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Vacunas

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Letter to the Editor

SARS CoV2 mRNA vaccines: Prolonged dosing intervals and anti-SARS-CoV-2 immunity status



Vacunas de ARNm del CoV2 del SRAS: Intervalos de dosificación prolongados y la inmunidad anti-SARS-CoV-2 status

Dear Editor,

The global number of cases infected with SARS-CoV-2 surpassed 433 million as well as 5.94 million deaths on 26 February 2022 (<http://covid19.who.int>). The mass vaccination is considered as the best strategy to fight with COVID-19 pandemic. However, immune system responses wane after vaccination. Furthermore, the durability of effective immune responses was varied among immunized individuals. Recent evidences suggested the effectiveness of ChAdOx1 (AstraZeneca) adenoviral as well as other non-replicating vaccines by increasing dosing intervals.¹ However, the magnitude and resilience of vaccine-induced immunity remains unclear particularly among mRNA vaccines.² Currently, regular schedule dosing intervals for BNT162b2 (Pfizer) and mRNA-1273 (Moderna) vaccines are 21 and 28 days, respectively.³ We provide a comprehensive literature search by ISI Web of Science, PubMed, and Scopus to demonstrate the SARS-CoV-2 antibody status after extended mRNA vaccine dosing intervals.

Firstly, Brockman et al. investigated humoral immune responses after one-month following one dose of the BNT162b2 mRNA COVID-19 vaccine in healthcare facilities. They found that after 30 days, the spike protein receptor binding domain (S/RBD) antibody titers were 4-fold lower than seronegative healthcare workers (HCW); However, convalescent HCW exhibited 7- to 20-fold higher levels of binding antibodies to neutralize live virus.⁴ Grunau et al. revealed the BNT162b2 and mRNA-1273 vaccines at dosing intervals of 6–7 weeks compared with a standard dosing interval of <4 weeks, could result in a significant increase of anti-spike antibodies concentrations (MSD ($t = 2.211$, $p = .028$); Roche ($t = 7.703$, $p < .0001$)) in vaccinated subjects.⁵

Recent studies suggested the role of extended dosing intervals in enhancing both humoral and cellular immunity against SARS-CoV-2 variants. Payne et al. declare extended dosing interval (6–14 weeks) for the BNT162b2 mRNA vaccine

can provide robust neutralizing antibody (NAb) responses to the spike protein, and augmentation of CD4+ T cells expressing interleukin-2 in peripheral blood samples of healthcare workers. They observed a reduction of SARS-CoV-2 infection in the extended dosing schedule (6–14 weeks) compared to the short dosing schedule (2–5 weeks) [55% vs. 66%, respectively].⁶ Tazuin et al. evaluated longitudinal humoral responses against the D614G strain and other variants of concern including B.1.1.7, B.1.351, P.1, and B.1.612.2, and B.1.526 in individuals who received the BNT162b2 mRNA vaccine at a 16-week interval between doses. Humoral immune responses significantly increased in naive individuals after a 16-week interval to the second dose, accomplishing analogous ranks as in previously infected patients. In addition, a 16-week interval induced more robust immune responses among vaccinated naive populations.⁷

This fact was assessed by Robinson et al., who compared the anti-spike protein neutralizing antibody concentration in healthy individuals as well as in cancer patients following BNT162b2, AZD1222, and mRNA-1273 administered at extended dosing intervals. The results showed a mean serum anti-spike protein antibody level was 382.4 BAU/ml (binding antibody unit) for control patients, 265.8 BAU/ml for solid cancer patients, and 168.2 BAU/ml in hematological cancer patients.⁸ Regarding effectiveness of extended mRNA vaccine dosing intervals with respect to various SARS-CoV-2 variants, another study, Grunau et al. revealed that a 100–120 days mRNA SARS-CoV-2 vaccine dosing intervals using BNT162b2 and mRNA-1273 can induce a significant immune response against the Wuhan, Beta, Gamma and Delta variants.⁹

In summary, extended mRNA-vaccine dosing intervals could better stimulate a robust immune response against circulating SARS-CoV-2 variants. The second dosage intervals of the Pfizer/BioNTech BNT162b2 and Oxford/AstraZeneca

was changed in the United Kingdom on December 31, 2020. Thus, optimizing mRNA vaccine dosage intervals can have influenced mRNA based-vaccine effectiveness against SARS-CoV-2 infection.

Conflict of interest statement

The authors have no conflict of interest.

REFERENCES

- Voysey M, Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, Angus B, Baillie VL, Barnabas SL, Bhorat QE, Bibi S, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet*. 2021;397(10277):881–91.
- Chu L, McPhee R, Huang W, Bennett H, Pajon R, Nestorova B, Leav B, mRNA-1273 Study Group, et al. A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine. *Vaccine*. 2021;39(20):2791–9.
- COVID C, Team R. SARS-CoV-2 B. 1.1. 529 (Omicron) Variant—United States, December 1– 8, 2021. *Morbidity and Mortality Weekly Report*, Vol. 70(50); 2021. p. 1731.
- Brockman MA, Mwimanzi F, Sang Y, Ng K, Agafitei O, Ennis S, Lapointe H, Young L, Umviligihozo G, Burns L, Brumme CJ, et al. Weak humoral immune reactivity among residents of long-term care facilities following one dose of the BNT162b2 mRNA COVID-19 vaccine. *medRxiv*. 2021.
- Grunau B, Asamoah-Boaheng M, Lavoie PM, Karim ME, Kirkham TL, Demers PA, Barakauskas V, Marquez AC, Jassem AN, O'Brien SF, Drews SJ, et al. A higher antibody response is generated with a 6-to 7-Week (vs Standard) Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccine Dosing Interval. *Clin Infect Dis*. 2021:ciab938.
- Payne RP, Longet S, Austin JA, Skelly DT, Dejnirattisai W, Adele S, Meardon N, Faustini S, Al-Taei S, Moore SC, Tipton T, et al. Immunogenicity of standard and extended dosing intervals of BNT162b2 mRNA vaccine. *Cell*. 2021;184(23):5699–714.
- Tauzin A, Gong SY, Beaudoin-Bussi eres G, V ezina D, Gasser R, Nault L, Marchitto L, Benlarbi M, Chatterjee D, Nayrac M, Laumaea A, et al. Strong humoral immune responses against SARS-CoV-2 Spike after BNT162b2 mRNA vaccination with a 16-week interval between doses. *Cell Host Microbe*. 2022;30(1):97–109.
- Robinson A, Mazurek A, Xu M, Gong Y. Quantitative Analysis of SARS-CoV-2 antibody status between patients with cancer and healthy individuals with extended vaccination dosing intervals in Canada. *Curr Oncol*. 2022;29(1):68–76.
- Grunau B, Goldfarb DM, Asamoah-Boaheng M, Golding L, Kirkham TL, Demers PA, Lavoie PM, et al. Immunogenicity of extended mRNA SARS-CoV-2 vaccine dosing intervals. *Jama*. 2022;327(3):279–81.

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<https://doi.org/10.1016/j.vacun.2022.03.001>
1576-9887/

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