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REVIEW ON OMICRON: A NEW EMERGING STRAIN OF COVID-19

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Abstract:

COVID-19 has brought about a worldwide threat to the public health. Recently, a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant B.1.1.529 has been found in South Africa and it leads to rapid increase in COVID-19 cases. On November 24, 2021, B.1.1.529 named Omicron was identified as a variant under monitoring (VUM) by World Health Organization. Two days later, the Omicron variant was categorised as a variant of concern (VOC). This variant harbour a large number of mutations, including 15 mutations in the receptor-binding domain (RBD) of spike. The Omicron variant of COVID-19 also shares variety of mutations with the previous VOC Alpha, Beta, and Gamma variants, which quickly raised global concerns about viral pathogenicity, transmissibility, and immune evasion. Here we described the discovery and characteristics of the Omicron variant, Third BNT162b2 Vaccination Neutralization of SARS-CoV-2 Omicron Infection, and further raised possible remedies to prevent and combat the prevalence of the Omicron variant.

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INTRODUCTION:

The Coronavirus disease 2019 (COVID-19) pandemic has been moving forward powerfully since almost two years. More than 260 million confirmed cases have been reported according to the numbers of the World Health Organization (WHO), including over five million deaths.[1] The original severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus that was identified at the end of 2019 had evolved and a variety of variants emerged. In order to prioritize monitoring and study of these variants, WHO has group them into three categories: variants of concern (VOCs), variants of interest (VOIs), and variants under monitoring (VUMs). The previous four VOCs include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2).[2] They all resulted in a new wave of pandemic and thousands of deaths in more than one country and area, and even across the entire world. On November 26, 2021, a new variant named Omicron (B.1.1.529) was identified as the fifth VOC by WHO, which immediately raised global concerns.

Arrival of omicron variant

According to the WHO reports, the first known confirmed infection by Omicron could be traced back to a sample collected on November 9, 2021.[3] The first Omicron sequence available, however, was from a sample collected on November 11, 2021, in Botswana. Ever since the finding of Omicron, the variant appears to rapidly spread. A recent genomic-sequence analysis on 77 virus specimen collected in Gauteng province of South Africa from November 12 to 20 showed that all the analysed variants were actually B.1.1.529,[4] showing that Omicron was becoming dominant in Gauteng. Furthermore, the identification of Omicron coincides with the recent sharp rise in the number of confirmed COVID-19 cases in South Africa. The mean number of COVID-19 cases per day increased from 280 to 800 after the Omicron variant was verified.[5] This number hits 2000 on November 26, 2021, and broke through 10,000 on December 3, 2021.[6] In addition, tracing the source of COVID-19 cases revealed that B.1.1.529 had probably spread in western Europe before the first cases were detected in southern Africa.[7] B.1.1.529 variant was first reported to WHO on November 24, 2021. On the day after receiving the report, WHO designated it as VUM and named it as Omicron variant (B.1.1.529). Only 2 days later, WHO grouped the Omicron variant as VOC, which recorded the shortest interval period of reclassifying a variant from VUM to VOC and subsequently brought about great public concerns. A few days after the identification of Omicron in Africa, the variant has emerged in the other continents. At the time of this writing, Omicron has been reported in 34 countries and areas, including Botswana, Hong Kong, South Africa, Israel, Belgium, Italy, and the USA.[8] Apparently, the variant has not stopped spreading to other countries.

Characteristics of omicron variant

Since early 2020, three big waves of COVID-19 pandemic outbreaks have been recorded in South Africa **(Figure 1A).** Among them, two are caused by the Beta and Delta variants respectively **(Figure 1B).** The epidemiological data indicates that the percentage of infections associated with the Beta variant increased to ~50% of the total daily infections within approximately 100 days since its outbreak **(Figure 2)**. The infection percentage of the Delta variant, however, raised to ~80% during the same period of time, echoing higher transmissibility among people for Delta than for the Beta variant. In contrast, the percentage of Omicron infection reached ~90% within approximately 25 days in South Africa. The early doubling time of the Beta, Delta, and Omicron variants was calculated to be about 1.7, 1.5, and 1.2 days, respectively. These data shows that the Omicron variant is probably more infection potential than the Delta and Beta variants. It is also noteworthy that a recent retrospective study based on the population-wide epidemiological data in South Africa indicates an increased risk of SARS-CoV-2 reinfection associated with Omicron.[9] The possibility of a new wave of COVID-19 epidemic in South Africa and even around the world therefore should not be avoided.

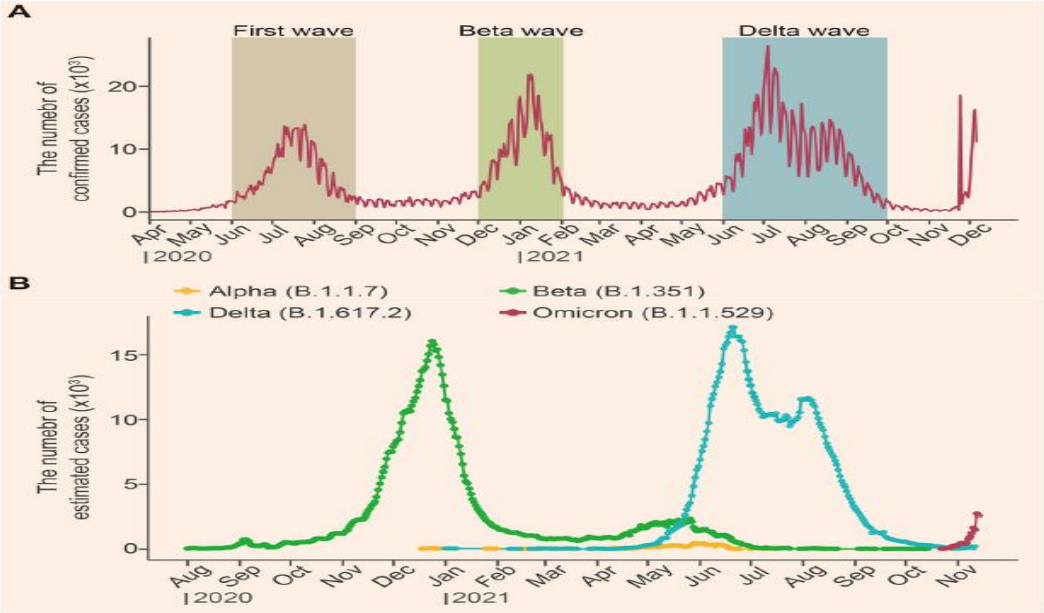

Figure 1: Waves of Coronavirus disease 2019 (COVID-19) pandemics recorded thus far in South Africa. (A) Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused three waves of epidemics in South Africa. The number of daily confirmed infection cases is plotted. (B) The number of estimated cases infected by the indicated variants of concern (VOCs) in South Africa.

Analysis of the genomic sequences of the Omicron variant has showed a high number of non-synonymous mutations, including several ones in spike that have been proved to be involved in disease severity, transmissibility, and immune escape. Overall, more than 60 substitutions/ deletions/insertions have been founded in the Omicron variant,[10] making Omicron a variant possessing the largest number of mutation sites of all SARS CoV- 2 variants characterized so far.

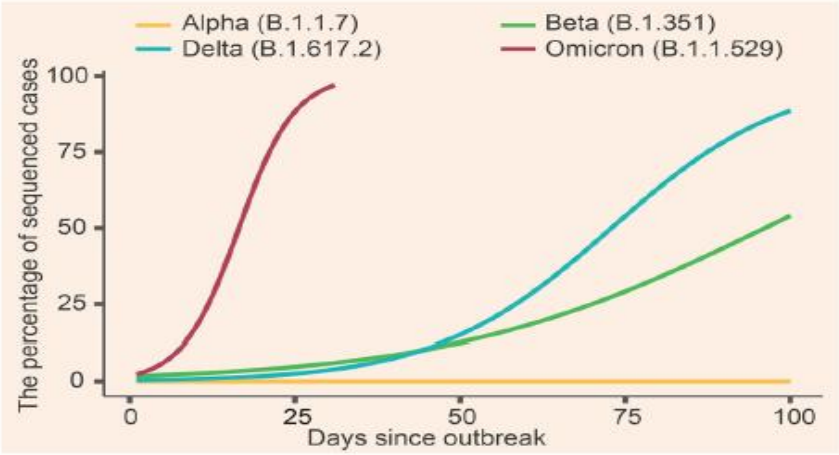

Figure 2: Omicron is spreading rapidly than other variants in South Africa.

It should also be noted that the spike receptor-binding domain (RBD) is the authentic virus entity that recognizes the ACE2 receptor to mediate virus entry.[11] While the currently predominant Delta variant only possesses the L452R and T478Kmutations in the RBD, 15 mutations have been accumulated in the RBD of the Omicron variant **(Figure 3)**. Among these substitutions, a bunch of residues is observed to locate nearby the bound ACE2 receptor. How these mutations would affect the receptor binding, however, remains to be investigated in the future. Whether or not and to what extent the Omicron variant can escape from immune recognition is another concern. It is notable that the spike RBD is the main site for neutralizing antibodies and that Omicron has accumulated 15 substitutions in the RBD region. It was noted that multiple antigenic sites have been characterized in RBD, featured with the RBS-A, RBS-B, RBS-C, the CR302, and the S309 sites.[12]

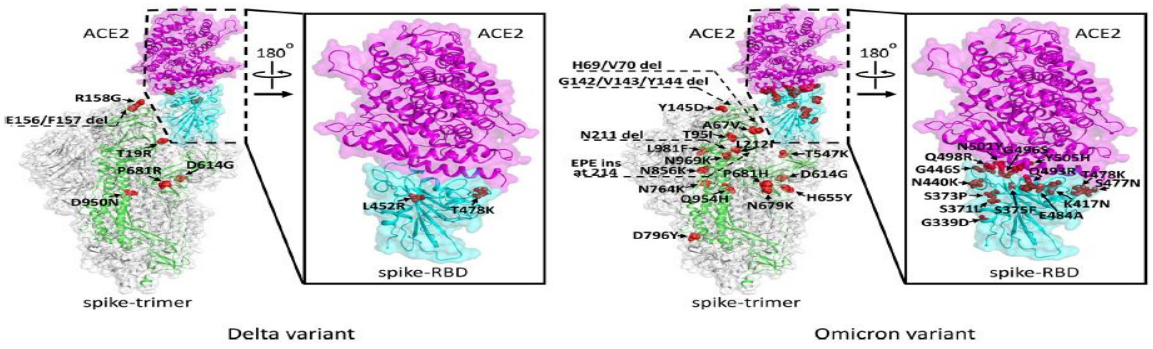

Figure 3: Landscape of spike mutations in the Delta (left) and Omicron (right) variants.

All the 15 mutations identified in Omicron spike RBD can be located to one or more of these antigenic sites, indicating potential resistance of Omicron to one or more of the monoclonal antibodies targeting these sites. As for the antibody treatment in clinical use, the cocktail consisting of LY-CoV555 (also known as Bamlanivimab) and LY-CoV016 (also known as Etesevimab) has been authorized for emergency use. Previous studies have revealed that the mutations at 484 and 417 positions of the spike are associated with immune evasion[13] and that both Beta and Gamma variants could escape the neutralization of LY-CoV555 (due to E484K) and LY-CoV016 (due to K417N/T).[14] Since the Omicron variant also contains E484A and K417N mutations, it is likely that Omicron would also resist these two antibodies.

Preventive measures to control the omicron variant

Development of variant oriented vaccines

It has been reported that the increased risk of SARS-CoV-2 reinfection is associated with the appearance of the Omicron variant in South Africa, showing that the Omicron variant may be associated with substantial capability to evade immunity from prior infection. Moreover, whether the current COVID-19 vaccines can provide protection against the Omicron variant attracts much attention. The most recent evidence showed that the current COVID-19 vaccines provided less immunity to the omicron variant than other VOCs.[15] Meanwhile, the sera from vaccinated individuals also had about 40 lower neutralizing ability against the Omicron variant compared to the wild-type SARS-CoV- 2.[16] These results indicates that the present COVID-19 vaccines might not be effective against the Omicron variant as other SARS-CoV-2 variants. More data about the effectiveness of current COVID-19 vaccines need to be further investigated in the future. Although the impact of the Omicron spike mutations on the effectiveness of currently available vaccines remains to be determined, it is well documented that vaccines developed based on wild-type SARS-CoV-2 are less effective in preventing variant infections. Previous study has shown that the vaccine based on the mutant spike would have a higher level of neutralizing antibodies against mutant viruses, but lower neutralizing antibodies against wild-type SARS-CoV-2.[17] These observations highlight the significance of developing variant-specific vaccines based on the mutated spike, especially towards the Omicron variant. Therefore, we are developing the specific vaccines against the SARS-CoV-2 Omicron variant based on the mutated spike of the Omicron variant. Alternatively, the vaccine candidates developed based on the other variants but containing one or more Omicron mutations might also be used to prevent the spread of Omicron infection and transmission. For example, some unofficial information indicates that Moderna has developed two multivalent vaccine candidates: candidate mRNA-1273.211 is believed to harbour several mutations observed in both the Omicron and Beta variants, andmRNA-1273.213 is believed to have included a certain number of mutations present in the Omicron, Beta and Delta variants.[18,19] The effectiveness of these candidate vaccines against the Omicron variant needs to be further investigation.

Determination of SARS-CoV-2 variant spread

At present, the detailed feature of the Omicron variant is unclear. In view of those spike mutations that are also observed in other VOCs, it is of particular concern that Omicron might have evolved with the capacity of easier spread among people and the ability to resist currently available vaccines. Such circumstance highlights the significance of maintaining present public health prevention measures, including wearing masks, frequent ventilation, keeping physical distance, and washing hands. These measures have been proved to be effective in preventing the transmission of other variants and should also be effective in dealing with the Omicron variant. In addition, early diagnosis and timely quarantine are key factors that can reduce virus transmission during a pandemic. There have been epidemiological evidence showing that the failure of PCR tests by targeting the spike gene is rising along with the increasing cases infected by Omicron. Thus,

improving diagnostic accuracy to enable timely isolation and treatment of diagnosed cases is also important to cut off the spread of the Omicron variant.

Third BNT162b2 Vaccination Neutralization of SARS-CoV-2 Omicron Infection

On November 26, 2021, the World Health Organization (WHO) named the B.1.1.529 (omicron) variant of SARS-CoV-2, first detected in South Africa, as a variant of concern. By November 29, 2021, three days after the announcement by the WHO, cases of infection with the omicron variant had already been detected in rest of the countries. Whether the BNT162b2 vaccine (Pfizer–BioNTech), which was previously shown to have 95% effectiveness against Covid-19 will effectively neutralize infection with the omicron variant is unclear. We compared neutralization of omicron-infected cells in serum samples obtained from participants who had received two doses of vaccine with neutralization in samples obtained from participants who had received three doses. Microneutralization assays with wild-type virus and B.1.351 (beta), B.1.617.2 (delta), and omicron variant isolates were determined with the use of serum samples obtained from two groups of 20 health care workers. One group comprised participants who had received two doses of the BNT162b2 vaccine (mean, 165.6 days since receipt of the second dose), and the second group comprised those who had received three vaccine doses (mean, 25 days since receipt of the third dose). Significance was assessed with the use of a Wilcoxon matched-pairs signedrank test. Receipt of three vaccine doses led to better neutralization of the wild-type virus and the three variants than receipt of two vaccine doses (Fig. 4). The geometric mean titers of the wildtype virus and the beta, delta, and omicron variants were 16.56, 1.27, 8.00, and 1.11, respectively, after receipt of the second vaccine dose and 891.4, 152.2, 430.5, and 107.6, respectively, after receipt of the third dose. A significantly lower neutralization efficiency of the BNT162b2 vaccine against all the tested variants of concern (beta, delta, and omicron) than against the wildtype virus was observed in samples obtained from participants who had received two doses than in those obtained from participants who had received three doses (Fig. 4B and 4D). The lower neutralization efficiency against the beta and omicron variants than against the wild-type virus was similar in samples obtained from participants who had received two doses and in those obtained from participants who had received three doses. The third dose of the BNT162b2 vaccine efficiently neutralized infection with the omicron variant (geometric mean titer, 1.11 after the second dose vs. 107.6 after the third dose) (Fig. 4A and 4C).

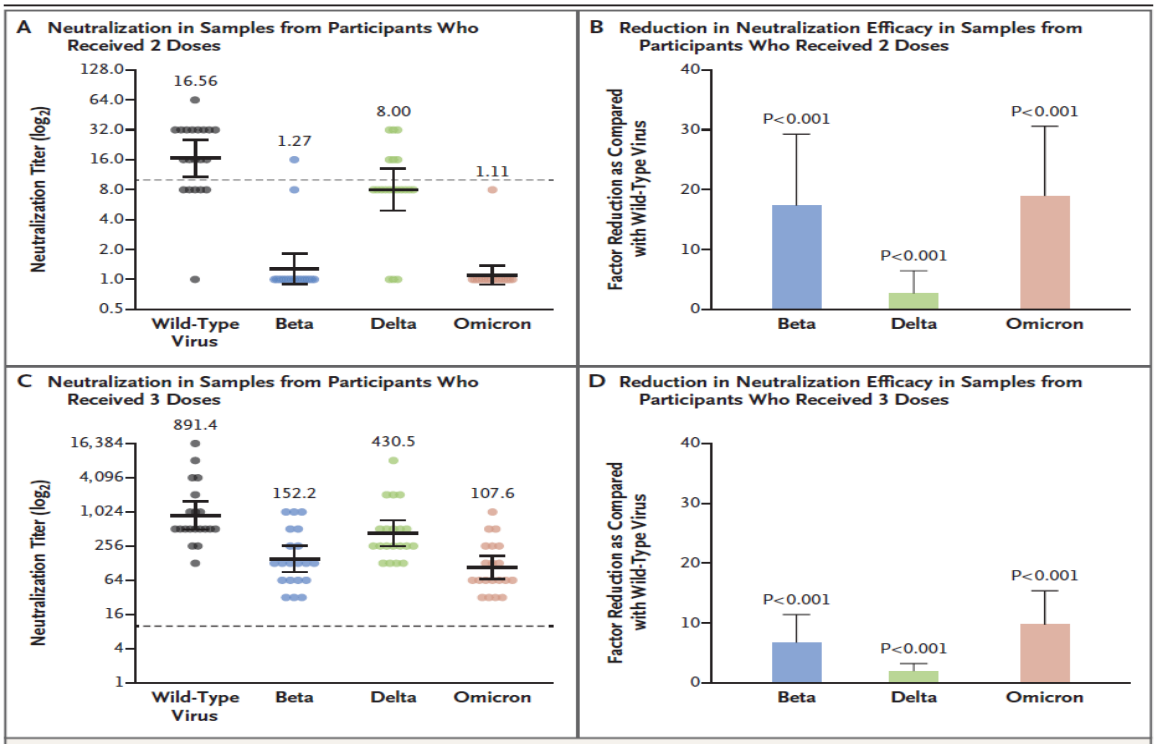

Figure 4: Neutralization Efficiency against Wild-Type Virus and the Beta, Delta, and Omicron Variants of Concern.

Serum samples were obtained from 20 front line healt workers who had received two doses of the BNT162b2 vaccine (Panels A and B) and from 20 who had received three doses (Panels C and D). Samples were tested by microneutralization against wild-type severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the B.1.351 (beta), B.1.617.2 (delta), and B.1.1.529 (omicron) variants of concern. Dashed lines in Panels A and C indicate the cutoff titer. Geometric mean titers (horizontal lines) with 95% confidence intervals (I bars) are presented, as well as the geometric mean titer value. Dots indicate individual serum samples. The factor reduction as compared with wildtype virus is shown for samples obtained from participants who had received two doses of vaccine (Panel B) and those obtained from participants who had received three doses (Panel D). For these analysis, the mean factor differences between wild-type SARS-CoV-2 and the variants of concern were calculated for each participant; the means of the individual values are shown here. Error bars in Panels B and D indicate the standard error.

The neutralization efficiency of the BNT162b2 vaccine against wild type SARSCoV- 2 and the beta, delta, and omicron variants of concern were analyzed. Limitations of the study include the small cohort tested and the fact that the test was only an in vitro assay. Nevertheless, they found low neutralization efficiency with two doses of the BNT162b2 vaccine against the wild-type virus and the delta variant, assessed more than 5 months after receipt of the second dose, and no neutralization efficiency against the omicron variant. The importance of a third vaccine dose is clear, owing to the higher neutralization efficiency (by a factor of 100) against the omicron variant after the third dose than after the second dose; however, even with three vaccine doses, neutralization against the omicron variant was lower (by a factor of 4) than that against the delta variant. The durability of the effect of the third dose of vaccine against Covid-19 is yet to be determined.

CONCLUSION:

With respect to Omicron emergence challenge, still it's an trending question regarding the origin, the immune-escape potential of the variant, and the transmission capacity. It is also not clear if new variants may be evolve on the basis of Omicron in the future. But there is no doubt that the Omicron variant will not be the last variant of SARS-CoV-2. The continuous emergence of new SARS-CoV-2 variants has made the control of the COVID-19 pandemic more challenging and at the same time complicated as well. With the help of various research, we have accumulated a lot of experiences and majors to deal with the novel coronavirus and we know what we need to do to stop the spread of virus variants. With global collaboration between all the countries and rapid data sharing, human society would definitely win the battle against COVID-19.

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