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The Omicron variant wave: Where are we now and what are the prospects?

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Abstract: The Omicron variant BA.2 is the dominant form of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak in many countries, including those that have already implemented the strictest quarantine mandates that effectively contained the spread of the previous variants. Although many individuals were partially or fully vaccinated, confirmed Omicron infections have far surpassed all other variants combined in just a couple of months since the Omicron variant emerged. The ChAdOx1-S (AstraZeneca), BNT162b2 (Pfizer-BioNTech), and mRNA-1273 (Moderna) vaccines offer protection against the severe illness of SARS-CoV-2 infection; however, these currently available vaccines are less effective in terms of preventing Omicron infections. As a result, a booster dose of BNT162b2 or mRNA-1273 is recommended for individuals >12 years old who had received their second dose of the approved vaccines for >5 months. Herein, we review the studies that assessed the clinical benefits of the booster dose of vaccines against Omicron infections. We also analyzed public data to address whether early booster vaccination effectively prevented the surge of the Omicron infections. Finally, we discuss the consideration of a fourth dose of vaccine as a way to prevent possible upcoming infections.

Keywords: BNT162b2; Booster-dose vaccine; mRNA-1273; Omicron variant; SARS-CoV-2

1. EMERGENCE OF THE OMICRON VARIANT

The emergence of the SARS-CoV-2 variant Omicron (B.1.1.529) was first reported to the World Health Organization in Southern Africa on November 24, 2021. Ever since the emergence of this variant, the world has been struggling to prevent the outbreak of this variant. The first known confirmed Omicron B.1.1.529 infection was from a specimen collected on November 9, 2021. In late November, cases of Omicron infection started to appear in Europe. At the beginning of December, the Omicron variant was detected in other parts of the world, including North and South America, Oceania, and Asia, and quickly became the dominant variant of the SARS-CoV-2 variant ever since.[1] The Omicron variant spread more easily than the earlier variants of SARS-CoV-2, including the Alpha and Delta variants, which, in some countries, directly led to travel bans to the areas affected by the Omicron variant. However, according to international statistics, the hospitalization rate, severe disease rate, and mortality rates of confirmed cases of Omicron variant infection are relatively low. Studies from South Africa indicated that patients infected with the Omicron variant were significantly less severe than those infected with the previous dominant variants, with lower hospital admission rates.[2]

2. CAN TWO BASAL SHOTS OF VACCINE PREVENT THE OMICRON PANDEMIC?

The Omicron virus first emerged in Gauteng province in South Africa and spread rapidly worldwide.[2] With >30 mutations in its spike antigen, concerns are raised regarding whether standard regimens of double vaccine administration, which are effective against the previous variants of the virus, will provide proper control of the spread of the Omicron infection. This concern was particularly relevant to the countries, including Taiwan, whose borders were protected against the encroaching infection since the outbreak of COVID-19. In this regard, studies conducted in other countries may provide pertinent information. Brazil was one of the countries most affected by COVID-19 between 2020 and 2021, with 30 502 501 cases and 663 816 deaths. Brazil adopted the strategy of being cautious about the quarantine measures of self-isolation and suspension of businesses. The vaccination program started in Brazil after most of the population was affected by COVID-19. A recent study showed that vaccine effectiveness in Brazil varied from 39.4% to 64.8% for a single dose of

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vaccine; however, it increased to 81.3%–89.7% after completion of a two-dose vaccination program.[3] A study conducted to assess the effectiveness of the Moderna mRNA-1273 vaccine against the Omicron variant showed that double vaccine administration elicited neutralization responses in children and adolescents 4 weeks after the second dose of a two-dose primary vaccination regimen with the mRNA-1273 vaccine but with less effectiveness in adults.[4] According to a large-scale statistics study in the United Kingdom, in patients with Omicron infection who had received the second dose, the vaccine efficacy was only 20%–30% after 10 weeks. The protective effect was completely lost after 20 weeks. This study recruited 886 774 participants infected with Omicron variants between November 27, 2021, and January 12, 2022. The vaccine effectiveness against the symptomatic disease was higher for the Delta variant than that for the omicron variant.[5] No noticeable effects against the Omicron variant were observed 20 weeks after the second vaccination dose.[5] Additionally, in a cohort of 35 768 individuals, one-third of whom were previously affected by SARS-CoV-2 infection in the United Kingdom, and showed that two doses of BNT162b2 vaccine administration were associated with higher short-term protection against COVID-19; however, this protective effect was significantly reduced after 6 months.[6] Therefore, two-dose vaccine administration seems to act favorably against Omicron infection; however, it cannot prevent the Omicron infection pandemic.

3. HOW SOLID IS THE CLINICAL EVIDENCE FOR THE COVID-19 BOOSTER DOSE TO EFFECTIVELY PROTECT SYMPTOMATIC ILLNESS FROM OMICRON VARIANT INFECTIONS?

The clinical value of the booster dose of the vaccine during the Omicron variant pandemic has been supported by several studies. As shown in a negative-test case-control study, the relative effectiveness against symptomatic COVID-19 increased from approximately 20% in patients receiving only a two-dose primary course of ChAdOx1-S (AstraZeneca) or BNT162b2 (Pfizer-BioNTech) vaccines to approximately 90% in patients with an additional booster dose of BNT162b2 or mRNA-1273 (Moderna) vaccine in all age groups. Booster vaccination also led to complete vaccine effectiveness of 94%–97% against Omicron infection-associated hospitalization or death, regardless of the primary vaccination course.[7] Another study involving a different population estimated that the effectiveness of the booster dose of the BNT162b2 vaccination was 93% for hospitalization, 92% for severe illness, and 81% for COVID-19-associated death.[8] Similar conclusions were also drawn from two other studies, which showed that patients receiving a third or booster dose of BNT162b2 or mRNA-1273 vaccine were less likely to develop severe SARS-CoV-2 infection compared to those receiving only two doses of vaccine.[9–11] Several studies have demonstrated that the Omicron variant is less sensitive to neutralization by patients' sera than other variants after two doses of mRNA-1273 vaccination. Furthermore, the neutralization potency of sera against the Omicron variant is higher in patients after a booster dose of the mRNA vaccination than in those without third-dose vaccines.[12–22] Collectively, these results highlight the importance of booster-dose vaccination using either homologous or heterogenous vaccines to provide sufficient protection against the Omicron variant.

4. WHETHER EARLY BOOSTER VACCINATION EFFECTIVELY PREVENTS THE OMICRON WAVE?

Although the clinical benefits of booster-dose vaccination against Omicron infections have been demonstrated, it is uncertain whether early booster vaccination effectively prevents the rapid surge in Omicron infection rate. Among Singapore, South Korea, Japan, and Hong Kong, which have similar socioeconomic and geographic conditions, Singapore had the highest booster vaccination rate, accounting for 25% of the total population, before the first appearance of the Omicron variant in South Africa on November 26, 2021. Singapore experienced the earliest Omicron infection outbreak, which began on January 20, 2022. As of April 29, 2022, Singapore also had the highest booster vaccination rate (approximately 67%) among these countries (South Korea, 57%; Japan, 52%; Hong Kong, 42%) (Figure). However, the percentage of confirmed cases in Singapore was 15% of the national population, similar to that of many other countries in the region. To date, data on the analysis of optimal vaccine coverage for blunt Omicron waves are limited. It is possible that timing, in addition to the vaccination coverage, correlates with the effectiveness of the booster dose of the vaccine.[23] Nonetheless, the fact that a booster vaccine is highly effective against severe illness and death proves its clinical value in preventing Omicron infections.

5. CAN WE BENEFIT FROM A FOURTH VACCINATION (SECOND BOOSTER-DOSE VACCINE)?

Since the waning effectiveness of the second vaccine warrants a booster-dose vaccination, the question is raised as to whether a fourth COVID-19 vaccine dose is inevitable before the end of the pandemic.[24] In this regard, two studies from Israel, which was the

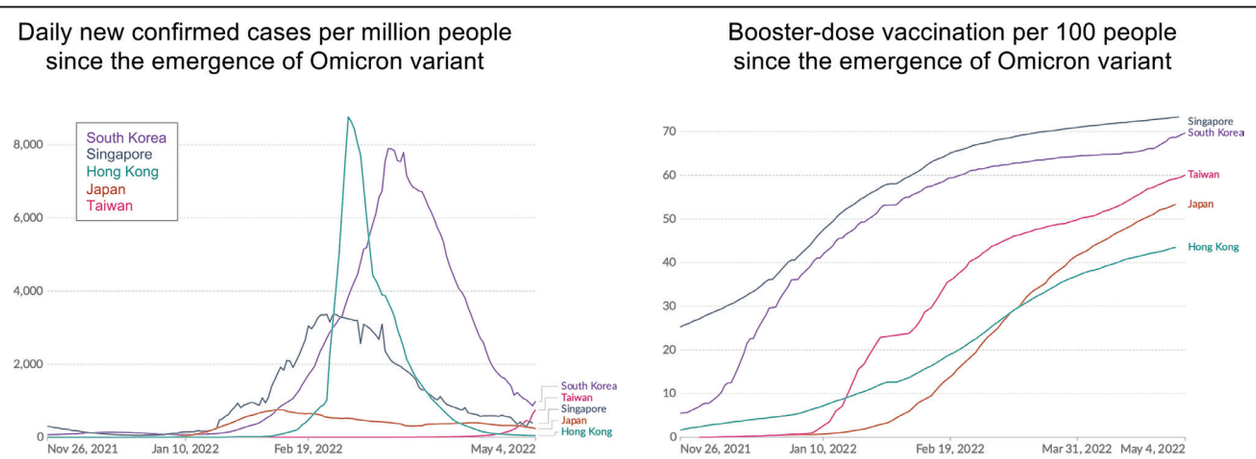

Fig. 1 Daily new confirmed cases per million people and booster-dose vaccination per 100 people since the emergence of the Omicron variant. The plots are acquired from the Our World in Data public database.

first country in the world to offer a third dose of COVID-19 vaccine in July 2021, reported that the fourth dose of mRNA vaccine following three doses of BNT162b2 vaccination effectively protected patients from severe symptomatic Omicron infections. The fourth vaccination restored antibody titers to the peak level after the third dose of vaccine.[24] Another study on patients with kidney transplantation showed that the antibody titer increased after the fourth dose of either the BNT162b2 or mRNA-1273 vaccine to approximately 143 BAU/mL, which is the level that conferred neutralization against some SARS-CoV-2 variants.[25] However, such an increase in the levels of neutralizing antibodies failed to meet the acceptable optimal cutoff values of 809 and 2208 BAU/mL for the Beta and Omicron variants, respectively. Accordingly, clinical evidence regarding the protection offered by the fourth dose of the vaccine is insufficient. Since there are no reports of severe complications following the fourth vaccination, elderly individuals with immunosuppression or in need of long-term care may still benefit from the fourth dose of the mRNA vaccine.

6. FUTURE PROSPECTS: WHAT CAN BE OUR STRATEGY FOR OVERCOMING THE CHALLENGE OF THE OMICRON VARIANT?

Although vaccines against SARS-CoV-2 were developed before the emergence of Omicron, this variant continues to spread rapidly in many countries, including China and Hong Kong, even though these countries have implemented the strictest quarantine mandates. While the development of Omicron-specific vaccines is underway, the imminent outbreak demands a critical review of current measures. COVID-19 vaccination protects against severe illness from the Omicron variant; however, neutralizing antibodies wane over time, even after a booster dose of the mRNA vaccine. From the review of available data, the timing of the booster dose may play a more critical role than the coverage rate in slowing the spread of the Omicron variant. Therefore, a prospective strategy for Taiwan, where there is high community infectivity at the moment, is to administer a third dose of vaccination to individuals who received two doses of the vaccine and a fourth dose of the vaccine to at-risk older adults or patients with chronic diseases.

In conclusion, the Omicron variant of SARS-CoV-2 is significantly distinct from the previous variants. As a result, while high vaccination coverage remains important in controlling the pandemic, other strategies to deal with the Omicron infection outbreak should be planned. Regardless of the debate on whether strict quarantine mandates work for containing the Omicron variant, it is vital to prevent the healthcare system from being overwhelmed by nonstratified patients with mild and severe disease progression. All citizens should be made aware of the benefits of COVID-19 vaccination. Hopefully, we will be rushed by the Omicron infection outbreak to sufficient immunity through vaccination or asymptomatic infection and move toward the end of the COVID-19 pandemic.

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