itun institut transplantation urologie néphrologie INSERM - UMR 643

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

Anti SARS-Cov-2 vaccination in kidney transplantation

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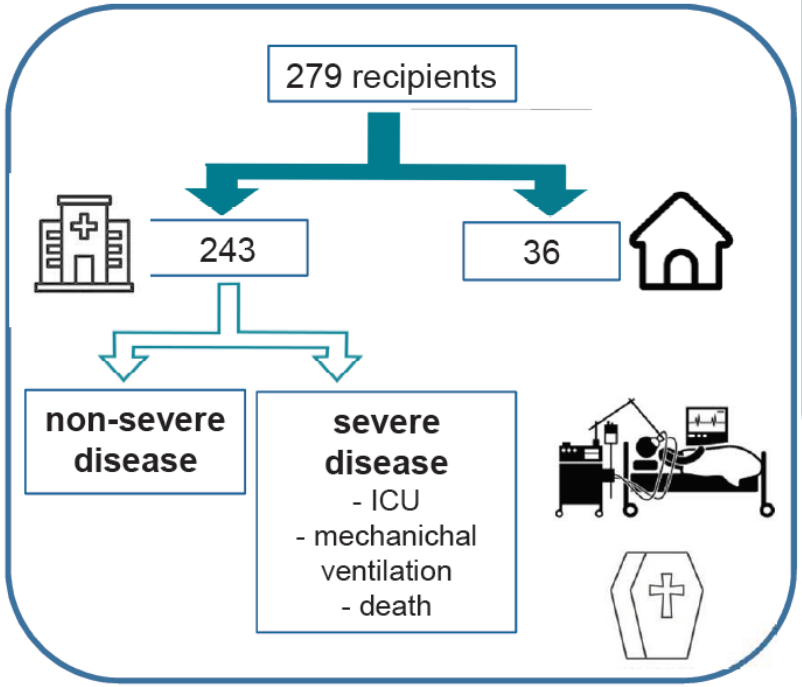
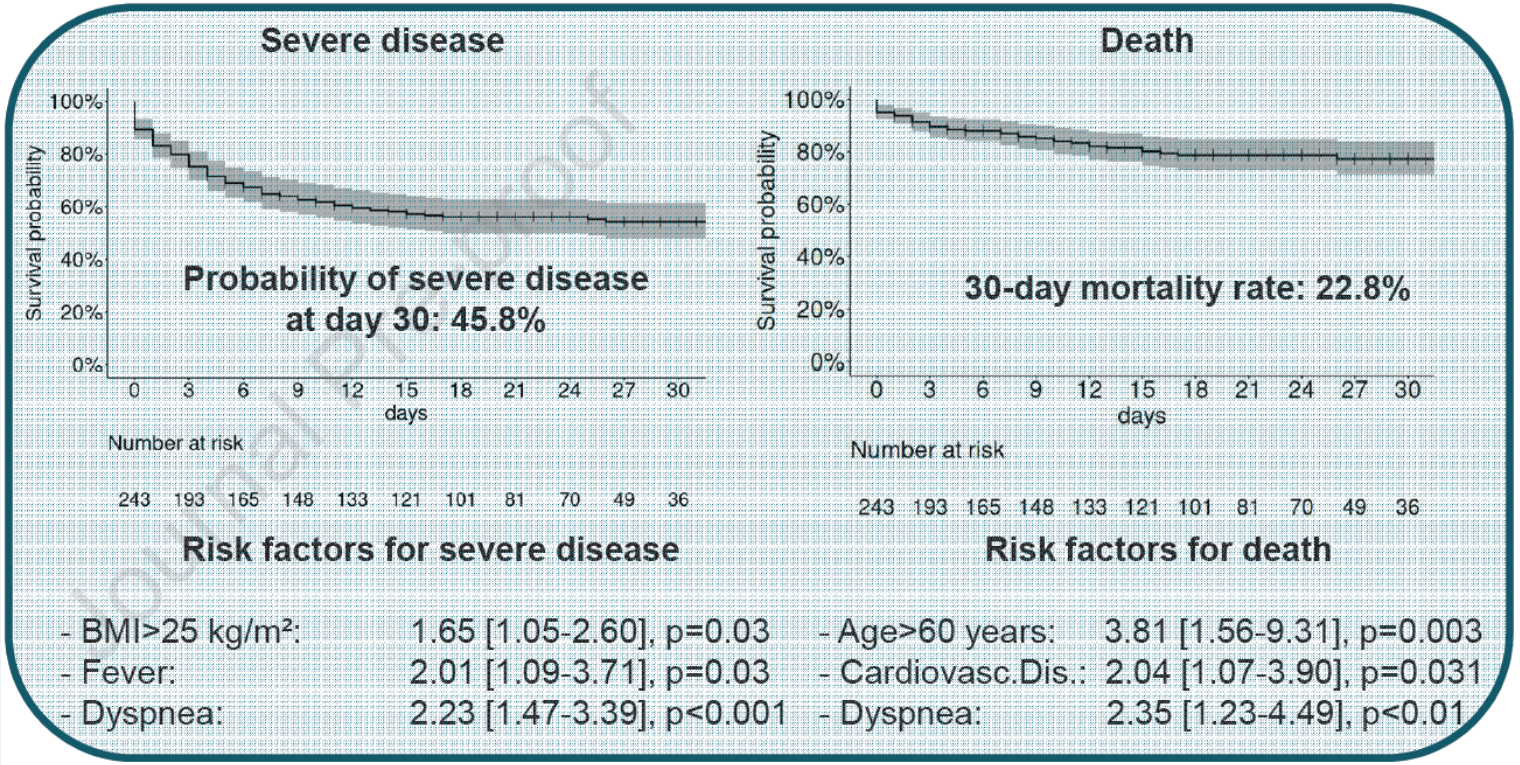
Conflicts of interest : none

An initial report from the French SOT COVID Registry suggests high mortality due to Covid-19 in recipients of kidney transplants.

A registry-based observational study to explore the characteristics and clinical outcomes of kidney transplant recipients included in the French nationwide Registry





CONCLUSION:

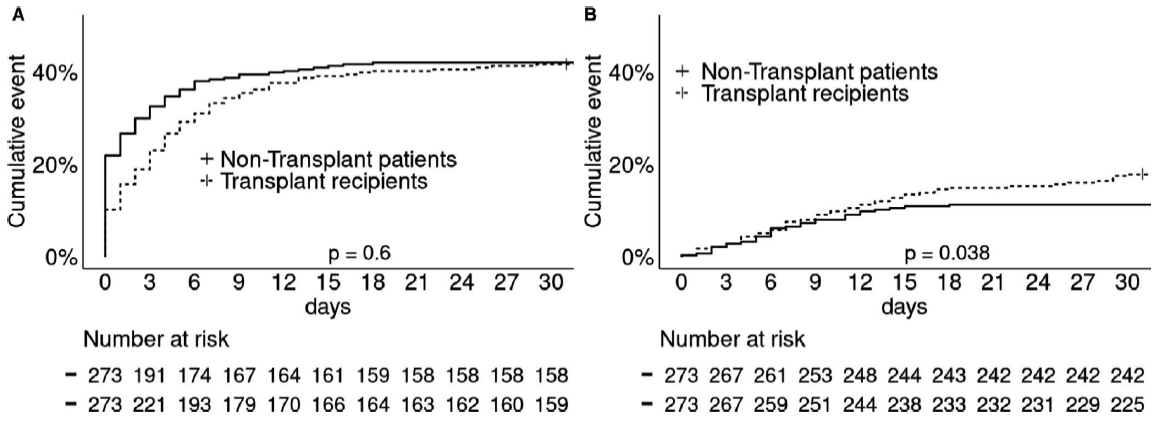
Covid-19 in KT recipients portends a high mortality rate. Risk factors for severe disease are closed to those of the general population. Proper management of immunosuppression and tailored treatment of this population remain challenging.

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

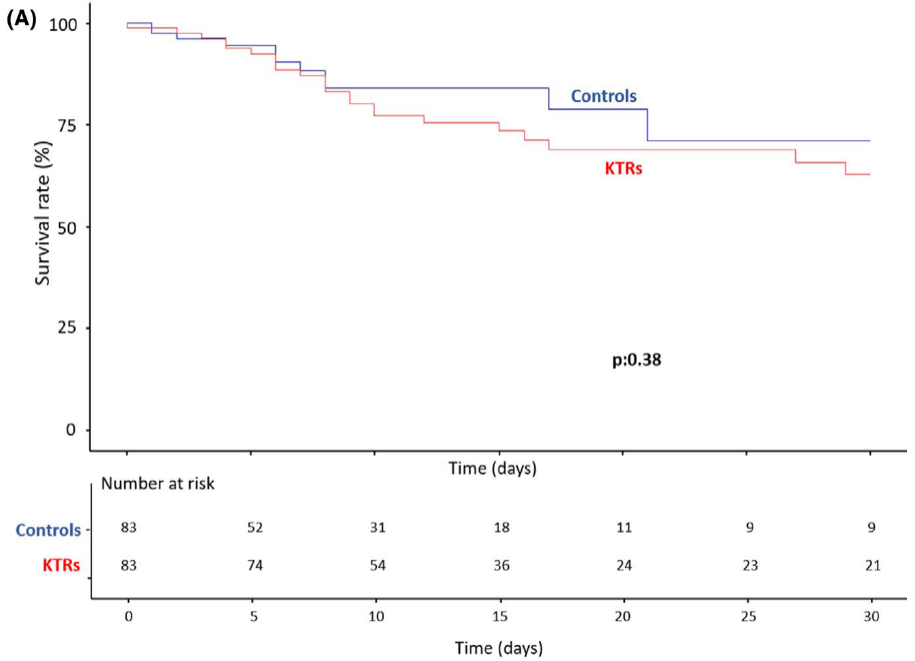
Caillard et al, 2020

Caillard et al, KI, 2020

Specific impact of immunosuppressive therapy ?



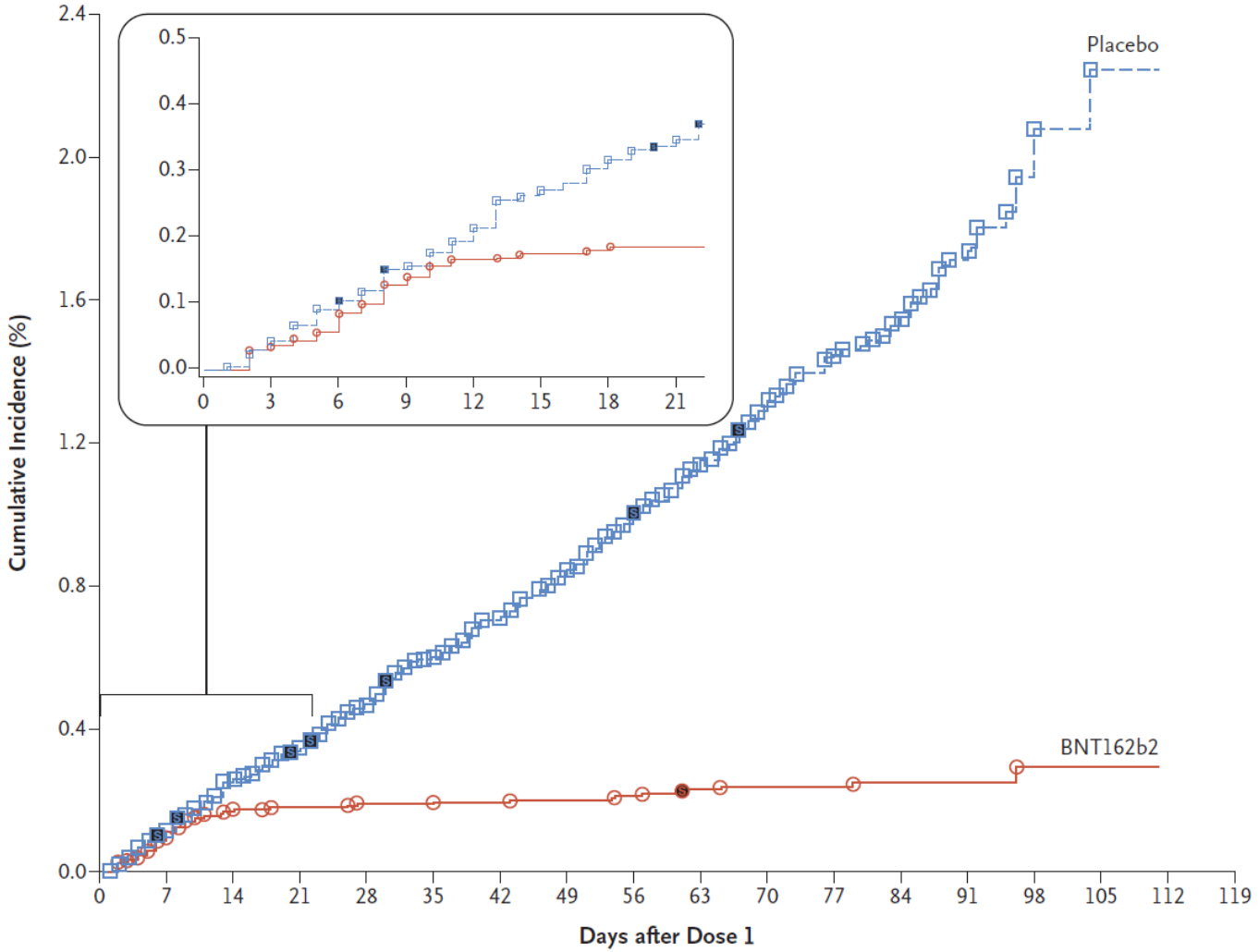
Caillard et al, AJT, 2020



Chavarot et al, AJT, 2020

ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time *person-yr (no. at risk)*	No. of participants	Surveillance time *person-yr (no. at risk)*	*percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

Polack et al, NEJM, 2020

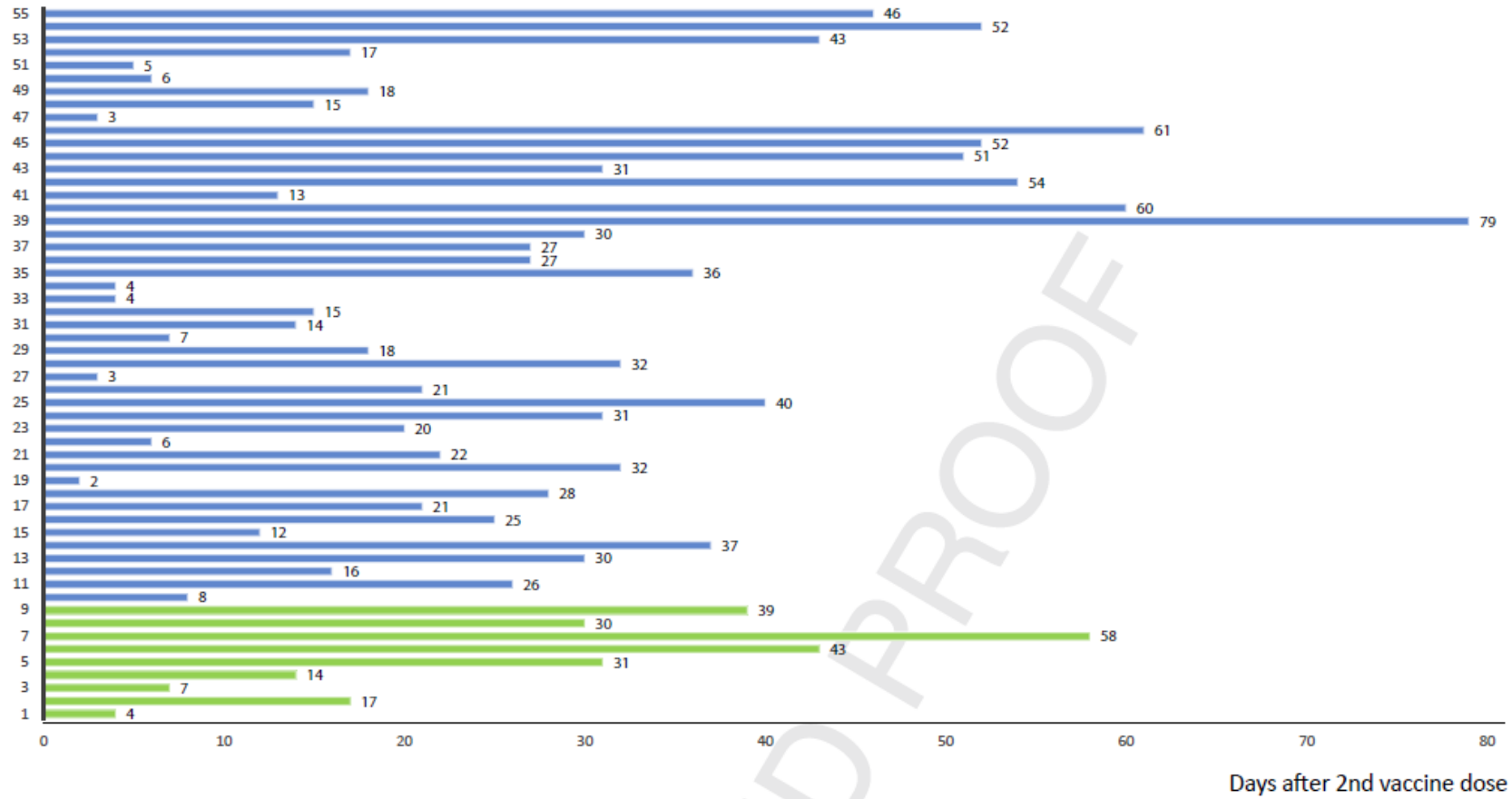


Figure 1| Time from the second vaccine dose to the onset of coronavirus 2019 (COVID-19) symptoms in each kidney transplant recipient. In all cases, the second dose was administered at a timepoint from February 8 to April 22, 2021. Green bars indicate patients who received the Moderna vaccine; blue bars indicate patients who received the Pfizer/BioNTech vaccine.

55 KTR Covid+ after 2nd mRNA vaccine

27% had hypoxemic pneumonia

6 were in ICU

3 died

Caillard et al, KI, 2021

Risk of Breakthrough SARS-CoV-2 Infections in Adult Transplant Recipients

Fully vaccinated

Breakthrough infections

Hospitalization

Death

18215 Transplant recipients in 17 centers	0.83%	0.48%	0.077%
	82x higher	**485x higher**	**485x higher**
101 million Adults in United States	0.0102%	0.0099%	0.00016%

Transplant recipients have lower protection from SARS-CoV-2 infection after vaccination.
Transplant recipients should get vaccinated & continue to practice all COVID safety precautions.

Qin et al. *Transplantation*. July 2021

@TransplantJrnl

Transplantation

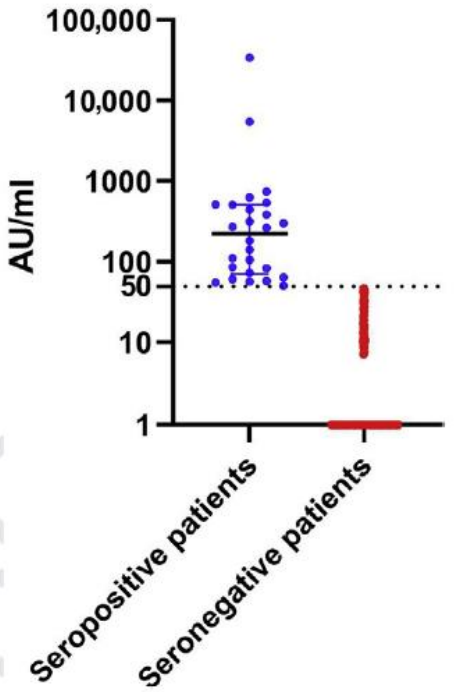
Humoral response after 1mRNA vaccine

Table. Demographic and Clinical Characteristics of Study Participants, Stratified by Immune Response to the First Dose of SARS-CoV-2 Messenger RNA Vaccine, and Associations With Developing an Antibody Response (N = 436)

	Antibody, No. (%)					
	Detectable (n = 76)	Undetectable (n = 360)	Bivariable IRR (95% CI)	*P* value	Adjusted multivariable IRR (95% CI)[a]	*P* value
Age group, y						
18-39	30 (39)	69 (19)	0.81 (0.71-0.93)[b]	.003	0.83 (0.73-0.93)	.002
40-59	18 (24)	132 (37)				
≥60	28 (37)	159 (44)				
Sex[c]						
Female	48 (64)	212 (59)	1.12 (0.73-1.73)[d]	.60		
Male	27 (36)	138 (41)				
Race[c,e]						
Non-White[f]	8 (11)	38 (11)	0.99 (0.51-1.94)[g]	.99		
White	67 (89)	312 (89)				
Type of organ transplant[h]						
Kidney	31 (41)	188 (53)	0.68 (0.45-1.04)[i]	.07		
Liver	28 (37)	50 (14)				
Heart	9 (12)	57 (16)				
Lung	4 (5)	45 (13)				
Pancreas	1 (1)	4 (1)				
Other (multiorgan)	2 (3)	12 (3)				
Time since transplant, y[j]						
<3	13 (17)	106 (30)	1.88 (1.21-2.93)[k]	.005	1.45 (0.96-2.20)	.08
3-6	12 (16)	77 (22)				
7-11	19 (25)	82 (23)				
≥12	31 (41)	89 (25)				
Type of regimen						
Includes anti-metabolite maintenance immunosuppression[l]	28 (37)	292 (81)	0.21 (0.14-0.32)[m]	<.001	0.22 (0.15-0.34)	<.001
Does not include anti-metabolite maintenance immunosuppression	48 (63)	68 (19)				
Vaccine[n]						
mRNA-1273 (Moderna)	52 (69)	152 (43)	2.14 (1.24-3.69)[o]	.006	2.15 (1.29-3.57)	.003
BNT162b2 (Pfizer-BioNTech)	23 (31)	200 (57)				
Enzyme immunoassay manufacturer[p]						
Roche Elecsys	64 (84)	266 (74)	1.71 (0.96-3.05)[q]	.07		
EUROIMMUN	12 (16)	94 (26)				

Boyarski et al, JAMA, 2021

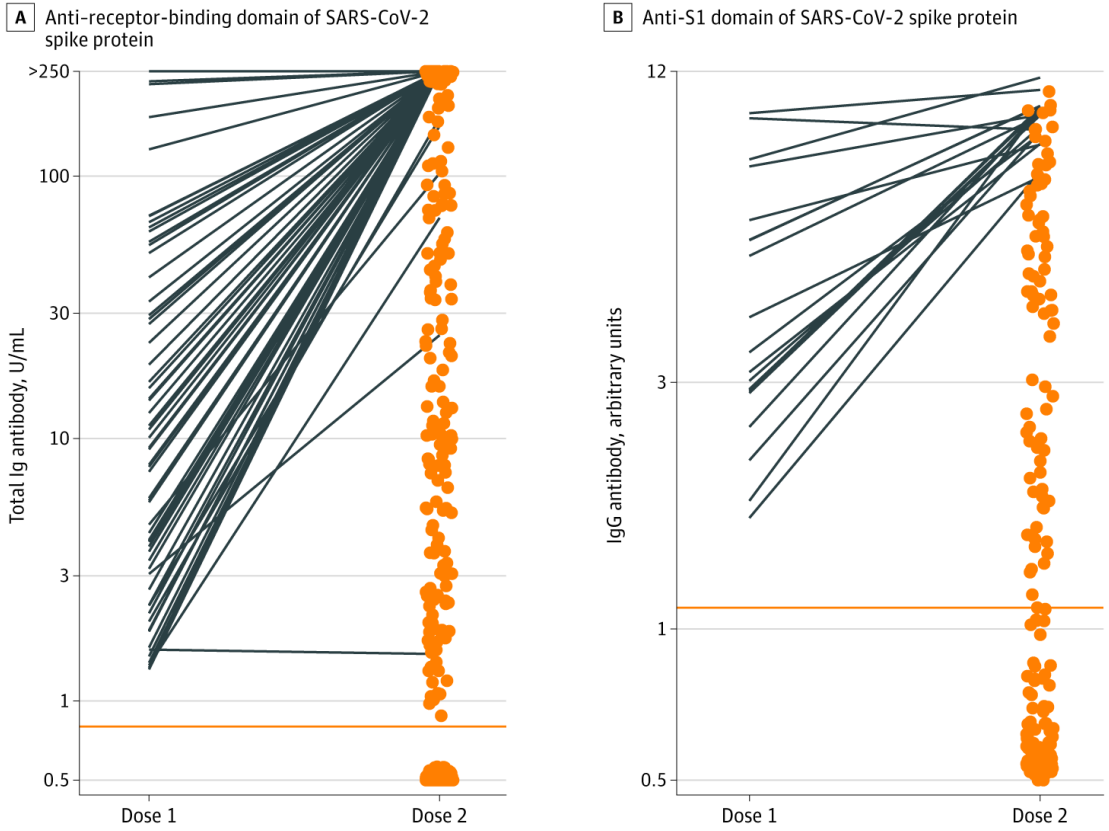
Seroconversion : 17.4%



Benotmane et al, KI, 2021

Seroconversion : 10.8%

Humoral response after 2mRNA vaccine



Boyarski et al, JAMA, 2021

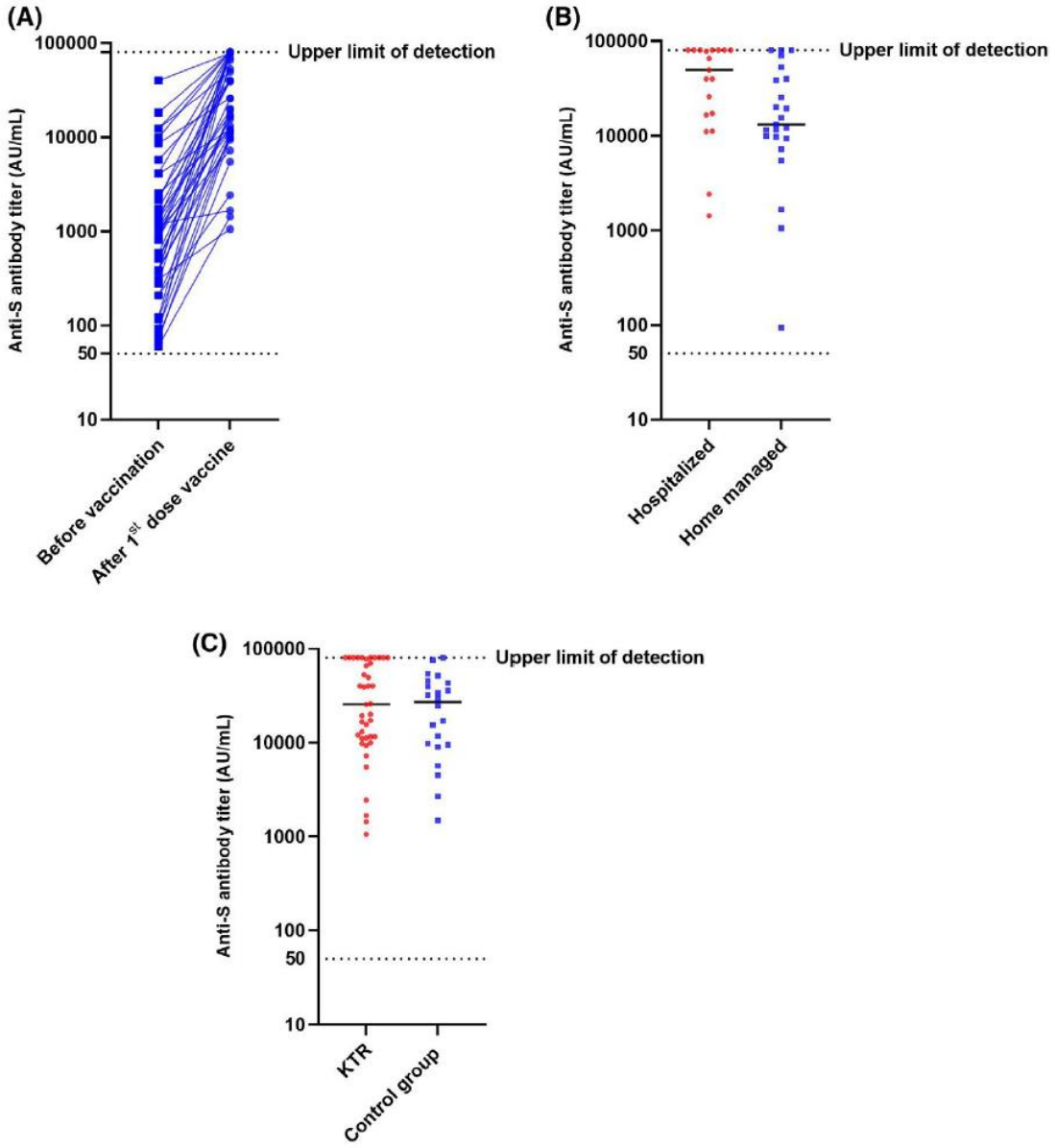
Seroconversion : 54%

Characteristics	Entire cohort (n = 204)[a]	SARS-CoV-2–seronegative patients (n = 106)	SARS-CoV-2–seropositive patients (n = 98)	P
Age, yr	57.7 (49.4–67.5)	58 (51–67.7)	57.3 (46.9–66.2)	0.45
Male sex	130 (63.8)	66 (62.3)	64 (65.3)	0.66
BMI, kg/m^2	25.6 (22.4–28.5)	25.4 (22.3–27.6)	25.9 (22.6–29.9)	0.3
Time from kidney transplantation, yr	6.2 (3–12.8)	5.4 (2.4–12)	7.1 (3.8–14.7)	0.04
First transplantation	170 (83.3)	80 (75.5)	90 (91.8)	0.002
Deceased donor	163 (79.9)	84 (79.3)	79 (80.6)	0.86
ABO group				0.1
O	84 (41.6)	38 (36.5)	46 (46.9)	
A	86 (42.6)	48 (46.2)	38 (38.8)	
B	11 (10.9)	15 (14.4)	7 (7.1)	
AB	10 (5)	3 (2.9)	7 (7.1)	
Induction treatment				0.5
Anti-thymocyte globulin	118 (60.5)	63 (61.8)	55 (59.1)	
Anti-CD25	70 (35.9)	37 (36.3)	33 (35.5)	
No induction	7 (3.6)	2 (2)	5 (5.4)	
CNI				0.13
Tacrolimus	115 (56.4)	67 (63.2)	48 (49)	
Cyclosporine	73 (35.8)	32 (30.2)	41 (41.8)	
No CNI	16 (7.8)	7 (6.6)	9 (9.2)	
MMF/MPA	161 (78.9)	91 (85.9)	70 (71.4)	0.02
Azathioprine	6 (2.9)	0	6 (6.12)	0.01
mTOR inhibitors	27 (13.2)	9 (8.5)	18 (18.4)	0.04
Steroids	122 (59.8)	69 (65.1)	53 (54.1)	0.12
Tacrolimus + MMF/MPA	98 (48)	60 (56.6)	38 (38.8)	0.001
Tacrolimus + MMF/MPA + steroids	64 (31.3)	46 (43.4)	18 (18.4)	0.0001
Belatacept	5 (2.5)	4 (3.8)	1 (1)	0.37
eGFR, ml/min per 1.73 m^2	57.1 (42.4–70.6)	54.4 (38.1–67.5)	62.5 (47.8–72.5)	0.004
Serum creatinine, µmol/L	120 (100–161)	137 (109–173)	110 (96–141)	0.0003

Benotmane et al, KI, 2021

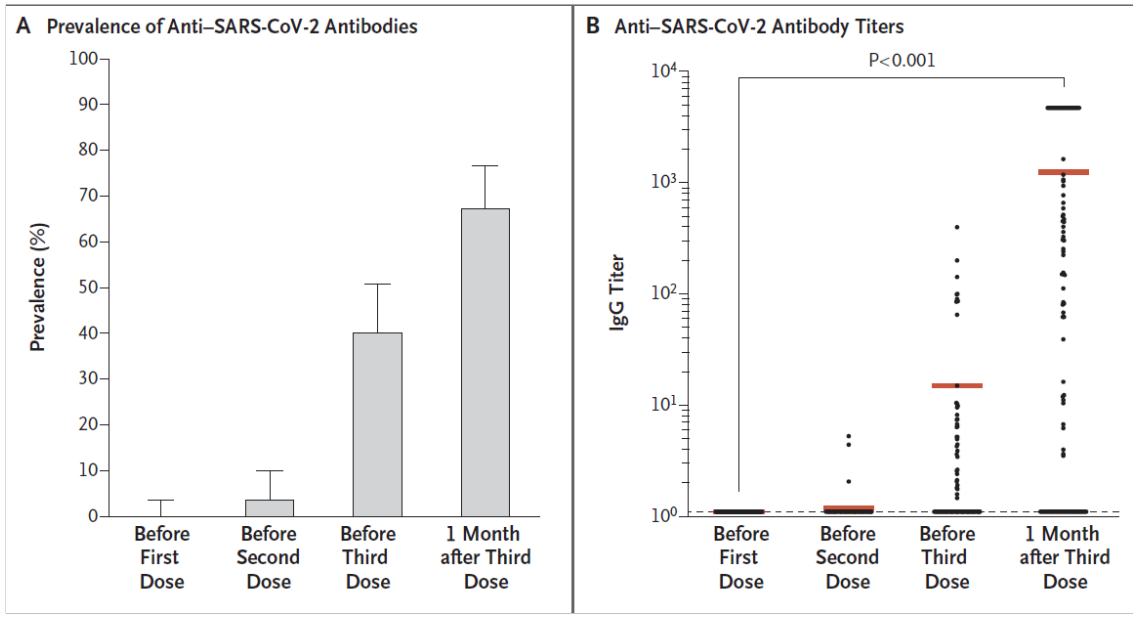
Seroconversion : 48.0%

Humoral response in previously infected KTR

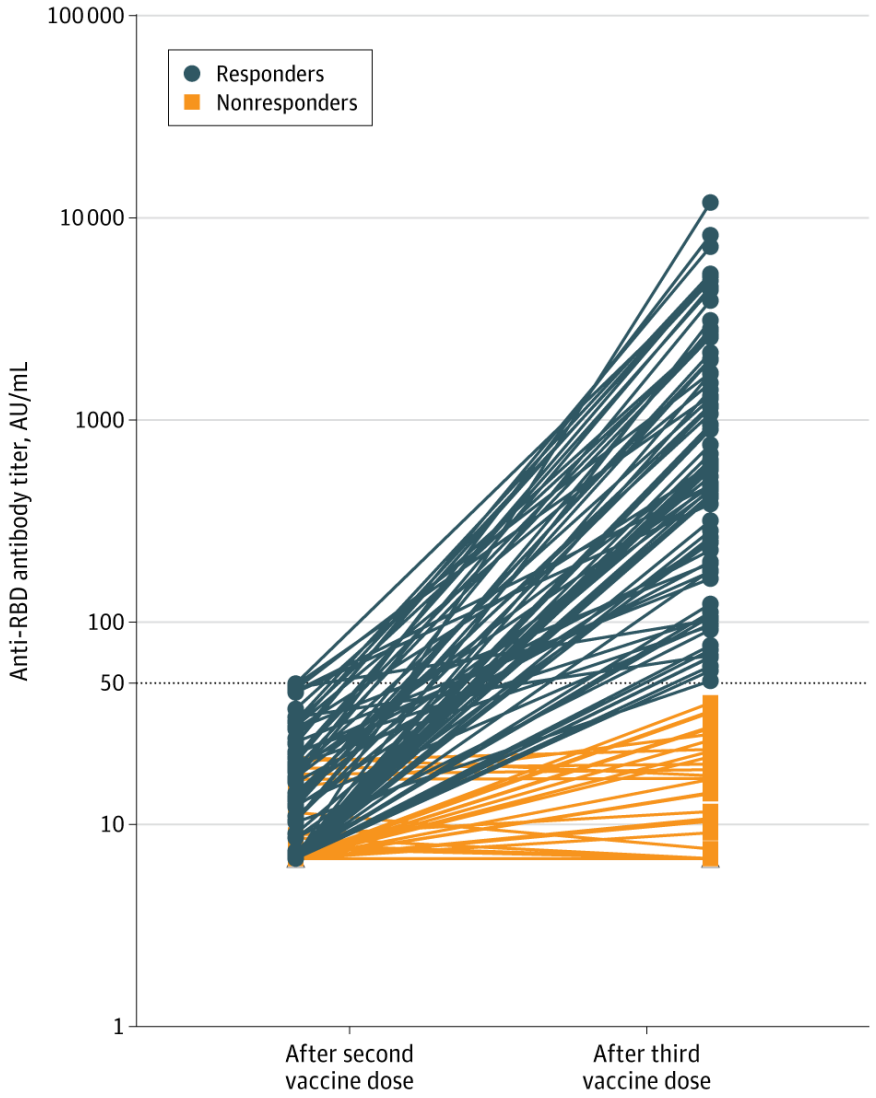


Benotmane et al, AJT, 2021

Humoral response after 3mRNA vaccines



Kamar et al,NEJM, 2021



Humoral response in 49% of seronegative patients after 2 doses

Benotmane et al, JAMA, 2021

Humoral response after 3mRNA vaccines

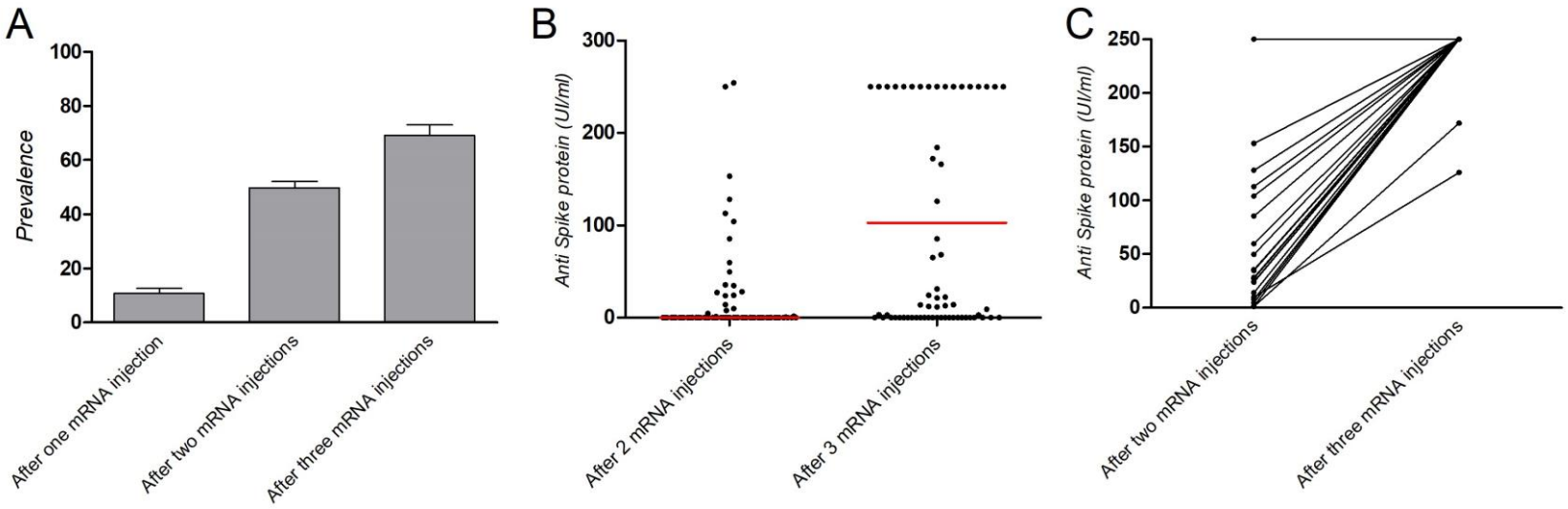


Table 2| Characteristics associated with risk of nonhumoral response to a second dose of mRNA COVID-19 vaccine after multivariate analysis (n = 394)

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

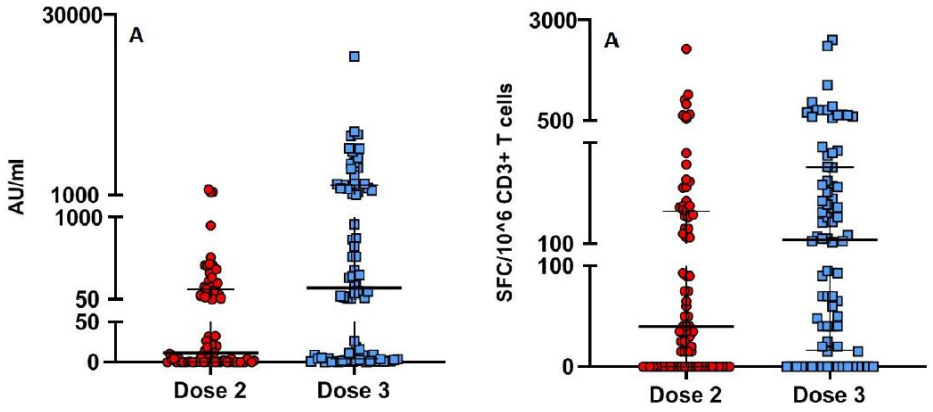
Table 4| Characteristics associated with risk of nonhumoral response to a third dose of mRNA COVID-19 vaccine after multivariate analysis (n = 129)

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**

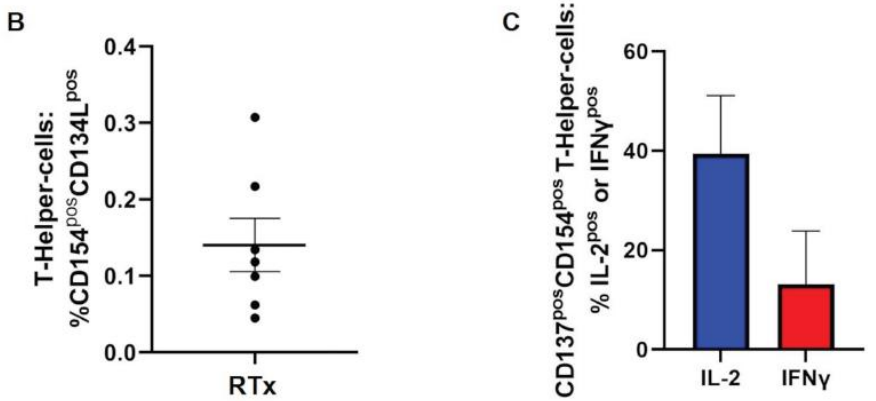
CI, confidence interval; COVID-19, coronavirus disease 2019;MDRD, Modification of Diet in Renal Disease; OR, odds ratio.

Masset et al, KI, 2021

Cellular response after 3mRNA vaccines



Bertrand et al, KI , 2021



Dolff et al, KI , 2021

Cellular response in seronegative KTR

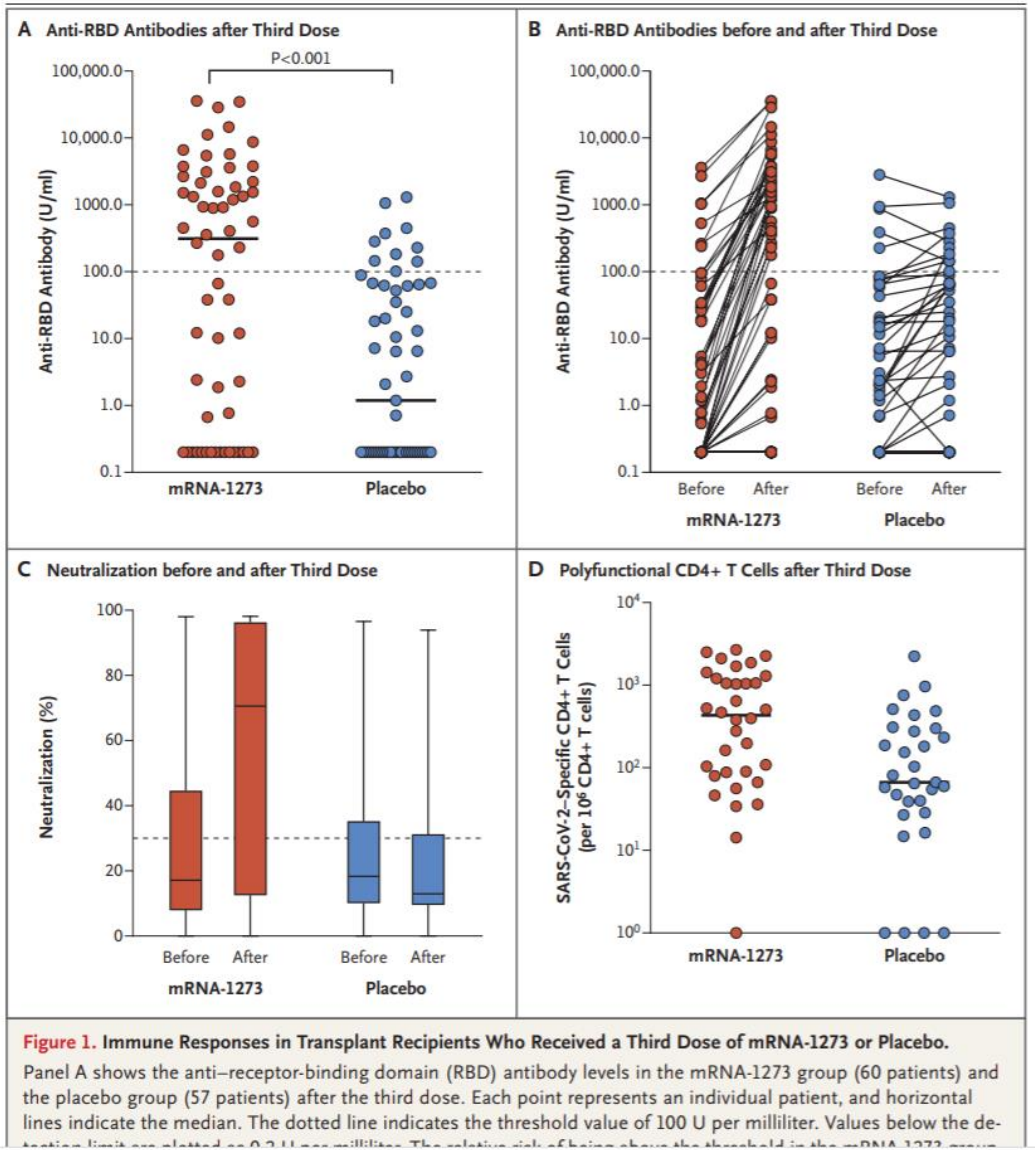
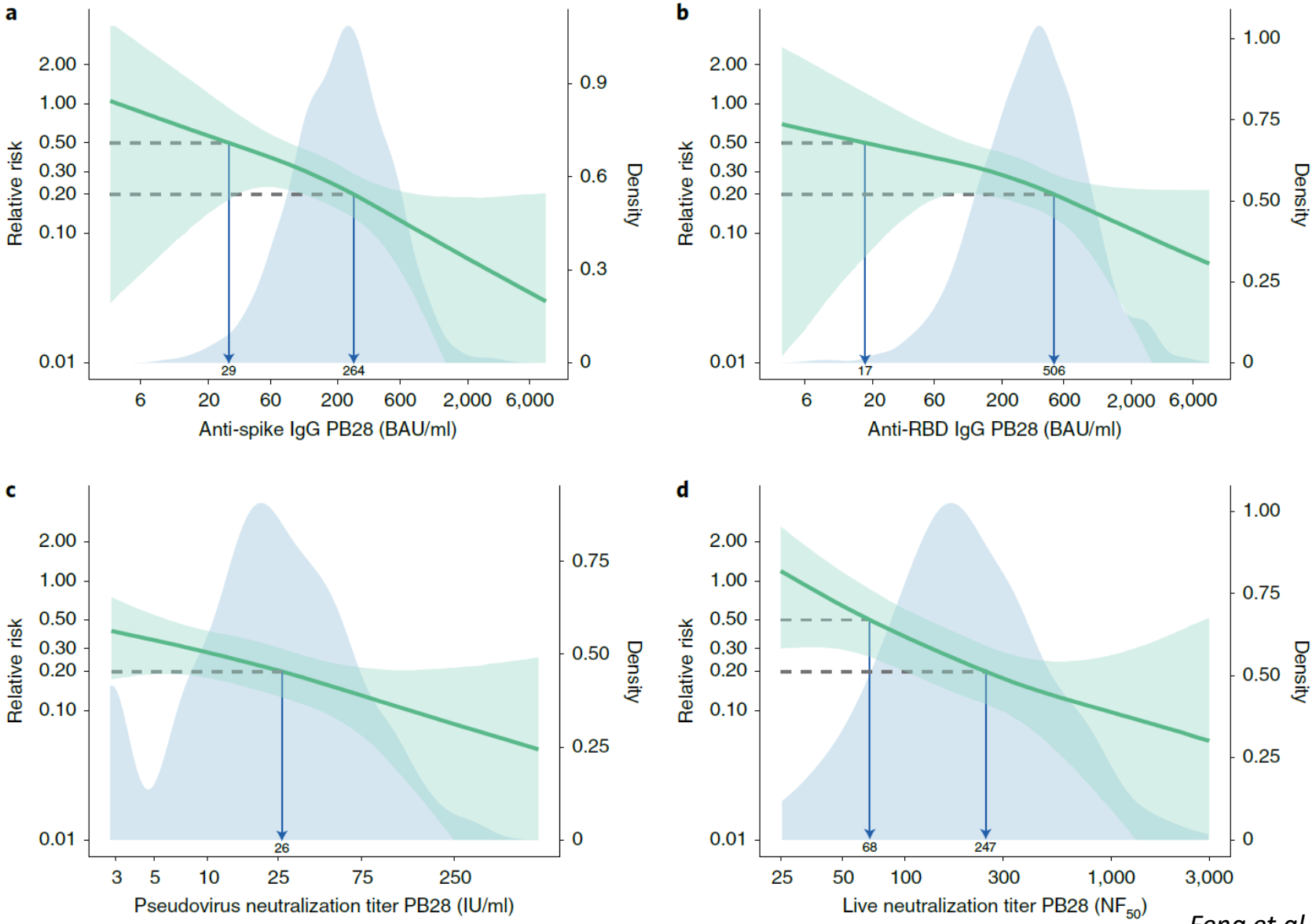


Figure 1. Immune Responses in Transplant Recipients Who Received a Third Dose of mRNA-1273 or Placebo.

Panel A shows the anti–receptor-binding domain (RBD) antibody levels in the mRNA-1273 group (60 patients) and the placebo group (57 patients) after the third dose. Each point represents an individual patient, and horizontal lines indicate the median. The dotted line indicates the threshold value of 100 U per milliliter. Values below the de-

Hall et al,NEJM, 2021

Risk of symptomatic Covid-19 depending on IgG level



Feng et al, Nature , 2021

Heterologous vaccination

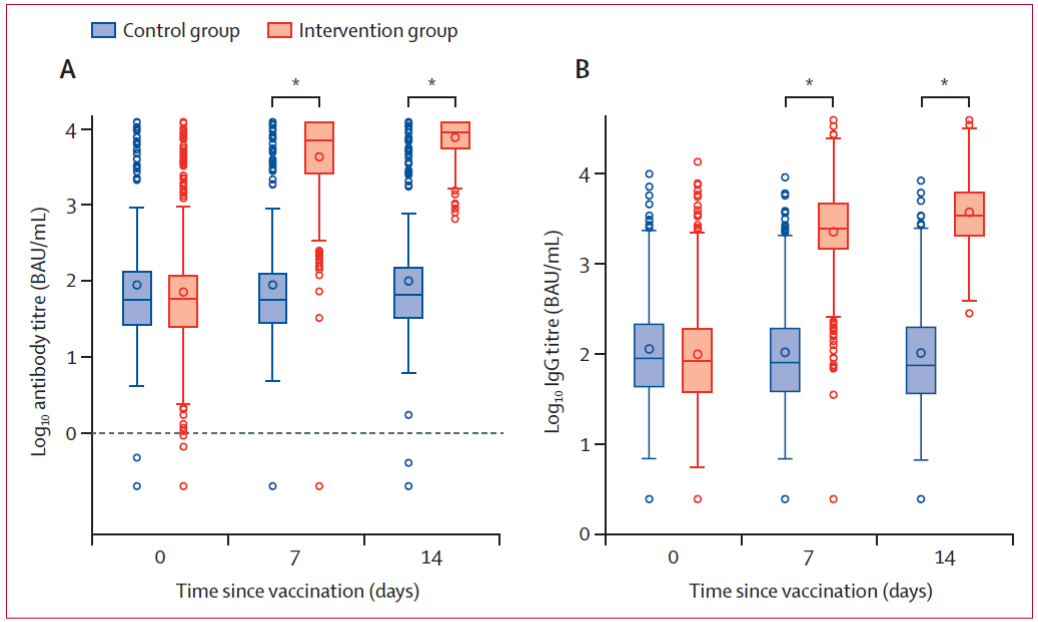
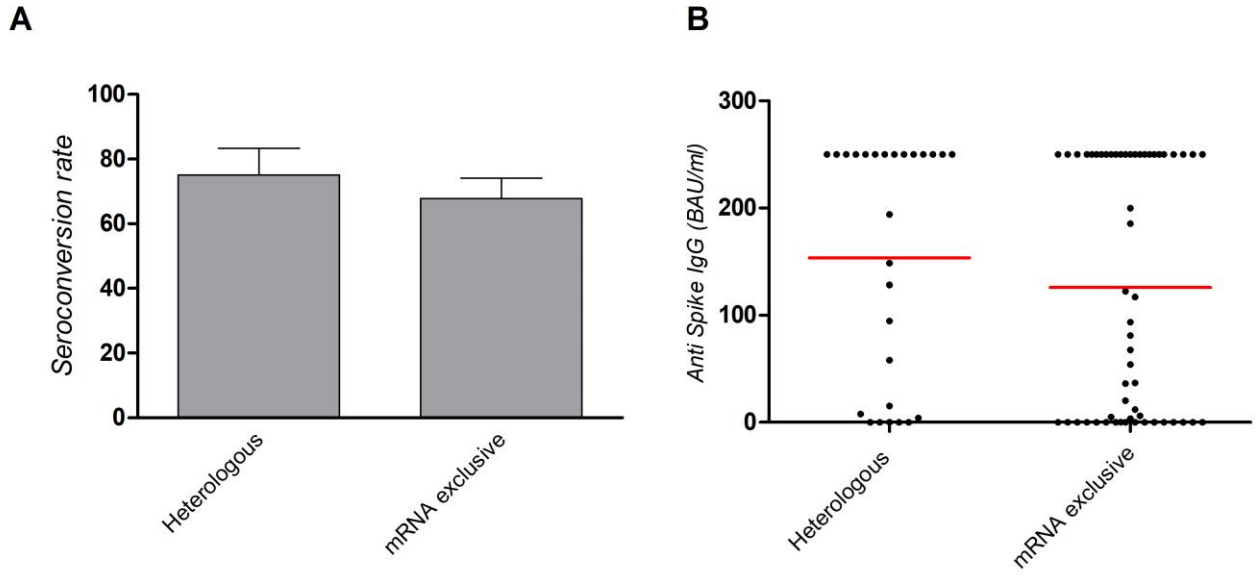


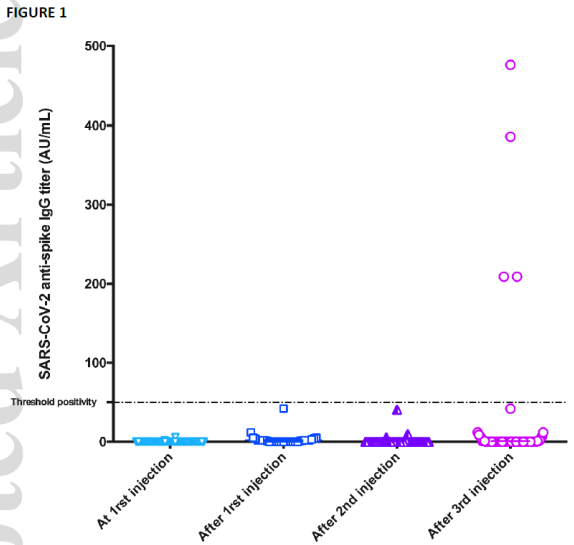
Figure 2: **Antibody titres**
Receptor-binding domain (anti-spike protein) antibody titres (A), and trimeric spike protein antibody titres (B), measured in both intervention and control groups on days 0, 7, and 14. *p<0·0001.

Borobia et al, Lancet, 2021



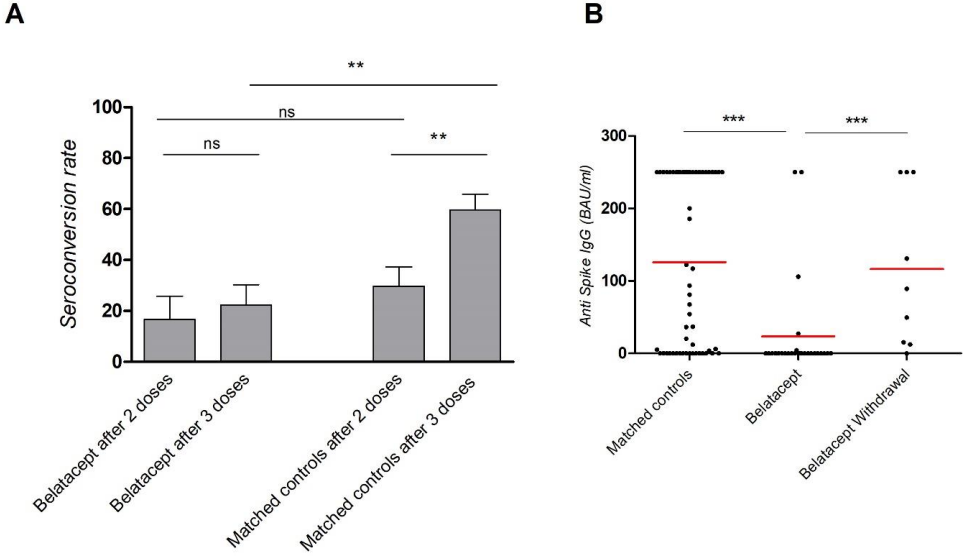
Masset et al, KI (reviewing), 2021

Impact of immunosuppression



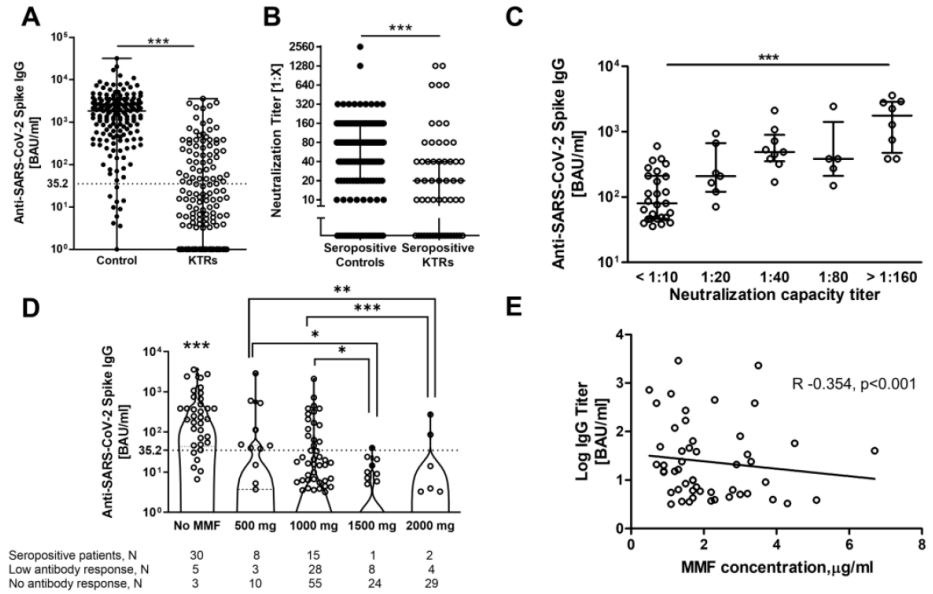
Chavarot et al, AJT, 2021

Belatacept Seroconversion : 6.4%



Masset et al, KI (reviewing), 2021

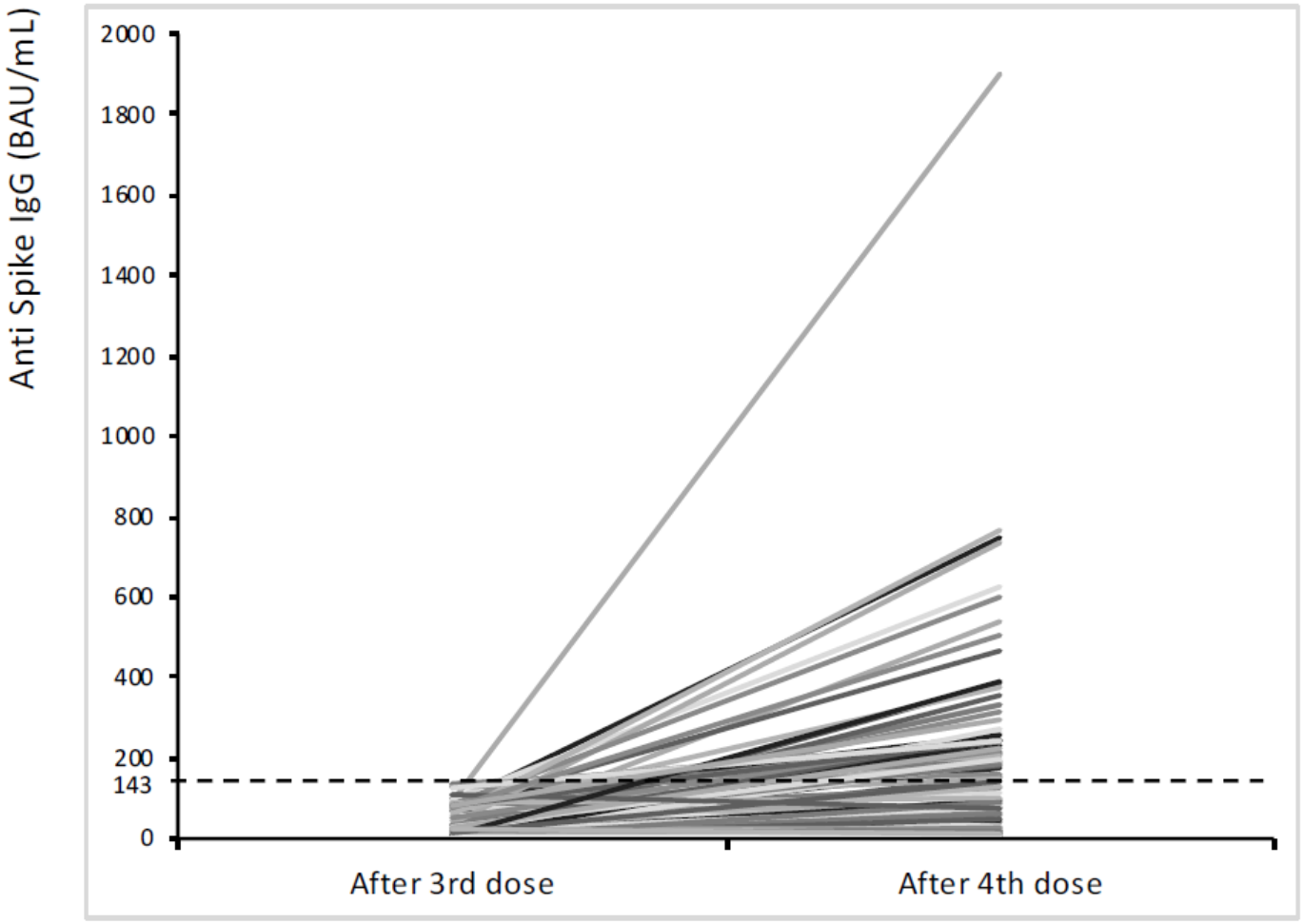
Belatacept Seroconversion : 22% vs 59% matched controls
Seroconversion 87% in belatacept withdrawal patients



Dose dependant effect of antiproliferative drugs

Kantauskaite et al, AJT, 2021

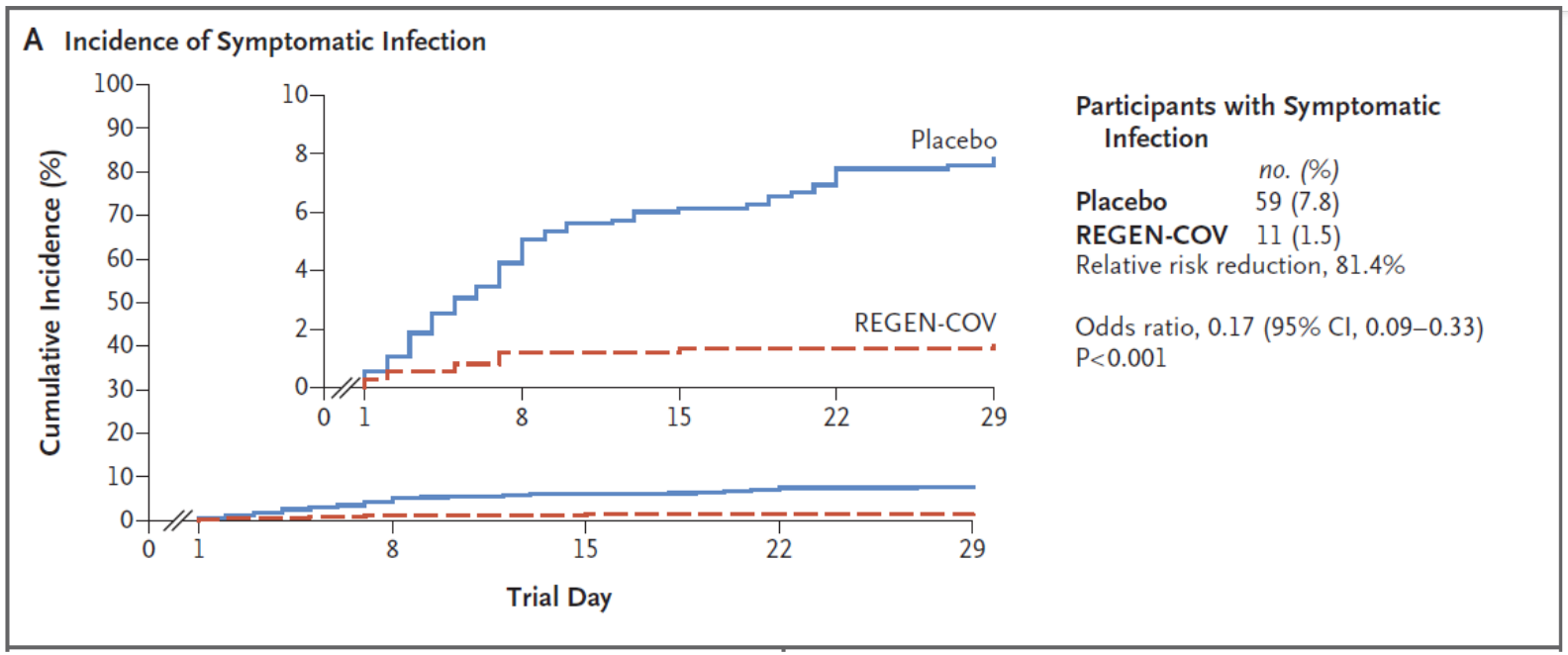
4th mRNA vaccine in weak positive SOT



Caillard et al, Annals of Internal Medecine (reviewing), 2021

ORIGINAL ARTICLE

Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19



HAS

Médicament | Vaccination | Dispositif | Évaluation économique | Moyens d'information | Agenda

RONAPREVE (casirivimab-imdevimab) (prophylaxie pré-exposition de l'infection à SARS-CoV-2)

DÉCISION D'ACCÈS PRÉCOCE - Mis en ligne le 06 août 2021

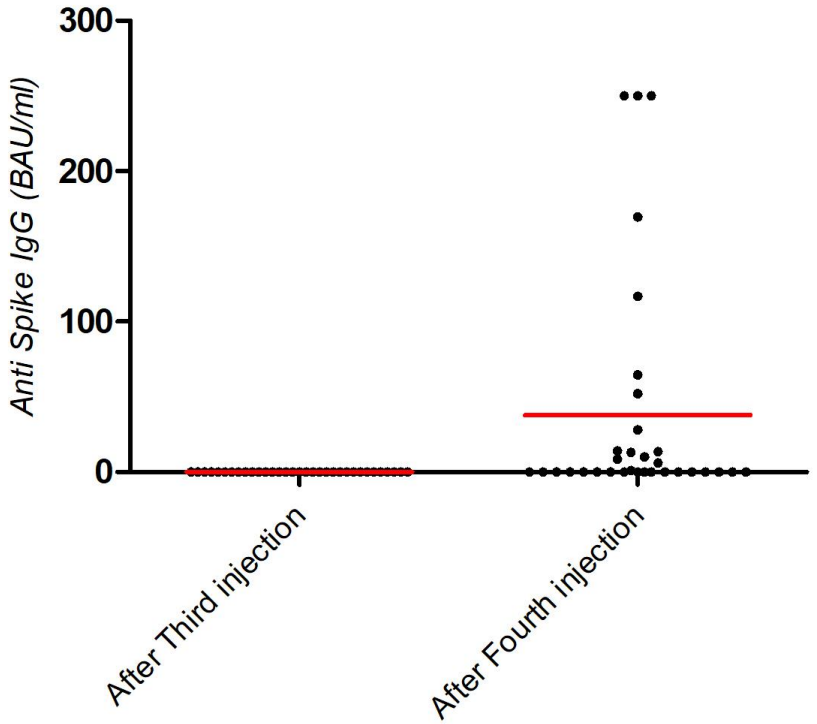
Autorisation d'accès précoce dans l'indication « en **prophylaxie pré-exposition de la COVID-19** chez les patients adultes et les enfants âgés de 12 ans et plus, n'ayant pas développé du fait de leur immunodépression une réponse vaccinale satisfaisante à un schéma complet de vaccination conformément aux recommandations en vigueur (patient non-répondeurs) ET appartenant à l'un des sous-groupes à très haut risque de forme sévère de COVID-19 tels que définis par l'ANRS-Maladies Infectieuses Emergentes :

- Receveurs de greffes d'organes solides
- Receveurs d'une greffe allogénique de cellules souches hématopoïétiques
- Hémopathies lymphoïdes : leucémies lymphoïdes chroniques traitées ou non, lymphomes non hodgkiniens et myélomes sous traitement, y compris les patients receveurs de thérapie cellulaire génique de type CAR-T cell ou d'anticorps thérapeutiques bi-phénotypiques
- Patients recevant un traitement par anticorps anti-CD20 ou inhibiteurs de BTK ou azathioprine, cyclophosphamide et mycophenolate mofetil
- Sujets porteurs d'un déficit immunitaire primitif

Ou les patients séronégatifs après un schéma vaccinal complet ou non éligibles à la vaccination **et** qui présentent une immunodépression sévère **et** qui sont à haut risque de forme grave de COVID-19.

O'Brian et al, NEJM, 2021

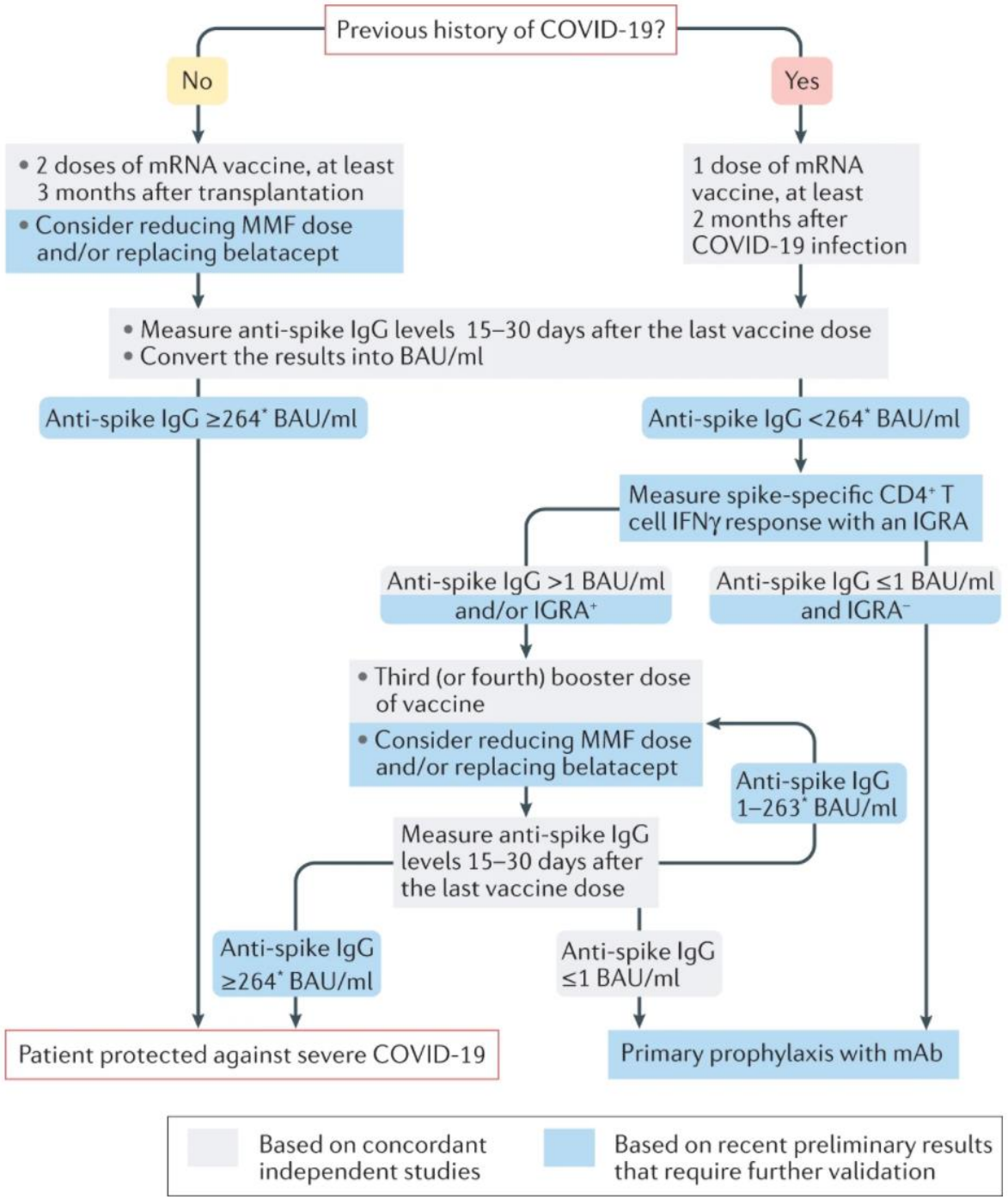
4th mRNA vaccine in seronegative SOT



	Negative (n=18)			Positive (n=15)			
	NA	n	%	NA	n	%	p-value
Male recipient	0	11	61.1	0	6	40	0.48
Transplant rank ≥ 2	0	2	11.1	0	2	13.3	1
Calcineurin inhibitor treatment	0	11	61.1	0	13	86.7	0.13
mTOR inhibitor treatment	0	0	0	0	0	6.7	0.45
Antimetabolite treatment	0	13	72.2	0	13	86.7	0.41
Steroid treatment	0	10	55.6	0	7	46.7	1
	NA	Mean	SD	NA	Mean	SD	p-value
Age (years)	0	65.0	9.4	0	61.7	13.2	0.62
Time from transplantation (years)	0	7.6	7.8	0	5.9	6.0	0.66
Lymphocyte count (/mm^3)	0	1269	490	0	1870	1297	0.46
Anti-spike IgG titer (BAU/ml)	0	0	0	0	73.0	86.7	< 0.001
Allograft function by MDRD (ml/min)	0	42.9	20.0	0	40.6	15.1	0.95

Seroconversion : 45.4%

Masset et al, unpublished data



Caillard et al, Nature Rev Nephrol, 2021