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# Humoral response after a third and fourth dose of mRNA-based SARS-CoV-2 vaccine in previously seronegative kidney transplant recipients

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**Summary** Growing evidence shows diminished response to mRNA-based SARS-CoV-2 vaccination in kidney transplant recipients. We aimed to investigate the seroconversion rate after a 3rd and 4th dose of mRNA vaccination in kidney transplant recipients without prior antibody response to two or three vaccination doses.
This retrospective study included 324 prevalent kidney transplant recipients of a single tertiary transplantation center of which 157 remained seronegative, defined as anti-spike-RBD-IgG antibody titer <7.1 BAU/ml, after two doses of mRNA-based SARS-CoV-2 vaccination. Maintenance immunosuppression was not changed. The median patient age was 60.6 years (IQR 51.4–68.1 years), 66.9% were male. Positivity for anti-spike-RBD-IgG (≥7.1 BAU/ml) was measured 4–5 weeks after administration of a 3rd and 4th vaccine dose.
Seroconversion rates were 63.9% after a 3rd dose and 29.3% after a 4th dose of vaccine. Cumulative prevalence of seropositivity was 51.5% after 2 doses, 80.5% after 3 doses and 84.2% after 4 doses.
In conclusion, seroconversion can be achieved in the majority of the kidney transplant recipients by administrating three or four doses of mRNA vaccine without changing maintenance immunosuppression.

**Keywords** Kidney transplantation · COVID-19 · Vaccination · MRNA · Immunogenicity

## Abbreviations

| | |
|---|---|
| ADPKD | Autosomal dominant polycystic kidney disease |
| BAU/ml | Binding antibody unit per milliliter |
| BMI | Body mass index |
| BPAR | Biopsy-proven acute rejection |
| IQR | Interquartile range |
| mRNA | Messenger ribonucleic acid |
| MTORi | Mammalian target of rapamycin inhibitor |
| PCR | Polymerase chain reaction |
| RBD | Receptor binding domain |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus type 2 |
| SD | Standard deviation |

## Introduction

The risk of severe COVID-19 is higher in kidney transplant recipients compared to the immunocompetent persons [1]. mRNA vaccination has shown to be highly efficient in a broad range of severe acute respiratory syndrome of coronavirus type 2 (SARS-CoV-2) in the general population [2]. Vaccine efficacy after the second vaccination was reported to be 92% for documented infection, 94% for symptomatic COVID-19, 87% for hospitalization and 92% for severe disease [2]. Nevertheless, growing evidence indicates dimin-

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ished responsiveness to mRNA vaccination in organ transplant recipients, especially after two doses [3, 4]. According to published data, the de novo detectable humoral response rate after the 3rd vaccination is about 50% in kidney transplant recipients, probably leaving many patients with little or no protection against COVID-19 [5]. This is of great clinical relevance, as COVID-19-related hospitalizations and deaths of transplant patients have been observed despite prior SARS-CoV-2 vaccinations [6, 7].

Herein, we report our center's (Ordensklinikum Linz, Elisabethinen Hospital) experience on seroconversion of prevalent kidney transplant recipients previously unresponsive to SARS-CoV-2 vaccinations who received a 3rd and 4th dose of SARS-CoV-2 mRNA vaccine.

## Methods

### Cohort

In this single center retrospective cohort study, 324 prevalent kidney transplant recipients in our COVID-19 vaccine program were included. Kidney transplant recipients were prioritized to receive COVID-19 vaccination as soon as vaccines became available in Austria in January 2021.

### Intervention

For the 1st and 2nd dose between 15 January and 30 June 2021, both mRNA vaccine types (mRNA-1273, Spikevax©, Moderna (Cambridge, Massachusetts, USA) and BNT162b2, Comirnaty©, Biontech (Mainz, Germany)/Pfizer (New York City, New York, USA)) were administered at standard dose (100 µg for mRNA-1273 and 30 µg for BNT162b2) and standard intervals (4 weeks for mRNA-1273 and 3 weeks for BNT162b2), depending on availability given the shortage of vaccines at the early stages of the vaccine program roll out in Austria ($n=74$, 22.8% mRNA-1273; $n=250$, 77.2% BNT162b2). After the 2nd dose 157 patients out of 324 (48.5%) remained seronegative. As recommended by joint statements of the Austrian Society of Transplantation and the Austrian Society of Nephrology, patients without seroconversion to prior vaccinations were invited to receive a 3rd dose of mRNA-based SARS-CoV-2 vaccine between 2 September and 21 October 2021 and a 4th dose between 18 October and 8 December 2021 [8, 9].

Based on published data and our own work showing higher odds of seroconversion after vaccination with mRNA-1273 compared to BNT162b2 in kidney transplant recipients, we preferred mRNA-1273 vaccine for the 3rd and 4th doses in seronegative patients [10]. The dose for the 3rd and 4th vaccination was 100 µg of mRNA-1273 or 30 µg of BNT162b2. The administration of the 3rd and 4th doses was conducted in our transplantation center, in outpatient clinics and vaccination centers depending on availability and the distance to the patients' residence. Blood samples for the assessment of the response to the vaccination were taken exclusively in our transplantation center outpatient clinic as part of routine checks. Maintenance immunosuppression was continued throughout the entire observation period according to center-specific standards. Importantly, immunosuppression was not modified or decreased in patients without seroconversion after SARS-CoV-2-vaccinations. Baseline patient characteristics were extracted from the medical records. The Austrian electronic vaccination card and electronic medical records were used to complete missing data. Patients who failed to appear for follow-up were contacted by telephone call and asked for their drop-out reasons.

### Measurement of humoral response

The humoral response to the vaccination was determined after each vaccination dose: titers of anti-SARS-CoV-2 antibodies directed against the receptor binding domain of the S1 subunit of the spike (S) protein were measured 37 days (IQR 32–40 days) after the administration of the 3rd and 26 days (IQR 26–27 days) after the 4th dose. SARS-CoV-2 IgG II Quant assay (Abbott Ireland Diagnostics Division, Sligo, Ireland) was used, results were reported in binding antibody units per ml (BAU/ml) [11]. A negative response was defined as a titer <7.1 BAU/ml according to the manufacturer in accordance with previous studies [10, 12]. The first detectable humoral response was defined as seroconversion. Antibody trajectories over time were not measured routinely due to transplantation center policy.

### COVID-19 infections

Screening for SARS-CoV-2 infections in asymptomatic patients was not performed in our transplantation center. SARS-CoV-2 infections in symptomatic patients (thus having COVID-19 per definition) were diagnosed by polymerase chain reaction (PCR) tests outside of our hospital and available only for analysis in patients self-reporting their infection. A COVID-19 infection was diagnosed in one seronegative kidney transplant recipient after two doses (asymptomatic infection) and in three seronegative kidney transplant recipients after three doses (two treated in hospital, one at home).

### Statistical analysis

Continuous variables were described by mean and standard deviation or median and interquartile range depending on data distribution. We calculated frequencies and proportions to describe count data. For explorative statistical analyses, proportions were compared using Fisher's exact test. Continuous variables

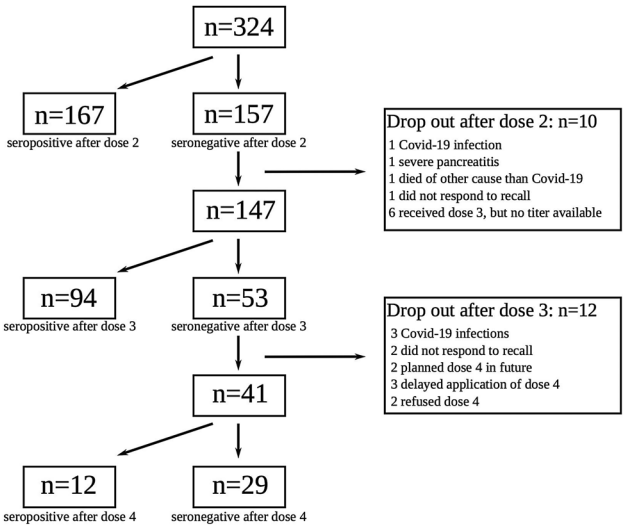


**Fig. 1** Patient flow chart for drop-out

were compared by the Student's t-test or the Mann-Whitney test depending on the distribution of data. A *P*-value $<0.05$ (two sided) was regarded as statistically significant. Because of the exploratory nature of the statistical analyses, no correction for multiple testing was performed. Data analysis was done using GraphPad Prism (GraphPad Software, San Diego, CA, USA) Version 9.3.1. The study was approved by the Ethics Committee (ID 1100/2021). Patients provided written informed consent.

## Results

Of 324 kidney transplant recipients participating in the study, 10 patients dropped out after dose 2 and 12 patients dropped out after dose 3. A patient flow chart including reasons for patient drop-out is shown in Fig. 1.

Of 147 kidney transplant recipients who remained seronegative after 2 vaccine doses and received a 3rd dose, 125 (85%) received mRNA-1273 and 22 (15%) received BNT162b2. After the 3rd vaccine dose, 94 (63.9%) patients developed detectable anti-Spike-RBD-IgG antibodies, with a median titer of 242.6 BAU/ml (IQR 39.9–821.1 BAU/ml). Characteristics of patients with or without seroconversion after a 3rd vaccine dose are shown in Table 1. In an exploratory statistical analysis, no significant differences between patients with and without seroconversion after a 3rd vaccine dose were detected for age ($p=0.18$), sex ($p=0.27$), mycophenolate use ($p=0.6$) or dose ($p=0.5$), kidney transplant vintage ($p=0.13$) or serum creatinine ($p=0.07$). An overview of *p*-values and the dose of immunosuppression are presented in supplementary tables 1 and 2.

Of 41 kidney transplant recipients who remained seronegative after 3 vaccine doses and received a 4th dose, 38 patients received mRNA-1273 (92.7%) and 3 patients (7.3%) received BNT162b2. After the 4th vaccine dose, 12 (29.3%) patients developed a humoral response with a median antibody titer of 44.7 BAU/ml (IQR 17.9–111.6 BAU/ml). The characteristics of seronegative and de novo seropositive patients after dose 4 are demonstrated in Table 1. In an exploratory statistical analysis, no significant differences between patients with and without seroconversion after a 4th vaccine dose were detected for age ($p=0.8$), sex ($p=0.7$), mycophenolate use ($p=0.9$) or dose ($p=0.12$), kidney transplant vintage ($p=0.9$) or serum creatinine ($p=0.6$). Seroconversion rates of seronegative kidney transplant recipients were 51.54% of $n=324$ patients after a 2nd dose, 63.95% of $n=147$ seronegative patients after a 3rd dose and 29.27% of $n=41$ seronegative patients after a 4th vaccine dose, as shown in Fig. 2.

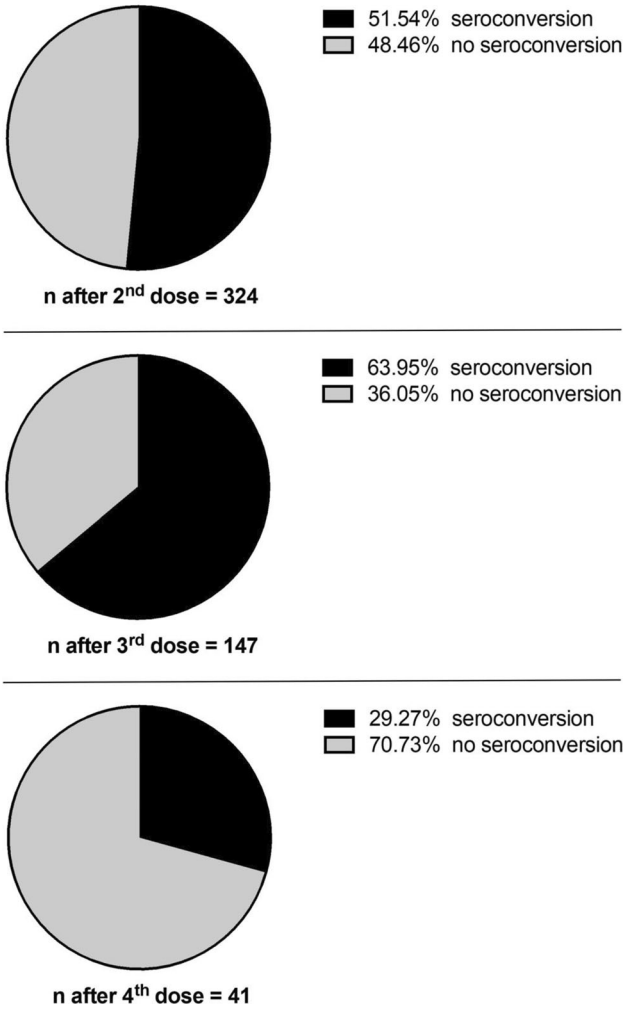


**Fig. 2** Seroconversion rates defined as anti-Spike-RBD-IgG antibody titer ≥7.1 (BAU/ml) after a 2nd ($n=324$; seroconversion rate of 51.5%), 3rd ($n=147$; seroconversion rate of 63.9%) and 4th ($n=41$; seroconversion rate of 29.2%) vaccine dose with mRNA -based SARS-CoV-2-vaccines in kidney transplant recipients without seroconversion after previous vaccinations. *RBD* receptor binding domain, *BAU/ml* binding antibody units per milliliter, *mRNA* messenger ribonucleid acid

**Table 1** Characteristics of the entire cohort of kidney transplant recipients before dose 1 and after doses 3 and 4 of mRNA-based vaccine

| | | Baseline | Remained seronegative after 3rd dose | Became seropositive after 3rd dose | Remained seronegative after 4th dose | Became seropositive after 4th dose |
|---|---|---|---|---|---|---|
| *Number of patients* | – | *n* = 324 | *n* = 53 | *n* = 94 | *n* = 29 | *n* = 12 |
| *Type of vaccine* | mRNA-1273 | *n* = 74; 22.84% | *n* = 51; 96.27% | *n* = 74; 78.72% | *n* = 26; 89.66% | *n* = 12; 100.0% |
| | BNT162b2 | *n* = 250; 77.16% | *n* = 2; 3.77% | *n* = 20; 21.28% | *n* = 3; 10.34% | *n* = 0; 0.0% |
| *Sex (male/female)* | – | *n* = 217; 66.98%/ *n* = 107; 33.02% | *n* = 32; 60.38%/ *n* = 21; 39.63% | *n* = 66; 70.21%/ *n* = 28; 29.79% | *n* = 19; 65.52%/ *n* = 10; 34.49% | *n* = 7; 58.33%/ *n* = 5; 41.67% |
| *Age (years) (median, IQR)* | – | 60.60 (51.43–68.18) | 65.10 (54.85–71.90) | 58.64 (51.80–64.63) | 66.80 (57.45–73.60) | 67.75 (56.28–70.83) |
| *BMI (kg/m²)* (median, IQR) | – | 26.08 (22.89–29.41) | 25.47 (23.04–29.11) | 25.88 (22.93–29.39) | 25.36 (23.04–28.22) | 25.54 (23.79–29.88) |
| *Primary renal disease* | Diabetes mellitus type 1 | *n* = 4; 1.24% | *n* = 0; 0.0% | *n* = 1; 1.06% | *n* = 0; 0.0% | *n* = 0; 0.0% |
| | Diabetes mellitus type 2 | *n* = 18; 5.56% | *n* = 6; 11.32% | *n* = 4; 4.26% | *n* = 5; 17.24% | *n* = 0; 0.0% |
| | Hypertensive/vascular | *n* = 19; 5.86% | *n* = 6; 11.32% | *n* = 5; 5.32% | *n* = 4; 13.79% | *n* = 1; 8.33% |
| | ADPKD | *n* = 48; 14.81% | *n* = 7; 13.21% | *n* = 17; 18.09% | *n* = 4; 13.79% | *n* = 1; 8.33% |
| | Glomerulonephritis | *n* = 136; 41.98% | *n* = 17; 32.08% | *n* = 42; 44.68% | *n* = 8; 27.59% | *n* = 5; 41.67% |
| | Reflux nephropathy/ pyelonephritis | *n* = 26; 8.02% | *n* = 3; 5.66% | *n* = 8; 8.51% | *n* = 1; 3.45% | *n* = 1; 8.33% |
| | Other | *n* = 73; 22.53% | *n* = 14; 26.42% | *n* = 17; 18.09% | *n* = 7; 24.14% | *n* = 4; 33.34% |
| *Comorbidities* | Diabetes | *n* = 84%; 25.93% | *n* = 14; 26.42% | *n* = 26; 27.66% | *n* = 9; 31.03% | *n* = 2; 16.67% |
| | Coronary artery disease | *n* = 95; 29.32% | *n* = 14; 26.42% | *n* = 28; 29.79% | *n* = 10; 34.48% | *n* = 2; 16.67% |
| | Congestive heart failure | *n* = 25; 7.71% | *n* = 5; 9.43% | *n* = 7; 7.45% | *n* = 1; 3.45% | *n* = 2; 16.67% |
| | Peripheral occlusive vascular disease | *n* = 53; 16.36% | *n* = 7; 13.21% | *n* = 15; 15.96% | *n* = 6; 20.69% | *n* = 0; 0.00% |
| | Cerebrovascular disease | *n* = 64; 19.75% | *n* = 12; 22.64% | *n* = 22; 23.40% | *n* = 8; 27.59% | *n* = 3; 25.00% |
| *Immunosuppressive therapy* | Tacrolimus | *n* = 251; 77.47% | *n* = 48; 90.57% | *n* = 81; 86.17% | *n* = 27; 93.10% | *n* = 11; 91.67% |
| | Mycophenolate | *n* = 228; 70.37% | *n* = 47; 88.68% | *n* = 87; 92.56% | *n* = 27; 93.10% | *n* = 11; 91.67% |
| | Cyclosporin A | *n* = 35; 10.80% | *n* = 3; 5.66% | *n* = 6; 6.38% | *n* = 1; 3.45% | *n* = 1; 8.33% |
| | Azathioprine | *n* = 26; 8.02% | *n* = 1; 1.89% | *n* = 3; 3.19% | *n* = 0; 0.0% | *n* = 1; 8.33% |
| | Glucocorticoids | *n* = 222; 68.52% | *n* = 40; 75.47% | *n* = 68; 72.34% | *n* = 21; 72.41% | *n* = 11; 91.67% |
| | mTORi | *n* = 30; 9.26% | *n* = 1; 1.89% | *n* = 4; 4.26% | *n* = 1; 3.45% | *n* = 0; 0.0% |
| | Belatacept | *n* = 5; 1.54% | *n* = 1; 1.89% | *n* = 1; 1.07% | *n* = 0; 0.0% | *n* = 0; 0.0% |
| *Donor type* | Living donor | *n* = 80; 24.69% | *n* = 11; 20.75% | *n* = 22; 23.40% | *n* = 4; 13.79% | *n* = 1; 8.33% |
| | Deceased donor | *n* = 244; 75.31% | *n* = 42; 79.25% | *n* = 72; 76.60% | *n* = 25; 86.21% | *n* = 11; 91.67% |
| *Number of kidney transplants* | 1 | *n* = 263; 81.17% | *n* = 46; 86.79% | *n* = 67; 71.28% | *n* = 25; 86.21% | *n* = 11; 91.67% |
| | 2 | *n* = 48; 14.81% | *n* = 7; 13.21% | *n* = 19; 20.21% | *n* = 4; 13.79% | *n* = 1; 8.33% |
| | 3+ | *n* = 13; 4.02% | *n* = 0; 0.0% | *n* = 8; 8.51% | *n* = 0; 0.0% | *n* = 0; 0.0% |
| *Time since transplantation (years)* | | | | | | |
| (median, IQR) | – | 7.00; 3.42–11.28 | 3.60; 1.4–10.0 | 5.15; 2.38–8.73 | 3.40; 1.40–10.60 | 4.40; 2.52–8.13 |
| *Blood parameters* | | | | | | |
| (median, IQR) | Creatinine (mg/dl) | 1.38; 1.11–1.83 | 1.54; 1.19–1.94 | 1.34; 1.10–1.75 | 1.54; 1.25–1.93 | 1.52; 1.21–1.88 |
| (mean ± SD) | Hemoglobin (g/dl) | 13.55 ± 1.84 | 13.03 ± 1.62 | 13.79 ± 1.69 | 12.93 ± 1.68 | 13.38 ± 1.53 |

*IQR* interquartile range, *BMI* body mass index, *ADPKD* autosomal dominant polycystic kidney disease, *SD* standard deviation

Of the entire cohort of 324 kidney transplant recipients, 84.2% (*n* = 273) ultimately developed anti-Spike-RBD-IgG antibodies after 2, 3 or 4 doses of mRNA vaccination (Fig. 3).

## Safety

The application of a 3rd or 4th vaccination elicited the typical local and systemic reactions, which were generally mild. One patient who received the first kidney transplantation approximately 1 year before receiving the 3rd vaccine dose was diagnosed with a biopsy-proven acute rejection (BPAR), classified as Banff Ia, 2 weeks after the 3rd vaccine dose. Another patient who received the first kidney transplant approximately 1.5 years before the 2nd vaccination was diagnosed with BPAR classified as Banff Ia with acute and chronic features 4 months after the 2nd vaccina-

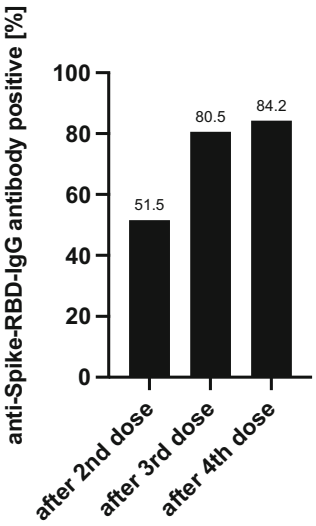


**Fig. 3** Cumulative seroprevalence of anti-Spike-RBD-IgG antibody positivity (≥7.1 BAU/ml) in prevalent kidney transplant recipients (KTR) after 2, 3 or 4 doses of mRNA-based SARS-CoV-2 vaccine. *RBD* receptor binding domain, *BAU/ml* binding antibody units per milliliter, *mRNA* messenger ribonucleic acid

tion. This patient had a history of self-reported nonadherence to immunosuppression.

Reasons for refusal of a 3rd or 4th vaccine dose are shown in Fig. 1 and did not appear to be related to adverse effects of SARS-CoV-2 vaccinations.

## Discussion

The main finding of this study is that seroconversion defined as anti-Spike-RBD-IgG antibodies ≥7.1 BAU/ml can be achieved in the majority (84.2%) of prevalent kidney transplant recipients without modification of maintenance immunosuppression. This may be of clinical importance as seroconversion rates are known to be very low in kidney transplant recipients after two doses of mRNA-based SARS-CoV-2 vaccine. An alternative approach to repeated vaccinations to increase seroconversion rates to SARS-CoV-2 vaccinations in kidney transplant recipients is transient reduction of immunosuppression. Several trials investigating this approach are currently ongoing (e.g. NCT05077254; NCT05060991), but results are not available yet. Therefore, it can currently not be concluded which vaccination strategy should be advocated in terms of efficacy (e.g. seroconversion rates) and safety (e.g. graft rejection).

Due to lack of reaching statistical significance, patient characteristics such as age, kidney transplant vintage or serum creatinine may not be fully suitable to predict (non)responsiveness after the 3rd dose, but still may influence vaccine responsiveness when studied in larger cohorts. Although the seroconversion rate was higher after the 3rd dose (63.9%) compared to the 4th dose (29.3%) in patients without seroconversion to previous vaccinations, our findings indicate that seroconversion can still be achieved in approximately one third of kidney transplant recipients who failed to develop anti-Spike-RBD-IgG antibodies to three previous vaccinations. Advocating a 3rd and 4th vaccine dose in patients without seroconversion to prior vaccinations therefore seems justifiable, despite the diagnosis of BPAR in two patients during the observation period. One patient developed BPAR shortly after receiving a 3rd vaccine dose without obvious reasons for graft rejection, rendering a causal relationship between vaccination and BPAR possible. The other patient had a history of self-reported nonadherence to immunosuppressive therapy and had also signs of chronic rejection in kidney graft histology, suggesting nonadherence as the major cause for graft rejection. The question of causal relationship between SARS-CoV-2 mRNA-based vaccination and BPAR needs to be addressed in further studies. Currently, only single cases of BPAR associated with SARS-CoV-2 vaccinations have been reported in kidney transplant recipients [13, 14].

Our study results are generally in line with findings reported by other research groups, but it might be worthwhile to highlight certain differences: Caillard et al. reported on anti-Spike antibody responses in prevalent kidney transplant recipients with anti-S titers <143, with the majority of patients already having detectable titers (median 16.4 BAU/mL, IQR 5.9–62.3 BAU/mL) [15]. This is different to the present study, as we report on seroconversion rates after a 3rd and 4th vaccination in patients without prior seroconversion (anti-Spike-RBD-IgG titer <7.1 BAU/ml). This has to be taken into account when comparing seroconversion rates, as it has been reported previously that transplant patients who develop low but detectable antibody responses are very likely to develop high antibody titers after additional vaccinations, whereas the majority of patients who were seronegative after two vaccinations remained seronegative after a 3rd vaccination [16, 17]. On the other hand, Caillard et al. aimed for anti-S antibody titers >143 BAU/ml, with the rationale that anti-S antibody titers which correlate with virus neutralization against the SARS-CoV-2 Delta variant need to be higher compared to the wild-type virus and the Alpha, Beta, and Gamma variants. In the present study, we defined seropositivity as anti-Spike-RBD-IgG antibody ≥7.1 BAU/ml in line with the assay manufacturers recommendation, which was defined as correlation with the presence of neutralizing antibodies against the wild-type variant. In this respect, the study reported by Kamar et al. on seroconversion rates after a 4th vaccination is more similar to our report. Kamar et al. included predominantly transplant patients without seroconversion after three vaccinations and reported a seroconversion rate (defined as any seropositivity) of 41.9% after a 4th dose, which is similar to our findings reported in this manuscript [18]; however, an important difference between the study by

Kamar et al. and our current report is that Kamar et al. included solid organ transplant recipients (kidney, liver, heart, pancreas), whereas we report on a homogeneous group of prevalent kidney transplant recipients. Differences in immunosuppressive regimes for different organ transplants might lead to relevant differences in seroconversion rates after SARS-CoV-2 vaccinations. Naylor et al. reported in a large population-based cohort study including over 12,000 organ transplant recipients a cumulative vaccination success rate of 72% after 3 doses of SARS-CoV-2 vaccination including mRNA-based vaccines and a vector-based vaccine (ChAdOx1). The findings of Naylor et al. regarding cumulative seroconversion after three doses are somewhat lower but still comparable to the 80.5% seroconversion rate in our cohort. An important difference to outline between the two studies is the inclusion of vector-based vaccine type in the cohort study of Naylor et al. [19].

A lower seroconversion rate after dose 3 was reported by Reindl-Schwaighofer et al., who showed no significant difference between mRNA vaccine and vector-based vaccine in a comparison of homogeneous and heterogeneous vaccine types used for the third dose [20].

Since the beginning of the SARS-CoV-2-pandemic it has been a matter of debate which anti-Spike-RBD-IgG antibody titers can be viewed as protective against COVID-19, especially against severe disease and whether a serological correlate of protection can be defined at all [21]. There is probably no straight answer to this question, as it may depend on genetic susceptibility of individuals to severe inflammatory response to a SARS-CoV-2 infection, underlying morbidities, concomitant medication, patient age and the SARS-CoV-2 virus variant, as well as perhaps additional factors [22, 23].

Furthermore, several therapeutic options for COVID-19 have become available (e.g. monoclonal antibodies [24], antiviral drugs [25]), which substantially ameliorate clinical outcomes.

Our study has limitations: as SARS-CoV-2 vaccinations and anti-Spike-RBD-IgG antibody titer measurements were performed as part of clinical routine, this study is formally of retrospective nature. Consequently, we do not have data available on cellular immune responses to SARS-CoV-2 vaccinations, as such assays are not part of routine clinical testing at our institution.

Within the prespecified vaccination program, antibody measurement was only routinely performed 3–4 weeks after each vaccination dose. Therefore, no structured statement on antibody waning is possible.

Time intervals between vaccination doses were determined by recommendations of national guidelines for nonresponders and therefore not consistent throughout the study period. Potential influences regarding epidemic peaks or strains may not have been considered adequately.

Furthermore, our reported SARS-CoV-2 infections need to be interpreted with caution as there was no systematic screening for SARS-Cov-2 positivity in our transplantation center.

## Conclusion

Seroconversion against SARS-CoV-2 can be achieved in the majority of prevalent kidney transplant recipients with up to four mRNA-based vaccinations without modification of maintenance immunosuppression.

**Conflict of interest** C. Brandstetter, M.C. Haller, J.M. Berger, H. Kerschner, P. Apfalter, and D. Cejka declare that they have no competing interests.

## References


1. Caillard S, Chavarot N, Francois H, Matignon M, Greze C, Kamar N, et al. Is COVID-19 infection more severe in kidney transplant recipients? Am J Transplant. 2021;21(3):1295–303.
2. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med. 2021; https://doi.org/10.1056/NEJMoa2101765.
3. Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Antibody response to 2-dose SARS-coV-2 mRNA vaccine series in solid organ transplant recipients. JAMA. 2021;325(21):2204–6.
4. Lee ARYB, Wong SY, Chai LYA, Lee SC, Lee MX, Muthiah MD, et al. Efficacy of covid-19 vaccines in immunocompromised patients: systematic review and meta-analysis. BMJ. 2022;376:e68632.
5. Benotmane I, Gautier G, Perrin P, Olagne J, Cognard N, Fafi-Kremer S, et al. Antibody response after a third dose of the mRNA-1273 SARS-coV-2 vaccine in kidney transplant recipients with minimal serologic response to 2 doses. JAMA. 2021; https://doi.org/10.1001/jama.2021.12339.
6. Tsapepas D, Paget K, Mohan S, Cohen DJ, Husain SA. Clinically Significant COVID-19 Following SARS-CoV-2 Vaccination in Kidney Transplant Recipients. Am J Kidney Dis. 2021;78(2):314–7.
7. Caillard S, Chavarot N, Bertrand D, Kamar N, Thaunat O, Moal V, et al. Occurrence of severe COVID-19 in vaccinated transplant patients. Kidney Int. 2021;100(2):477–9.
8. https://www.nephrologie.at/wp-content/uploads/OEGN-COVID-Impfung-270921.pdf. Accessed 19 Mar 2022.
9. https://www.nephrologie.at/wp-content/uploads/oegn-und-austrotransplant-stellungnahme-corona-schutzimpfung-update-2021-11-04.pdf. Accessed 17 Jan 2022.
10. Haller MC, Kaiser RA, Langthaler S, Brandstetter C, Apfalter P, Kerschner H, et al. Comparison of mRNA-1273 and BNT162b2 SARS-coV-2 mRNA vaccine Immunogenicity in kidney transplant recipients. Transpl Int. 2022; https://doi.org/10.3389/ti.2021.10026.
11. English E, Cook LE, Piec I, Dervisevic S, Fraser WD, John WG. Performance of the abbott SARS-coV-2 IgG II quantitative antibody assay including the new variants of concern, VOC 202012/V1 (united kingdom) and VOC 202012/V2 (south africa), and first steps towards global harmonization of COVID-19 antibody methods. J Clin Microbiol. 2021;59(9):e288–21.

12. Kaiser RA, Haller MC, Apfalter P, Kerschner H, Cejka D. Comparison of BNT162b2 (Pfizer-BioNtech) and mRNA-1273 (Moderna) SARS-CoV-2 mRNA vaccine immunogenicity in dialysis patients. Kidney Int. 2021;100(3):697–8.
13. Del Bello A, Marion O, Delas A, Congy-Jolivet N, Colombat M, Kamar N. Acute rejection after anti-SARS-CoV-2 mRNA vaccination in a patient who underwent a kidney transplant. Kidney Int. 2021;100(1):238–9.
14. Jang HW, Bae S, Ko Y, Lim SJ, Kwon HE, Jung JH, et al. Acute T cell-mediated rejection after administration of the BNT162b2 mRNA COVID-19 vaccine in a kidney transplant recipient: a case report. Korean J Transplant. 2021;35(4):253–6.
15. Caillard S, Thaunat O, Benotmane I, Masset C, Blancho G. Antibody response to a fourth messenger RNA COVID-19 vaccine dose in kidney transplant recipients: a case series. Ann Intern Med. 2022; https://doi.org/10.7326/L21-0598.
16. Werbel WA, Boyarsky BJ, Ou MT, Massie AB, Tobian AAR, Garonzik-Wang JM, et al. Safety and immunogenicity of a third dose of SARS-coV-2 vaccine in solid organ transplant recipients: a case series. Ann Intern Med. 2021;174(9):1330–2.
17. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. N Engl J Med. 2021;385(7):661–2.
18. Kamar N, Abravanel F, Marion O, Romieu-Mourez R, Couat C, Del Bello A, et al. Assessment of 4 doses of SARS-coV-2 messenger RNA-based vaccine in recipients of a solid organ transplant. JAMA Netw Open. 2021;4(11):e2136030.
19. Naylor KL, Kim SJ, Smith G, McArthur E, Kwong JC, Dixon SN, et al. Effectiveness of first, second, and third COVID-19 vaccine doses in solid organ transplant recipients: a population-based cohort study from Canada. Am J Transplant. 2022; https://doi.org/10.1111/ajt.17095.
20. Reindl-Schwaighofer R, Heinzel A, Mayrdorfer M, Jabbour R, Hofbauer TM, Merrelaar A, et al. Comparison of SARS-coV-2 antibody response 4 weeks after homologous vs Heterologous third vaccine dose in kidney transplant recipients. JAMA Intern Med. 2022;182(2):1–8.
21. Misra A, Theel ES. Immunity to SARS-CoV-2: what do we know and should we be testing for it? J Clin Microbiol. 2022; https://doi.org/10.1128/jcm.00482-21.
22. Ng WH, Tipih T, Makoah NA, Vermeulen JG, Goedhals D, Sempa JB, et al. Comorbidities in SARS-CoV-2 patients: a systematic review and meta-analysis. mBio. 2021;12(1):e3647–20.
23. Gao YD, Ding M, Dong X, Zhang JJ, Azkur KA, Azkur D, et al. Risk factors for severe and critically ill COVID-19 patients: a review. Allergy. 2021;76(2):428–55.
24. Heo YA. Sotrovimab: first approval. Drugs. 2022;82(4):477–84.
25. Wen W, Chen C, Tang J, Wang C, Zhou M, Cheng Y, et al. Efficacy and safety of three new oral antiviral treatment (molnupiravir, fluvoxamine and Paxlovid) for COVID-19:a meta-analysis. Ann Med. 2022;54(1):516–23.