COVID-19 Vaccine Development

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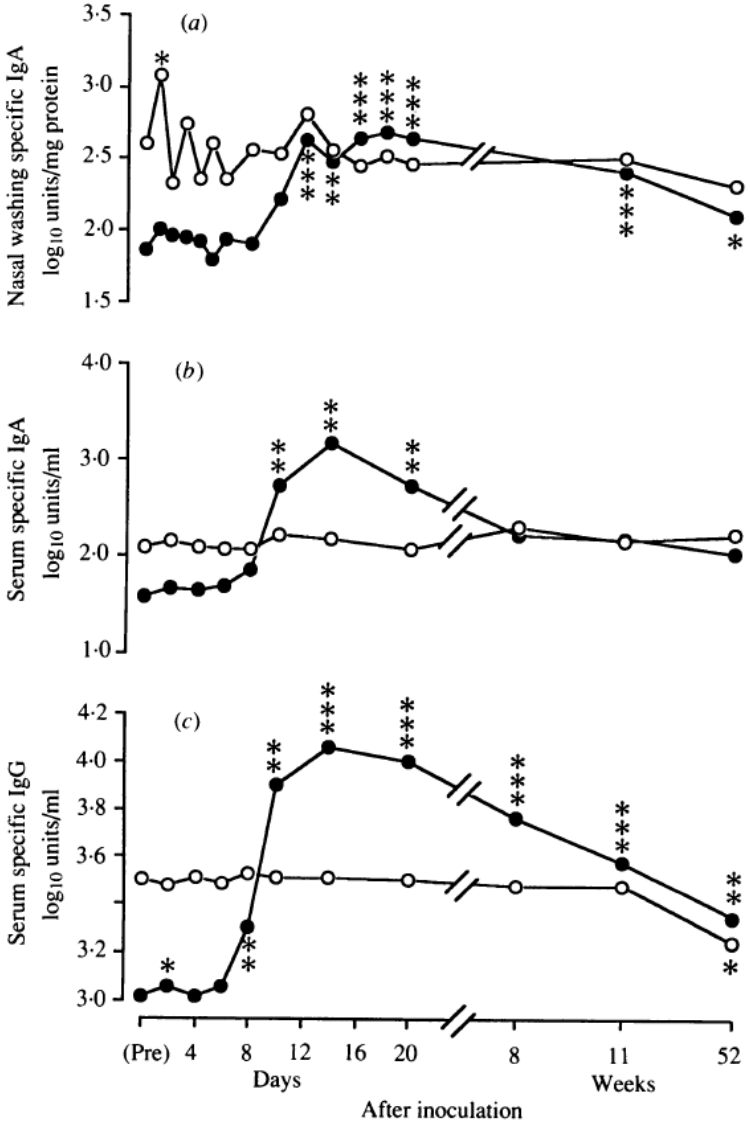
Humoral immune responses in experimental human HCoV-229E infection



- Volunteers intranasally inoculated with HCoV-229E: 10/15 Infected
  - 8/10 infections associated with cold sxs
  - Infected group had lower baseline Ab levels
  - Serum Ab declined over 1 yr
- Re-challenge with same HCoV-229E dose at 1 year: 11/14 Infected
  - Cold sxs less common 1/11
  - Duration of virus shedding shorter after re-challenge:
    - 5.6 d first infection vs 2.0 d second infection

Calloway Epidemiol Infect 1990 105, 435-446

Widespread naturally acquired immunity to SARS-CoV-2 would come at a high cost

291,104 confirmed cases (5% of population)

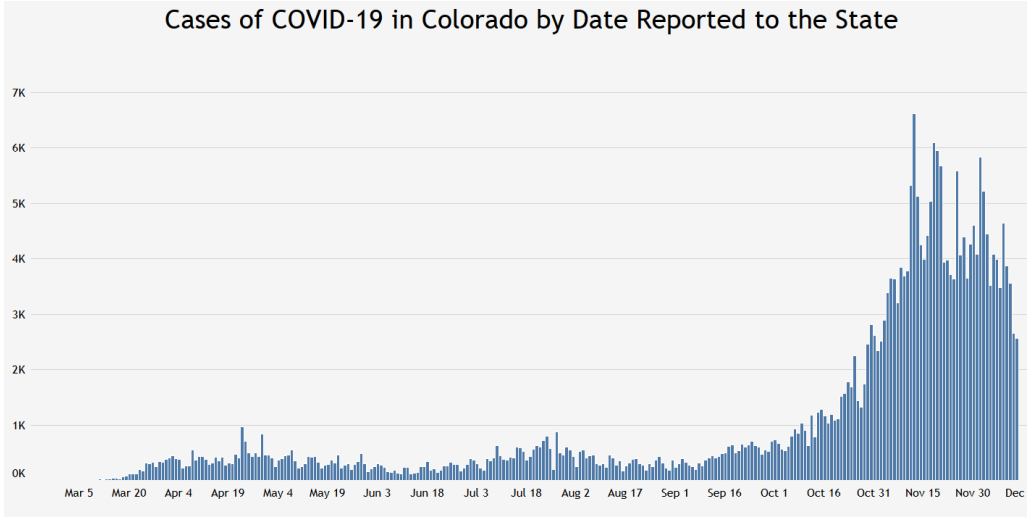
16,174 hospitalized cases (5.6% of confirmed cases)

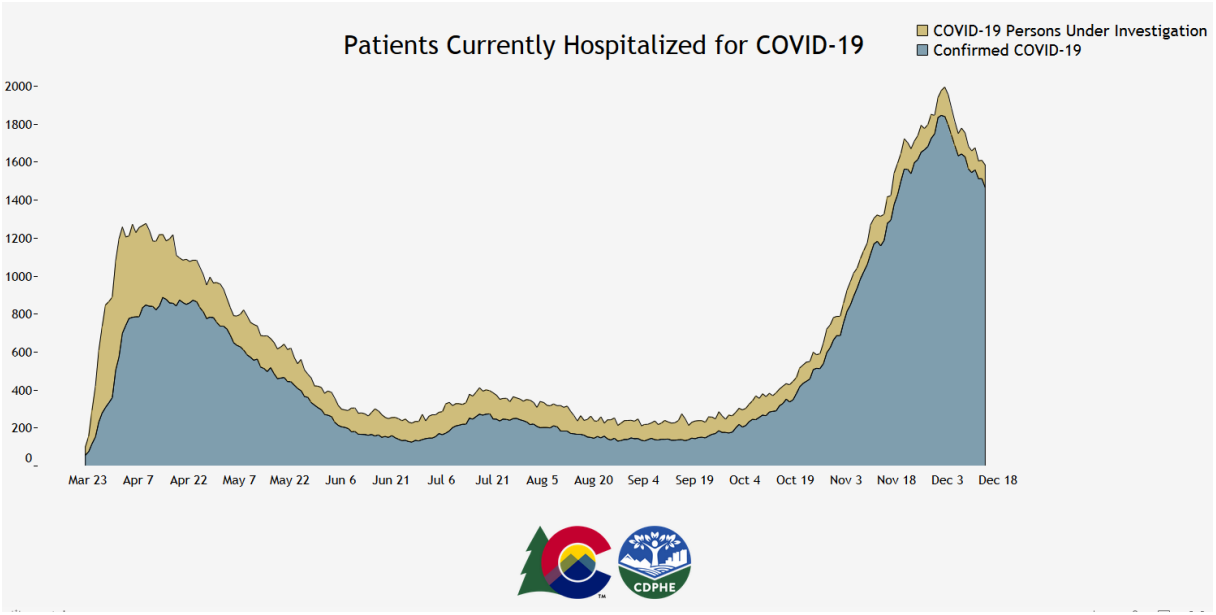
3,969 deaths among cases (1.3% of confirmed cases)

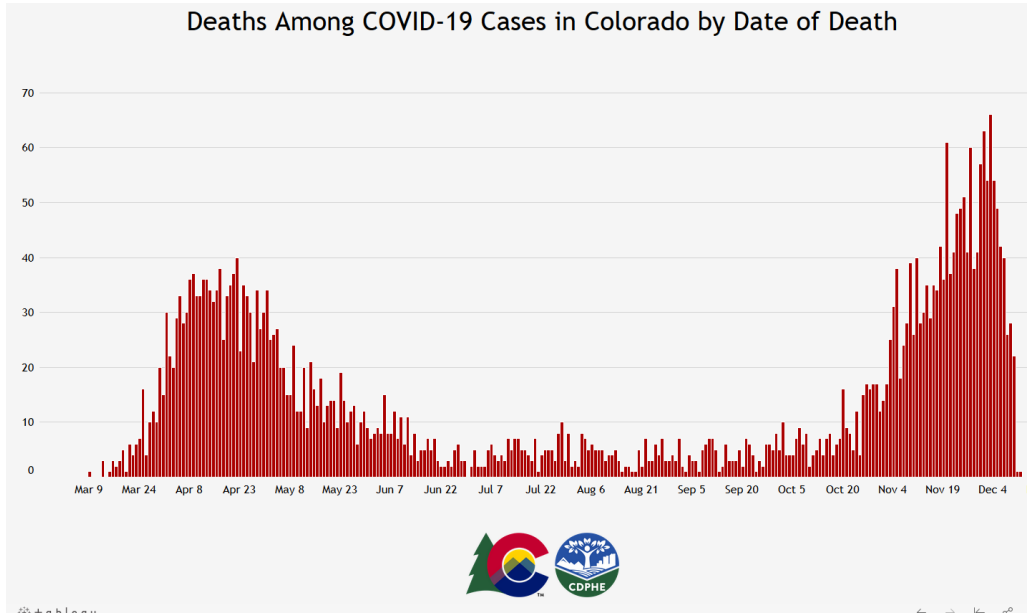
> 1 additional year to reach 1 million confirmed cases

> 50,000 additional hospitalizations in Colorado

> 13,000 additional deaths in Colorado

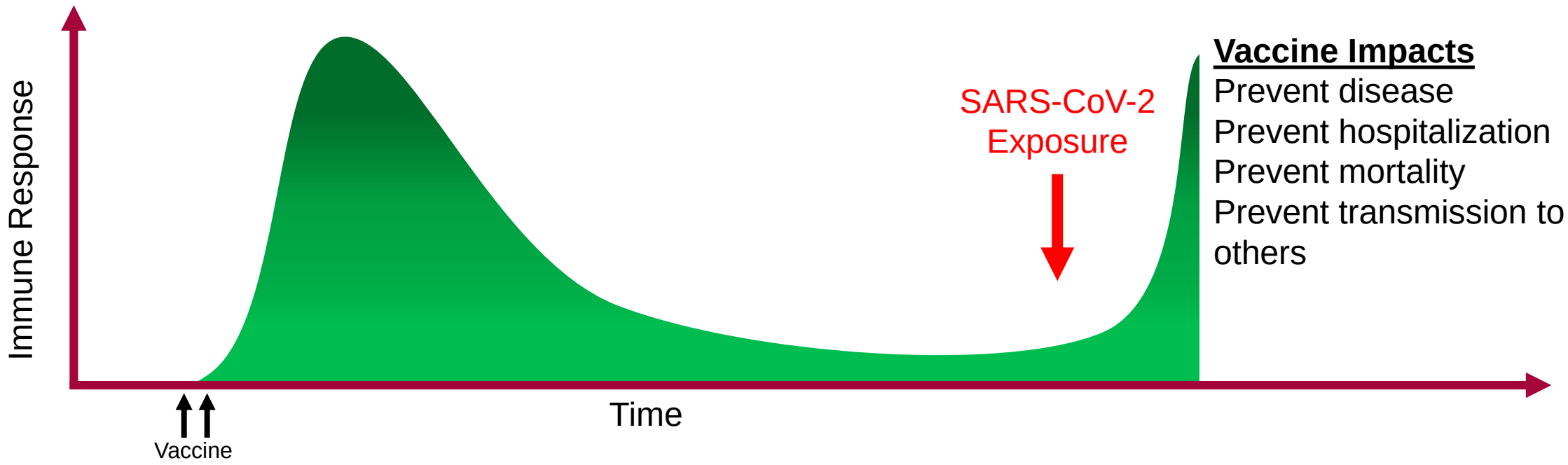






Source: https://covid19.colorado.gov/covid-19-data

Paradigm for an impactful COVID-19 vaccine



Important questions concerning candidate SARS-CoV-2 vaccines

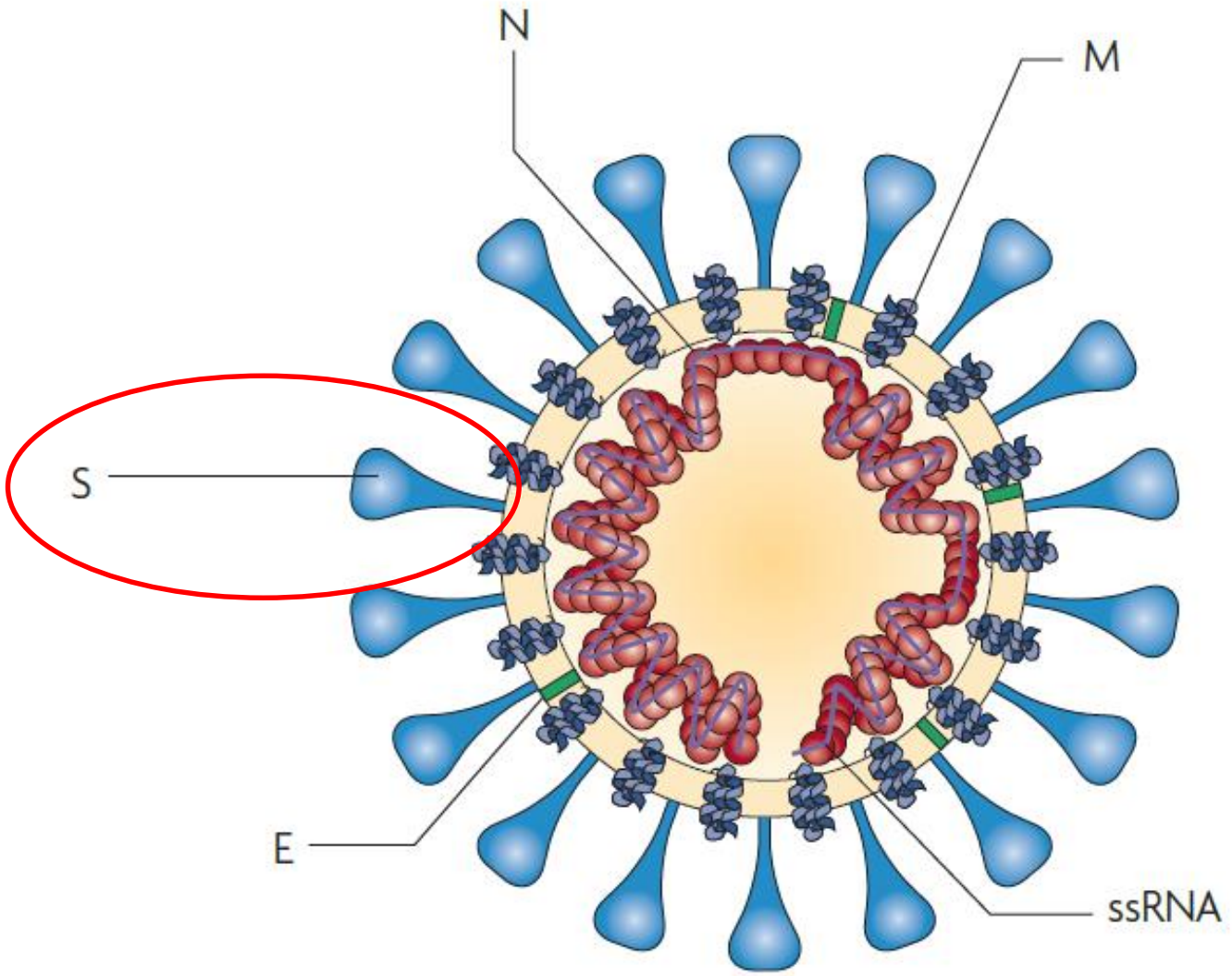
- Which viral protein(s) to target?
- Is the vaccine safe?
  - Short-term and long-term
  - Is there antibody dependent enhancement (ADE)?
  - Safety in special populations (pregnancy, children, immunocompromised)
- How do we define efficacy?
  - Prevention of SARS-CoV-2 infection?
  - Prevention of COVID-19 illness?
- Is the vaccine efficacious?
  - Efficacy in those at greatest risk
    - Elderly
    - Racial and ethnic minorities
    - Immunocompromised
- Is vaccine efficacy durable?

Candidate SARS-CoV-2 vaccines

- 198 candidate vaccines worldwide
- 44 candidate vaccines in clinical trials
- 6 candidate vaccines in phase 3 clinical trials in the US

Company	Technology	# Doses	Current Status	Colorado Site
AstraZeneca	Chimp Adenovirus	2	Phase 3 enrollment ongoing	UCHealth North
Janssen	Human Adenovirus	1	Phase 3 enrollment complete	AMC/Peds AMC/RMVA
Novavax	Protein subunit	2	Phase 3 pending	AMC/UCH
Sanofi	Protein subunit	2	Phase 3 to start 2021 Q2	AMC/Peds
Moderna	mRNA	2	Primary endpoint met EUA pending	AMC/UCH Lynn Institute Colo Sps
Pfizer	mRNA	2	Primary endpoint met EUA approved	Lynn Institute Denver

Potential SARS-CoV-2 vaccine targets



Perlman Nat Rev 2009 doi:10.1038/nrmicro2147

Moderna COVID mRNA vaccine (mRNA-1273)

RNA (U→pseudoU)

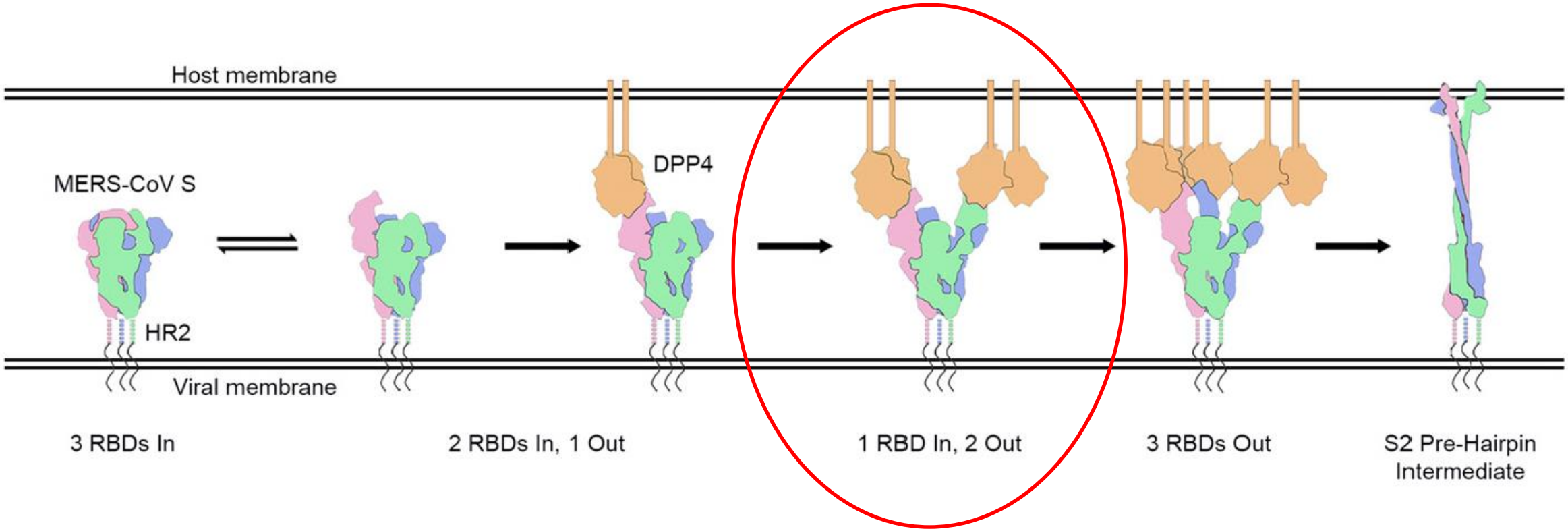
+

Lipid complex (2.5:1)

+

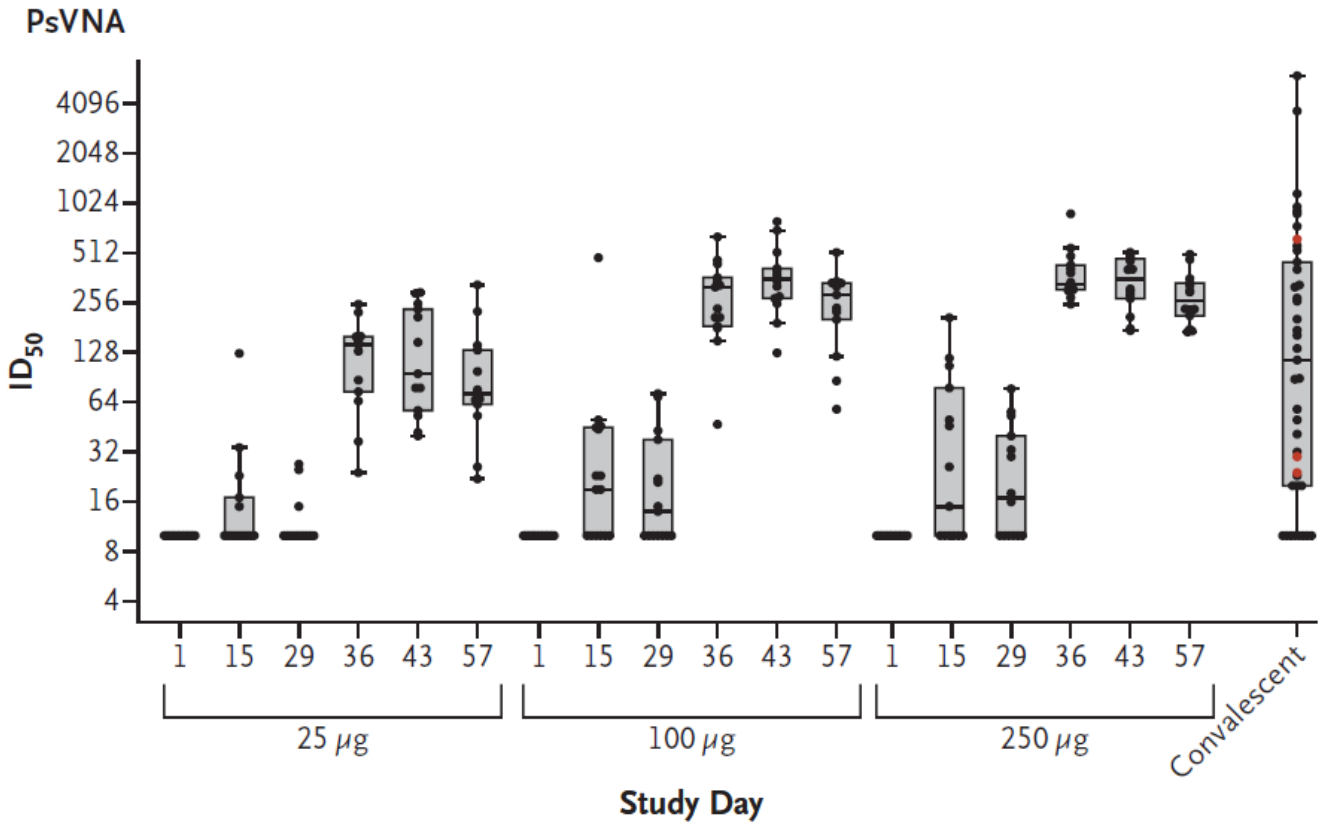
Salt, buffer, sucrose

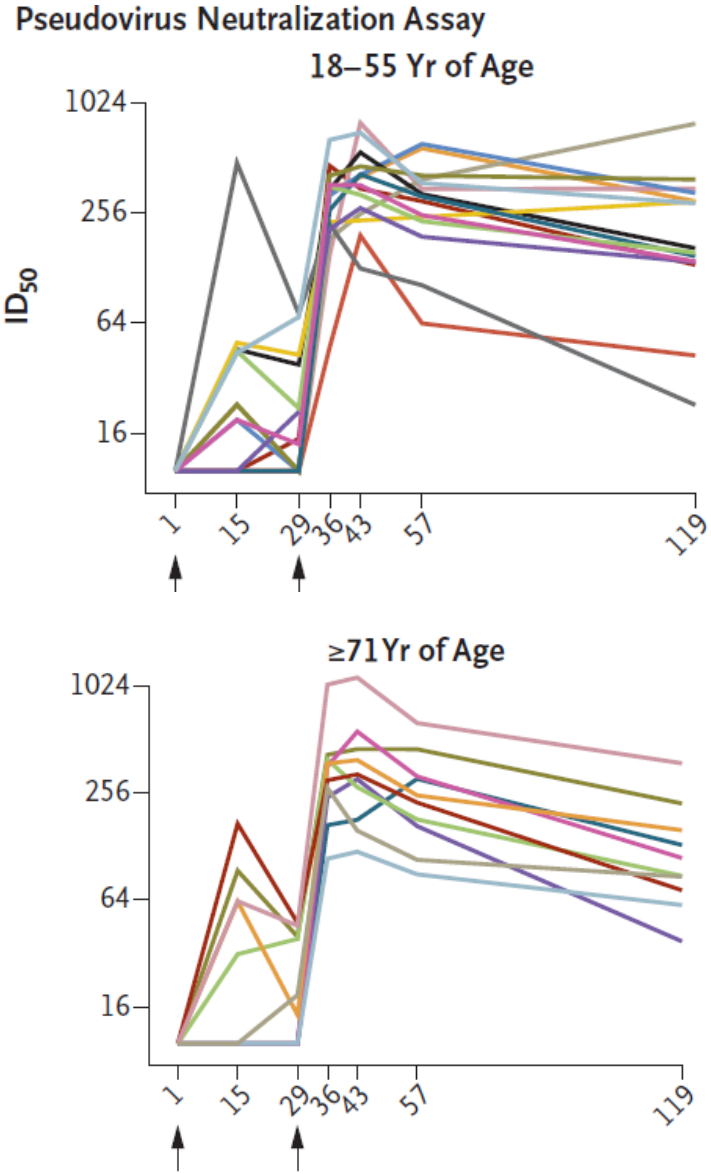
S2-P stabilizes Spike in open more immunogenic conformation



Pallesen et al., www.pnas.org/cgi/doi/10.1073/pnas.1707304114

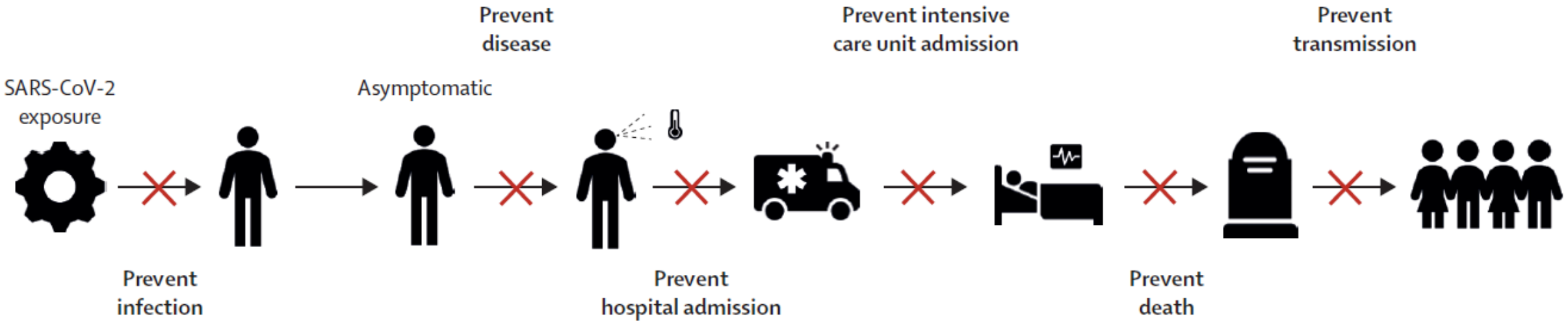
Phase 1 immunogenicity results: mRNA-1273 vaccine induction of neutralizing antibody





Jackson et al., NEJM 2020
Widge DOI: 10.1056/NEJMc2032195

Assessment of vaccine efficacy (or effectiveness)



Vaccine efficacy

- VE = $\frac{\text{Risk unvaccinated} - \text{Risk vaccinated}}{\text{Risk unvaccinated group}}$
- VE = proportionate reduction in outcome among the vaccinated group

Vaccine efficacy is measured in clinical trials

Vaccine effectiveness is measured on population level

Vaccine efficacy for other viral diseases

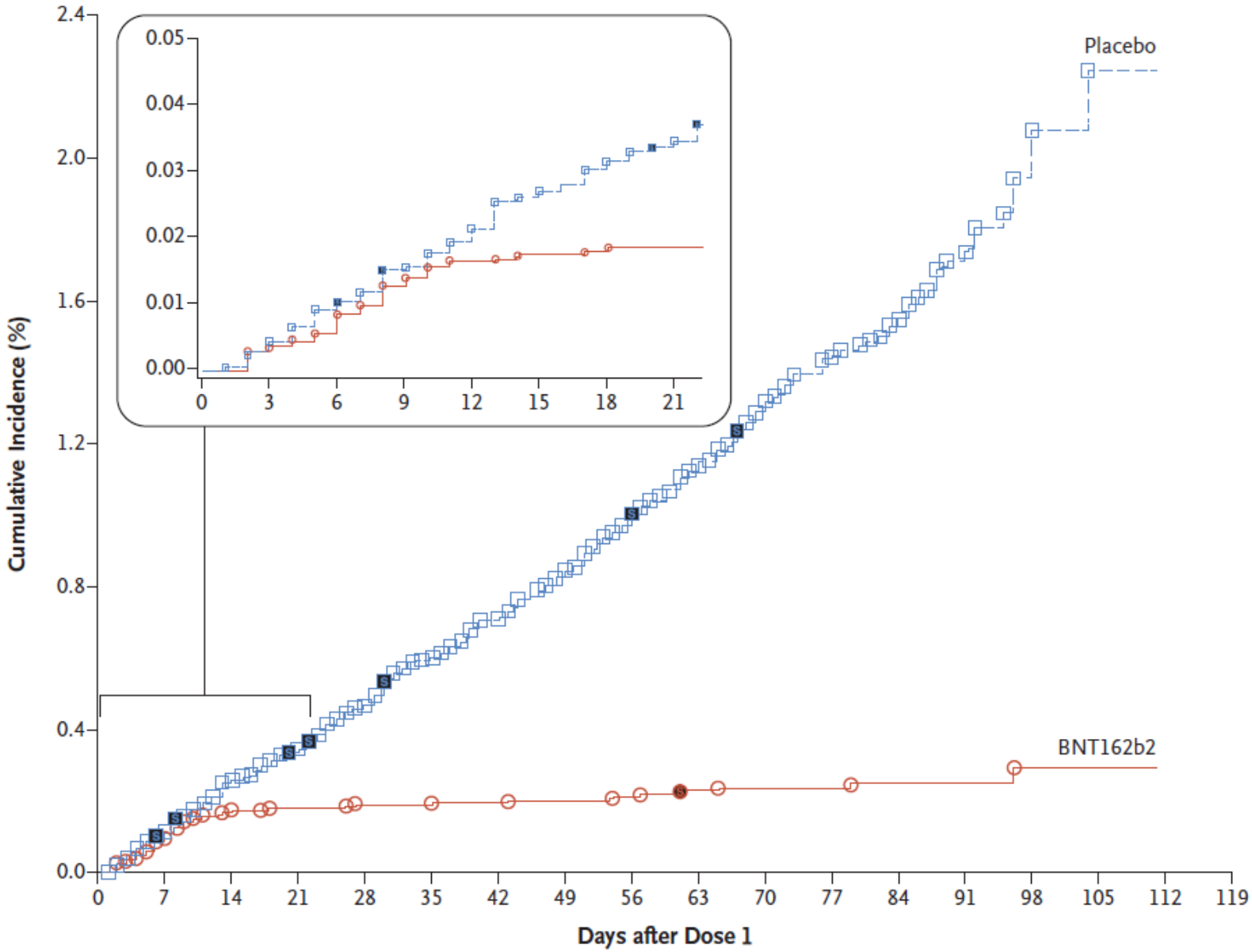
- HAV 94-100%
- HBV 80-100%
- Influenza 50-80%
- Mumps 66-95%
- Rotavirus 74-98%
- Varicella 70-100%

Hodgson Lancet 2020 https://doi.org/10.1016/S1473-3099(20)30773-8
https://www.cdc.gov/vaccines/pubs/pinkbook/index.html

Efficacy of Pfizer BNT162b2 mRNA COVID-19 Vaccine

Efficacy End Point	BNT162b2		Placebo		Vaccine Efficacy, % (95% Credible Interval)‡
	No. of Cases	Surveillance Time (n)†	No. of Cases	Surveillance Time (n)†	
		(N=18,198)		**(N=18,325)**	
Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection	8	2.214 (1,7411)	162	2.222 (17,511)	95.0 (90.3–97.6)
		(N=19,965)		**(N=20,172)**	
Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection	9	2.332 (18,559)	169	2.345 (18,708)	94.6 (89.9–97.3)

Polack et al., DOI: 10.1056/NEJMoa2034577



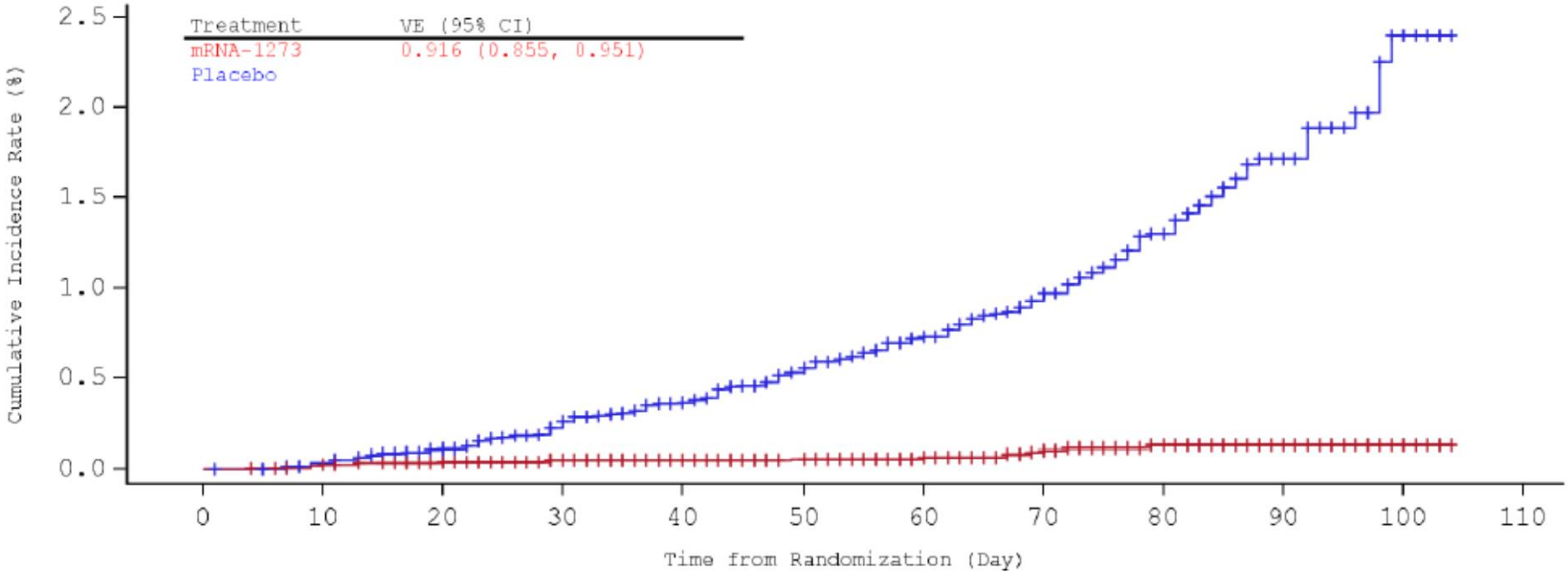
Polack et al., DOI: 10.1056/NEJMoa2034577

Moderna press release on 2nd interim analysis – November 30, 2020

- NIH DSMB review of 196 cases of confirmed COVID-19 illness
  - 11 cases in mRNA-1273 arm
  - 185 cases in placebo arm; P < 0.0001
  - VE = 94.1%
- Secondary endpoint of severe COVID-19 illness
  - 30 cases in placebo vs 0 in mRNA-1273 arms
  - No deaths

https://investors.modernatx.com/news-releases/news-release-details/modernas-covid-19-vaccine-candidate-meets-its-primary-efficacy

VE stratified by age group = 95.6% (95% CI: 90.6%, 97.9%) 18 to <65 years
= 86.4% (95% CI: 61.4%, 95.5%) ⩾65 years of age



Reactogenicity

Data from published Phase I/II trials

Adults 18–55 years of age

Moderna[1]

100µg	Post-dose 1			Post-dose 2		
N=15	Mild	Moderate	Severe	Mild	Moderate	Severe
Fever	—	—	—	5 (33%)	1 (7%)	—
Headache	4 (27%)	—	—	5 (33%)	4 (27%)	—
Myalgia	1 (7%)	—	—	2 (13%)	6 (40%)	—

Pfizer[2]

30µg	Post-dose 1			Post-dose 2		
N=12	Mild	Moderate	Severe	Mild	Moderate	Severe
Fever	1 (8%)	1 (8%)	—	—	2 (17%)	—
Headache	3 (25%)	1 (8%)	2 (17%)	6 (50%)	2 (17%)	—
Myalgia	1 (8%)	1 (8%)	1 (8%)	4 (33%)	3 (25%)	—

[1]Jackson et al. An mRNA Vaccine against SARS-CoV-2- Preliminary report. NEJM 2020;20:1920-1931.

[2]Walsh et al. Safety and immunogenicity of two RNA-Based COVID-19 vaccine candidates. NEJM 2020; online publication Oct 14.

https://www.cdc.gov/vaccines/acip/meetings/slides-2020-12-11.html

COVID Vaccine Status December 14, 2020

Pfizer/BioNTech

- Emergency Use Authorization approved 12/11/2020
- Vaccine administrations begun
- Expect to produce 50 million vaccine doses for global distribution in 2020; 1.3 billion doses in 2021

Moderna

- Submission for Emergency Use Authorization pending FDA review on 12/17/2020
- Expect to produce 20 million vaccine doses for US distribution in 2020; 0.5-1.0 billion doses in 2021

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-conclude-phase-3-study-covid-19-vaccine
https://investors.modernatx.com/news-releases/news-release-details/modernas-covid-19-vaccine-candidate-meets-its-primary-efficacy