Delta or Omicron BA.1/2-neutralizing antibody levels and T-cell reactivity after triple-vaccination or infection

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Letter

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To the editor,

In Germany, SARS-CoV-2 infections in fall 2021 were caused by the Delta variant of concern (VOC B.1.617.2), which was completely replaced by the Omicron VOC (BA.1, B.1.529.1/BA.2, B.1.529.2) in winter. Meanwhile, the BA.2 sublineage dominates, apparently having a selection advantage[1].

We studied the kinetics of anti-spike (S) protein IgG and Delta neutralizing antibodies (NA) as well as the release of interferon-gamma (IFN-γ) from SARS-CoV-2-specific T-cells in 152 individuals (117 women, 35 men, median age 41 years) who received two doses of vector vaccine (AstraZeneca, AZD, N=34), mRNA vaccine (BioNTech or Moderna, mRNA, N=62), or a combination of both (N=56) followed by an mRNA vaccine boost (N=81). In a subset of 15 age- and gender-matched vaccinees and in ten triple-vaccinated and two unvaccinated patients with previous BA.1 infection, the Delta- and Omicron BA.1/BA.2 NAs and T-cell reactivity were examined. For comparison, variant-specific antibody responses of unvaccinated patients after infection with Alpha- (N=10) or Beta VOCs (N=1) were included.

Within 279 days after the second vaccination, a decrease in anti-S IgG concentrations (Figures S 1A-C) and Delta NA titers (Figure 1A) was measured regardless of the immunization regimen. The booster vaccination led to a significant increase of anti-S IgG concentrations (Figures S1 D-F) and of Delta NA titers (Figure 1B). The IgG levels and Delta NAs reached four weeks after the mRNA vaccine booster were 1.3 - 1.7-fold higher than after the second mRNA dose, but this difference was significant only for IgG (Figures 1A, C; Figures S 1A-C, G-I). The release of IFN-γ as a measure of SARS-CoV-2 T-cell reactivity was demonstrated for months after second vaccination. In contrast to the Delta NA levels, IFN-γ concentrations were independent of the underlying vaccination schedule and increased slightly after the third immunization (Figures 1D, E). The parameters of humoral and cellular immunity decreased again after the booster vaccination (Figures 1C, F; Figures S 1G-I).

As reported by others [1-4], NAs to Omicron BA.1 were induced by the mRNA vaccine booster, but also against the predominant BA.2 sublineage, which was previously unclear. The BA.2 NA geometric mean titer (GMT) was higher than the BA.1 NA GMT (Figure 2A). With respect to the results presented in Figures 1C and

2B, we suspect that NAs against the Omicron VOC will decline rapidly after booster vaccination alone. High NA titers against Omicron BA.1/BA.2 and against Delta VOC were exclusively observed in triple-vaccinated individuals two to three weeks after Omicron breakthrough infection (Figure 2A). This indicates broadened immunity covering additional viral variants and may also explain why few BA.2 infections have occurred in this group of individuals to date [5]. Because Omicron is a distinct serotype [6], only NAs against this VOC were detectable in two unvaccinated BA.1-infected individuals (Figure 2A), while unvaccinated Alpha- and Beta VOC patients developed isolated NAs against the antigenically more related Delta VOC (Figure S 2A). Accordingly, both BA.1 patients had very low IgG levels against the receptor-binding domain (RBD) of a Wuhan-like virus (Figure S 2B), whereas IgGs against the higher preserved nucleocapsidprotein were barely affected (Figures S 2C, D). The results of a surrogate neutralization assay confirmed very limited humoral immunity after Omicron infection alone (Figure S 2E).

The increase of IFN-γ release by mRNA booster vaccination was moderate (Figures 1D, E), while the breakthrough infection insignificantly increased IFN-γ release by a factor of 1.9 - 2.6 (Figure 2C).

In conclusion, the importance of pre-existing vaccine-induced immunity is clearly demonstrated. The booster vaccination with the conventional mRNA vaccine resulted in measurable BA.1/BA.2 NAs. However, a multivalent vaccine could induce higher titers, which could provide better protection.

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Author contributions

Conceptualization, A.K.; methodology, A.K., F.N. and R.R.; investigation, C.B., F.N., F.S., M.S., R.R. and S.M.; resources, A.K., D.W., H.F., J.R., O.G., S.S. and T.L.; formal analysis, A.K., F.N. and R.R.; writing-original draft, A.K., F.N. and R.R.; writing-review and editing, all authors; visualization: A.K. and R.R.; supervision, A.K., H.F., O.G. and T.L.

Conflict of interest

The authors have no conflict of interest in relation to this work.

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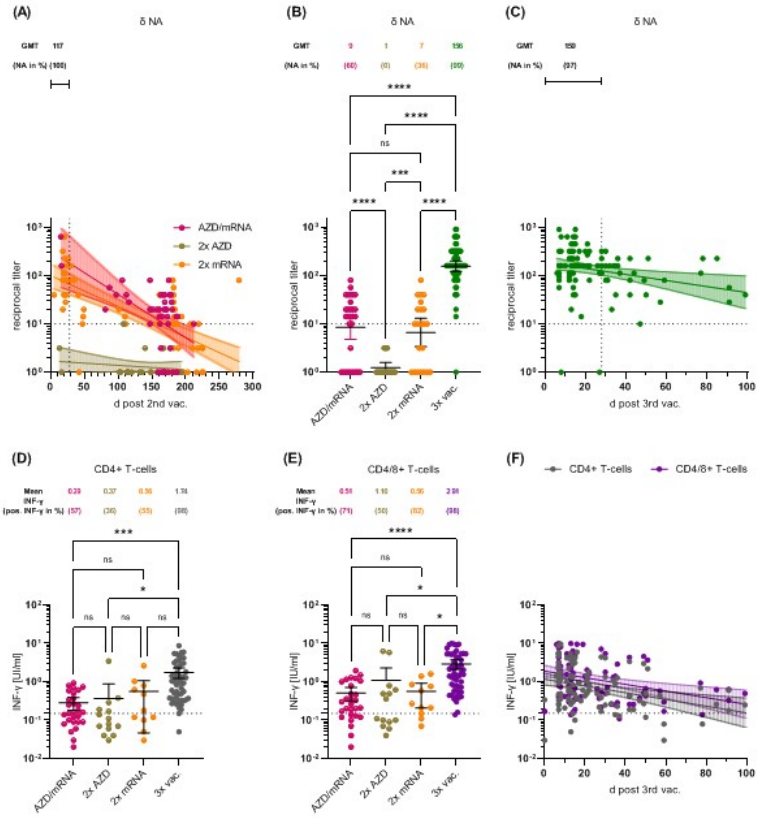

Figure 1 (A, B) Decrease in delta (δ) neutralizing antibody (NA) titers after baseline immunization, followed by their increase after mRNA booster. The geometric mean titers (GMT) and the prevalence of δ NA titers >1:10 are tabulated. **(C)** Renewed decline in titers. Four weeks after the third mRNA immunization, δ NAs tended to be higher than after the second immunization ($p = 0.27$).**(D, E)** Increase in CD4+ and CD4+/CD8+ T-cell reactivity after mRNA booster. **(F)** Renewed decrease in T-cell reactivity. ****: $p < 0.0001$; ***: $p < 0.001$; * $p < 0.05$. Horizontal dashed lines indicate test cut-off values.

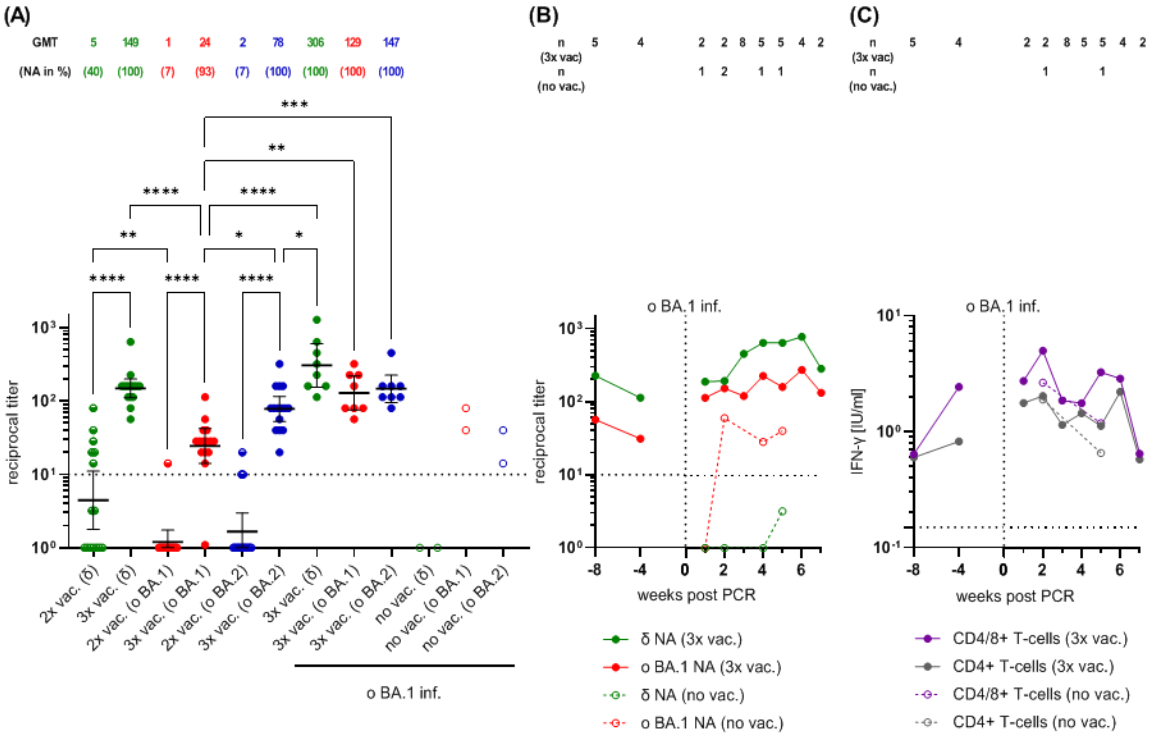

Figure 2 (A) Increase of Delta (δ)- and Omicron (*o*)- BA.1/BA.2 neutralizing antibody (NA) titers after mRNA booster in age- and gender-matched individuals pre-vaccinated with AZD/mRNA (N=5), AZD/AZD (N=5), and mRNA/mRNA (N=5). δ- and *o*-BA.1/BA.2-NA titers after BA.1 (breakthrough) infection in triple-vaccinated and unvaccinated individuals. **(B, C)** δ- and *o*-BA.1 NA titers and CD4+ or CD4/CD8+ T-cell reactivities before/after BA.1 (breakthrough) infection. Geometric mean titers (GMT), prevalence of NAs >1:10 or number of individuals tested are tabulated. ****: $p < 0.0001$; ***: $p < 0.001$ **: $p < 0.01$; * $p < 0.05$. Horizontal dashed lines indicate test cut-off values.

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