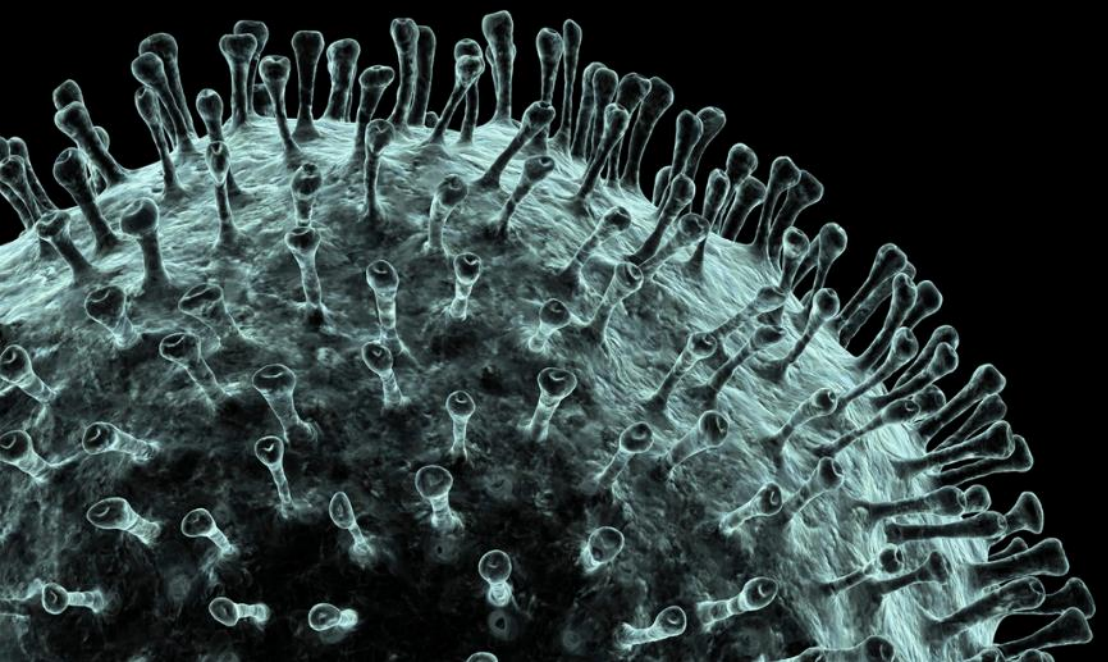
COVID-19 Conversations

Monica Gandhi

University of California, San Francisco
San Francisco General Hospital



COVID19Conversations.org
#COVID19Conversations

APHA
AMERICAN PUBLIC HEALTH ASSOCIATION
For science. For action. For health.

150 years NATIONAL ACADEMY of MEDICINE

COVID-19 vaccines: Do they halt transmission? Do they protect against variants? From CDC guidance to clinical practice

Monica Gandhi MD, MPH

Professor of Medicine, Division of HIV, Infectious Diseases and Global Medicine

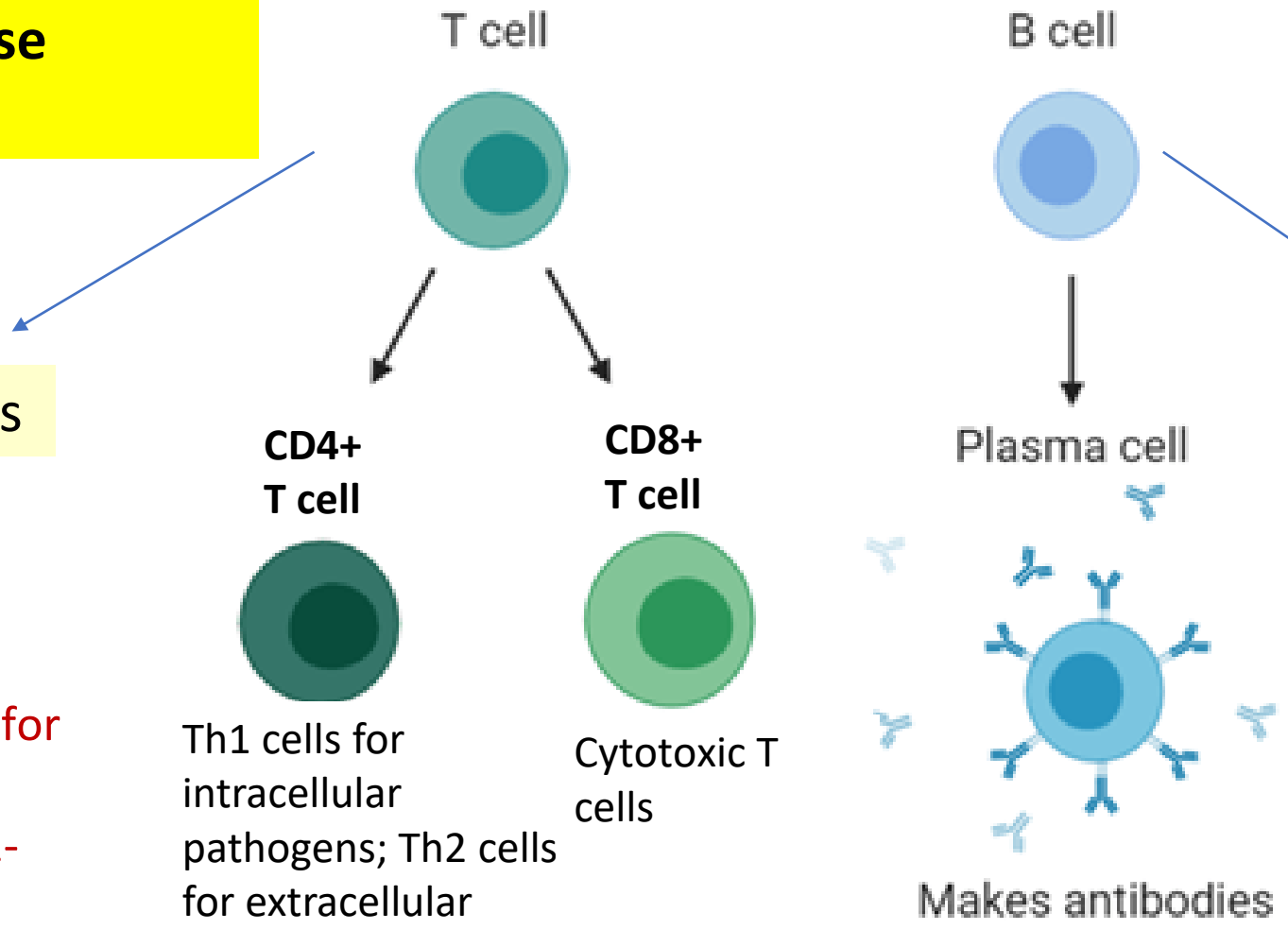
Medical Director, Ward 86 and Director, UCSF CFAR

NAM-APHA Webinar: COVID-19 Conversations: Variants and Vaccines

March 17, 2021

Remember immunity -antibodies and cell-mediated

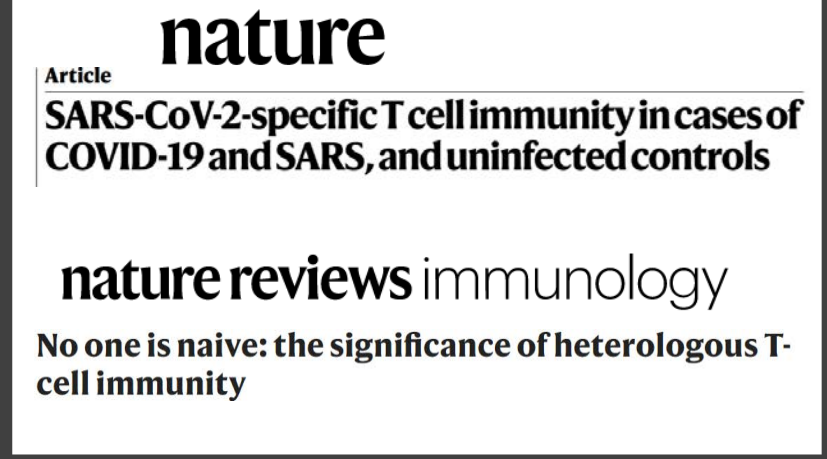
T cells are the major immune defense against viruses

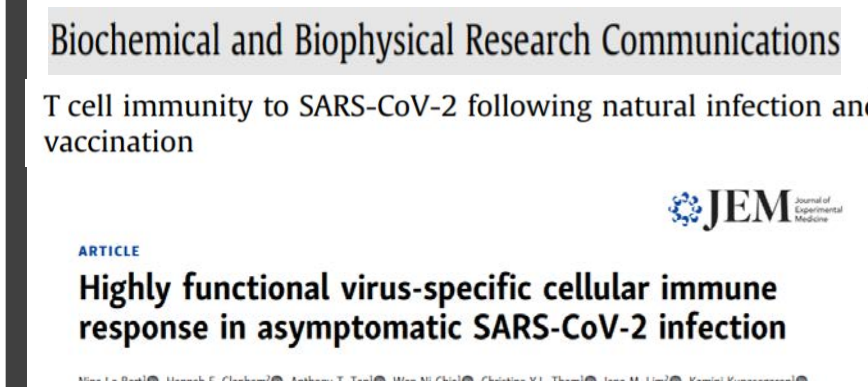


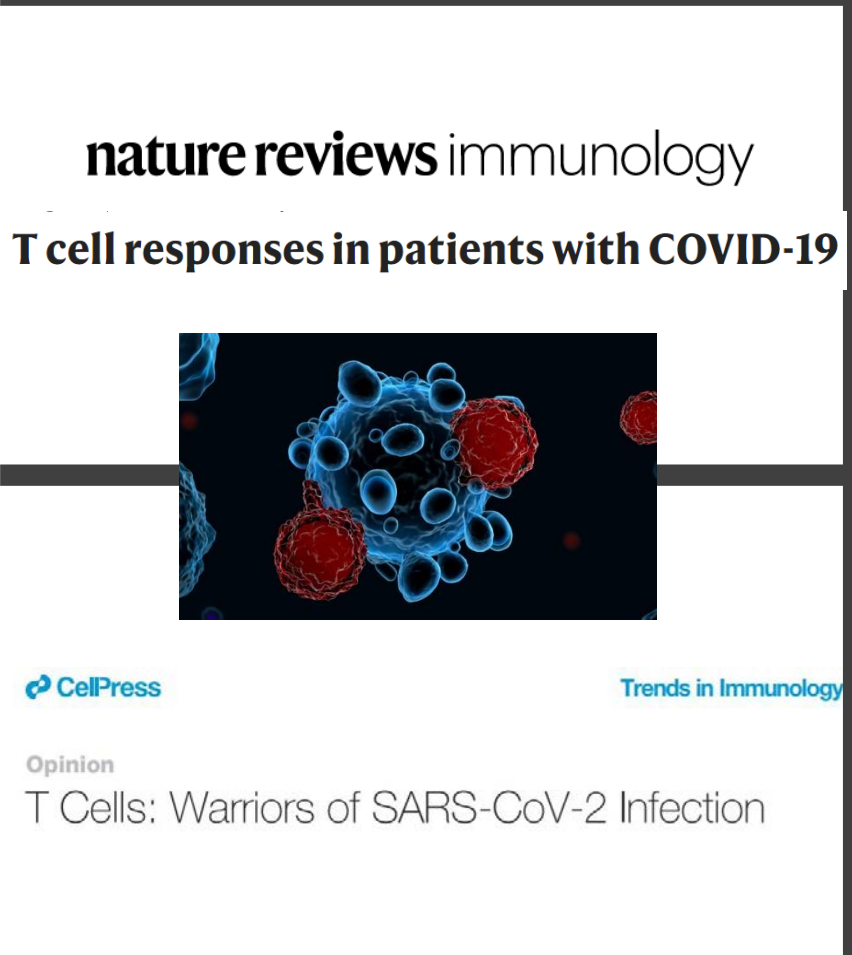
Of note, want Th1:Th2 ratio >>1 for viruses; Th2 CD4s block antiviral Th1-CD4s and CD8s

Most vaccine trials measured antibodies and T cell responses

Company	Platform	Doses	Non-clinical results	# who got vaccine	Protection from hospitalization from COVID-19	Protection from COVID severe dz (some at home)	Efficacy against milder COVID
moderna	mRNA-1273 mRNA in lipid nanoparticle	2	Neutralizing Abs; Strong Th1 CD4+, CD8+; protection from challenge (macaques)	~15,000	97% (1 in vaccine arm after 2nd dose hospitalized)	97% (30 cases in placebo arm; 0 in vaccine reported but 1 severe per FDA)	94.1%
Pfizer	BNT162b2 mRNA in lipid nanoparticle	2	Neutralizing Abs; Strong Th1 CD4+, CD8+; protection from challenge (macaques)	~18,600	100%	100% (9 cases in placebo arm; 0 in vaccine- 1 initially severe but not)	95%
Johnson & Johnson	JNJ-78436725 Non-replicating human adenovirus/DNA	1	Neutralizing Abs; Strong Th1 CD4+ > Th2; CD8+; challenge protection (macaque)	~22,000 US, Latin America, S. Africa	100%	85.4% across 3 sites (7 deaths, 16 hospitalizations, all in placebo arm)	72% US; 61% Latin America; 64% S. Africa (96% B1.351)
AstraZeneca	AZD 1222 Non-replicating Chimp Adenovirus-DNA	2	Neutralizing Abs; Strong Th1 CD4+ > Th2; CD8+; protection from challenge (macaques)	~8588	100%	100% (15 in placebo – all hospitalized; 0 in vaccine)	70% overall; 76% 1 dose; S. Africa trial halted for mild
NOVAVAX Creating Tomorrow's Vaccines Today	NVX-CoV2373 Spike protein/RBD + Matrix M adjuvant	2	Neutralizing Abs; Strong Th1 CD4 > Th2; challenge protection (macaques)	~8833 (Phase 3 UK; 2b SA)	100%	100% (10 severe in placebo in UK/SA; 0 in vaccine)	96.4% UK; 89% B117 UK; 55% SA (94% B1351)
Sputnik V	Ad26 and Ad5 adenovirus/DNA	2	NAbs; IFN-γ secretion PMBCs, cellular response	~14964	100%	100% (20 in placebo; 0 vaccine)	91.6%
sinovac							





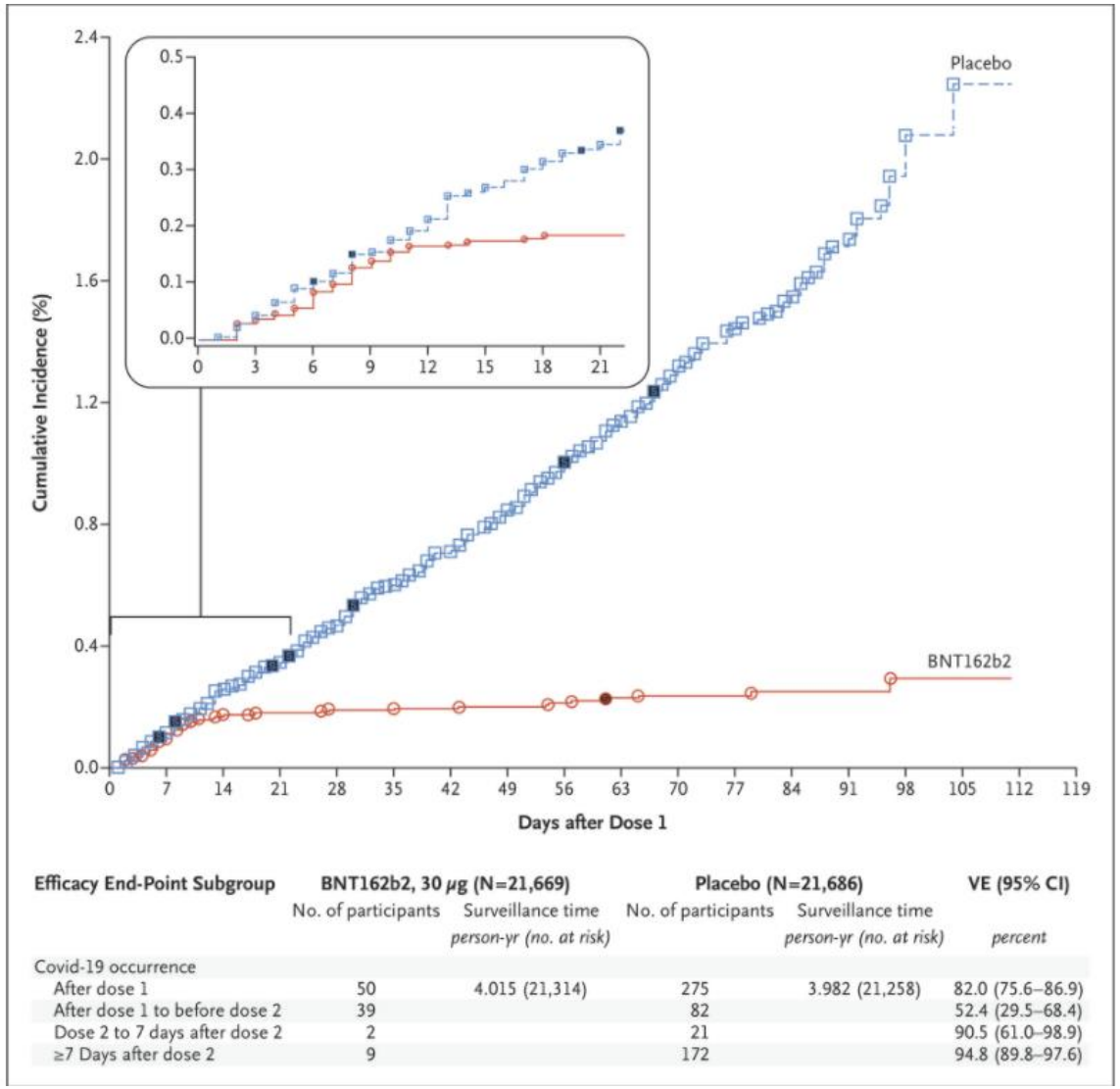


How does functional T-cell response modulate severity of disease?

- T cell responses modulate the severity of disease
- Strong T cell responses in all of these trials seem to have led to prevention of severe disease
- Even prior to vaccines, data indicating cross T-cell immunity from other coronaviruses led to more mild SARS-CoV-2 infection
- If you get re-infected after natural infection or vaccine (likely rare), should be mild if mounted good T-cell response
- Fun fact: Study from 1918 survivors of influenza pandemic show durable B cell immunity (memory B- Ab) 90 years later!

Pfizer/BioNTech trial

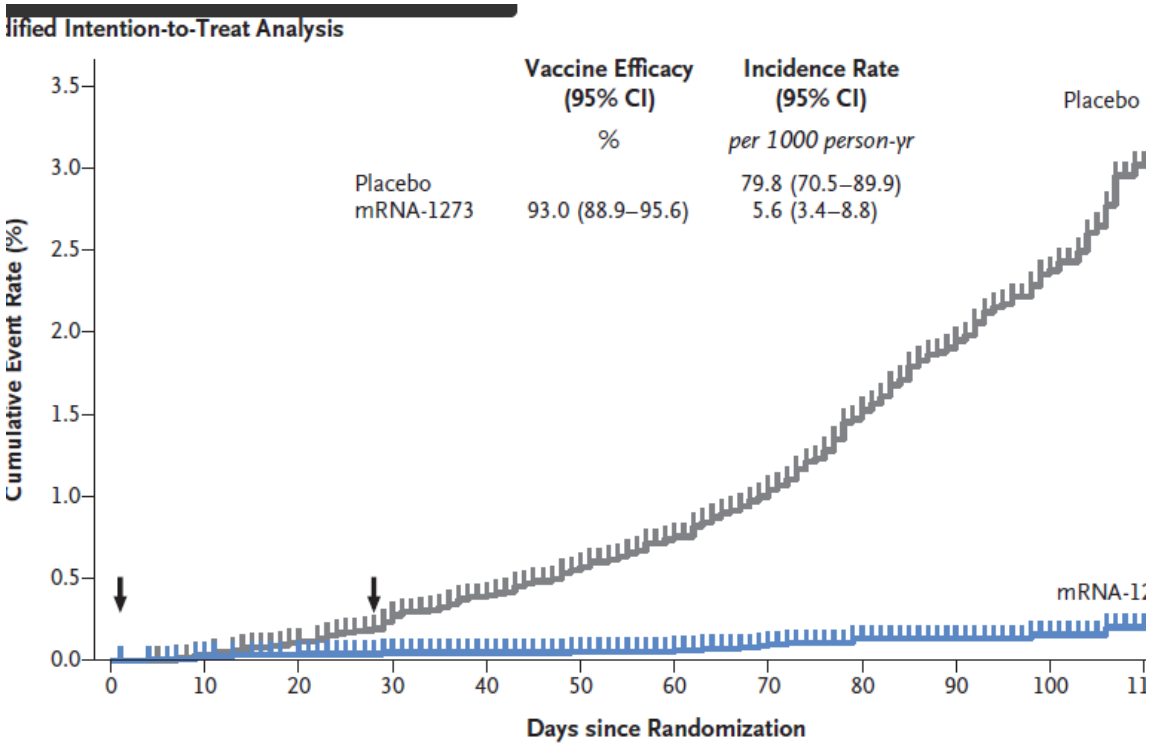
- 2 shots, 30μg, 3 weeks apart
- Of 37,706 reported on in NEJM, 49.4% females, 82.9% White, 9.83% AA, 28% Hispanic/Latino
- 21.4% >65 years, Median age 51
- Obesity (35.1%), diabetes 8.4%; pulmonary disease 7.8%
- Of 170 who became infected with COVID-19, 162 in placebo arm and 8 in vaccine arm so 95% effective (same level across subsets)
- Severe disease from COVID-19- 9 in placebo group; 0 in vaccine group (1 initially said severe, but FDA said not)



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)

Moderna vaccine trial

- Phase 3 enrolled 30,351 with data (15,170 in placebo, 15,181 in vaccine), >18 years of age
- 2 shots, 100µg, 4 weeks apart
- 47.3% female, 24.8%, ≥65 years of age, 36.5% of participants communities of color
- 22.3% participants high-risk (mean BMI 29.3)
- 196 final total symptomatic infections (e.g. 11 in vaccine group; 185 in placebo group), 94.1% efficacy
- Severe disease: 30 of the severe cases occurred in the placebo group (1 FDA reviewed in vaccine group)



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

Johnson and Johnson 1-dose phase 3 trial efficacy

468 cases symptomatic COVID

100% effective against hospitalization/death from COVID-19 (7 deaths & 14 hospitalizations in placebo)

85% effective against severe disease (could be O2 sat <93% but subset of severe disease included those hospitalized/died) across all 3 regions

89% efficacy against severe disease in South Africa where 95% of strains were B.1.351 (501Y.V2) variant

72% effective against moderate (>93% O_2 sat) disease in U.S., 64% in South Africa, 61% Latin America (66% overall)

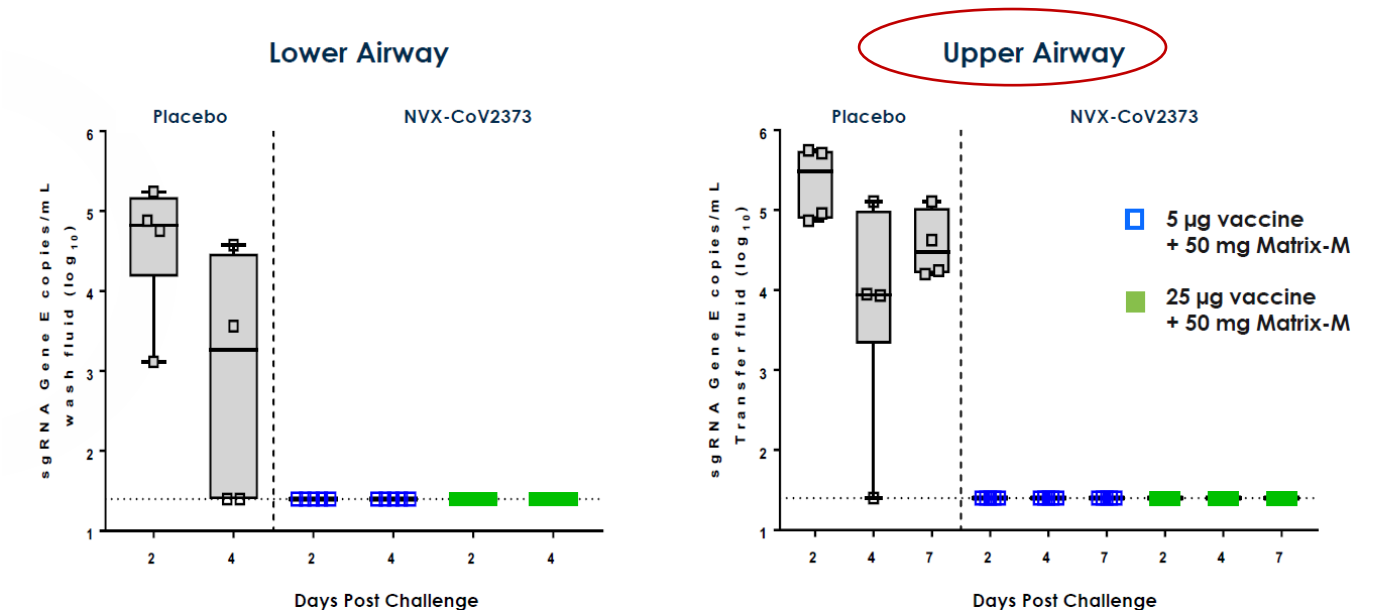
Immunogenicity data from NEJM phase I/II shows increases in immune responses over time, past 28 days

Press release: Phase 3 ENSEMBLE trial

Will vaccines halt transmission? Biological plausibility (4 main reasons)

NVX-CoV2373 Protected Lower & Upper Airways in Rhesus Macaques

No viral replication observed following Day 38 challenge with WT SARS-CoV-2



4. Challenge experiments with macaques in pre-clinical trials show blocking of viral replication (or no/low viral RNA) in BAL and nasal swabs (Mercado Nature J&J vax, 2020; Guebre-Xabier Vaccine Novavax 2020)

1. IgG antibodies measured in trials found in high levels in nasal mucosa

frontiers in IMMUNOLOGY

REVIEW ARTICLE
published: 16 July 2013
doi: 10.3389/fimmu.2013.00200

Antibodies and their receptors: different potential roles in mucosal defense

2. Systemic vaccines induce IgA (mucosal immunoglobulin) and recent study shows mRNA COVID-19 vaccines induce IgA

AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical and Vaccine Immunology

Parenteral Vaccination Can Be an Effective Means of Inducing Protective Mucosal Responses

BIOLOGICAL SCIENCES - ARTICLE

SARS-CoV-2 mRNA vaccines induce a robust germinal centre reaction in humans

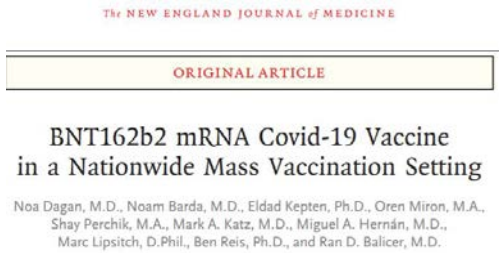
3. Monoclonal antibodies hasten viral clearance from airways

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

March 11, 2021- a year after WHO pandemic declared

REAL-WORLD EVIDENCE CONFIRMS HIGH EFFECTIVENESS OF PFIZER-BIONTECH COVID-19 VACCINE AND PROFOUND PUBLIC HEALTH IMPACT OF VACCINATION ONE YEAR AFTER PANDEMIC DECLARED



- Real-world roll-out data from Ministry of Health Israel, Pfizer vaccine
- 94% of asymptomatic infection prevented
- 97% effective against symptomatic COVID-19 cases, hospitalizations, severe and critical hospitalizations, and deaths
- Unvaccinated individuals 44 times more likely to develop symptomatic COVID-19 and 29 times more likely to die from COVID-19
- 80% of circulating virus during roll-out was B117 variant

Clinical Infectious Diseases

ACCEPTED MANUSCRIPT

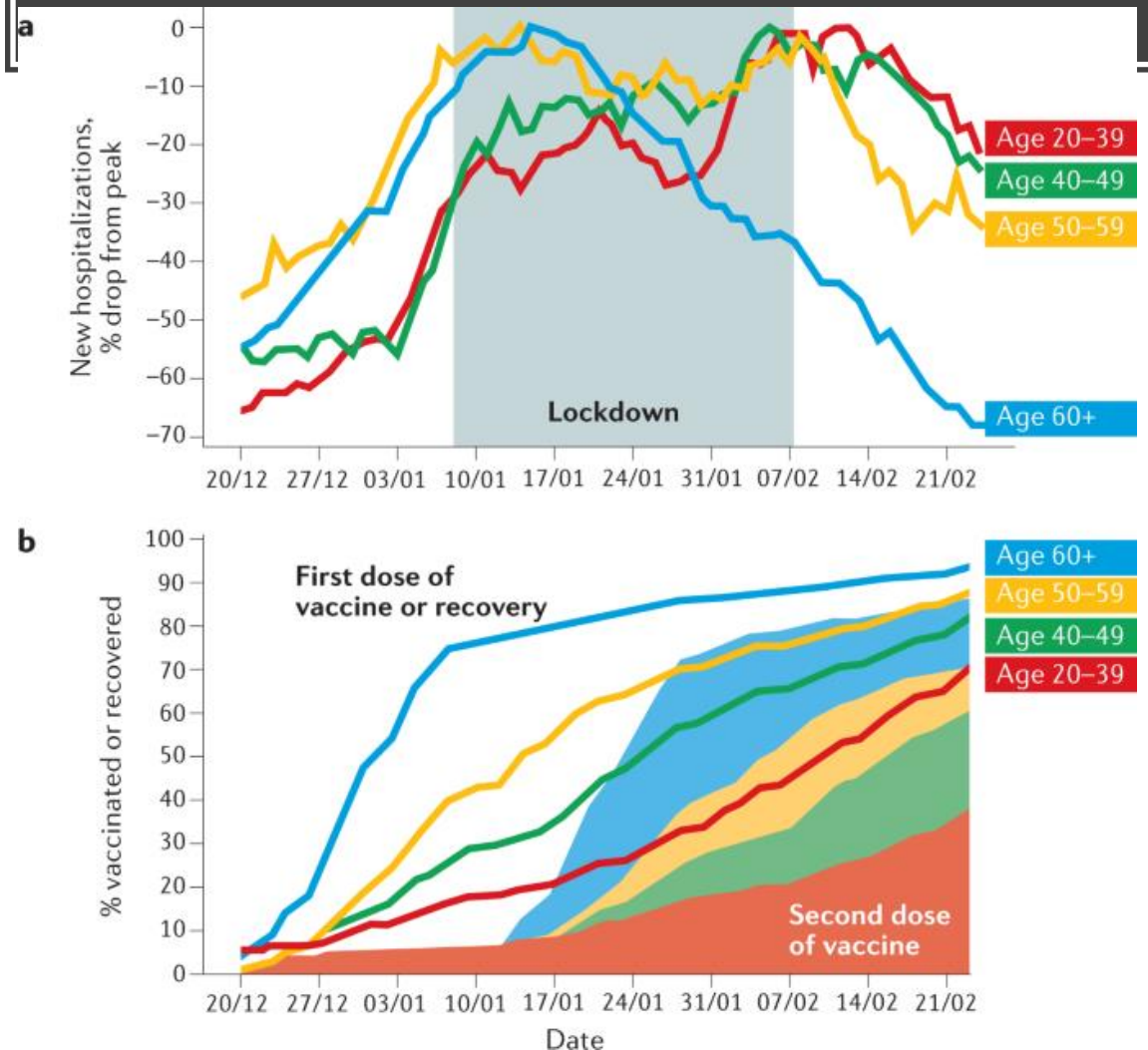
Impact of the COVID-19 Vaccine on Asymptomatic Infection Among Patients Undergoing Pre-Procedural COVID-19 Molecular Screening

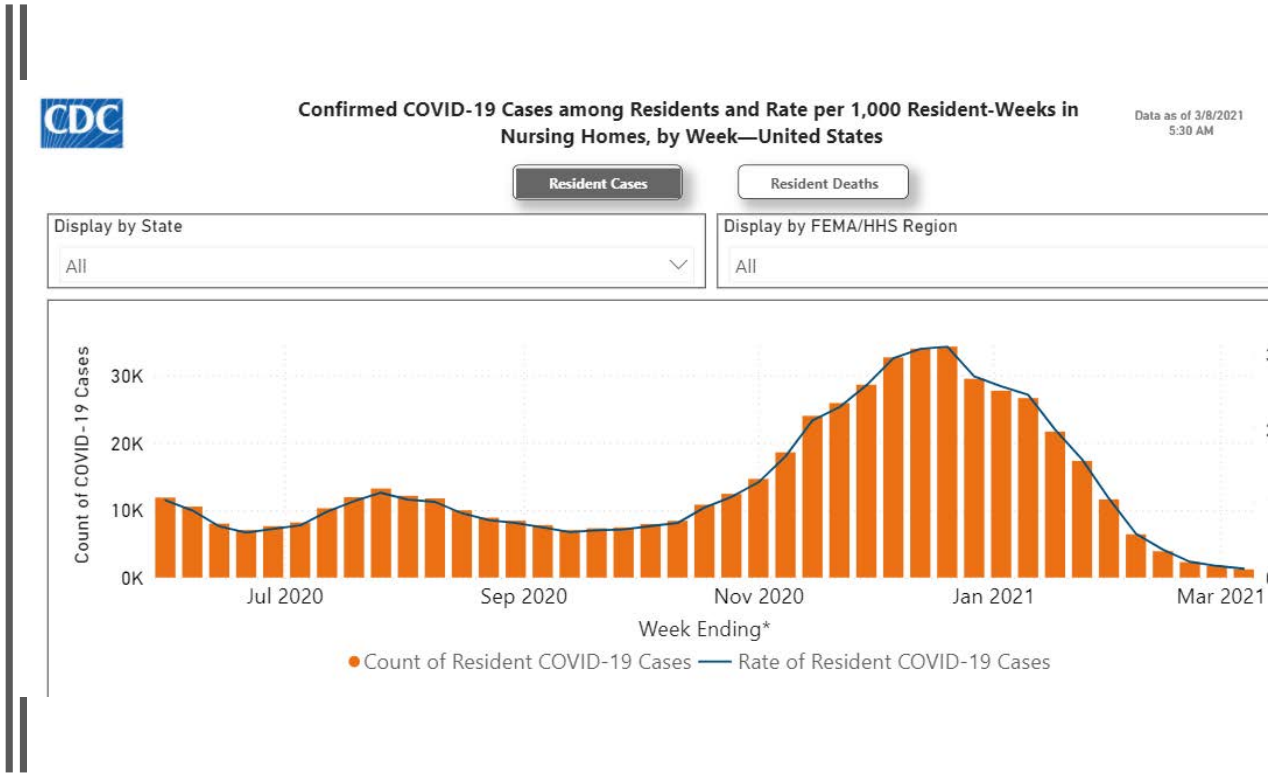
Aaron J Tande, MD ✉, Benjamin D Pollock, PhD, MSPH, Nilay D Shah, PhD,

- Swabbed pre-operative patients across the Mayo Clinic system
- Risk of asymptomatic infection was 80% lower after even 1 dose (and still after 2 doses) of mRNA vaccine than those unvaccinated
- As expected, symptomatic and asymptomatic infection reduced by vaccines

Seven Studies to date that showed COVID-19 vaccines reduce asymptomatic infection (transmission)		
Setting	Finding of xx% reduction in asymptomatic or infections that included asymptomatic	Reference
Healthcare workers in England	**86%**	**Hall SSRN, February 22, 2021**
Healthcare workers in Israel	**75%**	**Amit, Lancet, March 6, 2021**
Patients in Mayo Clinic health system	**88.7%**	**Pawlowski medRxiv, February 27, 2021**
Israel Ministry of Health (nationwide) Israel general population (Pfizer)	**94%** **90%**	**Pfizer press release, March 11, 2021** **Dagan NEJM, February 24, 2021**
Pre-surgical patients in Mayo Clinic health system	**80%**	**Tande Clin Inf Dis, March 10, 2021**
Healthcare workers in Cambridge University Hospitals	**75%**	**Weekes Authorea, February 24, 2021**
Moreover, nasal viral loads from post-vaccination exposures are low and likely noninfectious per CT values (use rapid Ag test)		

Real-world data amazing (US, UK, Israel)





Shiloh Nature Immunology Review 3/12/21; CDC Tracker

Will vaccines work against variants?

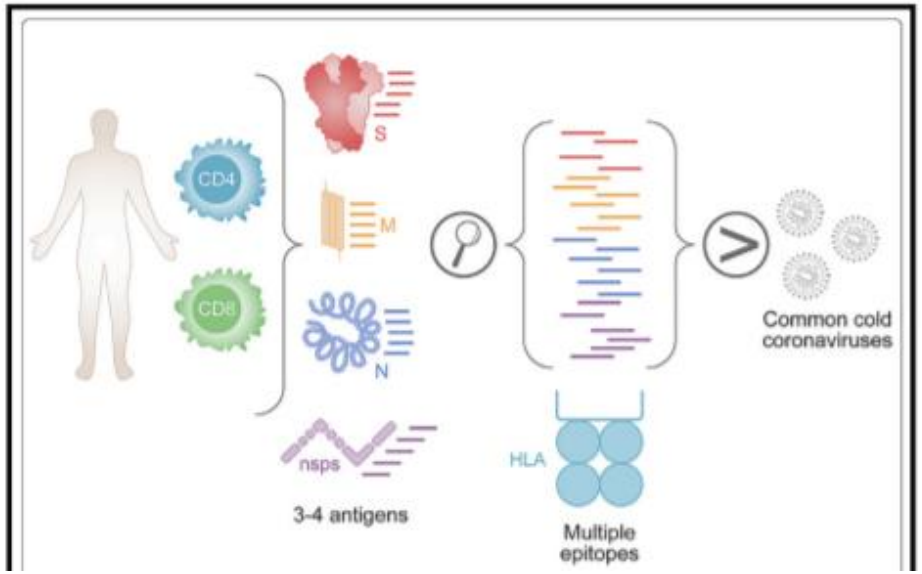
Why T cell response will work against variants? First look at natural infection

Cell Reports
Medicine

Article

Comprehensive analysis of T cell immunodominance and immunoprevalence of SARS-CoV-2 epitopes in COVID-19 cases

Graphical Abstract



Authors

Alison Tarke, John Sidney, Conner K. Kidd, ..., Daniela Weiskopf, Alba Grifoni, Alessandro Sette

Correspondence

agrifoni@lji.org (A.G.), alex@lji.org (A.S.)

In Brief

Tarke et al. show a broad T cell repertoire, suggesting that viral escape of T cell immunity is unlikely. CD4 immunodominant regions correlate with

Broad T cell repertoire (>19 CD4 epitopes; 17 CD8 epitopes) after infection. Means viral escape of T cell-immunity (from both natural infection and vaccination) unlikely, re-infection if happens mild

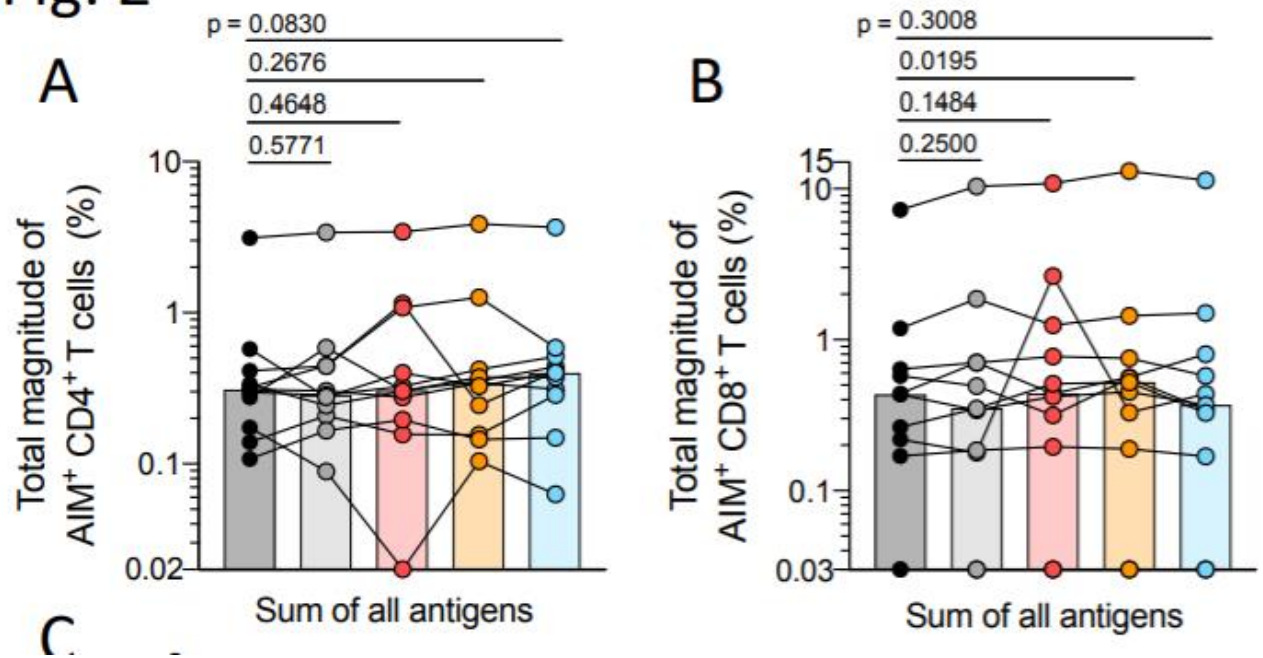
Then look at T-cell response to variants after vaccines- still intact

bioRxiv
THE PREPRINT SERVER FOR BIOLOGY

Negligible impact of SARS-CoV-2 variants on CD4+ and CD8+T cell reactivity in COVID-19 exposed donors and vaccinees.

Alison Tarke, John Sidney, Nils Methot, Yun Zhang, Jennifer M Dan, Benjamin Goodwin, Paul Rubiro,

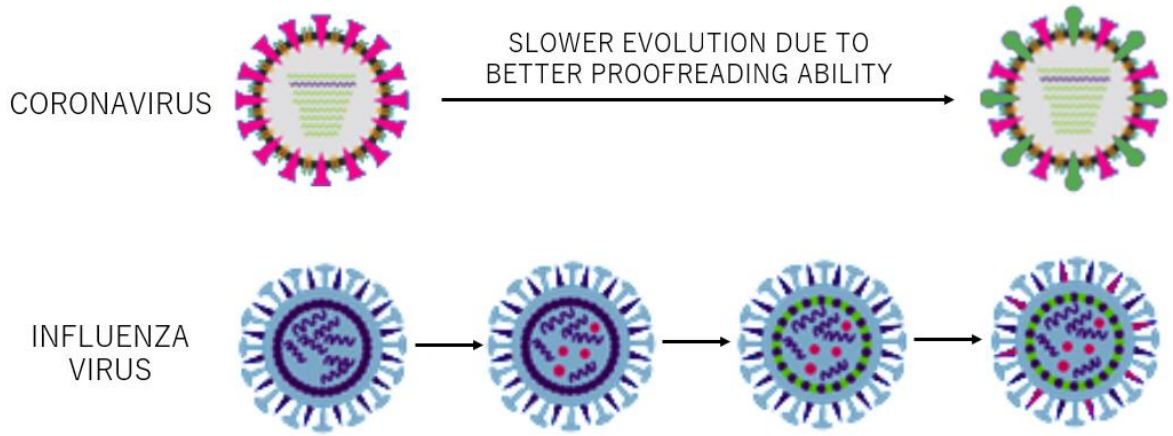
Fig. 2



- Looked at SARS-CoV-2-specific CD4+ & CD8+ T cell responses from those with natural infection with non-variant, compared to variants B.1.1.7, B.1.351, P.1, CAL.20C
- No difference seen between pool of spike protein peptides corresponding to ancestral sequence & those from variants
- T cell reactivity against those pools from variants remained intact if you had mRNA vaccination (Pfizer/Moderna) (or natural infection)

Why not to worry clinically too much about variants

- This is what RNA viruses do, mutate more readily than DNA viruses
- SARS-CoV-2 doesn’t mutate that fast, it is just transmitted a lot
- Neutralizing Ab titer information from Moderna/ Pfizer vaccines reassuring
- T cell responses and B cells and antibodies all elicited by vaccines; reassuring data about no hospitalizations/deaths in J&J (Brazil, S. Africa UK) and AZ trial (included Brazil, South Africa) and Novavax (S. Africa) suggests T cells mediating protection against severe infection
- mRNA vaccines and DNA vaccines can be readily “tweaked” (as they are being) from companies to code for new variant ‘boosters’ in future



That said, we want to tamp down transmission to increase efficacy of vaccine- peel off restrictions slowly!

COVID-19

By A. David Paltiel, Jason L. Schwartz, Amy Zheng, and Rochelle P. Walensky

DOI: 10.1377/hlthaff.2020.02054
HEALTH AFFAIRS 40, NO. 1 (2021): 42–52

Clinical Outcomes Of A COVID-19 Vaccine: Implementation Over Efficacy

Fauci urges COVID vaccinations to stop new strains: 'Viruses cannot mutate if they don't replicate'

Want to Motivate Vaccinations? Message Optimism, Not Doom

Monica Gandhi

OPINION ESSAY | COVID-19

- Vaccine optimism can reduce vaccine hesitancy
- Public is savvy enough to understand tiered messaging
- Philosophy of “give an inch, they will take a mile” is not harm reduction
- Lessons from HIV (“serosorting”)- we (or least the good ones) never messaged abstinence

CDC guidelines – March 8, 2021

Vaccinated and vaccinated? → Feel free to mingle with each other without restrictions

Importantly, no need to quarantine if exposed after vaccination if no symptoms

Vaccinated around unvaccinated and public? → Ok if privacy of home with non-susceptible persons; Keep masks, distancing in public; social norms

Unvaccinated and unvaccinated? → Keep all usual restrictions

European Commission @EU_Commission · Jan 18

"I'll do it to protect my father and organise a big family weekend get-together."

Prof. Dr. Steven Van Gucht,
Chief Scientific Adviser,

IDEAS

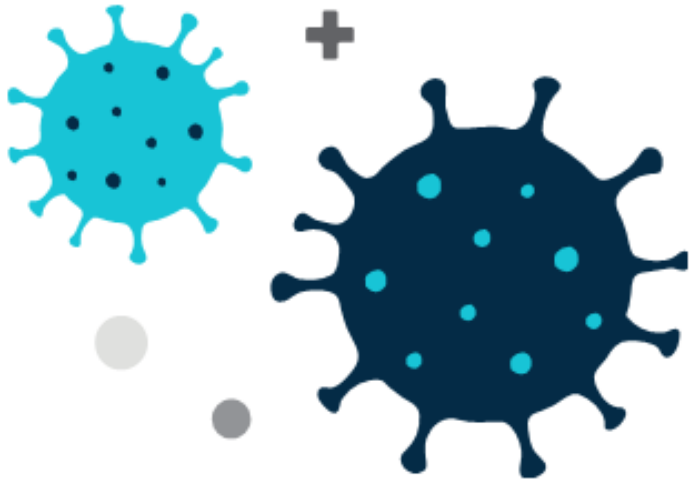
Vaccinated People Are Going to Hug Each Other

The vaccines are phenomenal. Belaboring their imperfections—and telling people who receive them never to let down their guard—carries its own risks.

JANUARY 27, 2021

Julia Marcus
Epidemiologist and professor at Harvard Medical School

Summary



- Vaccine trials show amazing efficacy and safety
- All vaccines reduce severe disease significantly, likely due to T-cell response – love the T cell
- Vaccines are almost certain to decrease transmission
- Variants can be managed- don’t worry
- Vaccine messaging can be tiered and optimistic