Review

Genetics, Structure, Transmission, Epidemiology, Immune response, and Vaccine Efficacies of the SARS-CoV-2 Delta variant: A Comprehensive Review

Running Title: COVID-19 Delta variant comprehensive review

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Summary

The SARS-CoV-2 Delta variant (B.1.617.2) was the predominant variant behind the surges of COVID-19 in the United States, Europe, and India in the second half of 2021. The information available regarding the defining mutations and their effects on the structure, transmission, and vaccine efficacy of SARS-CoV-2 is constantly evolving. With waning vaccine immunity and relaxation of social distancing policies across the globe driving the increased spread of the Delta variant, there is a great need for a resource aggregating the most recent information for clinicians and researchers concerning the Delta variant. Accordingly, this narrative review comprehensively reviews the genetics, structure, epidemiology, clinical course, and vaccine efficacy of the Delta variant. Comparison with the omicron variant is also discussed. The Delta variant is defined by 15 mutations in the Spike protein, most of which increase affinity for the ACE-2 receptor or enhance immune escape. The Delta variant causes similar symptoms to prototypical COVID-19, but it is more likely to be severe, with a greater inflammatory phenotype and viral load. The reproduction number is estimated to be approximately twice the prototypical strains during the early pandemic, and numerous breakthrough infections have been reported. Despite studies demonstrating breakthrough infection and reduced antibody neutralization, full vaccination effectively reduces the likelihood of severe illness and hospitalization.

Keywords: COVID-19; SARS-CoV-2; Delta variant; epidemiology; public health; virology;

List of Abbreviations: COVID-19, coronavirus disease of 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE-2, angiotensin-converting enzyme 2; CI, confidence interval, RBD, receptor binding domain; HR, Hazard Ratio; aOR, adjusted odds ratio;

Introduction

As of 1st of March 2022, SARS-CoV-2 has infected 437,693,348 cases and 5,978,017 deaths.[1] Complicating epidemiological control of the pandemic is the evolution of new variants with global transmission, which often have increased infectivity and immune evasion. An early dominant variant was D614G, which increased transmission due to an amino acid substitution in its Spike protein.[2] Subsequently, the Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), Gamma (P.1), and Omicron (B.1.1.529) variants have emerged as variants of concern by the WHO for their infectivity, evade detection, evade immunity, and reduce therapeutic effectiveness.[3] First identified in India in December 2020 as a sublineage of the B.1.617 variant, B.1.617.2 is particularly concerning for its rapid transmission among unvaccinated populations, as well as reports of breakthrough transmission in vaccinated individuals.[4] The Delta variant had emerged as the dominant contagion in the United States, United Kingdom, India, and Israel.[5] B.1.617.2 is up to 50% more transmissible than the B.1.1.7 variant, responsible for the infection waves in India and the UK.[6] Additionally, many countries have low vaccination acceptance due to their economic or cultural beliefs, which may have increased susceptibility to SARS-CoV-2 and its mutation.[7, 8]

Underlying its increased transmission are several amino acid substitutions in the Spike protein, allowing for enhanced affinity for the angiotensin-converting enzyme 2 (ACE2) receptor, immune evasion, and resistance to degradation.[6] The variants of concern all contain mutations that enhance receptor binding affinity for the ACE2 receptor.[9] The first variant of concern, the Alpha variant, contains eight mutations in the Spike protein, of which N501Y increases affinity for the ACE2 receptor. This variant tends to have higher mortality than its ancestor lineages. For the alpha variant, the BNT162b2 vaccine effectively reduces the likelihood of infection, reduces symptomatic infection, and reduces secondary

transmission once infected.[10] The Beta variant has three mutations that increase binding affinity for the ACE2 receptor and also demonstrates a comparable reduction in efficacy following two doses of the mRNA-1273 vaccine to wildtype SARS-CoV-2.[11] The Gamma variant hosts three affinity-boosting mutations in the Spike protein. Evidence concerning breakthrough infection by the Gamma variant is scarce. One small case series from French Guiana reported similar infection rates between vaccinated and unvaccinated miners.[12] The Omicron variant has more than 30 mutations in the Spike protein, which greatly increases the transmission and reinfection rates.[13] Although breakthrough infection and increased infectivity have been reported for all variants of concern, the Delta variant arouses particular concern because of 1) its emergence as a dominant strain in multiple waves of infection globally, even in the presence of other variants of concern and variants of interest;[9] and 2) early reports specifying a potentially high proportion of breakthrough infection.[14, 15]

Although individual studies have reported genetics, viral structure, clinical course, immune response, epidemiology, detection, and vaccine efficacy associated with the Delta variant, no comprehensive review of this kind has previously been reported. Despite the rapidly evolving and growing threat of Delta variant transmission, there exist few resources conglomerating the available information for clinicians and epidemiologists.

Accordingly, we performed a comprehensive review of the Delta variant genetics, structure, clinical course, immune response, epidemiology, transmission, vaccine efficacy, and breakthrough infection.

Genetics

Of the variants of concern, the Alpha variant was the first to emerge, described in the United Kingdom in December 2020. The Beta and Delta variants followed in South Africa and Maharashtra, India, respectively, in December 2020, the Gamma variant emerged in Brazil

in January 2021, and the Omicron variant was reported in November 2021 in South Africa. The Delta variant is a sublineage of variant B.1.617 out of three in total (B.1.617.1, B.1.617.2, B.1.617.3).

The precise number of mutations that distinguish the Delta strain is constantly evolving. The genetic diversity of the Delta variant amongst countries is greater than the Alpha variant, but to date, there are 15 defining mutations in the Spike protein that increase virulence: T19R, V70F*, T95I, G142D, E156del, F157del, R158G, A222V*, W258L*, K417N*, L452R, T478K, D614G, P681R, and D950N (* the mutation was detected in some sequences but not in all).[16, 17] Several mutations (V70F, T95I, G142D, A222V, W258L, K417N) are present at higher frequencies in the Delta plus variant, a descendent of the Delta variant. However, since distinguishing these variants was beyond the scope of this paper, these mutations are all discussed in the context of the Delta variant. Three of these (K417N*, L452R, T478K) are within the ACE2 receptor binding domain (RBD).[18] At least seven other structural mutations in the viral life cycle-associated membrane (I82T), nucleocapsid (R203M, D377Y), NS3 (S26L), and NS7a (V82a, T120l) are specific to the Delta variant.[17] D614G, as the defining mutation in the ancestor dominant variant, is present in all variants of concern and their sublineages. The other variants of concern do not share any identical amino acid substitutions with Delta (except D614G) but do share some amino acid substitutional positions. The Alpha variant has a P681H substitution, as opposed to the P681R of Delta, and both Beta and Gamma have substitutions at the K417 position.[19]

Figure 1 summarizes the unique and shared mutations of all sublineages of the B.1.617 variant. The Delta variant parent lineage (B.1.617) is defined by G142D, L452R, D614G, and P681R, and these four mutations are found in all its branching sublineages. Unlike the Delta variant, B.1.617.1 has the unique mutations E154K and Q107H. B.1.617.3 additionally shares T19R and D950N with B.1.617.2. Both B.1.617.1 and B.1.617.3 possess an E484Q,

which is not present in the Delta variant.[20] Despite the shared mutations encouraging transmissibility between all B.1.617 sublineages, only B.1.617.2 remains a dominant variant within Europe. Such differences in transmissibility may have resulted from the synergism in the B.1.617.2 unique mutations to increase cell entry and immune evasion.

Structure

The SARS-CoV-2 genome encodes 26 proteins. The four structural proteins include the Spike, Membrane, Nucleocapsid, and Envelope proteins. There are 16 non-structural proteins, NSP1 to NSP16, and six accessory proteins (NS3, NS6, NS7a, NS7b, NS8, and ORF10).[17] The Spike protein mediates SARS-CoV-2 cell entry and is a trimer with an S1 subunit that contains the RBD and an S2 subunit that contains peptides mediating cell fusion. The S protein is activated by cleavage of the S1/S2 site by host transmembrane protease serine 2 (TMPRSS2).[21]

Amino acids present at 438 to 506, a part of RBD, are responsible for higher virus transmission, infection, and immune escape.[22, 23] The most well-studied mutations currently include D614G, L452R, T478K, and P681R, located in the RBD or near the S1/S2 cleavage site. The D614G spike mutation significantly increases viral entry efficiency by a proposed mechanism that allows the Spike protein to adopt a more open conformation to bind ACE2.[24] Mutations in the RBD also drive a more positive electrostatic potential, further increasing affinity for the negatively charged ACE2 receptor.[25] Out of the RBD mutations, L452R and K417N allow immune escape. L452R facilitated neutralization escape from 14 of 34 monoclonal antibodies in one study.[26] K417N decreases ACE2 receptor binding but increases immune escape.[27] T478K increases ACE2 binding by further polarizing the RBD toward a positive electrostatic potential, which drives greater interaction with the negatively charged ACE2.[28] P681R, the closest substitution to the S1/S2 cleavage site, increases furin-mediated S cleavage by enhancing basicity and furin interaction.[29] In the N-terminal

domain, T19R, E156del, F157del, and W258L encourage antibody escape, while V70F increases S1/S2 cleavage.[30-33] Other mutations concentrated in the N-terminal domain and the S2 subunit have, to the best of our knowledge, as of yet, unclear effects on viral function. Table 1 summarizes the mutations unique to the Delta variant, their locations in the viral genome, and their proposed effects on structure and function.[24-35]

Clinical course and Immune Response

The Delta variant causes a greater rate of severe infection. In a cohort study in England with 43,338 SARS-CoV-2 positive patients, the Delta variant was associated with greater frequencies of hospital admission (adjusted HR 2.26) and combined hospital admission or visits to the emergency department (adjusted HR 1.45).[36] The EAVE II study in Scotland also showed that patients with the Delta variant were more likely to be hospitalized within 14 days compared to patients with the alpha variant (HR 1.85).[37] Combined surveillance and single-center study in Singapore demonstrated similar findings that the B.1.617.2 variant is associated with pneumonia (aOR 1.88), oxygen requirement, ICU admission, and death (aOR 4.90) compared to the wild-type. These findings are not demonstrated by the alpha or beta variants infections within the same cohort.[38] Another study was conducted using Washington Disease Reporting System from December 1, 2020, to July 30, 2021.[39] In this study, the Delta variant also showed a higher hospital admission frequency (HR 2.35). Table 2 summarizes the admission rate and hazard ratio of the Delta variant.[36, 37, 39] When aggregating the hazard ratios presented in the three articles above, the Delta variant had a higher risk of hospital admission than non-Delta variants (HR 2.09, 95% CI: 1.71 to 2.54).

B.1.617.2 does not appear to cause a notably different pattern of symptoms compared to wild-type counterparts, though it does associate with inflammation and severity. An epidemiological study monitoring seven transmission generations with confirmed B.1.617.2 infection in Guangzhou revealed that patients with the Delta variant had lower frequencies

of fever, dyspnea, cough, and vomiting compared to wild-type; however, the most common symptoms remained as cough, fever, and sputum production.[40] Patients with B.1.617.2 exhibited a greater inflammatory phenotype reflected in increased leukocytes, neutrophils, and decreased lymphocytes. The Delta patients had a greater proportion of patients < 18 years (16% vs. 3%).[40] Consistent with other findings demonstrating a more severe clinical course, this study also showed that the Delta variant led to a greater proportion of critical infections in the elderly.

Biological studies have demonstrated that Delta variant mutations confer the capability to evade the immune response, mediated significantly by the L452R and T478K residue mutations. L452R and T478K mutations increase intra-chain interactions within the spike protein, which may impede the binding of neutralizing antibodies.[41] L452R, specifically, has been shown by global phylogenetic analysis to be a common mutation across multiple highly proliferative and expanding strains.[35] In recombinant binding assays, L452R/E484Q led to lower mutant recognition from infection-induced antibodies but not vaccination-induced antibodies.[42] The G142D mutation in the spike protein RBD is also a highly preserved mutation in the B.1.617.2 lineage that permits immune evasion, based on a genomic study survey of Delta variant strains.[43] In vitro studies have revealed evasion of both humoral and cell-mediated immunity by B.1.617.2. Sera antibody neutralization studies from vaccinated and previously infected patients show decreased neutralizing activity against the B.1.617.2 variants.[44] A mutated epitope in B.1.617.2 containing L452R, D614G, P681R, T478K, D950N, T19R, E156-, F157-, and R158G led to significantly reduced CD8+ T cell activation from sera.[45]

Epidemiology and Transmission

The B.1.617.2 variant is more transmissible across epidemiological and clinical studies. The Delta variant was originally isolated in Maharashtra and West Bengal.[46] Over the period

from May to December, the Delta variant shifted from accounting for 0.2% of sequenced infection across all EU countries to 99.6% of sequenced infection.[47] The reproductive number (R0), which represents the average number of secondary contacts infected by an infectious host without epidemiological control efforts, is higher in the Delta variant. Most estimates for the R0 of the ancestral SARS-CoV-2 strains varied between two and four, while the estimates for B.1.617.2 variant R0 varied between 3.2 to 8, with a mean of 5.08.[48, 49] This spread seems to be mediated primarily by person-to-person transmission and in contexts defined by extended close-quarter contact.[48, 50] The secondary attack rate amongst household contacts was estimated to be 25% for vaccinated patients and 38% for unvaccinated patients, as shown in a UK study.[4] In Public Health England's technical briefing from August 6, 2021, the secondary attack rate was 10.4% for households and 6.2% for non-household community transmission, a finding similar to the alpha variant.[51] A stochastic model integrating survey data for K-12 school populations in California found that the Delta variant greatly increased the risk of school transmission compared to the Alpha variant, given school reopening policies.[52] In a study elucidating clinical characteristics of Delta variant infection in Guangzhou, China, viral shedding was detected six days longer from pharyngeal swab samples in the Delta variant compared to the wild-type (14 vs. eight days). Furthermore, it displayed an incubation of four days compared to the six days of wild-type incubation, and viral loads, as measured by cycle thresholds, are higher in the Delta variant.[40] To our knowledge, no systematic epidemiological study has been performed evaluating the nosocomial attack rate of the Delta variant across multiple hospitals, though preliminary case studies of individual hospital outbreaks suggest that the Delta variant is highly transmissible with the potential for breakthrough infection. One study in Israel described a nosocomial outbreak of 42 patients from a single primary case, with an attack rate of 10.6% among healthcare workers and 23.7% among patients, most of whom were vaccinated.[53] Similar outbreaks occurred in Finland and Canada, where they had massive

261 outbreaks of the Delta variant despite personal protective equipment and high vaccination
262 rates.[54, 55]

263 *Vaccine Efficacy and Breakthrough Infection*

264 The capacity for B.1.617.2 to evade antibody neutralization from several structural
265 substitutions, as well as several reported outbreaks in highly vaccinated populations, raises
266 concern for a potentially higher rate of breakthrough infection.[44, 53, 54] A UK study found
267 the household secondary attack rate to be 25% for vaccinated individuals.[4] In Israel, the
268 protection rates against COVID-19 decreased to 39% after the emergence of the Delta variant,
269 though protection against hospitalization and severe illness remained at 88% and 91.4%,
270 respectively.[56] In two case-control studies, mRNA-1273 was found to be slightly more
271 effective than the BNT162b2 at preventing any infection, and BNT162b2 was slightly more
272 effective than ChAdOx1 nCoV-19 at preventing symptomatic infection.[57, 58] Furthermore,
273 a single vaccine dose alone provides significantly reduced protection against the Delta variant
274 compared to the alpha variant.[57] Vaccine effectiveness declines with time and waning
275 immunity, specifically from 93% to 53% in after four months, though the decay rate of
276 vaccine effectiveness remains similar to non-Delta variants.[59] A systematic review and
277 meta-analysis extrapolating vaccine efficacy from antibody neutralization titers predicted
278 that the mRNA-1273 and ChAdOx1 nCoV-19 vaccines might be at least 25% less effective
279 for the Delta variant compared to prototype variants.[60] Bian et al. aggregated seven studies
280 from Canada, Scotland, Israel, India, and the UK and found a vaccine efficacy ranging from
281 59.8% to 87.9% after two doses, whereas the Alpha variant had a vaccine efficacy from
282 66.1% to 93.4% across the same studies.[56] Although it is possible that the moderate decline
283 in vaccine efficacy resulted from immune escape by B.1.617.2, such findings may also be
284 attributed to waning immunity, relaxation of social distancing policies, and heterogeneity
285 amongst study protocols and geographies.

Although the Delta variant seems to cause breakthrough infection at rates greater than other variants of concern, the severity of these infections are sufficiently attenuated by vaccination. COVID-19-related severe illness during surging Delta periods remain low in vaccinated individuals. Variant-specific data also demonstrate that mRNA and ChAdOx1 nCoV-19 vaccines provide >90% protection against severe illness, while Ad26.COV2.S provides 71% protection. The vaccine efficacies of each vaccine against hospitalization or severe illness from the Delta variant are shown in Table 3.[58, 59, 61-64]

The Delta variant is compared to the omicron variant.

On November 24 2021, a noble variant, B.1.1.529, the Omicron variant, emerged in South Africa and is becoming the leading variant around the world. It is analyzed that the Omicron variant is not mutated from the Delta variant, presuming it is derived from other animals and then reinfected in humans.[65] Compared to the Delta variant, it has more mutation residues (43 vs. 18) and higher transmissibility but has lower morbidity and mortality rate.[66] One study from Denmark has calculated the relative reproduction number of the Omicron variant compared to the Delta variant and concluded the rate to be 3.19 (95% CI: 2.82-3.61).[67] Some other studies also calculated the relative reproduction number of the Omicron compared to the Delta variant and estimated the number as 3 to 6.[66] Age of the patients in the Omicron infected group were middle-aged people (vs. Delta variant: children or elderly), and the vaccine efficacy of the Pfizer-BioNTech vaccines were 33%, which is extremely low compared to the Delta variant. The vaccine efficacy of Pfizer-BioNTech vaccines against severe illness and hospitalization was also decreased in the Omicron variant, which is 70% compared to 93% of the Delta variant. People infected with the Delta variant had a 40% relative risk of contracting the Omicron variant, which showed a protective immune response between the variants.[66]

Current treatment options

Many drugs were brought up to clinical trials and research, and countless articles have been published. In this review, we have summarized the drugs evidenced by randomized control trials, showing robust evidence. To start with, remdesvir, which was originally targeted for hepatitis C, had showed efficacy median recovery time in hospitalized COVID-19 patients. Taking 200mg loading dose of remdesvir on day 1 and continuing 100mg for 9 additional days has shortened the length of hospital stay from 15 days to 10 days (95% CI 9 to 11 days).[68] Moreover, adding baricitinib with remdesvir showed superiority compared to remdesvir alone.[69] Molnupiravir, a drug originally targeted for influenza virus, which induces lethal mutagenesis and escaping viral proofreading activities, also showed effect reducing the risk of hospitalization or death in unvaccinated adults with COVID-19 (risk difference -6.8 percentage points 95% CI -11.3 to -2.4).[70, 71] Nirmatrelvir/ritonavir, a novel per oral drug made by Pfizer, was approved by United States Food and Drug Administration as emergency use to COVID-19 patients. According to Pfizer, administering this new drug within 3 days has reduced the rate of hospitalization (0.8% in Nirmatrelvir/ritonavir group versus 7% in placebo group) but additional studies are needed.[72] Bamlanivimab/etesevimab also showed efficacy reducing hospitalization or death from any cause in mild to moderate COVID-19 patients (Bamlanivimab/etesevimab 2.1%, placebo 7%, absolute risk difference -4.8 percentage points, 95% CI: -7.4 to -2.3).[73] Dexamethasone, a potent corticosteroid, lowered mortality among the hospitalized COVID-19 patients with mechanical ventilation (age-adjusted rate ratio 0.83, 95% CI: 0.75 to 0.93).[74] Nebulizing interferon beta-1a resulted rapid recovery and greater odds of improvement in COVID-19 patients (odds ratio 2.32, 95% CI: 1.07 to 5.04).[75]

Apart from randomized controlled trials, a decent systematic review and network meta-analysis regarding medication options for COVID-19 was conducted and is currently being updated.[76] According to the study, corticosteroids, and interleukin-6 inhibitors showed

meaningful benefit with severe COVID-19 patients.[76] Additionally, janus kinase inhibitor ameliorated the risk and duration of mechanical ventilation but evidence is not robust.

Conclusions

SARS-CoV-2 remains a public health threat in no small part due to evolution into new, highly virulent variants. The Delta variant (B.1.617.2) had emerged as the dominant infection across multiple countries, including the United States and much of Europe. The Delta variant is afforded enhanced viral infectivity and antibody escape from 15 mutations in its Spike protein. These mutations grant this variant a reproductive number approximately twofold that of predecessor variants. The Delta variant is associated with more severe infection, with patients more likely to be hospitalized, require supplemental oxygen, and suffer longer infection course. Case reports suggest that the Delta variant allows for a greater proportion of breakthrough infection against vaccinated individuals, but the rate of serious breakthrough infection is sufficiently attenuated by vaccination across mRNA and vector-based vaccines. Nevertheless, development of a vaccine which could tackle the mutated SARS-CoV-2 is needed.

Table 1. Spike mutations in B.1.617.2 and proposed effects on structure.

Spike protein mutation	Genomic position	Structural effects
T19R[33]	N-terminal domain	Facilitate immune escape by altering epitopes
V70F*[32]	N-terminal domain	Increase S1/S2 cleavage
T95I	N-terminal domain	Unknown
G142D[31]	N-terminal domain	Affects side chain conformation in combination with R158G
E156del[30]	N-terminal domain	Increase immune escape
F157del[30]	N-terminal domain	Increase immune escape
R158G[31]	N-terminal domain	Affects side chain conformation in combination with G142D
A222V*[34]	N-terminal domain	Unknown, does not alter antigenicity or viral entry
W258L*[31]	N-terminal domain	Facilitates antibody escape by increasing antibody-epitope distance
K417N[27]	S1 subunit RBD	Decrease ACE2 affinity; facilitate immune escape
L452R[35]	S1 subunit RBD	Improve ACE2 binding and reduce antibody neutralizing activity
T478K[25, 28]	S1 subunit RBD	Increases ACE2 binding by driving a positive electrostatic charge
D614G[24]	S1 subunit C-terminal, near furin-cleavage site	Forces the S1 subunit to adopt a more open conformation that readily binds ACE2
P681R[26, 29]	S1 subunit C-terminal, near furin-cleavage site	Enhanced S1/S2 cleavage mediated by enhancing basicity of the poly-basic stretch and facilitation of interaction with furin
D950N[33]	S2 subunit, trimer interface	Proposed to affect spike protein dynamics

Abbreviations. RBD, receptor-binding domain

Table 2. Admission rate and hazard ratio of the Delta variant compared to non-delta variant

Author	Number of total patients	Number of admitted patients	Adjusted HR* and 95% CI
Twohig et al[36]	Non-Delta: 34,656 Delta: 8,682	Non-Delta: 764 (2.2%) Delta: 196 (2.3%)	2.26 [1.32-3.89]
Sheikh et al[37]	Non-Delta: 11,820 Delta: 7,723	Non-Delta: 243 (2.1%) Delta: 134 (1.7%)	1.85 [1.39-2.47]
Paredes et al[39]	Non-Delta: 22,068 Delta: 1,934	Non-Delta: 519 (2.4%) Delta: 63 (3.3%)	2.35 [1.72-3.22]

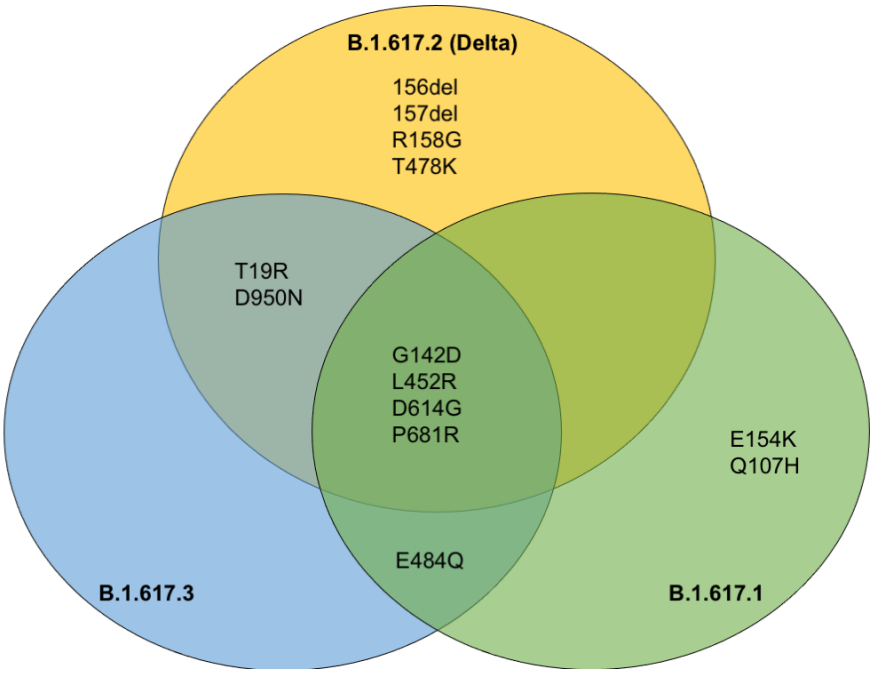
Abbreviations. HR, Hazard Ratio

* Hazard ratio for delta variant compared to non-delta variant was estimated using Cox regression

Table 3. Vaccine effectiveness against severe illness or hospitalization from Delta variant infection in vaccinated individuals.

Author	Country	Data source	Doses	Vaccine effectiveness against severe illness or hospitalization from Delta variant infection
Tang et al.[58]	Qatar	950,232	2	93.4% BNT162b2 96.1% mRNA-1273
Bruxvoort et al. [62]	US	8,153	2	97.6% mRNA-1273
Chia et al. [63]	Singapore	218	2	93% BNT162b2 or mRNA-1273
Tartof et al. [59]	US	4,920,549	2	93% BNT162b2
Sheikh et al.[64]	Scotland	114,706	2	91% ChAdOx1 nCoV-19 90% BNT162b2
Sisonke study[61]	South Africa	38,298	1	71% Ad26.COV2.S

Figure 1. Shared and unique mutations of the Delta and related variants.



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