Supplementary Methods

The serological response after the third vaccine dose was monitored in our entire kidney transplant cohort. Patients with a weak serological response one month after the third dose were eligible for a fourth injection of 100 μg of the mRNA-1273 (Moderna). Anti-SARS-CoV-2 spike protein receptor-binding domain (RBD) IgG titers were measured with an ARCHITECT IgG II Quant test (Abbott, Abbott Park, IL, USA). Results in Arbitrary Units (AU)/mL specific of this assay were converted into Binding Antibody Units (BAUs)/mL adapted to the WHO standard for SARS-CoV-2 immunoglobulin by multiplying them by the factor 0.142 (assay range: 1–11360 BAUs/mL). The sequence used for RBD was from the WH-Human 1 coronavirus. In light of previous data showing that IgG titers >100 BAUs/mL (704 AUs/mL) were associated with the presence of neutralizing antibodies against the wild-type virus and its common variants (alpha, beta, and gamma),[S5] titers <100 BAUs/mL were considered to reflect a weak humoral response. We also considered titers between 100 BAUs/mL and 143 BAUs/mL (1000 AUs/mL) as weak, thus posing an indication for a fourth vaccine dose. This decision was motivated by the willingness to protect frail patients who displayed titers slightly above 100 BAUs/mL against COVID-19. Neutralization of live viruses (delta strain) was investigated using a reporter cell line (S-Fuse cells) as previously described.[4] Following SARS-CoV-2-induced formation of syncytia, a GFP signal proportional to virus infectivity is generated. The percentage of neutralization was calculated using the number of syncytia according to the following formula: 100 × (1 − (value with serum − value in 'noninfected')/(value in 'no serum' − value in 'noninfected')). Neutralizing activity against the delta strain was expressed as the concentration capable of inhibiting 50% of the virus inoculum (inhibitory dilution 50, ID50; limit of detection: 7.5). A neutralizing ID50>30 was considered as positive. This threshold was used since the lowest dilution used for this assay in immunocompetent individuals is generally 1:30 – resulting in an ID50

detection threshold of 30.[4] On analyzing immunocompromised patients with a weak humoral response, an additional dilution was studied (1:7.5) to identify a more precise neutralizing ID50 titer. In an effort to improve comparability, we applied the same threshold to the study population. Anti-RBD IgG and neutralizing ID50 were quantified one month after the third and fourth vaccine doses, respectively. In order to rule out natural immunity, anti-SARS-CoV-2 nucleocapsid protein IgG titers were measured with an ARCHITECT SARS-CoV-2 IgG assay (Abbott) one month after the fourth vaccine dose. Continuous data are presented as medians and IQR and analyzed using the nonparametric Mann-Whitney *U* or Kruskal Wallis tests (for unmatched pairs) and the Wilcoxon signed rank tests (for matched pairs). Categorical variables are expressed as counts and percentages and compared using the Fisher's exact test. The Pearson's correlation coefficient (ρ) was used to express the correlation between neutralizing ID50 and IgG levels against the RBD. All calculations were performed using GraphPad Prism, version 8.0 (GraphPad Inc., San Diego, CA, USA). A two-sided P value < .05 was considered statistically significant. The study protocol was approved by the local Ethics Committee (identifier: DC-2013–1990) and written informed consent was obtained from all participants.

Supplementary References

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