Brief Communication

Omicron surge and the future of COVID-19 vaccinations

Erlina Burhan,[1] Rizky Abi Rachmadi[2]

Check for updates

pISSN: 0853-1773 • eISSN: 2252-8083
https://doi.org/10.13181/mji.bc.226066
Med J Indones. 2022;31:80–4

Received: January 31, 2022
Accepted: April 07, 2022

Authors' affiliations:
[1]Department of Pulmonology and Respirology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia,
[2]Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Corresponding author:
Rizky Abi Rachmadi
Faculty of Medicine, Universitas Indonesia, Jalan Salemba Raya No. 6, Kenari, Senen, Central Jakarta 10430, Jakarta, Indonesia
Tel/Fax: +62-21-3160493
E-mail: rizkyabirachmadi@gmail.com

ABSTRACT
The global surge of Omicron has caused significant concern. Omicron has caused new wave of infections in nations with adequate vaccine coverage. Omicron has around 30 mutations that are similar to the previous variant of concerns, possibly decreasing vaccine effectiveness (VE). Hence, the emergence of Omicron is predicted to be a significant public health challenge and may alter the future of COVID-19 vaccinations. Furthermore, other issues may affect vaccine policy in the future such as the never-ending vaccine inequity, waning immunity of current COVID-19 vaccines, decreasing VE against new emerging strains, and new findings regarding hybrid immunity. This literature review aimed to explore the possible steps forward using the most updated knowledge on COVID-19 vaccines and Omicron.

KEYWORDS COVID-19 vaccine, Omicron, SARS-CoV-2 vaccine

Omicron was first detected in South Africa on November 21st, 2021, with new waves of infection seen throughout the world.[1] Omicron has around 30 mutations that are similarly found in the Alpha, Beta, and Delta strains.[1] In addition to forming new waves in countries severely impacted by vaccine inequity such as the African nations, it is interesting to note that Omicron has also been spread to nations with good vaccine coverage, such as the UK, Germany, the US, Singapore, and many other nations. As of March 2022, Omicron BA.1 has been detected in 130 countries. Meanwhile, Omicron BA.2 has been detected in 57 countries by the end of January.[2]

Vaccination has been one of the major solutions in curbing this pandemic. Hence, it is logical to deduce that decreased vaccine effectiveness (VE) may present a significant public health problem in the future, especially when Omicron has made new waves of infections throughout the world, even in a nation with adequate vaccine coverage. This is a serious concern that may be caused by immune escape or/and waning immunity. This literature review aimed to explore the possible steps ahead in controlling this pandemic after the spread of Omicron, considering the possibilities of immune escape, waning immunity, and booster vaccinations.[1]

Vaccine protection against the Alpha, Beta, and Delta variants

A pre-printed systematic review compiled data from seven randomized controlled trials, 10 cohort studies, and 16 case-control studies researching live neutralization assays of eight coronavirus disease 2019 (COVID-19) vaccines (mRNA-1273, BNT162b2, ChAdOx1, Ad26.COV2.S, NVX-CoV2373, BBV152, CoronaVac, and BBIBP-CorV). A significant antibody neutralization escape was found in the Alpha, Beta, Gamma, and Delta variants with an average reduction of 1.4 fold, 4.1 fold,

Copyright @ 2022 Authors. This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original author and source are properly cited. For commercial use of this work, please see our terms at https://mji.ui.ac.id/journal/index.php/mji/copyright.

1.8 fold, and 3.2 fold, respectively. These findings are consistent with a decrease in VE against the emerging variants, compared with the original strain.[3]

Literature has shown significantly waning antibodies against COVID-19. In Israel, after 6 months of vaccination with BNT162b2, rapid decrease in IgG titers and neutralization antibodies were found in the first few months, continuing with a relatively consistent decrease afterward. This is a different finding compared to many published works regarding measles, mumps, and rubella vaccines, which observed a slight decrease of neutralization antibodies of 5–10% per year. Neutralization antibodies work by preventing virion attachment to the host cell.[4] Even though many studies have suggested that neutralization antibodies correlate with protection, the complete immune model has not yet been described as the procedure is complex.[5] It is important to note that antibodies are not the only component of the humoral immune system. The exploration of T-cell and B-cell immunity remains scarce due to the duration of the pandemic. In Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus (SARS-CoV), T-cell immunity was observed to last for 10–17 years. However, it is still unknown whether T-cell immunity may give efficient protection without antibodies.[4]

The efficacy of vaccines against the Alpha variants ranges from 70.4–85.6% for ChAdOx1 and NVX-CoV2373. A systematic review concluded that two doses of any COVID-19 vaccine would give adequate protection against the Alpha variant. The currently available vaccines provide greater efficacy against the Alpha variant, compared with the Delta variant.[6] This may explain the mutations that occurred in the Alpha variant, which has minimal effect in neutralizing antibody activities, as found in studies using sera of individuals vaccinated with BNT162b2 and mRNA-1273.[7] The Beta variant significantly decreased antibody neutralization activity. B.1.351 was found 6.5 fold more resistant to neutralization by sera from the population that was vaccinated with BNT162b2. In addition, antibody responses and memory B cells activity were decreased against COVID-19 in individuals vaccinated with mRNA-1273 and BNT162b2. This is attributed to the K417N and E484K mutations.[7]

A decrease in neutralization activity was also seen against the Delta variant. A large cohort of 8,690,825 vaccinated adults in New York City observed decreasing VE against COVID-19 from May to August 2021, when the Delta variant predominated.[8] Sharp declines in VE were reported since the Delta variant became the predominant strain in June 2021, falling from 91% to 66%.[6] A significant waning immunity of ChAdOx1 was observed in retrospective studies in Brazil and Scotland in the period when the Delta variant was the predominant strain. The rate ratio of COVID-19 infection increased to 5.43 in Scotland and 4.71 in Brazil at 18–19 weeks after the second dose of ChAdOx1. VE against COVID infection of ChAdOx1 in Scotland and Brazil dropped from 83.7% to 63.7% and from 86.4% to 42.2%, respectively, at 18–19 weeks after the second dose.[9]

Real-world data on COVID-19 vaccinations have consistently presented short-term protection against severe disease despite emerging variants. A recent meta-analysis on the real-world effectiveness of COVID-19 vaccines confirmed the short-term protection conferred by the vaccines against COVID-19 infection, severe disease, and COVD-19-related death. From 51 records on BNT162b2, ChAdOx1, CoronaVac and mRNA-1273 vaccine, and Ad26.COV2.S, pooled VE of 89.1% against COVID-19 infection, 97.2% against hospitalization, 97.4% against intensive care unit admission, and 99.0% from COVID-19-related death were found. However, the follow-up period was not feasible to research on long-term protection as most of the data were taken at <6 weeks after the second dose.[10] VE against COVID-19 infection of the Delta variant in the UK rapidly increased in the early weeks after administrating the second dose of BNT162b2 or ChAdOx1, then significantly decreased to 44.3% and 66.3%, respectively, after 20 weeks. The decrease was even greater in the elderly population. The decrease in VE was also observed against hospitalization but to a lesser extent. VE against hospitalization by the Delta variant was 80% and 91.7% for the ChAdOx1 and BNT162b2, respectively, at 20 weeks or more after the second dose.[11] The protection against COVID-19 infection may have significantly waned as time progresses. However, VE remains durable in protecting against severe disease, hospitalization, and COVID-19-related death from the Alpha, Beta, and Delta variants.

Vaccine protection against Omicron

The rapid spread of Omicron, including in nations with good vaccine coverage, indicates that Omicron is potentially more transmissible than the ancestral strain and previous strains and has greater immune escape potential. Preprint studies in South Africa,

the UK, and Scotland have shown unanimous results that Omicron is more transmissible but less severe than the Delta variant. Omicron has been associated with an increased risk of reinfection by 5.4 times.[2] By comparing the presence of S-genes, a preprint study estimated that Omicron has a reduced hospitalization risk of 67%, compared with the Delta variant.[12] The reason behind the decreased severity may be caused by the predilection of Omicron to infect the upper respiratory airways, compared with the Delta variant that more often targets the lower respiratory airways.[2]

A similar preprint study in South Africa found that S-gene positive infections are 80% less likely to be hospitalized, compared with S-gene negative infections.[13] These preliminary results indicate an early picture that Omicron may be more transmissible than the previous variants but less likely to cause severe disease. It is important to note that this may be caused by natural immunity caused by previous COVID-19 infection or completing two doses of vaccination.[14]

A preliminary study in South Africa compared the VE of BNT162b2 against COVID-19 in two different periods: the Omicron surge from the November 15th to December 17th and the pre-Omicron surge from September 1st to October 30th. The Omicron period observed a fall in VE to 70%, compared with the pre-Omicron period where VE was 93%.[15] Another South African study observed 41-fold lower neutralization antibodies against Omicron in patients vaccinated with BNT162b2, compared with the ancestral COVID strain. The UK's Com-COV2 study observed significantly reduced neutralization antibodies against Omicron in patients who received two doses of BNT162b2 or ChAdOx1.[16] In addition, T-cell capacity against Omicron seems to decrease, compared with the previous strains.[17] Studies of longer duration should be conducted to explore the Omicron's immunologic potential accurately.

Despite the reduced neutralization antibodies, cellular immunity induced by COVID-19 vaccines is conserved. Spike-specific CD8+ and CD4 T cells in 47 individuals who received the Ad26.COV2.S and BNT162b2 were durable and cross-reactive against the Delta variant and Omicron. Around 82–84% of the CD8+ T cells were cross-reactive against Omicron. In contrast, neutralizing antibodies increased rapidly in the first month and declined in the eighth month after receiving Ad26.COV2.S and BNT162b2. There were also minimal cross-reactive neutralizing antibodies.[18] The durability of cellular immunity against viral infections and post-vaccination is well documented and should be relevant against Omicron. This indicates that COVID-19 vaccinations elicit protection against severe disease despite rapidly decreasing neutralizing antibodies.[18]

VE against infection in Omicron significantly waned. Early data at 15 weeks after the second dose of BNT162b2 in the UK showed that VE against COVID-19 infection dropped to 35%, and a booster with BNT162b2 increased VE against COVID-19 infection to over 70%. This indicates that protection against infection is severely decreased against Omicron infection. However, the protection against severe disease and death remains high. Two doses of BNT162b2 and ChAdOx1 give protection against hospitalization against in Omicron cases at 63% and 74%.[19]

Are boosters required?

Boosters have been free and available for Indonesians since January 12th, 2022. The Indonesian Ministry of Health has announced the use of BNT162b2, mRNA-1273, ChAdOx1, and Sinovac vaccines as boosters. The Ministry of Health and National Agency of Food and Drug Control (*Badan Pengawas Obat dan Makanan* [BPOM]) in Indonesia have approved the use of half-dose booster and unmatched booster vaccines as an effort to curb the pandemic in Indonesia. Citizens who had primary vaccination with Sinovac may have a half-dose of BNT162b2 or ChAdOx1 as the booster, while citizens who had primary vaccination with ChAdOx1 may have a half-dose of mRNA-1273 as the booster.[20] The Omicron surge in Indonesia occurred when large proportions of the population were already vaccinated. This indicates that waning immunity might be one of the factors that led to the emergence of a new wave of COVID-19 infection in Indonesia and other nations.

The efficacy and effectiveness of the COVID-19 vaccine booster remain debated. In Israel, the number of infections and severe diseases was substantially less in the boosted group, compared with the unboosted group in people of over 60 years old.[21] The addition of boosters to the primary vaccinations indicates increased protection against all COVID-19 variants, as well as potentially against Omicron. However, the magnitude of this impact and the durability of the newfound protection remains unknown because the defined immunological mechanism of protection against COVID-19 has not yet been found.[17]

Research with data of over 44,000 subjects observed the administration of the third dose of

BNT162b2 in 6 months after the second dose. Protection against COVID-19 decreased from 96.2% to 83.7% after 6 months. After the third dose was administered, protection against COVID-19 was enhanced by 10%.[16] Additional vaccine doses correlate with increased protection against all variants; however, quantifying the magnitude and length of protection from these boosters remains an issue.[1] This enhanced protection is beneficial for the recipients. However, we need to look back to the public health goals of vaccine booster administrations. A choice should be made whether enhancing the immunity of the fully vaccinated population or preventing and reducing severe disease and mortality in the unvaccinated nations.[17] It is a well-documented concern that new variants will keep emerging if vaccine inequity persists.[22]

Is COVID-19 super immunity real?

From recent observations, the magnitude, breadth, and cross-reactivity of immune response elicited by vaccination and natural infection from COVID-19 is different. A recent cohort study in Qatar of over 1.5 million vaccinated individuals with BNT162b2 (BioNTech) and mRNA-1273 obtained a statistically significant decreased risk of breakthrough infections in individuals with prior natural infection to COVID-19.[23] In another study of 30 consecutive patients with autoimmune rheumatic disease, greater antibody titer against spike proteins and greater neutralization capacity were observed in patients with prior COVID-19 infection and a single dose of ChAdOx1, compared with patients with two doses of ChAdOx1 without prior infection.[24]

In theory, this concept is called hybrid immunity. Individuals previously infected with COVID-19 elicited antibody response with greater cross-reactivity to various mutant spikes and greater durability, compared with the immune response purely elicited by vaccination. It seems that natural infection presents antigen to the human body with a different mechanism, compared with vaccination. This immunologic mechanism may change the perspective on booster vaccinations, and the way we prime our immune system against future emerging variants.[25] Furthermore, a recent study observed serum-titers in 104 individuals with breakthrough infections, compared with the prior infected plus vaccinated group and the booster plus uninfected group. It was found that these three groups had similar robust neutralizing antibodies with nearly equal breadth and magnitude. This demonstrates that increased exposure to the SARS-CoV-2 antigen, whether naturally or via vaccination, will increase the breadth and the quality of neutralizing antibodies against COVID-19.[26] This indicates that booster vaccination can offer additional protection. One of the mechanisms is increasing the quality of the humoral immune response. As the pandemic progresses, the decreased mortality rates of Omicron around the world may be due to hybrid immunity, as a larger proportion of the population have been vaccinated more than two times and may have been infected with COVID-19 at least once.

In conclusion, the main goal of vaccination where supply is limited is to prevent severe disease and mortality. Secondly, it is aimed to decrease the social, economic, and health burden of the infection and reduce transmission.[1] Despite the decreased VE against COVID-19 infection, VE against severe disease and mortality remains high for all variants. Hence, the main public health goal is presently achieved amidst the rapid growth of Omicron.

It is recommended that booster vaccinations be used as necessary by prioritizing on the susceptible population such as the elderly, immunocompromised, and healthcare workers. The administration of booster doses would increase the recipient's exposure to the COVID-19 antigen, which should increase the quality of humoral immune response against COVID-19 and protection against infection, severe disease, and COVID-19-related death. Furthermore, vaccination and booster administration should be accompanied by public health interventions such as wearing masks, maintaining distance, and limiting travel options between nations when necessary.

Conflict of Interest
The authors affirm no conflict of interest in this study.

Acknowledgment
None.

Funding Sources
None.

REFERENCES

1. Center for Disease Control and Prevention. Potential rapid increase of Omicron variant infections in the United States. Center for Disease Control and Prevention; 2021.
2. Mahase E. Covid-19: what do we know about Omicron sublineages? BMJ. 2022;376:0358.
3. Zeng B, Gao L, Zhou Q, Yu K, Sun F. Effectiveness of COVID-19

vaccines against SARS-CoV-2 variants of concern: a systematic review and meta-analysis [Internet]. medRxiv [Preprint]. 2021. [posted 2021 Sep 26; cited 2022 Apr 5]. Available from: https://doi.org/10.1101/2021.09.23.21264048.
4. Hamady A, Lee J, Loboda ZA. Waning antibody responses in COVID-19: what can we learn from the analysis of other coronaviruses? Infection. 2022;50(1):11–25.
5. Levin EG, Lustig Y, Cohen C, Fluss R, Indenbaum V, Amit S, et al. Waning immune humoral response to BNT162b2 covid-19 vaccine over 6 months. N Engl J Med. 2021;385(24):e84.
6. Hayawi K, Shahriar S, Serhani MA, Alashwal H, Masud MM. Vaccine versus variants (3Vs): are the COVID-19 vaccines effective against the variants? A systematic review. Vaccines. 2021;9(11):1305.
7. Tregoning JS, Flight KE, Higham SL, Wang Z, Pierce BF. Progress of the COVID-19 vaccine effort: viruses, vaccines and variants versus efficacy, effectiveness and escape. Nat Rev Immunol. 2021;21(10):626–36.
8. Rosenberg ES, Dorabawila V, Easton D, Bauer UE, Kumar J, Hoen R, et al. Covid-19 vaccine effectiveness in New York State. N Engl J Med. 2022;386(2):116–27.
9. Leung K, Wu JT. Managing waning vaccine protection against SARS-CoV-2 variants. Lancet. 2022;399(10319):2–3.
10. Zheng C, Shao W, Chen X, Zhang B, Wang G, Zhang W. Real-world effectiveness of COVID-19 vaccines: a literature review and meta-analysis. Int J Infect Dis. 2022;114:252–60.
11. Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, et al. Duration of protection against mild and severe disease by covid-19 vaccines. N Engl J Med. 2022;386(4):340–50.
12. Sheikh A, Kerr S, Woolhouse M, Mcmenamin J, Robertson C. Severity of Omicron variant of concern and vaccine effectiveness against symptomatic disease: national cohort with nested test negative design study in Scotland [Internet]. The University of Edindurgh. [Preprint]. 2021. Available from: https://www.research.ed.ac.uk/en/publications/severity-of-omicron-variant-of-concern-and-vaccine-effectiveness.
13. Wolter N, Jassat W, Walaza S, Welch R, Moultrie H, Groome M, et al. Early assessment of the clinical severity of the SARS-CoV-2 Omicron variant in South Africa: a data linkage study. Lancet. 2022;399(10323):437–46.
14. Christie B. Covid-19: early studies give hope Omicron is milder than other variants. BMJ. 2021;375:n3144.
15. Collie S, Champion J, Moultrie H, Bekker LG, Gray G. Effectiveness of BNT162b2 vaccine against Omicron variant in South Africa. N Engl J Med. 2022;386(5):494–6.
16. Mahase E. Covid-19: Omicron and the need for boosters. BMJ. 2021;375:n3079.
17. Khan NA, Al-Thani H, El-Menyar A. The emergence of new SARS-CoV-2 variant (Omicron) and increasing calls for COVID-19 vaccine boosters-The debate continues. Travel Med Infect Dis. 2022;45:102246.
18. Liu J, Chandrashekar A, Sellers D, Barrett J, Jacob-Dolan C, Lifton M, et al. Vaccines elicit highly conserved cellular immunity to SARS-CoV-2 omicron. Nature. 2022;603:493–6.
19. Hart JD, Chokephaibulkit K, Mayxay M, Ong-Lim ALT, Saketa ST, Russell FM. COVID-19 vaccine boosters in the Asia-Pacific region in the context of Omicron. Lancet Reg Health West Pac. 2022:100404.
20. Putri SA. Mix-and-match, which covid-19 booster shot should I get? [Internet]. Jakarta's COVID-19 Response Team. 2022; [cited 2022 Mar 13]. Available from: https://corona.jakarta.go.id/en/artikel/cara-memilih-vaksin-booster-yang-tepat.
21. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Alroy-Preis S, et al. Protection against covid-19 by BNT162b2 booster across age groups. N Engl J Med. 2021;385(26):2421–30.
22. Rae M. Omicron: a failure to act with a global focus will continue the proliferation of new variants of covid-19. BMJ. 2021;375:n3095.
23. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, Yassine HM, Benslimane FM, Al Khatib HA, et al. Association of prior SARS-CoV-2 infection with risk of breakthrough infection following mRNA vaccination in Qatar. JAMA. 2021;326(19):1930–9.
24. Shenoy P, Ahmed S, Paul A, Cherian S, Umesh R, Shenoy V, et al. Hybrid immunity versus vaccine-induced immunity against SARS-CoV-2 in patients with autoimmune rheumatic diseases. Lancet Rheumatol. 2022;4(2):e80–2.
25. Callaway E. COVID super-immunity: one of the pandemic's great puzzles. Nature. 2021;598(7881):393–4.
26. Bates TA, McBride SK, Leier HC, Guzman G, Lyski ZL, Schoen D, et al. Vaccination before or after SARS-CoV-2 infection leads to robust humoral response and antibodies that effectively neutralize variants. Sci Immunol. 2022;7(68):eabn8014.