

Letter to the Editor

Fahad Imtiaz Rahman, Sadia Afruz Ether and Md. Rabiul Islam*

The “Delta Plus” COVID-19 variant has evolved to become the next potential variant of concern: mutation history and measures of prevention

<https://doi.org/10.1515/jbcpp-2021-0251>

Received August 17, 2021; accepted September 8, 2021;

published online September 27, 2021

Keywords: coronavirus; COVID-19 pandemic; Delta Plus; mutation; public health.

Dear Editor,

Since the first case of coronavirus disease 2019 (COVID-19) in Wuhan of Hubei province, China back in December 2019, waves of outbreak caused by the severe acute respiratory coronavirus 2 (SARS-CoV-2) have continued to claim lives in different regions of the world [1]. As of August 30, 2021, the World Health Organization (WHO) reports more than 216 million confirmed COVID-19 cases with almost 4.5 million casualties [2]. Although multiple vaccines have been discovered which are being administered worldwide, the virus continues to rage on, mainly due to its rapid mutations that keep enhancing its potency by imparting unique characteristics [3]. Viruses keep evolving as it replicates, and it is only natural for newer variants of a virus to develop over time. Since the pandemic began, numerous mutant strains of SARS-CoV-2 have been identified. They have been classified into three categories-variant of interest, variant of concern, and a variant of high consequence by the SARS-CoV-2 Inter-agency Group of the US Department of Health and Human Services [4]. In December 2020, the first reports of these variants of concern were emerging. The B.1.1.7 variant (WHO label: Alpha) had a mutation (N501Y) in the receptor-binding domain of its spike protein which increased its rate of transmission and caused an unexpected rise of

COVID-19 cases in the United Kingdom [5]. Another variant, B.1.351 (WHO label: Beta) has three concerning mutations (N501Y, E484K, and K417N) in its spike protein and it spread like wildfire in South Africa [6] due to its increased transmission rate and potential to escape antibodies [7]. Later on, the P.1 variant (WHO label: Gamma) discovered in Manaus, Brazil was found to have a set of mutations (N501Y, E484K, and K417T) in its spike protein which probably contributed to the country’s massive death toll from COVID-19 infection over the first half of 2021 [8]. However, the most concerning variant right now is B.1.617.2 (WHO label: Delta) that has become the predominant SARS-CoV-2 strain in the world with unique sets of mutations (T478K, P681R, and L452R) that makes it highly contagious and evade neutralizing antibodies in previously infected or vaccinated people [9].

Since the first detection of the Delta variant in India in late 2020, the strain has caused an upsurge of COVID-19 infection in different countries. It has continued to evolve as well, extending its lineage into various subtypes. On June 11, 2021, Public Health England began to report on the AY.1 sub-lineage of delta variant in its technical briefings, which has an additional K417N mutation in its spike protein [10]. This AY.1 variant, also known as the “Delta Plus” variant, is feared to have even more antibody escaping properties because of the K417N mutation which was previously seen in the Beta variant. As of August 31, 2021, 895 genome sequences of the Delta Plus variant have been identified in at least 32 countries around the world, the majority of them being in the United States [11]. The Delta Plus variant was found to have reduced neutralization in COVID-19 naïve or recovered patients who were vaccinated by the BBV152 (Covaxin) vaccine in India [12]. It has also been reported to resist monoclonal antibodies such as Casirivimab and Imdevimab which are used against COVID-19 and it has been suggested of having increased transmissibility and greater affinity to the mucosal lining of lungs compared to other variants [13]. India has already announced Delta Plus to be a variant of concern in June, after around 40 cases were reported in Maharashtra,

*Corresponding author: Dr. Md. Rabiul Islam, Department of Pharmacy, University of Asia Pacific, Dhaka, Bangladesh, Phone: +8801916031831, E-mail: robi.ayaan@gmail.com. <https://orcid.org/0000-0003-2820-3144>

Fahad Imtiaz Rahman, Department of Clinical Pharmacy and Pharmacology, University of Dhaka, Dhaka, Bangladesh

Sadia Afruz Ether, Department of Pharmacy, Daffodil International University, Dhaka, Bangladesh

Kerala, and Madhya Pradesh [14]. However, U.S. Centers for Disease Control and Prevention and the WHO have not done so yet as some experts believe that it is still unclear how dangerous the variant is [15]. We have presented epidemiological evidence of the current variants of concern and the Delta Plus variant in Table 1.

Table 1: Epidemiological evidence of SARS-CoV-2 variants of concern and the emerging Delta Plus variant based on latest updates by Centers for Disease Control and Prevention (CDC)⁴.

WHO name (Pango lineage)	Spike protein substitutions (key mutations in bold)	First detected	Transmissibility	Severity	Immune escape
Alpha (B.1.1.7)	69del, 70del, 144del, E484K , S494P, N501Y , A570D, D614G, P681H, T716I, S982A, D1118H K1191N.	United Kingdom Dec 2020	– Around 50% increased rate of transmission	– Increased hospitalization rates – Increased fatality rate	– Low impact on neutralization by sera antibodies of covid recovered and vaccinated individuals – No impact on emergency use authorization (EUA) monoclonal antibody treatments
Beta (B.1.351)	D80A, D215G, 241del, 242del, 243del, K417N , E484K , N501Y , D614G, A701V.	South Africa Sep 2020	– Around 50% increased rate of transmission	– More lethal compared to wild SARS-CoV-2 variant	– Reduced neutralization by sera antibodies of covid recovered and vaccinated individuals – Significantly reduced susceptibility to monoclonal antibody combinations of bamlanivimab and etesevimab
Gamma (P.1)	L18F, T20N, P26S, D138Y, R190S, K417T , E484K , N501Y , D614G, H655Y, T1027I.	Japan/ Brazil Dec 2020	– Not ascertained yet	– More lethal compared to wild SARS-CoV-2 variant	– Reduced neutralization by sera antibodies of covid recovered and vaccinated individuals – Significantly reduced susceptibility to monoclonal antibody combinations of bamlanivimab and etesevimab
Delta (B.1.617.2)	T19R, V70F, T95I, G142D, 156del, 157del, R158G, A222V, W258L, K417N , L452R , T478K, D614G, P681R, D950N.	India Dec 2020	– More than 2 times more contagious than previous variants	– Causes more severe illness than previous variants	– Reduced neutralization by sera antibodies of covid recovered and vaccinated individuals – Potential reduced susceptibility to some EUA monoclonal antibody treatments
Delta plus (AY.1)	T19R, E156G, 157del, 158del, W258L, K417N , L452R , T478K, D614G, P681R, D950N.	India Apr 2021	– Suggested of having increased transmissibility	– Not ascertained yet	– Reduced neutralization by sera antibodies of covid recovered and vaccinated individuals – Potential reduced susceptibility to some EUA monoclonal antibody treatments – Suggested of having greater affinity to the mucosal lining of lungs compared to other variants

The recent emergence of SARS-CoV-2 variants such as the Delta Plus is a concern. These variants can potentially lead to severe epidemic rebound in the future, as seen in South Africa, Brazil, India, etc. As many of these new variants are highly transmissible and can escape antibodies, they will continue to spread and evolve into more dangerous strains in the upcoming days. We recommend several measures that might be important to stem the resurgence of newer COVID-19 variants. First of all, vaccines need to be distributed equitably across the world. As first-world countries race to immunize their target population, they leave themselves vulnerable to the newer dangerous lineage of the SARS-CoV-2 variants that continue to evolve in unvaccinated low-income countries. This was evident in the recent surge of COVID-19 in the US, with cases reaching a six-month high in August, even though 51% of the population is fully vaccinated [16]. Higher vaccine coverage is required to ensure herd immunity across the world and children also have to be considered for vaccine shots as they can often be asymptomatic spreaders. Secondly, pharmaceutical interventions and treatment approaches need to be reevaluated considering the uniqueness of each new variant emerging. Therapeutic strategies that were successful in dealing with earlier strains of SARS-CoV-2 might be outdated already and need to be updated based on emerging medical trends. Thirdly, every country needs to begin genomic sequencing of SARS-CoV-2 variants to monitor their spread and evolution. In this regard, WHO and first-world countries can share variant-specific polymerase chain reaction (PCR) primers with resource-limited countries. Genetic sequences should also be uploaded and shared on international platforms such as GISAID for ease of access and analyses by researchers. Finally, current vaccines need to be adapted so that they can offer better protection against the newly emerging strains. Booster doses need to be developed and can be considered in regions that are heavily infected with the antibody escaping variants. This pandemic is unlikely to end anytime soon and is a reminder for us of what tremendous impact infectious diseases can have on our lives and economies. Global vaccine equity and prompt responsiveness of countries to outbreaks from newer strains are required for controlling the frequent surge of COVID-19 infection.

Acknowledgments: None.

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: Not applicable.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382:727–33.
2. WHO coronavirus disease (COVID-19) dashboard. World Health Organization. Available from: <https://covid19.who.int/> [Accessed 31 Aug 2021].
3. Li R, Liu J, Zhang H. The challenge of emerging SARS-CoV-2 mutants to vaccine development. *J Genet Genom* 2021;48:102–6.
4. SARS-CoV-2 variant classifications and definitions. Centers for Disease Control and Prevention. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html>. [Accessed 12 Aug 2021].
5. Volz E, Mishra S, Chand M, Barrett JC, Johnson R, Geidelberg L, et al. Transmission of SARS-CoV-2 Lineage B.1.1.7 in England: insights from linking epidemiological and genetic data. *medRxiv* 2021. <https://doi.org/10.1101/2020.12.30.20249034> [Epub ahead of print].
6. Tegally H, Wilkinson E, Giovanetti M, Iranzadeh A, Fonseca V, Giandhari J, et al. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. *medRxiv* 2020. <https://doi.org/10.1101/2020.12.21.20248640> [Epub ahead of print].
7. Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Oosthuysen B, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. *Nat Med* 2021;27:622–5.
8. Faria NR, Mellan TA, Whittaker C, Claro IM, Candido DD, Mishra S, et al. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. *Science* 2021;372:815–21.
9. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. *Nature* 2021;596:276–80.
10. SARS-CoV-2 variants of concern and variants under investigation in England: Technical briefing 15. Public Health England. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/993879/Variants_of_Concern_VOC_Technical_Briefing_15.pdf [Accessed 12 Aug 2021].
11. AY.1 Lineage Report. *Outbreak.info*. Available from: <https://outbreak.info/situation-reports?pango=AY.1&loc=IND&loc=GBR&loc=USA> [Accessed 31 August 2021].
12. Yadav PD, Sahay RR, Sapkal G, Nyayanit D, Shete AM, Deshpande G, et al. Comparable neutralization of SARS-CoV-2 Delta AY.1 and Delta in individuals sera vaccinated with BBV152. *bioRxiv* 2021. <https://doi.org/10.1101/2021.07.30.454511> [Epub ahead of print].
13. Roy B, Roy H. The Delta Plus variant of COVID-19: will it be the worst nightmare in the SARS-CoV-2 pandemic?. *J Biomed Sci* 2021;8:1–2.

14. Delta variant of Covid-19 mutates into delta Plus: all you need to know. The Times of India. Available from: <https://timesofindia.indiatimes.com/india/delta-variant-of-covid-19-mutates-into-delta-plus-all-you-need-to-know/articleshow/83538387.cms> [Accessed 12 Aug 2021].
15. Steenhuisen J. Explainer: beyond delta, scientists are watching new coronavirus variants. Reuters. Available from: <https://www.reuters.com/world/india/beyond-delta-scientists-are-watching-new-coronavirus-variants-2021-08-08/> [Accessed 12 Aug 2021].
16. Caspani M, Abraham RUS. COVID-19 cases reach six-month high, Florida grapples with surge. Reuters. Available from: <https://www.reuters.com/world/us/us-covid-19-cases-hit-six-month-high-over-100000-reuters-tally-2021-08-05/> [Accessed 12 Aug 2021].