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SARS-CoV-2 Variants have changed the end of pandemic

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ABSTRACT: Coronavirus Disease 2019 (COVID-19), imposed a huge burden on public health as well as global economies.Since late 2020, Genetic variants of SARS-CoV-2 have been emerging globally has been characterized by the emergence of sets of mutations in the spike (S) protein. There are reports of enhanced virulence, re-infection frequency, increased resistance to the action of monoclonal and polyclonal antibodies from convalescence sera and in vaccinated individuals in regions where the variants spread dominantly. There is increasing evidence of reduced neutralization insome severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)variants, a greater understanding is required to evaluate how this may impact vaccine effectiveness. However, pharmaceutical researchers are monitoring for a possible update of vaccine sequences, and it is crucial that information of genetic changes in the global virus population is essential to elucidate the phenotypic impacts of mutations. This article will review on understanding the different emerging SARS-CoV-2 variants that have thus far been identified in various parts of the world with mutational changes and biological properties as well as their impact in medical countermeasures and human health.

KEYWORDS:SARS-CoV-2Variants, orthocoronvirine, Nobecovirus

I. INTRODUCTION.

In the past two decades, the world has faced several infectious disease outbreaks, Ebola, Influenza A (H1N1), SARS, MERS, and Zika virus have had a massive global impact in terms of economic disruption, the strain on local and global public health. Most recently, the global outbreak of novel coronavirus 2019 (SARS-CoV-2) that causes COVID-19 is a newly discovered virus from the coronavirus family in Wuhan city, China, known to be a great threat to the public health systems. Coronavirus disease 2019 (COVID-19) pandemicfear and uncertainty enormous hope was placed in vaccines, the development of which progressed at unprecedented speed throughout 2020. The first clinical trials were started in March 2020 (of Moderna's mRNA-1273 vaccine) and the first licenses were granted in December 2020 (for mRNA vaccines from Moderna and Pfizer/BioNTech and the viral-vectored AstraZeneca vaccine). These achievements were the result of decades of scientific research in infectious diseases and vaccinology, latterly involving the development of adenoviral vectors and mRNA technology.Many countries are prompting large scale vaccination programs and these vaccines express the spike glycoprotein, the major target of neutralising antibodies in a natural infection.[1,2,3]The preliminary data suggestvaccination protect against disease and transmission.[4]

Current vaccines are based on a version of the spike glycoprotein from the start of the outbreak, but,genetic variants of SARS-CoV-2 have been emerging globally with an accumulation of a high number of mutations in the spike (S) protein, there are reports of enhanced virulence, re-infection frequency, and increased resistance to the action of monoclonal and polyclonal antibodies from convalescence sera and in vaccinated individuals in regions where the variants spread dominantly.[5,6]Fundamental questions remain around the vaccines ability of an old version of the spike glycoprotein to generate protective antibodies against newer emerging variants.This article reviews on understanding the different emerging SARS-CoV-2 variants that have thus far been identified in various parts of the world with mutational changes and biological properties as well as their impact in medical countermeasures and human health.

II.SARS-COV-2 GENOME STRUCTURE AND LIFE CYCLE

Coronaviruses (CoV) are a large family (Coronaviridae) of virusesNidovirales, further it is divided into two subfamilies: Letovirinae and Orthocoronavirinae. The orthocoronavirus subfamily is further divided into four genera: Alphacoronavirus, Betacoronavirus (has reported to

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five subgenera: Sarbecovirus, Hibecovirus, Nobecovirus, Merbecovirus, and Embecovirus), Gammacoronavirus, and Deltacoronavirus.[7, 8]The whole genome sequencing and phylogenetic analysis classified SARS-CoV-2 as Betacoronavirus from the sub-genus Sarbecovirus, which also includes SARS-CoV-1.[9, 10]The mutations, recombination and re-assortments routinely occur in the RNA viruses as a part of the evolutionary process for increasing the genetic diversity.

Coronavirus is a spherical or polymeric enveloped large (~30 kb), positive sense single-strand RNA genome encoding several open reading frames. It belongs to the Orthocoronavirinae subfamily, as the name, with the characteristic "crown-like" spikes proteins (S), membraneglycopteins (M)nuclocapsid protein (N), hemagglutinin-esterase dimer protein (HE), and envelope protein (E) on their surfaces ,several unidentified non-structuralopen reading frames (ORFs) and a poly (A) tail (Fig.1).[11, 12]

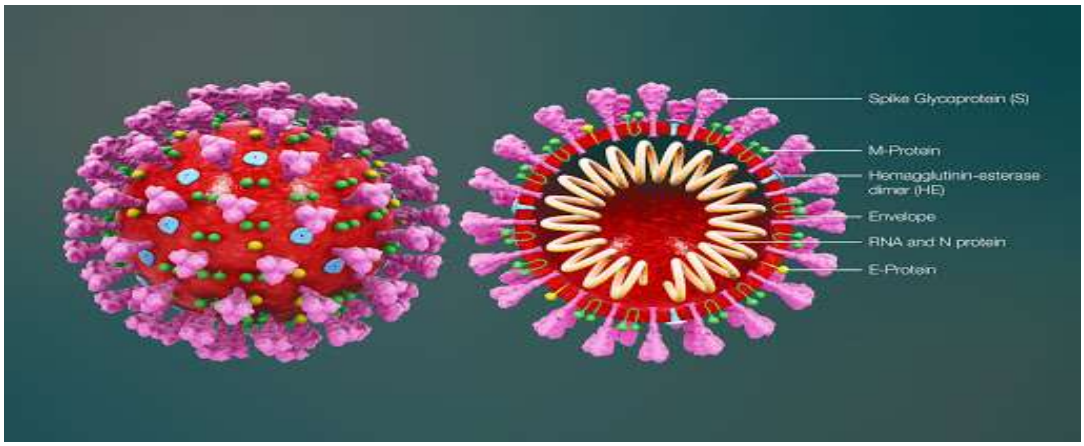

Figure 1. Schematic presentation of the SARS-CoV-2 genome Structure from sci-news.com (Image credit: Scientificanimations.com / CC BY-SA 4.0.)

The SARS-CoV-2 has 14 open reading frames (ORFs), which encodes for 27 different proteins.[13] The ORF1a gene is located at the 5′untranslated region (UTR), encodes for polyprotein pp1a, which contains 10 nsps and ORF1b gene, located next to ORF1a, encodes for polyprotein pp1ab which contains 16 nsps.[14]The pp1ab and pp1a protein undergoes autoproteolytic cleavage to form the viral replication complex. [15,16] The viral genome having a RBD for the interaction with host cell receptors is covered by the Spike glycoprotein.[17] The M glycoprotein is responsible for the assembly of viral particles has three domains, the cytoplasmic domain, the transmembrane domain, and the N hydrophilic domain.The Envelope protein is reported to play role in pathogenesis as it interacts with the tight junction related protein PALS1. The nucleocapsid protein packs the viral genome into a ribonucleoprotein complex, whichplays role in viral genome replication and the cell signaling pathway.[18,19]

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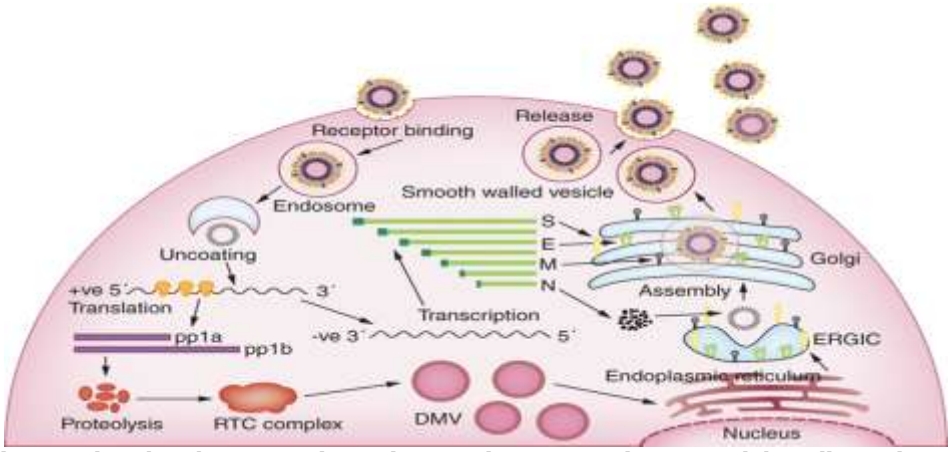

(The nucleocapsid, a phosphoprotein plays role in viral genome replication and the cell signaling pathway: Imagecredit: Future medicine.com)

III.HOST VIRAL INTERACTION AND REPLICATION OF SARS COV-2:

SARS-CoV virus cell entry in to host cells depends on binding of the viral S protein to the specific alveolar cell surface receptor (ACE2 receptor) present in the lungs. The ACE2 are used by SARS-CoV-1 and HCoV-NL63, whereas MERS uses dipeptidyl peptidase-4 (DPP4) and HCoV-229E uses aminopeptidase N (APN).[20,21,22,23]

All CoVs employ S glycoprotein for their internalization. SARS-CoVvirus S protein is subjected to proteolytic cleavages by host proteases (i.e., trypsin and furin), in two sites located at the boundary between the S1 and S2 subunits (S1/S2 site). In a later stage, the cleavage of the S2 domain (S2′ site) in order to release the fusion peptide which, trigger the activation of antibodies to find support on molecular targeting by utilizing the structural information of the binding region which is found in angiotensin-converting enzyme 2 receptor.[24,25]

Once entered the cytoplasm, it is suggested that COVID-19 employs a unique three-step method for membrane fusion, involving receptor-binding and induced conformational changes in Spike (S) glycoprotein followed by cathepsin L proteolysis through intracellular proteases and further activation of membrane fusion mechanism within endosomes.[26] Then, the endosome opens to release virus to the cytoplasm, and uncoating of viral nucleocapsid (N) via proteasomes which can hydrolyse and degrade endogenous proteins, as well as exogenous proteins.[27] The viral genetic material a single stranded positive sense RNA is released into the cytoplasm to undergo the replication and transcription processes which are mediated by the replication/transcription complex (RTC).[28]

The open reading frames viral genomes ORF1a and ORF1b, translate to non-structural proteins (nsps) in the cytoplasm. The ORF1a produces a polypeptide pp1a, which proteolytically cleaved to produce 10nsps while the -1PRF of SARS-CoV-2 allows continued translation till ORF1b and yields a larger polypeptide (pp1ab) which gets cleaved into 16 nsps. [29,30] The proteolytic cleavage of the polypeptides is carried out by the viral proteases 3CLpro and Mpro.[31,32] RTC complex is encoded in the viral genome believed to induce double-membrane structures in the cytoplasm of the infected cell.[33] The replication and transcription of the viral genome is mediated by the activity of RNA dependent RNA polymerase (RdRP/nsp12). The RdRP catalyzes the synthesis of viral RNA, with the assistance of nsp7 and nsp8 as cofactors.[34]

The positive RNA genome is translated to generate replicase proteins to generate full-length negative sense RNAs, which subsequently serve as templates in generating additional full length positive sense genomic RNAs (gRNA) and the sub-genomic RNA (sgRNA).Structural viral proteins, M, S and E are synthesized in the cytoplasm and then inserted into the endoplasmic reticulum (ER).[35]At the same time in cytoplasm nucleocapsids are formed from the encapsidation of replicated genomes by N protein, and as a result they coalesce within the ER membrane in order to self-assemble into new virions.[36] The SARS-CoV-2 expresses nine sgRNAs (S, 3a, E, M, 6, 7a, 7b, 8, and N) which form the structural and accessory

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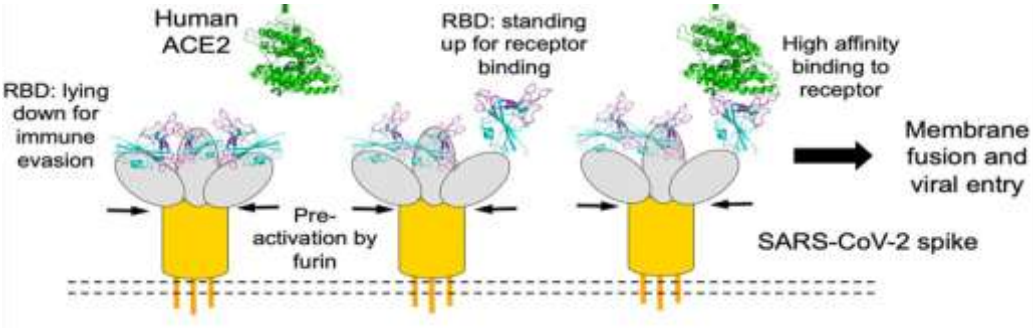
proteins. These sgRNAs are produced by the canonical Transcription Regulatory Sequence (TRS) mediated mechanism for discontinuous transcription.[37] Finally, novel virions induce a viral load stress to (ER) cause cell death and then are exported from infected cells by transport to the cell membrane by a process called exocytosis, so that can infect other cells.[38,39]



A schematic view of three unique features of SARS-CoV-2 entry: hidden RBD in the spike for immune evasion, RBD's high hACE2 binding affinity for efficient entry, and furin preactivation of the spike for enhanced entry into some cells.

Features of viral entry	SARS-CoV	SARS-CoV-2	Implications for SARS-CoV-2
Frequency of RBD standing up	High	Low	Immune evasion (hidden RBD)
Human ACE2-binding affinity by RBD	Low	High	Enhanced entry (compensation for hidden RBD)
Pre-activation by furin	No	Yes	Enhanced entry into some types of cells (compensation for hidden RBD)

A schematic view of implications of the cell entry mechanisms of SARS-CoV-2.[40]

IV EMERGING VARIANTS AND POTENTIAL CONSEQUENCES:

Mutations in SARS-CoV-2 are common: over 4,000 mutations have been detected in its spike protein alone, according to the COVID-19 Genomics UK (COG-UK) Consortium.[41]Viruses when acquire mutations over a time, giving rise to new variants and this new variant appears to be growing in a population, it can be labeled as an "emerging variant".[42]

Researchers have posted hundreds of thousands of complete SARS-CoV-2 genomes online since January 2020 and this number increases every day.[43]Some governments and media sources commonly named SARS-CoV-2 variants are often referring to by the country in which they were first identified, but the World Health Organization announced Greek-letter names for important strains on 31 May 2021, so they could be easily referred to in a geographically and politically neutral fashion.[44,45,46,47]

Centers for Disease Control and Prevention (CDC) has classified new variants which were under verification and validation of potential consequences on critical SARS-CoV-2 countermeasures may be labeled as "variants under investigation" or "variants of interest". The primary characteristic of a variant of interest, shows evidence that demonstrates it is the cause of an increased proportion of cases or unique outbreak clusters; but limited to prevalence or expansion at national levels, or the classification would be elevated to a "variant of concern". If there is clear evidence that the effectiveness of prevention or intervention measures for a particular variant is substantially reduced, that variant is termed as "variant of high consequence".[48,49]

Lineage B.1.525 Variant

B.1.525, also called VUI-21FEB-03(previously VUI-202102/03) and UK1188, carries the E484K-mutation (Eeek) refers to an exchange whereby the glutamic acid (E) is replaced by lysine (K) at position 484 and a new F888L mutation, a substitution of phenylalanine (F) with leucine (L) in the S2 domain of the spike

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protein.[50]E484K has been reported to be an escape mutation (i.e., a mutation that improves a virus's ability to evade the host's immune system)from monoclonal and serum derived antibodies against SARS-CoV-2 from 10 to 60 times less effective in neutralizing virus , indicating there may be a "possible change in antigenicity.[51,52]B.1.525 also carries the ΔH69/ΔV70 deletion (a deletion of the amino acids histidine and valine in positions 69 and 70) as found in B.1.1.7, N439K variant (B.1.141 and B.1.258) and Y453F variant (Cluster 5). As of now, Lineage B.1.525 has been detected in 23 countries, UK experts currently regarded it as a "variant under investigation"to understand how much of a risk it could be, butProf Ravi Gupta, from the University of Cambridge spoke to the BBC stated it may become a "variant of concern".[53,54,55]

Lineage B.1.526 Variant

B.1.526 variant(20C/S:484K), first detected in November and B.1.526.1(20C)October 2020 in New York city respectively, it had spread rapidly in the New York region accounted about one in four viral sequences.[56] The B.1.526 variant(20C/S:484K)variant has appeared with two notable mutations: the E484K spike mutation, which may help the virus evade antibodies, and the S477N mutation, (using molecular dynamics simulations of RBD) has shown to help theSARS-COV-2 virus spike to bind more tightly to hACE2 receptor of human cells. Reduced susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment were reported; however, the clinical implications of this are not known.[10]Alternative monoclonal antibody treatments are available.[57]Both the variants reduced neutralization by convalescent and post-vaccination sera. As of April 11, 2021, B.1.526 variant(20C/S:484K) variant has been detected in at least 48 U.S. states and 18 countries.[58,59]BioNTech vaccine developer referenced this amino acid exchange as relevant regarding future vaccine design.[60,61]

Gamma Lineage P.1 Variant

Lineage P.1, termed Variant of Concern by Public Health England and Nextstrain, was detected in Tokyo on 6 January 2021 by the National Institute of Infectious Diseases (NIID). P.1 lineage variant has 17 unique amino acid changes, 10 of which in its spike protein, including the three concerning mutations: N501Y (a change from asparagine (N) to tyrosine (Y) in amino-acid position 501 and has been nicknamed "Nelly"), E484K and K417T.[62,63]Lineage P.1 variants studies reported that infections can produce ten times more viral load,higher transmissibility and with the same ability to infect adults , older persons, younger humans irrespective of sex.Further, P.1 Variants infections are capable of evading (25–61%) inherited immunity from previous coronavirus diseases and the fatality ratio were also found to be (10–80%) more lethal.[64,65]A study found that people fully vaccinated with Pfizer or Moderna have significantly decreased neutralization effect against P.1, although the actual impact on the course of the disease is uncertain.[66]Preliminary studies datareported that the Oxford–AstraZeneca vaccine and Corona Vac is effective against the P.1 variant, although the exact level of efficacy is not yet released.[67,68]

P.2 Lineage variant termed “Variant of Interest”by CDC,identified in separate Brazilian study that harbours the E484K mutation but not the N501Y and K417T mutation. The P.2 lineage evolved independently in Rio de Janeiro without being directly related to the P.1 lineage from Manaus.[69]

Lineage P.3 variant designated on 13 March by the Department of Health of the Philippines, was first detected on 18thFebrauray 2021in Central Visayas having mutationE484K and N501Y.There were no official names for the variants and the full sequence was yet to be identified.Lineage P.3 variant's impact on vaccine efficacy and transmissibility is yet to be ascertained.[70]

Alpha Lineage B.1.1.7 Variant (Variant of Concern 20DEC-01)

Lineage B.1.1.7 referred as UK Variant or Kent Variant, first detected in October 2020 in Kent.[71]Lineage B.1.1.7, was previously known as the first Variant Under Investigation in December 2020 (VUI – 202012/01) and later notated as VOC-202012/01,reported to have 40% to 80% more transmissible than wild type SARS-CoV-2and Potential increased severity based on hospitalizations and case fatality rates.[72]VOC-202012/01 is defined by 23 mutations: 14 non-synonymous mutations, 3 deletions, and 6 synonymous mutations (i.e., there are 17 mutations that change proteins and six that do not.On 2 February 2021, Public Health England reported that they had detected E484K mutations in B.1.1.7 VOC-202012/01 genomes with E484K

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mutations",this mutation may reduce vaccine effectiveness, but minimal impact on neutralization by convalescent and post-vaccination sera.No impact on susceptibility to EUA monoclonal antibody treatments.[32]More recent work has found no evidence of increased virulence.[73]

Beta Lineage B.1.351 Variant

Lineage B.1.351 Variant (formerly VOC-202012/02) also known as South African Covid-29 Variant, was first detected in south Africa in October and health department reported on 18 December 2020, having three mutations in the receptor-binding domain (RBD) in the spike glycoprotein of the virus: N501Y,K417N, and E484K.[74] Scientists noted that the variant contains several mutations that allow it to attach more easily to human cellsand officials reported that the prevalence of the variant was higher among young people with no underlying health conditions, and by comparison with other variants it is more frequently resulting in serious illness in those cases. The health department of South Africa also indicated that the variant may be driving the second wave of the COVID-19 epidemic in the country due to the variant spreading at a more rapid pace than other earlier variants of the virus.Scientist reported Lineage B.1.351 Variant to have a significant decrease in susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment and reduced neutralization by convalescent and post-vaccination sera.[75]

Lineage B.1.429 Variant

Lineage B.1.429, also known as CAL.20C, CDC listed as "Variant of Concern" was first observed in July 2020 California ,is defined by five distinct mutations (I4205V and D1183Y in the ORF1ab-gene, and S13I, W152C, L452R in the spike proteins S-gene), of which the L452R (previously also detected in other unrelated lineages) was of particular concern.[76] B.1.429 is possibly~20% increase in viral transmissibility, modest decrease in susceptibility to the combination of bamlanivimab and etesevimab; however, the clinical implications of this decrease are not known and moderately reduce neutralization by plasma collected by people who have previously infected by the virus or who have received a vaccine against the virus.[77]

Lineage B.1.1.317 Variant

While B.1.1.317 which has been called Russian Variant ,though first discovered in Russia, but as on today it also reported from Germany (54.0%), Russia (21.0%), Estonia (4.0%), United States of America(2.0%), United Kingdom (2.0%)this variant is not currently classified as a variant of concerns not considered a variant of concern.[78]B.1.1.317 may be conferred by the (S:D138Y+S:S477N+S:A845S) combination; while the advantage of B.1.1.397+ may be conferred by the S:M153T change may affect the transmissibility further studies are needed to confirm it.The combinations of mutations observed in B.1.1.317, B.1.1.397+ and the three newly described lineages together with frequency increase of these lineages make them candidate variants of interest.[79]

Lineage B.1.1.318 Variant

Lineage B.1.1.318 was designated by PHE as a VUI (VUI-21FEB-04), containsE484 mutation on its spike protein which is also found in the Brazilian and South African variantsmay help it escape immunity.Lineage B.1.1.318 Variant's location of first detection is yet to be confirmed and it has been reported in 8 countries including UK.[80]

Delta Lineage B.1.617 Variant

Lineage B.1.617 Variant was discovered in India in October 2020PHE designated as a 'Variant under investigation', VUI-21APR-01, also known as "Double mutant"it has been reported with15 defining mutations,possessing common signature mutations D111D, G142D, L452R, E484Q, D614G and P681R, in the spike protein including within the receptor binding domain (RBD). Of these, the mutations at residue positions 452 (an exchange whereby the leucine (L) is replaced by arginine (R) at position 452), 484 (an exchange whereby the glutamic acid (E) is replaced by glutamine (Q) at position 484) and 681(an exchange whereby the proline (P) is replaced by arginine (R) at position 681)have been reported in other globally circulating lineages.[81,82] The structural analysis of RBD mutations L452R and E484Q along with P681R in the furin cleavage site, may possibly result in increased ACE2 binding and rate of S1-S2 cleavage resulting in better transmissibility. The same two RBD mutations indicated decreased binding to selected monoclonal antibodies (mAbs), may affect their neutralization potential andcould even make the coronavirus resistant to T cells that are class of cells necessary to target and destroy virus-infected cells.[50] Experimental validation and investigation is much needed to confirm its impact on SARS-CoV-2 counter measures, since it is reported that it had spread to at least 20 countries in all continents

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except Antarctica and South America. On 29 April 2021PHE added two further variants, VUI-21APR-02 and VUI-21APR-03, effectively B.1.617.2 and B.1.617.3.[83]

Lineage B.1.618 Variant

In October 2020, this variant was first isolated in West Bengal, having multiple mutations deletions of amino acid tyrosine and histidine at positions 145 and 146 of the spike protein, mutation E484K (same mutant of south African variant) that has been reported earlier to be contributing towards escape from immune response and D614G which was linked to increased infectivity.[84]Anurag Agrawal, director of the CSIR-Institute of Genomic and Integrative Biology in New Delhi. He described B.1.618 as a 'lineage of interest' and said it is being investigated. But there is no evidence yet that it is driving the Covid surge in India.[85]As of 23 April 2021, the CoV-Lineages database showed 135 sequences detected in India, with single-figure numbers in each of eight other countries worldwide.[86]"Its prevalence has increased over other variants in much of India, suggesting that it has better 'fitness' over those variants," says Shahid Jameel, a virologist at Ashoka University in Sonipat who chairs the scientific advisory group of the Indian SARS-CoV-2 Genome Sequencing Consortia (INSACOG).

CONCLUSIONS

It has been reported that change in antigenicity of the SARS-CoV-2 spike amino acid that impact neutralizing antibodies are present at significant frequencies in the global virus population, and there is emerging evidence of variants exhibiting resistance to antibody-mediated immunity elicited by vaccines. To monitor vaccine efficacy,it isbetter to understand the implications of antigenic variation for vaccine effectiveness, it is very important to collect information on vaccine status and viral genome sequence data from individuals infected with SARS-CoV-2.

Vaccines and antibody-based therapies target mainly the SARS-CoV-2 spike protein, the new variants carrying immune escape mutations generated in chronic infections, therefore, sequencing of viruses associated with prolonged infections will provide useful information on mutations that could contribute to increased transmissibility or escape from vaccine-mediated immunity.

The systematic surveillance of antigenicSARS-CoV-2 variants will help to guide the implementation of targeted control measures and further laboratory characterization.

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