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LETTER

Long-term effects of homologous and heterologous SARS-CoV-2 vaccination on humoral and cellular immune responses

To the Editor,

In the last 2 years, several studies investigated the immunological responses to SARS-CoV-2 infections and/or COVID-19 vaccinations,[1–6] but long-term immunological effects in response to different vaccination combinations are poorly defined. As recently demonstrated, humoral and cellular immune responses to SARS-CoV-2 vaccines wane with time.[7–9] Correspondingly, epidemiological data show a reduction in protection against (symptomatic) COVID-19 with increasing time following vaccination.[10,11] In the COV-ADAPT cohort, we recently studied the humoral and cellular immune responses and their interdependencies following different vaccine combinations before (T1) and up to 3 months after the second immunization (T2).[12] This follow-up investigated the stability of long-term immune responses and aimed to identify predictive markers. Thus, we assessed humoral (anti-spike-RBD-IgG, neutralization capacity and avidity) and cellular (spike-induced T-cell interferon-γ release) immune responses 3–7 months after the second immunization (T3) in blood samples of 320 healthcare workers of the COV-ADAPT cohort with previous homologous ChAdOx1 nCoV-19 (ChAdOx1, $n = 26$), homologous BNT162b2 ($n = 49$), heterologous ChAdOx1/BNT162b2 ($n = 243$) or heterologous ChAdOx1 /mRNA-1273 ($n = 2$) vaccinations (Figure S1; all participants provided written informed consent). The last group was not analyzed separately due to the low *n*-number (for characterization of study participants see Table S1). The study was approved by the local ethics committee (21/5/21) and registered with the German Clinical Trials Register (DRKS00026029). We detected no nucleocapsid (NCP)-IgG seroconversion between T2 and T3 indicating the absence of breakthrough infections (Figure S2). At T3, homologous ChAdOx1 vaccination resulted in significantly lower anti-spike-RBD-IgG vs. heterologous ChAdOx1/BNT162b2 and homologous BNT162b2 (Figure 1A, Table S1). ChAdOx1/BNT162b2 and BNT162b2/BNT162b2 did not significantly differ. Despite the decrease from T2 to T3 in all groups, anti-spike-RBD-IgG was still significantly higher at T3 vs. T1 (Figure 1A). T-cell interferon-γ release (i.e., the cellular response) also decreased from T2 to T3 in all regimes. Only the heterologous ChAdOx1/BNT162b2 group still showed significantly higher T-cell responses at T3 vs. T1 (Figure 1B), and no differences were observed between the regimes at T3 (Figure 1B, Table S1). For the groups with BNT162b2 as a second vaccination, anti-spike-RBD-IgG was negatively associated with the days elapsed since the second vaccination (Figure 1C, left panel) suggesting higher antibody dynamics for vaccination regimes including BNT162b2. Such an association was not found for the cellular response (Figure 1C, right panel). Similar to our previous findings at T1/T2, humoral and cellular immune responses showed significantly positive associations at T3 for the study population as a whole and the ChAdOx1/BNTb162b2 group (Figure S3). Between T2 and T3, strong associations with high predictive power were observed for cellular and humoral immune responses for all groups (Figure S4). The early cellular response (at T1) emerged as a predictor of long-term immune responses as it was significantly associated with late (T3) humoral (ChAdOx1/BNT162b2 and BNT162b2/BNT162b2) and cellular responses (all groups) (Figure 2). Antibody neutralization and avidity indices were significantly higher at T3 vs. T1 in all groups (Figure S5) indicating durable antibody quality. Neutralization capacity was higher in the groups with a second BNT162b2 vaccination vs. homologous ChAdOx1 at T3. Interestingly, subjects with a negative neutralization index (as per the manufacturer's instructions) did not present generally lower anti-spike-RBD-IgG levels (Table S2). In conclusion, we identified important long-term interactions between the humoral and the cellular immune systems and observed distinct long-term dynamics following different SARS-CoV-2 vaccination regimes. In this regard, vaccination regimes including BNT162b2 elicit strong immune responses with a more rapid decline, whereas vector-based vaccinations yield lower and comparably stable immunological effects. The immunological drawbacks of either homologous vaccination regime appear to be somewhat mitigated by the combination of both vaccination principles in the form of a heterologous vaccination. We additionally identified the early T-cell response to predict long-term immune responses in different vaccination regimes. It will be of utmost importance to determine how the observed interdependencies and long-term dynamics of immune response react to booster vaccinations and breakthrough infections.

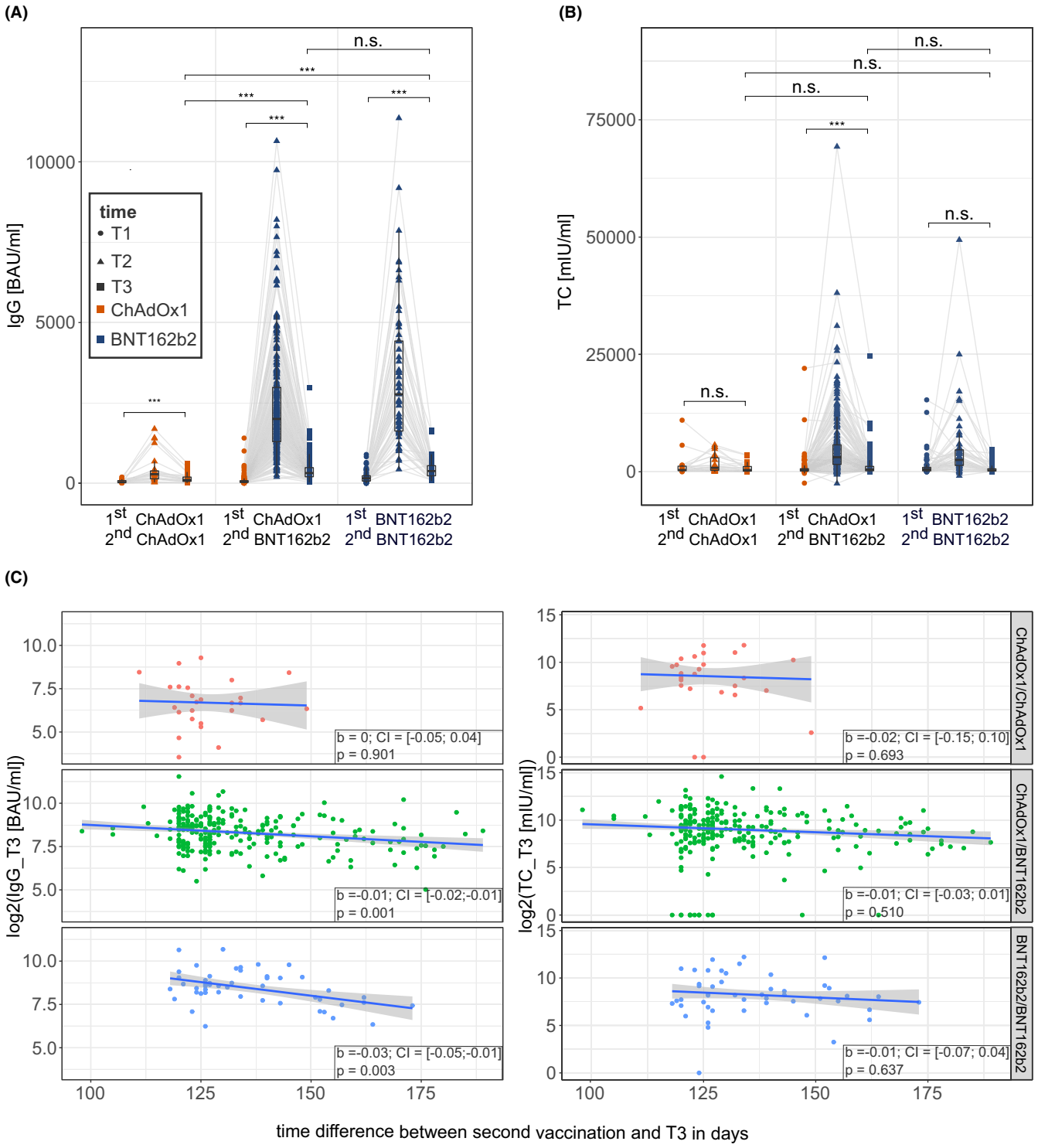

FIGURE 1 Anti-spike-RBD-IgG ≤2 weeks before (T1), 2 weeks–3 months (T2) and 3–7 months following second vaccination (T3) by vaccination regime. (A) Anti-spike-RBD-IgG (IgG) [BAU/ml], (B) spike-directed IFN-γ T-cell responses (TC) [mIU/ml] and (C) log2-association of IgG (left panels) and TC (right panels) with the duration [days] between second vaccination and T3. b = linear trend effect, p = p-value (adjusted using Holm's procedure), CI = confidence interval. ChAdOx1 = ChAdOx1 nCoV-19. ***$p < .001$; **$p < .01$; *$p < .05$; n.s.: not significant; calculated using linear mixed effect models with vaccination regime and time and their interaction as predictors, adjusted for age and sex

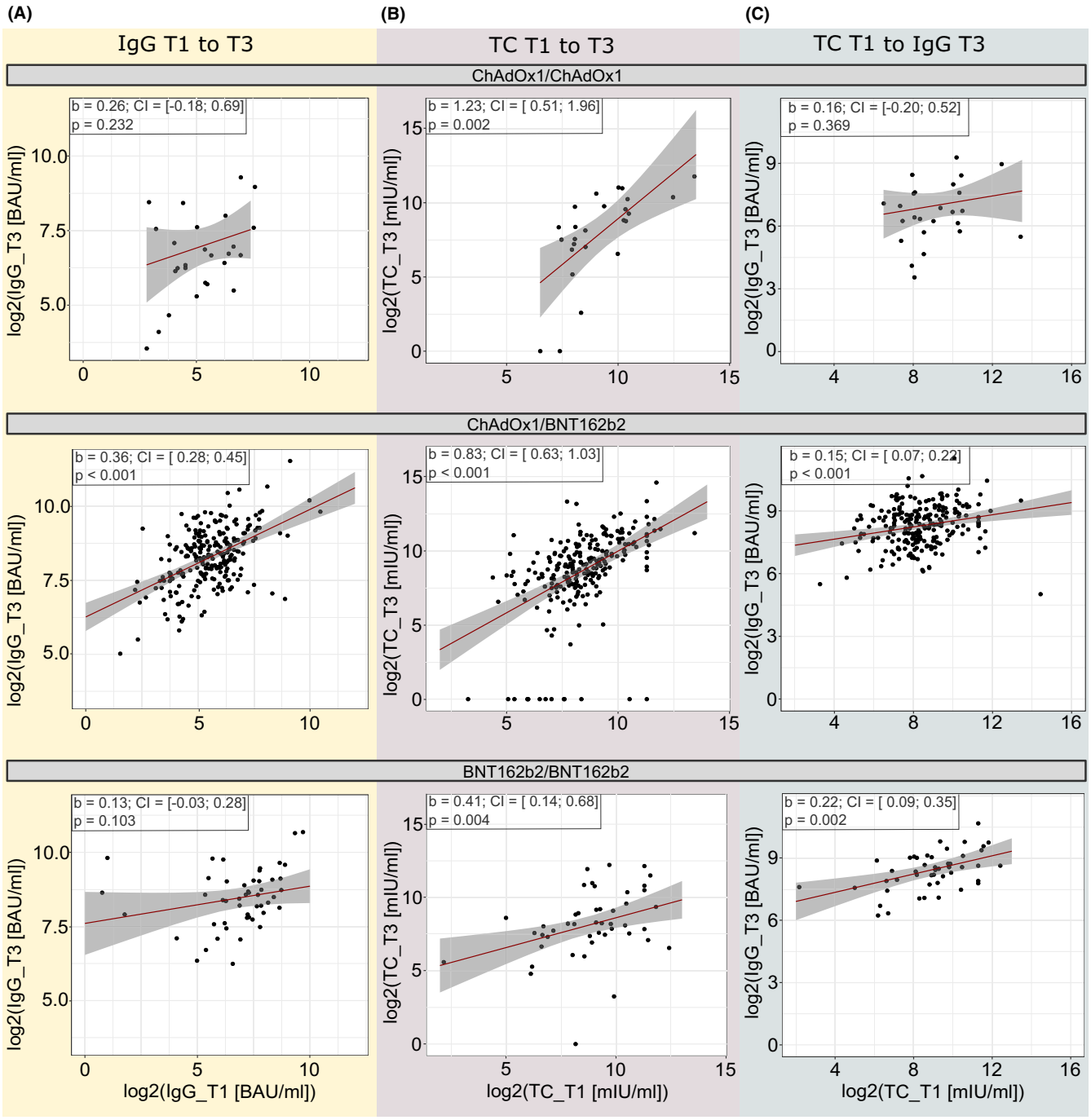

FIGURE 2 Associations of early and late humoral and cellular immune responses in the different vaccination regimes. (A) Anti-spike-RBD-IgG (IgG) at T1 (≤2 weeks before second vaccination) vs. IgG at T3 (3–7 months following second vaccination), (B) spike-directed IFN-γ T-cell responses (TC) at T1 vs. T3, and (C) TC at T1 vs. IgG at T3, all controlling for age, sex, and time between second vaccination and T3. b=linear trend effect, *p*=*p*-value (adjusted using Holm's procedure), CI=confidence interval. ChAdOx1=ChAdOx1 nCoV-19

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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