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.

Kidney International (2021) **100,** 1131–1132; https://doi.org/10.1016/j.kint.2021.08.018

A third injection of the BNT162b2 mRNA COVID-19 vaccine in kidney transplant recipients improves the humoral immune response

To the editor: Several reports have highlighted the poor humoral immune response of kidney transplant recipients following coronavirus disease 2019 (COVID-19) mRNA vaccination compared with immunocompetent patients.[1–3] Therefore, the French National Authority for Health has recommended the use of a third vaccine dose for immunosuppressed patients, such as solid organ transplant recipients. We retrospectively assessed the humoral response of all kidney and pancreas transplant recipients vaccinated with the BNT162b2 mRNA (Pfizer BioNTech) COVID-19 vaccine between January and May 2021 in our center. Patients with previous COVID-19 infection or positive pre-vaccination serology were excluded. The methods for detection of the anti-spike protein responses were dependent on laboratories' practices and included chemiluminescent microparticle immunoassay (Abbott Architect), chemiluminescence immunoassay (Siemens Atellica), and electrochemiluminescence immunoassay (Roche Elecsys). Anti-spike (IgG) responses were assessed 1 month after the

Table 1 | Characteristics associated with risk of nonhumoral response to a second dose of mRNA COVID-19 vaccine after univariate analysis (n = 456)

	Global (n = 456)			Negative (n = 229)			Positive (n = 227)			
Characteristics	**NA**	**n**	**%**	**NA**	**n**	**%**	**NA**	**n**	**%**	***P* value**
Transplantation ≤4 yr	0	336	73.7	0	146	63.8	0	190	83.7	**<0.0001**
Male recipient	0	275	60.3	0	130	56.8	0	145	63.9	0.1455
Transplant rank ≥2	0	81	17.8	0	40	17.5	0	41	18.1	0.9653
Transplant type (kidney vs. SPK/pancreas)	0	421	92.3	0	214	93.4	0	207	91.2	0.3845
Primitive kidney disease	0			0			0			0.5491
Unknown		39	8.6		15	6.6		24	10.6	
Glomerulonephritis		143	31.4		71	31		72	31.7	
Other		205	45		109	47.6		96	42.3	
Vascular disease		28	6.1		13	5.7		15	6.6	
Diabetes		41	9		21	9.2		20	8.8	
Deceased donor	0	376	82.5	0	196	85.6	0	180	79.3	0.1002
ABDR incompatibilities >4	0	102	22.4	0	59	25.8	0	43	18.9	0.0920
Blood type	0			0			0			0.4043
O		192	42.1		102	44.5		90	39.6	
A		206	45.2		103	45		103	45.4	
B		46	10.1		18	7.9		28	12.3	
AB		12	2.6		6	2.6		6	2.6	
Depleting induction	1	239	52.5	1	129	56.6	0	110	48.5	0.1009
Lymphocytes <1500/mm^3	36	220	52.4	20	126	60.3	16	94	44.5	**0.0017**
Calcineurin inhibitor treatment	20	369	84.6	11	191	87.6	9	178	81.7	0.1110
Belatacept treatment	18	11	2.6	10	9	4.4	8	2	0.9	**0.0343**
mTOR inhibitor treatment	20	68	15.6	11	20	9.2	9	48	22	**<0.0001**
Antimetabolite treatment	20	325	74.5	11	180	82.6	9	145	66.5	**0.0002**
Steroid treatment	20	150	34.4	11	94	43.1	9	56	25.7	**0.0002**
Diabetes history	0	79	17.3	0	46	20.1	0	33	14.5	0.1493
Cardiovascular history	0	179	39.3	0	94	41	0	85	37.4	0.4890
Neoplasia history	0	89	19.5	0	54	23.6	0	35	15.4	**0.0375**
DSA before transplant	136	21	6.6	47	16	8.8	89	5	3.6	0.1050
DSA *de novo*	6	56	12.4	5	26	11.6	1	30	13.3	0.6944
Episode of rejection	0	51	11.2	0	30	13.1	0	21	9.3	0.2479
	NA	**Mean**	**SD**	**NA**	**Mean**	**SD**	**NA**	**Mean**	**SD**	
Recipient age, yr	0	61.4	12.1	0	62.7	11.1	0	60.2	13.0	**0.0289**
Recipient BMI, kg/m^2	31	25.4	4.9	16	25.5	4.8	15	25.4	5.0	0.7514
Time from transplantation, yr	0	10.5	8.5	0	8.5	7.6	0	12.4	8.9	**<0.0001**
Allograft function by MDRD, ml/min	24	48.7	19.4	14	43.4	16.8	10	53.9	20.3	**<0.0001**
Total leukocyte count, G/L	30	32.1	376.2	18	57.9	534.0	12	6.7	2.0	0.1653
C0 cyclosporine, ng/ml	419	100.6	35.9	218	99.5	50.3	201	101.1	29.0	0.9217
C0 tacrolimus, ng/ml	193	5.9	1.9	83	6.1	2.0	110	5.6	1.7	**0.0239**

BMI, body mass index; C0, trough level; COVID-19, coronavirus disease 2019; DSA, donor-specific antibody; MDRD, Modification of Diet in Renal Disease; mTOR, mechanistic target of rapamycin; NA, not available; SPK, simultaneous pancreas–kidney.
Values in bold are significant ($P < 0.05$).

Table 2 | Characteristics associated with risk of nonhumoral response to a second dose of mRNA COVID-19 vaccine after multivariate analysis (n = 394)

Characteristics	OR	95% CI	*P* value
Recipient age at vaccination, yr	1.03	1.01–1.06	**0.0010**
Transplantation ≤4 yr	2.91	1.70–5.08	**0.0001**
Allograft function by MDRD, ml/min	0.98	0.96–0.99	**0.0011**
Calcineurin inhibitor treatment	1.55	0.73–3.30	0.2555
mTOR inhibitor treatment	0.73	0.33–1.62	0.4402
Antimetabolite treatment	5.74	2.99–11.48	**<0.0001**
Steroid treatment	3.68	2.10–6.66	**<0.0001**
Lymphocytes <1500/mm^3	1.48	0.93–2.35	0.0961

CI, confidence interval; COVID-19, coronavirus disease 2019; MDRD, Modification of Diet in Renal Disease; mTOR, mechanistic target of rapamycin; OR, odds ratio.
Values in bold are significant ($P < 0.05$).

second and third injection, and patients were considered positive if their anti-spike level was above the laboratory threshold. A total of 456 patients had a serologic assessment 1 month after the second injection, of whom 227 were positive, representing 49.7% of our cohort (Table 1). A total of 10.7% of these patients had a positive anti-spike protein 1 month after the first injection. Multivariate regression analysis (Table 2) revealed that there was an increased likelihood of being a nonresponder after the second mRNA injection for patients treated with antimetabolite drugs (odds ratio [OR], 5.74; 95% confidence interval [CI], 2.99–11.48; $P < 0.0001$) or steroids (OR, 3.68; 95% CI, 2.10–6.66; $P < 0.0001$), older recipients (OR, 1.03; 95% CI, 1.01–1.06; $P = 0.0010$), those with impaired allograft function (OR, 0.98; 95% CI, 0.96–0.99; $P = 0.0011$), and those with a transplant ≤4 years (OR, 2.91; 95% CI, 1.70–5.08; $P = 0.0001$). A total of 136 patients had a serologic assessment 1 month after the third injection (median, 30 days; quartile 1, 28 days; quartile 3, 32 days). The average time between the second and the third injection was 50 days. A total of 94 patients were positive, representing a 69.2% serologic conversion following the third mRNA injection (Figure 1a and Table 3). Among patients receiving a third dose, 85 had a serologic assessment after both second and third injections, and 34 of them (40%) became seropositive between the second and the third dose. The magnitude of immune response was investigated in 71 patients who had serologic assessment using electrochemiluminescence immunoassay (Roche Elecsys) after the second and third injections (Figure 1b and c). Nearly all patients with a positive serology after the second mRNA vaccine had a high titer of anti-spike antibody (>250 UI/L). Multivariate regression analysis (Table 4) determined that lymphocyte count <1500/mm^3 increased the likelihood of being a nonresponder after the third mRNA injection (OR, 3.84; 95% CI, 1.58–19.96; $P = 0.0039$), as impairment of allograft function (OR, 0.97; 95% CI, 0.94–0.99; $P = 0.0232$). Of note, the use of antiproliferative drugs and steroids no longer seemed to significantly impact the serologic conversion after the third mRNA vaccine injection. Male recipients were more likely to respond to the third mRNA vaccine injection in our cohort, without any clear explanation so far. Kidney transplant recipients respond poorly to COVID-19 mRNA vaccination, and although cellular responses to the vaccine seem better than humoral responses,[4] severe COVID-19 pneumonia can occur following 2 mRNA vaccine injections.[5] Our data support the use of a third mRNA injection to improve the humoral response to vaccination from about 50% to 70%, reducing the negative impact of antimetabolite drugs and steroids on seroconversion. Moreover, for previously seropositive patients, the third mRNA vaccine largely improved the intensity of humoral response, reaching titers suggestive of neutralizing antibody activity. Indeed, seropositive assessment (especially weak titers in immunocompromised patients) is not constantly associated with protective antibodies titers.[5] However, severe lymphopenia and impaired graft function remained as risk factors for a nonserologic response. In this particular situation, a fourth dose, with or without immunomodulation, could be discussed to improve the humoral response of this highly immunosuppressed population. These data will need confirmation from other series.

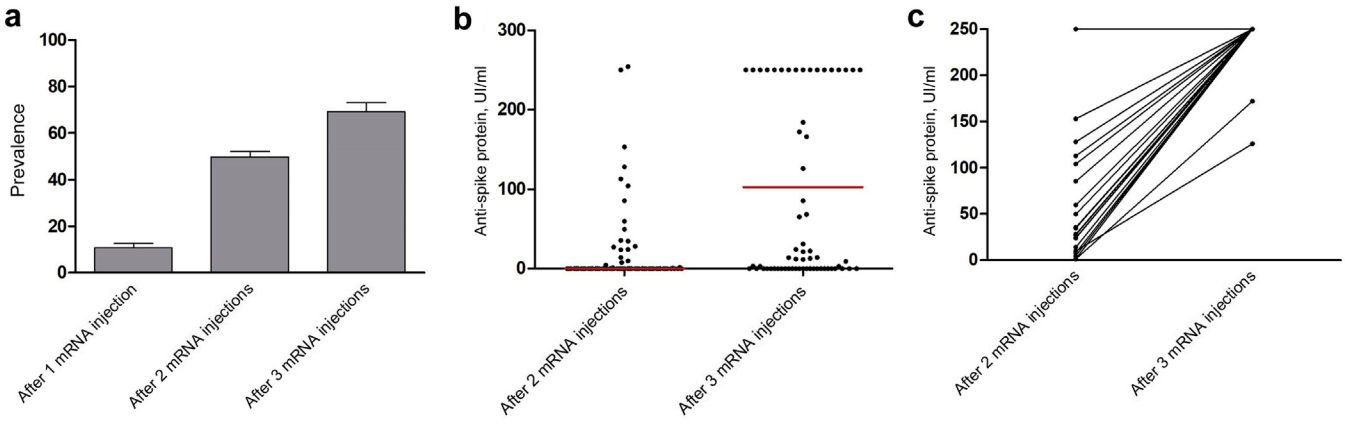

Figure 1 | (a) Prevalence of anti-spike IgG seroconversion following 1, 2, and 3 mRNA injections in kidney transplant recipients. (**b**) Antibodies titers (electrochemiluminescence immunoassay by Roche Elecsys) 1 month after the second and third mRNA injections. (**c**) The evolution of antibody titers in previously positive patients who received a third mRNA injection.

Table 3 | Characteristics associated with risk of nonhumoral response to a third dose of mRNA COVID-19 vaccine after univariate analysis (n = 136)

	Global (n = 136)			Negative (n = 42)			Positive (n = 94)			
Characteristics	NA	n	%	NA	n	%	NA	n	%	*P* value
Transplantation ≤4 yr	0	46	33.8	0	20	47.6	0	26	27.7	**0.0378**
Male recipient	0	86	63.2	0	17	40.5	0	69	73.4	**<0.0001**
Transplant rank ≥2	0	20	14.7	0	8	19.0	0	12	12.8	0.4879
Transplant type (kidney vs. SPK/pancreas)	0	124	91.2	0	38	90.5	0	86	91.5	1.0000
Primitive kidney disease	0			0			0			0.6077
Unknown		10	7.4		5	11.9		5	5.3	
Glomerulonephritis		44	32.4		12	28.6		32	34	
Other		54	39.7		15	35.7		39	41.5	
Vascular disease		12	8.8		4	9.5		8	8.5	
Diabetes		16	11.8		6	14.3		10	10.6	
Deceased donor	0	114	83.8	0	37	88.1	0	77	81.9	0.5142
ABDR incompatibilities >4	0	33	24.3	0	12	28.6	0	21	22.3	0.5167
Blood type	0			0			0			0.4838
O		52	38.2		20	47.6		32	34	
A		66	48.5		18	42.9		48	51.1	
B		14	10.3		3	7.1		11	11.7	
AB		4	2.9		1	2.4		3	3.2	
Depleting induction	0	80	58.8	0	29	69	0	51	54.3	0.1525
Lymphocytes <1500/mm^3	6	65	50	2	29	72.5	4	36	40	**0.0012**
Calcineurin inhibitor treatment	2	115	85.8	1	36	87.8	1	79	84.9	0.8662
mTOR inhibitor treatment	2	20	14.9	1	2	4.9	1	18	19.4	0.0569
Antimetabolite treatment	2	101	75.4	1	32	78	1	69	74.2	0.7950
Steroid treatment	2	43	32.1	1	18	43.9	1	25	26.9	0.0811
Diabetes history	0	28	20.6	0	11	26.2	0	17	18.1	0.3950
Cardiovascular history	0	56	41.2	0	17	40.5	0	39	41.5	1.0000
Neoplasia history	0	29	21.3	0	12	28.6	0	17	18.1	0.2490
DSA before transplant	35	8	7.9	8	4	11.8	27	4	6	0.4370
DSA *de novo*	5	17	13	2	6	15	3	11	12.1	0.8615
Episode of rejection	0	13	9.6	0	6	14.3	0	7	7.4	0.2207
	NA	**Mean**	**SD**	**NA**	**Mean**	**SD**	**NA**	**Mean**	**SD**	
Recipient age, yr	0	63.7	11.7	0	65.3	10.9	0	63.0	11.9	0.2679
Recipient BMI, kg/m^2	3	25.5	4.7	1	24.5	3.7	2	25.9	5.0	0.0642
Time from transplantation, yr	0	9.4	8.1	0	7.0	6.7	0	10.4	8.5	**0.0143**
Allograft function by MDRD, ml/min	3	49.1	19.3	1	41.1	15.1	2	52.6	20.0	**0.0004**
Total leukocyte count, G/L	5	6.6	2.2	1	6.7	2.4	4	6.5	2.2	0.7306
C0 cyclosporine, ng/ml	125	103.0	25.0	40	129.0	29.7	85	97.2	21.5	0.3526
C0 tacrolimus, ng/ml	55	6.0	1.8	13	6.2	1.9	42	5.9	1.8	0.5758

BMI, body mass index; C0, trough level; COVID-19, coronavirus disease 2019; DSA, donor-specific antibody; MDRD, Modification of Diet in Renal Disease; mTOR, mechanistic target of rapamycin; NA, not available; SPK, simultaneous pancreas–kidney.
Values in bold are significant ($P < 0.05$).

Table 4 | Characteristics associated with risk of nonhumoral response to a third dose of mRNA COVID-19 vaccine after multivariate analysis (n = 129)

Characteristics	OR	95% CI	*P* value
Male recipient	0.25	0.10–0.61	**0.0027**
Allograft function by MDRD, ml/min	0.97	0.94–0.99	**0.0232**
Antimetabolite treatment	1.76	0.59–5.64	0.3237
Steroid treatment	2.45	0.91–6.81	0.0795
Lymphocytes <1500/mm^3	3.84	1.58–9.96	**0.0039**

CI, confidence interval; COVID-19, coronavirus disease 2019; MDRD, Modification of Diet in Renal Disease; OR, odds ratio.
Values in bold are significant ($P < 0.05$).

1. Benotmane I, Gautier-Vargas G, Cognard N, et al. Low immunization rates among kidney transplant recipients who received 2 doses of the mRNA-1273 SARS-CoV-2 vaccine. *Kidney Int*. 2021;99:1498–1500.
2. Marion O, Del Bello A, Abravanel F, et al. Safety and immunogenicity of anti–SARS-CoV-2 messenger RNA vaccines in recipients of solid organ transplants. *Ann Intern Med*. 2021;174:1336–1338.
3. Müller L, Andrée M, Moskorz W, et al. Age-dependent immune response to the Biontech/Pfizer BNT162b2 COVID-19 vaccination [e-pub ahead of print]. *Clin Infect Dis*. https://doi.org/10.1093/cid/ciab381. Accessed September 14, 2021.
4. Cucchiari D, Egri N, Bodro M, et al. Cellular and humoral response after mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients. *Am J Transplant*. 2021;21:2727–2739.

5. Caillard S, Chavarot N, Bertrand D, et al. Occurrence of severe COVID-19 in vaccinated transplant patients. *Kidney Int*. 2021;100:477–479.

Christophe Masset[1,2], Clarisse Kerleau[1,2], Claire Garandeau[1], Simon Ville[1,2], Diego Cantarovich[1], Maryvonne Hourmant[1,2], Delphine Kervella[1,2], Aurélie Houzet[1], Cécile Guillot-Gueguen[1], Irène Guihard[1], Magali Giral[1,2], Jacques Dantal[1,2] and Gilles Blancho[1,2]

[1]*Institut de Transplantation Urologie Néphrologie, Service de Néphrologie et Immunologie, Clinique, Centre Hospitalier Universitaire Nantes, Nantes, France; and* [2]*Centre de Recherche en Transplantation et Immunologie Unité Mixte de Recherche 1064, INSERM, Université de Nantes, Nantes, France*

Correspondence: *Christophe Masset, 30 Blvd Jean Monnet, 44093 Nantes Cedex 01, France. E-mail: christophe.masset@chu-nantes.fr*

Kidney International (2021) **100,** 1132–1135; https://doi.org/10.1016/j.kint.2021.08.017

A third vaccine dose substantially improves humoral and cellular SARS-CoV-2 immunity in renal transplant recipients with primary humoral nonresponse

To the editor: Renal transplant recipients (RTRs) are at a high risk for fatal coronavirus disease 2019 (COVID-19).[1] Vaccinations are indispensable to protect this vulnerable population. Unfortunately, >50% of solid organ recipients do not mount antibody responses after 2 doses of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines.[2,3] We hypothesized that a third vaccine dose elicits protective humoral and cellular immune response in primary nonresponders. Ten RTRs under immunosuppression (Supplementary Table S1) without measurable SARS-CoV-2 spike antibodies 4 weeks after a second dose of BNT162b2 (Pfizer–

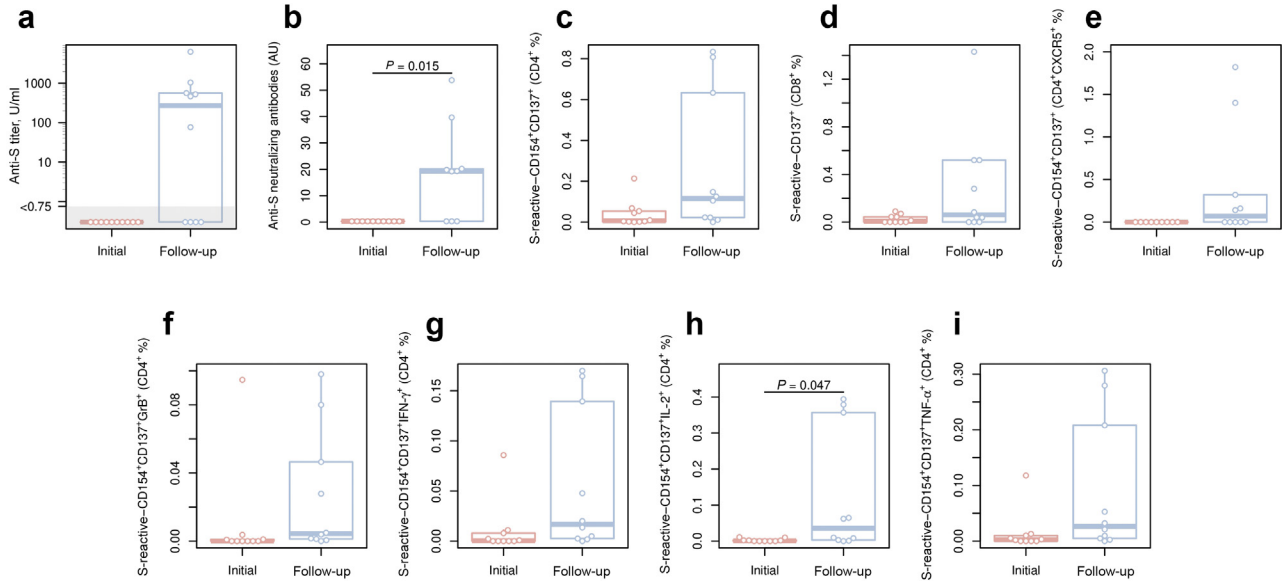

Figure 1 | Humoral and cellular response following the third vaccination in kidney transplant recipients in whom the primary vaccination failed. Renal transplant recipients with failed seroconversion after BNT162b2 (Pfizer–BioNTech) prime-boost vaccination were subjected to the third vaccination by mRNA-1273 (Moderna). Humoral and cellular immune responses before (red) and 2 weeks after (blue) the third vaccination are presented. Enzyme-linked immunosorbent assay (ELISA) was performed for the assessment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S)-protein–binding antibodies, and neutralizing antibody capacity was assessed by a pseudovirus system bearing the SARS-CoV-2 S-protein. S-protein–reactive T cells were analyzed by flow cytometry following an overnight stimulation of peripheral blood mononuclear cells with overlapping peptide pools (OPPs) spanning the S-protein of SARS-CoV-2. Activation markers CD154 and CD137 were used for the assessment and quantification of S-protein–reactive T cells within $CD3^+$ T cells. Expression levels of cytokines, interferon gamma (IFNγ), tumor necrosis factor alpha (TNFα), and interleukin 2 (IL-2), as well as the effector molecule granzyme B (GrB), were analyzed among activated $CD4^+$ T cells by intracellular staining and flow cytometry after stimulation with OPPs spanning the whole S-protein of SARS-CoV-2. Differences between the subcohorts were analyzed using the paired, 2-sided *t* test. The significance threshold was set at 0.05. Box plots depict the median and first and third quartiles of a variable; the maximum length of the whiskers corresponds to 1.5× the interquartile range. (**a**) Titers of anti–SARS-CoV-2 S-protein–binding antibodies assessed by ELISA. (**b**) Neutralizing antibody titers for the SARS-CoV-2 S-protein. (**c**) Frequencies of S-reactive $CD4^+$ T cells, as defined by $CD154^+CD137^+$ expression. (**d**) Frequencies of S-reactive $CD8^+$ T cells, as defined by CD137 expression and cytokine production. (**e**) Frequencies of S-reactive follicular $CD4^+$ T-helper cells, as defined by the expression of CXC chemokine receptor 5 (CXCR5). (**f–i**) Frequencies of S-reactive $CD4^+$ T cells producing (**f**) GrB, (**g**) IFNγ, (**h**) IL2, and (**i**) TNFα. AU, arbitrary unit.