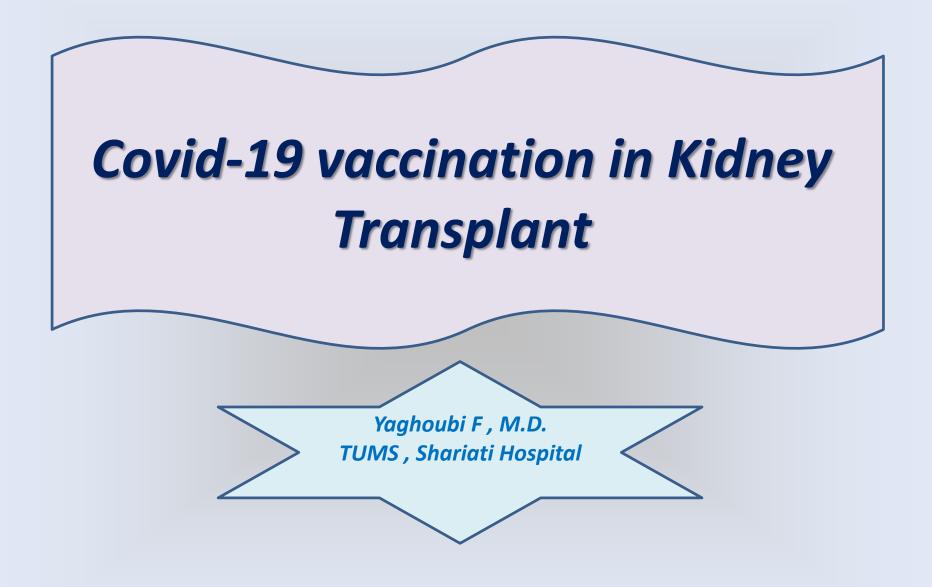
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INTRODUCTION

- Coronavirus disease 2019 (COVID-19) has had a major effect on kidney and other solid organ transplant recipients.
- In addition to public health measures , improved access to testing, and therapeutic developments, vaccination has emerged as a key tool for controlling the ongoing pandemic



Because of the known substantial risks of COVID-19–associated morbidity and mortality in recipients of kidney and other solid organs, and the long track record of safety of other vaccinations in such recipients, we anticipate the benefits of selected SARS-CoV-2 vaccines will far outweigh risks of vaccination.

INTRODUCTION

- Live (replication-competent)vaccines are generally contraindicated in immunocompromised individuals because of a risk of vaccine-acquired disease.
- The SARS-CoV-2 candidate vaccines that are furthest along in development do not contain replication-competent SARS-CoV-2 virus, and therefore do not carry risk of SARS-CoV-2 infection

SARS-CoV-2 vaccines& Infection

- There are, theoretical mechanisms by which replication-deficient viral vectorbased vaccines could become replication competent and cause disease, especially in immunocompromised individuals.
- For example, in cells concurrently infected with two different AdVes, homologous recombination of genetic elements could occur and result in the emergence of new, pathogenic, replication-competent AdV types.
- This has been observed in patients with advanced HIV disease during natural AdV infections, and is theoretically possible with AdV vector-based vaccines in patients who are immunocompromised with a concurrent wild-type AdV infection.
- Although infrequent, severe AdV infections, including allograft nephritis , can occur in kidney transplant recipients during natural infection.

SARS-CoV-2 vaccines& Infection

- It should be emphasized that, despite the theoretical concerns with replication-deficient viral vector-based vaccines, immunosuppression is not considered a contraindication to their use.
- Replication-competent viral vectored vaccines carry a greater risk of vaccine-derived vector infection in patients who are immunocompromised and should only be administered under carefully controlled circumstances.
- Other vaccine candidates that are in advanced stages of development, including mRNA, protein subunit, or whole virus—inactivated SARS-CoV-2 vaccines, do not contain intact virus and thus do not carry a risk of vaccine-associated infection.

Major SARS-CoV-2 platforms in development

| Vaccine Platform | Vaccine Name (Manufacturer) | Vehicle | Phase of Development | Adjuvant | ety and Efficacy in the General Population | Specific Considerations f Kidney Transplant Recipie |
|--|---|--|--|---|--|---|
| mRNA) | BNTb162b2 <mark>(Pfizer/</mark> BioNTech) mRNA-1273 (<mark>Moderna)</mark> | mRNA encapsulated in lipid nanoparticles | Authorized for emergency use in the United States and other countries | Unadjuvanted, but lipid nanopartides possess natural adjuvant activity ⁷ | 95% efficacy in phase 3 trials. ¹ Anaphylaxis has been reported. Avoid in patients with a known allergy to a vaccine component (e.g., polyethylene glycol). Close monitoring after administration for patients with a history of anaphylaxis to any food or drug. ³ | Does not contain live virus. evidence of vaccine- induced off-target immur responses in large phase clinical trials. ^{2,3} |
| Replication-defective viral vectors | AZD122 (Oxford/ AstraZeneca) | Human-chimpanzee adenovirus (ChAdOx 1) | Phase 3 | Unadjuvanted | 70%–90% efficacy depending on dose in phase 3 trials. ⁸ Transverse myelitis reported. ⁸ | Removal of genes necessar for replication reduces ris vaccine-associated AdV disease. ⁹ Theoretical risk |
| | JNJ78436735/ Ad26.COV2.S (Janssen) | Human adenovirus (Ad26) | Phase 3 | Unadjuvanted | Unknown | emergence of new AdV ty with replicative potential |
| | Convidecia (Ad5-nCov) | Human adenovirus (Ad5) | Approved for limited use in China | Unadjuvanted | Unknown | through homologous recombination, although |
| | <mark>(Sputnik V</mark> (Gamaleya) | Human adenovirus (Ad5 and Ad26 in consecutive doses) | Early use in Russia, Belarus, and Argentina | Unadjuvanted | Unknown | this has never been demonstrated to occur w AdV-vectored vaccines. ⁹ |
| Protein subunit | NVX-CoV2373 <mark>(Novavax)</mark> | Recombinant spike glycoprotein | Phase 3 | Matrix-M1 system plus an additional, unnamed adjuvant | Unknown | Does not contain live virus. Matrix-M1 contains the same QS21 saponin as th AS01B adjuvant system contained in the recombinant varicella zos vaccine. ⁷ |
| | SARS-CoV-2 recombinant protein formulation (GSK/Sanofi) | Recombinant spike protein | Phase 2 | AS03 adjuvant | Unknown | High incidence of anti-HLA antibodies in KTR vaccinated with AS03- adjuvanted influenza vaccines, but no associati between AS03 exposure a rejection. ^{3,10} |
| | EpiVacCorona (Vector Institute) | Peptide epitope | Early use in Russia | Unknown | | Limited data available |
| Whole-inactivated (killed) | BBIBP-CoV <mark>(Sinopharm)</mark> CoronaVac (SinoVac) | Whole-inactivated SARS- CoV-2 viral particles | Limited use in China and other countries | Unknown | Unknown | Does not contain live virus. Limited data available in peer-reviewed literature. |

SARS-CoV-2 vaccines&Rejection

- Induction of generalized systemic inflammation by either the vaccine antigen or an associated adjuvant, or by more specific cellular and humoral cross reactivity between vaccine epitopes and allograft antigens, theoretically could promote undesired allograft directed immune responses.
- AdV vectors elicit potent innate immune responses through complement activation and induce a diverse cytokine repertoire.
- Although this phenomenon is most prominent at the site of AdV-vector inoculation, systemic inflammation could promote vaccine-associated allograft rejection.

SARS-CoV-2 vaccines&Rejection

- Available data suggest acute allograft rejection is uncommon during COVID-19, despite frequent reduction in immunosuppression as a therapeutic strategy.
- In the absence of an observed association between natural SARS-CoV-2 infection and acute allograft rejection in kidney transplant recipients, it is unlikely that vaccine antigens would precipitate clinically significant immune responses to renal allografts.

SARS-CoV-2 vaccines &Rejection

- In general, adjuvants used to enhance vaccine immunogenicity also elicit nonspecific inflammatory responses, and thus have the potential to induce acute allograft rejection.
- Concern about adjuvant safety in organ transplant recipients arose from observations of an unusually high incidence of anti-HLA antibodies in kidney transplant recipients who received the 2009 influenza A(H1Na1) pdm09 vaccine, which contained the squalene-based AS03 adjuvant system.
- However, only a fraction of these anti- HLA antibodies were donor specific, and a subsequent investigation of >10,000 solid organ transplant recipients found no definitive association between the AS03 adjuvant system and acute allograft rejection.

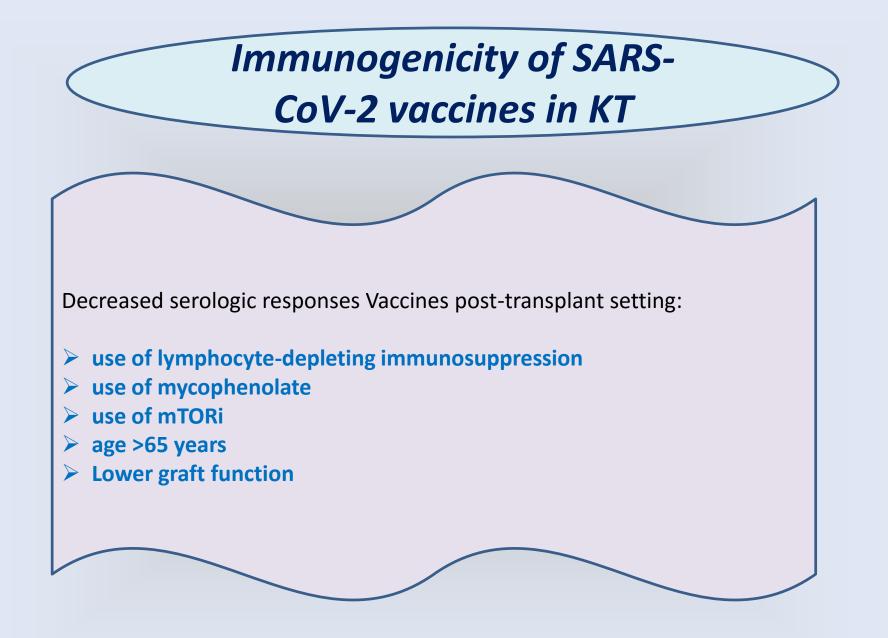
SARS-CoV-2

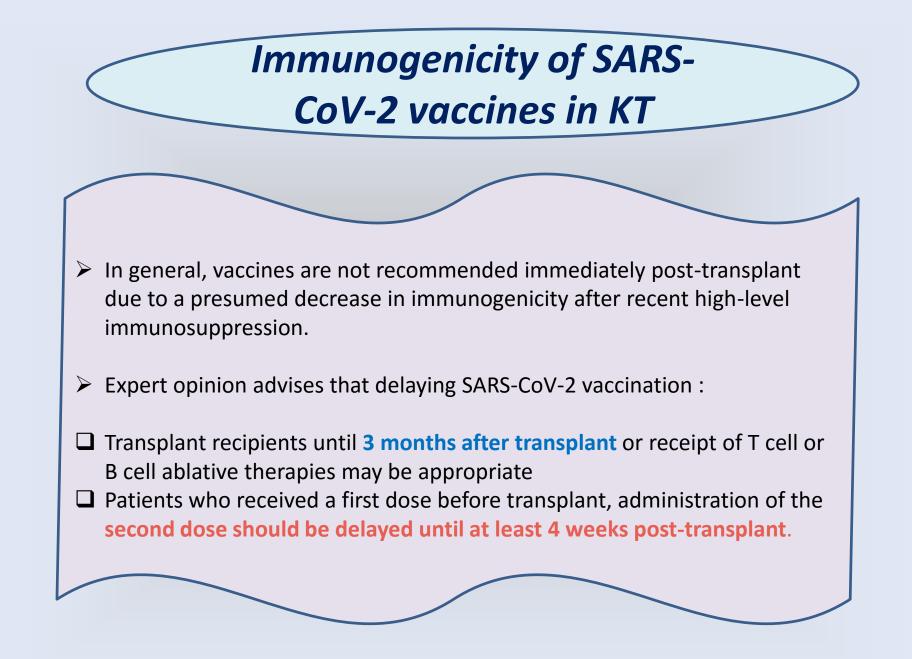
vaccines&Rejection

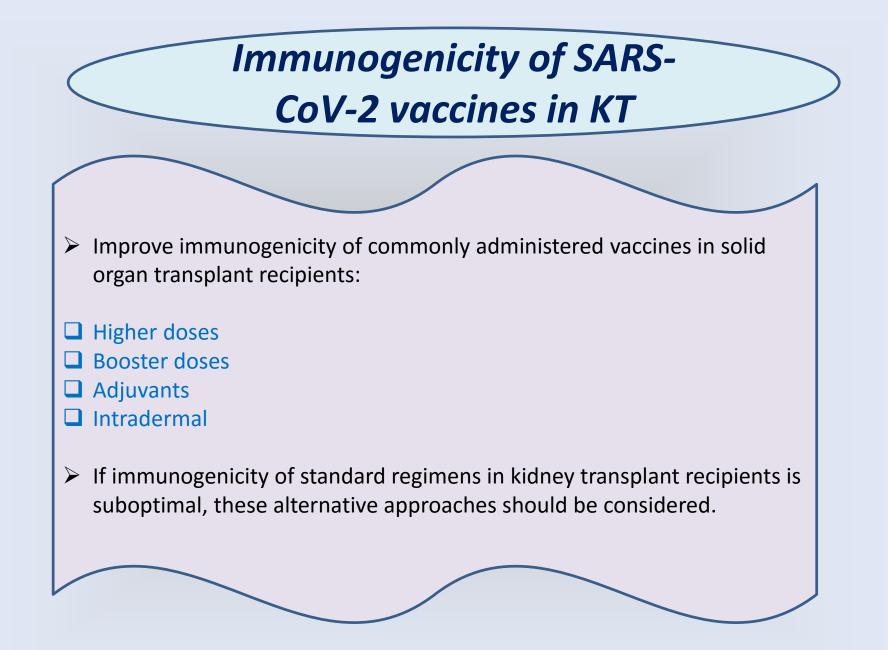
- The ASO1B adjuvant used in the recombinant varicella zoster virus vaccine contains a combination of Mono phosphoryl lipids and QS21, a saponin. This adjuvant induces a potent innate immune response and associated concerns for precipitating acute allograft rejection in kidney transplant recipients.
- Several recombinant spike protein SARS-CoV-2 vaccines contain adjuvants, such as AS03 and the novel Matrix M1 adjuvant, which contains the same QS21 saponin found in the recombinant varicella zoster vaccine.
- Viral-vectored and mRNA vaccines do not generally contain adjuvants, although lipid nanoparticle delivery devices used in the mRNA vaccines have natural adjuvant activity.



- Immunosuppression in kidney transplant recipients is anticipated to reduce the immunogenicity of SARS-CoV-2 vaccines, and immunogenicity may vary by vaccine platform.
- Available data across a broad range of vaccines in solid organ transplant recipients suggest they have relative humoral response rates that are approximately 50%–70% of those seen in non transplant populations.
- Patients with ESRD may have more a robust response to vaccines before rather than after kidney transplant, and when possible, SARS-CoV-2 vaccines should be given before transplantation.







Letters

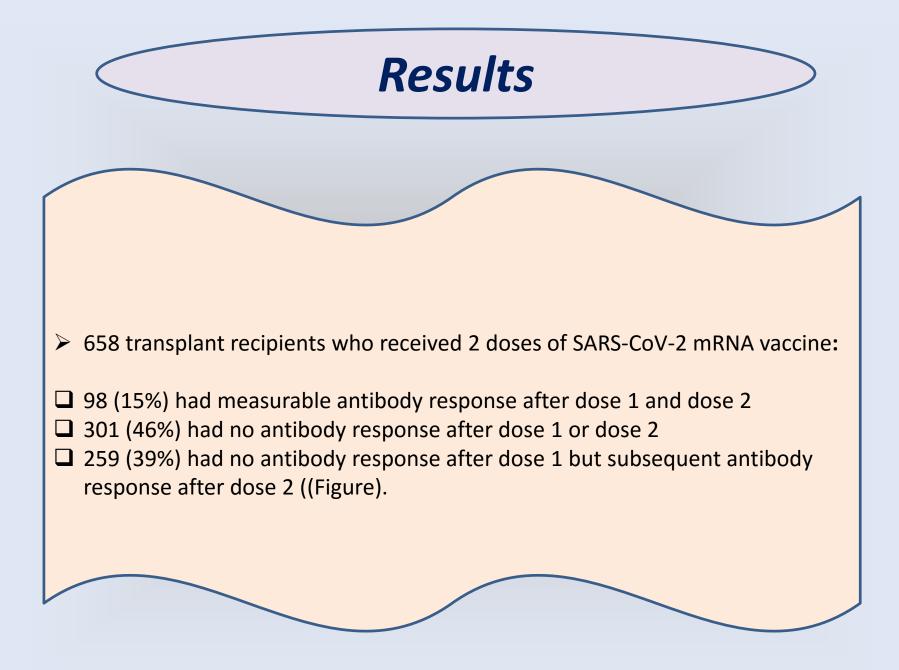
RESEARCH LETTER

Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients

In contrast to immunocompetent participants in vaccine trials,^{1,2} a low proportion (17%) of solid organ transplant recipients mounted a positive antibody response to the first dose of SARS-CoV-2 messenger RNA (mRNA) vaccines, with those receiving anti-metabolite maintenance immunosuppression less likely to respond.³ In this study, we assessed antibody response after the second dose.

Methods | Transplant recipients without prior polymerase chain reaction-confirmed COVID-19 were recruited from across the US to participate in this prospective cohort through a digital campaign. Those who completed the 2-dose SARS-CoV-2 mRNA vaccine series between December 16, 2020, and March 13, 2021, were included and followed up through April 13, 2021. As described previously,³ semiquantitative antispike serologic testing was undertaken with the Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay, positive cutoff of at least 0.8 U/mL, which tests for the receptor-binding domain of the SARS-CoV-2 spike protein,

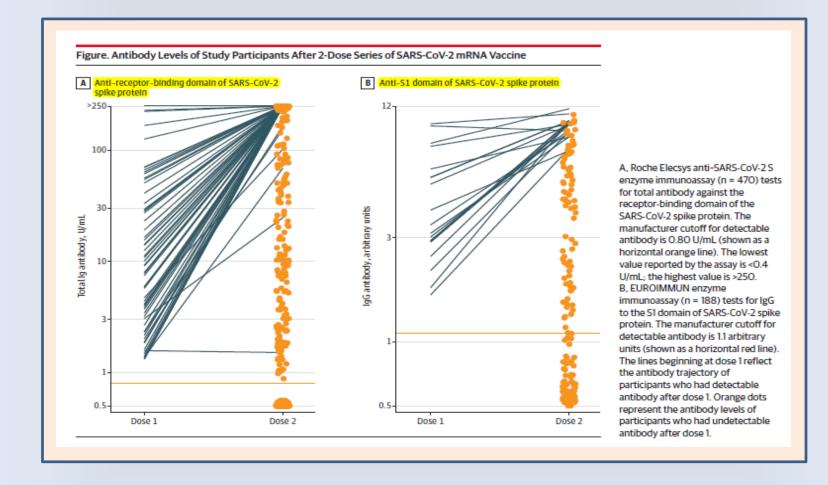
or the EUROIMMUN enzyme immunoassay, positive cutoff of at least 1.1 arbitrary units, which tests for the SI domain of SARS-CoV-2 spike protein, both key measures of humoral immune response.^{4,5} This study was approved by the Johns Hopkins institutional review board; participants provided informed consent electronically.



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| | No. (%) by pos | tvaccination antibod | y response | P value | |
|---|--------------------|----------------------|--------------------|--------------------|--|
| | Dose 1– Dose 2– | Dose 1– Dose 2+ | Dose 1+ Dose 2+ | | |
| No. | 301 (46) | 259 (39) | 98 (15) | | |
| Age category, y ^a | | | | | |
| 18-39 | 46 (41) | 35 (31) | 32 (28) | .002 ^b | |
| 40-59 | 86 (42) | 94 (46) | 26 (13) | | |
| ≥60 | 169 (50) | 129 (38) | 40 (12) | | |
| Sex ^c | | | | | |
| Female | 170 (45) | 152 (40) | 58 (15) | | |
| Male | 124 (46) | 103 (39) | 40 (15) | .92ª | |
| Race ^e | | | | | |
| White | 261 (45) | 228 (40) | 85 (15) | | |
| Black or African American | 11 (55) | 7 (35) | 2 (10) | | |
| Asian or Pacific Islander | 13 (39) | 12 (36) | 8 (24) | .74 ^d | |
| Other | 10 (48) | 8 (38) | 3 (14) | | |
| Organ ^r | | | | | |
| Kidney | 168 (52) | 118 (37) | 36(11) | | |
| Liver | 26 (20) | 62 (48) | 41 (32) | <.001 ^d | |
| Heart | 42 (43) | 45 (46) | 10(10) | | |
| Lung | 43 (61) | 22 (31) | 6 (8) | | |
| Pancreas | 4 (80) | 1 (20) | 0 | | |
| Other multiorgan | 15 (58) | 7 (27) | 4 (15) | | |
| Years since transplant ⁹ | | | | | |
| <3 | 114 (63) | 54 (30) | 13(7) | | |
| 3-6 | 69 (50) | 53 (39) | 15(11) | | |
| 7-11 | 54 (38) | 61 (43) | 26 (18) | .001 ^b | |
| ≥12 | 62 (33) | 85 (45) | 43 (23) | | |
| Maintenance immunosuppression regimen | | | | | |
| Includes antimetabolite ^h | 268 (57) | 167 (35) | 38 (8) | <.001 ^d | |
| Does not include antimetabolite ¹ | 33 (18) | 92 (50) | 60 (32) | | |
| Vaccinel | | | | | |
| mRNA-1273 (Moderna) 124 (40) 116 (38) 67 (22) | | 67 (22) | | | |
| BNT162b2 (Pfizer-BioNTech) | 175 (51) | 138 (40) | 29 (8) | <.001 ^d | |
| Enzyme immunossay ^k | | | | | |
| Roche Elecsys | 206 (44) | 188 (40) | 76 (16) | .19 | |
| EUROIMMUN | 95 (51) | 71 (38) | 22 (12) | | |

Table. Demographic and Clinical Characteristics of Study Participants, Stratified by Immune Response



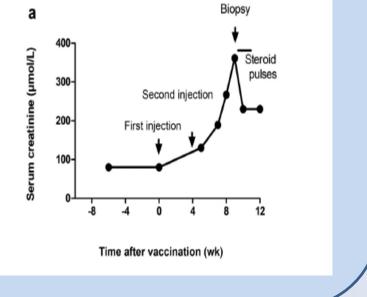
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letter to the editor

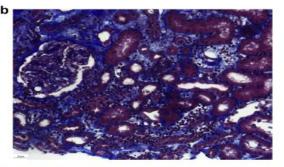
Acute rejection after anti-SARS-CoV-2 mRNA vaccination in a patient who underwent a kidney transplant

To the editor: Anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination is recommended in patients who underwent a transplant because of an increased risk of developing severe coronavirus disease 2019 (COVID-19), and mortality.¹ Because of a weak immunogenicity of mRNA 2-dose vaccines in transplant patients, the French Health Authority recommended to offer a third dose to immunosuppressed patients to boost the immune response.^{2,3} However, no



biological monitoring before and after vaccination is recommended. We report on the case of a 23-year-old non-human leukocyte antigen-sensitized patients who underwent a kidney transplant who presented an acute rejection after the second dose of the BNT162b2 mRNA COVID-19 Vaccine (Pfizer-BioNTech). She had undergone a deceased donor kidney transplantation for nephronophthisis 18 months earlier. The post-transplant period was uneventful. Her maintenance therapy was based on tacrolimus (target trough level, 5 ng/ml and 7 ng/ml), mycophenolic acid, and low-dose steroid. Fifteen days before the first dose, her serum creatinine level was at 80 µmol/L and anti-SARS-CoV-2 serology was negative. Eight days after the second dose, systematic blood tests revealed impaired kidney function at 130 µmol/L, which then raised to 360 µmol/L (Figure 1). A kidney biopsy revealed a cellular acute rejection. Donor-specific anti-human leukocyte antigen antibodies became detectable with a weak intensity, targeting donor human leukocyte antigen class II antigens. Anti-SARS-CoV-2 spike protein antibodies became positive. Tacrolimus trough level was unchanged at 5 ng/ml. At 10 days, after steroid pulses (500 mg/ d for 3 days), the patient's serum creatinine level had decreased to 230 µmol/L. Another kidney biopsy is planned to discuss the use of polyclonal antibodies. Hence, this report suggests that kidney function should be carefully monitored in kidney transplantation undergoing anti-SARS-CoV-2 vaccination, especially if a third boost dose is performed.

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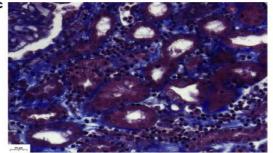


Figure 1 | (a) Outcome of kidney function before and after transplantation and (b,c) kidney pathology. Trichrome Masson staining exhibited inflammatory infiltration, tubulitis, edema, and peritubular capillaritis (original magnification $\times 20$ [b] and $\times 40$ [c]). Kidney biopsy was scored as follows, according to the 8ah [2019 classification⁴: 12, t2, v0, g0, ptc1, t1, HFTA0, C4d0, cg0, mm0, ah1, cv0, ci0, ct0. To optimize viewing of this image, please see the online version of this article at www.kidneyinternational.org.

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letter to the editor

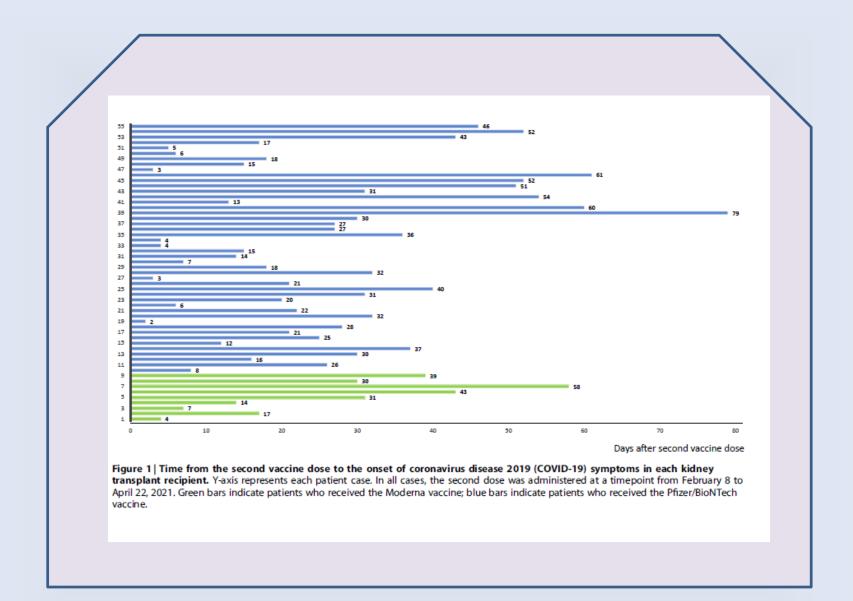
Occurrence of severe COVID-19 in vaccinated transplant patients

To the editor: Vaccination plays a paramount role in the current coronavirus disease 2019 (COVID-19) pandemic response. Although mRNA-based vaccines elicit a strong immune response in the general population, the immuniza-

sanitary protection measures. Other management strategies may include priority vaccination of the patients' households and the development of more-effective vaccination schemes.

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- 55 solid organ transplant recipients(52 kidney and 3 simultaneous kidney-pancreas) who developed COVID-19 after receiving 2 doses of mRNA based severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) vaccines.
- A total of 9 and 46 patients received the mRNA-1273 (Moderna) and the BNT162b2 (Pfizer-Bio-NTech) vaccine, respectively.
- The study sample included 32 men and 23 women (median age: 60 years, interquartile range: 49-67 years; mean time from transplantation: 66 months, interquartile range: 33-138 months).
- COVID-19 symptoms appeared after a median of 22 days after the second vaccine dose (interquartile range: 13-36 days;Figure 1).



- Of the 55 patients, 15 (27%) required hospitalization for oxygen therapy.
- Of these, 6 were admitted to an intensive care unit, and 3 died.
- Among the 25 patients with available data on anti–SARS-CoV-2 antibodies between the second vaccine dose and the onset of COVID-19 symptoms, 24 had negative serology, and 1 had positive results with weak antibodies levels (577 AU/L on the day of the second injection ; Architect Abbot test).
- SARS-CoV-2 sequencing, which was performed in 24 cases, revealed 5 wild-type viruses, 17 UK variants, 1 Marseille variant, and one B 1.160 variant.

- Growing evidence indicates that solid organ transplant recipients who receive mRNA-based vaccines have low immunization rates, with <50% of patients showing antibodies against the SARS-CoV-2 spike protein.
- Although immunosuppressive drugs are thought to play a key role in this phenomenon, the occurrence of severe COVID-19 after mRNA-based vaccination in immunocompetent or immunocompromised subjects has not yet been reported.
- A potential explanation for persisting disease susceptibility may lie in an absent humoral response, coupled with a limited or insufficient T-cell response, even after the second vaccine dose.

- Vulnerable immunocompromised patients who are nonresponsive to mRNA-based SARS-CoV-2 vaccines should undergo close serologic follow-up and/or maintain strict sanitary protection measures.
- Other management strategies may include priority vaccination of the patients' households and the development of more-effective vaccination schemes





Communication

Impaired Humoral Response in Renal Transplant Recipients to SARS-CoV-2 Vaccination with BNT162b2 (Pfizer-BioNTech)

Johannes Korth ^{1,*,†}, Michael Jahn ^{1,†}, Oliver Dorsch ², Olympia Evdoxia Anastasiou ³, Burkhard Sorge-Hädicke ⁴, Ute Eisenberger ¹, Anja Gäckler ¹, Ulf Dittmer ³, Oliver Witzke ⁵, Benjamin Wilde ¹, Sebastian Dolff ^{5,‡} and Andreas Kribben ^{1,‡}

Abstract: The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has a major impact on transplant recipients, with mortality rates up to 20%. Therefore, the effect of established messenger RNA (mRNA)-based SARS-CoV-2 vaccines have to be evaluated for solid organ transplant patients (SOT) since they are known to have poor responses after vaccination. We investigated the SARS-CoV-2 immune response via SARS-CoV-2 IgG detection in 23 renal transplant recipients after two doses of the mRNA-based SARS-CoV-2 vaccine BNT162b2 following the standard protocol. The antibody response was evaluated once with an anti-SARS-CoV-2 IgG CLIA 15.8 +/ – 3.0 days after the second dose. As a control, SARS-CoV-2 IgG was determined in 23 healthcare workers (HCW) and compared to the patient cohort. Only 5 of 23 (22%) renal transplant recipients were tested positive for SARS-CoV-2 IgG antibodies after the second dose. Thus, the humoral response of renal transplant recipients after two doses of the mRNA-based soft the mRNA-based soft the mRNA-based vaccine BNT162b2 (Pfizer-BioNTech, Kronach, Germany) is impaired and significantly lower compared to healthy controls (22% vs. 100%; p = 0.0001). Individual vaccination strategies might be beneficial in these vulnerable patients.



- Five of 23 (22%) renal transplant recipients tested positive for SARS-CoV-2 IgG at a mean of 15.8 +/- 3.0 days after the second dose of vaccine (Table 1).
- The mean SARS-CoV-2 lgG titer was 50.9 +/- 138.7 AU/mL.
- All 23 (100%)HCW tested positive for SARS-CoV-2 IgG at a mean of 13.7 +/- 1.8 days after the second dose.
- The mean SARS-CoV-2 lgG titer was 727.7 +/- 151.3 AU/mL.
- The mean SARS-CoV-2 antibody titer of the renal transplant recipients was significantly lower in comparison to the HCW(50.9 +/- 138.7 AU/mL vs. 727.7 +/- 151.3 AU/mL, p = 0.0001).

Table 1. Characteristics of patients after renal transplantation and healthcare workers after two doses of the mRNA-based SARS-CoV-2 vaccine BNT162b2. rtx renal transplant recipients; HCW, healthcare workers; n number; pos positive; neg negative; Ab antibody, CLIA Chemiluminescence Enzyme Immunoassays; AU Arbitrary Units; mL milliliter; Ab antibody.

| | rtx | HCW | |
|---|-------------------|-------------------|--------|
| n | 23 | 23 | р |
| female/male (n; %) | 12 (52%)/11 (48%) | 14 (61%)/9 (39%) | 0.76 |
| age (years) | 57.7 +/- 13.5 | 44.4 +/ - 9.2 | 0.0003 |
| immunosuppression (n) | | | |
| mycophenolate n (%) | 18, (78%) | | |
| corticosteroids n (%) | 14 (60%) | 14 (60%) | |
| tacrolimus n (%) | 14 (60%) | _ | |
| cyclosporine n (%) | 4 (17%) | | |
| sirolimus n (%) | 5 (22%) | | |
| everolimus n (%) | 1 (4%) | | |
| belatacept n (%) | 1 (4%) | | |
| azathioprine n (%) | 1 (4%) | | |
| years after rtx | 11.4 +/- 9.2 | - | |
| days between first and second dose (days) | 22.0 +/- 4.6 | 22.0 + / - 0 | |
| SARS-CoV-2 Ab detection after second dose (days) | 15.8 +/- 3.0 | 13.7 +/ - 1.8 | |
| SARS-CoV-2 Ab posCLIA (n; %) | 5 (22%) | 23 (100%) | 0.0001 |
| SARS-CoV-2 Ab negCLIA (n; %) | 18 (78%) | 0 (0%) | |
| Ab SARS-COV-2 CLIA (AU/mL) | 50.9 + / - 138.7 | 727.7 + / - 151.3 | 0.0001 |

| | SARS-CoV-2 IgG Positive | SARS-CoV-2 IgG Negative |
|--|-------------------------|-------------------------|
| n | 5 | 18 |
| female/male n (%) | 3 (60%)/2 (40%) | 9 (50%)/9 (50%) |
| age (years) | 57.0 +/ - 8.1 | 57.9 +/- 14.9 |
| time after rtx (years) | 17.6 +/ - 7.7 | 9.7 +/- 9.1 |
| mycophenolate n (%) | 3 (60%) | 15 (83%) |
| corticosteroids n (%) | 3 (60%) | 11 (61%) |
| tacrolimus n (%) | 2 (40%) | 12 (67%) |
| cyclosporine n (%) | 2 (40%) | 2 (11%) |
| sirolimus n (%) | 1 (20%) | 4 (22%) |
| everolimus n (%) | 1 (20%) | 0 |
| betalacept n (%) | 0 | 1 (6%) |
| azathioprine n (%) | 0 | 1 (6%) |
| number of immunosuppressive drugs n (%) | 2.4 +/ - 0.5 | 2.6 +/- 0.5 |

 Table 2. Characteristics of renal transplant recipients who tested positive and negative for SARS.CoV-2 IgG after two doses of the mRNA-based SARS-CoV-2 vaccine BNT162b2.

