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Overview of SARS COVID-2: An Emerging Spike Mutations in Variants and Immune Evasion

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Abstract

Severe acute respiratory syndrome Coronavirus 2 is a novel coronavirus strain that causes coronavirus illness was originally connected to a serious respiratory illness in late 2019 and since March 2020, has brought about a pandemic. The Coronaviridae family includes the beta coronavirus referred to as SARS-CoV-2. The family is made up of single-stranded (+) ribonucleic acid viruses. There are four coronavirus genera, with viruses known to damage humans located in the alpha and beta genera. These zoonotic viruses can spread from animals to humans. Coronaviruses' spike proteins help in the binding of ACE2 receptors and viral entrance into hosting cells. Although spike protein aids the entrance of viruses via receptors, additionally, it is crucial as an immunogen since it is the part that is easiest to access the virus structure. The four structural proteins of severe acute respiratory coronavirus are N (nucleocapsid), M (membrane), E (envelope), as well as S (spike). The original Wuhan strain was replaced by variants with a wide range of mutations, while 4000 mutations in the alterations in the Coronavirus S protein were recently discovered. Several additional varieties have subsequently evolved and become widely distributed, which include Alpha (B.1.1.7), which was initially discovered in the United Kingdom, Beta (B.1.351) in South Africa, Gamma (P.1 & P.2) in Brazil, Delta (B.1.617.2) in India, and Omicron in South Africa. Eight variants of interest have been identified by the World health organization since the start of the pandemic, including Epsilon (B.1.427 and B.1.429), Zeta (P.2), Eta (B.1.525), Theta (P.3), Iota (B.1.526), Kappa (B.1.617.1), Lambda (C.37), and Mu (B.1.621). Efficiency of vaccinations could be hindered by the quick emergence and expansion of SARS-Coronavirus-2 strain induced by receptor-binding domain and N-terminal domain alterations in the Beta spike protein, which could evade neutralizing antibodies and/or cell-mediated immunity. Although several COVID-19 vaccines, among these, are viral vector and mRNA vaccines, have been designed, more potent vaccines are still required to meet the needs on a global level. Modifying the medicine Remdesivir and Oseltamivir is the best method for creating potent treatments to eliminate COVID-19 and other viral human infections. The SARS-Coronavirus-2 S protein's most prominent alterations are reviewed in this article.

Keywords: COVID-19; SARS-CoV-2; Spike mutation; Variants; ACE2 receptor; Vaccines

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Introduction

History

SARS, also known as an acute respiratory syndrome, is a serious variation of SARS-CoV-2. It's a beta coronavirus from the Coronaviridae family. Four genera are used to classify coronaviruses with viruses known to cause human illness in the alpha and beta genera. These viruses are zoonotic, which means that they could spread from one animal to another. They are zoonotic viruses, which means they can spread from one animal to another as shown in figure 1. In the 1930s, coronaviruses were initially identified in chickens with respiratory illness (infectious bronchitis). In 2014, a swine coronavirus killed multiple thousand piglets in America [1].

The evolution of human coronaviruses began in 1965 when Tyrrell and Bynoe1 found they were able to propagate a virus known as B814. In 2002, SARS-CoV was found in humans for the first time in China [2]. The first Middle East respiratory syndrome (MERS) cases associated with a new coronavirus (CoV) were identified in Jordan in 2012 [3]. On the very last day of 2019, multiple cases of pneumonia were diagnosed by healthcare workers in Wuhan China, Several cases of pneumonia in Wuhan City were formally reported to the WHO, which is home to 11 million people and serves as central China's cultural and economic hub [4]. South Africa disclosed the first sequencing of a SARS-CoV-2 an Omicron-2 variant, in November 2021. The Omicron variant has currently replaced other COVID-19 strains as the primary epidemic strain globally. People who have received vaccinations and immunizations against earlier variants. According to etiological investigations that have shown that alterations in the spike protein generate increased pathogenicity of the coronavirus Omicron variant, all four RNA viruses (Alpha, Beta, Gamma, and Delta) are still vulnerable to the Omicron variation [5].

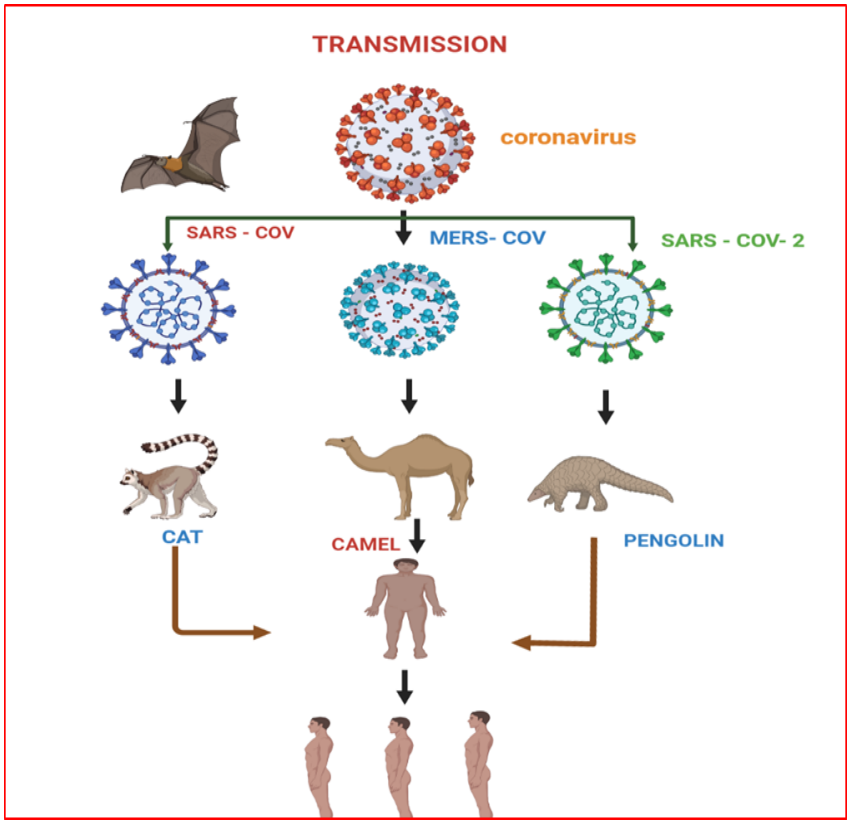

Figure 1: Transmission hierarchy of Coronavirus

Epidemiology

The distribution of viruses from one place to another is called epidemiology. The virus's transformation began at a seafood market in Wuhan, Hoebi Province. Coronaviruses are directly linked with this city and most of its people have died, which covers 81 percent of the whole number of deaths in the country. When the number increases, the WHO declares an emergency in the world [6]. The WHO reported 87,317 cases worldwide since about March 3, 2020. 2,977 (3.42%) of the cases have perished from the infection. China has recorded a vast number of incidences and fatalities. A number of 7,169 cases in 59 countries have been reported beyond China resulting from the pandemic's progressive nature [7]. The extensive migration has created ideal conditions for the spread of this complicated disease [8].

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COVID-19 had a risk of dying 4.9 percent during the first 6 months of the pandemic, which is lower than SARS (6.6%) and MERS (65%) [9]. Since February 23, 2014, SARS-COVID 2 instances have been identified within 6 states: Arizona (one incident), California (8 incidents), Illinois (1), Massachusetts (1), Washington (1), and Wisconsin (1), are the states with the most representatives (one). Out of the 14 cases, 12 were linked to immigration to Sino, and 2 were spread by immediate domestic connections of an individual with identified COVID-19 [10]. The scientific study of the higher infectivity of the Alpha version was formally disclosed as being more contagious in the early part of December 2020, resulting in an abrupt worldwide restriction of travel outside of the United Kingdom [11].

COVID-19 mortality has been most prevalent in the United States, with India and Brazil following closely behind. In 2020, after cancer and cardiovascular disease, Coronavirus disease became the third-leading cause of mortality in the US [12]. The first 2 Omicron episodes were discovered in Denmark on November 28, 2021, by South African immigrants coming from the continent. By the 9th of December, Denmark had recorded 785 Omicron cases [13]. On February 26, 2020, in Karachi, the first COVID-19 patient was discovered, and before January 2021, nearly half a million Pakistanis had contracted the disease. [14]. In Pakistan, a high prevalence (2.9/100,000) and several fatalities (1.7%) were seen till the middle of April 2020 [15].

In Pakistan, COVID-19 is apparently spreading, with an approximately 204.65 million people. On February 26, 2020, the first case of Coronavirus disease was discovered in Karachi. The virus has gradually spread to various areas across the nation and is already epidemic. By April 10, 2020, Pakistan had confirmed 4601 cases of COVID-19, there had been 727 successful recoveries and 66 fatalities [16]. Pakistan recorded no COVID-19 illnesses for eight weeks following the outbreak was declared, despite being close to China and Iran. One of the worst-affected nations and the outbreak's epicenter in the Eastern Mediterranean region announced its first confirmed case, which was connected to a person who had visited there. The eleven visitors who were leaving Pakistan for Iran, Saudi Arabia, Syria, and other Middle Eastern countries served as the main vectors for the introduction of viruses into that country. When many of the Iranian pilgrims who had returned and had been quarantined tested positive, there was an abrupt increase in Pakistan. Pakistan experienced a sub-exponential rise from March 10 through mid-May 2020, followed by exponential expansion, and then an overall decrease in cases. The worst were the provinces of Punjab and Sindh with more than 115 districts being impacted [17].

The 1179 cases of Coronavirus disease were identified in Pakistan as of March 26, 2020, the majority of which were in Sindh (421 cases), followed by Punjab (394 cases), Balochistan (139 cases), Khyber Pakhtunkhwa (123 cases), Gilgit-Baltistan (84 cases), Islamabad (1 case), Azad Jammu and Kashmir (1 case). Travel-related illnesses were the primary cause of the majority of severe acute coronavirus-2 infections in Pakistan during the early stages of the epidemic. Nevertheless, the number of instances of local viral transmission is growing daily. Nine fatalities have been linked to COVID-19. In comparison to China, Italy, the US, and Iran, the case mortality rate is lower at 0.8% [18]. On December 13, 2021, Pakistan experienced its first Omicron case, and since then, COVID-19 cases have started to increase. However, there is a lack of information on Omicron's genomic monitoring in Pakistan [19]. Between January 3, 2020, and June 23, 2022, there were 1,532,470 confirmed cases of COVID-19 in Pakistan, with 30,384 fatalities reported to WHO. A total of 258,021,731 vaccine doses have been given as of June 20, 2022. According to the NCOC report 2022, In Pakistan, the total number of COVID-19 cases has been estimated at 1.5 million. , with roughly 90% of cases being recovered and 2% being fatal. As of June 23, 2022, WHO had received reports of 6,324,112 deaths and 539,893,858 confirmed cases of COVID-19 worldwide [20].

In lower economic nations like Pakistan and the majority of Africa, younger populations may have a lower overall risk [21]. There are already a large number of naturally immune people, and they are multiplying quickly. It is well-known that COVID-19 presents fewer dangers to individuals under the age of 50 than it does to individuals over the age of 50, and that mild sickness or even silent infections are more frequent in younger individuals. This is crucial for many emerging nations with young populations. In the sub-Saharan region, for instance, at least half of the population is under 25, making the region's 95 percent of nations young. Accordingly, depending on the real number of convalescents, natural immunity could be a huge resource, especially in underdeveloped nations [22].

The COVID-19 pandemic has been particularly severe in nations like Italy, Spain, France, the UK, and the US, while Pakistan and most of Africa have seen fewer incidents. Low-income countries have been found to have higher COVID-19 resistance because of their warm environment, weaker virus strains due to mutation, and malarial cross-protection. Individuals in low-income nations are habituated to less hygienic living circumstances and have fewer accesses to healthcare throughout their lifetimes. As a result, they possess greater inherent immunity and greater resilience against a wide range of infectious diseases [23].

Genetics and Pathogenesis

SARS COV-2 variants are round, enclosed virus particles with a size varying from 80 to 160 nm. The overall virus particle surface (117nm) is covered in conspicuous surface projections of approximately 20 nm in length, lending it

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a corona appearance [24]. The severe acute respiratory syndrome has an ssRNA genome that is around 30 kilobases, similar to coronaviruses. Structured and non-structural peptides are both encoded in DNA [25] Its genomic architecture is quite close to that of other existing HCoVs, with a different number of ORFs (3a, 3d, 6, 7a, 7b, 8, 9b, 14, and ORF10) genes that are also fundamental genes that code for nine auxiliary proteins [26].

There are 16 NSP and four SPs. The NP, the MP, the S and the EP are the SP. Three out of four polypeptides are found within the viral envelope. The binding of virus particles to a particular receptor and subsequent fusion of virus and host cell membrane surfaces are both facilitated by the spike protein. The membrane proteins play a significant part in incorporating the viral nucleocapsid into viral particles. The envelope protein bends pre-Golgi membranes, to facilitate virus assembly. The fourth structural protein, N, forms a rnps complex with the viral RNA genome. The pp1a and pp1ab polyproteins are NSPs. Non-structural proteins 1–11 is exhibited by the non-structural protein pp1a, while NSP12–16 is exhibited by the non-structural protein pp1ab as shown in figure 3 [27].

Coronavirus particles adhere to cellular anchoring proteins and particular S linkages with the ACE2 receptor, in combination with host proteins (such as the plasma membrane serine protease TMPRSS2), facilitate viral absorption and integration into the cell or endosomal membrane. The initial translating of two big ORF1a-1b happens when the invading viral RNA is released and uncoated. The individuals (nsps) that make up the viral replication as well as the transcriptional complex are formed via co-translational and post-translational processing of the pp1a and pp1ab.

For the replication and transcription of viral ribonucleic acid and messenger RNAs, which include the embedded sequence of coronavirus messenger RNAs, the biogenesis of viral replication components serves as an efficient barrier. These components include perinuclear double-membrane vesicles, convoluted membranes, and small open double-membrane spherules. The walls of the ER receive the translated viral components and pass via ERGIC, in which they interface with N-encapsulated, newly generated genetic ribonucleic acid, causing budding into glandular vesicular compartment lumens. Exocytosis is then used by the infected host cell to release the virus particles [28].

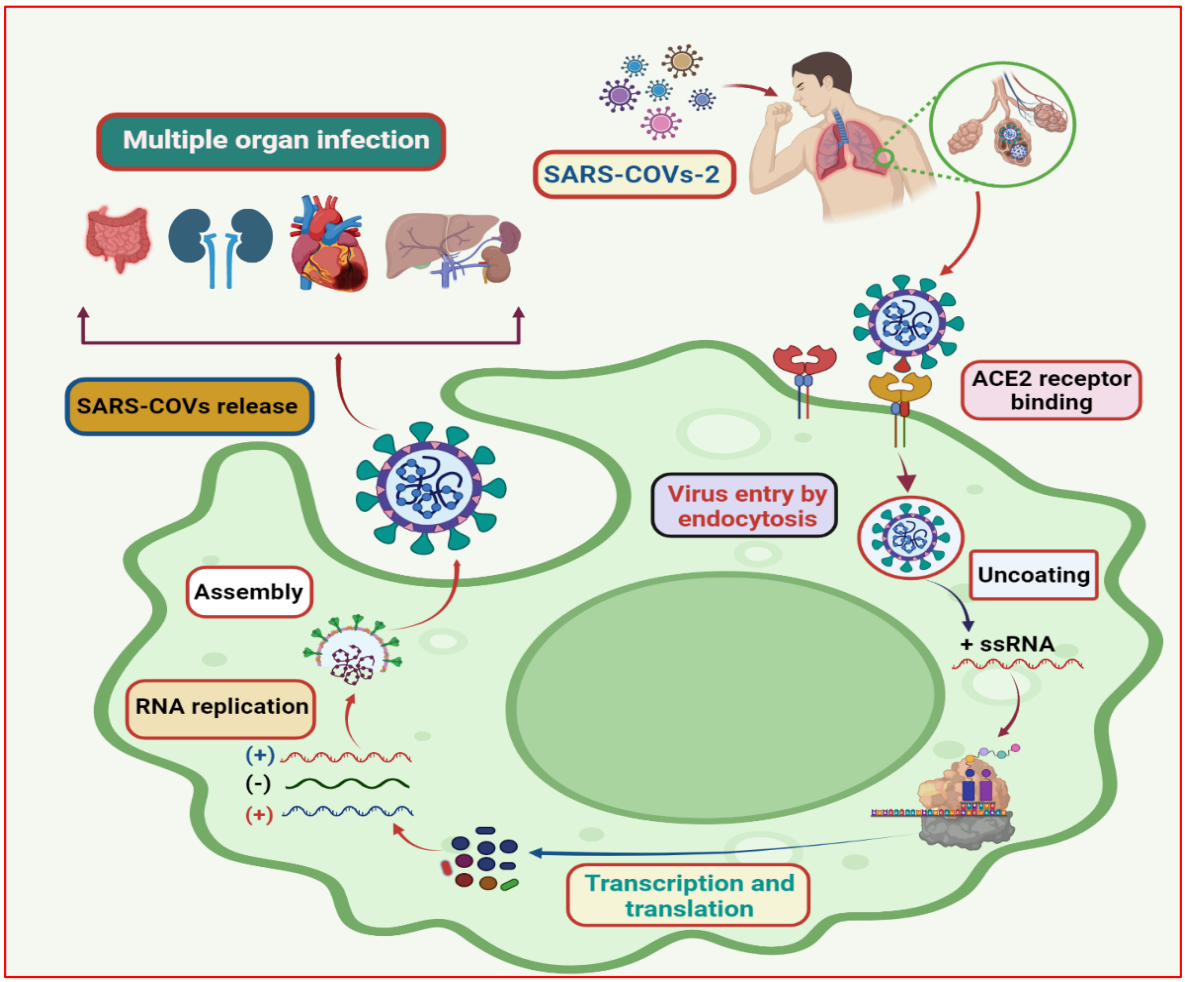

Figure 2: Pathogenesis of SARS-COV-2

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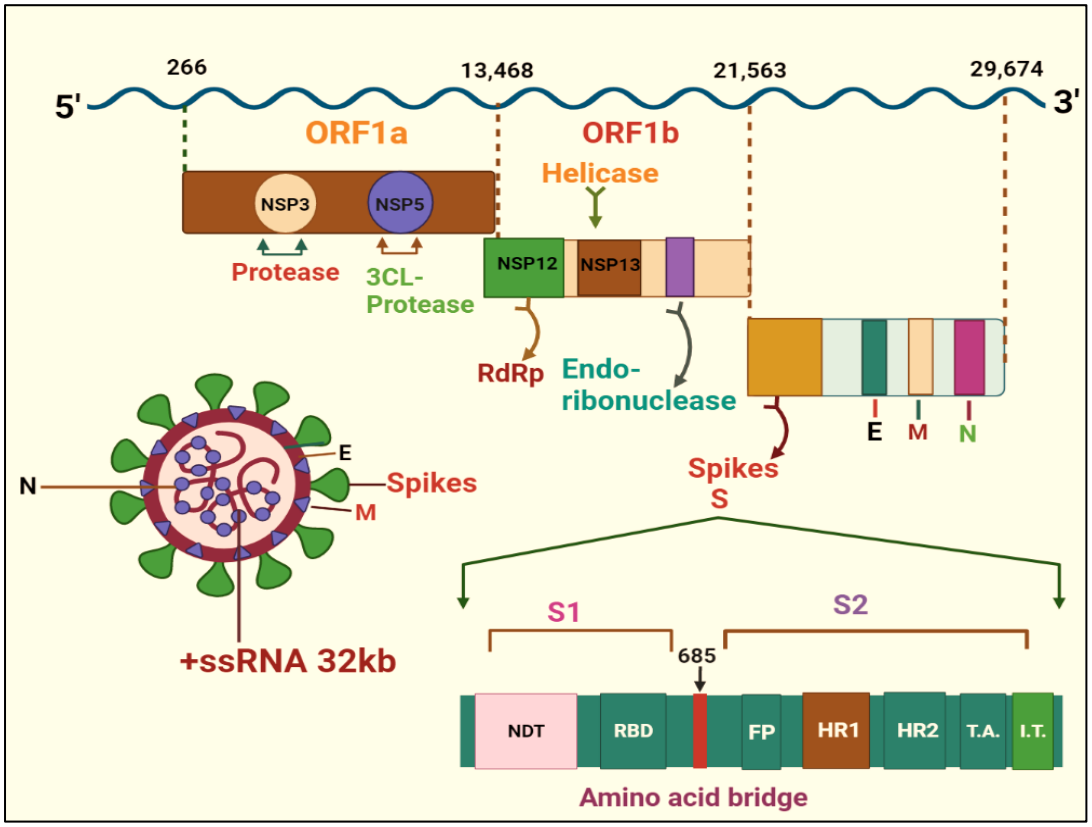

Figure 3: SARS Covid-2 Positive sRNA Genome

An enveloped virus belonging to the Coronaviridae family has a (+) ssRNA genome that is not segmented, has a cap at one end and a poly-A tail at the other, and functions as messenger RNA for the production of poly-proteins. According to an examination of the entire genome sequence, Beta-CoVs have four structural proteins, including spike, membrane, envelope, and nucleocapsid protein, and just a few nonstructural proteins. The coronavirus genome is said to be the biggest of the known coronaviruses, with a GC content of between 32 and 43 percent. The SARS-CoV-2 genome possesses 12 vacant reading frames (ORFs), which can be any length between 29.8 and 29.9 kilobases and can encode 27 distinct proteins. With the exception of the S-gene, which differs, greater than 90% of the amino acids in the four structural genes of SARS-CoV-2 are similar to those of coronavirus as shown in figure 2.

The gene for hemagglutinin-esterase that has been identified in a small number of Beta-CoVs [29] is not present in the SARS-CoV-2 genome. Approximately two-thirds of the RNA of SARS-CoV-2 contains the region ORF1a/b, which is thought to be the biggest ORF and contains 16 nonstructural proteins necessary for virus transcription and replication (pp1ab). Structure- and accessory-encoding ORFs can be found in the remaining one-third of the genome [30]. SARS- CoV-2's persistence and pathogenicity all depend on its genetic diversity. One study on the formation of SARS-CoV-2 revealed that the primary causes of the virus's genomic diversity are random mutation and recombination. SARS-CoV-2 has a very high rate of mutation for RNA viruses—approximately 8,104 nucleotides/genome per year. The sequence of SARS-genomic CoV-2 is 79% similar to Severe Acute Respiratory Syndrome and 50% similar to Middle East Respiratory Syndrome. The Severe Acute Respiratory Syndrome Coronavirus 2 spike proteins comprise 1273 amino acids, more than the Severe Acute Respiratory Syndrome Coronavirus (1255) and Bat Severe Acute Respiratory Syndrome-related Coronaviruses (1245–1269) [31].

Spike Mutation

Coronaviruses' spike protein aids receptor binding and viral penetration into host cells. The virus structural protein mutations are important for viral pathogenicity because they determine the development of antibody escape variants and cellular tropism [32]. The viruses appear to be constantly mutating, and their behavior and characteristics have changed in response to a variety of unknowns, including environmental and human-to-human interactions [33]. As a result, mutations that modify the spike protein's antigenicity are particularly important [34]. The supersite in the viral spike receptor's, anti-amino terminal domain antibodies can be recognized by the amino-terminal domain (NTD), while the 17 amino acids residues of the receptor binding domain establishes a bond with ACE2 and bind numerous neutralizing antibodies.

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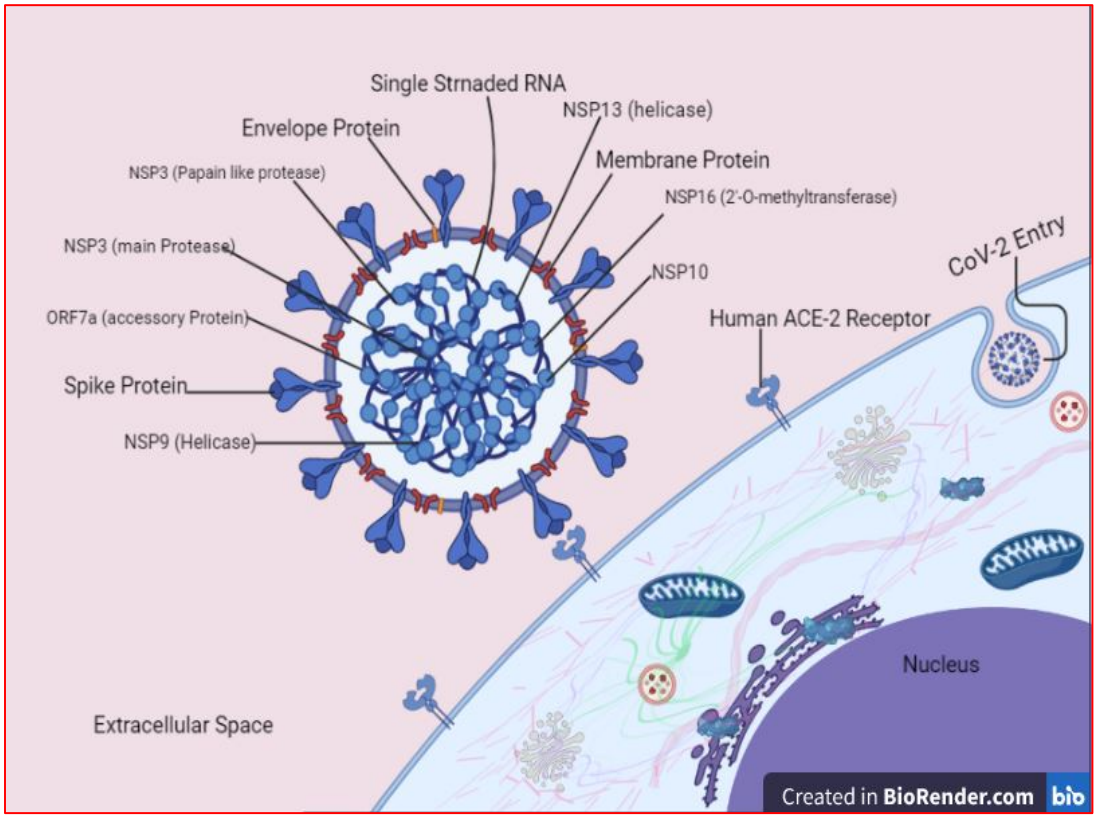

Figure 4: Genomic structure of Corona virus and the attachment of COVID-2 with ACE-2 Receptor

While NTD mutations appear to be highly different at first look, they always converge on the supersite's structure. The RBD mutations, on the other hand, focus on just a few critical locations (K417, L452, E484, N501) that function as allosteric control points, allowing spike to avoid neutralizing antibodies while retaining as well as increasing Ace2-binding activity as shown in figure 4 [35].

Severe acute respiratory coronavirus variants of concern (VOC) and variants of interest (VOI) began to be published in September 2020, with more unique substitutions than predicted given the virus's clock-like molecular evolution [36]. Variants that have undergone various mutations have replaced the original Wuhan strain. Several of these alterations can be found in the highly antigenic spike (S) protein. In the years since, a number of new varieties have developed and spread throughout the world, such as the British-discovered Alpha (B.1.1.7), the South African-discovered Beta (B.1.351), the Brazilian-discovered Gamma (P.1 and P.2), the Indian-discovered Delta (B.1.617.2), and the South African-discovered Omicron [37]. The B.1.1.7 pseudo typed virus's spike integration and entry efficiency are decreased when the H69 and V70 residues, which are naturally present in the alpha variant B.1.1.7 spike, are changed.B.1.1.7 spike, which is reliant on H69/V70, induces quicker cell-cell fusion kinetics than wild-type Wuhan-1 D614G. N501Y, which is a mutation in the RBD from asparagine (N) to tyrosine (Y), can boost Angiotensin II converting enzymes affinity for adhesion and Increase the virus's infectiousness. In certain immunocompromised individuals, the 69–70 deletion has escaped the immune response and is linked to other RBD changes [38].

The B.1.351 (also known as VOC-20DEC-02 and Beta) is a VOC lineage that was found in South Africa. The E484K alteration in S, which occurs in the receptor-binding domain and might produce inadequate immunological responses, is one of the most worrying mutations in Beta. Gamma (P.1): initially discovered in November 2020, demonstrating the existence of three alterations that increase a receptor's affinity for Angiotensin Converting Enzyme 2: K417T, E484K, and N501Y, which lead to a 40% increase in transmissibility over the previous variants [39]. WHO designated the B.1.617 lineage, which was discovered in India, as the fourth worldwide Variant of concern on May 10, 2021.B.1.617.1, B.1.617.2, and B.1.617.3 are the three sub-lineages of this lineage. The Delta variation features two distinguishing changes in the spike protein, in addition to the basic D614G genetic variation: position 452 in the RBD region and position 681 in the furin cleavage site between S1 and S2.

Coronavirus variant Omicron (B.1.1.529) has recently surfaced in southern Africa and numerous European nations. Many individuals were startled by the number of genetic changes in this variant's spike protein: 30 mutations, 3 deletions, and 1 insertion i.e NTD (G142D V143 Y144) and

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RBD (K417N N440K G446S S477N) mutations [40]. The nucleocapsid protein has the following revealed variations: T91 in the envelope, P13L, E31del, R32del, S33del, R203K, G204R in the matrix, D3G, Q19E, A63T in the nucleocapsid protein, N211del/L212I, Y145del, Y144del, Y143del, G142D, T95I, V70del Along with numerous additional mutations in the NSPs and spike protein, the spike has the following mutations: D796Y in the fusion peptide, L981F, N969K, and Q954H in the heptad repeat 1 of the spike.

The variant of interest is defined as a set of Spike protein changes that have been linked to increased infectivity and resistance to post-vaccinal/infection antibodies, increased transmissibility, and poor clinical outcomes. Three inbound Tanzanian visitors were put through a joint airport test in mid-February and found to have a new VOI. This novel VOI includes 31 amino acid changes (11 in spike) and three deletions and is currently known as A.VOI.V2 (all in spike). The receptor-binding domain has undergone three changes (R346K, T478R, and E484K) and five substitutions, and three deletions in the NTD are among the spike mutations as shown in figure 5 [41].

The WHO has outlined eight VOIs since the pandemic's start, including Epsilon (B.1.427 and B.1.429), Zeta (P.2), Eta (B.1.525), Theta (P.3), Iota (B.1.526), Kappa (B.1.617.1), Lambda (C.37), and Mu (B.1.621). When compared to wild-type circulating strains, the transmissibility of the Epsilon (B.1.427 and B.1.429) variants, also known as CAL.20C/L452R, increased by 18.6–24%. They first appeared in the United States around June 2020, and their prevalence increased from 0% to >50% of sequenced cases between September 1, 2020, and January 29, 2021. Specific mutations are present in these variations (B.1.427: L452R, D614G; B.1.429: S13I, W152C, L452R, D614G). This strain was identified by the CDC as a variation of concern in the US because of its heightened transmissibility [42].

In April 2020, the P.2 (Zeta) variant was discovered for the first time in Brazil. It also goes by the name B.1.1.28.2 and is a member of the B.1.1.28 lineage. The S-glycoprotein of this strain carries significant mutations (F565L, D614G, and V1176F). Besides S-glycoprotein, the RBD has undergone one significant mutation (E484K). In February 2021, P.3 (Theta) variants were discovered in Japan and the Philippines. It is also referred to as B.1.1.28.3, which corresponds to the B.1.1.28 lineage. The S-glycoprotein has several important mutations (141/143del, D614G, P681H, E1092K, H1101Y, and V1176F). The RBD contains two important alterations, E484K and N501, in addition to the S-glycoprotein [43].

Both the Eta (B.1.525) and Iota (B.1.526) variants, which were first found in November 2020 in New York, have critical spike mutations (B.1.525: A67V, 69/70, 144, E484K, D614G, Q677H, F888L; B.1.526: (L5F*), T95I, D253G, (S477N*), (E484K*), The Kappa(B.1.617.1) variation, initially identified in India, carries important alterations ((T95I), G142D, E154K, L452R, E484Q, D614G, P681R, and Q1071H). The CDC and WHO classifies it as an interesting variant. The Lambda (C.37) variant was discovered for the first time in Peru, and the WHO identified it as a VOI in June 2021 due to its growing prevalence in the South American region. The Mu (B.1.621) variant was found in Columbia and the WHO classified it as a Variant of interest in August 2021 [44].

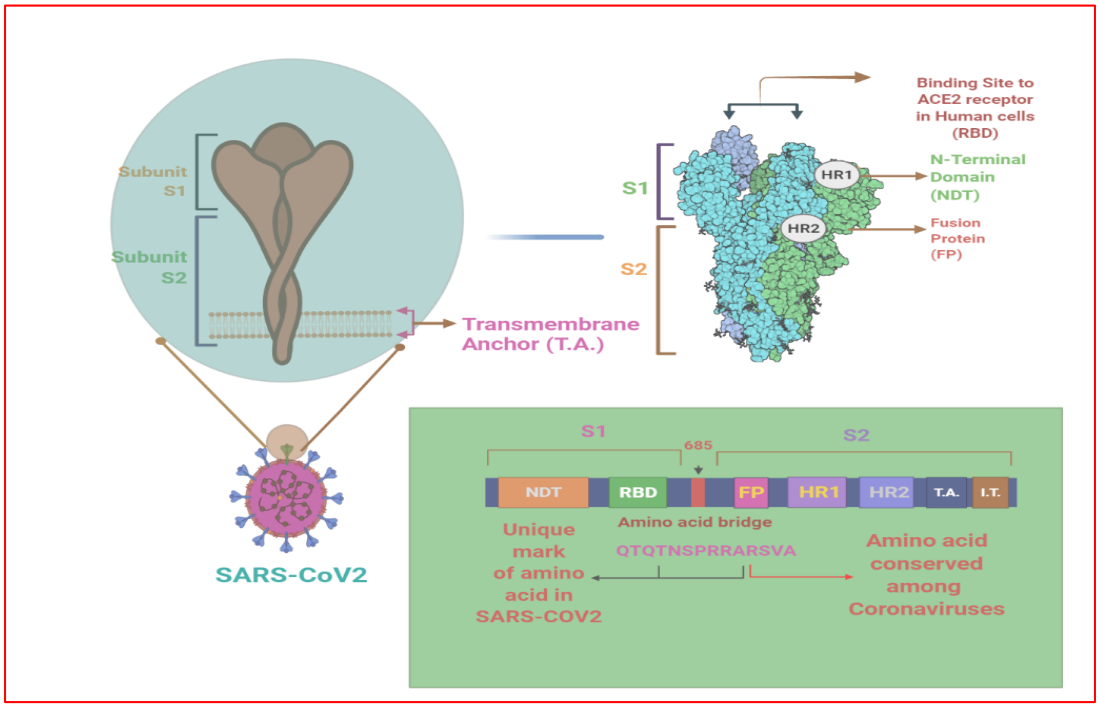

Figure 5: Spike Mutation

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Human immunity against COVID-19

When a coronavirus, such as SARS-Cov-2, comes into contact with the respiratory mucosa for the first time, it enters the cells through the Angiotensin Converting Enzyme 2 receptor and, after its RNA is translated, creates structural and NSPs. The nucleocapsid protein is one of those that can prevent interferon (IFN) synthesis and the effect it has on surrounding cells. In order to proliferate undetected by the body, the virus thus hijacks the host's initial innate immune response in the early days following infection. Many cells have already been infected, so symptoms, when they do appear, are frequently aggressive with a high temperature and overall malaise. The crucial period begins seven days after the onset of the first symptoms and is either when the immune system eradicates the virus, causing the patient to recover, or when the patient has a relapse. The virus spreads into the systemic circulation and the lungs, concentrating on type 2 pneumocytes, where it destroys the endothelium and causes oxidative stress [45]. In the advanced stages of the second week, this causes the inflammatory response to be overactive in around 3-5 percent of all patients, which is specifically brought on by interleukin (IL)-6, which activates macrophages, monocytes, and T cells, resulting in a "cytokine storm." The levels of cytokines in Coronavirus Disease 2019are 100–1000 times less than those in the actual cytokine storm syndrome. The innate immune system appears to play a crucial role in how COVID-19 will turn out, in addition to the body's overall viral load and the immune system's response to it.

By accessing the cells through the Angiotensin Converting Enzyme 2 receptor on their surfaces, Type 2 pneumocytes contract SARS-CoV-2 [46]. Contrary to the typical anti-viral response, which boosts Interferon type I and III production and, additionally, the neighboring cells' expression of genes set off by Interferon, so strengthening its anti-viral defense, the SARS-Cov-2 has techniques that suppress this anti-viral innate defense techniques. Furthermore, during a viral infection, chemotactic chemicals are generated that draw neutrophils, natural killer (NK) cells, and macrophages (M). Since the initial innate immune response is not fully completed during early COVID, it appears slow and insufficient. Following this initial innate response, dendritic cells stimulate specific Th1 lymphocytes, which in turn stimulate cytotoxic T cells to kill infected cells. These steps together generate adaptive immunity. T-cells play a significant role in the adaptive stage; SAR-CoV epitope pools detect helper T cells and cytotoxic T cells in 100% and 70%, respectively, of convalescent coronavirus-infected patients. Moreover, a distinct subgroup of B lymphocytes known as B-1a cells—which create autocrine natural immunoglobulin M and immunoglobulin G antibodies—might have a special use in medicine [47].

Vaccination and Immunity

Vaccination aims to stimulate an individual's immune response in a comparable way to a natural illness. Several vaccinations are currently being clinically tested and/or distributed to the target population. Because the spike protein is implicated in immune evasion, it is being studied as a vaccine and therapeutic target. Severe Acute Respiratory Syndrome Coronavirus 2 mutations at critical residues, particularly in the spike protein, elude immune responses, lowering vaccine immunogenicity and effectiveness, offering a serious challenge to preventive and control strategies [48]. The emergence of variations that are resistant to vaccine-induced antibody-mediated immunity. Because medicines (Vaccinations and antibody-based treatments) primarily target the Severe Acute Respiratory Syndrome Coronavirus 2 spike protein, in chronic infections, selection forces favor the development of novel variants with immune escape mutations. [49].

Several investigations have found that a mixture of RB proteins and Coronavirus N protein NTD alterations in the Beta spike protein significantly affects vaccine recipients' ability to neutralize activity. Vaccine effectiveness is less effective against the Beta version than against the B.1.1.7 variant. In December 2020, the Lambda (C.37) variant was first discovered in Peru. The spike RBD has the mutations L452Q and F490S. The F490S mutation is linked to a reduction in antibody neutralization susceptibility. This variation has 19 modifications that increase its transmissibility or resistance to antibodies generated by vaccination or past viral exposure [50]. The introduction of the Omicron (B.1.1.529) variant has raised severe concerns regarding vaccination effectiveness and the pandemic's potential trajectory [51]. The most severely altered SARS-Cov2, known as Omicron, is the most severely altered variant to date and is associated with an increase in infectivity and some opposition to vaccine-induced immunity. A number of cases in South Africa were caused by Omicron, which is now spreading globally [52]. Over 8.2 billion doses of SARS-Cov2 vaccination have been administered to over 4.3 billion people throughout the world. The emergence of the Omicron form, however, is cause for worry because it is resistant to the bulk of SARS-Cov2 neutralizing antibodies and reduces the immune protection generated by current Coronavirus infectious disease-19 infection and mRNA vaccines as shown in table in 1, [53].In South Africans who were vaccinated with Pfizer BNT162b2, Omicron evades antibody neutralization, whether they were previously infected with SARS-Cov2 or not (54).

Mechanism of Action

mRNA-based vaccines

The messenger Ribonucleic Acid-1273 vaccine by Moderna is an messenger Ribonucleic Acid vaccine, which consists of strands of mRNA carrying information that tells

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the cell how to produce a SP that is unique to coronavirus, which prompts the immune system to respond and create immunoglobulin to fight the virus. Two proline residues have been added to the spike protein (S2P) to maintain it in a prefusion conformation. The complete SP of SARS-CoV-2 is expressed by mRNA-1273. For immunoglobulins that prevent infection, the coronavirus spike protein is a popular target. It facilitates the virus's cellular binding and entry (via fusion). The mRNA vaccination BNT162b2 Pfizer works similarly to mRNA-1273 in that it transmits instructions to human cells that are unable to produce SP on their own. The BNT162b2 vaccine's mRNA instructions are read by the cells, which then direct the production of the spike protein that causes the immune system to mount a defense against SARS-Cov2 [55].

Inactivated SARS-COV-2-based vaccine

This vaccine is being developed by a state-owned corporation in China called Sinopharm. It is a vaccine that is inactive and enters the body as a dead SARS-CoV-2 replica. Then, using its expired antigens, antibodies are created to strengthen the immune system's defenses against viral assaults in the future. CoronaVac is a vaccine that has been inactivated and introduces the dead cells of the targeted virus into the subject's body after it has been confined by heat or chemicals. If the person contracts the virus once more in the future, the immune system will then learn from the dead antigens how to respond to living copies of them. In the instance of CoronaVac, the coronavirus contained inactivated SARS-CoV-2 and had been inactivated with beta-propiolactone [56].

Viral vector-based vaccine

The JNJ-78436735 vaccine was created using the PER. C6 and AdVac technologies from Jansen. The COVID-19 spike protein is expressed inside of cells using the vaccine's recombinant vector, which uses a human adenoviral vector. The adenovirus that causes the common cold is genetically altered so that it cannot reproduce in the body by including a fragment of coronavirus deoxyribonucleic acid [57]. Sputnik V (Russian Vaccine) is based on two distinct human adenoviral vectors (Ad 26 and Ad 5) that could produce a stronger and longer-lasting immune response than other vaccines that employ the same vector in two doses. The strategy is comparable to that used for the vaccines made by Johnson & Johnson and AstraZeneca. In actuality, a designed DNA fragment from an adenovirus infects the cells, which then use genetic instructions to build a duplicate of the coronavirus spike that can produce antibodies and T cells that protect people from upcoming infections. Adenovirus, the viral vector, cannot grow in human cells [58].

Coronavirus disease vaccine AstraZeneca is a monovalent vaccine made up of a single recombinant protein, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the spike protein of coronavirus. Because the coding sequence has not been altered, the SARS-CoV-2 S immunogen in the vaccine is expressed in the trimeric pre-fusion conformation, stabilizing the expressed S-protein. Following injection, Local expression of the coronavirus spike protein induces cellular immune responses and neutralizing antibodies. , which may help protect against COVID-19 [59]. Ad5-nCoV was created by Cansino Biologics, who also created the ground-breaking, widely distributed Ebola vaccine. It expresses the coronavirus disease 2019 spike protein using an adenovirus type with a replication defect. The vaccine is a genetically modified viral vector vaccine. The vaccine, like AZD1222, utilizes a compromised adenovirus (common cold virus) to provide cells with SARS-CoV-2 genetic instructions, enabling them to generate the spike protein that sets off an immune response where SARS-Cov2 specific Immunoglobulins are created [60].

Subunit protein-based vaccine

NVX-CoV2373, a NPs vaccine created by Novavax, is made up of trimeric prefusion stabilized full-length SARS-CoV-2 spike glycoproteins and the saponin-based MatrixM1 adjuvant [61]. The NVX-CoV2373 vaccine combines SP to create a knucklebone-shaped nanoparticle that can be injected. It also contains the company's patented Matrix-M adjuvant, which enhances antigen presentation in nearby lymph nodes and promotes the entry of APC into the injection site, having a potent and well-tolerated effect. thereby enhancing immune response [62].

Diagnosis

New diagnostic methods for the identification of the illness are being developed. Many molecular diagnostic assays, including RT-PCR, RT-LAMP, NGS, CRISPR, and MBA, as well as alternative approaches, including CT scan, biomarkers, biosensors, nanotechnology, Serology, ELISA. The detection of the viral nucleic acid test (NAT) using RT-qPCR is deemed sensitive, specific, and capable of processing large batches of samples. It has low sensitivity, especially in the latter stages of infection, and is highly dependent on the quality of the samples [63].

The most reliable way to identify coronavirus disease is currently positive severe acute respiratory coronavirus RNA findings by (RT-PCR), but the demand for testing a significant number of patients with suspected Coronavirus Disease 2019 may not be able to be met by the availability of test kits due to the time-consuming nature of this procedure. As a result, a speedy and reliable approach for differential identification of suspected coronavirus patients is required. A non-invasive, quick method of radiological evaluation, in particular thin-section chest computed tomography, offers the advantage of early detection of lung pathological alterations and reflecting the degree of disease. [64].

In Hong Kong, there is a RAD kit. Bio credit Coronavirus

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Disease 2019 antigen for the diagnosis of SARS-CoV2 infections when the assessment began. The Bio credit Coronavirus Disease 2019 antigen kit is intended for nasopharyngeal swab samples. To conduct the test, customized sample processing processes were used. Sputum and throat saliva can be collected and then either eluted in a viral transport medium or suspended in phosphate-buffered saline for analysis. These antibodies are now investigated using two methods: (ELISA) and (LFA). The first ELISA, the Euroimmun Immunoglobulin and Immunoglobulin Enzyme-linked immunosorbent assay gained CE certification at the end of March 2020. Although Immunoglobulin Enzyme-linked immunosorbent assay is a well-established technology for antibody detection, it has drawbacks such as a longer turnaround time, the necessity for a laboratory setting, and greater personnel costs [65].

It is not a new concept to utilize biosensors to detect human respiratory viruses; SARS-CoV, MERS, and influenza A have all been identified using EC, optical, and thermal biosensors, respectively. As a result, utilizing this biosensor technology may be broadened and effectively applied to the detection of additional viruses [66]. Biosensors can also be used to find SARS-CoV-2 illness. Several signal conversion methods, including electrolytic, photonic, and several more, are used to create biosensors. Electrochemical biosensors are mostly employed in the biomedical industry because they are low-cost, easy to use, and appropriate for mass production.

Graphene oxide functionalized with calixarene was reported as a DPV-based technique for targeting SARS-CoV-2 RNA. The ability to identify the RNA of coronavirus using a small electrochemical smartphone without the requirement for amplification or reverse transcription was proven. The architecture of this biosensor incorporates a capture, label, auxiliary probe, and target sequence [67]. For evaluating nucleic acids, rolling circle amplification (RCA) is frequently used. Using polymerases, the RCA method anneals Deoxyribonucleic Acid or Ribonucleic Acid primers to a circular Deoxyribonucleic Acid template. In about 90 minutes, RCA can synthesize 109-fold concatemers with minimal reagents that contain multiple repetitions of complementary sequences to the circular template (amplicons) [68].

Antiviral drugs against COVID-19 and their mode of action

The sole treatment for severe COVID-19 symptoms, if there aren't specialized therapies, is assistive care (such as oxygen treatment or mechanical breathing). The development of therapies based on already-existing antiviral drugs is a crucial technique to restrict viral multiplication in the initial stages of the disease and make it less severe. Following the coronaviruses' (SAR-coronavirus in 2003 and Middle East Respiratory Syndrome Coronavirus in 2012) quick appearance and development, significant attempts were made to discover medications that are directed at specific stages of the coronavirus life cycle, such as (a) dealings with ACE-2 receptors, (b) enzymes that catalyze S protein cleavage, (c) viral entry, (d) polyprotein processing, and (e) replication/transcription complex. These substances were quickly screened in severe acute respiratory syndrome coronavirus-2 infected cells, and many of them are currently undergoing testing in small animal models or clinical studies. [69].

Antibody neutralization

Preventing the viral spike protein's interaction with cell surface receptors is a useful therapeutic tactic for stopping the spread of viruses. Neutralizing antibodies (Abs) that can restrict coronavirus virus infection in vitro have recently been found in the sera of patients with coronavirus infection. Additionally, Plasma from recovering patients has shown some promise in the treatment of people with breathing difficulty, demonstrating that coronavirus infection may be decreased by passive immunity. The effectiveness of this approach is being tested in clinical trials utilizing plasmapheresis [70].

The first strategy involves employing chemicals that prevent virus-cell fusion to obstruct virus entry. This contains the antiviral compound umifenovir (Arbidol), which was initially created to treat influenza infection. Interestingly, umifenovir inhibits the invasion of other viruses and boosts the immune system to have broad-range antiviral efficacy. The most desirable antiviral substances are those that prevent RdRp activity from allowing viruses to replicate. Among the most promising classes of RdRp inhibitors are nucleotide and nucleoside analogues. Another promising anti-CoV agent is the cytidine analogue-d-N4-hydroxycytidine (NHC). NHC prevents the replication of MEES-CoV and SARS-CoV2 without what appears to be interference from nsp14's viral proofreading function. Reduced viral replication in infected cells was linked to an increase in mutation frequency [71].

The usage of ritonavir and lopinavir when treating coronavirus infection 2019 may be explained by the fact that it shares 79.6% of the genome with coronavirus and belongs to the same genus as SARS-CoV2, SARS-CoV, MERS-CoV and (Betacoronavirus). Both lopinavir and ritonavir have an equal ability to conjugate to the SARS-CoV 3CLpro enzyme's active site, which allows them to block the enzyme. According to a recent Coronavirus disease 2019 study, SARS-CoV2 uses the same cell entrance strategy as SAR-CoV, which depends on the Angiotensin Converting Enzyme 2receptor and TMPRSS2 to prime the spike protein [72].

Oseltamivir is another artificial prodrug used to treat COVID-19. The neuraminidase enzymes on the influenza virus particles' surface can be inhibited initially by this medication. It binds reversibly to the neuraminidase's active site and stops it from cleaving the host cell's surface-located sialic acid residues. As a result, less virus is shed and it is

less infectious. This also stops the virus from entering healthy cells and prevents the debut of recently created virions from infected cells [73].

Remdesivir (RDV; GS-5734) is a 1′-cyano-substituted adenosine nucleotide analogue prodrug developed by Gilead Sciences in 2017 as an Ebola virus infection treatment. It possesses broad-spectrum antiviral action on Ribo nucleic acid viruses such as the Ebola virus, Severe Acute Respiratory Syndrome Coronavirus, Middle East Respiratory Syndrome Coronavirus, Marburg, Nipah virus (NiV), respiratory syncytial virus (RSV), and Hendra virus, according to several studies. The virus-fighting system interferes with viral RNA polymerase activity, postponing chain termination, and decreasing viral RNA production. [74].

Favipiravir (FPV; T-705) has also been used to treat COVID-19 as a nucleotide analogue, which was created by Toyama Chemicals to cure infections caused by the influenza virus. Chain termination is how favipiravir, like remdesivir, prevents the synthesis of viral RNA. As the RNA strand grows, favipiravir is converted into the metabolite ribofuranosyl 5′-triphosphate (RTP). A single favipiravir-RTP molecule could only partially stop an RNA strand from extending, while the insertion of two of these molecules inhibited further extension entirely. This approach effectively blocks the operation of the RdRp [75].

Chloroquine (CQ), an antimalarial medication, is one of the treatment options that has effective inhibitory action on Severe Acute Respiratory Syndrome Coronavirus 2 at the cellular level, in contrast to remdesivir and favipiravir. It has been proven that chloroquine may have anti-coronavirus action. Chloroquine successfully stopped the viral replication of HCoV-229E, Severe Acute Respiratory Syndrome Coronavirus 2 Middle East Respiratory Syndrome Coronavirus and Ebolavirus [76].

Conclusion

SARS-CoV-2 is a zoonotic virus that propagates from an undisclosed infected animal to humans, causing disease in people and animals because of genetic drift in genetic RNA. Finally, the adaptation of the viral genetic material and the ongoing development of breakout variations indicate that coronavirus-2 has the chance to become a cyclical virus similar to influenza, necessitating the need to re-adjust vaccinations. It's also vital to know the pace and efficiency of alterations because they contribute to the virus evading the host immunity and building medication tolerance.

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