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.

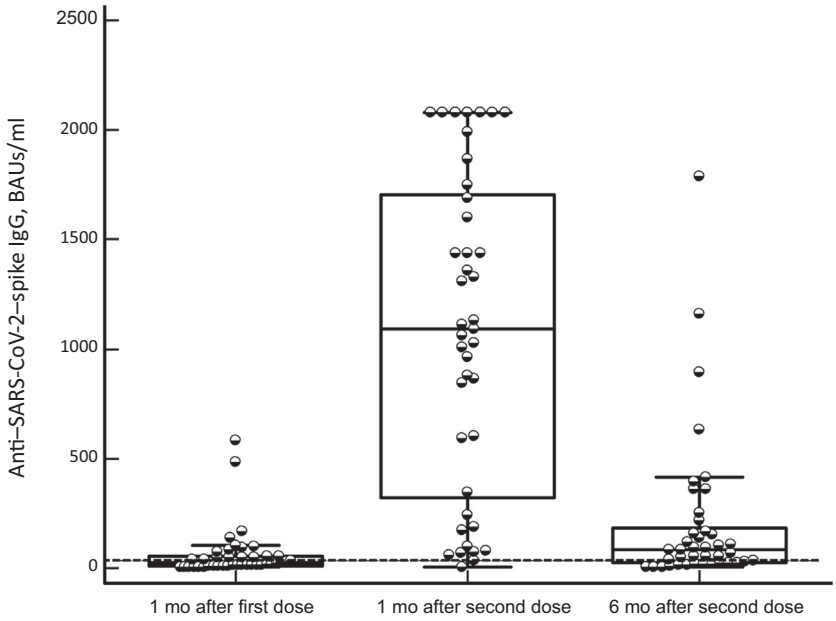

Figure 1 | Anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–spike IgG concentration after vaccination with the mRNA-BNT162b2 vaccine (Pfizer–BioNTech) in hemodialyis patients. Box-and-whisker plots including individual data points are displayed. The threshold for seropositivity (≥33.8 binding antibody units [BAUs]/ml) is represented by the dashed line.

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Improved cellular and humoral immunity upon a second BNT162b2 and mRNA-1273 boost in prime-boost vaccination no/low responders with end-stage renal disease

To the editor: Patients with end-stage renal disease (ESRD) develop inefficient immune responses upon vaccination and have a high risk of developing severe coronavirus disease 2019 (COVID-19). The globally expanding severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant of concern (VOC), B.1.6.17.2/Delta, evades immune responses and might constitute a particular threat to these patients.[1–3]

Herein, we evaluated the efficacy of a third dose (second boost) by BNT162b2 (Pfizer–BioNTech) or mRNA-1273 (Moderna) mRNA vaccines (Supplementary Table S1 and Supplementary Figure S1) in ESRD patients with no response/low response (NR/LR) after prime-boost BNT162b2 vaccination and compared with ESRD with high response (HR) following the regular prime-boost vaccination. Enzyme-linked immunosorbent assay, pseudovirus neutralization assay, and flow cytometry were applied to assess humoral and cellular immunity against the spike (S) protein of SARS-CoV-2 wild type (WT-S) and the Delta-VOC (Delta-VOC-S) before and 3 to 5 weeks following the last booster vaccination.

In NR/LR, 20 of 23 patients developed high-binding WT-S antibody titers (Figure 1a and Supplementary Figure S2A), with neutralizing capacity in 19 of 22 patients. The third vaccination led to an increase in WT-S protein-reactive $CD4^+$ T cells (Figure 1b) without differences between the applied vaccines (Supplementary Figure S2B and C). The higher frequency of S-reactive T follicular helper (Tfh) cells was the only difference observed in mRNA-1273–boosted patients (Supplementary Figure S2D).

Cellular immunity against WT-S and Delta-VOC-S was comparable irrespectively of helper or cytotoxic T cells or vaccine type (Figure 1e and f and Supplementary Figure S2E and F). In contrast, only 8 had neutralizing antibodies against Delta-VOC-S (Figure 1g). A clear association between cellular and humoral immunity was observed for each patient (Figure 1h). More important, when comparing the data

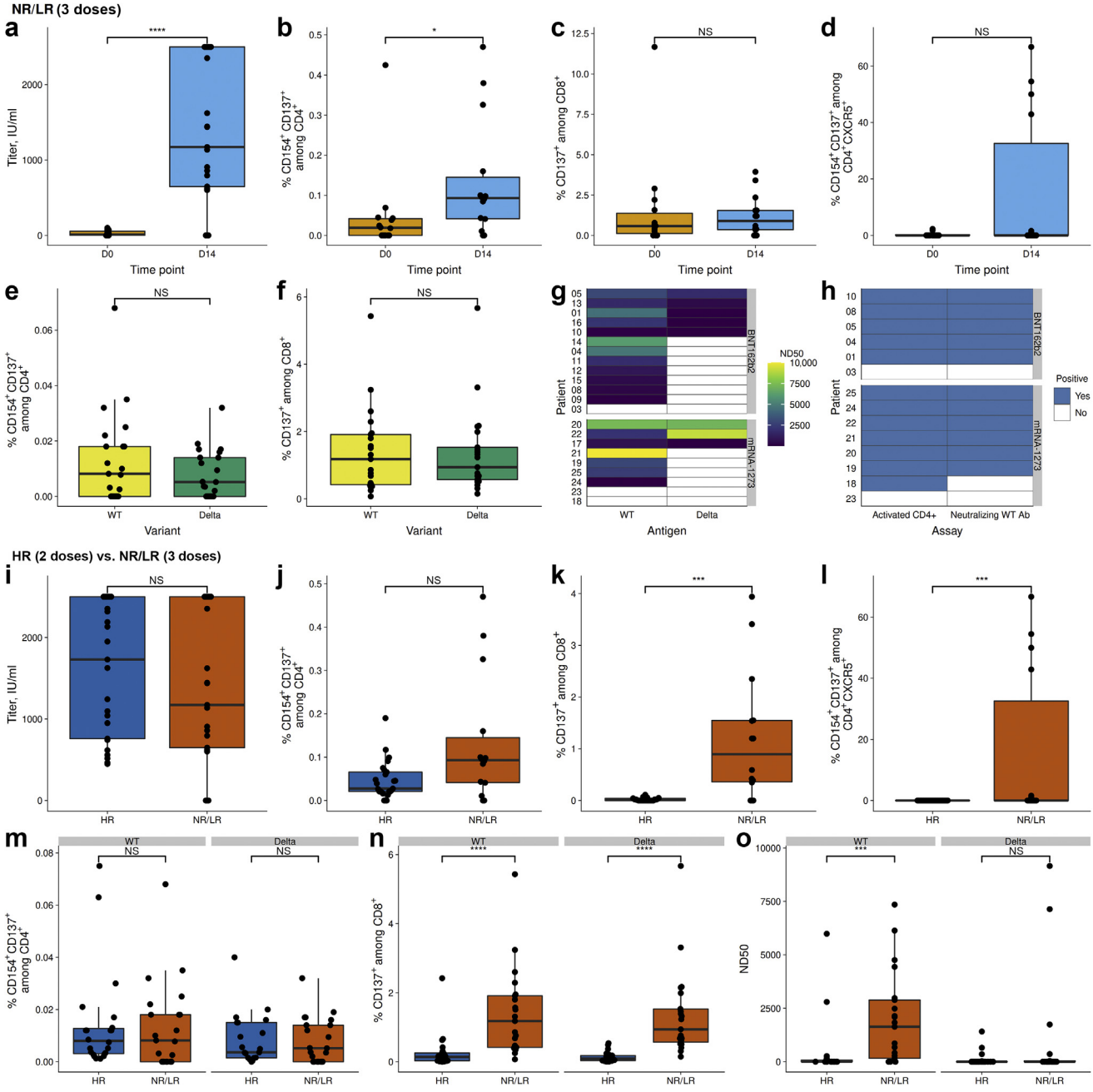

Figure 1 | The effect of a third severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccination boost. Patients with no response/low response (NR/LR) after a regular prime-boost SARS-CoV-2 mRNA vaccination (BNT162b2; Pfizer–BioNTech) scheme were given a second boost (3 doses). Patients with antibody titres >250 IU/ml after the first boost served as control group (high response [HR], 2 doses). (**a–h**) Comparison within NR/LR. (**a**) Antibody titers before and 3 to 5 weeks after the second SARS-CoV-2 mRNA vaccine boost. (**b–d**) Analysis of vaccine-reactive T-cell immunity following stimulation with SARS-CoV-2 Spike (S)-protein overlapping peptide pools. (**b**) The frequency of antigen-specific $CD4^+$ T cells. (**c**) The frequency of antigen-specific $CD8^+$ T cells. (**d**) The frequency of activated T follicular helper (Tfh) cells, as defined by CXC chemokine receptor 5 (CXCR5) expression. (**e,f**) Analysis of T-cell immunity following stimulation with (Delta-variant of concern [VOC]–S) peptides (Delta) and corresponding peptides from wild type (WT-S; Wuhan-1 isolate). (**e**) The frequency of antigen-specific $CD4^+$ T cells. (**f**) The frequency of antigen-specific $CD8^+$ T cells. (**g**) A comparison of neutralizing antibodies against pseudoviruses bearing WT-S or Delta-VOC-S. (**h**) The correlation between the activation of $CD4^+$ T cells and neutralization. White indicates no detection of humoral (antibody) or cellular (T-cell) immunity. (**i–o**) A comparison between HR (2 doses) and NR/LR (3 doses). (**i**) Antibody titers 3 to 5 weeks after the second SARS-CoV-2 mRNA vaccine boost. (**j,k**) Analysis of vaccine-reactive T-cell immunity following stimulation with SARS-CoV-2–S-protein overlapping peptide pools. (**j**) The frequency of antigen-specific $CD4^+$ T cells. (**k**) The frequency of antigen-specific $CD8^+$ T cells. (**l**) The frequency of activated Tfh cells, as defined by CXCR5 expression. (**m–o**) The analysis of T-cell immunity following stimulation with Delta-VOC-S peptides (Delta) and the corresponding peptides from WT-S (Wuhan-1 isolate). (**m**) The frequency of antigen-specific $CD4^+$ T cells. (**n**) The frequency of antigen-specific $CD8^+$ T cells. (**o**) Neutralizing antibodies against pseudoviruses bearing WT-S or Delta-VOC-S. The box plots indicate the 75th, 50th, and 25th quantiles, and the whiskers indicate 1.5× the interquartile range. *$P \leq 0.05$, ***$P \leq 0.001$, ****$P \leq 0.0001$. D0, day 0; D14, day 14; ND50, 50% neutralization dose; NS, not significant.

obtained from NR/LR following the third dose with ESRD HR after the second dose, overall, superior results in cellular immunity and WT neutralizing capacity were observed. Although S-binding antibody titers and S-reactive $CD4^+$ T cells were comparable between both cohorts (Figure 1i and j), WT neutralizing capacity and S-WT– and Delta-reactive $CD8^+$ T cells and S-reactive Tfh cells were significantly higher in NR/LR after the second booster (third dose) compared with HR requiring only 1 booster (2 doses; Figure 1g, h, n, and o).

Our data demonstrate that patients with ESRD can benefit from a second vaccination boost by improving their cellular and humoral immunity not only to the vaccination-specific strain but also against the globally expanding Delta-VOC.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Figure S1. Comparison of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) adaptive immunity to the wild-type (WT) variant or Delta variant of concern (VOC) in hemodialysis patients requiring a second vaccine booster. Patients with no/low titers after a regular prime-boost SARS-CoV-2 mRNA vaccination (BNT162b2; Pfizer–BioNTech) scheme were given a second boost (2 boosts). (**A**) Antibody titers before and 3 to 5 weeks after the final SARS-CoV-2 mRNA vaccine boost. (**B–D**) Analysis of vaccine-reactive T-cell immunity following stimulation with SARS-CoV-2 spike (S)-protein overlapping peptide pools. (**B**) Frequency of SARS-CoV-2 S-reactive $CD4^+$ T cells. (**C**) Frequency of SARS-CoV-2 S-reactive $CD8^+$ T cells. (**D**) Frequency of SARS-CoV-2 S-reactive Tfh cells as defined by CXC chemokine receptor 5 (CXCR5) expression. (**E,F**) Analysis of T-cell immunity following stimulation with Delta-VOC–S peptides (Delta) and corresponding peptides from WT-S (Wuhan-1 isolate). (**E**) The frequency of antigen (WT or Delta)–reactive $CD4^+$ T cells. (**F**) Frequency of WT or Delta–reactive $CD8^+$ T cells. The box plots indicate the 75th, 50th, and 25th quantiles, and the whiskers indicate 1.5× the interquartile range.

Figure S2. Gating strategy to identify spike (S)-protein reactive T cells. Peripheral blood mononuclear cells (PBMCs) were incubated for 16 hours with overlapping peptide pools (OPPs) of the complete severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) wild-type (WT) S-protein. Brefeldin A was added after 2 hours. The reactivity to the Delta variant of concern (VOC) mutations was evaluated using OPP peptides covering the Delta VOC mutations and the corresponding WT peptides. Stimulation with peptide diluent and *Staphylococcus aureus* enterotoxin B (SEB) as polyclonal stimulus served as negative and positive controls, respectively. Cells were acquired using a Cytoflex flow cytometer.

Table S1. Patient characteristics. Patients with no/low titers after a regular prime-boost severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccination (BNT162b2; Pfizer–BioNTech) scheme were given a second boost. Patients not requiring this additional boost (binding antibody titers > 250 IU/ml) serve as a control group (1 boost).

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Antibody and T-cell response to a third dose of SARS-CoV-2 mRNA BNT162b2 vaccine in kidney transplant recipients

To the editor: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination has become the standard of care for the prevention of severe coronavirus disease 2019 (COVID-19), with a strongly positive impact in countries in which vaccination has been effectively promoted.[S1] In kidney