 DOI: 10.1002/eji.202149645 Eur. J. Immunol. 2022. 52: 356–359

Clinical

European Journal of Immunology

Notes and Insights

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Robust induction of neutralizing antibodies against the SARS-CoV-2 Delta variant after homologous Spikevax or heterologous Vaxzevria-Spikevax vaccination

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Keywords: antibodies · vaccination · SARS-CoV-2

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Although various variants of concerns (VoC) dominated the coronavirus pandemic at different times in different regions, all currently licensed vaccines are designed based on the spike (S) protein of the original Wuhan strain. Currently, the Delta variant (B.1.617.2) is dominating in large parts of the world causing increasing infection rates even in those individuals that had been completely vaccinated albeit at strongly reduced frequencies compared to non-vaccinated individuals [1–3]. The adenoviral vector vaccines Vaxzevria (ChAd) and Janssen COVID-19 Vaccine were reported to induce less Delta-neutralizing antibodies compared to Spikevax (MOD) and Comirnaty (BNT) [1,2,4]. In several European countries, vaccination campaigns faced an additional level of complexity since vaccination with ChAd was halted due to an increased risk of thrombotic events after millions of people received their first shot. The affected vaccinees were offered booster immunizations with mRNA-based vaccines or given the opportunity to freely select their booster vaccine. Interestingly, several studies reported that such heterologous prime-boost regimens resulted in vigorous humoral and cellular immunity [5–7], even against the Alpha, Beta, and Gamma VoC [8]. However, data regarding the neutralization capacities against the Delta variant induced by heterologous immunization protocols are rare.

In this study, sera of vaccinees collected during the course of a clinical study conducted at the Medical Faculty of the Otto-von-Guericke-University Magdeburg were tested for their potential to neutralize the Delta variant applying a surrogate virus neutralization test (sVNT). The sVNT is an ELISA-based assay that quantitatively determines the ability of serum antibodies to inhibit a

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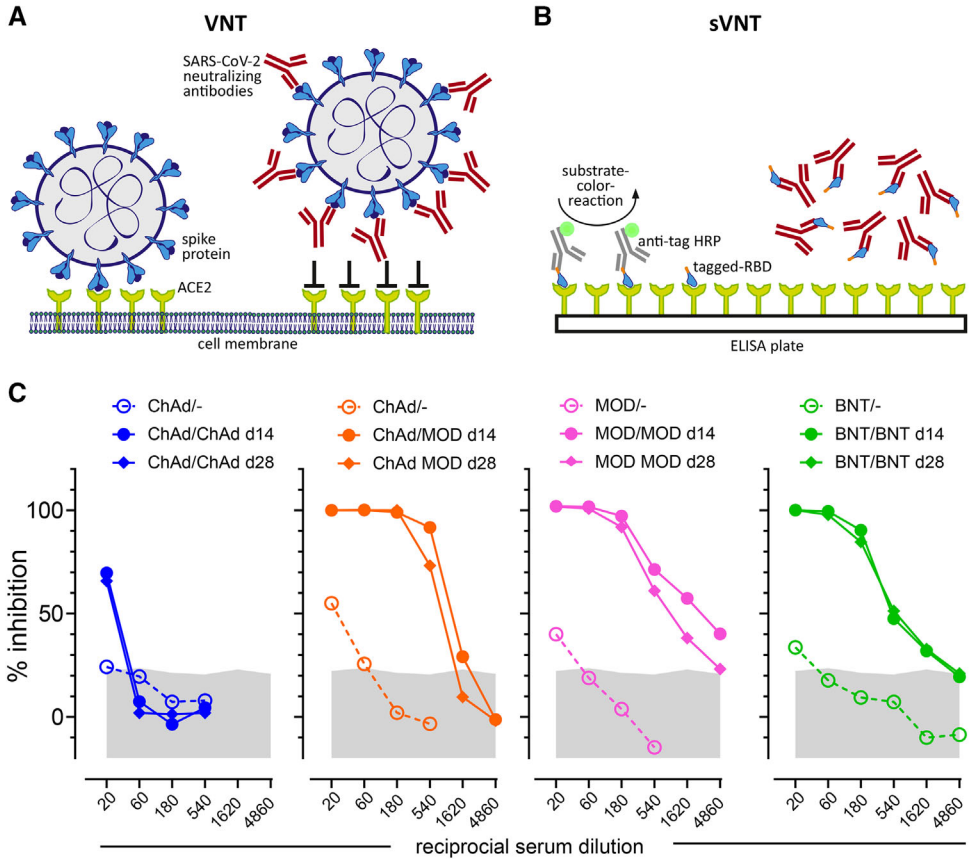

Figure 1. Experimental setup. Schematic depiction of **(A)** a virus neutralization test (VNT) and **(B)** a surrogate virus neutralization test (sVNT). **(C)** Examples for interaction inhibition of SARS-CoV-2 Delta RBD with plate-bound ACE2 by the addition of sera from vaccinees before boost (open circles) and 14 days (filled circles) and 28 days (diamonds) after boost with the vaccination regimens indicated. Shaded area show mean ± 2SD of pooled negative controls.

tagged spike receptor-binding domain (RBD) to bind to coated ACE2 that serves as a cellular receptor for SARS-CoV-2 (Fig. 1a-b). This assay, therefore, does not determine neutralizing antibodies binding to the S protein outside the RBD domain. Participants received prime injections with ChAd, MOD, or BNT. Homologous booster doses were applied 28 and 41 days after MOD and BNT primes, respectively. Following ChAd prime, participants could choose to either receive a MOD or ChAd boost approximately 12 weeks post prime (Supporting Information Fig. S1 and Table S1). These various boosting intervals corresponded to the recommendations of the German Standing Committee on Vaccination (Ständige Impfkommission, STIKO) at that time. Sera were taken one day before boosting as well as mean 14 days and mean 28 days after boosting (Supplementary Fig. S1).

As reported before [9], a considerable proportion of ChAd pre-boost sera did not contain a measurable Delta RBD-blocking activity (Fig. 1C; Fig. 2A). Although titers significantly increased at days 14 and 28 after homologous boosting, the median neutralization titer stayed at a 1/20 dilution at both time points analyzed (Fig. 2A). In contrast, after heterologous immunization with MOD, the median RBD-blocking titers increased to 1/540 and 1/180 at day 14 and day 28 after boosting, respectively, indicating a high immunogenicity of this mRNA vaccine for induction of neutralizing antibodies against the Delta variant (Fig. 1C; Fig. 2A). The effectiveness of MOD to induce antibodies that block Delta RBD binding was even more pronounced after homologous immunization. Here, the median blocking titer increased to 1/1620 on both days 14 and 28 after boosting (Fig. 1C; Fig. 2A). As reported before [9], with titers of 1/540 at day 14 and 28 after boosting, the Delta RBD-blocking capacity after homologous BNT vaccination was also very efficient, but significantly less pronounced than after homologous MOD vaccination (Fig. 1). Notwithstanding it has to be taken into account that the mean boosting intervals differ after ChAd priming (78 and 80 days), MOD priming (29 days), and BNT priming (41 days), which might be of particular importance when comparing results from pre-boost sera (Fig. 1C; Fig. 2A). We next compared the amount of anti-S1 day 28 serum antibodies, as determined by quantitative ELISA, with their ability to block binding of Delta RBD (Fig. 2B). Overall, the ability to block RBD binding to ACE2 went along - to a considerable degree - with amounts of anti-S1 antibodies present in the sera. Here, vaccinees receiving two injections of ChAd had the lowest, while vaccinees receiving two injections of MOD had overall the highest level of anti-S1 antibodies (Fig 2B).

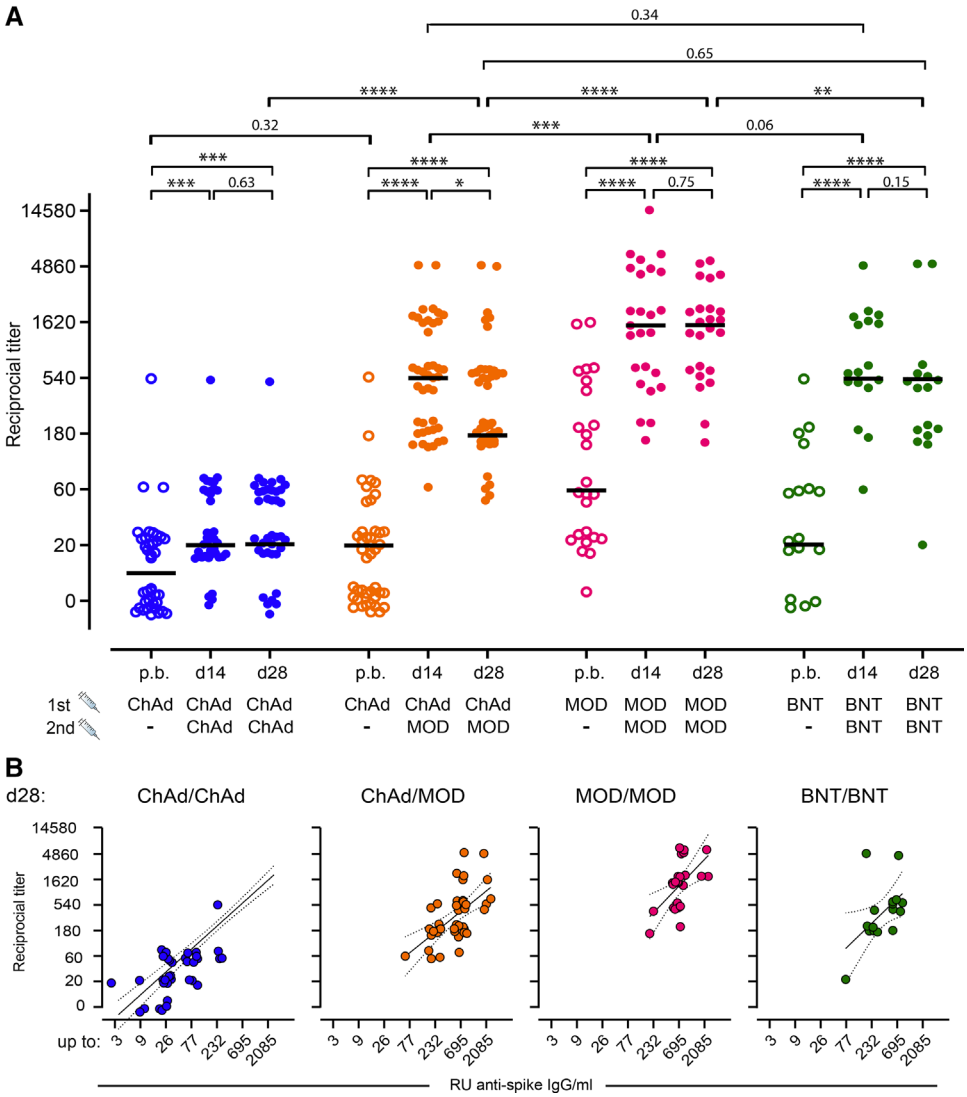

Figure 2. Strongest humoral immune responses against the SARS-CoV-2 Delta variant following homologous MOD / MOD vaccination. **(A)** Reciprocal titers of Delta RBD-blocking antibodies measured using a surrogate virus neutralization test (sVNT). Data are from n=38 biologically independent samples from the ChAd/ChAd group, n=42 biologically independent samples from the ChAd/MOD group, n=25 biological independent samples from the MOD/MOD group, and n=17 biological independent samples from the BNT/BNT group. Dots represent individual vaccinees, lines represent group median. Open symbols: pre-boost (p.b.) sera; filled symbols, post-boost collected 14 days (d14) and 28 days (d28) after boost. For better visualization of identical titer values, data were randomly and proportionally adjusted closely around the precise titer result. Chi-square test for trend; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$. **(B)** Correlation of SARS-CoV-2 ant-S1 IgG serum antibodies with Delta RBD-blocking activity of samples collected 28d after booster immunization from vaccinees immunized with vaccination regimens indicated.

Data from the present study confirm that homologous vaccination with ChAd induces limited amounts of antibodies able to neutralize the Delta VoC [9]. As reported before for BNT [9], the immune response in ChAd-primed individuals could be strongly increased by a boost immunization with another mRNA-based COVID-19 vaccine, MOD. Interestingly, of all vaccination regimens tested in the present study, homologous immunization with the MOD vaccine appears to induce the highest levels of antibodies able to neutralize the Delta variant of SARS-CoV-2 and that even heterologous immunization with ChAd/MOD induces titers similar to those found after vaccination with BNT/BNT. It is currently unclear why only the median titers of the ChAd/MOD group dropped by one dilution step from day 14 to day 28. Data from additional cohorts have to show whether this heterologous vaccination approach induces less long-lived humoral immunity compared to other vaccination regimens. Although our data indicate that individuals receiving homologous ChAd immunization have lower levels of Delta-neutralizing antibodies, it is currently unclear whether these vaccinees are more prone to vaccination breakthroughs than those that developed higher titers of antibodies due to homologous or heterologous immunization with mRNA-based vaccines.

In conclusion, MOD alone or in combination with Adenoviral vector vaccines provides a powerful approach to combat the Delta variant.

Acknowledgments: The study was supported by Deutsches Zentrum für Infektionsforschung, DZIF, TTU 01.938 (grant 80018019238 to R.F.), by Deutsches Zentrum für Lungenforschung, DZL (grant 82DZL002B1 to R.F.), by Deutsche Forschungsgemeinschaft, DFG, grants: EXC 2155 "RESIST" (Project ID39087428 to R.F.), SFB 900/3 (Projects B1, 158989968) and FO334/7-1 to R.F., by the State of Lower Saxony (14-76103-184 CORONA-11/20 to R.F.), by Bundesministerium für Bildung und Forschung, BMBF (NaFoUniMedCovid19 FKZ: 01KX2021. Project B-FAST to R.F.) and by the State of Saxony-Anhalt (SI-2 and SI-3) to B.S.
Open access funding enabled and organized by Projekt DEAL.

Conflict of interest: The authors have declared that no conflict of interest exists.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request. The complete data are not publicly available due to privacy or ethical restrictions.

Peer review: The peer review history for this article is available at https://publons.com/publon/10.1002/eji.202149645

References

1 **Puranik, A., Lenehan, P., Silvert, E., Niesen, M. J., Corchado-Garcia, J., O'Horo, J. C., Virk, A. et al.,** Comparison of Two Highly-Effective mRNA Vaccines for COVID-19 During Periods of Alpha and Delta Variant Prevalence. *medRxiv*. 2021: 10.1101/2021.08.06.21261707.

2 **Lopez Bernal, J., Andrews, N., Gower, C., Gallagher, E., Simmons, R., Thelwall, S., Stowe, J. et al.,** Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. *N. Engl. J. Med.* 2021. **385**: 585–594.

3 **Planas, D., Veyer, D., Baidaliuk, A., Staropoli, I., Guivel-Benhassine, F., Rajah, M. M., Planchais, C. et al.,** Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. *Nature*. 2021. **596**: 276–280.

4 **Sheikh, A., McMenamin, J., Taylor, B. and Robertson, C.** SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *Lancet*. 2021. **397**: 2461–2462.

5 **Borobia, A. M., Carcas, A. J., Pérez-Olmeda, M., Castaño, L., Bertran, M. J., García-Pérez, J., Campins, M. et al.,** Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS): a multicentre, open-label, randomised, controlled, phase 2 trial. *Lancet*. 2021. **398**: 121–130.

6 **Normark, J., Vikström, L., Gwon, Y. -. D., Persson, I. -. L., Edin, A., Björsell, T., Dernstedt, A. et al.,** Heterologous ChAdOx1 nCoV-19 and mRNA-1273 Vaccination. *N. Engl. J. Med.* 2021. **385**: 1049–1051.

7 **Schmidt, T., Klemis, V., Schub, D., Mihm, J., Hielscher, F., Marx, S., Abu-Omar, A. et al.,** Immunogenicity and reactogenicity of heterologous ChAdOx1 nCoV-19/mRNA vaccination. *Nat. Med.* 2021 **27**: 1530–1535.

8 **Barros-Martins, J., Hammerschmidt, S. I., Cossmann, A., Odak, I., Stankov, M. V., Morillas Ramos, G., Dopfer-Jablonka, A. et al.,** Immune responses against SARS-CoV-2 variants after heterologous and homologous ChAdOx1 nCoV-19/BNT162b2 vaccination. *Nat. Med.* 2021. **27**: 1525–1529.

9 **Hammerschmidt, S. I., Bosnjak, B., Bernhardt, G., Friedrichsen, M., Ravens, I., Dopfer-Jablonka, A., Hoffmann, M. et al.,** Neutralization of the SARS-CoV-2 Delta variant after heterologous and homologous BNT162b2 or ChAdOx1 nCoV-19 vaccination. *Cell. Mol. Immunol.* 2021. **18**: 2455–2456.

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Received: 20/9/2021
Revised: 18/10/2021
Accepted: 2/12/2021
Accepted article online: 6/12/2021