Review Article

New Strain SARS CoV2

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Under severe strain for nine months of 2020, with 1.8 million deaths through Covid 19 and 85 million people infected, we were all hoping 2021 would show us the light at the end of the tunnel. The "new variant" of SARS-CoV-2 and its confirmed rapid transmission properties has once more setback our hopes. The start of vaccinations in the last week has been a source of relief although the benefits of the same will only be known with the passage of time. New variants and mutations against which the vaccines have not been prepared will continue to be challenges on a daily basis for scientists epidemiologists and administrators. Despite treating Covid 19 patients of all spectrums with a variety of therapeutic agents only a few like oxygen and steroids have acquired some evidence basis while others have not met the same threshold. The public have suffered including through anxiety and education, livelihood and social structure have suffered to the point of breaking in these tumultuous times. Patience is a virtue and prevention measures– hand hygiene wearing of masks social distancing and avoiding unnecessary human contact will eventually see us through with vaccines being the added layer of protection and prevention.

[*J Indian Med Assoc* 2021; **119(1):** 31-6]

Key words **: "new variant" of SARS-CoV-2, Vaccinations, Covid 19, Self Isolation, Masks.**

SARS-CoV-2 has infected more than 85 million persons and caused more than 1.85 million deaths approximately till early January 2021. Hopes have risen with the commencement of vaccination against the virus which have commenced in the UK initially and next in the US with other countries including India to follow shortly. However new strains including the recently identified "variant of concern (VOC)" in UK which clearly has a higher transmissibility has raised concerns from a public health standpoint.

The genetics of this novel RNA virus merits closer attention by the medical community at large so that we all have a clear understanding of the RNA virus pathogenesis, virulence, transmissibility and now the level of protection achieved through vaccination programs[1]. Mutations in RNA viruses are inevitable as they replicate and circulate. Most mutations are of no consequence while others may be neutral or of a positive survival advantage to the virus. Many thousands of mutations have been identified in the SARS-CoV-2genome. Novel combinations of mutations are appearing. While the most mutations had no apparent effect on the virus,a minority can change the virus by increasing its infectivity or cause a change in the clinical severity or in the way the virus interacts with the immune system including the vaccine response. Most attention has been paid to mutations in the genes that encode the spike protein and therefore determine immunity and vaccine efficacy.

Editor's Comment :

- **Preventative measures are paramount and the basic principles of hand hygiene, wearing of masks, staying apart physically and avoiding unnecessary travel and social congregation unless legally authorised and seeking medical help and self isolating at the earliest warning signs of Covid 19 infection remain the cornerstones of our fight against the coronavirus.**
- **Vaccination will certainly help against strains that are sensitive to it and it is hoped the new mutants and variants will also be protected against.**
- **The World Health Organisation and our respective national governments efforts, people's togetherness and the strength of the global human race will surely manage to beat back the ravages caused by this tiny RNA virus.**

History of SARS-CoV-2 genomics: the virus probably originated in bats and strains found in Wuhan, China showed very less genetic diversity meaning that the virus may have been introduced from a single source[2]. Early zoonotic variants in the novel coronavirusSARS-CoV that emerged in 2003 targeted the receptor binding domain (RBD) of the spike protein and thereby increased entry through the human angiotensin-converting enzyme 2 (hACE2) receptor[3]. The spike protein RBD of earlySARS-CoV-2 strains were shown to affect the hACE2 receptors early on[2].

In the UK, the COVID-19 genomics UK

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Received on : 06/01/2021
Accepted on : 10/01/2021

consortium(COG-UK) has been maintaining a close watch on the evolving genetics of SARS-CoV-2 since the onset of infections. COG-UK undertakes sequencing of SARS-CoV-2 samples from about 10% of confirmed cases in the UK. Public Health England and New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) work in close association with COG – UK to be able to adviseScientific Advisory Group for Emergencies (SAGE) of the best advice the British government can give to UK citizens and advice the global community via the World Health Organisation to provide advance genomic information on this pandemic virus to prevent its further spread.

Historically in late February 2020 D614G mutation affecting the spike glycoprotein SARS-CoV-2 from southern Europe was found, and this variant has since has become the most common genotype worldwide[4]. This variant had higher viral loads in the upper respiratory tract than poeple with the virus strains without the mutation although the disease severity was not affected[5].

On 8 December 2020, an increasing incidence of COVID 19 cases was detected in Kent, England as part of epidemiological surveillance of the genomic data that revealed the Kent cluster[6]. This cluster was phylogenetically very distinct from the rest of the UK data set. These cases were concentrated in Kent and north-east London with limited spread into rest of London, Anglia and Essex. This variant(familiar now as the "new variant") was designated as a variant under investigation (VUI) redesignated as VOC –202012/01 on 18 December 2020[7]. The lineage of this new SARS-Cov-2 was termed B.1.1.7 which was first observed in the UK in September 2020 and had spread to at least 244 of 317 English local authorities by December 13, 2020[8]. Initially high prevalence was seen in the south-east of England and was contributing to an increasing share of cases locally and nationally. High transmissibility relative to other circulating lineages (estimated to be 1.5 to 1.7-fold higher) despite the English lockdown between November 5 and December 2, 2020 during which case numbers was generally contracting was noted[9].

The particular feature of this "new variant" of SARS-CoV-2 genomics[10] was the appearance of 23 mutations: 13 non-synonymous mutations, four deletions and six synonymous mutations[11]. Non-synonymous mutations and deletions inferred to occur on the branch leading to lineage B.1.1.7 lineageare enumerated in table 1and others in the open reading frame and one in the M gene. This was the appearance of an unusually large number of mutations in a single cluster so far (Table 1a. Priority mutations tracked by COG-UK,Table 1b. Priority lineages tracked by COG-UK)Most mutations are not concerning because they do not result in a change in one of the nucleotides that generate the proteins the virus is made of. When they do that becomes serious specially when the mutations occur in a region of the virus that could change the way it interacts with its human host. In this case changes in the spike protein which projects outside the virus and is the mechanism by which it attaches to enter the host cell where it can replicate becomes of great interest. The lineage B 1.1.7 has one mutation termedN501Y [12](denotes the wildtype N Asparagine replacement with amino acid Y Tyrosine)that had been shown to increase how tightly the protein combines to a receptor on the surface of the human cell. A second change (69 – 70 deletion) had been identified in viruses that evolved to evade the natural immune response in some immune compromised patients. How this large cluster of mutations occurred simultaneously is a conjecture including viral replication under selective pressures in an alternative host (for example the Danish cluster in minks) or possibly in an immune compromised patientwho was chronically infected with the virus and able to replicate and evolve in them over a long period of time. These hypotheses remain unproven.

Potential impact of spike variant N501Y[13] :

(a) Transmissibility: the new variant has increased transmissibility characterised by an absolute increase in the R value of between 0.39 -0.93. This is likely through the N501Y affecting the receptor binding affinity of the spike protein is enhancing the transmissibility of the virus.

(b) Antigenicity: position 501 is in the receptor binding domain where neutralising antibodies most frequently act and therefore it is possible that variants at this position affect the efficacy of neutralisation of the virus.

(c) The growth rate from genomic data suggests that it is 71% higher than other variants.

(d) The PCR ct values suggest a decrease of cyclical time value of around two with the new variant

(e) the emergence and subsequent dominance of the new variant does suggest that the new variant has a selective advantage over other variants.

(f) The stability and growth potential of the new strain during a period when National lockdown measures were taken suggests a higher replicative potential of the new strain.

As of the 18 December 2020 NERVTAG[14]opined that there was currently insufficient data to draw any conclusions on:

Table 1 — *Non-synonymous mutations and deletions inferred to occur on the branch leading to lineage B.1.1.7 lineage.(Ref: ICOG – UK - COVID 19 genomics UK Consortium)*

Gene	Nucleotide	Amino acid
ORF1ab	C3267T	T1001I
	C5388A	A1708D
	T6954C	I2230T
	11288-11296 deletion	SGF 3675-3677 deletion
Spike	21765-21770 deletion	HV 69-70 deletion
	21991-21993 deletion	Y144 deletion
	A23063T	N501Y
	C23271A	A570D
	C23604A	P681H
	C23709T	T716I
	T24506G	S982A
	G24914C	D1118H
Orf8	C27972T	Q27stop
	G28048T	R52I
	A28111G	Y73C
N	28280 GAT->CTA	D3L
	C28977T	S235F

(1) underlying mechanisms of increased transmissibility

(2) the age distribution of cases

(3) disease severity (4 deaths from around 1000 cases till 18/12/2020)

(4) antigenic escape: the location of the mutations in the receptor binding domain of the spike glycoprotein which raises the possibility that this variant is antigenically distinct from prior variants. Four probable reinfections have been identified among 915 subjects with this variant and further work was needed to compare this reinfection rate with compatible data sets.

(5) Within the UK the variant was concentrated in the London, south-east and East of England but had been detected in various parts of the UK as part of its spread.

(6) Few cases of this variant have been reported internationally including export from the UK to Australia and to India. (As of 30 December, VOC-202012/01 variant has been reported in 31 other countries/territories/areas in five of the six WHO regions.)[13]The UK sequencing capabilityis acknowledged to be very robust for new genotypes as well as for epidemiological surveillance.

(7) NERVTAG endorsed the actions proposed by Public Health England and suggested better comparative data on reinfection, readmission and case fatality rates acquisitions, better data on age distribution of infections and in vitrio data on the ability of convalescent and post-immunisation sera to neutralise the new variant.

Effect of Vaccinations :

With vaccinations being rolled out in the UK there is no evidence so far to suggest that the current vaccination targets are not effective against the new variant. However, this is subject to confirmation and in the absence of genotype testing prior to mass vaccination the Chief medical Officer Sir Chris Whitty[15] has advised routine vaccination. The Prime Minister Mr Boris Johnson on 19 December 2020 also endorsed the same view where he reported absence of evidence to suggest the vaccine will be any less effective against the new variant. In the light of this resurgence of "new variant" SARS-CoV-2 infections fresh lockdown and tiered containment strategies are again in force throughout the UK. The PM Mr Johnson reluctantly to save lives announced a third lockdown on and from 5

Table 1a — *Priority mutations being tracked by COG-UK(Ref: ICOG – UK - COVID 19 genomics UK Consortium)*

Mutation	Predominant Lineage	Reasons for tracking	Cumulative number in UK	Number over last 28 days (13/11/2020 - 10/12/2020)
D614G	B.1	Moderate effect on transmissibility	118,906	11,447
A222V	B1.177	Fast growing lineage but no evidence of mutation effect	46,710	7,856
N439K	B.1.141 B.1.258	(1) Increased binding affinity to hACE2receptor	3,320	246
		(2) Escape to somemAbs	3,504	1,228
Δ69-70	B.1.1 B.1.258	Possible escape to some mAbs		
N501Y	B.1.1.7	Fast growing lineage & increased binding affinity to hACE2 receptor	2,057	1,182
N501Y+Δ69-70	B.1.1.7	Likely to maintain characteristics described for N501Y and 69-70del	1,524	1,034
N439K+Δ69-70	B.1.258	Likely to maintain characteristics described for N439Y and 69-70del	1,895	176
Y453F	B.1.1 B.1.1.298	(1) Increase binding affinity to hACE2receptor		
		(2) Escape to somem Abs Human/ minkassociated	0	0

Cumulative number as of December 15 based on data deposited into CLIMB. Caution is required since the data will not include information from the last 2 weeks.

Jan 2021[16] to enable the vaccine to take effect and in the meantime to avoid loss of lives and overwhelming the health services that are on the brink and particularly the ITU's and Ventilatory care services. The country since the onset of the pandemic has been divided into four tier zones and presently about 80% of the country is in the higher tiers with the South of England predominantly in Tier 4 with severe restrictions to avoid viral transmission. As a consequence, all social mixing has been curtailed both indoors and outdoors with contacts limited to close family only and a total ban on congregations at public places. Advice on hand hygiene, the wearing of masks, social distancing and avoiding congregation is what one is regularly reminded of on the media waves. Schools remain closed and working from home unless otherwise mandatory remains the ongoing order for the last nine months. Experience from brief relaxations of the above restrictions have only demonstrated how intensively transmissible this virus and its variants are the moment we let our guard down. This precaution against spread and ultra-vigilance has become the order of the day.

Will the vaccine still work?[17] The new variant has mutations to the spike protein that the three leading vaccines are

Appendix (Ref: ICOG – UK - COVID 19 genomics UK Consortium)

The extent to which SARS-CoV-2 may evolve to escape immunity induced by infection or vaccination is not currently known. Determining phenotype from genetic data is a fundamental challenge. **Figure 1a** shows the localisation of the selected mutations in a three dimensional structure of the Spike protein. A222V and the 69-70 deletion are localised relatively far from the receptor-binding site in comparison with amino acid residues 453, 439 and 501 which are in the RBD region. For each amino acid present in the Spike structure, an antibody accessibility score was calculated in **Figure 1b**. High antibody accessibility scores for 501, 439 and 70 correspond to sites that sit on the surface of the protein and that are more easily accessible to antibodies. Antibodies (Ab) are known to recognise specific regions of the Spike protein known as epitopes. Depending on the areas that Abs target there are 4 classes for the RBD region and 1 class for the N-terminal domain (NTD) near to where 69-70 sit (**Figure 1c-d**).

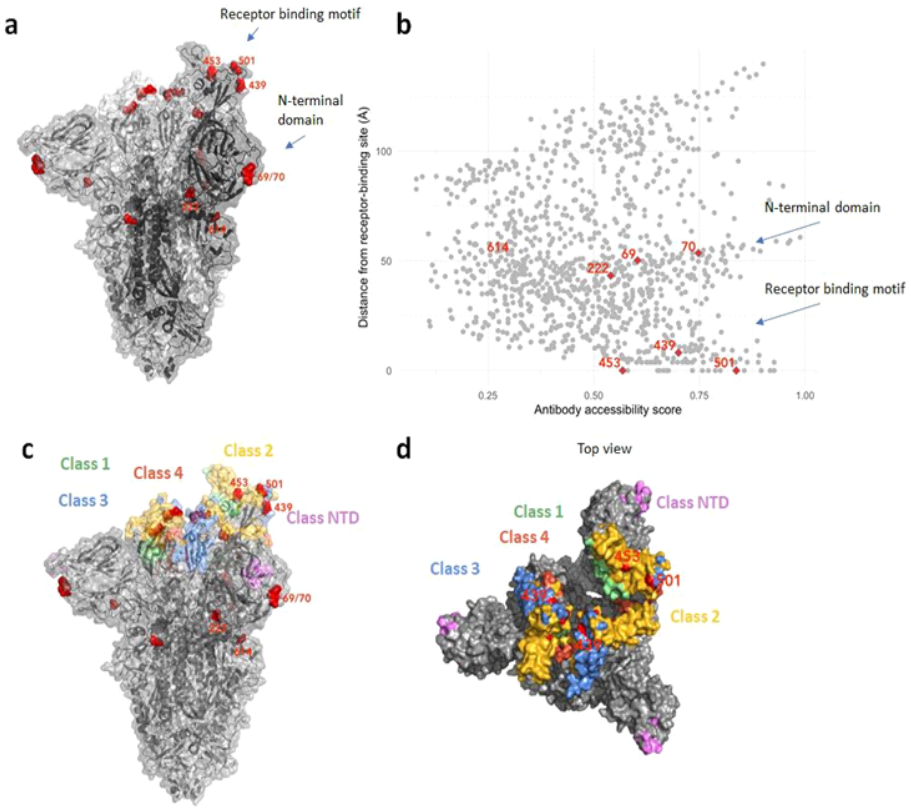

Fig 1 — Localisation of mutations in the Spike structure. a) Spike heterotrimer in open conformation (PDB: 6ZGG, Wrobel et al. 2020). Locations of deleted residues His69 and Val70 and the residues involved in substitutions (A222V, N439K, Y453F, and N501Y) are highlighted in red; b) Each point represents a Spike protein amino acid residue positioned according to distance from the hACE2 receptor-binding site and an antibody accessibility score. Residues associated with high interest amino acid substitution or deletions are highlighted with red diamonds. Residues belonging to the receptor-binding site defined as those with atoms within 4Å in Spike:hACE2 complex and distance to these residues based on closed conformation Spike. Antibody accessibility score represents surface accessibility and amino acid identity of target residue and weighted average of nearby residues and is scaled between minimum 0 and maximum 1, calculated across Spike in open and closed conformations; residues are positioned according to their maximum score across Spike in either open and closed conformations; c-d) Highlighted in colours regions target by different classes of Abs. 453, 501 and 439 are localised in the regions targeted by some classes of mAbs. 69-70 is near a region targeted by other mAbs and deletion might alter the structure of neighbouring amino acids. green = class 1: ACE2 blocking, bind open RBD only; yellow = class 2: ACE2 blocking, bind open and closed RBD; blue = class 3: non-ACE2 blocking, bind open and closed RBD; orange = class 4: non_ACE2 blocking, bind open RBD only). Epitope residues described in the NTD are coloured in magenta.

targeting. However, vaccines produce antibodies against many areas in the spike protein, so a single change would not make the vaccine less effective.

Over time, with more mutations , the vaccine may need to be changed. This happens with seasonal flu, which mutates every year, and the vaccine is altered accordingly. The SARS-CoV-2 virus does not mutate as often as the flu virus, and the vaccines that have so far proved effective in trials are types that can easily be modified if necessary. In India, several vaccines are being rolled out with different targets and different schedules. It is hoped that the mutations do not affect the efficacy of the vaccine and the vaccine effect is lasting – these are matters that are yet to be accurately fathomed.

Herd immunity[18] : at the onset of the pandemic in UK, the public health strategy was to build up herd immunity. However, when the virulence of the virus andunpredictability in its clinical manifestations in various age groups became apparent and the healthcare resources were getting overwhelmed including infections among medical personnel, the above lockdown/containment initiatives were initiated to avoid the number of deaths and to avoid overwhelming the health services. However new variants like this one and the other virus mutations that are being regularly monitored and tracked by COG-UK have regularly nearly pushed health resources to the brink.

As scientists and epidemiologists work overtime to determine the genetic changes theSARS-CoV-2 acquires and vaccines that have been produced in a fast tracked manner are rolled out to develop population immunity against the specified vaccine viral components, it is hoped the population will acquire the basic immunity againstSARS-CoV-2 and its various variants, mutations and lineages to build up herd immunity to stop its spread among nations despite strict travel restrictions and domestic population containment strategies that have been in force for several months now. As vaccines are given it will be important to sequence SARS-CoV-2 virus from infected people who have been vaccinated or had a second infection with the aim to detect variants that are evading the immune system produced by past infection or vaccination. The extent to whichSARS-CoV-2 may evolve to escape immunity induced by infection or vaccination is not currently known. Determining phenotype from genetic data is challenging. – localisation of mutations in the spike structure – appendix 2.

Epidemiological studies have confirmed that new infection rates decline with strict infection-control measures unless "new variants" with higher transmissibility and infectivity and new relations with the host immunity set the clock back and generate clinical cases to the detriment of people's lives and healthcare resource. This seesaw battle with the virus has been the feature of our struggle for nearly all of 2020 as people, businesses and social activities continued to suffer globally.

Priority mutations being tracked by COG-UK[19]: in addition to the "new variant" arising from mutation N501Y and deletions 69 – 70 of the predominant lineage B.1.1.7 a few other mutations and the "cluster five variant" (Danish mink variant) are also being tracked on a matter of priority from the public health point of health protection strategy. A major impediment is our lack of understanding of the various mutations including

Table 1b — *Priority lineages being tracked by COG-UK(Ref: ICOG – UK - COVID 19 genomics UK Consortium)*

Variant	*Reason for tracking*	*Cumulative number in the UK*	*Number overlast 28 days (13/11/2020 - 10/12/2020)*
'Cluster 5 variant'	Danish Mink variant. Contains 4 mutations including: Y453F, 69-70del, I692V and M1229I. Cluster 5 variants may be able to escape the effect of convalescent plasma. Y453F has increased binding affinity to the human ACE2 receptor in laboratory experiments	0	0
B.1.1.7 (variant)[1]	Has 17 mutations (14 replacements and 3 deletions) including: T1001I, A1708D, I2230T, SGF 3675-3677 del In the ORF1ab; 69-70 del, Y144 del, N501Y, A570D, P681H, T716I,S982Aand D1118H in the Spike; Q27stop, R52I and Y73C in ORF8; D3L and S235F in the N. Noteworthy N501Y enhances ACE2 binding affinity, 69-70del has immunological role and it is associated with some diagnostics failures,and P681H occurs at the furin cleavage site, known for biological significance in membranefusion	1416	945

[1]Named by Public Health England as VUI-202012/01 (the first "Variant Under Investigation" in December 2020)

of potentially structurally important areas of the spike protein and the interactions of the virus with the host.

Way forward as of 5 Jan 2021 in the UK[20]: The PM Mr Boris Johnson announced a third national lockdown last night at 8 pm to save lives and avoid the National Health Service getting overwhelmed. It is hoped that the massive rollout of the vaccination programme with build-up of population immunity in the next 2-3 weeks to prevent spread of the virus and clinical illness. In the meantime, we must all wear face masks, wash our hands for 20 secs and or use hand gel, have 2 m social distancing, avoid all unnecessary travel and congregation and listen to administration guidelines to save and protect lives. In India it is hoped the new variant is contained pre-emptively as it spreads very fast and its clinical manifestations and response to current vaccination targets are yet not certain. With the new variant already spread to 31 countries we can only rely on extreme vigilance and caution to save ourselves and all around us and cooperate with administration at all times.

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