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Unravelling the Complexity of SARS-CoV-2 and COVID-19: A Comprehensive Review

[1]Aman Bhatia and [2]Dr. Gaurav Kapoor*

Author's Affiliation:
[1]Research Scholar, Department of Zoology, Sardar Patel University, Mandi, Himachal Pradesh 175001, India
E-mail: iamaman221b@gmail.com
[2]Assistant Professor, Department of Zoology, Sardar Patel University, Mandi, Himachal Pradesh 175001, India
E-mail: drgauravk@spumandi.ac.in

***Corresponding author:**
Dr. Gaurav Kapoor
Assistant Professor, Department of Zoology, Sardar Patel University, Mandi, Himachal Pradesh 175001, India
E-mail: drgauravk@spumandi.ac.in, iamaman221b@gmail.com

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ABSTRACT:
The recent pandemic of CoVID-19 was due to severe acute respiratory syndrome 2 (SARS-CoV-2) and its various viral variants and their evolutionled to a global pandemic. SARS-CoV-2 is categorised under enveloped viruses consisting of single stranded, non-segmented, linear, positive sense strand RNA which functions as its genetic material. Further sub categorised into five important variants of concern namely, Alpha, Beta, Gamma, Delta, and Omicron. Ribovirus interacts with various receptors in human body most prominently ACE2, APN, NEU-5, results in occurrence and transmission. It is accompanied by induced hypercytokinemia, also known as a cytokine storm. Various cytokine and interlukins associated with it results in acute respiratory distress syndrome (ARDS). This review contains a summarized account of recent advancements regarding epidemiological, clinical and pathological attributes of COVID-19 along with recent progress in treatment and vaccine development.

Keywords:
COVID-19, Cytokine storm, SARS-CoV-2, VOC (variant of concern), Hypercytokinaemia.

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INTRODUCTION

It is clear, from past 2 years, that infectious diseases are being regarded to be the most serious health threats that will become a challenge in the foreseeable future. Following the Severe acute respiratory syndrome (SARS-CoV) and the Middle-East respiratory syndrome (MERS-CoV), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) became the third coronavirus outbreak in the past 20 years along with other viral outbreaks such as Zika virus and Ebola virus that caused the transformation of various aspects at the individual, societal, and legislative levels that appears unavoidable in order to combat such situations (Jazieh & Kozlakidis, 2020). Sanyaolu et al., 2021 reported that Wuhan, China in December 2019, saw a sudden surge of pneumonia cases amongst its populace due to appearance of another coronavirus, SARS-CoV-2. In 2019 December, Wei Guixian, a 57-year-old female shrimp vendor in Wuhan was traced as patient zero because of common cold symptoms (Agrahari et al., 2021). The World Health Organization (WHO) termed severe acute

respiratory syndrome coronavirus-2 (SARS-CoV-2) a global pandemic and the disease was named as CoVID-19 (Coronavirus Disease 2019) on March 11, 2020, as a result of rapid global expansion of the virus (Sanyaolu et al., 2021). It was hypothesised that COVID-19 has a zoonotic origin because the infected individuals were linked to an animal market of Wuhan City, China. The ongoing COVID-19 that SARS-CoV-2 causes, is the culprit of the epidemic (Rothan & Byrareddy, 2020).

It has been established that there are six separate coronavirus strains that infect humans but a new seventh one, known as SARS-CoV-2, having similar genetic characteristics as of SARS coronavirus came into limelight recently. The virus belongs to the family of enveloped viruses with genetic material that is linear, non-segmented, single stranded, and positive sense strand RNA (Agrahari et al., 2021). Even though the SARS and MERS viruses belongs to the same viral family as that of SARS-CoV-2, still comparatively the SARS-CoV-2 is less pathogenic (Rabaan et al., 2020). According to studies done by Rabaan et al., 2020, SARS-CoV-2 and SARS-CoV are highly similar as per their structure and pathogenicity, while exhibiting slight differences in their most crucial structural protein, known as spike protein (S). When compared to other beta coronaviruses, the SARS-CoV-2 also exhibit a furin-like cleavage site that helps the S protein to prime easily and may help the virus in more effective dissemination. Hence Furin inhibitors can be used as targets for SARS-CoV-2 pharmacological treatments (Rabaan et al., 2020).

Worldwide, 771,191,203 were infected due to COVID-19, and 6,961,014 mortalities were observed by WHO till the month of October in 2023. 13,513,324,853 dosages of vaccine were administered till October, 2023. India exhibited a total of 44,999,328 patients due to COVID-19 in India as stated by WHO from January 2020 to October 2023 and 532,034 mortalities. 2,206,737,729 dosages of vaccine were administered from June, 2023 (WHO, 2023). It was found out that a major population of patients was formed by people having underlying illnesses such diabetes, hypertension, or cardiovascular disease (Ren et al., 2020). Global economy experienced catastrophic effects, while derailing aspects of human day to day lives including employment, physical and mental health, education, of individuals, etc. Due to lack of medicine or effective vaccine to counter it, global efforts were made, and still are being made as per the available data (Guo et al., 2020; Jazieh & Kozlakidis, 2020).

This review paper aims to provide a brief understanding about the origin, taxonomy, epidemiology and therapeutic techniques deployed by various national and international organisations to combat the pandemic by significantly altering the morbidity and mortality rate exhibited by SARS-CoV-2 virus and its variants.

HISTORY

On April 1, 1967, Tyrell and June Almeida, both from the Department of Medical Microbiology at St. Thomas' Hospital Medical School in London, discovered three unnamed respiratory viruses, two of which had never before been linked to human illnesses. They claimed that the particles of avian infectious bronchitis and two of the viruses, 229E and B814 were undistinguishable. Subsequently, in 1968, Almeida and Tyrell published a study in Nature stating that a group of viruses were responsible for human upper respiratory tract illnesses as well as murine hepatitis and avian bronchitis. They named it as Coronaviruses due to 'crown-like appearance' of its morphology (CEBM, 2022; Rothan & Byrareddy, 2020). Coronaviruses are known to infect humans, pigs, chickens, leading to disorders of different organ systems (McIntosh, 1974). SARS-CoV-2 variant instead of the original virus infected mice. By increasing the receptor binding domains (RBD) affinity to mouse angiotensin-converting enzyme 2 (mACE2), mice infection was seen in B.1.351 variant. There are evidences that show the mutation(s) in RBD acts as a driving force in the development of SARS-CoV-2 variants which further are transmitted zoonotic and anthropologically, leading to the expansion of their host range among vertebrates (Pan et al., 2021).

There have been two significant coronavirus epidemics in the previous 20 years, including the SARS-CoV (2002) and MERS (2012) (Rabaan et al., 2020). Zaki et al., 2012 found that before 2003, only two human coronaviruses, HCoV-229E and HCoV-OC43, were identified. Following discovery of the SARS-CoV in the year 2003, new human coronaviruses, HCoV-NL63 and HCoV-HKU1, were found. SARS was first reported in Southern China in the year 2002 and its infection reached upto 29 nations causing 8096 cases and 774 deaths. This was controlled within a time span of 7 months of its original dissemination due to incredible global public health endeavour (Cherry, 2004). Hung, 2003 reported that people were supposed to put on a mask and practise social distancing while those who had direct contact were required to practise quarantine for 14 days regardless of symptoms and control of the viral spread was accomplished through various health measures including hand washings.

First confirmed cases of Middle East respiratory disease (MERS) were retroactively documented in Jordan in the year 2012 and the first public record came from Jeddah, of the Kingdom of Saudi Arabia (KSA). Later, MERS-CoV were discovered in bats and numerous dromedary camels (DC) as its primary reservoir. (Mackay & Arden, 2015). According to WHO, 35% rate of death was seen and camels served as the main host for human transmission. (Mackay & Arden, 2015).

TAXONOMY AND MORPHOLOGY

The term "coronavirus" was first used in 1968 and later classified via International Committee on the Taxonomy of Viruses (1975) by placing it in the order "Nidovirales" under the family "Coronaviridiae" due to the discovery of a crown-like morphology through electron microscopy. A per serological cross-reactivity, it was classified into groups I, II, and III, which are three distinct genera (Fig. 1). Group I respiratory diseases occur due to porcine respiratory corona virus (PRCV), feline corona virus (FECoV), porcine epidemic diarrhoea virus (PEDV), transmissible gastroenteritis virus (TEGV), canine coronavirus (CCoV), feline infectious peritonitis virus (FIPV), human coronavirus HCoV-229E, and HCoVNL63. Human respiratory infections occur due to Group II viruses such as HCoV-OC43, HCoV-HKU1, and Murine Hepatitis Virus (MHV) (Woods & Wesley, 1988). The mildly pathogenic HCV-229E and HCV-NL63, HCV-HKU1 and HCV-OC43, and SARS CoV-2, as well as other CoVs, can infect humans and cause symptoms like a cold and a cough, according to prior studies on the seven CoVs. But SARS-CoV and MERS-CoV led to serious, deadly respiratory diseases (Li et al., 2020).

Morphologically, coronavirus has unique protein structure consisting of single-stranded, positive-sense, non-segmented, encapsulated RNA without DNA stages. There are linear and helical capsids on the coronavirus's surface and the nucleocapsid is located inside the virion's envelope containing spike proteins (S-proteins) or pleomorphic RNA peplomers of size 80–160 nm and positive polarity 27–33 kb (Sahin et al., 2020). The unique striking detail in coronaviruses that gives it its distinctive nomenclature is the resemblance with solar corona are the mace-like barbs that protrude on its surface. These viruses' essential structural components are encoded as the spike protein (S), membrane protein (M), 16s nucleo-capsid protein (N), and envelope protein (E) at the 3' end of the viral genome. Three or four viral proteins are present in the coronavirus membrane. The most common structural protein is the membrane (M) glycoprotein. The spike protein (S) constitutes peplomers, is a membrane glycoprotein of type I nature. Actually, main persuaderin neutralising antibodies is S protein. The development and composition of coronaviral membrane is most likely influenced by the molecular interaction between the envelope proteins. (Fig. 2) (Mousavizadeh & Ghasemi, 2021). Coronaviruses (CoV) categorisation is grouped in four types, α/β/γ/δ-CoV. SARS-CoV and SARS-CoV-2 infect humans through binding to the ACE2 receptor (Guo et al., 2020). Delta and Gamma chiefly infect avian life form, while alpha and beta target mammals, including humans (Wertheim et al., 2013). The coronaviruses infecting humans HCoV229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 are all members of the genus alpha- and beta-coronavirus. SARS-

CoV-1, MERS-CoV, HCoV-OC43, HCoV-229E, HCoVNL63, and HCoV-HKU1 are additional beta family members (Li et al., 2020; Woods & Wesley, 1988).

Figure 1: Coronaviruses and their groups. (Agrahari et al., 2021)

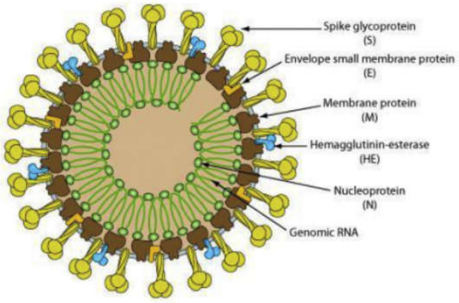

Figure 2: Coronavirus Structure (Mousavizadeh & Ghasemi, 2021). From Biowiki (http://ruleof6ix.fieldofscience.com/2012/09/a-new-coronavirus-should-youcare.html).

On the viral surface, the trimeric N-linked glycosylated spike protein (S) of about 150 kDa causes signals from N-terminal to route in the direction of endoplasmic reticulum of host. S protein is made up of two sub units. S2 creates the stalk, which gives the spike its structure, whereas S1 functions as the domain for binding of receptor. The M protein (25–31 kDa) endodomain has larger C–terminal and ectodomain possess less glycosylated N–

terminal, determines the structure. Moreover, nucleocapsids possessdual domains and is attached to N protein through CTD and NTD (C, N terminal domain), each exhibiting a unique form of binding (Jaimes & Whittaker, 2018). Hemagglutinin-Esterase (HE) of β-Coronaviruses, fixes with sialic acids found on the surface of glycoproteins with acetyl esterase activity increase the virus's entrance into mucosal tissue through the spike protein. Continuous mutation in their transcription occurs far more frequently than in the host—nearly millions of times more frequently (Kim et al., 2020). Kim et al., 2020 also stated that abrupt alterations in the nucleic acids cause the release of highly virulent components, make detection procedures harder, and increase evolvability.

Sarbeco viruses subgenus includes SARS-CoV and SARS-CoV-2 that exhibits recurrent recombination and have localised genetic variation. SARS-CoV-2 receptor-binding domain is crucial for specificity to ACE2 receptors in humans that seems to be a bat virus ancestor rather than a more recent mutation (Boni et al., 2020). The genome sequence in the RNA-dependent RNA polymerase (RdRp) in bat coronavirus (BatCoV RaTG13) and the disease-causing COVID-19 agent, with 87.6-89% nucleotide identity, exhibits how closely it is related to the bat-origin SARS-like coronavirus (bat-SLCoVZC45) and was assumed that this virus was the initial source of infection. But, as bats were not previously sold in stores, the infection may have come from similar animals (Guo et al., 2020; Ren et al., 2020).

RECEPTOR RECOGNITION

Viral infections (including coronavirus) start with receptor recognition that leads to prediction of cross-species infection which is the main focus of antiviral treatment. Both the N-terminal domain (S1-NTD) and the C-terminal domain (S1-CTD) have the ability to be a receptor-binding motif which are two different domains that make up the receptor-binding S1 subunit on coronavirus spike proteins (RBDs). Four protein and three sugar receptors are found on S1-NTDs and S1-CTDs from three of the main coronavirus genera and they exhibit a complicated pattern of receptor recognition (Li, 2015). Further explaining it, Li, 2015 reported separate coronavirus S1-CTDs from separate genera recognises the similar receptor while S1-CTDs from the similar genus can recognise various receptors. Furthermore, coronavirus S1-NTDs can detect either sugar or protein receptors.

Despite belonging to different genera, HCoV-NL63 and SARS-CoV's S1-CTDs recognise the angiotensin-converting enzyme 2 receptor (ACE2) (Hofmann et al., 2006). ACE2 belongs to type I transmembrane amino-peptidase being primarily presenton the apical surface of gastrointestinal cells, heart, and blood vessels. The heart and type II alveolar cells of the lungs also express ACE2 at significant levels (Zhou et al., 2020). ACE2 receptor was first discovered in 2000 and it shares structural similarity (42%) with angiotensin-converting 1 (ACE1) (Rice et al., 2004). The substrate for ACE2 is Angiotensin (Ang II) that accumulates if the ACE2 receptor is down regulated. Accumulated Ang II then boosts vascular permeability and cause neutrophils to aggregate more eventually leading to pulmonary oedema along with acute respiratory distress syndrome (ARDS) exacerbation. Three important coronavirus genera have following receptors (Fig. 3) (Li, 2015). Upon entering human cells, SARS-CoV and SARS-CoV-2 on host cells use the ACE2 receptor, MHV binds to carcino-embryonic antigen-related cell adhesion molecule 1 (CEACAM1), and MERS-CoV binds to dipeptidyl-peptidase 4 (DPP4) (Fehr & Perlman, 2015). According to Kubo et al., 1994 both MHV and BCoV are members of the β-genus, their S1NTDs distinguish between sugar and carcino-embryonic antigen-related cell adhesion molecule 1 (CEACAM1). Additionally, the S1-NTDs of the genera TGEV and IBV both recognise sugar.

A critical study done by Hoffmann et al., 2020 showed that cellular serine protease TMPRSS2 (transmembrane protease serine 2) inhibitor, could also block entry of SARS-CoV-2 in host cell by ACE-2. Thus, ACE-2 and protease inhibitors are possible counteractants to intercede the SARS-CoV-2 transmission.

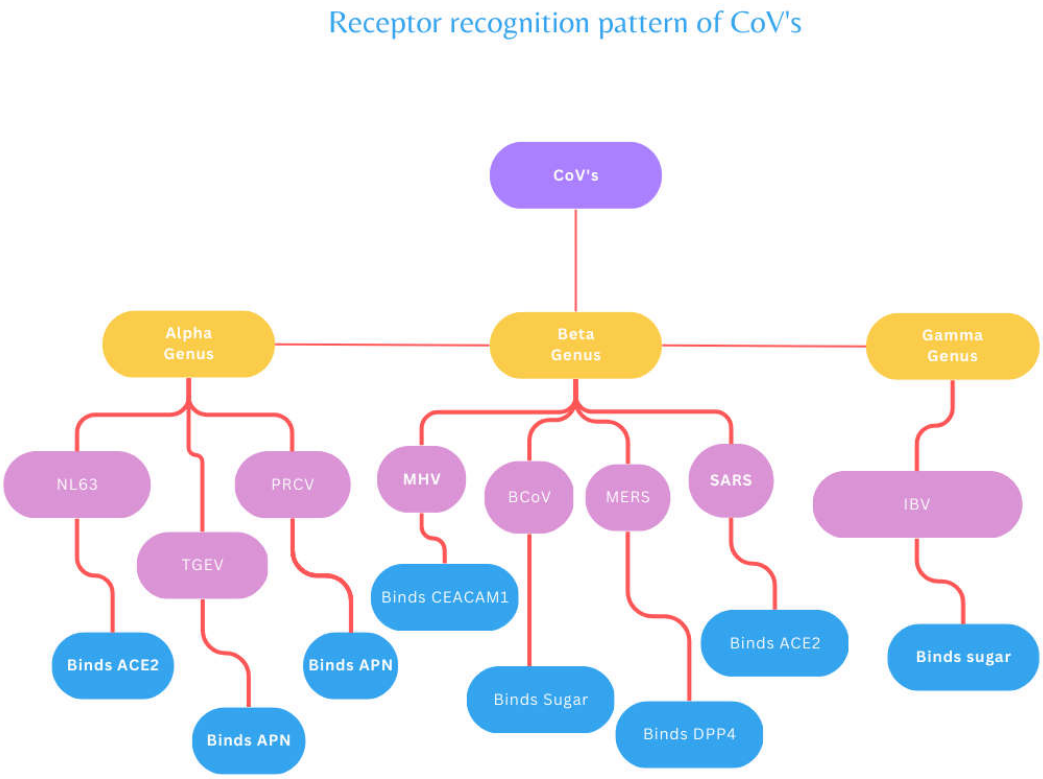

Figure 3: Receptor recognition pattern of CoV's (Li, 2015).

EPIDEMIOLOGY

A novel epidemic causing respiratory tract infection, reported in 2019 December from the Wuhan region of China, suggested possible links to seafood market alongside speculations of bats being the reservoirs of SARS-CoV-2 (McIntosh, 1974; Pan et al., 2021). No such evidences that show links between the origin of SARS-CoV-2 and bats are found. Rather, bats serve as a reservoir of an array of CoVs which includes SARS-CoV-like and MERS-CoV-like viruses (Banerjee et al., 2019). Upon virus genome sequencing by F. Wu et al., 2020, the genome of BatCoV RaTG13 and CoVID-19 exhibited 96.2% genome sequence similarity, leading to popular theory that bat CoV and human SARS-CoV-2 ancestrally have similar lineages, but bats were not sold in this seafood market.

Fresh samples of individual bat feces collected during the birthing season were subjected to real-time PCR screening revealing viral RNA even after three months of the bats had departing the cave and suggested that CoV shedding in bats may enhance the likelihood of spillover (Joffrin et al., 2022). As per Helen, 2020, the local community visits the bats' habitat to gather guano and use it as fertilizer for their crops and knowledge of the infections that bats carry is crucial because they may be transmitted to people as stated by Dr. Elizabeth Gori.

Animal and human Coronavirus cross-pollination had resulted in serious human sickness over the past 20 years. Initially coronavirus was documented in 2002–2003, and after that a second one (COVID-19), became the largest outbreak till date (Sahin et al., 2020). After the Centre for Disease and Control (CDC) investigated an infected sample, WHO categorised it as new coronavirus in the year 2020, and later termed it as COVID-19. The WHO classified this epidemic as the fifth pandemic in the previous ten years. In addition to pneumonia, infected individuals have shown signs of severe acute respiratory syndrome, among other significant consequences (Ghosh et al., 2020).

The 2'nd most populous nation, China, has recorded more fatalities due to the CoVID-19 than two previous epidemics of SARS and MERS, the coronavirus has been highly pathogenic and virulent to humans for the past 20 years. This pandemic primarily affected older people or persons with acute medical problems like respiratory disorders, diabetes, and cardiovascular disease (Letko et al., 2020).

PATHOGENESIS

Various environmental and biological factors contribute to immuno-pathogenesis in CoVID-19. The immune system of hostalong with its reaction towards the illness play fundamental role in preventing and treating Corona infections. The disease is extremely debilitating and typically spreads from person to person by aerosol. The spike protein connects via ACE2 receptor on host's cell and viral RNA is thus released when host and SARS-CoV-2 come into contact (Fig. 4) (Letko et al., 2020). Both the innate as well as adaptive immune response can be caused due to SARS-CoV-2. Harmful tissue damage may result from unchecked innate immune responses and inflammation. A typical symptom of individuals with severe COVID-19 is lymphopenia (blood disorder resulting in lack of white blood cells/lymphocytes), which is characterised by significantly decreased levels of CD4+ T cells, CD8+ T cells, B cells, natural killer (NK), monocytes, eosinophils, and basophils (Huang et al., 2020; Qin et al., 2020). An enhanced IgG response and a greater number of antibodies are frequently seen in patients, raising potential of antibody-dependent enhancement (ADE) of SARS-CoV-2 infection (Zheng et al., 2020). Zheng et al., 2020 also stated increased viral entry of antibody and a strong inflammatory response are two characteristics of the immunopathological effects of ADE.

Entry into cell: Spike protein (S) in SARS-CoV-2 is structurally similar to SARS-CoV, is a key viral determinant for host tropism. It is achieved through controlling cell entry by engaging cellular receptors and causing fusion, which leads to infection (Hoffmann et al., 2020). Studies done by Hoffmann et al., 2020 stated that cellular transmembrane protein ACE-2, binds with S protein in order to promotes priming of host protease which is necessary in entry. ACE-2 has shown high affinity towards S protein and this attachment further leads towards proteolytic cleavage, revealing fusion peptide which is carried out by a cellular enzyme known as transmembrane protease serine 2 (TMPRSS-2) (Yan et al., 2020). Biochemical and crystallographic studies resulted in identification of the critical SARS-CoV-2 region responsible for interactions between virus and ACE-2 receptor of humans called S1 c-terminal domain. These investigations showed that SARS-CoV-2 possess stronger affinity towards the ACE-2 receptor than SARS-CoV. The S protein could not be contained by monoclonal antibodies or murine polyclonal antisera contrary to SARS S1/ RBD, revealing variations in antigenicity between SARS-CoV and SARS-CoV-2 (Baig et al., 2020; Cao et al., 2020; Yan et al., 2020). Therefore, for the binding and internalisation of viral S proteins, ACE-2 receptors are crucial. The priming process causes S proteins to undergo conformational change, depends heavily on host cell proteases. A study showed that the cellular serine protease TMPRSS2 inhibitor could prevent the SARS-CoV-2 entry into host cell through ACE-2. As a result, inhibitors of ACE-2 and protease may be employed as possible solution to stop the fast transmission of SARS-CoV-2 (Hoffmann et al., 2020; W. Wang et al., 2020).

Patients with severe COVID-19 showed cytokine storm because of significantly high levels of pro-inflammatory cytokines in their serum such IL-6 and IL-1, as well as IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1, MIP1 (also known as CCL3) and TNF. High concentrations of these cytokines results in shock, tissue damage leading in failure of organs. They also play a role in the severe pulmonary disease that results in significant neutrophil and macrophage infiltration, diffuse alveolar destruction, and thickening of walls of alveoli. In the deceased patients, atrophy in their spleen and mortification of lymph node was evident due to immune system destruction (Cao, 2020; Qin et al., 2020; Zheng et al., 2020).

Lung microvascular and alveolar epithelial cell barrier was damaged during viral infections because of the abnormal levels in pro-

inflammatory factors, leading in vascular leakage, alveolar edoema, and hypoxia. Reactive oxygen species along with the uncontrolled synthesis of chemokines like CCL2, CCL-5, IP-10, and CCL3, as well as factors like IL-6, IL-8, IL-1, and GM-CSF, induce ARDS, which results in lung fibrosis and death of patients (Reghunathan et al., 2005). Additionally, patients with COVID-19 are more likely to develop severe disease if they also have diabetes or hypertension. The anti-inflammatory and anti-apoptotic properties of mesenchymal stem cells (MSCs) can rebuild the cells of pulmonary epithelium and aid in clearing of the alveolar fluid. Development of a viable strong vaccine to produce effective cellular and humoral responses in a population have been raised concerns as age (beyond 50 years) became an important risk factor for this disease (Cao, 2020). Cytokines (IFN-, IL-1, IL-6, IL-12, and TGF) and chemokines (CCL2, CXCL10, CXCL9, and IL-8) serum levels were shown to be higher in SARS-CoV infected individuals with disease than in patients with non-severe SARS (CHIEN et al., 2006). The neurotropism (ability to invade and live in neural tissue) of SARS-CoV-2 had been established by numerous investigations. The brain tissue of COVID-19 patients' autopsy samples have been reported to be hyperemic (increased amount of blood in the vessels of an organ or tissue) and edematous (swelling caused by excess fluid in body tissues), and measurable virus particles were present along with neuronal death (Huang et al., 2020; Machhi et al., 2020). Virion particles reached brain through meningeal endothelial lining due to the ACE-2 receptor of endothelium, where they engage with neuroglia cells' ACE-2 receptors to spread the virus and harm neurons. Similarly, SARS-CoV-2 can infect brain via the olfactory pathway and impair sense of smell (Baig et al., 2020; Machhi et al., 2020).

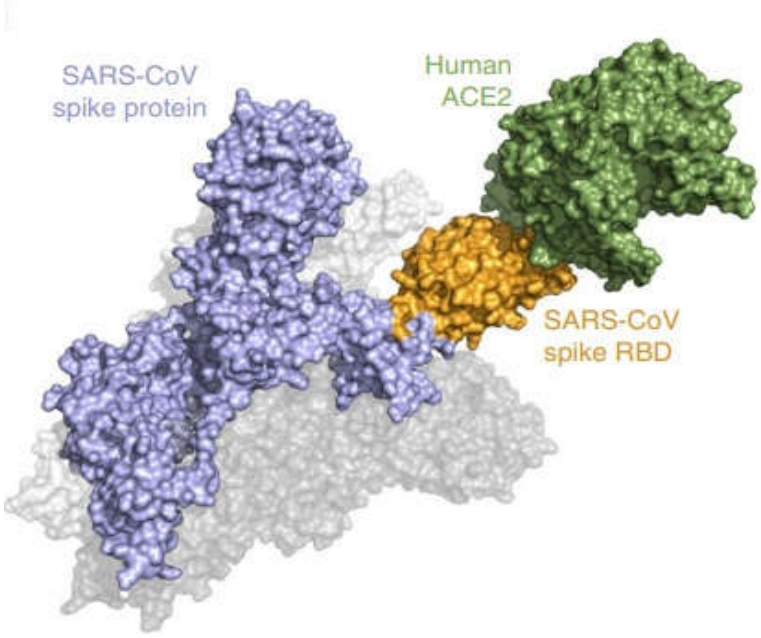

Figure 4: Host-cell receptor interaction through RBD in spike (Letko et al., 2020).

a.) Cytokine Storm

The lethal inflammation due to high levels of cytokines leading to immune-cell hyper activation is known as cytokine storm and is brought on by infections, malignancies, autoimmune diseases, and monogenic disorders (Fajgenbaum & June, 2020). Historically, cytokine storm was described as an influenza-like condition that occur after sepsis and same was seen in other major pandemics, such as Black Death that was resulted by *Yersinia pestis* infection causing alveolar macrophages to release an excessive quantity of cytokines leading to cytokine storms (Pechous et al., 2013).

Small proteins of cytokines like IL-6, IL-8, and TNF-α, as stated by Moore & June, 2020, are released to signal the immune cells of body to combat forigen virus. In order to defend itself against any infection, this reaction is crucial for body. In immunocompetent people, severe pneumonia brought on by pathogenic human coronaviruses (HCoV) is frequently followed by hypercytokinemia, (cytokine storm) which is unchecked overproduction in amounts of inflammatory cytokines causing severe damage to lungs and acute respiratory distress syndrome (ARDS) (Zhang et al., 2020). Acute respiratory distress syndrome (ARDS) according to Rocco et al., 2009 is the most dreadful form of the acute lung injury (ALI) and is defined as fibroproliferation of alveolar capillaries. Acute respiratory distress syndrome (ARDS) is caused by production of excessive cytokines in COVID-19 instances, which significantly boost leukocyte release to several bodily organs, especially the lung cells (Zhang et al., 2020). The neutrophil-to-lymphocyte ratio (NLR), which rises in the blood because of the raised cytokine levels, is the primary indication of cytokine storms (hypercytokinaemia). SARS-CoV-2 can infect dendritic cells, lymphocytes, monocytes, and macrophages, all of which are essential for the formation of cytokine storms (Machhi et al., 2020; Yuki et al., 2020).

Various inflammatory cytokines released theough various cells such as macrophages, dendritic cells, fibroblast, etc. lead to varying immunological response. For instance, IFN-γ leads to fever, dizziness, and fatigue; TNF-α leads to symptoms similar to that of common cold comparable to IFN-γ, nonetheless also exhibiting some vascular outflow, cardiomyopathy and acute-phase protein synthesis. The chemicals released by various cytokines, also known as Cytokine Release Syndrome (CRS), leads to clinical symptoms development. The coagulation cascade, complement activation, and vascular leakage caused by IL-6, an important part of adoptive cell therapy-induced CRS, result in diffuse intravascular coagulation (DIC), one of the hallmark signs of severe CRS. It is important to emphasise that IL-6 is probably responsible for cardiomyopathy which is frequently seen in people with CRS (Hunter & Jones, 2015). In addition, one of the characteristics of severe CRS as stated by D. Wang et al., 2020 also include endothelial cell activation. Hypotension, coagulopathy, and capillary leakage can all be caused by endothelial dysfunction. Fatal pneumonia post HCoV infections is primarily caused by virus-induced immunopathological events (Table. 1).

In essence, a cytokine storm that results from the uncontrolled production of many cytokines appears to cause harm to organs even as the immune system aims in reducing and killing of virus. Such cytokine storms are not a novel occurrence; they can occur in primary or secondary hemophagocytic lymphohistiocytosis, influenza, SARS, MERS, and other viral infections (Machhi et al., 2020).

Table 1: Tabular representation of cytokine and symptoms in SARS-CoV-2 (Sun et al., 2020).

Cells	*Cytokine*	*Clinical Features*
Macrophage	IL-1β IL-6 IL-18	Decreased serum protein. Fever. Severe injury to kidney. Anaemia
Dendritic Cells	TNF-α	Fever. Hematopoietic dysfunction. Intravascular coagulation imapred. Protein levels in serum is decreased.
T Cells	IFN-γ TNF-α IL-6 IL-18	Fever. Intravascular coagulation imapred. Protein levels in serum is decreased. Hyperlipidemia.

		Liver damage.
Fibroblast	IL-6 IL-18	Fever. Severe injury to kidney injury. Anaemia.
Endothelium	IL-18 IL-1β	Acute phase protein. Fever. Acute kidney damage.

b.) Histopathology

SARS-CoV-2 links to ACE2 toll-like motif on pneumocytes, a number of pathogenic events happen at the same time. Immune system of host gets stimulated during virus' genome replication, which causes release of inflammatory cells, the generation of cytokines and chemokines, and the maturation of dendritic cells. Immune system is constantly stimulated as a result of the genomic replication of virus, which leads to an out-of-control reaction that is fatal to host cells (Channappanavar & Perlman, 2017; Matthay et al., 2019).

Histopathologically, SARS-CoV-2 causes diffused alveolar damage (DAD) resulting in ARDS sub-divided into two phases: 1.) exudative phase, 2.) proliferative phase. In exudative phase hyaline membrane is formed by polymerization of fibrin in plasma fluid further seeps into interstitial/alveolar space. The alveolar-capillary barrier is then injured leading to leakage of red blood cell into surrounding spaces causing extravasation. Later the intra-alveolar spaces experience an intense inflammatory cells infiltration. In proliferative phase a rapid increase in the fibroblast and myofibroblast occurs leading to acute fibrinous organizing pneumonia along with extracellular matrix deposition, causing parenchymal remodelling and pulmonary fibrosis along with pneumocytes squamous metaplasia (Fox et al., 2020; Xu et al., 2020).

When SARS-CoV-2 attaches itself to the ACE2 motif on type II pneumocytes, immune system of the host gets triggered. The recruitment of monocytes results in the pro-inflammatory cytokines release leading to pneumocyte apoptosis; recruitment of macrophages results in the release of additional cytokines that increase capillary permeability and prompt the recruitment of neutrophils; the migration of neutrophils to interstitial space causes permanent injury of pneumocytes and endothelial cells and disrupts the capillary barrier of alveoli further resulting in intestinal and alveolar edema (Agrahari et al., 2021; Batah & Fabro, 2021).

TREATMENT AND THERAPEUTICS

Early diagnosis included reporting, isolation, and supportive therapy that were previously recommended as crucial lines of defence against COVID-19 infections. The foremost tool in our arsenal for defence against the COVID-19 pandemic continues to be personal hygiene improvement, wearing masks or facial coverings, getting enough rest, and maintaining well-ventilated rooms. Later social practises also include timely epidemic information release and upholding social norms. To prevent the illness or to treat the viral infection, there were no proven effective vaccinations or medicinal treatments initially. Comorbid infection control strategies and prevention or therapy were used in clinical care. Additionally, mechanical ventilator support or extracorporeal membrane oxygenation were used when necessary (Agrahari et al., 2021; R. Wu et al., 2020). As per Pillaiyar et al., 2020, using soap so as to wash hands reduce the number of microorganisms on hands, which is not achievable with items like hand.

Antibiotics, antiviral therapy, systemic corticosteroids, and anti-inflammatory medications (including anti-arthritis medications) were frequently utilised in the treatment regimens for ARDS, which is then followed by secondary infections.

Neuraminidase inhibitors, RNA synthesis inhibitors, convalescent plasma, and conventional herbal remedies have all been used to treat COVID-19 in addition to antiviral interferers and antibiotics (Lu, 2020).

The therapy of COVID-19 with chloroquine (hydroxy chloroquine/Plaquenil), previously used in malaria and arthritis treatment, was sanctioned as per US Food and Drug Administration (FDA) (Mehra et al., 2020). According to the WHO, two HIV medications in combination, lopinavir and ritonavir, and four additional very potent antiviral substances, including Remdesivir, chloroquine, and hydroxychloroquine, which are used to treat malaria can effectively treat CoVID-19 (W. Wang et al., 2020). The National Medical Products Administration of China sanctioned antiviral, Favilavir (Cai et al., 2020). Yavuz & Ünal, 2020 stated combination therapy using animals and clinical trials including Lopinavir/Ritonavir, Remdesivir, Lopinavir/Ritonavir (licenced HIV treatments) alongside Intergalactic beta-1a, and Chloroquine or Hydroxychloroquine. Favipiravir or Avigan, was used in Japan to combact CoVID-19 initially.

VACCINE

The age-old adage "prevention is better than cure" is particularly true in regards of the continuing CoVID-19 outbreak. Vaccines became one of the most important weapons in the battle against this extremely contagious disease as a result of the virus' rapid spread. Vaccines can aid in preventing infection, hospitalisation, and potentially fatal consequences from COVID-19 by immunising against SARS-CoV-2. By administering a safe version of a pathogen vaccination becomes one of the most efficient ways to contain the virus and its potentially harmful effects, strengthening the immune system and preparing it to recognise and combat the real pathogen in the future. Additionally, vaccinations have been essential in decreasing the virus's transmission and minimising its effects on global healthcare systems, economies, and society. The COVID-19 pandemic can be contained as vaccination initiatives are currently being conducted all across the world.

SARS-CoV-2 binds with the host angiotensin-converting enzyme 2 (ACE2) moiety, same as that of SARS-CoV (Lan et al., 2020). SARS-CoV-2 has undergone continuous and significant development, providing difficulties to combat the public health crisis, and making the availability and dispersal of vaccines a challenging task. (World Health Organisation, 2023a). Vaccines continue to offer strong defence in order to combat the illness due to SARS-CoV-2 variants, even Omicron (World Health Organisation, 2023b)

The Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) was established by the World Health Organization (WHO) on September 2021 to evaluate the effects of forthcoming SARS-CoV-2 variants of concern (VOC) on the efficacy of vaccines of COVID-19 and to recommend composition changes to vaccine's antigen (Organisation, 2023a). 18 specialists make up the autonomous, multidisciplinary TAG-CO-VAC. TAG-CO-VAC functions as advisory board and makes recommendations regarding the need for vaccine composition to ensure that VOC protection is still offered safely. The Technical Advisory Group on SARS-CoV-2 Virus Evolution's recommendation that VOCs be designated by the WHO, which started the advisory group's present decision-making process, (TAG-VE) (Subissi et al., 2022).

Protease inhibitors, monoclonal antibodies, and antiviral drugs are examples of potential therapies that are available in the market (Gillenwater et al., 2020). Symptoms start within a week of infection, phase 2 clinical trial about mixed therapy of interferon-beta-1b, oral lopinavir-ritonavir and oral ribavirin was superior to lopinavir-ritonavir alone in symptoms suppression (Hung et al., 2020). An advanced antiviral medication that was being used for COVID-19 is Remdesivir, as stated by Gillenwater et al., 2020 is a nucleoside analog drug created by Gilead (NCT04292899, NCT04292730, NCT04280705, NCT04315948, NCT04257656).

Types

COVID-19 vaccine ranges from conventional to new-generation vaccines.

Live-attenuated vaccines consist of live pathogens with reduced severity, while inactivated vaccines includes thermally or chemically inactivated form of pathogen. Two types of traditional whole-pathogen vaccines that are used most often. Both have relatively simple development methods that includes a powerful immune response along with long-lasting immunological memory which delivers a mild infection that mimics the genuine disease. The main disadvantage of live-attenuated vaccinations is the safety due to presence of inactivated strains. Compared to recombinant protein-based vaccinations, live-attenuated vaccines frequently have higher reactivity, and their viruses can potentially infect persons with weakened immune systems (Hanley, 2011).

Inactivated vaccines are more often than not a safer option as there are no live microorganisms involved, but their immunogenicity can be lower and they frequently need numerous doses in order to build immunological memory. Recombinant protein vaccines along with vector-based vaccinations are examples of newer vaccines that only include a particular pathogenic antigen or antigens instead of entire pathogen (Table. 2) (Vartak & Sucheck, 2016).

Table 2: Types of Vaccine for SARS-CoV-2 (J. Wang et al., 2020)

Vaccine type	Mechanism	Features
Live-attenuated	Immunological response is strong. Protection is long term. Reactogenicity occurs.	Proper development process already established. Live virus is required.
Inactivated vaccines	Reactogenicity is low. Weak immune response as compared to live-attenuated vaccines. Multiple dosages required.	Proper development process already established. Live virus is required
Recombinant protein based and vector based vaccines	Immune system responds precisely. Immune response provoked is low. Additional adjuvants are needed.	Complex in formation of vehicle as well as epitope selection. Lack of prior mass production.
Trained immunity based Vaccine	Innate immunity strengthens against a spectrum of infections. Vaccine Efficacy and mechanism at initial stages.	Cosmopolitan in distribution. Non-traditional specific adaptive immunity inducing vaccine.

Proper storage is essential for vaccine safety and effectiveness. The proper vaccination will come as ready-to-use dosage exhibiting long shelf life at room temperature. Routinely used vaccines has to be refrigerated from + 2 to + 8°C temperature range (World Health, 2006). Cold chain alone leads up to 80% of total expenses, and in order for shipping, vaccines require temperatures below + 2°C. Liquid vaccines if frozen will put stress on the colloids. Freezing leads to nucleation of water which in turns causes solutes to displace in the water crystals, causing irreversible cluster formation (Niu & Panyam, 2017).

Various CoVID-19 vaccines as per emergency use authorisation. (Table. 3)

Table 3: Vaccines under emergency use authorization (Kumar & Kumar, 2022).

S. No.	Vaccine name	Company	Technology platform
1.	BNT162b2 or Comirnaty	Pfizer-BioNTech, USA	mRNA in lipid nanoparticle.
2.	mRNA-1273	Moderna, USA	mRNA in lipid nanoparticle
3.	Covishield or AZD1222	AstraZeneca and University of Oxford, UK	Chimpanzee adenovirus-based vector containing gene for S-protein (non-replicating)
4.	Covaxin or BBV152	Bharat Biotech, India	Inactivated virus
5.	Ad26.COV2.S	Janssen/Johnson & Johnson, USA	Recombinant non-replicating adenovirus 26 containing DNA for spike protein
6.	Sputnik V	Gamaleya Research Institute, Russia	Recombinant non-replicating adenovirus 26 and adenovirus 5 vector containing DNA for spike protein
7.	CoronaVac	Sinovac, China	Inactivated virus
8.	BBIBP-CorV	Beijing Institute of Biological Products, China	Inactivated virus
9.	Convidicea	CanSino Biologics, China	Recombinant type 5 adenovirus

BNT162b2 (Pfizer/BioNTech), Ad26.COV2.S (Janssen), mRNA-1273 (Moderna), ChAdOx1 nCoV-19 (Oxford/AstraZeneca), and other widely available COVID-19 vaccines are potent to combat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, symptoms of COVID-19, hospitalisation and death (for Immunization, 2021).

As per Di Fusco et al., 2022, the effective CoVID-19 vaccines such as BNT162b2 (Pfizer/BioNTech) (Abu-Raddad et al., 2021), mRNA-1273 (Moderna) (Chemaitelly et al., 2021), Ad26.COV2.S (Janssen) (Polinski et al., 2021), and ChAdOx1 nCoV-19 (Oxford/AstraZeneca) (Whitaker et al., 2022), is under 64% to 90% against SARS-CoV-2 infection, 73% to 84% against symptoms, and 70% to 100% against death. Immunocompromised (IC) populations that were immunised were found to be protected against serious disease under range 63% to 100% against COVID-19. The IC group of people were found to have COVID-19 vaccine efficacy below the rate possessed by general populations and needs more preventative steps to avoid COVID-19 infection and related illness (Di Fusco et al., 2022).

Recombinant, viral vector-based vaccine ChAdOx1 nCoV-19 (AstraZeneca/Covishield) expresses the S protein, which is produced by chimpanzee adenovirus. This modified adenovirus is a comparatively safer technique in order to incorporate the antigenic elements present in SARS-CoV-2, into host cell because the gene that causes virion to assemble is removed hence the transformed adenoviruses are not able to multiply in the host body. This causes S protein to be expressed by host cells, further activating an effective humoral and cell-mediated immune response (Wong et al., 2022). The SARS-CoV-2 virus' spike protein (S) is determined by the nucleoside-modified messenger RNA (mRNA) known as BNT162b2 that is expressed in lipid nanoparticles (LNP). The S antigen expression of the SARS-CoV-2 results from RNA's ability to enter host cells

through the lipid particles. The encoding of S protein is stabilized by using proline Additional protection against COVID-19 is provided by the antibody response to SARS-CoV-2 S antigens (Padda & Parmar, 2021; Wong et al., 2022).

There is still a significant lack of trust in vaccines in the populace leading to vaccine hesitancy. In 23 countries (including India), a study on the hesitancy to administer the COVID-19 vaccine found that 79.1% of people were willing. While hesitancy rose in eight nations, from as low as 1.0% (United Kingdom) upto 21.1% (South Africa). 12.1% of respondents who had received their vaccinations were unsure about booster shots. The majority of parents' were in favour of immunising kids under the age of 18 with only a marginal improvement, while it decreased among those who were personally apprehensive (Lazarus et al., 2023).

Both vaccine efficacy (VE) measured as per clinical trials and also vaccine effectiveness (VE) calculated on field show a degree of risk of disease amongst both, vaccinated and unvaccinated individuals (Dicker et al., 2006). For people with one or more immunodeficiency (IC) conditions, numerous nations throughout the world have put out endorsements for greater vaccine protection; also covering other population groups (such as the elderly) patients with IC who have suppressed immunity brought on by medical diseases, such as active malignancies, advanced/untreated HIV infections, or active immunosuppressive medication use (Sadoff et al., 2021).

COVID VARIANTS

RNA viruses lack the ability of proofreading and hence are always changing and adapting. The structure of a virus has the capacity to alter each time it modifies by replication. "Mutations" includes each of the modifications. A "variant" of a virus includes virus that has undertaken single or multiple mutations. These result in changes to the virus's essential properties, such as those that alter how easily it spreads or how likely it is to cause more serious sickness and even death. SARS-CoV-2 showed an extraordinary versatile evolutionary adaptability since its late 2019 inception, first in the context of unconstrained global dissemination and then with factors such as immune response as a result of vaccine and monoclonal antibodies (mAbs).

Replication-related genetic mistakes (mutations), consist of viral genomic recombinants and selection environmental factors that favour one form over another are the causes of virus evolution, despite every virus group (RNA and DNA) exhibiting specific life cycle leading to its evolution. Since RNA-dependent RNA polymerases is low fidelity and a lacks a proper repair mechanisms such as proofreading and mismatch repair, RNA viruses are well recognised for their flexibility (Dolan et al., 2018). Innate adaptability is a characteristic of viruses that can cross species barriers. When different viral variants are infecting a particular host leading to reproduction within same cell, viral recombinants develop. Polymerase of virus may switch in between the genome of virus leading to dual infection, thus creating a hybrid genome. Recombinants thus produced, if stable, can join the progeny further infecting and reproducing. Viable recombination has been considered as the evolutionary process responsible for the formation of SARS-CoV-2 because a noticeable alteration in virulence, transmissibility, and immune evasion is caused (Simon-Loriere & Holmes, 2011).

Jackson et al., 2021 stated that RNA viruses, particularly coronaviruses, frequently recombine especially when transmission levels are high and many variations coexist. It is hardly unexpected that viral recombinants have been discovered considering the SARS-CoV-2 variations' quick and widespread transmission. The US CDC and WHO, alongside numerous national as well as international public health organisations, kept tabs on variations that could lead to major health repercussions as SARS-CoV-2 recombination came into light. CDC states that a variant becomes as a variant of concern (VOC) if its transmission rate becomes significantly high and it (a) influences illness or prevention; (b) transmission is increased; and/or (c) increase in the frequency of disease (CDC, 2022).

aVarient

The Alpha (B.1.1.7) VOC, discovered in UK on September of 2020 and officially was recognised VOC in December 2020. Extremely high frequency of mutations was observed. It exhibits a total of 13 mutations which are non-synonymous and 4 deletions. Spike contained six alterations and two deletions, forming a hypothesis that infection in host with immunocompromised body led to Alpha evolution (Hill et al., 2022). When compared to D614G by Abu-Raddad et al., 2021, Alpha was found to be about 50% more contagious and to have a higher incidence of unfavourable outcomes like death. However, immune evasion of greater significance was not seen.

The 69/70 deletion is a significant genetic alteration that has been detected independently and repeatedly. It has been hypothesised to help evade N-terminal domain (NTD)-specific antibodies that are crucial for SARS-CoV-2 protection (McCarthy et al., 2021). N501Y mutation in Alpha RBD increases transmission ability by improving binding to ACE2 receptor on host. In addition, because of receptor binding domain (RBD) on S protein is immunodominant, essential for ACE2 receptor binding, and produced as the immunogen in the majority of currently used vaccines, genetic mutation in this region has significant consequences (Starr et al., 2020).

β Varient

The CDC classified Beta (B.1.351), along with Alpha, as a VOC in December 2020 after it was discovered in South Africa in May 2020. In South Africa, beta sparked a significant outbreak of illness very soon (Tegally et al., 2020). Preliminary assessments of the Spike substitutions done by Lin et al., 2021 revealed widespread immune evasion, which was supported by drops in neutralising antibody titers in serum from individuals who had previously been exposed to other CoVID variants and it was found that beta was far more infectious and to produce illness of greater severity compared to ancestral form.

Some have hypothesised that the advantage of Beta in South Africa stemmed from the population's level of immunity at the time of its formation. The nation had recently undergone a significant wave of diseases that resulted in high immunity amongst it population. Immune circumvention capabilities in VOC are not valued in other global societies without such immunity. Moreover, this concept would imply that immunological pressure played a role in the selection and development of Beta (Weisblum et al., 2020). Substitutions in RBD such as—K417N, E484K, and N501Y—have been implicated in Beta's immunological resistance. It has been demonstrated by Wibmer et al., 2021 that the changes E484K and K417N decrease antibody neutralisation whereas N501Y increases binding to ACE2 and increases transmissibility.

γ Varient

Gamma (P.1), discovered in Brazil in the month of November in 2020. January 2021 it was termed as VOC. Just like Beta, it caused localised rise in cases while not exhibiting having a significant global impact. Analysis done by Faria et al., 2021 revealed that it was more contagious and fatal than other versions that were coexisting. Gamma has three amino acid changes in the RBD similar to Beta (K417T instead of K417N, E484K, and N501Y), promoting infectivity and allow humoral immune evasion. Manaus region in Brazil exhibited high SARS-CoV-2 infection further supported these characteristics (Sabino et al., 2021). It appeared to indicate convergent evolution when the RBD mutations of—K417N/T, E484K, and N501Y—appeared in two different VOCs. According to Faria et al., 2021 the emergence and global distribution of extremely diverse VOCs have disproved this notion.

δ Varient

After Alpha, Delta (B.1.617.2) became first variety to transmitglobally, replacing Alpha as the predominant variant in most areas. Delta was first discovered in samples from India in the month of October in year 2020, later classified VOC during May (Fisman & Tuite, 2021). The global rollout of vaccines took place during this time. Contradictory information exists regarding the disease severity of Alpha and Delta. A CDC analysis revealed that severity of Delta did not surpass that of Alpha as determined by hospital

data despite some reports suggesting otherwise (Twohig et al., 2022).

More infections in populations with poor vaccination rates were blamed for the increased hospitalisation rate. Because of its quick global dissemination, Delta's heightened transmissibility was instantly apparent, and numerous studies have conclusively shown Delta to be most contagious VOC (Lechien & Saussez, 2022). Using cycle threshold (Ct) and quantitative reverse transcription polymerase chain reaction (qRT-PCR), a study linked increased transmissibility to higher viral concentrations in the respiratory tract. Laboratory research on Delta viral isolates revealed faster growth kinetics, more released virions, and more cleaved spike than on Alpha, explaining why virus levels are higher (Mlcochova et al., 2021).

Blood test of people that were infected and had been vaccinated people to neutralise genuine or pseudo typed virus further proved Delta to be eluding immune responses by host body. Spike substitutions along with RBD changes in Delta, combined with increased infections on vaccine recipients, gave rise to this theory (Mlcochova et al., 2021). L452R and T478K, two changes found on RBD Spike of delta, along with no increase in ACE2 binding, but they have been demonstrated to confer a fivefold reduction in predisposition to polyclonal antibodies on plasma from vaccine recipients. Moreover, at least ten times as many NTD alterations (G142D, E156G, and del 157/158) inside antigenic supersites decrease the antibody binding of NTD-specific mAbs (McCallum et al., 2021).

Omicron

In May 2022, Omicron (B.1.1.529) became the latest VOC to be discovered. Earliest samples discovered in November of 2021, later that month it was formally labelled a VOC. Omicron has an astonishing array of Spike mutations (>30), along with substitutions found earlier onother variants (Figure 5). Moreover, there are 69/70 deletion, which has been detected in several earlier variants including Alpha (Martin et al., 2022).

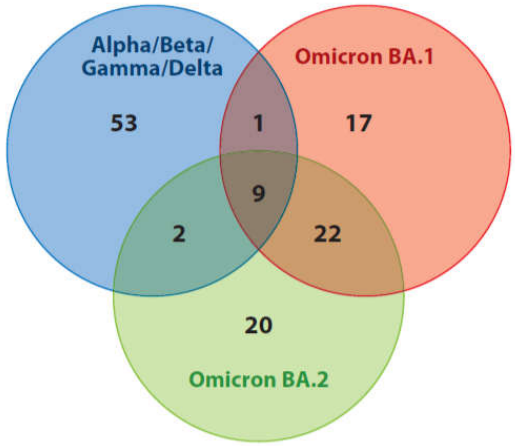

Figure 5: Substitutions in variants of concern alongside original SARS-CoV-2 (Jacobs et al., 2023).

Omicron also has the N501Y alteration, which increases infectivity, alongside E484A (instead of K), and K417N, three modifications that decreased sensitivity to antibodies on other variants. The changes localised around host cell receptor activation area are expected to work together to increase viral contagivity (Martin et al., 2022). Hui et al., 2022 stated increased transmissibility in omicron is probably a result of confluence of larger virus concentrations in the upper respiratory tract.

People suffering from this variant showed a lesser degree of severity in terms of infection and epidemiological analyses revealed an increased transmittance than earlier variants, may be due to lower rate replication (McMahan et al., 2022). Despite the lesser deaths

attributable to Omicron, overall mortality is still large due to high transmittance (Iuliano et al., 2022).

Omicron's sub lineages that are BA.1, BA.2, and BA.3, all appeared about the same period. Whereas BA.1 earlier was the dominant one worldwide, later BA.2 surpassed BA.1 around many continents such as Asia, Europe, and the United States. BA.3 did not cover larger early distances. BA.2 was hypothesize to be more contagious when compared to BA.1 (Yamasoba et al., 2022). Immunity from earlier infections, including those with BA.1, as well as vaccination, were effective against BA.2 (Yu et al., 2022). The three primary hypotheses on how it became a severely mutated variety according to Martin et al., 2022 are (a) transmission remained unnoticed in a solitary population that gradually picked up mutations; and (b) reservoirs of animals were resurfaced..

CONCLUSION

The global lockdown because of pandemic resulted in waning in the level of soil, air, water pollution and fauna migration into the streets worldwide. Since the rapid development of vaccine was need of the hour, still the need of further and detailed study of CoVID-19 is required. In summary, COVID-19 was the result of SARS-CoV-2, exhibiting greater contagious characteristics while in the meantime also reduced levels of virulence than SARS and MERS as per the rates of morbidity and mortality. Bats were thought to be reservoir of CoVID 19 earlier due to presence of BatCoV RaTG13, exhibited 96.2% similarity in its overall genomic structure, leading people to believe that bat CoV alongside human SARS-CoV-2 might have similar ancestral connections, but due to lack of direct evidence of CoVID 19 infection transmission from bats to humans these claims are not widely accepted. ACE2 receptors acts as the binding site of SARS-CoV-2 which infect humans. Most vulnerable section of society comprised the elderly alongside people exhibiting comorbidities. Neonatal were not at the risk of infection due to non-development of ACE2 receptors. Infection leads to hypercytokinemia, also known as a cytokine storm which is unchecked inflammatory response of cytokines leading to acute lung damage along with acute respiratory distress syndrome (ARDS). A "variant" is a virus exhibiting more than one mutation. Certain mutations can result in changes to the virus's essential properties, such as those that alter how easily it spreads or how likely it is to cause more serious sickness and even death. Recombination rate is high when transmission rates are high alongside one or more variation occupies the host. Additional elaborate studies to predict and detect the SARS-CoV-2 variants as well as enactment of trials to limit its dispersal are perilous for international global communal health. COVID-19 can serve as a reagent for change in public health interventions, hastening their implementation and adoption. As a result, new models of healthcare delivery need to be developed, with a greater focus on preventive measures, remote care, and significant technological reliance. The society is way too much dependent on the health care provisions, than preventing disease in the first place. This pandemic has reminded us the importance of public health in dealing with large scale and global issues requires robust and resilient public health infrastructure

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