

# Characteristics and Vaccines: Five Variants of Concern of SARS-CoV-2

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**Abstract.** Since the detection of the novel coronavirus in 2019, all countries in the world have been affected, the economy has declined, and people's health has been greatly threatened. Although with the in-depth study of the virus, several vaccines have been developed and put into use. However, due to the characteristics of the virus itself, its mutation speed is very fast, resulting in the delay of the vaccine relative to the virus. This article outlines and summarizes the evolutionary route and each important mutation point of the mutant strains, as well as their impact on the characteristics and vaccine development, so as to find out or predict the variation law of novel coronavirus or the trend of its transmissibility and pathogenicity, and provide new ideas on how to develop effective vaccines and how people finally deal with sars-cov-2.

**Keywords:** SARS-CoV-2, Variants of Concern, Vaccine.

## 1. Introduction

Since a novel coronavirus had been first detected and caused severe pneumonia cases in Wuhan, China in December 2019, it spread and transmitted all over the world and badly affected people's lives. According to the latest data updated by World Health Organization (WHO), COVID-19 has caused cumulative 509,531,232 cases and 6,230,357 deaths globally. Due to its high transmissibility and fatality, scientists are keeping exploring safe and efficacious vaccines to immune the population. However, the true efficacy is not as high as they expected. Even in some countries such as Singapore and Korea, where each person inoculates more than 2 doses on average and most people got fully vaccinated with doses of primary series, there are still tens of thousands of new cases emerging every day. Though there are effective diagnostic and therapeutic tools like aptamers [1] and oral antiviral drug treatments like molnupiravir, the developments of vaccines are imperative in order to prevent infection from the beginning.

During these years when SARS-CoV-2 kept traveling and evolving, it developed massive variants, among which there are five Variants of Concern (VOC) designated by WHO, including alpha, beta, gamma, delta, and omicron. Each variant changes its pathogenicity or transmissibility to a new stage, so they require simultaneous development of diagnosis and treatment methods to control and eliminate them. As an mRNA virus, its characteristic is its high mutation rate and rapid evolving speed. Thus, it is quite difficult that scientists to develop corresponding vaccines and get people widely vaccinated before the virus evolves to the next variant. Usually, an effective vaccine for one variant doesn't have the same effect on others. Therefore, this article aims to outline and summarize the VOCs evolving route and each one's important mutation points, their impact on characteristics, and vaccine developments. The main content will focus on what specific changes a variant had made compared with the last one. Through such work, the law of how it mutates or the trend of its transmissibility and pathogenicity may be figured out or at least predicted. Therefore, it will provide new ideas about how to develop an efficacious vaccine and how can people finally deal with Sars-Cov-2.

## 2. Five VOCs of SARS-CoV-2

### 2.1. Alpha VOC

This new variant was detected for the first time in the United Kingdom in September 2020. It was ascertained to the B.1.1.7 lineage, which WHO has designated as Alpha. SARS-CoV-2, just as other CoVs, is a single-stranded positive-sense RNA virus. The basic function of the genome is to encode four structural and essential proteins: envelope, membrane, nucleocapsid, and spike (S). [2] The mutation of the gene encoding S protein is the most critical element in viral diversity among them. Most of the mutation points are in the S1 subunits. In the Alpha variant, there are a total of 10 mutations in S protein, 7 in the S1 subunit, and 3 in the S2 subunit. Mutation P681H is the unique one, only detected in Alpha VOC. It affects the virus's capacity to fuse membranes, making it easier for it to escape the immune system. [3] The N501Y mutation is a pivotal contact residue that has a tighter combination with an important protein, human angiotensin-converting enzyme 2 (ACE2), through which enhances its infectivity. Furthermore, it was proved that the transmissibility of Alpha VOC appeared much higher than other 307 lineages at that time, about 43%-90% more transmissible, and correspondingly caused increasing mortality.

Since there was no specific medicine to cure the disease, scientists were keep exploring appropriate vaccines for humans. The mRNA vaccine BNT162b2 was developed and proved to be the most efficacious vaccine against Alpha VOC. [4] A single dose of vaccine has relatively low efficacy against virus infection and severe diseases, but two doses can enhance the efficacy up to 89.5% against infection and even 100% against fatal disease, as seen more than 14 days after the second dose. Another vaccination, mRNA-1273 can also induce abundant neutralizing antibodies against B.1.1.7. Other types of vaccines, such as Ad26.COV2.S, a recombinant human adenovirus type 26 vector, has an efficacy of 72% against Alpha. Its safety was also demonstrated, for only less than 1% of people got slight side effects like site-injection pain, headache, fatigue, etc. There were merely 3 deaths that occurred and none of them are covid-19 related. [5]

### 2.2. Beta VOC

In May 2020, this variant was detected for the first time in South Africa. It was ascertained to the B.1.351 lineage and then classified as Beta VOC by WHO. Though it emerged earlier than Alpha, it almost prevailed in many places during the same period. This variant contains 10 mutation points, among which 7 are missense mutations and the left 3 are continuous amino-acid deletions. 9 of them congregate in S1 subunits. [3] Both Alpha and Beta VOCs are discovered to have the p.N501Y and p.D614G mutations, indicating that Beta's infectivity may be similar to or perhaps greater than Alpha's. p.K417N and p.E484K are two novel mutation points in the S protein's receptor-binding domain (RBD). Together with p.N501Y, this combination allows a higher degree of structural variation when RBD combine with ACE2, increasing their affinity. Therefore, the transmissibility and infectivity of Beta VOC are both greater than Alpha, and it is more likely to escape from the immunologic defense. [6] However, the three amino-acid deletions have little effect, for the S protein remains in its normal sequence and structure.

The three vaccines mentioned in Alpha VOC approximately have the same effect towards Beta. There is only a little difference in the specific data. The BNT162b2 vaccine is shown to be 75% effective against B.1.351 infection after the second dose and 14 days of monitoring. For the severe disease caused by Beta VOC, this vaccine has the same 100% effectiveness as it against Alpha. [4] Vaccine mRNA-1273 has a more powerful effect on B.1.351. It can lower the titer by 6-9 folds compared with wild-type viruses. The vaccine Ad26.COV2.S was estimated that its effectiveness against severe disease could reach 64% with a single dose, at 28 days after administration. [5] Since Alpha and Beta VOC prevailed in the same period, scientists often compared the vaccine's efficacy on both variants.

### 2.3. Gamma VOC

In November of 2020, this variant was firstly recorded and rapidly spread out in Brazil. It belongs to lineage P.1 and was given the name Gamma by WHO in January 2021. It contains 12 missense mutations on S protein, 10 of which are on S1 subunits. Similar to Alpha and Beta VOC, it also shares a few common mutation points with the previous variants, p.N501Y and p.D614G. Besides, Beta and Gamma both have two common mutation points, p.K417N and p.E484K. Thus, it could be predicted that the affinity of RBD and ACE2 was increased and its transmissibility grew to a new level. [7] It was also more likely to elude the immune system and neutralize antibodies generated by vaccinations. The evolution of the SARS-CoV-2 continued to move toward increasing transmissibility and infectivity until the Gamma prevalence period.

A demonstrated effective vaccine against Gamma VOC is mRNA-1273. Just like the previous variants, this vaccine also has a great impact on decreasing the virus' neutralizing activity. [8] CoronaVoc vaccine is an aluminium hydroxide adjuvant vaccine, constituted by inactivated virus. Its efficacy ranged from 50% to 91% in scientific research from different countries, so the data may not be absolutely convincing. In Brazil, when it was at Gamma VOC prevalence period, the reports showed that CoronaVoc had merely a 50.4% efficacy rate. The SARS-CoV-2 infection rate decreased by 0.51-fold after at least one dose of immunization. The data indicated that the Gamma variant had a certain possibility to escape from antibody neutralization induced by the vaccine.

### 2.4. Delta VOC

In India, his variant was first detected and recorded among the public in October 2020, almost at the same time as Gamma VOC. It belongs to lineage B.1.617.2 and was given the name Delta by WHO. It also has 10 missense mutations on its S protein, and 9 of them on the S1 subunit. However, Delta VOC changed dramatically from the previous three VOCs, for it only shares one common mutation point with them, p.D614G. Besides, it carries a few new mutations, such as p.L452R, p.T478K, and p.G142D. These new mutations made Delta VOC much easier to bind with the ACE2 receptor and drastically increase its infectivity and ability to escape from antibodies neutralization after vaccination. Studies showed that Delta VOC's most obvious feature is its extremely high transmissibility. [9] Compared with Alpha VOC, the emerging speed of Delta VOC was up to 1.37-2.63 fold, and its transmissibility was enhanced by 63%-167%. SARS-CoV-2 kept evolving toward higher infectivity and transmissibility.

Though the fact is that the vaccines' efficacy was keep falling as the virus evolved, the difference was rather small from Alpha to Delta. For example, vaccine BNT162b2 has efficacy at 93.7% after two doses injected among Alpha VOC patients while as 88.0% against Delta VOC. Using the ChAdOx1 nCoV-19 vaccine had a similar result. After two doses, the efficacy against Alpha VOC was 74.5% while against Delta was 67.0%. [10] Therefore, it is feasible that people accept the same vaccines to prevent several variants, but a single dose usually has little effect. So it is critical to encourage people to get vaccinated in at least two doses. However, vaccines such as ChAdOx1 nCoV-19 still don't possess a satisfying efficacy and need further improvement.

### 2.5. Omicron VOC

This variant was recently the newest VOC, first detected in a few different countries in November 2021. It belongs to lineage B.1.1.529, named Omicron VOC by WHO not long after it was discovered. Hitherto, it is the variant that has the highest transmissibility and traveled to 80 countries in a month after it was named. It contains 30 mutation points on its S protein, most located in the RBD of the S1 subunit, much more than each previous VOC. Some common mutations such as p.N501Y and p.D614G functioning together with the new mutations can further increase the risk of reinfection and decrease the efficacy of vaccines. [11] Omicron also shares common p.K417N and p.T478K mutation with Delta VOC, which contribute to immune evasion. Though Omicron has a high reproduction rate and travels rapidly, it is observed that compared with a year ago, COVID-19-related hospital

admission and ICU admission have dramatically decreased by 82% and 84% respectively, indicating that its pathogenicity has weakened. [12]

Recently, new vaccine developments targeted at Omicron VOC are still scarce. Because of the wide range of mutations in S protein, Omicron can easily escape from neutralizing antibodies from current vaccines. Among the people who received BNT162b2 vaccines, only 20% and 24% of them can be detected out neutralizing antibodies respectively against the Omicron variant HKU691 and HKU344-R346K. Astoundingly, there are no neutralizing antibodies found in persons who got the Coronavac vaccine. [13] Thus, developing new efficacious vaccines is extremely imperative.

### 3. Conclusion

SARS-CoV-2 is a highly transmissible and contagious virus, that has caused numerous people's death. Hitherto, thousands of variants have emerged and spread to every corner of the world. It is crucial to know how the virus mutates and the trend of its evolution, so that people can develop efficacious vaccines and get it controlled. Through summarizing each VOC's feature, it can be revealed that from Alpha to Omicron, transmissibility is keep enhancing, while pathogenicity gradually become weaker. This discovery indicates that this virus is sacrificing its pathogenicity to increase its transmissibility. Thus, it can be predicted that the next VOC maybe even more infectious and will cause less severe disease. At last, SARS-CoV-2 may reach coexistence with humans like a common disease, just like having a cold. However, it is still important to develop vaccines for susceptible groups such as the elderly and children. Given the fast speed of the virus mutation, the development of new vaccines maybe cannot catch up with it. Therefore, it may give them the inspiration that they can predict the new mutations and synthesize a fake virus for developing vaccines, or find out the invariable feature and target on it. In conclusion, great efforts are needed to figure out the method of developing an efficacious vaccine. In near future, scientists are expected to solve this problem.

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