THOMAS FRIEDRICH

7 OCTOBER 2021

WISCONSIN
UNIVERSITY OF WISCONSIN–MADISON

ENDEMIC COVID

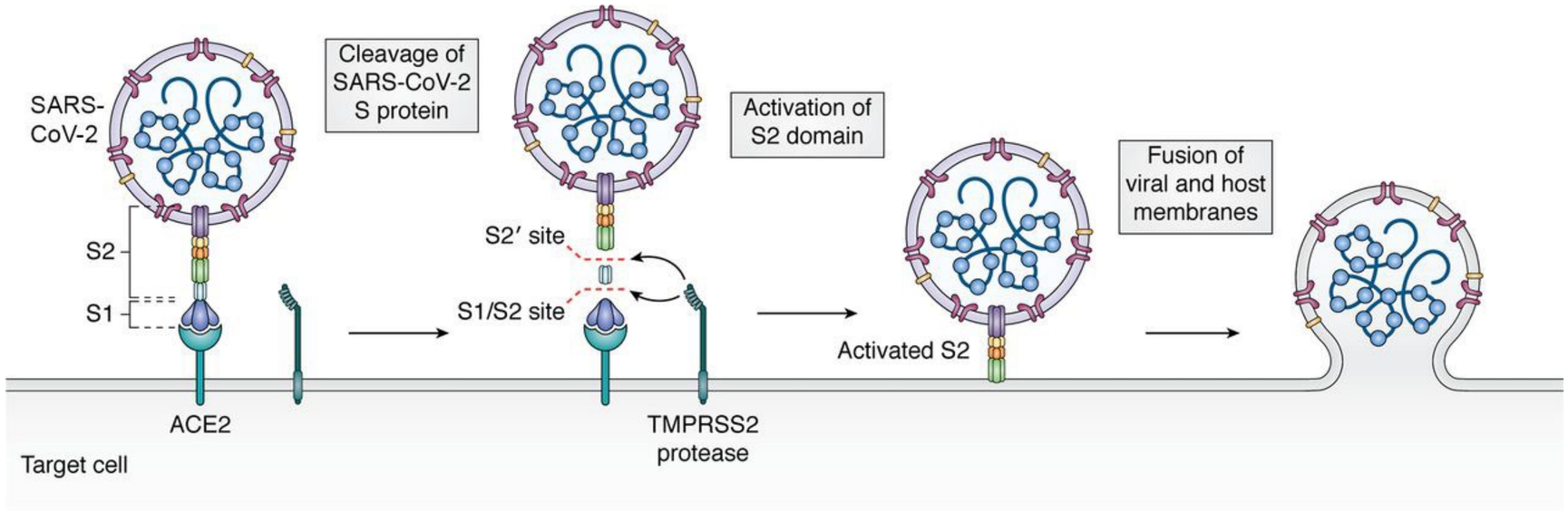
EVOLVING VIRUSES, CHANGING IMMUNITY

Prospects and challenges for controlling COVID-19

- How can vaccines protect against SARS-CoV-2? What does “protection” mean?
- “Breakthrough” infections and potential for transmission
- Do we need boosters now?
- Thoughts on current and future SARS-CoV-2 evolution, with implications for vaccines
- Discussion

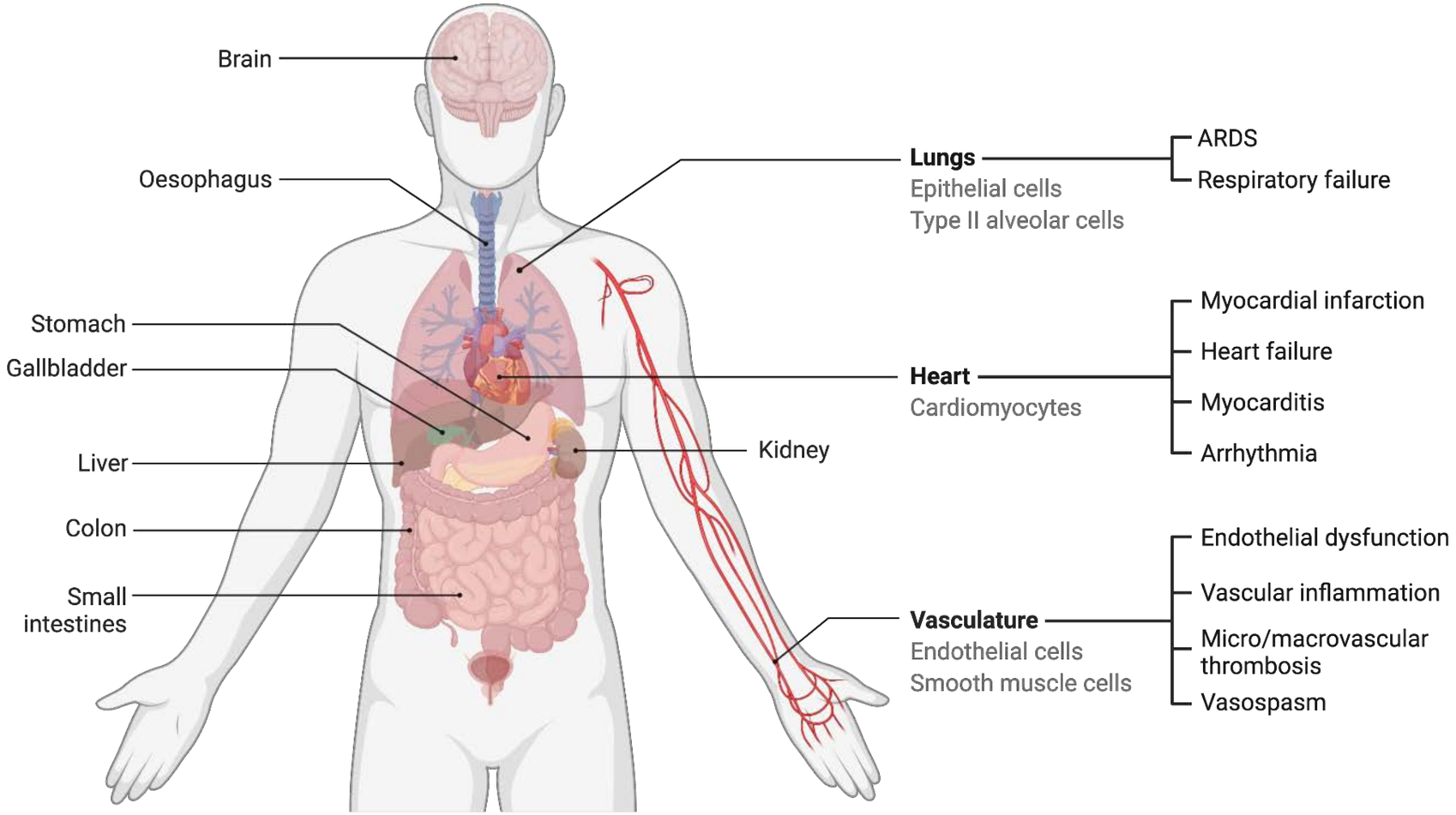
WHAT DOES A COVID VACCINE NEED TO DO?

SARS-CoV-2 binds ACE2 receptors to enter cells



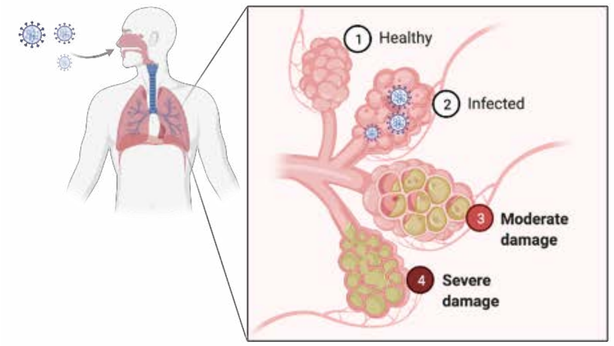
hartenian et al j biol chem 2020: https://doi.org/10.1074/jbc.REV120.013930

ACE2 is expressed in many tissues of the body

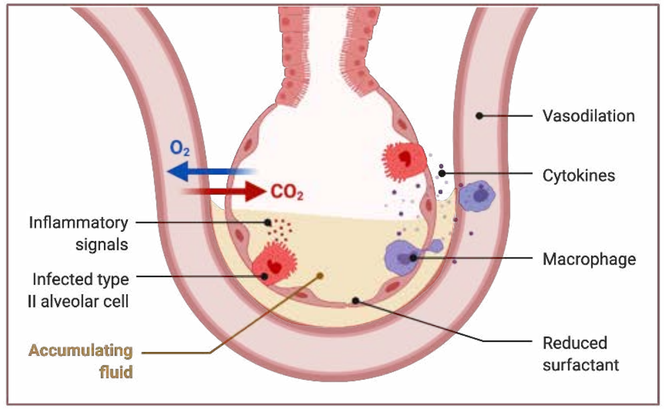


Vaccines must protect the lower respiratory tract

- Virus is transmitted from upper respiratory tract (URT)
- Severe disease occurs when virus and the immune response damage the lower respiratory tract (LRT)
- Protection of LRT prevents severe disease
- Virus replication in URT may still allow vaccinated person to transmit



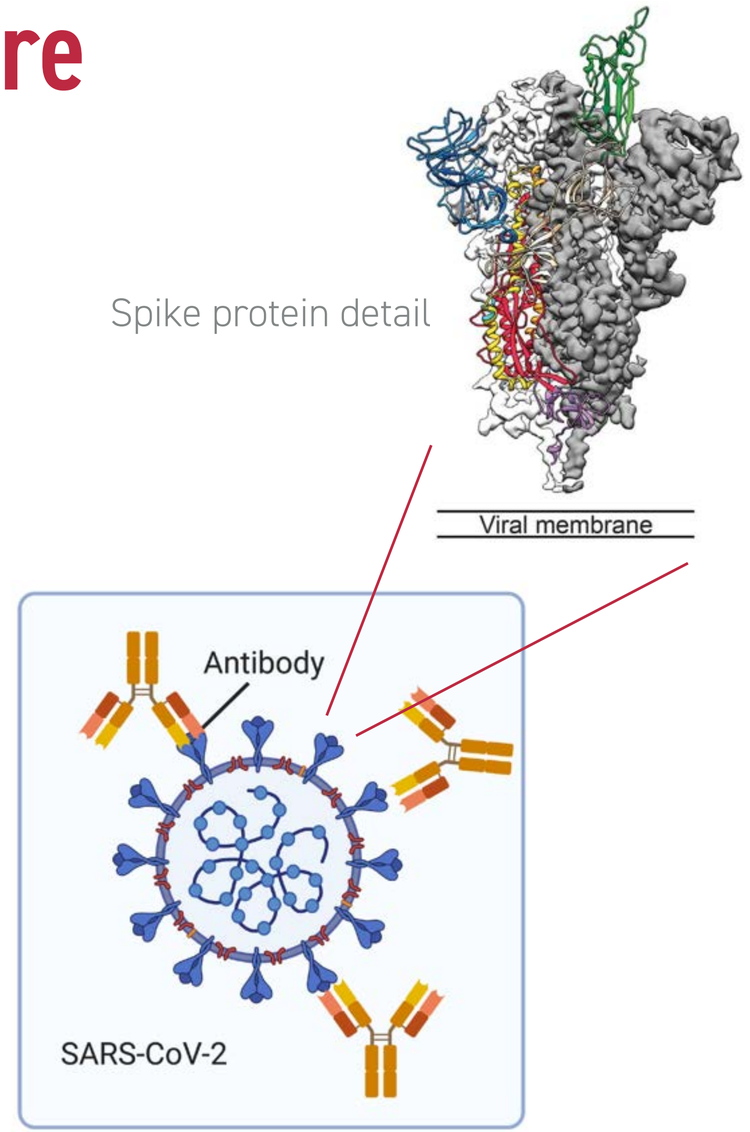
3 Moderate damage: Accumulating fluid, reduced gas exchange



biorender

SARS-CoV-2 Spike protein structure

- Antibodies that bind Spike protein block virus' ability to attach to ACE2
- Such "neutralizing antibodies" can prevent infection of cells
- **Vaccines present Spike protein to immune system to elicit antibodies**

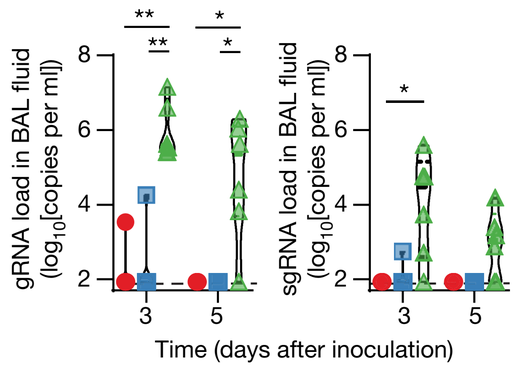


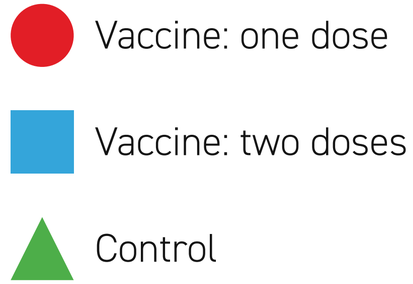
Biorender; Wrapp D et al. 2020. Science. 367:1260-1263. doi:10.1126/science.abb2507

Vaccines may protect LRT, but not URT

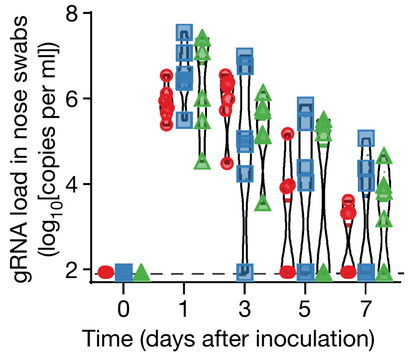
- Vaccines given intramuscularly are not expected to induce potent URT immunity
- In a preclinical trial, the AstraZeneca vaccine gave robust protection to LRT
- But there was no difference in virus in URT vs. controls
- This is why we are concerned about transmission in vaccinated people

lung





nose



van doremalen et al nature 2020: https://doi.org/10.1038/s41586-020-2608-y

What is “protection?”

- Vaccines can “protect” against many things — note how this is defined!
- Individual-level protection
  - Against any infection, with or without symptoms
  - Against any symptomatic illness
  - Against severe disease, hospitalization, or death
- Population-level protection
  - Are vaccinated people less likely to infect others?

COULD VACCINATED PEOPLE TRANSMIT?

Can people with post-vaccination infections transmit SARS-CoV-2?

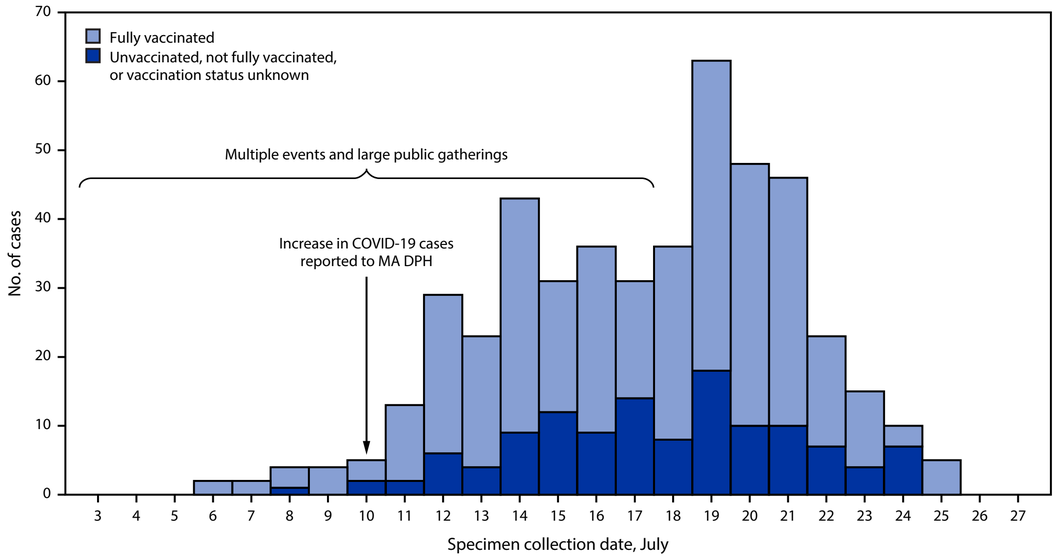
- Is viral load in vaccinees lower than in unvaccinated? (Sequencing implications)
- July 2021: outbreak in Provincetown associated with large gatherings
- 346 of 469 (74%) fully vaccinated
- CDC and local public health changed mask recommendations
- Other outbreaks involving transmission from vaccinated persons have since been described

Morbidity and Mortality Weekly Report

Outbreak of SARS-CoV-2 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings — Barnstable County, Massachusetts, July 2021

Catherine M. Brown, DVM[1]; Johanna Vostok, MPH[1]; Hillary Johnson, MHS[1]; Meagan Burns, MPH[1]; Radhika Gharpure, DVM[2]; Samira Sami, DrPH[2]; Rebecca T. Sabo, MPH[2]; Noemi Hall, PhD[2]; Anne Foreman, PhD[2]; Petra L. Schubert, MPH[1]; Glen R. Gallagher PhD[1]; Timelia Fink[1]; Lawrence C. Madoff, MD[1]; Stacey B. Gabriel, PhD[3]; Bronwyn MacInnis, PhD[3]; Daniel J. Park, PhD[3]; Katherine J. Siddle, PhD[3]; Vaira Harik, MS[4]; Deirdre Arvidson, MSN[4]; Taylor Brock-Fisher, MSc[5]; Molly Dunn, DVM[5]; Amanda Kearns[5]; A. Scott Laney, PhD[2]

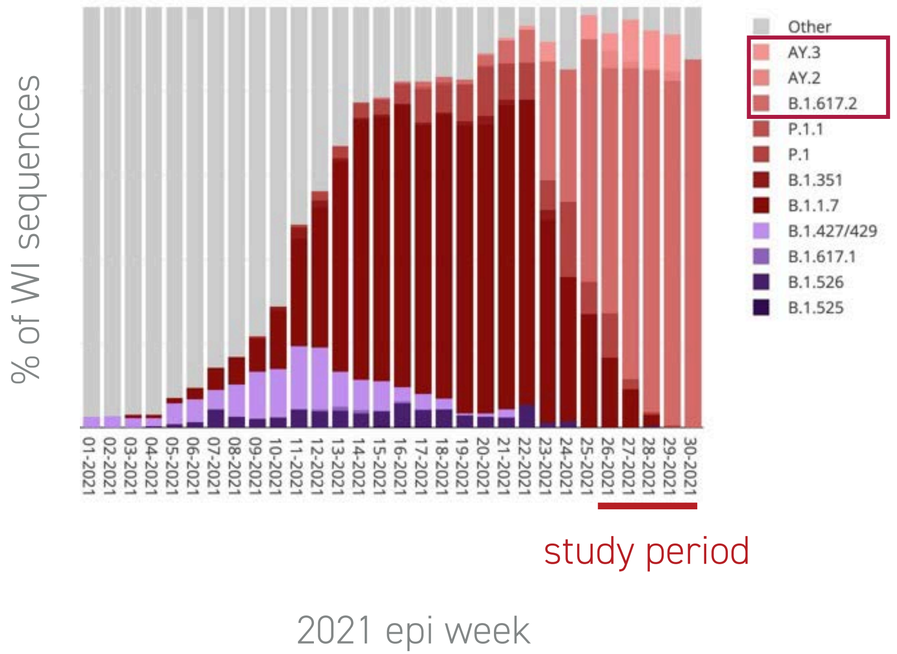
FIGURE 1. SARS-CoV-2 infections (N = 469) associated with large public gatherings, by date of specimen collection and vaccination status* — Barnstable County, Massachusetts, July 2021



brown et al. mmwr 6 aug 2021 doi:10.15585/mmwr.mm7031e2

Delta prevalence in Wisconsin increased dramatically in July

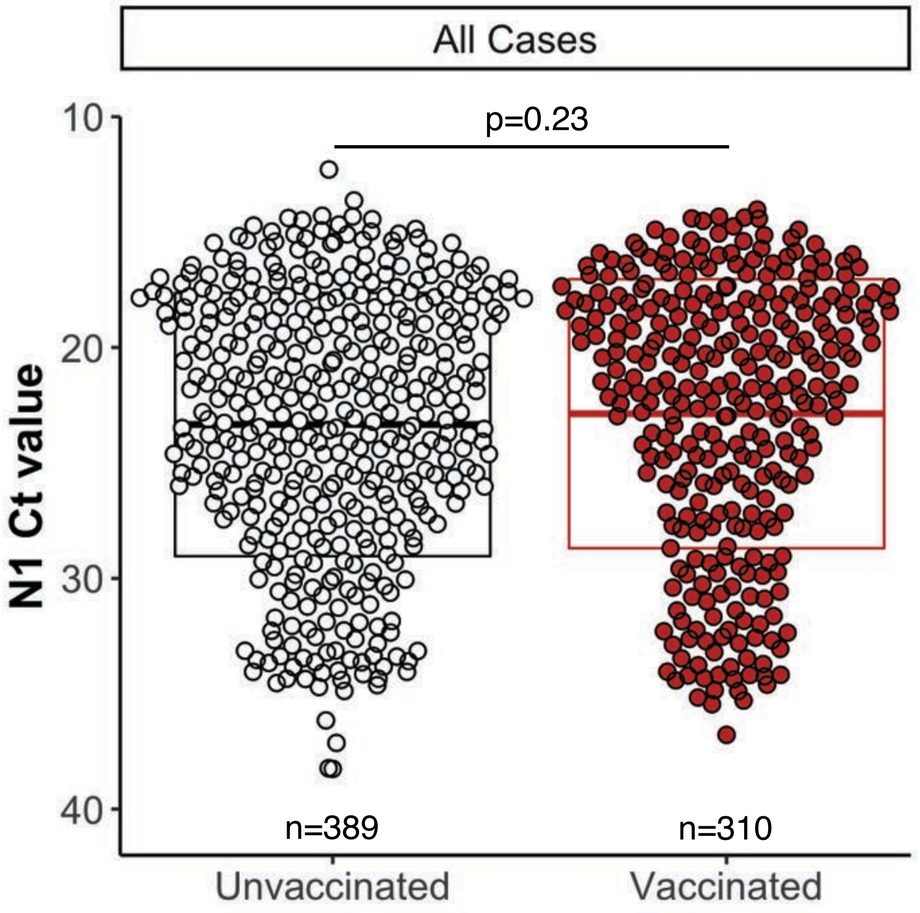
- We examined **n=699 specimens** collected 28 June – 31 July 2021
- Estimated prevalence of Delta lineages increased from 69%–95%
- 110 of 122 samples we sequenced (90%) were Delta
- A single contract lab performed PCR testing on all 699 specimens



kelsey florek: https://dataportal.slh.wisc.edu/sc2dashboard

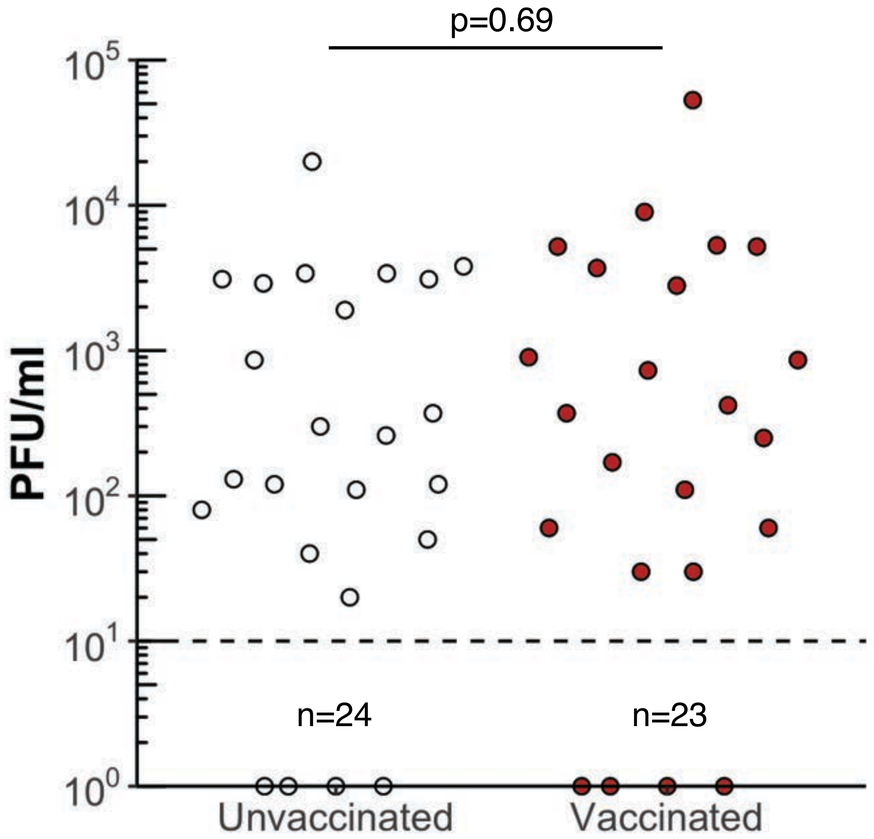
Fully vaccinated and unvaccinated have similar Ct values

- Threshold cycle (Ct) in PCR test gives an estimate of viral RNA level
- No significant difference in Ct value by vaccine status
- **Fully vaccinated and unvaccinated individuals had similar viral loads**
- **212 of 310 people with post-vaccination infections (68%) had Ct <25**



Vaccinated and unvaccinated have similar infectious virus titers

- Inoculated specimens with Ct < 25 onto a “lawn” of cells in culture
- Specimens had undergone a freeze-thaw
- Where virus infects cells, “plaques” form in the cell “lawn”
- Vaccinated and unvaccinated people have similar levels of infectious virus.



Plaque assay on Vero E6 TMPRSS2

Vaccinated and unvaccinated have similar infectious virus titers

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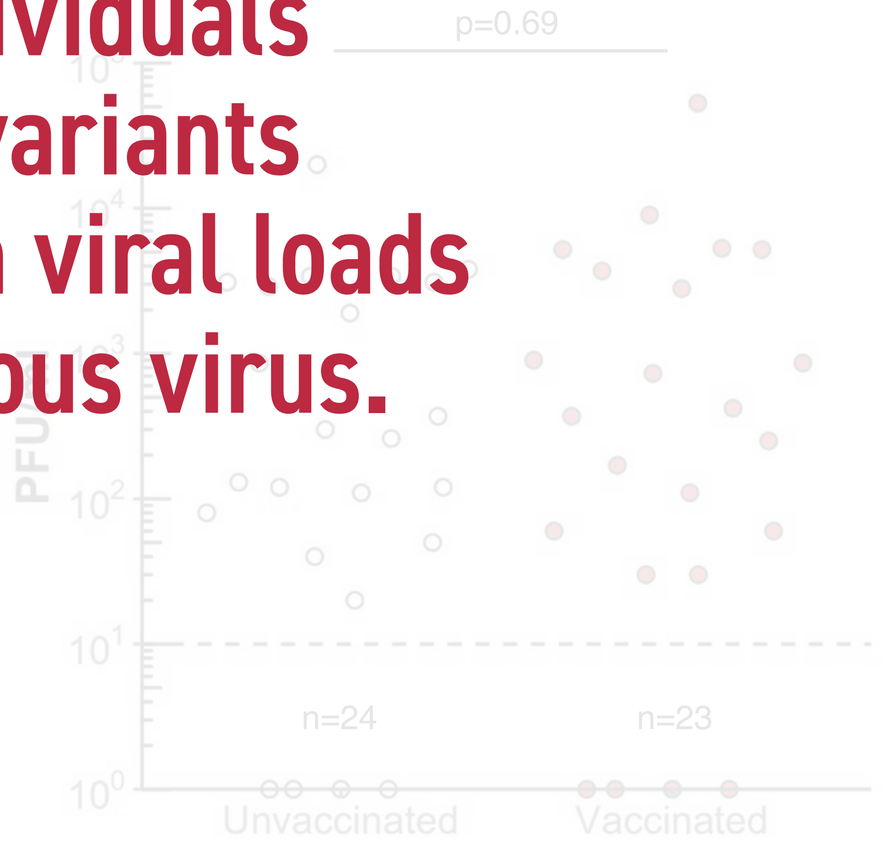
- Specimens had undergone a freeze-thaw
- Where virus infects cells, "plaques" form in the cell "lawn"
- Vaccinated and unvaccinated people have similar levels of infectious virus.

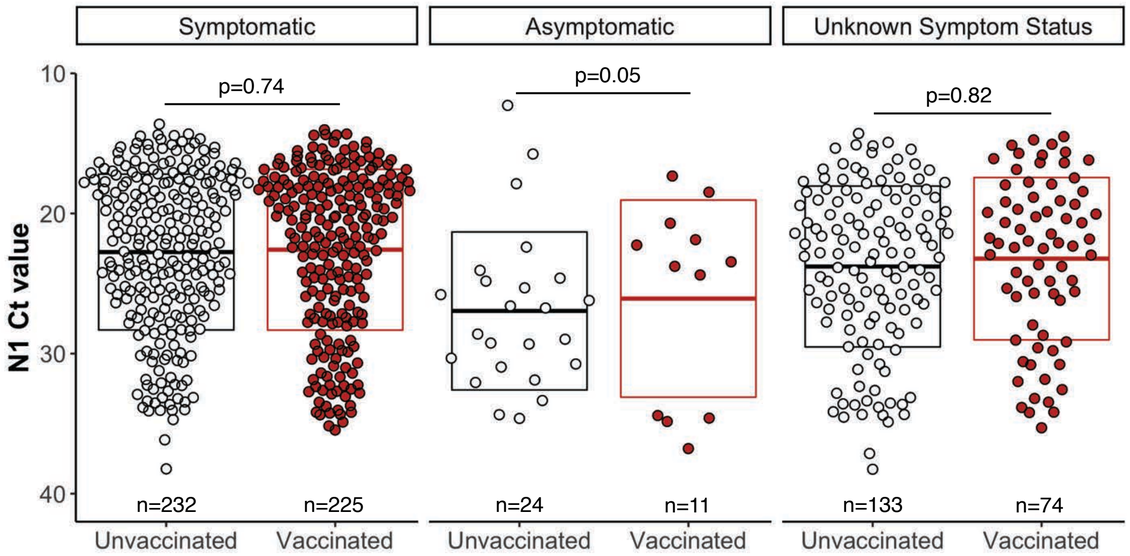
Fully vaccinated individuals infected with Delta variants frequently have high viral loads and can shed infectious virus.



peter halfmann

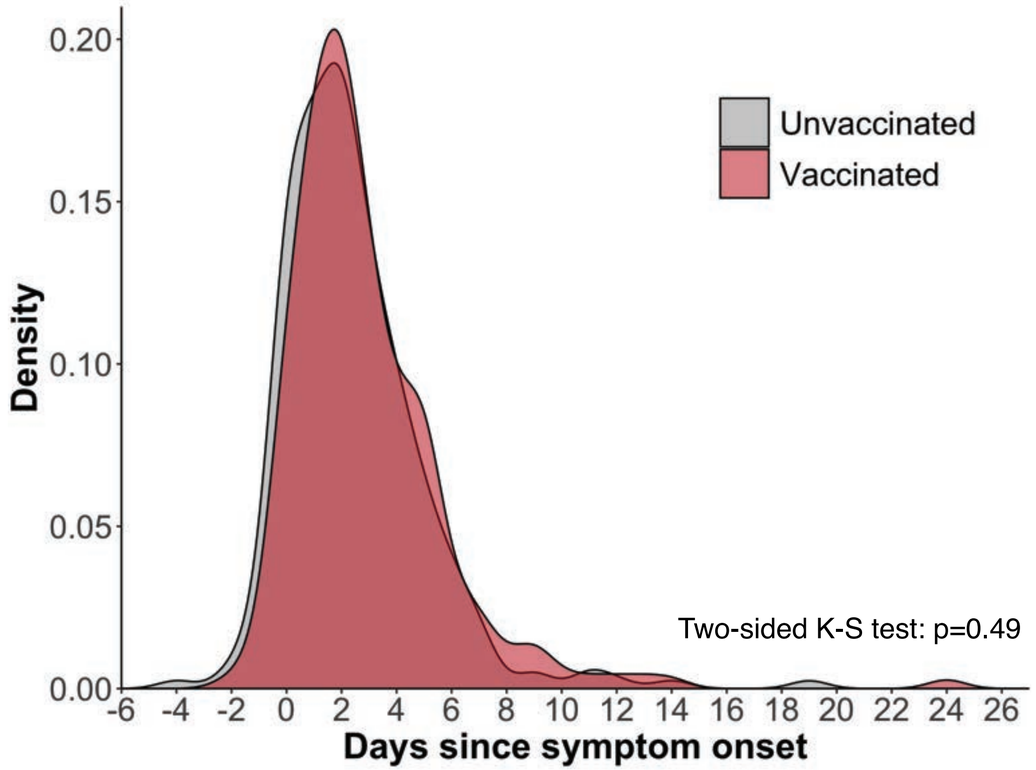
Ct values are similar in vaccinated and unvaccinated, regardless of symptom status

- Data on symptom status at the time of testing were available for 492 of 699
- In unvaccinated and fully vaccinated individuals **Ct values were similar, regardless of symptom status**
- No info on specific symptoms or severity
- **At least 8 fully vaccinated individuals were asymptomatic with Ct <25**



Both vaccinated and unvaccinated seek testing within ~2 days

- Do vaccinated people wait longer to be tested?
- Median time to testing is 2 days for both vaccinated and unvaccinated
- 91% of specimens were collected within 6 days of illness onset
- Findings unlikely to be biased by differences in test-seeking behavior for people with symptoms



Individuals with post-vaccination infection can transmit Delta

- Within 6 days of illness onset, Ct values are similar in fully vaccinated and unvaccinated individuals
- In our study 68% of fully vaccinated individuals had Ct <25 at the time of testing, including 8 of 12 who reported no symptoms
- Infectious virus was present at similar levels in vaccinated and unvaccinated
- Our study and others show that vaccinated individuals can transmit Delta, perhaps even without symptoms, and should take precautions accordingly

https://www.medrxiv.org/content/10.1101/2021.07.31.21261387v3

Shedding of Infectious SARS-CoV-2 Despite Vaccination

Overview of attention for article published in medRxiv

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SUMMARY | News | Blogs | Policy documents | Twitter | Facebook | Wikipedia | Video | Dimensions citations

Title	Shedding of Infectious SARS-CoV-2 Despite Vaccination
Published in	medRxiv
DOI	10.1101/2021.07.31.21261387
Authors	Riemersma, Kasen K., Grogan, Brittany E., Kita-Yarbro, Amanda, Halfmann, Peter J., Segaloff... [show]

View on publisher site

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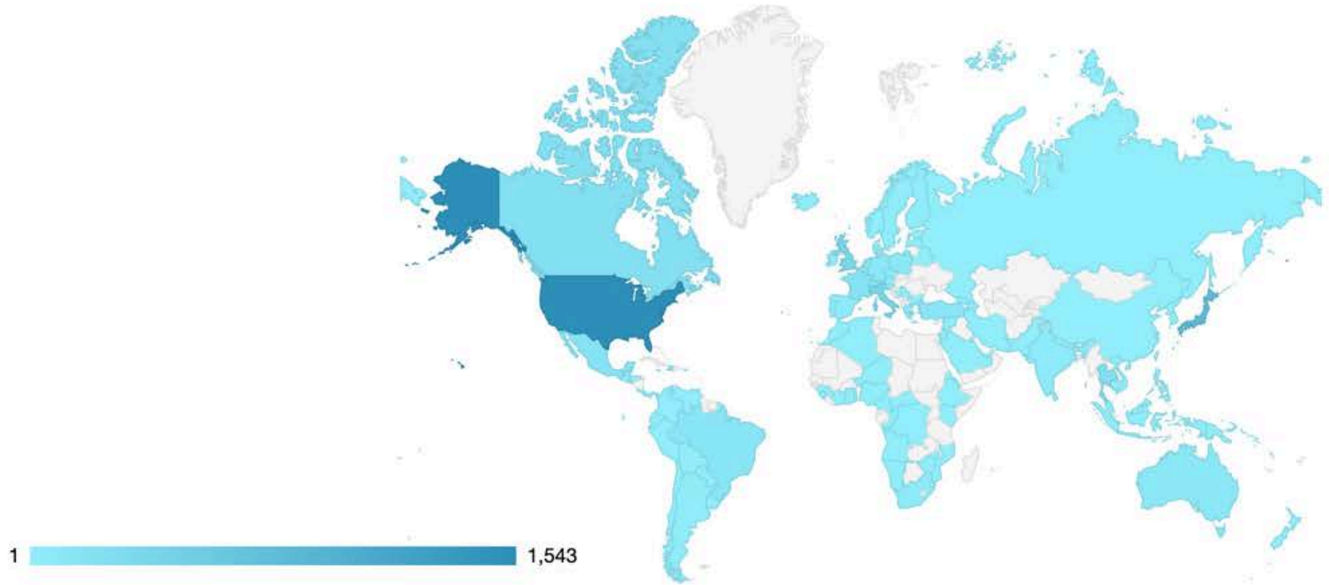
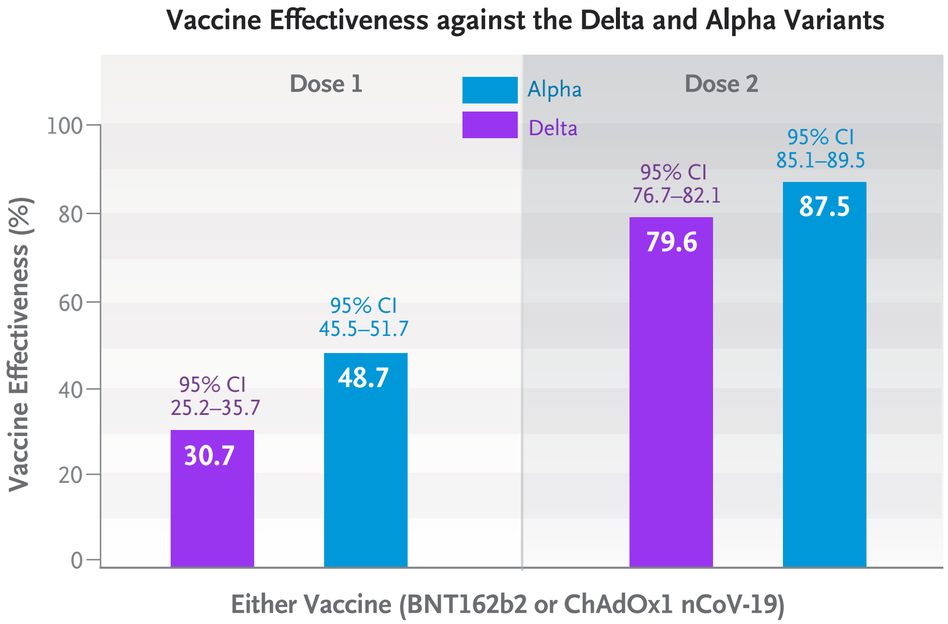
The data shown below were collected from the profiles of **14,805** tweeters who shared this research output. Click here to find out more about how the information was compiled.

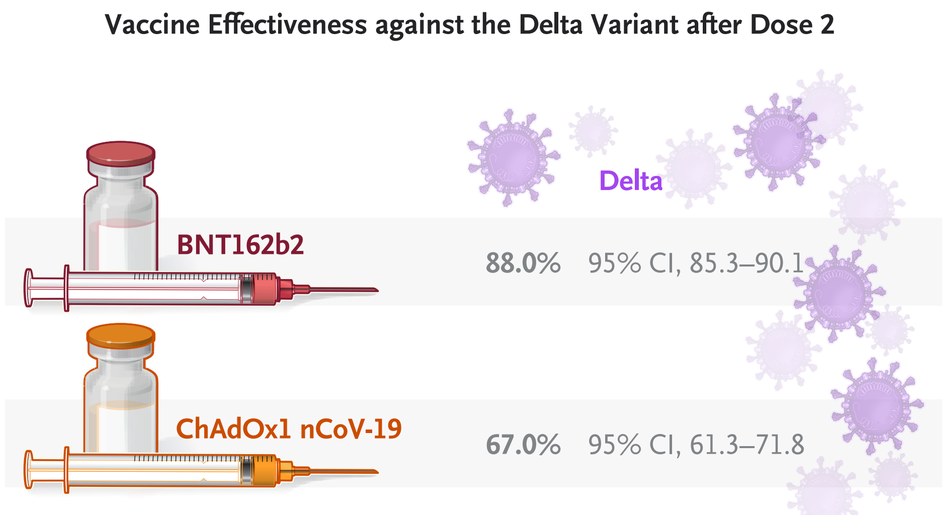



If it moves I'll trade it
@HuntingStops
@arielstulberg @mWylliecrypto @TheVisionEx @ErikVoorhees Do you honestly not know that the vaccinated and the non-vaccinated are equal vectors for spreading the virus? https://t.co/BjBSnEl1kz
02:23AM

DOES VACCINATION REDUCE TRANSMISSION?

COVID-19 vaccines prevent infection with Delta*



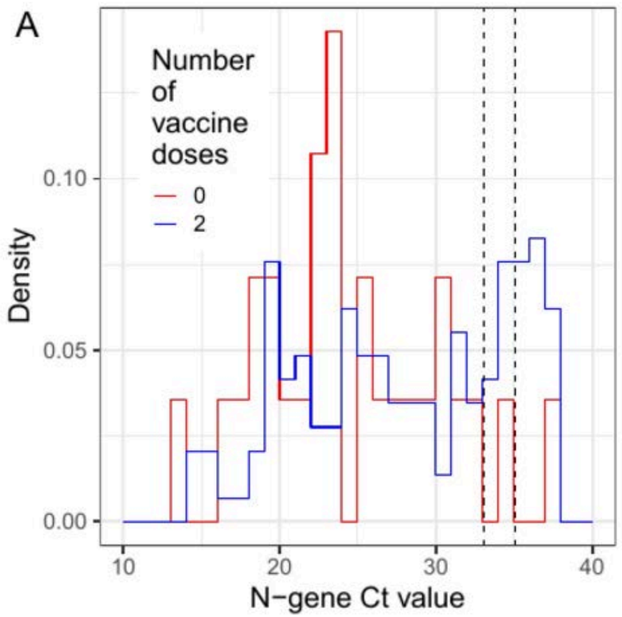


*Though effectiveness is waning -- more on this later

summary of lopez bernal et al nejm 2021. https://www.nejm.org/doi/10.1056/NEJMoa2108891

Some positive vaccinees may have very low virus loads.

- The UK REACT study rounds 12–13, 20 May – 12 July 2021
- Very high Delta prevalence
- Disproportionate number of positives with high Ct values among vaccinees
- Could these be **asymptomatic** infections despite vaccination?



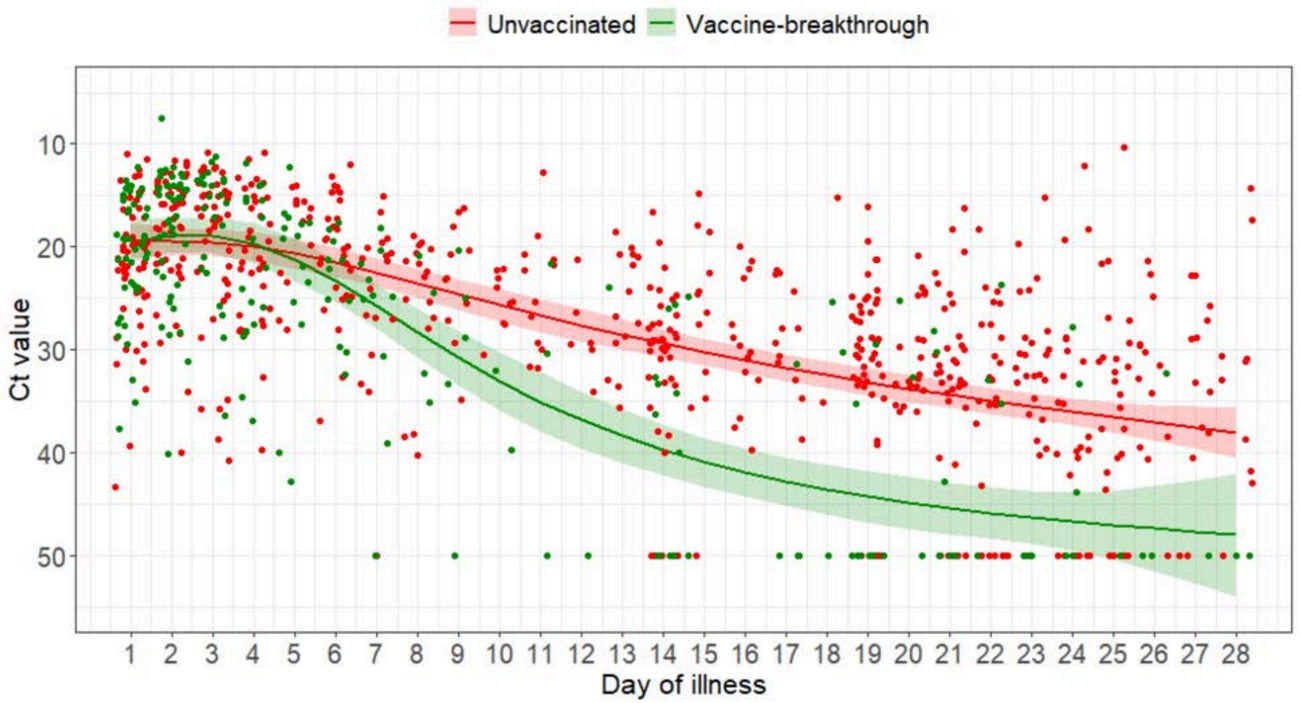
unvaccinated

fully vaccinated

https://spiral.imperial.ac.uk/bitstream/10044/1/90800/2/react1_r13_final_preprint_final.pdf

Vaccinees likely control SARS-CoV-2 faster

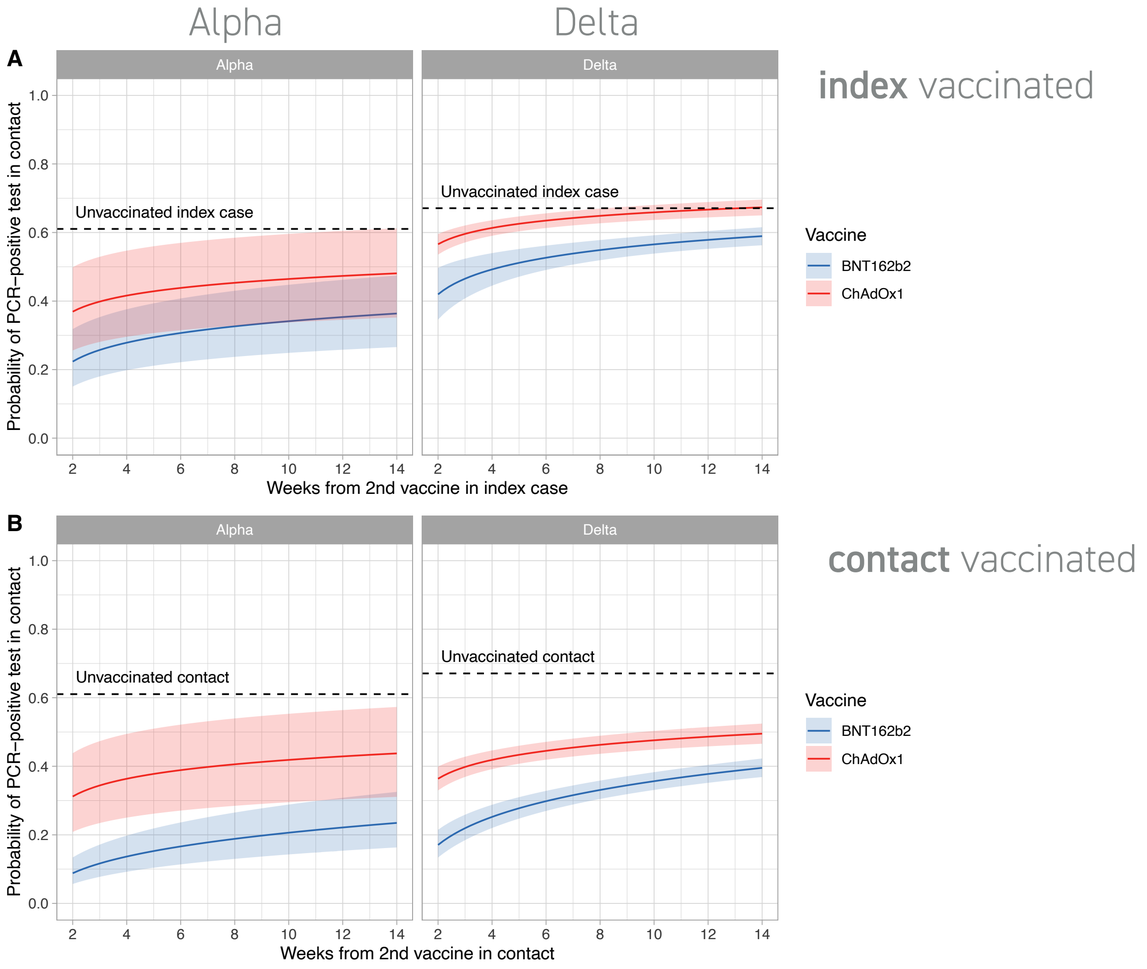
- Multi-center study in Singapore measured viral load kinetics among persons infected with Delta despite full vaccination
- Compared to retrospective study of Delta viral load kinetics among unvaccinated persons
- Ct values diverge 6-7 days after illness onset



chia et al 2021: www.medrxiv.org/content/10.1101/2021.07.28.21261295v1

Vaccination reduces rates of transmission to contacts

- Compared risk of SARS-CoV-2 transmission in vaccinated vs. unvaccinated
- Top: vaccinated index cases less likely to transmit to contacts
- Bottom: vaccinated contacts less likely to get infected from index
- Note: protection wanes with time after vaccination!



eyre et al, biorxiv 2021. http://dx.doi.org/10.1101/2021.09.28.21264260

Vaccination reduces rates of transmission to contacts

- Compared risk of SARS-CoV-2 transmission in [illegible] unvaccinated
- Top: vaccinated index cases less likely to transmit to contacts
- Bottom: vaccinated contacts less likely to get infected from index
- Note: protection wanes with time after vaccination!

COVID-19 vaccines reduce transmission of SARS-CoV-2!

But, vaccinated people who become infected may still transmit the virus to others.

index vaccinated

contact vaccinated

eyre et al, biorxiv 2021. http://dx.doi.org/10.1101/2021.09.28.21264260

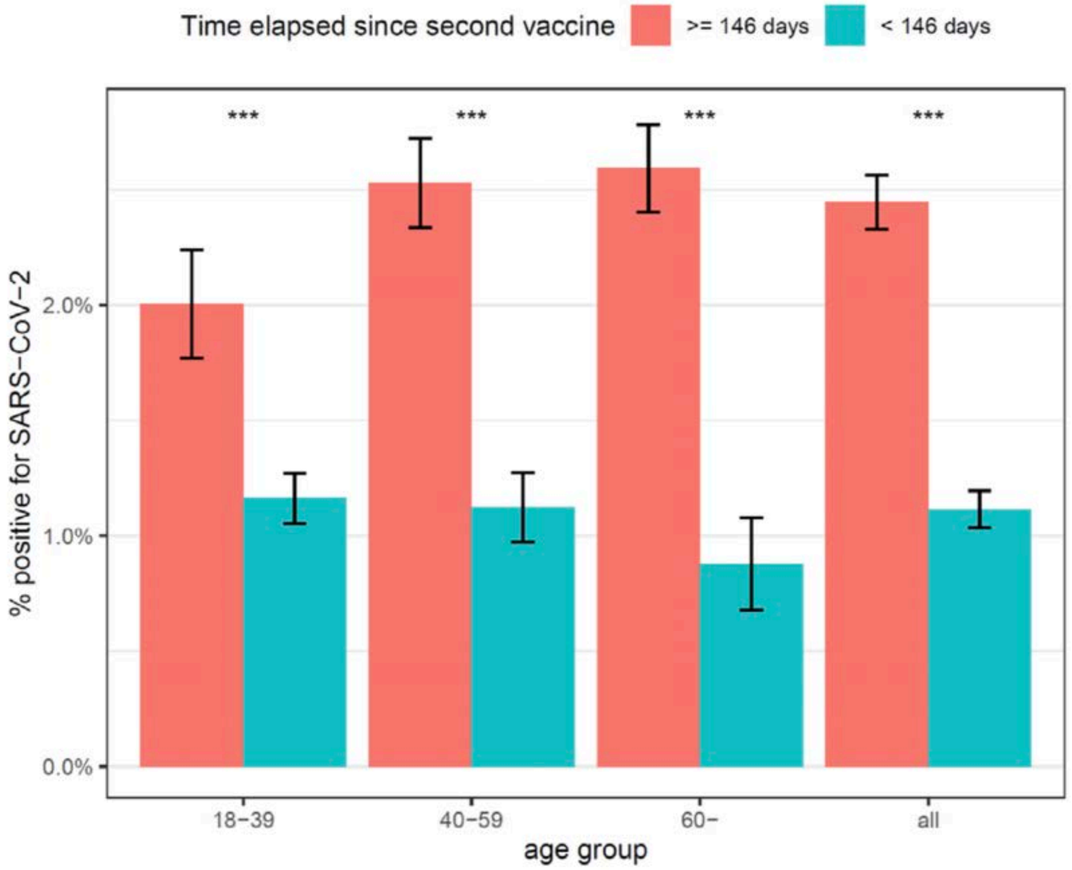
Vaccination and SARS-CoV-2 transmission: questions

- Why does vaccine breakthrough happen? Viral immune escape, weak immune response, or a combination of factors?
- What is the role of fully vaccinated individuals in transmission? Answers may differ by location, depending on factors like vaccination rates, local patterns of transmission, etc.
- Can boosters reduce breakthrough infections and transmission from the vaccinated?

DOES IMMUNITY WANE WITH TIME?

Protection wanes with time since full vaccination

- SARS-CoV-2 rates compared in 33,993 fully vaccinated adults (Pfizer) between May 15 and July 26, 2021
- Median time since vaccination = 146 days
- ~90% delta during this time period
- Significantly higher rates of infection in those fully vaccinated < 146 days prior
- How to disentangle waning immunity from delta immune escape?



israel et al, medrxiv 2021. https://www.medrxiv.org/content/10.1101/2021.08.03.21261496v1

*** P<0.001

It's not just Delta.

- SARS-CoV-2 rates compared in 3.4 million people receiving care from Kaiser, 14 Dec 2020 through 8 Aug 2021
- Viral sequencing available in a subset
- Vaccine effectiveness against infection wanes with time for all viruses, including Delta.

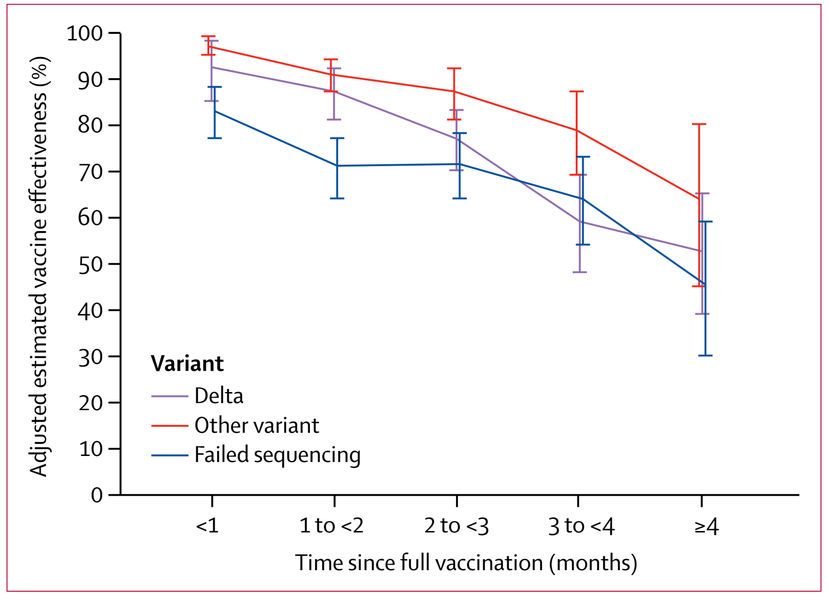


***Figure 3*: Adjusted estimated vaccine effectiveness against SARS-CoV-2 infection by variant**
Data are shown for number of months since being fully vaccinated with BNT162b2 with 95% CIs.

tartof et al, lancet 2021. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02183-8/fulltext

Protection against severe disease persists!

- Stratified participants by age group and assessed vaccine effectiveness against infection (testing positive) and severe disease (hospitalization)
- Overall vaccine effectiveness wanes with time, in all age groups (less so in 12-15?)
- Protection against hospitalization remains strong!

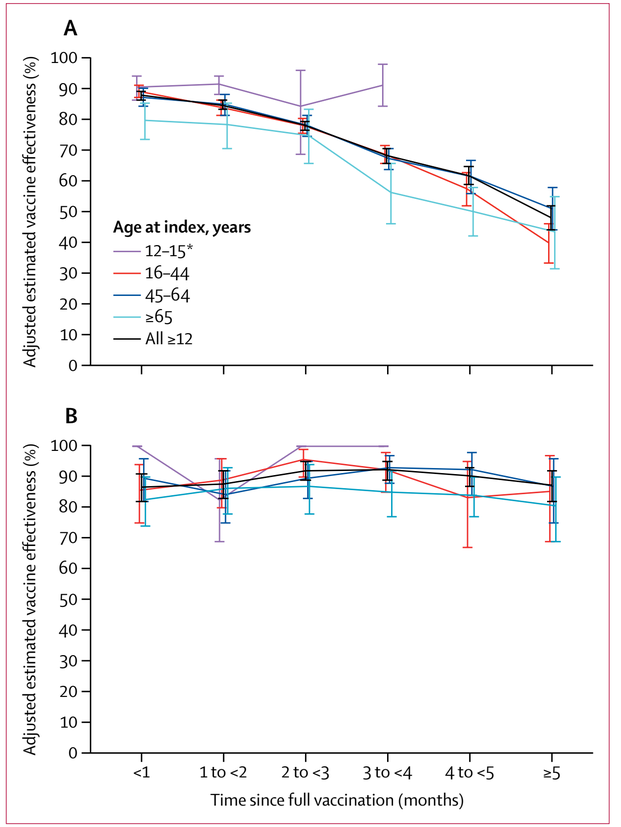


Figure 2: **Adjusted estimated vaccine effectiveness against SARS-CoV-2 infection and hospital admissions**
Vaccine effectiveness (95% CI) against SARS-CoV-2 infection (A) and COVID-19 hospital admission (B) by age group and number of months since being fully vaccinated with BNT162b2. *BNT162b2 authorised for those aged 12–15 years in May, 2021, limiting follow-up time for this age group.

tartof et al, lancet 2021. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02183-8/fulltext

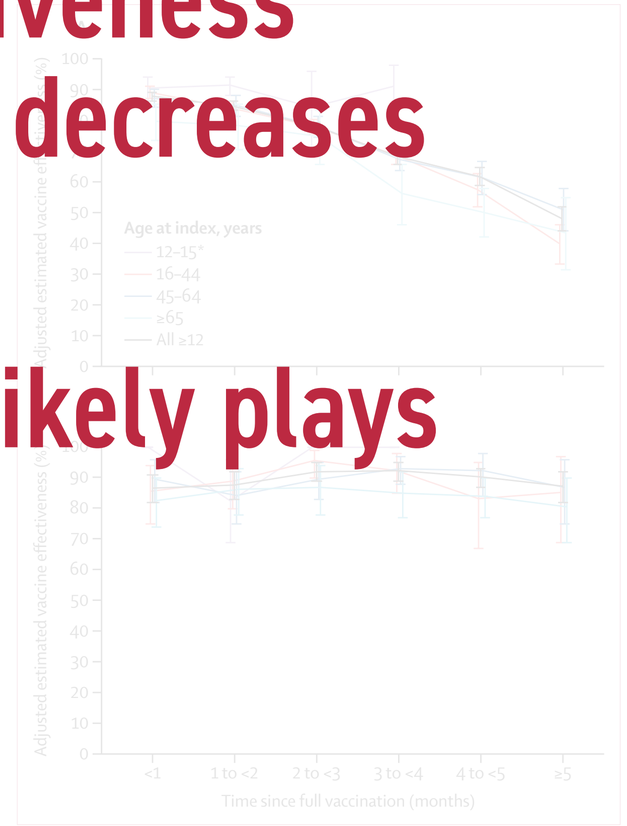
Retrospective study of individuals receiving Pfizer vaccine via Kaiser Permanente

Protection against severe disease persists!

- Stratified participants by age group and assessed vaccine effectiveness against infection (testing positive) and severe disease (hospitalization)
- Overall vaccine effectiveness waned with time, in all age groups (less so in 12-15?)
- Protection against hospitalization remains strong!

COVID vaccine effectiveness against any infection decreases with time.

"Waning immunity" likely plays a key role.



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tartof et al, lancet 2021. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02183-8/fulltext

SHOULD WE BOOST EVERYONE?

Vaccine boosters: experience from Israel

- Israel has had a strong vaccination campaign. Almost entirely Pfizer.
- Over-60s who received their second dose of vaccine at least five months previously became eligible for a **third dose (booster)** 30 July 2021
- Everyone over 12 became eligible for a third dose 30 August 2021
- Data from first month of third dose program published in NEJM 15 September 2021

ORIGINAL ARTICLE

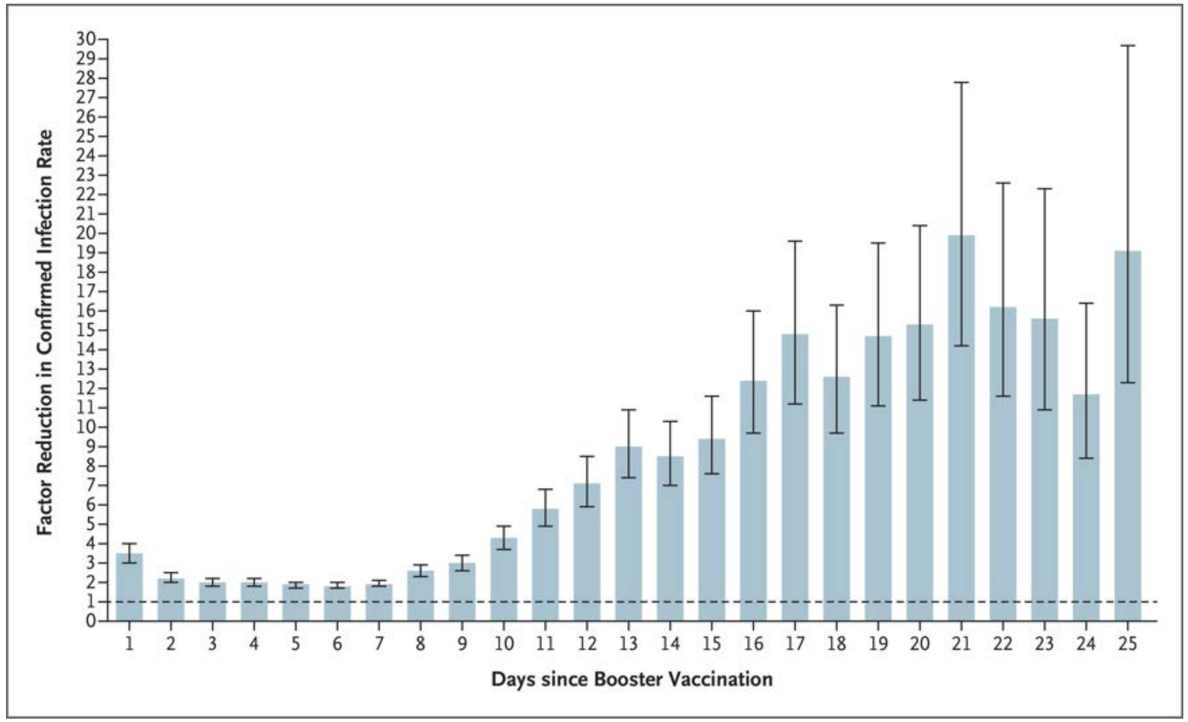
Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel

Yinon M. Bar-On, M.Sc., Yair Goldberg, Ph.D., Micha Mandel, Ph.D., Omri Bodenheimer, M.Sc., Laurence Freedman, Ph.D., Nir Kalkstein, B.Sc., Barak Mizrahi, M.Sc., Sharon Alroy-Preis, M.D., Nachman Ash, M.D., Ron Milo, Ph.D., and Amit Huppert, Ph.D.

doi:10.1056/NEJMoa2114255

Third dose of Pfizer vaccine reduces infection risk

- Over 1.1 million participants received second dose before 1 March 2021
- Compared relative risk of infection using national test registry
- Beginning 12 days after third dose:
  - 11.3-fold reduction in infections
  - 19.5-fold reduction in severe illness

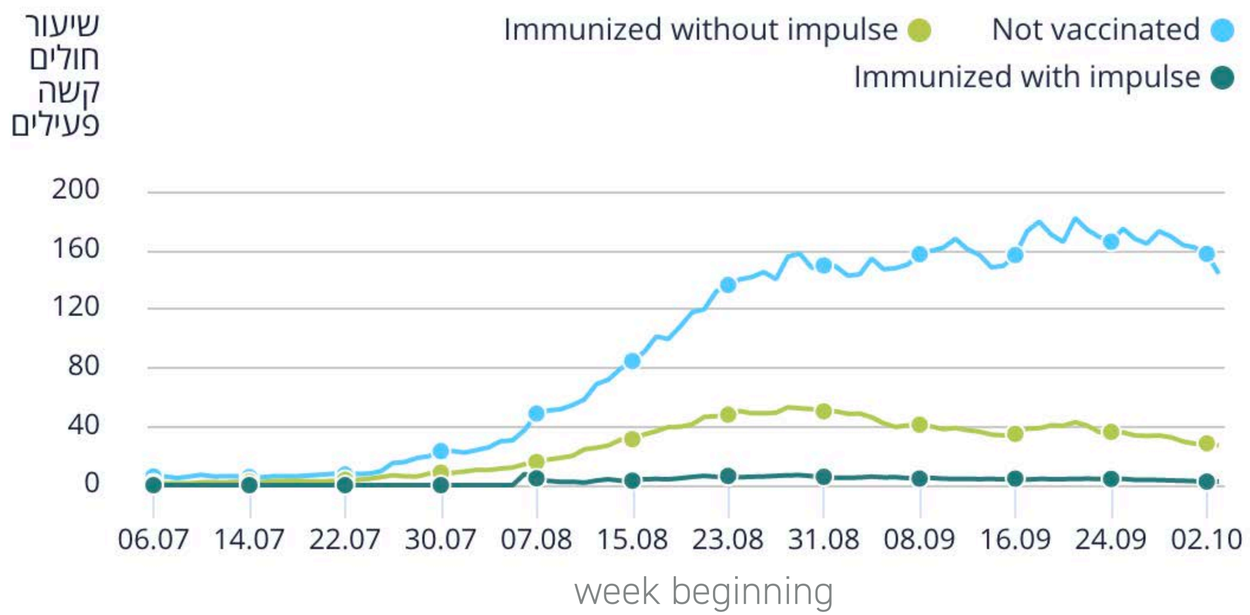


bar-on et al, nejm 2021. https://www.nejm.org/doi/full/10.1056/NEJMoa2114255

Third doses reduce risk of severe illness

- Addition of **third doses** reduced **severe illnesses** relative to **2 doses** and **no vaccine** in both older and younger individuals
- Note that 2 doses still offer protection from severe disease

Rate of over-60s with severe illness per 100k by vaccine status



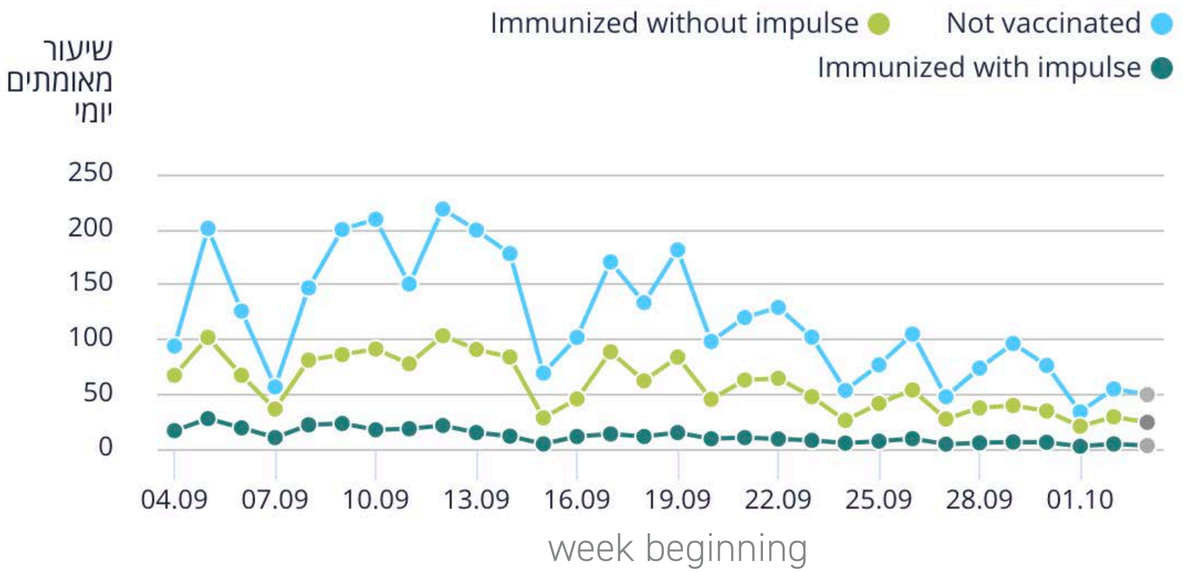
"Impulse" = third dose

https://datadashboard.health.gov.il/COVID-19/general? (translated from Hebrew)

Third doses reduce risk of infections

- Addition of **third doses reduced infections** among both older and younger individuals
- Second vaccine dose provides limited protection from infection in younger individuals

New test-positive cases per day per 100k in those under 60



"Impulse" = third dose

https://datadashboard.health.gov.il/COVID-19/general? (translated from Hebrew)

Boosters of all authorized vaccines increase immunity

PFIZER/BIONTECH

Dolsten said that early data from the company's own studies shows that a third booster dose generates antibody levels that are five to 10-fold higher than after the second dose, suggesting that a third dose will offer promising protection.

MODERNA

An additional analysis showed that a booster dose of mRNA-1273 at the 50 µg dose level induced robust antibody responses and significantly increased geometric mean titers (GMT) for all variants of concern including Beta (B.1.351) by 32- fold, Gamma (P.1) by 43.6-fold and Delta (B.1.617.2) by 42.3-fold.

JOHNSON & JOHNSON

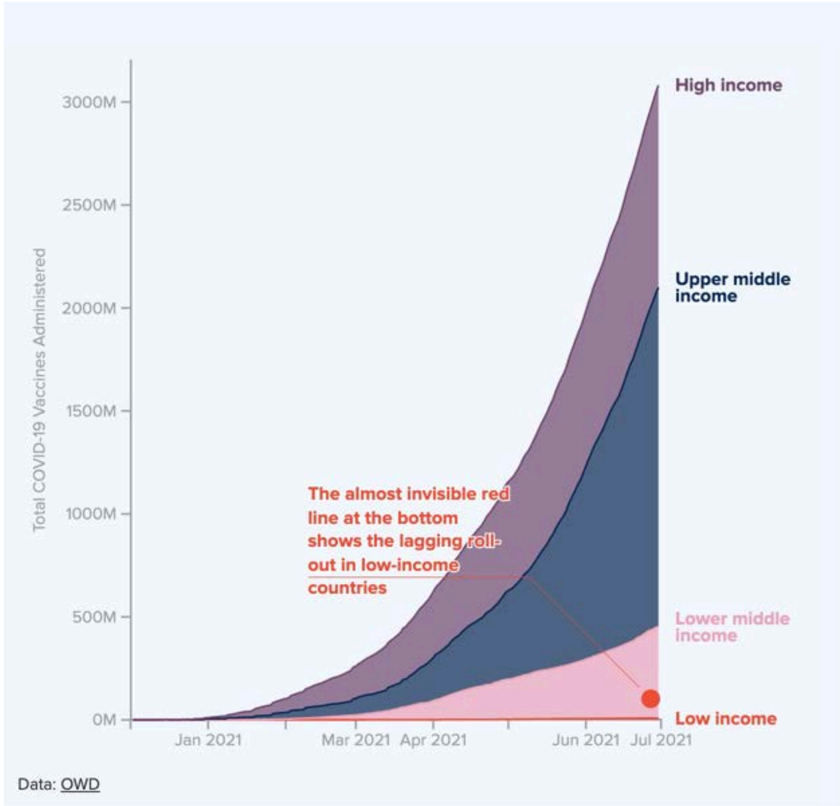
When a booster of the Johnson & Johnson COVID-19 vaccine was given six months after the single shot, antibody levels increased nine-fold one week after the booster and continued to climb to 12-fold higher four weeks after the booster. All rises were irrespective of age.

Third doses can be effective at reducing transmission

- Israel is at 70% vaccinated more than seven months after reaching 50%
- US is at 62% vaccinated more than four months after reaching 50%
- Hospitalizations and deaths are concentrated in the unvaccinated
  - Adults are not being vaccinated quickly, except when motivated by employment or other mandates
  - Kids and immunocompromised remain at risk
- A 90% reduction in transmission after third doses in the vaccine willing would reduce community transmission and risk to all

Global vaccine equity remains a challenge

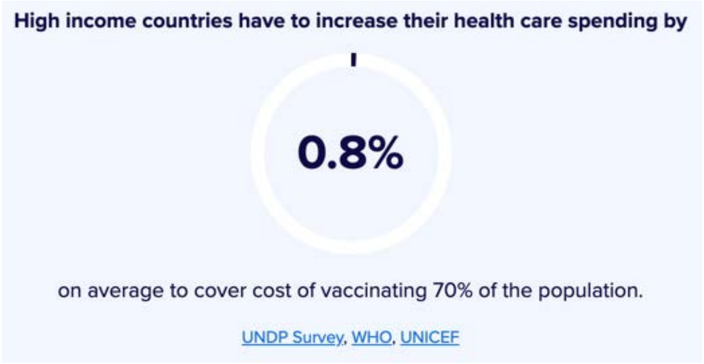
- The vast majority of the >3bn vaccine doses given worldwide have been given in richer countries

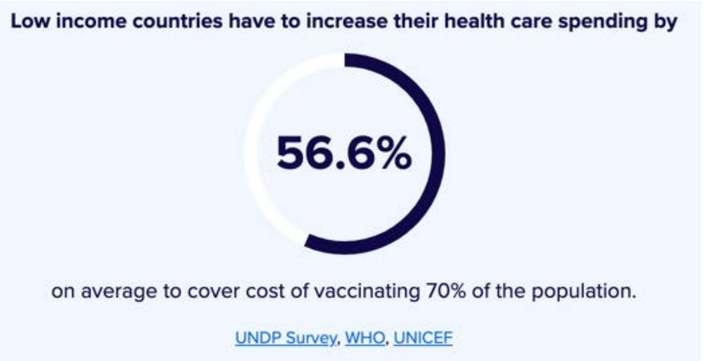


who, un development program, oxford university: https://data.undp.org/vaccine-equity/

Global vaccine equity remains a challenge

- The vast majority of the >3bn vaccine doses given worldwide have been given in richer countries
- Average annual health care expenditure per capita in low-income countries is $41
- Average cost to deliver 2 vaccine doses is $35
- Rich countries need to subsidize vaccine for lower-income countries, but challenges go beyond just vaccine supply.





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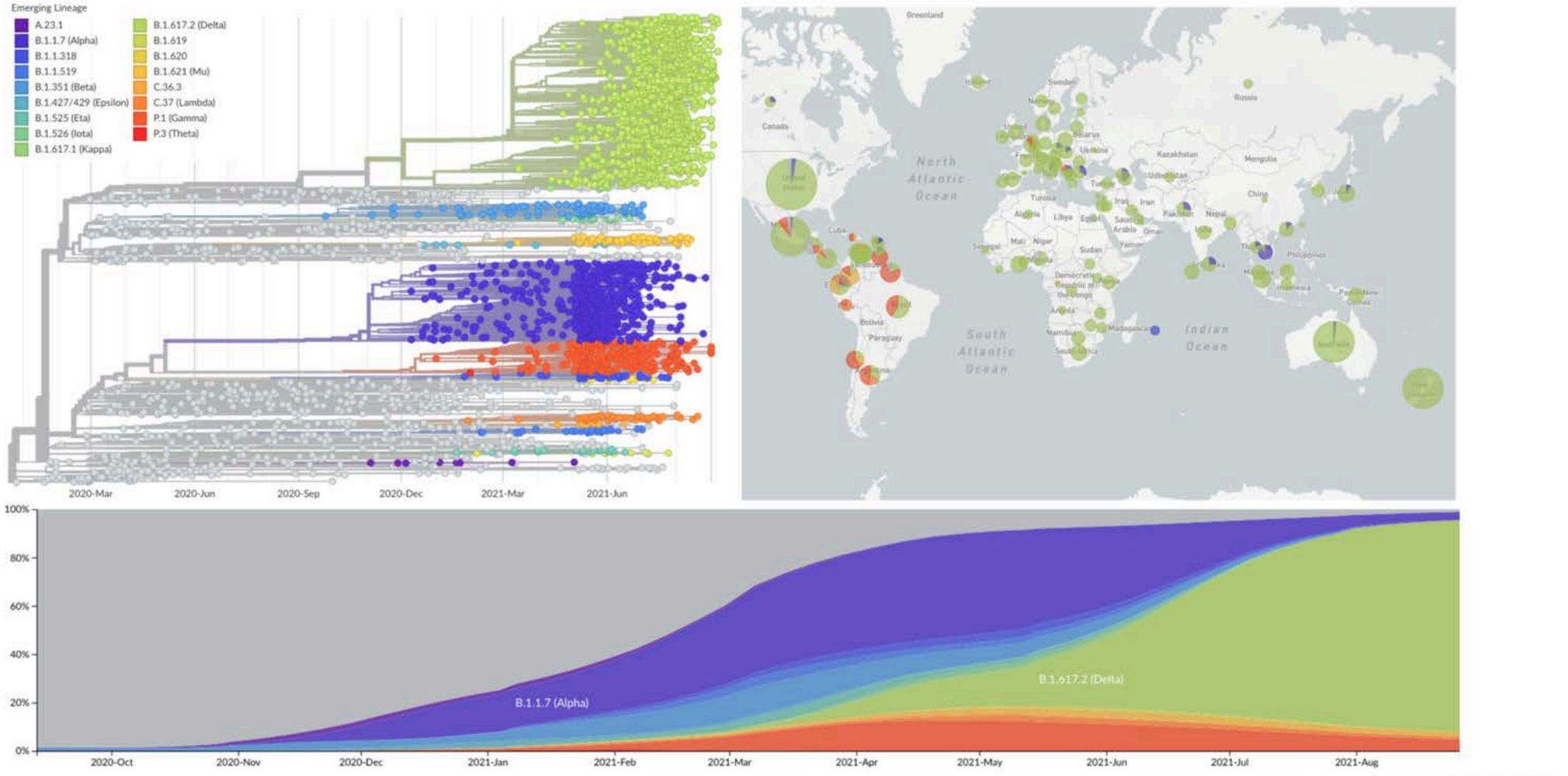
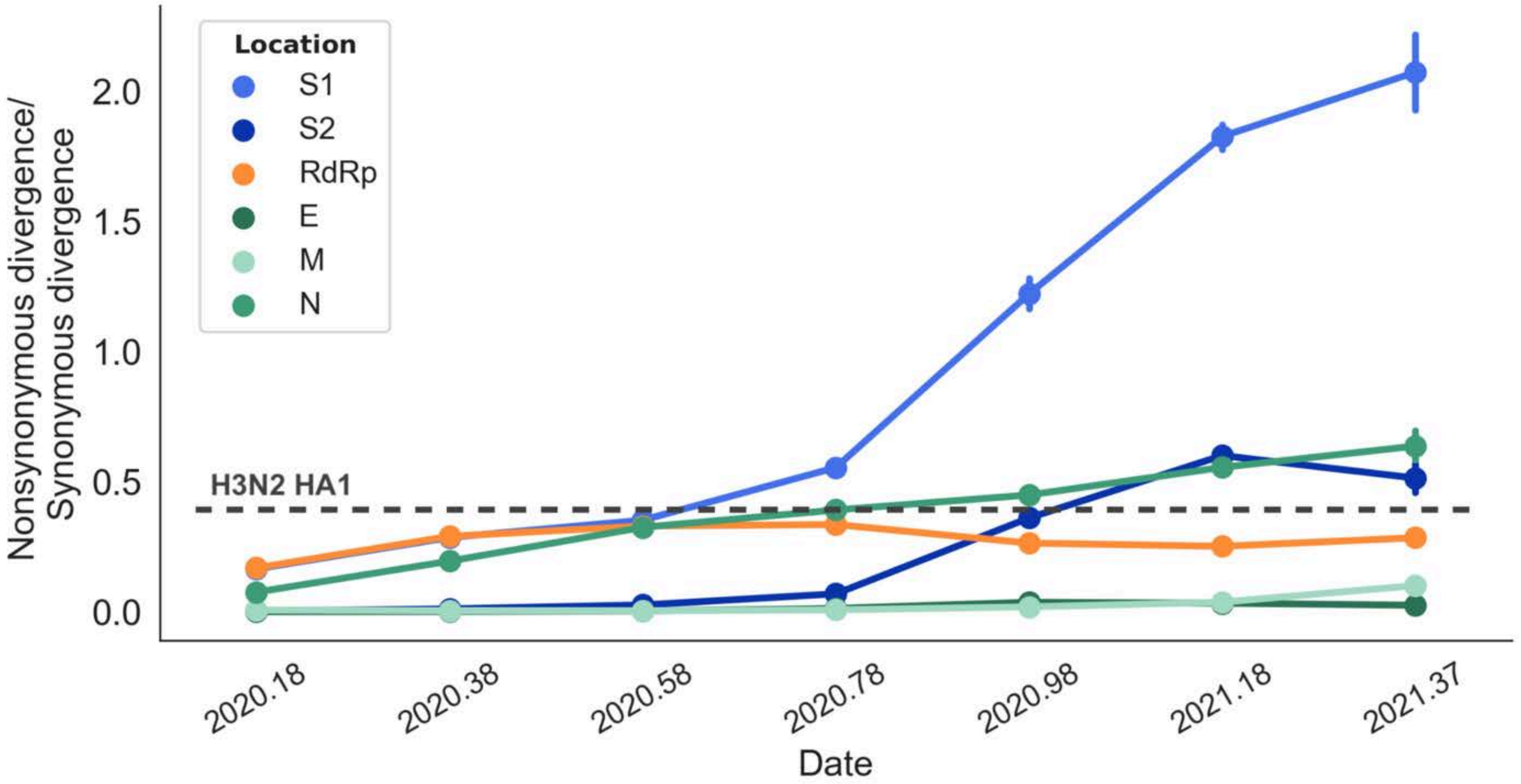
WILL WE NEED VACCINE UPDATES?

Delta is outcompeting other variants and is on track to sweep



trevor bedford: https://bedford.io/talks/sars-cov-2-evolutionary-dynamics-vidd/#/24

Natural selection appears to be driving evolution of Spike S1

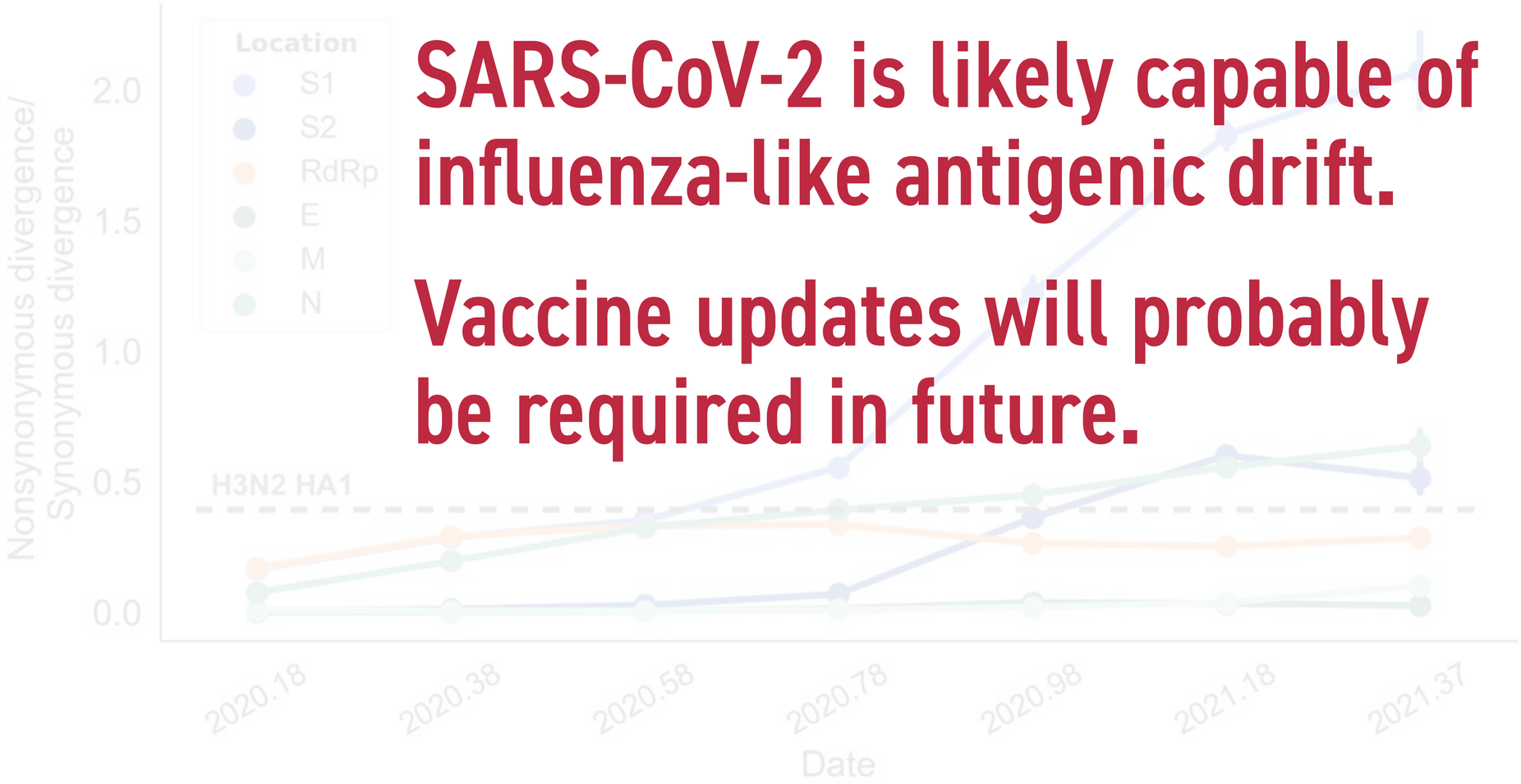


trevor bedford: https://bedford.io/talks/sars-cov-2-evolutionary-dynamics-vidd/#/36

Kistler et al. 2021. bioRxiv.

Excess nonsynonymous (amino-acid-changing) mutations indicate adaptive evolution

Natural selection appears to be driving evolution of Spike S1



SARS-CoV-2 is likely capable of influenza-like antigenic drift.

Vaccine updates will probably be required in future.

trevor bedford: https://bedford.io/talks/sars-cov-2-evolutionary-dynamics-vida/#/30

Kistler et al. 2021. bioRxiv.

Final thoughts

- SARS-CoV-2 is likely to become the most severe seasonal respiratory infection. Control efforts must continue to evolve along with the virus.
- Two vaccine doses remain effective against severe disease, but protection against any infection wanes (half-life ~110 days?) and vaccinated people can transmit
- “Remote” boosters enhance immunity and help prevent community spread—particularly important in partially vaccinated communities below herd immunity?
- Need to balance benefit of boosters with need to vaccinate the unvaccinated. Will wealthy countries increase funding to administer COVID-19 vaccines globally?