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SARS-CoV-2 Variants of Concern

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Since the COVID-19 pandemic first began in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has continuously evolved with many variants emerging across the world. These variants are categorized as the variant of interest (VOI), variant of concern (VOC), and variant under monitoring (VUM). As of September 15, 2021, there are four SARS-CoV-2 lineages designated as the VOC (alpha, beta, gamma, and delta variants). VOCs have increased transmissibility compared to the original virus, and have the potential for increasing disease severity. In addition, VOCs exhibit decreased susceptibility to vaccine-induced and infection-induced immune responses, and thus possess the ability to reinfect previously infected and recovered individuals. Given their ability to evade immune responses, VOC are less susceptible to monoclonal antibody treatments. VOCs can also impact the effectiveness of mRNA and adenovirus vector vaccines, although the currently authorized COVID-19 vaccines are still effective in preventing infection and severe disease. Current measures to reduce transmission as well as efforts to monitor and understand the impact of variants should be continued. Here, we review the molecular features, epidemiology, impact on transmissibility, disease severity, and vaccine effectiveness of VOCs.

Key Words: SARS-CoV-2, COVID-19, variant, variant of concern, delta variant, alpha variant, vaccine

INTRODUCTION

All viruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), evolve over time. Although the rate of evolution of coronavirus is slower compared to other RNA viruses, such as HIV-1 or influenza virus, antigenic drift occurred during the SARS-CoV-1 outbreak in 2003. In particular, an amino acid mutation of D480 A/G within the receptor binding domain (RBD) of the Spike (S) protein of SARS-CoV-1, which had the ability to escape from neutralizing antibodies, became the dominant variant as the outbreak proceeded.[1] For SARS-CoV-2, the mutation rate was approximately two mutations per month, and variants with clinical implication were not considered to be able to emerge at such a slow rate within a short period;[2] however, chronic viral shedding in the setting of immunocompromised hosts produced viruses with multiple mutations, including in the S protein.[3,4]

It became clear in the early phase of the pandemic that viral evolution was going to be an issue. In February 2020, the D614G mutation within the RBD of S protein was detected in Europe, and variants carrying the D614G mutation rapidly became the dominant viral strains across the world.[5] Studies showed that the D614G mutation is associated with higher viral loads, enhancing the binding of the virus spike to the angiotensin-converting enzyme 2 (ACE2) receptor and increased infectivity.[5,6] Since the emergence of D614G variant, several major variants with additional infectious and clinical implications have been identified worldwide.

The nomenclature systems for naming SARS-COV-2 lineage by GISAID, Nextstrain, and Pango are currently used by researchers. While the scientific lineage nomenclatures have their advantages, these scientific names can be difficult to say and recall, and are prone to being misreported. As a result, people often resort to calling variants by the places where they are detected, which is stigmatizing and discriminatory. To avoid

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this and to simplify public communication, the WHO Virus Evolution Working Group has recommended using letters of the Greek alphabet for naming variants of SARS-CoV-2.[7] The classification of variants of SARS-CoV-2 includes variant of interest (VOI), variant of concern (VOC), and variant under monitoring (VUM).[8] The classification of variant may differ according to each country's situation.

VOI is defined as a SARS-CoV-2 variant with genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; and identified to cause significant community transmission or multiple clusters of infected persons, in multiple countries with increasing relative prevalence as well as increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health.

VOC is defined as a SARS-CoV-2 variant that meets the definition of a VOI and has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance: 1) increase in transmissibility or detrimental change in COVID-19 epidemiology; 2) increase in virulence or change in clinical disease presentation; or 3) decrease in effectiveness of public health and social measures or available diagnostics, vaccines, and therapeutics. As of August 30, 2021, four VOCs (alpha, beta, gamma, and delta) have been designated by the WHO (Table 1). Based on the WHO epidemiological update, as of Aug 31, 2021, the alpha, beta, gamma, and delta variants have spread to 193, 141, 91, and 170 countries, respectively (Fig. 1).[9]

A previously designated VOI or VOC, which has conclusively demonstrated to no longer pose a major added risk to the global public health compared to other circulating SARS-CoV-2 variants, can be reclassified. VUM is a SARS-CoV-2 variant with genetic changes that are suspected to affect virus characteristics with some indication that it may pose a future risk; however, the evidence of phenotypic or epidemiological impact is currently unclear, requiring enhanced monitoring and repeat assessment pending new evidence.

Here, we have reviewed the VOC.

Alpha VOC

On December 14, 2020, the United Kingdom (UK) reported a SARS-CoV-2 VOC, lineage B.1.1.7, which became known as the "alpha" variant according to the WHO.[10] The alpha VOC likely emerged in September 2020, and had quickly become the dominant circulating variant in the UK within a few months and then was exported around the world,[11] implicating a fitness advantage over the original strain. The alpha variant includes 17 mutations (14 nonsynonymous point mutations and three deletions) in the viral genome. Among these, eight mutations (Δ69-70 deletion, Δ144 deletion, N501Y, A570D, P681H, T716I, S982A, and D1118H) are in the S protein.[12] Of those mutations, N501Y within the RBD enhances virus binding affinity to ACE2 receptor of host cells,[12,13] and P681H is adjacent to the furin cleavage site in spike, which is a key determinant for transmission.[14] Additionally, the deletion H69/V70 in the S protein is linked to immune escape and may cause testing kit failures.[15]

A modeling study from UK showed that the alpha VOC has a 43%–90% [95% confidence interval (CI), 38–130] higher reproduction number compared to preexisting variants.[12] However, the initial assessment by the Public Health England (PHE) of disease severity through a matched case-control study reported no significant difference in the risk of hospitalization or death in people infected with confirmed alpha variant infection versus those infected with preexisting variants other variants.[10] However, another matched cohort analysis by PHE suggested the possibility of increased death risk for individuals infected with the alpha variant compared to non-alpha variants, with a risk ratio of 1.65 (95% CI, 1.21–2.25).[16]

Regarding implications for treatment, several mutations found in the alpha variant reduce the neutralizing activity of several monoclonal antibody-based therapies. A study showed

Table 1. Variants of Concern (as of August 31, 2021)

WHO label	Lineage+ additional mutations	Country first detected	Spike mutations of interest	Year and month first detected	Number of countries where variants are detected	Impact on transmissibility	Impact on vaccine immunogenicity or effectiveness	Impact on disease severity
Alpha	B.1.1.7	United Kingdom	N501Y, D614G, P681H	Sep-20	193	Yes[12-14,25]	No[19-23]	Yes[10,16]
	B.1.1.7+E484K	United Kingdom	E484K, N501Y, D614G, P681H	Dec-20		Yes[12-14,25]	Yes[19-23]	Yes[10,16]
Beta	B.1.351	South Africa	K417N, E484K, N501Y, D614G, A701V	Sep-20	141	Yes[12,13,28,29,32]	Yes[24,31,37,38]	Yes[33]
Gamma	P.1	Brazil	K417T, E484K, N501Y, D614G, H655Y	Dec-20	91	Yes[12,13,42]	Yes[44,45]	Yes[33]
Delta	B.1.617.2	India	L452R, T478K, D614G, P681R	Dec-20	170	Yes[47,49-53,55]	Yes[22,57-61]	Yes[22]

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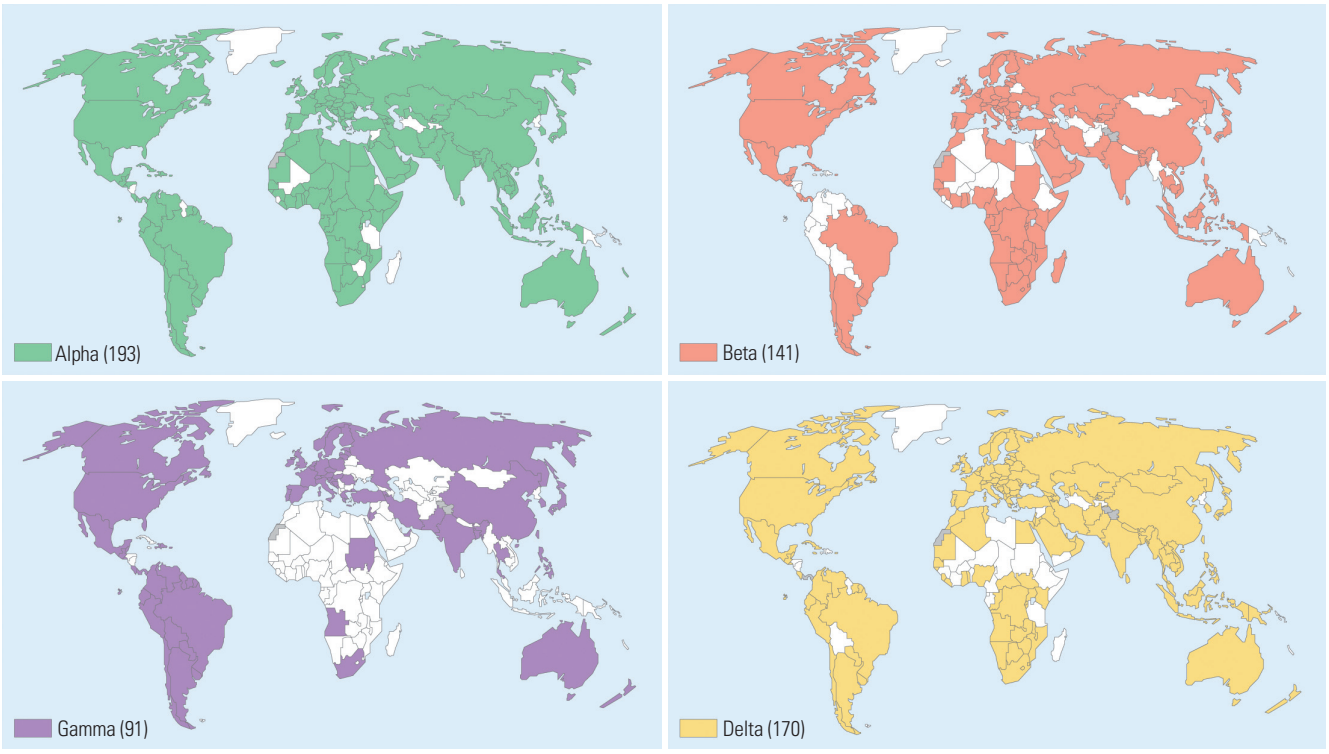

Fig. 1. Regions where variants of concern have been reported (as of August 31, 2021).[9] Regions highlighted with color are regions where the alpha, beta, gamma, and delta variants were detected. The number within parentheses is the number of countries in which the variant was found.

some neutralizing monoclonal antibodies to the RBD or N-terminal domain demonstrated diminished activity against the alpha variant.[17] Another study showed that the alpha variant is refractory to neutralization by most monoclonal antibodies to the N-terminal domain of the spike protein and is relatively resistant to several monoclonal antibodies to the RBD.[18]

Regarding implications for vaccines, a study which evaluated the neutralizing activity of mRNA vaccine-elicited antibodies against the alpha variant after the first and second vaccination with the mRNA-based vaccine, BNT162b2 (Pfizer-BioNTech),[19] found that the sera from individuals who received the vaccine exhibited modestly reduced neutralizing activities against the alpha variant. This reduction was also evident in the convalescent sera of some individuals who recovered from COVID-19. Introduction of the mutation that encodes the E484K substitution in the alpha variant background led to a more-substantial loss of neutralizing activity by vaccine-elicited antibodies and monoclonal antibodies compared with the loss of neutralizing activity conferred by the mutations in alpha variant alone. However, according to another study from the United States, the neutralization activity against the alpha variant of serum from BNT162b2 vaccinees was roughly equivalent to the activity against USA-WA1/2020, a relatively early isolate of SARS-CoV-2.[20] Another study showed that the sera of individuals vaccinated with mRNA vaccines [BNT162b2 and mRNA-1273 (Moderna)] and adenovirus-vector vaccine [Ad26.COV.S (Janssen)] significantly neutralized the alpha variant, as compared to the D614G variant.[21]

A study from the UK evaluated the effectiveness of the BNT162b2 and ChAdOx1 nCoV-19 (AstraZeneca) vaccines against symptomatic disease.[22] Effectiveness after one dose of vaccines (BNT162b2 or ChAdOx1 nCoV-19) against symptomatic disease by the alpha variant was 48.7% (95% CI, 45.5–51.7), and the effectiveness of two doses of vaccines were 93.7% (95% CI, 91.6–95.3) and 74.5% (95% CI, 68.4–79.4), respectively. Another study in Qatar evaluated the effectiveness of the mRNA-1273 vaccine against PCR-positive infection by the alpha and beta variants.[23] The study showed that vaccine effectiveness against the alpha variant infection was 88.1% (95% CI, 83.7–91.5) ≥14 days after the first dose but before the second dose, and was 100% (95% CI, 91.8–100) ≥14 days after the second dose. Interim results released from trials of the Novavax vaccine showed that Novavax was 85.6% effective against the symptomatic COVID-19 with the alpha variant (85.6%).[24]

Regarding infectiousness, an ecological study from the UK estimated a 0.7% (95% CI, 0.6–0.8) risk of SARS-CoV-2 reinfection in the UK between September 28 and December 27, 2020.[25] Possible reinfection was defined as the presence of two reported episodes of laboratory-confirmed COVID-19 separated by more than 90 das with a period of reporting no symptoms for more than 7 days before the second positive test . The study concluded that the risk of reinfection by the alpha variant may not be higher than that by ancestral lineages.

Beta VOC

On December 18, 2020, researchers from South Africa reported SARS-CoV-2 lineage B.1.351 (also known as 501Y.V2), which was labeled as the beta variant according to the WHO.[26] This variant was identified in South Africa after the first wave of the epidemic in a severely affected metropolitan area (Nelson Mandela Bay) located on the coast of the Eastern Cape province. The investigators analyzed 2882 whole genomes of SARS-CoV-2 from South Africa, which were collected between March 5 and December 10, 2020; and they identified a previously unrecognized monophyletic cluster (beta VOC) that contained 341 sequences from samples collected between October 8 and December 10, 2020 in KwaZulu–Natal, Eastern Cape, Western Cape, and Northern Cape. Within a short period, the beta variant was also detected in other countries, with probable connection to travelers from South Africa.[27] The beta variant includes nine mutations (L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, and A701V) in the S protein, of which three mutations (K417N, E484K, and N501Y) are located in the RBD. The N501Y substitution was also identified in the alpha variant in the UK, and the mutation has previously been shown to enhance the binding affinity to human ACE2.[12,13] The E484K and K417N substitutions also increase the binding affinity to human ACE2, and the combination of N501Y, E484K, and K417K enhances the binding affinity further.[28,29] It seems that mutations in the beta variant have little to no effect on the performance of RT-PCR assays.[30]

The E484K mutation, which was first found in the beta VOC, has a number of concerning characteristics. For example, a study found that post-vaccination sera from individuals who received two doses of the BNT162b2 vaccine neutralize E484K recombinant SARS-CoV-2 less efficiently, compared to the USA-WA1/2020 strain.[31] Data showed the neutralization efficiency of convalescent sera with low or moderate immunoglobulin G (IgG) against the SARS-CoV-2 spike protein could result in loss of neutralization of the E484K recombinant stain. This suggests that, in order to enhance protection against variants with E484K, the vaccine-induced antibody titers should be high. Human sera with high neutralization antibody titers against the USA-WA1/2020 strain was still able to neutralize the virus with E484K mutation.

Regarding infectiousness, a mathematical modelling study estimated the transmissibility and severity of the beta variant.[32] The study estimated the beta VOC was 50% (95% CI, 20–113) more transmissible than previously circulating variants in South Africa assuming past exposures would provide complete cross-protection.

Regarding disease severity, another study from the European Centre for Disease Prevention and Control (ECDC) compared the disease severity between VOC cases and non-variant cases reported in seven European countries.[33] The study showed that cases with the beta variant had significantly higher adjusted odds ratio for hospitalization (3.6, 95% CI, 2.1–6.2); however, the risks for ICU admission and death were not significantly higher compared to non-variant cases [i.e., odds ratios for ICU admission and death were 3.3 (95% CI, 1.9–5.7) and 1.1 (95% CI, 0.4–3.4), respectively].

Regarding treatments, a few studies showed that mutations within the beta variant cause partial or complete escape from therapeutic monoclonal antibodies and neutralizing antibodies in the convalescent plasma.[34,35] Also, significantly reduced susceptibility of the beta variant to the combination of bamlanivimab and etesevimab monoclonal antibody treatment has been reported.[36]

Regarding vaccines, multiple studies have shown that the neutralizing antibody titers for the beta variant of sera of individuals vaccinated with mRNA vaccines (BNT162b2 and mRNA-1273) and adenovirus-vector vaccine (Ad26.COV.S) were decreased relative to the D614G strain.[37,38] A study from Qatar showed that the effectiveness of the mRNA-1273 vaccine against beta variant infection (defined as PCR positivity) was 61.3% after the first dose (95% CI, 56.5–65.5) and 96.4% after the second dose (95% CI, 91.9–98.7). Interim results from Novavax vaccine trials showed that the vaccine is 60% effective against the beta variant.[24]

Gamma VOC

Lineage P.1, which is the gamma variant according to the WHO label, was first detected in four travelers returning to Japan from Amazonas state of Brazil on January 2, 2021.[39] A molecular epidemiology study on 250 SARS-CoV-2 genome sequences from different Amazonas municipalities sampled between March 2020 and January 2021 showed that the gamma variant was evolved from a local B.1.1.28 clade in late November 2020 and replaced the parental lineage in less than 2 months.[40] The gamma VOC harbors 10 mutations in the S protein (L18F, T20N, P26S, D138Y, R190S, H655Y, T1027I V1176, K417T, E484K, and N501Y),[41] and three of these mutations (L18F, K417N, and E484K) are located in the RBD, similar to the beta variant. The N501Y, K417N, and E484K mutations, which are also found in the alpha and beta variants, have been associated with enhanced binding affinity to human ACE2 as well as increased transmissibility.[12,13,42]

Regarding infectiousness and disease severity, the abrupt increase in the number of COVID-19 hospitalizations and deaths in Manaus, Brazil in January 2021 was unexpected, as a previous study of blood donors indicated that 76% of the population had been infected with SARS-CoV-2 by October 2020, and the estimated SARS-CoV-2 attack rate in Manaus would be above the theoretical herd immunity threshold.[42] One explanation for the expected surge was that the gamma variant identified in Manaus may have higher transmissibility compared to pre-existing lineages. The gamma variant accounted for 42% (13/31) of samples sequenced from a cluster of COVID-19 cases in Manaus in December 2020, but it was absent in 26 samples collected in Manaus from March to November 2020. Another study from the

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ECDC compared the disease severity between VOC and non-VOC cases, and showed that cases with the gamma variant had significantly higher adjusted odds ratio for hospitalization (2.6, 95% CI, 1.4–4.8) and ICU admission (2.2, 95% CI, 1.8–2.9).[33]

Regarding treatments, the gamma VOC has significantly reduced susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment;[36] however, casirivimab and imdevimab together retained neutralization activity against pseudotype virus-like particles expressing the K417T, E484K, or N501Y mutations found in the gamma variant.[43] A study reported that the gamma variant is not only refractory to multiple neutralizing monoclonal antibodies, but also more resistant to neutralization by convalescent plasma (3.4 fold).[44] As mentioned earlier, SARS-CoV-2 variants with the E484K mutation might escape neutralization by antibodies from the convalescent plasma of recovered COVID-19 patients who were infected with earlier strains;[17] and the gamma variant, containing E484K, could also increase the risk of re-infection.[42]

Regarding vaccines, a study reported that the gamma variant is more resistant to neutralization by the vaccinee sera (3.8–4.8 fold) collected from people who received BNT162b2 or mRNA-1273 vaccines.[44] Moreover, a nationwide case-control study from France assessed the effectiveness of two doses of mRNA COVID-19 vaccines (BNT162b2 and mRNA-1273) against COVID-19, using the original virus and other variants (the alpha, beta, and gamma variants) circulating in France.[45] The study showed that the mRNA vaccine effectiveness at 7 days after the second dose was estimated as 88% (95% CI, 81–92), 86% (95% CI, 81–90), and 77% (95% CI, 63–86) against COVID-19 with the original virus, the alpha, beta, and gamma VOC, respectively.

Delta VOC

On March 24, 2021, the Ministry of Health and Family Welfare of India first reported a SARS-CoV-2 variant with E484Q and L452R mutations in the spike protein.[46] The analysis of samples from Maharashtra revealed that, compared to December 2020, the proportion of samples with the E484Q and L452R mutations had increased, and the mutations did not match any of the previously catalogued VOC. Within a few months, the variant was detected in other countries, and was named lineage B.1.617. The lineage B.1.617 contains three sublineages of B.1.617.1, B.1.617.2, and B.1.617.3. On May 11, 2021, the sublineage B.1.617.2, which is also known as the delta variant according to the WHO label, was designated as VOC, since its transmissibility was assessed to be at least equivalent to that of the alpha variant.[47] In a short period, the delta variant spread quickly across the globe, and it has now become the most dominant strain worldwide.[48] Common mutations within the S protein across the sublineages of B.1.617 include L452R, P681R, and D614G. In addition, B.1.617.1 and B.1.617.3 carry the E484Q and G142D mutations, and some sequences of the delta VOC may have G142D. Notably, the L452R mutation may stabilize the interaction between the spike protein and the ACE2 receptor of host cell, and thereby increase infectivity.[49-51] Although the L452 residue does not directly contact the ACE2 receptor, unlike the N501 residue, L452 is positioned in a hydrophobic patch of the spike RBD, and the L452R mutation may cause structural changes that promote the interaction between the spike protein and ACE2 receptor. In addition, the P681R mutation, which is also found in the alpha variant, is situated near the furin cleavage site and has been shown to optimize spike cleavage by furin with potentially enhanced transmissibility.[47]

Regarding infectiousness, a matched case-control study from the UK estimated the odds of household transmission for delta variant index cases compared to alpha variant cases using the national surveillance data between March and May 2021.[52] The study showed the adjusted odds ratio of household transmission was 1.64 among delta variant cases (95% CI, 1.26–2.13) compared to alpha variant cases. Another modelling study form the UK estimated the reproduction number (R) of the delta variant as 1.64 (95% CI, 1.61–1.67).[53] Another modelling study from the UK showed the S-gene-positives as proxy of the delta VOC may have 1.4-fold higher transmissibility compared to other lineages.[54] An outbreak study on delta variant cases from a gymnastic facility in Oklahoma, USA suggested that the attack rate of the delta variant is higher than those of other lineages.[55] The attack rate among the exposed gymnasts and staff members in this outbreak was 20%, and the household attack rates in this outbreak (53%) were higher than the reported secondary attack rates associated with other SARS-CoV-2 lineages (16.6%).[55,56]

Regarding disease severity, a study from Singapore found that, after adjusting for age and sex, infection with the delta variant was associated with higher odds of oxygen requirement, ICU admission, and death [adjusted odds ratio 4.90 (95% CI, 1.43–30.78)].[57] Cases with the delta variant also had significantly higher viral loads [i.e., lower PCR cyclic threshold (Ct) value] and longer duration of Ct value ≤30. Another study from Canada evaluated the virulence of VOCs compared to non-VOC SARS-CoV-2 infections, as measured by the risk of hospitalization, intensive care unit admission, and death, using a retrospective cohort of COVID-19 patients in Ontario between February 7 and June 22, 2021.[58] Compared to non-VOC SARS-CoV-2 strains, the risks of disease severity associated with the delta variant were more remarkable than those for other variants [i.e. adjusted odd ratios were 2.2 (95% CI, 1.93–2.53) for hospitalization; 3.87 (95% CI, 2.98–4.99) for ICU admission; and 2.37 (95% CI, 1.5–3.3) for death].

Regarding treatments, a study examined the sensitivity of the delta variant to monoclonal antibodies and to antibodies present in the sera from convalescent individuals or those who had received a COVID-19 vaccine.[59] The delta variant was resistant to neutralization by some anti-N-terminal domain and anti-RBD monoclonal antibodies, including bamlanivimab, and these antibodies showed impaired binding to the spike protein. Moreover, the sera collected from convalescent individuals

up to 12 months after the onset of symptoms were four times less potent against the delta variant compared to the alpha variant. Another study showed that in vitro, the delta variant was six times less sensitive to serum neutralizing antibodies from recovered individuals, and eight times less sensitive to vaccine-elicited antibodies compared to wild type D614G.[60] The B.1.617.2 spike pseudotyped viruses showed compromised sensitivity to monoclonal antibodies against the RBD and N-terminal domain.

Regarding vaccines, the administration of two doses of vaccines (BNT162b2 or ChAdOx1 nCoV-19) generated a neutralizing response in 95% of individuals, with titers three- to five-fold lower against the delta variant than against the alpha variant.[59] Also, a study from the UK evaluated the effectiveness of BNT162b2 and ChAdOx1 nCoV-19 vaccines against symptomatic disease with alpha and delta variants.[22] The study showed that the effectiveness after one dose of vaccine (BNT162b2 or ChAdOx1 nCoV-19) against symptomatic disease by the delta variant was 30.7% (95% CI, 25.2–35.7), and the effectiveness of two doses with the BNT162b2 and ChAdOx1 nCoV-19 vaccines against symptomatic COVID-19 caused by delta variant were 88.0% (95% CI, 85.3–90.1) and 67.0% (95% CI, 61.3–71.8), respectively. Of note, these estimates were only modestly lower than the estimated vaccine effectiveness against the alpha variant. Another study from Scotland estimated the effectiveness of BNT162b2 and ChAdOx1 nCoV-19 vaccines against COVID-19 hospitalization by alpha and delta variants as 72% (95% CI, 57–82) and 62% (95% CI, 42–76), respectively.[61] The study showed that both BNT162b2 and ChAdOx1 nCoV-19 vaccines were effective in reducing the risk of SARS-CoV-2 infection and COVID-19 hospitalization in people with the delta variant, but these effects on infection appeared to be diminished when compared to those with the alpha variant.

CONCLUSIONS

As of September 15, 2021, there are four SARS-CoV-2 lineages designated as the VOC. VOCs significantly increase transmissibility, and have the potential for increasing transmission and disease severity. In addition, VOCs show decreased susceptibility to monoclonal antibodies and convalescent plasma, and possess the ability to cause reinfection in individuals who recovered from previous infections. VOCs can also impact the effectiveness of mRNA and adenovirus vector vaccines, although the currently authorized COVID-19 vaccines are still effective in preventing infection and severe disease. If a variant with more significant impact on the global public health emerges, it would pose further threat to humanity; therefore, measures to reduce virus transmission and efforts to monitor and understand the impact of variants should continue.

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