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Insights into COVID-19 Delta variant (B.1.617.2)

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Abstract: Since beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), different variants of concern (VOC) have been discovered. One of the variants that stood out was the Delta variant (B.1.617.2), first found in India. It caught worldwide attention due to its greater transmissibility than the progenitor strain and the first variant of concern (VOC)- Alpha variant (B.1.1.7). B.1.617.2 spread rapidly across the globe and became a VOC due to its high transmissibility, clinical implications, and impact on vaccine efficacy. This review discusses the background and prevalence of B.1.617.2 and its sensitivity to convalescent sera and vaccinated individuals. We will provide an insight into the impact B.1.617.2 has on vaccine efficacy and discuss the level and type of protection an individual could get by being vaccinated. We will also discuss briefly on the COVID-19 vaccine booster doses and whether it is needed.

Keywords: SARS-CoV-2, Delta (B.1.617.2), variants of concern (VOC), transmissibility, vaccine, booster

1. Introduction

The COVID-19 global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that took place in 2020 has yet to come to an end[1–4]. Throughout the pandemic, the SARS-CoV-2 spike protein is continuously mutating, leading to the discovery of more and more new variants. Four of the many variants discovered have

been listed as variants of concern (VOC). This includes variants B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta) and P.1 (Gamma)[5].

B.1.617.2 was initially given the designation as a variant of interest (VOI) by the World Health Organization (WHO) in April 2021, which quickly turned into a VOC in May 2021[6]. Interestingly, as the Delta variant became the predominant lineage in many countries, its sub-lineages are given the alias AY. This separates B.1.617.2 into smaller related clusters, allowing for better monitoring of diversity and enhancing the identification of newly emerging clades. New AY lineages are phylogenetically defined and treated as Delta variants. Their designation to a sub-lineage does not necessarily imply any functional biological differences compared to B.1.617.2 unless stated otherwise by other health bodies or the WHO[7].

On a side note, in recent months, a new variant called the Delta plus (B.1.617.2.1 and AY.1) has emerged from India and has spread to a few other countries, including the United States (US). An analysis showed that this variant traveled to the US via England and Japan, with the first case reported in Washington state on the 3rd May 2021. Research, however, found AY.1 to be more than just a Delta variant with an additional K417N mutation, and compared to B.1.617.2, AY.1 has a distinct mutation profile[8]. This review focuses only on B.1.617.2 which gained widespread attention due to its sudden emergence, rapid transmission, and severe clinical implications. In comparison to previous circulating variants, B.1.617.2 seems to be a more virulent variant. It is deemed to have greater transmissibility, increased severity risk, and is more resistant to current vaccines. Based on the weekly epidemiological update of COVID-19 on 31st August 2021 published by the WHO, B.1.617.2 has been reported in 170 countries[9]. Hence, we aim to discuss the background and prevalence of B.1.617.2 and provide valuable insights into how this variant caused the crisis, planting fear in people worldwide. We will also discuss concerns regarding covid vaccines against the B.1.617.2.

2. Background and Prevalence of B.1.617.2

B.1.617.2 first emerged in India in December 2020[5], causing the second wave of COVID-19 in India, which resulted in a health crisis affecting millions of people[10]. The confirmed daily new cases in India spiked from 53 per million population (up to March 2021) to >200 per million population (after mid-March 2021). On the contrary, the ratio of daily recoveries to daily new cases from the beginning of March declined sharply, indicating the severe burden on India's healthcare system. Shortages in essential supplies were seen in leading hospitals and the number of deaths of COVID-19 patients in intensive care increased in >130 cities as a result of oxygen and medicine shortage[11]. On the 1st of May 2021, India became the first country to record >400,000 new COVID-19 cases within 24 hours since the pandemic[12]. B.1.617.2 quickly became the most prevalent variant in many other countries, including the United Kingdom (UK) and the US. In the UK, B.1.617.2 emerged in mid-April and later accounted for 95% of all new cases[13], in the US, it accounted for 99% of new cases[14], while in Portugal, it accounted for 70% of cases in Lisbon[13]. It also leads to new

record highs for COVID-19 cases and deaths in many Southeast Asian countries, including Malaysia, Myanmar, and Indonesia[15].

B.1.617.2 is one of the three sub-lineage of the B.1.617 lineage[5]. It has several spike mutations, including D614G, P681R, L452R, T19R, T478K, A222V, R158G, G142D; 156–157 deletion in the N- terminal domain (NTD) and S2 substitution D950N[16]. Regarding some of the mutations, a study found D614G is linked to higher viral loads in the respiratory tract of infected individuals, increased human host infectivity, and possibly a higher transmission efficiency to SARS-CoV-2[17,18]. It has also been shown to strengthen cleavage efficiency due to substitution on spike conformational diversity[19,20]. P681R is in the S1-S2 furin cleavage site[21]. Similarly, mutation at the P681 position also contributes to SARS-CoV-2 transmission and infection[22,23]. On the other hand, L452R and T478K present in B.1.617.2 have been associated with vaccine escape and increased transmissibility[24]. Several studies showed that the L452R increases infectivity by stabilizing the SARS-CoV-2 spike glycoprotein and human angiotensin-converting enzyme 2 (ACE2) receptor interaction[25-27]. The stronger cell-virus attachment and increased infectivity result as the L452R mutation causes huge increments in free energy at the receptor-binding domain (RBD) and ACE2 binding complex[26,28]. Other studies also demonstrated that L452R mutant could evade the human leukocyte antigen (HLA)-24 limited cellular immunity, boost viral infectivity, and possibly increase viral replication[29]. Together, these mutations contribute to the increased transmissibility, infectivity and immune evasion characteristics of B.1.617.2.

Research indicated that B.1.617.2 is 60% more transmissible than the B.1.1.7 which is already more transmissible than the progenitor strain[30]. In addition, when most countries enforced lockdown measures, the B.1.617.2 was found to have a mean basic reproductive number ($R0$) value of 5.08 while the ancestral strain's $R0$ is 2.79[31]. A China study has proposed that B.1.617.2 has a higher viral replication rate, resulting in their infections having a 1000 times higher viral load than the 19A/19B strains (during the initial 2020 epidemic) infections when the day testing turns positive. Hence, greater infectivity during the early stages[32]. A Singapore study also associated B.1.617.2 with a lower polymerase chain reaction (PCR) cycle threshold (Ct) value and a longer viral shedding, possibly providing a mechanism for increased transmissibility[33]. Hence, suggesting the need for a greater vaccination rate.

Furthermore, B.1.617.2 has a higher risk of hospitalization and greater disease severity than B.1.1.7[34–36]. Studies from both England and Scotland were consistent that those infected with the delta variant have twice the risk of hospitalization than those infected with the alpha variant. Based on a cohort study in England where 74% of COVID-19 patients were unvaccinated, they found that within 14 days of testing, those infected with B.1.617.2 have a higher risk of hospitalization and greater disease severity than those infected with the B.1.1.7 variant[36]. A Singapore study was comparing patients with B.1.1.7, B.1.351, and B.1.617.2 also found B.1.617.2 was associated with higher odds of oxygen requirement, intensive unit care (ICU) admission, or death[33]. A UK report also stated B.1.617.2 has a higher secondary attack rate compared to B.1.1.7 in both household and non-household

contacts and traveler and non-traveler cases. In contrast, the 28-day case fatality for B.1.617.2 stays low at 0.1% compared to B.1.1.7, which is at 1.9%[37].

Recently, there are also concerns about whether children have an increased risk of getting infected with B.1.617.2. It seems that the increased cases in children were most likely because they are not yet fully vaccinated. Moreover, in a press conference, the Centers for Disease Control and Prevention (CDC) head Rochelle Walensky said although there are increased pediatric cases and increased overall cases, there was no increased severity in pediatric cases[38]. (Table 1)

Table 1. Summary of the background and prevalence of B.1.617.2

	Delta/ B.1.617.2	**References**
Country first detected	India	[5]
Month+Year detected	December 2020	[5]
Confirmed Daily New Cases in India (up to March 2021)	53 per million population increased to >200 per million population	[11]
Ratio of Daily Recoveries to Daily New Cases in India (from mid-March 2021)	Significant reduction	[11]
Total countries affected	170	[9]
Mutations	D614G, P681R, L452R, T19R, T478K, A222V, R158G, G142D; 156–157 deletion in the N-terminal domain (NTD) and S2 substitution D950N	[16]
Transmissibility	60% more transmissible than B.1.1.7	[30]
Basic reproductive number (*R*0)	5.08 while ancestral strain's *R*0 is 2.79	[31]
Risk of hospitalization and Disease severity	Twice the risk of hospitalization and a greater disease severity compared to B.1.1.7	[36]
Secondary attack rate	Higher than B.1.1.7 in both household and non-household contacts and traveller and non-traveller cases	[37]
Are children at an increased risk?	Unlikely. Probably due to being unvaccinated	[38]

3. Sensitivity of B.1.617.2 to Convalescent Sera and Vaccinated Individuals

In a month 12 cohort study in France, individuals vaccinated with a single dose of either Pfizer, AstraZeneca, and Moderna vaccines demonstrated greater neutralizing antibody (Nab) titers against Alpha, Beta, and Delta variants than those convalescents of unvaccinated individuals. Hence, a single dose of vaccine boosts cross-neutralizing antibody responses to the Delta variant. However, those vaccinated with a single dose of Pfizer or AstraZeneca showed low efficiency against Delta variant with the percentage of sera of individuals vaccinated with Pfizer or AstraZeneca neutralizing B.1.617.2 to be 13% and 9% respectively. An efficient neutralizing response was generated only after the second dose[39]. An India study also showed that relative to the prototype strain (D614G), there is a 3.2 (two dose)-4.5 (one dose) fold reduction in NAb titer in the sera of Covishield vaccinees against the B.1.617.2, indicating the significance of a second dose. Moreover, it also showed that the NAbs in breakthrough participants and COVID-19 recovered individuals with one or two

vaccine doses showed higher protection against B.1.617.2 than vaccinees who received one or two vaccine doses[10]. Another study also evaluated the neutralization of sera collected from COVID-19 recovered patients (post 5-20 weeks of infection) and individuals (post 28 days) vaccinated with two doses of Bharat Biotech's Covaxin (BBV152) against B.1.617.2. Findings demonstrated a 4.6-fold and 2.7-fold reduction in neutralization titer compared to the B.1 strain (D614G) with sera of COVID-19 recovered patients and Covaxin vaccinees. Studies have shown that against B.1.617.2, although there is a decrease in neutralization titer with Covaxin vaccinees sera, the neutralization potential is yet to be established. The broad epitope coverage in an inactivated vaccine (BBV152) reduces the magnitude of decreased neutralization against emerging variants by inducing an immune response against whole virion[40].

Besides that, studies have demonstrated the effectiveness of two shots of Pfizer vaccine against B.1.617.2 infection[41,42]. One study showed two shots of Pfizer vaccine demonstrated 88% efficacy two weeks after the second dose, while two shots of AstraZeneca vaccine could provide 60% protection against symptomatic disease from B.1.617.2[43]. Therefore, although B.1.617.2 has demonstrated immune evasion characteristics, vaccines still offer protections against B.1.617.2 to some extent.

4. Understanding the B.1.617.2 Variant

There is an association between the emergence of new variants and epidemic severity and SARS-CoV-2 transmission. The high transmission rate is a prognostic factor for genomic variations. As a consequence, outbreaks happen following large gatherings[5,44]. The emergence of the B.1.617.2 has been raising concerns globally due to its high transmissibility, increased disease severity, and immune evasion ability. With the emergence of the COVID-19 pandemic, several types of vaccines have been developed, consisting of inactivated virus vaccines, a protein subunit vaccine, mRNA vaccines, and viral vector recombinant vaccines[45]. The COVID-19 vaccines enable the activation of the immune response upon binding to the spike protein[5]. However, mutations on the RBD that are present in many new emerging variants are responsible for most of the escape from vaccine-induced neutralization[46]. Thus, concerns on vaccine efficacy arise as new variants with mutations on the spike protein emerge. In addition, the durability of antibody response in semi and fully vaccinated individuals are not yet fully understood.

The toll B.1.617.2 takes depends mainly on the population's vaccination status and the number of people having immunity from previous infection[13]. For instance, in the UK with a high vaccination rate, fatality did not increase with increased cases. However, in countries with low vaccination rates such as Thailand and Indonesia, the COVID-19 cases are more serious. New cases in the US also were focused on unvaccinated individuals[47]. Another example is in Israel, the estimated Pfizer vaccine effectiveness against SARS-CoV-2 infection was 95.3% $\geq$ 7 days after the second dose[48]. However, the Israeli Ministry of Health stated that the efficacy of the Pfizer vaccine dropped to 39% due to B.1.617.2. Even so, there is still 88% protection against infection, progressing to hospitalization, and 94.1%

against severe illness[47]. Thus, demonstrating vaccination still plays a role in alleviating the disease burden.

According to data from the Coronavirus Resource Center, John Hopkins University of Medicine, many countries have initiated a national vaccination process. Many have indeed had a high percentage of the population vaccinated. However, there are still a handful of countries whose vaccination rate is still far below the world average[49]. Not to forget, as mentioned earlier, B.1.617.2 has a much higher reproduction number compared to the ancestral strain, which means a much higher vaccine coverage needs to be achieved compared to the assumed initially 60–70% vaccine coverage for the ancestral strain. A reproductive number of 5 would mean a vaccine coverage of 80% will be needed based on the equation $q=1-1/R0$, assuming a 100% vaccine efficacy[31]. B.1.617.2, having high infectivity means more people need to be vaccinated to reduce its spread and disease burden. Hence, it is crucial to increase vaccination coverage to control the spread B.1.617.2.

Now, for some countries where most of the population had been fully vaccinated with two doses of COVID-19 vaccine, this brings us to the issue of COVID-19 vaccine booster doses. Currently, the CDC and the Food and Drug Administration (FDA) have approved the booster shot of the Pfizer-BioNTech COVID-19 vaccine in specific populations and those in high-risk occupational and institutional settings, while booster shots of COVID-19 vaccines by Moderna and Johnson & Johnson will be evaluated in the coming weeks. According to the statement released by the CDC on 24th September 2021, with the dominance of B.1.617.2 and the increase in COVID-19 cases in the US, booster shots can strengthen protection against severe disease in those with high-risk exposure to COVID-19 or complications for severe disease[50]. With that, Israel is the first country in the world to administer Covid-19 vaccine (Pfizer) booster doses to adults with weak immune systems following the announcement by the Israeli Ministry of Health on the 11th July 2021[47].

However, some believe booster doses should not be prioritized over primary vaccination. The clinical trials lead for the vaccine and director of the Oxford Vaccine Group, Andrew Pollard emphasized "urgent priority" should be given to those who have not got their first dose before initiating a third booster dose[51]. In line with that, a statement released by the WHO on the 4th August stated that 4 billion vaccine doses had been administered globally, in which >80% went to upper-middle- and high-income countries even though they accounted for <50% of the world's population. Although booster doses may help combat the Delta variant, people from low-income countries should not be left unprotected[52,53]. Moreover, current evidence is limited and inconclusive on the widespread need for booster doses after receiving primary vaccination[54].

5. Conclusion

Despite the concerns mentioned regarding the B.1.617.2, national and international vaccination is still crucial for containing this global SARS-CoV-2 pandemic, as vaccines induce neutralizing antibodies and block the viral RBD from binding to the ACE2 receptor. Although there is a reduction in vaccine efficacy against the B.1.617.2, vaccines can still

provide a considerable amount of protection, decreasing the risk of hospitalization and moderating the severity[5]. Nonetheless, the government should implement testing campaigns, mass vaccination, efficient contact-tracing, restricting gatherings, have strict quarantine of international travelers and strict traveling bans[55–58]. Furthermore, reminders and awareness within the community could increase compliance to preventive measures[59]. With the continuous emergence of new variants, there is a need for constant surveillance of the evolutionary changes of SARS-CoV-2 and how mutations of the spike protein contribute to immune escape[60]. This could allow for better definition and implementation of countermeasures. Last but not least, we must continue practicing safety measures to protect ourselves and others from COVID-19 infection and slow its transmission[5,61].

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