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.

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Letter to the Editor

Developing new COVID-19 vaccine against the variants is urgently needed rather than boosters: A longitudinal cohort study

Dear Editor,

A new wave of COVID-19 cases caused by the highly transmissible Omicron variant is exacerbating the worldwide public health crisis and has led to the consideration of the potential need for and optimal timing of booster doses for vaccinated populations.[1,2] In this journal, our team evaluated the dynamic response and duration of anti-SARS-CoV-2 antibodies within 180 days after a third dose of inactivated CoronaVac vaccine was administered. The results suggested that there is no need to rush to deploy a fourth vaccination strategy.[3] We continued long-term follow-up of this cohort population and studied the immunogenicity profile with three-doses schedule of the CoronaVac vaccine over 552 days. We specifically assessed the decay of antibodies. We look forward to presenting evolving data to ensure that decisions about the next booster dose (fourth dose) are based upon scientific evidence.

The 32 participants were the same as those who participated in a previous study.[4] They gave blood samples at 20 serial time points during the course of three doses of CoronaVac vaccine within 552 days (Fig. 1A). The first and second doses were defined as the primary immunization according to the serial immunization regimen, and the third dose was defined as the secondary immunization.[5] The kinetics of neutralizing antibody, total antibody, and IgG antibody were serially evaluated, and the decay of antibodies was analyzed using a power law model.

A robust correlation was reported between neutralizing antibody titer and COVID-19 vaccine efficacy.[6] The neutralizing antibody concentration showed a small response after the first dose, peaking at 207.40 IU/mL 2 weeks after the second dose (42 days) and then declining as relatively fast to 4.75 IU/mL (≥54.00 IU/mL considered as positive[4]) at 276 days (about 9 months) during the primary immunization. After the third dose, the level rapidly increased and peaked at 711.90 IU/mL at 2 weeks and then began to very slowly decline, remaining at 115.23 IU/mL at 276 days (about 9 months) during the secondary immunization (Fig. 1B), which was significantly higher than that of 9 months after the primary immunization ($p< 0.001$). The concentration was maintained at about half of the highest value of primary immunization. The third dose could quickly evoke the immune memory and increase response.

The response for total antibodies after vaccination was similar to that for neutralizing antibodies. The level of total antibodies decreased from a peak of 174.90 AU/mL (42 days) to 4.69 AU/mL at 276 days during the primary immunization, and from a peak of 563.00 AU/mL to 197.89 AU/mL at 276 days after the third dose (during secondary immunization), which was significantly higher than that of 9 months, and the concentration was higher than the maximum during the primary immunization ($p < 0.001$) (Fig. 1C). IgG antibody was the main component of total antibody, and strongly correlated with neutralizing antibody as a predictor of seropositivity for anti–SARS-CoV-2 neutralizing antibody.[7] Analogously, compared with the primary immunization, the secondary immunization greatly delayed the attenuation of IgG antibody. IgG antibody decreased to 0.48 S/CO on the 276th day of primary immunization and remained at 9.37 S/CO on the 276th day after secondary immunization (Fig. 1D).

Furthermore, the power law model was fitted to compare the attenuation of anti-SARS-CoV-2 antibodies in the primary and secondary immunization.[8] The neutralizing antibody, total antibody, and IgG antibody levels declined over time, with half-lives of 71.01 days, 88.93 days, and 64.00 days within 276 days after primary immunization (Fig. 2A-C), respectively. Further, after secondary immunization, the half-lives of neutralizing antibody, total antibody, and IgG antibody further extended to 191.57 days, 410.37 days, and 449.28 days, respectively (Fig. 2D-F), which were 2.7-fold, 4.6-fold and 7.0-fold higher than those in the primary immunization, respectively. Obviously, anti-SARS-CoV-2 antibodies in the secondary immunization had a higher likelihood of antibody persistence and produced stronger response than primary response, and the concentration of these antibodies may be starting to stabilize and align with real observations after 276 days during the secondary immunization, which was similar to that after 180 days.[3]

Establishing immune memory is essential in the defense against SARS-CoV-2 infection. This cohort study showed that the third dose (secondary immunization) of CoronaVac inactivated vaccine could quickly evoke the immune memory. The anti-SARS-CoV-2 antibody titers at 9 months after the third dose of vaccine were still significant and decayed slowly. However, laboratory and real-world studies had shown evidence of waning immunity as early as 10 weeks after the third dose of mRNA vaccination.[9] mRNA boosters were highly effective against symptomatic Delta infection (with an 86.1% reduction in the incidence), but they were less effective against symptomatic Omicron infection (with a 49.4% reduction in the incidence).[10] In addition, a report about booster dose also indicated that the fourth dose of the original vaccines may not generate robust protection against infection in the form of neutralizing antibodies against Omicron.[2] Thus, a longer-term strategy for a global response is the development and administration of a new generation of broadly effective vaccines against SARS-CoV-2 variants rather than continuing with a strategy of repeated booster vaccination with existing vaccines. It can be expected that repeated booster vaccination will again stimulate a strong immune response. However, facing a broad range of existing and future SARS-CoV-2 variants, these boosters may mainly provide protection against COVID-19-related hospitalization and death, rather than achieving the goal of herd immunity.

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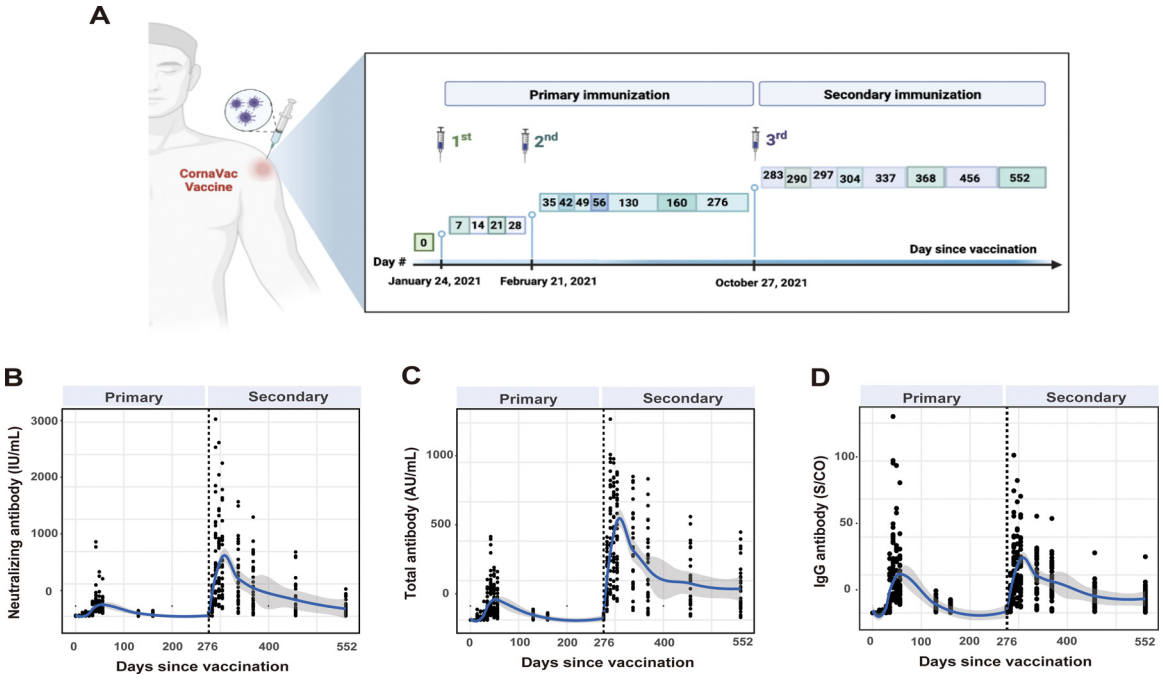

Fig. 1. Longitudinal anti-SARS-CoV-2 antibodies responses. A. Schedule of vaccination procedures and blood sample collection at 20 serial time points during the course of three-doses CoronaVac vaccine within 552 days. B-D. The levels of neutralizing antibody (B), total antibody (C), and IgG antibody (D) were measured at 20 serial time points.

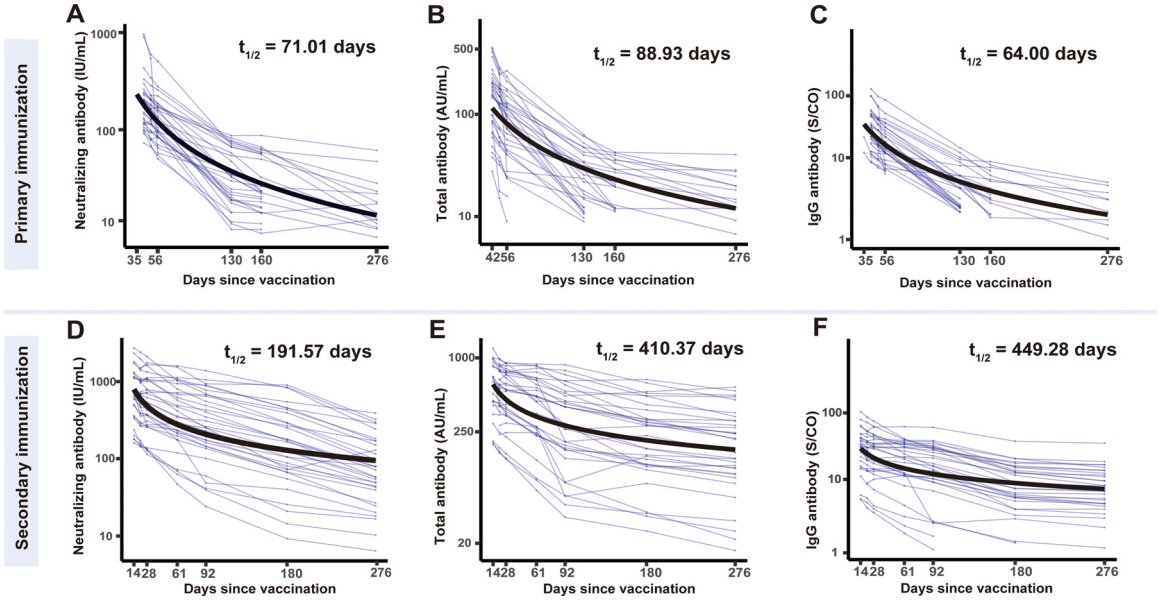

Fig. 2. The attenuation of anti-SARS-CoV-2 antibodies in the primary and secondary immunization estimated by a power law model at day 120. A-C: Neutralizing antibody (A), total antibody (B), and IgG antibody (C) decay curves and half-lives of primary immunization. D-F: Neutralizing antibody (D), total antibody (E), and IgG antibody (F) decay curves and half-lives of secondary immunization.

Current evidence of our study again proved that secondary immunization (i.e., the third dose of vaccine) awakened the memory of primary immunization, improved the immune response, and significantly prolonged the half-life of antibody attenuation. However, considering the rapid development of new COVID-19 variants worldwide, it is imperative that attention be focused on developing new vaccines to combat the new variants, rather than on strategies for a fourth dose of the existing vaccines.

Declaration of Competing Interest

The authors declare no competing interest in this work.

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