

## SHORT COMMUNICATION

# COVID-19 Delta variants—Current status and implications as of August 2021

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## Abstract

The SARS-CoV-2 Delta variant has evolved as the dominant strain of the current pandemic. Studies have shown that this variant has increased infectivity/viral load, and reduced neutralization by the host antibodies from convalescent patients/vaccinees. Clinically, Delta variant infection has been observed/documentated in convalescent patients/vaccinees, although with less incidence of severe diseases, but can serve as reservoir to spread the infection to the unvaccinated. The current understanding (as of 18 August 2021) on the virologic aspect (including the amino acid substitutions), clinical implications, and public health implications will be discussed in this mini review, and recommendations to health authorities will be provided.

**Key words:** SARS-CoV-2; COVID-19; coronavirus; Delta variant; transmissibility; vaccine

## Introduction

Since its emergence in December 2019, COVID-19 has evolved into a pandemic.<sup>1</sup> As of 18 August 2021, there are >200 million people with confirmed infection globally (actual number likely much higher), contributing to >4 million deaths.<sup>2</sup>

SARS-CoV-2, closely related to the SARS-CoV, is a member of the genus Betacoronavirus.<sup>3,4</sup> A positive-sense, single-stranded RNA virus of around 30 000 bases,<sup>5</sup> it replicates using the viral RNA-dependent RNA polymerase, which lacks proof-reading activity. Therefore, the virus can easily generate genetic variations,

allowing a genetically diverse population that can be selected through gained fitness and/or adaptation to the environment.<sup>6</sup> Hence, rapid development of variants with increased infectivity and/or escape from the host immune response is to be expected, especially with a huge pool of infected subjects globally. Note that the genetic variations may or may not lead to amino acid substitutions/variations (known as synonymous and non-synonymous substitutions).<sup>7,8</sup>

Even with estimated genetic variation/mutation rate of one nucleotide substitution for every 10 replications, a single infected person, presumed to carry >10 billion

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copies of the virus, can produce billions of variations per day.<sup>9</sup> When multiplied by the number of infected subjects globally, an enormous number of variants will be created. As the genetic scrambling is relatively random, most variants will have no impact. However, if the variant has increased infectivity/replication rate/genome stability, and/or can escape the host immune response, these variants can evolve as the dominant viral strain quickly.

The US government SARS-CoV-2 Interagency Group developed a Variant Classification that defines three types of variants: variant of interest (VOI), variant of concern (VOC), and variant of high consequences (VOHC).<sup>10</sup> As of 18 August 2021, four VOCs have been reported (Table 1).<sup>10</sup> The Alpha variant that initially emerged in UK has since spread to >185 countries.<sup>10,11</sup> Studies have shown its increased transmission ability (50% increase), secondary infection attack rate, along with increased severity based on hospitalization rates. However, this variant has minimal impact on neutralization by convalescent and post-vaccination sera.<sup>10,11</sup> The Beta strain was first described in South Africa, displaying both increased transmission and host antibody neutralization escape.<sup>10</sup> The origin of the Gamma variant was traced to Japan/Brazil, and this variant has shown increased immune escape to neutralization antibodies.<sup>10,12</sup>

The Delta strain, or B.1.617.2 variant of SARS-CoV-2, was first described in India in October 2020.<sup>13</sup> By mid-2021, it had been detected in >142 countries.<sup>11</sup> An additional spike amino acid change, K417N, was reported on 11 June (classified as the Delta Plus).<sup>14</sup> As of 6 July 2021, this variant and another sub-lineage have been aggregated with the Delta variant.<sup>15</sup> As of 17 August, >98% of the newly diagnosed COVID-19 cases in the USA result from the Delta variant.<sup>16</sup> This mini review, with specific emphasis on the biology, clinical and public implications of the Delta variant, will provide the latest information related to the Delta variant as of 18 August 2021 to complement our previous review so that readers can have an update on the latest on COVID-19.

## Amino acid substitutions in the Delta variant (B.1.617.2 variant)

COVID-19 gets its spike protein features from the coronavirus family.<sup>17</sup> The spike proteins are flexible and hinge at three different points, thereby allowing easier access to the receptors on human cells.<sup>18</sup> The receptor-binding domain (RBD) of the spike protein is the key binding element to the human angiotensin-converting enzyme 2 (hACE2) receptor.<sup>18</sup> Two glycans play a key role in the positioning of the RBD and binding affinity to the hACE2 receptors, and there is evidence that the unique presence of the furin cleavage site found in SARS-CoV-2 is associated with its high infectivity in lungs.<sup>18</sup>

There are a number of amino acid substitutions observed with the Delta variant,<sup>15</sup> and the amino acid

**Table 1.** Some characteristics of the current four VOC of SARS-CoV-2 (as of 14 August 2021).

Variant	Alpha, B.1.1.7	Beta, B.1.351	Gamma, P.1	Delta, B.617
Date/location	September 2020, UK	September 2020, South Africa	December 2020, Japan/Brazil	October 2020, India
Global dominance	185 countries	136 countries	81 countries	142 countries
Spike protein amino acid substitutions	69-79del, 144del, (E484K*), (S494P*), N501Y, A570D, D614G, P681H, T716I, S982A, D1119H, (K1191N*)	D80A, D215G, 241-243del, K417N, E484K, N501Y, D614G, A701V	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I	T19R, V70F, T95I, G142D, E156-, F157-, R158G, (A222V*), (W258L*), (K417N*), L452R, T478K, D614G, P681R, D960N L452R, D614G, T478K
Enhanced binding to HACE2/infectivity	N501Y, D614G	K417N/N501Y, D614G	N501Y, D614G	E484Q (possible), T478K (possible) P681R
Immune escape	E484K	E484K	E484K	
Furin cleavage	P681H			
Transmission	Increase ~50%+ secondary attack rate	Increase ~50%	Increased	Increased + secondary attack rate, similar rate between vaccinees and unvaccinated
Reinfection risk	Risk remains similar	Increased	Increased, and in vaccinees	Increased, and in vaccinees
Disease severity/hospitalization	Possible increase/increase	Increased in-hospital mortality	Possible increase	Increased risk of hospitalization
Pfizer vaccine efficacy	93.40%			42% (infectious)

Information gathered from references.<sup>10,11,13,19,20,22,24,25,45,51,52,53</sup> L452R is highlighted as a key amino acid substitution in the Delta variant. The amino acid mutations with a (\*) indicate that the mutation of this particular amino acid may or may not occur, and will not affect a variant designation. The amino acid mutations not in a (\*) are invariable mutations, which must be present in a specific variant.

substitutions observed on the spike protein are summarized in Table 1. Some of the notable mutations found in the Delta variant such as D614G, L452R, E484Q, P681R, and T478K, can also be linked to other variants. Since the first description of the D614G mutation in China, this amino acid substitution has remained in all subsequent VOCs, with the main attribute being enhanced binding to hACE2 receptors.<sup>19</sup> A key feature is L452R, which was discovered to enhance infectivity and decrease the neutralization ability of immune sera.<sup>20</sup> Further studies also reported that L452R enhances membrane fusion, viral replication, and evades the HLA-A24 cell immunity.<sup>21</sup> When L452R combined with E484Q, only a slight decrease in neutralization activity of immune sera was observed *in vitro*.<sup>22</sup> The E484Q mutation has been observed to share similar immune neutralization escape properties with the E484K mutation in the Beta and Gamma variants. There were reports of reinfection being linked to the E484K mutation.<sup>23</sup> As E484K and E484Q are close to each other, there is the concern regarding the reinfection potential of the Delta variant in convalescent patients and vaccinees. The P681R in the Delta variant is located near the furin cleavage site, similar to the P681H observed in the Alpha (UK) variant. Studies have shown that although P681R had decreased infectivity, it facilitates furin-mediated S cleavage, thereby enhancing viral fusion to ACE, promoting syncytia formation, and possibly facilitating immune escape.<sup>24</sup>

T478K mutation is also found in the B.1.1.519 and B.1.214.3 lineages, located within the interaction domain of ACE2, and can possibly alter the electrostatic surface of the protein which greatly influences how treatments interact with the virus.<sup>25</sup> An *in vitro* experiment suggested the mutation can escape immune recognition.<sup>25</sup> An additional amino acid substitution K417N was also reported on 11 June 2021 with the new variant Delta Plus/AY.1.<sup>14,26</sup> This variant has already spread to >30 countries by August 2021 and has been classified as a VOC in India.<sup>13,26</sup>

## Clinical implications

First identified in India, the Delta variant has evolved as the major viral strain in the current pandemic. Studies have shown that clinically, in addition to increased transmissibility, the variant has a shortened incubation time, enhanced replication abilities, and is more infectious compared to non-VOCs.<sup>27</sup> A recent study reported that viral load is 1260 times higher in Delta variant patients than the original COVID-19 strain.<sup>27</sup>

In India, the major Delta variant-driven wave of infection started in March 2021 and started to recede by early July.<sup>28</sup> In the UK where vaccination rate was high (76% adults), the Delta variant-driven surge started in July and had begun to recede by August.<sup>28,29</sup> Overall, there was a 10% global increase in the number of infections and a 3% increase in deaths reported in the week of 13 July

that were believed to relate mainly to the Delta variant surge (compared to the previous nine weeks with a steady decline in COVID-19 incidents).<sup>30</sup>

In the US (with 50% of the population fully vaccinated), which had 8%–14% (7-day average of 13 500 COVID-19 cases/day) caused by the Delta variant in early June 2021, there was an increase to 80%–87% (7-day average of 92 000 COVID-19 cases/day) in the last two weeks of July.<sup>31</sup> The Delta variant has evolved as the main driver for this pandemic in the US. Computer models have predicted that this surge may peak sometime in September and could increase the number of new infections significantly.<sup>31</sup>

A key question regarding the Delta variant is whether it can infect vaccinees. A recent study on the Delta variant-driven outbreak in Provincetown, Massachusetts, published in CDC's *Morbidity and Mortality Weekly Report*, reported that fully vaccinated people accounted for 74% of nearly 469 COVID-19 cases (4/5 subjects hospitalized were fully vaccinated; and no one died).<sup>32</sup> Importantly, this study found that fully vaccinated people carried the same amount of Delta variant virus in their noses/throats as the unvaccinated.<sup>32</sup>

From a scientific perspective, one can imagine that vaccinated people may still carry a significant load of a viral variant known to have better infectivity/replication/reduced neutralization by host antibodies. A short spell of rapid viral replication can still cause symptoms, but the host immune system (both B-cells and T-cells) can be activated again to control/clear the viral infection.<sup>33</sup> Scientists in Singapore found that although vaccinated and unvaccinated patients infected with Delta variant had similar viral loads when diagnosed, those loads declined more rapidly in the vaccinated.<sup>34</sup>

As for clinical features, despite the increased transmissibility, secondary attack rate, infection with Delta variant does not stray from the general set of COVID-19 symptoms, although there were reports suggesting less cough/loss of smell/cold-like symptoms, and reports suggesting potentially more severe disease in the unvaccinated.<sup>35,36</sup>

## Public health implications

The observation that the Delta variant can infect vaccinees (therefore, can spread the infection) led CDC to change their recommendation that even fully vaccinated people should wear masks in indoor public places and in areas where transmission is high.<sup>37</sup> The upcoming public health challenges will be when children are back at school, and when people move indoors during the coming fall and winter. We expect that there will soon be changes in public policy. Even before these challenges, the US has already seen a major wave of new infections coming, with several states reporting overloads of intensive care units.<sup>38,39</sup>

Remdesivir is the first antiviral drug authorized for emergency use (EUA) by US FDA for the treatment of COVID-19.<sup>40,41</sup> There are as yet no published data on the efficacy of remdesivir against the Delta variant. Currently, there are three sets of monoclonal antibodies against SARS-CoV-2 with EUAs: bamlanivimab/etesevimab, casirivimab/imdevimab, and sotrovimab.<sup>42</sup> Bamlanivimab/etesevimab have been put on hold because of reduced efficacy against the Beta and Gamma strains, and the impact with the Delta variant is currently being studied.<sup>42</sup>

A recent update on the effects of Pfizer mRNA 2 dose vaccination regime showed a reduction in hospital admissions (i.e. their efficacy endpoint) from 95% to 87.9%, while the prevalence of the Delta variant is increasing.<sup>19</sup> As the host immune response is polyclonal against different B-cell/T-cell epitopes on the RBD based vaccine, it was not surprising that the vaccinees are still protected, and although some epitopes might be impacted by amino acid substitutions, exposure to vaccines enhances the host immune system and prevents development of severe COVID-19.<sup>43</sup> Recently, there was an updated report that the Pfizer vaccine has 64% efficacy against infection and preventing symptomatic cases, but is 93% effective at preventing hospitalization/severe disease caused by the Delta variant.<sup>44</sup> As of August 2021, another set of data showed that Moderna dropped from 86% to 76% efficacy against infection and Pfizer has dropped to 42%, while the Delta variant is evolving as the dominant strain.<sup>45,46</sup> The Johnson and Johnson (JNJ) vaccine demonstrated 73.1% efficacy in preventing severe disease/hospitalization/death but no sub-analysis was performed for its efficacy against the Delta variant.<sup>47</sup> Against the Beta variant, however, the efficacy of JNJ vaccine dropped to 52%.<sup>47</sup>

Pfizer and BioNTech released a statement in early July 2021 that their booster trial showed neutralization titers 5 to 10 times higher against wild types and the Beta variant (no data on Delta variant yet) compared with their two-dose mRNA regime.<sup>48</sup> An updated vaccine targeting the Delta variant and new regimens with booster shots to provide high levels of protection are currently projected to begin in August 2021.<sup>48</sup>

As vaccinees may still have some level of protection against the Delta variant, with most vaccinees infected with Delta variant being asymptomatic/having mild diseases, and a vast majority of hospitalizations are unvaccinated individuals, the current COVID-19 pandemic has evolved to be a pandemic of the unvaccinated.<sup>49</sup>

Nasally administered vaccines are also in development, and it is possible that this may enhance local immune response to better protect the upper airways, which is where the body is first exposed to the virus.<sup>50</sup> There are no approved inhalational vaccines yet, but in non-human primates, early humoral IgA immune responses has been shown to reduce viral shedding/transmission.<sup>50</sup>

It is also important to emphasize that these variants will sustain the current pandemic, and there will

certainly be more long-term social/psychological/mental implications.

## Conclusions

The SARS-CoV-2 Delta variant is a VOC and is currently the dominant strain in the prevailing COVID-19 pandemic. The high infectivity/viral load in infected subjects, and the enhanced susceptibility of the vaccinees to infection are concerning. Public health measures including continued use of facemasks/social distancing in public areas should be considered by health authorities. Governments should strongly encourage all their citizens to be vaccinated. Clinics/hospitals should prepare for the new wave of infection caused by the Delta variant. Vaccines based on the Delta variant should be developed as soon as possible. The rapid evolution of SARS-CoV-2 variants suggests that we may see more SARS-CoV-2 variants of higher infectivity and/or reduced neutralizing activity of the convalescent/vaccinees in the future. A concerted effort to break the spread of the virus globally may be the only way to combat this pandemic.

## Conflict of interests

The authors declare no competing financial interests. Besides, as a Co-EIC of *Precision Clinical Medicine*, the corresponding author Dr. Kang Zhang was blinded from reviewing or making decisions on this manuscript.

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