Comparing the Omicron Mutations with other Sars-CoV-2 Variant of Concerns

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Abstract:

Two years after the emergence of the SARS-CoV-2 pandemic, multiple variants of the virus have emerged such as Alpha, Beta, Gamma and Delta variants. The latest variant of SARS-CoV-2, B.1.1.529 (Omicron), was first reported to the World Health Organization (WHO) by South Africa on November 24, 2021, and was classified as a variant of concern two days later. However, Omicron exhibits even higher mutation levels than previous SARS-CoV-2 variants, with 37 amino acid substitutions in the spike (S) protein, 15 of which are in the receptor-binding domain(RBD). Due to numerous mutations in the spike protein, Omicron is capable of increasing viral transmissibility, conferring resistance to therapeutics, or partially escaping infection or vaccine-induced immunity. This review summarizes the mutations in Omicron and other Variant of concern (VOCs) (Alpha, Beta, Gamma, Delta), the global VOC transmission using Pango, the impact on vaccine development monoclonal antibodies, and compares Omicron's mutation impact on B cell and T cell response.

Keywords: SARS-CoV-2, Omicron Mutations, Variants of Concern (VOCs) Mutation

Introduction:

It is possible for a viral genome to undergo evolutionary changes over time, and even a single amino acid exchange can cause the virus to become immune-evading, complicating vaccine development (Giovanetti, Benedetti et al. 2021). As a RNA virus, SARS-Cov-2 will evolve genetically through mutations over time as it adapts to its new host, which would lead to the emergence of many variants that may differ significantly from the ancient strain.

In the early stages of the pandemic, relatively little change occurred in the genetic makeup of SARS-CoV-2. The appearance of a globally dominant genetic variant, the D614G mutation in the S protein , resulted in an increased transmission without enhanced virulence.(Korber, Fischer et al. 2020)For the past two years, new genetic variants of SARS-CoV-2 have been identified utilizing periodic genomic sequencing of viral samples. A few are considered variants of concern (VOCs), due to their impact on public health which are associated with increased virulence, the ability to evade detection, a reduction in neutralization by antibodies, or decreased efficacy of therapeutics or vaccines. Five SARS-CoV-2 VOCs have been designated since the beginning of the pandemic by WHO on December 11, 2021. They are Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) and Omicron (B.1.1.529).

Mutations in the receptor binding domain (RBD) and the N terminal domain (NTD) are found in the five VOCs. The N501Y mutation in RBD is not shared in the Delta variant, which increases viral attachment through affinity for Angiotensin-converting enzyme 2 (ACE2) receptors and facilitates entry into host cells (Harvey, Carabelli et al. 2021)

The continued mutations of this RNA virus have significantly blocked the progress of the fasting speed of vaccine development and mass vaccination efforts against COVID19 made so far in curtailing the SARS-CoV-2 transmission. In this review, we will investigate the efficacy of different available vaccines against this virus and its new variants. We highlight the mutations in Omicron and other VOCs (Alpha, Beta, Gamma, Delta), their global transmission using Pango, (https://cov-lineages.org/) the impact on vaccine development monoclonal antibodies, and the comparison of Omicron's mutation impact on B cell and T cell responses.

How SARS CoV-2 Variants are Named:

Scientists continue to use the established nomenclature systems to name and track SARS-CoV-2 genetic lineages by GISAID, Nextstrain, and Pango. The WHO Technical Advisory Group on Virus Evolution, comprised of scientists from the WHO Virus Evolution Working Group (now called the Technical Advisory Group on Virus Evolution), the WHO COVID-19 reference laboratory network, as well as experts from GISAID, NextStreet, Pango, and other countries and agencies in microbial nomenclature, communication, and virology, convened to consider easy-to-pronounce and non-stigmatizing labels for VOCs and VOIs (Virant of interested). This expert group assembled by the World Health Organization (WHO) has recommended utilizing letters of the Greek alphabet, i.e., Alpha, Beta, Gamma, and Delta, which are easier and more practical to discuss by individuals who are not scientists.

SARS Cov-2 Variants of Concern (VOC):

Thousands of SARS-CoV-2 variants have emerged since China's report began in December 2019. SARS-CoV-2 variant of concerns (VOC) are defined by the WHO as having increased transmissibility, virulence, and decreased response to diagnostics, vaccines, and therapeutics.

Current VOCs include Alpha, Beta, Gamma, Delta and Omicron (Table 1 details the 5 variants of concern).

Table 1: Sars Cov 2 variant of concern (VOCs):

WHO Label	Pango lineage	Location Earliest Documented	Date First Detected	Spike Mutations of Interest:
Alpha	**B.1.1.7**	**United Kingdom**	**September 2020**	**N501Y, A570D, D614G, P681H, T716I, S982A, D1118H**
Beta	**B.1.351**	**South Africa**	**October 2020**	**K417N, E484K, N501Y, D614G, A701V**
Gamma	**P.1**	**Brazil**	**January 2021**	**K417T, E484K, N501Y, D614G, H655Y**
Delta	**B.1.617.2**	**India**	**October 2020**	**L452R, T478K, D614G, P681R**
Omicron	**B.1.1.529**	**Multiple Countries**	**December 2021**	**A67V, Δ69-70, T95I, G142D, Δ143-145, N211I, Δ212, ins215EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F**

Table description:

1. WHO label: A WHO proposal was published on 31st May 2021 for the labeling of global SARS-CoV-2 variants of concern and variants of interest alongside scientific nomenclature. This list includes variants on WHO's global list of VOCs, and is updated as WHO's list changes.
2. Lineage and additional mutations: The variant designation is specified by one or more Pango lineages, as well as any additional characteristics of its spike protein. Each lineage in the table is linked to the respective lineage page on the Pango lineages website.

3. Location earliest documented: The first country of detection.
4. Date first detected: The first date of detection
5. Spike mutations of interest: Not all spike protein amino acid changes are included but includes changes to spike protein residues 319-541 (receptor binding domain) and 613-705 (the S1 part of the S1/S2 junction and a small stretch on the S2 side), and any additional unusual changes specific to the variant.

Epidemiological update of VOCs:

During the week of January 24, 2022, there were over 22 million new cases and over 59 000 new deaths reported globally (WHO, 2022). Over 370 million cases and over 5.6 million deaths have been reported as of March 2022. In the Western Pacific, the Eastern Mediterranean, and the European regions, new cases have risen, while in the Americas and South-East Asia regions, cases have declined. The number of new cases reported in the African Region remained stable while weekly deaths continued to increase in the South-East Asia Region, the Eastern Mediterranean Region and the Region of the Americas. There has been a decrease in the incidence of deaths reported in the African region, while numbers in the European and Western Pacific regions remained similar to the previous week. The WHO website may need to be re-visited for new updates to these numbers.

SARS Cov-2 Variants of interest (VOI):

Variants of interest carry specific genetic markers associated with receptor binding, reduced neutralization by antibodies against previous infections or vaccinations, reduction in treatment efficacy, potential diagnostic impact, or predicted increases in disease transmission or severity. Although genomic properties, epidemiological evidence, and in-vitro evidence exist for these variants that could indicate significant impacts on transmission, severity, and/or immunity, the evidence is preliminary or associated with significant uncertainty. Variants of interest may require public health measures, such as surveillance or epidemiological investigations to assess how quickly the virus spreads, the severity of the disease, the effectiveness of therapeutics, and whether vaccines are effective (CDC 2021).

SARS Cov-2 Variants Under Monitoring (VUM):

The SARS-CoV-2 variants under monitoring have been detected as signals through epidemic intelligence, rules-based genomic variant screening, or preliminary scientific evidence. WHO, CDC and ECDC haven't yet assessed whether they have properties similar to VOCs, but some evidence indicates they might. It is required that the variants listed here have been present in at least one outbreak, detected in at least one community within the European Economic Area, or there must be proof that the variant is transmitted internationally (ECDC 2022).

Omicron Mutations in comparison to other Sars-CoV-2 Variants of Concern:

In a number of countries and areas, researchers and public health agencies use Pango nomenclature to identify SARS-CoV-2 variants of concern and track their transmission and spread. Figure 1 showed the spike (S) protein mutations of the omicron and other four variants of concern (VOCs). (Alpha, Beta, Gamma, Delta variants) discovered between the end of 2020 and the beginning of 2021 share many similar amino acid mutations (Tao, Tzou et al. 2021). The mutations include substitutions, deletions, and insertions.

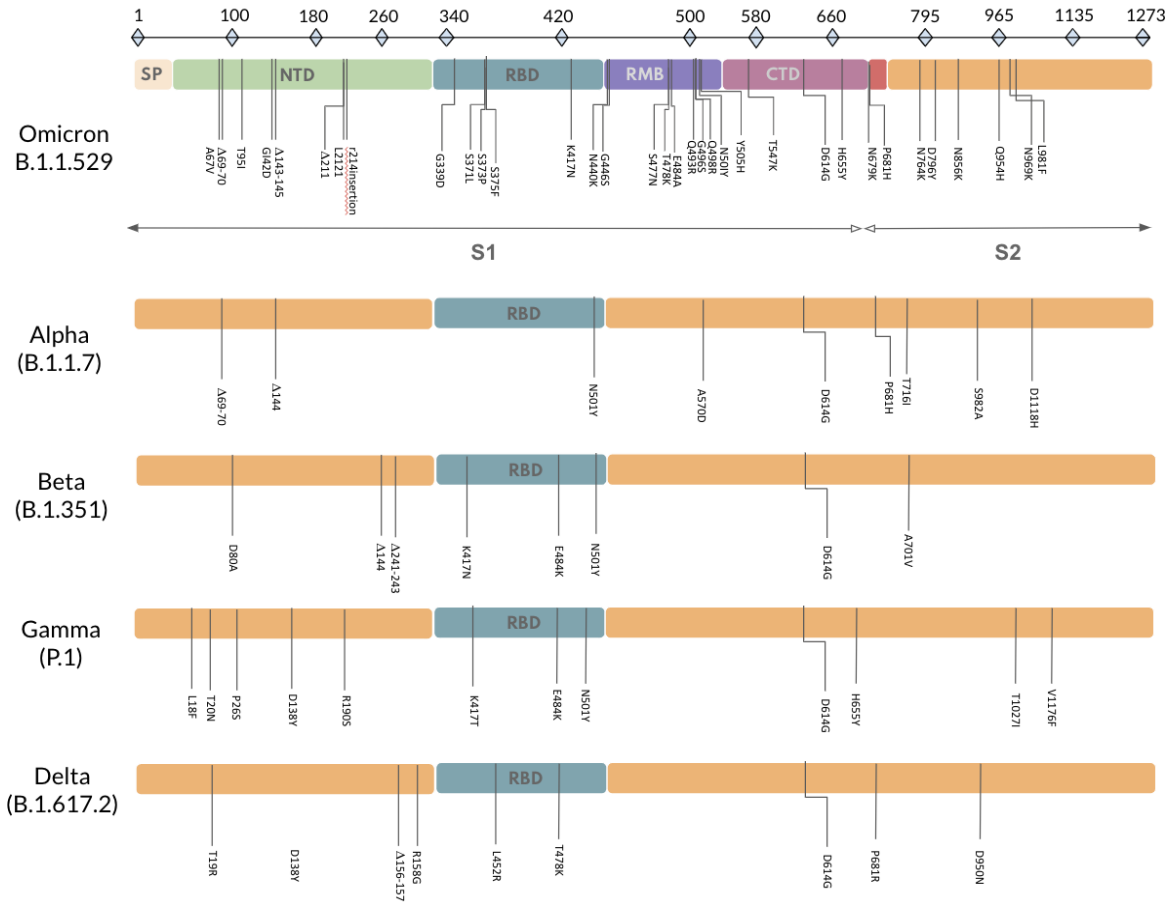

Fig 1: This figure illustrates the Amino acid changes to the spike (S) protein in SARS-CoV-2 variants of concern (VOCs). The variants shown include Omicron, Alpha, Beta, Gamma and Delta with the RBD (receptor binding domain) specified. The mutations, including substitutions, deletions, and insertions, are from the covariants database at https://covariants.org.

There are four descendants of Pango lineage B.1.1.529 in Omicron: BA.1, BA.1.1, BA.2, and BA.3 (Desingu and Nagarajan 2022) The Omicron-defining mutations from Pango lineage BA.1 account for the majority of sequences found. Consequently, most of the information we have regarding VOC Omicron pertains to Pango lineage BA.1. However, studies of BA.2, which exhibit

immune escape properties and virulence, were prioritized independently of BA.1 as it is becoming more prevalent (WHO, 2022).

The lineage BA.2 was first identified in early December and has since spread to 49 countries including the United States. BA.2 like Omicron has multiple changes (28 mutations) concentrated in the spike protein, the part of the virus that's targeted by vaccines (VanBlargan, Errico et al. 2021). In contrast to Omicron, however, it is nicknamed “the stealth variant” as it does not show a spike gene deletion at 69-70 that causes S-gene target failure (Rahimi and Talebi Bezmin Abadi 2022), which means it may look like other SARS-CoV-2 variants at first glance. Whereas the BA.1 family is causing nearly all Omicron infections in the U.S, the BA.2 clade is present in 40 countries and appearing mainly in India, Denmark, South Africa, and the United Kingdom.

BA.1 and BA.2 possess 34 and 28 mutations in the S glycoprotein, respectively, raising concerns whether they are more likely to transmit, escape immunity, and be more virulent than other circulating SARS-CoV-2 strains. However, no indication exists that BA.2 causes a more severe disease or spreads more readily than the original strain of Omicron, and it's been proven that current vaccines protect as well against BA.2 as they do against its original variant, with improved protection against symptoms (WHO 2022).

Several non-synonymous mutations have been found in the genome of the Omicron variant, among them several ones in spike that have been implicated in virulence, disease propensity and immune evasion. The Omicron variant has been identified as having over 60 substitutions/deletions/insertions, making it the variant with the highest number of mutation sites of all SARS-CoV-2 variants studied so far.

There are six substitutions within ORF1a in the Omicron variant including K856R, L2084I, A2710T, T3255I, P3395H, and I3758V. It also has two deletions, making a total of four amino acids (2083 and 3674–3676). Two substitutions are found within ORF1b including P314L and I1566V. A P10S substitution and a deletion of three residues at positions 27–29 can be observed in ORF9b. A T91 substitution can be found in the envelope, three D3G substitutions (Q19E, A63T, and D3G) in the membrane, and three substitutions and a three-residue deletion in the nucleocapsid proteins.

In the Omicron virus, more than half of the mutations are seen in the spike. There is one insertion of three amino acids at position 214, and three deletions including H69/V70, G142/V143/Y144 and N211. Additionally, there are 30 substitutions including 67V, T95I, Y145D, L212I, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F(Quaglia, Salladini et al. 2022).

These deletions and mutations have been found to increase viral binding affinity, increase antibody escape, and increase transmissibility. Among other omicron mutations known to affect binding affinity and transmissibility, some confer increased vaccine escape. Moreover, we do not know how most of the remaining omicron mutations will affect viral behavior and vulnerability to natural and vaccine-mediated immunity since most of the remaining mutations are not known.

It has been shown that D614G in S protein is correlated with viral loads in the upper respiratory tract along with reduced age. In the spikes of all VOCs, this amino acid change is observed. Study findings have shown that mutation N501Y enhances the binding between spike and angiotensin-converting enzyme 2 (ACE2) and increases the transmission of the disease (Yang, Yu et al. 2021).This mutation is shared between Omicron, Alpha, Beta and Gamma variants and might be further enhance the transmissibility with the H69/V70 deletion. A cleavage site for furin can be further facilitated by basic amino acids, thereby allowing the spike to be cleaved into S1 and S2 components, thus enhancing virus infection. As a matter of fact, the P681H mutation has also been identified in the Alpha variant (Fig 1).

Omicron has some deletions and more than 30 mutations, several of which (eg, 69–70del, T95I, G142D/143–145del, K417N, T478K, N501Y, N655Y, N679K, and P681H) overlap with those in the alpha, beta, gamma, or delta VOCs. These deletions and mutations are known to lead to increased transmissibility, higher viral binding affinity, and higher antibody escape. Some of the other omicron mutations with known effects confer increased transmissibility and affect binding affinity. Importantly, the effects of most of the remaining omicron mutations are not known, resulting in a high level of uncertainty about how the full combination of deletions and mutations will affect viral behaviour and susceptibility to natural and vaccine-mediated immunity. (Karim and Karim 2021)

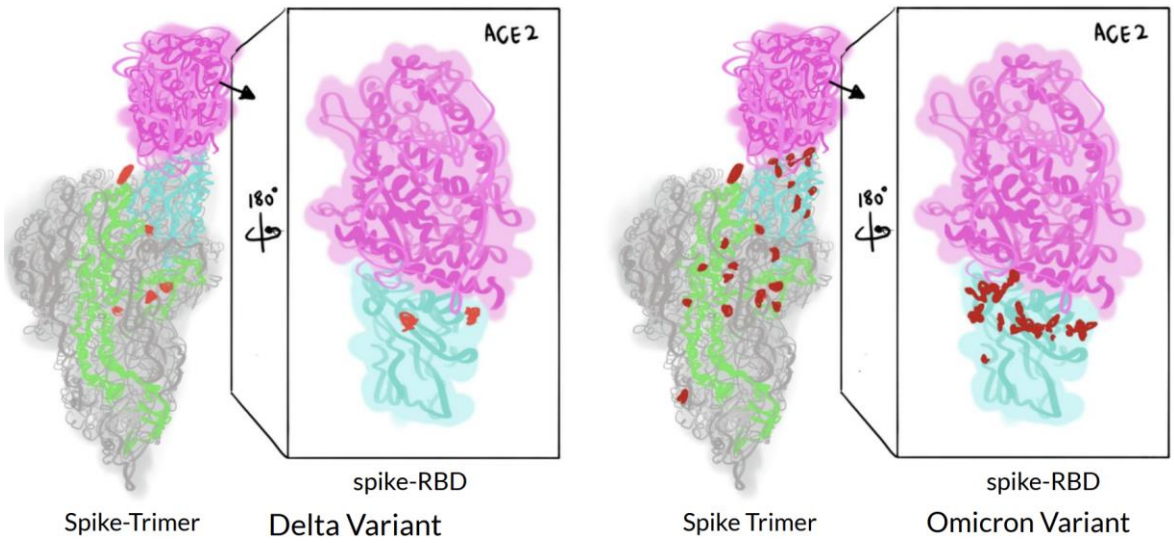

Figure 2: shows the mutation landscape in the Delta and Omicron variants. The structures are depicted based on the cryo-electron microscopy spike trimer structure of the protein data bank code 6VVB and the crustal RBD/ACE2 complex structure of PDB code 6LGZ. The protomer of the spike trimer is highlighted in green, and the RBD in cyan. The ACE2 receptor is magenta, and the mutations in both variants are highlighted in red (He, Hong et al. 2021)

There is evidence that Omicron may increase SARS-CoV-2's infectivity. There are only two RBD mutations present in the Delta variant, the L452R and the T478K, while 15 mutations have been accumulated in the RBD of the Omicron variant (He, Xuemei et al. 2021). In particular, it is noteworthy that the spike RBD region is the major target for neutralizing antibodies, and Omicron has acquired 15 substitutions within the spike RBD over time. (Fig2?=Fig 4) Close to the bound ACE2 receptor, various residues are seen to locate closeby among Omicron's numerous substitutions.

Immune escape, B cell response and the omicron's mutation

An increase in reinfection was reported and this immune escape is another concern based on information on positive PCR tests in people who have previously tested positive. However, it has become more difficult to interpret test positivity rates, which are four times the previous rate after the increased use of rapid antigen tests and incomplete capture of negative results. Despite this limitation, our growing number of repeat infections is consistent with omicron's mutations that allow it to escape immune surveillance.

Clinical trials have reported lower efficacy for some vaccine variants that are dominant in COVID-19 vaccines, despite conflicting reports on whether all four VOCs prior to omicron have consistently retained high efficacy. As a result of previous variants, vaccine efficacy has been decreased - for instance, the D614G variant of the ChAdOx1 vaccine in the UK produced 70% protection against clinical infections, while the beta variant in South Africa produced 10% protection (Madhi, Baillie et al. 2021). In spite of this, both the beta and D614G variants of BNT162b2 were effective in preventing clinical infections. The presence of more mutations in omicron compared with previous VoCs may have an adverse effect on the clinical efficacy of vaccines.

T cell response and the omicron's mutation

In the absence of severe COVID-19, hospitalization, and death, most COVID-19 vaccines have remained effective because this efficacy may be due more to T-cell immune responses than antibodies (Tenforde, Self et al. 2021). There was more than 90% efficacy of the vaccine in preventing hospital admissions even six months after vaccination, based on observational studies from Qatar and Kaiser Permanente (Bruxvoort, Sy et al. 2021). A study from the state of New York, USA showed high vaccine efficacy in preventing severe disease in people over the age of 65. Among all of the vaccines tested, protection varied, including 95% for BNT162b2, 97% for

mRNA-1273, and 86% for Ad26.COV2.S, with minimal declines in protection six months after the vaccine was given (Rosenberg, Dorabawila et al. 2022).

Omicron mutation and transmission

The impact on RBD and ACE2 binding free energy (BFE) has shown that the mutation of Omicron directly impacts transmission.T478K, Q493K, and Q498R three substitutions, significantly contribute to the binding energies and almost doubled the electrostatic potential (ELE) of the RBDOmic−ACE2 complexMany of the most concerning mutations occur in the virus's receptor-binding domain, and these mutations may affect the spike protein's affinity for ACE 2 (ACE2). The binding ability to ACE2 remains a critical aspect of the virus's pathogenicity. The specific concern is when mutations enhance their binding ability to these cell surface receptor proteins. The Omicron variant has two mutations that may increase the spike protein's affinity to ACE2, contributing to the current concern. Omicron RBD binds ACE2 ~2.5 times stronger than prototype SARS-CoV-2 confirmed by Computational mutagenesis and free energy perturbation.

Omicron mutation impact on Monoclonal Antibody Treatments

Currently, there are no virus-specific data available to assess whether monoclonal antibody treatments will retain efficacy against the Omicron variant. Based on data from other variants with significantly fewer changes in the RBD, the expectation is that the Omicron variant will remain susceptible to some monoclonal antibody treatments, while others may have less potency. Mutations within the RBD are most relevant for monoclonal antibody therapeutics available under Emergency Use Authorization (EUA) (CDC2021)

Impact on Vaccine-Induced Immunity or Immunity from Previous Infection：

Currently, there is no data available to assess the ability of sera from vaccinated persons or those with previous SARS-CoV-2 infection to neutralize the Omicron variant. However, the U.S. Government SIG and global public health partners are working to generate these data in laboratory settings and will also continue to monitor epidemiological and clinical indicators. The spike protein is the primary target of vaccine-induced immunity. The Omicron variant contains more changes in the spike protein than have been observed in other variants, including 15 in the RBD. Based on the number of substitutions, the location of these substitutions, and data from other variants with similar spike protein substitutions, significant reductions in neutralizing activity of sera from vaccinated or previously infected individuals, which may indicate reduced protection from infection, are anticipated.

Laboratory and epidemiological studies are needed to assess the impact of the Omicron variant on vaccine effectiveness and breakthrough infections, including in individuals who have received booster doses. However, vaccination is anticipated to continue to offer protection against

hospitalization and death, and vaccines continue to play a critical role in controlling the COVID-19 pandemic.

Summary, so the residue substitution in E484 as well as other D614G, N501Y, K417N, P681H, and K417N mutations has been shown to result in enhanced binding affinity with ACE2, enhanced transmissibility, and reduced ability of neutralization by monoclonal antibodies and immune evasion (Cheng, Krieger et al. 2022). The cocktail consisting of Bamlanivimab and Etesevimab that is used in clinical applications for antibody therapy has been authorized for emergency use. There have been previous studies demonstrating that the mutations at 484 and 417 positions of the spike could be involved in immune evasion. Both Beta and Gamma variants have been observed to resist the neutralization of LY-CoV555 and LY-CoV016 due to mutations E484A and K417N. Since the Omicron variant also contains E484A and K417N mutations, it is likely that Omicron would also resist these two antibodies (He, Hong et al. 2021).

Other Sars-CoV-2 Variant of Concerns

Alpha variant (B.1.1.7)

The B.1.1.7 alpha variant was reported on 2020-09-03, which was originally associated with a UK lineage, which carried mutations including N501Y, P681H, and numerous others. Its rapid growth in the UK and internationally has been attributed to its higher transmissibility than other lineages (PHO 2022).

Beta variant (B.1.351)

The B.1.351 Beta variant is a lineage first detected in South Africa and has been characterized by the new variant of concern 501Y.V2 (Tegally, Wilkinson et al. 2021) An additional sublineage of SARS-CoV-2 (501Y.V2) can be defined by eight mutations in the spike protein, including three found in the receptor-binding domain that could be functionally significant (K417N, E484K, and N501Y). Nelson Mandela Bay, located on the coast of the Eastern Cape Province, was severely affected by the first epidemic wave, which gave rise to this lineage. A lineage of this strain quickly spread, becoming the dominant lineage in both the Eastern Cape and Western Cape within weeks. Even though the full significance of the mutations has not yet been determined, the genomic data indicating that this lineage is displacing other lineages indicates a possible link to increased transmissibility.

Gamma variant (P.1 B.1.1.28)

The P.1 strain reported in January 2021, is an alias of the B.1.1.28.1 strain first identified in Brazil with variants E484K, N501Y and K417T) (Sahay, Patil et al. 2022). This variant was first observed in December in Manaus, Amazonas state in north Brazil, where very high attack rates have previously been estimated. This new lineage, named P.1 (descendant of B.1.1.28), exhibits a constellation of specific mutations that define the lineage. These mutations, such as E484K,

K417T, and N501Y, have been shown to be of biological significantly (Henriques-Santos, Farjun et al. 2021). The P.1 lineage was identified in 42% of RT-PCR positive samples extracted between 15 and 23 December, but it was not detected in 26 publicly available genome surveillance samples collected in Manaus between March and November 2020. According to these results, a new lineage from the Amazon region has been transmitted locally and may have recently increased in frequency. There is an increasing concern due to variants with multiple shared mutations in spike that convergent evolution may result in a new phenotype that is associated with an increase in infection potential or re-infection. The P.1 variant, containing mutation E484K, may increase the risk of re-infection or infection in vaccinated individuals containing earlier strains of SARS-CoV-2 by aiding SARS-CoV-2 variants to evade antibodies (PHO, 2021).

Delta variant

The Delta variant (B.1.617.2 lineage) was identified in December 2020 in India and was responsible for the second wave of COVID-19 infections in April 2021 (Page, M. L. 2021). However, this variant rapidly spread around the world prompting the WHO to classify it as a VOC in May 202. This variant became the dominant SARS-CoV-2 strain in the US until Omicron was identified in November of 2021 being replaced in December 2021. This variant consists of ten mutations including T19R, G142D, 156del, 157del, R158G, L452R, T478K, D614G, P681R, D950N in its spike protein.

Discussion and Conclusion

By virtue of their increased transmissibility, virulence, and evasion of vaccine and natural immunity, VOCs present new global threats to health in the midst of COVID-19's transition from pandemic to an endemic disease. Similar to the nature of all viruses, the evolution of SARS-CoV-2 virus changes with time. It is generally true that, while viruses change their forms, their properties remain the same or are not radically different. The World Health Organization (WHO) has recently reported the latest SARS-CoV-2 variant called Omicron, which differs from other SARS-CoV-2 variants like Alpha, Beta, Gamma, and Delta. Thus, the scientific community is investigating the impact of this variant on SARS-CoV-2, such as its transmissibility, disease severity, diagnostic method, efficacy of existing vaccines, and other COVID-19 protocols. Additionally, SARS-CoV-2 spike protein antigenicity and amino acid changes affecting antibody neutralization are now clearly evident. Viruses worldwide show significant variations in amino acid substitutions and deletions affecting neutralizing antibodies. There is further evidence that some virus variants may be resistant to antibody-mediated immunity induced by vaccines while T cell mediated immunity induced by vaccines still have a protective role. Despite the inclusion of the new variant Omicron with the previous variant of concern, recent research indicates no rapid changes or sudden acceleration in the pattern of epidemic curves. Using present studies, we can answer the question of whether new Omicron variants can evade vaccine-induced immunity, but the consistency of results depends on the answer to that question (Gowrisankar A, Priyanka TMC, Banerjee S. 2022)

The emergence of the Omicron variant indicates that surveillance of SARS-CoV-2 variants should be conducted in economically underdeveloped countries and in the environment to avoid

the continuous emergence of new variants of unknown origin. Understanding the threat posed by the Omicron variant will require researchers to gather and analyze a great deal more data in a brief period. Determining the origin of Omicron requires surveillance of animals, especially rodents, because they may have come into contact with humans carrying a strain of the virus with adaptive mutations. Future work should focus on SARS-CoV-2 variants isolated from other wild animals to investigate the evolutionary trajectories and biological properties of these variants both in vitro and in vivo. If Omicron is determined to have been derived from animals, the implications of it circulating among non-human hosts will pose new challenges in the prevention and control of the epidemic.[1]

References:

1. Aleem A, Akbar Samad AB, Slenker AK. Emerging Variants of SARS-CoV-2 And Novel Therapeutics Against Coronavirus (COVID-19). 2022 Feb 6. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 34033342.
2. Karim SSA, Karim QA. Omicron SARS-CoV-2 variant: a new chapter in the COVID-19 pandemic. Lancet. 2021 Dec 11;398(10317):2126-2128. doi: 10.1016/S0140-6736(21)02758-6. Epub 2021 Dec 3. Erratum in: Lancet. 2022 Jan 8;399(10320):142. PMID: 34871545; PMCID: PMC8640673.
3. Gowrisankar A, Priyanka TMC, Banerjee S. Omicron: a mysterious variant of concern. Eur Phys J Plus. 2022;137(1):100. doi: 10.1140/epjp/s13360-021-02321-y. Epub 2022 Jan 10. PMID: 35036269; PMCID: PMC8743750.
4. SIB Swiss Institute of Bioinformatics. 2022, February 9. SIB Swiss Institute of Bioinformatics. SIB Swiss Institute of Bioinformatics | Disclaimer. Retrieved March 26, 2022, from https://viralzone.expasy.org/9556
5. COVID-19 P.1 Variant of Concern– What We Know So Far. Public Health Ontario. March 3,2021.https://www.publichealthontario.ca/-/media/documents/ncov/covid-wwksf/2021/02/wwksf-covid-19-p1-variant-of-concern.pdf?la=en
6. Tegally, H., Wilkinson, E., Giovanetti, M., Iranzadeh, A., Fonseca, V., Giandhari, J., Doolabh, D., Pillay, S., San, E. J., Msomi, N., Mlisana, K., von Gottberg, A., Walaza, S., Allam, M., Ismail, A., Mohale, T., Glass, A. J., Engelbrecht, S., Van Zyl, G., … de Oliveira, T. (2021, March 9). Detection of a SARS-COV-2 variant of concern in South Africa. Nature News. Retrieved March 25, 2022, from https://www.nature.com/articles/s41586-021-03402-9
7. Page, M. L. (2021, November 9). Delta covid-19 variant (b.1.617). New Scientist. Retrieved March 25, 2022, from https://www.newscientist.com/definition/indian-covid-19-variant-b-1-617/
8. SARS-COV-2 variants of concern as of 24 March 2022. European Centre for Disease Prevention and Control. (2022, March 25). Retrieved March 25, 2022, from https://www.ecdc.europa.eu/en/covid-19/variants-concern

[1]

9. Salim S Abdool Karim, Quarraisha Abdool Karim Omicron SARS-CoV-2 variant: a new chapter in the COVID-19 pandemic Lancet. 2021 11-17 December; 398(10317): 2126–2128.
10. Giovanetti M, Benedetti F, Campisi G, Ciccozzi A, Fabris S, Ceccarelli G, Tambone V, Caruso A, Angeletti S, Zella D, Ciccozzi M. Evolution patterns of SARS-CoV-2: Snapshot on its genome variants. Biochem Biophys Res Commun. 2021 Jan 29;538:88-91. [PMC free article] [PubMed])
11. nuno_faria. (2021, January 12). Genomic characterisation of an emergent SARS-COV-2 lineage in manaus: Preliminary findings. Virological. Retrieved March 25, 2022, from https://virological.org/t/genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-manaus-preliminary-findings/586
12. World Health Organization. (2022, February 22). Statement on Omicron sublineage BA.2. World Health Organization. Retrieved March 26, 2022, from https://www.who.int/news/item/22-02-2022-statement-on-omicron-sublineage-ba.2
13. #2-Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, Hengartner N, Giorgi EE, Bhattacharya T, Foley B, Hastie KM, Parker MD, Partridge DG, Evans CM, Freeman TM, de Silva TI, Sheffield COVID-19Genomics Group. McDanal C, Perez LG, Tang H, Moon-Walker A, Whelan SP, LaBranche CC, Saphire EO,Montefiori DC. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of theCOVID-19 Virus. Cell. 2020 Aug 20;182(4):812-827.e19. [PMC free article: PMC7332439] [PubMed: 32697968]
14. He, Xuemei et al. "SARS-CoV-2 Omicron variant: Characteristics and prevention." MedComm, vol. 2,4 838–845. 16 Dec. 2021, doi:10.1002/mco2.110
15. Aleem A, Akbar Samad AB, Slenker AK. Emerging Variants of SARS-CoV-2 And Novel Therapeutics Against Coronavirus (COVID-19). 2022 Feb 6. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 34033342.
16. "Socio-Economic Inequality in Science Is on the Rise." Nature News. Nature Publishing Group, September 21, 2016. https://www.nature.com/articles/537450a.
17. Harvey, W.T., Carabelli, A.M., Jackson, B. et al. SARS-CoV-2 variants, spike mutations and immune escape. Nat Rev Microbiol 19, 409–424 (2021). https://doi.org/10.1038/s41579-021-00573-0
18. Bruxvoort, K. (2021, November 25). Real-world effectiveness of the mRNA-1273 vaccine against COVID-19: Interim results from a prospective observational cohort study. The Lancet. Retrieved March 26, 2022, from https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(21)00130-7/fulltext
19. Rosenberg, E. S., Al., E., Author AffiliationsFrom the New York State Department of Health, Others, M. R. S. and, Others, K. L. W. and, Others, J. N. J. and, Others, G. R.-Y. and, Others, J. Y. and, & King, T. E. (1970, March 24). Covid-19 vaccine effectiveness in New York State: Nejm. New England Journal of Medicine. Retrieved March 26, 2022, from https://www.nejm.org/doi/full/10.1056/NEJMoa2116063
20. P.1 2022-03-25. Cov. (n.d.). Retrieved March 25, 2022, from https://cov-lineages.org/global_report_P.1.html

21. “Lineages.org.” Cov. Accessed March 13, 2022. https://cov-lineages.org/.
22. Ontario Agency for Health Protection and Promotion (Public Health Ontario). COVID-19 B.1.351 (501Y.V2) variant of concern – what we know so far. Toronto, ON: Queen's Printer for Ontario; 2021. [cited 2021 Feb 14]. Available from: https://www.publichealthontario.ca/- /media/documents/ncov/covid-wwksf/2021/02/wwksf-covid-19-b1351501yv2-variant-ofconcern.pdf?la=en
23. Mark W. Tenforde, M. D. (2021, November 23). Association of COVID-19 mrna vaccination with hospitalizations and disease severity. JAMA. Retrieved March 26, 2022, from https://jamanetwork.com/journals/jama/fullarticle/2786039
24. Wang P, Lihong L, Iketani S, Luo Y, Guo Y, Wang M, et al. Increased resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7 to antibody neutralization. bioRxiv 428137 [Preprint]. 2021 Jan 26 [cited 2021 Feb 02]. Available from: https://doi.org/10.1101/2021.01.25.428137
25. Zhang S. A troubling new pattern among the coronavirus variants. The Atlantic [Internet], 2021 Jan 18 [cited 2021 Feb 01]; Health. Available from: https://www.theatlantic.com/health/archive/2021/01/coronavirus-evolving-same-mutations-aroundworld/617721/
26. Rahimi, Farid, and Amin Talebi Bezmin Abadi. “The Omicron subvariant BA.2: Birth of a new challenge during the COVID-19 pandemic.” International journal of surgery (London, England) vol. 99 (2022): 106261. doi:10.1016/j.ijsu.2022.106261
27.
28. Zimmer K. A guide to emerging SARS-CoV-2 variants. The Scientist [Internet], 2021 Jan 26 [cited 2021 Feb 02]. Available from: https://www.the-scientist.com/news-opinion/a-guide-to-emerging-sars-cov-2- variants-68387
29. Pan American Health Organization; World Health Organization. Epidemiological update: variants of SARS-CoV-2 in the Americas: 26 January 2021 [Internet]. Washington, DC: PAHO/WHO; 2021 [cited 2021 Feb 03]. Available from: https://www.paho.org/en/file/81085/download?token=iVEppahk
30. Aleem, Abdul. “Emerging Variants of SARS-COV-2 and Novel Therapeutics against Coronavirus (COVID-19).” National Center for Biotechnology Information. U.S. National Library of Medicine, February 6, 2022. https://www.ncbi.nlm.nih.gov/books/NBK570580/?report=printable.
31. “Enhancing Response to Omicron SARS-COV-2 Variant.” World Health Organization. World Health Organization, January 21, 2022. https://www.who.int/publications/m/item/enhancing-readiness-for-omicron-(b.1.1.529)-technical-brief-and-priority-actions-for-member-states.
32. Desingu, Perumal A. “Omicron Ba.2 Lineage Spreads in Clusters and Is ...” Wiley Online Library, 2022. https://onlinelibrary.wiley.com/doi/full/10.1002/jmv.27659.
33. Yang T-J, Yu P-Y, Chang Y-C, et al. Impacts on the structure-function relationship of SARS-CoV-2 spike by B.1.1.7 mutations. bioRxiv. Published online May 12, 2021. https://doi.org/10.1101/2021.05.11.443686.

34. Karim, Salim S Abdool, and Quarraisha Abdool Karim. “Omicron SARS-CoV-2 variant: a new chapter in the COVID-19 pandemic.” Lancet (London, England) vol. 398,10317 (2021): 2126-2128. doi:10.1016/S0140-6736(21)02758-6
35. VanBlargan, L.A., Errico, J.M., Halfmann, P.J. et al. An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralization by therapeutic monoclonal antibodies. Nat Med 28, 490–495 (2022). https://doi.org/10.1038/s41591-021-01678-y
36. Centers for Disease Control and Prevention. (2021, December 1). SARS-COV-2 variant classifications and definitions. Centers for Disease Control and Prevention. Retrieved

Cheng, M. H., et al. (2022). "Impact of new variants on SARS-CoV-2 infectivity and neutralization: A molecular assessment of the alterations in the spike-host protein interactions." iScience **25**(3): 103939.

Desingu, P. A. and K. Nagarajan (2022). "Omicron BA.2 lineage spreads in clusters and is concentrated in Denmark." J Med Virol.

Giovanetti, M., et al. (2021). "Evolution patterns of SARS-CoV-2: Snapshot on its genome variants." Biochem Biophys Res Commun **538**: 88-91.

Harvey, W. T., et al. (2021). "SARS-CoV-2 variants, spike mutations and immune escape." Nat Rev Microbiol **19**(7): 409-424.

He, X., et al. (2021). "SARS-CoV-2 Omicron variant: Characteristics and prevention." MedComm (2020).

Henriques-Santos, B. M., et al. (2021). "SARS-CoV-2 Variant Determination Through SNP Assays in Samples From Industry Workers From Rio de Janeiro, Brazil." Front Microbiol **12**: 757783.

Karim, S. S. A. and Q. A. Karim (2021). "Omicron SARS-CoV-2 variant: a new chapter in the COVID-19 pandemic." The Lancet **398**(10317): 2126-2128.

Korber, B., et al. (2020). "Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus." Cell **182**(4): 812-827 e819.

Madhi, S. A., et al. (2021). "Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant." N Engl J Med **384**(20): 1885-1898.

Quaglia, F., et al. (2022). "SARS-CoV-2 variants preferentially emerge at intrinsically disordered protein sites helping immune evasion." FEBS J.

Rahimi, F. and A. Talebi Bezmin Abadi (2022). "The Omicron subvariant BA.2: Birth of a new challenge during the COVID-19 pandemic." Int J Surg **99**: 106261.

Rosenberg, E. S., et al. (2022). "Covid-19 Vaccine Effectiveness in New York State." N Engl J Med **386**(2): 116-127.

Sahay, R. R., et al. (2022). "SARS-CoV-2 Delta and delta derivatives impact on neutralization of Covishield recipient sera." J Infect.

Tao, K., et al. (2021). "The biological and clinical significance of emerging SARS-CoV-2 variants." Nat Rev Genet **22**(12): 757-773.

Tegally, H., et al. (2021). "Detection of a SARS-CoV-2 variant of concern in South Africa." Nature **592**(7854): 438-443.

Tenforde, M. W., et al. (2021). "Association Between mRNA Vaccination and COVID-19 Hospitalization and Disease Severity." JAMA **326**(20): 2043-2054.

Yang, T. J., et al. (2021). "Effect of SARS-CoV-2 B.1.1.7 mutations on spike protein structure and function." Nat Struct Mol Biol **28**(9): 731-739.