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Delta variant - A new phase of COVID-19 in India

S.S.Sreenivas

ICAR-CTRI Research Station, Hunsur 571 105, Karnataka, India

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Abstract *- SARS-CoV-2 virus first reported from Wuhan City of Hubei Province of China became COVID-19 pandemic throughout the world. A variant of SARS-CoV-2 was noticed in India in late 2020, spread throughout India and other countries. The variant became dominant in India and the United Kingdom. The delta variant is now present in almost 100 countries. This variant of SARS-CoV-2 was assigned sub-lineage B.1.617.2 (Delta), of B.1.617. Variant Delta has around nine critical mutations with altered amino-acid sequences of the proteins it encodes and linked to increased ACE2 binding and enhanced escape from neutralizing antibodies. The global emergence of L452R independently in several lineages since November/December 2020 suggests a role in immune-evasion as an adaptation. Delta variant with an additional K417N mutation resulted in a new variant B.1.617.2.1 (Delta plus). The impact of mutation E484Q in Delta plus is similar to that of E484K, which was reported to diminish antibody binding, including those elicited by vaccination.*

Keywords *— COVID-19, SARS-CoV-2, Delta variant, mutation, Delta plus*

I. INTRODUCTION

COVID-19 first reported in Wuhan City of Hubei Province of China and affected millions of individuals worldwide is primarily a severe acute respiratory infection caused by coronavirus 2 (SARS-CoV-2)[1-7] Coronaviruses of family *Coronaviridae* are known to infect hosts in a species-specific manner with acute or persistent infections. Infection is transmitted mainly via respiratory and fecal-oral routes. COVID-19 can be transmitted by both asymptomatic and mildly symptomatic individuals. Reviews on molecular aspects of coronaviruses have appeared in the Advances in Virus Research series [8-11]. Spike-like projections on virus surfaces give them a crown-like appearance and hence coronaviruses[12]. The virus SARS CoV-2 is known to mutate, and the first variant was reported from China [13-18]. Coronavirus employs a complex gene expression and pathway system unique among RNA viruses and makes relatively fewer mutations than most RNA and DNA viruses because they encode an enzyme exoribonuclease domain (ExoN) to proofread errors[19]. Infectivity, human-to-human transmission, pathogenesis, and immune escape are known to be influenced by select mutations in the receptor-binding motif (RBM)[20,21]. Spike (S) proteins facilitate invasion of host cells and bind to host cell receptor, angiotensin-converting enzyme-2 (ACE2), which regulates blood pressure and fluid salt balance. Six amino acid residues of Receptor Binding Domain (RBD) viz., L455, F486, Q493, S494, N501, and Y505 are critical for the binding capacity of SARS-CoV-2 to ACE2 receptors [22]. Residues N501 contribute to the increased binding ability to ACE2[23,24] by interacting with a salt bridge D38-K353 of ACE2 [17]. WHO notified Variants of Concern (VOCs) and Variants of Interest (VOIs) through monitoring and assessing the evolution of SARS-CoV-2 (Table 1). Based on certain attributes like increased transmissibility, virulence, clinical disease aspects, potential reduction in neutralization by some EUA monoclonal antibody treatments,[25,26] reduced neutralization by post-vaccination sera[27,28]and decrease in the effectiveness of preventive measures presently available variants are being described as variants of concern. Variants of Interest (VOI) are isolated with genomic change or suspected phenotypic changes with presence in multiple countries. Genetic variants of SARS-CoV-2 are routinely monitored through sequence-based surveillance, laboratory studies, and epidemiological investigations. ECDC was regularly monitoring variants based genomic screening performed using an open-source algorithm[29]. Currently, genetic lineages by a 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 1)[30].

II. METHODOLOGY

A review of research work carried on the COVID-19 virus SARS CoV-2 variant Delta and its evolution was made. Based on available published research, a review was made to summarize information on the variant Delta of coronavirus, its response to monoclonal antibodies, and currently developed vaccines against the virus. Information was sourced from WHO and other official websites on different aspects of the Delta variant.

III. PHYLOGENY OF DELTA VARIANT

The emergence of variants from the lineage of B.1.1.7 has raised global concern. A new variant emerged in the state of Maharashtra in late 2020, spread throughout India and many countries. The variant also became dominant in India and the United Kingdom[31-35] and was assigned sub-lineage B.1.617.2, of B.1.617. Initially, noted as the 21A clade under the *Nextstrain* phylogenetic classification system later designated as Delta by WHO on 31 May 2021[36]. Recent variants are noted to have multiple mutations in RBD, such as N501Y, E484K, and K417N/T37[18,37,38]. Delta has around nine key mutations which altered the amino-acid sequences of the proteins it encodes [39], with four of them in the virus's spike protein (SP) and is of serious concern. SARS-CoV-2 Spike protein (SP) alteration reported a substitution of T478K, P681R, and L452R[40,41] known to affect transmissibility. The variant also shares D614G substitution noted in Alpha, Beta, and Gamma shown to result in significantly higher infectivity and more transmission of the virus[42-44] (Tables 2&3)

Table 1: Variants of Concern (VOC)

WHO label	Pango lineage	GISAID clade/lineage	Nextstrain clade
Alpha	B.1.1.7	GRY (formerly GR/501Y.V1)	20I/S:501Y.V1
Beta	B.1.351	GH/501Y.V2	20H/S:501Y.V2
Gamma	P.1	GR/501Y.V3	20J/S:501Y.V3
Delta	B.1.617.2	G/452R.V3	21A/S:478K

IV. SENSITIVITY TO ANTIBODY NEUTRALIZATION

An interesting finding on substitution of L452R, which mediates a stronger affinity for the ACE2 receptor and P681R enhances cell level infectivity, makes the Delta variant distinct. Mutations T19R, G142D, E156G, 99 F157Δ, and R158Δ were reported to contain epitopes for neutralizing antibodies[45-48], mutation L452R with Leucine to arginine substitution[49-51] reduce antibody-mediated neutralization[52,53]. The K417N mutation also detected in Beta variant with the exchange of lysine-to- asparagine substitution is reported to be associated with immune escape[54]. Investigation of the effect of RBD mutations on the binding of convalescent plasma by deep mutational scanning suggests the impact of E484Q is similar to that of E484K, which diminished antibody binding, including those elicited by vaccination[55,56]. Significantly reduced sensitivity of B.1.617.2 to convalescent sera and vaccine-elicited antibodies, manifested in Indian vaccinated healthcare workers (HCW) was reported recently[57]. Epidemiological studies indicate that a combination of evasion of neutralizing antibodies in previously infected individuals by Wuhan-1 D614G in 2020 and increased virus infectivity led to the dominance of the Delta variant in India[58]. The structural analysis of RBD mutations L452R and E484Q along with P681R in the furin cleavage site reveals that these may possibly result in increased ACE2 binding and rate of S1-S2 cleavage resulting in better transmissibility[59]. The same two RBD mutations indicated decreased binding to select monoclonal antibodies (mAbs) and may affect their neutralization potential[60-62]. Studies have shown that Delta is less sensitive to sera from naturally immunized individuals, while vaccination of convalescent individuals boosted the humoral immune response well. Delta with an additional K417N mutation corresponding to lineages AY.1 and AY.2 resulted in a new variant B.1.617.2.1 (Delta plus) [63,64]. Symptoms caused by the delta variant differ from the original virus and other mutations. Some key mutations in the delta variant E484Q, L452R, and P614R, along with earlier N501Ymake easier for the virus spike to attach to ACE-2 receptors. The K417N mutation also detected in Beta variant[65] with the exchange of lysine-to- asparagine substitution is reported to be associated with immune escape.

Table 2: Phylogeny of Delta variant

Sub-lineage	Spike Protein Substitutions	Name*
B.1.617.1 Kappa India-2020	(T95I), G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H	20A/S:154K
B.1.617.2 Delta India-2020	T19R, (V70F*), T95I, G142D, E156-, F157-, R158G, (A222V*), (W258L*), (K417N*), L452R, T478K, D614G, P681R, D950N	21A/S:478K
B.1.617.3 India-2020	T19R, G142D, L452R, E484Q, D614G, P681R, D950N	20A

*Nextstrainexternal icon

Table 3: Critical mutations in Delta variant

Mutation	Position
T19R, G142D, E156G, F157Δ & R158Δ	N-terminal domain of S1
D614G	Between RBD and S1/S2 cleavage at 614
T478K	Receptor binding domain (RBD) at 478
L452R	Receptor binding domain (RBD) at 452
P681R	Receptor binding domain (RBD) at 681

V. RESPONSE TO VACCINES

Immune evasion enhanced colon and lung cell entry and augmented syncytium formation by B.1.617.2 has been reported[66]. Both sub-lineage B.1.617.1 and B.1.617.2 share

the presence of L452R spike mutation with 'California Variant' B.1.429. Further, the two-dose effectiveness of the ChAdOX1 vaccine is reduced to 59.8% following exposure to B.1.617.2[67]. Transmissibility studies with animal models revealed chief dependent on the polybasic cleavage site (PBCS) between S1 and S2, unlike endosomal entry route[68,69]. No significant vaccine efficacy against the Delta variant is reported so far. Neutralizing antibodies from symptomatic infection of covid-19 are highly protective[70,71]. Recently published studies in which sera from subjects who received the Moderna, Pfizer-BioNTech, or Oxford-AstraZeneca COVID-19 vaccines, the reduction in neutralization titer was greater for the Beta (B.1.351) than observed for the Delta (B.1.617.2) variant. According to Public Health England (PHE) effectiveness of the BNT162b2 vaccine is reduced to 33.5% and 87.9% after the first and two doses, respectively, while it is 59.8% after two doses of the ChAdOX1 vaccine following exposure to B.1.617.2[67]. At the same time, the Public Health England (PHE) reported that Pfizer-BioNTech vaccine against Delta is 96% and Oxford-AstraZeneca vaccine is 92% effective against hospitalization after 2 doses of vaccine[72]. Global emergence of L452R independently in several lineages since November/December 2020 suggests a role in immune-evasion as an adaptation[73]. Studies show that the Delta variant is less sensitive to sera from naturally immunized individuals, while vaccination of convalescent individuals boosted the humoral immune response well[67]. Compared to unvaccinated convalescents, vaccinated participants showed cross-neutralizing antibody responses to Delta[74,75].

VI. Conclusions

The emergence of variant B.1.617.2 in the state of Maharashtra in late 2020 and later spread throughout India has raised the alarm to be notified as VOC by WHO. The variant with around nine crucial mutations of altered amino-acid sequences of the proteins is subject to the reason for the faster spread. The substitution of L452R, which mediates a stronger affinity for the ACE2 receptor, and P681R, which enhances cell level infectivity, makes the Delta variant distinct. The emergence of L452R independently in several lineages since November/December 2020 suggests a role in immune-evasion as an adaptation. These two mutations could make the virus more transmissible as well as help it evade human-made antibodies such as Casirivimab and Imdevimab, which are the mark of monoclonal antibody cocktails currently under emergency use for Covid-19 treatment in India is a major health concern. India has registered 56 cases of the Delta Plus variant in 12 states till June 2021. The government of India declared the 'Delta Plus' virus is causing Covid-19 as a 'variant of concern' in India. Scaling up of studies with monoclonal antibodies (mAbs) is a priority to understand the viral mutations. Surveillance and close monitoring of the genomic sequence of SARS-CoV-2 is an important process in developing a broad and effective intervention to check the virus. Hastening the process of vaccination is vital to bring herd immunity to safeguard vulnerable groups, especially children.

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