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

Is the fourth COVID-19 vaccine dose urgently needed? Revelation from a prospective cohort study

Dear editor,

Vaccines have proven to be safe, effective, and able to reduce the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its variants, as well as abrogate the serious clinical consequences of coronavirus disease 2019 (COVID-19).[1,2] In this Journal, the report by Liu and co-workers evaluated the persistence of immunogenicity of seven COVID-19 vaccine, not including CoronaVac vaccine, at three months after third dose boosters, showing that the decay rates of humoral response vary among vaccines.[3] We undertook a study to evaluated the dynamic response and duration of anti-SARS-CoV-2 antibodies after a third dose of inactivated CoronaVac vaccine within 180 days and specifically assessed the decay of antibodies.

A prospective cohort study design was employed as we previously reported.[4] 41 participants received the three-dose CoronaVac vaccine (Fig. 1A) and provided blood donation at 8 serial time points within 180 days after the third dose. This study was approved by the Institutional Ethics Committee of Zhongshan Hospital of Xiamen University, School of Medicine, Xiamen University. All participants provided written informed consent. The neutralizing antibody, anti-RBD total antibody, anti-Spike IgG titers were serially determined to evaluate the immune response and duration. Mixed effects exponential and power law models were used to analyze antibody waning.

The seropositive rate of neutralizing antibody was 2.44% after the second dose (248 days). After the third dose, the seropositive rate reached 100% at two weeks, maintained for approximately 2 months and began to slowly decrease, dropping to 80.49% at 180 days (Fig. 1B). On the other hand, the level of antibody concentration rapidly increased from a base value of 5.03 IU/mL and peaked at 707.20 IU/mL at two weeks and then also began to slowly decline, remaining at 175.29 IU/mL at 180 days (Fig. 1C).

For the anti-RBD total antibody, the seropositive rate was 39.02% after the second dose, peaked at 100.00% one week after the third dose and was maintained within 180 days (Fig. 1B). The level of anti-RBD total antibody rapidly increased from a base value of 5.13 AU/mL to 177.27 AU/mL at one week after the third dose, peaked at 534.35 AU/mL within the three weeks, and then began to decline, dropping to 198.54 AU/mL at 180 days (Fig. 1D). The response for anti-Spike IgG after vaccination was similar to that for the anti-RBD total antibody (Fig. 1E).

To measure anti-SARS-CoV-2 antibody waning after vaccination, two mixed effects models were fitted. First, the neutralizing antibody, anti-RBD total antibody, and anti-Spike IgG levels declined over time, with half-lives of 81.14 days, 105.66 days, and 104.76 days within 180 days after the third dose, respectively, as estimated by an exponential decay model, which increased 2–4 fold compared with those after the second dose[5] and were longer than those within 3 months after the third dose in our previous study.[4] The power law model estimated half-lives for the neutralizing antibody of 293.88 days, anti-RBD total antibody of 468.98 days, and anti-Spike IgG of 467.28 days, which were longer than those estimated by the exponential decay model (Fig. 2A-C), indicating that the concentration of these antibodies may be starting to stabilize. Different antibodies were classified into two subgroups (younger participants ($\leq$33 years) and older participants ($>$33 years)) based on age. The results of two mixed effects models showed that younger participants had a higher likelihood of antibody persistence than older participants (Fig. 2D-F).

The findings of this study showed that 41 participants who received the third dose of the CoronaVac inactivated vaccine exhibited relatively good responses and durations of neutralizing antibody, anti-RBD total antibody and anti-Spike IgG and prolonged decay time, which were higher than expected.

Neutralizing antibody levels are highly predictive of immune protection.[6,7] Our results showed that the seropositive rate for neutralizing antibody was 80.49% at 180 days after the third dose vaccination, which was higher than that after the second dose that we had previously studied at this point in time.[5] The neutralizing antibody level declined over time which increased approximately 2-fold compared with that after the second dose[5] and was also longer than that within 3 months of the third dose in our previous study.[4] Our real-world data supported that the recall responses to boost doses in individuals with preexisting immunity primarily increased antibody levels and substantially altered antibody decay rates. More specifically, the importance of these observations is that neutralizing antibodies in vaccinees may persist, albeit with a relatively low rate of decay, and may act as the first line of defense against future encounters with the omicron variant or future variants evolved from omicron.

Although vaccination is key to preventing infections, vaccine responses are often found to be lower in elderly adults. Our results suggest that younger participants had a higher likelihood of neutralizing antibody persistence than older participants. The markedly reduced vaccine success in older adults has been attributed to adaptive immunosenescence.[8]

Limitations of this study include short follow-up time, small sample of persons, no detection of cellular responses and evaluated only homologous inactivated vaccinations and so on.

In conclusion, our results showed that the third vaccine dose dramatically increased antibody levels and prolonged the decay time, which were higher than we expected. Therefore, antibodies decay slowly in terms of immunity persistence such that there is no need to rush to deploy a fourth vaccination strategy, or a booster dose could be given to vulnerable groups first.

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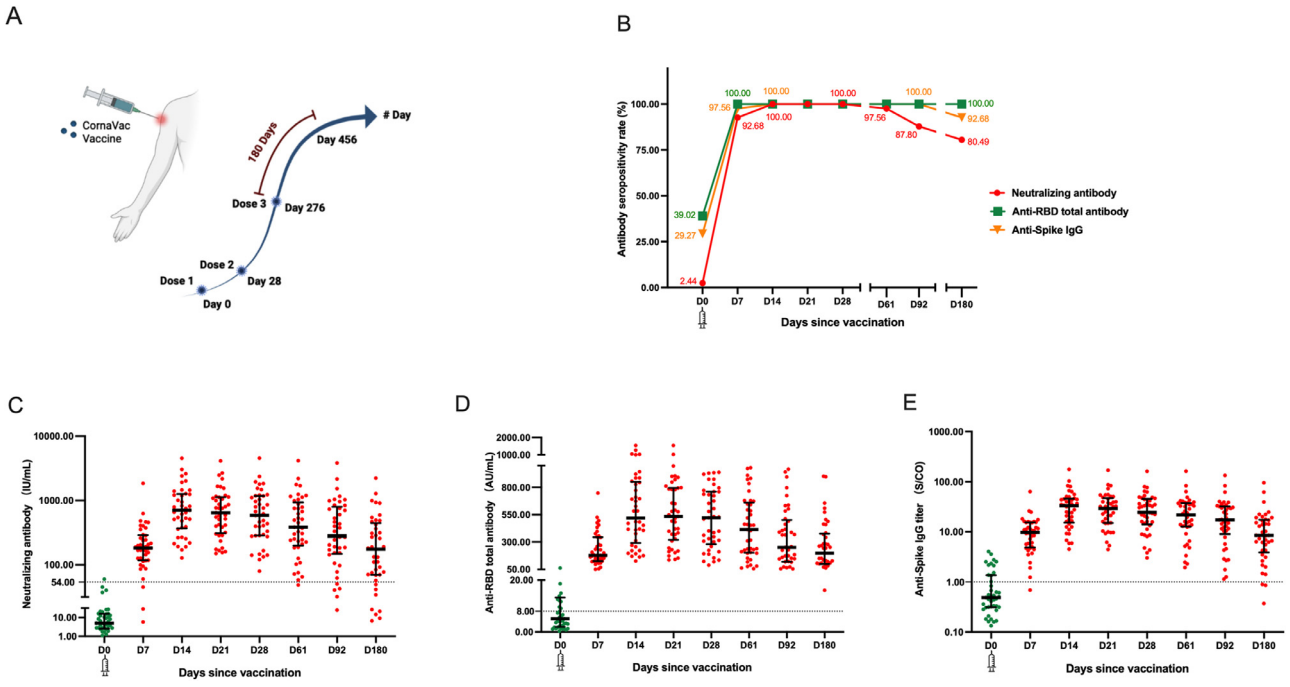

Fig. 1. Anti-SARS-CoV-2 antibody response after the third dose vaccination. A. Schedule of vaccination procedures. B. The seropositive rate changes of antibodies. C-E. The levels of neutralizing antibody (C), anti-RBD total antibody (D) and anti-Spike IgG (E) were measured at 8 serial time points. The antibody-positive judgement threshold is marked with a dotted line.

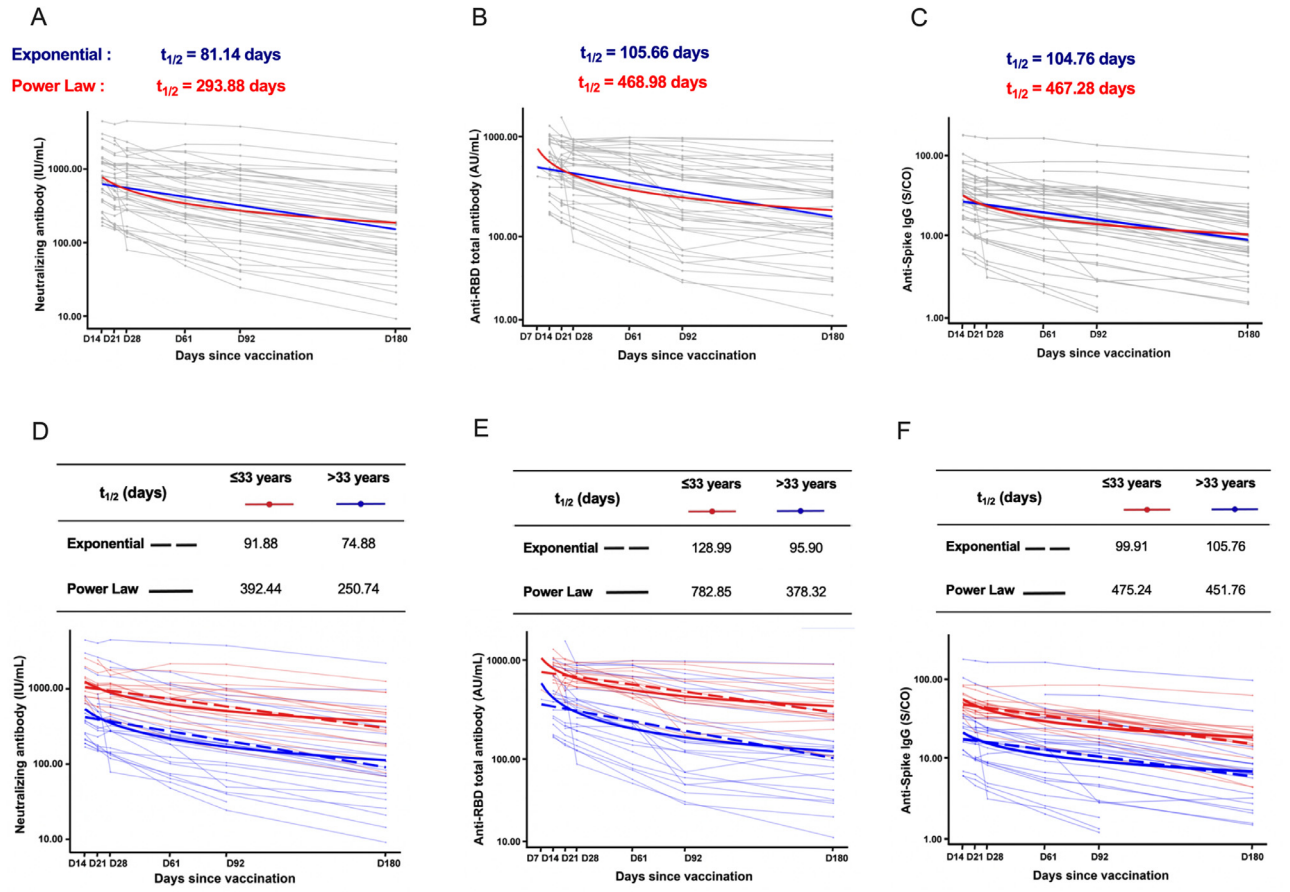

Fig. 2. The exponential and power law model of decay half-lives. A–C: A. Neutralizing antibody; B. Anti-RBD total antibody; C. Anti-Spike IgG. Antibody decay curves and half-lives estimated by an exponential decay model are shown in blue, and the decay curves and half-lives at day 120 estimated by a power law model are shown in red. D-F: D. Neutralizing antibody; E. Anti-RBD total antibody; F. Anti-Spike IgG. Antibody decay curves and half-lives estimated for younger participants (≤33 years) are shown in red, and older participants (>33 years) are shown in blue. Dotted lines represent exponential models, and solid lines represent power law model.

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Declaration of Competing Interest

All the authors declare no competing interest in this work.

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