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LETTER TO THE EDITOR

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Omicron (B.1.1.529) variant of SARS-CoV-2: Concerns, challenges, and recent updates

Dear Editor,

A very huge surge in Omicron cases in the past few weeks and a massive increase of coronavirus disease (COVID-19) cases worldwide have altogether raised paramount concerns in scientific and medical communities, and created high fear and panic in the public across the globe. Extensive mutations in the genome of the Omicron variant have been implicated to facilitate evasion of the protective immunity in the vaccinated individuals and events of failures in monoclonal antibodies-based immunotherapies, thus potentially magnifying the aggravated risk of COVID-19. The continuous emergence of newer variants of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), mainly the Variants of Concerns (VoCs), are resulting in the consecutive waves of COVID-19 pandemic worldwide and potentially causing high morbidity and mortality owing to high surge in cases.[1–6] The recently emerged Omicron (B.1.1.529) variant, a highly mutated SARS-CoV-2 variant, classified as VOC by World Health Organization (WHO) on November 26, 2021, has now spread to nearly 150 countries and territories, owing to its very high transmissibility and infectivity.[7–11] Enhancing genomic sequencing facilities to confirm infection with variants on a larger proportion of COVID-19 cases could reveal more numbers of Omicron as well as Delta cases than reported as of now. Real-time spread of Omicron needs to be tracked with molecular data.[12] The variants such as Alpha, Delta, and Omicron have high transmissibility.[5,10] Soon after the emergence of the Omicron variant, a very rapid and high surge in COVID-19 cases on a daily basis is being observed worldwide with cumulative cases crossing the mark of 350 million confirmed cases and over 5.6 million deaths as of January 24, 2022. Notably, more than 3.5 million cases are being reported per day that is adding to an ever higher peak during the ongoing pandemic.[5,8,9,13,14]

The Omicron variant is found more contagious but less deadly than the Delta variant. The main clinical manifestations are those of a "mild infection" such as headache, body ache, muscles ache, cough, fever, generalized myalgia, and fatigue, therefore hospital admission is less likely but a higher transmission rate of Omicron will be a major concern.[9,15–19] Mutations in the receptor-binding domain (RBD) of the Omicron variant's spike (S) protein result in a stronger binding to the human ACE2 receptor, through which the virus gains entry into the cells of the body. The relatively effective reproduction number of this variant has been reported to be 3.19 (95% confidence interval 2.82–3.61) times greater than the Delta variant. Therefore, a rapid increase in Omicron cases is being witnessed across the globe immediately after its introduction to any country due to the considerable advantage of higher transmissibility and infectivity.[19–21]

More recently, some news has come up with regard to the possibility of a highly transmissible SARS-CoV-2 double variant (Delmicron), suspected to be created by the combination of the two existing VOCs (most deadly Delta and most mutated Omicron variant), and a double infection of flu virus with SARS-CoV-2 (COVID-19) (Flurona). Such news requires further explorative investigations and timely attention of researchers under the probable threats of future emergence of newer variants and double infections that may trigger a complicated, worrisome, and alarming situation amid the ongoing pandemic.[22–28] SARS-CoV-2 infections normally involve a single mutant strain, but two strains may also infect simultaneously, though such an event to happen is an extremely rare case. The new super-variant of SARS-CoV-2 would be created if the two existing variants infect someone at the same time. Delmicron is believed to be not a new variant but possibly seems to be a combination of basically twin viral spikes (S protein) and is being blamed in for a fresh surge of COVID-19 cases in North America, Europe and maybe spreading in other countries, however, such assumptions are yet not confirmed and need to be investigated in details to reach to any conclusion. Worldwide countries have earlier witnessed waves of COVID-19 pandemic due to SARS-CoV-2 emerging variants and mutants, and currently, both the Delta and Omicron variants are affecting several countries very speedily, resulting in an ever high surge in COVID-19 cases.[2,4–7,11] Hence, the scientists fear that these two variants (Delta and Omicron) and any possible combination of such double variant(s) might trigger a more dangerous situation in terms of COVID-19 pandemic tsunami across the globe. It may be possible that both the strains can swap genes and trigger a more dangerous variant.[24] Research conducted by Commonwealth Scientific and Industrial Research Organisation (CSIRO, Australia) has revealed that the variants containing both N501Y (Omicron) and P681R (Delta) mutations did not spread.[29] However, the study was conducted as of November 1, 2021, hence, more recent studies on genome sequences are required to understand such situations of concern in a better way.

Additionally, simultaneous infection of COVID-19 and flu has been reported more recently in a young pregnant woman from Israel and has been given the name "Flurona."[25–27] As per the report, the young woman was COVID-19 unvaccinated and the copresence of both the pathogens (Flu virus and SARS-CoV-2) was detected in her body. The simultaneous infection of COVID-19 and influenza A (H1N1) virus was also confirmed earlier in a 21-year-old woman in

Egypt.[30] Due to the simultaneous attack of two viruses, the body's immunity system may be compromised. As per WHO, a person may be infected by both the strains (COVID-19 and influenza) at the same time which could be catastrophic to the immune system.[31] Such simultaneous attacks of flu and COVID-19 may cause more respiratory failure and damage to other organs. As per CDC, COVID-19 and flu can attack simultaneously to the lungs and potentially cause pneumonia, and finally respiratory failure.[32] This may also cause cardiac injury, sepsis, and inflammation of the brain, heart, and (or) muscle tissues.[32] Due to the limited information available, it is not completely understood. The scientists are trying to find out more about the possibility of dual variants, a combination of two variants and what exactly does double infections mean, and their health concerns amid the pandemic.

Another variant IHU (B.1.640.2) having 46 mutations has been documented in France in mid-November 2021, which is now under surveillance. This variant was found in 12 people in the country and hasn't posed much of a threat yet.[28] However, it is highly recommended to understand its rate of infectivity and the risk of vaccine-induced immunity. The first IHU infected patient has a travel history to Cameroon.[33] This variant has not been identified in other countries yet. As per a recent study, fourteen amino acid substitutions with N501Y and E484K are located in the 'S' protein of the IHU variant. Both N501Y and E484K mutations were also seen earlier in Beta, Gamma, Theta, and Omicron variants.[34] This is another example of the unpredictability of the emergence of SARS-CoV-2 variants.

Despite developing few vaccine candidates and the progressive vaccine drives being carried out globally to vaccinate the mass population at the earliest for achieving herd immunity and desired protection from severe illness, the COVID-19 pandemic is flaring up due to emerging variants. Particularly, variants such as Delta and Omicron, both of which have high transmissibility and infectivity, and Omicron possessing higher immune evading properties, results in a reduction in vaccine-induced immunity with lowering efficacy of the available vaccines (Table 1). Omicron can also overpower the protection rendered by antibodies-based immunotherapies through escaping the neutralization potential of therapeutic monoclonal antibodies (mABs), therefore some mAbs currently available for use in clinics may lose efficacy and will not be useful in treating Omicron-infected patients (Table 1). These properties are causing larger breakthrough infections in vaccinated individuals, reinfection in recovered patients, immunotherapy-based treatment failures, and a consequent high surge in COVID-19 cases.[6,19,51–62] To counter immune escape of Omicron and rising fears in the presently evolving scenario of the ongoing pandemic with a very high increase in cases of this variant and COVID-19, researchers and vaccine manufacturers have emphasized adding up of booster vaccine dose in the progressive vaccine drives being carried out worldwide. Booster shots have been found to significantly boost achieving high neutralizing antibody titers, thus increasing the levels of protective immunity in vaccinated individuals for the long term against infection with SARS-CoV-2 and its variants, and ameliorate severe COVID-19 illness.[63–68] More research works are required to evaluate the impact of Omicron on the efficacy of existing vaccines as well as assessing the durability of protection rendered by booster shots under ages of Omicron and other SARS-CoV-2 variants. Additionally, challenges of vaccine hesitancy, achieving global equitable access of vaccines to all the countries, especially low-income countries, are needed to be addressed appropriately so as to enhance the proportion of vaccinated people across the globe.[69–71]

VanBlargan et al. have tested the anti-RBD mAbs which are in clinical use by AstraZeneca, Vir Biotechnology, Eli Lilly, Regeneron, and Celltrion for their ability to neutralize an infectious Omicron (B.1.1.529) isolate.[72] As per the study, most of the mAbs lost completely the neutralizing activity against Omicron in both Vero-hACE2-TMPRSS2 and Vero-TMPRSS2 cells. Ma et al. studied the infection features and immune escape efficiency of the highly mutated global dominant B.1.1.529 strain with the Omicron pseudovirus, wherein Omicron displayed slightly higher infectivity as compared to the Delta variant.[73] Moreover, Omicron also displayed reduced fusogenicity as compared to the original strain and the Delta variant in both BHK21-ACE2and Vero-E6 cells. Furthermore, the Wuhan convalescents' sera displayed a dramatic reduction of neutralization against Omicron (10.15-fold) than Delta (1.79-fold) as compared with the original strain (D614G). However, three vaccine shots considerably improved the convalescents' immunity against this B.1.1.529 strain as the sera neutralizing activity increased significantly after three shots of inactivated-vaccine. A very recent study also indicated that the Omicron variant is less sensitive to the booster shot.[74]

Furthermore, Gao et al.[75] have reported that SARS-CoV-2 spike-specific T cells (CD8+ and CD4+) induced by vaccination (BNT162b2) or prior infection provide extensive immune coverage against Omicron. The median relative frequencies was recorded for CD4+ (84% and 91%) and CD8+ (70% and 92%) T cells that cross-recognized B.1.1.529 in previously infected or vaccinated (BNT162b2) individuals.[75] Hirabara et al.[76] have discussed the characteristics of five SARS-CoV-2 VOCs (B.1.1.7, B.1.351, P.1, B.1.617.2, and B.1.1.529) with mutations in the S gene. They also highlighted the possible evasion from neutralizing antibodies generated through the previous infection, or vaccination, which may be helpful to reduce the impact of such new variants during the pandemic.[76]

Various repurposed drugs, antivirals, and immunotherapies have been recommended for use in emergency purposes to lessen the disease severity in COVID-19 patients, and many drugs and therapies are under development and clinical trials, however, the choice of drug and optimal treatment option is yet awaited.[77–79] Recently, the development of powerful oral antiviral drugs such as Molnupiravir (Lagevrio®) and Paxlovid (nirmatrelvir/ritonavir, PF-07321332 + ritonavir - Pfizer) have shown promising clinical results and raised new hopes of COVID-19 treatment. These oral drugs could protect from serious illness and reduce hospitalization, and thus can help to change the course of the ongoing pandemic that is presently under severe threats of Omicron, Delta, and other variants.[80–84]

Early and rapid detection, strengthening of genomic surveillance, tracking, and monitoring, and contact tracing of variant infected individuals need to be given due attention.[85] Enhancing COVID-19 vaccination campaigns and booster doses of vaccines, updating current vaccines, and developing highly effective newer vaccines to keep pace against the emergence of variants are the basic needs to counter Omicron.[86,87] Considering the potential benefit of booster vaccines, the third dose as a booster shot is necessarily required to facilitate vigorous neutralizing antibody responses against Omicron.[63,65,68] Of note, amidst the threats of highly evolving SARS-CoV-2 with its newer variants coming up continuously, the currently available vaccines are not being proven as silver bullets and neither mAbs are acting as magic bullets for prevention and treatment purposes. In such an adverse situation, newer strategies to develop next-generation mutation-proof SARS-CoV-2 vaccines and designing more effective and additional mAbs are required that would be more robust in countering highly mutated variants. Additionally, exploring more effective drugs and treatable options are the need of the hour.[77–79,88,89]

The airborne transmission and extensive environmental contamination associated with the Omicron variant have been demonstrated by Wong et al. (2021), which may pose a greater challenge.[90] To maximize the flow rate of air exhaust, increase in fresh air supply, air purifiers in corridors, quarantine camp with individual isolation unit and natural ventilation in the open area may

TABLE 1 Efficacy of vaccines and antibodies-based therapies against Delta and Omicron variants

Monoclonal antibody/natural infection/vaccination	Delta variant of concern (B1.617.1, B.1.617.2 and B.1.617.3)	Omicron variant of concern (B.1.1.529)
Anti-NTD and anti-RBD monoclonal antibodies (mAbs), bamlanivimab, Imdevimab), broadly neutralizing sarbecovirus mAbs, cocktails[35,36]	Negligible neutralization effect[35]	Some neutralization effect[36]
Non-RBD Abs[37]	Almost no neutralizing effect[37]	Almost no neutralizing effect
Convalescent sera[35]	Four to six-fold less effective neutralizing antibodies[35]	More than eight-fold reduction in neutralizing antibodies[38]
One-dose ChAdOx1 (Oxford/AstraZeneca)[35]	Almost no neutralizing effect[35]	Almost no neutralizing effect[39]
Two-doses of ChAdOx1 (Oxford/AstraZeneca) vaccine[35]	Considerable neutralization effect/protection[35]	Almost no neutralizing effect[39]
Two-dose of ChAdOx1 (Oxford/AstraZeneca) vaccinees[37]	Some neutralization effect[37,40]	Almost no neutralizing effect[39]
Two-dose of BNT162b2 (Pfizer/BioNTech) vaccinees and CoronaVac (Sinovac)[37,41,42]	Better neutralization effect as compared to ChAdOx1 vaccinees,[37] some neutralization effect,[41] can still cause breakthrough infections[41]	Some/no neutralization effect[42] More than 40-fold reduction in neutralizing antibodies[43]
One-dose Ad26.COV2.S vaccine (Johnson & Johnson–Janssen)[44]	Almost no neutralizing effect[44]	Almost no neutralizing effect[44]
2- dose of ChAdOx1 (Oxford/AstraZeneca), BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), NVX-CoV2373 vaccine (Novavax), other mRNA vaccines[45,46]	Asymptomatic and mild infections[45]	Some neutralization effect[44,47] More than eight-fold reduction in neutralizing antibodies[38] Only 17% protection against infection[46]
Booster dose after 6-months with mRNA-1273 (Moderna), and CoronaVac/PiCoVacc (Sinovac) and other mRNA based vaccines[45,48]	Considerable neutralization effect/protection[45]	Considerable neutralization effect/protection[44,47,48]
Infected people who later took a single dose of mRNA vaccination [39,45]	Considerable neutralization effect/protection[45]	Some neutralization effect[39,44]
BNT162b2 (Pfizer/BioNTech) vaccinees later infected with Delta variant[39,49]	Considerable neutralization effect/protection[49]	Some neutralization effect[39,44]
Infected and later completed 3-doses of mRNA vaccination[44]	Considerable neutralization effect/protection[44]	Considerable neutralization effect/protection[44]
Mix-and-match vaccines (Oxford (AZD1222), Pfizer (BNT162b2), Moderna (mRNA-1273) and Novavax (NVX-CoV2373), CoronaVac (DB15806), Janssen (JNJ-78436735), CanSino (AD5-nCOV))[50]	Potential for improved protection, pending further studies on adverse effects[50]	Need studies[50]

Abbreviations: mRNA, messenger RNA; RBD, receptor-binding domain.

be considered to counter the Omicron associated airborne infection. It's time again to wear face masks really tight, follow regular hand hygiene and recommended disinfection procedures, and take social distancing measures with seriousness, along with avoiding crowded places, gatherings, and mass events to avoid infection with Omicron. The emergence of newer and newer SARS-CoV-2 variants may pose a never-ending pandemic scenario, and to counter such a scenario the recommended COVID-19 prevention and control strategies are required to be implemented adequately and strictly.[91–94] These would facilitate limiting the spread of SARS-CoV-2 and its emerging variants to a minimum level and effectively control the COVID-19 pandemic in the coming time. Besides these, there is utmost necessity to formulate action plans and proactive control strategies immediately before the Omicron grips the world with its high transmission ability and may give rise to very huge surges in COVID-19 cases amid the ongoing pandemic along with other variants such as Delta. Lastly, formulating appropriate preparedness plans for the future to restrain the ongoing pandemic under the threats of continuously emerging variants and fears of any new super-variant is to be given high priority.

Mankind may be forced to live with COVID-19, therefore vaccination campaigns will need to continue, appropriate routine behavioral changes will become more and more vital for adopting safety measures and other necessary disease prevention and control measures as the "new normal" lifestyle of the modern world.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript. RKM and KD wrote the first draft with the inputs from AKS, RT, and MRI. RKM and KD updated, reviewed, and edited the manuscript. All the authors reviewed and approved the final submission.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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