Outline

- The science behind COVID-19 vaccines
- Common side effects from COVID-19 vaccines
- New variants & COVID-19 vaccines
- Vaccine booster trials

Disclosure: I serve as sub investigator for AstraZeneca phase 3 study. No financial disclosures

How did we get to this point?

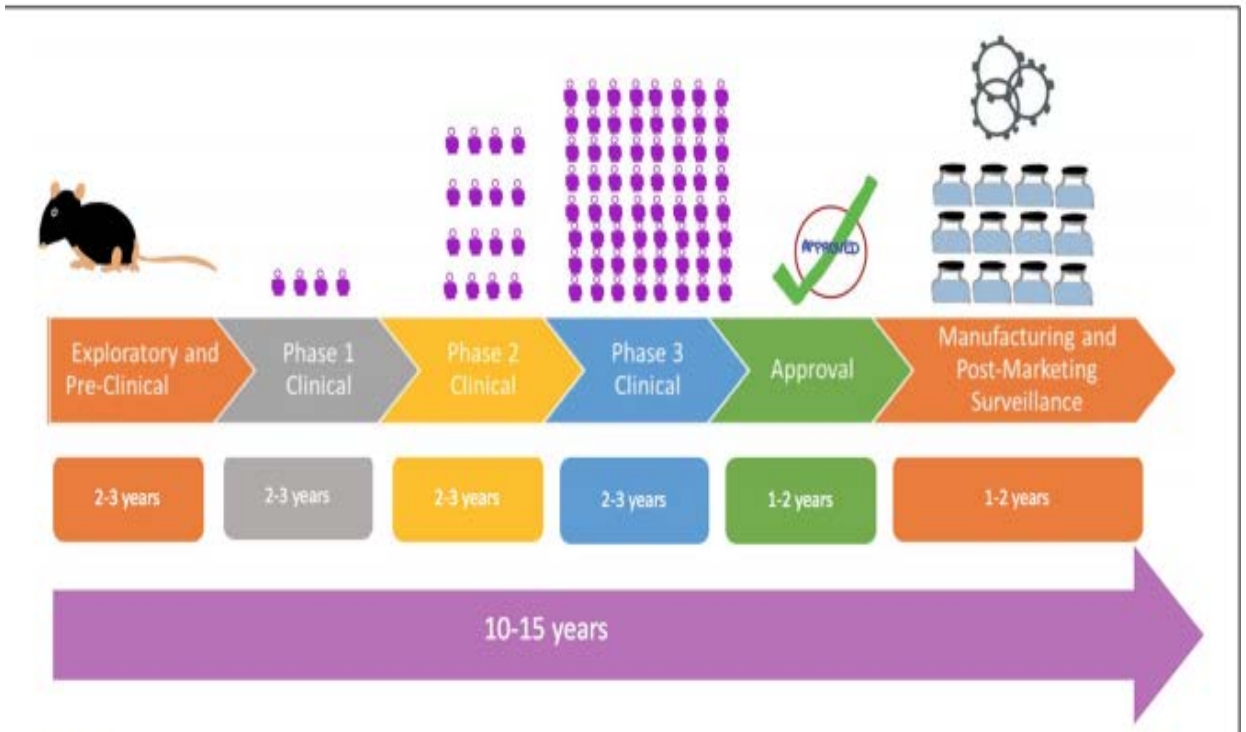


FIGURE 1 | Flowchart showing traditional process of vaccine development from exploratory, pre-clinical studies to Phase 1 studies in a comparatively few control volunteers as depicted by the figure to larger Phase 2 and Phase 3 studies. The symbol is a representation of the number of human subjects in trials.

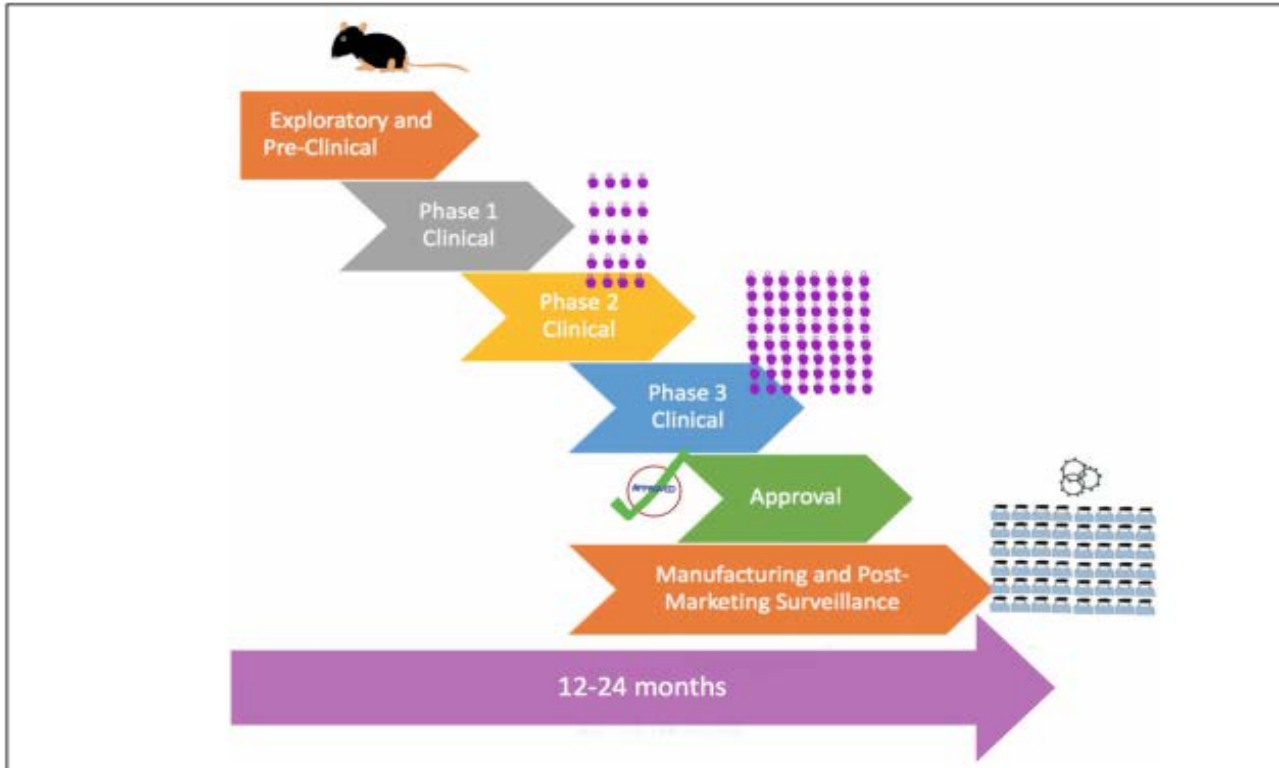
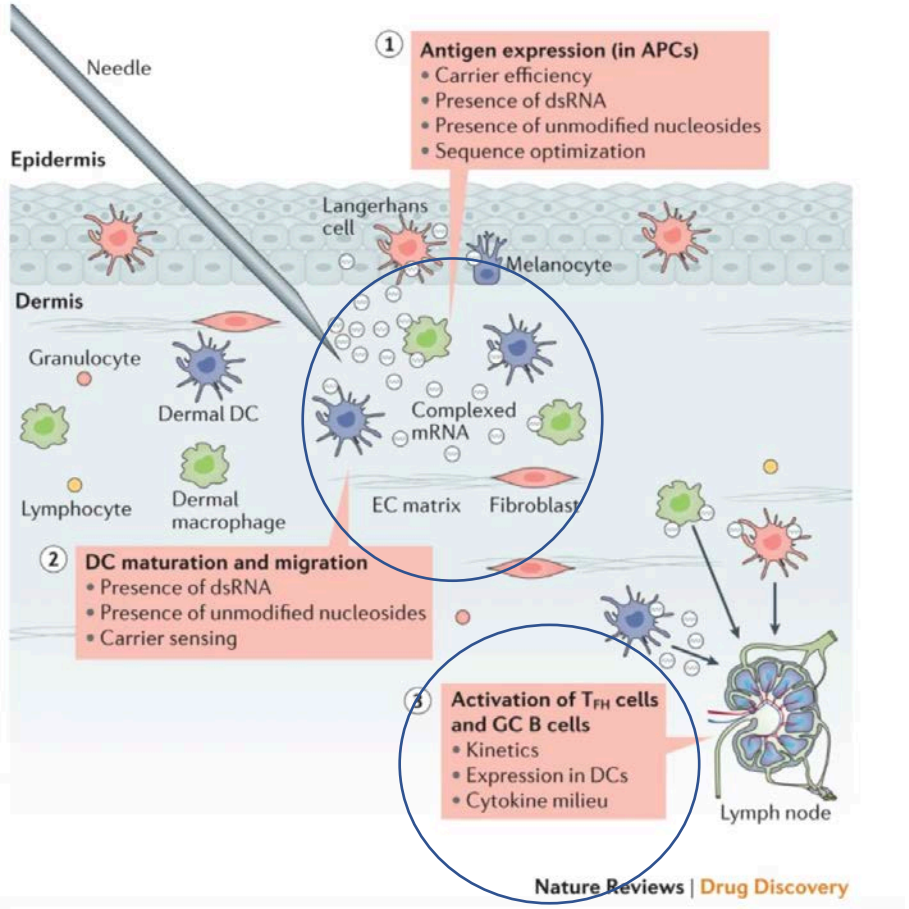


FIGURE 2 | Flowchart showing accelerated process of vaccine development in a pandemic with combined phases, pre-approval, and rapid large-scale manufacturing. The symbol is a representation of the number of human subjects in trials.

Sharma O, Front Immunol 2020.

Steps in generating an immune response: mRNA vaccines

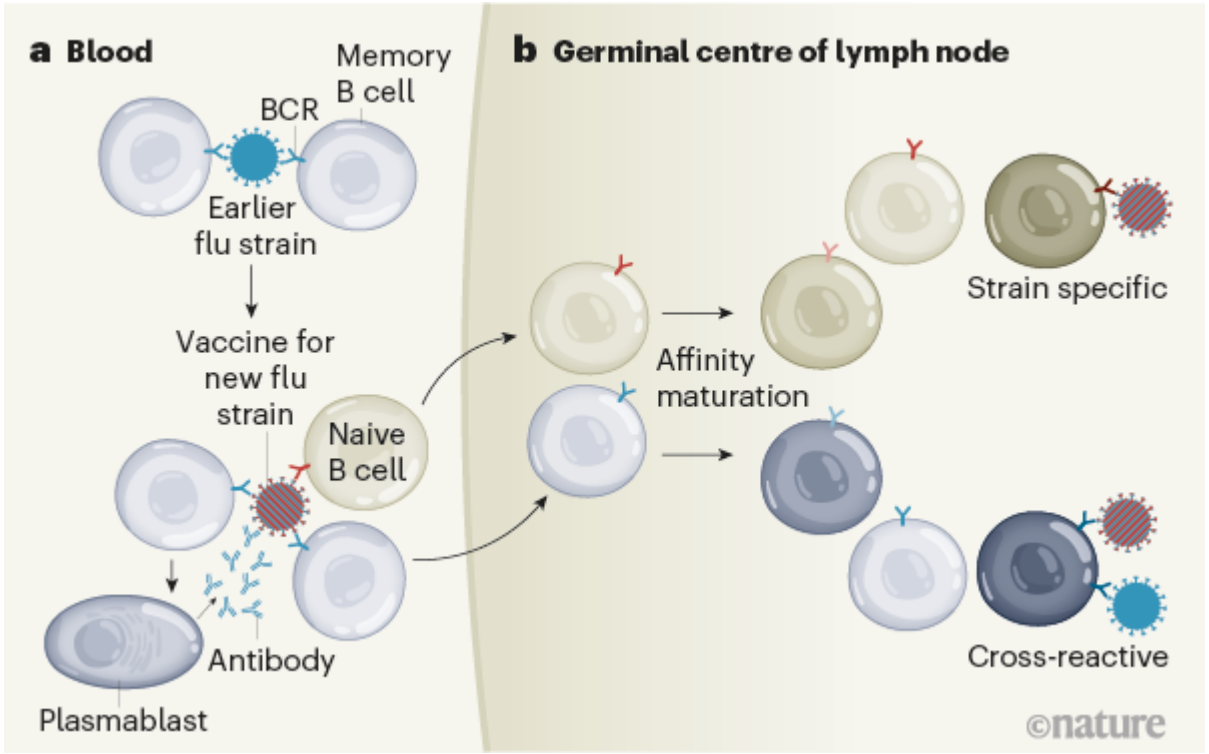
- 1) Injection of vaccine (in this case mRNA encased in lipid nanoparticles)
- 2) Uptake into cytoplasms of local antigen presenting cells (APCs)
- 3) Expression of SARS-CoV-2 Spike protein by APCs
- 4) Generation of robust, multifaceted, including T & B cell immune response

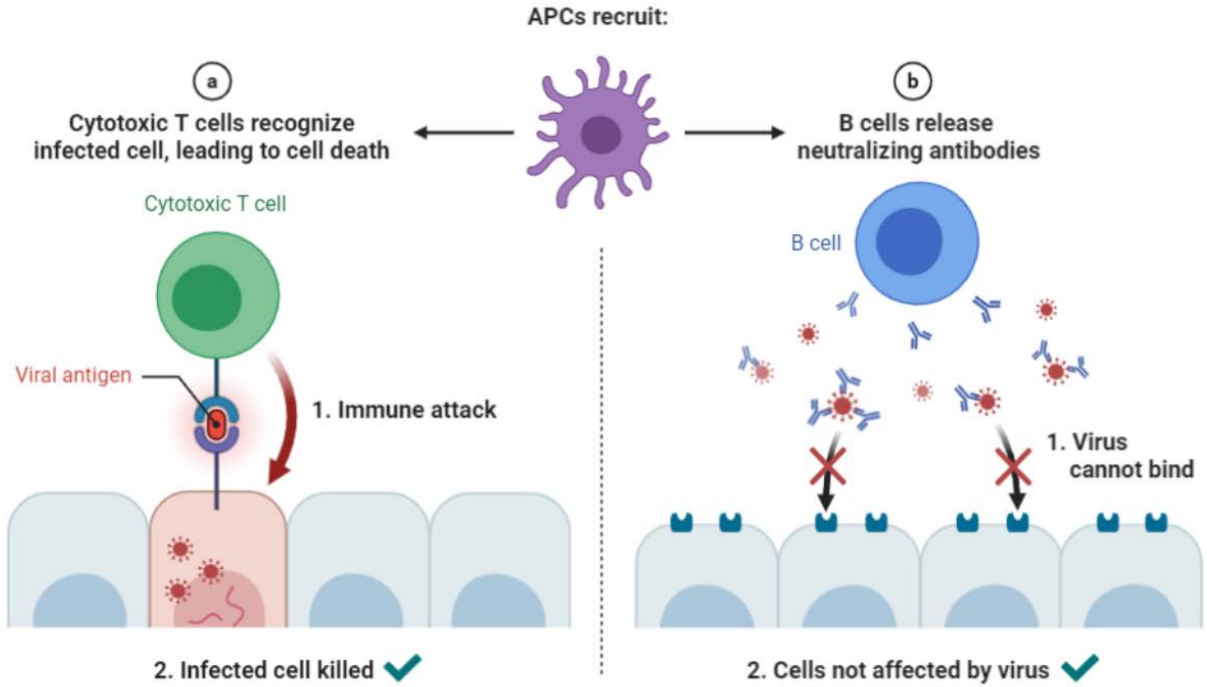


Pardi *Nat Rev Drug Discov* 2018 doi: 10.1038/nrd.2017.243

Vaccines and immunogenicity

- T cell response
- B cell response





Immunogenicity = ability of vaccine to produce immune (antibody) response

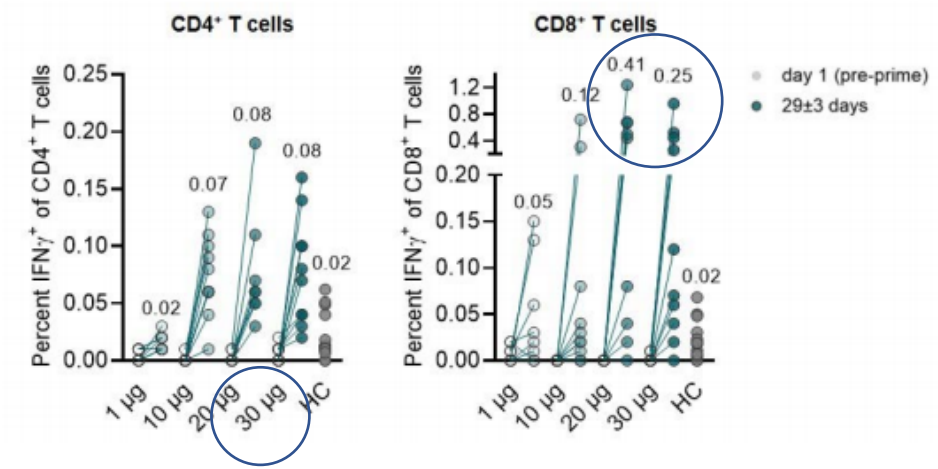
Efficacy = ability of vaccine to reduce incidence of disease in vaccinated population compared to unvaccinated population

Rodda LB. Nature. 2019.
Baraniuk C. Scientist. 2020.

Pfizer/BioNTech vaccine

- Formerly known as BNT162b2
- Lipid nanoparticle-encapsulated mRNA vaccine against SARS-CoV-2 spike glycoprotein antigen
- 2 doses, 21 days apart
- Storage at -20C

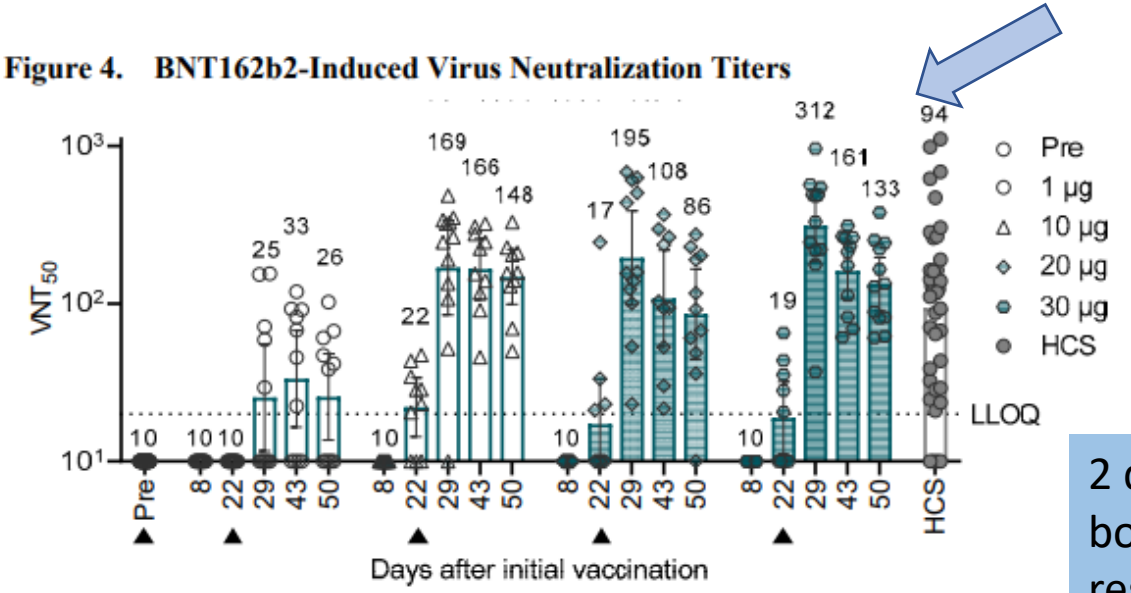
Figure 2. Frequency and Magnitude of BNT162b2-induced CD4⁺ and CD8⁺ T Cell Responses



PBMCs of BNT162b2-immunized participants were obtained on Day 1 (pre-prime) and on Day 29 (7 days post dose 2) (coh... OVID-19-recovered human convalescent donors (HC, n=18) were stimulat... nting the N-terminal portion of the wild-type sequence of SARS-CoV-2 S ... intracellular cytokine staining flow cytometry analysis. Frequency of S-specific CD4+ and CD8+ T cells producing IFNγ in response to S pool 1 as a fraction of total circulating CD4 and CD8 T ce... are shown. Numbers indicated in the graphs are the arithmetic mean fractions.

Dose Finding: 30ug

Figure 4. BNT162b2-Induced Virus Neutralization Titers

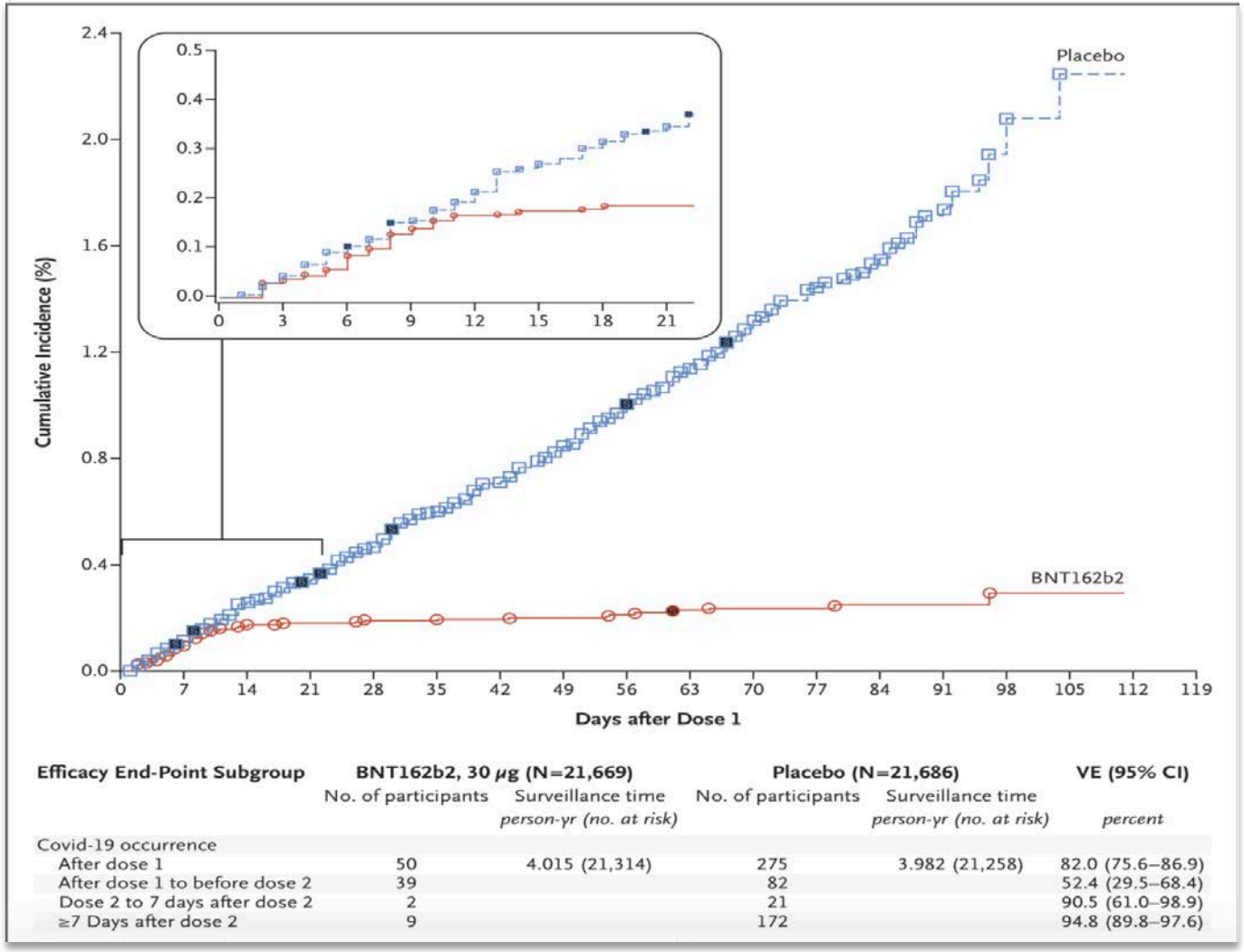


Arrowheads indicate days of vaccination. a, SARS-CoV-2 50% neutralization titers (VNT50) in immunized participants and HCS. Each serum was tested in duplicate and geometric mean titer plotted. For values below the lower limit of quantification (LLOQ) = 20, LLOQ/2 values were plotted. Group geometric mean titers (values above bars) with 95% confidence interval.

2 doses: boosted response

Mulligan MJ. Nature. Nov 2020.

The Pfizer/BioNTech Vaccine: Safety & Efficacy



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669) No. of participants	BNT162b2, 30 μg (N=21,669) Surveillance time *person-yr (no. at risk)*	Placebo (N=21,686) No. of participants	Placebo (N=21,686) Surveillance time *person-yr (no. at risk)*	VE (95% CI) *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)

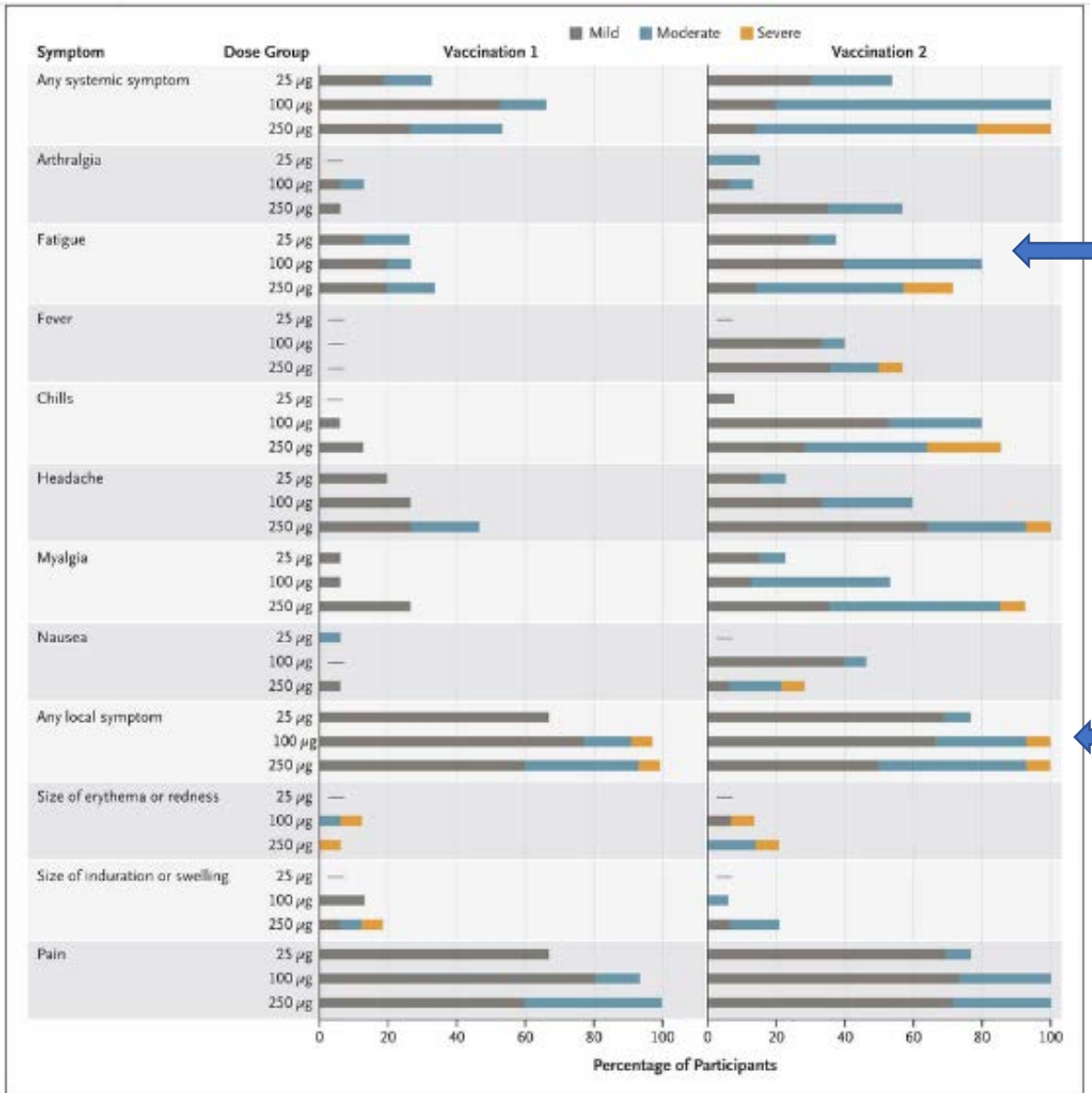
- Primary efficacy endpoints:
  - 1) Safety (AEs): 43,448
  - 2) Efficacy: 36,523 (1:1 randomization)
    - new confirmed COVID-19 cases >7 days after dose 2
- Safety:
  - Reactogenicity common, resolved quickly
  - Any AE: 27% in vaccine vs 12% in placebo
  - Serious AE: 0.6% vs 0.5%
- Efficacy
  - 162 cases in placebo, 8 cases in vaccine
  - **95% [**CI 89.9-97.3]
- Efficacy after one dose = 52%
  - Severe cases after dose one: 1 in vaccine vs 9 in placebo

VE = (%Cases Plcb-%Cases Vax) / %Cases Plcb

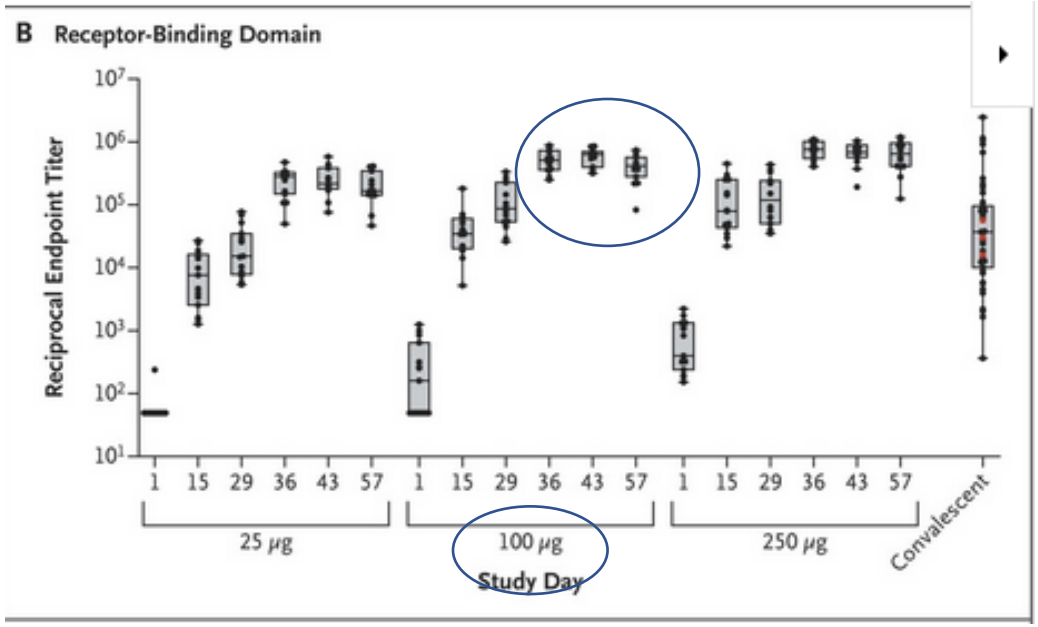
VE = 100x 1-[risk among vaccinated / risk among unvaccinated]

Polack FP et al. NEJM. 31 Dec 2020

Moderna vaccine



- Formerly known as mRNA 1273
- Lipid nanoparticle encapsulated RNA based vaccine targeting spike protein
  - 100ug dose
- 2 doses, 28 days apart*
- Storage temp -20C



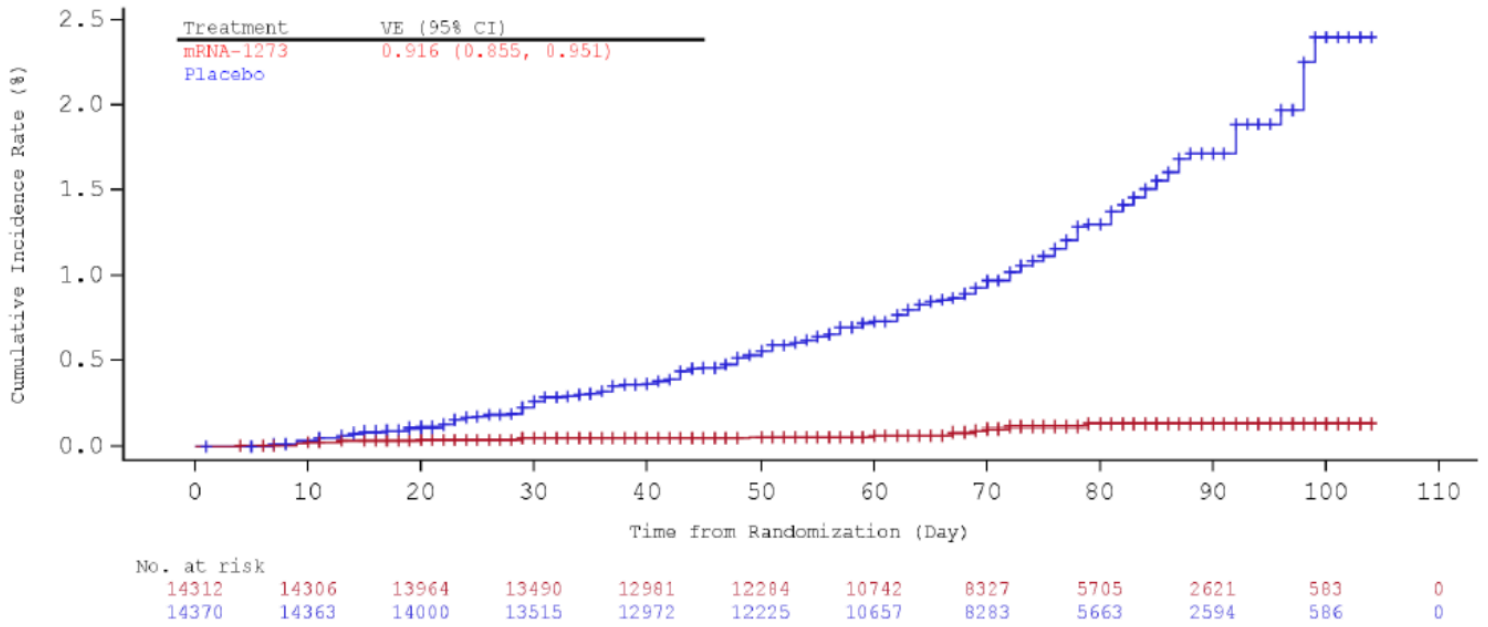
Jackson et al. NEJM. 12 Nov 2020.

Moderna vaccine: Safety & Efficacy

- Primary efficacy endpoint: reduction in incidence of COVID-19 among COVID-uninfected people after 14 days beyond dose 2
- Interim analysis: 27,817 included, 1:1 placebo (13,934) to vaccine (13,883)
  - 90 *symptomatic* cases in placebo, 5 in vaccine → 94.5% EFFICACY
- Severe COVID-19
  - 11 in the placebo, 0 in the vaccine arm
- Prevention after the first dose?

- **Final** efficacy analysis: **94.1**%
  - 185 cases in placebo, 11 cases in vaccine
  - 95.6% VE in 18-64yo
  - 86.4% VE in age >65 (ltd by #)

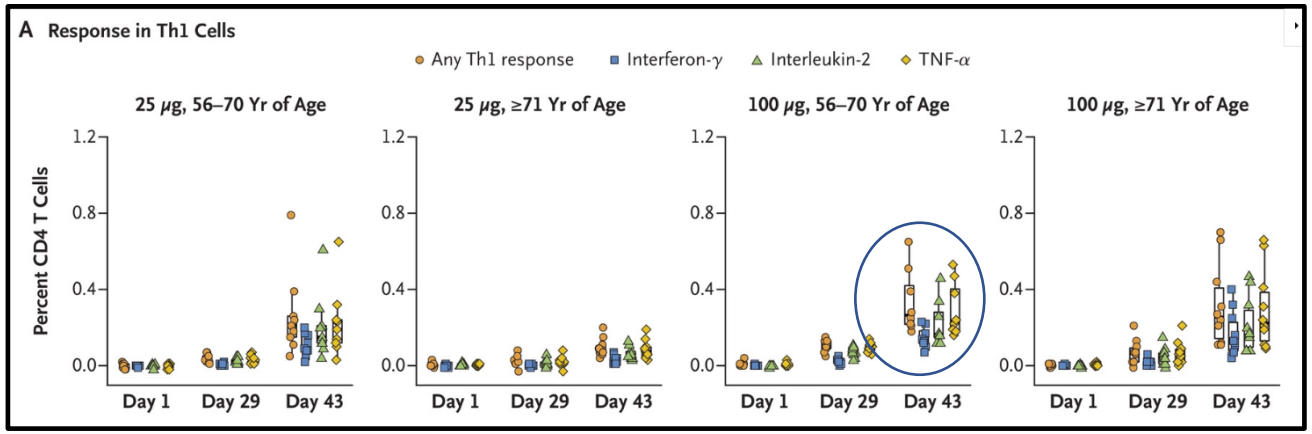
Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Randomization, mITT Set

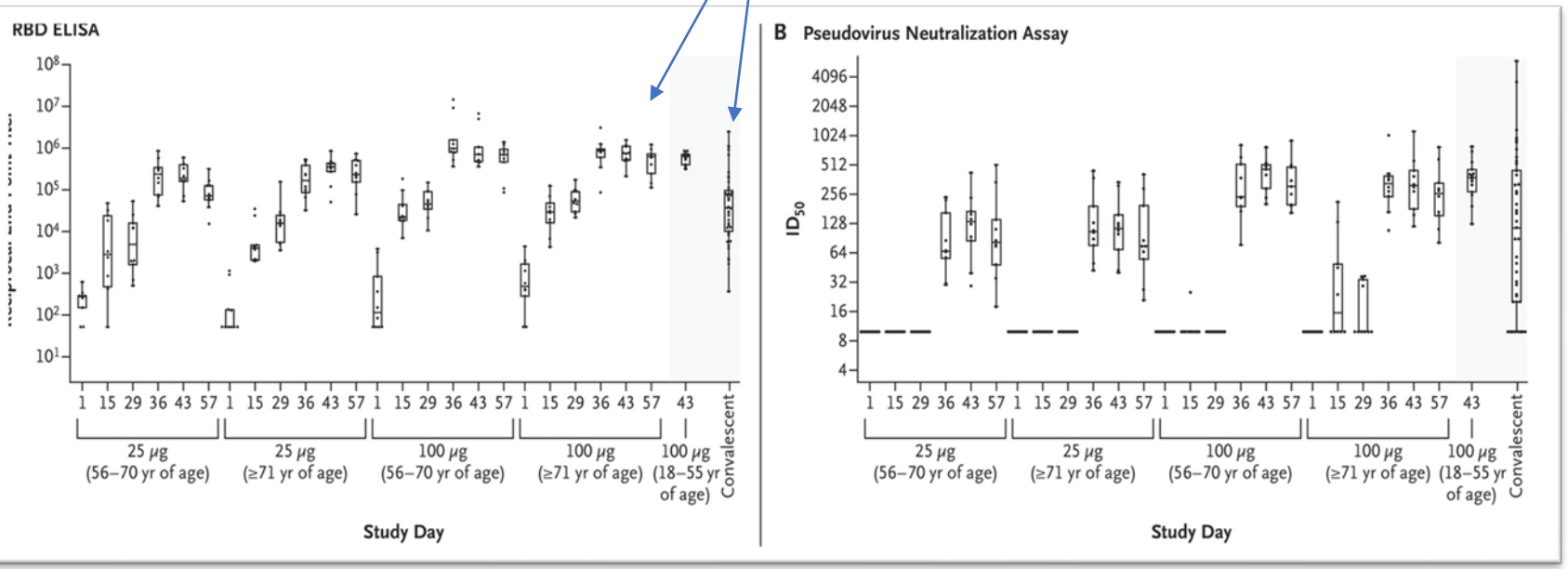


Baden, LR et al. NEJM.(2020).

Moderna Vaccine in Older Adults

- Substudy of 40 ppl >55yo in phase 2/3
- Neuralization and binding antibody titers similar to natural infection





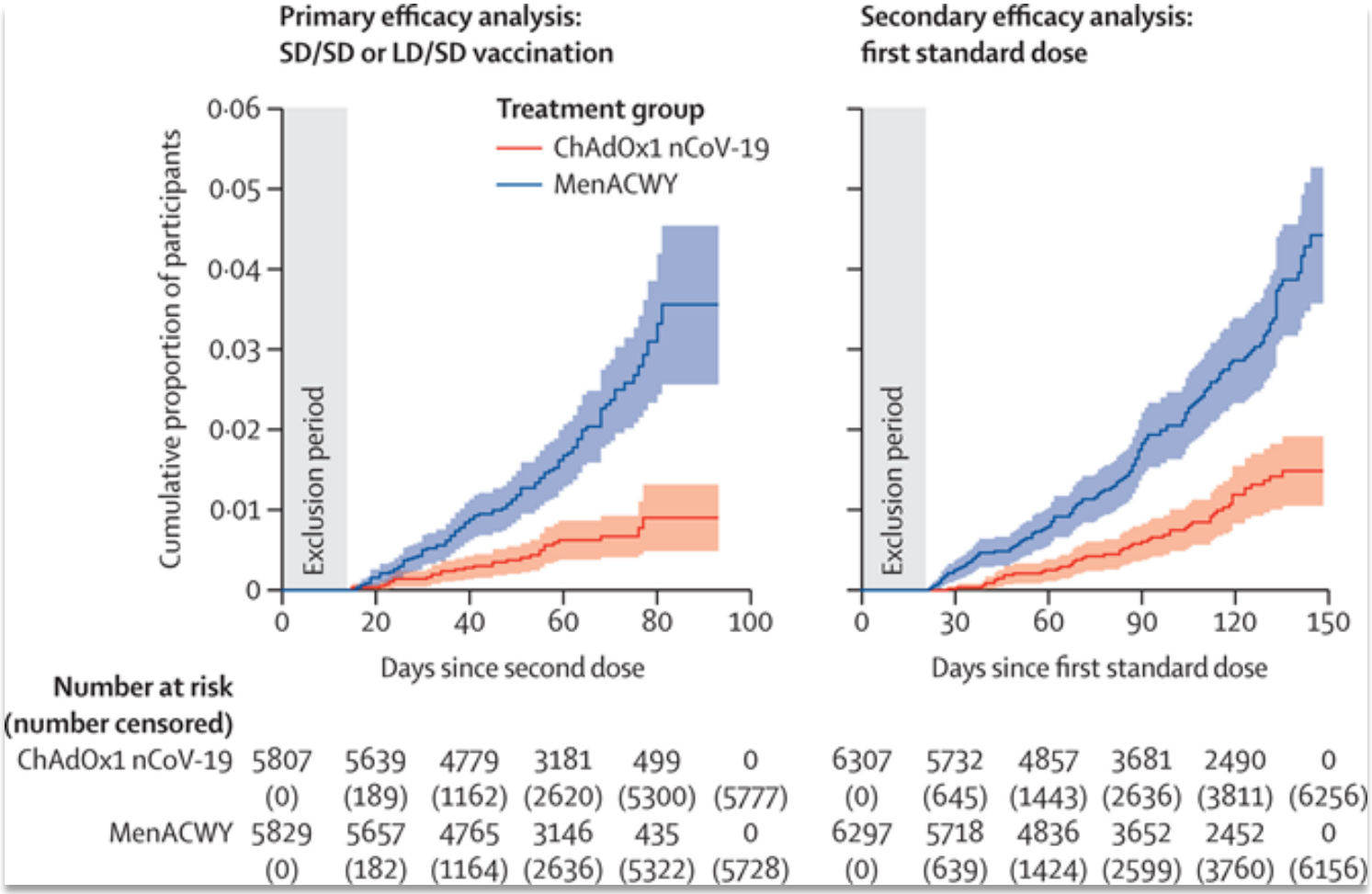
- Better titers with 100ug vs 25ug dose
- Good T cell response
- AEs were mainly mild to moderate

Anderson EJ. N Engl J Med. 2020 Dec 17.

COVID-19 Vaccine Astra Zeneca

Control: Menactra vaccine

- Formerly known as ChAdOx1-nCoV19 and AZD1222
- Chimpanzee adenovirus vector (AZD1222) against spike protein
  - Not capable of viral replication
- 2 doses, one month apart
  - Std dose vs low dose
- Storage 2-8C (refrigerator)
- Efficacy: 70.4%
  - 62.1% in std dose/Std dose
  - 90% in low dose/Std dose
  - 0 hospitalized in ChAdOx1 arm
  - 10 hospitalized in control, 1 death
- Few AEs

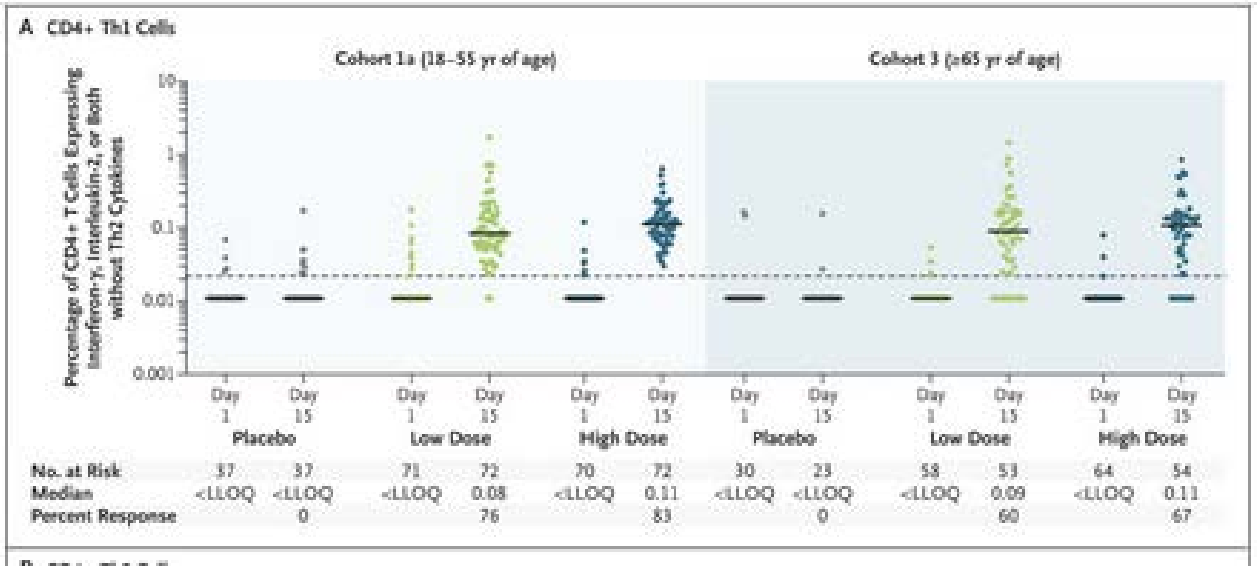


Primary outcome: symptomatic COVID

Voysey M, et al.. Lancet. 2020 Dec 8.

J&J /Janssen Vaccine

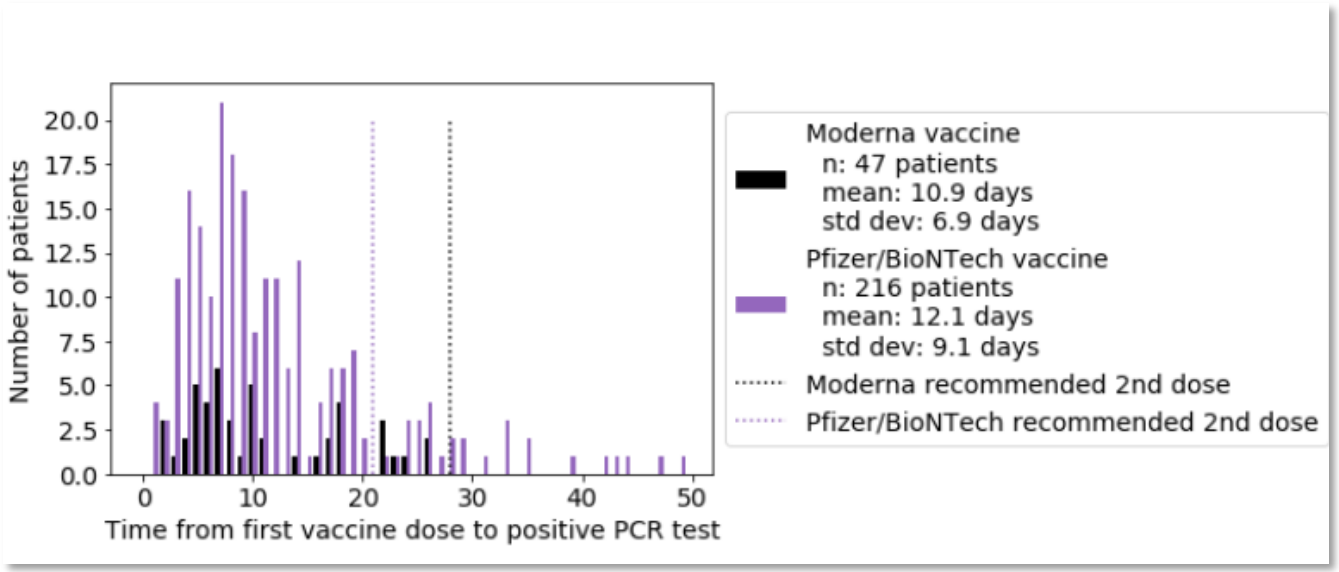
- Also known as Ad26.CoV2.S
- Non-replicating adenovirus 26 vaccine
- Stored at -20C or fridge, 1 dose
- Phase ½: 1 dose vs 2 dose vs placebo
  - Reactogenicity lower after 2nd dose
  - 100% neutr Ab titers by day 57
  - Th1 skewed T cell response
- Phase 3: 2 doses
  - 43,783 participants → 468 symptomatic cases
  - Overall well tolerated; 9% fever rate, no anaphylaxis
- 72% effective in US at preventing moderate to severe COVID-19
  - 28 days after vaccine dose
  - 66% overall VE
- No hospitalization or death after day 28
  - Protection from severe disease



Johnson & Johnson Press Release. 19 Feb 2021.
Sadoff J et al. NEJM 2021.

Real-world mRNA COVID-19 Vaccine Efficacy

- 31,069 non-trial vaccine recipients (>=1 dose) vs. 31,069 unvaccinated
  - 8041 had received 2 doses
  - Propensity matched:
    - demographics
    - zip code
    - prior test #
- 2 doses = **88.7%** [CI 68.4-97.1%] effective in preventing *infection*
  - > 36 days from first dose
  - Decreased hospitalization - RR 0.4

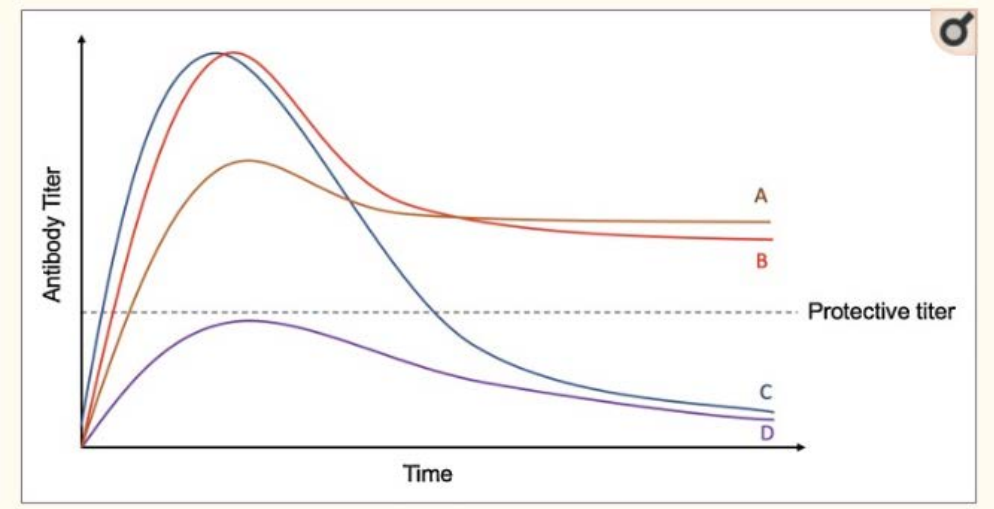


Outcome	**Moderna or Pfizer 1+ dose, COVID positive** (263 patients)	**Matched unvaccinated, COVID positive** (2630 patients)	**Relative Risk** (95% CI)	**Fisher Exact test p-value**
Number of patients with at least 14 days of follow-up	191	2348		
14-Day Hospital admission rate	7 / 191 (3.7%)	217 / 2348 (9.2%)	0.4 (0.21, 0.86)	0.0074**
14-Day ICU admission rate	2 / 191 (1%)	30 / 2348 (1.3%)	0.82 (0.28, 3.6)	1
14-Day Mortality rate	0 / 191 (0%)	2 / 2348 (0.085%)	0 (0, 51)	1

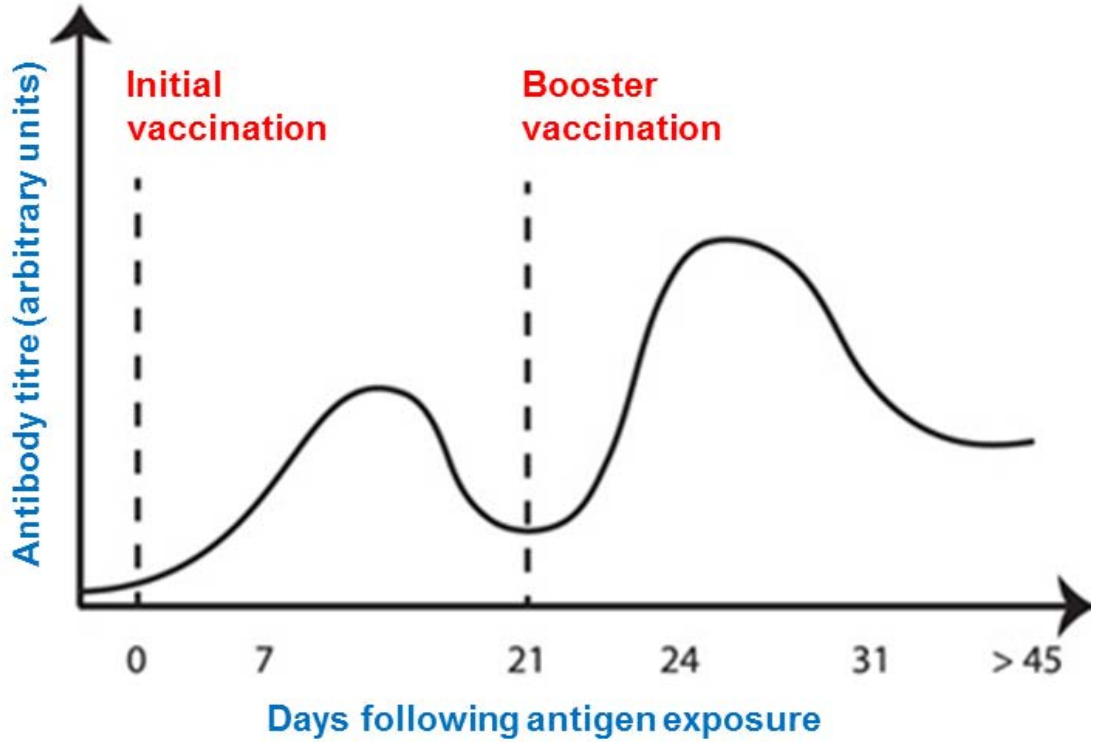
Pawlowski C et al. medRxiv [preprint] 18 Feb 2021.

Why would a vaccine be designed with 2 doses?

- Affinity maturation
  - Antibody quality + quantity
- Durability of response



The durability of antibody responses over time in 4 different infection/vaccination scenarios.

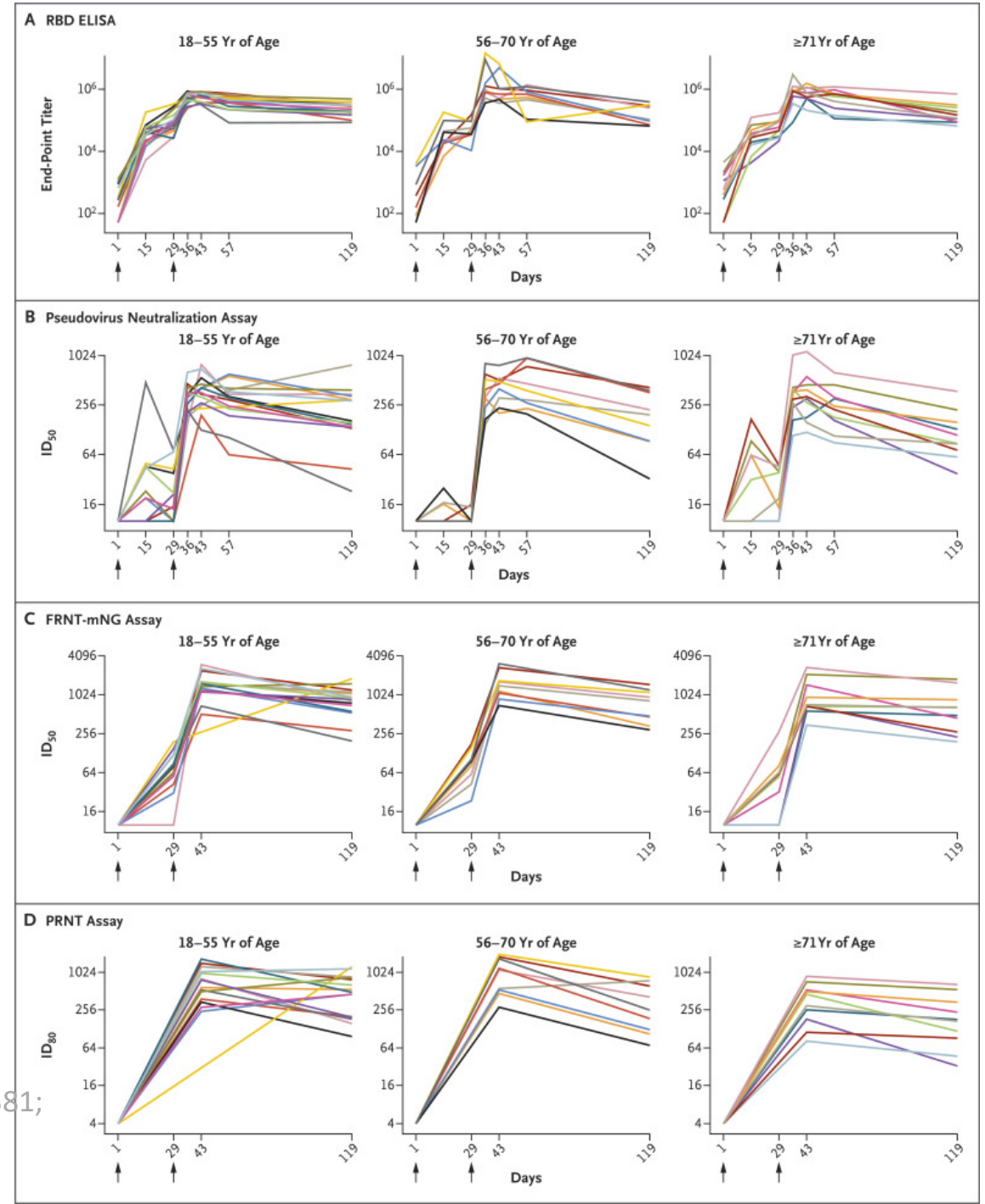


Grigoryan L. Semin Immunol. 2020.

https://www2.le.ac.uk/projects/vgec/highereducation/topics/microbial-genetics-1/vaccines-1

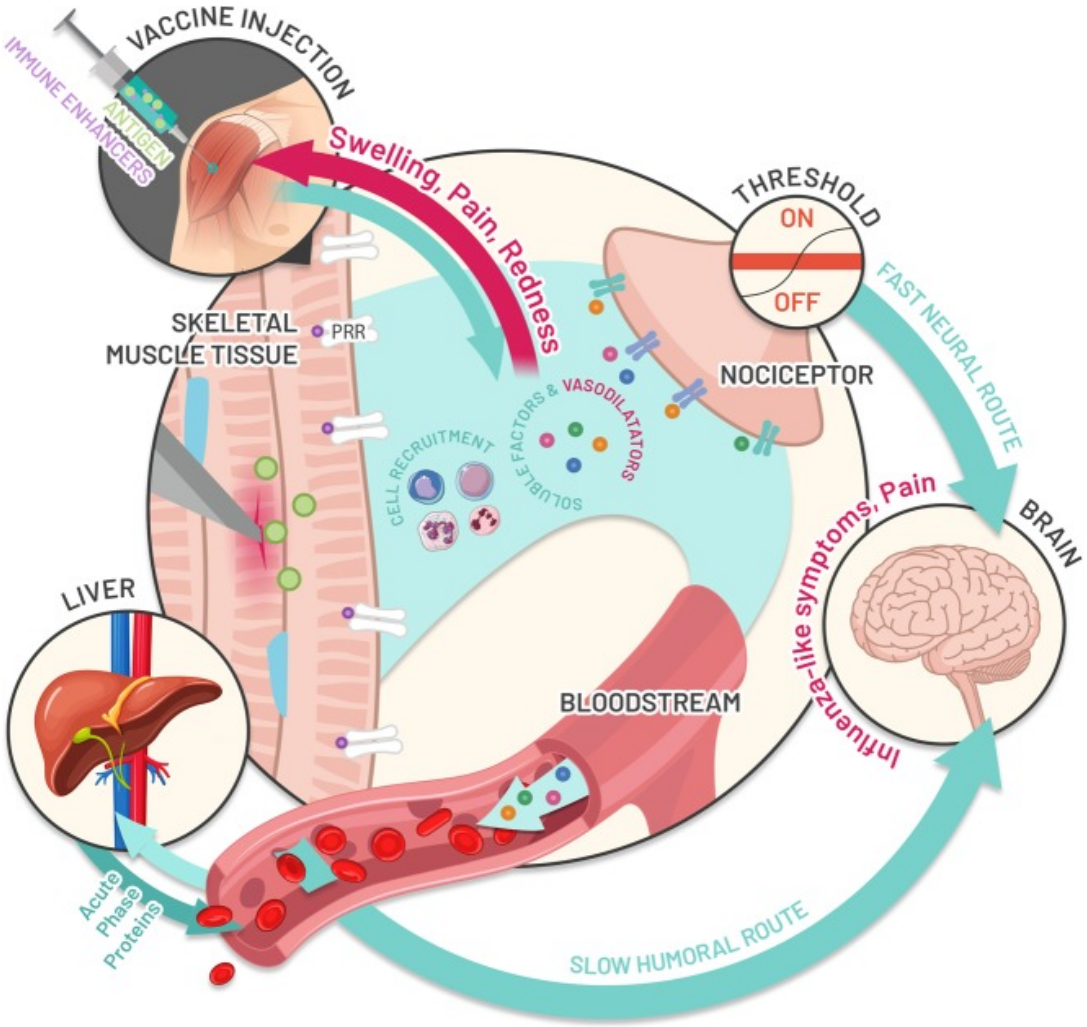
Durability of vaccine antibody response

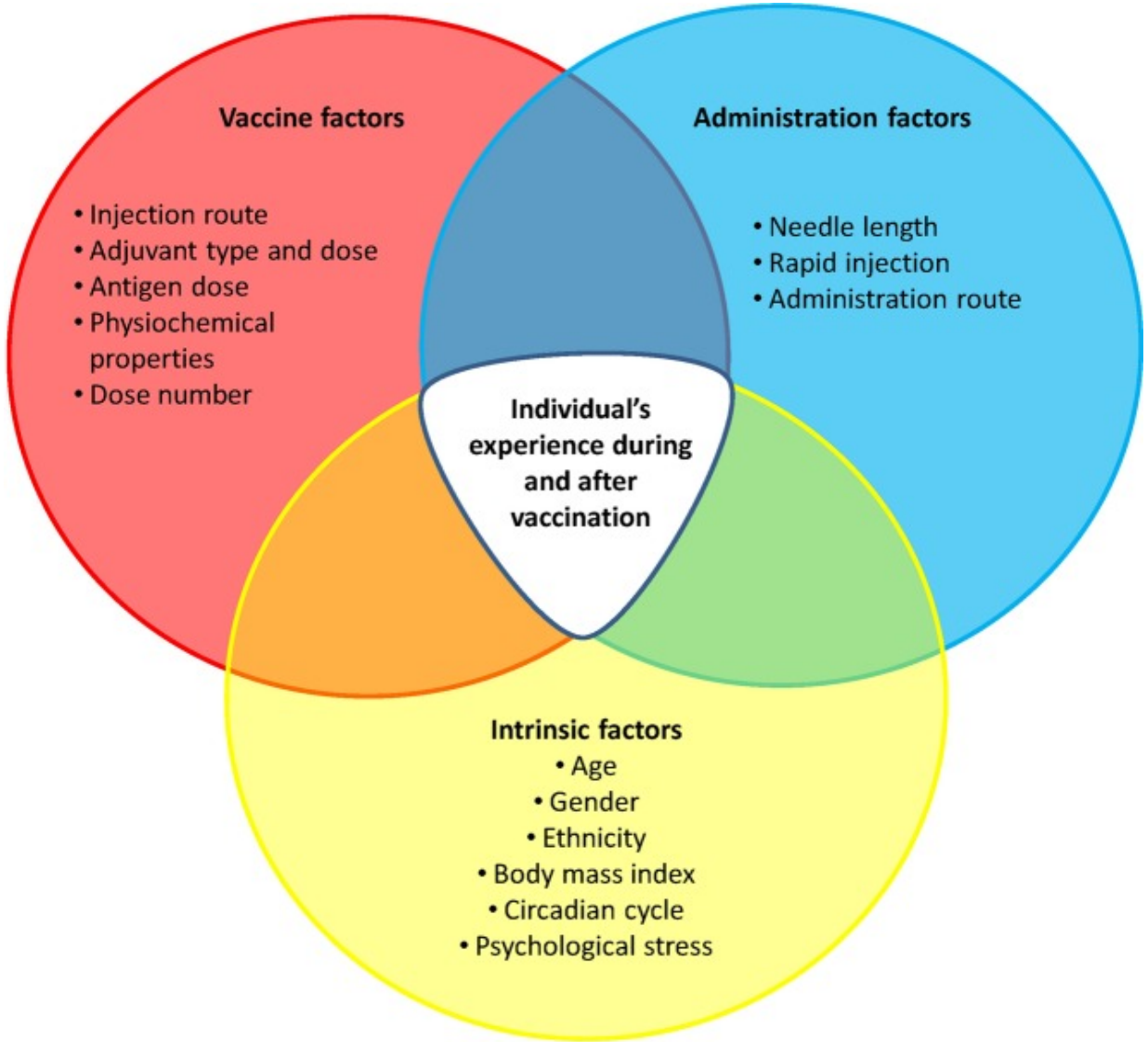
- Moderna:
  - Vaccine-induced neutralizing antibody titers were higher than the controls (people recovering from natural COVID) at 3 mo (n=44)
- Pfizer:
  - 6 mo data showed 91.3% efficacy against symptomatic disease (77 infections in vaccine, 850 in placebo)



Widge AT, Rouphael NG, Jackson LA, ...; mRNA-1273 Study Group. Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. N Engl J Med. 2020 Dec 3:NEJMc2032195. doi: 10.1056/NEJMc2032195. Epub ahead of print. PMID: 33270381; PMCID: PMC7727324.

Reactogenicity





Hervé C, et al. NPJ Vaccines. 2019.

Comparison of reported side effects for various vaccines

Vaccine Side Effects Compared

(<55 yr, after Dose 2 – highest side effect group found)

	SHINGRIX (ZOSTER VACCINE RECOMBINANT, ADJUVANTED) Shingrix	moderna messenger therapeutics COVID-19 mRNA-1273	Pfizer COVID-19 BNT162b2	Influenza Vaccine FLUCELVAX QUADRIVALENT Flu
Local Pain	88.4%	90.1%	77.8%	45.4%
Redness	38.7%	9.0%	5.9%	13.4%
Swelling	30.5%	12.6%	6.3%	11.6%
Myalgia	56.9%	61.3%	37.3%	15.4%
Fatigue	57%	67.6%	59.4%	17.8%
Headache	50.6%	62.8%	51.7%	18.7%
Chills	35.8%	48.3%	35.1%	6.2%
Fever	27.8%	17.4%	15.8%	0.8%
Overall Grade 3%	5.2%	4.1%	1.5%	0.5%
Overall SE %	48%	46%	36%	15%
	1	2	3	4

@JesseOSheaMD

Graphic from Dr. Jesse O'Shea MD, MSc from Emory

CDC COVID-19 Vaccine Safety Monitoring

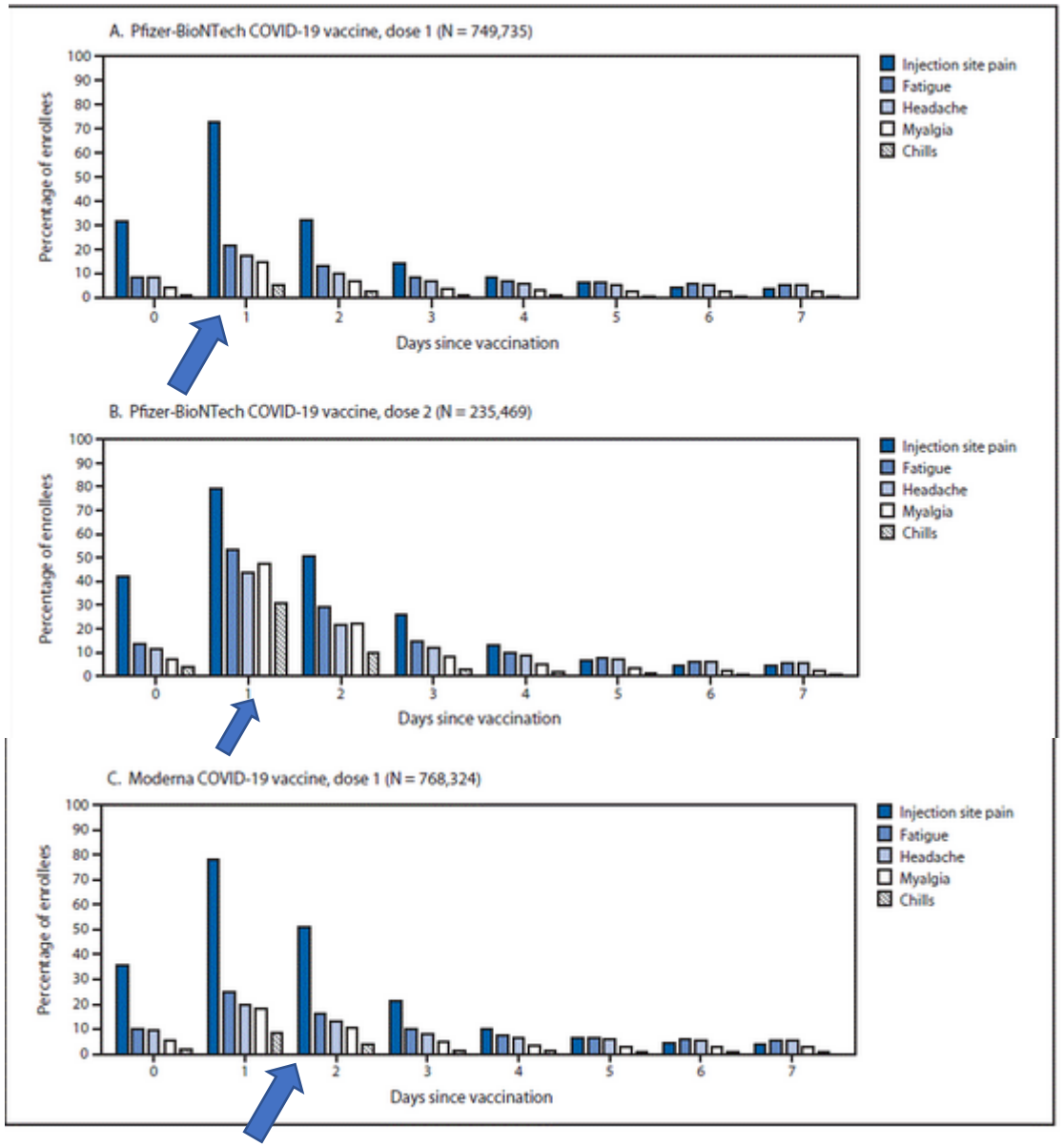


TABLE 2. Percentage of v-safe enrollees who completed at least one survey (N = 1,602,065) with local and systemic reactions reported for day 0–7 and for day 1 after receiving Pfizer-BioNTech and Moderna COVID-19 vaccines — v-safe,* United States, December 14, 2020–January 13, 2021

	Percentage of v-safe enrollees reporting reactions			
	Both vaccines	Pfizer-BioNTech vaccine		Moderna vaccine
Local and systemic reaction	Day 0–7	Dose 1, day 1	Dose 2, day 1	Dose 1, day 1
Injection site pain	70.9	72.9	79.3	78.1
Fatigue	33.5	21.9	53.5	25.1
Headache	29.5	17.5	43.4	19.9
Myalgia	22.9	14.7	47.2	18.3
Chills	11.6	5.5	30.6	8.4
Fever	11.4	5.8	29.2	8.2
Injection site swelling	10.8	6.2	8.6	12.6
Joint pain	10.4	5.3	23.5	7.3
Nausea	8.9	4.2	14.0	5.5

Gee J et al. MMWR. 19 Feb 2021; 70.

What about mutations?

- All RNA viruses mutate
- SARS-CoV-2 mutates slowly, at a rate of 1-2 mutations/month
- Mutations are random but may be seen more frequently if:
  - By chance (founder effect, overdispersion, superspreading events)
  - Adaptive advantage to virus (i.e., binds more easily to ACE2, more transmissible, allows virus to replicate more efficiently)
  - Could arise in setting of selective pressure (e.g., N439K escapes from some monoclonal antibodies, D484Y in RdRP is a remdesivir mutation)
- May emerge more rapidly with infection in immunocompromised hosts where there can be prolonged viral replication

Genetic variants: unlikely to affect vaccines

- Our antibody and cellular immune response to vaccination is broad, and unlikely to be affected by variant in small area of the spike protein
  - Available vaccines have been protective against all variants to date
- If there were enough mutations accumulated to escape the vaccine immune response, we could change an mRNA vaccine easily to address new mutations
  - But will it? Has not accumulated too many mutations despite infecting many millions in last year
- Degree to which vaccine efficacy is affected by variants may depend on magnitude of neutralizing antibody titer induced by vaccination

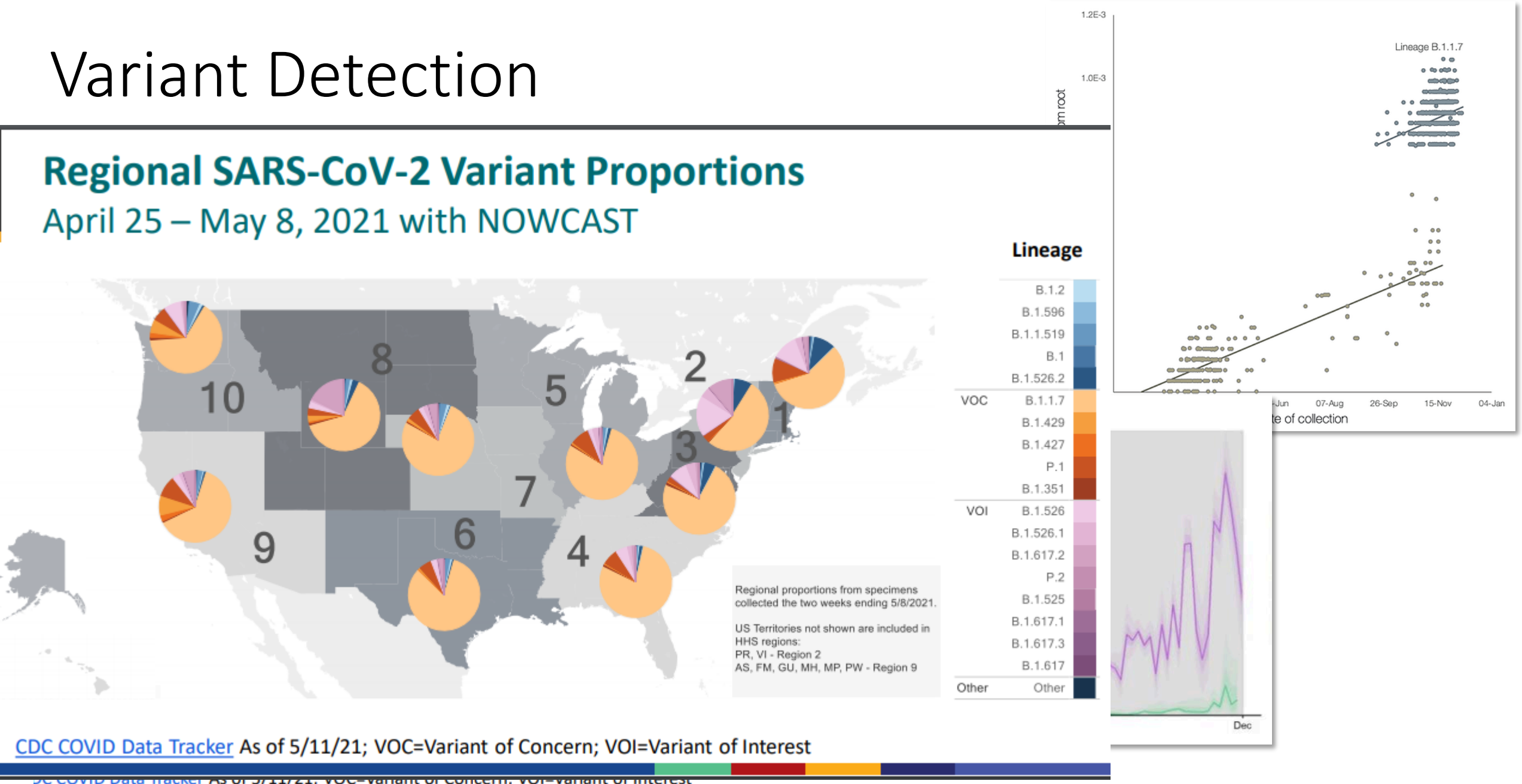
SARS-CoV-2 Variants

Variant of Concern	Mutation	First identified in	Mutation locations	Concerning Characteristics
B.1.351	N501.Y.V2	South Africa	3 in RBD of spike 5 in NTD	50% more transmissible Reduced efficacy of some Abs
B.1.1.7	N501Y E484K Del 69-70	UK	RBD	53% increased transmissibility Minimal impact on Ab neutralization Reinfection rate 0.7%
P.1	E484K, K417N	Brazil	10 mutations in spike	Reduced efficacy of some antibodies
B.1.4127 , B.1.4129	L452R	California		20% increased transmission
B.1.167	E484Q, L452R	India	3-10	Possibly reduced Ab efficacy
B.1.256	S477N E484K	Bronx NY	3-7 spike mutations	Reduced neutralization by CP

RBD = Receptor Binding Domain -- the target of much of vaccine-elicited neutralization
NTD = N-terminal Domain

Graham et al. medRxiv 2021.
Volz et al. medRxiv 2021
Greaney et al. bioRxiv 2021
Wang et al. bioRxiv 2021
Cele et al. medRxiv 2021

Variant Detection



Scobie H. CDC/ACIP Meeting COVID-19 Vaccines Update. 12 May 2021.

Davies N. **[Pre-Print]** CMMID repository. 23 Dec 2020
Virological.org. 2020

Vaccine Efficacy against Variants

Vaccine Efficacy or Effectiveness (VE) Against Variants

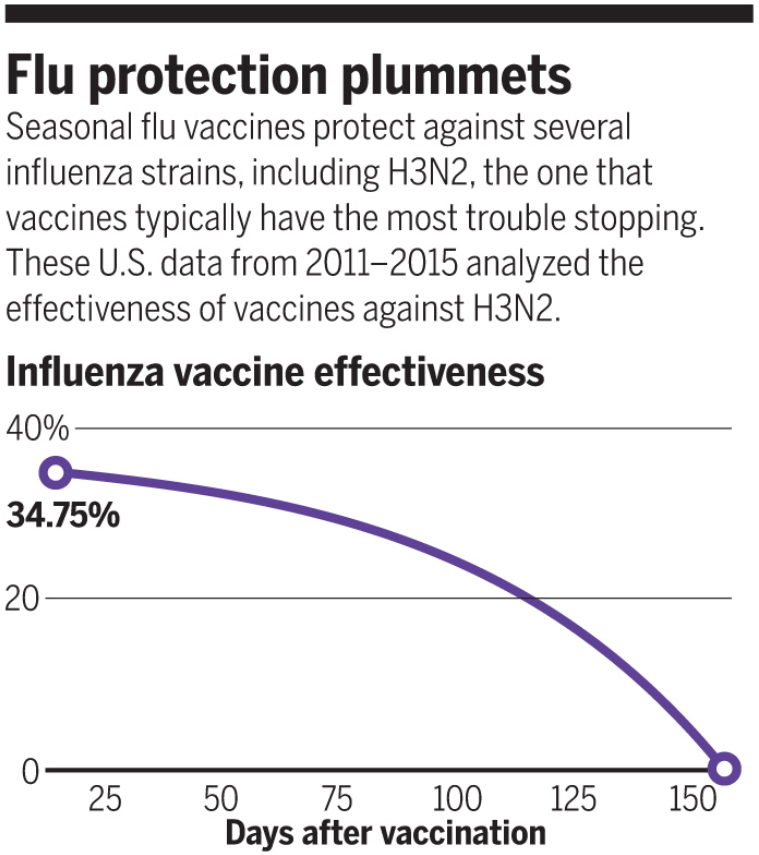
Vaccine	Study type	VE	
Pfizer	Post-EUA	• 90% against B.1.1.7 in Qatar* • 75% against B.1.351 in Qatar	100% for severe/ critical disease
Janssen	Pre-EUA	• 74% in U.S. • 66% in Brazil • 52% in S. Africa	73-82% for severe/critical disease in each country
Novavax	Pre-EUA Pre-EUA	• 96% against non-B.1.1.7 in UK • 86% against B.1.1.7 in UK • 51% against B.1.351 in S. Africa	
AstraZeneca	Pre-EUA Pre-EUA	• 84% against non-B.1.1.7 in UK • 75% against B.1.1.7 in UK • 10% against B.1.351 in South Africa*	

* >85% in UK & Israel (predominate B.1.1.7): https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html
Abu-Radad and Butt. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants | NEJM
https://www.fda.gov/media/146217/download
Novavax.: https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3
Shinde et al. Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant | NEJM
Madhi et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant | NEJM
Emary et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): The Lancet **mild/moderate illness

Scobie H. CDC/ACIP Meeting COVID-19 Vaccines Update. 12 May 2021.

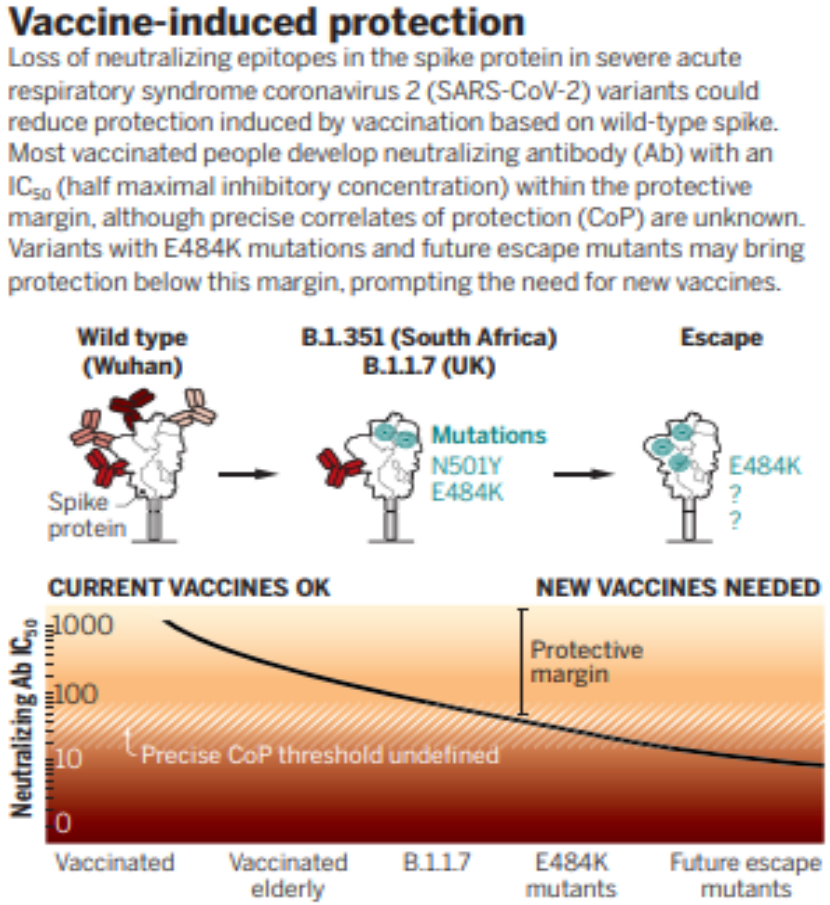
Why would we need a booster dose of a vaccine?

(1) To increase nAb titers because waning immunity



Cohen J. Science. 2019

(2) To provide more specific immune response to new variants of the virus



Altmann et al. Science Mag. 2021.

Vaccine booster trials

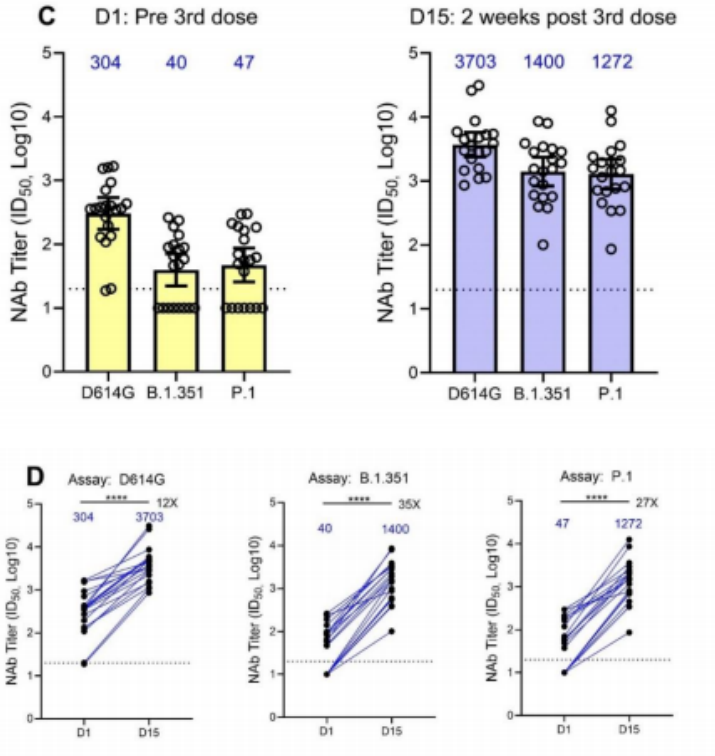
Moderna:

- Booster with 3rd dose mRNA 1273 (original)
- mRNA 1273.351 = a B1.351 VOC-specific vaccine booster
- mRNA 1273.211 = multivalent booster candidate (50% original + 50% 1273.351)

[Pfizer, J&J and others are doing similar trials]

Figure 3C and D: Immunogenicity After Boosting with 50 µg of mRNA-1273.351

273



Legend: Neutralization of recombinant SARS-CoV-2 VSV-based pseudoviruses (D614G, B.1.351 and P.1) by serum from participants before (D1) and 15 days after boosting (D15) with 50 µg of mRNA-1273 **(A and B)** and mRNA-1273.351 **(C and D)**. The geometric mean neutralizing antibody titer is denoted by the top of the box and the 95% confidence intervals are shown by the brackets. The titers for individual participants are shown by the circles. The fold increases for day 15/day 1 are shown above the bars. The horizonal dotted lines indicate the lower limit of quantification (LLOQ). **** = p<0.0001 by the Wilcoxon matched-pairs signed rank test.

Wu et al. MedRXiv. [preprint]
https://www.medrxiv.org/content/10.1101/2021.05.05.21256716v1.full.pdf

https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-positive-initial-booster-data-against-sars-cov

Summary: COVID-19 and the immune system

- COVID-19 vaccines: efficacy and immunogenicity
  - Overview of data on efficacy / antibody production and durability
  - Data on vaccines in older populations: blunted response, likely mortality benefit
- Side effects of COVID-19 vaccines are common, but most are mild and self limited
  - Amount of reactogenicity does not = immunogenicity
- New variants vs the vaccine
  - So far our vaccines are working against them, but only a matter of time / mutations
- Future directions for prevention
  - Boosters of same? Annual update?

COVID-19 vaccines and allergic reactions

Relevant medications with polysorbate (PS80, PS20) or PEG	
Alemtuzumab	Infliximab
Blinatumomab	Nivolumab
Brentuximab	Pembrolizumab
Bevacizumab	Rituximab
Elotuzumab	Trastuzumab
	Gardasil
Vancomycin	Depo provera
Lorazepam	Hand soap
Herceptin	Cough medicine
Cleaning agents	Gemcitabine

Vaccine allergies are **rare** (1/100000) and typically to excipients

- Polysorbate
- Polyethylene glycol

Appendix A: Triage of persons presenting for mRNA COVID-19 vaccination

	MAY PROCEED WITH VACCINATION	PRECAUTION TO VACCINATION	CONTRAINDICATION TO VACCINATION
CONDITIONS	CONDITIONS • Immunocompromising conditions • Pregnancy • Lactation ACTIONS • Additional information provided* • 15 minute observation period	CONDITIONS • Moderate/severe acute illness ACTIONS • Risk assessment • Potential deferral of vaccination • 15-minute observation period if vaccinated	CONDITIONS • None ACTIONS • N/A
ALLERGIES	ALLERGIES History of allergies that are unrelated to components of an mRNA COVID-19 vaccine†, other vaccines, injectable therapies, or polysorbate, such as: • Allergy to oral medications (including the oral equivalent of an injectable medication) • History of food, pet, insect, venom, environmental, latex, etc., allergies • Family history of allergies ACTIONS • 30-minute observation period: Persons with a history of anaphylaxis (due to any cause) • 15-minute observation period: All other persons	ALLERGIES • History of any immediate allergic reaction† to vaccines or injectable therapies (except those related to component of mRNA COVID-19 vaccines‡ or polysorbate, as these are contraindicated) ACTIONS: • Risk assessment • Consider deferral of vaccination and/or referral to allergist-immunologist • 30-minute observation period if vaccinated	ALLERGIES History of the following are contraindications to receiving either of the mRNA COVID-19 vaccines‡: • Severe allergic reaction (e.g., anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or any of its components • Immediate allergic reaction† of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components‡ (including polyethylene glycol)# • Immediate allergic reaction of any severity to polysorbate‡# ACTIONS • Do not vaccinate# • Consider referral to allergist-immunologist

* See Special Populations section for information on patient counseling in these groups

Caballero ML. J Investig Allergol Clim Immunol 2021.

Schwartzberg LS. Adv Ther. 2018 Jun.

CDC. 21 Jan 2021. www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html.