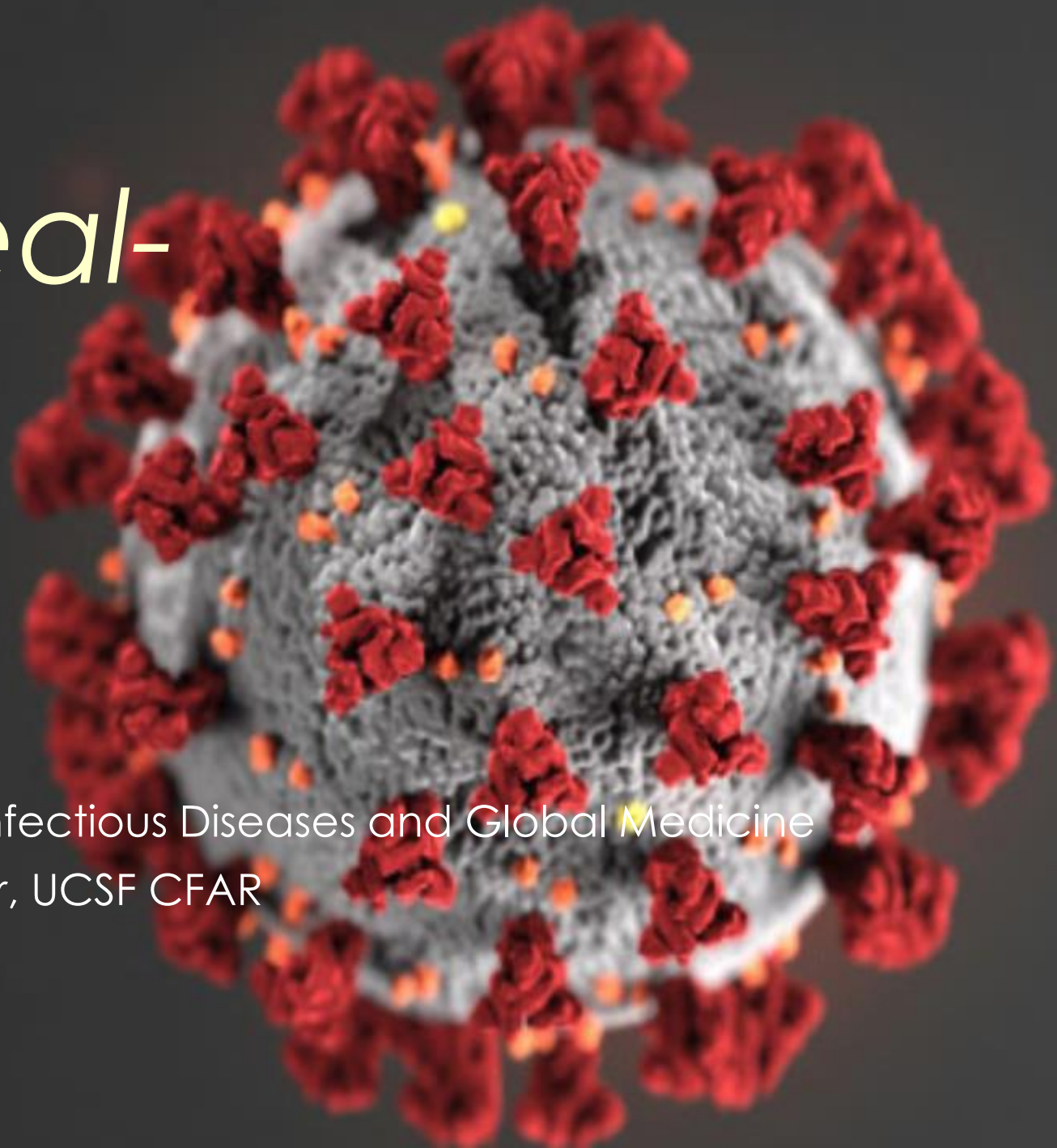
COVID-19 vaccines: Real-world data



Monica Gandhi MD, MPH
Professor of Medicine, Division of HIV, Infectious Diseases and Global Medicine
Medical Director, Ward 86 and Director, UCSF CFAR
April 28, 2021

Disclosure

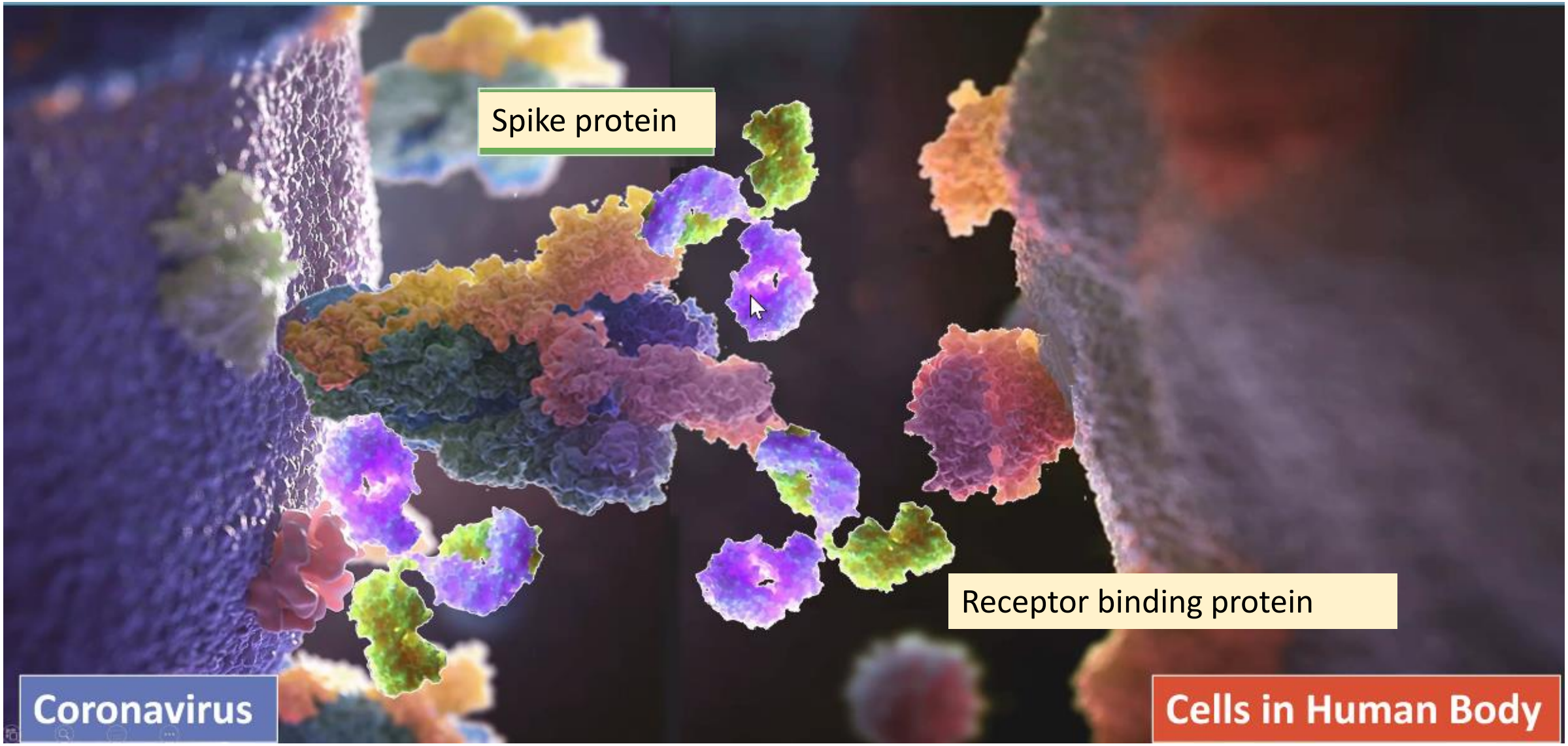
- Neither I nor any member of my immediate family has a financial relationship or interest (currently or within the past 12 months) with any proprietary entity producing health care goods or services consumed by, or used on, patients related to the content of this CME activity.

- I do not intend to discuss an unapproved/investigative use of a commercial product/device.

Company or name	Form of publication for phase 3 data	Reference
moderna	Peer reviewed publication	Baden NEJM, Feb 4, 2021
Pfizer	Peer reviewed publication	Polack NEJM, December 31, 2020
Johnson & Johnson	Press release only	J&J press release January 29, 2021; FDA document Feb 24
AstraZeneca	Two peer-reviewed publications but ongoing	Voysey Lancet December 8, 2020; Preprint Feb 1, 2021
NOVAVAX Creating Tomorrow's Vaccines Today	Press release and abstract only (phase 3 UK; phase 2b S. Africa)	Novavax press release 1/28 and NYAS abstract 2/2/21
Sputnik V	Peer-reviewed publication	Logunov Lancet, February 2, 2021
sinovac	Press release (scanter details)	Sinopharm, January 16, 2021
SINOPHARM	Press release (scanter details)	Sinovac, February 5, 2021
BHARAT	Press release (scanter details)	Bharat Covaxin, March 3, 2021

There are actually 9 vaccines out there for COVID-19, three authorized in U.S.

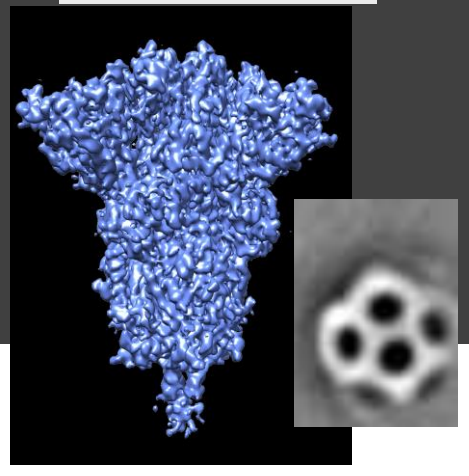
6 vaccine candidates to date involve spike protein and receptor binding domain of SARS-CoV-2 - either mRNA or adenoviral-vector DNA vaccines or protein adjuvant itself; 2 inactivated virus

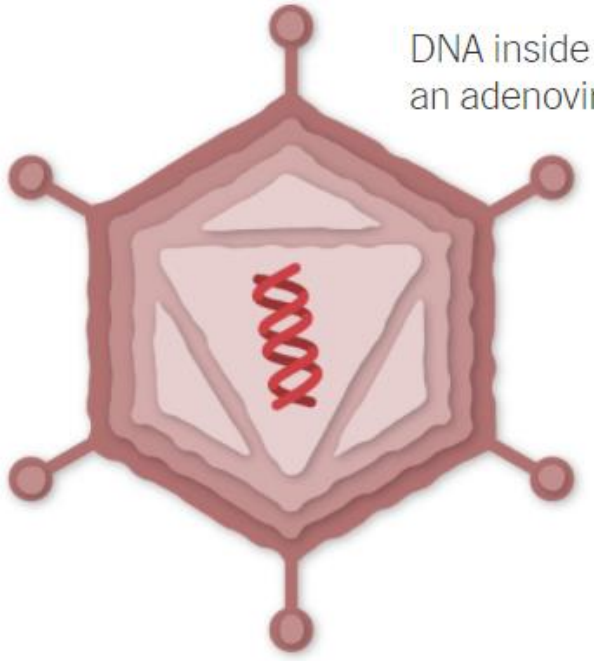


Three types of vaccines involving spike protein

- mRNA vaccines (2)
- Adenoviral vector DNA vaccines (3)
- Spike protein + M-adjuvant vaccine (1)

NOVAVAX
Creating Tomorrow's Vaccines Today

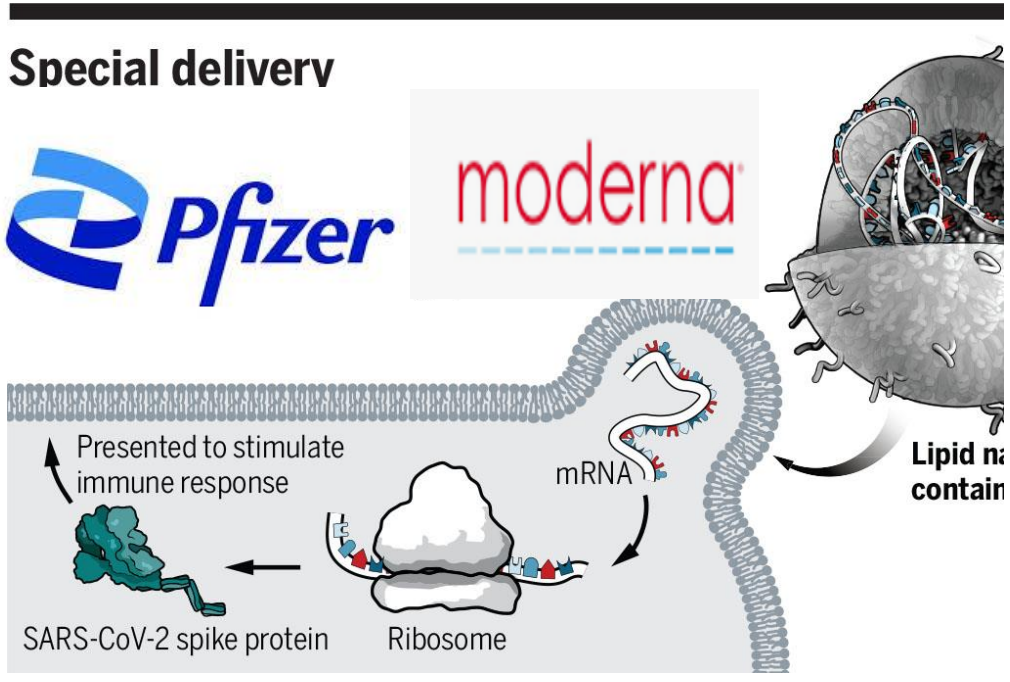




Johnson & Johnson

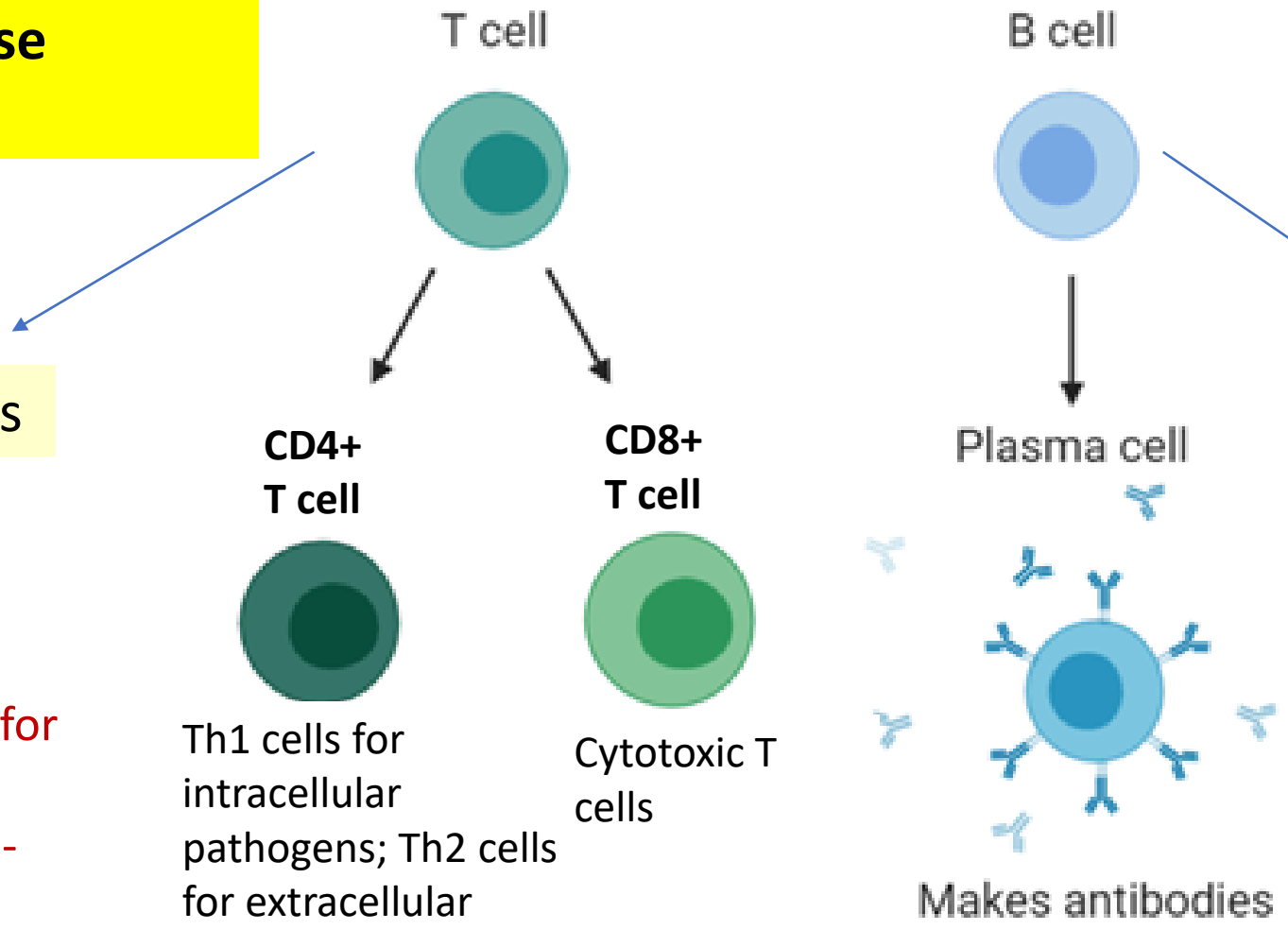
AstraZeneca

Sputnik V



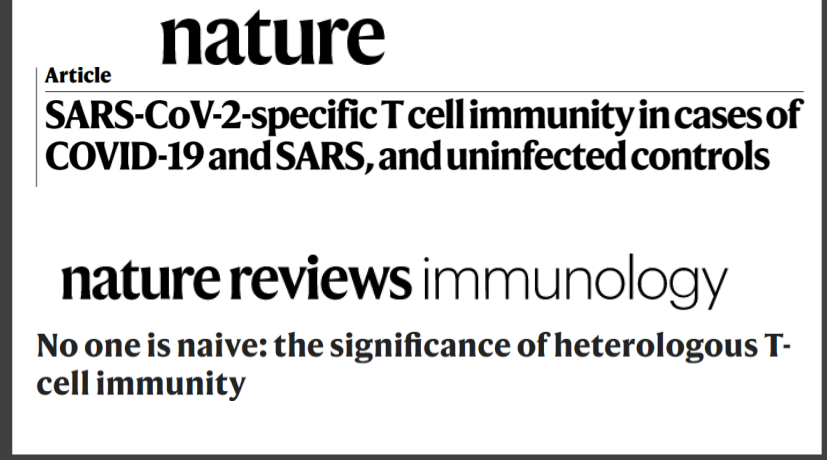
Remember immunity -antibodies and cell-mediated

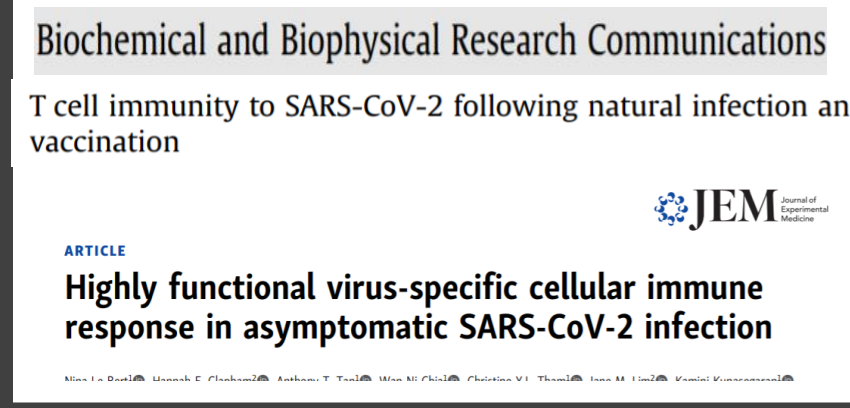
T cells are the major immune defense against viruses

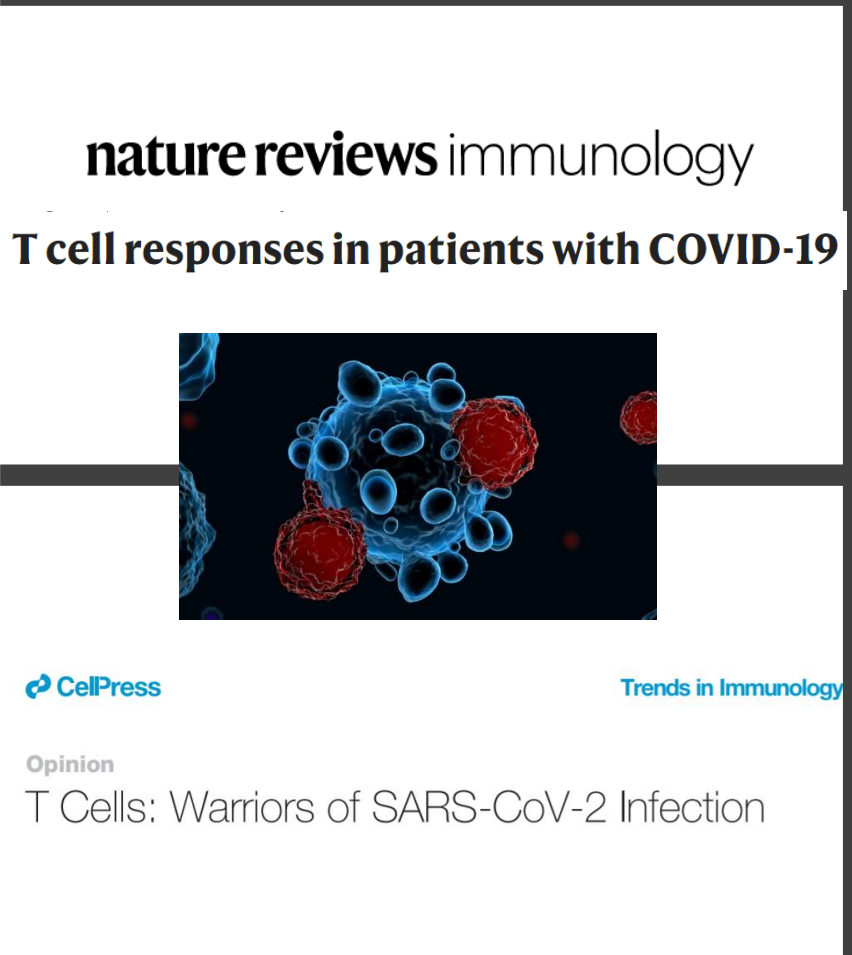


Of note, want Th1:Th2 ratio >>1 for viruses; Th2 CD4s block antiviral Th1-CD4s and CD8s

Most vaccine trials measured antibodies and T cell responses





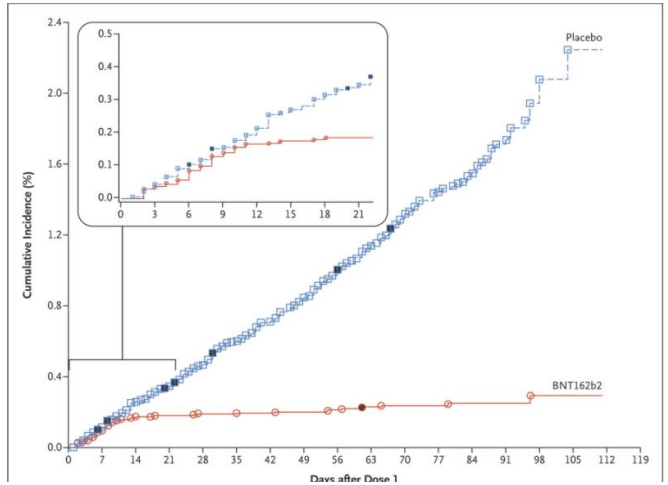


How does functional T-cell response modulate severity of disease?

- 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!

Company	Platform	Doses	Non-clinical results	# with vaccine (same placebo)	Protection from COVID-19 hospitalization	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+ protection from challenge (macaques)	~15,000	90% (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 (95% B1.351)
AstraZeneca	AZD 1222 Non-replicating Chimp Adenovirus-DNA	2	Neutralizing Abs; Strong Th1 CD4+ > Th2; CD8+; protection from challenge (macaques)	~28,588 (UK, SA, US/Peru/ Chili)	100%	100% (UK, 15 placebo arm hospitalized, 0 in vaccine; US, 8 severe in placebo, 0 vaccine)	76% US (85% in >65 yrs); 70% UK; S. Africa halted for mild
NOVAVAX Creating Tomorrow's Vaccines Today	NVX-CoV2373 Spike protein/RBD + Matrix M adjuvant	2	Neutralizing Abs; Strong Th1 CD4 > Th2; macaque challenge protection	~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%

Two mRNA vaccines clinical trials



Pfizer

- 2 shots, 3 weeks apart
- Trial participants: half female, 83% White; 9.9% African America; 28% Hispanic/Latino
- 21% >65 years
- Some risk factors for severe illness: obesity (35%), diabetes 8%; pulmonary disease 8%
- 170 symptomatic COVID-19, 162 in placebo arm and 8 in vaccine arm so 95% effective
- 9 cases of severe disease all in placebo

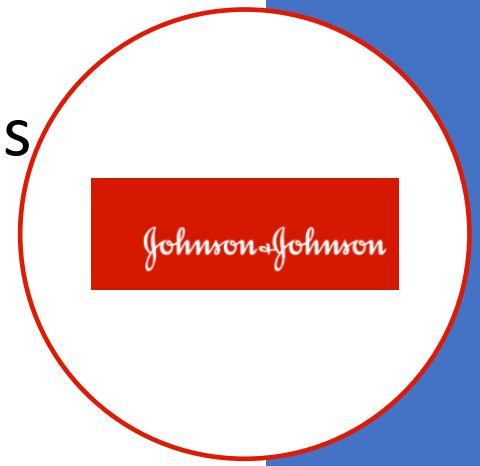
moderna

- 2 shots, 4 weeks apart
- ~half female, 36.5% of participants communities of color
- 25%, ≥65 years of age
- Some risk factors for severe illness, including obesity (mean BMI 29.3)
- 196 symptomatic COVID-19, 185 in placebo arm and 11 in vaccine arm so 94.1% effective
- 30 cases of severe disease in placebo; 1 in vaccine arm

NEJM 2020

Johnson and Johnson 1-dose phase 3 trial

- 43,783 participants, 44% from US, 41% Central and South America, 15% South Africa
- 59% White; 45% Hispanic and/or Latinx; 17.2% AA or African; 9% Native American, 3% Asian
- 41% risk factors for severe illness, e.g. obesity or diabetes
- 486 cases symptomatic COVID-19
- All hospitalizations (16) and deaths (9) from COVID-19 in placebo arm
- High efficacy against variants (95% B.1.351 S. Africa; 69% P1 Brazil) and 85% effective against all severe disease
- Variable against mild disease (72% U.S., 64% in South Africa, 61% Latin America)



Press release: Phase 3 ENSEMBLE trial; FDA document February 24, 2021

Will vaccines work against variants?
Short answer: yes

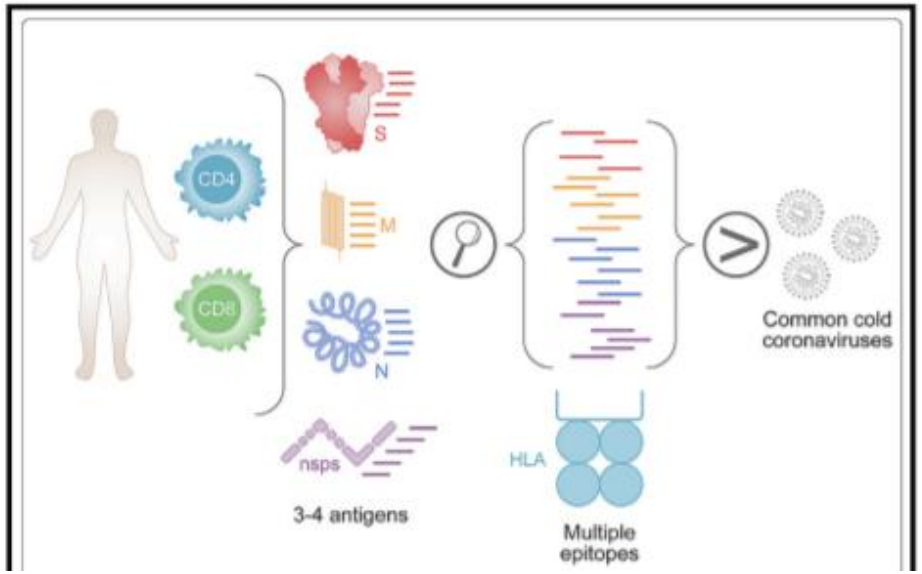
Why T cell response will work against variants? First look at natural infection

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

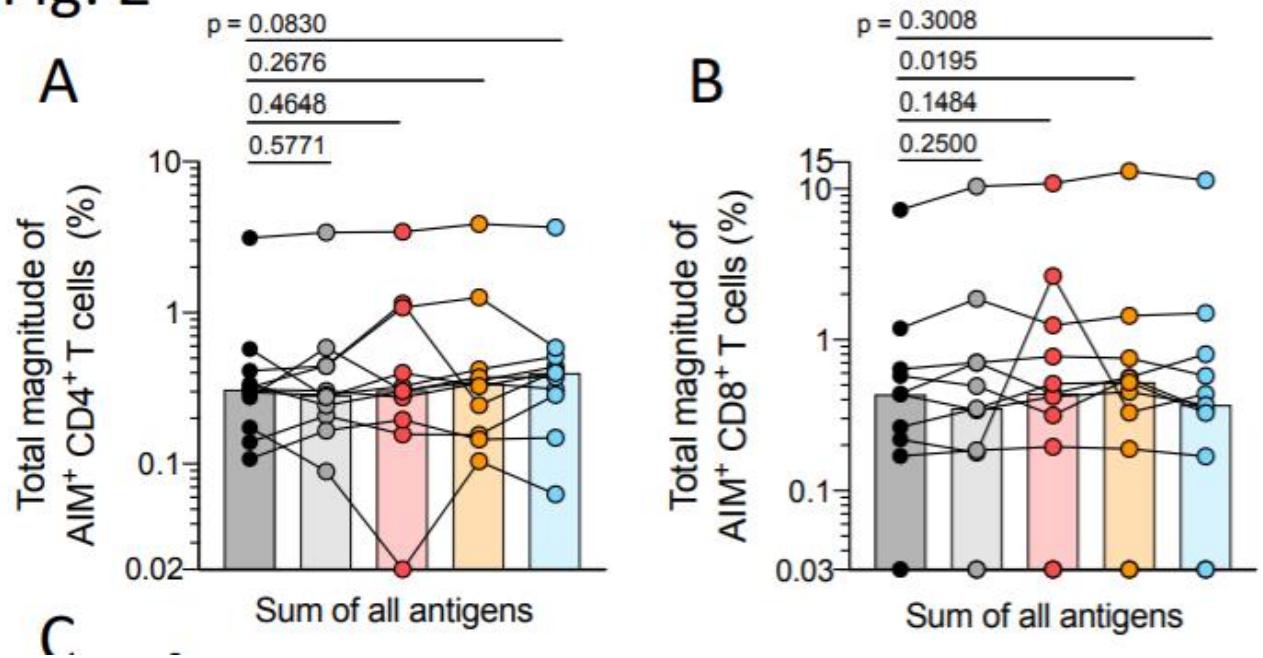
Then look at T-cell response to variants after vaccines- still intact

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 & examined activity against B.1.1.7, B.1.351, P.1, CAL.20C
- T cell reactivity against those variants remained intact if you had natural infection or mRNA vaccination (Pfizer/Moderna)
- CD4/CD8 responses in South Africa AztraZeneca trial[1] showed 75 out of 87 T cell epitopes in the spike protein remained unaffected by B.1.351 mutations

[1]Madhi. NEJM. March 16, 2021

National Institutes of Health
Turning Discovery Into Health

NEWS RELEASES

ACCEPTED MANUSCRIPT

CD8+ T cell responses in COVID-19 convalescent individuals target conserve epitopes from multiple prominent SARS-CoV-2 circulating variants

Andrew D Redd ✉, Alessandra Nardin, Hassen Kared, Evan M Bloch,

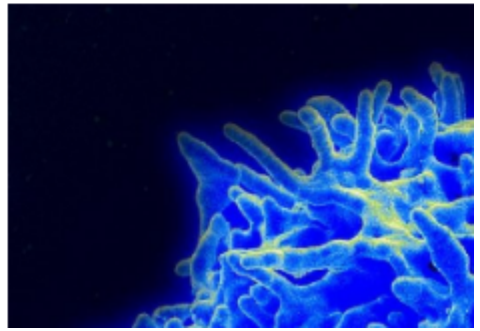
Tuesday, March 30, 2021

T cells recognize recent SARS-CoV-2 variants

52 epitopes for CD8 cells after infection & 51/52 preserved against B.1.351, B.1.1.7, P.1

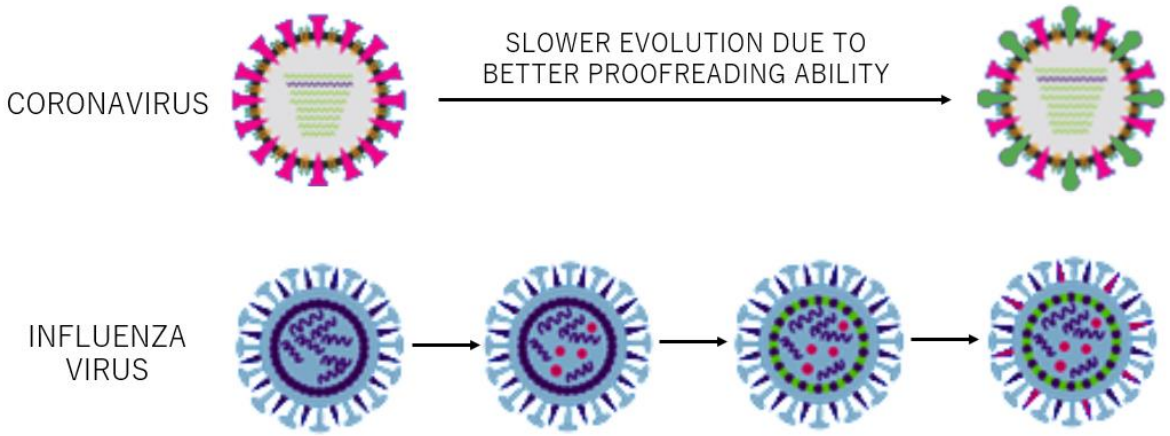
What

When variants of SARS-CoV-2 (the virus that causes COVID-19) emerged in late 2020, concern arose that they might elude protective immune responses generated by prior infection or vaccination, potentially making



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
- T cell responses preserved against variants
- mRNA vaccines and DNA vaccines can be readily "tweaked" (as they are being) from companies to code for new variant 'boosters' in future if needed (don't think needed)

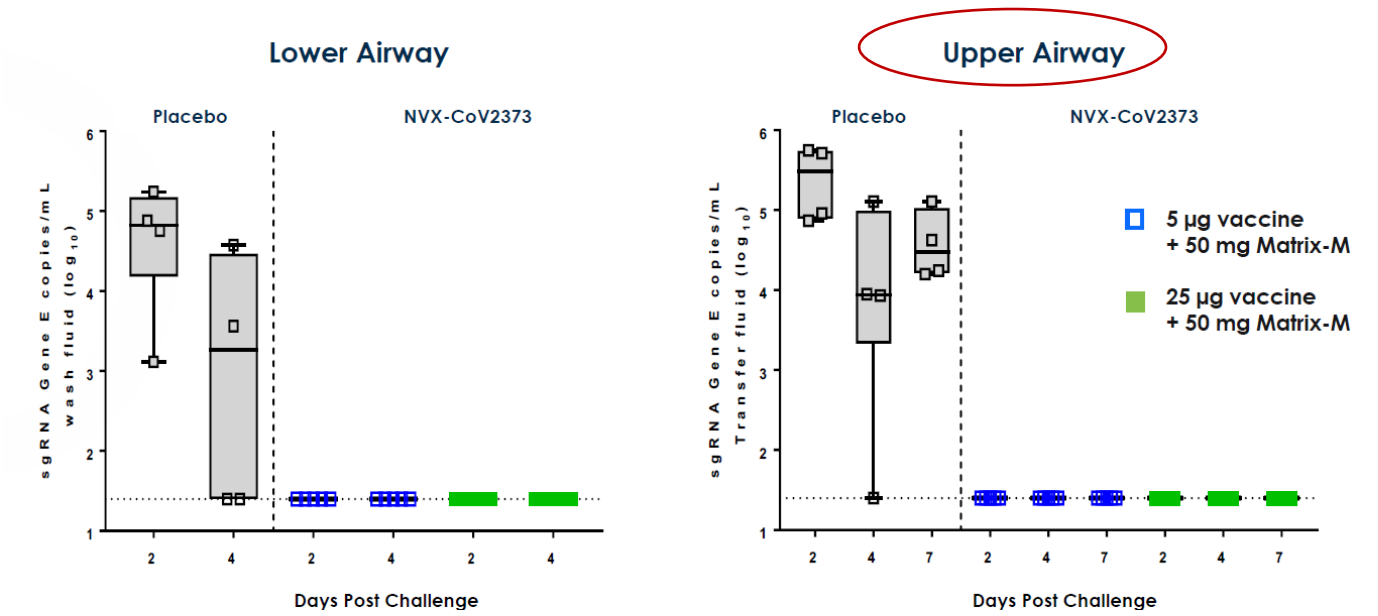


Do vaccines reduce transmission?
Short answer: yes

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

NVX-CoV2373 Protected Lower & Upper Airways in Rhesus Macaques

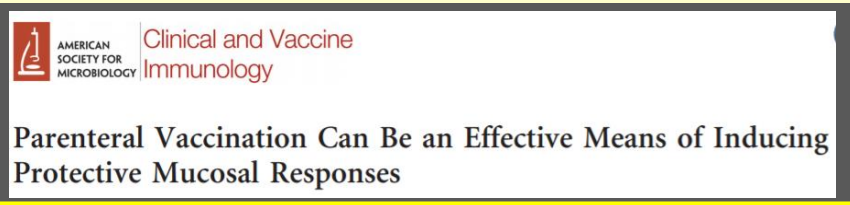
No viral replication observed following Day 38 challenge with WT SARS-CoV-2

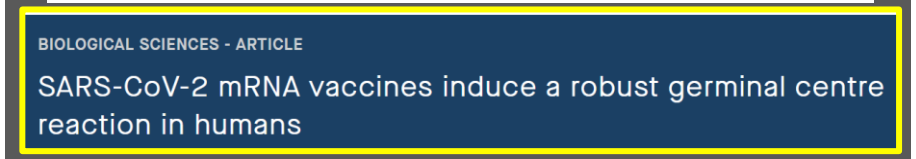


4. Challenge experiments with macaques in pre-clinical trials show blocking of viral replication (or no/low viral RNA) in BAL and nasal swabs (Mercado Nature J&J vax, 2020; Guebre-Xabier Vaccine Novavax 2020)

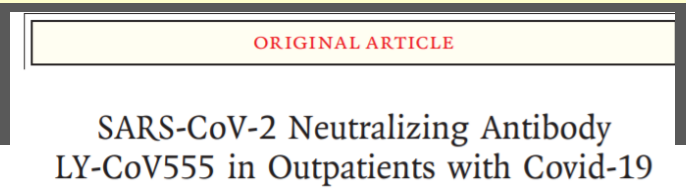
1. IgG antibodies measured in trials found in high levels in nasal mucosa

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





3. Monoclonal antibodies hasten viral clearance from airways



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

Studies to date that showed COVID-19 vaccines reduce asymptomatic infection (transmission)

Setting	Finding of xx% reduction in asymptomatic	Reference
Healthcare workers in England	**85%**	**Hall Lancet, April 23, 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% (largest study)** **90%**	**Pfizer press release, March 11, 2021 (and Goldberg Medrxiv, April 24, 2021)** **Dagan NEJM, February 24, 2021**
Pre-surgical patients in Mayo Clinic system swabbed asymptomatically	**80%**	**Tande Clin Inf Dis, March 10, 2021**
Healthcare workers in Cambridge University Hospitals	**75%**	**Weekes Authorea, February 24, 2021**
First-line responders and HCWs in US	**90%**	**Thompson A. MMWR, March 30, 2021**
Israel population (>16) with children unvaccinated	**For every 20-point increase in adult vaccination, rates of kids testing positive halves**	**Milman O. Medrxiv. March 31, 2021**
Long-term care facility, Spain	**90%**	**Salazar P. Medrxiv. April 13, 2021**
Nursing home, U.S.	**100%**	**Cavanaugh MMWR, April 21, 2021**

Nasal viral load values are most important determinant of transmissibility (Lancet study); Nasal viral loads from post-vaccination exposures are low and likely noninfectious per CT values (use rapid antigen tests after vaccination if want to test symptomatic)

March 30, 2021

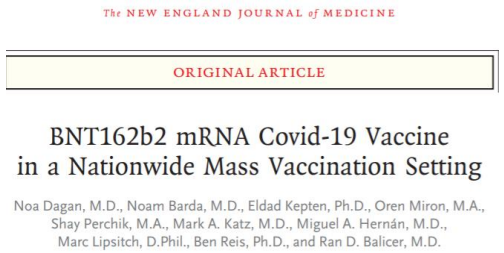
CDC Director Dr. Rochelle Walensky: "Our data from the CDC today suggest that vaccinated people do not carry the virus."

What do real world studies show us?
Vaccine effectiveness even better than efficacy

March 11, 2021- a year after WHO 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

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


The NEW ENGLAND JOURNAL of MEDICINE

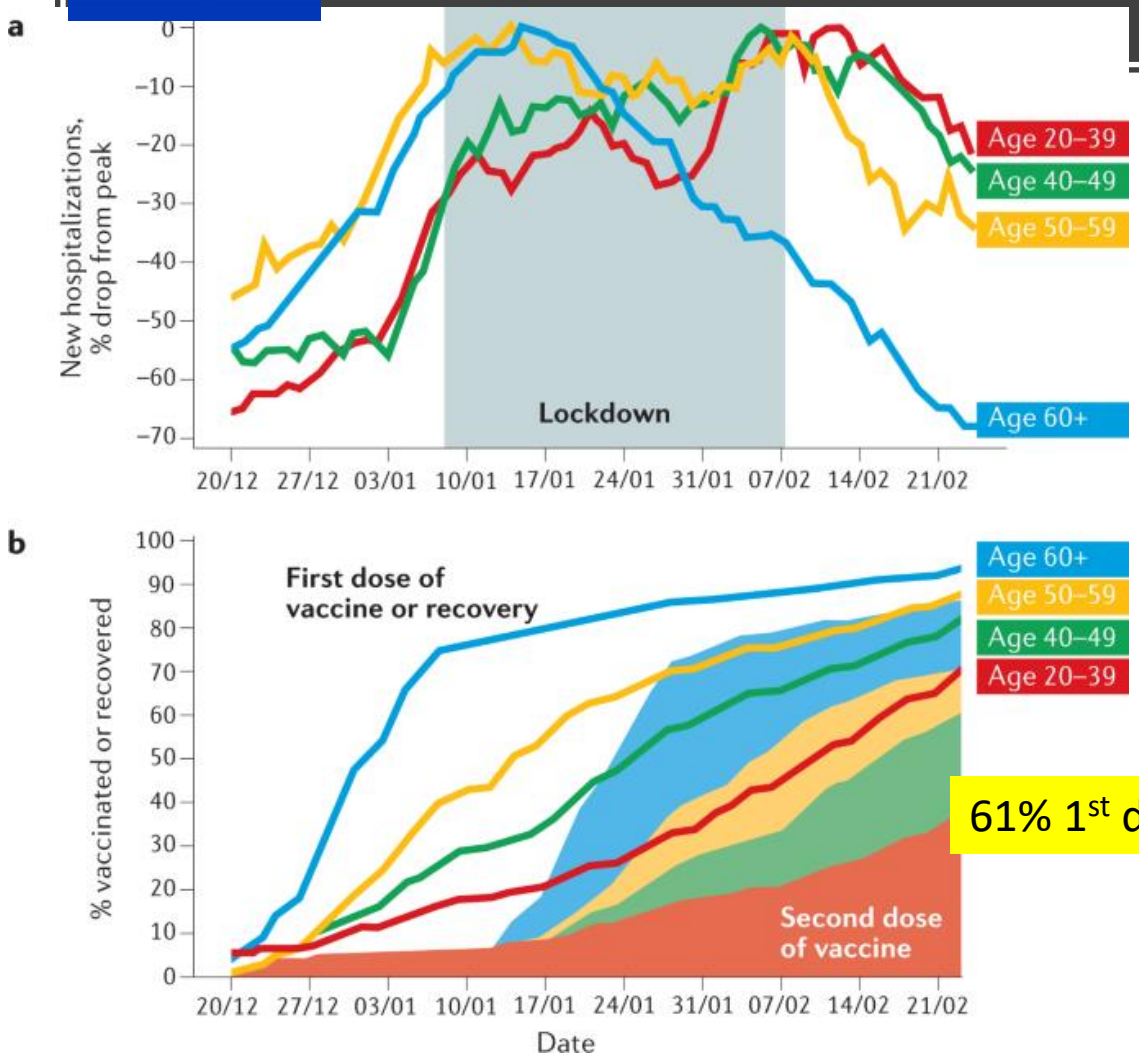
ORIGINAL ARTICLE

BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting

Noa Dagan, M.D., Noam Barda, M.D., Eldad Kepten, Ph.D., Oren Miron, M.A., Shay Perchik, M.A., Mark A. Katz, M.D., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Ben Reis, Ph.D., and Ran D. Balicer, M.D.

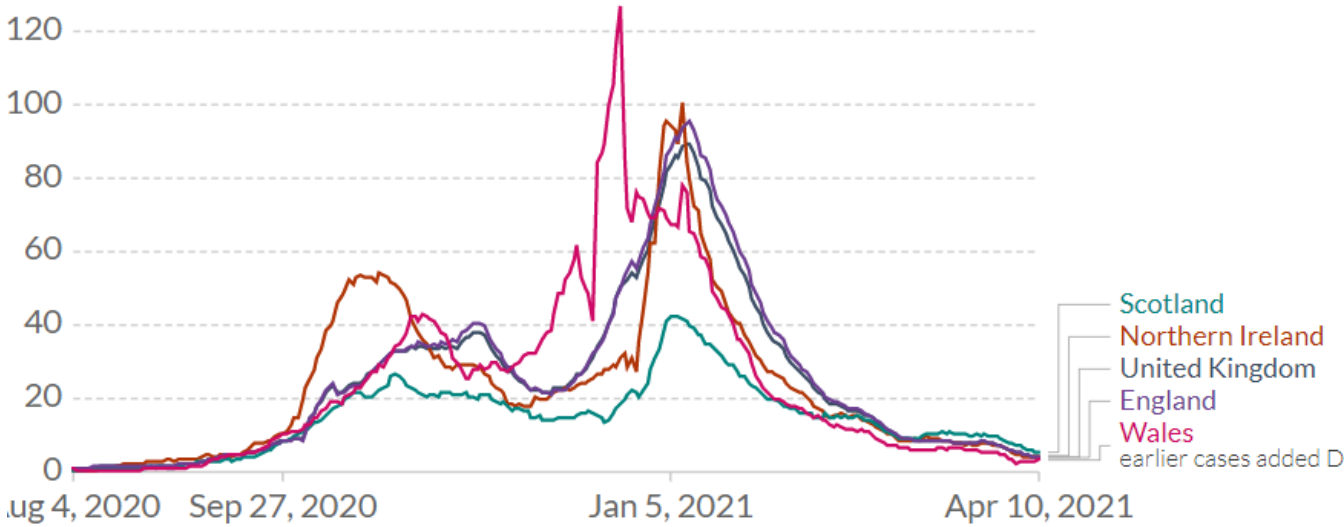
Real-world data amazing (UK, Israel fastest vaccinators)

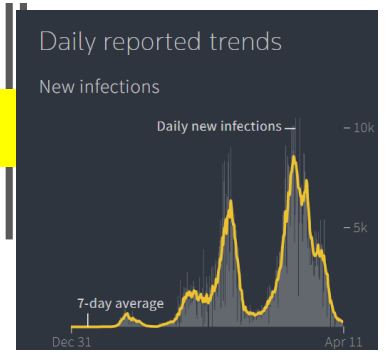
Shiloh Nature Immunology Review



61% 1st dose

51% 1st dose

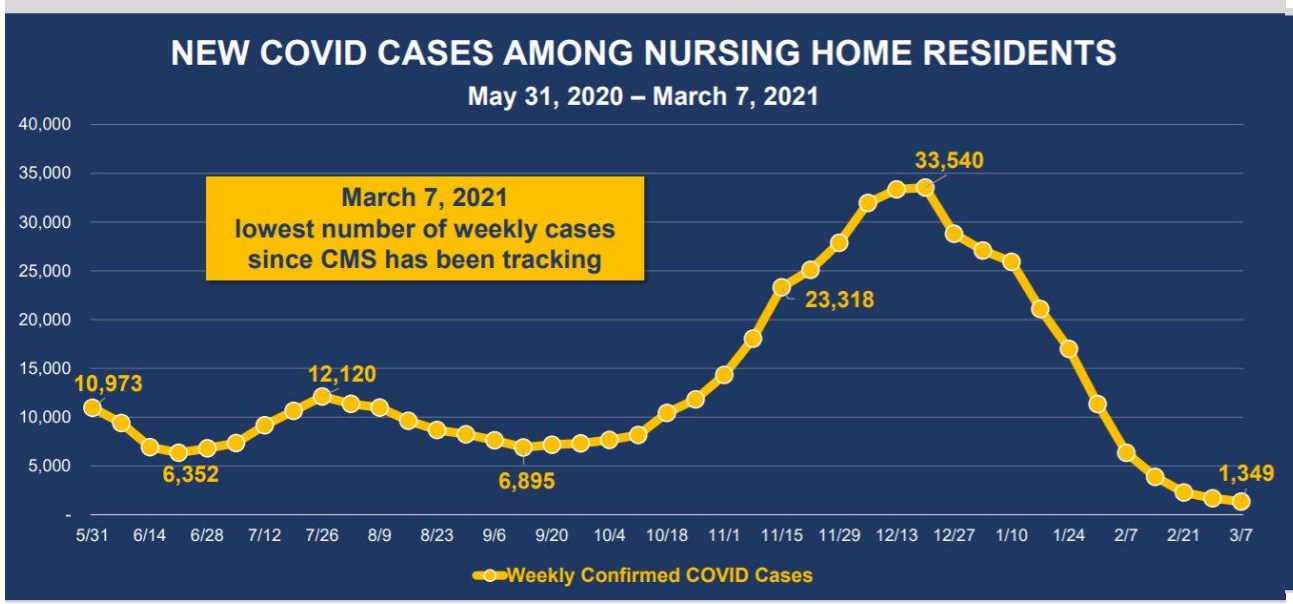


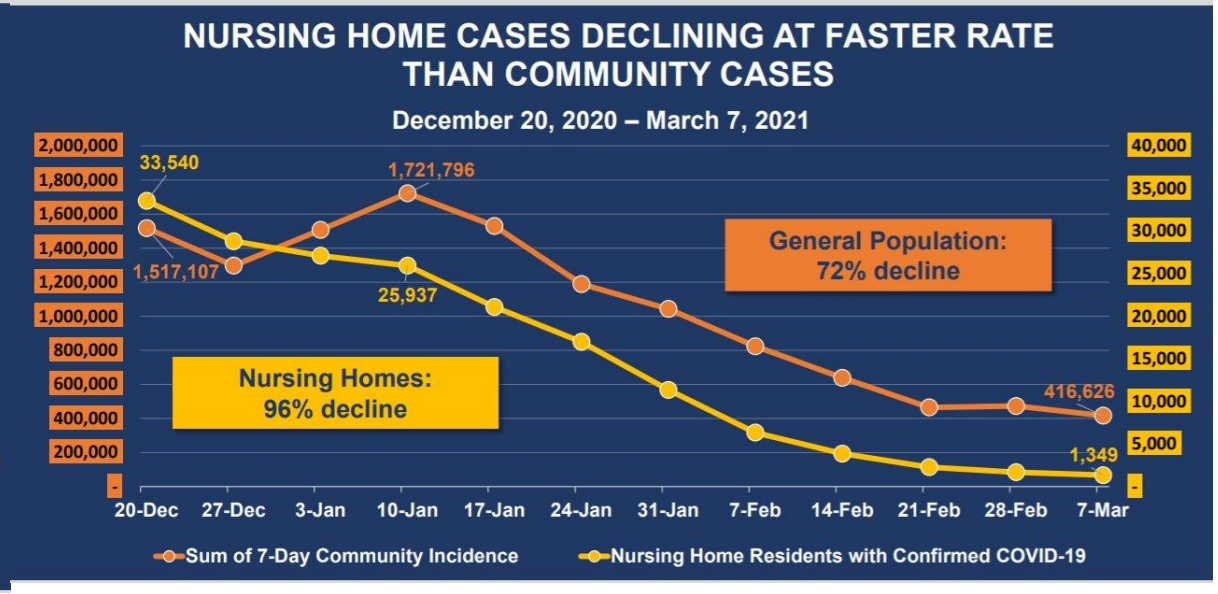


Israel has 4 cases per 100K population; UK has 4.2 per 100K (actually so does CA)

This is what mass vaccinated settings look like in the U.S.

Nursing homes





March 30, CMA data

The NEW ENGLAND JOURNAL of MEDICINE

March 23, 2021

CORRESPONDENCE

SARS-CoV-2 Infection after Vaccination in Health Care Workers in California

UCSD and UCLA began vaccinating HCWs December 16, 2020
Weekly asymptomatic testing at UCSD
Optional asymptomatic testing program at UCLA

379 Vaccinated HCWs tested positive between Dec 16 – Feb 9

- 71% tested positive within the first 2 weeks after 1st dose
- 7 out of 14,990 HCWs who were > 2 weeks after 2nd dose tested positive (0.05%)

Keehner et al, *NEJM* 2021; Daniel et al, *NEJM* 2021

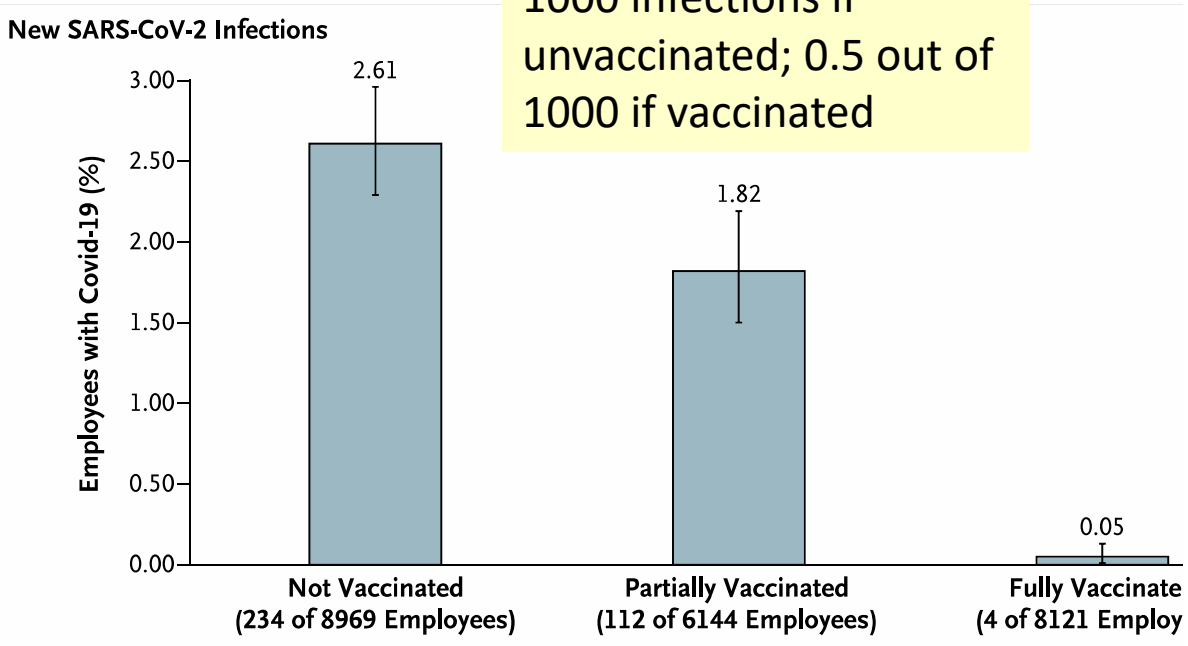
CORRESPONDENCE

Early Evidence of the Effect of SARS-CoV-2 Vaccine at One Medical Center

Evaluation of SARS-CoV-2 infections at UT Southwestern
December 15 – January 28 by vaccination status

- 4/8121 fully vaccinated employees (0.05%)

To put simply, 26 out of 1000 infections if unvaccinated; 0.5 out of 1000 if vaccinated



Morbidity and Mortality Weekly Report (*MMWR*)

CDC

Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March 2021

Early Release / March 29, 2021 / 70

To put simply, 161 COVID infections out of 1000 unvaccinated; 1 out of 1000 if vaccinated

April 1 press release, 100% effectiveness in real-world against severe disease even against B.1.351

Pfizer and BioNTech Confirm High Efficacy and No Serious Safety Concerns Through Up to Six Months Following Second Dose in Updated Topline Analysis of Landmark COVID-19 Vaccine Study

- *Analysis of 927 confirmed symptomatic cases of COVID-19 demonstrates BNT162b2 is highly effective with 91.3% vaccine efficacy observed against COVID-19, measured seven days through up to six months after the second dose*
- *Vaccine was 100% effective in preventing severe disease as defined by the U.S. Centers for Disease Control and Prevention and 95.3% effective in preventing severe disease as defined by the U.S. Food and Drug Administration*
- *Vaccine was 100% effective in preventing COVID-19 cases in South Africa, where the B.1.351 lineage is prevalent*
- *Vaccine safety now evaluated in more than 44,000 participants 16 years of age and older, with more than 12,000 vaccinated participants having at least six months follow-up after their second dose*

Mayo Clinic HCWs Florida, Minnesota, AZ

ACCEPTED MANUSCRIPT

Effectiveness of mRNA COVID-19 vaccines against SARS-CoV-2 infection in a cohort of healthcare personnel

Melanie D Swift ✉, Laura E Breeher, Aaron J Tande, Christopher P Tommas
Caitlin M Hainy, Haitao Chu, PhD, MD, M Hassan Murad, Elie F Berbari,
Abinash Virk

Clinical Infectious Diseases, ciab361, https://doi.org/10.1093/cid/ciab361
Published: 26 April 2021 **Article history** ▾

Unvaccinated cohort 23,931
2-dose vax cohort 44,011
(Moderna/Pfizer)

- 96.8% effectiveness for Pfizer vaccine; 98.6% effectiveness for Moderna in real-world cohort (for both disease & asymptomatic infection)

To put simply, 36 symptomatic COVID infections out of 1000 unvaccinated; 0.4 out of 1000 if vaccinated (42 symptomatic+ symptomatic out of 1000 unvaccinated; 0.7 all infections out of 1000 if vaccinated)

CDC breakthrough data

- CDC keeping track of breakthrough infections in U.S
- Out of 87 million Americans who are fully vaccinated against COVID-19
  - 5079 symptomatic breakthroughs (0.005%)
  - Only 0.0003% hospitalizations for COVID-19
  - Deaths 0.0001% for COVID-19

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? → Mingle with each other without masks, distancing

Importantly, no need to quarantine if exposed after vaccination if no symptoms (nor test)

Vaccinated around unvaccinated and public? → Ok if privacy of home; Keep masks and distancing in public for social norms until all who want to can get vax

Unvaccinated and unvaccinated? → Keep all usual restrictions

IDEAS

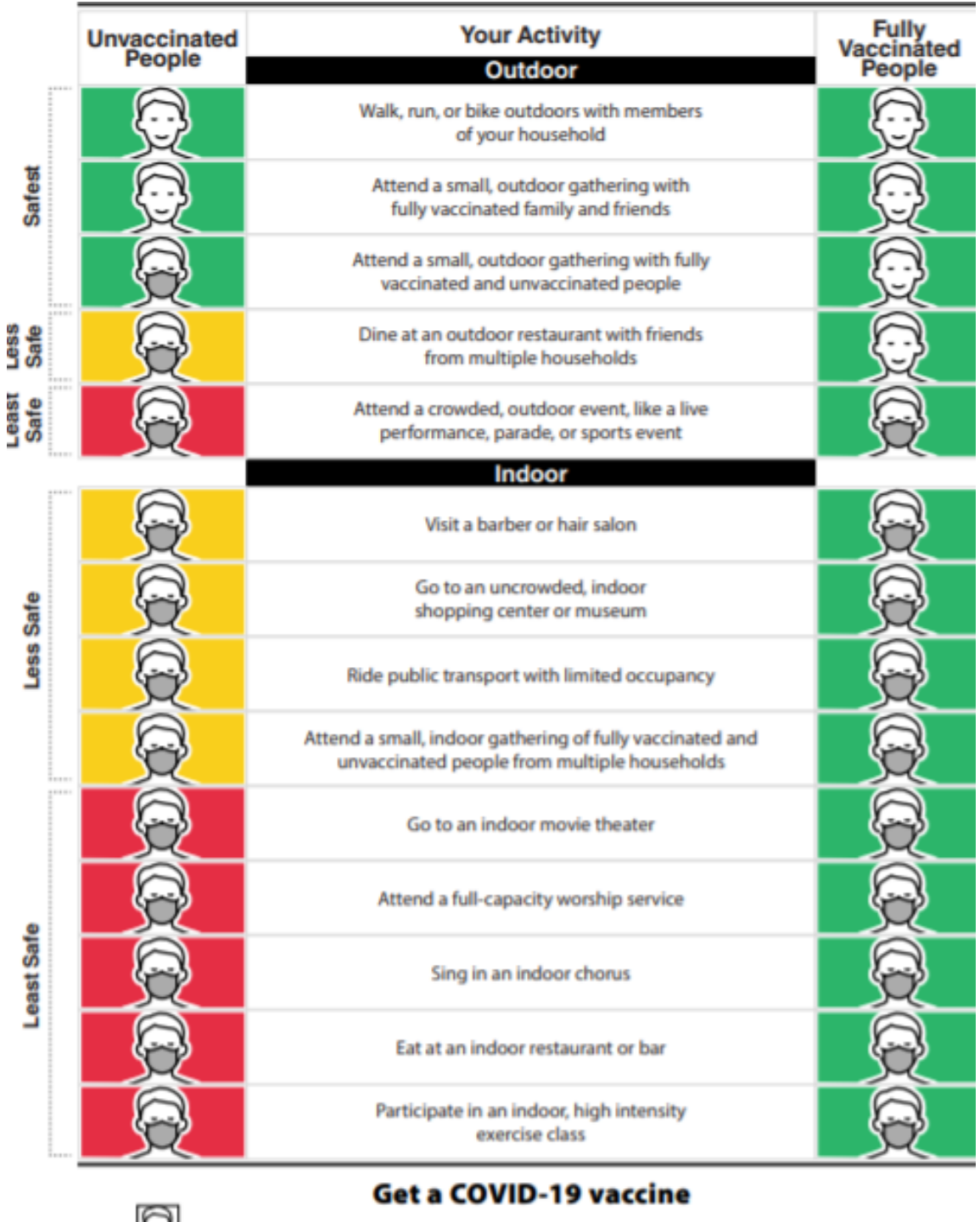
Vaccinated People Are Going to Hug Each Other

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

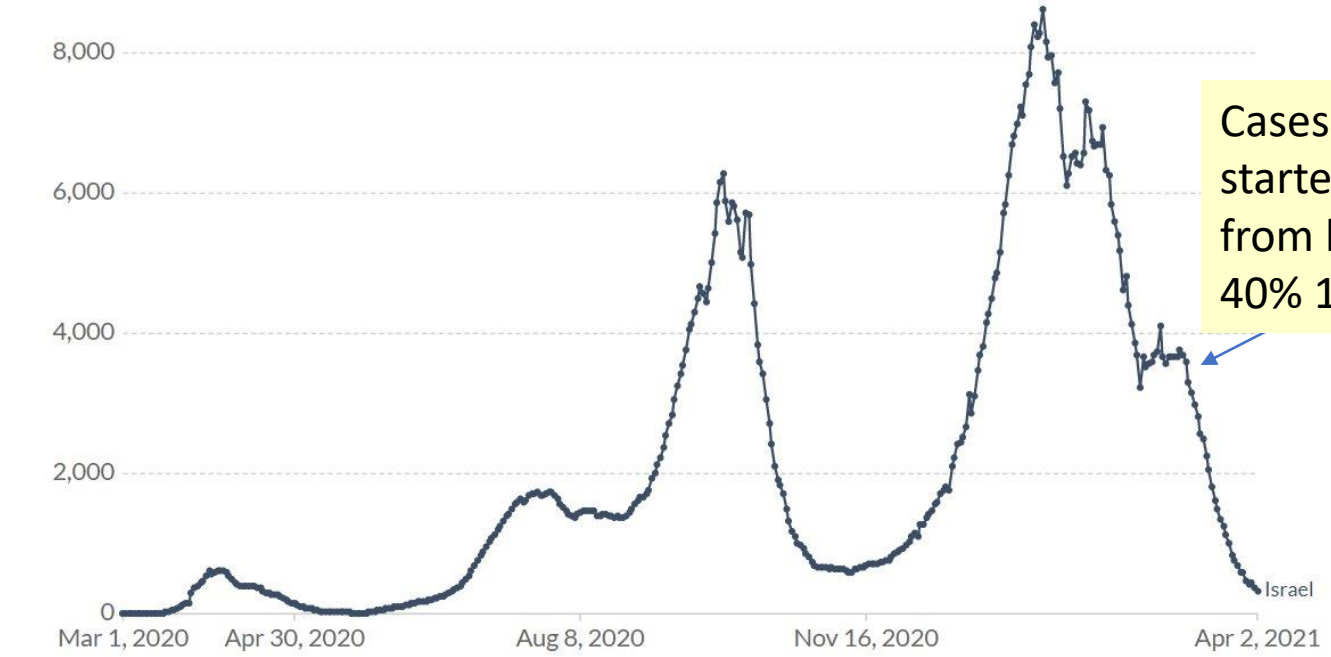
Julia Marcus
Epidemiologist and professor at Harvard Medical School

April 27, 2021

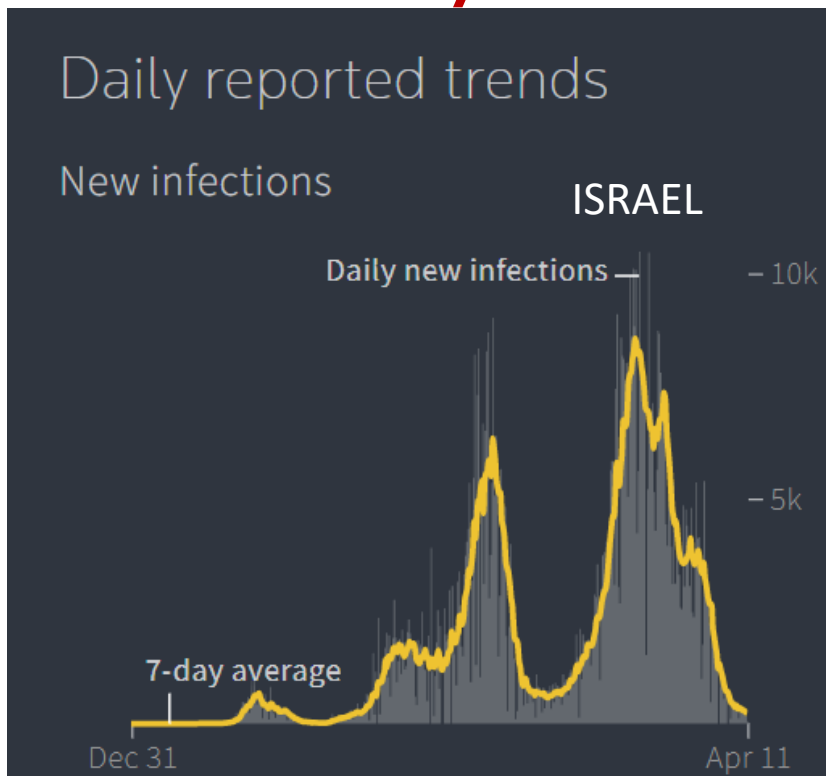


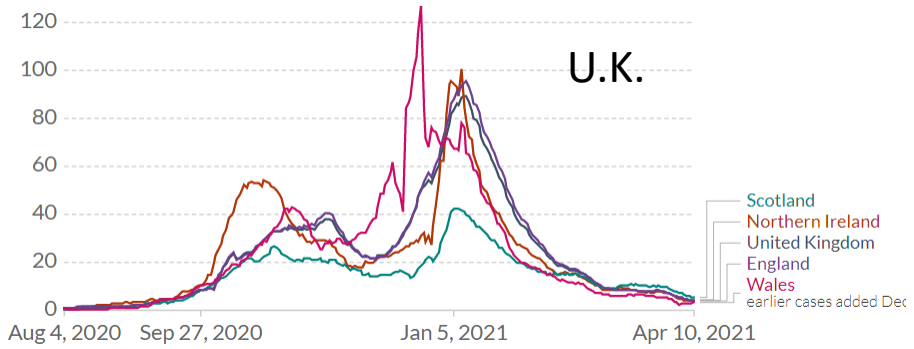
Giving 1 dose first to get to herd immunity faster

What is inflection point of keeping cases low and of herd immunity?



Cases in Israel started falling from high rate at 40% 1st dose





Tap to know more	Infections % of peak	Deaths % of peak	Percent of population given at least one dose of vaccine	Vaccination phase
Israel	3% ▼	13%	58%	1 of 1
United Kingdom	4% ▼	3%	47%	

Israel has 18 cases per 100K population; UK has 4.2 per 100K

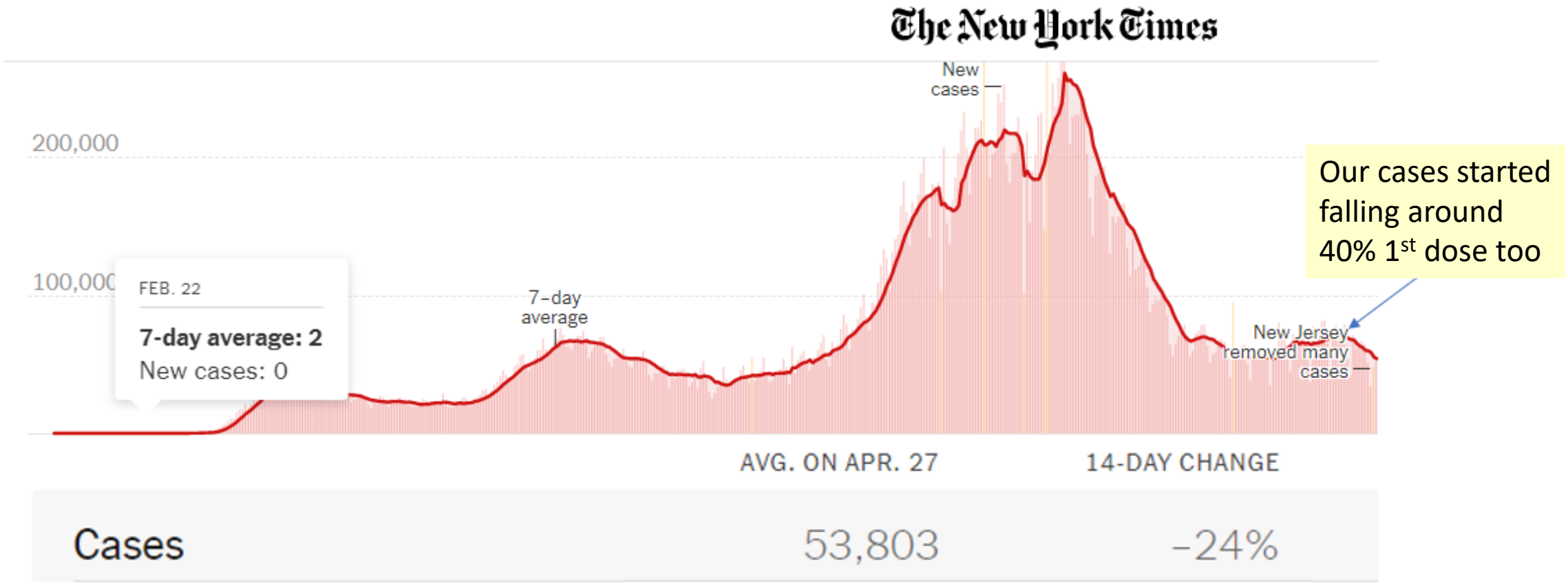
Accelerate Coronavirus Disease 2019 (COVID-19) Vaccine Rollout by Delaying the Second Dose of mRNA Vaccines FREE

Stanley A Plotkin ✉, Neal Halsey

Clinical Infectious Diseases, ciab068, https://doi.org/10.1093/cid/ciab068

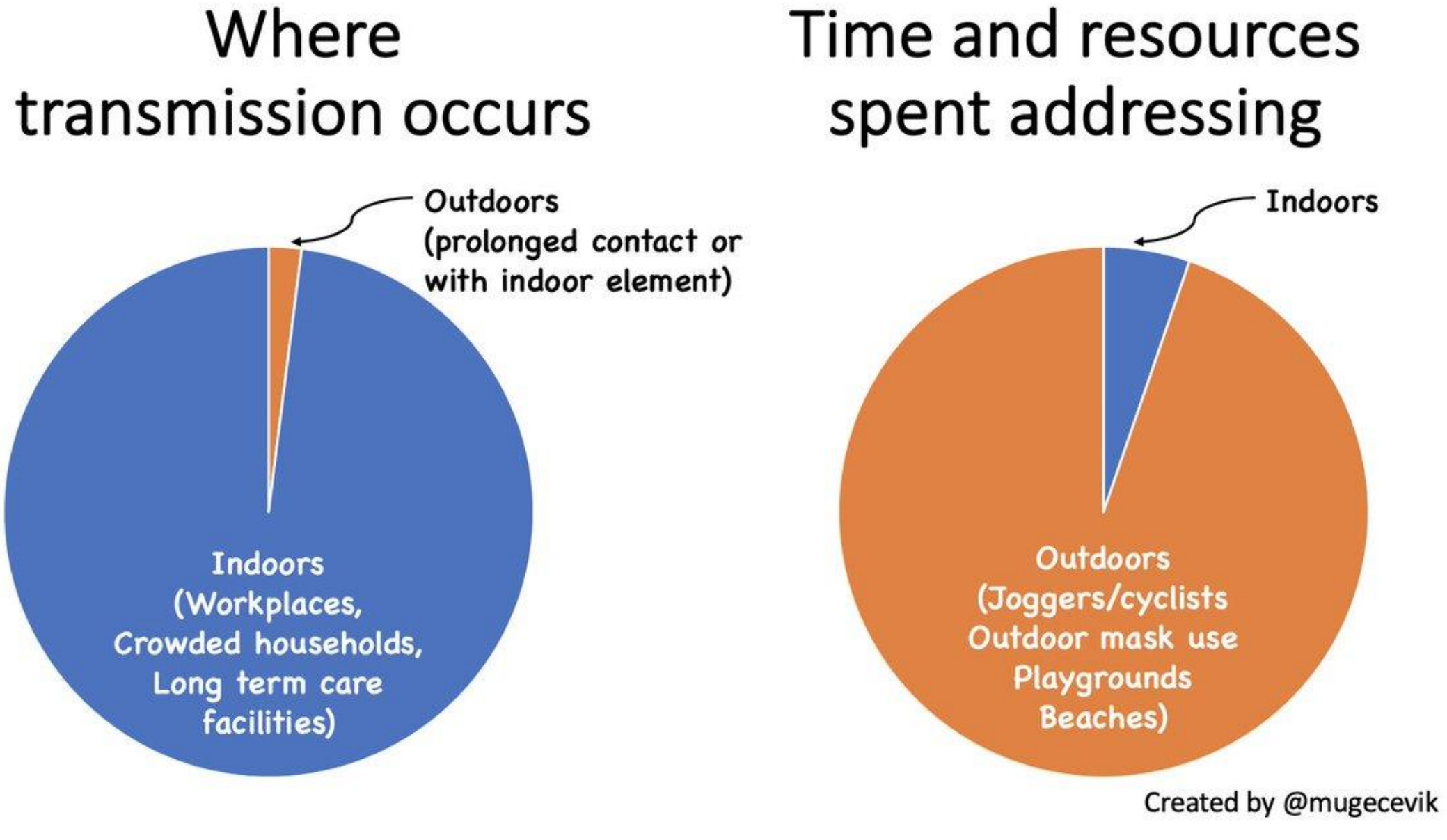
Published: 27 January 2021 **Article history** ▾

- Based on immunologic principles, sensitization with single doses would still allow boosting with a 2nd dose
- B-cell memory after mRNA vaccination has been clearly demonstrated, which supports the idea that antibodies will be boosted by a second mRNA dose given months later
- Priming of the immune system generates good responses to second doses of most vaccines for at least 6 months and perhaps longer
- Good efficacy of 84-92% after 1st dose- waiting 6 weeks (CDC guidelines) will allow first dose faster


The New York Times
New cases
200,000
100,000
FEB. 22
7-day average: 2
New cases: 0
7-day average
New Jersey removed many cases
Our cases started falling around 40% 1st dose too
AVG. ON APR. 27
14-DAY CHANGE
Cases
53,803
-24%

Mask mandates

Outside transmission rare



Outside transmission rare

- Viral particles disperse effectively in the outside air (inside 5000x more)
- A study in Wuhan, China, which involved careful contact tracing, discovered that just *one* of 7,324 infection events investigated was linked to outdoor transmission.
- In a recent analysis of over 232,000 infections in Ireland, only one case of COVID-19 in every thousand was traced to outdoor transmission.
- Scoping review from the University of Canterbury concluded that outdoor transmission was rare, citing the opportunity costs of not encouraging the public to congregate outdoors

Mask mandates?

EDITOR'S CHOICE

The Time for Universal Masking of the Public for Coronavirus Disease 2019 Is Now

Monica Gandhi ✉, Diane Havlir

Open Forum Infectious Diseases, Volume 7, Issue 4, April 2020, ofaa131, https://doi.org/10.1093/ofid/ofaa131

- Outside lifted by CDC on April 27, 2021
- For every 20 point increase in vaccinations in adults, risk to children halves (because vaccines block transmission)
- Very low rates in cities/states with high vaccination rates (SF 70% 1st vax rate; 30 cases out of 896K people; 2 hospitalization/100K
- Indoor mask mandates likely should be lifted when either 1) metric of hospitalization met or 2) everyone >16 in country has chance to get vaccine x 2 doses

SARS-CoV-2 infection risk among unvaccinated is negatively associated with community-level vaccination rates

Oren Milman, Idan Yelin, Noga Aharony, Rachel Katz, Esma Herzel, Amir Ben-Tov, J

These are the metrics that will tell us when we can safely lift restrictions

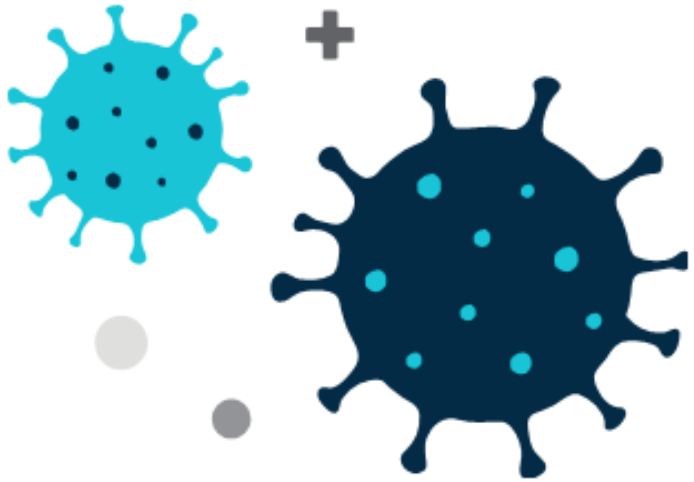
Rising vaccination rates and dropping hospitalization rates are what to look for.

By **Syra Madad**, **Monica Gandhi** and **Ashish K. Jha**

April 7, 2021 at 7:51 a.m. PDT

The Washington Post

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 decrease transmission
- Real world effectiveness even better than efficacy
- Variants can be managed
- 1st dose FIRST worked in UK but we didn't adopt here
- Outdoor very safe!