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Mini-Review

Omicron, a new variant of SARS COV-2 and the impact of immunization on it — all that we know so far

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ABSTRACT

Introduction: The latest variant of SARS COV-2 has been identified in South Africa for the first time and was subsequently reported to the World Health Organization on 24th November 2021. A couple of days later, the WHO named this variant Omicron as well as declared it to be a Variant of Concern (VoC). This variant evolved during a crucial phase of the current pandemic where vaccination-induced immunity development has been kept as the topmost priority to combat the current scenario. **Areas Covered**: Approximately 50 genomic mutations have rendered this variant as more transmissible with larger replicating potentiality, as well as acquiring an immune escape property with additional features of vaccine-based innate immunity and a monoclonal antibody neutralizing capability. Information on its disease transmissibility as well as the disease severity caused by this new variant is still limited. Heterogenous data is available regarding its vaccine neutralizing capability as well as the impact on the clinical outcome by treating the variant with monoclonal antibodies. All leading vaccine manufacturers are putting in their best efforts to introduce new versions of the available Covid vaccines at the earliest point possible to counteract this new strain. **Commentary**: In spite of this, all international health regulatory bodies believe that Covid Appropriate Behaviors (CAB) still remain the most important step in reducing the mortality, morbidity, and further spread of this new variant.

Key words: SARS COV-2, Variant, mutation, immune-escape, transmissibility

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INTRODUCTION

The B.1.1.529 variant was first discovered in Botswana on November 11th, 2021 and in South Africa on November 14th, 2021. On November 26th, 2021, the World Health Organization (WHO) identified lineage B.1.1.529 of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) as a Variant of Concern (VOC)[1]. The United Kingdom Health Security Agency identified B.1.1.529 as a Variant Under Monitoring (VUI21-NOV-01) on November 25th, 2021[2]. The Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-VE) met on November 26th, 2021 to examine B.1.1.529[3]. The TAG-VE recommended that this variant be identified as a Variant of Concern (VOC). The WHO called it Omicron, after the fifteenth letter of the Greek alphabet[4,5]. Although earlier VoCs appeared in a world where natural immunity to COVID-19 infections was frequent, the fifth VoC appeared at a time when vaccination-induced immunity is developing globally. The first incidence of B.1.1.529 was reported in the United States on December 1st, 2021 in a person returning from a trip to South Africa. On December 2nd, 2021, a second case was reported in an individual with no prior overseas travel history who had similarly attended a convention. In addition to Europe, the Omicron variation has been found in instances involving travel in Australia, Brazil, Canada, Hong Kong, Israel, Japan, Nigeria, Norway, Sweden, the United Kingdom, and India.

GENOMIC FEATURES

Although clear immunological and clinical evidence is still lacking, little information is available regarding its transmissibility, mutations, and escape from immunity. Omicron has approximately 50 mutations in its genome, including 32 mutations in the spike protein[6]. The spike protein contains the following mutations: A67V, 69-70, T95I, G142D/143-145, 211/L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498R, and N501Y[7,8]. Three alterations (H655Y, N679K, and P681H) near the furin cleavage site may improve its transmissibility and replication[9]. Six mutations in the N-terminal region have been linked to innate, vaccine-based, or monoclonal antibody neutralization.

The T478K (also discovered in the Delta variant), N501Y (also found in the Alpha, Beta, and Gamma variants), and Q498R (not previously found in any of the VOCs) alterations in the receptor-binding domain

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may improve the virus's affinity for the ACE2 receptors of the host cells[10,11] and encourage the development of immunological escape mechanisms. The nsp6 deletion 105-107 (also observed in the Alpha, Beta, and Gamma VOCs) may be linked to its additional evasion of innate immunity and increased transmissibility outside of the spike protein[12]. R203K and G204R's nucleocapsid alterations (also identified in the Alpha and Gamma VOCs) may be linked to higher infectivity[13]. In comparison to the original Wuhan variety, the Omicron variant has 60 mutations: 50 nonsynonymous mutations, 8 synonymous mutations, and 2 non-coding mutations[14]. At least one new mutation may have been acquired from one of the coronaviruses that causes the common cold (HCoV-229E) or the human immunodeficiency virus (HIV) since that particular genetic sequence is known to exist in both of these viruses. South Africa likewise has the world's highest incidence of HIV infection, creating a high likelihood of concurrent infection[15].

WHY A VARIANT OF CONCERN (VOC)?

The WHO classified Omicron as a VOC based on epidemiological evidence that showed there to have been a surge in illness in South Africa in recent weeks, coinciding with Omicron detection. The US Department of Health and Human Services formed the SARS-CoV-2 Interagency Group (SIG) which is in charge of variant classifications in the US. The SIG meets on a regular basis to assess the risk posed by SARS-CoV-2 variants circulating in the United States and around the world, as well to offer suggestions on variant classification. The SIG decided to identify the Omicron version as a Variant of Concern on November 30th, 2021 (VoC). This decision is based on a number of factors including the detection of Omicron-related cases in multiple countries, as well as among those with no prior travel history, the transmission and replacement of Delta as the predominant variant in South Africa, the number and locations of substitutions in the spike protein, and the available data on the other variants with fewer substitutions in the spike protein, indicating a reduction in neutralization due to the available vaccines and convalescent sera. In South Africa, the average number of COVID-19 cases per day jumped from 280 cases per day the week before Omicron was discovered to 800 cases per day the following week. This was owing in part to greater surveillance. The number of COVID-19 cases are rapidly increasing in South Africa's Gauteng area; the fourth wave's early doubling time is faster than that of the prior three waves[16].

DISEASE TRANSMISSIBILITY

It is currently unknown how quickly the Omicron variant can transmit from one person to another. The replacement of Delta by Omicron as the most common variant in South Africa has raised concerns that the Omicron variant being more transmissible than Delta. However, due to the small number of cases in South Africa when Omicron first appeared, it is unclear whether this variant is in fact more transmissible than Delta. Furthermore, estimating transmissibility is problematic due to the small number of cases described to date. The differences in the spike protein suggest that the Omicron variety is more transmissible than the original SARS-CoV-2 virus but it's difficult to say if it's more transmissible than Delta. N501Y increases the ACE2 receptor binding which may improve transmission, and the combination of N501Y and Q498R may boost binding even more; nevertheless, other Omicron spike protein changes are expected to diminish ACE2 receptor binding. As a result, the whole range of spike protein changes present in the Omicron variation must be used to measure the receptor binding affinity. Because H655Y is close to the furin cleavage point, it may accelerate spike cleavage, aiding transmission. N679K is close to the furin cleavage site and contributes to its polybasic character which may enhance the spike cleavage and help transmission. Spike cleavage has been observed to be enhanced by P681H which could assist transmission. This mutation is found in the Alpha variant but a different mutation (P681R) is found in Delta. Omicron's effect on transmissibility is a matter of serious concern. Higher transmissibility is expected if the overlapping Omicron mutations maintain their known effects, especially because of mutations near the furin cleavage site. Early epidemiological evidence suggests that instances are increasing in South Africa as PCR tests fail to target the S-gene. However, preliminary evidence suggests that it is spreading rapidly against a backdrop of continued Delta variant transmission and a high natural immunity to the Delta variation. If the current trends continue, Omicron is expected to supplant Delta as the most common variant in South Africa.

R is the average number of new cases created by each infection and it is used by epidemiologists to track the spread of an epidemic. R is the average number of new cases created by each infection[17]. According to Tom Wenseleers, an evolutionary biologist at the Catholic University of Leuven in Belgium, Gauteng's R value was well below 1 in September when Delta was the predominant variant and cases were falling, indicating that Omicron has the potential to spread much

faster and infect far more people than Delta. The R in South Africa was expected to have climbed to 3% on November 26th, 2021 across all provinces [18].

IMMUNE ESCAPE

Another issue to consider is immune escape. Preliminary findings from the nationwide PCR testing program could provide some clues in the absence of data following the observational vaccination effectiveness and antibody-neutralization tests of vaccinee sera. Positive PCR tests among patients who have previously tested positive suggests an increase in cases of reinfection in South Africa. However, the increased use of fast antigen testing, as well as the incomplete recording of negative results, have both made it more difficult to interpret potential test positivity rates which have climbed to nearly four times the prior rate in the last week. Despite this limitation, the rise in reinfection instances is consistent with the immune escape alterations found in Omicron.

DISEASE SEVERITY

It is still unknown if infection with the Omicron variant causes a more severe disease. According to the preliminary data from South Africa, there are no special symptoms linked with Omicron variant infection. Some patients are asymptomatic, as with the other variants [19]. As of November 2021, it is unknown how the variant will spread in immune-compromised populations or whether the Omicron variant causes either a milder or more severe COVID-19 infection [20]. At this time, the anecdotal data from South African medics working on the front lines suggests that patients with Omicron are younger persons with a clinical presentation comparable to that of the previous variations. Although more nations are identifying the Omicron variety, affluent countries have the capacity to quickly sequence viruses from positive COVID-19 testing, skewing the early statistics on Omicron's distribution as a result. The South African Medical Research Council reported on 4th December that inpatients at a hospital complex in Tshwane were younger than in the previous waves from 14^{th} to 29^{th} November 2021, and that the ICU and oxygen therapy rates were lower than in the previous waves. These findings are not conclusive, and the clinical profile may alter in the coming days, allowing for a more precise disease severity assessment [21].

IMPACT OF IMMUNIZATION ON OMICRON

There are currently not enough data available to examine the ability of sera from vaccinated people or those who have previously been infected with SARS-CoV-2 to neutralize the Omicron variant. However, the US Government SIG and worldwide public health partners are trying to generate this data in laboratory settings, and the epidemiological and clinical markers will continue to be monitored.

Vaccine-induced immunity mostly targets the spike protein. The spike protein in the Omicron version contains more modifications than in the other variants, including 15 in the RBD. Significant reductions in the neutralizing activity of sera from vaccinated or previously infected individuals may suggest a lower protection from infection. This is based on the number of substitutions, their position, and evidence from other variations with similar spike protein mutations. To examine the influence of the Omicron variant on vaccine efficacy and outbreak infections, laboratory and epidemiological investigations are needed, especially in those who have received booster doses. Vaccination, on the other hand, is expected to continue to provide protection against hospitalization and mortality, and vaccines will continue to play a crucial part in the COVID-19 pandemic's containment. Clinical trials found there to be a decreasing efficacy of some vaccinations in the transmission of SARS COV-2 when the Beta variant is prevalent but conflicting findings have been observed for whether COVID-19 vaccines have consistently preserved the high efficacy for each of the four VoCs preceding Omicron.

Previous mutations have reduced vaccine efficacy. For example, the ChAdOx1 vaccine was 70% successful in preventing clinical infections in the UK for the D614G variant but just 10% effective in South Africa for the Beta version [22]. BNT162b2 vaccine's efficacy in preventing clinical infections was maintained in both the D614G and Beta versions. The influence of Omicron on the clinical efficacy of COVID-19 vaccines for mild infections is unclear. It's uncertain whether or not Omicron can evade vaccination-induced immunity and if so, to what extent. Only 24% of the population in South Africa, one of the nations where Omicron infections are on the rise, has been fully vaccinated [23], and it is unclear how many of the infected cases have been vaccinated at this time. There have been media reports of B.1.1.529 breakthrough infections in fully vaccinated travelers among Botswana [24] and Israel.

There have also been reports of 61 out of 624 South African travelers testing positive for COVID-19 on arrival in Amsterdam, including those infected with Omicron [25]. Other parts of the immune system, including T cells, may be less affected than antibody

responses by Omicron's mutations. T cells and another immunological player known as natural killer cells, which may be especially crucial for protection against severe COVID-19, will be measured by researchers in South Africa. All three vaccinations delivered in South Africa — Johnson & Johnson, Pfizer–BioNTech, and Oxford–AstraZeneca — have anecdotal evidence of breakthrough infections. The neutralizing-antibody levels generated by the booster dose immunization will likely act as a barrier to Omicron's capacity to escape these antibodies. People who have recovered from COVID-19 months before receiving their vaccines had antibodies capable of neutralizing the mutant spike protein. Those who have been exposed to SARS-spike CoV-2's protein multiple times, whether through infection or a booster dosage, are "very likely to have [a] neutralizing activity against Omicron."

Recently, an observational study was conducted in the UK to estimate the vaccine effectiveness against the Omicron variant in comparison to the Delta variant among currently available vaccines. Effectiveness was adjusted in the logistic regression models for age, sex, ethnic group, the index of multiple deprivation, period etc. A total 581 Omicron cases were tested against 56439 eligible Delta cases and 130867 negative controls. The results showed that the effectiveness against symptomatic Omicron cases was lower than with the Delta variant. Two doses of BNT162b2 or ChAdOx1 were not sufficient to provide adequate protection in mild cases of Omicron. Further larger follow-up studies with mild, moderate, and severe cases are required to comment properly [26].

Concerns regarding reduced vaccine efficacy due to a new variant have shifted our perspective on the COVID-19 endgame, dispelling the myth that worldwide vaccination is sufficient to suppress SARS-CoV-2 infection. As a gateway to viral endemicity, VoCs have emphasized the necessity of vaccination in tandem with established public health preventative measures, such as masks [27]. The ability of vaccines and convalescent sera to neutralize the Omicron variant, the variant's vulnerability to therapies, and the ability of vaccine-induced immunity to protect against sickness and death are all being investigated in clinical trials.

CONCLUSION

Global efforts to improve vaccination coverage, particularly in low and middle-income countries with limited resources to prevent and control COVID-19 transmission, are also a critical measure to combat VOC spread because each transmission event contributes to the virus mutations that risk the emergence of new variants [28]. On November 29^{th}, Novavax announced that it was working on a new vaccination for the Omicron form which it projected to be ready for testing and manufacturing in a few weeks. The vaccine would require two doses [29]. On the same day, Sinovac announced that it can swiftly mass-produce an inactivated vaccine against the variant and, apart from monitoring the clinical trials, it is also collecting variant samples to see if a new vaccine is needed [30]. Officials representing the Gamaleya Institute have stated that they will begin developing a modified version of Sputnik V which should be ready for mass production in 45 days [31]. To limit SARS-COV-2 transmission and to avert the COVID-19 pandemic, we must employ all available prevention techniques such as masks, improved ventilation, distancing, handwashing, and testing, as we continue to increase the vaccination levels nationwide and globally. In public indoor venues in areas of substantial or high transmission, the CDC recommends that everyone over the age of two, including those who have been completely vaccinated, wear masks. New findings and information on Omicron are expected to emerge quickly, necessitating constant monitoring to inform the public health response. Given the concerns about Omicron's increased transmissibility and mutations that could lead to vaccine/immune escape, as well as uncertainty about its virulence (i.e., the clinical severity among those who have the disease), a temporary containment strategy could be used as a precautionary measure to help delay the VoC's importation and spread.

ABBREVIATIONS

None

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All authors equally contributed to this work, read and approved the final manuscript.

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The authors declare that they have no competing interests.

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