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Immunosuppression is critical to prevent rejection episodes in kidney transplant recipients (KTRs) and entails a reduced resistance to infections and efficacy of vaccines. The reduced efficacy of vaccines has challenged COVID-19 vaccination strategies for KTRs.[1] This patient group displays a lower-than-normal antibody response against the COVID-19 vaccines, which has left a large proportion with low levels of spike antibodies even after several booster doses.[2–5] In addition, SARS-CoV-2 has shown an exceptional ability to adapt to the original vaccines, which has gradually rendered vaccine-induced antibodies less neutralizing.[5] Together, this has generated the need for updated COVID-19 vaccines with restored efficacy against newer SARS-CoV-2 subvariants, in particular the Omicron variant of concern, which has dominated the pandemic since late 2021. During 2022, Pfizer-BioNTech adapted their original BNT162b2 mRNA COVID-19 vaccine to target the Omicron BA.1 and later the BA.4/BA.5 subvariants, in addition to the Wuhan-1 index strain. The resulting bivalent mRNA vaccines were approved during autumn 2022 and recommended to vulnerable patients including KTRs. Since then, the more transmissible Omicron subvariant XBB.1.5 has rapidly replaced the BA.1/BA.4/BA5 subvariants, in particular in the United States where XBB.1.5 prevalence is 88% at the time of writing (April 10, 2023).[6] Consequently, this has raised concerns about whether the updated vaccines still provide the intended protection against COVID-19 in this patient group. To answer this question, we analyzed the capacity of KTRs to neutralize authentic Omicron XBB.1.5 after receiving the bivalent vaccine from Pfizer-BioNTech.

Sera from 46 KTRs collected 1 month after receiving a BNT162b2 bivalent mRNA vaccination from Pfizer-BioNTech as a fifth dose were tested for neutralization of SARS-CoV-2 Omicron XBB.1.5. In addition, serum-neutralization against ancestral SARS-CoV-2, BA.1, BA.5, and XBB.1.5 were measured in a subgroup of representative KTRs ($n = 21$) before and after receiving the bivalent vaccine. For reference, sera from healthy individuals ($n = 26$) and KTRs ($n = 25$) were tested against XBB.1.5 one month after the third BNT162b2 monovalent vaccination. All participants were nucleocapsid IgG antibody seronegative, indicating not previously infected. All groups were matched on the basis of time from vaccination to serum collection (median 33 days, interquartile range 30–39 days). The KTRs were matched according to age (median 67 years, interquartile range 59–73 years) whereas the healthy controls were younger (median 48 years, interquartile range 38–57 years). The neutralization capacity was measured using a microneutralization assay as recently described.[7] In this assay, cultured Vero E6 cells are challenged with authentic SARS-CoV-

2 isolates in 2-fold serially diluted serum. The highest dilution protecting more than 90% of the cells from virus-induced cytopathic effects is designated the ED90 titer. A dilution of 10 was used as a threshold of a neutralizing response, because a titer of 8.8 in microneutralization assays has been suggested to indicate real-world protection against Omicron.[8] The SARS-CoV-2 strains were clinical isolates identified by whole-genome sequencing. The samples were analyzed for spike antibodies using the Liaison TrimericS IgG Quantitative immunoassay (Diasorin, Saluggia, Italy). For details on patient groups, SARS-CoV-2 strains, immunoassays, and statistics, see Supplementary Material. A flow chart showing selection criteria for KTRs is shown in Supplementary Figure S1.

Clinical characteristics of the KTRs are shown in Table 1 and the spike antibody levels in Figure 1a. Overall, bivalent vaccination increased the fraction of KTRs with above-threshold neutralizing capacity against XBB.1.5 from 52% (11/21) to 76% (35/46) ($P = 0.09$, Fisher Exact test) and increased the geometric mean titer (GMT) from 9.1 (95% confidence interval [CI] 6.6–12.5) to 22.2 (95% CI 15.4–32.1) ($P = 0.0025$, Mann-Whitney test). This was significantly more than the responding fractions and the GMT of both KTRs (4%, GMT = 5.1) and healthy controls (35%, GMT = 6.9) after the third monovalent booster ($P < 0.0001$ and 0.0002, respectively, Mann-Whitney test) (Figure 1b). Spike antibody levels after bivalent vaccination (geometric mean 3654 binding antibody units/ml, 95% CI 1956–6825 binding antibody units/ml) correlated with the XBB.1.5 neutralization capacity ($r = 0.80$, $P < 0.0001$, Spearman's correlation, Figure 1a and b). After bivalent vaccination the serum-GMT for the KTR subgroup ($n = 21$), were for ancestral SARS-CoV-2: 154.8 (95% CI 75.1–318.9); for BA.1: 77.4 (95% CI 35.0–171.4), for BA.5: 52.1 (95% CI 25.6–105.8), and for XBB.1.5: 17.5 (95% CI 9.7–31.8). These differences were statistically significant ($P < 0.0001$, Friedmans test). However, the increases in GMT induced against these subvariants following bivalent vaccination were not significantly different (GMT increase x1.8-x2.6, $P = 0.05$, Friedmans test, Figure 1c). Neither induction nor maintenance immunosuppression were associated with the bivalent vaccine response ($P = 0.852$ and $P = 0.122$, respectively, Fisher exact test).

We recently found that the Pfizer-BioNTech bivalent mRNA vaccine largely failed to protect immune-compromised cancer patients against XBB.1.5.[7] Similarly, a considerable fraction of the KTRs analyzed here remained below neutralization threshold after receiving a bivalent vaccine. Still, compared to younger healthy individuals and KTRs after 3 monovalent BNT162b2 doses, the bivalent boosted KTRs were overall better protected against XBB.1.5. This is encouraging because KTRs throughout the pandemic have struggled with evoking a protective humoral immune response after vaccination as compared to healthy controls.[1–5] Moreover, our data show that bivalent vaccination, as intended, elicits a neutralizing humoral response across both new and old SARS-CoV-2 variants in the KTRs. The study is limited by the small sample size, groups are not fully comparable with respect to treatment history, no KTR group vaccinated with a fourth or fifth dose of the monovalent vaccine were included, and an ED90 threshold value indicating real-world protection against XBB.1.5 is not yet available. Overall, our data indicate that KTRs benefit from bivalent vaccination, but the most immune deficient may require additional boosters to reach a neutralizing humoral response.

Table 1. Characteristics of kidney transplant recipients

Demographic characteristics	Monovalent (3rd dose)[a]	Bivalent (5th dose)[b]
Numbers (%)	25 (35)	46 (65)
Age Y (IQR)	65 (57–74)	67 (59–72)
Female (%)	11 (44)	19 (41)
TX characteristics		
Time from TX Y (IQR)	6 (3–12)	9 (6–16)
TX number		
First TX (%)	20 (80)	37 (80)
Second TX (%)	5 (20)	8 (17)
Third TX (%)	0 (0)	1 (2)
Deceased donor (%)	17 (68)	34 (74)
Induction		
Rituximab (%)	0 (0)	1 (2)
anti-CD25 (%)	13 (52)	35 (76)
anti-CD25 + Rituxmab (%)	2 (8)	3 (7)
Thymoglobuline (%)	6 (24)	3 (7)
Thymoglobuline + Rituxmab (%)	3 (12)	2 (4)
Unknown	1 (4)	2 (4)
Maintenance		
Tacrolimus (%)	19 (76)	36 (78)
Ciclosporin A (%)	4 (16)	9 (20)
MMF (%)	24 (96)	39 (85)
Azathioprine (%)	1 (4)	6 (13)
Steroids (%)	5 (20)	8 (17)
Renal function		
eGFR ml/min (IQR)	41 (25–62)	45 (35–68)
Underlying disease		
[c]Non-immune disease (%)	10 (40)	25 (54)
[d]Immune disease (%)	9 (36)	13 (28)
Diabetes mellitus (%)	2 (8)	4 (9)
Unknown (%)	4 (16)	4 (9)

eGFR, estimated glomerular filtration rate; IQR, interquartile range; MMF, mycophenolate mofetil; N/A, not applicable; TX, transplant; Y, years.
[a]KTRs who received 3 vaccine doses with the monovalent BNT162b2 (Pfizer-BioNTech).
[b]KTRs who received 4 monovalent BNT162b2 vaccine doses followed by 1 bivalent BNT162b2 (Pfizer-BioNTech) mRNA vaccination.
[c]Immune disease designate diseases such as glomerulonefritis, systemic lupus, ANCA associated vasculitis etc.
[d]Nonimmune disease designate diseases such as cystic kidney diseases, Alports disease, urinary outlet obstruction etc.

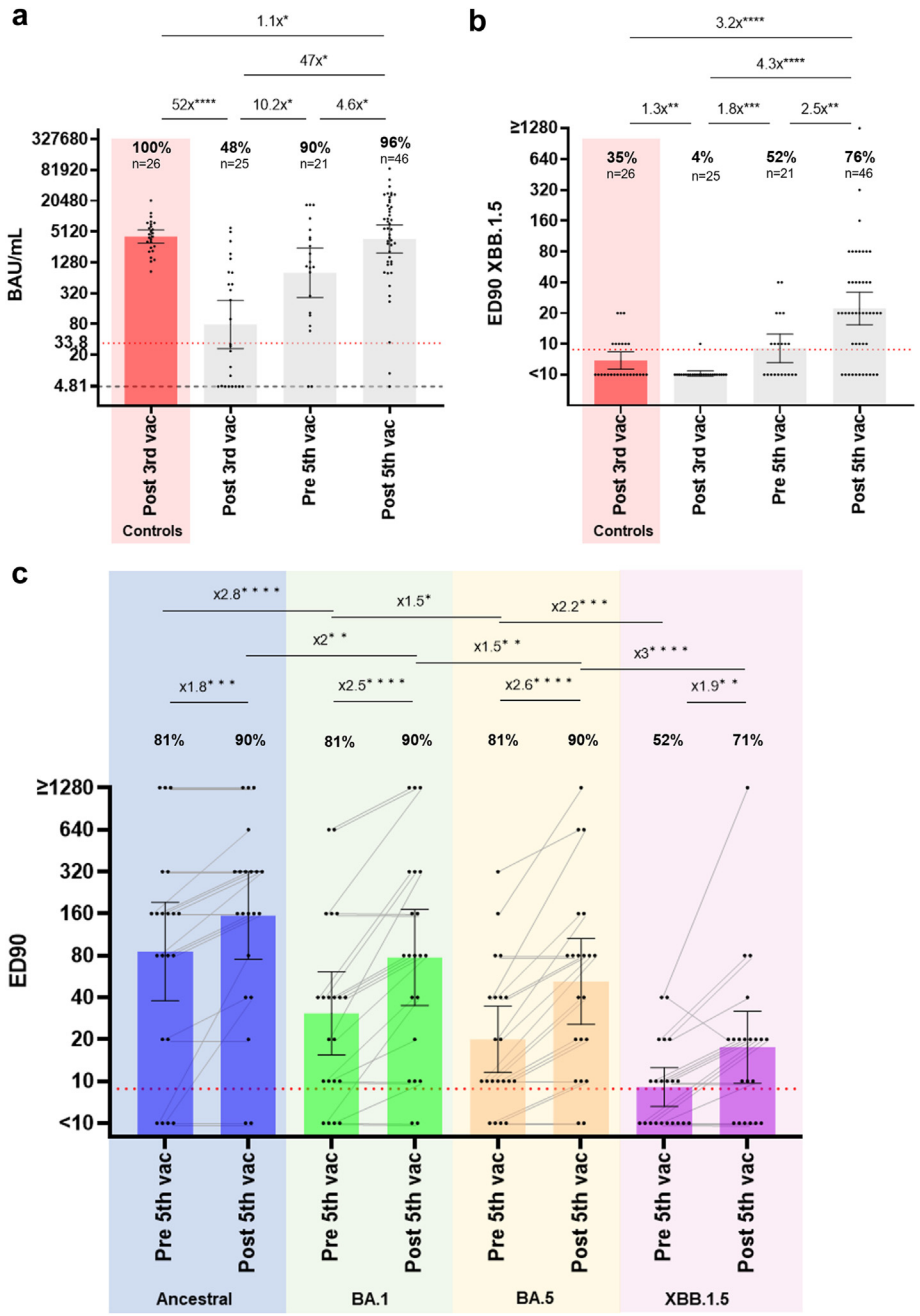

Figure 1. Antispike antibody levels and neutralization capacity in kidney transplant recipients against SARS-CoV-2 Omicron subvariants after Pfizer-BioNTech bivalent mRNA vaccination. (a) Anti-SARS-CoV-2 spike specific IgG antibody levels in kidney transplant recipients (KTRs) and healthy controls after the third Pfizer-BioNTech monovalent mRNA vaccine booster (Post 3rd vac) and before and after Pfizer-BioNTech bivalent mRNA vaccination (Pre 5th vac and Post 5th vac, respectively). Bars indicate geometric mean and error bars indicate 95% confidence interval. The red dotted line indicates the threshold of seropositivity as provided by the manufacturer. The black dotted line indicates lower level of detection. Controls: healthy controls. The 4 groups were initially compared using 1-way ANOVA followed by one-to-one comparison using the unpaired t-test. The antibody levels in healthy controls and in KTRs after the third vaccination were extracted from our previous study.[5] (b) Virus neutralization titers of authentic XBB.1.5 measured as effective dilution 90% (ED90) using sera from KTRs and healthy controls at the indicated levels of vaccination. Bars indicate geometric mean titers (titers <10 counted as 5 and ≥ 1280 as 1280) and error bars indicate 95% confidence interval. The red dotted line indicates the neutralizing threshold titer of 1:8.8. Controls: healthy controls. The 4 groups were initially compared using the Kruskal-Wallis test followed by one-to-one comparison using the Mann-Whitney test. (c) ED90 titers of KTR sera ($n = 21$) against ancestral SARS-CoV-2, BA.1, BA.5, and XBB.1.5 Omicron subvariants. The bars indicate geometric mean titers and error bars indicate 95% confidence interval. Changes in neutralization capacity in individual patients from before to after the bivalent vaccination are indicated with gray lines. The 4 groups were initially compared using the Friedman test followed by one-to-one comparison using the Wilcoxon test. The red dotted line indicates the neutralizing threshold titer of 1:8.8. Fold differences between groups are indicated together with levels of significance: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$. The percentage of samples with antibody levels (a) or neutralizing titers (b and c) above their respective thresholds are indicated above each column. BAU, binding antibody units.

DISCLOSURE

All the authors declared no competing interests.

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Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Patient Groups.

SARS-CoV-2 strains, Immunoassays, Statistics.

Figure S1. Flow chart showing selection criteria for KTRs.

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