

MINI-REVIEW



## Delta variant (B.1.617.2) of SARS-CoV-2: Mutations, impact, challenges and possible solutions

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### ABSTRACT

Since commencement of COVID-19 pandemic, several SARS-CoV-2 variants have emerged amid containment efforts *via* vaccination. The Delta variant (B.1.617.2), discovered in October 2020, was designated as a VOC by the WHO on May 11, 2021. The enhanced transmissibility of Delta variant has been associated with critical mutations such as D614G, L452R, P681R, and T478K in the S-protein. The increased affinity of the S-protein and ACE2 has been postulated as a key reason for decreased vaccine efficacy. As per evidence, the Delta variant possesses increased transmissibility and decreased vaccine efficacy compared to other VOCs like Alpha and Beta. This has led to concerns regarding the acquisition of novel mutations in the Delta variant and outbreaks in vulnerable communities, including vaccinated people. In this mini-review of Delta variant, we have explained its evolution and characteristics, the impact of spike mutations on infectivity and immune evasion, and measures to combat future outbreaks.

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### Introduction

Since the COVID-19 pandemic began, many SARS-CoV-2 mutations have been discovered and reported.<sup>1–6</sup> These rapid alterations were aided by recombination, selection pressure and point mutations.<sup>4,7</sup> SARS-CoV-2 mutations affect the neutralizing activity of vaccine-elicited antibodies and monoclonal antibodies (MAbs), resulting in a mild-to-significant loss of effectiveness.<sup>8–11</sup> They may also affect viral transmission, treatment efficacy, and diagnosis. According to the US Department of Health and Human Services, the SARS-CoV-2 variants fall into three broad categories: the variant of interest (VOI), the variant of concern (VOC), and the variant of high consequence.<sup>1,12–14</sup>

According to recent studies, the Delta variant (B.1.617.2) emerged during India's second wave of infections with a unique set of mutations (T478K, P681R, and L452R) that make it exceptionally infectious and immune to neutralizing antibodies in previously infected or vaccinated people.<sup>2,6,15</sup> Despite the fact that the Delta variant was first found in India in late 2020, it has caused a rise in COVID-19 infection in several other nations.<sup>16,17</sup> The Delta variant has progressed effectively, expanding its ancestry into various subgroups or sublineages such as AY.1, AY.2, AY.3, AY.33, AY.34. The AY.1 sub-lineage of delta variant, which contains an extra K417N mutation in its spike protein, has been reported in England.<sup>18</sup> The AY.1 variant known as the Delta Plus variant is thought to

be the most lethal. It has been postulated that the Delta Plus variant has even more antibody escaping properties because of the K417N mutation. A K417N mutation has been reported in the Beta variant previously.<sup>18,19</sup> Furthermore, in comparison to other VOCs, the Delta plus strain has been found to possess a greater risk of transmission and a high affinity to lung epithelial cells.<sup>19</sup>

However, recent genome sequencing research has confirmed that the Delta variant has spread across at least 32 nations worldwide, the bulk of which are in the United States.<sup>18,20</sup>

According to a recent comparison analysis, the Delta Plus variant exhibited a much higher number of high-prevalence mutations (20%) than the Delta variant. The Delta Plus version has a higher proportion of signature mutations in Spike (G142D, A222V, and T95I) than the Delta variant. Three spike mutations (K417N, V70F, and W258L) were found only in the Delta Plus version.<sup>19,21</sup> A novel mutation in ORF1a (A1146T) was discovered, which was exclusively seen in the Delta Plus variant with a 58% frequency.<sup>19</sup> Apart from that other four mutations detected in the ORF1a, i.e., P1604L, A3209V, V3718S, and T3750I,<sup>19,21</sup> Delta Plus variant had much more alterations, such as T95I, A222V, G142D, R158G, and K417N than the Delta variant.<sup>19</sup> According to structural analysis, mutations alter the sidechain conformation, weakening the antibody interactions.<sup>22</sup> Delta Plus originated in India



Delta variant's S-protein has shown the most substantial alterations. These alterations are thought to be responsible for the Delta variant being the most transmissible. There is no doubt that the Omicron variant has been widely altered thus far.<sup>9,12,26</sup> However, mutations in the Delta variant have been theorized to be more harmful than the Omicron variant. With updated knowledge on mutations and their impact, individually and in combination, on overall viral fitness, researchers will be able to better and more quickly predict the behavior of novel variants of SARS-CoV-2. Additionally, this will be an important consideration when assessing the ramifications of vaccination modifications and booster regimens.<sup>17</sup> The S-protein domain spike gene mutations in the Delta variant are D614G, L452R, P681R, and T478K, and these mutations are also recorded in other VOCs and VOIs (Table 1).<sup>26,29,30</sup> These mutations are highly likely to influence viral infectivity/transmissibility and resistance of the convalescent plasma (CP) or monoclonal antibodies (MAbs).<sup>14,31,32</sup>

The asparagine-to-glycine substitution at amino acid position 614 in the viral spike protein (D614G) is one of the most critical mutations that has been reported in the current circulating viral strains. Transitions from D614 to G614 happened asynchronously in many parts of the world, including local epidemics where the WT D614 virus was well-established prior to developing the G614 variation.<sup>33</sup> This suggests that the D614G change is not the result of an unintentional founder effect or genetic drift. There has been no clinical evidence of a difference in illness severity linked with the D614G alteration because S-protein influences the host range, tissue tropism, and pathogenicity by interacting with the host cell receptors ACE2. However, recent studies have suggested that D614G mutation improved the viral resilience in human hosts, resulting in greater dissemination in the community.<sup>34</sup>

Furthermore, several analyses, such as the clinical studies, have shown that the D614G mutation significantly increases the replication of the viral particles in the respiratory tract, notably in the upper region of the respiratory tract, which can be associated with the enhanced transmissible potential of the Delta variant. Nevertheless, it is essential to note that the D164G mutation does not lead to the increased severity of the infection. In addition, the enhanced viral replication has been associated with the changes that have occurred in the RBD of the S-protein due to the D614G mutation. In addition,

it has been shown through the neutralizing antibody data that the D614G mutation is unlikely to undermine the vaccine effectiveness, but it may influence the potency of therapeutic MAbs in an epitope-dependent way.<sup>34</sup> Furthermore, a recent genetic analysis in Qatar showed that the D614G mutation was more dominating and prevalent (approximately 80%) among 2634 SARS-CoV-2 genome sequences.<sup>35</sup> In addition, the SARS-CoV-2 variant with D614G mutation has been recorded to have modifications in the viral viability, which improve the dissemination of the Delta variant relative to the WT SARS-CoV-2.<sup>33</sup> However, the severity of the infection induced by the variant with D164G mutation may not be affected by this type of mutation.<sup>33,36</sup>

Another vital mutation in the Delta variant is at position 452, and the L452R mutation substitutes a leucine with an arginine. The L452 residue does not directly contact the ACE2 receptor. Because it is found in the spike protein's hydrophobic plaques, mutations create structural alterations that increase its interaction with the ACE-2 receptor.<sup>37,38</sup> It also aids viral replication by boosting spike persistence, viral transmissibility, and viral fusion.<sup>39</sup> Additionally, a pseudovirus analysis demonstrated that the L452R mutation is linked to significant enhancement in the binding of the S-protein to ACE-2 receptors.<sup>40</sup> The capacity of a pseudovirus harboring the L452R mutation to infect 293T cells improves by 7 to 23 times, and the ability to infect HAO-ACE2 cells rises about 6 to 15 folds relative to the D614G mutation only.<sup>40</sup> Moreover, L452R mutation can cause the vaccine-induced serum neutralizing antibody titer against the pseudovirus to decrease by 3–6 times<sup>39,41</sup> and the pseudovirus can evade several permitted MAbs based therapeutics.<sup>41,42</sup>

Another notable mutation in the Delta variant is the substitution of proline for arginine at position 681. The P681R mutation promotes the furin-mediated cleavage of the S-protein, which leads to the enhanced fusion of the viral particle with the host cell.<sup>28</sup> Compared to the strains lacking this mutation, this would allow for better viral fusion and integration into the host cell.<sup>29,30,43</sup> *In vitro* assays showed that P681R mutation does not increase the infectiousness of the Delta variant. However, the viral strain with P681R mutation exhibits higher pathogenicity in infected hamsters than the WT SARS-CoV-2 strain.<sup>43</sup>

**Table 1.** Major mutation of Spike protein (S-protein) of the Delta variant and their various impact on viral features such as transmissible nature and capability to evade the immune response and vaccine induced neutralizing antibodies (NABs).

S. No.	Major Mutation in the Spike-protein (S-protein)	Impact on transmissibility	Impact on severity	Impact on vaccine Effectiveness	Reference
1.	D614G	Significantly enhances the transmission	Non-significant impact on severity	Significant reduction in the vaccine effectiveness. The serum neutralizing antibody (NABs) titer against the pseudovirus decreased by 3–6 times as a result of the vaccine.	34,41
2.	L452R	Improves transmission	Significantly increases the severity	Help in the evasion of vaccines induced NABs	39–42
3.	P681R	Improves transmission	Non-significant impact on the severity	Partial decrease the vaccine effectiveness by evading NABs.	95
4.	T478K	Improves transmission	Increase in severity	Decrease in the sensitivity toward the Nabs elicited by vaccines	29,44
5.	K417N	Improves transmission (Based on Preliminary investigation)	Significant increase on severity (Based on preliminary data)	Significant reduction in the susceptibility of the virus to NABs by more than ten times	96–98



Recent studies have shown a partial reduction in neutralizing antibodies (NAbs) due to the P681R mutation in the Delta variant. The presence of both D614G and P681R mutation in the viral strain showed moderate (approximately 1.5 times) resilience to some important MAbs against the RBD region of the S-protein, according to a recent pseudovirus neutralization assay.<sup>43</sup> In addition, a significant reduction has been observed in neutralizing antibody (NAb) titer of serum elicited by the BNT162b2 vaccination against the D614G/P681R virus.<sup>43</sup> It's worth noting that this neutralization assay implies that the existence of many mutations in the virus strain might have negative repercussions.<sup>30</sup>

Another substitution (T478K) of the uncharged threonine (T) to a charged amino acid, lysine (K), is a crucial mutation that increases the electrostatic potential of surface S-protein of viral variant. This leads to a more positive value in the region of the S-protein, which directly interacts with the host cell receptor (ACE2). Additionally, the larger side chain of lysine is predicted to increase the steric hindrance of the delta variant, which can be a plausible reason for the significant increment in the interaction of S-protein with the ACE2 receptor.<sup>44</sup>

Another recent report suggests that the location of T478K increases the interaction of the S-protein with human ACE2 receptors, which leads to enhanced infectiousness of the Delta variant.<sup>45,46</sup> Moreover, it has been postulated that this mutation has led to the enhanced infectivity of the Mexican variant (B.1.1.222) of SARS-CoV-2.<sup>45</sup> According to the recent information by the global GISAID database, the presence of T478K mutation in the variant may enhance the adaptability of the variant in European countries.<sup>44</sup> Moreover, an *in vitro* analysis has suggested that the presence of this mutation can lead to immune evasion and reduce the sensitivity toward the NAbs (Figure 2).<sup>47</sup>

### Impact on the transmissibility and severity

A recent study has investigated the dissemination of the Delta variant of SARS-CoV-2 in China.<sup>48</sup> One hundred sixty-seven patients infected with the Delta variant were tracked back to the index case, and the viral load was recorded on a daily basis. Sequential polymerase chain reaction tests were used to retrieve the viral load in the patients. According to the investigators, the initial positive test of patients infected with the Delta variant had a viral load 1000 times greater than patients with 19A/19B strain infection, which led to the pandemic in early 2020.<sup>48</sup> This suggests that the Delta variant (B.1.617.2) possesses an enhanced capability of viral replication. In addition, the Delta variant is significantly more infectious than the parental strain of SARS-CoV-2.<sup>34</sup>

$R_0$  ( $R$ -naught) is the primary reproduction number, also known as the basic reproduction ratio or rate, which is an epidemiological metric used to measure the transmissibility of infectious agents.<sup>49</sup> The contagiousness of an infectious disease is usually measured by this epidemiological term known as  $R_0$ .  $R_0$  is calculated using the patient's duration of infectivity after infection, the mechanism of transmission, and the contact rate.<sup>49</sup>  $R_0$  of the initial COVID-19 strain discovered in Wuhan was 2.4–2.6, according to reports.<sup>49,50</sup> The  $R_0$  for the Alpha (B.1.617.2) strain was 4–5, whereas the  $R_0$  for the Delta (B.1.617.2) strain was 5–8.

This means that someone infected with the Delta variant of SARS-CoV-2 can infect up to eight other persons. It also suggests that the Delta variant can be twice as transmissible (or perhaps more) as the parental strain of SARS-CoV-2.<sup>51</sup>

In addition, it has been ascertained that the Delta variant of SARS-CoV-2 (B.1.617.2) is more infectious than smallpox, which has an  $R_0$  of 3.5–4.6.<sup>52</sup> Furthermore, it has been reported that the vaccination can provide a lesser amount of protection against asymptomatic community transmission of the Delta variant compared to the other variants reported so far.<sup>53,54</sup> Moreover, scientists believe that the higher dissemination or the circulation of the Delta variant in the community can lead to high rates of mutations. This, in turn, may enforce the emergence of novel variants of SARS-CoV-2. It has been suggested that because of the emergence of novel variants of SARS-CoV-2, the vaccine manufacturers such as Moderna and Pfizer may have to produce booster doses for their vaccines.<sup>30</sup>

### Immune escape or the resistance to convalescent plasma (CP)

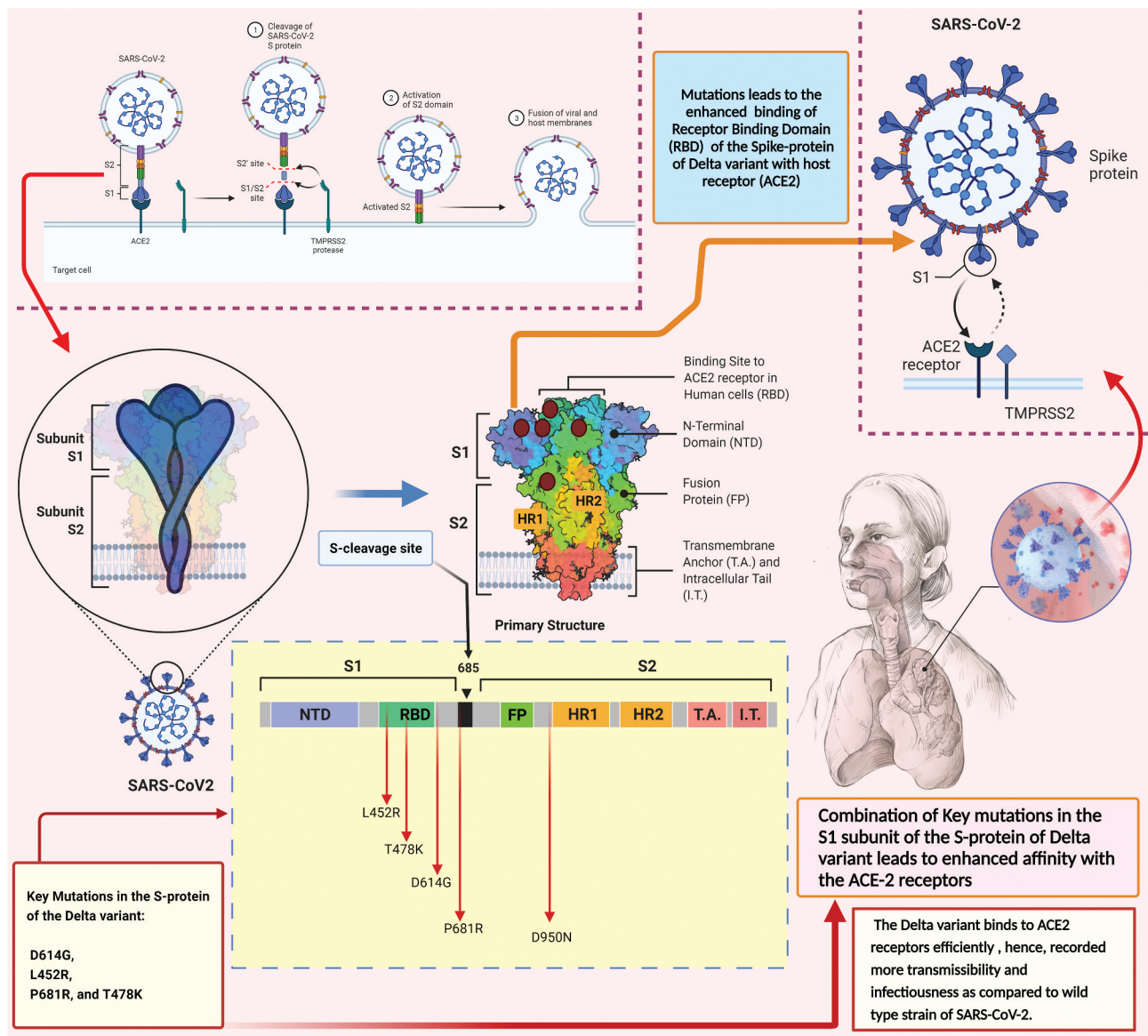
Earlier the E484 mutation was observed in the Beta and Gamma variants of SARS-CoV-2, which was linked to their ability to elude the immunological response, notably the neutralizing effectiveness of CP. However, it is yet unclear how far these variants can evade the neutralizing powers of CP in recovered and vaccinated individuals. Intriguingly, double mutations in the Delta variant's S-protein, such as E484Q and L452R, have been associated with immunological evasion, thus causing global havoc. The presence of E484 residue as a repulsive residue has been considered as a critical mutation as it is present at the RBD-ACE2 interface,<sup>55</sup> which might influence the attachment capabilities of RBD of S-protein with the ACE2.

The E484 and L452 mutations are linked with the resistance capabilities of the Delta variant against the neutralizing antibodies (NAbs) in the sera of convalescent people.<sup>56</sup> Hence, the variants including B.1.617, B.1.617.1, and B.1.617.3, possessing the E484 and L452 mutations, were initially considered to be strongly resistant to the body's immune response.

A two-fold resistance against the NAbs of CP has been observed in the variants such as B.1.617 and B.1.617.1. However, B.1.617.2 (Delta variant) is approximately six to eight times more resistant toward the CP of naturally infected and vaccinated individuals.<sup>57–59</sup> Moreover, a significant reduction was reported in the neutralization potentialities of the sera from COVID-19 convalescents against the Delta variant compared to the Alpha and Beta variants.<sup>12</sup> In addition, a recent study has revealed that the sera derived from persons immunized with one dose of Pfizer or AstraZeneca have inadequate neutralizing capacities against the Delta variant.<sup>12</sup>

### Influence on the vaccine efficacy (VE)

VOCs, particularly the Delta variant, have a direct influence on COVID-19 vaccines and immunotherapeutics because they can impair the neutralizing activity of vaccine-elicited antibodies and monoclonal antibodies (MAb), leading to a mild-to-significant loss of effectiveness.<sup>60–62</sup> BNT162b2 is a well-known mRNA-based vaccine developed by Pfizer and is widely used in



**Figure 2.** A schematic representation of the mutations in the Spike protein (S-protein) of Delta B.1.617.2 variant. The combination of mutations induces a conformational changes in the S-protein which leads to the substantial increase in the affinity of S-protein to the ACE2 receptors. The increased affinity between the S-protein and ACE2 receptors is a key factor in increased transmission and severity of the Delta variant.

the vaccination programs of several countries. Recent comparison studies have raised questions regarding the vaccine's efficacy, although the two booster doses of this vaccine offer a comparable degree of protection against the Delta strain.<sup>12,29,63</sup> Both BNT162b2 and ChAdOx1 nCoV-9 vaccines have been recorded to have reduced effectiveness in the individuals infected with the Delta variant compared to the other VOCs. It is essential to consider that these results were obtained with the individuals given a single dose of the vaccine.

Further analysis with two doses of the vaccine have shown the apparent effectiveness of the major vaccines against the Delta variant. The efficacy of two doses of the BNT162b2 vaccine was 93.7% in people with the Alpha variant and 88% in people with the Delta variant. The efficacy of two doses of the ChAdOx1 nCoV-19 vaccine was 74.5% in people with the Alpha variant and 67.0% in people with the Delta variant. After receiving the two vaccine doses, minor changes in vaccine

efficacy were seen between the Delta and Alpha variants. After the first dosage, absolute variations in the vaccine efficacy were more noticeable. This finding would encourage attempts to increase vaccination uptake among vulnerable groups by administering two doses.<sup>64</sup>

Recently, it has been claimed that the Delta variant has caused a significant increase in vaccine breakthrough infections featuring elevated viral load and transmissibility and has impaired the establishment of effective vaccines.<sup>65</sup> In this context, recent research has found a Delta variant outbreak in an ADSC (adult day service center) with a high vaccination coverage rate characterized by a high infection rate, high transmissibility, and mild clinical severity. The outbreak spread to unprotected or partly vaccinated household members, highlighting the need to immunize the high-risk populations' close contacts.<sup>66</sup> In addition, it has also been postulated that the vaccination lowers the chance of infection with the Delta

variant and speeds up viral clearance.<sup>67</sup> However, it is essential to consider that the fully vaccinated persons with breakthrough infections recorded a high viral load similar to unprotected people and can efficiently spread illness in the household, even among the fully vaccinated people.<sup>67</sup> These disparities may possibly be resolved in the future with more immunological studies to find the exact reasons.

In a similar way, numerous recent discoveries in India have found breakthrough infections caused by the Delta variant in people who had been completely vaccinated. However, in the vaccinated group, the proportion of patients who have developed severe illness and died was lower. Both vaccinated and unvaccinated people are at risk of contracting the Delta variant. On the other hand, vaccination appears to stop the disease from progressing. Thus the non-pharmaceutical therapies must also continue to curb the spread of the disease. In order to prevent the pandemic from spreading further, the rate and scope of vaccination must be boosted.<sup>68</sup>

### **Effectiveness of various available vaccines against Delta variant**

In phase III studies, BNT162b2, mRNA-1273, and Sputnik V exhibited significant effectiveness (>90%) in avoiding symptomatic instances after two doses. COVID-19 symptomatic illnesses and severe diseases with Alpha, Beta, Gamma, or Delta variants were prevented by mRNA vaccines, AZD1222, and CoronaVac. Complete vaccination with mRNA vaccines with AZD1222 appears to either successfully prevent SARS-CoV-2 infection even against parental strain, Alpha, and Beta strains, however with lower efficiency against the Delta variant, according to real-life observational data. BNT162b2 and AZD1222 both showed a decrease in infection protection after six months.<sup>69</sup>

### **Effectiveness of various vaccines against infection caused by Delta variant**

Fiolet et al., (2022) recently summarized the effectiveness of various available vaccines to protect against SARS-CoV-2 infection by Delta variant in fully vaccinated individuals.<sup>69</sup> BNT162b2 recorded 42–79% protection,<sup>70,71</sup> mRNA-1273 vaccine recorded 76–84%.<sup>72,73</sup> On the other hand, mRNA-vaccines were reported for 64% protection,<sup>74</sup> and mRNA-vaccines/Janssen reported 47–79%.<sup>75,76</sup> AZD1222 was reported to provide 60–67% protection,<sup>70,71</sup> and mRNA/AZD-1222 were shown to provide only 49% protection against the Delta variant.<sup>77</sup>

### **Efficacy of vaccines to reduce COVID-19 hospitalization and death**

Ad26.COV1.S vaccine is reported to provide 60 to 85% protection against hospitalization in patients infected Delta variant of SARS-CoV-2.<sup>78,79</sup> On the other hand, mRNA-vaccines such as mRNA1273 provided 95% protection to reduce hospitalization and death in patients infected with Delta variant.<sup>78–80</sup>

### **Effects on other notable drugs**

Recently, the Delta variant has been recorded to possess increased resistance against various effective monoclonal antibodies (MAbs) such as Bamlanivimab. The resistance against MAbs has been associated with changes in the RBD of the S-protein.<sup>42</sup> Additionally, the alterations in the N-terminal domain (NTD) of S-protein are significant in the development of resistance against several important therapeutic regimens. However, the neutralizing capacity of three additional therapeutically authorized MAbs, including Etesivimab, Basirivimab, and Imdevimab, against the Delta variant was retained. Furthermore, combining numerous neutralizing MAbs that can recognize and bind to distinct and non overlapping epitopes of the S-protein might reduce the loss of individual antibody-mediated neutralization capacities.<sup>81,82</sup>

### **Clinical differences among patients infected with Wild type and Delta strain of SARS-CoV-2**

According to a recent study, the infection caused by the Delta variant was associated with a lower incidence of symptoms than wild-type infection. Coughing and fever are still the most common symptoms, although gastrointestinal problems have become far less common.<sup>83</sup> Moreover, these findings were in agreement with previously published findings.<sup>45</sup> Patients infected with the Delta variant of SARS-CoV-2 have also reported sore throats, which were not prevalent in patients infected with wild-type SARS-CoV-2. But the Sore throat symptoms have been reported in a significant proportion of patients infected with a wild-type strain of SARS-CoV-2. In terms of hematological data, patients infected with Delta variant (those who were not vaccinated) reported to have lesser leukocytosis and neutrophilia as compared to the patients infected with a parental strain of SARS-CoV-2. In addition, the lower levels of C-reactive protein (CRP), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactic dehydrogenase (LDH), procalcitonin (PCT) and D-dimer have been reported.<sup>83</sup> Importantly, varied outcomes were observed in the cases of monocytosis and thrombocytopenia, as well as in the levels of ALP, creatinine, CPK, thrombin time, and fibrinogen, among other parameters.<sup>83</sup>

However, there is still a lot of work to be done on these clinical symptoms. It is interesting to consider that the partial vaccination did not significantly reduce the severity of Delta variant infection; full vaccination did so by alleviating coagulation dysfunction and mitigating the viremic impact on major organs (as evidenced by lower levels of adenosine deaminase (ADA), blood urea nitrogen (BUN), creatinine, and liver deaminase (LDH)).<sup>83</sup> It was concluded from these findings that COVID-19 immunization is associated with a considerable reduction in hospitalization and illness progression, despite its decreased efficiency against the Delta variant.<sup>68,84</sup>

### **Future concerns/threats**

According to current statistics, the Omicron variant is undeniably the most common among the population of numerous countries, including England. However, the Delta variant still



exists in several communities and may emerge as a plausible threat in the future *via* acquiring more mutations in the S-protein or by infecting people who fall on the vulnerability list. In this context, it has recently been suggested that pregnant women are among the most susceptible populations during the Delta variant outbreak, with higher hospitalization, pneumonia, respiratory assistance, and admission to critical care units. Viral infection due to the Delta variant is more likely to occur in pregnant women with gestational diabetes mellitus (GDM). GDM patients are nine and three times more likely to be infected with viral infection compared to pregnant women with diabetes and cardiovascular diseases, and hypertension, respectively. Moreover, it has also been found that pregnant women with GDM are more susceptible to infection of Delta variant than other VOCs and wild-type strains of SARS-CoV-2.<sup>85</sup>

Furthermore, it has recently been proposed that a single viral strain can only cause SARS-CoV-2 infection, but it is essential to consider that the two strains of SARS-CoV-2 may infect the host at the same time, but this is an exceedingly unusual occurrence.<sup>13</sup> In addition, according to some recent information and media coverage, a newly identified Delmicron double variant has been postulated. However, further investigations are required before any conclusions can be drawn. This so-called new super-variant might be created if both variants, including Delta and Omicron variants, infect individuals at the very same time, and people with weakened immune systems can harbor both variants of SARS-CoV-2. The Delmicron variant is considered to have been created by combining the most lethal Delta and most modified Omicron variants of SARS-CoV-2, which is now being blamed for a new outbreak of COVID-19 cases in North America, Europe, and potentially India and other nations.<sup>13</sup> However, if such assumptions are proved, they will necessitate more research and certification by the WHO. Because genomic sequencing is used to validate the mutations, which is done on only a tiny fraction of COVID-19 cases, the actual number of Omicron and Delta cases is expected to be much greater than the number of verified instances published thus far.<sup>13,86,87</sup> Hence, there is an urgent need to halt the circulations of the variants among the vast population to stop the emergence of any potential viral strain.

## Preventive measures

Several reports have clearly shown that the Delta variant is significantly infectious compared to smallpox, with an R0 value of 3.5–4.6. Hence, people must comply with physical distancing and other precautionary measures to take better control of the infection caused by the Delta variant.<sup>52</sup>

However, we cannot overlook that BNT162b2, mRNA-1273, ChAdOx1, and other commonly used vaccines in European countries and the United States have reported a certain amount of protectiveness against the Delta variant in the people administered with two doses of the vaccine. It is essential to consider that after two doses, the protection rates against diverse SARS-CoV-2 variants, including the Delta variant, were much higher than the single dose of the vaccine. Hence, it is vital to raise the number of completely vaccinated

persons to successfully prevent the spread of SARS-CoV-2 internationally.<sup>29</sup> Rather than spontaneous infection, vaccination is the only way to establish significant herd immunity against SARS-CoV-2. As a result, global efforts should focus on developing a vaccination program that uses a highly effective vaccine to achieve the largest possible coverage,<sup>27</sup> which could serve as an efficient measure to reduce any plausible consequences caused by the Delta variant outbreak.

Moreover, vulnerable people like pregnant women should prioritize self-care and get vaccinated against SARS-CoV-2 as soon as possible. Pregnant women should be prioritized in a rapid immunization campaign.<sup>85,88</sup> Until data from the trial bases studies, including the pregnant women, is available, pregnant women and their obstetricians should be informed of the latest facts, including the benefits and risks of the COVID-19 vaccinations.<sup>89</sup> Though pregnant women with COVID-19 have a comparable risk of problems than non-pregnant women, intensive care is required in middle and low-income nations. Pregnant women should follow all precautionary measures, with vaccination being a major priority.<sup>89,90</sup>

Moreover, it is essential to consider that even with the development of effective COVID-19 vaccines, considerable obstacles such as vaccine hesitancy and inequalities in vaccine distribution are still prevalent among several countries.<sup>9</sup> All nations should actively evaluate and solve these issues to inhibit the spread of SARS-CoV-2, particularly the Delta variant, and the development of additional SARS-CoV-2 variants.<sup>91</sup> Furthermore, the genomic surveillance and evolutionary dynamics studies should be done more quickly, and contact tracing of variants should be done more often as well. This will help a lot to improve our knowledge of VOCs, particularly the Delta variant, so that scientists can update the COVID-19 vaccines and make second-generation vaccines. In addition, the use of booster doses and the development of effective treatment regimens can lessen the risks of the infection with the Delta variant, which possesses a significant advantage of enhanced dissemination potentials. Scientists should keep monitoring and evaluating the Delta variant along with the Omicron variant around the world.<sup>13,87,90,92</sup>

Genomic surveillance makes use of next-generation sequencing techniques, provides whole-genome data accessible, and improves phylogenetic approaches. These technologies provide new ways to detect phenotypically or antigenically distinct variations.<sup>93,94</sup> Genomic monitoring is critical in the fight against COVID-19, and it must be deployed globally in a thorough and coordinated manner. It can give the relevant data needed to develop a more tailored public health plan that targets local priorities through stakeholder engagement and mitigation initiatives while waiting for herd immunity to be achieved through vaccination. Increased international collaboration offers unique prospects for achieving quick genomic monitoring and leveraging the expertise of high-income nations, particularly the United Kingdom, and deploying these to low- and middle-income countries around the globe. Genomic surveillance will allow for better early detection of SARS-CoV-2 mutations and many other new viral strains, as well as the development of effective ways to attenuate and limit epidemics.<sup>93</sup>

## Conclusions and future directions

Since the beginning of the COVID-19 pandemic, which was caused by SARS-CoV-2, the causative agent has undergone several mutations due to recombination, selection pressure, and point mutations. Till now, several variants of concern (VOCs) such as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) have been discovered and reported in various parts of the world. These variants may have the potential to significantly influence the dissemination capabilities of the virus, along with reducing the efficacy of presently available vaccines, therapeutic regimens, and diagnostic procedures. The emergence of VOCs has led to challenges in controlling the pandemic amid serious worldwide efforts. However, due to the increased transmissibility and virulence of the Delta variant (B.1.617.2), it has been considered as a major concern and threat to humankind. Recent findings have concluded that the current immunization approaches and the available vaccines may not prevent the Delta variant infection and morbidity. However, they may reduce the severity of the infection hence reducing the mortality rates according to real-world data from various nations. The Delta variant's enhanced infectivity appears to be the result of a combination of critical changes/mutations that enable the spike protein (S-protein) to interact with the host receptor (ACE-2) more efficiently. The increased affinity of the S-protein toward the ACE-2 receptors leads to lesser effectiveness of the vaccines and a significantly higher number of viral loads in infected people. Moreover, the Delta variant has been reported to exhibit significantly increased resistance to the neutralization by several anti-NTD and anti-RBD monoclonal antibodies such as Etesivimab, Basirivimab, and Imdevimab. In addition, these MAbs have shown decreased affinity to the S-protein of the Delta variant.

Furthermore, the clinical signs of individuals infected with the Delta variant of SARS-CoV-2 are still being worked out. In individuals infected with the Delta variant and wild type SARS-CoV-2, it is critical to distinguish clinical and biochemical markers. There is no doubt that how clinical symptoms differ among individuals infected with sublineages of the Delta variant, such as the Delta plus variant, is still a conundrum. All of these questions, hopefully, will be answered in the future through well-designed and elaborated clinical trials.

Moreover, sera obtained from convalescent people have been found to be four times less effective against the Delta variant than the Alpha variant (B.1.1.7). Even the plasma from those who had received one dose of either the Pfizer or AstraZeneca vaccines have been reported to exhibit a negligible neutralization of the Delta variant. Thus the decline in vaccine effectiveness against the Delta variant is a serious issue, and immunization against COVID-19 should be increased internationally to deal with the Delta variant's high frequency. With the considerable decrease in the neutralization of the Delta variant with neutralizing antibodies elicited by various available vaccines, it is questionable how vaccinated individuals and vaccine inequalities across the globe will shift the trajectory of the COVID-19 pandemic.

The most critical method to prevent and control the spread of the Delta variant is to increase vaccination coverage. The mortality rate has not ascended in nations with high vaccination rates, such as the United Kingdom, despite the rising incidence, but the pandemic is more dangerous in countries with poor vaccination rates, such as South Africa, India, Thailand, and Indonesia. Among the United States, the reported COVID-19 cases reported are primarily found in the unvaccinated community. As a result, managing the worldwide pandemic would require an accelerated vaccination pace and coverage, with an emphasis on the vaccine-deficient countries.

## Abbreviations

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WHO	World Health Organisation
VOC	variant of concern
S-protein	spike protein
ACE-2	angiotensin-converting enzyme-2
VE	vaccine efficacy
VOI	variant of interest
VOC	variant of concern
Mab	monoclonal antibody
ORF1a	open reading frame 1a
NAb	neutralizing antibody
R0	R naught
CP	convalescent plasma
ADSC	adult day service center
NTD	N-terminal domain
RBD	receptor binding domain
GDM	gestational diabetes mellitus

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## Authors' contributions

MD did the ideation, conceptualization, data curation, writing original draft, reviewing and editing. PR executed the conceptualization, writing original draft, reviewing and editing. AS, NT, TKR, OPC did the reviewing and editing. All authors critically reviewed and approved the final version of the manuscript.

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This article does not require any human/animal subjects to acquire such approval.

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