Detailed Description of Global Misfortune: The SARS-CoV-2 Infection

Fiza Farooq[1,*], Atif Ahmed[1], Samran Sardar[1], Samawia Ifrahim[2], Kinza[3], Wajiha Ali[3], Aimenara Shafiq[3], Maryam Mustaid[3] and Saleha Tahir[4]

[1]Centre of Excellence in Molecular Biology (CEMB), University of the Punjab, Lahore, Pakistan
[2]School of Chemical Engineering, Yeungnam University, South Korea
[3]Dr Ikram ul Haq Institute of Industrial Biotechnology, Government College University, Lahore, Pakistan
[4]Department of Parasitology, University of Agriculture Faisalabad, Pakistan
*Corresponding author: fizafarooq66@gmail.com

Abstract

The emergence of SARS-CoV-2 is the third major reason for the outbreak of a coronavirus in the 21st century since the two previously recorded threats were severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Different from all its predecessors, this SARS-CoV-2 became an instance of lightning-speed pandemic transmission around the world, resulting in severe large-scale mortality and high morbidity. The pandemic has expanded its boundaries from global health systems to socioeconomic structures and in particular, it has lasting impacts on public health, economic stability, and mental well-being in different regions across the world. In response, an unprecedented global mobilization was put into action, including extensive research into viral transmission, the development of vaccines, and therapeutic approaches. Despite these worthwhile endeavors, the continual mutation of SARS-CoV-2 demands vigilant observation and adaptive strategies. This paper firmly emphasizes international cooperation for the longer term, innovative research, and effective infrastructural public health to alleviate the effects of the pandemic and better prepare for future viral threats.

Keywords: SARS-CoV-2, COVID-19, Pandemic, Molecular biology, Pathogenesis, Treatment,

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Introduction

SARS-CoV-2 represents the third major outbreak caused by a coronavirus, following severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (Zeidler & Karpinski, 2020). The continuous evolution of SARS-CoV-2 has led to unprecedented adverse effects on public health and the global economy. To date, there have been over 776.8 million confirmed cases of COVID-19, with the virus responsible for more than 7 million deaths. Beyond acute disease and mortality, the COVID-19 pandemic has impacted various aspects of life, including economic stability, mental health, and the provision of healthcare services for other conditions, thereby contributing to increased mortality from non-COVID-related diseases (Dang et al., 2022). Significant advancements have been achieved in understanding the transmission mechanisms, preventive strategies, vaccinations, and therapeutic interventions for COVID-19. Despite these strides, COVID-19 continues to pose a major healthcare challenge, resulting in substantial morbidity, mortality, and economic impact globally. Furthermore, the continuous emergence of novel strains undermines progress in prevention and treatment, as viral evolution often leads to immune evasion and antiviral resistance.

The chronic sequelae of COVID-19, commonly referred to as long COVID, affect at least 10% of infected individuals and represent a global health challenge (Davis et al., 2023). Over 200 symptoms have been documented, impacting multiple organ systems, with many patients experiencing concurrent symptoms that significantly impair their quality of life (Klein et al., 2023). Unfortunately, there are currently no validated effective treatments for long COVID. The objective of this manuscript is to elucidate all aspects of COVID-19 in a clear and accessible manner to enhance public understanding and awareness.

Molecular Biology

Coronaviruses are single stranded, pleomorphic, enveloped, RNA viruses ranging between 60nm to 140nm in diameter. It contains the largest genome size in RNA viruses ranging from 26 to 32kb in length. The order *Nidovirales*, the family *Coronaviridae* and the class *orthocoronavirinae* is assigned to SARS-CoV-2 in taxonomical hierarchy. The whole genome analysis of novel coronavirus-2 reveals 82% similarity with SARS-CoV (Naqvi et al., 2020) and 50% resemblance with MERS-CoV (Mehta et al., 2020).

The genome of SARS-CoV-2 is organized into 14 open reading frames which are translated into 27 structural and non-structural proteins. The ORF-1 is the longest ORF in the genome which is present at 5' end and encodes for large polyprotein. Subsequently, the polyprotein cleaves into numerous non-structural proteins (NSP) (Wu & McGoogan, 2020) which are functionally involved in replicase-transcriptase complex

(RTC) (Malik, 2020). However, the remaining structural and accessory proteins are encoded by residual 13 ORFs present towards 3' terminal of the genome (Wu & McGoogan, 2020). The proteins translated by the S, M, N and E genes are structural proteins (Gordon et al., 2020) and their role in viral entry, assembly and release. While the accessory proteins are orf3a, orf3b, orf6, orf7a, orf7b, orf8, orf9b, orf9c and orf10 which collectively participates in the pathogenesis (Gordon et al., 2020; Lan et al., 2020). Moreover, the genomic RNA is protected by 5'-cap and poly-A tail. Additionally, the genome contains uniquely designed sequences called untranslated regions (UTR) at both 5' and 3' end which play a significant role in RNA replication and translation. Table 1 represents the function of Non-Structural Proteins of SARS-CoV-2

Table 1: Function of Non-Structural Proteins of SARS-CoV-2 (Malik, 2020; Yoshimoto, 2020)

Name	Amino Acids	Functions
NSP1	180	Cleavage of host mRNA, blocks translation by interacting with 40S rRNA
NSP2	638	Binds to prohibitin protein 1,2
NSP3	1945	Papain like proteinase, cleaves viral polyprotein
NSP4	500	Important component of DMVs
NSP5	306	Cleaves viral polyprotein
NSP6	290	Generates autophagosomes
NSP7	83	Dimerizes with NSP8, supports NSP12
NSP8	198	Forms complex with NSP7, stimulates NSP12, may act as primase
NSP9	113	RNA binding protein
NSP10	139	Co-factor for NSP14 and NSP 16, stimulates exonuclease activity
NSP11	13	Unknown
NSP12	932	RNA dependent RNA polymerase
NSP13	601	RNA helicase, 5' triphosphatase
NSP14	527	3' to 5' exonuclease, guanine N7-methyltransferase
NSP15	346	Viral endoribonuclease
NSP16	298	2'-O-ribose-methyltransferase

Viral Entry

The viral entry is a critical step for coronavirus infection and pathogenesis. Initially, coronaviruses bind to cell surface receptor for viral attachment followed by endocytosis in endosomes and eventually viral membrane fuses with the lysosomal membrane to finish the penetration into the host cell (Li, 2016). The S protein of SARS-CoV-2 is essential facilitator for host cell entry by binding to the ACE_2 receptor. Apart from ACE_2, host cell membrane bound HSPGs, such as syndecans 1-4, glycosylphosphatidylinositol-anchored proteoglycans, betaglycan, neuropilin-1 and CD44 may also serve as alternative receptors but the affinity varies among binding molecules (Hoffmann et al., 2020).

The envelop-anchored spike protein takes the virulent particle towards the host cell containing respective receptors. The spike has two distinctive configurations: the pre-fusion configuration, the actual arrangement of mature virion and the post-fusion configuration, the form after the fusion of two membranes has been accomplished (Shang et al., 2020). The pre-fusion structure of spike is a homo-trimer, with three receptor binding S1 heads sitting on top of trimeric membrane fusion S2 stalk (Yuan et al., 2017).

The S1 subunit contains N-terminal domain (S1-NTD) and C-terminal domain (S1-CTD). The N-terminal domain usually recognize the sugar receptors (Shang et al., 2020) while C-terminal domain is specialized to bind with the protein receptors. Although, only S1-CTD acts as receptor binding domain (RBD) for novel coronavirus (Shang et al., 2020). The RBD constantly switches between two structural conformations, the standing up and lying down. The standing-up configuration enables receptor binding while lying down configuration unable to bind with the receptor and evade immune surveillance (Yuan et al., 2017). There are six crucial amino acids in RBD which are critical for cellular attachment. However, a recent study confirms that five out of six amino acids are different in SAR-CoV-2 contrast to SARS-CoV. Although its five substituted amino acids in RBD, it can still have an efficient interaction with ACE_2 (Andersen et al., 2020). The RBD of SARS-CoV-2 has significantly enhanced binding affinity towards ACE_2 than SARS-CoV (Yuan et al., 2017) whereas the SARS-CoV-2 spike binds less potently than SARS-CoV spike.

The S protein comprises of two major domains, the receptor binding domain (RBD) and fusion domain. During the process of attachment, the $TMPRSS_2$ cleaves the S protein in two step process. In the first step, the $TMPRSS_2$ cleaves the RBD, thus pushing the S1 to side and exposing fusion peptide. Subsequently, fusion subunit forms a hairpin which is embedded in the membrane of target cell. In the second step, the fusion subunit consists of hydrophobic amino acids get activated. The subsequent folding of embedded hairpin drags the viral envelop very close to target cell membrane followed by fusion. This process occur either at plasma membrane leading to release of nucleocapsid or virus particle is endocytosed in endosome (Kim et al., 2017). Afterwards, the endosome fuse with lysosome to put out viral nucleocapsid in the cytoplasm.

The host cell factors also promote coronavirus infection in humans. The pro-protein convertase (PPC) has crucial role in elevated virulence in avian influenza virus. Similarly, SARS-CoV-2 PPC ensures efficient viral penetration into the host cell. Furthermore, the lysosomal proteases and cell surface proteases also aid in novel coronavirus entry. The entry-initiating proteases include cell surface $TMPRSS_2$ and lysosomal cathepsins (Shang et al., 2020). Despite the strong attraction of RBD to human ACE_2, the SARS-CoV-2 still has less affinity towards host cell receptors for attachment.

The expression pattern of ACE_2 is amplified in few conditions which facilitates the viral entry. The healthy tissues of heart, lungs, kidneys, liver and colon extensively express the ACE_2 and $TMPRSS_2$ in normal condition. Mostly, smokers express elevated number of ACE_2 in their air passage ways than healthy ones (Leung et al., 2020), however, the expression levels of ACE_2 in patients with pre-existing asthma is almost unaltered. The tremendous expression of ACE_2 is observed in obesity in renal tissues. Moreover, we notice the significant increase in ACE_2 in

patients who had suffered heart failure with diabetes comorbidity. Apart from various viral and host cell membrane factors which facilitates viral penetration, the raised ACE_2 expression increased the risk of viral binding.

Pathogenesis

SARS-CoV-2 has specific mode of pathogenesis which are varied between three clinical stages, presymptomatic, mild or moderate and severe. Mostly cases of Covid-19 are asymptomatic or symptomatic with non-severe phase (Guan et al., 2020). The switching of moderate to violent disease progression depends upon the response by the individual's immune system to virus. Commonly reported complications are acute myocarditis, acute respiratory distress syndrome and septic shock. Mostly the critical patients have underlying comorbidities. The condition is more exaggerated when bacterial, fungal or viral coinfections are reported. The SARS-CoV-2 lifecycle is summarized in Figure 1, highlighting key stages such as ACE2-mediated entry and viral assembly.

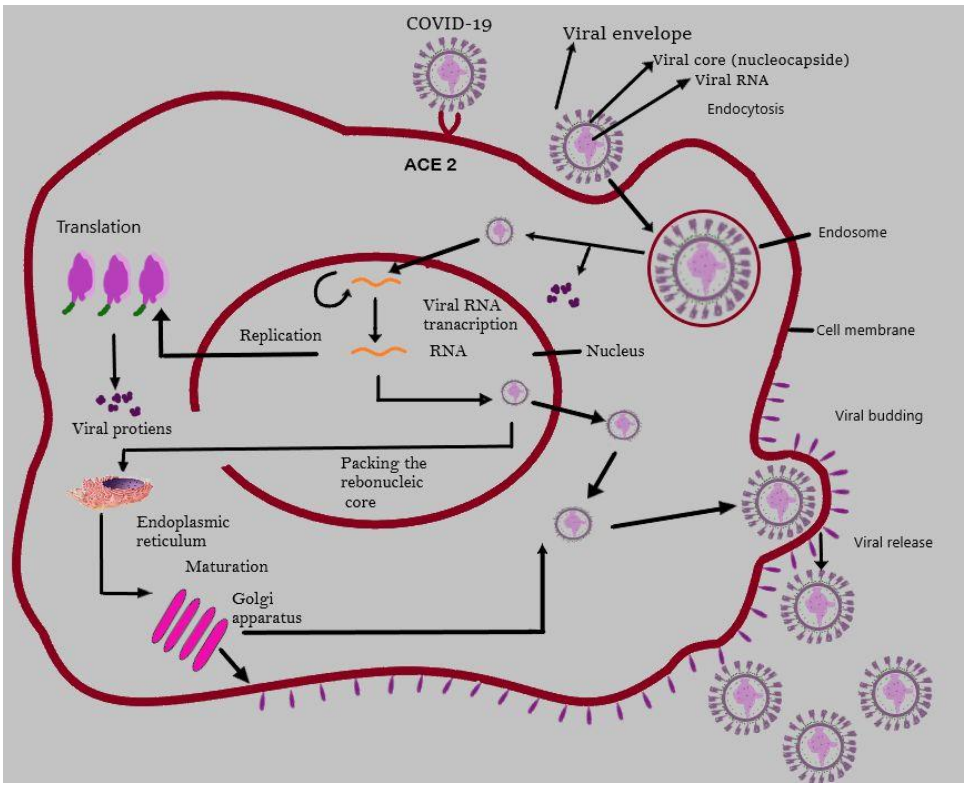

Fig. 1: Life Cycle of SARS-CoV-2 (Retrieved from biorender)

The SARS-CoV-2 infection is also involved in gastrointestinal disturbances along with the severe respiratory inflammation. Critical Covid-19 patients show higher incidence of gastrointestinal manifestations including diarrhea, nausea, vomiting (Guan et al., 2020), anorexia and abdominal pain with more serious acute hemorrhagic colitis (Carvalho et al., 2020). Injury mucosal membrane of esophagus and numerous plasma cells and lymphocyte infiltrates are observed in lamina propria of stomach, duodenum and rectum during histological examination (Pan et al., 2020). An increase in hepatic enzymes such as, alanine aminotransferase and aspartate aminotransferase and total bilirubin level commonly seen in patients who take intensive care. In more severe cases, impairment in hepatic function occur and rarely it take towards lung injury (Guan et al., 2020). The expression of ACE_2 in esophageal stratified epithelial cells is considered to be responsible for esophagitis during Covid-19. Moreover, the researchers are relating the high level of ACE_2 expression in absorptive enterocytes of ileum and colon with SARS-CoV-2 induce diarrhea.

Symptoms

The commonly detected signs on admission of patients are cough, fever and shortness of breath. Other common symptoms include headache, sore throat, diarrhea, chest pain; myalgia and muscle ache. Mostly the symptoms are related to pulmonary pathway; however, 2-10% patients suffer with gastro-intestinal symptoms including vomiting, diarrhea and abdominal discomfort. The patients remain pre-symptomatic for first four days, the onset of symptoms occur at 5^{th} day with coughing, dyspnea and fever. The witnessed complications involve acute lung injury, ARDS, acute renal injury and septic shock (Singhal, 2020). Mostly children's cases are asymptomatic or moderate cases, only a few have symptoms of dyspnea, cyanosis and less oxygen saturation. The fatal outcomes are extremely rare in children (Ludvigsson, 2020).

Transmission

During breathing, talking, sneezing and coughing, the tiny infectious droplets transferred from one person to several susceptible hosts. The chain of transmission elongates further in the communities thus disseminates the infection in cities and countries. Direct transmission

transfers the virus from the infected host to susceptible host. It ensures the contact between the both individuals such as hand shaking. In contrast, the indirect transmission implicates transmission through fomites and contaminated objects. Coughing release the infectious particles with enough pressure, thus they can travels average distance of 2.48m, while maximum distance traverses 4.5m (Loh et al., 2020).

The virus can survives in infectious aerosols for hours whereas viability on the surfaces could be up to days (Asadi et al., 2020). The chance of getting infection through non-living surfaces is approximately rare and people get infection only when a person sneezes or coughs and someone else touches within 1-2 hour before drying. Fomite transmission is more significant in case of hospitals because third world have limited resources and difficult to apply infection control strategies.

The zoonotic coronavirus is probably originated from the bats and transmits in humans through intermediary hosts. It was proposed that coronavirus transmits in human from intermediate hosts which are none-bats. The hidden pathogen infected naturally the small animals such as, dogs, cats, tigers, lion and farmed mink likely transmits from human to animals. Moreover, experiments in lab animals including, Egyptian fruit bats, ferrets, golden Syrian hamsters and cats can pass on infection within the same species. The chances of zoonotic transmission would be increased in case of close human and pet interactions (Newman, 2020). Two feline SARS-CoV-2 cases were reported in USA likely to be transmitted from human to animals. By connecting the dots, the experts analyze that these cats have epidemiological linkages to human COVID-19 patients. These findings led to one health investigations by the stakeholders who assume that no such transmission can be possible (Newman, 2020).

The coronavirus uses various routes of transmission. Disease can be transmitted through feco-oral route but it is nearly irrelevant. Sometimes, the patients with COVID-19 shed SARS-CoV-2 in their stools. Improper hand washing may contaminate the fomites and increase the risk of exposure. In addition to feco-oral route, respiratory pathway has superiority for being quickly infected due to its massive potential of transmission. Moreover, no case was revealed about Vertical transmission. Similarly no evidence found about presence of virus in urine, genital fluids, amniotic fluid and breast milk (Lopez-Alcalde et al., 2020).

Diagnosis

The accurate and efficient diagnostic methods of SARS CoV-2 and treatment strategies can help us to reduce the effects of virus. Early diagnosis can be very effective for individual health. Biological specimens that are commonly used for viral detection include feaces, saliva, blood, upper (nasopharynx) and lower respiratory tract (sputum and lung tissue). Among aforementioned specimens, upper and lower respiratory tract samples are preferably considered for diagnosis. Diagnostic assays are generally categorized into two types i.e., Nucleic Acid Amplification Tests (NAAT) and Serological Testing (Corman et al., 2020).

Nucleic Acid Amplification Tests

Nucleic Acid Amplification Tests include RT-PCR, Genome Sequencing, Microarray and Loop Mediated Isothermal based testing. Among these approaches, Reverse Transcriptase polymerase chain reaction (RT-PCR) is considered to be a gold standard for viral detection. It involves isolation of RNA followed by complementary DNA synthesis and amplification of that DNA. Many primers have been designed to carry out differential diagnosis with other flu causing viruses and the mainly targeted regions for designing probes include S (spike protein), N (Nucleocapsid Protein), E (envelope) and membrane protein. Sensitivity of RT-PCR depends on type of biological specimen used. False negative results reported in different samples like nasal, throat and sputum are 27%, 40% and 11% respectively (Linton et al., 2020). Occurrence of false negative results can be mainly due to mutations in viral genome. Other limitations include requirement of instrumentation and personal expertise to carry out the test. Many studies have been done for increasing sensitivity of the diagnostic protocols. It is reported that by applying RT-PCR after optimizing RNA extraction methods, sensitivity of the tests can be enhanced and early diagnosis of the virus can be carried out.

Loop Mediated Isothermal Amplification method mainly based upon nucleic acid amplification that uses 4 to 6 different primers for recognition of 4 to 6 specific regions of target gene in the same reaction with the help of bst DNA polymerase enzyme under isothermal conditions and identification of product through fluorescence (Rai et al., 2021). Many loop Mediated Isothermal Amplification Assays have been developed till now. LAMP assay without RNA extraction step with the detection limit of more than 1.43×10^3 copies has been developed (Yoshikawa et al., 2020). To overcome false positive results, colorimetric and Fluorometric LAMP assay utilizing 5 primers with detection limit of 20 copies per µl has been developed (Alhamid et al., 2023).

Serological Assays

Although genome based diagnostic approaches are considered to be gold standard for viral detection but they are unable to determine true number of infected individuals and asymptomatic infections. Serological tests can be utilized to determine these parameters. They depend on detection of antibodies to determine the status of diseases. Such tests are also known as immunoassays. These tests are employed for rapid and early detection of viral infection to prevent its spread. They are developed to detect antibodies against SARS-CoV-2. These tests can be performed after a week of infection when particles of virus start reducing and RT-PCR gives false negative results but cannot be used as diagnostic tools as the sensitivity of these tests is very less (Guevara-Hoyer et al., 2021). They help us to detect active infection and previous exposure to the virus. Immunoassay based approaches are divided into Enzyme linked immunosorbent assay (ELISA), Immunofluorescence Assays and Immunochromatographic Assays.

ELISA test is widely used for diagnostic purposes and quantification of different molecules like antibodies, proteins and hormones in biomedical research. It utilizes the basic principle of antigen and antibody interaction. The micro well plate is coated with target antigen and allowed to react with patient's serum containing antibodies. Wells are then washed to remove any unbound antibody. Then animal antibody conjugated with enzyme also known as secondary antibody is allowed to interact with human antibody called primary antibody. The well plate is again washed to remove any unbound secondary antibody. Later, enzyme specific substrate is added resulting in color change. There are different types of Elisa tests including direct Elisa, Indirect Elisa and Sandwich Elisa. Traditional Elisa lacks multiplexing detection capability and it requires expensive instrumentation so many advancements have been made to increase its efficacy, specificity and sensitivity (Peng et

al., 2022). Elisa providing not only qualitative but also quantitative results against IgM, IgG and IgA antibodies have been developed to determine their level (Roy et al., 2020). Development of optimized Elisa with more than 99% specificity, 96% sensitivity and minimum cross reactivity with other coronaviruses against SARS- CoV-2 Spike protein has been reported (Freeman et al., 2020).

Immunofluorescence is a technique based on detection of target antigens via fluorescently labelled antibodies. It is categorized into direct immunofluorescence and indirect immunofluorescence. In direct immunofluorescence, fluorescently labelled antibody binds directly to the target antigen while in indirect immunofluorescence, primary unlabeled antibody bound to the target antigen is detected via fluorescently labelled secondary antibody. Many immunofluorescence assays have been developed for more accurate and rapid diagnosis of COVID-19. An indirect immunofluorescence assay to determine serological status of SARS- CoV-2 infection through IgG, IgA and IgM antibodies was developed in France (Edouard et al., 2021).

Immunochromatographic assays are also known as Lateral flow immunoassay or strip tests. It has four basic components including sample pad for sample, conjugate pad for combining labeling elements, membrane for antigen antibody interaction and absorbent pad for wastes. Different materials like nanoparticles including gold and carbon nanoparticles, enzymes and quantum dots are used for labeling (Zhao et al., 2021). Different versions of lateral flow immunoassay are available.

Treatment

1. General Treatment of COVID-19

Initially treatment of COVID-19 starts after the confirmation of the positive infection. During early stages when viral infection is not severe, bed rest, enough water and calorie intake is recommended to reduce chances of dehydration (Hultström et al., 2022). Water electrolytes and homeostasis are maintained along with checking any vital signs and O_2 saturation in the patient. According to the severity of the COVID-19 infection, different tests are conducted such as chest imaging, urine test, and blood test, along with checking blood biochemical indexes for determining the functions of vital organ. For the patients showing symptoms like high fever (greater than 38.5 °C), warm bath and the antipyretic drug treatment is recommended. Drugs such as ibuprofen, acetaminophen should be given orally (Vandenberg et al., 2021).

Symptomatic Treatment

As the levels of SARS-CoV-2 are much higher in the upper respiratory tract even during moderate infection therefore, most effective therapy which is recommended is the antiviral therapy (Gandhi et al., 2020). But if infection is severe to such an extent that patient has to be hospitalized due to excessive inflammation and can face multiple clinical features such as hypoxemia: during which oxygen supplements are required, thrombosis or maybe multi-organ failure, it necessitates the use of ventilator (Martinez, 2020). In critical condition, immunomodulators are administered as chief supportive treatment alongside the critical care of the ones who suffer respiratory failure (Nabi-Afjadi et al., 2022). During hospitalization, prophylactic anticoagulants are administered: while therapeutic anticoagulation may also help but the window is narrow.

A. Antiviral Agents

The reported antiviral agents used against COVID-19 primarily include protease inhibitors, polymerase inhibitors, inhibitors of nucleoside and nucleotide reverse transcriptase, entry and uncoating inhibitors, and others.

1. Protease Inhibitors

For the processing of polyproteins of the coronavirus, protease is graded as one of the vital enzymes. Recently, many studies have been conducted on exploiting the protease inhibitors for the treatment of COVID-19. Lopinavir is a common example of protease inhibitors which is used for the treatment of human immunodeficiency virus (HIV). It has been studied that the concentration of lopinavir in serum can be increased in vivo by ritonavir, so the both products are used in combination (Yao et al., 2020). Using ritonavir/lopinavir in combination with the ribavirin and interferon β1b, which had reduced symptoms of the COVID-19 patients, limited the shedding time and hospital stay, and is characterized as safe (Hung et al., 2020)

2. Polymerase Inhibitors

Remdesivir, a polymerase inhibitor, is FDA approved for COVID-19 due to its ability to inhibit viral RNA although its antiviral effect in clinical setting remains controversial. Researcher observed that when remdesivir was combined with baricitinib, the antiviral effect was more prominent than remdesivir given alone (Kalil et al., 2021). Additionally, Favipiravir also inhibits the RNA polymerase of the viruses but selectively. It is an antiviral drug which shows its antiviral effect on a number of viruses.

3. Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

One of the important nucleoside reverse transcriptase inhibitors is Azvudin, which has an antiviral broad-spectrum activity. Azvudine was approved by NMPA for treating COVID-19 among adults depending upon the clinical trials. Furthermore, Molnupiravir is an N-hydroxycytidine derived ribonucleoside prodrug and is effective against COVID-19 which can be administered in case of emergency by FDA for patients suffering from moderate COVID-19 (Wahl et al., 2021). It has potential to reduce 50 percent deaths among non-hospitalized adults who suffer from moderate COVID-19 (Mahase, 2021).

4. Entry and Uncoating Inhibitor

For blocking the viral replication in its early stage, Amantadine inhibitor is commonly used which has potential of crossing lysosomal membrane and inhibiting the RNA of the virus to be released into the cell (Smieszek et al., 2020). The small-scale study explored that

Adamantanes can be used against COVID-19 but the study had some limitations and for confirming the claim, further large-scale research must be conducted. Moreover, Enfuvirtide, which is the fusion inhibitor peptide of HIV-I, is potentially used against SARS-CoV-2 as fusion inhibitor (Rejdak & Grieb, 2020; Ahmadi et al., 2022).

Preventions and Precautions

For combating covid-19 effectively, it is critical to abide by the guidelines of local heath authority and stay informed with the current information issued by world health organization (WHO). By adhering to this approach, spread of secondary infections, man-to-man transmission and worldwide spread of covid-19 infection can be prevented (Ahmad, 2022). Although majority of the covid-19 patients recover from the illness after experiences moderate signs and symptoms but a considerable number of individuals may experience severe covid-19 disease. For safeguarding personal as well as community health, extensive preventive measures must be adopted.

Conclusion

The SARS-CoV-2 pandemic, characterized by rapid worldwide spread and evolving variants, represents the critical interplay of virology, public health, and societal adaptability. Its complex morphology, particularly the spike protein's ACE2 binding and immune system evasion strategies are highly problematic. The virus's pathogenesis, causing respiratory, gastrointestinal, and systemic complications, along with the emergence of long COVID, highlights its multifaceted impact on host health. Advancements in diagnostics, particularly NAATs like RT-PCR and serological assays, have played vital role in curbing transmission, while therapeutic strategies—ranging from antiviral agents (e.g., remdesivir, molnupiravir) to immunomodulators—have reduced morbidity and mortality. However, challenges like viral mutations and the lack of targeted therapies for long COVID still persist. Fair access to vaccines, sustained genomic surveillance, and healthcare strategies remain crucial. This crisis highlights the need of global collaboration for novel interventions, and robust health infrastructure to reduce the severity of ongoing effects and prepare for future pandemics

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