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Asclepius

SARS-CoV-2 Variants of Concern (VOC): A Review

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ABSTRACT

Nearly two years since the start of the SARS-CoV-2 pandemic, which has caused over 5 million deaths, the world continues to be on high COVID-19 alert. The World Health Organization (WHO), in collaboration with national authorities, public health institutions and scientists have been closely monitoring and assessing the evolution of SARS-CoV-2 since January 2020. The emergences of specific SARS-CoV-2 variants were characterized as Variant of Interest (VOI) and Variant of Concern (VOC), to prioritize global monitoring and research, and to inform the ongoing global response to the COVID-19 pandemic. The WHO and its international sequencing networks continuously monitor SARS-CoV-2 mutations and inform countries about any changes that may be needed to respond to the variant, and prevent its spread where feasible. Multiple variants of the virus have emerged and become dominant in many countries since January 2021, with the Alpha, Beta, Gamma, Delta and Omicron variants being the most prominent to date. The paper was aimed to review the SARS-CoV-2 variants of concern (VOC).

Key words: COVID-19, alpha, beta, gamma, delta, omicron

INTRODUCTION

Viruses innately have the ability to mutate constantly and lead to variants. Some variants emerge and disappear while some persist. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a beta coronavirus that belongs to the Coronavirus family. The family is composed of single-stranded positive ribonucleic acid (RNA) viruses [1]. Coronaviruses have four genera, and the alpha and beta genera have viruses known to cause human disease. They are zoonotic viruses that can be transmitted from animal to human; and the first time that occurs, it is referred to as a spillover event. The SARS-CoV-2 has been found to be closely related to coronaviruses found in the bat population and to the SARS-CoV[2]. Two corona viruses found in bat populations, RaTG13 and RmYN02 were found to have 96.2% and 93.3% sequence homology, respectively with SARS-CoV-2 [3,4]. Coronaviruses in Malayan pangolins have also been found to have sequence homology to SARS-CoV-2 [5]. The zoonotic source for SARS-CoV-2 is yet to

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be established. The bat and pangolin coronaviruses lack the polybasic cleavage site and mutations in the spike (S) protein, which SARS-CoV-2 possesses making the theory of human to human transmission at undetectable rates post spillover, a possibility for the virus to have acquired these genomic features prior to starting off the pandemic [6]. December 31, 2019 was the day the World Health Organization (WHO) China Country Office was made aware of cases of pneumonia of an unknown etiology occurring in the city of Wuhan in the Hubei Province of China [7]. The virus once isolated from the airway epithelial cells of the infected patients was temporarily assigned the name 2019-nCoV [8]. Once it was determined that the virus is related to SARS-CoV, it was designated the name SARS-CoV-2 by the Coronavirus Research Group (CSG) of the International Committee for the classification of viruses on February 11, 2020 [9].

MICROBIOLOGY OF SARS-COV-2

SARS-CoV-2 is an enveloped spherical-shaped virus [1]. It has four structural proteins and 16 nonstructural proteins. The structural proteins are the nucleocapsid (N) protein, the membrane (M), the S protein and the envelope (E) protein as seen in figure 1. The RNA is oriented in a 5'-3'direction which makes it a positive sense RNA virus, and the RNA can be read directly as a messenger RNA. The RNA replicase is encoded at the 5' terminal end. The nonstructural protein 14 (nsp14) has proofreading activity which allows the rate of mutations to stay low. The S protein causes the attachment of the virus to the host cell at the angiotensin-converting enzyme 2 (ACE2) receptor which is present on membrane of the host cell [10]. The ACE2 receptors are found in abundance on alveolar cells. The attachment causes fusion of the viral lipid membrane with the cell membrane of the host thus internalizing the virus. The host machinery translates the viral RNA and leads to the production of the replicase and structural proteins of the virus. The replicase is cleaved into nonstructural proteins of which RNA-dependent RNA polymerase (RdRp) is one of them. Viralreplication and amplification is carried out and assembly of the virions is carried out in the host cell endoplasmic reticulum and Golgi apparatus. During the process of replication, errors can occur in the genome leading to mutations which give rise to variants. The virions are finally released out of the cell by exocytosis [11, 12].

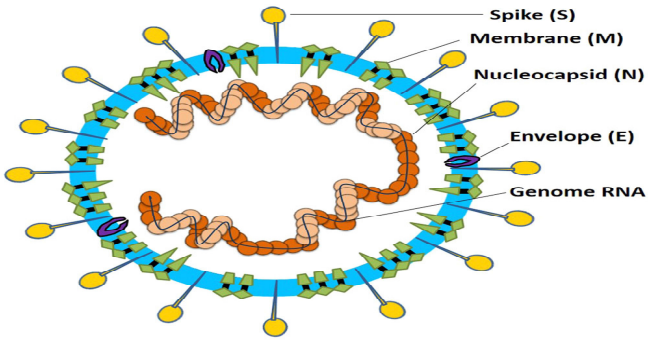

Figure 1: Molecular structure of Corona virus [13].

SARS-COV-2 VARIANTS OF CONCERN (VOC)

As SARS-CoV-2, the virus that causes COVID-19, has spread widely over time, a number of new variants have been identified globally. According to the Centers for Disease Control and Prevention (CDC), "a new virus variant has one or more mutations that differentiate it from the wild-type or predominant virus variants already circulating among the general population." Genetic variation in circulating viruses is expected, especially with RNA viruses like SARS-CoV-2, which have high rates of mutation generally. When a virus infects its host, it uses the host cell machinery to replicate itself. This replication process is error prone and offers chances to introduce changes to the virus's genetic code. Many of these changes are inconsequential, but a few improve the fitness of the virus, providing a selective advantage and establishing new strains of the virus, which would be expected to increase in prevalence over time. Although they may occur in any part of the viral genome, changes in the genetic code for the virus part that locks onto the host cell, known as the "spike protein," have been noted in certain SARS-CoV-2 variants. These changes appear to strengthen viral attachment to the host cell, which can result in more efficient viral transmission (increased infectiousness). This type of change does not have to correlate with a change in the clinical severity of infection (virulence), although it may [14].

The Beta (B.1.351 in Pango nomenclature) and, to a lesser extent, Gamma (P.1) variants were associated with immune evasion *in vitro* and spread locally but never dominated globally. In contrast, the Alpha (B.1.1.7) and Delta (B.1.617.2) VOCs attained a worldwide distribution and were responsible for significant waves of infections associated with an increase in reproduction number (R_0). Both variants harbour mutations at position 681 within the

polybasic furin cleavage site (a histidine in Alpha and an arginine in Delta); changes associated with enhanced cell entry that likely confer an intrinsic transmission advantage. Alpha displayed lower immune evasion properties compared to Beta but higher transmission. Alpha was in turn replaced by the Delta variant that displayed more significant immune evasion in addition to enhanced furin cleavage. Omicron is the fifth variant to be named as a VOC by the World Health Organization (WHO) and the third (after Alpha and Delta) to achieve global dominance [15].

Table 1: SARS-CoV-2 Variants of Concern (VOC)

SARS-CoV-2 Variants	WHO Date of Designation	Pangolineage	Additional amino acid changes monitored	Country of origin of first documented samples
Alpha	18 Dec 2020	B.1.1.7	+ S:484K + S:452R	Sept 2020 United Kingdom
Beta	18 Dec 2020	B.1.351	+ S:L18F	May 2020 South Africa
Gamma	11 Jan 2021	P.1	+ S:681H	Nov 2020 Brazil
Delta	11 May 2020	B.1.617.2	+ S:417N + S:484K	Oct 2020 India
Omicron	26 Nov 2021	B.1.1.529		Nov 2021 South Africa

Alpha or UK variant (B.1.1.7)

B.1.1.7, also known as VOC202012/01 was detected in September, 2020 in the UK. It has 23 mutations compared to the original strain found in Wuhan, China. Eight of these mutations were found to be in the S protein. Its notable mutations are N501Y, 69/70 deletion and P681H. The N501Y mutation appears to allow for the S protein to bind more tightly to the ACE2 receptor [16]. It is 40-80% more transmissible [17]. According to the report by Davies et al, nearly 5,000 out of 17,452 COVID-19 deaths during the months September to February were due to this variant. They also estimated that the mortality was approximately 55% higher when compared to other variants [18]. Similarly, the scientific reports in January 2021 indicated that there was an increased rate of death with this variant [19]. As of April 1, 2021, there were 12,505 reported cases across 51 jurisdictions [20]. It has been identified in 82 countries [21]. There are studies going on to determine the effectiveness of antivirals and anti-inflammatory medications in the treatment of UK strain [22].

Beta or South African variant (B.1.351)

The B.1.351 variant, also known as 501Y.V2 was first identified as early as October 2020 in Nelson Mandela Bay in South Africa. By December 2020 it was also detected in Zambia. By April 1 2021, there were 323 reported cases in 31 jurisdictions in the USA. There are 23 mutations with 17 amino acid changes but the notable mutations in this variant are K417N, E484K, and N501Y on the S protein. It is suggested to have increased transmissibility and most commonly seen in young people without underlying diseases [20]. The mutation E484K in this variant mediates the antibody escape is the main reason for the reduced sensitivity to vaccines [23]. The mRNA vaccines (Pfizer and Moderna) were authorized in the USA before the identification of this strain inthe country [24]. According to the latest studies, these two vaccineselicited lower neutralizing antibodies than that of the previous strains. Novavax, Janssen, and Astra-Zeneca conducted trials in South Africa that have dominant B.1.351 mutated strains. These studies demonstrated the lower vaccine efficacy compared to that of the other variants where this strain was not dominant [25].

Gamma or Brazilian variant (P.1)

P.1 variant also known as B.1.1.28.1 was first detected in North Brazil in the city of Manaus in the Amazonas state in December 2020. By January 2021, it was identified just outside Tokyo at Haneda airport among four travelers from Brazil during routine screening of passengers in samples analyzed at National Institute of Infectious Diseases (NIID) in Japan. As of April 1, 2021, there were 224 reported cases in 22 jurisdictions in the USA [20]. It has 35 mutations with 17 amino acid changes. Its notable mutations are K417T, E484K, and N501Y [20]. In a study by Naveca et al, it was found that this variant is 2.2 times higher transmissible that led to a few cases of reinfection who recovered from COVID-19, and almost has a similar rate infection in the younger (18 - 59 years old) and older (> 60 years old) patients [26,27]. B.1.351 and P.1 consist of similar receptor binding

mutations and hence, the vaccine efficacy against P.1 strain is assumed to be similar to B.1.351. As the studies demonstrated reduced vaccine efficacy against B.1.351, it is likely that the efficacy against P. 1 strain is reduced [28]. Sinovac Biotech has initiated the clinical trials which demonstrated that the CoronoVac vaccine is 50% effective in preventing infection with the P.1 variant in Brazil [29].

Delta variant (B.1.617.2)

Delta variant (B.1.617.2)(SARS-CoV-2) was first identified in the state of Maharashtra in late 2020 and spread throughout India, outcompeting pre-existing lineages including B.1.617.1 (Kappa) andB.1.1.7 (Alpha)1. In vitro, B.1.617.2 is six fold less sensitive to serum neutralizing antibodies from recovered individuals, and eightfold less sensitive to vaccine-elicited antibodies, compared with wild-type Wuhan-1 bearing D614G. Serum neutralizingtitres against B.1.617.2 were lower in ChAdOx1 vaccines than in BNT162b2 vaccines.B.1.617.2 spike pseudo-typed viruses exhibited compromised sensitivity tomonoclonal antibodies to the receptor-binding domain and the amino-terminaldomain. B.1.617.2 demonstrated higher replication efficiency than B.1.1.7 in both airway organoid and human airway epithelial systems, associated with B.1.617.2 spikebeing in a predominantly cleaved state compared with B.1.1.7 spike. The B.1.617.2 spikeprotein was able to mediate highly efficient syncytium formation that was lesssensitive to inhibition by neutralizing antibody, compared with that of wild-typespike. The B.1.617.2 had higher replication and spike-mediated entrythan B.1.617.1, potentially explaining the B.1.617.2 dominance. In an analysis of more than 130 SARS-CoV-2-infected health care workers across three centers in India during a period of mixed lineage circulation, it has been observed a reduced ChAdOx1 vaccine effectiveness against B.1.617.2 relative to non-B.1.617.2, with the caveat of possible residual confounding. Compromised vaccine efficacy against the highly fit and immune-evasive B.1.617.2 Delta variant warrants continued infection control measures in the post-vaccination era [30, 31, and 32].

Omicron (B.1.1.529)

On Friday 26 November 2021, the WHO announced [33] that a new SARS-CoV-2 Variant of Concern, named Omicron (initially named B.1.1.529), appeared to be increasing in almost all of South Africa's provinces, particularly Gauteng. The rapid spread, especially among the younger age group, in Gauteng, South Africa, has placed WHO and global health systems on high alert. The SARS-COV-2 VOC was first reported to the WHO from South Africa on 24 November, 2021. Cases of VOC Omicron had also been identified in Botswana, Belgium, Hong Kong and Israel. On 29 November, 2021, three days after the announcement by WHO, cases of VOC Omicron have been detected in Austria, Australia, Belgium, Canada, Czech Republic, Denmark, France, Germany, Italy, the Netherlands and the United Kingdom. The global public health community applauds scientists in South Africa and other countries which have reported the new VOC for the speed with which they have identified, sequenced and characterized SARS-CoV-2 strains, and their transparency andopenness in reporting quickly to WHO [33]. Their SARSCoV-2 sequencing work has been exemplar [34, 35]. As of November 28, 2021, 17:00 CET, 127 viral genomes (VOC Omicron GR/484A) have been entered into the GISAID databases [36]. Several receptor binding domains (RBD) and N-terminal domains (NTD) mutations hypothesized to be associated with resistance to neutralizing antibodies and increased transmissibility are of concern.

The Omicron lineage (B.1.1.529) has split into three divergent sub-lineages (BA.1, BA.2 and BA.3) of which BA.1 has spread rapidly around the world. The BA.1 Omicron genome encodes 30 amino acid substitutions relative to Wuhan-Hu-1 within the spike glycoprotein, 15 of which are in the receptor-binding domain (RBD) and 9 within the receptor-binding motif (RBM), the RBD sub domain that interacts with the human ACE2 receptor. Six of these mutations (G339D, N440K, S477N, T478K, Q498R and N501Y) enhance binding affinity to the human ACE2 receptor. Combinations such as Q498R and N501Y may enhance ACE2 binding additively. Overall, the Omicron RBD binds to the human ACE2 with approximately double the affinity (x2.4) of the Wuhan RBD9. Seven Omicron RBD mutations (K417N, G446S, E484A, Q493R, G496S, Q498R and N501Y) are associated with decreased antibody binding, importantly falling in epitopes corresponding to the three principal classes of RBD-specific neutralizing antibodies [20].

CONCLUSION

As SARS-CoV-2, the virus that causes COVID-19, has spread widely over time, a number of new variants have been identified globally. Multiple variants of the virus have emerged and become dominant in many countries since January 2021, with the Alpha, Beta, Gamma, Delta and Omicron variants being the most prominent to date.

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