
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

# Omicron-adapted vaccines might require longer follow-up to reveal true benefits

Endless SARS-CoV-2 omicron subvariants with drifting antigens highlight the importance of the neutralisation breadth of antibodies that confer protection to current and future SARS-CoV-2 variants.[1] Due to the metabolic cost, natural expansion of neutralisation breadth is time-limited and might be saturated by repeated antigen exposures.[2,3] Current vaccination strategies thus rely on artificial expansion of neutralisation breadth using variant antigens (eg, the upcoming bivalent Wuhan-Hu-1-omicron BA.5 vaccine).

Intriguingly, data on the bivalent Wuhan-Hu-1-omicron BA.1 vaccine mRNA-1273.214 showed a less than two-times increase in neutralising antibody titres against omicron BA.1, BA.4, and BA.5 subvariants compared with the Wuhan-Hu-1-only mRNA-1273 vaccine, both administered as a second booster dose.[4] Such a marginal advantage over existing vaccines is disappointing when omicron-adapted vaccines are hoped to effectively block transmission. However, we reason that the short follow-up time of 29 days might overlook later benefits of omicron-adapted vaccines.

Durability of antibody responses after vaccination or infection is limited by the lifespan of antibody-secreting cells. Meanwhile, the affinity maturation process selects B cells with a higher and broader affinity to the exposed antigen, which partly compensates the loss of antibody-secreting cells in convalescing or vaccinated individuals.[3,5] When these individuals are exposed to omicron BA.1 antigens, as in the mRNA-1273.214 study, neutralising antibodies would initially be secreted by cells derived from existing Wuhan-Hu-1-trained B cells with suboptimal affinity to BA.1 antigens.[6] The affinity maturation process would more efficiently select clones with optimal affinity to BA.1 and other subvariants from these BA.1-neutralising cells rather than from the pre-boosted Wuhan-Hu-1-trained pool (appendix p2).[7] This prolonged process was evident in breakthrough infections and a bivalent beta vaccine study in primates, with both showing increased neutralisation breadth 60 days after exposure.[8,9] By contrast, omicron neutralisation after Wuhan-Hu-1 booster vaccination would rely on less efficient affinity maturation of the Wuhan-Hu-1-trained pool.[5] Therefore, longer follow-up might reveal a larger difference in omicron neutralisation titres between omicron-adapted and Wuhan-Hu-1 booster recipients.

Omicron-adapted booster vaccination might extend the duration of immune protection by compensating immune decay. A previous study showed that, although antibody levels gradually declined after infection, neutralisation titres against Wuhan-Hu-1 and variants remained stable up to 1-year after infection thanks to the compensatory increase in neutralisation potency and breadth.[10] A longer affinity maturation process since first exposure in Wuhan-Hu-1 booster recipients might also contribute to more durable neutralisation activity against omicron subvariants than in primary vaccination recipients.[11] We expect more long-term than immediate benefits after omicron-adapted booster vaccination, which, given sufficient time, might better protect against current and emerging omicron subvariants than Wuhan-Hu-1 boosters.

We declare no competing interests.



*Lu Tang, Ruihua Zhang, Miao Cui, *Peng Hong*

**peng.hong@downstate.edu**

Department of Research, The Seventh Affiliated Hospital, Sun Yat-sen University School of Medicine, Shenzhen, China (LT, PH); Immunology Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA (RZ); Department of Pathology, Mount Sinai St Luke's Roosevelt Hospital Center, New York, NY, USA (MC); Division of Research and Development, US Department of Veterans Affairs New York Harbor Healthcare System, Brooklyn, NY 11209, USA (PH); Department of Cell Biology, State University of New York Downstate Health Sciences University, Brooklyn, NY, USA (PH)

1 Muecksch F, Weisblum Y, Barnes CO, et al. Affinity maturation of SARS-CoV-2 neutralizing antibodies confers potency, breadth, and resilience to viral escape mutations. *Immunity* 2021; **54:** 1853–68

2 Chardès V, Vergassola M, Walczak AM, Mora T. Affinity maturation for an optimal balance between long-term immune coverage and short-term resource constraints. *Proc Natl Acad Sci USA* 2022; **119:** e2113512119.

3 Zhu Y, Lu Y, Tang L, et al. Finite neutralisation breadth of omicron after repeated vaccination. *Lancet Microbe* 2022; **3:** e729.

4 Chalkias S, Harper C, Vrbicky K, et al. A bivalent omicron-containing booster vaccine against COVID-19. *N Engl J Med* 2022; published online Sept 16. https://doi.org/10.1056/NEJMoa2208343.

5 Muecksch F, Wang Z, Cho A, et al. Increased memory B cell potency and breadth after a SARS-CoV-2 mRNA boost. *Nature* 2022; **607:** 128–34.

6 Koutsakos M, Lee WS, Reynaldi A, et al. The magnitude and timing of recalled immunity after breakthrough infection is shaped by SARS-CoV-2 variants. *Immunity* 2022; **55:** 1316–26.

7 Kaku CI, Bergeron AJ, Ahlm C, et al. Recall of preexisting cross-reactive B cell memory after Omicron BA.1 breakthrough infection. *Sci Immunol* 2022; **7:** eabq3511.

8 Walls AC, Sprouse KR, Bowen JE, et al. SARS-CoV-2 breakthrough infections elicit potent, broad, and durable neutralizing antibody responses. *Cell* 2022; **185:** 872–80.

9 Yuan Y, Zhang X, Chen R, et al. A bivalent nanoparticle vaccine exhibits potent cross-protection against the variants of SARS-CoV-2. *Cell Rep* 2022; **38:** 110256.

10 Wang Z, Muecksch F, Schaefer-Babajew D, et al. Naturally enhanced neutralizing breadth against SARS-CoV-2 one year after infection. *Nature* 2021; **595:** 426–31.

11 Qu P, Faraone JN, Evans JP, et al. Durability of the neutralizing antibody response to mRNA booster vaccination against SARS-CoV-2 BA.2.12.1 and BA.4/5 variants. *bioRxiv* 2022; published online July 22. https://doi.org/10.1101/2022.07.21.501010 (preprint).

*Lancet Microbe* 2022

Published **Online** October 13, 2022 https://doi.org/10.1016/S2666-5247(22)00292-0

See **Online** for appendix