani, P., Mesters, J. R., and Hilgenfeld, R. Coronavirus main proteinase (3CLpro) structure: Basis for design of anti-SARS drugs. *Science*, 300(5626): 1763–1767, 2003. https://doi.org/10.1126/science.1085658.

[300]. Su, H., Zhou, F., Huang, Z., Ma, X., Natarajan, K., Zhang, M., Huang, Y., and Su, H. Molecular insights into small molecule drug discovery for SARS-CoV-2. *Angewandte Chemie*, 133(18): 9873–9886, 2020. https://doi.org/10.1002/ange.202008835

[301]. Zhang, L., Lin, D., Sun, X., Curth, U., Drosten, C., Sauerhering, L., Becker, S., Rox, K., and Hilgenfeld, R. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. *Science*, 368(6489): 409–412, 2020. https://doi.org/10.1126/science.abb3405

[302]. Mengist, H. M., Dilnessa, T., and Jin, T. Structural Basis of Potential Inhibitors Targeting SARS-CoV-2 Main Protease. *Frontiers in Chemistry*, 9: 622898, 2021. https://www.frontiersin.org/articles/10.3389/fchem.2021.622898

[303]. Abdellatiif, M. H., Ali, A., Ali, A., and Hussien, M. A. Computational studies by molecular docking of some antiviral drugs with COVID-19 receptors are an approach to medication for COVID-19. *Open Chemistry*, 19(1): 245-264, 2021. https://doi.org/10.1515/chem-2021-0024

[304]. Muralidharan, N., Sakthivel, R., Velmurugan, D., and Gromiha, M. M. Computational studies of drug repurposing and synergism of lopinavir, oseltamivir and ritonavir binding with SARS-CoV-2 protease against COVID-19. *Journal of Biomolecular Structure and Dynamics*, 39(7): 2673-2678, 2021. http://doi.org/10.1080/07391102.2020.1752802

[305]. Mongia, A., Saha, S. K., Chouzenoux, E., and Majumdar, A. A computational approach to aid clinicians in selecting antiviral drugs for COVID-19 trials. *Scientific Reports*, 11(1): 9047, 2021. https://doi.org/10.1038/s41598-021-88153-3

[306]. Behera, S. K., Vhora, N., Contractor, D., Shard, A., Kumar, D., Kalia, K., and Jain. A. Computational drug repurposing study elucidating simultaneous inhibition of entry and replication of novel corona virus by Grazoprevir. *Scientific Reports*, 11(1): 7307, 2021. https://doi.org/10.1038/s41598-021-86712-2

[307]. Egieyeh, S., Egieyeh, E., Malan, S., Christofells, A., and Fielding, B. Computational drug repurposing strategy predicted peptide-based drugs that can potentially inhibit the interaction of SARS-CoV-2 spike protein with its target (humanACE2). *PLoS one*, 16(1): e0245258, 2021. https://doi.org/10.1371/journal.pone.0245258

[308]. Mikitsh, J. L., and Chacko, A. M. Pathways for small molecule delivery to the central nervous system across the blood-brain barrier. *Perspectives in Medicinal Chemistry*, 16(6): 11-24, 2014. https://doi.org/10.4137/PMC.S13384

[309]. Goodwin, D., Simerska, P., and Toth, I. Peptides as therapeutics with enhanced bioactivity. *Current medicinal chemistry*, 19(26): 4451–4461, 2012. https://doi.org/10.2174/092986712803251548

[310]. WHO coronavirus disease (covid-19) dashboard. *Bangladesh Physiotherapy Journal*, 10(1): 2020. https://doi.org/10.46945/bpj.10.1.03.01

[311]. Zang, Y., Su, M., Wang, Q., Cheng, X., Zhang, W., Zhao, Y., Chen, T., Jiang, Y., Shen, Q., Du, J., Tan, Q., Wang, P., Gao, L., Jin, Z., Zhang, M., Li, C., Zhu, Y., Feng, B., Tang, B., Xie, H.,

Wang, M. W., Zheng, M., Pan, X., Yang, H., Xu, Y., Wu, B., Zhang, L., Rao, Z., Yang, X., Jiang, H., Xiao, G., Zhao, Q., and Li, J. High-throughput screening of SARS-CoV-2 main and papain-like protease inhibitors. *Protein & Cell*, 14(1): 17–27, 2023. https://doi.org/10.1093/procel/pwac016

[312]. Owen, D. R., Allerton, C. M. N., Anderson, A. S., Aschenbrenner, L., Avery, M., Berritt, S., Boras, B., Cardin, R. D., Carlo, A., Coffman, K. J., Dantonio, A., Di, L., Eng, H., Ferre, R., Gajiwala, K. S., Gibson, S. A., Greasley, S. E., Hurst, B. L., Kadar, E. P., Kalgutkar, A. S., Lee, J. C., Lee, J., Liu, W., Mason, S. W., Noell, S., Novak, J. J., Obach, R. S., Ogilvie, K., Patel, N. C., Pettersson, M., Rai, D. K., Reese, M. R., Sammons, M. F., Sathish, J. G., Singh, R. S. P., Steppan, C. M., Stewart, A. E., Tuttle, J. B., Updyke, L., Verhoest, P. R., Wei, L., Yang, Q., and Zhu, Y. An oral SARS-CoV-2 Mpro inhibitor clinical candidate for the treatment of COVID-19. *Science*, 374(6575): 1586–1593, 2021. https://doi.org/10.1126/science.abl4784

[313]. Beigel, J. H., Tomashek, K. M., Dodd, L. E., Mehta, A. K., Zingman, B. S., Kalil, A. C., Hohmann, E., Chu, H. Y., Luetkemeyer, A., Kline, S., Lopez de Castilla, D., Finberg, R. W., Dierberg, K., Tapson, V., Hsieh, L., Patterson, T. F., Paredes, R., Sweeney, D. A., Short, W. R., Touloumi, G., Lye, D. C., Ohmagari, N., Oh, M., Palacios, G. M. R., Benfield, T., Fätkenheuer, G., Kortepeter, M. G., Atmar, R. L., Creech, C. B., Lundgren, J., Babiker, A.G., Pett, S., Neaton, J.D., Burgess, T.H., Bonnett, T., Green, M., Makowski, M., Osinusi, A., Nayak, S., and Lane, H. C. Remdesivir for the Treatment of Covid-19 - Final Report. *The New England journal of medicine*, 383(19): 1813–1826, 2020. https://doi.org/10.1056/NEJMoa2007764

[314]. Hosseinzadeh, M. H., Shamshirian, A., and Ebrahimzadeh, M. A. Dexamethasone vs Covid-19: An experimental study in line with the preliminary findings of a large trial. *The International Journal of Clinical Practice*, 75(6): e13943, 2021. https://doi.org/10.1111/ijcp.13943

[315]. Nangaku, M., Kadowaki, T., Yotsuyanagi, H., Ohmagari, N., Egi, M., Sasaki, J., Sakamoto, T., Hasegawa, Y., Ogura, T., Chiba, S., Node, K., Suzuki, R., Yamaguchi, Y., Murashima, A., Ikeda, N., Morishita, E., Yuzawa, K., Moriuchi, H., Hayakawa, S., Nishi, D., Irisawa, A., Miyamoto, T., Suzuki, H., Sone, H., and Fujino, Y. The Japanese Medical Science Federation COVID-19 Expert Opinion English Version. *JMA journal*, 4(2): 148–162, 2021. https://doi.org/10.31662/jmaj.2021-0002

[316]. Andreoni, M., Sticchi, L., Nozza, S., Sarmati, L., Gori, A., Tavio, M., and Society for Infectious and Tropical Diseases (SIMIT). Recommendations of the Italian society for infectious and tropical diseases (SIMIT) for adult vaccinations. *Human vaccines & immunotherapeutics*, 17(11): 4265–4282, 2021. https://doi.org/10.1080/21645515.2021.1971473

[317]. Zhu, K. W. Deuremidevir and Simnotrelvir-Ritonavir for the Treatment of COVID-19. *ACS pharmacology & translational science*, 6(9): 1306–1309, 2023.

https://doi.org/10.1021/acsptsci.3c00134

[318]. Williamson, B. N., Feldmann, F., Schwarz, B., Meade-White, K., Porter, D. P., Schulz, J., van Doremalen, N., Leighton, I., Yinda, C. K., Pérez-Pérez, L., Okumura, A., Lovaglio, J., Hanley, P. W., Saturday, G., Bosio, C. M., Anzick, S., Barbian, K., Cihlar, T., Martens, C., Scott, D. P., Munster, V. J., and de Wit, E. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. *Nature*, 585(7824): 273–276, 2020. https://doi.org/10.1038/s41586-020-2423-5

[319]. Wahl, A., Gralinski, L. E., Johnson, C. E., Yao, W., Kovarova, M., Dinnon III, K. H., Liu, H., Madden, V. J., Krzystek, H. M., De, C., White, K. K., Gully, K., Schafer, A., Zaman, T., Leist, S. R., Grant, P. O., Bluemling, G. R., Kolykhalov, A. A., Natchus, M. G., Askin, F. B., Painter, G., Browne, E. P., Jones, C. D., Pickles, R. J., Baric, R. S., and Garcia, J. V. SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801. *Nature*, 591(7850): 451–457, 2021. https://doi.org/10.1038/s41586-021-03312-w

[320]. Xie, Y., Yin, W., Zhang, Y., Shang, W., Wang, Z., Luan, X., Tian, G., Aisa, H. A., Xu, Y., Xiao, G., Li, J., Jiang, H., Zhang, S., Zhang, L., Xu, H. E., and Shen, J. Design and development of an oral remdesivir derivative VV116 against SARS-CoV-2. *Cell research*, 31(11): 1212–1214, 2021. https://doi.org/10.1038/s41422-021-00570-1

[321]. Zhang, J. L., Li, Y. H., Wang, L. L., Liu, H. Q., Lu, S. Y., Liu, Y., Li, K., Liu, B., Li, S. Y., Shao, F. M., Wang, K., Sheng, N., Li, R., Cui, J. J., Sun, P. C., Ma, C. X., Zhu, B., Wang, Z., Wan, Y. H., Yu, S. S., Che, Y., Wang, C. Y., Wang, C., Zhang, Q., Zhao, L. M., Peng, X. Z., Cheng, Z., Chang, J. B., and Jiang, J. D. Azvudine is a thymus-homing anti-SARS-CoV-2 drug effective in treating COVID-19 patients. *Signal transduction and targeted therapy*, 6(1): 414, 2021. https://doi.org/10.1038/s41392-021-00835-6

[322]. Unoh, Y., Uehara, S., Nakahara, K., Nobori, H., Yamatsu, Y., Yamamoto, S., Maruyama, Y., Taoda, Y., Kasamatsu, K., Suto, T., Kouki, K., Nakahashi, A., Kawashima, S., Sanaki, T., Toba, S., Uemura, K., Mizutare, T., Ando, S., Sasaki, M., Orba, Y., Sawa, H., Sato, A., Sato, T., Kato, T., and Tachibana, Y. Discovery of S-217622, a Noncovalent Oral SARS-CoV-2 3CL Protease Inhibitor Clinical Candidate for Treating COVID-19. *Journal of Medicinal Chemistry*, 65(9): 6499-6512, 2022. https://doi.org/10.1021/acs.jmedchem.2c00117

[323]. Yan, V. C., and Muller, F. L. Why Remdesivir Failed: Preclinical Assumptions Overestimate the Clinical Efficacy of Remdesivir for COVID-19 and Ebola. *Antimicrobial agents and chemotherapy*, 65(10): 10-1128, 2021. https://doi.org/10.1128/AAC.01117-21

[324]. Sachan, A. K. R., Kumar, S., Kumari, K., and Singh, D. Medicinal uses of our spices used in our traditional culture: Worldwide. *Journal of Medicinal Plants Studies*, 6(3): 116–122, 2018.

[325]. Umesh, Kundu, D., Selvaraj, C., Singh, S. K., and Dubey, V. K. Identification of new anti-nCoV drug chemical compounds from Indian spices exploiting SARS-CoV-2 main protease as target. *Journal of biomolecular structure and dynamics*, 39(9): 3428-3434, 2020. https://doi.org/10.1080/07391102.2020.1763202

[326]. Cui, W., Yang, K., and Yang, H. Recent Progress in the Drug Development Targeting SARS-CoV-2 Main Protease as Treatment for COVID-19. *Frontiers in Molecular Biosciences*, 7: 616341, 2020. https://doi.org/10.3389/fmolb.2020.616341

[327]. Alsamri, H., Hasasna, H. E., Baby, B., Alneyadi, A., Dhaheri, Y. A., Ayoub, M. A., Eid, A. H., Vijayan, R., and Iratni, R. Carnosol Is a Novel Inhibitor of p300 Acetyltransferase in Breast Cancer. *Frontiers in Oncology*, 11: 664403, 2021. https://doi.org/10.3389/fonc.2021.664403

[328]. Lo, A. H., Liang, Y. C., Shiau, S. Y. L., Ho, C. T., and Lin, J. K. Carnosol, an antioxidant in rosemary, suppresses inducible nitric oxide synthase through down-regulating nuclear factor-κB in mouse macrophages. *Carcinogenesis*, 23(6): 983–991, 2002. https://doi.org/10.1093/carcin/23.6.983