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Variations from SARS-CoV-2 to Omicron: A new threat knocking at world's door

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ABSTRACT

The public health threat posed by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has persisted since December 2019. Many countries were able to manage SARS-CoV-2 due to various strategies, like masking, social distancing, and vaccinations. Virus mutations are one of the most significant barriers to the disease's eradication; as a result, various variants have emerged (Alpha, Beta, Gamma, Delta, etc.) from time to time with higher mortality. Omicron, a variant identified from South Africa, has put the world on high alert. In this context, we have reviewed some reports on Omicron along with other variants. This new variant has been designated as a variant of concern by the World Health Organization. The preliminary reports revealed that Omicron is heavily mutated with more than 30 mutations (A67V, del69-70, T95I, del142-144, Y145D, etc.) in its spike protein. Despite vaccination with the most efficacious Pfizer candidate, Omicron infection was reported in South Africa. Bioactive lipids, such as arachidonic acid, alpha-linolenic acid, docosahexaenoic acid, eicosapentaenoic acid, and others have been reported to be the key components in inactivating the virus, so their future role is imperative. Ongoing research for the development of new or modification of existing vaccines must continue.

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic began in Wuhan, China, in December 2019, and has posed a serious threat to public health around the world (Zhu *et al.*, 2020). SARS-CoV-2 or COVID-19 is a Betacoronavirus belonging to the *Coronaviridae* family that causes cough, tiredness, myalgia, and fever (Chen *et al.*, 2020; Wu *et al.*, 2020; Wu and McGoogan, 2020). The World Health Organization (WHO) has classified SARS-CoV-2 as a public health emergency at the international level. As of December 3, 2021, a total of 263,563,622 COVID-19 cases had been documented worldwide, with 5,232,562 fatalities (WHO, 2021a). COVID-19 had a massive impact on society, the environment, and the global economy, posing a grave threat to human survival.

Several investigations and approaches have been undertaken to prevent COVID-19 from spreading further and developing safe and effective medications and vaccines. AstraZeneca, Johnson & Johnson, Gamaleya, Novavax, Sinopharm, Sinovac, Moderna, and Pfizer have all produced vaccines to prevent the COVID-19 pandemic (Balkrishna *et al.*, 2021). While current vaccines are assisting in keeping the pandemic under control in some countries, it is also vital to remain prepared for SARS-CoV-2 mutations, as RNA viruses like the coronavirus tend to change and mutate over time (Bollinger and Ray, 2021; WHO, 2021c). Due to mutations in the SARS-CoV-2, the world has seen numerous peaks of the COVID-19 pandemic with higher infectivity and transmissibility.

SARS-CoV-2 variations such as Alpha, Beta, Delta, Eta, Theta, and others have already been identified. In terms of transmissibility and infectivity, the SARS-CoV-2 Delta variant or B.1.617.2, has had the largest impact. In December 2020, it was initially reported in India, and it rapidly spread to 98 countries around the world (CDC, 2021a). On November 13, 2021, Thomas Peacock, a postdoctoral fellow at Imperial College London

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in the United Kingdom, revealed the sequencing of a novel variant (B.1.1.529) of SARS-CoV-2 acquired from an immune-compromised patient in South Africa (FDA, 2021a). WHO categorized variant B.1.1.529 or Omicron as a variant of concern (VOC) on November 26, 2021 (WHO, 2021c). The B.1.1.529 variant is now most prevalent in COVID-19 patients in South Africa; unfortunately, it has also been documented in more than 20 other countries including Botswana, Belgium, Hong Kong, Israel, etc. (Callaway and Ledford, 2021; Choudhary *et al.*, 2021). SARS-CoV-2 variants are rapidly evolving; this review gives an insight into SARS-CoV-2 variants, with a focus on the highly mutated form Omicron. The importance of bioactive lipids in the battle against COVID-19 is also emphasized.

CATEGORIZATION OF SARS-COV-2 VARIANTS AND ASSOCIATED MUTATIONS

A mutation is defined by the Center for Disease Control and Prevention (CDC) as a change in a virus's genetic code that occurs naturally over time when an animal or person becomes infected (CDC, 2021a). Viruses like COVID-19 are emerging consistently as alterations in the genetic code (genetic mutations) that arise upon genome replication. These alterations are categorized as lineage and variants. Furthermore, a lineage is a group of viral variations that have a common ancestor and are genetically related, wherein a variation is differentiated from other SARS-CoV-2 variants by one or many mutations (CDC, 2021d). The different variants from SARS-CoV-2 to Omicron, along with their first identification detail are shown in Figure 1.

The WHO and CDC have classified coronavirus variants into the following categories:

Variants of interest (VOI)

The genetic variations in SARS-CoV-2 are considered as VOI when they are observed to alter its characteristics such as immunological escape, the severity of disease, therapeutic or diagnostic escape, enhanced transmissibility, and decreased neutralization by antibodies developed in response to past infection or immunization. The second component is when the SARS-CoV-2 variation is found to produce considerable community transmission or multiple clusters in different nations, with increasing case numbers over time, or other evident epidemiological repercussions, indicating an expanding concern to global public health. VOI may necessitate appropriate public health actions like increasing sequential monitoring, enhancing lab characterization, or epidemiological assessments to identify how conveniently the virus is spreading, the magnitude of disease, the efficiency of therapeutics, and whether commercially available or accredited immunizations offer protection (CDC, 2021d; WHO, 2021c). Lambda and Mu are considered as VOI by WHO (2021c).

Variant of concern (VOC)

VOC is the one that infects people who have been vaccinated or previously infected. These variations are more likely to enhance transmissibility, cause severe illness (e.g., elevated hospitalizations or mortalities), show resistance against antiviral therapy, circumvent diagnosis or substantially reduce antibodies neutralization produced throughout vaccination or previous infection. Concerning variants may necessitate relevant public health interventions, like reporting to the CDC or intimation to WHO, regional attempts to prevent transmission, rapid diagnosis, or experimentation to assess the efficacy of vaccines and therapies

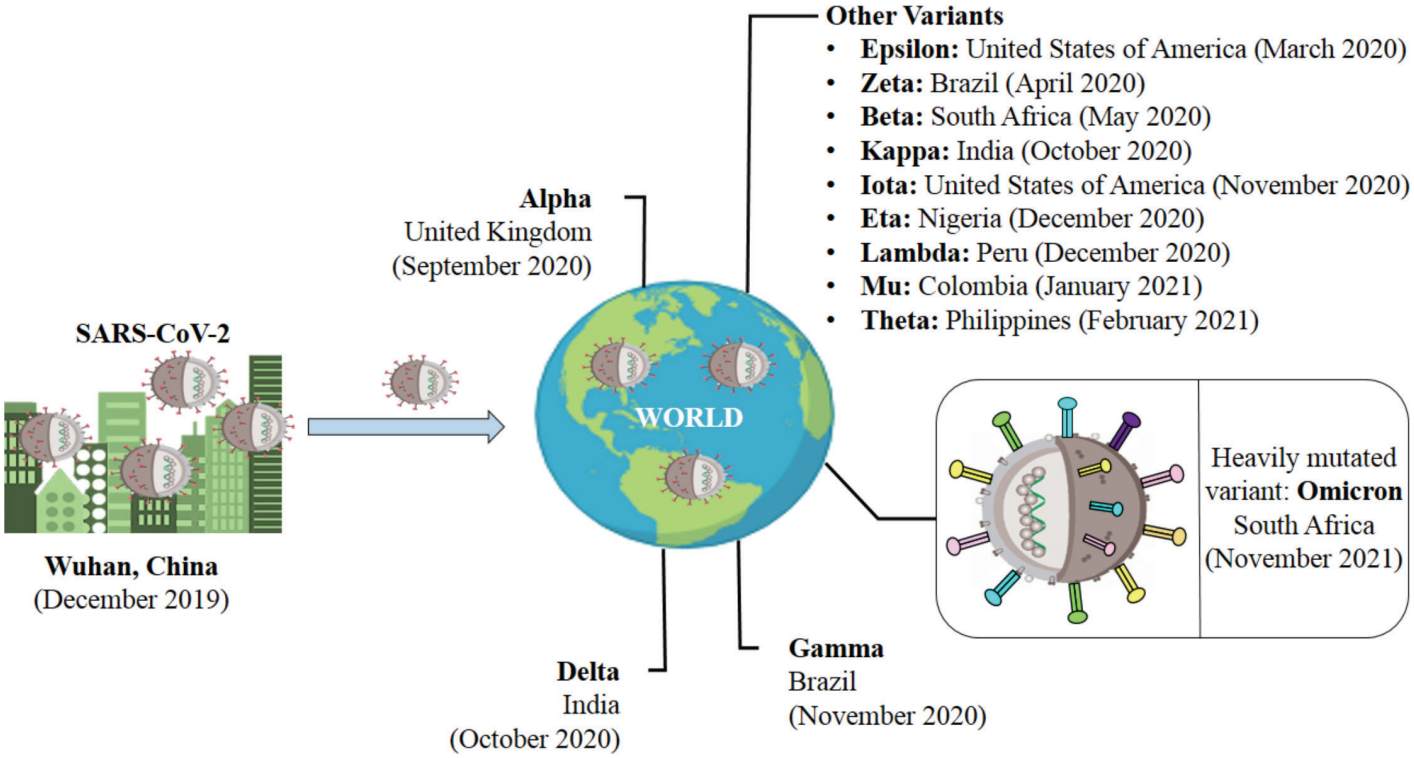

Figure 1. An overview of variations from SARS-CoV-2 (Wuhan) to Omicron (South Africa).

against it. Additional considerations could include developing new diagnostics or altering immunizations or medicines based on the characteristics of the variant (CDC, 2021d; WHO, 2021c). WHO classifies Alpha, Beta, Gamma, Delta (B.1.617.2 and AY lineages), and Omicron (B.1.1.529) as VOC (WHO, 2021c).

Variant of high consequence (VOHC)

VOHC is one against which existing vaccinations provide no protection. VOHC contains clear proof that precautionary measures or medicinal interventions are much less effective than formerly existing versions. A VOHC would involve information to WHO, reporting to the CDC, disclosure of prevention or containment activities, and considerations to improve therapy and vaccinations (CDC, 2021d; WHO, 2021c). There are no substantial SARS-CoV-2 variations to evaluate under VOHC at this time (CDC, 2021d).

Variants being monitored (VBM)

VBM variations are those for which data implies a possible or apparent influence on allowed or permitted medical treatments, or that have been linked to higher rates of catastrophic disease or transmissions but are no longer detectable, or that exist in relatively small amounts. These variations do not constitute a major or immediate health risk. VOI or VOC may be included in this list after a considerable and consistent decrease in proportions over time or if additional research suggests that the variant will not pose a serious hazard to public health. Alpha (Q lineages and B.1.1.7), Beta (B.1.351 and descendent lineages), Gamma (P.1 and descendent lineages), Epsilon (B.1.427 and B.1.429), Eta (B.1.525), Iota (B.1.526), Kappa (B.1.617.1), Zeta (P.2), Mu (B.1.621.1, B.1.621) are all VBM variations (CDC, 2021d). Table 1 provides a quick review of various mutations found in several SARS-CoV-2 variants.

The majority of the variants were found to be more prevalent in Brazil, South Africa, India, and the United States of America, and these variants were also more transmissible. The B.1.1.529 lineage still has the greatest spike substitutions as compared to previously reported ones, as seen in Table 1, which could affect transmissibility and antibody potency. Stopping Omicron as soon as possible is the only method to prevent future lethal variants.

EFFICACY OF EXISTING VACCINES AGAINST OMICRON: A MAJOR CONCERN

In recent weeks, with the identification of the B.1.1.529 strain (Omicron), the infections have increased tremendously. There are a lot of mutations in this variant, including the novel spike mutations and antigenic distinctiveness from preceding strains. The variant's rapid spread in South Africa indicated that it might be immune-evading (WHO, 2021a). The individuals who received any of the three types of vaccinations available in South Africa (Pfizer-BioNTech, Johnson & Johnson, and Oxford-AstraZeneca) have developed breakthrough infections, posing a public health risk. The variant's rapid transmission in South Africa suggests that it may be able to bypass immunity and existing vaccines. Around a quarter of South Africans are fully vaccinated, and many have been infected in previous COVID-19 waves (Callaway and Ledford, 2021). According to one source, in Hong Kong, two quarantined passengers were found positive for the novel variant even after immunization with the Pfizer vaccine. One of them had come from South Africa (Callaway and Ledford, 2021).

Against all COVID-19 variants, including the super spreader Delta variant, vaccines continue to be crucial in lowering severe illness and mortality. According to WHO, a total of 7,864,123,038 vaccination doses were administered globally up to December 2, 2021 (WHO, 2021a). The role of current immunizations against the Omicron variant is still obscure. To understand the efficacy of current vaccines, researchers are closely tracking the effects of current vaccines on Omicron mutations. They intend to evaluate the virus's capacity to avoid infection-fighting antibodies and other immunological reactions. Because of the threat posed by Omicron, several rich nations, like the United Kingdom, have accelerated and expanded the distribution of COVID vaccination booster doses. However, it is unknown how successful these dosages will be toward this variant. The novel development of Omicron underscores the significance of immunization and booster shots (CDC, 2021c).

BIOACTIVE LIPIDS AGAINST SARS-COV-2: A RAY OF HOPE

To stop the SARS-CoV-2 pandemic, tremendous attempts are being undertaken to establish both prophylactic and treatment strategies. The scarcity of antiviral drugs, fewer vaccines, and emerging variants necessitates the development of new therapeutic approaches to tackle SARS-CoV-2. Polyunsaturated fatty acids and their derivatives (also known as bioactive lipids) could play an important role in this context. The bioactive lipids include alpha-linolenic acid (ALA), arachidonic acid (AA), dihomo- γ-linolenic acid, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), linolenic acid, γ-linolenic acid, leukotrienes, lipoxins, maresins, prostaglandins, protectins, resolvins, and thromboxanes (Das, 2021). Das (2020) suggested that AA and other unsaturated fatty acids, as well as their derivatives, may act as endogenous antiviral agents, and their insufficiency could make individuals vulnerable to SARS-CoV-2. In addition, fatty acids also aid in the inactivation of enveloped viruses (Mousavizadeh and Ghasemi, 2021).

The omega-3 polyunsaturated fatty acids (ALA, EPA, and DHA) were found to have immunomodulatory properties (Chang *et al.*, 2020). Their anti-viral potential is mediated through the inhibition of replication (Shakoor *et al.*, 2021). The underlying mechanism by which unsaturated fatty acids (AA, EPA, and DHA) inactivate the virus is still unknown; nonetheless, the fatty acids trigger bilayer lipid envelope breakdown with enhanced efficacy (Aryan *et al.*, 2021). Das (2021) revealed that AA could be a crucial player in the prevention and management of SARS-CoV-2. He demonstrated multiple mechanisms, such as the production of AA and other bioactive lipids in the lungs inactivate viral pathogens; derivatives of AA (prostaglandin E2, leukotrienes, lipoxin A4), EPA and DHA (maresins, protectins, and resolvins) stimulate the release of pro-inflammatory and anti-inflammatory macrophages. Moreover, AA derivatives and other bioactive lipids also inhibit the production of tumor necrosis factor-α and interleukin-6. These bioactive lipids could be used in the management of new variants of SARS-CoV-2.

Table 1. An overview of various variants of SARS-CoV-2.

Variants	Lineages	First reporting nation (month, year)	Mutations	Attributes	References
Epsilon	B.1.427/ B.1.429	United States of America (March 2020)	RBD mutation L452R	20% more contagious than co-circulating lineages, 2-fold greater upper-airway virus load	Deng *et al.* (2021); Peng *et al.* (2021); WHO, (2021c)
Zeta	P.2	Brazil (April 2020)	RBD mutation E484K, D614G, and V1176F	Low prevalence and is no longer considered a variant of interest by the WHO	WHO, (2021c, b); Stanford University, (2021)
Beta	B.1.351	South Africa (May 2020)	RBD mutations N501Y, K417N, and E484K 5 NTD mutations, together with a deletion at 242-244 positions	It is more transmissible than the earlier reported lineages E484K influences the binding of multiple RBM (class 1, 2) mAbs, whereas K417N inhibits the binding of several RBM (1) mAbs, resulting in lower susceptibility to a variety of mAbs	Tegally *et al.* (2021); Zhou *et al.* (2021a); Wang *et al.* (2021c); Li *et al.* (2020); Hoffman *et al.* (2021); WHO, (2021c)
Alpha	B.1.1.7	United Kingdom (September 2020)	RBD mutation P681H, N501Y NTD deletions at 69–70 and 144 position Non-spike variations, nsp6:Δ106–108 Nucleocapsid mutation G204R, D3L, and R203K	Neutralizing mAbs, and plasma samples from previously infected people can neutralize it RBD mutation E484K, F490S, and S494P have been found in many Alpha variant sub-lineages, potentially increasing the likelihood of reinfection and vaccination failure	Martin *et al.* (2021); Jiang *et al.* (2020); Thorne *et al.* (2021); Parker *et al.* (2021); Chen *et al.* (2021); Supasa *et al.* (2021); Wang *et al.* (2021c, a); Rees-Spear *et al.* (2021); Grabowski *et al.* (2021); Collier *et al.* (2021); Betton *et al.* (2021); Planas *et al.* (2021a); Edara *et al.* (2021); WHO, (2021c)
Delta	B.1.617.2	India (October 2020)	RBD mutation L452R P681R mutation in the proximal furin cleavage site *Orf*3, *orf*7a, and the nucleocapsid gene mutations Several mutations within *orf*1a/b, spike NTD, and S2 domains Spike protein substitutions: T19R, (V70F *), F157, T95I, R158G, D950N, E156, (A222V *), T478K, (W258L *), D614G, (K417N *), G142D, L452R, P681R	Greater transmissibility, rapidly replacing the Alpha variant High-level decreased bamlanivimab susceptibility among the FDA EUA-approved mAbs	CDC, (2021b); Deng *et al.* (2021); Weisblum *et al.* (2020); Ferreira *et al.* (2021); Liu *et al.* (2021); Planas *et al.* (2021b); WHO, (2021c)
Kappa	B.1.617.1	India (October 2020)	RBD mutation E484Q *Orf*3, *orf*7a, and the nucleocapsid gene mutation Several mutations within orf1a/b, spike NTD, and S2 domains	Highly capable of evading humoral immunity Lower susceptibility to casirivimab and bamlanivima	Liu *et al.* (2021); Weisblum *et al.* (2020); Edara *et al.* (2021); Zhang *et al.* (2021a); Ferreira *et al.* (2021)
Gamma	P.1	Brazil (November 2020)	RBD mutations E484K, N501Y and K417T	It is suspected of infecting and spreading disease to those who have already been attacked with the other variants Gamma variant's resistance profile to FDA EUA-approved mAbs is similar to that of Beta variants	Faria *et al.* (2021); Buss *et al.* (2021); Sabino *et al.* (2021); Dejnirattisai *et al.* (2021); Copin *et al.* (2021); FDA, (2021b); Wang *et al.* (2021b)
Iota	B.1.526	United States of America (November 2020)	RBD mutation E484K nsp6 deletion	About 40% of convalescent plasma samples had reduced Iota variant neutralizing activity by 3 to 10-fold, while 10% have reduced the same by >10-fold	Zhang *et al.* (2021b); Annavajhala *et al.* (2021); Zhou *et al.* (2021b)

Continued

Variants	Lineages	First reporting nation (month, year)	Mutations	Attributes	References
Eta	B.1.525	Nigeria (December 2020)	RBD mutation E484K ΔH69/ΔV70 deletion A new F888L mutation	Eta is distinguished from all other variations by the presence of both the E484K mutation and a novel F888L mutation	GISAID, (2021); Cov-Lineages, (2021)
Lambda	C.37	Peru (December 2020)	Spike mutations (F490S and L452Q) within the RBD Δ246-252 NTD deletion	Reduced susceptibility to the locally used CoronaVac vaccine	Wink *et al.* (2021); Acevedo *et al.* (2021)
Mu	B.1.621, B.1.621.1	Colombia (January 2021)	E484K, T95I, Y145N, Y144S, R346K, or the escape mutation N501Y, P681H, D950N, and D614G	Multiple outbreak clusters in different nations	Latif *et al.* (2021)
Theta	P.3	Philippines (February 2021)	N501Y, P681H, E484K NTD deletion at 141-143	Variation is less susceptible to neutralizing antibodies, including those acquired by vaccination	Bascos *et al.* (2021); CNN Philippines, (2015); The Japan Times, (2021); Tablizo *et al.* (2021)
Omicron	B.1.1.529	South Africa (November 2021)	Spike protein substitutions: del69-70, A67V, del142-144, T95I, Y145D, L981F, del211, ins214EPE, L212I, G339D, S371L, S375F, N440K, K417N, T478K, G446S, S477N, G496S, E484A, Y505H, Q493R, Q498R, Q954H, T547K, N764K, D614G, H655Y, N501Y, N679K, D796Y, P681H, N969K, N856K, S373P	Prospect of enhanced transmissibility Some EUA monoclonal antibody therapy may reduce neutralization Neutralization by post-vaccination sera may be reduced	CDC, (2021d); WHO, (2021b)

RBD: Receptor-binding domains; mAbs: Monoclonal antibodies; NTD: Amino-terminal domain*: Indicates a mutation that may or may not occur as per the CDC.

CONCLUSION AND RECOMMENDATIONS

Undoubtedly, it would take days to weeks to determine the severity of the Omicron. Although it is too early to determine Omicron's fatality potential based on preliminary findings, its rapid transmission cannot be ignored, as evidenced by the increase in cases in South Africa. Despite vaccination, the rate of transmission has increased, raising concerns among researchers and nations. Many developed nations are detecting this variant through genome sequencing; however, accurate data about Omicron appears to be a significant issue in the developing countries due to poor infrastructure. Omicron was discovered to be the heavily mutant variant. Until the facts regarding the Omicron are exposed, masking, social distancing, and vaccination are strongly suggested. To acquire a better understanding of Omicron's transmissibility, researchers are monitoring how it spreads in the rest of South Africa and around the world. To halt Omicron from spreading further, governments and researchers must play a critical role. The interplay between bioactive lipids and SARS-CoV-2 has opened up a new front in the fight against the pandemic.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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