COVID-19:Lessons Learned? Variants and Vaccines

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History of Variants

Name	Date of Emergence	Origen	Genotype
Wild Type	October 2019	China	
Alpha	September 2020	UK	B.1.1.7
Beta	May 2020	South Africa	B.1.351
Gamma	November 2020	Brazil	P.1
Delta	October 2020	India	B.1.617.2
Lambda	June 2021	Peru	C.37
Mu	June 2021	Columbia	B1.621
Iota	November 2020	New York	B.1.526

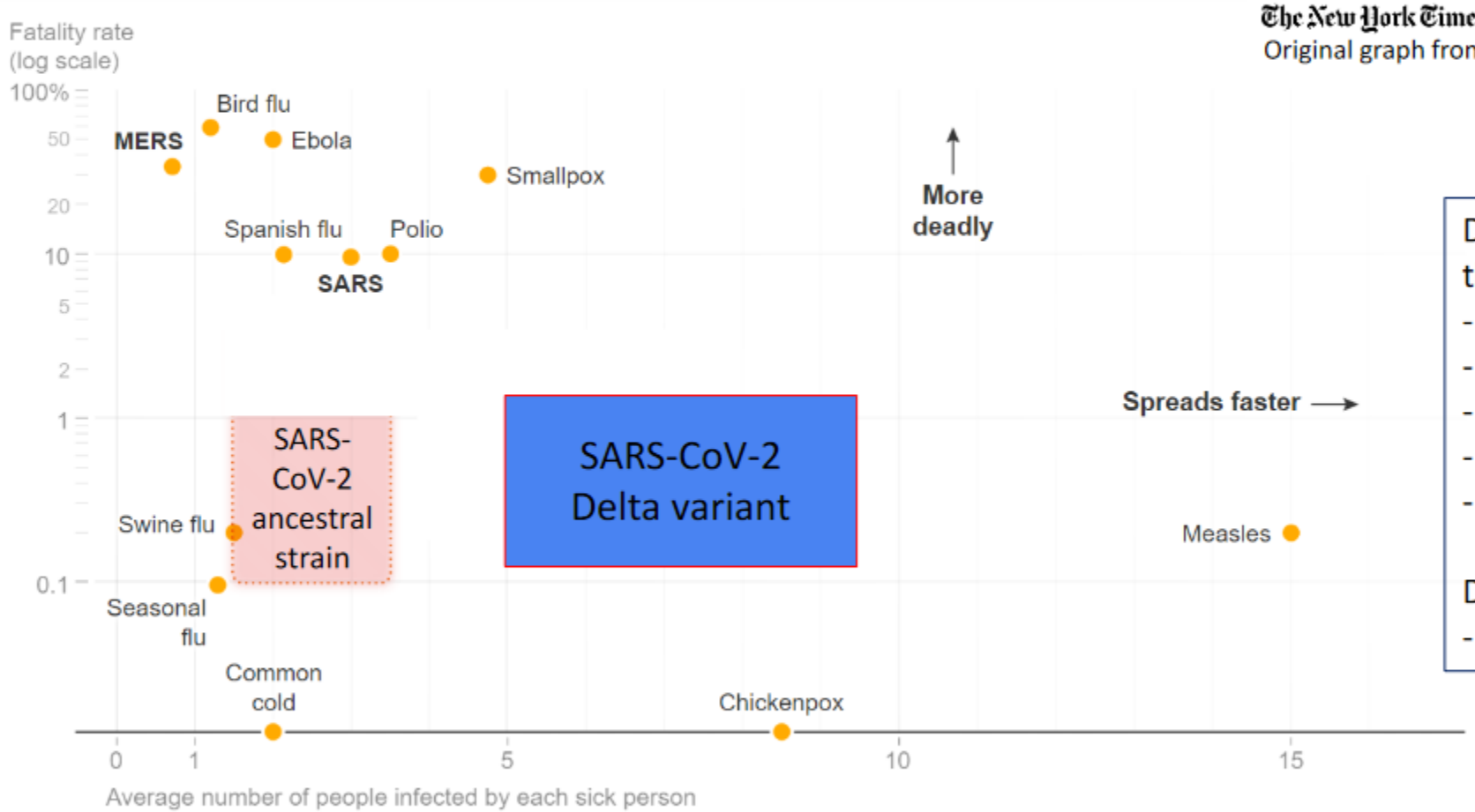
Variants
A Few Specifics

- Alpha-
  - Binds more tightly to ACE2 binding receptor (N501Y)
  - 50% more contagious than wild type
  - May have been driven by convalescent plasma and monoclonal antibodies
- Beta-
  - Has N501Y (increased transmission)
  - Also has E484K (decreased neutralization by antibody)
- Gamma-
  - Increased transmission (N501Y)
  - Resists proteolytic cleavage (D614G) of spike protein

Variants

- Delta-
  - Now dominant variant in most of the world
  - **Markely** increased transmission- (similar to chicken pox)
  - Produces higher viral loads than previous variants
  - Produces longer duration of shedding
  - Evades immune response to previous (non-delta) infections
  - Less sensitive to neutralizing antibodies
  - Lower vaccine efficacy

Transmission of Delta variant vs. ancestral strain and other infectious diseases



Delta variant is **more** transmissible than:
- MERS & SARS
- Ebola
- Common cold
- Seasonal flu & 1918 (“Spanish”) flu
- Smallpox

Delta variant is **as** transmissible as:
- Chicken Pox

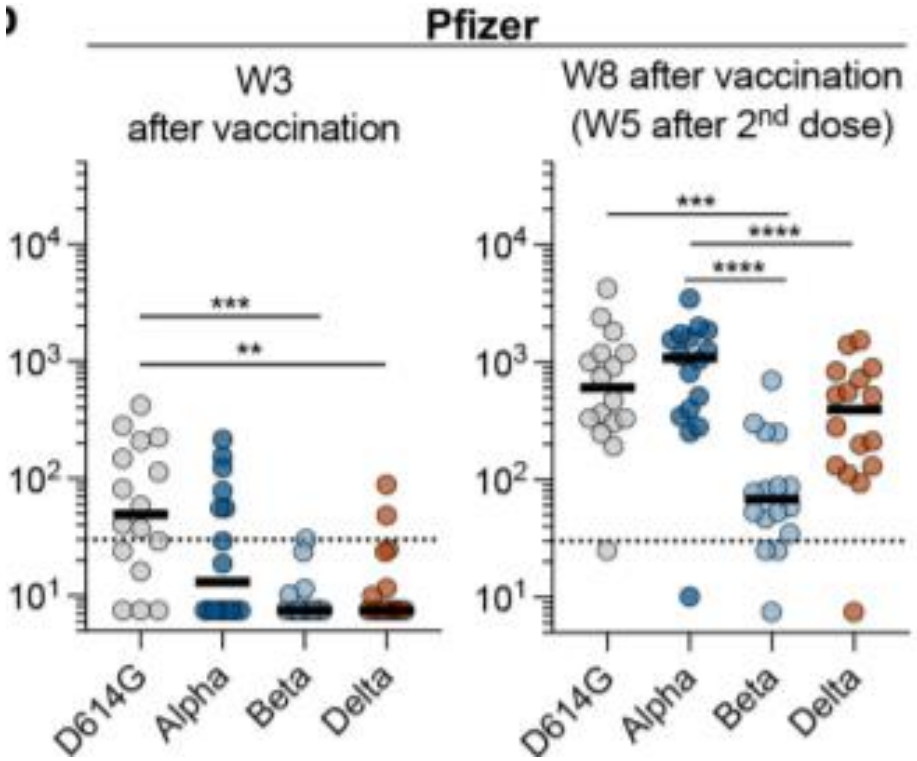
The coming of Delta - Vaccines

Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant

Julia Stowe[1], Nick Andrews[1,2], Charlotte Gower[1], Eileen Gallagher[1], Lara Utsi[1], Ruth Simmons[1], Simon Thelwall[1], Elise Tessier[1], Natalie Groves[1], Gavin Dabrera[1], Richard Myers[1], Colin Campbell[1,2], Gayatri Amirthalingam[1,2], Matt Edmunds[1], Maria Zambon[1,3], Kevin Brown[1,2], Susan Hopkins[1,4], Meera Chand[1,5], Mary Ramsay[1,2], Jamie Lopez Bernal[1,2,3]

- Single dose BioNTech/Pfizer vaccine (PHE June 2021)
  - 33% protection against symptomatic disease (Alpha > 50%)
  - 75% protection against hospitalization
- Fully vaccinated (2 weeks after second dose)
  - 80% protection against infection
  - 88% protection against symptomatic disease (Alpha 93%)
  - 94% protection against hospitalization

Variant sensitivity to neutralizing antibodies



- Sera from individuals having received one dose of Pfizer vaccine barely inhibited variants Delta and Beta
- Two doses generated a neutralizing response in 95% of individuals, with titers 3-5 fold lower against Delta than Alpha
- Delta spread is associated with an escape to antibodies targeting non-RBD and RBD Spike

https://www.nature.com/articles/s41586-021-03777-9

Variants

- Lambda-
  - More transmissible than alpha or gamma, but not as transmissible as delta
  - More resistant to vaccines than alpha or gamma
  - More resistant to neutralizing antibodies
- Mu-
  - More resistant to vaccines and natural immunity
  - Less transmissible than delta
- Delta plus (B.1.617.2AY1/2)
  - Spreads more easily; binds better to lung tissue
  - May not be more deadly than delta
  - AY1 or 2 adds to immune escape
  - May be a serious problem for monoclonal antibodies
  - May become the first “Variant of High Consequence”

Variants
So What??

- Variants can arise spontaneously or in response to selective pressure
- Variants can lead to increased spread or virulence
- We could be 1-2 mutations from making current vaccines ineffective
- Increasing vaccine coverage is crucial to prevent worse mutations

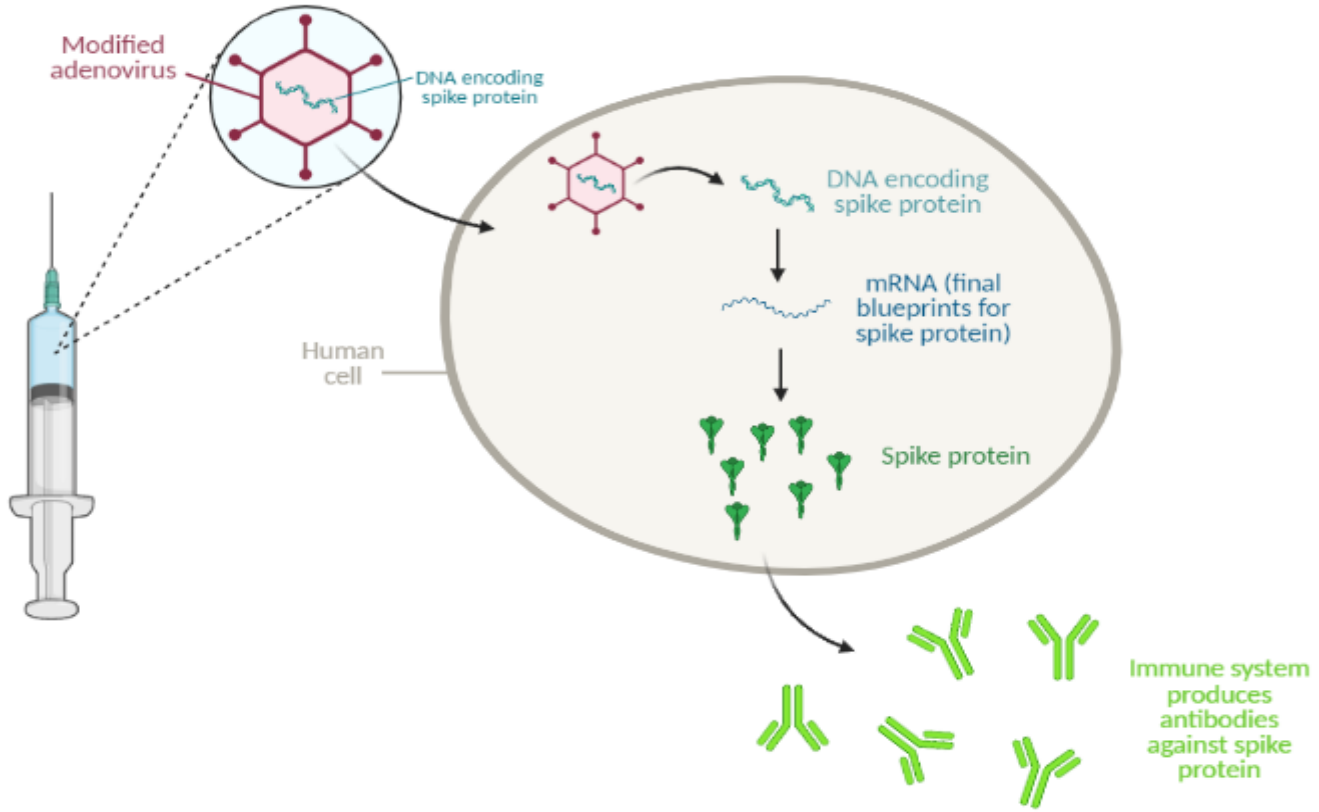
COVID-19 Vaccines (Real and Potential)

- Killed Virus Vaccines
- Live Virus Vaccines
- Split Virus Vaccines
- DNA Vaccines
- Adenovirus Vector Vaccines
- mRNA Vaccines

Adenovirus Vector Vaccine

- Splice DNA of spike protein into adenovirus
- Adenovirus infects vaccine recipient
- Spike protein produced along with viral replication
- Spike protein interacts with host immune system
- Anti-spike protein antibodies are produced.

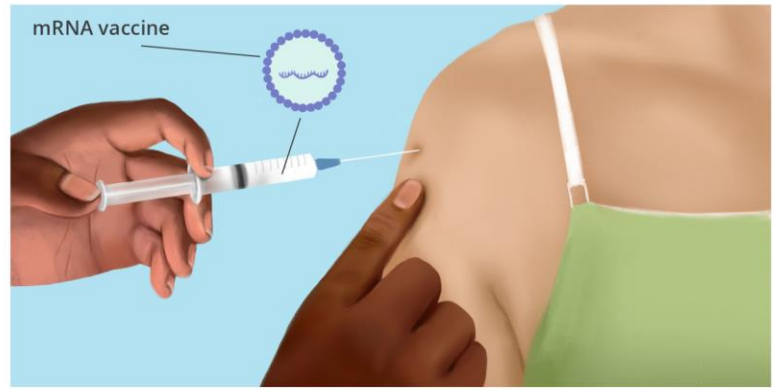
Adenovirus Vector Vaccine



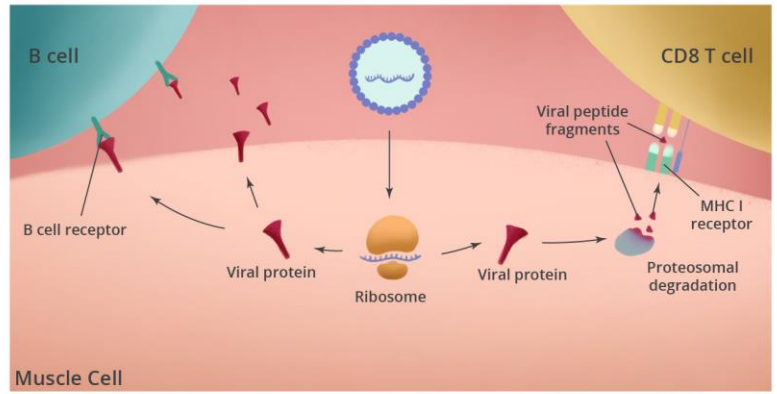
mRNA Vaccine

- mRNA packaged to prevent degradation
- Packaged mRNA injected into recipient
- mRNA is transcribed by tRNA to make spike protein
- Spike protein interacts with immune system
- Anti-spike antibodies are produced

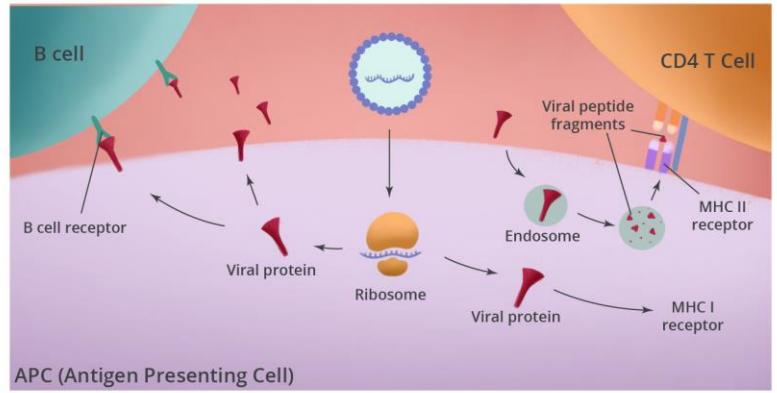
mRNA Vaccine Technology



In Deltoid Muscle

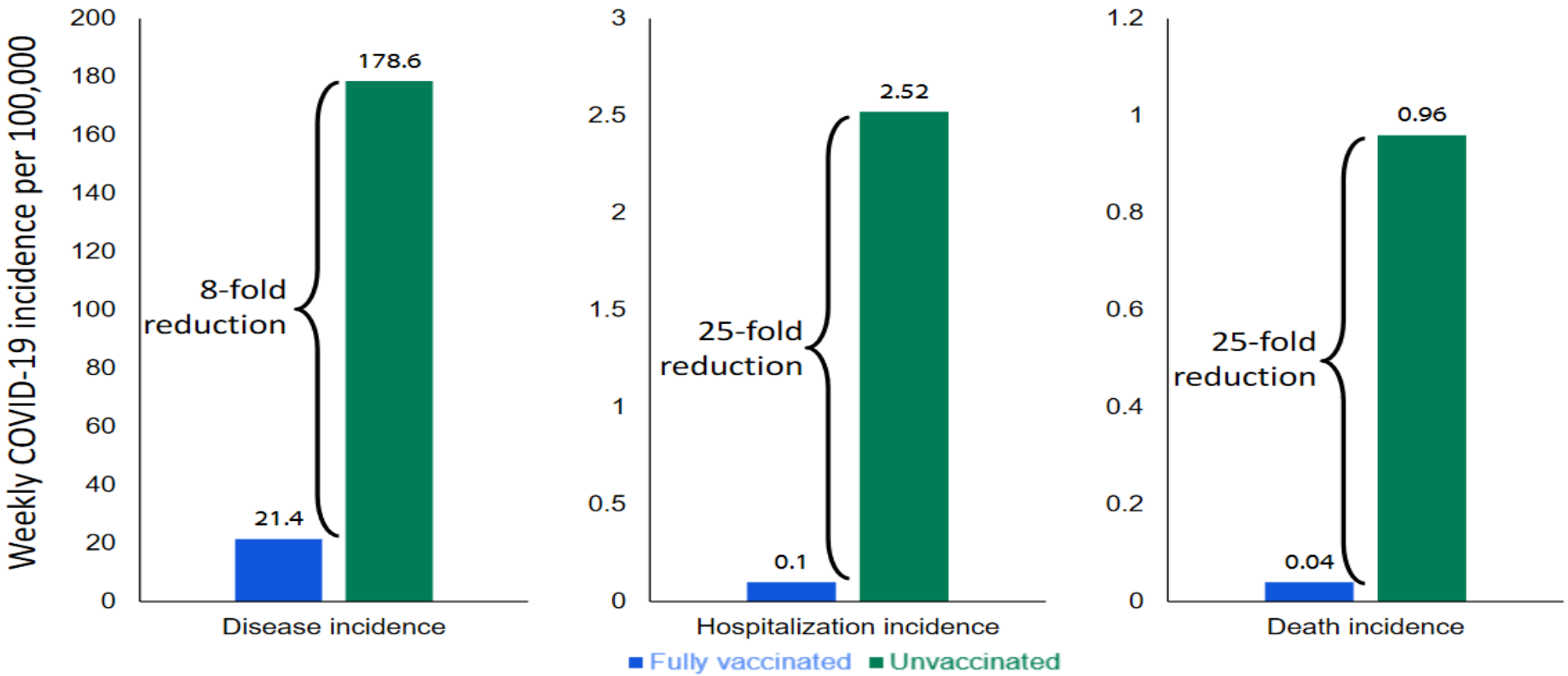


In Deltoid Muscle and Lymph Nodes



Vaccine Efficacy

Greater risk of disease, hospitalization and death among unvaccinated vs. vaccinated people: National estimates



At current incidence, 35,000 symptomatic infections per week among 162 million vaccinated Americans

Data from COVID Tracker as of July 24, 2021. Average incidence 100 cases per 100,000 persons per week. Vaccine effectiveness against symptomatic illness = 88% (Lopez Bernal et al. NEJM 2021), where risk is [1 – VE] or 12%. Vaccine effectiveness hospitalization (or death) = 96% (Stowe et al. PHE preprint), where risk is [1 – VE] or 4%. Rate in unvaccinated = Community rate/((1-fully vaccinated coverage) + (1-VE)*fully vaccinated coverage). Rate in fully vaccinated=(1-VE)*Rate in unvaccinated. Fully vaccinated coverage proportions were from COVID Data Tracker as of July 24, 2021 (50% for US,).

Lower estimates of VE for mRNA vaccines among immunocompromised populations: Published evidence

- 71% (CI 37-87%) **against SARS-CoV-2 infection** 7-27 days after 2nd dose of Pfizer-BioNTech vaccine among immunosuppressed* people vs. 90% (CI 83-96%) overall[1]
- 80% **against SARS-CoV-2 infection** ≥7 days after 2nd dose of mRNA vaccine among people with IBD on immunosuppressive medication[2]
- 75% (CI 44-88%) **against symptomatic COVID-19** 7-27 days after 2nd dose of Pfizer-BioNTech vaccine among immunosuppressed* people vs. 94% (CI 87-97%) overall[1]
- 59% **against COVID-19 hospitalization** among immunocompromised ≥14 days after 2nd dose of mRNA vaccine[3] vs. 91% (CI 86-95%) without immune compromise[3]

*Immunocompromised conditions (e.g., recipients of hematopoietic cell or solid organs transplant, patients under immunosuppressive therapy, asplenia, and chronic renal failure: advanced kidney disease, dialysis, or nephrotic syndrome)

1. Chodick et al. *Clinical Infectious Diseases*, ciab438, https://doi.org/10.1093/cid/ciab438; **2.** Khan et al. Gastroenterology (2021). https://www.gastrojournal.org/article/S0016-5085(21)03066-3/pdf; **3.** Tenforde et al. medRxiv preprint: https://doi.org/10.1101/2021.07.08.21259776

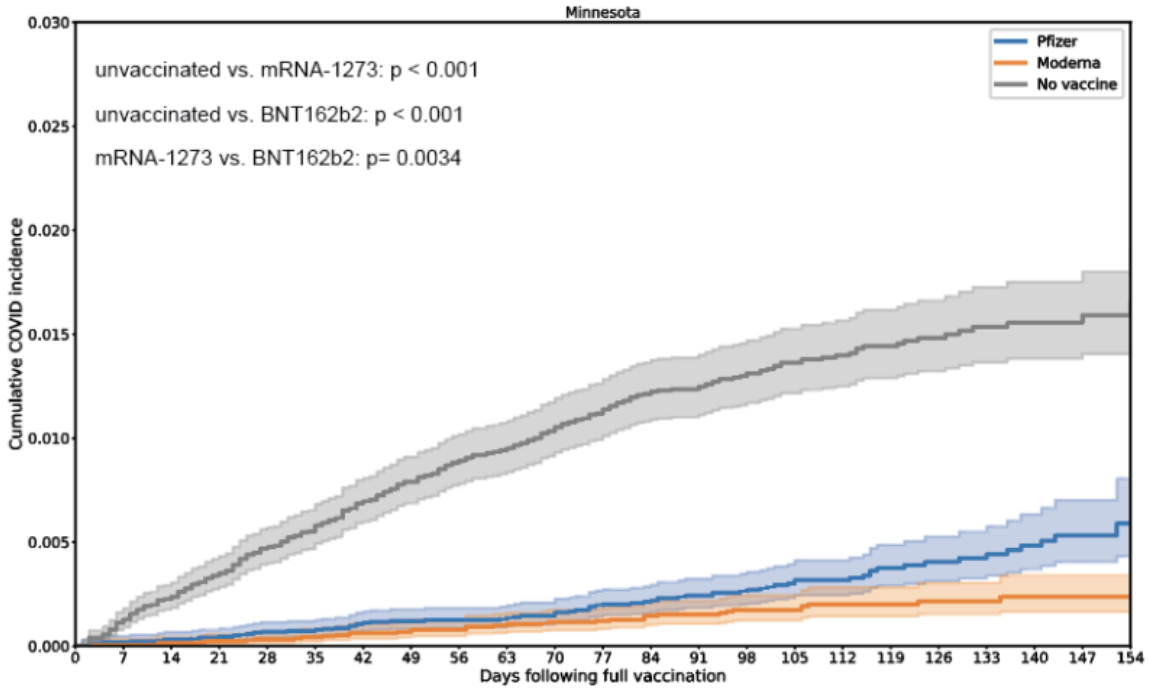
Is Moderna better than BioNTech/Pfizer

Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence

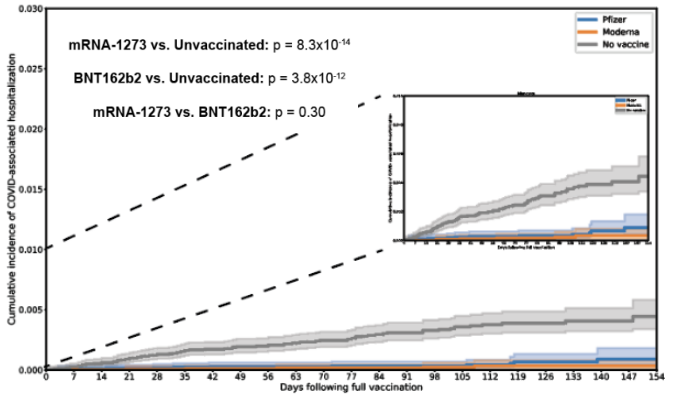
Arjun Puranik, Patrick J. Lenehan, Eli Silvert, Michiel J.M. Niesen, Juan Corchado-Garcia, John C. O'Horo, Abinash Virk, Melanie D. Swift, John Halamka, Andrew D. Badley, A.J. Venkatakrishnan, Venky Soundararajan

doi: https://doi.org/10.1101/2021.08.06.21261707

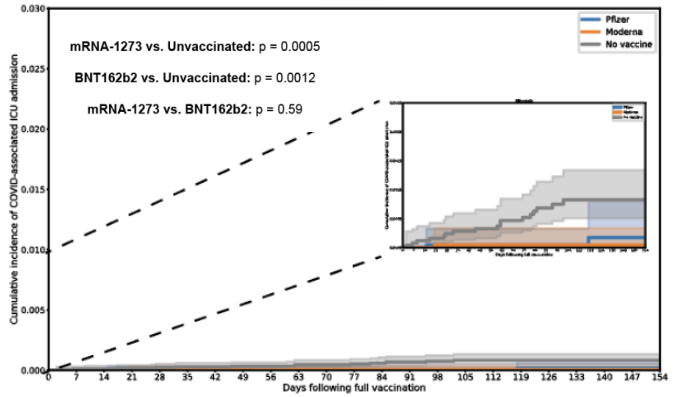
Comparison of cumulative incidence of SARS-CoV-2 infection between propensity-matched individuals in Minnesota



COVID-19 Associated Hospitalization



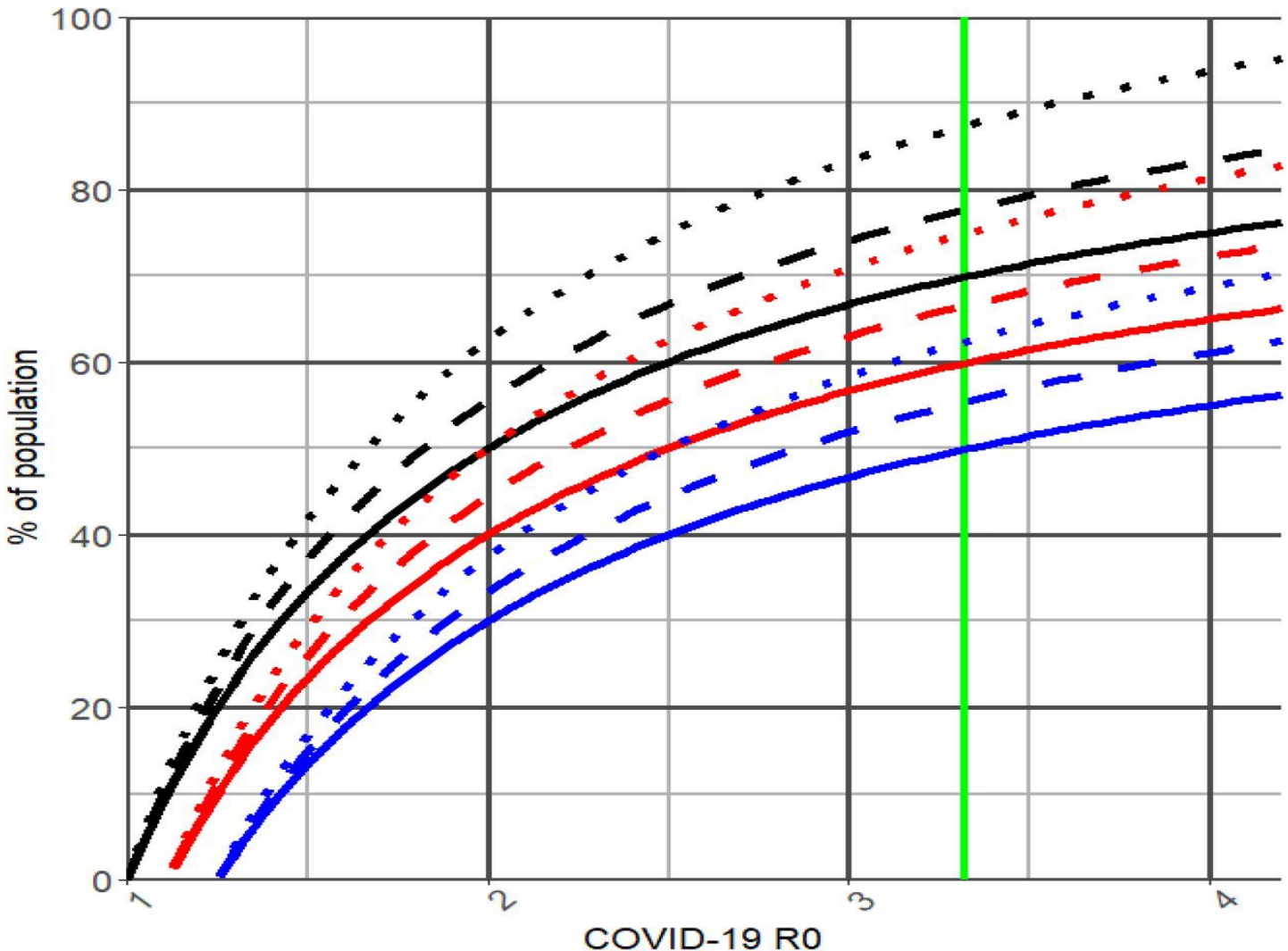
COVID-19 Associated ICU Admission



Herd Immunity

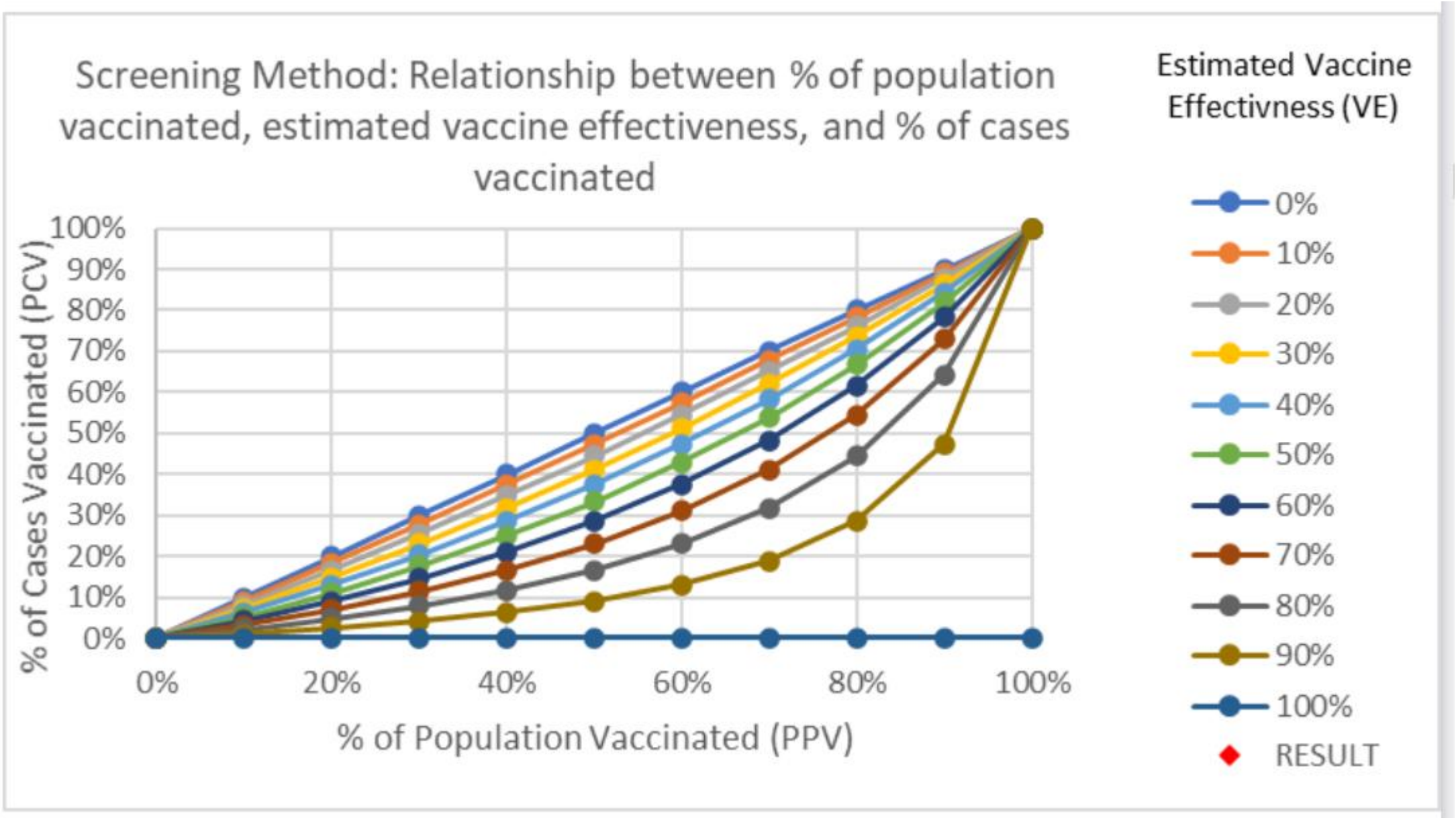
- May not be achievable by vaccination alone
- Decreasing vaccine efficacy increases the vaccine coverage required
- Complicated by asymptomatic infections
- Based on interaction of Ro, vaccine coverage, vaccine efficacy, and natural immunity in population

Herd Immunity

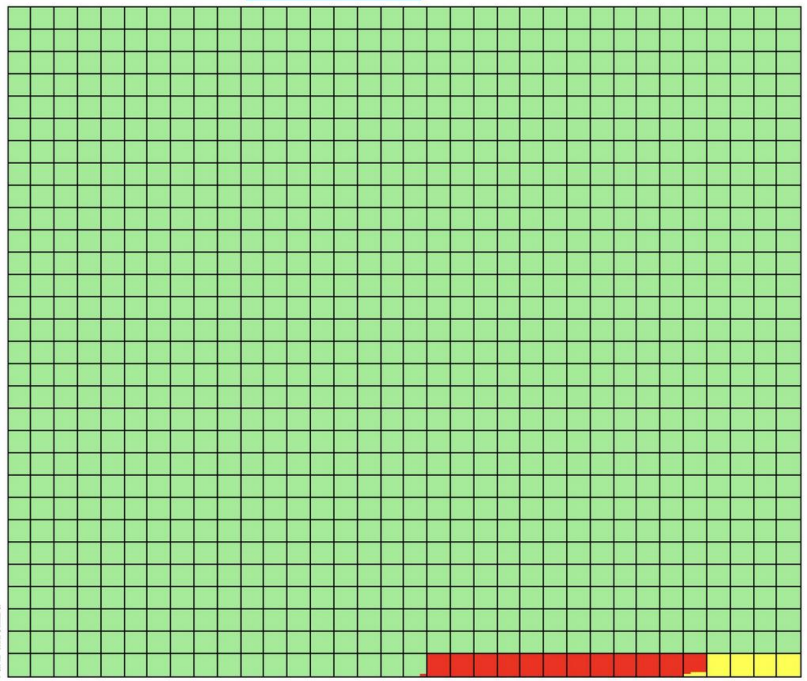


Breakthrough Infections

- Unavoidable if vaccine is less than 100% effective
- Becomes more common as vaccine coverage increases
- Depends on interaction of vaccine uptake, vaccine efficacy and (possibly) Ro
- Despite breakthroughs, there is still a 25-fold higher rate of hospitalization and death among unvaccinated


Screening Method: Relationship between % of population vaccinated, estimated vaccine effectiveness, and % of cases vaccinated
% of Cases Vaccinated (PCV)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0%
20%
40%
60%
80%
100%
% of Population Vaccinated (PPV)
Estimated Vaccine Effectivness (VE)
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
RESULT

Serious unvaccinated COVID-19 infections



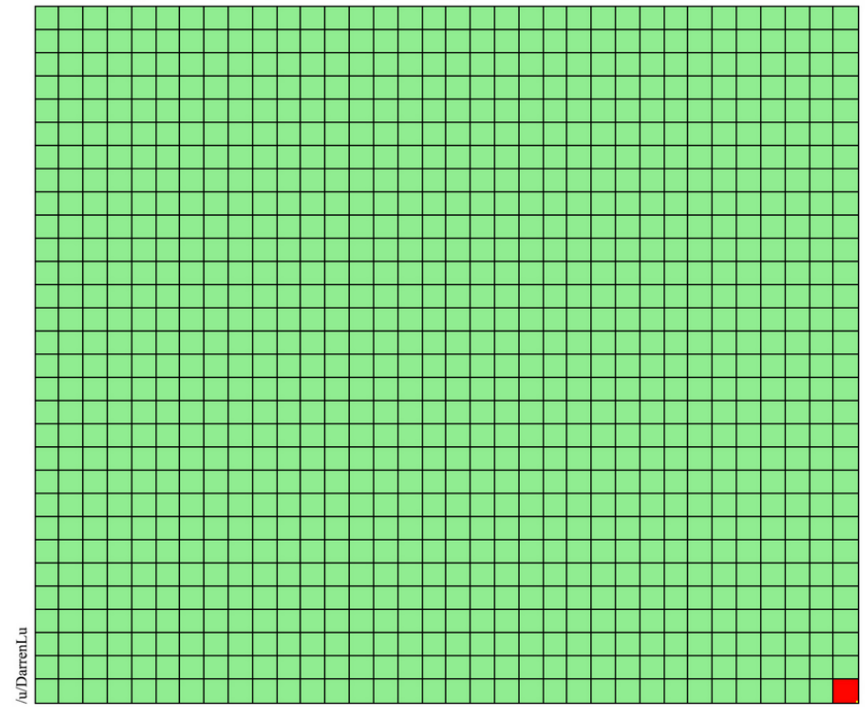
/u/DarrenLu

As of 21 July 2021 in the U.S...
For every 102K UN-vaccinated
There have been a TOTAL
of 1,603 new hospitalizations
And 417 COVID-19 deaths

IMPORTANT NOTES:
1. These are snapshots in time and compare different TOTALS over different time periods. It also compares mere sypmtomatic infections to more severe ones that lead to hospitalization. This DATA does NOT imply the chances getting infected or the severity of the infections. It means that as of last week, only about 1 in 1000 of ALL fully-vaccinated had symptomaticinfections. The likely reason is that, until recently, a combination of masking, social distancing, vaccinations, and milder spring/summer weather drove vaccinated AND unvaccinated infection rates to an all-time low. There is every reason to believe that the Delta variant WILL infect a lot of vaccinated people.
2. BUT the vaccines are INCREDIBLY effective at preventing and reducing the severity of infections. Because Delta has 1,000X the viral load of Alpha/regular COVID, there will be CLUSTERS of vaccinated people who get infected, but their disease will be much less severe than if they were unvaccinated.

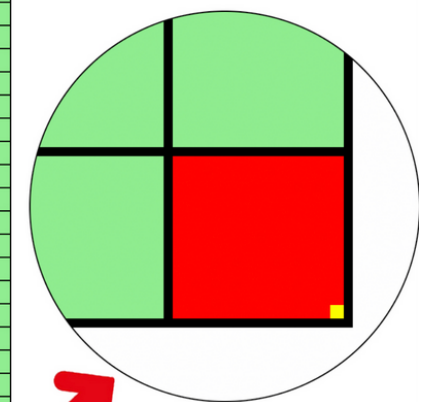
as of 21 July 2021, source: CDC COVID Data Tracker Weekly Review
https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html
Google Sheet worksheet: https://bit.ly/2TDs81Lt

Symptomatic breakthrough COVID-19 infections



/u/DarrenLu

Currently...
For every 102K vaccinated
There are 100 symptomatic
breakthrough infections
And ONE death

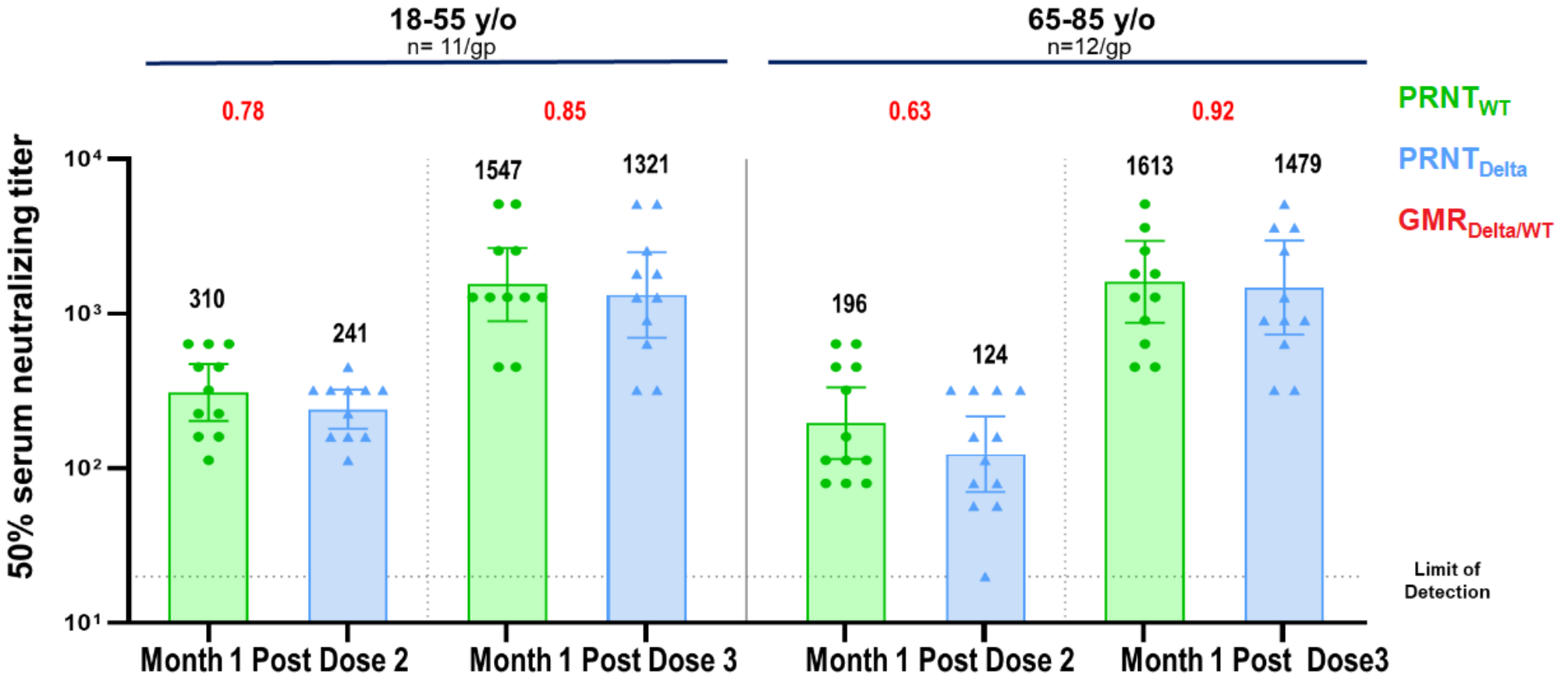


as of 26 July 2021, source: https://abcn.ws/3y9lpvv

Boosters

- We have no idea about the proper dosing regime
- Antibody titers decrease after 6-8 months
- 3rd vaccination significantly increases antibody titers
- We don’t know the significance of antibody titers.
- 3rd doses decrease the odds of testing positive for COVID-19 for at least 3 weeks.
- There are few data on significant endpoints.

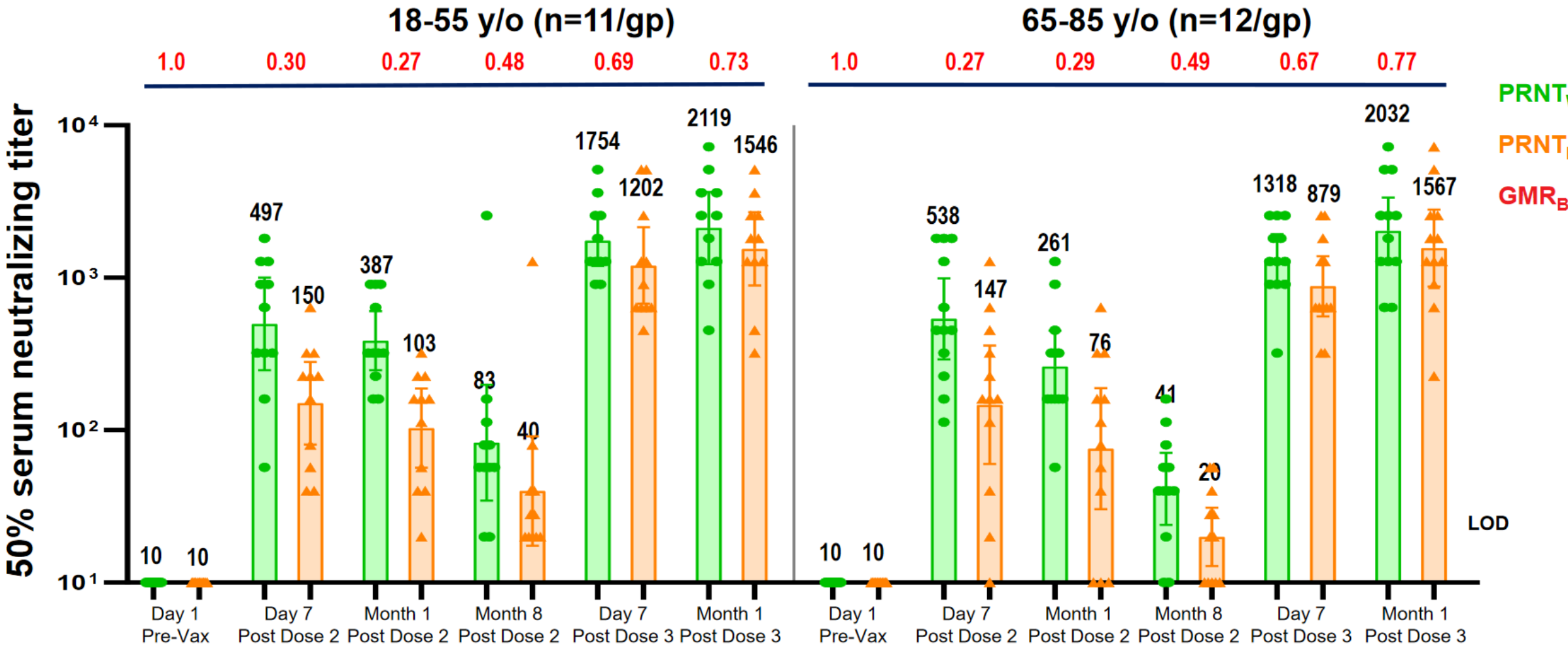
COVID-19 Vaccine: 3rd Dose Strongly Boosts Neutralizing Titers Against Delta Strain[1,2]



- Post dose 3 titers vs. the Delta variant are **>5-fold post dose 2 titers** in 18-55 y/o & **>11-fold post dose 2 titers** in 65-85 y/o
- Estimated potential for up to **100-fold increase in Delta neutralization post-dose three** compared to **pre-dose three**

1. Initial data; 2. Samples were tested against each variant separately; PRNT: Plaque Reduction Neutralizing Test; Wt: Wild Type; GMR: Geometric Mean Ratio

COVID-19 Vaccine: Neutralization Titers Much Higher Post 3rd Dose Than Post 2nd for Wild Type and Beta Variants[1,2]



1. Initial data, Phase 1 sentinel subjects received dose 1 & 2 of 30mcg BNT162b2 21 days apart, subjects then came back and received BNT162b2 30 mcg as a 3rd booster dose;
2. Samples were tested against each variant separately; PRNT: Plaque Reduction Neutralizing Test; GMR: Geometric Mean Ratio; WT: Wild Type; LOD: Limit of Detection