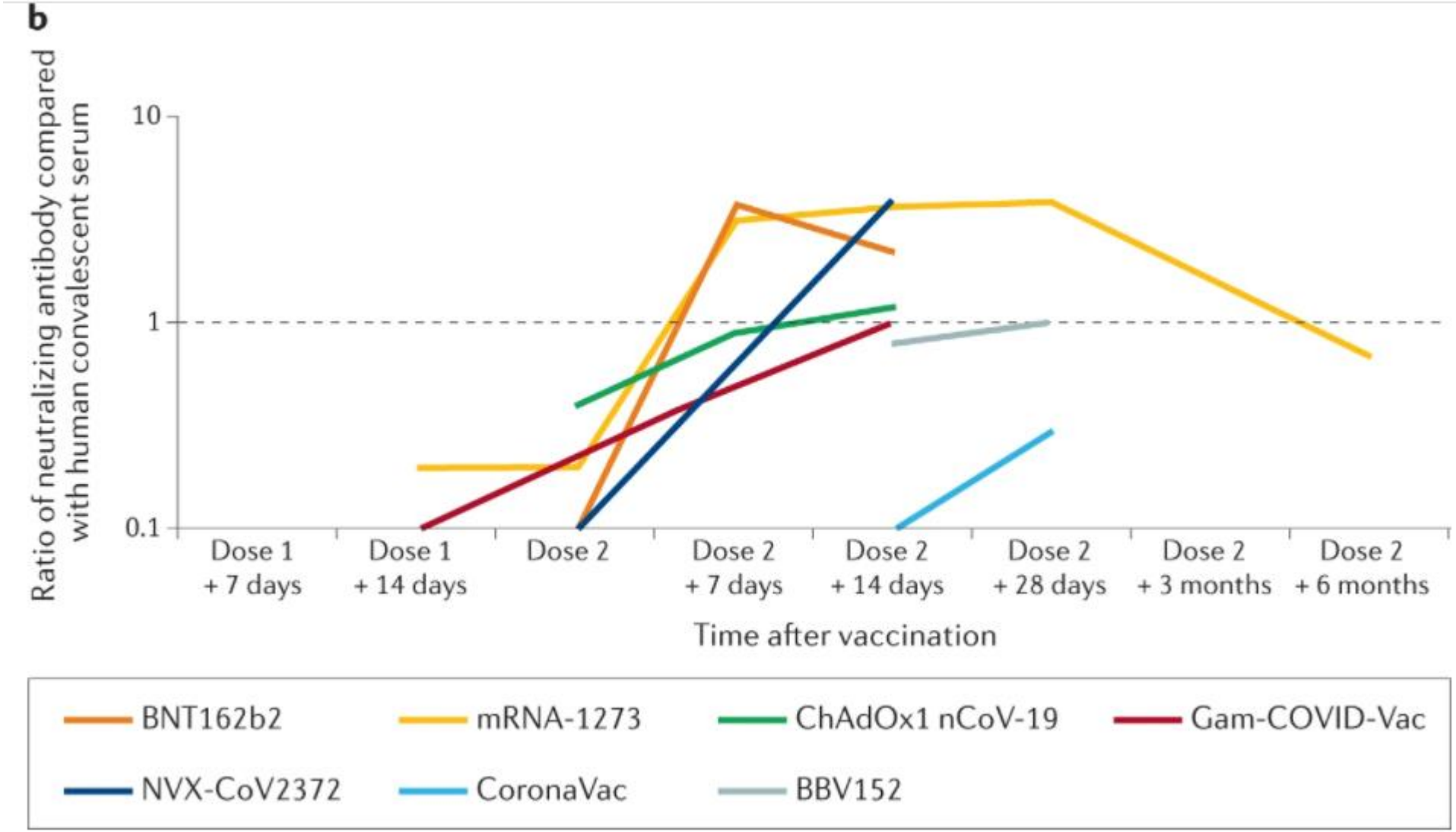
Convegno
GIORNATE INFETTIVOLOGICHE "LUIGI SACCO" 2021
18-19 Ottobre 2021
Hybrid Edition

Risposta immunitaria alla vaccinazione anti-SARS-CoV-2 nei soggetti fragili

Mara Biasin

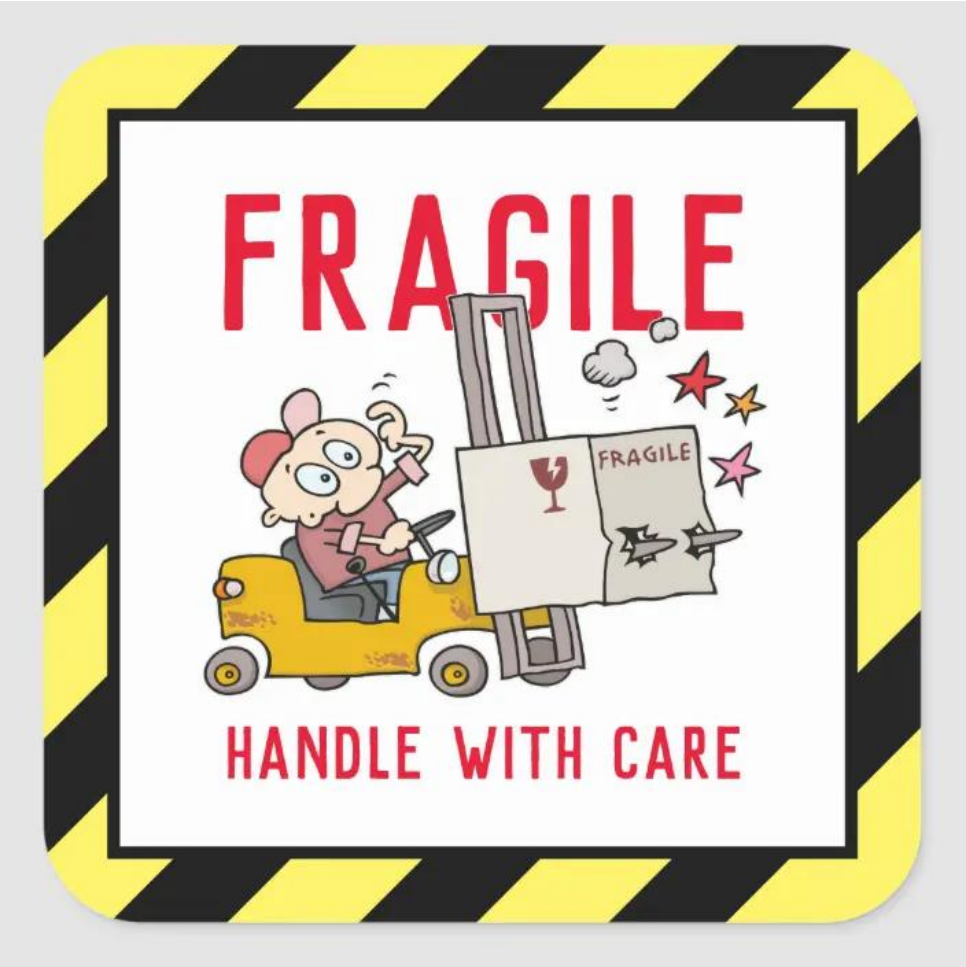
Dipartimento di Scienze Biomediche e Cliniche «L. Sacco»- Università degli Studi di Milano

Antibody responses induced by different SARS-CoV-2 vaccines



Sadarangani, Nature Reviews Immunology 2021

Studies on vaccine immunogenicity in Fragile Patients are missing



Patients diagnosed with:

- Malignancies
- Neurological and immunological disorders
- Transplanted patients
- Primary Immunodeficency (i.e.DiGeorge, Wiskott-Aldrich)
- Secondary immunodeficency (i.e. Pharmacologycal)
- Dialysis and severe chronic renal failure
- Acquired immunodeficiency syndrome (AIDS)

SARS-CoV-2 Vaccination in Fragile Patients: open questions

- What's the kinetic of immune response and its persistence?
- Should fragile patients receive additional doses of vaccine? When?
- What's the most effective vaccine?
- Which therapies should be avoided or interrupted?
- Does the vaccine interfere with any therapy?

«Waning immunity» in vaccinated fragile patients

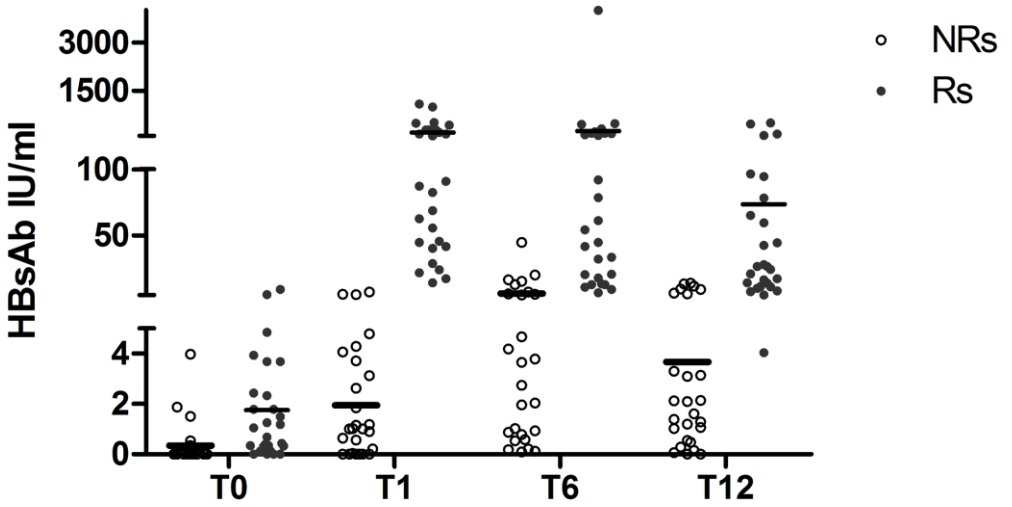
PLOS ONE

RESEARCH ARTICLE

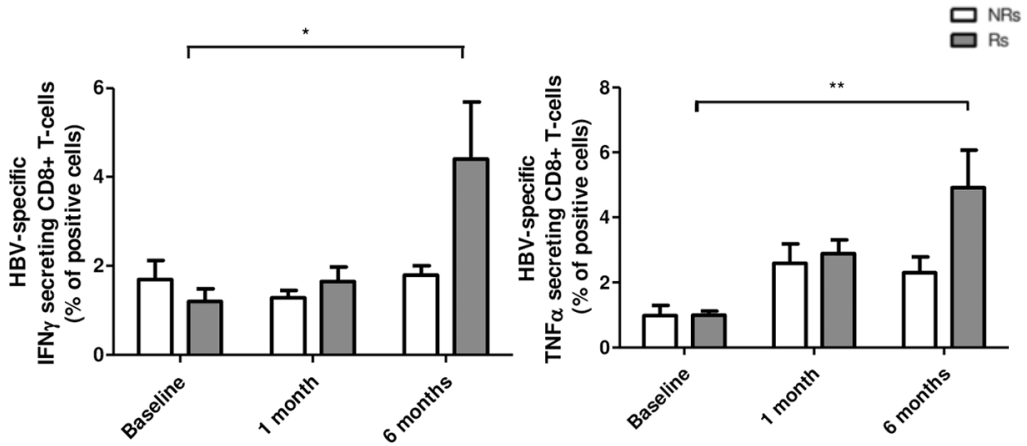
Humoral and cell-mediated immune responses after a booster dose of HBV vaccine in HIV-infected children, adolescents and young adults

Vania Giacomet[1]*, Michela Masetti[2,3], Pilar Nannini[1], Federica Forlanini[1,4], Mario Clerici[3,5], Gian Vincenzo Zuccotti[1,4], Daria Trabattoni[2]

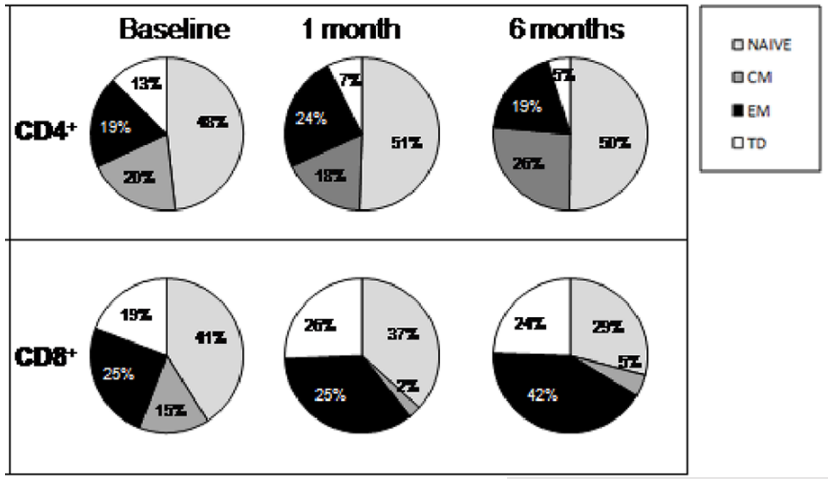
HBsAb



HBV-specific CD8+ T cells

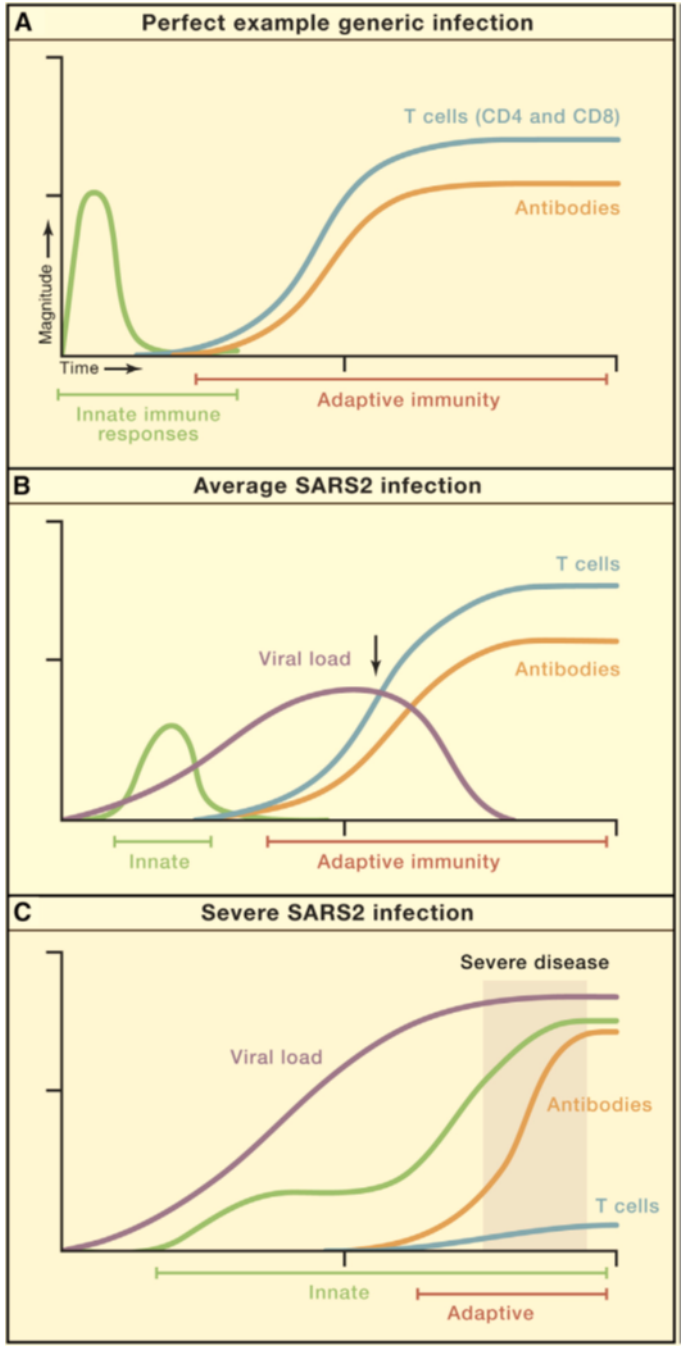


HBV-Specific T cell memory

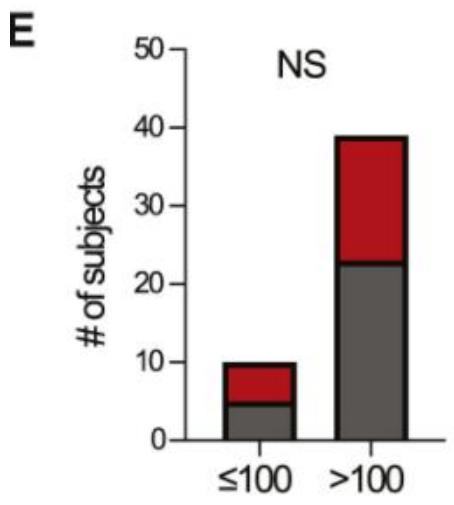


Giacomet, PlosOne 2018

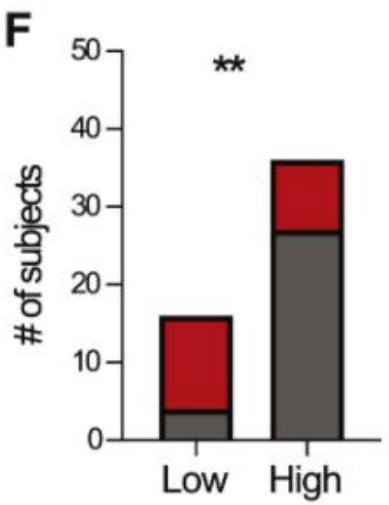
Immune response to SARS-CoV-2 infection



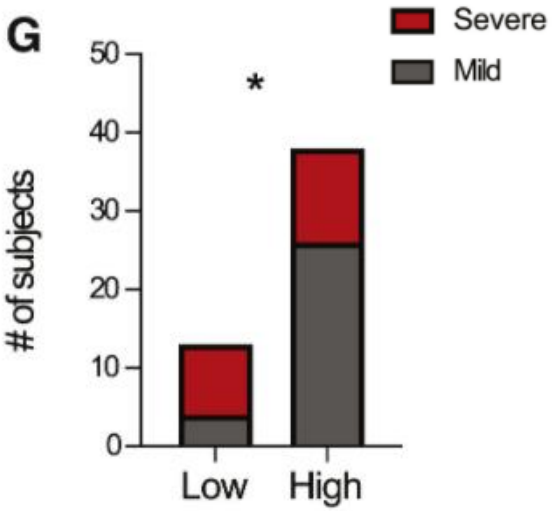
Sette, Cell 2021



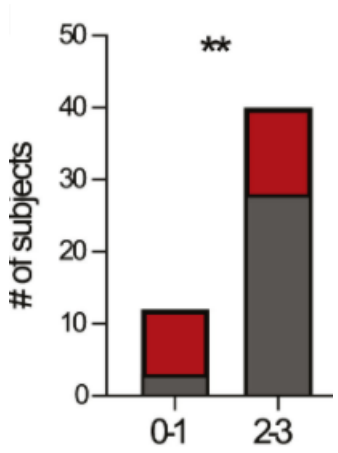
SARS-CoV-2 nAbs



SARS-CoV-2 CD4+



SARS-CoV-2 CD8+



ADIM

ADIM:
SARS-CoV-2 antigen-specific adaptive immune responses

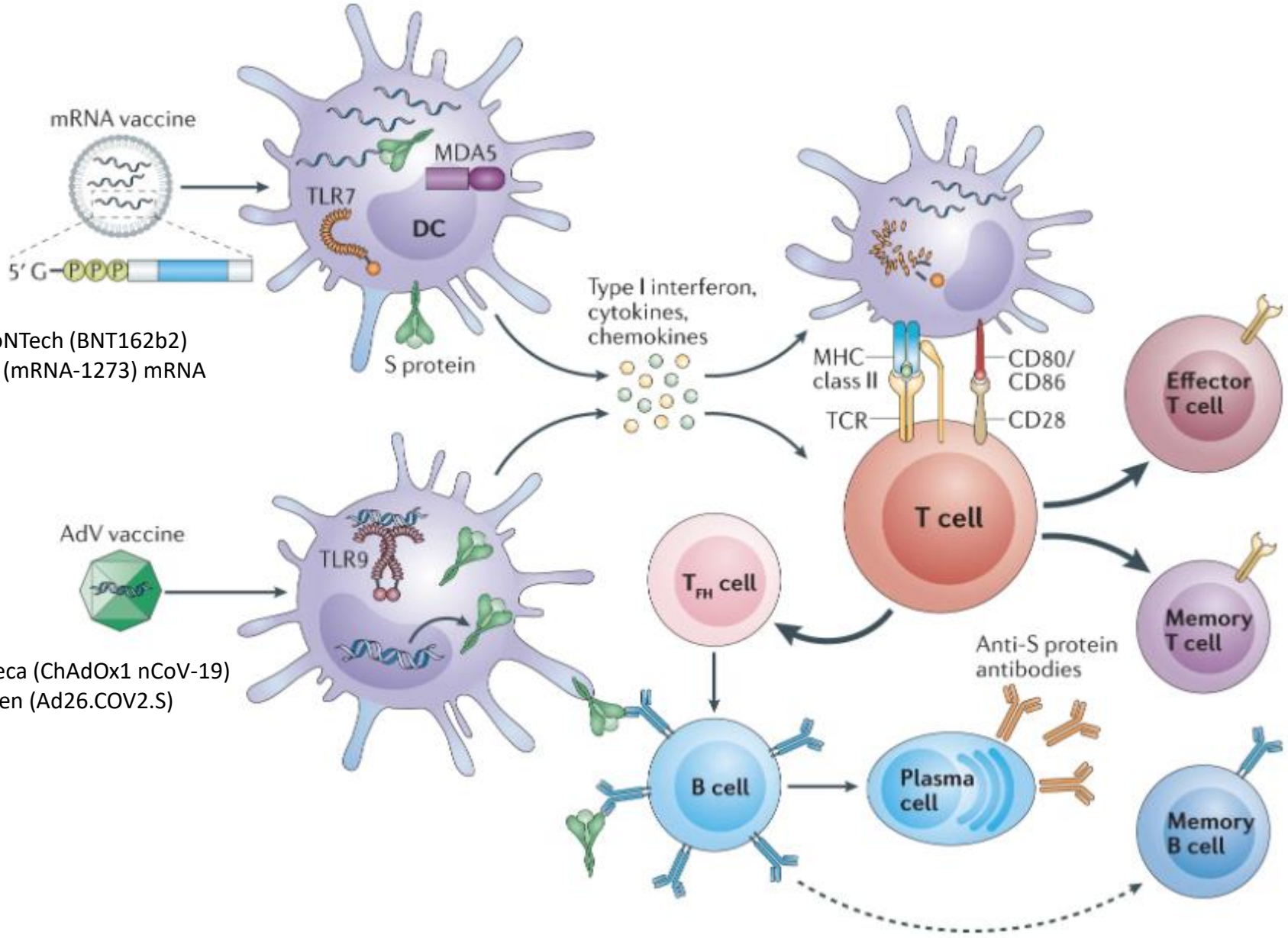
- Antibody
- SARS-CoV-2 specific CD4+ T cells
- SARS-CoV-2 specific CD8+ T cells

Rydyznski Moderbacher, Cell 2020

Modes of immune activation in SARS-CoV-2 vaccines

- Pfizer/BioNTech (BNT162b2)
- Moderna (mRNA-1273) mRNA

- AstraZeneca (ChAdOx1 nCoV-19)
- J&J/Janssen (Ad26.COV2.S)



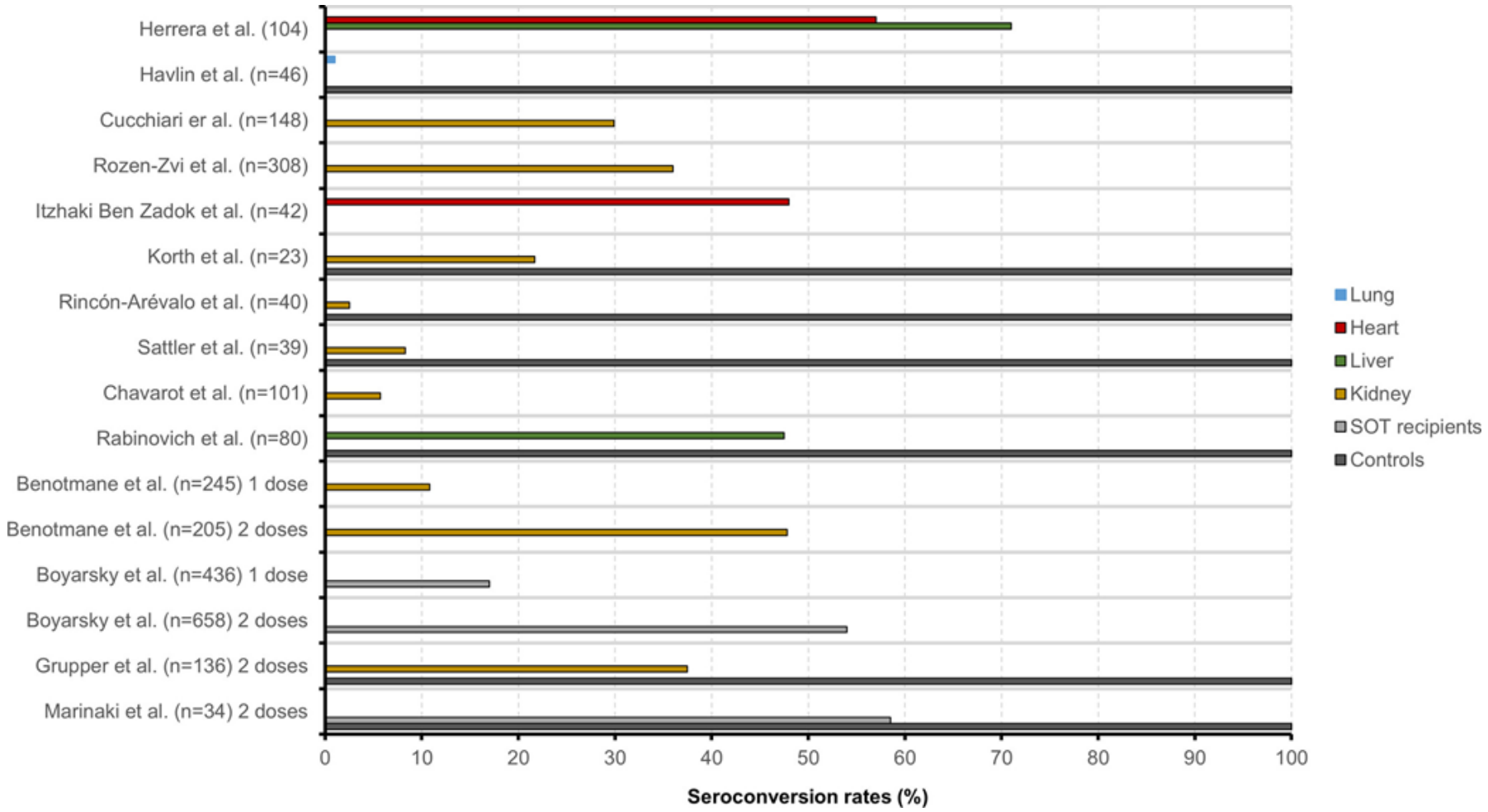
Teijaro, NAture Reviews | ImmuNology 2021

Immune responses in SARS-CoV-2 vaccinated fragile patients

Author	Disease	Vaccines	n	Immune assessment	Timing of assessment		Vaccine responders	Comments
					1^ dose (n)	2^ dose (n)		
Monin-Aldama L, 2021 (5)	Solid and haematological malignancies	BNT162b2	151	Antibody seroconversion, T cell responses, and neutralisation of SARS-CoV-2 Wuhan strain and of a variant of concern (B.1.1.7)	X (118)	X (30)	15%-40%	Efficacy increased by boosting at 21-days (95% within 2 weeks of boost) in solid cancer patients .
Bird S, 2021 (6)	Multiple Myeloma	BNT162b2 ChAdOx1 nCoV-19	93	SARS-CoV-2 IgG antibodies directed against the Spike-protein	X (93)		70%	
Boyarsky BJ, 2021 (7)	Organ transplant	BNT162b2mRNA-1273	436	SARS-CoV-2 IgG antibodies directed against the Spike-protein	X (427)		31% (BNT162b2) 69% (mRNA-1273)	Increased antibody response in young, in absence of immunosuppressive therapy, and with mRNA-1273.
Herishanu Y, 2021 (8)	CLL	BNT162b2	167	SARS-CoV-2 IgG antibodies directed against the Spike-protein		X (167)	39.5%	Vaccine responders: 79.2% among complete disease responders, 55.2% in treatment-naïve, and 16% in patients under treatment.
Agha M, 2021 (9)	Haematological malignancies	BNT162b2 mRNA-1273	67	SARS-CoV-2 Ig Ma and IgG antibodies directed against the Spike-protein		X (67)	54%	
Wong SI, 2021 (10)	Inflammatory bowel disease	BNT162b2 mRNA-1273	48	SARS-CoV-2 IgG antibodies directed against the Spike-protein, and Nucleocapsid-protein	X (22)	X (26)	71.4 and 100% after the 1^ and 2^ dose	Decreased antibody titers in patients receiving anti-TNF therapies.
Geisen UM, 2021 (11)	CID	BNT162b2 mRNA-1273	26	SARS-CoV-2 IgG antibodies directed against the Spike-protein; neutralising antibodies ELISA-based neutralisation test system; SARS-CoV-2 IgA antibodies		X (26)	100%	IgG titres lower in patients with CID as compared with healthy controls. No patients experienced flare up of CID.
Rabinowich L, 2021 (12)	Organ transplant	BNT162b2	80	SARS-CoV-2 IgG antibodies directed against the Spike-protein, and Nucleocapsid-protein		X (80)	47.5%	
Grupper A, 2021 (13)	Organ transplant	BNT162b2	136	SARS-CoV-2 IgG antibodies directed against the Spike-protein		X (136)	37.5%	
Chavarot N, 2021 (14)	Organ transplant	BNT162b2 mRNA-1273	101	SARS-CoV-2 IgG antibodies directed against the Spike-protein	X (101)	X (35)	2% and 5.7% after the 1^ and 2^ dose	

Agrati, Frontiers in Immunology 2021

Humoral response in SARS-CoV-2 vaccinated solid organ transplant (SOT) recipients



Antibody levels and seroconversion rates to the SARS-CoV-2 mRNA vaccines are lower in SOT

Giannella, Transplant international 2021

Cellular response in SARS-CoV-2 vaccinated solid organ transplant (SOT) recipients

TABLE 2 Vaccine-induced immune responses and reported adverse events in the study population

	Post vaccination 1			Post vaccination 2		
	Controls	Transplant recipients		Controls	Transplant recipients	
	n = 70	n = 38*	*p*-value	n = 70	n = 34*	*p*-value
Individuals with SARS-CoV-2 spike-specific immunity						
IgG (≥35.2 BAU/ml), n (%)	56 (80.0)	2 (5.3)	< .0001	70 (100.0)	12 (35.3)	< .0001
Neutralizing antibodies (IH ≥35%), n (%)	18 (25.7)	0 (0)	.0002	68 (97.1)	10 (29.4)	< .0001
CD4 T cells, n (%)	52 (74.3)	5 (13.2)	< .0001	64 (91.4)	21 (61.8)	.0007
CD8 T cells, n (%)	49 (70.0)	5 (13.2)	< .0001	53 (75.7)	14 (41.2)	.0009
Combined cellular and/or humoral analysis						
CD4 and/or CD8 T cells, n (%)	59 (84.3)	9 (23.7)	< .0001	67 (95.7)	22 (64.7)	< .0001
T cells and/or IgG; n (%)	67 (95.7)	10 (26.3)	< .0001	70 (100.0)	24 (70.6)	< .0001
Adverse events	n = 70	n = 38*	.018#	n = 70	n = 34*	.140#
None, n (%)	8 (11.4)	12 (31.6)		13 (18.6)	11 (32.4)	
Local, n (%)	11 (15.7)	4 (10.5)		16 (22.9)	9 (26.5)	
Systemic, n (%)	17 (24.3)	11 (28.9)		8 (11.4)	2 (5.9)	
Local and systemic, n (%)	34 (48.6)	11 (28.9)		33 (47.1)	12 (35.3)	

Humoral immunity

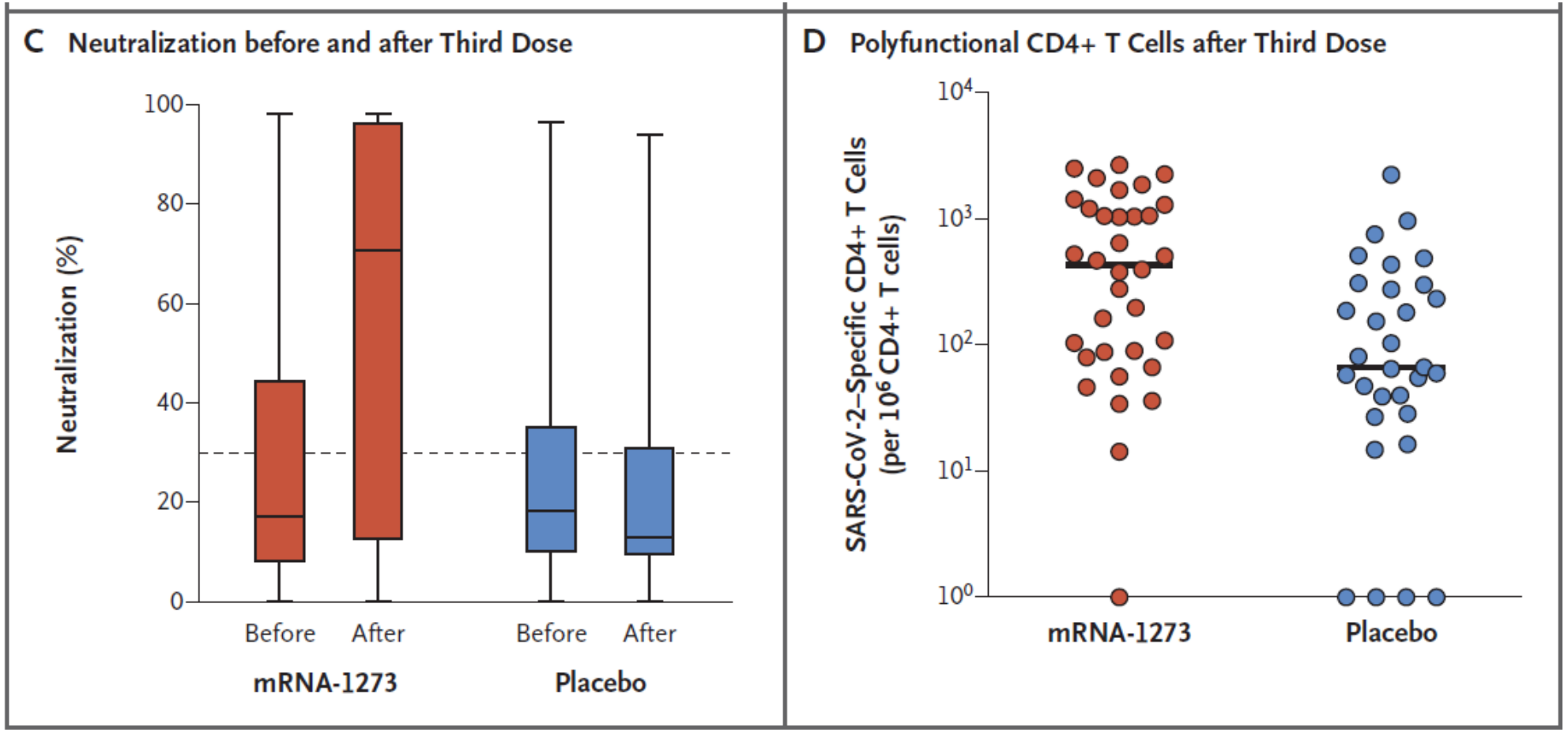
Cellular immunity

- 40 SOT
- 70 Controls.
- **two doses BNT162b2**
- **two doses ChAdOx1**

The exclusive assessment of antibodies is insufficient to identify COVID-19-vaccine responders

Schmidt, Am. J. Transplant 2021

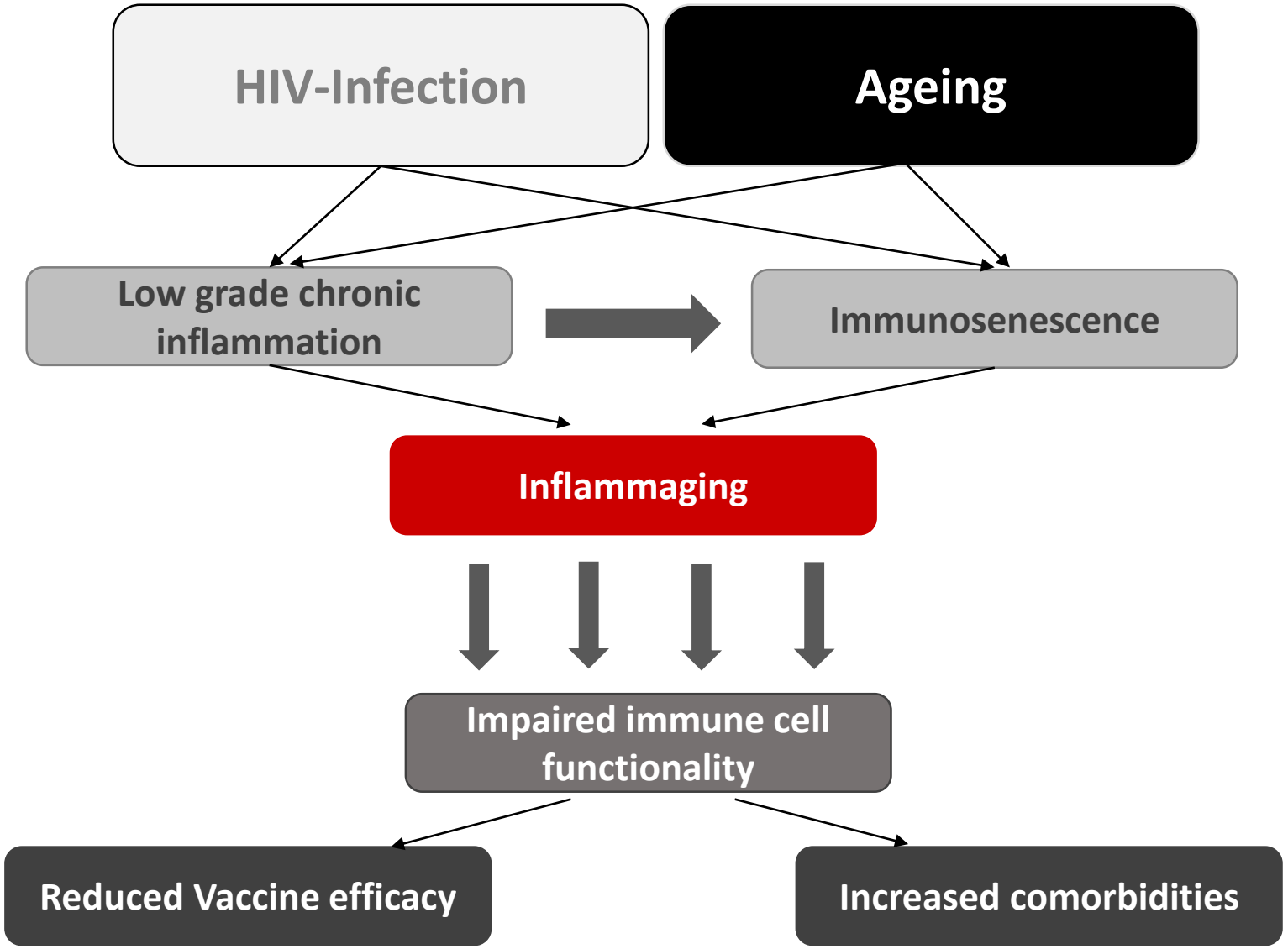
Third dose of SARS-CoV-2 vaccine in solid organ transplant (SOT) recipients



An additional COVID-19 vaccine dose in SOT enhances antibody and T cell response and increases the proportion of responders

Hall, NEJM 2021

Immune responses in SARS-CoV-2 vaccinated HIV-patients



Immune responses in SARS-CoV-2 vaccinated HIV-patients

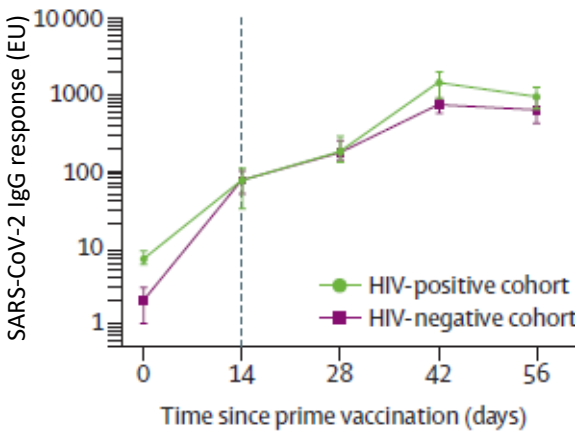
Frater, Lancet HIV 2021

- 54 HIV (all male, median age 42·5 years)
- on antiretroviral therapy (ART),
- HIV viral loads <50 copies per mL
- CD4 counts > 350 cells per µL.
- **two doses ChAdOx1** 4–6 weeks apart

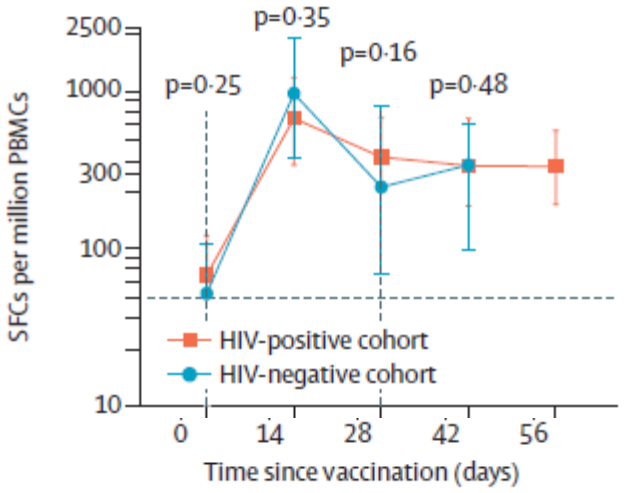
Bezawit, CDI 2021

- 12 HIV (median age 52 years)
- on antiretroviral therapy (ART),
- HIV viral loads <70 copies per mL
- Median CD4 counts 913 cells per µL.
- **two doses BNT162b2** 28 days apart

Humoral response

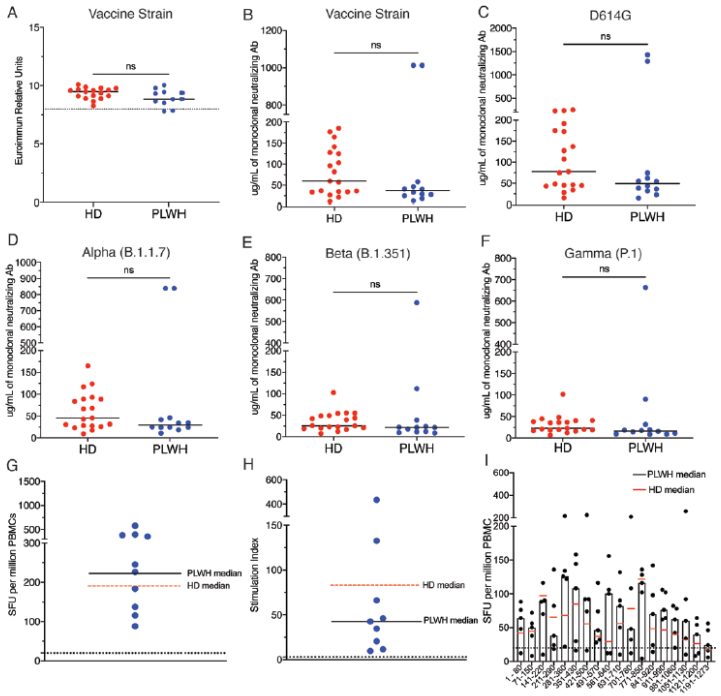


Cellular response



Humoral response

Cellular response



No differences in humoral and cellular responses to COVID-19 vaccines between HIV patients and healthy donors

Immune responses in SARS-CoV-2 vaccinated HIV-patients

Failure to seroconvert after two doses of BNT162b2 SARS-CoV-2 vaccine in a patient with uncontrolled HIV

SARS-CoV-2 infection elicits similar antibody responses in HIV-negative individuals and people living with HIV that is well controlled by antiretroviral therapy (ART).[1] SARS-CoV-2 vaccines, including the mRNA vaccine BNT162b2, are efficacious in clinical trials, inducing antibodies and T cells specific to the spike protein.[2–4] However, vaccine responses in people living with HIV have been assessed only in those stable on ART.[5] Immune function in people with HIV and uncontrolled HIV replication is impaired due to destruction of the CD4 T cells that help B cells during an antibody response. Immune responses to vaccines (eg, against influenza and hepatitis B) in people living with HIV are inferior to those in the general population.[6] We present a case of one individual with uncontrolled HIV replication who did not respond to two doses of the BNT162b2 SARS-CoV-2 vaccine.

The index patient, with advanced HIV, was recruited to a cohort study, along with 13 people living with HIV suppressed on ART (median CD4 count 590 cells per µL [SD 202; range 310–940]) and 43 HIV-negative controls, all of whom had received one or two doses of BNT162b2.[1] The index patient had no history of SARS-CoV-2 infection or AIDS-defining conditions and had already received two doses of BNT162b2 24 days apart. Blood samples were obtained 16 days and 44 days after the second dose (appendix p 2). At day 16, the patient's HIV viral load was 831 764 copies per mL and CD4 count was 20 cells per µL (CD4% 4·6%; CD4/CD8 0·05). ART with bictegravir, emtricitabine, and tenofovir alafenamide and prophylaxis for opportunistic infections were initiated at day 16. At day 44 (29 days after ART initiation), HIV viral load was undetectable and CD4 count was 70 cells per µL.

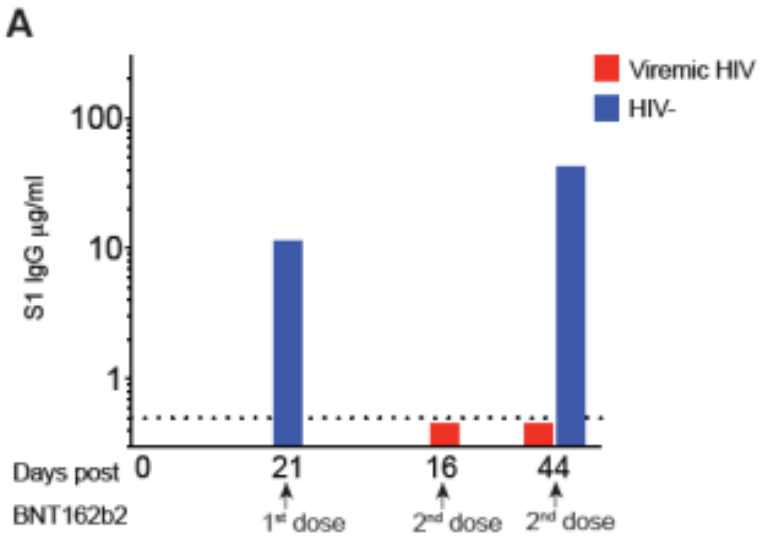
Post-vaccine samples from the index patient showed no IgG reactivity against the S1 subunit of the spike protein by an in-house ELISA (appendix pp 1–2).[7] By contrast, an HIV-negative, SARS-CoV-2-naive participant had an S1-specific IgG titre of 43·4 µg/mL 44 days after the second dose of BNT162b2, consistent with the binding titres across the wider cohort, in which all participants produced S1-specific IgG, even after only one dose (appendix pp 1–2). No SARS-CoV-2-specific neutralisation was observed at either timepoint for the index patient. By contrast, the HIV-negative, SARS-CoV-2-naive vaccine recipient had a neutralisation titre of 1/656 after the second dose. No quantifiable spike protein-specific T cells, evaluated via ELISpot (MAIPN4550; Merck Millipore, Darmstadt, Germany), were observed in the index patient compared with the HIV-negative control participant, sampled 44 days after the second dose, and a subsample of people living with well controlled, stable HIV after one dose of BNT162b2 (appendix p 2). Although no spike protein-specific T cells were detected via intracellular cytokine staining in the index patient, responses against cytomegalovirus pp65 were dominated by CD8 T cells, strikingly so after ART (appendix p 2). The profound peripheral immune cell perturbations in the index patient were accompanied by increased frequencies of CD8 T cells with a terminally differentiated effector memory phenotype (CCR-7$^-$ and CD45RA$^+$) and an inverted CD4/CD8 ratio, which could influence the size of T-cell responses to SARS-CoV-2.[1]

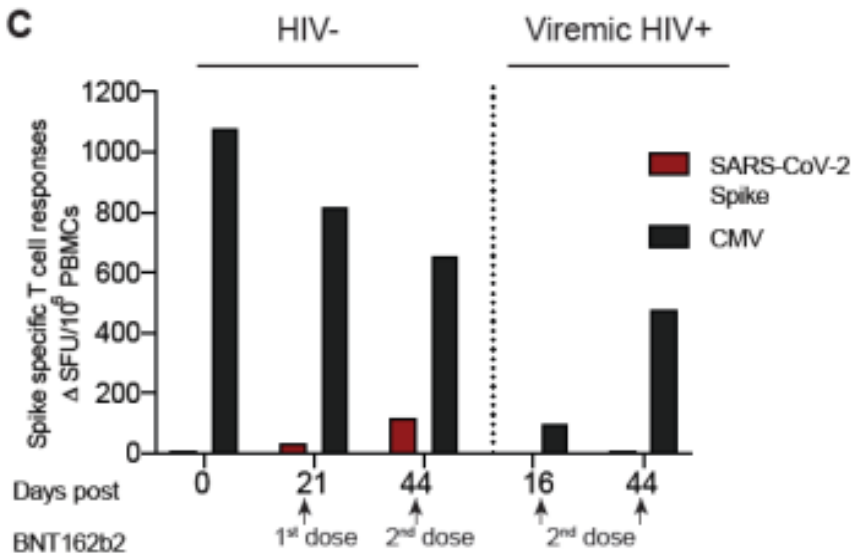
In conclusion, an individual with profound HIV-related immune dysfunction did not seroconvert to a SARS-CoV-2 vaccine. We suggest monitoring SARS-CoV-2 seroconversion in people with advanced HIV and considering repeat vaccination upon HIV suppression and CD4 count improvement with ART. This case highlights an urgent need to establish correlates of vaccine efficacy in people living with HIV, particularly in those with suboptimal viral suppression or ongoing perturbed immune function, to better inform clinical management and guidelines.

LEM has received honorarium for lectures from the London School of Hygiene and Tropical Medicine. SR-J has received honorarium for lectures from the London School of Hygiene and Tropical Medicine, declares additional grant support from UK Research and Innovation, EDCTP, Kumamoto University, the Rosetrees Trust, and the Global Challenges Research Fund, and is a trustee and past president of the Royal Society of Tropical Medicine and Hygiene. RKG has received consulting fees from UMOVIS Lab and Janssen. FB has received payment for teaching research methods from Gilead Sciences. LW has received honorarium for participation in advisory boards, speaker fees, or both from Gilead Sciences, ViiV, Janssen, MSD, Theratechnologies, Mylan, and Cipla, and has also received conference attendance support from ViiV. All other authors declare no competing interests. ET and AA contributed equally to this Correspondence. This Correspondence was supported by a Medical Research Council (MRC) grant to LEM (MR/R008698/1), a MRC studentship (MR/N013867/1), and a MRC grant (MR/M008614) and a National Institutes of Health grant (R01AI55182) to DP. We thank Peter Cherepanov of the Francis Crick Institute (London, UK) for supplying recombinant S1 antigen. We are grateful to Rebecca Matthews, Paulina Prymas, Marzia Fiorini, Thomas Fernandez, Nnenna Ngwu, the clinical research teams at the Mortimer Market Centre (London, UK) and the Ian Charleson Day Centre (London, UK), and all the clinic staff and participants.

*Emma Touizer, Aljawharah Alrubayyi, Chloe Rees-Spear, Natasha Fisher-Pearson, Sarah A Griffith, Luke Muir, Pierre Pellegrino, Laura Waters, Fiona Burns, Sabine Kinloch, Sarah Rowland-Jones, Ravindra K Gupta, Richard Gilson, *Dimitra Peppa, *Laura E McCoy*
dimitra.peppa@ndm.ox.ac.uk; l.mccoy@ucl.ac.uk

Division of Infection and Immunity (ET, C-RS, SAG, LM, LEM), Department of Immunology, Royal Free Campus (SK), and Institute for Global Health (FB, RG), University College London, London WC1E 6BT, UK; Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK (AA, NF-P, SR-J, DP); The Mortimer Market Centre, Department of HIV, CNWL NHS Foundation Trust, London, UK (PP, LW, DP); Department of Infection and Immunity (SK) and Department of HIV Medicine (FB), Royal Free NHS Foundation Trust, London, UK; Department of Medicine, University of Cambridge, Cambridge, UK (RKG)



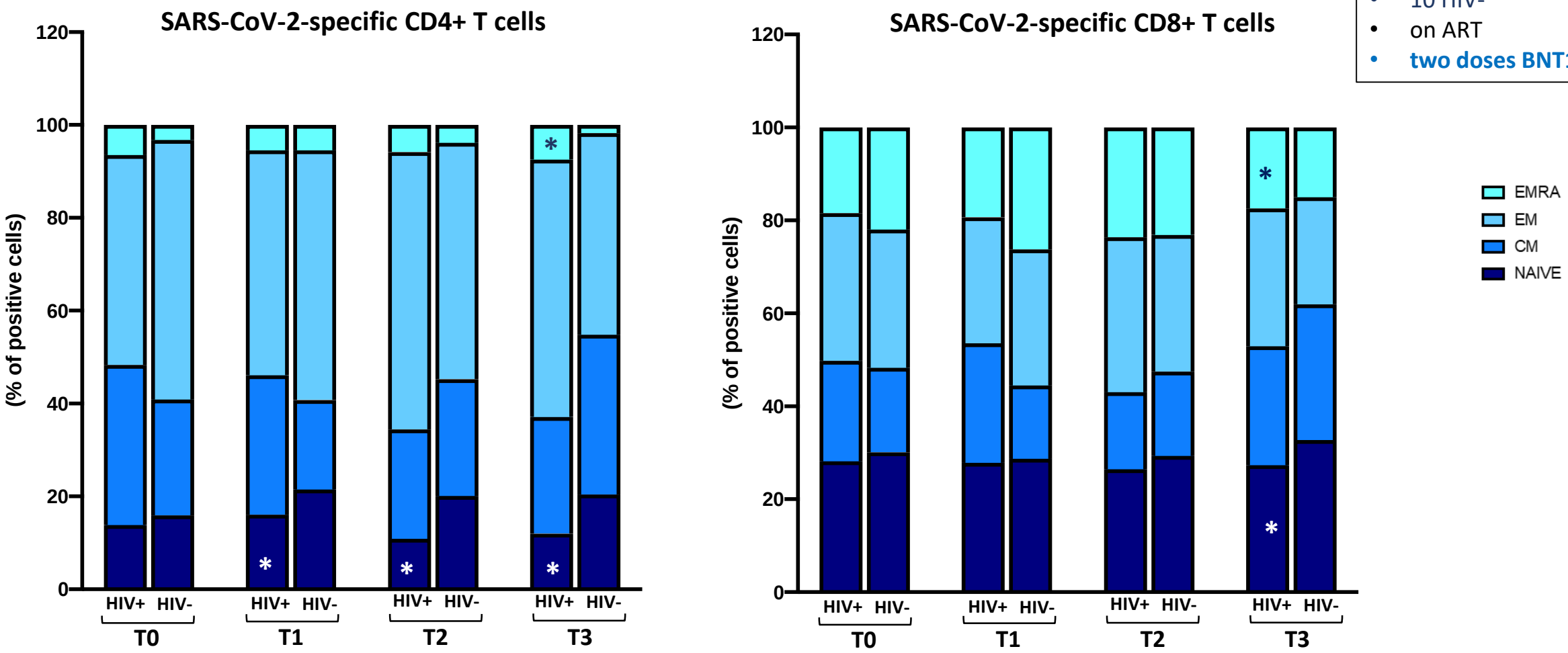


Patient with uncontrolled HIV replication do not respond to two doses of the BNT162b2 SARS-CoV-2 vaccine

Touizer, Lancet HIV 2021

Immunological memory in SARS-CoV-2 vaccinated HIV-patients

- 7 HIV+
- 10 HIV-
- on ART
- **two doses BNT162b2**

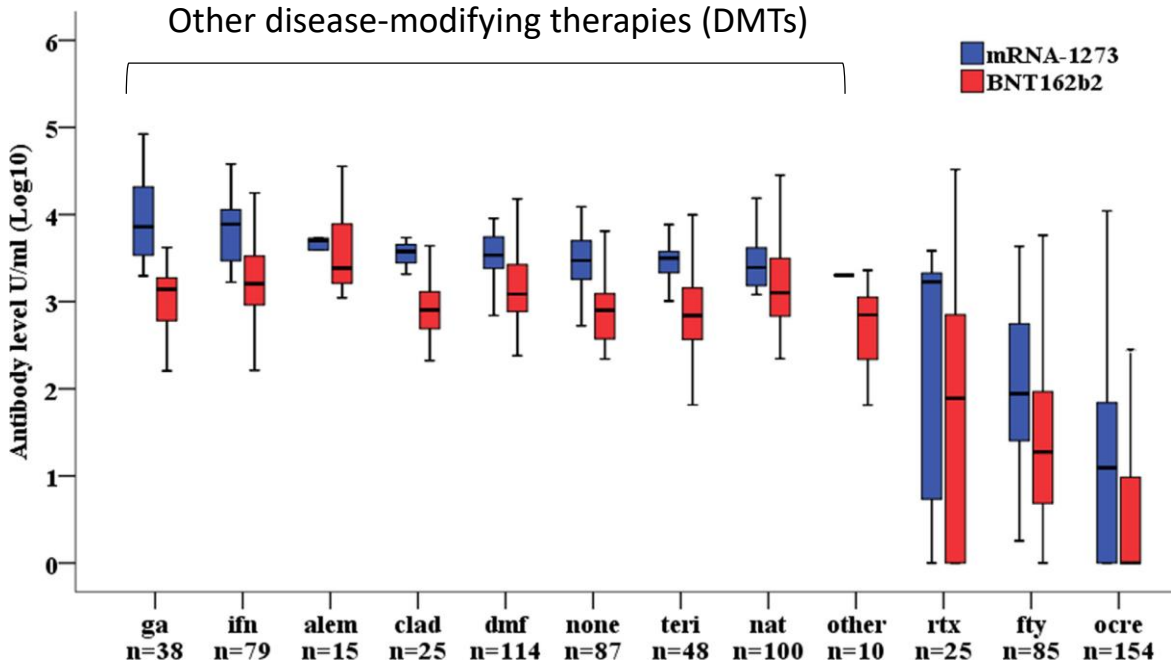


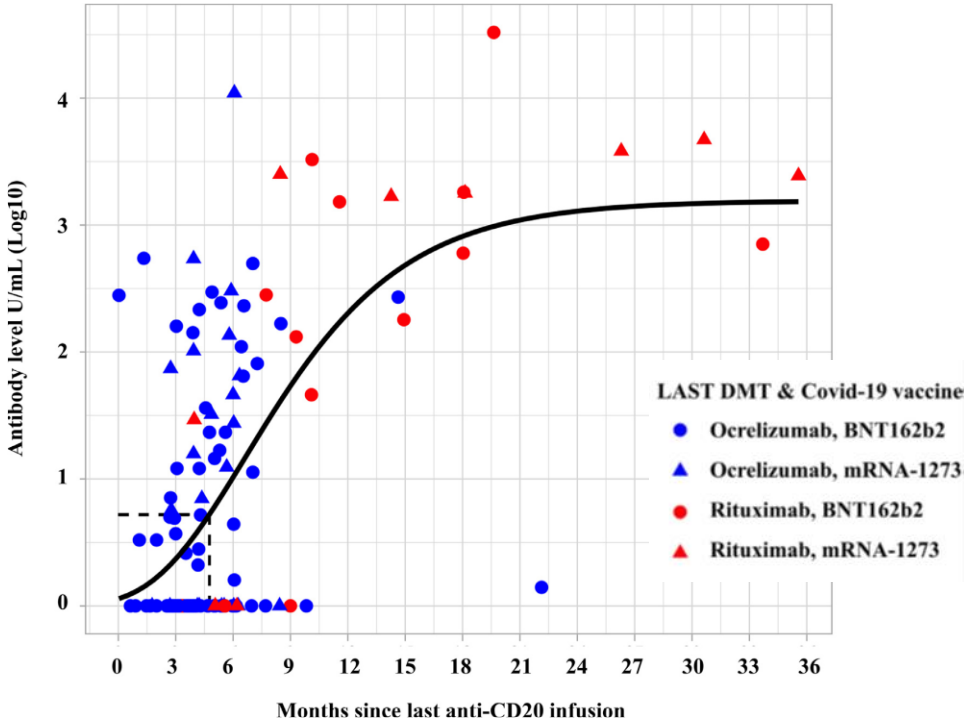
“Waning immunity “ profile in T lymphocyte from HIV+ SARS-CoV-2 Vaccinated subjects

Biasin, in preparation 2021

Immune responses in SARS-CoV-2 vaccinated MS-patients

- 740 MS patients
- 76% **BNT162b2** and 24% **mRNA-1273**
- 87 untreated, 154 on ocrelizumab, 25 on rituximab, 85 on fingolimod, 25 on cladribine and 404 (51¢7%) on other DMTs





Impaired response to COVID-19 mRNA in patients under anti-CD20 therapies, positively correlates with time from therapy infusion

Sormani, EBioMedicine 2021

Immune responses in SARS-CoV-2 vaccinated MS-patients

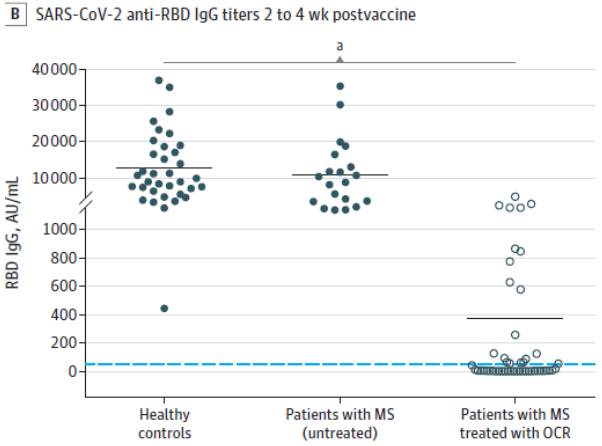
- 112 MS patients
- 2 doses **BNT162b2**
- 49 on Ocrelizumab

Brill, Jama Neurology 2021

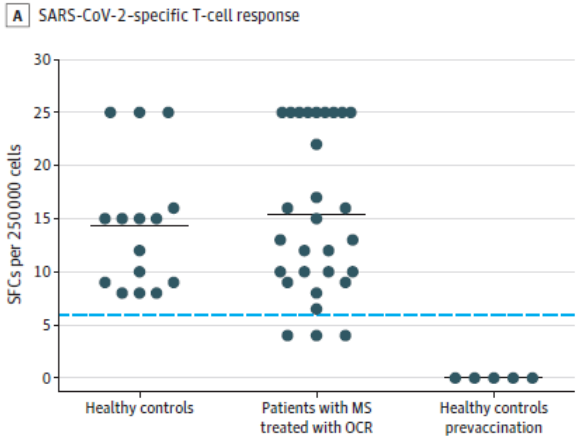
- 20 MS patients
- **BNT162b2** or **mRNA-1273**
- 19 on Ocrelizumab 1 on Rituximab

Apostolidis, Nature Medicine 2021

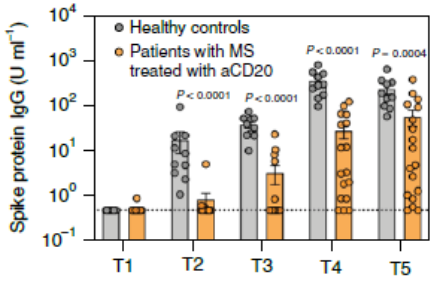
Humoral response

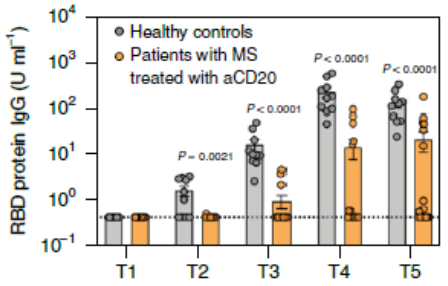


Cellular response

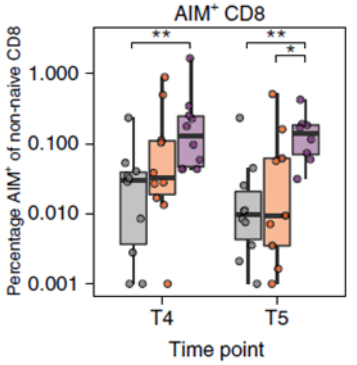


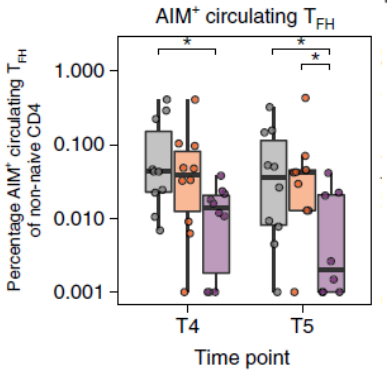
Humoral response



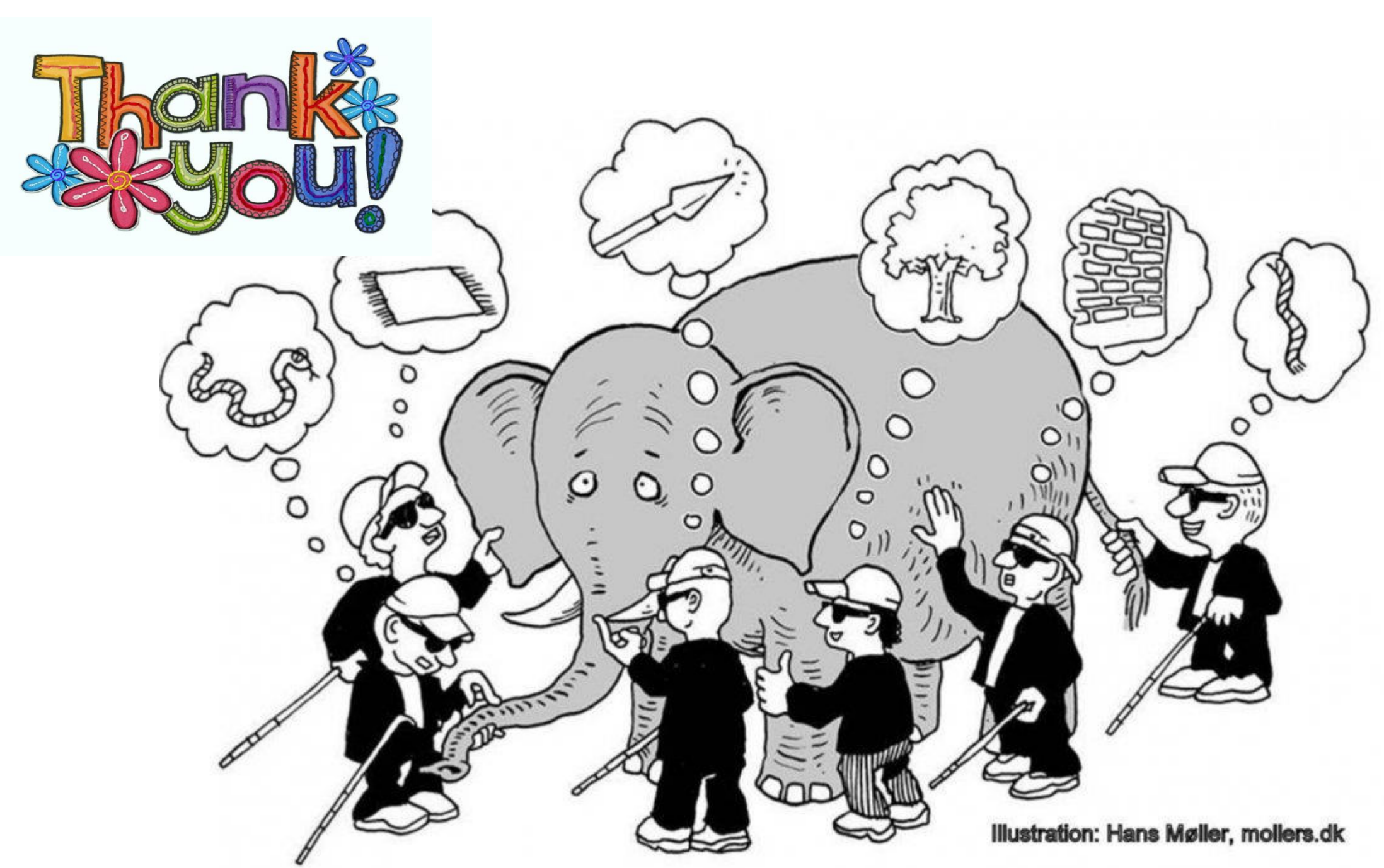


Cellular response





Patients with MS under anti-CD20 therapies generated comparable SARS-CoV-2–specific T-cell responses with healthy controls


Thank you!
Illustration: Hans Møller, mollers.dk