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.

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).

Supplementary References.

1. Stumpf J, Siepmann T, Lindner T, et al. Humoral and cellular immunity to SARS-CoV-2 vaccination in renal transplant versus dialysis patients: a prospective, multicenter observational study using mRNA-1273 or BNT162b2 mRNA vaccine. *Lancet Reg Health Eur*. 2021;9:100178.
2. Thieme C, Blazquez-Navarro A, Safi L, et al. Impaired humoral but substantial cellular immune response to variants of concern B1.1.7 and B.1.351 in hemodialysis patients after vaccination with BNT162b2. *J Am Soc Nephrol*, in press.
3. Blazquez-Navarro A, Safi L, Meister TL, et al. Superior cellular and humoral immunity toward SARS-CoV-2 reference and alpha and beta VOC strains in COVID-19 convalescent as compared to the prime boost BNT162b2-vaccinated dialysis patients. *Kidney Int*. 2021;100:698–700.

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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

Table 1 | Baseline characteristics of patients and according to the immune response after the third dose of mRNA BNT162b2 vaccine (Pfizer–BioNTech)

Variable	Entire cohort (n = 80)	S^+/E^+ (n = 43)	S^+/E^- (n = 6)	S^-/E^+ (n = 13)	S^-/E^- (n = 18)
Age, yr, mean ± SD	63.6 ± 15.7	60.3 ± 14.9	66.7 ± 15.6	64.3 ± 18.1	70.2 ± 14.6
Sex (M/F), n	48/32	24/19	5/1	8/5	11/7
Time from transplantation, yr, median (IQR)	7.3 (3.4–14.1)	10.3 (4.7–16)	6.8 (3.5–17.5)	6.6 (1.6–14.2)	4.4 (1.7–6.8)
eGFR, ml/min per 1.73 m^2, mean ± SD	44.8 ± 17.2	50.2 ± 14.2	46.6 ± 17.3	44.0 ± 21.6	32.0 ± 14.8
IS regimen, n (%)					
Tacrolimus	46 (57.5)	22 (51.2)	6 (100)	10 (76.9)	8 (44.4)
Cyclosporine	14 (17.5)	13 (30.2)	0 (0)	1 (7.7)	0 (0)
MMF	61 (76.2)	32 (74.4)	4 (66.7)	13 (100)	12 (66.7)
AZA	9 (11.2)	6 (13.9)	0 (0)	0 (0)	3 (16.7)
mTOR inhibitors	10 (12.5)	7 (16.3)	1 (16.7)	1 (7.7)	1 (5.6)
Belatacept	12 (15)	1 (2.3)	0 (0)	1 (7.7)	10 (55.6)
Steroids	32 (40)	16 (37.2)	3 (50)	4 (30.8)	9 (50)

AZA, azathioprine; E, enzyme-linked immunosorbent spot; eGFR, estimated glomerular filtration rate; F, female; IQR, interquartile range; IS, immunosuppressive; M, male; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; S, serology.

transplant recipients (KTRs), SARS-CoV-2 vaccination has been recommended through international guidelines.[S2] Unfortunately, the data reported in KTRs are disappointing, with a low rate of seroconversion after 2 doses,[1] whereas the occurrence of severe infection after vaccination[2] is of concern. In this context, as of April 6, 2021, the French Administration recommends that solid organ transplant recipients receive a third mRNA vaccine dose at least 4 weeks after the second dose. Herein, we report the evaluation of humoral and cellular responses induced after the second and third doses of BNT162b2 (Pfizer–BioNTech) in 80 KTRs (see Supplementary Methods).

Baseline characteristics of the 80 KTRs are described in Table 1. After the second dose, 30 KTRs (37.5%) had anti–spike IgG antibodies; and 49 KTRs (61.2%) had these antibodies after the third injection ($P < 0.0001$) (Figure 1a). In patients already seropositive after the second dose (Figure 1b), median antibody titers increased from 217.1 arbitrary units (AU)/ml (interquartile range [IQR], 120.2–443.8 AU/ml) to 2238.3 AU/ml (IQR, 1934.4–7220.6 AU/ml; $P < 0.0001$). Forty-one KTRs (51.2%) displayed a significant number of IFN-γ–producing spike-reactive T cells after the second injection, and 56 (70%) displayed these cells after the third injection ($P < 0.0001$ compared with the second dose). No response to N, M, ORF3A, and ORF7A was evidenced, excluding a potential SARS-CoV-2 infection between the second and up to 1 month after the third dose. In these 41 patients, the median number of spike-reactive T cells increased from 225 spot-forming cells (SFCs)/10^6 CD3+ T cells (IQR, 90–355 SFCs/10^6 $CD3^+$ T cells) to 330 SFCs/10^6 CD3+ T cells (IQR, 187–610 SFCs/10^6 $CD3^+$ T cells; $P < 0.0001$) after the third dose (Figure 2b). Vaccination status after the third dose is summarized in Supplementary Figure S1.

Baseline characteristics and immune response after the third dose, according to baseline immunosuppressive regimen, are described in Supplementary Tables S1 and S2 and Supplementary Figure S2.

Two KTRs presented with symptomatic COVID-19 67 and 72 days, respectively, after the third vaccine injection. One KTR was hospitalized but did not require intensive care. Both KTRs had a low number of spike-reactive T cells after the third dose (65 and 50 SFCs/10^6 $CD3^+$ T cells), and only the second KTR had a low titer of anti-spike antibodies (145 AU/ml).

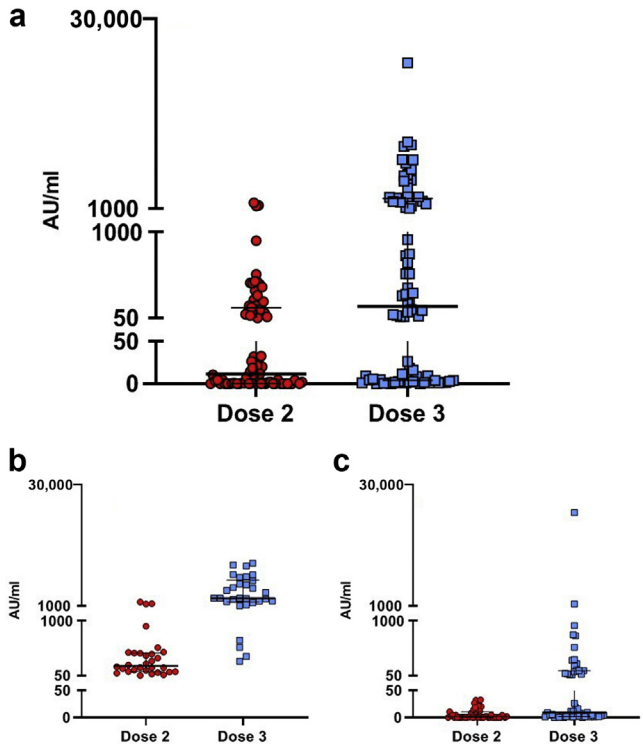

Figure 1 | Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) anti-spike (S) antibody response in kidney transplant recipients (KTRs) following a second and third injection of SARS-CoV-2 mRNA BNT162b2 vaccine (Pfizer–BioNTech). Median and interquartile range for anti–S IgG antibody titers are shown. The threshold for antibody positivity is 50 arbitrary units (AUs)/ml. (**a**) S IgG antibody titers in all 80 KTRs. (**b**) S IgG titers in the 30 KTRs who were seropositive after the second dose. (**c**) S IgG titers in the 50 KTRs who were seronegative after the second dose.

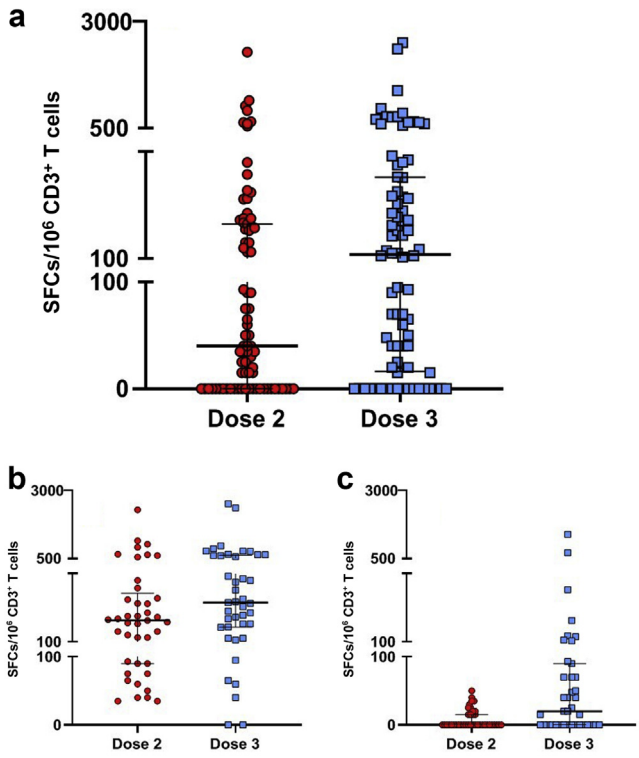

Figure 2 | Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–reactive interferon-γ–producing T cells in kidney transplant recipients (KTRs) following the second and third injection of the SARS-CoV-2 mRNA BNT162b2 vaccine (Pfizer–BioNTech). (**a**) Total numbers of T cells (expressed as spot-forming cells [SFCs]/10^6 $CD3^+$ T cells) reactive to overlapping peptide pools spanning the SARS-CoV-2 structural spike protein S (pools S1 and S2) in all 80 KTRs. Median and interquartile range are shown. (**b**) T-cell response in the 40 KTRs showing significant anti-spike T-cell numbers after the second dose. (**c**) T-cell response in the 40 KTRs without a significant T-cell response after the second dose (cutoffs for significant T-cell numbers were 25 and 40 SFCs/10^6 $CD3^+$ T cells for pools S1 and S2, respectively).

We did not report any severe adverse events after the third vaccine dose. None of the patients presented an acute rejection after vaccination. We did not report any *de novo* donor-specific antibodies until 1 month after the third dose.

We provide herein the largest cohort of KTRs explored for both humoral and T-cell responses after a third dose of BNT162b2 vaccine. The seropositivity rate increased, with an important increase in median antibody titers in responders, reaching levels that have been found associated with the presence of neutralizing antibodies.[S3,S4] Our results are in line with other reports in solid-organ transplant recipients.[3,S5,S6] Hall *et al.*,[4] in a double-blind, randomized, placebo-controlled trial of a third dose of mRNA-1273 vaccine (Moderna), found that seroconversion, virus neutralization, and specific T-cell counts were statistically higher in the mRNA-1273 group. In our study, the rate of positive T-cell response increased from 51.2% to 70% after the third dose, with a median spike-reactive T-cell number comparable to that observed in the general population after 2 doses.[S7]

Our results suggest that the immune response to a third BNT262b2 dose is highly influenced by the intensity of the immunosuppressive regimen. As already reported,[S8] belatacept-treated patients were the worst responders, developing no antibodies and no or only few specific T cells. Mycophenolic acid by itself appears associated with a lower seroconversion rate.[S5] However, in our study, KTRs on cyclosporine were more likely to develop humoral and cellular responses than KTRs on tacrolimus (Supplementary Table S2), regardless of mycophenolate mofetil coadministration.

In addition, the BNT262b2 vaccine appears safe with regard to acute rejection and *de novo* donor-specific antibodies, a potent risk factors for antibody-mediated rejection and graft loss,[S9] up to 1 month after the third dose.

In conclusion, a third dose of the SARS-CoV-2 mRNA BNT162b2 vaccine in KTRs increases the rate of positive antibody and T-cell responses in nonresponsive patients after the second dose and improves the magnitude of these responses in already seropositive patients. In patients without significant response after a third dose, anti–SARS-CoV-2 monoclonal antibodies could be proposed in prophylaxis,[S10] as recommended by the French Administration since August 6, 2021.

DATA STATEMENT

All relevant data are within the article.

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AUTHOR CONTRIBUTIONS

SC and DB designed the study; JL performed enzyme-linked immunosorbent spot assays; SC and DB collected data; MHam, SC, and DB analyzed the data; SC and DB wrote the article; and all authors provided feedback and critical review.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Figure S1. Flowchart of the humoral and cellular response to the third dose of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA BNT162b2 (Pfizer–BioNTech) vaccine in kidney transplant recipients (KTRs).

Figure S2. Anti-spike antibody and T-cell responses in kidney transplant recipients (KTRs) following the second and third injections of the BNT162b2 vaccine (Pfizer–BioNTech), according to the immunosuppressive regimen.

Table S1. Baseline characteristics of kidney transplant recipients (KTRs) and the immune response after the third dose, according to the immunosuppressive regimen.

Table S2. Baseline characteristics of kidney transplant recipients (KTRs) and the immune response after the third dose, according to the immunosuppressive regimen tacrolimus (Tac) + mycophenolate mofetil (MMF; n = 32) or cyclosporine + MMF (n = 10).

Supplementary References.

1. Bertrand D, Hamzaoui M, Lemée V, et al. Antibody and T cell response to SARS-CoV-2 messenger RNA BNT162b2 vaccine in kidney transplant recipients and hemodialysis patients. *J Am Soc Nephrol*. 2021;32:2147–2152.
2. Caillard S, Chavarot N, Bertrand D, et al. Occurrence of severe COVID-19 in vaccinated transplant patients. *Kidney Int*. 2021;100:477–479.
3. Kamar N, Abravanel F, Marion O, et al. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. *N Engl J Med*. 2021;385:661–662.
4. Hall VG, Ferreira VH, Ku T, et al. Randomized trial of a third dose of mRNA-1273 vaccine in transplant recipients. *N Engl J Med*. 2021;385:1244–1246.

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New-onset systemic lupus erythematosus beginning as class V lupus nephritis after COVID-19 vaccination

To the editor: We read the report by Tuschen *et al.* of a 42-year-old woman with a previous diagnosis of systemic lupus erythematosus (SLE) and class V lupus nephritis (LN) that developed a flare 1 week after vaccination with the mRNA coronavirus disease 2019 (COVID-19) vaccine BNT162b2 (Pfizer–BioNTech).[1] Here, we report a case of a 23-year-old woman who presented with nephrotic syndrome 1 week after vaccination with the first dose of the AZD1222 (ChAdOx1-S) nCoV-19 vaccine (AstraZeneca).

She had no previous medical history of disease and was taking no medications. She had not been previously infected by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Her family history was negative for autoimmune diseases. On July 21, 2021, she was vaccinated, without major adverse events. One week later, she developed abrupt eyelid edema and foamy urine that progressed to anasarca within days. She also experienced hair loss. Physical examination showed normal blood pressure and pitting edema up to the thighs. Her laboratory tests showed lymphopenia (1000 × 10^3/ml), a serum creatinine level of 0.8 mg/dl (estimated glomerular filtration rate of 104 ml/min per 1.73 m^2), a serum albumin level of 1.57 g/dl, a total cholesterol level of 351 mg/dl, proteinuria of 12.6 g/24 h (protein-to-creatinine ratio of 11.0 mg/mg), a complement C3 level of 85 mg/dl (reference, 87–200 mg/dl), and a C4 level of 12 mg/dl (reference, 19–52 mg/dl). Antinuclear antibody (ANA) titer was a 1:1280 homogeneous pattern; the anti-dsDNA-IgG level was 17.1 IU/ml; and antiphospholipid antibody panel was negative. Serology for SARS-CoV-2 demonstrated negative IgM and IgG antibodies to the nucleocapsid antigen (NCP), suggesting no previous infection by this virus. Anti–SARS-CoV-2–Spike IgG antibodies in response to vaccination were quantified at 32.8 UI/ml (reference, <1 UI/ml), suggesting an appropriate response to vaccination.

The kidney biopsy performed 1 week after the start of symptoms (2 weeks post-vaccination) demonstrated secondary membranous nephropathy, with diffuse thickening of the basement glomerular membrane and mild mesangial expansion. One of 13 glomeruli had sclerosis, and interstitial fibrosis was less than 10%, with no tubular atrophy, and normal vessels. Direct immunofluorescence revealed deposits of IgG, IgM, C1q, C3c, kappa, and lambda chains in the subepithelial and mesangial space. Electron microscopy showed mesangial and subepithelial electron-dense deposits (Figure 1). A diagnosis of SLE with class V LN was established. We started treatment with mycophenolate mofetil, high-dose glucocorticoids, hydroxychloroquine, and diuretics. After 3 weeks of follow-up, edema has improved and the patient continues follow-up.

Diverse glomerular diseases have been reported in association with COVID-19 vaccination, particularly podocytopathies, IgA nephropathy, and anti-neutrophil cytoplasmic antibody (ANCA) vasculitis.[2] For SLE, the Vaccination Against COVID in Systemic Lupus (VACOLUP) study[3] reported 2 renal flares (with no specification of the type of LN), and the report by Tuschen *et al.*[1] also corresponded to a class V LN flare. In animal models, the loss of the T-helper type 1 (Th1)/T-helper type 2 (Th2) balance is crucial for the development of LN, and may even determine the phenotype of the glomerulonephritis.[4] For example, the lack of the *WSX-1* gene in the MRL/lpr SLE mice model increases both the Th2 response, with increased interleukin-4, and the development of a disease resembling human membranous nephropathy with IgG1-dominant electro-dense deposits in the subepithelial space.[5] Moreover, the Th1 response has been associated with the development of LN proliferative variants.[6]

T cells are key to stimulating the immune response to vaccination. From phase 1 and 2 trials of the AZD1222 nCoV-19 vaccine, it has been shown that the spike-specific effector T-cell response presents early, from day 8 post-vaccination through day 56.[7] There is a robust Th1 response with an expansion of CD8+ T cells, with increases in cytokines such as tumor necrosis factor, interleukin-2, and interferon gamma. However, no Th2 response has been found after AZD1222 nCoV-19 vaccination.[8]