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SARS CoV-2 VARIANTS – META – ANALYSIS

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A

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In

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By

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DEDICATED TO

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INTRODUCTION

INTRODUCTION

SARS-COV-2, or severe acute respiratory syndrome coronavirus 2, is an acronym. It belongs to the genus, the Coronavirinae subfamily, and the Coronaviridae family. Coronaviruses are spiky, crown-shaped particles with a surface. (1) The 29.9 kb single-stranded RNA genome of SARS-CoV-2 has 14 ORFs that code for four structural and sixteen non-structural proteins. Proteins (nsp 1-16), Examples of structural proteins include the spike protein (S), envelope protein (E), membrane protein (M), and nucleoprotein (N). Through the formation of an RNA synthesis complex in which nsp12 functions as an RNA-dependent RNA polymerase, nonstructural proteins participate in viral RNA replication and gene expression.(2) Contrary to other RNA viruses, coronaviruses include RNA proofreading machinery to fix genetic mutations brought on by the action of the nsp14 3′-5′ exonuclease. (3) However, it is estimated that SARS-CoV-2 experiences 3 10-6 changes per nucleotide during each replication cycle. (4)

RNA viruses come in five distinct varieties. (5-6) A few viral groups in one branch could be connected to or functionally similar to viruses in another branch. Branch 1 is made up of leviviruses and their eukaryotic counterparts, including as mitoviruses, narnaviruses, and ourmiaviruses; Branch 2 is made up of a number of eukaryotic +RNA virus families (e.g., the orders Picornavirales and Nidovirales and the families Caliciviridae, Potyviridae, Astroviridae, and Solemoviridae) The alphavirus and offlavivirus supergroups, nodaviruses, tombusviruses, and several other novel and tiny groups are among the +RNA viruses that may be discovered in branch 3. RNA viruses are found in branch 5, while dsRNA viruses including totiviruses, reoviruses, and cystoviruses are found in branch 4. (5)

Coronaviruses, which belong to the order Nidovirales and family Coronaviridae, are most likely connected to branch 2.

In 2018, the Orthocoronavirinae and Letovirinae subfamilies of the Coronaviridae were established by the International Committee on Virus Taxonomy.

Based on the hosts they attack, coronaviruses are further divided into animal and human coronaviruses. Numerous animal coronaviruses, such as the canine respiratory coronavirus, which causes respiratory illness in dogs, are known to infect pets and cause sickness. Highly pathogenic human coronaviruses can be found in the Coronavirinae subfamily of the Coronaviridae family.

Four genera—Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus—are used to group the viruses that make up this subfamily. Both the betacoronavirus subgroups and the alphacoronavirus subgroups are designated by the letters 2a–2d. At the moment, seven coronaviruses, including the recently identified SARS-CoV-2, infect people.

Human coronavirus (HCoV)-229E, HCoV-NL63, HCoV-OC43, or HCoV-HKU1 all only cause the common cold (7), in contrast to SARS-CoV or Middle East respiratory syndrome coronavirus (MERS-CoV), which both cause a disproportionately high mortality rate and first appeared in 2002 (8) and 2012 (9), respectively. One pandemic is being caused by SARS-CoV-2 in particular. Betacoronavirus subgroups 2b and 2c are home to SARS-CoV, MERS-CoV, and SARS-CoV, respectively. SARS-CoV-2, a newly discovered member of the betacoronavirus family, also lives alongside SARS-CoV and MERS-CoV. MERS-CoV.(11)

The four genera of this viral subfamily are as follows: When compared to other ssRNA viruses, the mutation rates of the coronavirus (CoV) are thought to be moderate to high. (1) The SARS-CoV contains two variable gene loci. The spike (S) protein gene has one of these locations. The second significant point of variation is located in the accessory gene ORF8's open reading frame.

The primary variations between SARS-CoV and MERS-CoV include the SARS-CoV-2-S gene sequence, three brief insertions in the N-terminal domain, and modifications to four of the five critical residues in the receptor binding motif. (11) The genome organisation and gene expression are consistent across all coronavirus genomes. Other ORFs at the 3′ end code for structural proteins such S, envelope (E), membrane (M), and nucleocapsid; ORF1a/b encodes 16 nonstructural proteins (NSPs) (called NSP1-NSP16) (N).

The closest putative bat progenitors of SARS-CoV-2, SARS-CoV and BatCoV-RaTG13 surface proteins, exhibit 76 and 97 percent sequence similarity with SARS-CoV-2, respectively. (12) SARS-antigenic CoV-2's surface is notably different from SARS- CoV's. Subsequently its emergence in late 2019, SARS-CoV-2 has undergone genome-wide changes, and hundreds of viral variants have since spread over the globe.

The third coronavirus to be linked to severe acute respiratory illness in people in the past 20 years is SARS-CoV-2. (13-15)

The most virulent human coronavirus, SARS-CoV, is responsible for a potentially deadly lung condition in people.(16-18)

Most likely, infected civet cats from a wildlife reservoir—most likely bats—transmitted SARS-CoV to people (19-20).

SARS-CoV amply established the capacity of a new coronavirus to penetrate the species barrier and cause major morbidity and mortality in humans in 2003, when it caused about 8,000 illnesses and at least 800 fatalities.

The coronavirus disease 2019 (COVID-19), brought on by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has devastated the whole world, causing havoc on healthcare systems and taking millions of lives. This is in contrast to MERS and SARS, which only affect smaller populations. (21-23) Critical illnesses include conditions including acute respiratory distress syndrome, coagulopathies, septic shock, and numerous organ injuries, such as heart injury(24), kidney injury(25), liver injury(26), and gastrointestinal symptoms. (27)

As of September 22, 2021, COVID-19 has spread quickly to more than 200 nations, with 229373963 confirmed cases, including 4705111 fatalities. WHO reported 537591764 confirmed cases and 6319395 fatalities as of June 20, 2022.

EPIDEMIOLOGY

On December 29, 2019, the city of Wuhan, Hubei Province, China, reported the first four cases of acute respiratory syndrome of unknown aetiology among people connected to a local fish market. ("damp market") (28) More research into the transmissibility, severity, and other characteristics of COVID-19 (29) is being conducted. The majority of the early cases appear

to have had some sort of contact with the original fish market. (30-32) Human-to-human transmission through close contact was quickly identified as a secondary source of infection.

Following that, reports suggested a possible outbreak of a new coronavirus with a reproductive number ranging from 2.24 to 3.58. (33)

Initially, 5 patients (one of whom died) with acute breathing distress syndrome were admitted to the hospital between December 18 and December 29 (34), 2019. On January 2, 2020, 41 patients from the same hospital were diagnosed with COVID-19, with more than half having underlying illnesses such as cardiovascular disease and diabetes. As a result, a nosocomial SARS-CoV-2 contamination at this health centre is suspected. (36) By January 22, the total number of confirmed infections had risen to 571 in 25 Chinese provinces, with 17 deaths.

There was an increase in infected people who had no history of contact with wildlife or visiting Wuhan, and there were several cases of infection among medical professionals. (36-38)

According to a study of the dynamics of early virus transmission, the average age of patients was 59 years, with a range of 15 to 89 years, and the majority (59 percent) were male. People with weakened immune systems, such as the elderly and those with kidney and liver disease, may be the most vulnerable.

SARS-CoV-2 infections have spread rapidly around the world, resulting in a global pandemic. (38) Outside of China, WHO reported 82 new confirmed cases as of January 30, 2020, including Japan, the Republic of Korea, Vietnam, Singapore, Australia, Malaysia, Cambodia, the Philippines, Thailand, Nepal, Sri Lanka, India, and the United States from America, Canada, France, Italy, Finland, Germany, and the United Arab Emirates. Since

then, the number of confirmed COVID-19 cases has increased exponentially, reaching 122,992,844 on March 22, 2021, with 2,711,021 deaths worldwide, distributed among 54,127,466 in America, 42,674,788 in Europe, 14,236.990 in Southeast Asia, 3,006,474 in Africa, and 1,786,689 in the Western Pacific.

RISK FACTORS

Children and young adults are more likely to be resistant than older people, adults, and newborns. Immunocompromised children and adolescents without underlying diseases, such as impaired lung function, appear to be less susceptible to SARS-CoV-2 infection and frequently develop mild disease.

However, an impaired immune system response promotes the spread of SARS-CoV-2 and massive tissue destruction, which may explain the severity of cases in the elderly and infected patients with comorbidities. Increased virus exposure and viral load can both worsen the disease.

A large genome-wide association study included over 1900 patients with severe COVID-19 symptoms (with respiratory failure). They found two genomic regions that were linked to severe COVID-19 disease. The first is located on chromosome 3 (locus 3p21.31) and is made up of six genes. A 50-kb genomic segment passed down from Neanderthals is responsible for the risk. The second is found on chromosome 9 (locus 9q34.2) and corresponds to ABO blood groups (higher risk in blood group A and protective effect in blood group O).

TRANSMISSION

Concerning COVID-19, it was reported that the first patients were linked to the Huanan Seafood Market in Wuhan, China, implying that these early infections were caused by animal-to-human transmission. Later cases, however, have been reported among medical workers and others who have not previously been exposed to this market or visited Wuhan, which has been interpreted as evidence of human-to-human transmission. (28, 39,34-36)

COVID-19 transmission modes were outlined in the guidance as (1) droplet transmission, (2) contact transmission, and (3) aerosol transmission. Droplet transmission has been observed when respiratory droplets (such as those produced when an infected person coughs or sneezes) are ingested or inhaled by people nearby. Contact transmission occurs when a person comes into contact with a virus-infected surface or object and then touches their mouth, nose, or eyes; and aerosol transmission occurs when respiratory droplets mix with air to form aerosols, which cause infection when large doses of aerosols are inhaled into the lungs in a relatively closed environment.

CLINICAL FEATURES

Fever, cough, myalgia or fatigue, pneumonia, and complicated dyspnea are the most commonly reported symptoms, while headache, diarrhoea, coughing up blood, runny nose, and cough with sputum are less common. (42) Patients with mild symptoms reportedly recovered within a week, whereas severe cases experienced progressive respiratory failure due to virus-induced alveolar damage, which can result in death. (43)

VARIANTS OF SARS-CoV-2

The virus's fast rate of mutation has resulted in the formation of multiple coronavirus subtypes. These mutations cause a distinct clinical picture in the patient, and there is also a danger that the vaccination will fail with these variants. The WHO further categorised the coronavirus into Variants of Concern and Variants of Interest based on its severity and pandemic potential.

SARS-CoV-2, like other RNA viruses, undergoes genome change as a result of viral replication. In addition to VOCs, the CDC has created a new categorization for novel variations, which comprises three groups: VOIs, VOCs, and high-consequence variants (VOHC). (43)

The three worldwide VOCs are B.1.1.7 (Alpha), B.1.351 (Beta), and P.1 (Gamma), which first occurred in the United Kingdom, South Africa, and Brazil, in that order. (44-46) The WHO has named B.1.617.2 (Delta), a variety of concern first found in India last year, a variant of global concern, and early research shows that it is spreading faster than prior variants. This fourth type was identified as a worldwide threat on May 10, 2021.

B.1.1.7 VARIANT (Alpha)

The first case was discovered in London and Kent, UK, in mid-September 2020, and as of December 2020, 1,108 instances of infection with this variant have been found in the UK.

The Alpha form became popular in 21 nations on March 16, 2021: the United Kingdom, Ireland, Bulgaria, Slovakia, Israel, Luxembourg, Portugal, Denmark, the Netherlands, Norway, Italy, Belgium, France, Austria, Switzerland, Liechtenstein, Germany, Sweden, Spain, Malta, and Poland. Variant alpha initially appeared in the United States in November 2020, and the number of cases climbed from 76 in 12 states on January 13 to 7,501 in all 50 states on March 23. (47)

B.1.351 VARIANT (Beta)

The beta edition debuted in Nelson Mandela Bay in early October 2020. (a metropolitan area in the Eastern Cape province of South Africa). The new 501Y.V2 variety is also known as the B.1.351 line or the 20H/501Y.V2 Next Strain Clade. It has spread to Botswana, France, Scotland, South Korea, Sweden, Switzerland, and the United Kingdom by December 2020. (48)

P.1 VARIANT (Gamma)

The P.1 line, also known as 20J/501Y.V3, Variant of Concern 202101/02 (VOC-202101/02), or the Brazilian variant, was discovered on January 6, 2021 in patients who arrived in Tokyo after visiting Amazonas, Brazil, by the National Institute of Infectious Diseases (NIID), Japan. It spread across the city of Manaus, causing widespread illness. (49) The gamma variation resulted in greater viral loads and 1.4 to 2.2 times more transmissibility than prior strains, particularly in young individuals.

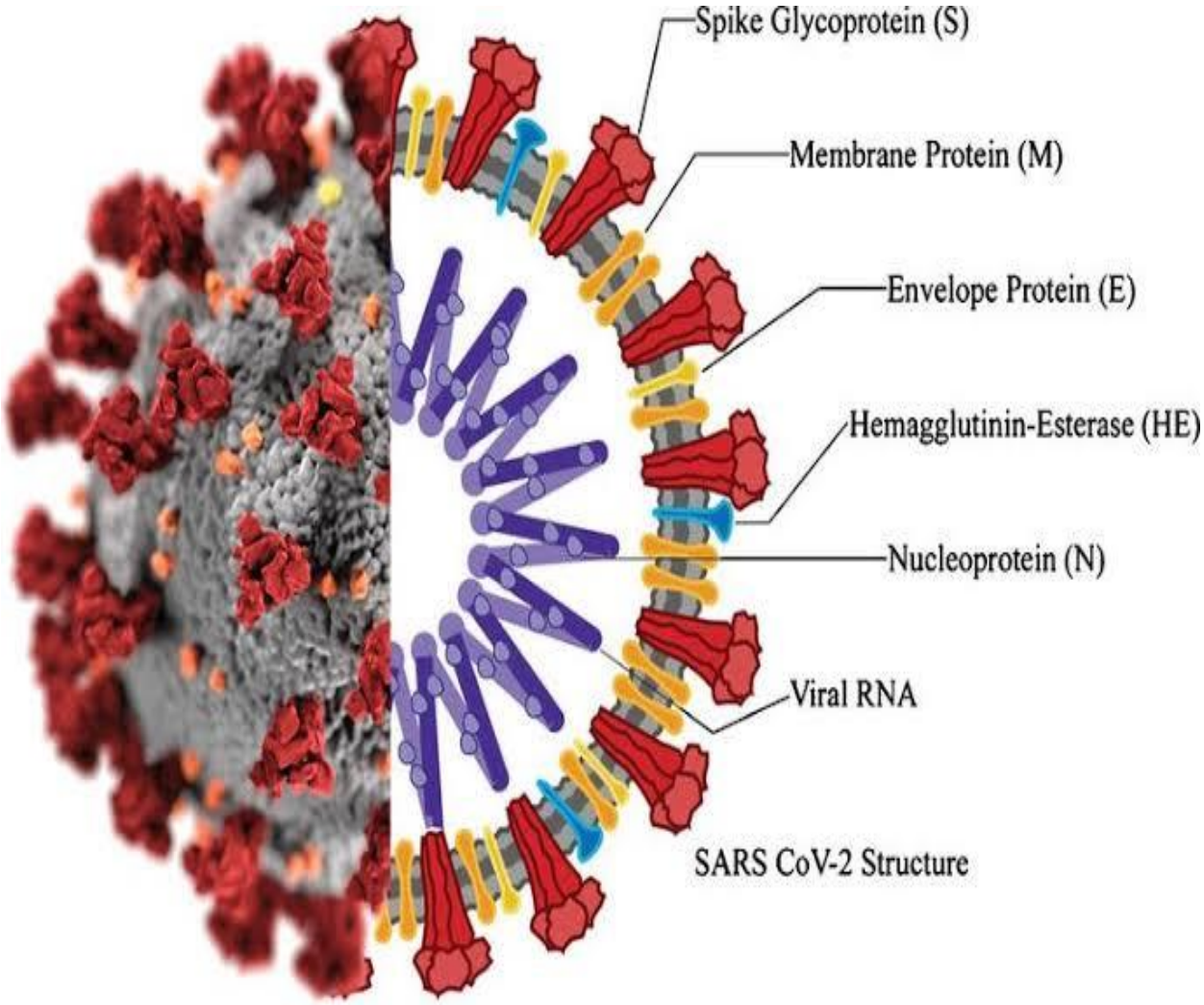
B.1.617.2 VARIANT (Delta)

On May 10, 2021, the WHO designated lineage B.1.617, which was discovered in India, as the fourth worldwide VOC. This line is divided into three sections: B.1.617.1, B.1.617.2, and B.1, 617.3. Along with the core mutation D614G, the delta variation has two distinctive mutations in the spike protein, at positions 452 in the RBD area and 681 in the furin cleavage site between S1 and S2. The Delta variation is an outlier in the B.1.617 line, with no alteration at residue 484. (50-51). The WHO stated on June 1, 2021, that only B.1.617.2, identified as the Delta variation, remained a VOC, while the B.1.617.1 subline was designated as the Kappa variant and categorised as a VOI. b.1, 617.3 were either unlabeled or reclassified. (52)

B.1.1.529 OMICRON VARIANT

On 11 November 2021, the first instance of sequenced omicron was recorded in Botswana, and a few days after, a tourist from South Africa was reported in Hong Kong. (56) Following the first discovery that the novel variation was associated with failure of the S gene target in a particular PCR experiment due to a 69-70 del deletion identical to that seen in the alpha variant, other South African sequences were identified. (53)

Omicron possesses a few deletions and over 30 mutations, some of which overlap with those of alpha, beta, gamma, or delta VoC (e.g., 69-70del, T95I, G142D/143-145del, K417N, T478K, N501Y, N655Y, N679K, and P681H). (54) These deletions and mutations have been shown to enhance viral transmissibility, viral binding affinity, and antibody leakage. (55, 56)



SARS CoV-2 STRUCTURE-

Siavash (2020), Nano-and biosensor for the detection of SARS-C0V-2:challenges and opportunities.,2020,1,3092-3103 http://doi.org/10.1039/D0MA00702A

REVIEW

OF

LITERATURE

REVIEW OF LITERATURE

So far in this century, man has faced a number of epidemics, each of which has had a detrimental influence on a variety of levels, including health, the economy, and even psychology and human behaviour. More preventative methods should be provided in the future to help people and communities in good disaster response and to maintain social stability, physical and mental health. Furthermore, research on the coronavirus and illness outbreaks should be expanded in order to better prepare future reactions, medical treatments, vaccinations, and strategies to reduce human concern.

Many viruses have long been thought to reside in their natural reservoirs. Human actions, such as current farming methods and urbanisation, are primarily to blame for the continuous spread of viruses from natural hosts to people and other animals. As a result, maintaining barriers between natural reservoirs and human civilization while keeping the One Health idea in mind is the most efficient strategy to avoid viral zoonosis.

SARS-CoV most likely evolved in bats by consecutive bat-SARSr-CoV recombination, according to data collected on genetic evolution, receptor binding, and pathophysiology. Before SARS-CoV was imported to Guangdong province from Yunnan via infected civet cats or other sick animals, recombination most likely happened in bats. The imported SARS-CoV underwent fast alterations in S and orf8 and disseminated well in market civet cats. A similar situation might have occurred in the case of MERS-CoV.

MERS-CoV and associated viruses (HKU4 and HKU5) have been detected in several bat species on five continents since its outbreak in 2012.

Although these viruses' ORF1ab and MERS-ORF1ab CoV's are quite similar, their S proteins differ significantly. Unexpectedly, some bat MERS-CoV and -HKU strains can share the same DPP4 receptor as MERS-CoV. According to recent studies, SHC014 was not the target of anti-SARS-CoV efforts, rather WIV1. Additionally, there is limited information on strains linked to HKU3, which have a considerably larger geographic distribution and have truncations in their RBD. Similar to this, MERS-CoV anti-S antibodies could not offer protection against infection with MERSr-CoV, a bat-borne pseudovirus. (57)

The SARS-CoV and SARS-CoV-2 cellular receptors are ACE2 plus CD147 for SARS-CoV-2, and DPP4 for MERS-CoV. (CD26). All evolved a way to avoid detection by the host cell's immune system. SARS-CoV and SARS-CoV-2 impact the RAS system by inhibiting ACE2, causing symptoms to emerge. MERS-CoV induces symptoms in the body by producing inflammatory cytokines and infiltrating T cells. SARS-CoV, MERS-CoV, and SARS-CoV-2 infections all cause comparable symptoms such as fever, cough, myalgia, and shortness of breath. Current SARS treatments mostly involve IFN-, antiviral medicines (e.g., Ribavirin), plasma therapy, host-directed therapies, and systemic corticosteroids.

Drugs targeting protein S, nonstructural proteins (3CLpro, PLpro, helicase, and RdRp), and viral RNA synthesis blockers such as remdesivir and ribavirin are among the options for COVID-19. DNA vaccines, mRNA vaccines, and recombinant vaccinations are being produced at a rapid pace. (58)

Although novel coronaviruses are detected in a high percentage of URTIs and LRTIs, there is no indication that these viruses may cause common colds in healthy individuals. The

discovery of these viruses in persons suffering from the common cold may give the required proof that these viruses are not that unlike to "ancient" viruses. Only HCoV-NL63 has been connected to a specific childhood respiratory disorder, croup, to yet. The claimed association between HCoV-NL63 and Kawasaki illness is still questionable. The relationship between HCoV-KKU1 and febrile seizures is intriguing, but more research is needed. To that purpose, children who do not have febrile seizures should be checked. Only then is the required proof presented that an infection is strongly connected with a clinical symptom. (59)

Viruses change in order to adapt and survive in the environment. Non-spike variants should be studied more broadly due to their function in overcoming innate immunity and boosting SARS-CoV-2 proliferation, as well as their importance to viral survival. Because viral variations can circumvent both naturally acquired and vaccine-induced immunity, the primary objective is to develop next-generation vaccinations that have a substantially neutralising impact against existing and future SARS-CoV-2 variants. There is an urgent need for a proven vaccination approach that is effective against the majority of VOCs. Nasal vaccination should also be considered by researchers since it delivers localised immunity. At the time, this meant remaining vigilant in monitoring all prophylactic steps to restrict SARS-Co-2 transmission (60)

The host's immunological response is undoubtedly a source of selection pressure for the virus to evolve, and the virus is very capable of doing so. Because of its RdRp-independent proofreading activity, the mutation rate of SARS-CoV-2 is rather modest. Despite the faithfulness of its RdRp, the fact that the virus infects at least 330,000 people globally every day gives it a rich field for mutant emergence. A portion of memory B cells resistant to the

original RBD are predicted to react with RBD variations for the time being, however this remains to be seen with the novel Omicron variant. (61)

None of the aforementioned respiratory pathogens have been consistently identified. However, a novel coronavirus was discovered in SARS patients. Vero E6 cells injected with a mouth swab samples showed cytopathologic characteristics. Ultra-structural characteristics of coronaviruses were identified using electron microscopy. Reactivity with group I coronavirus polyclonal antibodies was seen in immunohistochemical and fluorescent staining. We detected several identical nucleotide sequences in 12 individuals at multiple locales using particular diagnostic RT-PCR primers, indicating a point source epidemic. To establish a virus-specific serological response, the novel Isolates were employed in indirect fluorescent antibody tests and enzyme-linked immunosorbent assays. This virus may have never previously infected the US population. (62)

Variations with greater transmissibility infiltrate vulnerable populations quickly, but variants with partial immune escape do not. The latter can occasionally cause a second wave of infection, but only in healed and vaccinated patients with mild disease. Although partial immune escape has a minor impact on the overall scale of the epidemic, variants with a combination of enhanced transmissibility and immune escape not only increase the overall scale of the epidemic, but also increase the number of primary infections in susceptible hosts, which are more likely to result in severe disease or death. As a result, partial immune escape can have catastrophic repercussions, particularly when combined with enhanced transmissibility.

Although the CDC would classify variations with strong evidence of a substantial vaccination epidemic as "high consequence variants," they are not normally assigned a clear danger level. Our findings indicate that mutations with greater transmissibility have a high invasive potential and can greatly worsen an epidemic. Without improved transmissibility, partly immune escape becomes a substantial feature of the epidemic only when population immunity is strong enough to impose effective selection but not strong enough to ensure Control transmission, and when an invasion occurs. The variation is mostly responsible for minor intercurrent infections and re-infections.

The findings are consistent with widespread sweeps of the highly transmissible Alpha and Delta variants, as well as Beta's failure to achieve high frequencies in most locations (showing symptoms of partial immunological escape). The ability to discover risk patterns by modelling different variations in different circumstances shows that this is a good strategy for finding variant phenotypes of special concern. (63)

A coronavirus-positive virus culture was found in the majority of pre-mortem nasopharyngeal aspirates (five out of six) and post-mortem lung tissue samples (two out of seven). In the majority of patients, virus particles consistent with the coronavirus have been found in lung pneumocytes. These characteristics showed that pneumocytes are most likely the primary target of infection. The pathologic characteristics were characterised by widespread alveolar destruction, with multinucleated pneumocytes present. In certain cases, fibrogranulation tissue proliferated in tiny airways and air gaps (bronchiolitis obliterans with pneumonia-like lesions) at subpleural locations. Autopsy allows for tissue sample for virological and ultrastructural analyses, which, when paired with lung morphological abnormalities, is useful

for verifying the diagnosis of SARSCoV, particularly in clinically asymptomatic or suspected but unconfirmed patients. (64)

SARS-CoV-2 infection poses a serious hazard to human health, according to researchers in this field. In this regard, a growing number of clinical treatments and scientific methodologies are being used against SARS-CoV-2, spanning from virtual drug screening to molecular mechanisms, vaccine design to platform development. Computational methods are quite attractive. There is now sufficient research on modifying the antigenicity of SARS-CoV-2 spike proteins as well as amino acid alterations that can impact antibody neutralisation. Spike amino acid alterations and deletions have an effect on the effectiveness of neutralising antibodies in the global virus population. (65)

In terms of hospitalizations, intensive care unit admissions, and death, the alpha, beta, gamma, and delta variants are all more severe than the wild-type virus, with the beta and delta variants being at greater risk than the alpha and Gamma variants. The random effects of the wild-type virus beta variant on hospitalisation rate, serious illness rate, and mortality rate are 2.16 (95 percent CI: 1.19-3.14), 2.23 (IC 95 percent: 1,31-3,15), and y 1.50 (IC 95 percent: 1,26-1.74), respectively, and the random effects of the delta variant for wild-type virus are 2.08 (95 percent CI: 1.77-2.39), 3.35 (IC 95 percent: 2.5-4.2), and 2.33 (95 Although vaccinations have reduced the threat posed by SARS-CoV-2 variations, they remain extremely significant, particularly the beta and delta variants.

Results of research reporting SARS-COV-2 VOC illness severity from June 1, 2020 to October 15, 2021 and processing pertinent data. In comparison to the wild-type virus, beta and delta variants had a greater risk of hospitalisation, intensive care unit admission, and

death, and all are SARS-COV VOCs.2 exposed to a higher risk. The risk of illness severity is higher than with the wild-type virus. (66)

Emerging variants of SARS-CoV-2 alpha (A), beta (B), and delta (D) were evaluated for infection performance in single variant and co-infections to acquire insight into their replication dynamics. Thapsigargin (TG), a new broad-spectrum antiviral agent, was also tested against these variations. The replication rate of variant D was more than 4-fold that of variant A and 9-fold that of variant B at 24 hours post-infection (hpi), based on progeny viral RNA production. Variant D boosted the replication of its co-infected partners at the price of its own initial performance in co-infections. Furthermore, co-infection with either the AD or AB combination resulted in replication synergy, with total progeny (RNA) generation exceeding that of the corresponding single variant infections. Every variation was particularly sensitive to TG inhibition. Priming only once before infection At 72 hpi, the TG dosage successfully stopped all single variant infections as well as all combinations (AB, AD, BD variations) of co-infection by more than 95% (relative to controls). Similarly, TG inhibited any variety of an active pre-existing infection. In conclusion, in the current setting of the dominant D version, which may be exacerbated further by the synergy of co-infection with novel variations, the increasing list of viruses sensitive to TG, a potential host-targeted antiviral, is now a spectrum of Contemporary SARS includes the -CoV-2 virus. (67)

In theory, variations can originate by evolution inside the host in immunological deficient people (quasi-species evolution) or through antigenic evolution under selection pressure in immune competent individuals. Any substantial mutation that changes the structure of the spike has the potential to disrupt the virus's adaptability to the human host, resulting in

vaccination resistance and re-infection. As a result, a vigorous worldwide immunisation campaign is required to prevent the formation of new VOCs.

The antigenic development of the viral spike in human coronavirus 229E, notably in the receptor-binding domain, is to blame for lower neutralisation of 'future' viruses.

SARS-CoV-2 is under intense selection pressure from two sources: immunological responses and therapies. Natural infection and vaccination can both induce an efficient immune response, but novel variations that elude immunisation can lower protection from neutralising antibodies.

Strong selection pressure can inhibit viral reproduction, whereas mild selection pressure allows the virus to multiply easily. The issue is aggravated when weak vaccinations result in inadequate neutralising antibody response or when vaccine doses are separated by a lengthy period of time. Such settings favour the creation of novel SARS-CoV-2 subtypes (68)

D614G, N501Y, L452R, N439K, S477N, HV69-70del, E484K/Q, K417N/T, S477N, Y144Del, LLA242.24Del, P681H/R, ORF3a Mutations, N439K, S477N, L452Q, T76I, del247-252, F490S These mutations modify the biological activity of the VOC and VOI variations, including higher transmissibility, increased risk of hospitalisation and fatality, and stronger immune responses than the wild-type strain. Furthermore, the Delta version may be more easily transmissible and has a greater risk of hospitalisation and fatality than other VOC variants (B.1.1.7, B.1, 351 and variant P.1). (69)

Vaccine-induced memory T and B cells, however, may protect vaccinated people against severe illness against presently circulating variations, including VOC, variants of interest, and monitoring variants, even if neutralising activity declines after immunisation. Additionally, it is anticipated that the vaccine's formulation and delivery techniques would effectively trigger a response from the germinal centre. Neutralizing antibodies and vaccines must be continuously investigated for their efficacy against novel variations in order to stay on top of highly harmful variants. Neutralizing antibody detection and upcoming vaccine design both require constant monitoring of variations.(70)

SARS-CoV and MERS-CoV appear to have bats as a common natural source. Although the clinical characteristics are similar, MERS develops into respiratory failure considerably more quickly than SARS. The fatality rate from MERS is substantially greater and is probably due to older age and concomitant conditions in sporadic instances, despite the projected pandemic potential of MERS-CoV being lower than that of SARS-CoV,144 which is lower. It's also critical to be on the lookout for potential mutations in other groups of SARS-like CoVs that are circulating in bat populations and may endanger human health. (71)

Indian SARS-CoV-2 GISAID sequences from the dates of collection and shipping in January 2021 to the dates in May 2021.

The amount of deposited genomic sequences varied across the eight Indian states with GISAID sequences that were available. The percentage of sequences that were examined for the regional distribution of the distinctive mutations in the spike protein L452R, E484Q, and P681R from western to eastern India is displayed. The western state of Maharashtra had a nucleoprotein substitution prevalence of just 0.18 percent (n=202) compared to the eastern

state of West Bengal's incidence of 42.3 percent (n=357). 20I and 20B were the most common locations for the 203K replacement.

There were 80 percent, 40 percent, 25 percent, and 16 percent N-terminal domain (NTD) mutations of the H69del spike protein in Europe, Oceania, the US, and South America, respectively. Between January and April 2021, it was found in 216 genomic sequences in India at a frequency of 7% (n=216). All twelve clades of the gene had H69del, which was most often present in 20I and showed up in 20A, 20B, 20C, 20D, 19B, and 21A. Y144del/Y145del (n=129), V70del (n=215), A67del (n=5), and I68del (n = 3) were the other notable mutations found in the N-terminal domain (NTD) of the spike protein.

The sequences from India were assigned to the clade 21A or B.1.617.1/B.1.617.2, which is likely the reason for the high transmission, when the phylogenetic categorization and clade assignment were focused on. Twelve more variations were found, and among those, 20H, 20I, and 20J were of concern. On May 11, 2021, B.1.617 was assigned the variation Global Concern and the letters Kappa and Delta to sublines 1 and 2, respectively. Greater portability is linked to both sublineages. The development of antigen detection kits and medication discovery both rely on the tracking of the mutation. (72)

There is now unmistakable proof that the SARS-CoV-2 spike protein's antigenicity is evolving and that amino acid variations impact antibody neutralisation. There is recent proof of variations that display resistance to vaccine-evoked antibody-mediated immunity. Spiking amino acid changes and deletions that impact neutralising antibodies are found with high frequency in the worldwide virus population.

Potential selective pressure put on SARS-CoV-2 progression in immune deficient patients by plasma and mAb therapies given to convalescents. The SARS-CoV-2 spike protein is the primary target of therapeutics (vaccines and antibody-based therapies), so the selection pressure favouring the emergence of new variants carrying immune-escape mutations developed during chronic infections will be similar to that in the Selection for mutations that allow re-infection within the general population.

It is very challenging to predict the mutational routes that a virus like SARS-CoV-2 would follow as it evolves. Nevertheless, the body of information about the effects of SARS-CoV-2 spike mutations on antigenicity and other facets of viral biology is quickly expanding. It may be easier to automatically find low frequency variations of potential concern with the use of this data and fresh SARS-CoV-2 sequences. (73)

The results demonstrate that SARS-CoV is the primary cause of SARS with the aid of Koch's postulate. The most frequent concurrent infection in SARS patients was human metapneumovirus The respiratory system was the primary site of viral infection in experimentally infected macaques, as is probably the case in humans, according to virological analysis of clinical and post-mortem tissues. These macaques did not have SARS-CoV in their urine or faeces, in contrast to SARS patients, despite the faeces testing positive in a prior trial. Since SARS-CoV RNA was found in the faeces of late-convalescent SARS patients, the early cut-off point of the experiment (6 days post-infection), which suggested a spill from other tissues implies, for example, through the blood, may help to explain this discovery. SARS-CoV isolation from a macaque kidney supports viral replication at this location, although immunohistochemistry was unable to support this hypothesis. The lower respiratory

tract's epithelium is most impacted by SARS-CoV infection, which might have negative effects on breathing. (74)

explains how the delta variant spike protein's L452R, T478K, and P681R mutations affect its biological characteristics. The biological characteristics of the Delta variant are impacted by these alterations, including enhanced transmissibility and immunological evasion. Patients with Delta-infected COVID-19 are more likely to be hospitalised and admitted to the ICU than patients with other VOCs (B1.1.17, B.1.351, and P.1) and wild-type strains. The delta form, which may be the most readily transmissible VOC, is starting to take centre stage in the epidemic in many developed nations. (75)

In the previous 20 years, three CoV subspecies have interbred with humans, and the current pandemic is not expected to be the last. Scientists will be able to determine if vaccines and other treatments require regular updating through routine worldwide surveillance of SARS-CoV-2 variations and their effects on virulence and presently used therapeutics. Infection of unvaccinated people by new variations can overcome herd immunity and lead to their death or serious disease, whereas vaccination escape can be made easier by new variants.

The necessity for more fast vaccine distribution and implementation in impoverished places like Africa has been highlighted by evidence supporting the use of merely a single dose of immunisation to avoid severe delta sickness in the UK. Additionally, more research is required to determine the causes of newly emergent illnesses, the potential for weakened immunity to SARS-CoV-2, and the potential preventative value of booster doses.

In nations like South Africa, where the incidence of comorbidities like HIV is high and may have a role in the formation of variations, a multifaceted treatment strategy should be maintained. This will not only prevent unnecessary deaths, but it will also leave little room for the infection to spread. Even while it might not be feasible to forecast what the subsequent VOCs would be, we can still benefit from lessons learned from the past to better handle the current circumstance. (76)

The process of viral evolution is ongoing and has the potential to enhance "viral fitness" and selective adaption. Authorities and researchers from all around the world have faced difficulties as a result of new SARS-CoV-2 mutations. Vaccines presently provide excellent levels of protection against all VOCs, but ongoing evaluation of vaccine efficacy is necessary to battle the main SARS-CoV-2 strains and perhaps new variations.

The main issues are that a VOC may partially or completely evade the immune response, increase re-infection in people already infected with previous strains, vaccine protection is limited, and the effectiveness of plasma or monoclonal nAb-based therapies in convalescents reduced and consequently increased risk of future COVID-19 pandemic waves. In fact, it has been hypothesised that the COVID19 pandemic would last for a very long period, with new mutations and VOCs developing.

There are certain measures for prevention and control that could stop the establishment of new SARS-CoV-2 subtypes.

To prevent future infections, there should be an immediate and widespread COVID-19

immunisation campaign. This argument is supported by the fact that reducing viral transmission makes viral mutations and the emergence of new variations less likely.

Continuous and active worldwide monitoring, detection, and characterisation of circulating and developing VOCs. Rapid identification, isolation, and reaction to novel VOCs are made possible by effective monitoring systems, avoiding their unchecked spread and upcoming pandemic waves. Evaluation of vaccination efficiency and development of VOC-neutralizing antibodies. Periodic vaccine updates or modifications are necessary when immunizations do not completely protect against viral variations, as is the situation with the H1N1 vaccine.

Create plasma stocks using samples from people who have had various COVID-19 infections and vaccinations. The purpose of this step is to quickly assess the activity of nAbs against novel VOCs and the likelihood of immune evasion.

Monitoring for re-infections, particularly in those who have already had a shot or been exposed. This measurement may be a useful method for determining if novel VOCs may be immune evading.

Combination vaccination studies to increase protection and effectiveness. A defence against newly developing VOCs appears to be conferred by high levels of protein S nAb in completely immunised people, therefore monitoring these levels may be useful for protection. (77)

Nine vaccinations obtained emergency or conditional marketing clearance, bringing the total number of SARS-CoV-2 vaccines into clinical testing to 19 within a year. But it is extremely

difficult to stop this outbreak because of SARS-CoV-2 mutations. Questions have been raised concerning the efficacy of the vaccinations currently utilised in mass vaccine introduction due to the B.1.351 and the P.1, which have the potential to cause re-infections and immune evasion. For assessing the capacity to neutralise infectious cDNA clones or wild-type viruses and establishing protective effectiveness in clinical studies, standardisation of test procedures is urgently required and very beneficial.

It describes the main SARS-CoV-2 mutations and their effects on the neutralising activity of serum from patients and vaccines. Given that certain vaccinations continue to offer protection against B.1.351 variations, there is a need to keep distributing SARS-CoV-2 vaccines quickly and widely while closely tracking any changes in their genetic makeup. The development of monovalent or multivalent vaccinations against variations, as well as increasing the number of doses and rotating vaccines to increase immunogenicity, are other response techniques that have been suggested.

Responding to SARS-CoV-2 outbreaks would enhance both the ability to quickly and effectively develop vaccines as well as the strategies and tactics for responding to new infectious diseases. (78)

A radically new picture of the epidemic is emerging. When they become available, we'll be able to tell if vaccinations to successfully stop the spread of the SARS-CoV-2 virus are still a long way off. In the latter scenario, the equal distribution of vaccinations around the world and their accessibility will be the next hot subject. A number of international organisations will be working to promote a more fair distribution in all nations of the globe, which will conflict with the predatory national policy focused at obtaining the first doses of vaccines

accessible to the people of their country. The political importance the COVID-19 vaccine is gaining contrasts sharply with this admirable endeavour. Politicians or the nation that develops the first therapeutic vaccination may take use of this to assert their power to defend their population as well as those of allied nations. As a result, the vaccination may be misused as a gauge of authority. Cynically, it may just be a never-ending predatory race to receive the first doses of the vaccine that, in a short amount of time, could lead to a fair distribution of excess vaccinations to less developed countries. (79)

Based on the year 2020, at that time there was no vaccination on the market. Nine SARS-CoV-2 vaccines obtained approved for emergency use in 2020, and approximately 19 vaccines against the disease began clinical development. The diminished protective impact of the current vaccination programmes and the considerable loss of neutralising power, however, point to a potential immunological escape of these SARS-CoV-2 variants. However, the immunological flight brought on by the mutational dynamics of SARS-CoV-2 variants poses an unforeseen threat to the entire world.

SARS-CoV-2 is evolving into new strains, yet there is some effectiveness of the existing vaccinations against these variant strains. In order to reduce the likelihood of new variant strains arising, it is now advisable to require the use of existing vaccinations to immunise a bigger population. The development of next-generation vaccinations, such as multivalent vaccines or nasal vaccines, as well as increasing the number of doses and rotating vaccines might be other possible approaches to dealing with these mutations. Research on gene mutations should be closely monitored. By adopting the necessary steps as soon as possible, it will assist to swiftly contain the new varieties.(80)

The appearance of novel variations shows that SARS-CoV-2 is changing and adapting to the human population. Increased transmissibility and a certain amount of resistance to antibody-mediated neutralisation are conferred by mutations in the spike protein of SARS-CoV-2 variants. Recurrent attenuating mutations including P323L, L37F, G251V, and Q27stop, which have also been discovered and are thought to lessen disease severity, have also been identified. Asymptomatic, presymptomatic, or undetected cases of SARS-CoV-2 are the main causes of the present epidemic. The emergence of the current endemic, low pathogenic HCoV might have resulted from a similar evolutionary trajectory.

It is important to research mutations thought to diminish immunological recognition, for example, to increase resistance to acquired immunity or vaccination-induced immunity. Further research should be done on additional aspects that might have a big impact on evolution, such B. zoonotic and zooanthroponotic transmission of SARS-CoV-2, cross protection through immunity to endemic HCoVs, and the potential development of new animal reservoirs through zooanthroponosis. SARSCoV-2 and COVID-19 pandemic progression. (81)

The morbidity and mortality risk from COVID-19 is significant for people with haematological malignancies. Patients with chronic lymphocytic leukaemia do not often respond well to vaccinations. Less than 50% of patients show an antibody response, indicating that even after vaccination, they are still at risk of contracting SARS-CoV-2. Immune dysregulation caused by the disease as well as patient- and therapy-related variables are some of the several causes of the chronic lymphocytic leukaemia population's poor response to the COVID-19 vaccine. Hypogammaglobulinemia, advanced age, active

treatment currently being received, and anti-CD20 monoclonal antibodies from earlier therapy are all poor predictors of vaccination response.

People with CLL are especially sensitive to SARS-CoV-2 infection and a subpar response to immunisation due to a confluence of illness, patient, and treatment-related variables. We are experiencing an era of quick learning regarding factors that indicate a poor response to a vaccination as well as fresh methods for overcoming present treatment limits. Vaccines continue to be the mainstay of COVID-19 prophylaxis despite the significant non-response rate in individuals with haematological malignancies. Patients with CLL, regardless of vaccination status, must adhere to stringent preventative measures until herd immunity is developed or the COVID-19 pandemic has passed. (82)

The development of new viruses with a high genetic diversity and unexpected changes in virulence during human infections is the result of recombination events occurring often in CoVs. The likelihood that the next recombinant CoV will develop and start a new epidemic in humans is probably not if, but when, given the variety of CoV strains that are circulating in nature among many animal species that can contact with each other continually. As a result, the following are some crucial topics for further study: I the prevalence of HCoVs that are already present in the animal population; (ii) the similarity of coronavirus recombination in animals; (iii) the possibility that animals could act as mixing vessels for the creation of new recombinant CoVs; and (iv) a surveillance network to track and foresee the potential emergence of a highly virulent recombinant CoV from animals. Furthermore, in order to adequately prepare for the next CoV outbreak, the lessons from the SARS-CoV and MERS-CoV outbreaks must be understood in advance. (83)

This paper provides a comprehensive overview of the state-of-the-art investigation of the COVID-19 epidemic. Numerous investigations on the epidemiology, aetiology, clinical presentation, diagnosis, control, and prevention of the new coronavirus have been published in this early stage. However, research into preventative and control strategies has increasingly grown. In order to lessen the effects of the pandemic, studies in this area are urgently needed. For COVID-19 to be contained or stopped from spreading further, local, regional, and/or national public policies have to swiftly updated to reflect the most recent scientific findings. We urge the academic community to carry out further study to identify legitimate and trustworthy approaches to deal with these kinds of public health catastrophes both immediately and over the long run. (84)

Numerous investigations have now demonstrated that newly emergent SARS-CoV-2 variants have enhanced virulence, transmissibility, and immune evasion. The WT strain and variations that first appeared during the early stages of the pandemic may have created important epidemiological hurdles that these variants may have the ability to overcome, according to strong evidence. Recent population-level changes, including viral dynamics brought on by the selection of adaptive mutations, may make control efforts ineffectual. To curb the spread of the most dangerous varieties, swift and forceful intervention is required.

In order to quickly detect these variations, the use of variant-specific PCR kits is crucial and critically needed. The creation of monoclonal antibodies and vaccines that specifically target the most conserved regions of the spike protein, immunisation of the populace against the dominant variants, the administration of booster doses to those who have received the vaccine, and the priority vaccination of non-exposed and vulnerable groups are additional crucial aspects of necessary actions that must be taken as a matter of priority. (85)

We have discovered structural mutational patterns that set apart dangerous SARS-CoV-2 subtypes. The majority of the distinctive mutations in the of interest variants are arranged in a pattern in the spike protein's galectin-like NTD. The RBD/ACE2 region has a distinct pattern of mutations in variations of interest, which are largely present to avoid neutralising antibodies. Within the trimer of the spike protein, a notable mutational pattern at inter-strand junctions was discovered. Alpha and delta, the most contagious variations of interest, exhibit an additional pattern: mutations at the furin cleavage site. The interesting variations exhibit the same distinctive mutational pattern as the interesting variants. It is anticipated that new mutations in these distinguishing patterns would improve the fitness of SARS-CoV-2 (86)

Since the start of the COVID-19 pandemic, SARS-CoV-2 VOCs have appeared that are more readily transmissible and may be more pathogenic. The SARS-CoV-2 S protein is the principal target of the antibody response in the vaccinations and antibody treatments now being used. The SARS-CoV-2 virus has been under selection pressure to develop, adapt to the human host, and avoid immune responses, principally through changes in the S protein, as a result of widespread infection. A benefit is the quick adoption of monoclonal antibody vaccinations and treatments, which were successful in lowering the severity and mortality risk of SARS-CoV-2 illness.

In this study, the once-distributed SARS-CoV-2 VOCs' S-related immune evasion was examined. We wanted to present an overview of the consequences of cumulative mutations on the overall conformational balance and local structures of S that induce changes in its antibody recognition and receptor binding based on the structures of S VOCs that are currently known. Structure-assisted design of S-centric vaccine boosters and therapeutics to

curb the COVID-19 pandemic is influenced by knowledge of the relationship between structural changes in S and increased viral transmissibility and immune evasion of SARS-CoV-2 VOCs throughout viral evolution. (87)

The COVID-19 catastrophe is a global tragedy that has claimed several lives. Fighting off this illness is a difficult task. The main challenge in managing and containing the pandemic is the emergence of different mutations in the virus' genome, which have resulted in the creation of new viral strains. The spike gene, which enhances affinity for the spike protein and ACE2 receptor, undergoes the most important of these modifications, increasing the prevalence and toxicity of new strains. In addition, medication responses to individuals with various strains of SARS-CoV-2 infection have changed as a result of changes in the viral genome. Vaccination, on the other hand, has been proven to considerably lower acute sickness and death. The efficacy of different vaccinations has been altered, nevertheless, by the emergence of new strains. (88)

As a consequence of natural selection leading to mutations within the lengthy RNA sequence (30,000 nucleotides) of coronaviruses, SARS-CoV-2 variants have emerged, which is not an unexpected virological finding. Despite viral proofreading exonuclease, the population contains a number of variations, but only those that have an advantage in viral replication and dissemination are able to survive. Because the viral genome contains genes that encode antagonists of host defence systems, such as B. inhibiting the activity of interferon and other immune stimulatory molecules, the high prevalence of infection rates in humans is made worse. In an effort to block the host's reaction, the virus mutates itself.

It has been demonstrated that present and upcoming vaccinations can manage variation control and potential viral eradication. In this context, the findings from Israel about the high efficiency of Pfizer's vaccine against SARS-CoV-2 infection, in a nation where the British variety is widely prevalent, are encouraging. We won't be able to completely stop SARS-CoV-2 infections until we have a thorough grasp of viral biology, structure, and development of vaccines. (89)

SARS-CoV2 has astonished several evolutionary virologists during the present epidemic because of its capacity to produce variants that have quickly accumulated 10 to 20 additional mutations, encoding novel phenotypes that result in greater transmission, immune evasion, or higher toxicity. Currently, these variations are mostly vulnerable to the immunity provided by viral infection with the parental strains and available vaccinations. Even while certain genotypes show some protective antibody leakage brought on by a genuine infection, T cell responses are still present. Immune escape mutations will still happen, although vaccination-induced immunity now offers significant benefits in defending against variations. Nevertheless, it appears certain that SARS-CoV-2 will continue to adapt to human transmission and immune evasion. A crucial and urgent public health goal continues to be the quick global availability of vaccinations that have been proven to be both safe and efficacious. (90)

SARS-CoV-2 variations vary in terms of illness severity, humoral immune resistance, and the potential to spread. Due to immune evasion and probable larger viral concentrations brought on by antagonistic innate immunity, the alpha and delta variants are each linked to enhanced transmissibility and disease severity. Because they may bypass humoral immunity and spread infection again, beta and gamma variations are linked to greater transmissibility. Neutralizing

mAb levels produced by mRNA vaccinations have been high and will probably continue to be higher than those required to defend against even the most resistant circulating variations for many months to come. The results of epidemiological research show a correlation between neutralising antibody titers against prevariant and variant SARS-CoV-2 isolates and resistance to infection. It is unclear whether this results from the fact that neutralising antibodies are the main method of viral defence or from the correlation between these titers and other components of protective immunity, such as memory B cells, antibody-mediated effector functions, and T cell immunity.

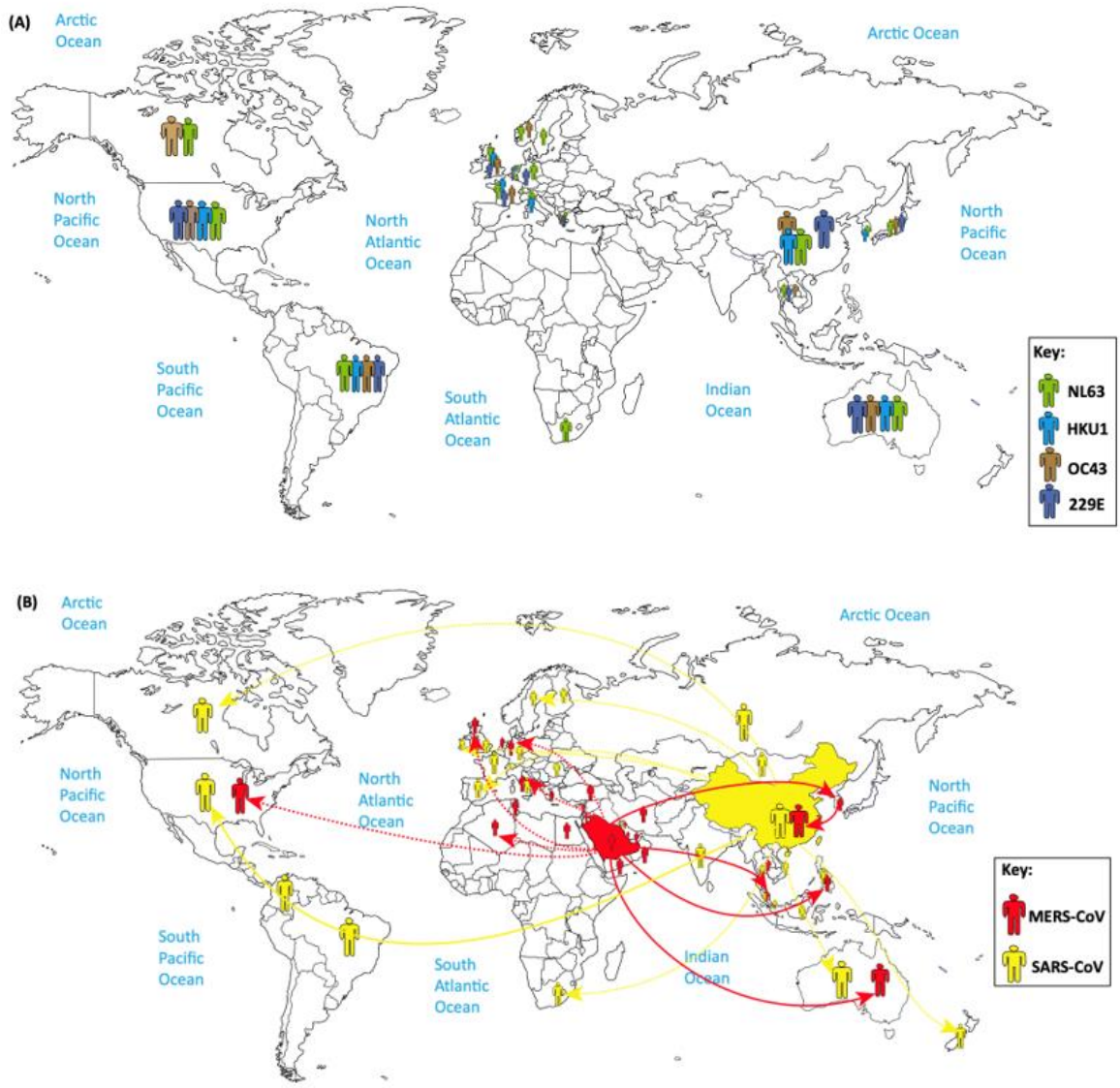
According to a recent study, when given to previously immunised mice, an mRNA vaccine (mRNA1273.351; Moderma) containing the majority of the spike mutations found in the beta variant boosted the titers of beta-variant and pre-variant-specific neutralising antibodies. mRNA-1273 vaccination. Furthermore, it is crucial that as many cytotoxic and helper T cell epitopes as possible be incorporated in upcoming vaccine formulations because it has been shown that the spike protein contains several of both. (91)

Emerging VOCs may have an effect on clinical outcomes and overall health, which highlights the necessity for a genome-specific treatment strategy in the future. Therefore, we suggest that a combined approach focusing on several viral cycle components and the host immune response may be essential but underutilised in the battle against SARS-CoV-2 VOCs. (92)

Millions of people have died as a result of the communicable SARS-CoV-2 (COVID-19) virus globally. It is the root of a pandemic that affects the entire world, and its mutations lead to genetic variations that are still poorly understood. In order to determine how novel

variations may affect transmission rate, resilience, and mortality, it is also essential to comprehend them.

These variations' propensity to disseminate effectively is what has led to the current increase in COVID-19 cases. They are more resistant and have a better affinity for binding receptor proteins than the initial strain due to their pathological makeup. However, further investigation is required to completely comprehend these variations and improve the accuracy of life-saving interventions. To have the best chance of preventing the illness, the public should think about being vaccinated with laws requiring people to wash their hands often, wear face masks, and use social isolation. (93)



Human Coronaviruses' Global Distribution

A) The colours green, blue, brown, and purple represent the global distribution of the human coronaviruses NL63, HKU1, OC43, and 229E, respectively.

B) The global distributions of MERS-CoV and SARS-CoV are represented in red and yellow, respectively.Ref:- https://doi.org/10.1007/s00705-022-05365-2

AIMS

AND

OBJECTIVE

AIMS AND OBJECTIVE

AIMS:-

The aim of this study is to review the spread of current variants of SARS-CoV-2 viruses.

OBJECTIVE:-

To look at the disease profile of different variants of SARS CoV-2 Virus.

To look at the current variants of SARS CoV-2 Virus prevalent in different parts of the world.

MATERIALS AND METHODS

METHODOLOGY

TYPE OF STUDY:- A Meta analysis of corona virus and its variants related articles published in various indexed journals.

DATA TYPE:- Data for this meta analysis will be collected from following sources.

a) Data from various publications in indexed journals.

b) Data from recent editions of textbooks.

c) Data from website of CDC, NCDC, WHO.

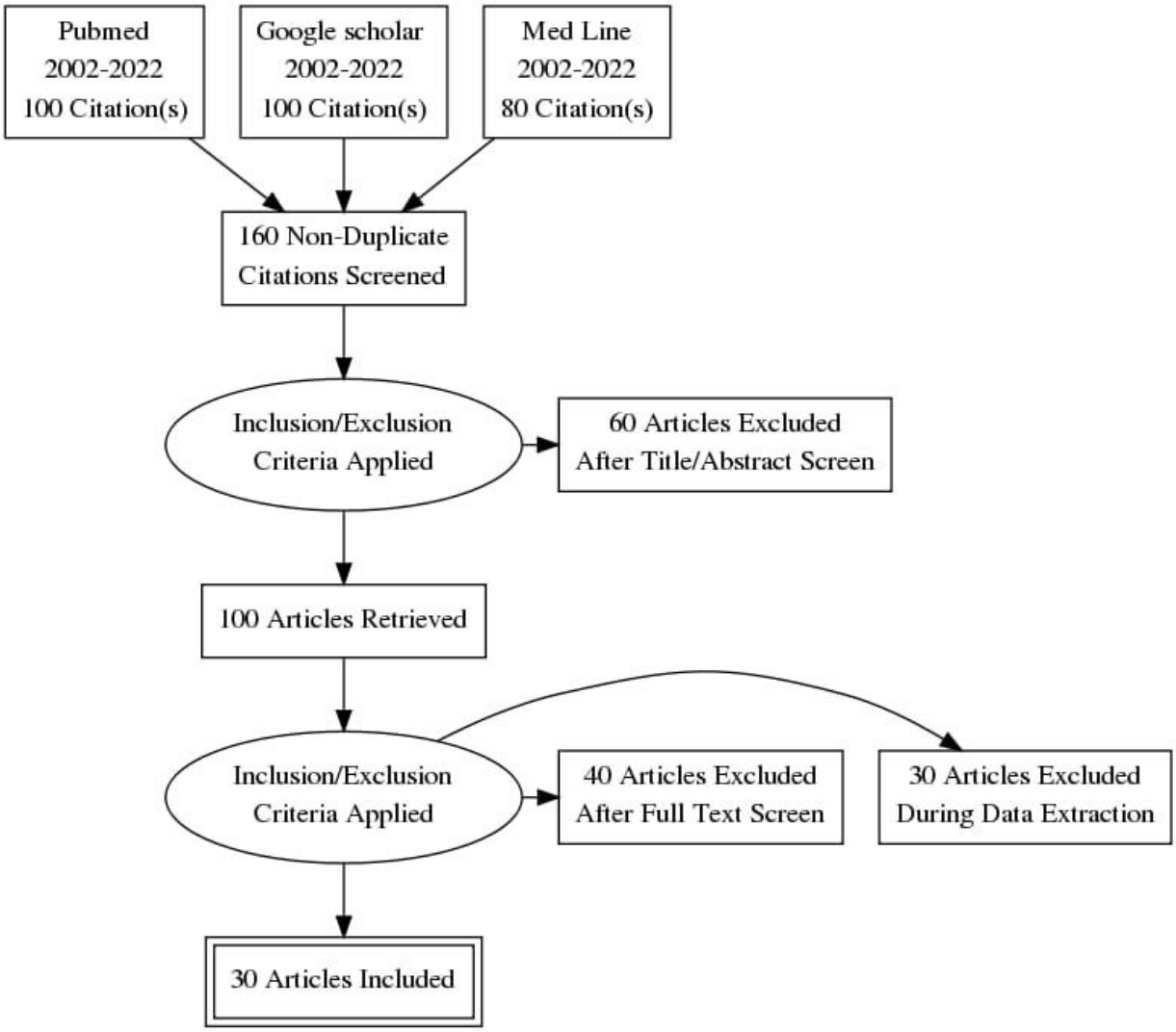
TIME FRAME:- All the studies in the indexed journal from year 2003 to 2022

SEARCH STRATEGY:- This meta-analysis followed the PRISMA guidelines. Articles were searched on Pubmed, Google scholar, Web of Science, Science Direct and scopus sing term related to covid, variants, MERS, pandemic, SARS 2003. Boolean AND, OR, and NOT were used.

INCLUSION CRITERIA:- Article titles and abstracts were screened to include relevant articles. The SARS-CoV-2 Variants, Current status of Corona Virus, Treatment and Prevention of Pandemic, Vaccines of Covid-19.

EXCLUSION CRITERIA:- Article titles and abstracts were screened by researchers independently to exclude irrelevant articles.

STUDY SELECTION PROCESS:- Follow by Prisma, at first stage of the search, 280 article were found, and after reviewing the titles of the articles, 120 duplicate and overlapping articles were deleted and 160 articles remained. In total, 60 articles were removed due to noncompliance with the criteria, the extract of 30 potentially related articles were reviewed, and 40 articles were excluded due to lack of access to the full text articles. Finally, 30 appropriate papers were selected to enter the meta-analysis stage.



OBSERVATION

AND

RESULTS

RESULTS

	AUTHOR	YEAR	COUNTARY / CITY	STUDY FINDING
01.	Jalen Singh et al.,	2021	Canada	Mutations in the spike protein of SARS-CoV-2 variants shows increased resistance and transmission. P323L, L37F, G251V, and Q27 stop attenuating mutation have also been found Because of attenuating mutation SARS-CoV became less harmful.
02.	Jie Cui et al.,	2919	China, USA	WIV1 susceptible to anti-SARS CoV measures; SHC014 not susceptible. Strains linked to HKU3 have RBD truncations and have larger worldwide distribution. MERS, CoV anti-S antibodies showed ineffective for preventing infection by a pseudovirus carrying the bat MERSr-CoV S.
03.	Shuo Su et al.,	2016	China, USA	SARSCoV recombined with alpha- and gamma CoV lineages. Nucleotides 13 392-13 610, 15 259-15 342, and 15 974-16 108 at these positions, smaller recombinant and distinct breakpoint of RNA dependent and RNA polymerase have seen. It is based on the sequence of the SARS CoV-TOR2 strain.
04.	Bin Chen et al.,	2020	China	SARS-CoV-2 may spread more rapidly in comparison to other known viruses. The reason is human ACE2 protein's affinity which is 10 to 20 times stronger for the new coronavirus' RBD than it is for the SARS virus.
O5.	Lia van der Hoek et al.,	2007	Netherlands	Pharmaceuticals that target protein S, nonstructural proteins (3CLpro, PLpro, Helicase, and RdRp), and agents that prevent viral RNA production are the key COVID-19 options. One specific respiratory condition in infants, croup, has only been associated with HCoV-NL63.

06.	Sandro M. Hirabara et al.,	2022	Canada	The significant VOC-related concerns were addressed: Aspects of VOCs that have S gene mutations include: a) characteristics; b) potential evasion of neutralising antibodies produced by immunotherapies, vaccination or infection c) chances of new pandemic in the world; and d) Hope for research in future and some actions to stop new COVID-19.
07.	William T. Harvey et al.,	2021	UK	Mutations in the spike protein of SARS-CoV-2 has been reviewed. The main antigen, and discuss them in relation to reported mutation frequencies in large-scale sequencing data sets. The study basically focused on changes affect antigenicity and place them within the context of protein structure.
08.	Thomas G.Ksiazek et al.,	2003	England	Coronavirus was found in those patients who fits in the description of SARS case. Vero E6 cells showed cytopathologic characteristics after being injected with a mouth swab sample. The sequence obtained using consensus coronavirus primers used in reverse transcription polymerase chain reaction (RT-PCR) to amplify a fragment of the polymerase gene distinctly identifies the isolate as a single coronavirus that is only distantly related to previously sequenced coronaviruses.
09.	David S. Hui, MD et al.,	2016	Hong kong, China	SARS-CoV and MERS-CoV appear to have bats as a common natural source. The clinical characteristics are similar, In comparison to SARS, MERS develops rapidely into respiratory failure. It is connected to old age and have high fatality rate, despite the projected pandemic potential of MERS-CoV being lower than that of SARS-CoV.
10.	Thijs Kuiken et al.,	2003	Hong Kong	In SARS case criteria 436 people fits in which 329 (73%) person had SARS-CoV; metapneumovirus case was 41 (12%). Limited case of respiratory illness. The macaques which are infected, excrete the virus from different parts like mouth & nose after 2 days of infection. In compare to report of SARS patients out of 4, 3 macaques have alveolar enjury, which is characterised as pneumocyte hyperplasia, epithelial necrosis etc.

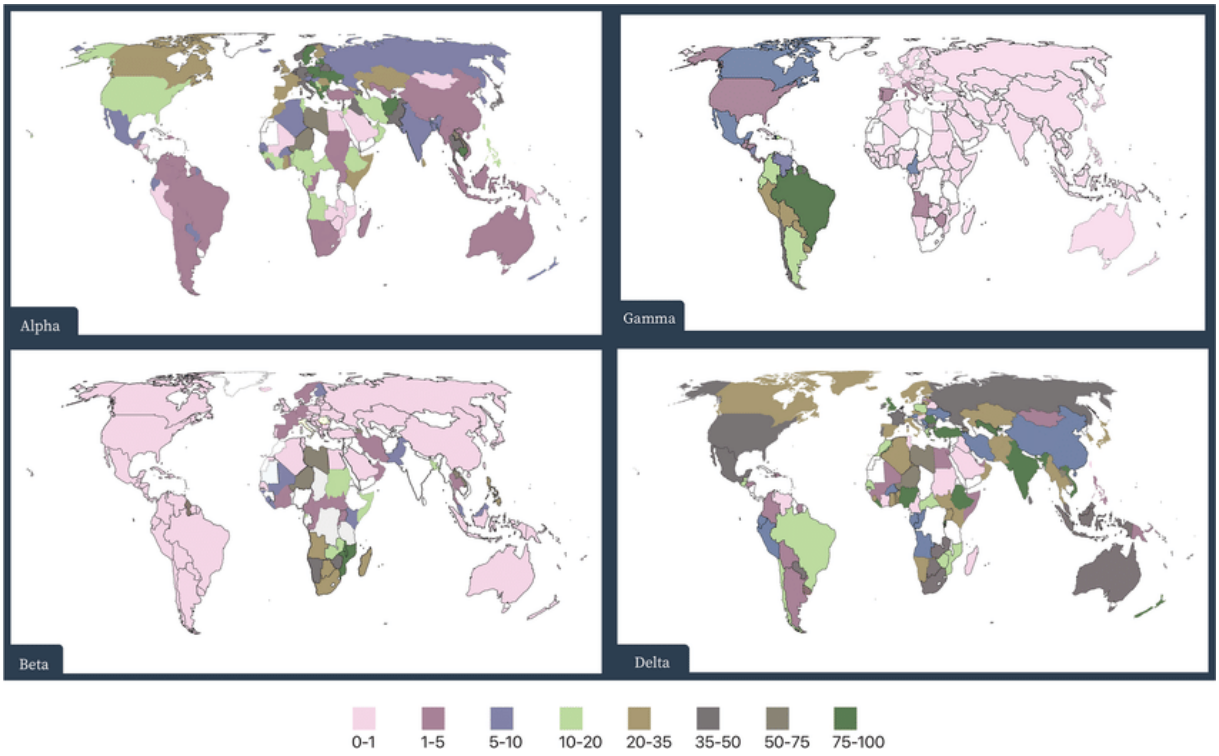
11.	J Clin Pathol et al.,	2003	China	2 out of 7 culture is positive of coronavirus, sample is from lung tissue of post-mortem and nasopharyngeal aspirate of pre-mortem which has 5 out of 6 samples. Coronavirus virus like particles found in pneumocytes of lungs in most of the patients. In pathologic characteristic alveolar distruction and multinucleaded pneumocytes were seen.
12.	Priyal Mistry et al.,	2022	Italy	Vaccination and treatments needs some update by the researcher if possible. Often by routine global surveillance of SARS-CoV-2 variations and their effects on virulence and existing medicines. Variations have the capacity to undermine herd immunity. Those who not get vaccinated, got infect and phase some life threatening conditions.
13.	Desh Deepak Singh et al.,	2001	India	The antigenicity of the SARS-CoV-2 spike protein and the impact of amino acid changes on antibody neutralisation have been sufficiently studied. The efficiency of neutralising antibodies within the world's viral population is impacted by spike amino acid deletions and substitutions. SARS-CoV-2, however, is mostly unknown to us. There is no proven course of therapy, and anti-SARSCoV-2 strategies have achieved their ultimate form. Infection prevention and pandemic crisis management require further clinical research.
14.	Kensaku Murano et al.,	2021	Japan	To stop the epidemic, the production and distribution of vaccines have increased. New variants impacted on efficiency of vaccines and the way the CoV-2 is treated with neutralising antibodies. Currently circulating VOCs is not able to cause any sever illness because of vaccination. There vaccine-induced memory T and B cell may protect them.

15.	Vivek P. Chavda et al.,	2022	India	In general, non-spike variants need to be on focus study because it helps in overcome innate immunity. Variants have capability to avoid naturally acquired and vaccine-induced immunity. The primary goal is to develop a next-generation vaccine which provide neutralising response against current SARS-CoV variants.
16.	Sarah Al-Beltagi et al.,	2021	UK	Replication synergy occurred when AB & AB variants were co-infected. Sum of infection with the separate variation generated by increasing the total quantity of progeny(RNA). Each variation to TG inhibition shows quite high sensitivity. More than 95% shows those who get priming dose of TG get prevented from all the single variants infections and combinations like (AB, AD, BD) of co-infection under 72 hours. The TG inhibit the pre-existing infection very effectively. Because of that modern SARS spectrum added in the list of viruses sensitive to TG.
17.	Lixin Lin et al.,	2021	China	In alpha and gamma variants the beta and delta variants of SARS-CoV-2 causes more chances of ICU unit admission and hospitalization and even death. It is higher in comparision to other wild type virus.
18.	Rama Adiga et al.,	2021	India	In India 21A, B.1.617 or Delta is the most prevalent lineage, which have 67.7% of the genome. 22.5%, 10.9% and 12.2% these are the 3 main clade it is collected from Jan 2021 and April 2021. It is for 20A, 20B and 20I respectively. The remaining sequence is 20H, 20J, 20D, 20C, 20G, 20E, 19A, and 19B. The highest mutations frequency in Maharastra, India L452R, E484Q, and P681R were 61.5 percent, 65.6 percent, and 62.4 percent, respectively. Deletion of spike protein's N-terminal domaine were discovered in 2 district.

19.	Dandan Tian et al.,	2001	China	The biological properties of the delta variant spike protein L452R, T478K, and P681R mutations are discussed in this article. Compared to patients infected with other VOCs (B1.1.17, B.1.351, and P.1) and wild-type strains, patients with Delta-infected COVID-19 have a greater risk of hospitalisation and ICU admission. The delta variation, which may be the most contagious VOC, is quickly becoming the predominant pandemic form in many nations throughout the world.
20.	Mary Bushman, et al.,	2021	USA	The dynamics of SARS-CoV-2 wild-type and mutant strains are simulated in the setting of vaccine administration and non-pharmaceutical treatments using a mathematical model. Variants with partial immune escape may not spread widely which results re-infection commonly worsen the severity of the epidemic. The effects of vaccination decreases and epidemic increases when both traits come together, a variants can spread even as population immunity increases.
21.	Dandan Tian et al.,	2021	China	Multiple amino acid mutations, such as D614G, N501Y, L452R, N439K, S477N, HV69-70del, E484K/Q, K417N/T, S477N, Y144Del, LLA242-244Del, P681H/R, and ORF3a - Mutations, have different properties in RBDs, NTDs, furin protease cleavage sites. There is lots of mutational changes occurs like biological behaviour, hospitalization risk and fatality etc. in VOC & VOI.
22.	Haolin Liu et al.,	2022	United States	The proofreading activity of SARS-CoV-2 is independent of RdRp, which contributes to its relatively low mutation rate. Everyday new viral infection occurs at global level which is about 330,000 infections, which provide favourable condition for mutations. If this has to be seen in relation to the novel Omicron mutation a fraction of memory B cells against ancestral RBD are still expected to respond with RBD variations

23.	M. WAHID et al.,	2021	Saudi Arabia	Research on genetic alterations should be closely monitored. With established techniques every country should routinely sequence the genomes of circulating SARS-CoV-2 strains. The appropriate procedures should be put into action as soon as possible to help control the new kinds quickly.
24.	Mostafa Salehi-Vaziri et al.,	2022	Austria	Vaccine accessibility, affordability, and availability should be major priorities everywhere. The countries who had less resources they have to wait until 2023 or 24 to get vaccinated because of the high income nations who ordered 9 doses of vaccines for every citizens. Population get categorised in immunized and unimmunized due to uneven distribution of vaccination. The escape variants will spread all over the world and re-infect vaccines recipient in wealthy nations.
25.	Marta Morawska et al.,	2021	Poland	The patients with hematolgical malignancies have high risk of morbidity and death from corona. The immunization response is low in people with chronic lymphocytic leukemia. Some of the people still shows the risk of infection after receiving the vaccines. Some individuals with chronic lymphocytic leukaemia do not react after receiving booster doses and receiving heterologous vaccination to improve humoral and cellular immunity.
26.	Guido Forni et al.,	2021	Italy	The certain vaccines will prove to be more effective for particular populations of people because of various technical and conceptual framework is used. Because of the short development period and the novelty of the technology utilised the vaccines have a number of unresolved issues that can only be resolved over time.

27.	Lianlian Bian et al.,	2021	Beijing	For emergency use 9 vaccines have been approved. Making 19 SARS-CoV-2 vaccines based on parental strains already in clinical development. Some of recently developed variations have impact on protective effect. AstraZeneca, Novartis etc are no longer effective for B.1.351. The vaccination-based SARS-CoV-2 pandemic prevention and control plan face a serious challenge due to spread of variants.
28.	Lukman Prayitno et al.,	2020	Indonesia	Six antivirals have been employed to treat virus related disease. All 6 antivirus programmes can be helpful because none of the special antivirus discovered due to pandemic. On patient's severity many antiviral regimens are depended. Necessary supporting drugs are prompted by the severity difference.
29.	Zhen Cui et al.,	2022	Beijing	The breach of the reported epidemiological barriers may have been caused by the predicted modifications in the virus-host interactions given by mutations in the RBD sequence. Host-cell expressions of ACE2 and other proteases influence susceptibility to SARS-CoV2 infection as well as the course of the disease. The increasing data shows that the variants have decreased neutralisation by both naturally occurring and vaccine-induced antibodies. It suggesting that recurrent chronic illnesses resistant to vaccines might become major health issues in the upcoming pandemic
30.	Veronica Roxana et al.,	2022	Switzerland	The S1 domain of the spike protein has been altered in the majority of the new viral variations, which increases the spike protein's interaction with ACE2 and, as a result, decreases the potency of neutralising antibodies.



- The global prevalence of the VOCs- ALPHA, BETA, GAMMA, and DELTA.
- The colours indicate % of prevalence as shown in picture.
- Ref- https://doi.org/10.1007/s00705-022-05365-2

DISCUSSION

Covid-19 pandemic has spread all over the world which covers from health crises to economics crises. It affects every individual all over the world but some of the people and group are more severely affected. The virus has both rapid spread and chronic imbalances. This virus impacted immediately and over time.

So many variants are appeared since the SARS-CoV-2 outbreak happened. These viral aspects seems to be more accurate in their sign and symptoms of the illness which they produce. So many research studies showed that the alpha variants had a high risk of mortality and morbidity in comparison to other wild type virus. It increases the risk of ICU admission, hospitalization and in worse condition death occurs.

It affects more than 9000 people in more than 30 countries with 9.3% of fatality rate. This is the tough illness, it is a infectious disease which is dominated by SARS. The result of the disease is pulmonary fibrosis underlying lung damage.

It is proved that that the 2^{nd} wave of SARS-CoV-2 lineage is more severe than the initial waves. The study about the virus increased our understanding about how much harm will caused by the different variants.

For the confirmation of the connection between the virus and SARS, the coronavirus get isolated from the respiratory secretion of SARS patients and also for the future viral or serological symptoms in additions to SARS patients.

The illness that affects human and domestic animal which includes lower respiratory, upper respiratory and gastroenteritis illness are recognised coronavirus which are linked.

In order to improve the pathogens for detection of coronavirus traditional tissue lifestyle isolation was used. After analysis of SARS pandemic we can use positive modelling to predict the epidemiological and laboratory response for upcoming pandemic or infectious disease. The rapid identification of coronavirus which is related to SARS has allowed fot timely development of diagnosis assays. To understand how these viruses spread and how to prevent it the testing and studies will help and make easier to understand. If we detect the new coronavirus early, then it will also made possible to quickly perform antiviral chemical research and start development of vaccine.

It is now necessary to keep close look at the development and mutations of any variants which are circulating, because if don't then it might be jeopardise human health as well.

CONCLUSION

There are several different coronaviruses, most of which are spread by animals. In total of 7 viruses which infect people 4 of them are responsible for cold symptoms. In last 2 decades coronavirus has crossed the animal-to-human barrier which causes severe illness.

The deadly respiratory illness is spread from the live market in China and then quickly spread all over the world as well as in China. In December 2019, it was initial discovery and it announced new coronavirus in Wuhan, China. Tens of thousands of people acquired from infection because it was extremely infectious throughout the China.

The fact is first report of new coronavirus infection are linked to travel from wuhan but 177 countries across the world have already been infected by the virus. To stop the spread of the virus public health officials are using so many methods like social isolation, quarantines and restructions in travels etc. On Jan 30 WHO declared the covid 19 epidemic a pandemic on march 11, 2020.

The vast majority of people have gotten one of the several anti-virus shots that are presently offered. There are presently a relatively small number of ongoing COVID cases worldwide. The recovery rate is much better than it was the prior year since more people were vaccinated and immunised during the epidemic.

After COVID19, there have been calls for the world to be more prepared for the impending epidemic. The COVID-19 has brought into harsh focus the flaws in past initiatives and the need for a more thorough and long-lasting approach to readiness.

The COVID-19 has brought to light the shortcomings of prior initiatives and the demand for a more ambitious and long-term strategy to readiness.

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