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AN OVERVIEW OF THE SARS-COV-2 MUTATIONAL PROFILE IN RELATION TO VARIANT OF CONCERNS (VOC): A NARRATIVE REVIEW

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Abstract: The current review provides an overview of SARS-CoV-2 variants and mutations that are of interest. The SARS-CoV-2 pandemic has affected the whole world at a significant influence on all levels. Variants of concern (VOC) of SARS-CoV-2 are more transmissible, with the potential to increase infection severity and reduce vaccination efficacy. To date, seven varieties of concern (VOCs) have emerged from the evolution of the SARS-CoV-2 virus during the COVID-19 pandemic: Alpha, Beta, Gamma, Delta, Lambda, Omicron and Mu. In relation to VOCs, there is strong agreement that developing a more effective COVID-19 vaccine is the most important way to push the COVID-19 pandemic to endemic phase. The rapid development of vaccine candidates and beginning of vaccination trials is the consequence of an extraordinary scientific effort and worldwide collaboration. Apart from the vaccination as a preventive measure, several antibodies are being tested or developed as treatment options for COVID-19. But it is important to anticipate whether the new emerging VOCs will remain receptive to antibody therapy or vaccines when they emerge. There is a possible expectation that the worldwide immunization campaign and treatment options will put the COVID-19 pandemic to an endemic era. However, still there are questions regarding what kind of long-term effects the virus and its VOCs will have on humans. Pockets of susceptible individuals and waning immunity after infection or vaccination and recovery, changes in the virus through antigenic drift that decreases the protection, and re-entries from zoonotic reservoirs may all contribute to COVID-19 persistence as an endemic virus, possibly with seasonal epidemic peaks.

Keywords: COVID-19; Corona virus; Mutant, Omicron; Pandemic.

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), also known as the pathogen for COVID-19, was first diagnosed in December, 2019, and was responsible for the worldwide coronavirus pandemic [1]. In the beginning of 2021, SARS-CoV-2 was responsible for about 143 million infections and over three million fatalities globally [2]. With time, the genome of the virus becomes more mutated. When it comes to mutation accumulation, there are a number of elements to consider, including the rate of mutation and the influence mutations have on viral dynamics in both individual hosts and the population [3,4]. In comparison with each other, these factors influence the emergence and spread of viral variations and intensity of the pandemic. As with many other RNA viruses, SARS-CoV-2 has evolved into new mutated strains, having a genomic length of 29,891 nucleotides, which is differentiated by the presence of four structural proteins and sixteen nonstructural proteins (NSP) with regulatory activities [5]. Most of RNA viruses except SARS-CoV-2 like other coronaviruses has a proofreading domain that decreases its mutation rate (such as influenza, HIV, and hepatitis C viruses) [6]. There are 1.87 nucleotide changes per site per day (10^6 per cycle) in the SARS-CoV-2 genome, which is nearly five times less than influenza A/10.9 H3N2's 10^6 nucleotide alteration per site each day. There are around 20 genetic mutations every year that arise in SARS-CoV-2 30,000 base-pair (bp) genome [5].

Moderate mutation rates of 9.06×10^7 subs/site/cycle for SARS-CoV and 2.5×10^6 cycle for the mouse hepatitis virus have been observed, both below the predicted range for RNA viruses. Because of its 3'-5' exonuclease (ExoN) activity, this is compatible with NSP 14 playing a role in RNA proofreading or repair [7]. CoV RNA has a big genome, which means that deletions and recombination events may occur, which could allow the virus to adapt to new host conditions, as is the case when a species jumps from one host to another [8]. In the open reading frame (ORF) of the SARS-CoV after human-to-human transmission, a single naturally occurring deletion on 29 nucleotides has been linked to attenuation [9].

Rapid spread in the human population could be explained by the low mutation rate, strong human-to-human transmissibility (R0 =2.2), and absence of human pre-existing immunity against SARS-CoV-

2 (99.9% sequence identity) (sequence published in the repository sequence data banks, GISAID and GenBank [10]. Coronavirus disease-19 (COVID-19) has spurred scientists around the world to create a solution in record time because of the virus's high pathogenicity, the severity of the illness, and the lack of an effective antiviral treatment or vaccine [5]. A variant of concern (VOC) is designated because of having higher transmissibility, illness severity (more hospitalizations or deaths), less neutralization by previous infection or immunization antibodies, decreased treatment or vaccine efficiency, or diagnostic detection failures [11]. The World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), and the European Centre for Disease Prevention and Control (ECDPC) have identified four variations as VOCs based on their epidemiological characteristics and spike mutation patterns (ECDC) [12]. Since the first year of the pandemic, many other nations have recognized these strains as the main circulating strains, including the United Kingdom, South Africa, Brazil, and India. Alpha B.1.1.7 was the first VOC that was discovered in September 2020 [13].
Scientists monitor all variants, but some are observed more closely than others, with specific concern that emergence of variants could limit the effectiveness of some vaccines or available therapeutics [14]. Some variants spread more quickly than others, increasing the risk of COVID-19 waves [15,16]. A rise in instances will strain healthcare resources, increase hospitalizations, and even deaths [17]. Delta variant; that was first detected in India; caused severe disease and death [18]. Vaccines are useful in averting serious illness, hospitalization, and death. Evidence suggests fully vaccinated people who contract the Delta variant can infect others [19]. Vaccines approved by the FDA protect against serious illness, hospitalization, and death [20]. Nearly all US variations respond to FDA-approved monoclonal antibody therapies (except the Omicron variant). Omicron variety was discovered in South Africa in late 2021[21,22]. While there were concerns about vaccines efficacy with the Omicron surge [23], still, vaccines continued to be useful in averting serious illness, hospitalization, and death. A recent study found that persons who get the Omicron version can spread it to others [24]. Nevertheless, the FDA-approved vaccines remained capable of preventing serious illness, hospitalizations and fatalities. The latest Omicron variation highlights the necessity of immunization and boosters [25,26]. The figure 1 shows the human innate immunity/immune responses to COVID-19.

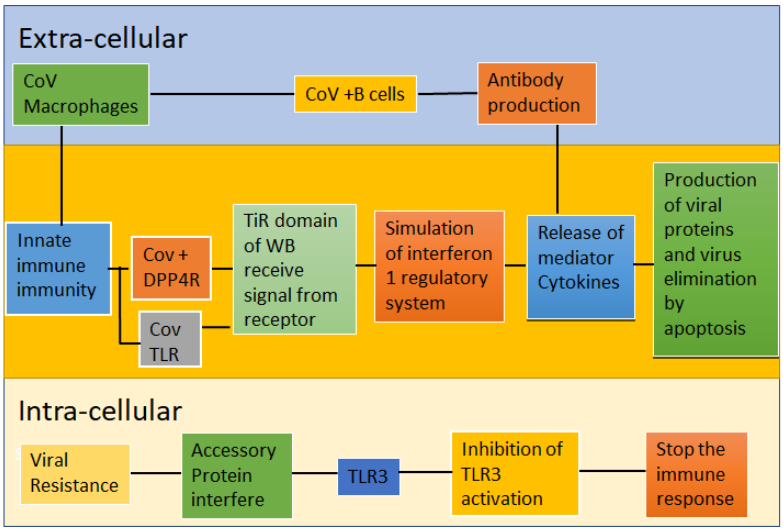

Figure 1. Innate immunity responses to SARS-CoV-2.

1.1 Genetic diversity of SARS-CoV-2:

SARS-CoV-2 (a new coronavirus) is sweeping the globe since 2020. Although the virus first appeared in 2019 at wholesale market of seafood, the number of affected patients has been steadily increasing. SARS-CoV-2 transmission from person to person has been evidenced [27,28]. Detection of virus has been observed in nasopharyngeal swabs, saliva, throat, bronchoalveolar-lavage, as well as sputum.

The most essential process of viral evolution has been postulated to be nucleotide substitution in nature. Exponential dissemination of SARS-CoV-2 poses fascinating concerns, such as whether mutations are driving its development. Eighty-six nearly complete or whole genomes of SARS-CoV-2 had been obtained from GISAID to examine genetic alterations [29]. SARS-CoV-2 strains had been reported in cases from Vietnam (1), Belgium (1), Germany (1), South Korea (1), Taiwan (2), England (2), Singapore (3), France (4), Japan (5), Australia (5), United States (11) and China (50) [30]. ClustalX2 was used to perform nucleotide sequence arrangement (pairwise) by using sequence of China/WHU01/2020/EPI ISL 406716 strains as a reference genome. SARS CoV-2 genome represents lengthy polyprotein (ORF1ab) at 5′ end accompanied by 4 important structural proteins such as: nucleocapsid protein, matrix protein, small envelop protein as well as spike surface glycoprotein [31]. Phan conducted genomic study of SARS-Cov-2 isolates from Australia (Victoria), United States (Wisconsin) and Japan (Aichi) observing 3 deletions in their genomes[29]. ORF1ab polyprotein reported two deletions (3 and 24 nucleotides), whereas 3′ end of genome had one deletion (ten nucleotides). It's worth noting that Phan reported 93 mutations across the whole SARS-CoV-2 genome by nucleotide sequence arrangement [32,33]. Excluding envelope protein, 42 missense alterations had been reported in all of the main structural as well as non-structural proteins. Nucleocapsid proteins had 4 missense mutations, matrix protein had one, spike surface glycoprotein had 8 and ORF1ab polyprotein had 29 [34,35]. Three noteworthy variations, F367, D354 and Y364, have been identified in the spike surface glycoprotein receptor-binding domain. Spike surface glycoprotein is crucial in regulating host tropism as well as binding to host cell receptors. It is also a primary focus in neutralization of antibodies [36]. Spike surface glycoprotein alterations may cause conformational modifications, which would likely result in a shift in an antigenicity. To present, there is no research on the location of amino acids involved in the conformational variations of the SARS-CoV-2 spike surface glycoprotein structure. The finding of these amino acids is significant and warrants further investigation [37,38]. The main regions of mutations identified in SARS-CoV-2 in eastern and southern Asian countries have been showed in Table 1.

Table 1. Regions of mutations among COVID-19 from Eastern and Southern Asia.

No.	Country of study	Regions of mutation	Reference
1	China	ORF1ab, 5'UTR, S, N, ORF8, ORF3a,	Du et al 2020 [39]
2	China	N, S, orf1ab, ORF3a, ORF8, ORF10	Chen et al 2020 [40]
3	China	E gene	Sun et al 2020 [41]
4	China	ORF1ab gene, S, and N gene	Zhang et al 2020 [42]
5	Taiwan	ORF1ab, ORF3a, ORF8, Spike gene	Gong et al 2020 [43]
6	Hong Kong	Spike	Ip et al 2020 [44]
7	Hong Kong	ORF1ab, ORF3a, Spike	Leung et al 2021 [45]
8	Korea	Spike gene	Kim et al 2020 [46]
9	Bangladesh	Non-structural protein 2, N-gene, Non-structural protein 3, Spike gene, Non-structural protein 12,	Akter et al 2020 [47]
10	Bangladesh	ORF1a, N gene, Spike,	Parvez et al 2021 [48]
11	Bangladesh	EndoRNase, NSP2, NSP3, NSP4, NSP5, NSP6, NSP8, RRDP, Helicase, 3'-to-5' exonuclease, ORF3a, Spike, Matrix, Nucleocapsid, ORF6, ORF7a, ORF8,	Saha et al 2020 [49]
12	India	ORF1ab, ORF8, S, and N	Devendran et al 2021 [50]
13	India	ORF+K25:K261, ORF3a, ORF7a, ORF8, S, M, N	Hassan et al 2020 [51]
14	India	Spike	Jacob et al 2020 [52]
15	India	orf1ab, S gene, N gene, 5-UTR, ORF3a, M gene, ORF6, ORF7b, ORF84, ORF10	Raghav et al 2020 [53]
16	India	Membrane, 5'UTR, Nucleocapsid, ORF1ab, Spike, ORF3a	Saha et al 2020 [54]

2. CoVariants

When a virus mutates, it can produce a new strain. Viruses are continually evolving and changing. While some varieties appear and then fade away, there are others that continue to exist. There will

always be new variations [10,55]. The CDC and other public health organizations throughout the world keep tabs on all possible strains of the virus that causes COVID-19 [56].

2.1 20I (Alpha, V1)

Alpha V1, also known as B.1.17 and 201/501Y.V1, emerged with a large number of genetic mutations [57]. This variant was identified in England in late 2020. And spread rapidly around the country and in present it has spread over 114 countries worldwide causing fear of international surge [58] and worries whether the current COVID-19 vaccines were effective in preventing it, because this variant showed 30-50% more transmissibility than previously identified species [59]. Multiple mutations were observed in its spike and most significant from them was the spike protein where asparagine was replaced with tyrosine at position of 501, and deletion of 69 and 70 amino acids. The change in 501 position was the responsible of enhanced transmissibility [19].

Clinical manifestation

Its spike protein binds with angiotensin-converting enzyme 2 (ACE2) receptors present on epithelial cells of human airway, especially on the upper respiratory track, where this variant multiplies and causes SARS like disease [60].

Probable Transmission

Its transmission mainly depends on its ability to bind human cells, as described this variant got amino acid 501 position mutations on a spike which act as receptor binding protein. This described mutation can enhance its ability to bind strongly with receptors present on Human cells [61]. This is the main reason that this variant can spread more easily than other variants, in UK it was observed it has ability to transfer from one to another more than 30% as compared to other variants. In United States, it was observed even to be more transmissible than in the UK [62], having 50% more transmission ability. Rate of spreading was increasing more than 7% a day, and in the end of the march 2021, it had spread in many US states [63].

Epidemiology

This variant was first discovered in the South-East England in the last month of 2020. Due to its fast-spreading ability, till March 2021, it had spread all around the country and to more than 114 countries as well, including the US[63]. There have been reports of variation Alpha in 170 nations, territories, and/or locations around the world [64].

Relevant genetic/Mutational profile

This Alpha variant possesses multiple mutations specially in the spike protein region. Most common mutations in the alpha variant are SN501 which identified independently multiple times in the previous studies [24,65].

2.2. 20H (Beta, V2)

It was originated from South Africa in late 2020. Like alpha V1, it also gained SN501Y mutation in the spike that made it a highly transmissible virus. But this strain also possesses E484K, S: L18F, S: K417N and S: D18A mutation [66]. Deletion of 243 and 241 position was also reported, but these deletions did not show any amino acid change. Due to it transmission speed, it triggered a second wave of COVID-19 in South Africa. The variation was associated with an increase in in-hospital mortality, that was 20% higher in the second wave than in the first wave[67]. Table 2 shows the fatality rate of COVID-19 infections in patients with different co-morbidities.

Table 2. Fatality rate with Co-Morbidities.

Co-morbidity	Fatality rate	References
With no co-morbidity	0.9 %	[68-73]
Cardiovascular Disorder	4.9 %	
Diabetes and hypertension	16.8 %	
Chronic respiratory Disorder	27.2 %	
Septic shocks	2.8 %	
Myocardial infarction	0.6 %	
Cancer	5.6 %	

The majority of the leading antibody therapy for Covid-19 have showed no evidence of decreased efficacy when compared to the South African form [15]. Various monoclonal antibodies have been combined in order to combat the disease; for example, the Casirivimab and imdevimab antibody cocktail (Regeneron) appeared to be effective against the South African variety [74]. Efforts to determine the susceptibility of variations discovered through worldwide surveillance and in people treated with bamlanivimab are now underway. It was discovered that pseudoviruses with the E484K mutation exhibited decreased susceptibility to bamlanivimab. E484K significantly reduced bamlanivimab neutralisation by more than 2000-fold. Still, many additional studies are required to provide clarity on these issues [75].

Pathogenic patterns of B.1.1.7 (alpha) and B.1.351 (beta) variants in K18-hACE2 transgenic mice: SARS-CoV-2 VOCs including B.1.1.7 (alpha) and B.1.351 (beta) have greater antibody neutralizing resistance as well as transmissibility. Rabaan et al., (2021) demonstrated that B.1.351 and B.1.1.7 are 100 times more deadly than original SARS-CoV-2 carrying 614D in K18-hACE2 transgenic mice [17]. In K18-hACE2 mice, B.1.351 and B.1.1.7 generate acute organ lesions than prior SARS-CoV-2 strains carrying 614G or 614D. Reduced pulmonary hypoxia signaling before death, increased D-dimer accumulation in major organs as well as different tissue-specific cytokine identifications are consequences of infection with B.1.351 and B.1.1.7 [5]. Even though with lower antibody titers against VOCs than prior variants, K18-hACE2 mice found to be resistant having deadly reinfection of B.1.351 or B.1.1.7, because of the intramuscular vaccination of receptor binding domain or viral spike and past infection with prior SARS-CoV-2 variants. Prior SARS-Cov-2 variants and B.1.351 as well as B.1.1.7 infection induced pathogenic patterns had been identified in K18-hACE2 mice and they help informing prospective COVID-19 medicinal therapies [31,48].

2.3. 20J (Gamma, V3)

Initially isolated from Brazil, also known as P.1 which is particularly associated with Manaus Amazonas. Like alpha and beta this variant also has spike protein mutation S: N501Y and S: E484K. some other mutations also found like S: L18F, S: K417T and S: H655Y [30]. Some mutation in Nucleocapsid also present like deletion of ORF1a at 3675-3677 position and N: P80R. During the first half of 2021, this variant was expected to be the most prevalent SARS-CoV-2 lineage in Brazil, as estimated [27].

The launch of the immunization program in Brazil coincided with an increase in the proportion of COVID-19 cases caused by the Gamma variant in early 2021 [74]. The possibility that the Gamma form could circumvent the prior SARS-CoV-2 immune response was explored in this context [15]. In Brazil, the surge in Gamma variant instances coincided with a rise in COVID-19 incidence in younger individuals. COVID-19 infection induced by the Gamma variant had distinct symptoms from COVID-19 infections caused by the non-VoC variant [67]. Because of a decrease in the frequency of hyposmia/anosmia and dysgeusia, a rise in Gamma variant cases should raise awareness that COVID-19 may present more frequently with cold-like symptoms [65].

2.4. 21A (Delta)

Known as B.1.617.2. very first it was isolated in India and spread very rapidly till it was found in every country at the end of 2021 [76]. This variant got mutations in spike S: L452R and S: P681. These two mutations have role in antibody binding. Some other Spike mutations are S: D950N, S: R158G, S: T478K and S: T19R. Some deletions in Spike are also found S: F157 and F156. Some deletions in Open Reading Frame 8 at F120 and D119 [60,77].

It was observed in India that 78% of COVID-19 infection was caused by 21A-Delta and 21B-Kappa variants from April 2021 to May 2021 [76]. In infected hamsters, the B.1.617.2/Delta variant is highly fusogenic and significantly more pathogenic than prototypic SARS-CoV-2. The P681R mutation in the spike protein, which is largely conserved in this lineage, improves viral fusogenicity by facilitating spike protein cleavage [78]. The P681R mutation is a feature of the B.1.617.2/Delta variant's virological phenotype and is linked to increased pathogenicity [79].

21J (Delta)

Associated with a variant of concern is a subclade of already described variant which spread very rapidly in Europe, America and Africa [80]. It was observed that this variant almost has all mutations of 21A Delta variant, with same clinical features as well. Infection of this variant was on the peak in October 2021 throughout the World, and decreasing trend was seen just before January 2022 [81].

Pathogenesis of SARS-CoV-2 Delta Variant:

During COVID-19 pandemic, a plethora of variations have occurred across the genome of SARS-CoV-2 and four VOCs are regarded as potentially harmful for the human society [82]. Newly discovered B.1.617.2/Delta VOC is linked to COVID-19 outburst that emerged in India in the spring of 2021. In infected hamsters B.1.617.2/Delta variant is much more pathogenic, as well as highly fusogenic, as compared to prior SARS-CoV-2 [83]. Highly conserved P681R variation in S protein in this ancestry, increases viral fusogenicity as well as promotes disintegration of S protein [63]. Furthermore, Saito et al., reported that virus carrying P681R variation, has a greater pathogenicity as compared to prototypic virus [84]. P681R variation is a feature of B.1.617.2/Delta variant's virological profile and is linked to increased pathogenicity. SARS-CoV-2 Omicron variant has reduced pathogenicity as well as fusogenicity [64]. In fully-vaccinated individuals, severe infections with Delta variant were significantly reduced [85].

2.5. 21K (Omicron)

The WHO designated this as variant of concern, very first case was identified in Africa [86]. Early cases were detected in South Africa and later on Botswana and Hong Kong were also reported for same variant cases [87].

This variant of concern also has a large number of spike gene mutations that results in increased transmissibility and adhesion ability. Some of the variant reported with receptor binding domain and N-terminal domain that plays a key role in ACE2 receptor binding [88].

In spike gene at position 214, three amino acid insertions were reported as EPE, that later on were known as the insertion hotspot [59]. Deletion of H69 and V70 in spike gene were also reported [63]. In Open Reading Frame, 3 amino acid deletions were also present. Cases of this variants started from December 2021, surged rapidly, and to date it is going down as per country-wide data showed [89].

21L (Omicron)

It is number five variant of concern. It belongs to 21M, which is a large distinct group from previous variants. Both 21L and 21K are included in same group. Both variants share 38 mutations but 21L has an additional 27. Both variant share spike mutation of 21 amino acid with 6 deletion or insertions [90]. 69/70 deletion is missing in this variant. This variant spread all around the world, predominantly being reported in Denmark. Phylogeny revealed that these genomes were distributed in three distinct

clusters, with the most closely related genomes coming from England and South Africa, Singapore and Nepal, or France and Denmark [18]. The structural predictions revealed a considerable increase and flattening of the 21L/BA.2 N-terminal domain surface when compared to the 21K/BA.2 Omicron variation, which may promote early viral interactions with lipid rafts. With rapid surge in cases, close monitoring of the incidence and clinical outcome of the 21L/BA.2 Omicron variation is warranted at the global, national, and regional levels [91].

Pathological features of Omicron

The advent of SARS-CoV-2 Omicron strain is a major worldwide health concern. Omicron has expanded faster than Delta strain in various nations, including South Africa [92]. Omicron was shown to be less fusogenic as compared to prototypic SARS-CoV-2 and Delta variant in cell culture assays [10]. However, cell-cell fusion is facilitated by disintegration of Delta S protein into two subunits. Less effective disintegration of S protein of Omicron was observed as compared to prototypic SARS-CoV-2 as well as Delta S proteins [63]. Moreover, Omicron was less pathogenic as compared to prototypic SARS-CoV-2 as well as Delta and had lower lung infectivity, in hamster model [93,94].

2.6. 21G (Lambda)

In late 2020, it appears to have emerged in South America. The earliest sequences are primarily from Peru and Chile [95]. It was eventually found throughout North America, Europe, and the Middle East. In April 2021, it accounted for 97% of the Peruvian public genomes [96,97]. C.37 was classified as a Variant of Interest (VOI) Lambda by the WHO on June 15, 2021 [98,99]. It got the spike mutation L452Q as L452R. Also has 7 amino acid deletions in spike protein and 3 amino acid deletions in ORF1a between 3675-3677 [100-102].

2.7. 21H (Mu)

In early 2021, it appears to have emerged in South America. The first sections are mostly from Colombia. It has now been discovered throughout North America and Europe [103]. It has the mutations that make it a variant of concern, Namely in the spike protein P681H, N501Y, E484k and T95I. Spike protein has a 3 nucleotide/1 amino acid insertion [104]. In the spike protein, this is sometimes reported as Y144T and Y145S with an insertion 'N' at position 146 [105]. The B.1.621 lineage emerged as a variation of interest (VOI) as a result of the accumulation of numerous mutations altering the spike protein, including amino acid alterations [106].

3. Mechanism of COVID-19 transmission in relation to Variant of Concerns (VOC):

Recent reviews have discussed consequences of variations reported in multiple VOC strains, which include increased binding affinity of the spike protein to the host ACE2 receptor, evasion of neutralizing antibodies increased viral loads enhanced shedding duration, enhanced viral loads, evasion of neutralizing antibodies and enhanced spike protein's binding affinity to host ACE2 receptors [10]. All these are potentials for ongoing research on prevention and treatment for disease caused by VOCs. Alpha, for instance, comprises variations may be possibly related to viral fusion (P681H), immunological evasion (perhaps directly or indirectly connected to spike identification at position and ACE2 receptor binding affinity (N501Y) [75]. Beta has K417N & E484K variations, which inhibit the binding of certain antibodies as well as some of the variations identical to Alpha. The K417T & K417N variations have been shown to diminish affinity of ACE2 receptor; although, when paired with N501Y variation, they exhibit a net increase in ACE2 receptor affinity, in contrast to a non-VOC strain [63]. N501Y & E484K variations are possessed by Gamma, which increases affinity of ACE2 receptor and the propensity for immunological evasion (specifically of therapeutic antibodies) [61]. Despite the possibility of immunological escape, antibodies-based neutralization, from previous infection or immunization, remains overall successful, and no substantial rise in

reinfection rates for VOCs in general has been recorded [59,63]. The figure 2 shows the mechanism of SARS-CoV-2 for possible destruction of human cells and their replication in human body.

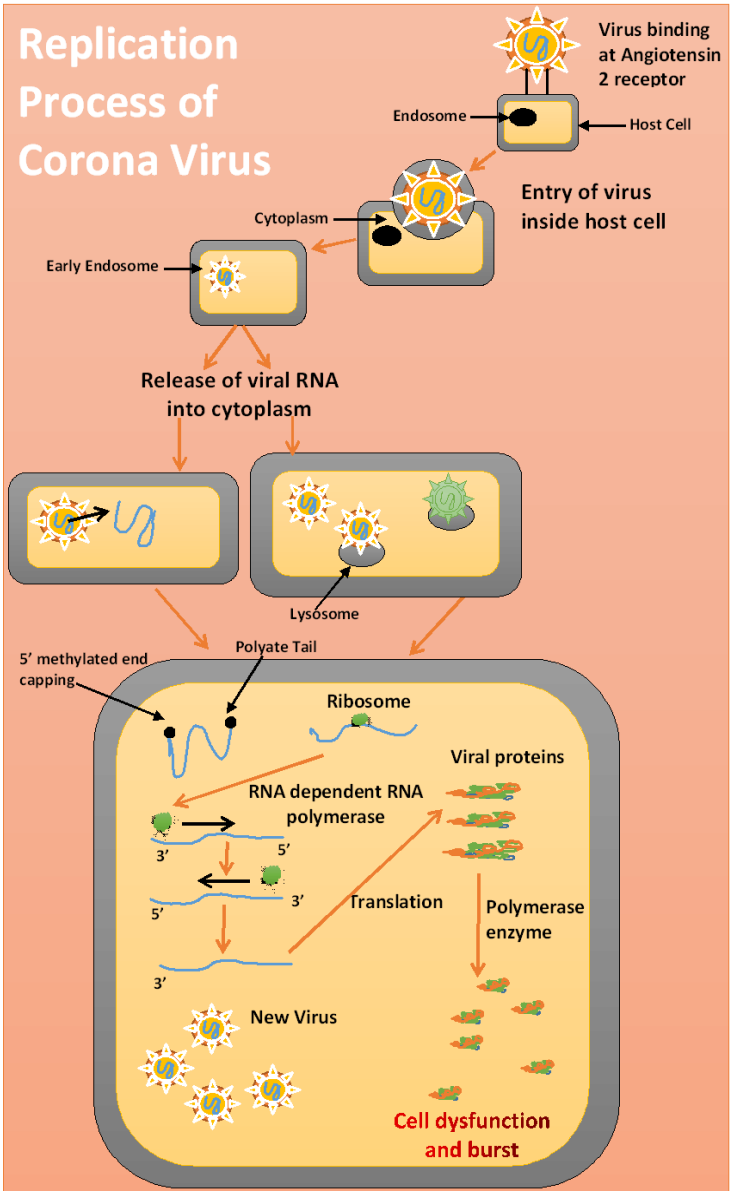

Figure 2. Mechanism of replication and destruction of human cell among SARS-CoV-2.

Because of asymmetric heterotypic immunity, antibodies generated against infection with one strain cannot offer adequate immunity against other strains [63]. Immune evasion of Beta seems to be a perturbation for patients who have already been diagnosed by other strains and for those who have been vaccinated; nonetheless, convalescent sera from people who have been affected with Beta exhibit strong cross-reactivity to other VOCs. There are comparable perturbations of Gamma reinfection due to immunological evasion [81]. A plethora of investigations on VOC's transmissibility have not been undertaken in communities with greater rates of natural protection or vaccination. When greater percentages of people are vaccinated, the extent and significance of vaccination innovation/interruption from natural protection will become increasingly evident or from locations with severely affected populations, as well as VOCs transmission in these groups continues to be examined [80]. However, real-world vaccination efficacy report from Ontario have thus far revealed enormously increased vaccine efficacy against SARS-CoV-2, particularly from a completed series of mRNA vaccines (E484K-positive VOCs) [64]. According to a report of meta-analysis from Denmark,

Ontario and the UK, the Alpha disease severity was expected to be greater. Report incorporated all VOCs, although the most prevalent disseminated VOC was found to be Alpha, as well as evaluations revealed, an accelerated risk of intensive care unit (ICU) admission (RR 2.03, 95 percent CI 1.69 to 2.45), a 56% increase in all-cause mortality (RR 1.56, 95 percent CI 1.30 to 1.87), as well as a 63% increased risk of hospitalization (RR 1.63, 95 percent CI 1.44-1.83) [64]. Beta may be associated with greater severity of disease; however, evidence is muddled by the absence of different demography as well as hospital services. Impact of severity of disease on transmission is unclear; nonetheless, a greater viral load is linked to greater likelihood of transmission as well as more severe disease [63]. There have been contradictory indications about Alpha's prolonged length of shedding as well as higher viral loads. One-page table (June 10, 2021) had been released by Public Health England, that is often updated in terms of Delta immunity, severity of disease as well as transmission [98]. Based on in vitro evidence, their present evaluation predicts replication advantages, immunological escape as well as probably enhanced disease severity, which are comparable pathways to Alpha. The statement, although, implies that Delta is found to be highly transmissible as compared to Alpha. Also, Technical Briefing 15 of Public Health England indicates Delta is the primary disseminating VOC at that time [17]. According to a fusion study conducted utilizing HEK293 cells transfected by D614G/P681R against HEK293 cells transfected by D614G, the P681R variation in Delta, identical to P681H variation in Alpha, presumably confers greater viral fusion. Other variations incorporate, other spike protein variations (D950N, T19R, Δ157/158), T478K (linked to ACE2 binding affinity), L452R (linked to immune escape as well as ACE2 binding affinity), G142D (linked to immune escape) and D614G (linked to greater viral load) [96]. The clinical manifestations of SARS-CoV-2 has been shown in figure 3.

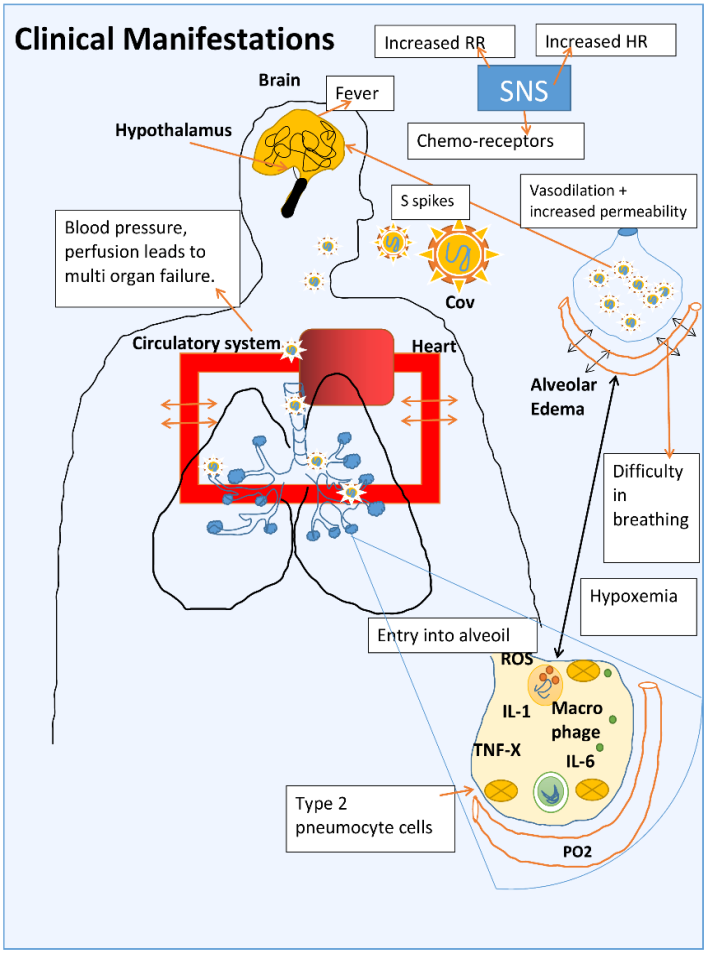

Figure 3. Clinical Manifestations of SARS-CoV-2.

4. Pathogenicity of COVID-19 in relation to Variant of Concern (VOC):

Because of their great transmissibility, the introduction of novel variations is causing alarm throughout the world, with new challenges to achieving herd immunity to control the pandemic [107]. The scope of recurrent deletions in 4 distinct locations of the N-terminal domain (NTD) as well as their genetic variations in spike (S) gene confers resistance to antibody neutralization, consequence in antigenic change as well as selective pressure, destroying the immunity offered by vaccines as well as mAb treatments and giving rise to confluent evolution [60]. The selection pressure most likely resulted in variations that have fitness benefits in replication, infection as well as transmission effectiveness. According to one research, possible antibody escape may be related to a consequence of immunological pressure during chronic SARS-Cov-2, in an individual [8]. Confluent evolution develops to avoid shared selection pressure, as indicated by continuing population transmission when phylogenetic research revealed separate unique branches of varied origins. Despite the fact that an exoribonuclease with a proofreading activity during replication is encoded by SARS-Cov-2, the virus's genome continues to be mutated [10].

VOCs have established themselves as dominant strain in afflicted locations as well as spread around the world. This rapid growth of the SARS-CoV-2 genomic diversity has resulted in viral sequence surveillance, including by the CDC in the US, COG-UK in the UK, and GISAID [82,102]. This advanced modification of SARS-CoV-2 genomic diversity resulted in viral sequence surveillance, encompassing by GISAID, COG-UK in UK and CDC in the US. Despite the fact that variant B.1.351 appears irrespective of B.1.1.7 variant, they do exhibit significant characteristics [62]. Before the prevalence of B.1.351 as well as B.1.1.7 strains with both deletions and 501Y, a significant population of NTD deletion-only mutants as well as N501Y-only mutants was discovered in both South Africa and UK. P.1, B.1.617.2, B.1.351, and B.1.1.7 possess variations in NTD and have considerable genetic divergence, with each showing more than 8 missense variations in spike (S) protein [64]. P.1 contains six amino acid variations; B.1.617.2 contains a deletion (Δ156–157), B.1.351 contains one deletion as well as 4 amino acid variations (Δ242–244) and B.1.1.7 incorporates 2 deletions (Δ69–70 and Δ144). Because NTD is attacked by several incredibly strong neutralizing antibodies, variations at NTD might be problematic. Binding sites of neutralizing anti-NTD antibodies are impaired by deletions, where anti-NTD mAb 159 unable to neutralize [18,92]. Furthermore, both P.1 as well as B.1.351 exhibit similar three variations: K417N/T, E4848K and N501Y. P.1 as well as B.1.351 have also been connected to an accelerated rise in cases in areas with a high prior attack rate. Finally, all four VOCs possess a plethora of variations throughout the genome, such as: deletion in ORF1b (del11288–11296 (3675–3677 SGF)) as well as few in S protein and its RBD. SARS-CoV-2 cell entrance, binding affinity, infectivity, vaccination effectiveness as well as neutralization are all affected by these alterations [10,100].

5. Vaccination

The vaccine formulation must reflect current knowledge of the SARS-CoV-2-and immune system interaction that includes selection of antigen, vaccine adjuvants and platforms, dosage regimens and administration rout (Immunological considerations for COVID-19 vaccine strategies). [55].

5.1. Types of vaccination

COVID-19 vaccination can be categorized in two sections, either it could be whole genome vaccine or any component like spike protein. Basic aim to any vaccine is to develop immunity against COVID-19 [55].

5.1.1 Complete pathogen approach

Attenuated live virus

This vaccine comprises an attenuated SARS-CoV-2 virus that the immune system recognizes and responds to without triggering COVID-19 sickness. This response strengthens immunological

memory, allowing your body to combat SARS-CoV-2 sinopharm and sinovac both are example of attenuated virus vaccine [109].

5.1.2 Viral components

Vector

This vaccination introduces a harmless, modified version of the virus – known as "the vector" – to deliver the antigen's genetic coding. The "vector" in a COVID-19 vaccine is the spike proteins located on the coronavirus's surface. When the body's cells get "infected," they are taught to create a huge number of antigens, which triggers an immune response examples are Oxford, AstraZeneca and Spuntik V [110].

Genomic approach

The COVID-19 RNA vaccine is made up of laboratory-created mRNA molecules that code for elements of the SARS-CoV-2 virus, specifically the virus' spike protein. When mRNA is injected into the body, it tells cells to make antigens, such as the spike protein discussed earlier, which are then identified by immune cells, causing a response by the body's lymphocytesv [111]. Because of the pandemic, research has progressed quickly, and several COVID-19 mRNA vaccines are now approved for emergency use, which means they can be administered to patients instead of just in clinical trials [112]. For example, Pfizer, Moderna and BioNtech.

Viral Subunit approach

To elicit an immune response, the protein subunit vaccine comprises purified "pieces" of a disease rather than the entire organism. The danger of side effects is expected to be reduced by confining the immune system to the entire pathogen examples are Novavax[10]. Virus components that the immune system recognizes were employed for this purpose [56].

6. The shifting sands of COVID-19

COVID-19's variation capabilities continue to be its most dangerous threat. Within a few months during the pandemic, national as well as local variations emerged [96]. In 2021, the Delta type remains the most dangerous with efficient projections, causing coronavirus outbreaks in nations ranging from the US to UK, including most of Europe as well as Asia. Similarly, while variations continue to be a prominent component of COVID-19, a more organized transformation is also occurring, involving coronavirus switching from pandemic to an endemic virus [90]. This transformation has both advantages and disadvantages. The advantages argue that strong public policy mandating double immunizations of adults and a vaccination/booster for children of 12–15-year-olds, along with continuing non-pharmacological precautions, such as compliance with PPE in unventilated/indoor spaces as well as social distancing, will strongly outweigh most combative characteristics of COVID-19's transmissible nature [24]. The disadvantages, on the other hand, necessitate serious consideration of the makeup of a post-pandemic society, both domestically and worldwide [19,74].

Although, no society has yet successfully declared full victory over the epidemic, several communities as well as societies are exhibiting policies, practices and comprehensible attitudes that will allow COVID-19 to be managed on a daily basis in medium as well as long term [18]. To recapitulate, they are increasingly considering COVID-19 as an endemic rather than a pandemic. Endemism or indigenous illnesses are widespread, prevalent, and inborn [80,81]. In this respect, they are persevering, especially during specific times of the year, as well as eventually reduced rate, but only in places with greater immunization rates. Because of prevalence of pandemic COVID-19 intersecting with frequent outbreaks of general variants of influenzas, post immunization booster doses, for both COVID-19 and other respiratory viruses like the Influenza vaccines, will be critical in moving countries and communities to that level of the end game [56,64].

However, what can be inferred from pandemic-endemic shift? Pandemic ceases when virtually every individual possess optimal immunity, since they were immunized or alternately, as they survived the SARS-CoV-2 infection [24]. This describes the transformation regarding immunity-derived coverage; nevertheless, additional information is required, implicating a refresher on terminology. The WHO definitively defined COVID-19 as a 'universal dissemination of a new illness' in March 2020, on the basis of decidedly trans-national epidemiology at work, which has both the potential to afflict an infinite number of individuals as well as nearly global spectrum [88]. Pandemics are productive in terms of and likelihood of geographical spread, speed and spectrum [96]. Ongoing surveillance and alertness are warranted to optimize early detection of future variants to control their spread.

7. Conclusions

COVID-19 pandemic has reached its third calendar year with newly reported VOCs. Indeed, COVID's transition from pandemic to endemic state is part of the normal course of many infections among different populations, as previously Tuberculosis and HIV infections scenarios. The Endemic doesn't mean that COVID-19 threat is no anymore, as the virus can rise up again with new mutational profiles and may be this time become more powerful. To some extent, the Delta variant played an important role in aspect of transitioning from pandemic to endemic status by enhancing the human immunity. The capacity to manage the future change from pandemic to endemic within the confines of our overall public health policy will determine how we reduce the transmission, hospitalization, and mortality rates. Furthermore, with the rapid changes in the mutational profile of SARS-CoV-2, it is very important to keep an eye on the occurrence of novel mutations since they may have an impact on disease severity, transmissibility, antiviral medication resistance, and also efficacy of vaccines.

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