Current understanding of mechanisms of vaccine-induced protection

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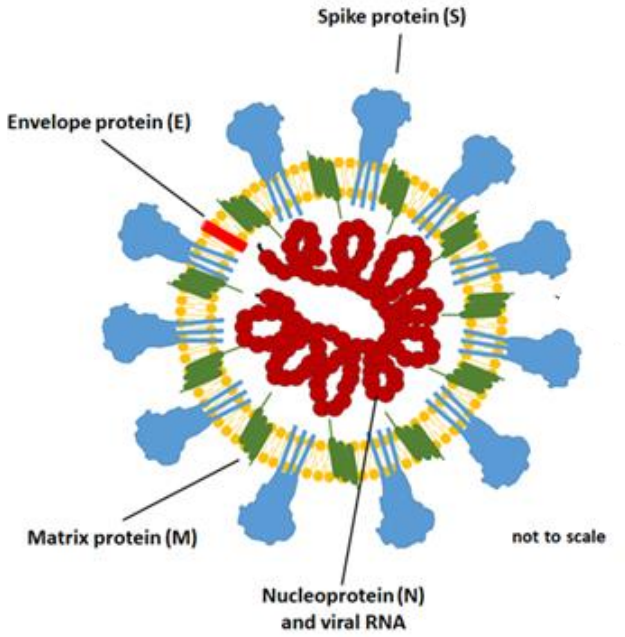
WHO meeting on COVID vaccines research

August 13th, 2020

Mount Sinai

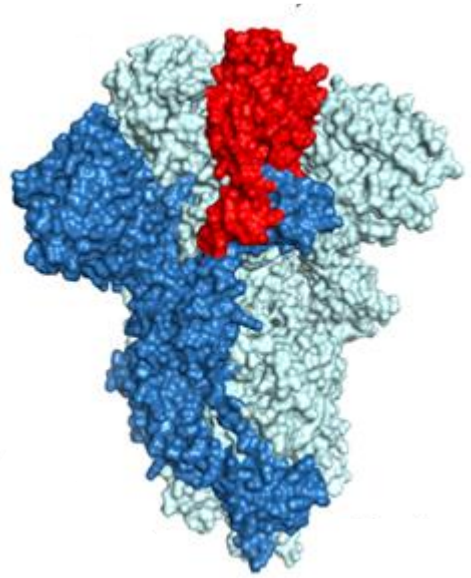
Infection-induced immunity



+ all other nonstructural proteins
likely some intra-host sequence diversity
potentially longer presence of antigen

systemic immunity
mucosal immunity

Vaccine-induced immunity



***except inactivated vaccines**

one consensus spike

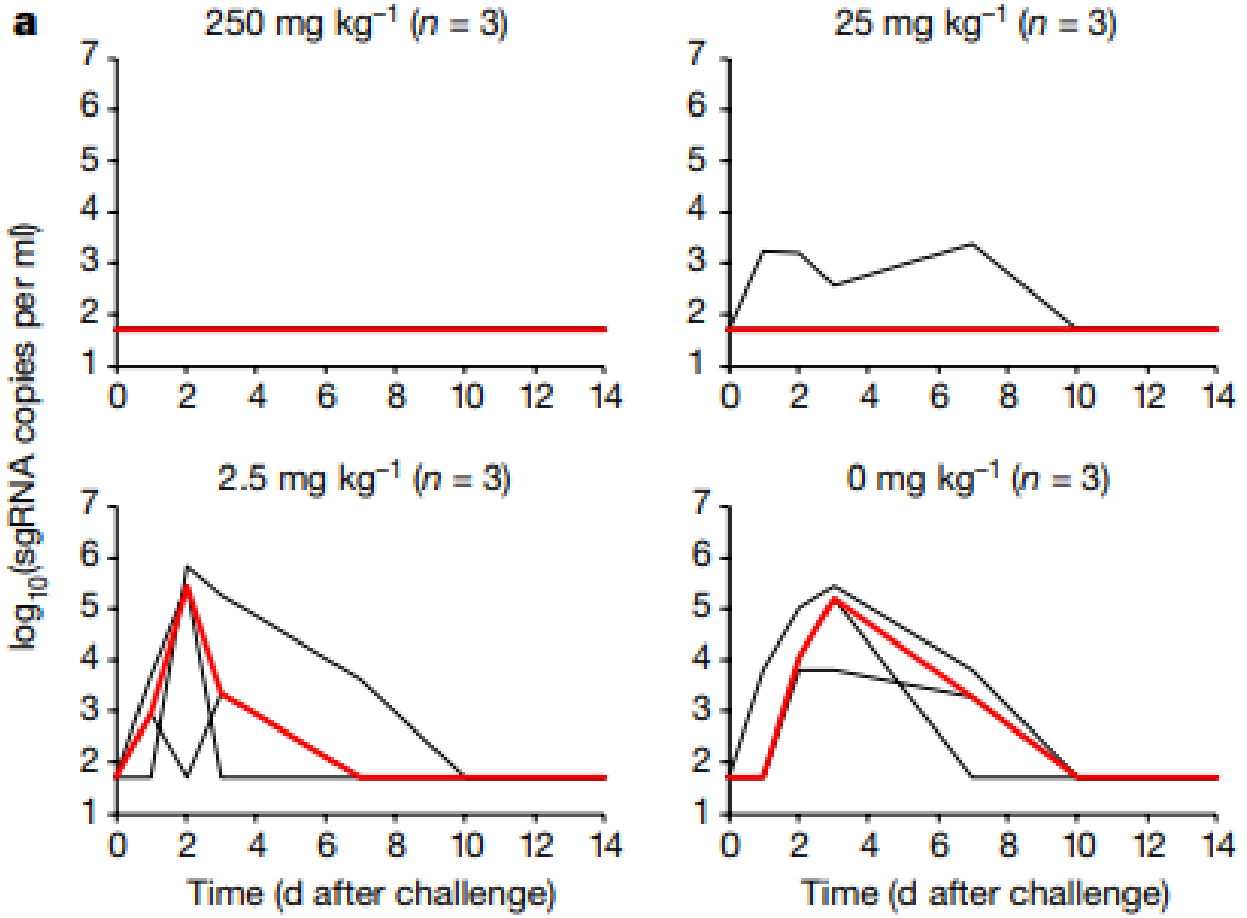
systemic immunity

Antibody based immunity

- Antibodies neutralize SARS-CoV-2
- Antibodies may protect through Fc-dependent effector functions

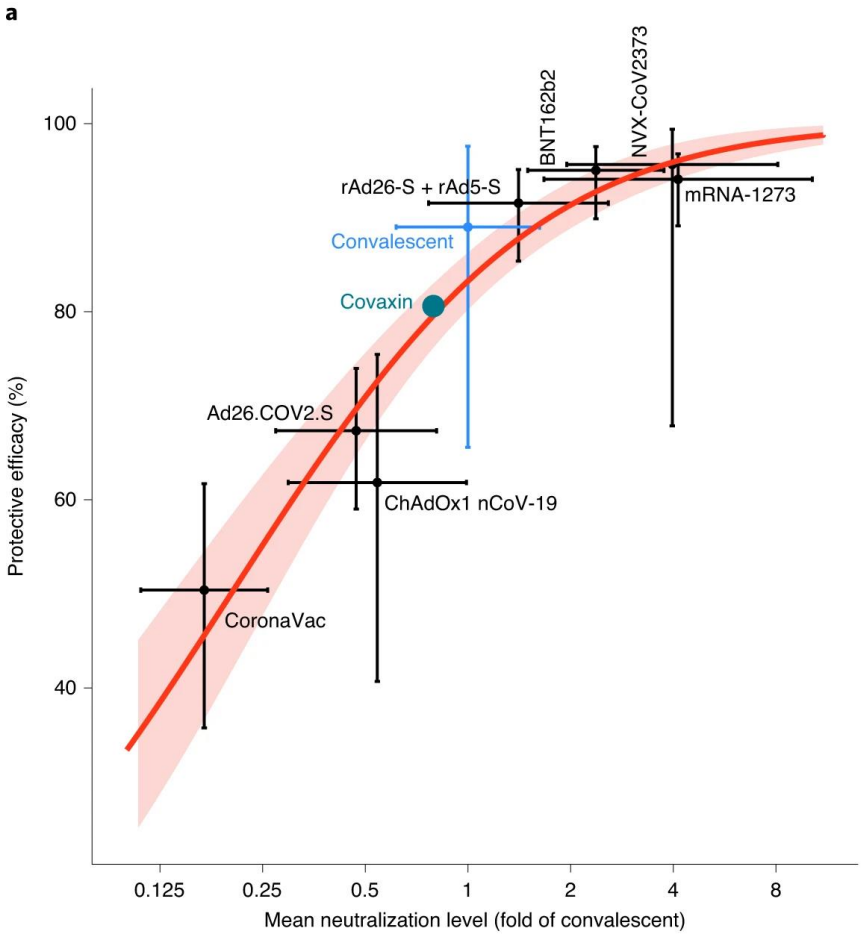
- mAb prophylactics and therapeutics work!

NHP are protected from challenge by passive transfer of antibody in a dose dependent manner

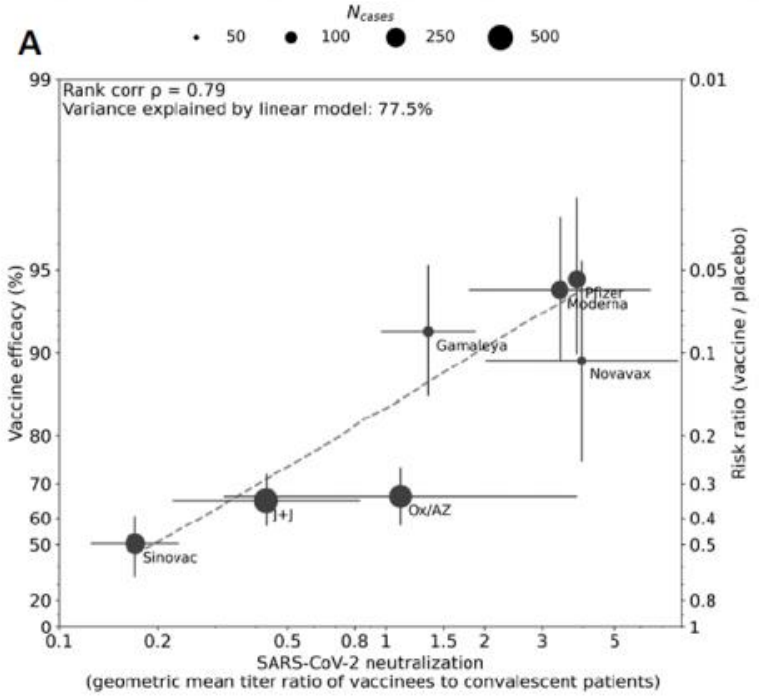


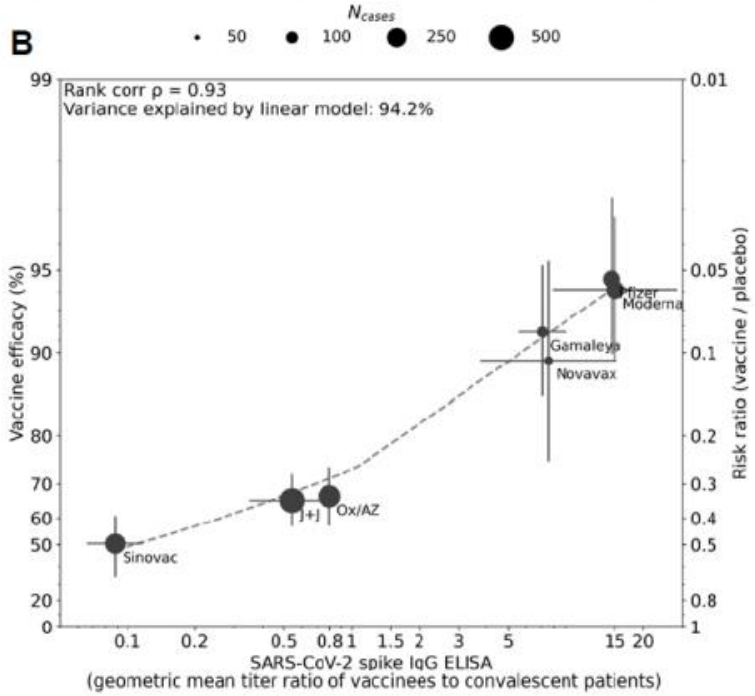
McMahan *et al.*, Nature 2021

From a ‘global’ perspective, antibody levels correlate with vaccine efficacy



Khoury *et al.*, Nat Med, 2021

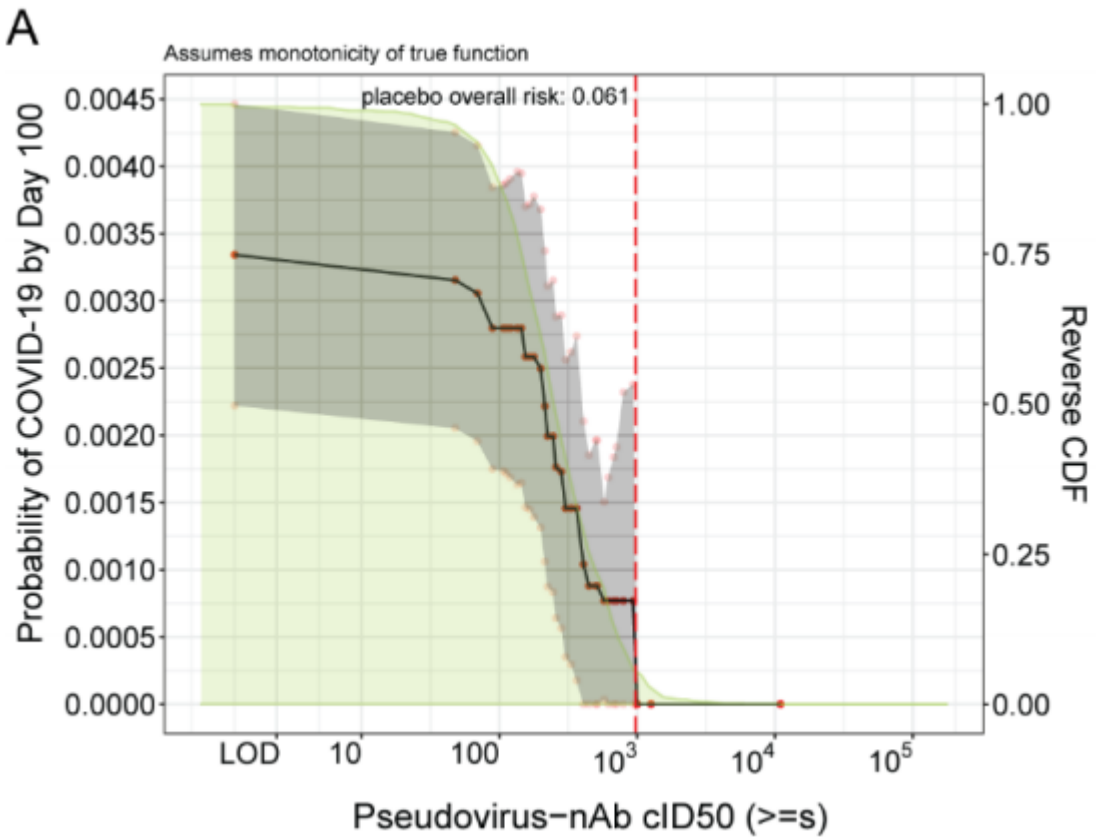




Earle *et al.*, Vaccine, 2021

Antibodies do seem to be a correlate of protection at an individual level as well

COVE Immunologic Marker	Tertile¶	No. cases / No. at-risk§	Attack rate	Haz. Ratio Pt. Est.	Haz. Ratio 95% CI	P-value (2-sided)	Overall P-value	Overall q-value†	Overall FWER
Anti Spike IgG (IU/ml)	Low	25/4,573	0.0055	1	N/A	N/A	0.006	0.014	0.010
	Medium	14/4,804	0.0029	0.45	(0.20,1.01)	0.053			
	High	8/4,687	0.0017	0.23	(0.09,0.60)	0.002			
Anti RBD IgG (IU/ml)	Low	25/4,620	0.0054	1	N/A	N/A	0.009	0.014	0.014
	Medium	13/4,745	0.0027	0.45	(0.20,1.01)	0.052			
	High	9/4,699	0.0019	0.28	(0.12,0.67)	0.004			
Pseudovirus-nAb cID50	Low	21/4,727	0.0044	1	N/A	N/A	0.052	0.042	0.054
	Medium	18/4,681	0.0038	0.82	(0.39,1.72)	0.599			
	High	8/4,656	0.0017	0.31	(0.12,0.80)	0.016			
Pseudovirus-nAb cID80	Low	20/4,742	0.0042	1	N/A	N/A	0.012	0.014	0.015
	Medium	22/4,715	0.0047	1.00	(0.49,2.03)	1.000			
	High	5/4,607	0.0011	0.20	(0.07,0.61)	0.004			
Placebo		646/13,758	0.0470						

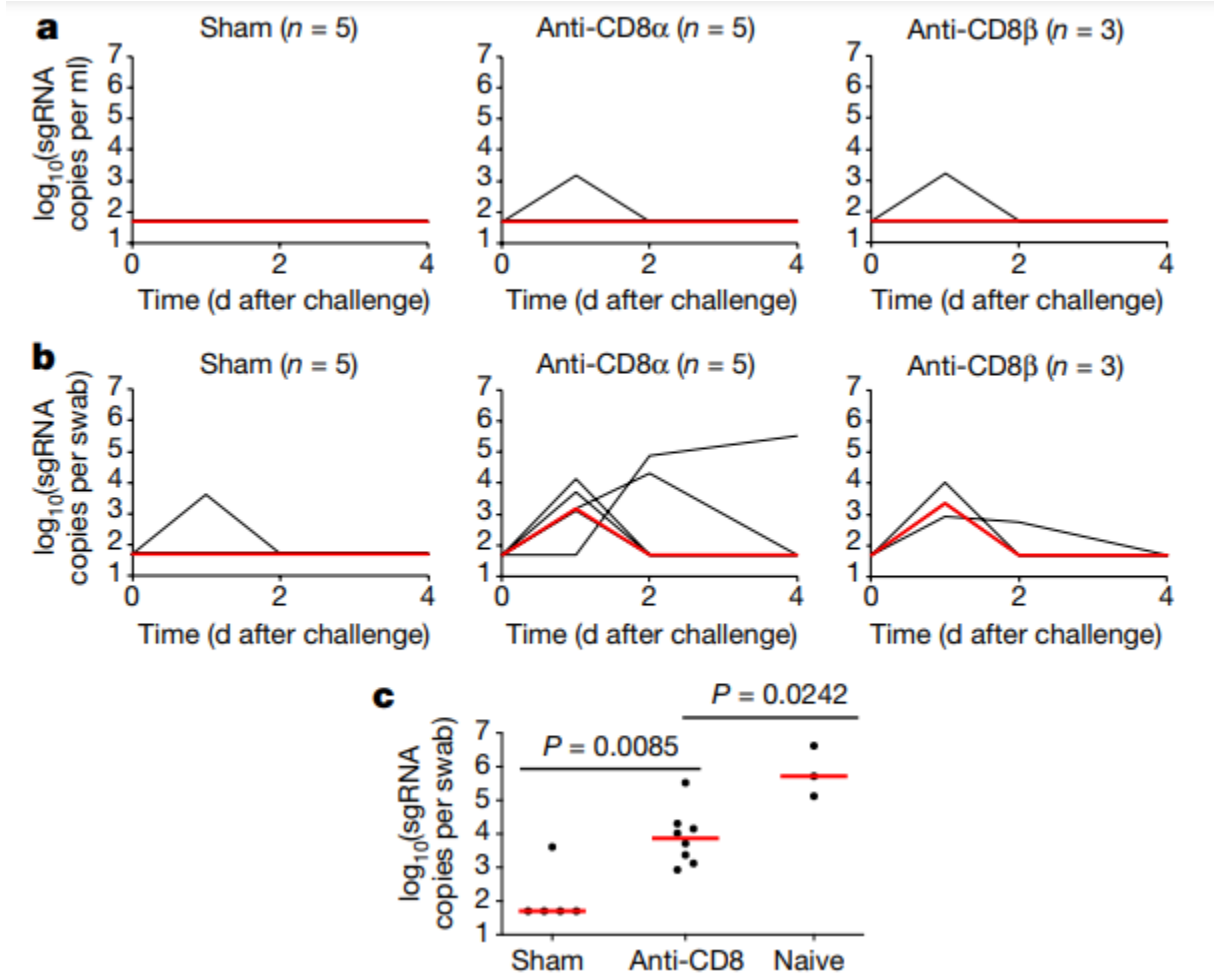


https://www.medrxiv.org/content/10.1101/2021.08.09.21261290v1.full.pdf

T cell based immunity

- Vaccination induces strong CD4+ and somewhat lower CD8+ T-cell responses with most currently used vaccines

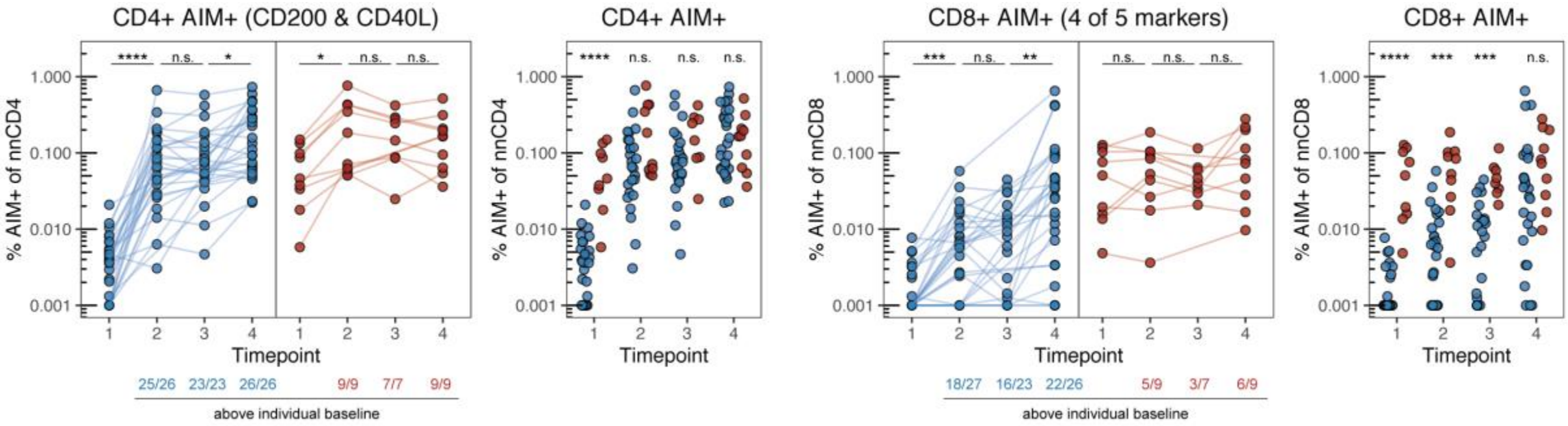
Depletion of CD8 T-cells in NHPs with low antibody titers facilitates breakthrough infections



McMahan *et al.*, Nature 2021

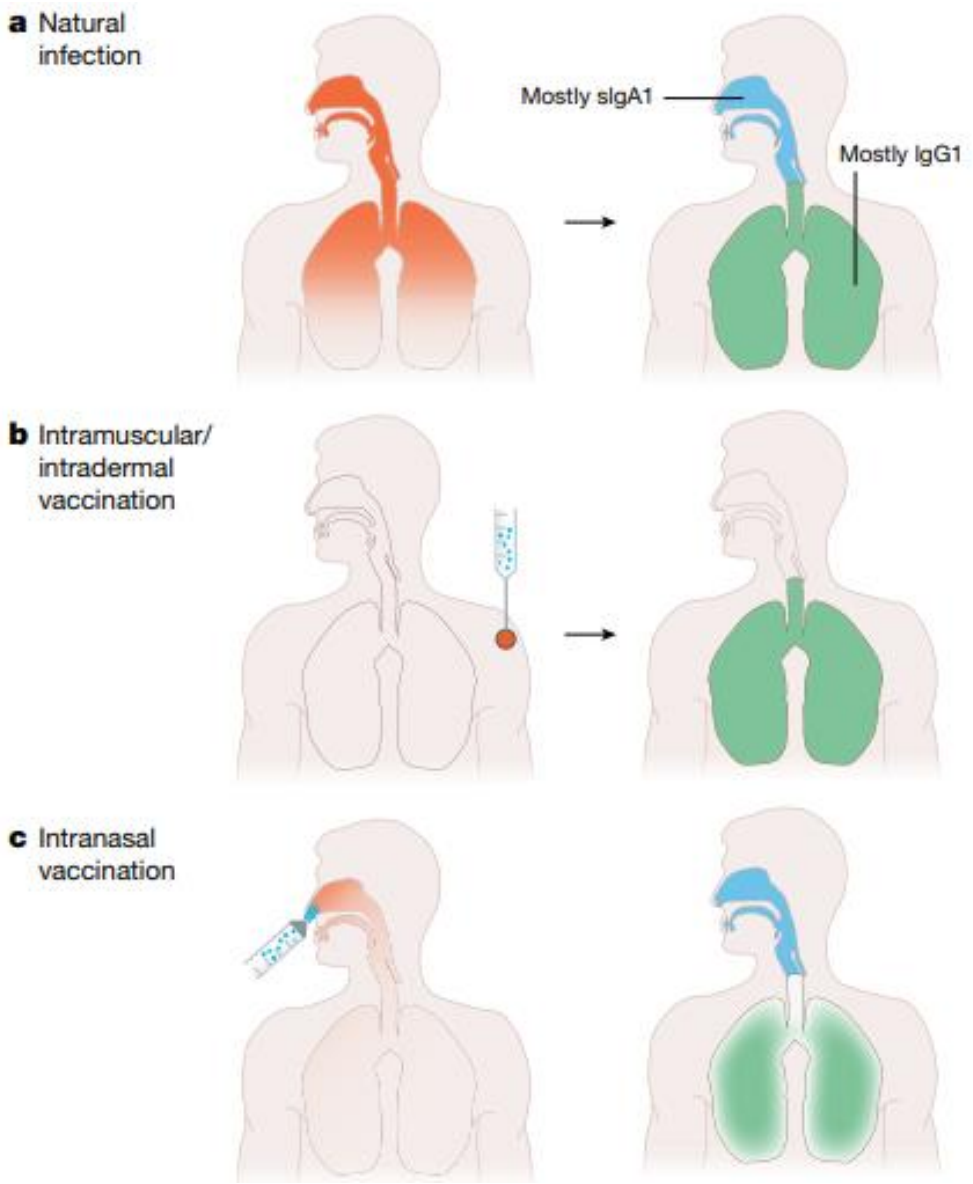
T cell based immunity

CD4+ and CD8+ T-cell responses in naive and recovered indiviuals post mRNA vaccination



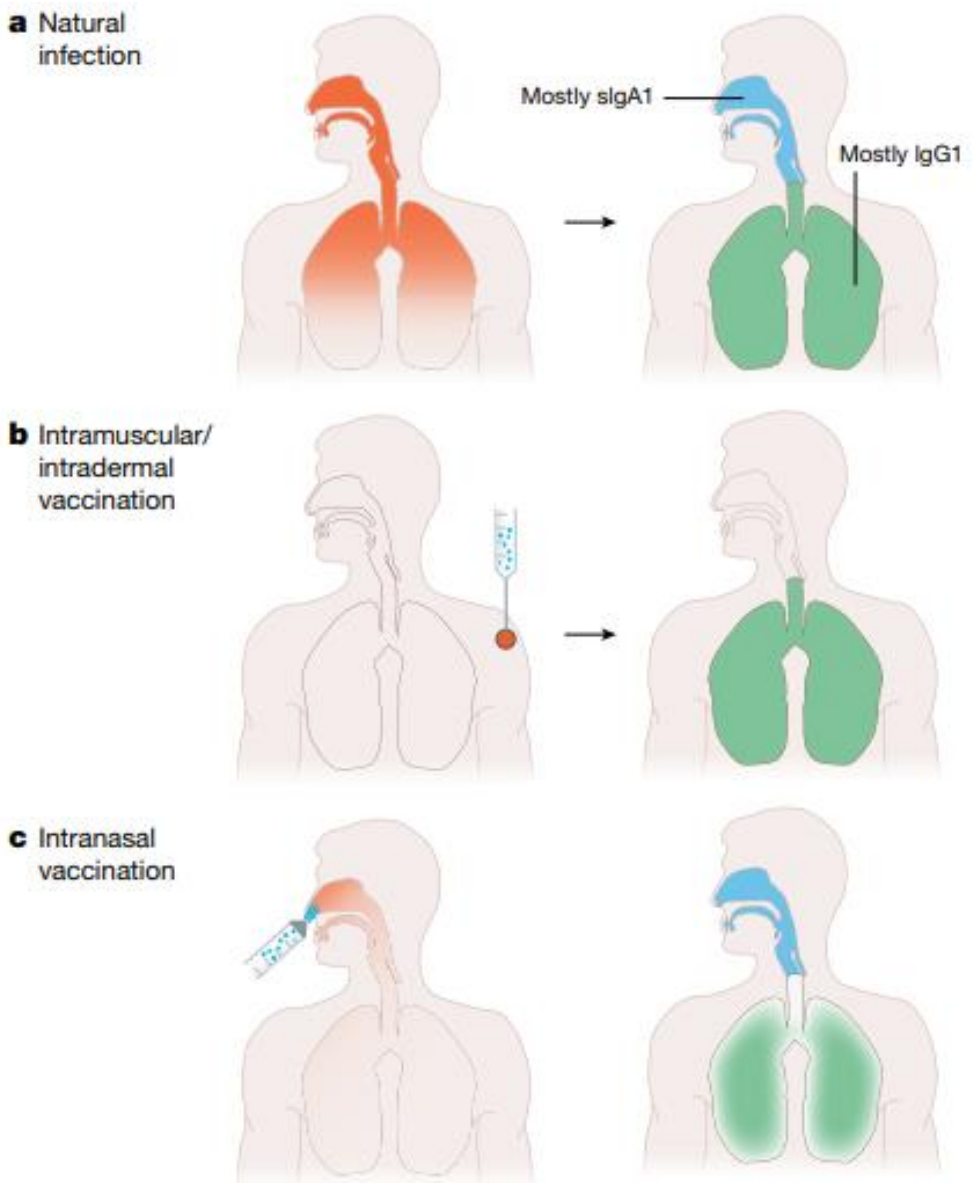
https://www.biorxiv.org/content/10.1101/2021.04.21.440862v1.full.pdf

Mucosal immunity



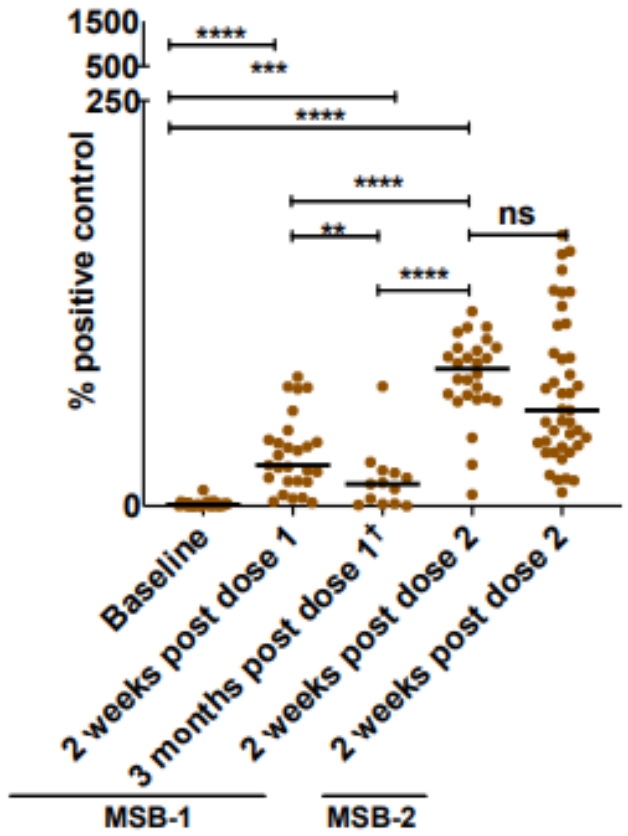
Krammer, Nature, 2020

Mucosal immunity



Krammer, Nature, 2020

Spike IgG in saliva



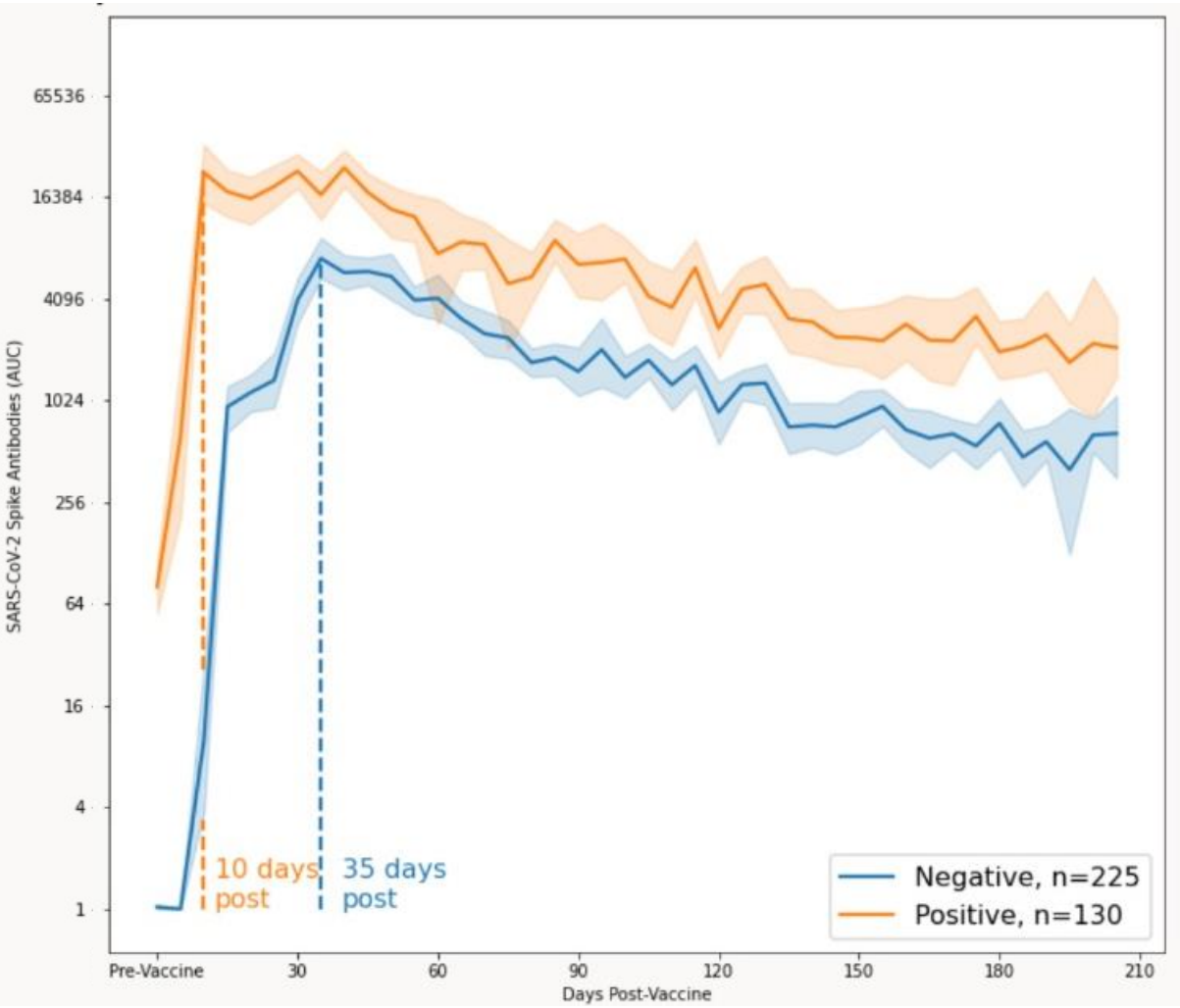
Gommerman lab
https://www.medrxiv.org/content/10.1101/2021.08.01.21261297v1.full.pdf

Mucosal immunity

Table 1 | Overview of NHP results

Company (ref.)	Vaccine candidate (type)	Dose range (route)	Neut. titre after prime	Neut. titre after boost	T cell response	Challenge dose (route)	URT protection	LRT protection	Species
Sinovac[34]	PiCoVacc (inactivated virion + aluminium hydroxide)	3–6 μg (i.m.)	None[a]	1:10 range[a] after first boost; 1:50 range[a] after second boost	ND	10^6 $TCID_{50}$ (i.t.)	Partial[b]	Partial (low dose)[b] Complete (high dose)	Rhesus macaques
Beijing Institute of Biological Products[33]	BBIBP-CorV (inactivated virion + aluminium hydroxide)	4–8 μg (i.m.)	1:100 range[a]	1:200 range[a]	ND	10^6 $TCID_{50}$ (i.t.)	Partial[b]	Complete[b]	Cynomolgus macaques
AstraZeneca[49]	ChAdOxnCoV-19 (non-replicating AdV)	2.4×10^{10} VP; 1× or 2× (i.m.)	1:5–1:40 range[a]	1:10–1:160 range[a]	Yes	2.6×10^6 $TCID_{50}$ (i.t., oral, i.n., ocular)	None (1×)[c] None (2×)[c]	Partial (1×)[c] Complete (2×)[c]	Rhesus macaques
Janssen[41]	Ad26COVS1 (non-replicating AdV)	1×10^{11} VP (i.m.)	1:100 range[d]	NA	Low	10^5 $TCID_{50}$ (i.n, i.t.)	Complete in S.PP group[c]	Complete in S.PP group[c]	Rhesus macaques
Moderna[57]	mRNA-1273 (mRNA via LNPs)	2× 10–100 μg (i.m.)	ND[e]	1:501–1:3,481 range[d]	Yes, CD4, T_{FH}	7.6×10^5 $TCID_{50}$ (i.n., i.t.)	None (10 μg)[c] Partial (100 μg)[c]	Partial (10 μg)[c] Complete (100 μg)[c]	Rhesus macaques
Novavax[79]	NVX CoV2373 (spike protein + Matrix-M)	2× 2.5–25 μg	Not reported	17,920–23,040 range[a]	ND	10^4 plaque-forming units (i.n., i.t.)	Partial (low dose)[c] Complete (higher doses)[c]	Complete[c]	Cynomolgus macaques

Persistence of immune responses



NIAID PARIS New York cohort

Moderna/Pfizer vaccinated

Provided by Dr. Viviana Simon

Factors that may negatively impact on protection from variants

- Partial escape from neutralizing antibodies
  - Through mutation that decrease antibody affinity for spike
  - Through mutations that increase affinity of spike for ACE2
  - Through mutations that increase/alter fusogenicity
- Partial escape from T-cell responses
- Higher replication capacity
- Shorter incubation time
- Exposure to higher viral loads
- Waning of IgG on mucosal surfaces (protection from infection)
- Waning of immune responses in general (protection from illness)

(Many) remaining questions

- What is the absolute correlate of protection for antibody responses (how high does the titer need to be) for protection from
  - Infection
  - Illness
  - Severe illness
- What is the role of the anamnestic response (T-cells, memory B-cells) and to which degree is that role influenced by shorter incubation times (e.g. for B.1.617.2/Delta)
- What is the contribution of vaccine induced CD4+ and CD8+ T-cells in protection from
  - Infection
  - Illness
  - Severe Illness
- How much difference in these mechanisms is there between vaccines and vaccine platforms?

Acknowledgements

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Thank you to all the study participants!

Department of Microbiology/
Icahn School of Medicine at Mount Sinai
Peter Palese

PARIS and SPARTA teams!!!

John Kubale and Aubree Gordon

Viviana Simon

Komal Srivastava, Charles Gleason and the Personalized Virology Initiative

Kantaro

CIVICs
Collaborative Influenza Vaccine Innovation Centers

CEIRS
NIAID Centers of Excellence for Influenza Research and Surveillance

Ania Wajnberg
(Mount Sinai Hospital)

Carlos Cordon-Cardo
Adolfo Firpo
Rao Mendu
(Mount Sinai Hospital)

Harm van Bakel
(ISMMS)

Mia Sordillo
David Reich
Judy Aberg
(Mount Sinai Hospital)

Adolfo García-Sastre
Lisa Miorin
Teresa Aydillo

Tom Moran

Katherine Kedzierska (U Melbourne)
Jussi Hepojoki (U Helsinki)
Olli Vapalahti (U Helsinki)