Delta Variant: The New Challenge of COVID-19 Pandemic, an Overview of Epidemiological, Clinical, and Immune Characteristics

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Abstract. The SARS-CoV-2 genome has undergone several mutations since the beginning of the pandemic in December 2019. A number of these mutants were associated with higher transmissibility, higher mortality, or hospitalization rates, which were named the variants of concern. B.1.617.2 or the Delta variant has made a lot of concern as it has been responsible for the most recent COVID-19 outbreaks throughout the world. Higher transmissibility, a 60 percent increase in hospitalization rates compared to the wild type, higher viral loads, and reduced response to available vaccines are among the key factors why this variant has become a variant of concern. 148 countries are currently fighting with this variant, hoping to better understand the epidemiological, immunological, and clinical characteristics of this disease in order to find the best way to overcome these new outbreaks. Although reduced efficiency of vaccines on this variant and its higher pre-symptomatic transmissibility have made it complicated to control the disease, higher vaccination coverage and following sanitation rules can help control the outbreaks. (www.actabiomedica.it)

Key words: COVID-19, SARS-CoV-2, Vaccine, Epidemiology, Immunology

Introduction

Since December 2019, when a novel beta coronavirus emerged to cause a significant number of pneumonia cases in Wuhan, China (1), the world has been challenging to overcome this pandemic. To date, more than 216 million people have been infected with this virus, and more than 4.5 million deaths have been reported from SARS-CoV-2 infection (2). A lot of advances have been made in better understanding the genomic structure of the virus, and many successful attempts have been made in developing efficient vaccines against this disease (3).

Despite the administration of COVID-19 vaccines, we are still facing new daily cases partly due to low immunization coverage in most countries, that can also be a consequence of the adaptive mutations that have happened in the SARS-CoV-2 genome amending its pathogenicity, virulence, and infectivity (4).

Mutations happen during the replication process,

which is five times more common in RNA viruses than DNA viruses. Owing to enzyme possession, coronaviruses undergo fewer mutations compared to other RNA viruses. During the natural selection process, mutations that are in favor of virus existence, making them more transmissible or more virulent, are chosen, and the other mutants disappear from the community of circulating viruses over time (5–7).

More than 4000 mutations have been identified in the spike protein of SARS-CoV-2 since the beginning of the pandemic; nevertheless, only a limited number of these mutations have been able to alter the virus' immune characteristics. The most significant variants impacting virus function have been originated from the United Kingdom, South Africa, Brazil, and India (7,8).

B1.1.7, also known as the UK variant or alpha variant, was one of the first distinguishable variants that underwent 23 mutations, and made a great concern in September 2020 as it was 56% more transmissible than other variants. Another aggressive variant emerged in South Africa in October 2020, known as B.1.351 or beta variant, and was reported to be 50% more transmissible. Unfortunately, those affected by the B1.1.7 variant were not immune against the South African type, as antibodies formed against the UK variant were ineffective against B.1.351 (7).

Another variant of concern was distinguished in Brazil in January 2021, known as the P1 descendent of B.1.1.28 or gamma variant, which was reported to be two times more transmissible than the original virus, and which could cause reinfections in people once affected by COVID-19 (6,8). Variants with reported potential to cause reinfections also raise significant concern about the effectiveness of available vaccines against them, and studies have shown that a slight decline in vaccine efficacy against new variants should be predicted (9,10).

The current variant of concern, B.1.617.2, also known as the Delta variant, emerged in India in late 2020, and is currently one of the main circulating variants throughout the world (11,12). Hence, a great concern remains over epidemiological, clinical, and immune characteristics of this variant and whether the available vaccines are effective against this variant which will be reviewed in this article

Epidemiological Characteristics

Mutations in the genome of all viruses, including SARS-CoV-2, are inevitable. There is no significant effect of most changes on the properties of the virus. However, some mutations result in new strains with higher transmission and infection rates, like the variant of SARS-CoV-2 known as Delta or the lineage B.1.617, which has recently drawn worldwide attention (13,14). This variant has been shown to have a higher transmission rate than the previous variants, even in fully vaccinated people, and it is estimated that the Delta variant is twice as contagious compared to the previous types (15).

For the first time, this mutant variant was identified among Indian citizens in Maharashtra in October 2020. As a result of the advent of this strain, the number of coronavirus infections in India dramatically increased, leading to a huge epidemic situation accompanied by many record-breaking cases and deaths. More than 400,000 new cases and 4,000 deaths were reported in one day; consequently, it became the first country to be in this situation (16,17).

Within a short time, cases were reported in over 100 countries because of its rapid spread, particularly in the U.K, due to numerous travels from India to this country (18,19).

In April 2021, this variant was first detected in the U.K. Despite vaccination, it spread rapidly, and accounted for more than 95% of the new cases that led to a devastating new wave in the UK and other European countries (20,21).

From another perspective, due to India's common border with Nepal, Bangladesh, and Pakistan, this strain was quickly transferred to these countries, and caused a similar disaster (22).

Continuing this trend, the high growth rate and transmission allowed it to spread quickly to more distant countries like Hong Kong, China, Singapore, Indonesia, Russia, the United States, and Australia (11,23–25).

This rapid outbreak of the SARS-CoV-2 Delta variant highlighted its high transmissibility, which led to it being labeled as a Variant Of Concern (VOC) (19,26). Infections with higher growth rates and more contagion indicate a change in the epidemiological

characteristics of viruses. Although this characteristic has not been definitively identified, several studies have attempted to determine it. Basically, increased growth rate of an epidemic could be due to changes in different characteristics, for example, reduced Generation time or increased reproduction number (27).

In a study conducted in China with 68 cases of infection, the epidemiological profile and transmission dynamics of the SARS-CoV-2 Delta variant were assessed and measured. Results showed the generation time (GT) between primary and secondary cases is 2.9 days which has become shorter in comparison to previous variants. (28).

On the other hand, several studies hinted that this variant is 60% more transmissible than the alpha variant (B.1.1.7), which is also 60% more contagious than the original virus first identified in China. Besides, it is known that the potential reproduction number (R0), the number of people a sick person will infect, for the wild type of SARS-CoV-2, is 2.5; hence, considering the transmissibility of the Delta variant, the R0 is calculated between 6 and 7, meaning the virus can spread to 6 to 7 individuals from each infected person (29). Therefore, changes in these two characteristics confirm the increase in growth rate, and in this regard, concerns about what is happening have grown.

Recently, researchers reported that the viral load, which represents the density of viral particles in the body, is 1,000 times higher in people infected with the Delta virus compared to people infected with prior versions of the Coronavirus and according to the resulting data. This could be related to its increased transmissibility rather than its increased pathogenicity (30,31). Furthermore, according to data from the United States, the United Kingdom, and Singapore, vaccinated and non-vaccinated individuals have the same viral load when infected with the Delta variant, but may stay infectious for a shorter duration (15,32).

In order to evaluate other epidemiological characteristics, a study in France examined one of the important characteristics of epidemics, called doubling time, which is defined as the sequence of intervals at which the cumulative incidence doubles (33). For a two-week period, this parameter is computed to be approximately 10 days. If the measurement period is increased to 21 days, it may increase significantly, probably because the data collection may be delayed (34).

Several studies show that, compared with the ancestral strain of the virus or the variant first detected in the U.K, individuals affected by the Delta variant are approximately two times more likely to be hospitalized, although it seems to cause more mortality, it has been reported that the fatality-case ratio (the number of deaths divided by the total number of cases) is about 1.7% compared to the main strain which was 3%. Thus, we can conclude that while more deaths have occurred, this is due to a significant increase in the number of cases, and the death case ratio is lower (35). Other studies also confirm that the risk of hospitalization is two times higher than the alpha variant, even in fully vaccinated, the same as the higher risk of infection (36).

Altogether, it seems that this strain is more infectious and has a high potential of transmission than previous types due to its greater adaptability to humans, and occurs more frequently among young people (36) who have not been vaccinated or have received only one dose. Because of these features, The World Health Organization called it “the fastest and the fittest”. Centers for Disease Control and Prevention (CDC) guidelines were updated after the spread of the new SARS-CoV-2 variant, and it is now recommended that fully vaccinated individuals wear masks in high-risk public places (15).

As of now, the Delta variant or the lineage B.1.617.2 has become the largest circulating virus, and is predominant in 135 countries, including the United Kingdom and Iran, which have reported the highest number of cases (37).

Clinical Characteristics

Signs and Symptoms

The symptoms of the SARS-CoV-2 Delta variant appear to be the same as those of the original form. On the other hand, physicians are noticing people become ill more quickly, particularly among the young. According to one study, the Delta variant develops faster

and to much higher levels in the respiratory system (30).

A study found that the incubation period, the time between exposure and the onset of symptoms, is 4 days, compared to 6 days for the ancestral strain (28). Patients infected with the delta variant can spread the virus from two days before the first symptoms of disease appear (38).

When vaccinated people are infected with the Delta variant, they are usually asymptomatic or have minor symptoms. Their symptoms are similar to those of a common cold, such as cough, fever, and headache, but a significant loss of smell and cough are less commonly reported in this variant (39).

Mucormycosis related with the SARS-CoV-2 Delta variant

Several instances of mucormycosis, aspergillosis, and candidiasis were recorded in India during the outbreak of the Delta variant (40).

As of 25th May 2021, the Indian government reported that 11,700 individuals had acquired mucormycosis. Even before the COVID-19 epidemic, mucormycosis rates in India were believed to be about 70 times more than anywhere else on the globe (41).

Mucormycosis is a rare but dangerous illness that may exacerbate the symptoms of severe COVID-19. Diabetes mellitus, concurrent glucocorticoid treatment, longer ICU stays, treatment with voriconazole, cancer, and other comorbidities have been associated with higher risks of developing mucormycosis in COVID-19 patients (42,43). Mucormycosis has been reported mostly in males, as male patients with COVID-19 accounted for about 80% of all cases. Furthermore 80% of COVID-19 patients with mucormycosis had a history of diabetes mellitus, and about 76% of cases were treated with glucocorticoids (44).

Mucormycosis has been reported with different clinical manifestations in respect of anatomical involvement. Rhino-orbital-cerebral mucormycosis (ROCM), cutaneous form, pulmonary involvement, and renal involvement are the most common reported clinical forms in COVID-19 patients, respectively. Mucormycosis can also manifest as a disseminated infection or involve the heart, ear, spine or breasts (43).

For better treatment results, high suspicion, early diagnosis, and immediate treatment initiation are important. In most cases, surgical debridement of the necrotic tissue is also a crucial part of the treatment (45).

Diagnosis & Treatment

Studies have shown that the Alpha and Beta variant have had no impact on the result of Rt-PCR test. However, to date, there has been no available report of the impact of the delta variant on RT-PCR (46).

Like other variants, no specific therapy has been found for the Delta variant, and supportive therapy is still the main part of treatment. World Health Organization (WHO) and CDC believe that some monoclonal antibody therapies are ineffective against this variant. This has the potential to have a significant impact on the usage of monoclonal antibodies (15,47).

Bamlanivimab, a monoclonal antibody, is no longer used since it is ineffective against the SARS-CoV-2 Delta variant. Monoclonal antibodies are not recommended for usage in life-threatening situations (47). Casirivimab, etesevimab, and imdevimab appear to be efficacious at high enough concentrations (15). Those infected with the Delta variant are more likely to develop pneumonia, or demand oxygen than those infected with the wild-type or the Alpha variant (48). A study done in Singapore found that more severe pneumonia cases were associated with the delta variant compared to the previous variants, and the use of supplemental oxygen, remdesivir, and corticosteroids have been higher in these patients rather than the ones infected with other VOCs (48).

Prognosis

Those infected with the Delta variant developed the first manifestations of the disease much faster than the other variants. Increased viral load and likelihood of pre-symptomatic transmission suggest that controlling infections with the Delta variant would be complicated (49).

According to one research, the Delta variant is associated with a 60% greater chance of household transmission than the alpha variant, which was already significantly more transmissible than the original virus (50).

SARS-CoV-2 Delta variant is sixty percent more infectious, which draws a lot of attention as it can act as a key factor in determining how fast the subsequent disease waves arrive. The fact that this virus appears to be causing about 60% more hospitalizations than the prior variants is also worrisome (51). Delta variant has been associated with a 120 percent increased risk of hospitalization, a 287 percent increased risk of intensive care unit admission, and a 137 percent increased mortality risk compared to non-variant of concern SARS-CoV-2 strains (52).

This variant had a case fatality rate (CFR) of 0.2 percent in England, while the Alpha variant had a case fatality rate of 1.9 percent. However, reports have indicated that case fatality rates are not comparable across variants because they peaked at different points during the pandemic, and thus differ in background hospital pressure, vaccination availability and rates, and case profiles, as well as treatment options (50).

People infected with the Delta virus had 1,000 times more copies of the virus in their respiratory tracts than those infected with the Wuhan strain; and it took an average of four days for people infected with the Delta virus to be detectable, compared to six days for those infected with the Wuhan strain (30).

According to preliminary results from a research conducted with 100,000 volunteers in the United Kingdom between May and July 2021, the time in which the Delta variant was spreading fast, vaccinated individuals who tested positive for COVID-19, including asymptomatic cases, had a reduced viral load on average.

The efficacy of existing vaccines on the Delta variant suggests that illnesses are milder post-vaccination (32).

Immune Characteristics

Characterization of the SARS-CoV-2 Delta variant

B.1.677 lineage variants were documented in India in October 2020 (36,53,54). The second sublineage, B.1.617.2 (Delta), was classified as a variant of concern (VOC) by the world health organization (WHO) (55). Studies regarding the SARS-CoV-2 Delta variant are limited, but reports clearly showed it is more infectious and spreads faster than the wild type of SARS-CoV-2. At the time writing this manuscript, the latest epidemiological update on COVID-19, published by WHO on 17th August 2020, indicates that the Delta variant has been identified in 148 countries worldwide (56), it is twice worse in hospitalization and infection than the Alpha variant, and it has been led to a new wave of cases in all the countries(57). As mentioned before, the lineage includes three primary subtypes (B1.617.1, B.1.617.2, and B.1.617.3), each of which has mutations in the SARS-CoV-2 spike protein's N-terminal domain (NTD) and receptor-binding domain (RBD) that may boost the variants' immune evasion capability.

Assessment of the structure of the Delta variant and comparing it with other variants showed that the spike protein of the Delta variant includes 8 mutations. T19R, G142D, Δ56–157, and R158G alterations in the NTD, two in the RBD (L452R and T478K), one in the furin-cleavage site (P681R), and one in the S2 area (D950N) (49). This group of alterations was distinct from those seen in other B.1.617 lineage members and other VOCs. In addition, it should be noted that mutations in the receptor-binding domain of the SARS-CoV-2 spike protein, such as L452R and P681R, have been linked to enhanced transmissibility in the Delta variant. Scientists found that in sera from recovered individuals, the Delta variation is less vulnerable to neutralizing antibodies, and compared to the Alpha form, this variant has a better replication efficiency (34,53,58–60).

Entry Ability of the Delta Variant into the Host Cell

Precise functions of SARS-CoV-2 Delta variant mutations have yet to be investigated scientifically. So far, it has been discovered that they allow the virus to adhere to human cells more easily and bypass some immune responses (61).

Researchers used African green monkey kidney cells as well as human kidney, colon, and lung cells that express endogenous ACE2 in a series of studies to see if B.1.617.2 has a better ability to infiltrate host cells (62,63).

According to the assessment of various research results, B.1.617.2 can enter human and monkey kid-

ney cells with the same efficiency as the wild-type. In comparison to the wild-type, B.1.617.2 has 1.5-fold, and 2-fold increased invading ability in human colon and lung cells, respectively. Therefore, these findings suggest that spike protein-mediated host cell entrance varies by cell type, with B.1.617.2 being more invasive in lung and colon cells. Increased entry of B.1.617.2 into colon and lung cells is not mediated by increased ACE2 binding because the spike protein of B.1.617.2 did not display increased ACE2 binding (64).

Efficacy of COVID-19's Vaccines on the Delta Variant

The start of vaccination against COVID-19 has led to a decrease in the rate of new cases and deaths in many countries; however, emergence of the Delta variant has caused a lot of concern. Since March 2021, roughly 17 percent of the SARS-CoV-2 Delta variant cases have occurred in vaccinated patients in Houston, Texas, where a Houston Methodist Hospital team has been sequencing and documenting SARS-CoV-2 variations for practically every COVID-19 case in the hospital system (65). Limited studies have assessed the efficacy of different vaccines against the SARS-CoV-2 Delta variant, and still, high contradictory information has been published during this period.

Sinopharm vaccine

One study evaluated the ability of the Sinopharm vaccine against the Delta variant, and the results showed that this vaccine is very effective against Delta species. Immunogenicity in people under 40 years of age was quite significant in 98% of people, and in over 60 years, the success rate was high in 93% of people (66).

Sputnik V

Studies have shown that neutralizing antibodies against the SARS-CoV-2 delta variant were significantly reduced in the Delta variant (67).

Available data from vaccinated healthcare workers in Iran, who were vaccinated with Sputnik V or Sinopharm vaccine suggested that there has been a reduced efficacy of these vaccines against the SARS-CoV-2 Delta variant as even the fully vaccinated healthcare workers became symptomatically infected with the delta variant (55).

Pfizer and AstraZeneca vaccines

According to data published from Israel, the Pfizer vaccine efficiency against infection fell from 94% to 64% after the Delta variant prevalence (68).

Jamie Lopez Bernal et al. evaluated the effectiveness of the BNT162b2 and ChAdOx1 nCoV-19 vaccines against the Delta variant in a study that was published in The New England Journal of Medicine (Table 1)(16). The efficacy after a single dose of Pfizer (BNT162b2) and AstraZeneca (ChAdOx1 nCoV-19) vaccine in people infected with the Delta variant was significantly lower than that in alpha variant infected patients. In addition, it has been shown that two doses of the Pfizer vaccine are more effective than two doses of the AstraZeneca vaccine. The Pfizer-BioNTech vaccine was found to be 88 percent effective against the Delta variant after two doses. However, after one vaccine dose, effectiveness dropped to around 36% (16).

The results of a study that has been published in the Nature scientific journal demonstrated clearly that a single treatment of a two-dose vaccine-like Pfizer-BioNTech or AstraZeneca, "hardly" provided any protection (69). In another study, researchers stated that when Delta was dominant, the efficacy of AstraZeneca (AZN) vaccination was lower than Pfizer (PFE), but the Pfizer vaccine's efficacy fell over time, and the authors estimated that both vaccines would be equally effective against the Delta variant four to five months after receiving a second dose (70).

Moderna vaccine

Some studies showed that individuals who were fully vaccinated with Moderna's mRNA-1273 product were much less likely than unvaccinated individuals to acquire moderate or severe outcomes following B.1.617.2 infection (71).

The Moderna vaccine was found to be capable of providing protection against the Delta form and other variants evaluated in lab research, despite the fact that it was substantially less effective than the alpha variant (69). Also, the efficiency of the Pfizer and Moderna vaccine was estimated 94% against the SARS-CoV-2 Delta variant by researchers of a lab (72).

Johnson & Johnson vaccine

A recent study evaluated the power of the John-

son & Johnson vaccine against this variant, and the results showed that the single-shot J&J vaccine offered 91% to 96.2% protection against death, and when the Delta variant dominates, the protection against hospitalization is roughly 71%(73). A trial study estimated that the efficiency of the Johnson & Johnson vaccine against the Delta variant is about 85%, and it also revealed that the J&J vaccine-elicited larger levels of "neutralizing antibody activity" against the Delta variant than the beta variant, which prevents the virus from infecting healthy cells.

Conclusion

Mutations are always predictable in all viruses, and SARS-CoV-2 is no exception (5). The Delta variant has proved to be associated with higher viral loads in both vaccinated and non-vaccinated people, more transmissibility, and higher hospitalization rates (74). Nevertheless, although studies have shown reduced overall efficiency on this variant, available vaccines are still effective enough to prevent a disaster. Hence, vaccinating larger percentages of the communities, together with following the public rules for protecting oneself and others against COVID-19, like wearing masks and frequent hand washing, can help us defeat the outbreaks caused by new variations irrespective of their higher transmissibility.

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