COVID-19 vaccinations in renal disease: an update

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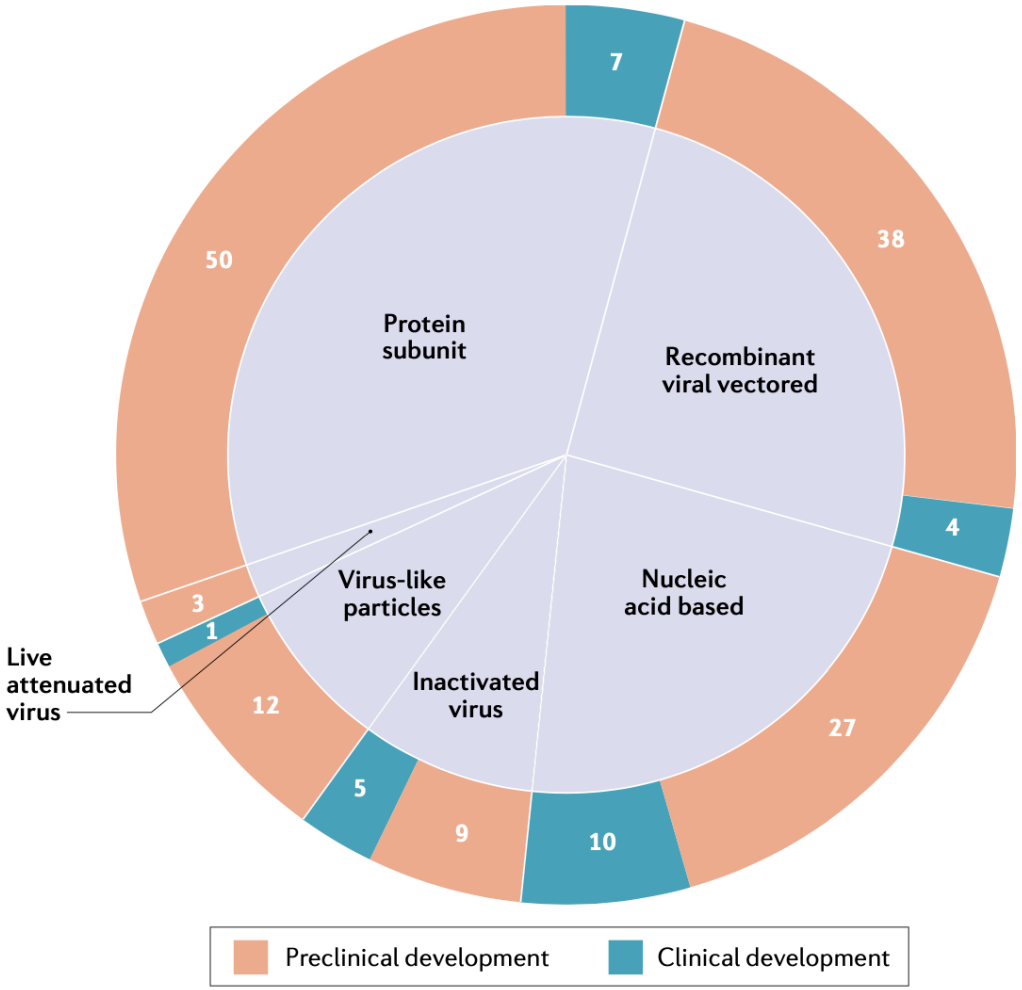
… for frequent updates on preprints/publications please visit

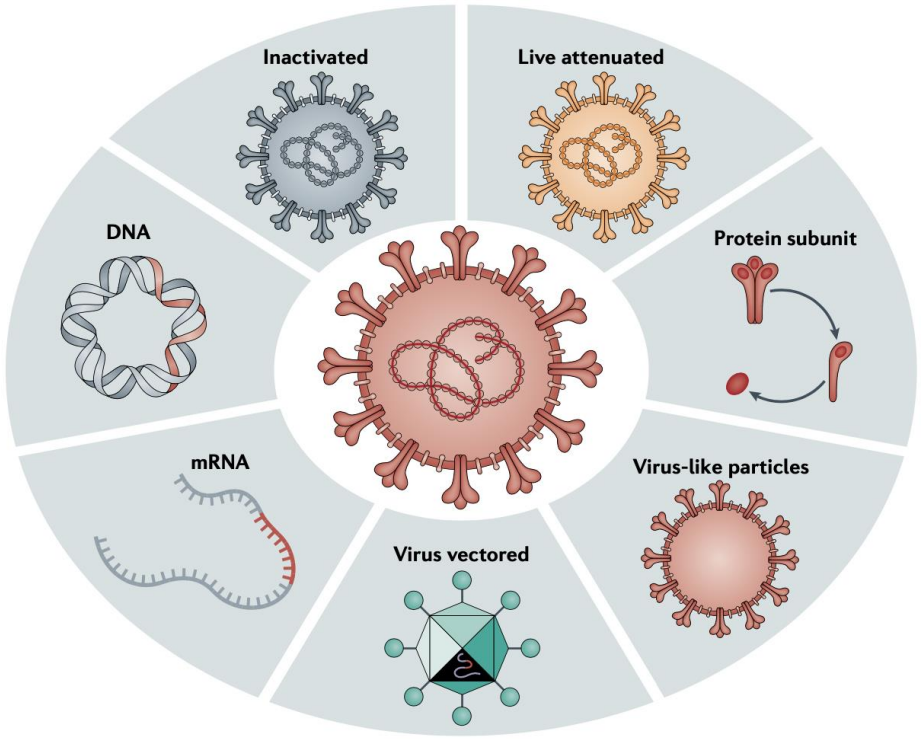
http://www.nephjc.com/news/covid-vaccine

COVID-19 vaccine pipeline (*Oct. 2020*)



Jeyanathan M, et al. Nat Rev Immunol 2020; 20:615-632

COVID-19 vaccine pipeline



Inactivated virus vaccine

Preservation of the integrity of the virus particle, which serves as the immunogen

VLP or nanoparticle vaccines

Viral proteins are co-expressed to form non-infectious particles (lack the viral genome)

Protein subunit vaccines

Key viral proteins/peptides that can be manufactured *in vitro* (i.e. in bacteria)

Virus-vectored vaccines

Gene(s) encoding pathogen antigen(s) are cloned into non-replicating or replicating virus vectors (such as adenovirus)

DNA and mRNA vaccines

DNA: viral antigen(s) encoded by a recombinant DNA plasmid are produced in host cells via a sequential transcription-to-translation process
mRNA: synthesized by in vitro transcription and produce viral antigen(s) in the cytoplasm through direct protein translation *in vivo*

Live-attenuated virus vaccines

Virus is attenuated by *in vitro* or *in vivo* passage or reverse-genetic mutagenesis
The resulting virus becomes non-pathogenic or weakly pathogenic

Dai L, et al. Nat Rev Immunol 2021; 21:73-82

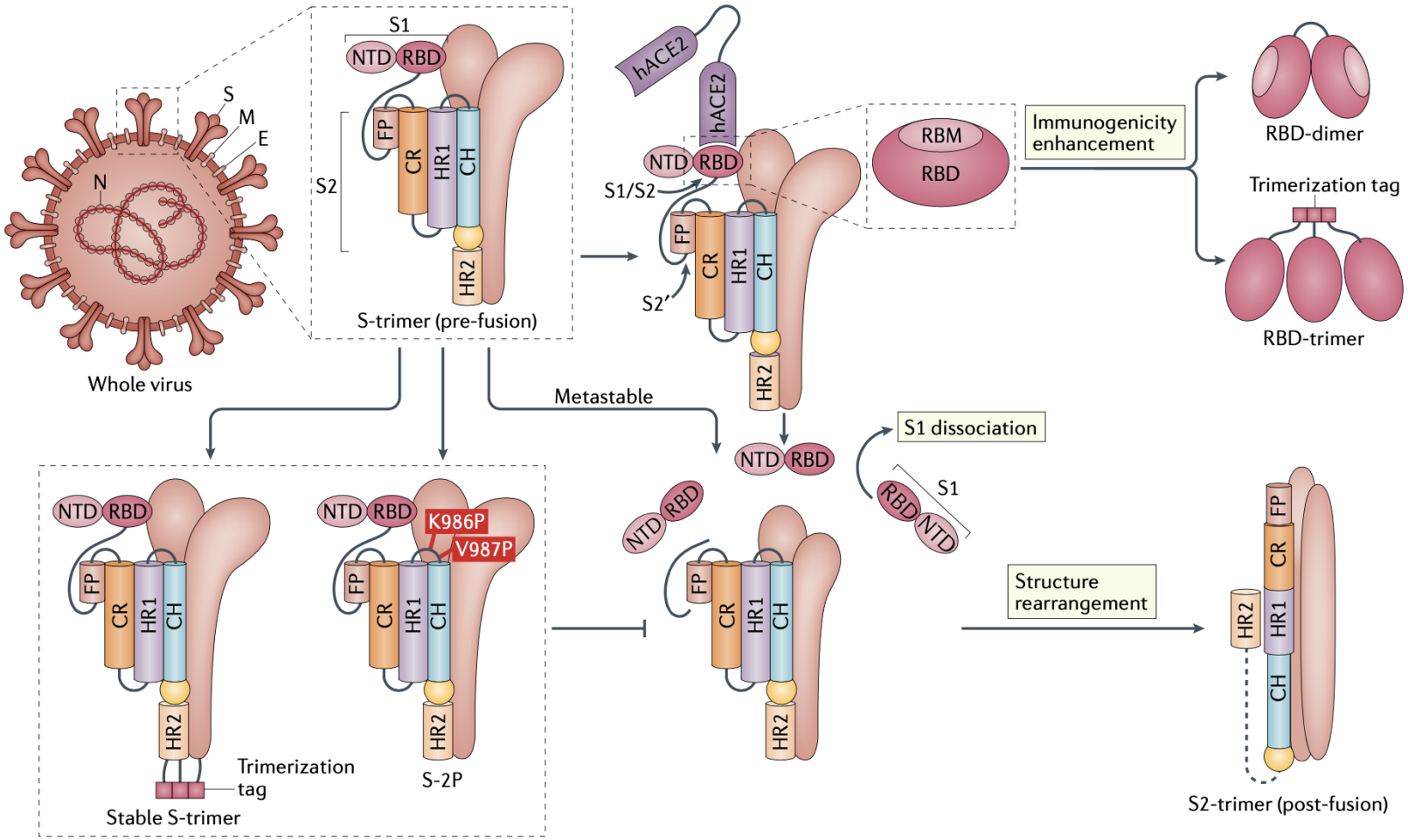
COVID-19 vaccine pipeline

Vaccine platform	SARS-CoV-2 antigens	Neutralizing antibody response	T cell response			Pre-existing antivector immunity	Route of vaccination	Overall immunogenicity	Other attributes
			$CD4^+$ T_H cells	$CD8^+$ T cells	Lung T_{RM} cells				
Viral-vectored vaccines									
Ad5 (non-replicating)	S protein	Quality and durability affected by pre-existing antivector immunity	T_H1 cell	Potent response; negative effects from pre-existing antivector immunity	Induced by RM but not IM route	High, age-dependent, prevalence in blood; low prevalence in respiratory tract	Parenteral (IM) in clinical trials	Strong with single delivery but hindered by pre-existing antivector immunity	Ample human safety data; RM delivery helps bypass antivector immunity; can be delivered by inhaled aerosol
Ad26 (non-replicating)	S protein	Quality and durability affected by pre-existing antivector immunity	T_H1 cell	Moderate response; negative effects from pre-existing antivector immunity	Induced by RM but not IM route	Medium prevalence	Parenteral (IM) in planned clinical trials	Weak; requires repeated or heterologous boost vaccination	Established human safety from HIV and Ebola vaccine trials; RM delivery helps bypass antivector immunity
ChAd (non-replicating)	S protein	Unimpeded owing to lack of pre-existing antivector immunity	T_H1 cell	Potent response	Induced by RM but not IM route	Very low prevalence	Parenteral (IM) in clinical trials	Strong with single delivery	Well-established human safety data; amenable to RM delivery; can be used as a stand-alone vaccine or in prime–boost regimens
Other vaccines									
mRNA-based vaccine	S protein or RBD encapsulated in lipid nanoparticle	Unimpeded owing to lack of pre-existing antivector immunity	T_H1 cell or T_H2 cell depending on adjuvant	Depends on choice of adjuvant and formulation	Not induced by parenteral route	None	Parenteral (IM) in clinical trials	Requires repeated delivery	Adjuvant required; unclear whether it is amenable to RM vaccination

IM (intramuscular), RBD (receptor-binding domain), RM (respiratory mucosal)

Jeyanathan M, et al. Nat Rev Immunol 2020; 20:615-632

COVID-19 vaccine targets



***4 major structure proteins*:**
S (spike)
M (membrane)
E (envelope)
N (nucleocapsid)

S-protein:
S1 subunit
(RBD, receptor-binding domain)
S2 subunit

SARS-CoV-2 S protein binds to its host receptor, the dimeric human angiotensin-converting enzyme 2 (hACE2), and dissociates the S1 subunits

Structure rearrangement of the S2 subunit, required for virus-host membrane fusion

RBD is an attractive vaccine target; RBD-dimer/-trimer has been shown to enhance the immunogenicity of RBD-based vaccines

Dai L, et al. Nat Rev Immunol 2021; 21:73-82

COVID-19 vaccines

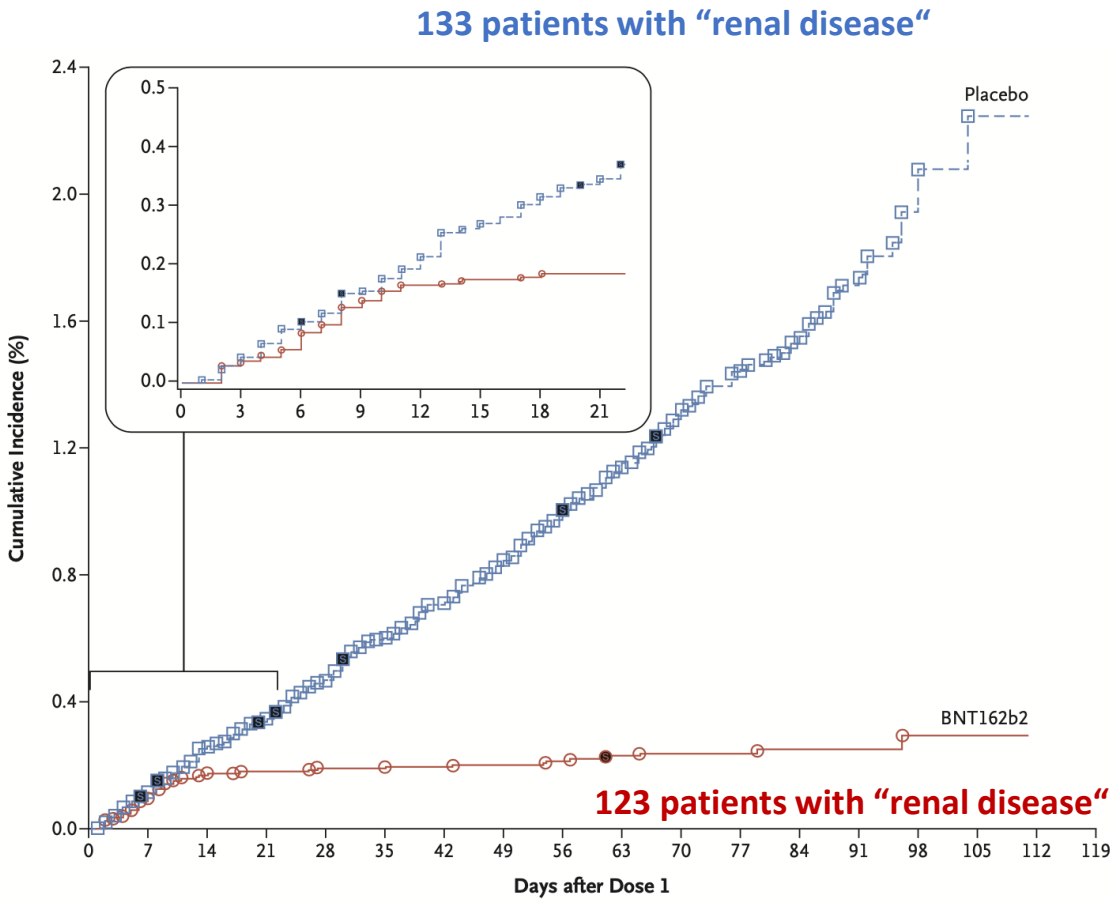
How do approved vaccines perform in “healthy individuals“?

Vaccine (manufacturer)	Participants (vaccine/control group)	Efficacy	Infections (vaccine vs. control arm)	Duration (months)	Countries involved in trial	Number of doses	Storage
		Purified protein					
NVX-CoV2373 (Novavax)	-	89.3%*	6 vs. 56		UK	2	2-8°C
		Replication-defective viral vector vaccine					
ChaAdOx1 nCoV-19 (Oxford-Astra Zeneca)	5,807 vs. 5,829	70.4% (LD/SD: 90.0%; SD/SD: 62.1%)	30 vs. 101*[2]	3.4	UK, Brazil	1-2	2-8%
Gam-COVID-Vac/Sputnik V (Gamaleya)	16,501 vs. 5,476	91.6%	16 vs. 62*[3]	1.6	Russia	2	2-8%
Ad26.COV2.S (Janssen/Johnson & Johnson)		72%, 66%, 57%* (USA, Latin America, South Africa)	116 vs. 348		USA, Central/South America, South Africa	1	2-8%
		mRNA vaccines					
BNT162b2 (Pfizer/BioNTech)	18,860 vs. 18,846	95%	8 vs. 162*[4]	2	USA, Brazil, Argentina, South Africa	2	-20%/-70%
mRNA-1273 (Moderna)	15,181 vs. 15,170	94.1%	11 vs. 185*[2]	2.1	USA	2	-20%

*based on press releases

Windpessl M, et al. Nat Rev Nephrol 2021; online ahead of print.
Kronbichler A, et al. Nephrol Dial Transplant 2021; online ahead of print.

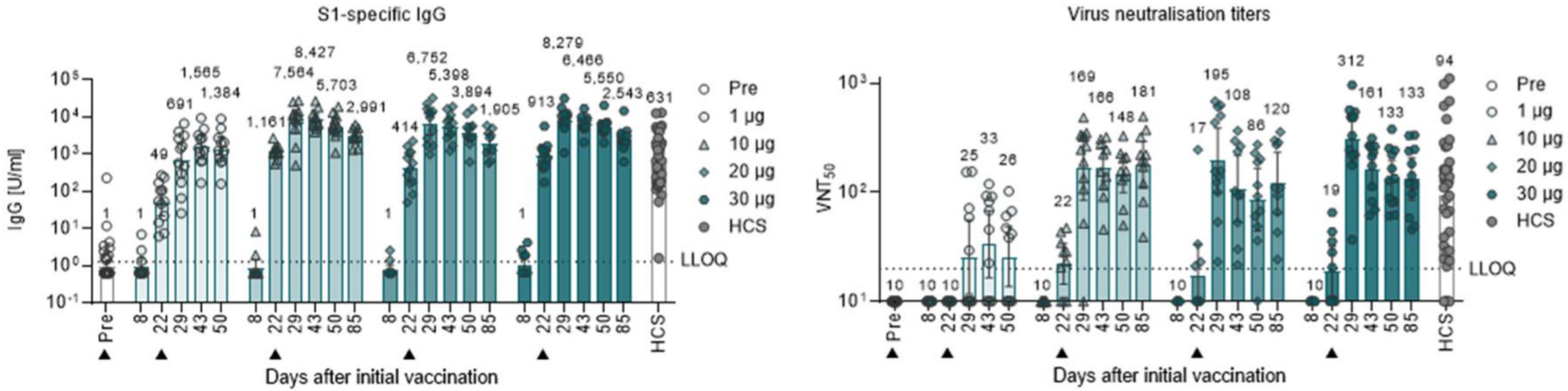
Limited data on patients with renal diseases



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 FP, et al. N Engl J Med 2020; 383:2603-2615

Longevity of antibody response (*BNT162b2*)



HCS (panel of sera from SARS-CoV-2 convalescent patients)

Sahin U, et al. medRxiv preprint, doi: 10.1101/2020.12.09.20245175

Is a single dose sufficient?

In healthy individuals probably YES

Moderna

Covid-19 Onset	Placebo (N=14,598)	mRNA-1273 (N=14,550)
Randomization to 14 days after dose 1	11	5
14 Days after dose 1 to dose 2	35	2
Dose 2 to 14 days after dose 2	19	0
Starting 14 days after dose 2	204	12
Total (any time after randomization)	269	19

Pfizer-BioNTech

Analysis Period	Vaccine (N=21,669)	Placebo (N=21,686)	Vaccine Efficacy, % (95% CI)*
	no. of cases		
After dose 1 to before dose 2 (per Polack et al.[1])	39	82	52.4 (29.5–68.4)
Beginning 7 days after dose 1 to before dose 2 (derived†)‡	18	57	68.5 (46.5–81.5)
Beginning 14 days after dose 1 to before dose 2 (derived†)§	2	27	92.6 (69.0–98.3)
≥7 Days after dose 2 (per Polack et al.[1])	9	172	94.8 (89.8–97.6)

Baden LR, et al. N Engl J Med 2021; 384:403-16
Skowronski DM, et al. N Engl J Med 2021, online ahead of print.

	Specific question?	Answers
1	Is vaccination recommended to patients with kidney disease?	We do recommend vaccination for everyone (except for those with known allergic reactions to any of the vaccine components).
2	Is one vaccine better than others?	Full trial publications of BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and Gam-COVID-Vac (Sputnik V, Gamaleya) showed a high efficacy on preventing symptomatic and severe COVID-19, while the duration of protection and the potential of the available vaccines to prevent asymptomatic SARS-Cov-2 infection has not yet been fully explored. It is also not known, if any single vaccine offers advantage for specific patient populations.
3	I had COVID-19 recently. Should I be vaccinated?	Antibodies are decreasing over time, so theoretically there is a benefit, but data on the number of booster injections and an optimal time-point for vaccination after infection are scarce.
4	Can I be vaccinated while taking immunosuppression?	States of immunodeficiency, hereditary or acquired, can reduce vaccine responses. A recent dose of rituximab or higher doses of other immunosuppressants may specifically impair vaccine responses. Likely, it is wise for many patients to wait with vaccination until steroid doses are tapered to below 20 mg prednisone equivalent a day and 6 months have eclipsed since last rituximab dose.
5	Are there specific side effects of vaccines?	The approved vaccines are generally well tolerated. Some report "flu-like symptoms" one or several days following the second dose. Local reactions are frequently reported as with other vaccines.
6	Is there a possibility that the vaccine induces an activation of my disease?	Patients with autoimmune diseases were excluded in the early studies. There are insufficient data, but the vaccines seem to be safe and experience from previous vaccine studies does not indicate an increased risk for relapse/recurrence.
7	Should I get vaccinated even if there are existing allergies?	In general, "yes", the whole process is supervised. We advise against the use of currently available vaccines in patients with known PEG or polysorbate allergies.
8	Am I having a lifelong protection against COVID-19 after vaccination?	For now, there is no information about the longevity of immunity following vaccination. Booster injections may become necessary to maintain anti-SARS-CoV-2 immunity. Viral mutations are frequent, and newer/modified vaccines may be used to protect against these variants.
9	I failed to mount an adequate immune response to my first COVID-19 vaccine. Is it possible to receive another vaccine platform?	Yes, with the approval of more vaccines, there could be other options (such as respiratory booster vaccines under investigation), which might induce immunity.
10	Can I expect interference of the COVID-19 vaccine with my medication?	No, no such interactions are expected.
11	After receiving my first vaccine shot, do I still need to shield and can I infect others?	Vaccinated patients should continue to follow current guidance to protect themselves from exposure to COVID-19. While providing the vaccine to patients and their caregivers will reduce risk for infection or clinical COVID-19 disease, they must continue practices of wearing masks, social distancing, and maintaining good hand hygiene even after vaccination.
12	I received another vaccine a week ago. Should I get vaccinated against COVID-19 now?	There should be a delay of at least two weeks before you should receive your COVID-19 vaccine. We advise that non-urgent vaccinations may be postponed, with the exception of meningococcal/pneumococcal vaccination when eculizumab/ravulizumab are used.
13	Does the formation of antibodies reflect antiviral immunity?	This is unclear at the moment. The formation of antibodies is perceived as a surrogate biomarker for antiviral protection but whether the detected antibodies are of a neutralizing type or whether protective immunity is present even at low or absent antibody levels will remain uncertain. Therefore, antibody testing has of yet not generally been recommended.

Kronbichler A, et al. Nephrol Dial Transplant 2021; online ahead of print.

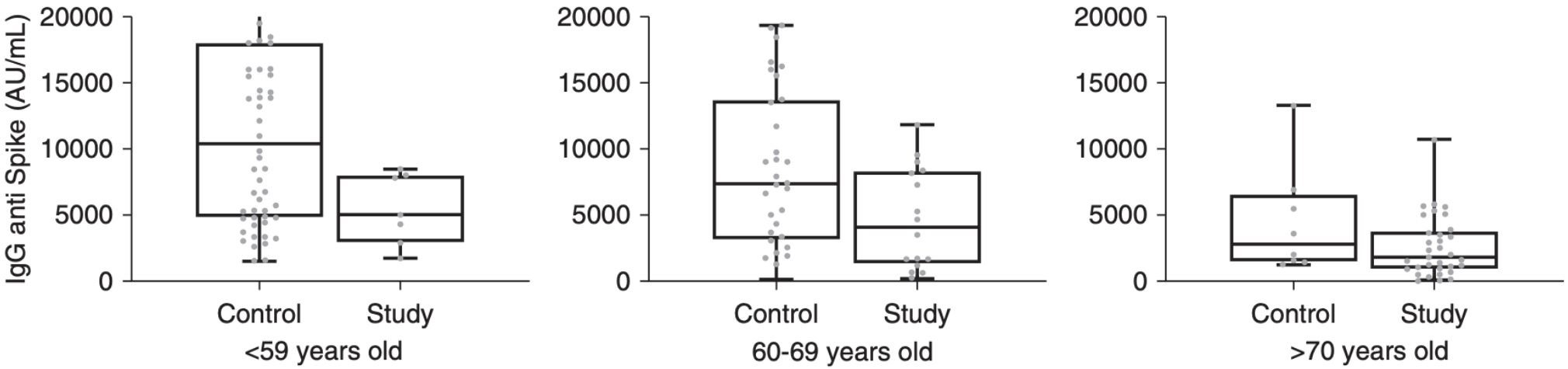
Measurement of vaccine efficacy

Humoral response to structural proteins	
IgG/IgM against Spike protein	ELISA - Most commonly reported; Correlate with infection severity; Likely reflects subsequent response; Unclear disease prevention and efficacy
IgG against Receptor binding domain (RBD)	
IgG against membrane protein	
Neutralization assay	Most time consuming
Pseudo-virus	SARS-CoV-2 Spiked lentivirus
Live virus	Read-out usually reflects half maximal inhibitory concentration (IC50)
Focus reduction neutralization assay	
Plaque reduction neutralization assay	
Cellular response	
ELISpot – either T or B cell	Activation of single cells by specific Ag, i.e. Spike protein, Membrane protein, or a panel of SARS-CoV-2 related peptides
	Requires PBMC
Cytokine response	IFNg, TNF, IL-2, etc
Ag-specific T cells	CD4/CD8+ cells
Memory B cell responses	Flow cytometry using tetramer staining

Alp Ikizler T, et al. Kidney Int 2021, online ahead of print.

Vaccine efficacy in dialysis patients (*BNT162b2*)

Israel (Abbott antibody test)

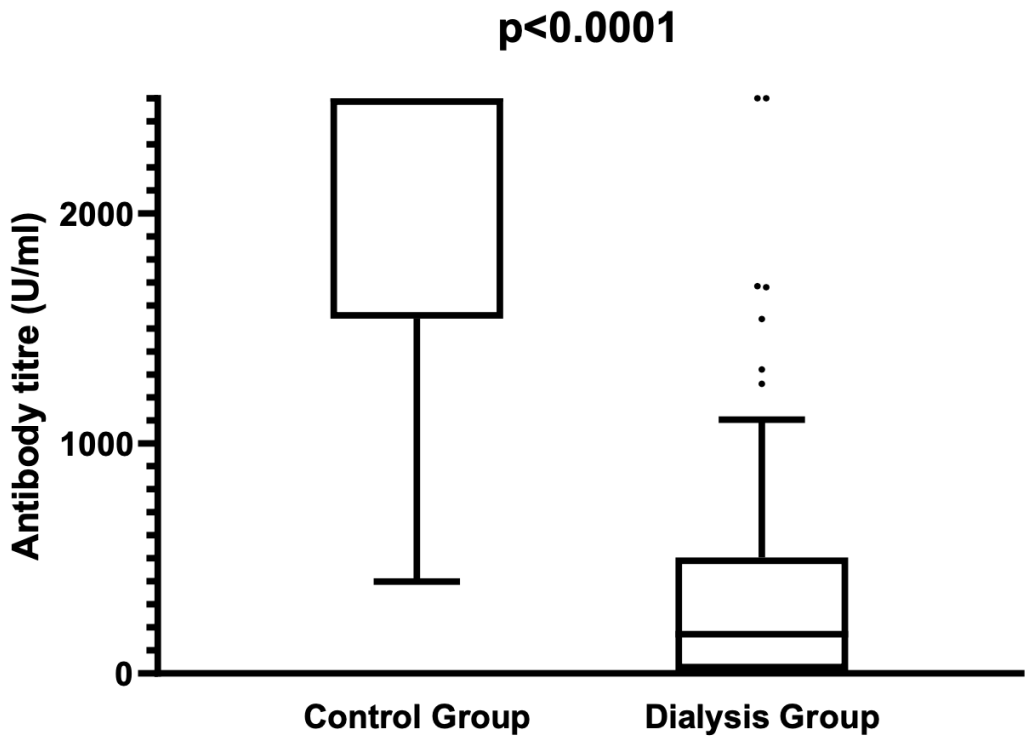


Antibodies measured at least 7 days after second dose
54/56 dialysis patients (96%) had an antibody response (Abbott test, 50 AU/ml or higher)
IgG levels 2900 in dialysis patients, 7401 in the control group ($p<0.001$)
Age was an independent predictor of a reduced antibody response

Grupper A, et al. Clin J Am Soc Nephrol 2021, online ahead of print.

Vaccine efficacy in dialysis patients (*BNT162b2*)

Austria (Roche antibody test)



Antibodies were measured 3 weeks after second dose

171 U/ml versus 2500 U/ml (Roche Elecsys®)

Age again a predictor of poor response

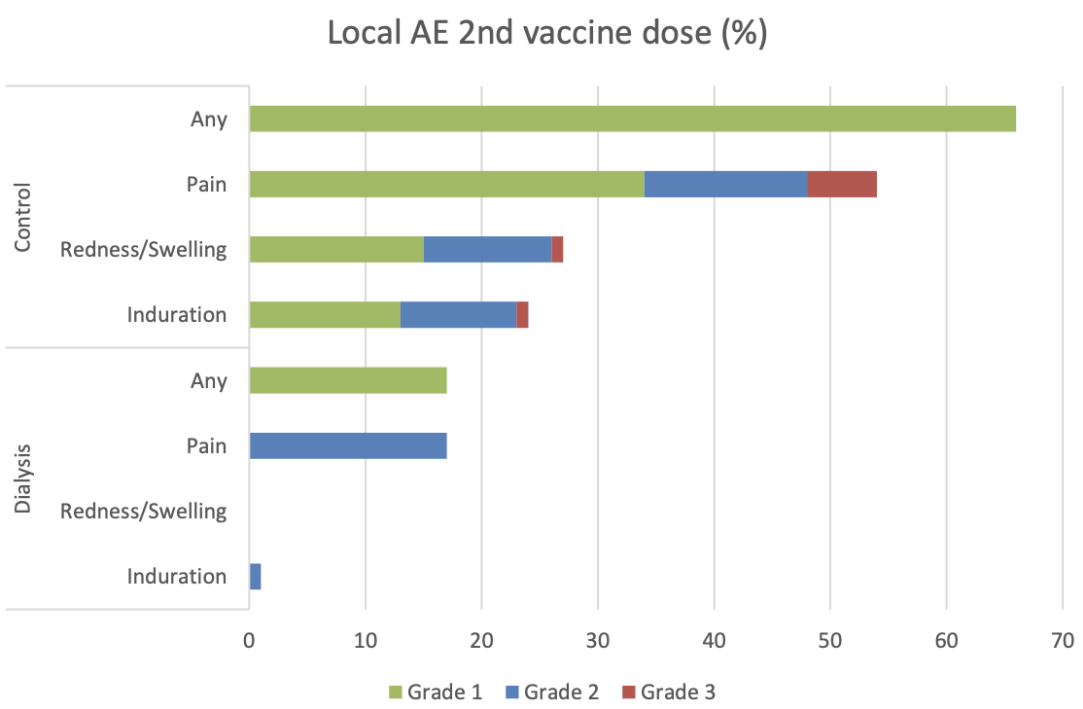
Patients with a response to hepatitis B vaccine have higher SARS CoV-2 antibody titers (non-significant)

Simon B, et al. medRxiv preprint (10.1101/2021.03.26.21254259)

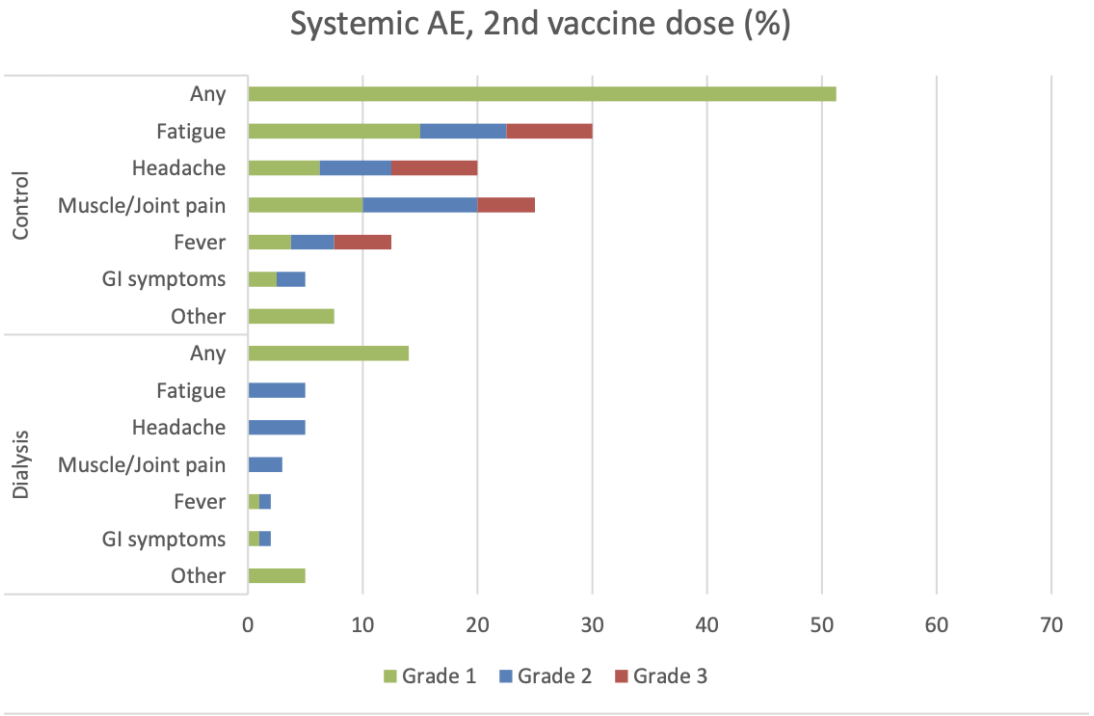
Side effects in dialysis patients (*BNT162b2*)

After the second dose

LOCAL AEs



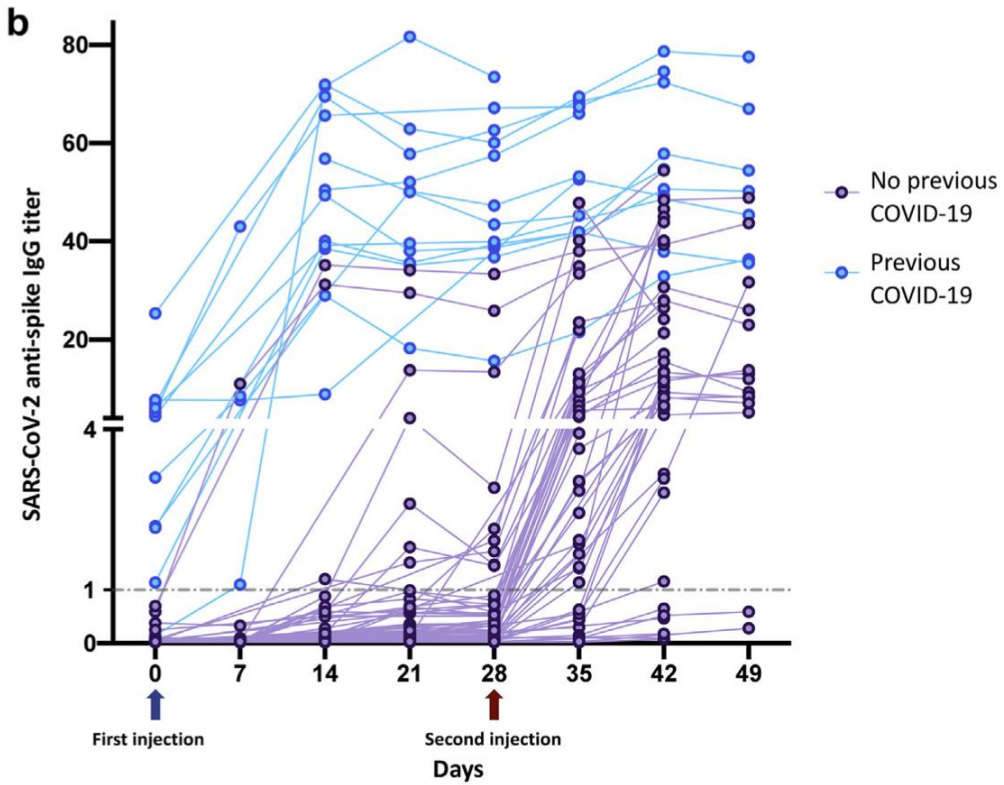
SYSTEMIC AEs



Grade 1: mild, does not interfere with activity
Grade 2: moderate, interferes with activity
Grade 3: severe, prevents daily activity

Simon B, et al. medRxiv preprint (10.1101/2021.03.26.21254259)

Efficacy over time in dialysis patients (*BNT162b2*)



13 patients with a history of COVID-19

56 COVID-19 naive patients

Seropositivity rate at last follow-up 86%
Age > 70 years associated with lower seroresponse rates (75%)

Seropositivity rate was 10/56 (18%) before second injection and 43/52 (82%) at last follow-up

Attias P, et al. Kidney Int 2021, online ahead of print.

Vaccine efficacy in transplantation (*mRNA vaccines*)

14-21 days after dose 1 (EUROIMMUN/Roche assays)

	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)				
40-59	18 (24)	132 (37)	0.81 (0.71-0.93)[b]	.003	0.83 (0.73-0.93)	.002
≥60	28 (37)	159 (44)				
Time since transplant, y[j]						
<3	13 (17)	106 (30)				
3-6	12 (16)	77 (22)				
7-11	19 (25)	82 (23)	1.88 (1.21-2.93)[k]	.005	1.45 (0.96-2.20)	.08
≥12	31 (41)	89 (25)				
Type of regimen						
Includes anti-metabolite maintenance immunosuppression[l]	28 (37)	292 (81)				
Does not include anti-metabolite maintenance immunosuppression	48 (63)	68 (19)	0.21 (0.14-0.32)[m]	<.001	0.22 (0.15-0.34)	<.001
Vaccine[n]						
mRNA-1273 (Moderna)	52 (69)	152 (43)				
BNT162b2 (Pfizer-BioNTech)	23 (31)	200 (57)	2.14 (1.24-3.69)[o]	.006	2.15 (1.29-3.57)	.003

Boyarsky BJ, et al. JAMA 2021, online ahead of print.

Vaccine efficacy in transplantation (*mRNA vaccines*)

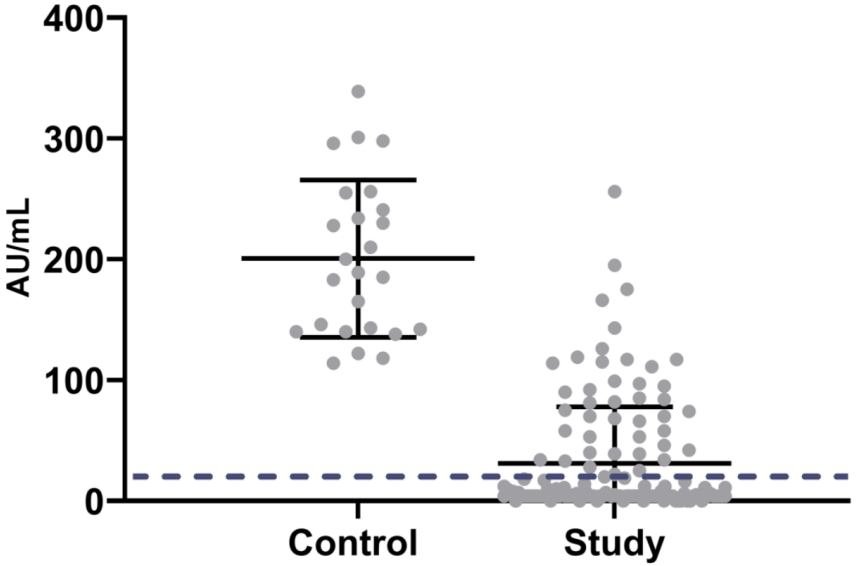
29 days after dose 2 (EUROIMMUN/Roche assays)

	No. (%) by postvaccination antibody response			
	Dose 1− Dose 2−	Dose 1− Dose 2+	Dose 1+ Dose 2+	*P* value
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)	
Organ[f]				
Kidney	168 (52)	118 (37)	36 (11)	<.001[d]
Liver	26 (20)	62 (48)	41 (32)	
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[g]				
<3	114 (63)	54 (30)	13 (7)	.001[b]
3-6	69 (50)	53 (39)	15 (11)	
7-11	54 (38)	61 (43)	26 (18)	
≥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[i]	33 (18)	92 (50)	60 (32)	
Vaccine[j]				
mRNA-1273 (Moderna)	124 (40)	116 (38)	67 (22)	<.001[d]
BNT162b2 (Pfizer-BioNTech)	175 (51)	138 (40)	29 (8)	

Boyarsky BJ, et al. JAMA 2021, online ahead of print.

Vaccine efficacy in transplantation (*mRNA vaccines*)

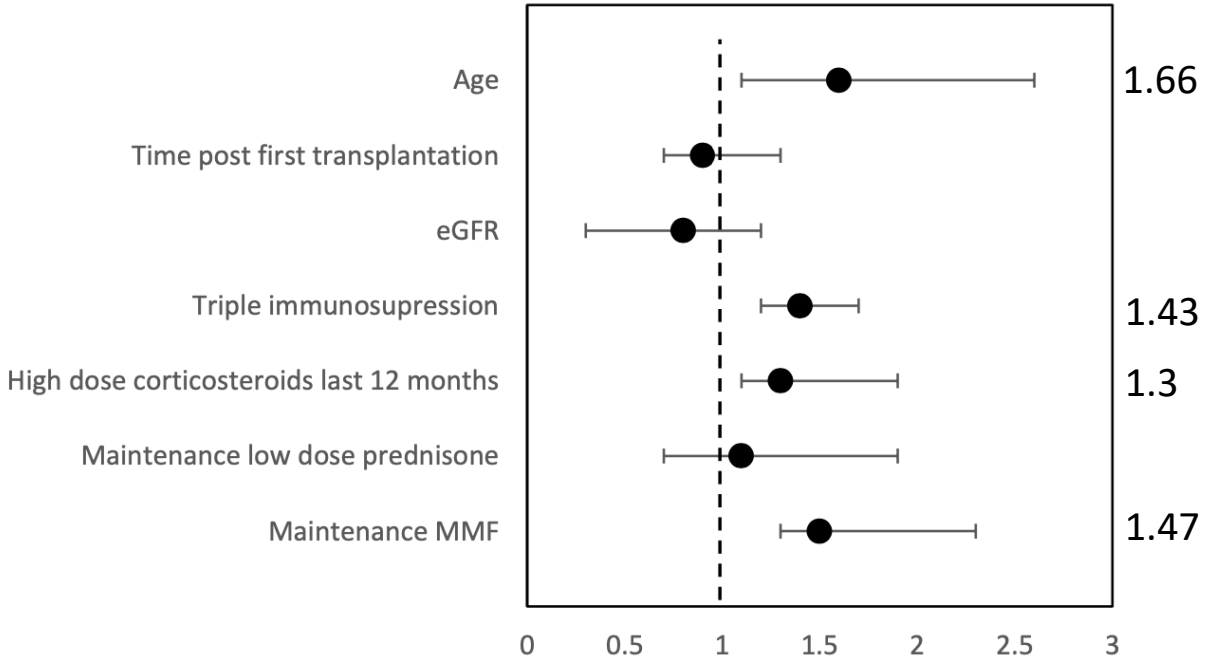
10-20 days after 2nd dose (DiaSorin SpA LIAISON SARS-CoV-2 S1/S2 assay)



100% *37.5%*

51/136

median 189.0 5.9

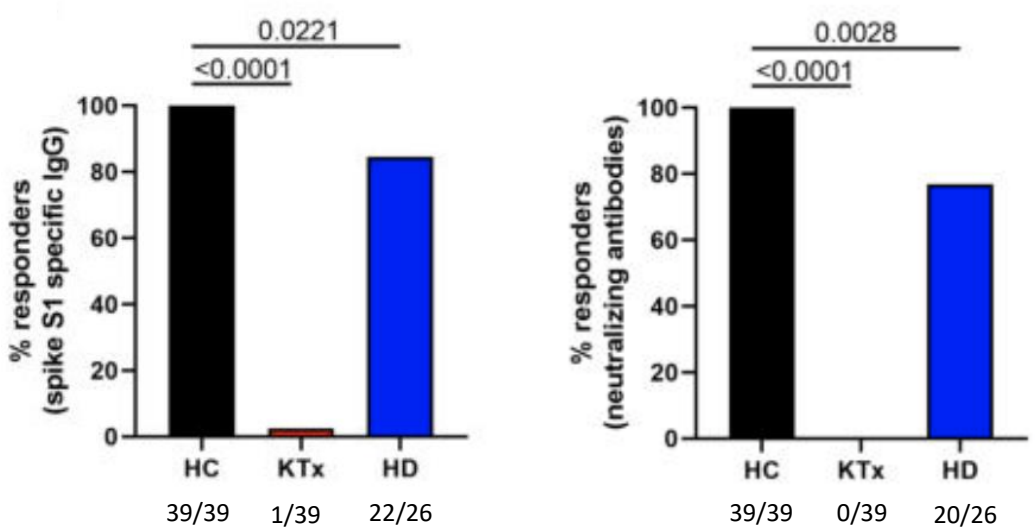


Grupper A, et al. Am J Transplant, online ahead of print.

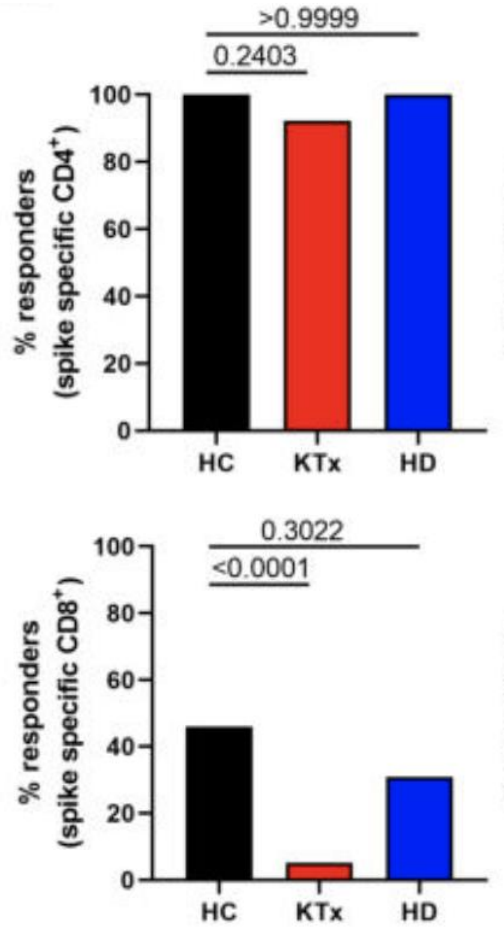
Vaccine efficacy in transplantation (*mRNA vaccines*)

1 week after booster vaccination (BNT162b2)

Antibody response



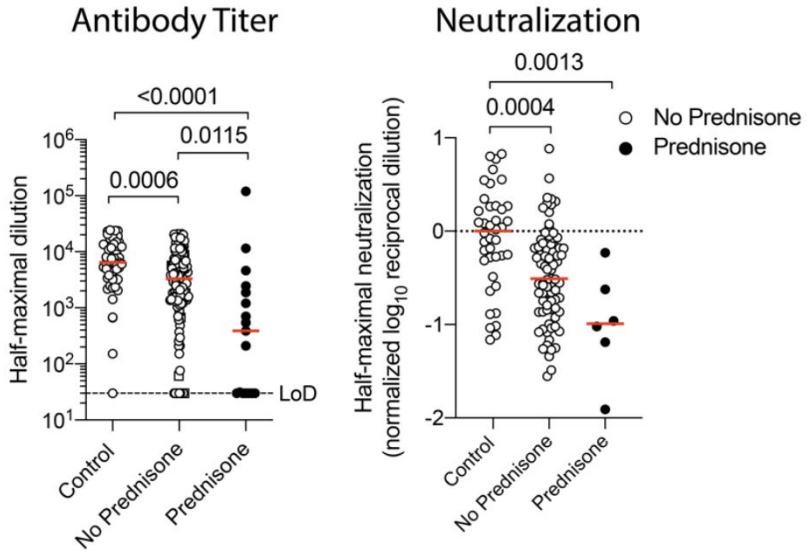
T-cell response



Sattler A, et al. medRxiv preprint; doi: 10.1101/2021.04.06.21254963.

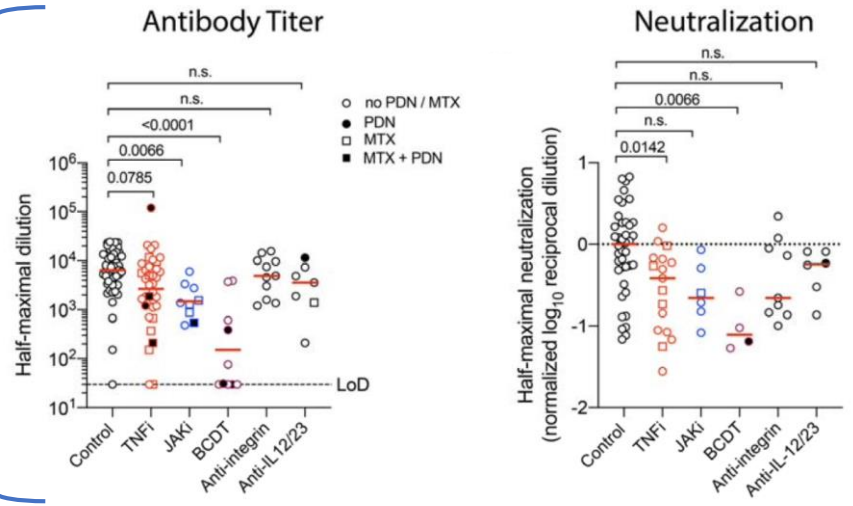
Vaccine efficacy during intake of immunosuppression (*mRNA vaccines*)

Prednisone



10-fold reduction in titers
Seropositivity decreased from 92% in patients off prednisone to 65% in prednisone-users

B-cell depletion



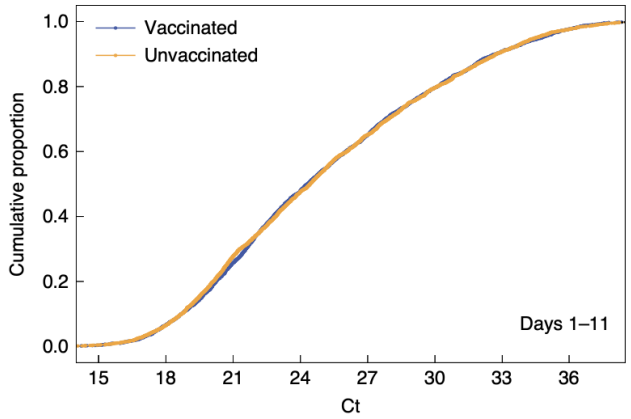
BCDT within 6 months
36-fold reduction in titers
10 patients received BCDT, only 50% with seropositivity

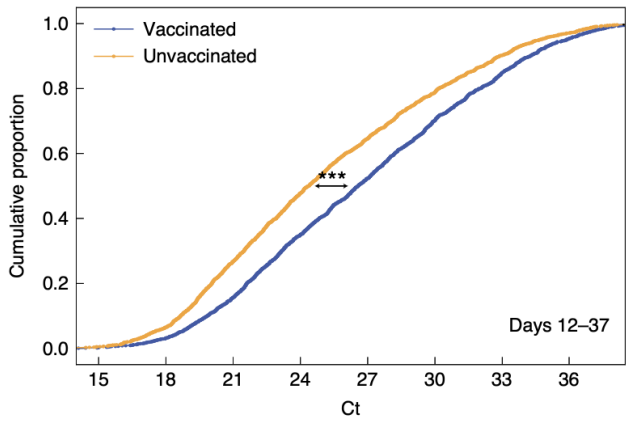
Deepak P, et al. medRxiv preprint. doi: 10.1101/2021.04.05.21254656.

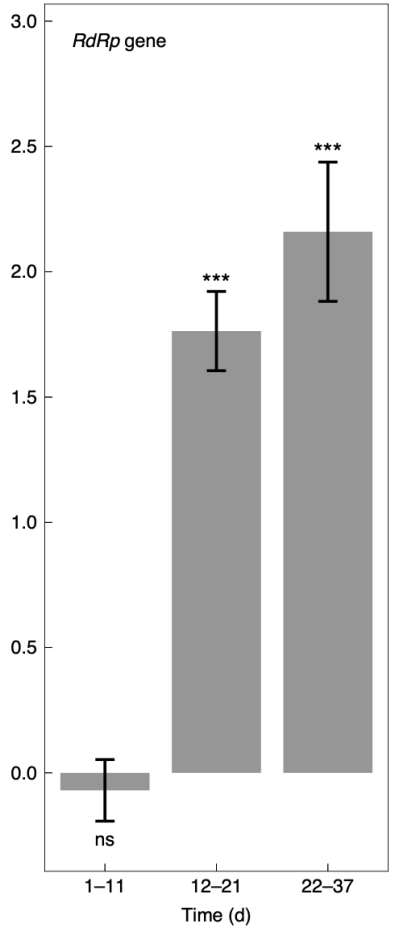
Can mRNA vaccines stop transmission?

It seems to reduce the spread of COVID-19

Infection cycle threshold (**Ct**)



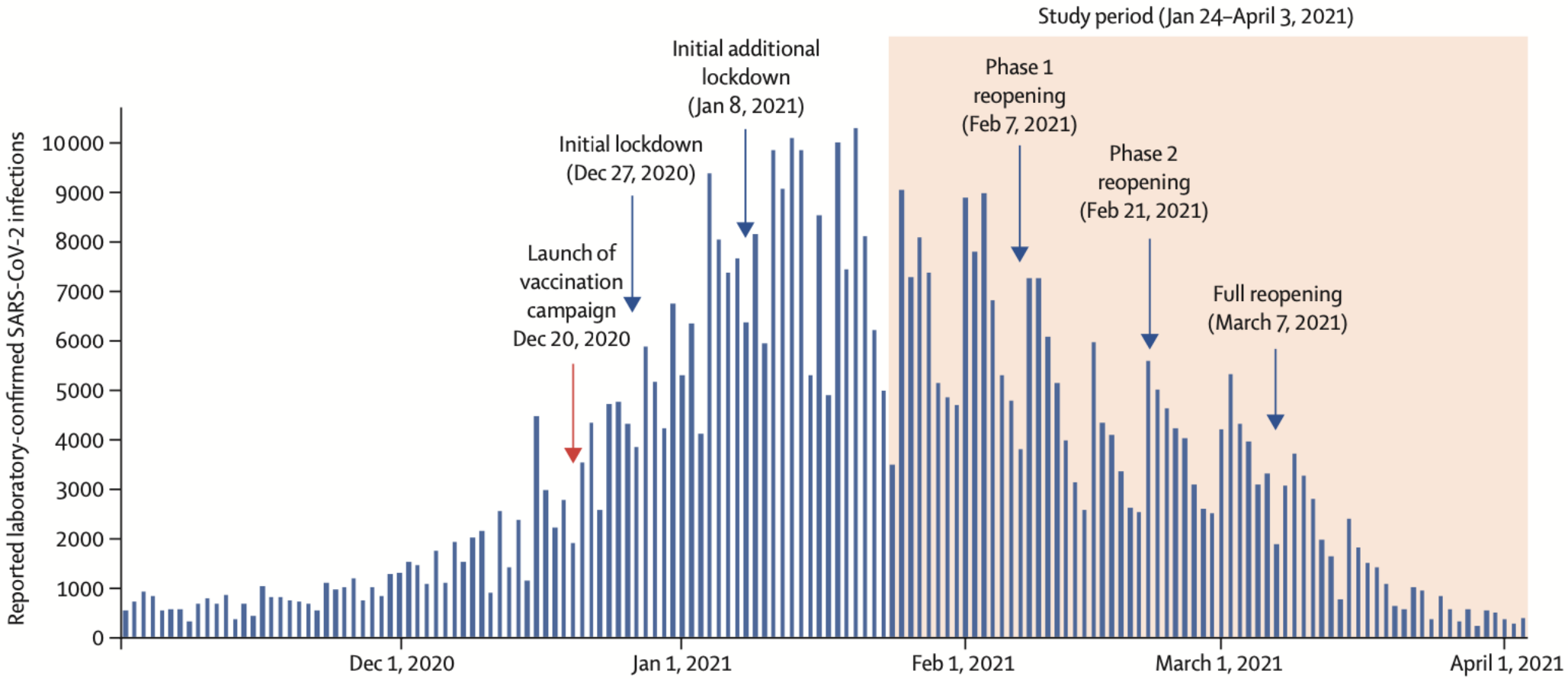




Levine-Tiefenbrun M, Nat Med. Doi: 10.1038/s41591-021-01316-7.

Can mRNA vaccines stop transmission?

Real-life data from Israel



Haas EJ, Lancet 2021, online ahead of print.

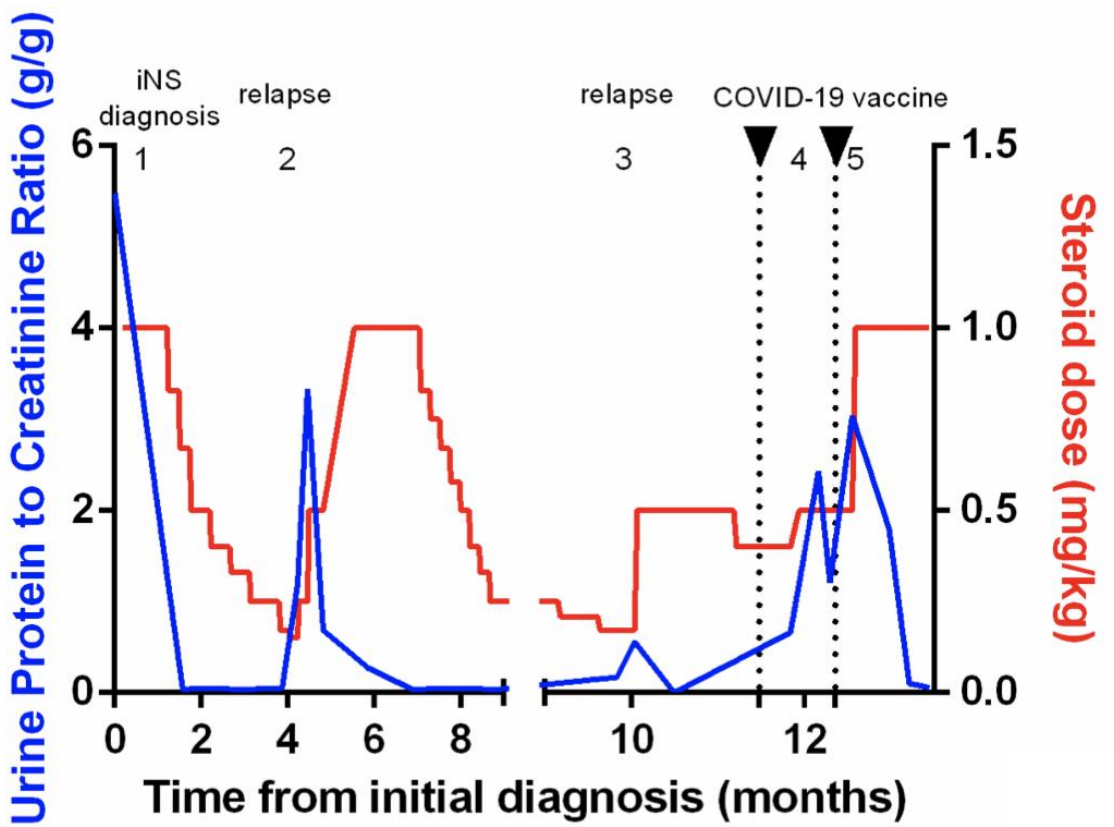
Can mRNA vaccines stop transmission?

Real-life data from Israel

	Vaccine effectiveness*		
	Age ≥65 years	Age ≥75 years	Age ≥85 years
SARS-CoV-2 infection†	94·8% (93·9–95·5)	95·1% (93·9–96·0)	94·1% (91·9–95·7)
Asymptomatic SARS-CoV-2 infection	88·5% (86·4–90·3)	87·5% (84·2–90·1)	83·2% (76·3–88·1)
Symptomatic COVID-19	96·4% (95·9–97·0)	96·7% (95·9–97·4)	96·6% (95·2–97·6)
COVID-19-related hospitalisation	96·8% (96·2–97·3)	97·0% (96·2–97·7)	96·9% (95·5 –97·9)
Severe or critical COVID-19-related hospitalisation	97·3% (96·8–97·8)	97·6% (96·8–98·1)	97·4% (95·9 –98·3)
COVID-19-related death	96·9% (96·0–97·6)	97·1% (96·0–97·9)	97·0% (94·9–98·3)

Haas EJ, Lancet 2021, online ahead of print.

Are vaccines provoking relapses/rejections?



Kervella D, Kidney Int 2021, online ahead of print.

Discussion/Outlook

Where do we go from here?

Patients with kidney diseases have a weaker antibody response and there are more non-responders (measurement of cellular immunity?). We need to learn the impact of non-response on COVID-19 infectious risk and severity thereof

What is the most potent vaccine in our cohorts (Moderna/mRNA-1273?)

What is the best timing to vaccinate patients (MMF users? Rituximab users?)?

Defining the ideal time point to booster our patients! Switch to other vaccine platforms in non-responders (ethical considerations)