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Research Paper

SARS-Cov-2 Variants and Current Status

S.S.SREENIVAS
ICAR-CTRI Research Station, Hunsur 571 105, Karnataka, India

ABSTRACT: *COVID-19 virus, SARS-CoV-2 first reported from Wuhan City of Hubei Province of China became pandemic infectious disease of severe respiratory disorder. Globally 17.8 Cr population was effected within a short span of period leading to 38.6 L deaths. Coronoviruses are large enveloped RNA viruses of Coronaviridae. Coronavirus employs a complex gene expression and pathway system unique among RNA viruses. SARA-CoV-2 is reported to mutate and variants reported to have one specific mutation, D614G which is makes to spread faster. WHO is monitoring and assessing the evolution of SARS-CoV-2 and notified Variants of Concern (VOCs) and Variants of Interest (VOIs), in order to prioritise the activities globally on containing COVID-19 pandemic. Currently genetic lineages by GISAID, Nextstrain and Pango are in use to code variants detected and being labeled using letters of the Greek Alphabet, i.e., Alpha, Beta, Gamma and Delta etc. Presently 15 vaccines were developed based on the SARS-CoV-2 spike protein, of original Wuhan-hu-1 and being administered in different countries. Surveillance and monitoring of the genomic sequence of SARS-CoV-2 is being done on a priority as virus is mutating for development of effective vaccine or therapeutic measures. Only 0.8% of people in low-income countries have received a single dose out of 20.8% of the world population which is a big concern for vulnerable groups.*

KEYWORDS: *SARS-CoV-2, COVID-19, surveillance, variants, neutralizing antibodies*

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I. INTRODUCTION

Ever since, China reported cases of pneumonia with unknown aetiology on December 31, 2019 and WHO declaring COVID-19 pandemic, several countries have reported incidence of SARS-CoV-2[1]. Globally the epidemic taken toll of 38.6 L deaths and infection spread to more countries. SARS-CoV-2, reported to have originated in bat and entered to another animal, possibly the pangolin, which then passed it on to humans. Later the virus spread between humans without any animal intermediary. Detailed guidelines for critical care management for COVID-19 have been directed by the WHO. Some of the most commonly used tests to detect the infection are molecular tests or RT-PCR, COVID-19 antigen test and COVID-19 antibody test. Chest CT scan is done in abnormal cases where patient had no positive molecular test to diagnose COVID-19. Coronaviruses are classified under the family *Coronaviridae* along with *toroviruses*[2] and known to infect animals and humans. This group became importance in the last few years owing to the identification of coronavirus as causal agent for acute respiratory syndrome (SARS) and neurologic illness or hepatitis[3]. Coronaviruses usually infect hosts in a species-specific manner with acute or persistent infections. Infections are transmitted mainly via respiratory and faecal-oral routes. Coronaviruses employ a complex gene expression and pathway system unique among RNA viruses. Reviews on molecular aspects of coronaviruses have appeared in the Advances in Virus Research series[4-6]. The name coronavirus was christened based on the Spike like projections on its surface which gives a crown like appearance[7]. Coronaviruses are roughly spherical with an average diameter of 80-120nm with genome of extremely large, non-segmented, single-stranded RNA molecules of positive sense, that is, the same sense as mRNA[8-11]. RNA viruses typically have higher mutation rates than DNA viruses which is a natural process. However, Coronaviruses make fewer mutations than most RNA viruses because they encode an enzyme to correct some of the errors unlike influenza virus. The chances of getting a mutant are high because so many replications happen in the host. Mutations in genetic material of the virus may pose problem in an antibody or PCR test. Under co-infection of virus, there is a possibility of coronaviruses can recombine, a chance factor given the exponential replication of virus. Individual pieces of RNA may reassort in a dual infection leading to the production of new genotypes.

II. METHODOLOGY

The paper is a review of research made on the COVID-19 virus SARS CoV-2 and its evolution through mutations. Based on available information on electronic media and published research around the world a review was made to brief information on the variants of coronovirus and their response to currently available vaccines against the virus. Information was sourced from WHO and other official websites on different aspects of virus, its mutation and response to vaccine.

III. SURVEILLANCE AND MONITORING

Reports on variants, more spread rate, infectivity and less sensitivity to vaccines raised alarm at global level. More than one million SARS- CoV-2 sequences available via the Global Initiative on Sharing All Influenza Data (GISAID), permitting near real- time surveillance of the unfolding pandemic[12]. Variants of Concern have reported to be more wide spread and have some common substitution in their spike glycol protein. The initial reports from various laboratories have been reviewed by WHO suggest that variants have differential response to presently advocated vaccines[13,14] and proposed guidelines for monitoring variants. The variants are reported based on the response to following conditions: a.Increased transmissibility; b. Increased morbidity; c. Increased mortality; d. Ability to evade detection by diagnostic tests; e. Decreased susceptibility to antiviral drugs; f. Decreased susceptibility to neutralizing antibodies, either therapeutic (convalescent plasma or monoclonal antibodies) or in laboratory experiments; g. Ability to evade natural immunity causing re-infections; h. Ability to infect vaccinated individuals; i. Increased risk of particular conditions such as multisystem inflammatory syndrome; j. Increased affinity for particular demographic or clinical groups, such as children or immune-compromised individuals. Variants that meet one or more of these criteria may be labelled "variants under investigation" or "variants of interest" prior to verification and validation of these properties. Some variations and substitution in spike protein leading to new strains have been reported and found substantial spread in different countries.

IV. EVOLUTION SARS-COV-2 VIRUS

RNA viruses typically have higher mutation rates than DNA viruses which is a natural process[15]. However, Coronaviruses make fewer mutations than most RNA viruses because they encode an enzyme exoribonuclease domain (ExoN) to proof read errors. Mutations may change virus receptor site due to changed outer surface leading to antigen drift and antibodies produced by previous infection with the ancestor strain may fail. Spike (S) proteins that facilitate invasion of host cells bind to the host cell receptor, angiotensin-converting enzyme 2 (ACE2), which regulates blood pressure and fluid salt balance. COVID-19 can be transmitted by both asymptomatic and mildly symptomatic individuals. It is found that six amino acid residues of RBD viz., L455, F486, Q493, S494, N501, and Y505 are critical for the binding capacity of SARS-CoV-2 to ACE2 receptors [16]. Residues N501 interact with a salt bridge D38-K353 of ACE2 [17] which contributes to increasing the binding ability to ACE2[18]. SARA-CoV-2 is reported to mutate, first in China and earliest variants have one specific mutation, D614G which makes to spread faster[19-24]. D614G is an aspartic acid-to-glycine substitution at position 614 of the spike glycoprotein. The genome is reported to be of 27-31kb in length increasing chances of more mutations. Studies indicate that D614G gives a moderate advantage for infectivity and transmissibility[25-27]. Spike protein is responsible for attachment to host cell-surface receptor and fusion[28]. Same is the principal target while neutralizing antibodies under virus infection. WHO is monitoring and assessing the evolution of SARS-CoV-2 and notified Variants of Concern (VOCs) and Variants of Interest (VOIs). Based on certain attributes like increased transmissibility, virulence, clinical disease aspects, potential reduction in neutralization by some EUA monoclonal antibody treatments,[29,30] and reduced neutralization by post-vaccination sera[31,32]and decrease in effectiveness of preventive measures presently available variants are being described as variants of concern. Variants of Interest (VOI) are an isolates with genomic change or suspected phenotypic changes with presence in multiple countries. Genetic variants of SARS-CoV-2 emerging around the world are being routinely monitored through sequence-based surveillance, laboratory studies, and epidemiological investigations. ECDC regularly monitors variants based genomic screening performed using an open source algorithm[33]. Currently genetic lineages by database of viral genomes from Global initiative on sharing all influenza data (*GISAID*), *Nextstrain* and Phylogenetic Assignment of Named Global Outbreak Lineages (PANGOLIN) (*Pango*) are being used to code variants detected and being labeled using Greek letters *Alphabet*, i.e., *Alpha*, *Beta*, *Gamma* and *Delta* (Table 1and 2)[34].

V. SARS-COV-2 VARIANTS AND KEY MUTATIONS

Mutations are common in SARS-CoV-2, according to COVID-19 Genomic UK (COG-UK) Consortium 4,000 mutations have been detected in its spike protein alone[35]. *Alpha* variant, of B.1.1.7 lineage, is a variant of SARS-CoV-2 of particular importance. Some stains of this group reported to have E484K substitution in the spike protein. Studies on epidemiology revealed that Alpha variant spreads 56% faster than

the wild type strain[36,37]. Apart from D614G mutation, the B.1.1.7 variant evolved with 23 mutations and different phylogeneticity. *Beta* (lineage B.1.351) has combination of K417N, E484K, N501Y and E484K substitutions in the spike protein. There are three mutations K417N, E484K and N501Y of particular interest in the spike region of the lineage B.1.351 genome and a further five spike mutations L18F, D80A, D215G, R246I, A701V which have so far generated less concern. Away from spike region also, carries K1655N, SGF 3675-3677, deletion P71L, and T205I[38,39]. E484K amino acid change, a receptor-binding-domain (RBD) mutation, was reported to escape from neutralising antibodies which adversely affect the efficacy of present vaccines targeting spike protein. Reports confirm that B.1.351 and B.1.1.7 variants share the N501Y mutation, located in the RBD domain of the spike protein. *Gamma* (P1) has combination of K417T, E484K, N501Y and E484K substitution in the spike protein. Lineage P.1 comprises two distinct sub-variants 28-AM-1 and 28-AM-2, which carry the K417T, E484K, N501Y mutations, and both developed independently of each other within the same Amazonas region ofBrazil[40]. The *Delta* variant, also known as B.1.617.2, G/452R.V3, 21A or 21A/S:478K was first reported in India and spread internationally. Initially, noted as the 21A clade under the Nextstrain phylogenetic classification system later designated as *Delta* by WHO. This has a lineage B.1.617, which also includes the Kappa (variant under investigation). There are three sub-lineages B.1.617.1 (VUI-21APR-01), B.1.617.2 (VUI-21APR-02) and B.1.617.3 (VUI-21APR-03). Variant B.1.617.1 (VUI-21APR-01) was designated a Variant Under Investigation. Later, two other variants B.1.617.2 (VUI-21APR-02) and B.1.617.3 (VUI-21APR-03) were designated as Variants Under Investigation. B.1.617.3 shares the L452R and E484Q mutations found in B.1.617.1, B.1.617.2 lacks the E484Q mutation. B.1.617.2 has the T478K mutation, not found in B.1.617.1 and B.1.617.3[41-43]. Compared to the *Delta* variant an additional K417N mutation resulted in a new variant B.1.617.2.1 (*Delta plus*).[44]. Some key mutations in the delta variant E484Q, L452R and P614R make easier for the virus spike to attach to ACE-2 receptors. The K417N mutation was earlier detected in the *Beta* variant[45]. K417N mutation has been associated with immune escape.

Genomic and epidemiologic investigation in Netherland's early outbreak revealed human-mink-mink-mink and mink to human transmission cycle (Cross-species transmission)[46,47]. It is first variant of interest with the presence of several spike mutations, and referred to as B.1.1.298 (cluster 5) [48]. SARS-CoV-2 sequences from the Netherlands and Danish outbreaks had an Y453F mutation in the RBD of spike, which might mediate increased binding affinity for mink ACE2. Variant termed cluster 5, which had 3 additional mutations in spike (del69_70, I692V, and M1229I) was recorded in Danish. Investigation of human convalescent serum samples suggested a modest and variably statistically significant reduction in neutralization activity against cluster 5 viruses. This is a cause of concern because of continued evolution of the virus in an animal reservoir.

Table 1: Variants of Concern (VOCs)

WHO label	Pango lineage	GISAID clade/lineage	Nextstrain clade	Earliest documented samples	Date of designation
Alpha	B.1.1.7	GRY (formerly GR/501Y.V1)	20I/S:501Y.V1	United Kingdom, Sep-2020	18-Dec-2020
Beta	B.1.351	GH/501Y.V2	20H/S:501Y.V2	South Africa, May-2020	18-Dec-2020
Gamma	P.1	GR/501Y.V3	20J/S:501Y.V3	Brazil, Nov-2020	11-Jan-2021
Delta	B.1.617.2	G/452R.V3	21A/S:478K	India, Oct-2020	VOI: 4-Apr-2021 VOC: 11-May-2021

Vaccines presently developed against SARS-CoV-2 are supposed to be effective against variants also, as they incite an immune response to the entire spike. Evidence suggest that E484K and D614G spike mutation enhances SARS CoV-2 susceptibility to neutralization to post-vaccination sera[49,50]. Some studies found that sera from convalescent individuals showed effective cross-neutralization of both wild type and D614G variants[51,52]. B.1.1.7 with seven missense mutations along with D614G in receptor-binding domain (RBD) reported to be more infectious than D614G[53,54]. Also, strains, B.1.1.7, B.1.1.298, or B.1.429 escaped vaccine-induced humoral immunity even with individual RBD mutations. However, studies confirmed that vaccination or antibodies from wild-type SARS-CoV-2 may still provide protection against B.1.1.7 variants[55-58]. Similarly, P.1 strain, which has three RBD mutations, escaped neutralization effect[59,60]. B.1.351 variant with three mutations in RBD exhibited remarkable resistance to neutralization. Studies revealed that B.1.351 is more resistant to neutralization due to E484K mutation that also exists in P.1.variant from Brazil, a dominant variant in Brazil. SARS-CoV-2 is evolving to become more transmissible. Notably the Alpha variant and the Delta variant are both more transmissible than the original virus identified round Wuhan in China. There are many variants of SARS-CoV-2, sub-types of the virus are put into larger groupings such as lineages or clades. Internationally

three main nomenclatures have been proposed and few missense mutations have also been found in circulation in various parts of different countries (Table 3&4).

VI. VACCINES AND SARS-COV-2 VARIANTS

COVID-19 vaccines are based on the SARS-CoV-2 spike protein, *Wuhan-hu-1*. Around 15 vaccines have been developed around the world and currently being administered. Currently four types of technologies are being used in vaccine making viz., whole virus, RNA vaccines, vector (using an adenovirus shell based) and protein sub-unit vaccines. Perusal of literature and reviews are a clear indication that COVID-19 virus fast mutating and evolving globally[61-63]. WHO prepared COVID-19 surveillance and monitoring guidelines and is co-ordinating the research on SARS-CoV-2 virus mutants reported from different countries[,64,65]. Coronavirus replicase gene encodes16 non-structural proteins with multiple enzymatic activity. Eight of these are involved in unique metabolic path ways for replication and interfere with cellular functions and antiviral host responses making development of therapeutics difficult[66]. Initial studies have confirmed differential reaction of variants against present vaccines. Serological analyses studies of infected with SARS-CoV-2 indicated that serum neutralizing antibody activity targets the spike receptor-binding domain (RBD)[67]. Post-vaccination sera of persons immunized with Moderna or BNT162b2 (Pfizer–BioNTech) showed high binding titres for anti-SARS-CoV-2 spike IgM and IgG with plasma neutralizing activity and relative numbers of RBD-specific antibodies equivalent to those in natural infection and is similar to plasma from individuals who had recovered from natural SARS-CoV-2 infection[68].

Table 2: Variants of Interest (VOIs)

WHO label	Pango lineage	GISAID clade/lineage	Nextstrain clade	Earliest documented samples	Date of designation
Epsilon	B.1.427/B.1.429	GH/452R.V1	20C/S.452R	United States of America, Mar-2020	5-Mar-2021
Zeta	P.2	GR	20B/S.484K	Brazil, Apr-2020	17-Mar-2021
Eta	B.1.525	G/484K.V3	20A/S484K	Multiple countries, Dec-2020	17-Mar-2021
Theta	P.3	GR	20B/S:265C	Philippines, Jan-2021	24-Mar-2021
Iota	B.1.526	GH	20C/S:484K	United States of America, Nov-2020	24-Mar-2021
Kappa	B.1.617.1	G/452R.V3	21A/S:154K	India, Oct-2020	4-Apr-2021

Preliminary studies reviewed by the WHO indicate retained effectiveness against Alpha variant with the Oxford–AstraZeneca vaccine, Pfizer–BioNTech and Novavax, Studies have also indicated retained antibody neutralization against Alpha with most of the widely distributed vaccines (Sputnik V, Pfizer–BioNTech, Moderna, CoronaVac, BBIBP-CorV, Covaxin), minimal to moderate reduction with the Oxford–AstraZeneca. One study indicated that the Oxford–AstraZeneca vaccine had an efficacy of 42–89% against Alpha, versus 71–91% against other variants. While, clinical trials indicated that the Novavax vaccine is ~96% effective against the original variant and ~86% against Alpha andBeta. Preliminary studies reviewed by the WHO have indicated reduced effectiveness reduced antibody neutralization against Beta with most of the widely distributed vaccines (Oxford–AstraZeneca, Sputnik V, Johnson & Johnson, Pfizer–BioNTech, Moderna, Novavax; minimal to substantial reduction) except CoronaVac and BBIBP-CorV (minimal to modest reduction).

WHO reported CoronaVac and BBIBP-CorV, likely retained effectiveness against Gamma. Also, indicated retained antibody neutralization against Gamma with Oxford–AstraZeneca and CoronaVac (no to minimal reduction) and slightly reduced neutralization with Pfizer–BioNTech and Moderna (minimal to moderate reduction). The Gamma variant or lineage P.1 variant (also known as 20J/501Y.V3), initially identified in Brazil, showed partial escape to vaccination with the Pfizer-BioNTech vaccine. The K417N mutation detected in the Beta variant has been associated with immune escape, or evasion, that leaves it less susceptible, or more immune, to the vaccine or any form of drug therapy. Variants of Concern, Beta, or B.1.351 and Gamma, or P.1 variant have the K417N mutation, though the B.1.617.2 Delta variant doesn't carry this mutation. The E484K mutation in B.1.351, B.1.1.28.1, B.1.525, and B.1.526 at critical sites in RBD directly

affects the binding to the human ACE2 receptor[69] and significantly reduced neutralizing activity of human convalescent and post-vaccination sera[70] adversely affecting efficacy of present vaccines targeting spike protein. Studies found that L452R mutation weakens the binding ability of convalescent patients' antibodies and serum to spike protein[71-73]. Data indicates that the 501Y.V2 showed more resistance to the vaccine serum[74]. The biotech firm recently disclosed the Reports from Novavax from phase III clinical trial of NVX-CoV2373 is graded for variants 501Y. V1 (B.1.1.7) and 501Y. V2 (B.1.351). The effectiveness against 501Y.V1 is more than 85% and <50% against 501Y.V2[75,76]. This suggests reduced immunity by present recombinant protein vaccine against SARS-CoV-2 variants.

VII. CONCLUSIONS

Variants being evolved have in common a higher rate of transmissibility. They are reported to have more mutations in the spike (S) protein of the amino terminal domain (NTD) and the receptor binding domain (RBD). Augmenting Covid-19 surveillance is vital for detection, containing spread and ending pandemic. As of now 20.8% of the world population has received at least one dose of a COVID-19 vaccine. 2.4 billion doses have been administered globally and 32.6 million are now administered each day. Only 0.8% of people in low-income countries have received at least one dose. The vaccine administered is on an average of 31 doses for every 100 people. As there is an un-equal distribution of presently developed vaccines and gap in the vaccination drive among different nations arriving at community immunity may be a slow process. Also, results from different locations suggest potential of variants to escape from neutralizing humoral immunity and stress the need for broad protective interventions against the evolving variants. Surveillance and close monitoring of the genomic sequence of SARS-CoV-2 is an important process to be followed for attempting any vaccine or therapeutic measures.

Table 3: SARS-CoV-2 corresponding nomenclatures

PANGO lineages	Notes to PANGO lineages	Nextstrain clades,2021	GISAID clades	Notable variants
A.1–A.6		19B	S	Contains "reference sequence" WIV04/2019
B.3– B.7, B.9, B.10, B.13– B.16		19A	L O	
B.2			V	
B.1	B.1.5–B.1.72	20A	G	Lineage B.1 in the PANGO Lineages nomenclature system; includes Delta B.1.617
	B.1.9, B.1.13, B.1.22, B.1.26, B.1.37			
		20C	GH	Includes Epsilon B.1.427/B.1.429/CAL.20C and Eta/B.1.525
	B.1.3–B.1.66	20G		Predominant in US generally, Jan '21
		20H		Includes Beta/B.1.351 aka20H/501Y.V2 or 501.V2 lineage
		20B		Includes Bi.1.1207
		20D		
	B.1.1	20J	GR	Includes Gamma/P.1 and Zeta/P.2
		20F		
		20I		Includes Alpha/B.1.1.7 aka VOC-202012/01, VOC-20DEC-01 or 20I/50Y.V1
	B.1.177	20E (EU1)	GV	Derived from 20A

Table 4: Notable missense mutations

Mutated variant	Description of mutation site
N440K	Aspargine (N) is replaced by lysine (k) at position 440 India reported largest proportion of N440K mutated variants followed by the US and Germany
L452R	Leucine (L) is replaced by arginine (L) at position 452. 2021 all across India caused in part by lineage B.1.617, referred to as a "double mutant". Makes the coronavirus resistant to T cells
S477G/N	Position S477 shows the highest flexibility among them. it has been shown that both S477G and S477N strengthen the binding of the SARS-COV-2 spike with the hACE2 receptor
E484K	Gluatamic acid (E) is replaced by Lysine (K) at position 484 and reported in UK
E484Q	Glutamic acid (E) is replaced by glutamic acid (E) at position 484. E484Q may enhance ACE2 receptor binding ability and may reduce vaccine-stimulated antibodies from attaching to this altered spike protein
N501Y	Change from Aspargine (N) to tyrosine (Y) at position 501. Dominant form of the virus is reported in Columbus of USA
D614G	Glysine (G) replaced Aspartic acid (D) at position 614. Prevalent globally
P681H	P681H', a characteristic feature of the Alpha variant and lineage B.1.1.207. Global prevalence
P681R	Exchange, where Proline (P) is replaced by arginine (R) at position 681. Reported in India
A701V	mutation has the amino acid alanine substituted by valine at position 701 in the spike protein. Reported in Malaysia

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