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Short Communication

Impact of various vaccine boosters on neutralization against omicron following prime vaccinations with inactivated or adenovirus-vectored vaccine

Qingrui Huang [a,1], Jiawei Zeng [a,b,1], Qingyun Lang [a,c,1], Feng Gao [d,1], Dejun Liu [d,1], Siyu Tian [a,b], Rui Shi [a], Ling Luo [a,c], Hao Wang [a,b], Liping Hu [a,e], Linrui Jiang [a], Yawei Liu [d], Kailiang Li [d], Yunbo Wu [d], Junjie Xu [d], Wenxi Jiang [d], Ning Guo [c], Zhihai Chen [f], Xiaohua Hao [f], Ronghua Jin [f,*], Jinghua Yan [a,b,*], Yufa Sun [d,*]

[a] CAS Key Laboratory of Pathogenic Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences, Beijing 100101, China
[b] University of Chinese Academy of Sciences, Beijing 101408, China
[c] College of Life Sciences, Anhui Agricultural University, Hefei 230036, China
[d] Health Service Department of the Guard Bureau of the General Office of the Central Committee of the Communist Party of China, Beijing 100017, China
[e] Institute of Physical Science and Information, Anhui University, Hefei 230039, China
[f] National Center for Infectious Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing 100015, China

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As of this writing, the world is currently experiencing a huge wave of infection with the Omicron variant of SARS-CoV-2. Two SARS-CoV-2 inactivated vaccines (IAVs, CoronaVac by Sinovac and BBIBP-CorV by Sinopharm) with a two-dose vaccination regimen, one recombinant protein subunit vaccine (PRV, ZF2001 by Anhui Zhifei Longcom) with a three-dose vaccination regimen, and one single-dose recombinant adenovirus-vectored vaccine (AdV, Convidecia by CanSino) have been given conditional approval for general public use or approved for emergency use by China [1]. These four vaccines form the core of China's vaccination program. It has been reported that Omicron extensively escapes vaccine neutralization, and a booster shot seems to be necessary [2,3]. It is urgent to discover a superior booster strategy in China's current vaccination program context to fight against the Omicron variant.

Considering the wide use of vaccines in China, this study aims to investigate what booster strategy can maximally improve neutralization against the Omicron variant. The study has been reviewed and approved by the Ethics Committee of the Institute of Microbiology of the Chinese Academy of Sciences (APIMCAS2021159). Some serum specimens were from a single-center, open-label, and randomized controlled clinical trial at Beijing Ditan Hospital (approval No. IRB#2021-(024)-02; Trial Registration: www.chictr.org.cn, ChiCTR2100051998). Informed consent was obtained from all participants.

To investigate the Omicron BA.1 variant's sensitivity to immunity elicited by infection or full-course vaccination, we measured the binding, blocking, and neutralizing activities of a series of human sera obtained from convalescent individuals or vaccine recipients (Table S1 online). Among convalescent individuals, there were 3 asymptomatic, 5 mild, and 17 moderate cases. For all of the serum specimens, the binding antibody titers were 5–15 times lower for the Omicron than for the prototype strain (Fig. S1a online). Notably, except for 1 specimen from an individual receiving PRV vaccinations scored as positive, all of the other specimens lost the blocking activity against the Omicron variant, whereas nearly all of the specimens exhibited positive blocking activity against the prototype strain (Fig. S1b online). Pseudovirus-based neutralization assays demonstrated that geometric means of 50% neutralizing titers (NT_{50}) against the Omicron variant were 20, 10, 6, and 4 folds lower than those against the prototype strain in serum specimens from convalescent patients, IAV recipients, AdV recipients, and PRV recipients, respectively (Fig. 1a). In addition, despite being obtained 6 months following full-course vaccination, the serum samples from individuals who had received PRV vaccinations had the highest NT_{50} titers against the Omicron variant, but these titers were approximately 1/5 of the titer of convalescent sera against the prototype strain (Fig. 1a). In contrast, the neutralizing activity against the Omicron variant afforded by full-

* Corresponding authors.
E-mail addresses: ronghuajin@ccmu.edu.cn (R. Jin), yanjh@im.ac.cn (J. Yan), dafa20136725@163.com (Y. Sun).
[1] These authors contributed equally to this work.

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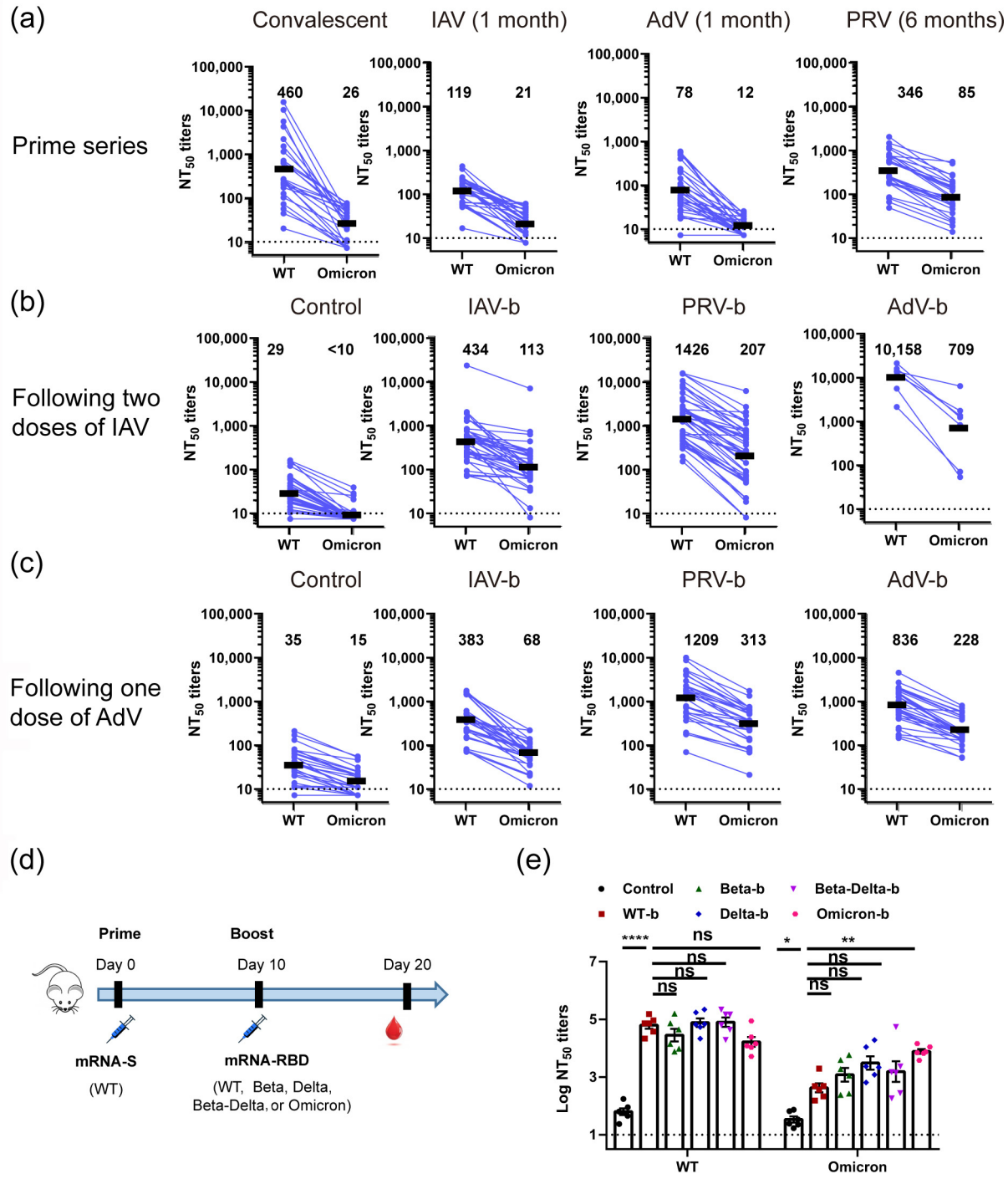

Fig. 1. Serum neutralizing antibody titers of convalescents and vaccinated individuals and mice against SARS-CoV-2 prototype strain or Omicron BA.1 variant. (a) Samples included sera obtained from convalescents (n = 25), 1 month after two-dose vaccination with IAV (n = 30) or a single-dose AdV (n = 30), and 6 months after three-dose vaccination with PRV (n = 28). (b) Samples were obtained from participants without vaccine booster (n = 42), with IAV (IAV-b, n = 39), AdV (AdV-b, n = 7), or PRV (PRV-b, n = 45) boosters following two-dose prime vaccination with IAV 4–8 months earlier. (c) Samples were obtained from participants without vaccine booster (n = 30), with IAV (IAV-b, n = 30), AdV (AdV-b, n = 30), or PRV (PRV-b, n = 30) boosters following a single-dose prime vaccination with IAV 4–8 months earlier. IAV represents inactivated vaccines (CoronaVac and BBIBP-CorV). PRV represents recombinant protein subunit vaccine (ZF2001). AdV represents adenovirus-vectored vaccine (Convidecia). (d) BALB/c mouse immunization schedule. (e) Serum pseudovirus neutralization titers in mice with various RBD-encoded mRNA vaccine boosters based on SARS-CoV-2 prototype, Beta, Delta, Beta plus Delta, and Omicron following a single prime injection. The pseudoviruses used in the study included wild-type strain and Omicron. The dotted line indicates the limit of detection (>10). P values were analyzed with one-way analysis of variance (ns, non-significant, $^{*}P$ <0.05, $^{**}P$ <0.01, and $^{****}P$ <0.0001). Experiments were repeated at least twice, and the results from one representative experiment are presented.

course vaccination with IAV or AdV was less than 1/20 of the activity of convalescent sera against the prototype strain (Fig. 1a), suggesting a potential of neutralizing insufficiency against Omicron infection. However, it should be noted that all subjects in the IAV group were aged >59 years with a mean age of 67.8 years, whereas all participants in the AdV and PRV groups were aged 18–59 years

with mean ages of 37.5 and 32.0 years, respectively (Table S1 online). As IAVs usually exhibit weaker immunogenicity in the elderly than in young adults, neutralizing antibody levels of full-course IAV vaccinations against WT and Omicron were likely to be underestimated.

To explore the impact of a homologous or heterologous booster at 4–8 months following IAV full-course vaccination on vaccine-induced antibodies against the Omicron variant, we obtained serum specimens from participants receiving no vaccine booster, homologous IAV booster (IAV-b), heterologous PRV booster (PRV-b), or AdV booster (AdV-b) (Table S1 online). Binding, blocking, and neutralizing antibodies titers in all of the groups were markedly higher against the prototype strain than against the Omicron variant (Fig. 1b and Fig. S2 online). The booster dose with IAV, PRV, and AdV vaccine induced 3-, 7-, and 40-fold increase in Omicron-binding antibody titers compared with the no-booster control (Fig. S2a online). At 4–8 months after full-course vaccination with IAV, Omicron-blocking antibodies were close to or below the lower limit of detection (4-fold dilution of plasma), and the blocking positive rate was only 2% (Figs. S2b and S3 online). The IAV, PRV, and AdV vaccine boosters led to an increase in blocking positive rates to 54%, 71%, and 57%, respectively (Figs. S2b and S3 online). For neutralizing antibodies against the Omicron variant, the genomic mean NT_{50} titers were below the lower limit of detection (10-fold dilution of plasma) in the control group, whereas the titers rose to 113, 207, and 709 in the IAV, PRV, and AdV booster groups, respectively (Fig. 1b and Fig. S4 online), indicating that the heterologous vaccine booster with AdV was superior to the homologous IAV vaccine booster in improving the neutralizing activity against the Omicron variant.

To examine the effect of various booster vaccinations following a single-dose prime vaccination with AdV, we conducted similar tests with serum specimens from individuals receiving no booster, IAV-b, PRV-b, or AdV-b at 4–8 months following the primary AdV vaccination (Table S1 online). The Omicron-binding antibody titers were boosted 4-, 25-, and 16-fold by the booster injection of heterologous IAV and PRV vaccines or homologous AdV vaccine, respectively, compared with the no-booster control (Fig. S5a online). For Omicron-blocking antibodies, the PRV and AdV booster groups exhibited an identical blocking positive rate (80%) that was higher than that of the control (3%) or the IAV booster group (53%) (Figs. S5b and S6 online). The neutralizing NT_{50} titers for the Omicron variant in the control group and the IAV, PRV, and AdV booster groups were 1568, 313, and 228, respectively (Fig. 1c and Fig. S7 online). Notably, a heterologous PRV booster induced the highest degree of neutralizing immunity against both the prototype and the Omicron strains compared with the no-booster control and the other two boosters (Fig. 1c and Fig. S7 online).

All four of the above-mentioned vaccines have been developed based on the prototype strain. Next, we developed various receptor binding domain (RBD)-encoding mRNA vaccine candidates based on the prototype, Beta, Delta, and Omicron strains as booster shots in BALB/c mice following a single-dose prime injection with a prototype S-encoding mRNA vaccine candidate, to assess the impact on humoral immunity against the Omicron variant (Fig. 1d). Beta-Delta represents a combination of Beta and Delta vaccine candidate with either half the other vaccine booster dose. The mice receiving a prime injection developed binding and neutralizing but no detectable blocking antibodies against the Omicron variant, whereas all binding, neutralizing, and blocking antibodies against the prototype were detected in those mice (Fig. 1e and Fig. S8 online). The mice immunized with all types of booster shots had significantly elevated anti-prototype strain binding, blocking, and neutralizing antibody titers, as well as anti-Omicron binding and neutralizing antibody titers (Fig. 1e and Fig. S8 online). In addition, all of the booster groups induced significantly higher anti-Beta and anti-Delta binding antibody titers compared with the no-booster control group (Figs. S9 and S10 online). However, only mice immunized with Delta and Omicron boosters developed significantly higher anti-Omicron blocking antibody titers compared with no booster control (Fig. 1e). Notably, the prototype, Beta, Delta, Beta-Delta, and Omicron vaccine boosters elicited Omicron-neutralizing NT_{50} titers with values of 423, 1202, 3073, 1548, and 7710, respectively, and only those elicited by the Omicron booster were significantly higher than those by the prototype booster (Fig. 1e), suggesting that the Omicron-based mRNA vaccine booster is superior to the prototype-based mRNA vaccine booster in elevating Omicron-neutralizing immunity.

A correlation between neutralizing antibody levels and vaccine efficacy against symptomatic COVID-19 has been observed at the population level [4]. Our results indicate that homologous or heterologous vaccine boosters after IAV or Ad5 prime vaccinations markedly improve neutralizing antibody levels against the Omicron variant compared to no booster control, implying higher efficacy against symptomatic COVID-19 caused by Omicron. Moreover, our findings suggest that recipients of primary IAV and AdV vaccines may consider heterologous AdV and PRV vaccine boosters, respectively, to achieve superior efficacy against symptomatic COVID-19 caused by Omicron. With previous variants, vaccine efficacy against severe disease and death has been higher and has been retained longer than effectiveness against mild disease [5,6]. Thus, the efficacy of various vaccine boosters against severe disease and mortality is likely to be higher and more convergent than their corresponding efficacy against symptomatic disease. Although our immunogenicity study may provide a rapid assessment of the potential protective effects of various vaccine booster strategies against the emerging Omicron variant, accurate vaccine efficacy needs to be determined by further clinical trials.

One limitation of our study is that human serum specimens were not collected from a rationally designed clinical trial. Such trials usually set strict inclusion and exclusion criteria for participants and then randomly divide all participants into subgroups to maximize comparability. Since the specimens in our study were pieced together by multiple institutions, there may be a potential bias in comparability. Another limitation of our study is that the neutralization assays used here were conducted in the absence of complement or Fc receptor-bearing cells, which may enable antibody-dependent cell-mediate cytotoxicity, potentially leading to an underestimation of protection afforded by serum specimens. Moreover, cellular immunity elicited by booster vaccination, which is usually more cross-reactive than humoral immunity, is not included in this study.

Here, we showed that the Omicron variant remarkedly escaped from neutralizing antibody response elicited by full-course vaccinations of approved IAV and AdV vaccines. To boost anti-Omicron response to sufficiently high titers to provide some protection against Omicron infection, a booster shot may be necessary. We further showed that for prime vaccinations with IAV and AdV, a heterologous vaccine booster with AdV and PRV, respectively, generated the highest increase in Omicron-neutralizing antibody titers. Although the sample number in AdV booster with prime IAV vaccinations was small (n = 7), the robust increase in the Omicron-neutralizing activity supports the heterologous AdV booster administration. Currently, all of the approved vaccines have been developed based on the SARS-CoV-2 prototype strain. Using the mouse model, we demonstrated that prototype booster significantly increased the prototype vaccine-elicited Omicron-neutralizing activity. Moreover, it is only the Omicron-based, but not the Beta- or Delta-based vaccine booster, that exhibited a significantly stronger ability to improve Omicron-neutralizing immunity.

Conflict of interest

The authors declare that they have no conflict of interest.

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Author contributions

Jinghua Yan, Yufa Sun, and Qingrui Huang designed the study; Feng Gao, Dejun Liu, Yawei Liu, Kailiang Li, Yunbo Wu, Junjie Xu, Wenxi Jiang, Xiaohua Hao, Zhihai Chen, and Ronghua Jin collected human serum specimens; Jiawei Zeng, Qingyun Lang, Siyu Tian, Ling Luo, Hao Wang, Liping Hu, and Linrui Jiang conducted all assays. Jinghua Yan, Qingrui Huang, and Ning Guo analyzed and interpreted the data. Qingrui Huang wrote the manuscript. Qingrui Huang and Jinghua Yan discussed and edited the manuscript.

Appendix A. Supplementary materials

Supplementary materials to this short communication can be found online at https://doi.org/10.1016/j.scib.2022.05.010.

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Qingrui Huang is an associate professor at Institute of Microbiology, Chinese Academy of Sciences. He received his Ph.D. degree from Institute of Process Engineering, Chinese Academy of Sciences. His research interest mainly focuses on the development of vaccines against bacteria and viruses, especially mRNA vaccines and protein subunit vaccines.

Jiawei Zeng received his B.S. degree from Hainan University in 2018 and is now a Ph.D. candidate at the Institute of Microbiology, Chinese Academy of Sciences. His research interest mainly focuses on the structure-based vaccine design for infectious diseases including herpes zoster, influenza, and COVID-19.

Qingyun Lang received her B.S. degree from Bengbu University in 2020. She is currently pursuing her M.S. degree in Biology at Anhui Agricultural University and studying at the Institute of Microbiology, Chinese Academy of Sciences. Her research interest mainly focuses on the mechanisms of infection and intervention methods for pathogenic microorganisms, and her efforts are currently focusing on COVID-19.

Dejun Liu is a chief physician at Health Service Department of the Guard Bureau of the General Office of the Central Committee of the Communist Party of China. He received his Ph.D. degree from Chinese PLA General Hospital. His research interest mainly focuses on Geriatrics.

Feng Gao is a chief physician at Health Service Department of the Guard Bureau of the General Office of the Central Committee of the Communist Party of China. He received his M.S. degree from Chinese PLA General Hospital. His research interest mainly focuses on Geriatrics.

Ronghua Jin is a professor, and chief physician at Beijing Ditan Hospital, Capital Medical University. His research interest mainly focuses on diagnosis and treatment strategy, clinical characteristics, and pathogenesis of emerging infectious diseases.

Jinghua Yan is a professor and principal investigator at Institute of Microbiology, Chinese Academy of Sciences. She obtained her Ph.D. degree from Institute of Bioengineering, Academy of Military Medical Sciences. Her research interest mainly focuses on the development of vaccines and therapeutic antibodies against emerging viruses.

Yufa Sun is a chief physician at Health Service Department of the Guard Bureau of the General Office of the Central Committee of the Communist Party of China. He received his Ph.D. degree from Chinese PLA General Hospital. His research interest mainly focuses on Geriatrics.