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SARS-CoV-2 Virus and its initial Variants of Concern (VoC): A Short Communication

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Abstract

A new and highly pathogenic virus came into existence and caused a severe outbreak in Wuhan city of China. This virus is the well-knownSevere Acute Respiratory Syndrome Coronavirus-2(SARS CoV-2), commonly known as the coronavirus. The outbreak started around December 2019 and had quickly spread over other countries all around the world. The virus had posed a serious global public health emergency and it was declared a pandemic by WHO and most of the countries of the world had declared lockdown to prevent the spreading of this deadly virus.

Keywords: COVID, Infectious diseases, Virus, Pandemic, Immunology

1. Introduction

Patients infected by this novel coronavirus showed a varied range of symptoms including dry cough, headache, dyspnea, and pneumonia with an estimated mortal rate of 3 - 5 %[1-6]. China had confirmed 80565 cases of Covid-19 and 3015 deaths due to it till 5th March 2020.Globally, as of 4:00pm CET, 28 January 2022, there have been 364,191,494 confirmed cases of COVID-19, including 5,631,457 deaths, reported to WHO.Currently, the maximum number of cases registered is in the USA followed by India [7,8]. Most people show mild symptoms but some develop ARDS – Acute Respiratory Distress Syndrome. ARDS can be precipitated by cytokine storms[9], multi-organ failure, septic shock, and blood clots. Long-term infection may cause damage to organs mainly, to the lungs and heart [10-13]. The virus spreads via numerous means, mostly involving saliva and other human body fluids and excretions. These fluids can form droplets and aerosols, which can spread when a covid infected person speaks, sneezes, coughs, etc. The virus may also spread from contaminated surfaces or can spread if a healthy individual comes in direct contact with an infected patient. People generally remain infected for up to ten days in moderate cases, and two weeks in severe cases of the disease. The standard method for the

detection of this disease is by real-time reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab.

Covering of face using masks and face shields is now mandatory at public places to reduce the chances of transmission of the virus. Currently at present, various vaccines has been developed by different countries of the world namely Covaxin, Covishield, SputnikV, Pfizer, Moderna, etc. As of 27 January 2022, a total of 9,854,237,363 vaccine doses have been administered.

2. Basic Structure of the SARS-CoV-2 Particle

SARS CoV-2 is a member of the genus *Betacoronavirus*. The closest relative of SARS CoV-2 is Bat coronavirus RaTG13, and these have 96% sequence identity. Other members of the coronavirus family are distinct and having a sequence identity of less than 80%. SARS-CoV-2 has 79.6% sequence identity with SARS-CoV-1[1].

To bind to the cellular receptors, the coronaviruses use homotrimeric glycoproteins that are present on the virus envelope. These are known as spike proteins. Each spike protein monomer consists of 2 subunits – S1 and S2. Earlier cryo-electron microscopy studies of the spike protein of SARS-CoV and its interaction with cell receptor hACE2 have suggested that binding of the receptor induces dissociation of S1 with ACE2 and promoting S2 to transform from a metastable pre-fusion state to a post-fusion state of higher stability that is important for the membrane fusion[18-24]. In vitro binding studies have also suggested that the SARS-CoV-2 RBD binds to hACE2 with an affinity in the low nanomolar range, indicating that the RBD is the key functional component present within the S1 subunit of the spike protein that is responsible for the binding of SARS-CoV-2 by ACE2 [22, 25].

3. Three most important initial Variants of Concern of the SARS-CoV-2 Virus:

In March 2020, a new variant was detected that had an increased transmissibility and rate virus replication [26-28]. This strain of had a single D614G mutation in the spike (S) glycoprotein. Since December 2020, many different variants of the virus have been detected in different parts of the world with multiple mutations in the spike protein. The term “variant of concern” (VOC) for SARS-CoV-2 virus refers to viral variants with mutations in their spike protein receptor-binding domain (RBD) that dramatically improve binding affinity in the RBD-hACE2 complex while also causing fast dissemination in human

populations. Increased viral replication increases the likelihood of SARS-CoV-2 mutations forming.

4. B.1.1.7 (VOC 202012/01 or 20B/501Y.V1) Variant

This variant was first detected in the United Kingdom on 14th December 2020. This caused an increased rate of infection in the areas of eastern and south eastern parts of England and the London metropolitan area. Epidemiological studies and mathematical modelling studies have revealed that this new strain had 56% higher rate of spreading than the previous strain and results in a much higher nasopharyngeal viral load than the wild-type[29]. Observational and statistical studies showed that this variant increased the death risk by an average of 35% which indicated that this strain can cause a much more serious disease [30]. In contrast to the previous strain that had the D614G mutation, this new variant had a total of 23 mutations. It was interesting to note that it was not phylogenetically related to the variant of virus that was circulating in the UK before the detection of this strain. Of these mutations, 14 are non-synonymous: [[T1001I, A1708D, and I2230T] in open reading frame (ORF)1ab; [N501Y, A570D, P681H, T716I, S982A, and D1118H] in the spike (S) protein; [Q27stop, R52I, and Y73C] in ORF8; and [D3L and S235F] in the nucleocapsid (N) protein]; 6 are synonymous: [[C913T, C5986T, C14676T, C15279T, and T16176C] in ORF1ab; and [T26801C] in M (membrane) gene]; and 3 are deletions: [[SGF 3675-3677del] in ORF1ab; and [H69-V70del and Y144del] in S protein][31]. 47% of the mutations that occurred in the B.1.1.7 variant is in the gene, that codes for the spike protein containing the receptor binding domain (RBD). The spike protein is the main target of neutralizing antibodies and, hence, it has been used as the vaccine antigen in most of the vaccines under development and in the licensed vaccines that are being administered globally. All these mutations as a whole can induce structural changes in the spike protein that might alter the mode of interaction of the spike protein to the hACE2 receptor. The three mutations of B.1.1.7 that can affect the biological behaviour to the greatest potential of the virus are: H69-V70del, N501Y, and P681H. H69/V70 deletion is one of the recurrent mutations observed in the amino terminal domain (NTD) of the spike protein and was found in at least six lineages of the SARS-CoV-2 virus prevalent in Europe. Protein structure displaying shows that H69/V70 cancellation could be a "lenient" change

that alters the immunodominant epitopes situated at variable circles inside the amino terminal space, that gives protection from balance by serum from both improving patients and inoculated people. The N501Y transformation is of main pressing issue since it includes one of the six key amino corrosive deposits deciding a tight association of the SARS-CoV-2 RBD with ACE2 receptor[32].Modelling examination showed that the N501Y change would permit a potential fragrant ring-ring collaboration and an extra hydrogen connection among RBD and ACE2 and, thus, there is an expansion in the limiting fondness of SARS-CoV-2 Spike protein for the human angiotensin changing over catalyst 2 receptor. The N501Y mutation has also shown an increased infectivity and virulence in ferret and mouse models. The function of the P681H has not yet been discovered.

5. B.1.351 (20H/501Y.V2) Variant

It was first identified in the Republic of South Africa on eighteenth December 2020. Whenever contrasted with the strain, that was first recognized in Wuhan, this variation had 12 non-interchangeable changes and one erasure. 77% of these changes were found in the spike protein of the infection [L18F, D80A, D215G, LAL 242-244 del, R246I, K417N, E484K, N501Y, D614G, and A701V] while the excess ones are situated in ORF1a [K1655N], envelope (E) [P71L], and N [T205I] viral proteins. The large number of changes inside two of the most immunodominant districts of S protein, like the NTD and the RBD spaces, proposes that it very well may be a break variation to neutralization[33]. Both the B.1.351 and B.1.1.7 variations share the N501Y transformation, which is situated in the receptor restricting space of the spike protein. As referenced over, this change gives an expanded restricting fondness of the spike RBD for the human ACE2 receptor, raising the transmission pace of the virus.Other than these, the B.1.351 variation likewise has two extra transformations in the receptor restricting area (K417N and E484K) that assume an imperative part in both the connection with the receptor and avoidance of resistant reaction. The E484K change is available in only<0.02% of successions outside the Republic of South Africa. This change can liberally work on the limiting proclivity of the infection to the hACE2 receptor. Essentially, in spite of the fact that K417 buildup is an exceptional SARS-CoV-2 S RBD buildup that connects with ACE2 adding to an improved liking of the infection for the receptor, a mutational examining study proposes that the amino

corrosive difference in K by N insignificantly influences this binding[34]. In addition, an investigation of sub-atomic elements simulation revealed that both E484K and N501Y transformations increment proclivity of spike RBD for hACE2 and E484K specifically turns the charge on the adaptable circle district of spike RBD, which keeps an eye on the development of newfavourable contacts. In addition, the blend of E484K, K417N, and N501Y transformations results in the most noteworthy conformational changes of thespike protein RBD when bound to hACE2, contrasted with either E484K or N501Y alone, permitting the infection a more successful getaway to neutralization[35]. It ought to be considered that different transformations of the B.1.351 variation are situated in the N-terminal area locale of the SARS-CoV 2 spike (L18F, D80A, D215G, LAL 242-244 del, and R246I), inside or close to the adaptable variable circles that acknowledges the progressions in arrangement without adjusting the underlying and utilitarian spaces of the spike protein. This N-terminal area is likewise goes about as an objective for antibodies that are confined from healing patients or from people who have been immunized. Studies proposes that a blend of receptor restricting space and N-terminal area transformations in the B.1.351 spike protein fundamentally influences the balance of this variation by both mAbs focusing on these locales and resistant sera got from recovering or immunized patients[32].

6. P.1 (B.1.1.28.1) Variant

Japan's National Institute of Infectious Diseases first reported the existence of this strain of the virus on 6th January 2021. They isolated this train from 4 visitors from the continent of South America (Brazil) who landed at the Tokyo airport. This variant was then identified in Brazil later on, and then it had become the dominant strain of the virus[36]. P1 belonged to the ancestral lineage of B.1.1.28 and contains it contains 17 non-synonymous mutations: [L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, and V1176F] in spike protein, [S1188L, K1795Q, and E5665D] in ORF1ab, [E92K] in ORF8, and [P80K] in N protein; 1 deletion: [SGF 3675-3677del] in ORF1ab; and 4 synonymous mutations. P.1 has 12 mutations in the spike protein, which was the highest till then. The N501Y mutation was there in the all the three mentioned variants, whereas the mutations: L18F, K417T, E484K, and D614G mutations were only shared with

the variant B1.351[32]. As stated previously, this set of mutations in the spike protein hadsignificant implications for infection rates, and evasion of antibody-mediated immune response. One of the highest mutations of concern in terms of evasion of immune response was the E484K, which was shared by the P.1 and the B.1.351 variants. The effect of this mutation has been estimated in the neutralization ability of serum from convalescent or vaccinated patients considering their SARS-CoV-2 spike immunoglobulin G (IgG) antibody titer. The efficacy of serum neutralization against the virus carrying the E484K mutation was reduced in both vaccination samples and convalescent sera. However, serum with high anti-Spike IgG titers were able to neutralize the virus which contained the mutation, elucidating that it was important to induce the highest possible levels of specific antibodies through vaccination to improve protection against emerging SARS-CoV-2 variants[37].

Variants	**B.1.1.7**	**B.1.351**	**P.1**
1st detection	September 2020	8 October 2020	2 January 2021
Detection site	United Kingdom	South Africa	Japan/Brazil
Mutations in S protein	7 mutations: **N501Y**, A570D, **D614G**, P681H, T716I, S982A, D1118H 2 deletions: H69-V70del, Y144del	9 mutations: L18F, D80A, D215G, R246I, K417N, E484K, **N501Y**, **D614G**, A701V 1 deletion: LAL 242-244 del	12 mutations: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, **N501Y**, **D614G**, H655Y, T1027I, V1176F
Countries reported cases	82	40	19
Countries with sequences	64	35	14
Potential risk	- Higher transmission - Higher disease severity - Modest reduction in the neutralization efficacy of sera from convalescent patients or vaccinees	- Higher transmission - Higher reinfection rates - Significant reduction in the neutralization efficacy of sera from convalescent patients or vaccinees	- Higher transmission - Higher reinfection rates - Significant reduction in the neutralization efficacy of sera from convalescent patients or vaccinees

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7999234/

At present, the two most important variants of concern are the Delta (B.1.617.2) and Omicron Variant (B.1.1.529). The delta variant (B.1.617.2) had emerged during the second wave of infections in India and it has grown dominant internationally and is still evolving. WHO had detected and identified another variant of SARS-CoV-2, B.1.1.529 on 26th of November, 2021. They declared it a variant of concern and given the name “Omicron” to it. However, the severityand mode of transmission of this variant is still under cover.It has been found that the Omicron variant had a greater affinity for hACE2 than the Delta due to a considerable number of mutations found in the spike RBD, pointing at a higher risk for infection. Based on docking studies, the following mutations: Q493R, N501Y, S371L, S373P, S375F, Q498R, and T478K are present in the Omicron and not in the Delta, which qualifies as a reason for the higher affinity of Omicron for the hACE2.

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