

### Breakthrough Infections and Omicron Variant: Dealing with the Dilemma

About two years have elapsed since the first official SARS-CoV-2 infection was reported in Wuhan. The introduction of vaccines, along with efforts around masking and social distancing has raised the hopes that the SARS-Coronavirus-2 pandemic can be contained. However, the continuous emergence of new variants of the virus, breakthrough infections, and sustained vaccine hesitancy pose considerable challenges to our efforts towards ending the current pandemic. Since the beginning of the coronavirus disease-2019 (COVID-19) pandemic, the emergence and circulation of a large number of variants that may harbor one or more mutations have been reported. Some of these variants are designated as a 'Variant of Concern' or a 'Variant of Interest' due to shared attributes and characteristics that warrant public health attention. These variants may have possible effects on virulence, transmissibility, viral replication, reinfection etc.

The Omicron variant of SARS COV-2 was first identified in Botswana and South Africa and was reported to the World Health Organization (WHO) on 24th November 2021 and was convened by WHO as SARS-CoV-2 variant of concern (B.1.1.529) on 26 November 2021. SARS-CoV-2 has undergone over 50 genetic mutations including 15 mutations in the receptor-binding domain (RBD) of the viral spike protein which has led to the increased potential for transmissibility, immune escape, and infectivity of the omicron variant.<sup>1,2</sup> It is presently the most common variant rapidly replacing the Delta variant of the virus and is prevalent in nearly all countries.

The screening test by real-time PCR for detection of omicron variant for SARS-CoV-2 shows S gene dropout /target failure and detection of other targets such as ORF 1ab and N gene etc. as a marker indicating SARS-COV2 positive infection by Omicron variant which may be further confirmed by genetic sequencing.

Omicron has surprised the world by rapidly spreading and infecting the double-dose vaccinated individuals even when 60% of the world population has received at least one dose of COVID-19 vaccine and many countries are at the level of achieving a fair percentage of their population being fully vaccinated against COVID-19. Omicron has a definite growth advantage over the Delta variant, sustained transmissibility potential, and causes reinfections owing to its property of immune evasion.<sup>3,4</sup> These reinfections could also be due to antibody escape by the variant coupled with the waning of neutralizing antibodies over the three to six months that intervened between vaccination and omicron infection. Data released by Pfizer demonstrated that three doses of the Pfizer-BioNTech COVID-19 vaccine neutralize the Omicron variant while two doses show significantly reduced neutralization titers. But, as 80% of epitopes in the spike protein recognized by CD8+ T cells are not affected by the mutations in the Omicron variant, two doses may still induce protection against severe disease. In an *in vitro* study of live virus neutralization assay, omicron was able to escape neutralization by Pfizer mRNA vaccine (Pfizer-BioNTech) raising concern over the possible risk of reinfections with this variant.<sup>5</sup> Other studies have also reported low vaccine effectiveness against omicron infection, with only 57% effectiveness at preventing hospitalization following more than six months duration since completion of two-dose primary immunization. Another study showed reduced vaccine effectiveness of 70 % against hospital admission with Omicron.<sup>6</sup> The Lancet has reported the first documented report of symptomatic breakthrough infections with omicron variant in a group of 7 German visitors to South Africa in November 2021. All of them had received three doses of SARS-CoV-2 vaccines, including at least two doses of an mRNA vaccine. Infections were mild to moderate in all the individuals suggesting protection offered by the booster dose against severe disease and hospitalization by omicron variant. The individuals demonstrated high serum levels of neutralizing IgG levels as well as strong T cell responses.<sup>7</sup>

Even though breakthrough infections with Omicron variant may pose a low risk to millions of vaccinated individuals in terms of the severity of the disease, natural infection with the variant could be dangerous for the unvaccinated population. Millions of immunocompromised, elderly, and medically vulnerable people are still at higher-than-average risk. Surety of lifelong immunity with any of the current COVID vaccines was never promised. Instead, the crucial objective of vaccination is to prevent COVID-19 deaths. Due to the waning of immunity observed 6–9 months post-vaccination with primary series, there is definite usefulness of providing booster vaccines to the high-risk group individuals such as elderly, healthcare workers, and immunocompromised individuals for protection against severe disease and deaths with breakthrough infections. However, there is currently no evidence of the immediate need to provide booster doses to the entire population of the countries.

High-income countries are way ahead of low-income countries in COVID-19 vaccination coverage and globally, 3 billion people have still not received their first dose of the vaccine. These unvaccinated populations provide a good opportunity for the SARS-COV-2 virus to multiply, evolve and mutate further, which may even lead to the emergence of deadly variants and so it is these groups who will majorly shape and drive the course of the pandemic. Therefore, the focus of the countries should be on accelerating the vaccination coverage of its unvaccinated or additional booster doses to high-risk populations and not on offering additional doses to all the primary vaccinated individuals who are not at high risk.

The future of the pandemic will decide the need for the development and rollout of variant-specific SARS-COV-2 vaccines, depending upon the lethality of future variants, herd immunity of the population, and cost-effectiveness of the approach.

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