SARS-CoV-2 Vaccines

Florian Krammer

Mount Sinai Professor in Vaccinology

Icahn School of Medicine at Mount Sinai

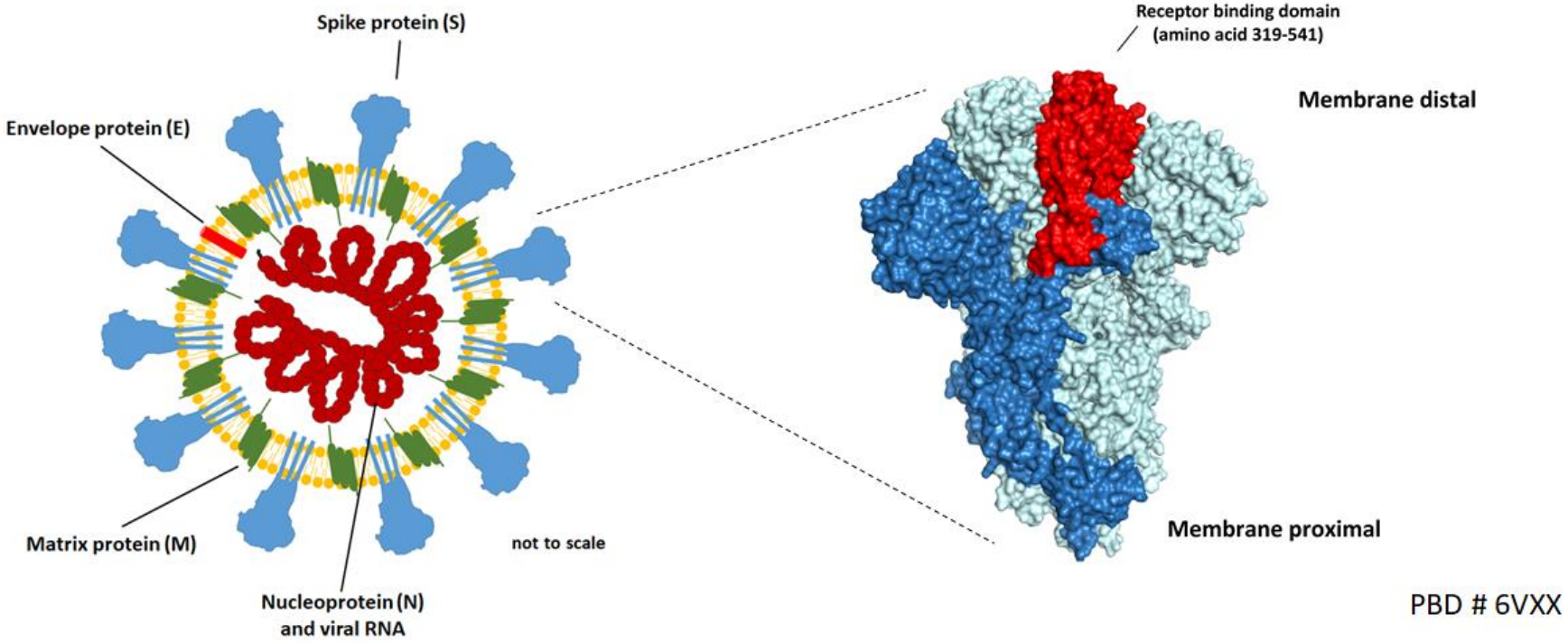
Workshop on Vaccine Efficacy & Safety

DHS UNIVERSITY CENTERS OF EXCELLENCE VIRTUAL WORKSHOPS

January 7, 2021

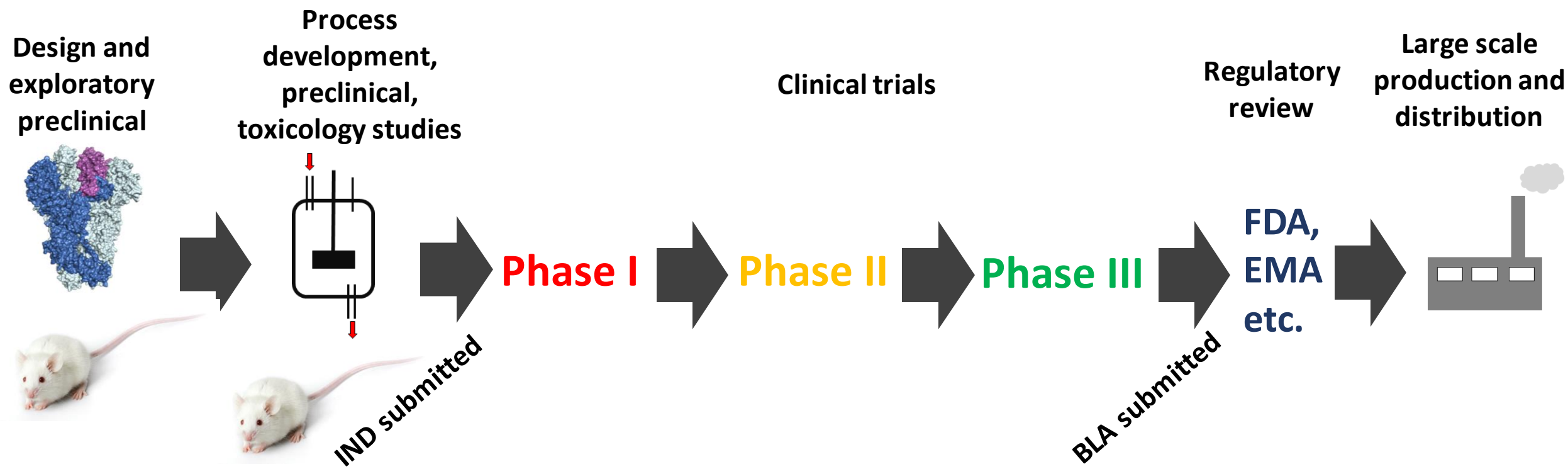
Mount Sinai

Immunity?



- **Antibody responses target the spike protein including the receptor binding domain as well as the nucleoprotein and other targets**
  - **Anti-spike (and RBD) antibodies are neutralizing and correlate with protection**
  - **NP antibodies are not neutralizing (we do not know if they are helpful)**
- **T-cell responses target several proteins**
  - **Strong CD4+ response**
  - **Relatively weak CD8+ response**

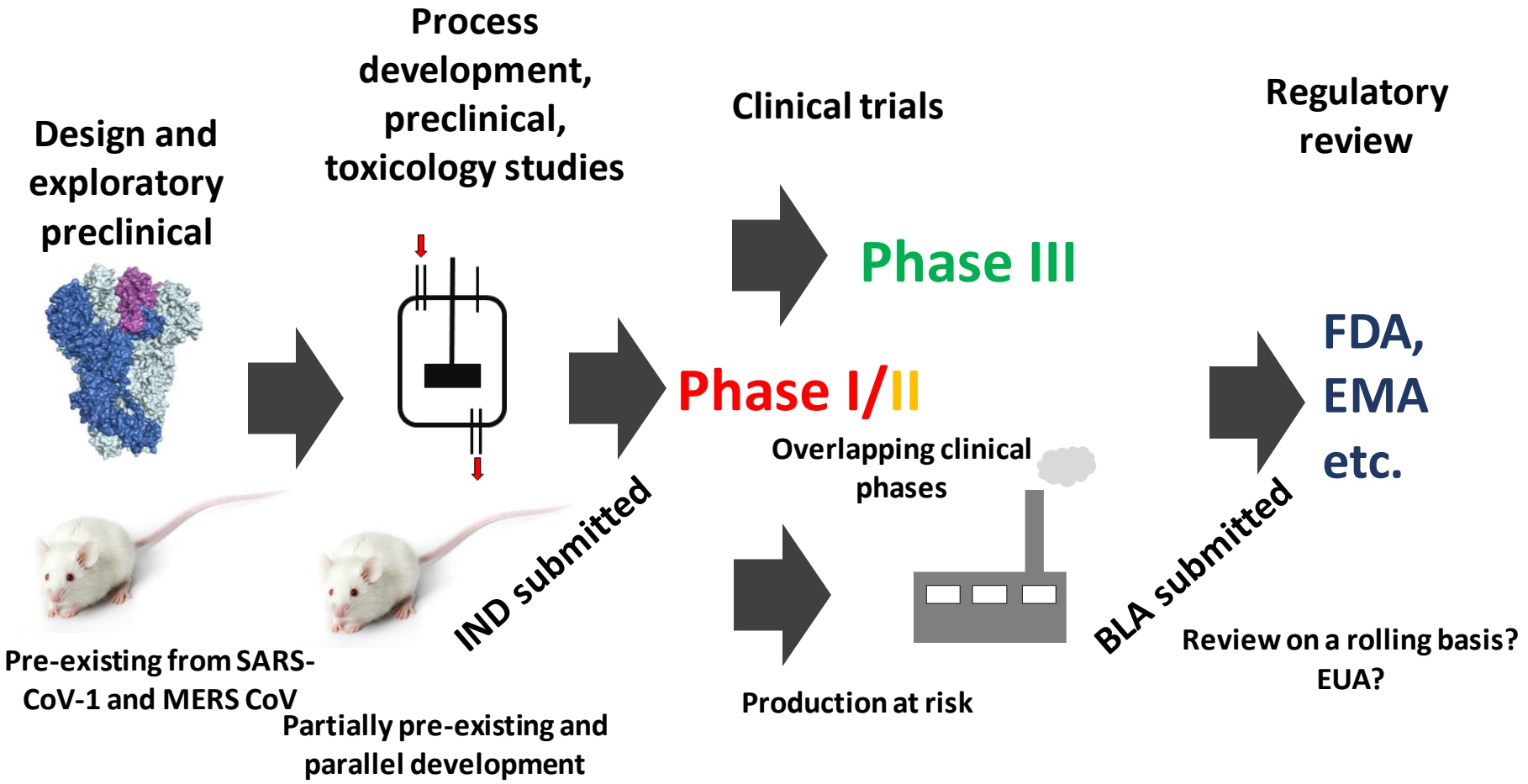
Vaccine development usually happens at a glacial pace



Years	2-4 years	1-2 years	2 years	2-3 years	1-2 years

15 years

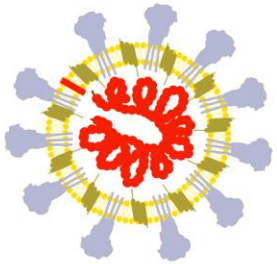
COVID-19 vaccine development



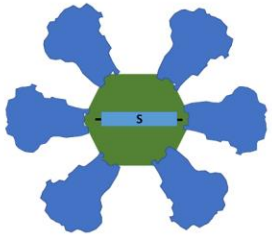
months months months

10 months to 1.5 years

C Inactivated vaccines are made of SARS-CoV-2 that is grown in cell culture and then chemically inactivated



J Inactivated vector vaccines carry copies of the spike on their surface but have been chemically inactivated



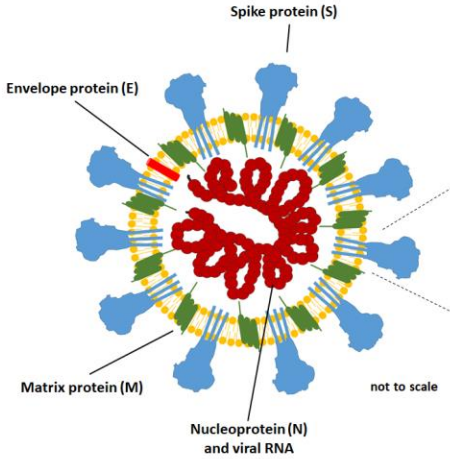
F Recombinant RBD protein based vaccines

E Recombinant spike protein based vaccines

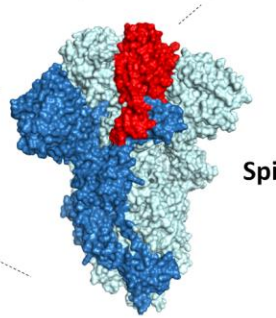
D Live attenuated vaccines are made of genetically weakened versions of SARS-CoV-2 that is grown in cell culture

SARS-CoV-2

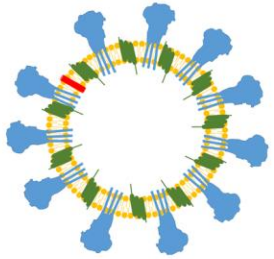
A



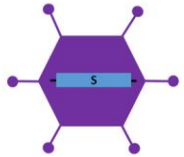
B Receptor binding domain (RBD)



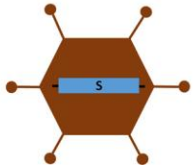
G Virus-like particles (VLPs) carry no genome but display the spike on their surface



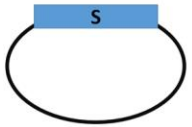
H Replication competent vector vaccines can propagate to some extend in the vaccinee's cells and express the spike protein there.



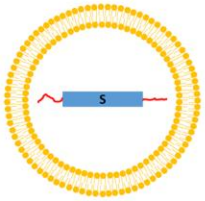
I Non-replication competent vector vaccines cannot propagate in the vaccinee's cells but express the spike protein there



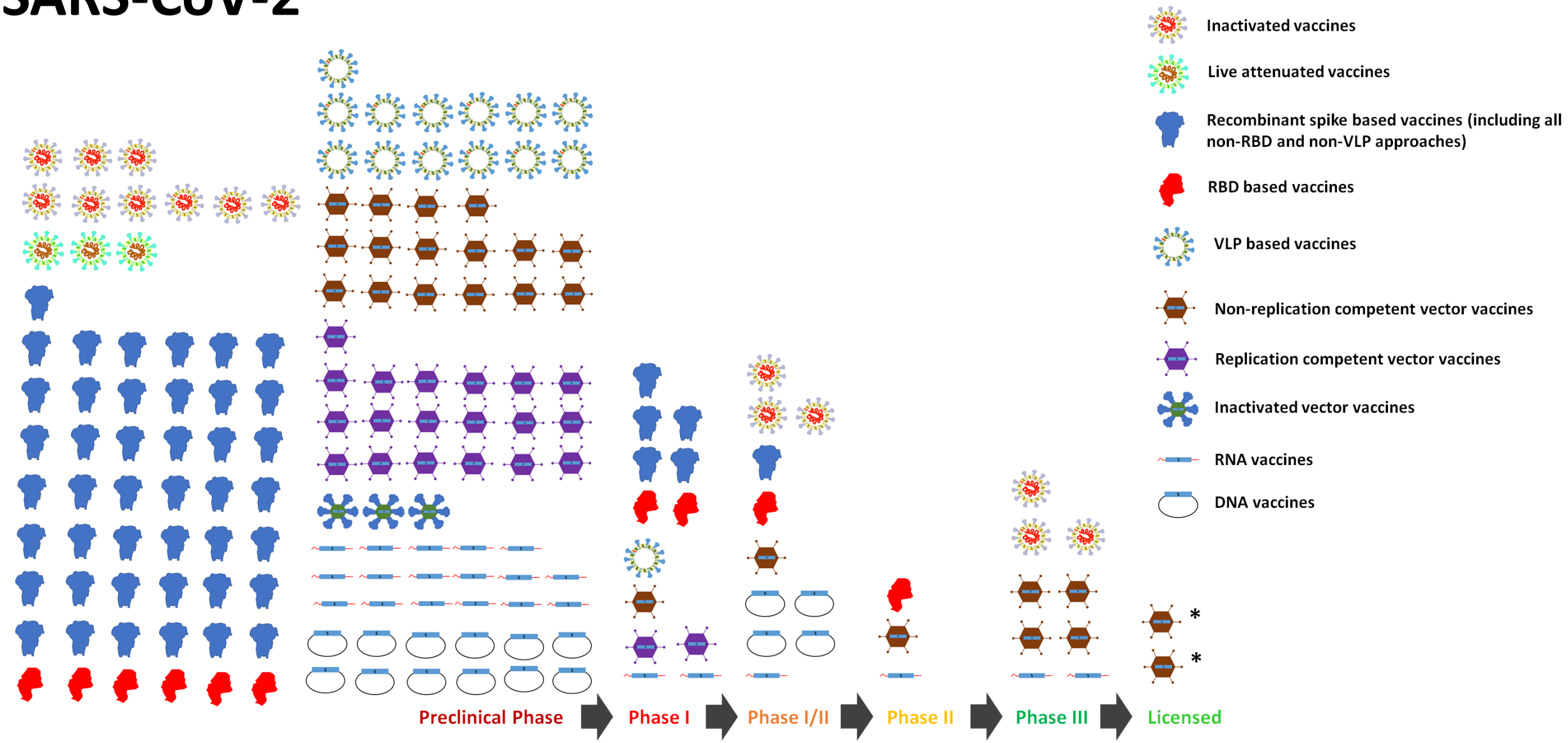
K DNA vaccines consist of plasmid DNA coding for the spike gene under a mammalian promotor



L RNA vaccines consist of RNA encoding for the spike protein and are typically packaged in lipid nanoparticles (LNPs)



Current vaccine development pipeline for SARS-CoV-2



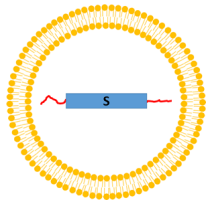
Data from non-human primate challenge experiments

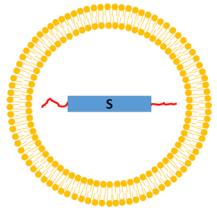
Company (ref.)	Vaccine candidate (type)	Dose range (route)	Neut. titre after prime	Neut. titre after boost	T cell response	Challenge dose (route)	URT protection	LRT protection	Species
Sinovac[34]	PiCoVacc (inactivated virion + aluminium hydroxide)	3–6 µg (i.m.)	None[a]	1:10 range[a] (1:15 range[a] after 2nd boost)	ND	10^6 $TCID_{50}$ (i.t.)	Partial[b]	Incomplete (low dose)[b] Yes (high dose)	Rhesus macaques
Beijing Institute of Biological Products[33]	BBIBP-CorV (inactivated virion + aluminium hydroxide)	4–8 µg (i.m.)	1:100 range[a]	1:200 range[a]	ND	10^6 $TCID_{50}$ (i.t.)	Partial[b]	Complete[b]	Cynomolgus macaques
AstraZeneca[49]	ChAdOxnCoV-19 (non-replicating AdV)	2.4 x 10^{10} VP; 1x or 2x (i.m.)	1:5–1:40 range[a]	1:10–1:160 range[a]	Yes	2.6 x 10^6 $TCID_{50}$ (i.t., oral, i.n., ocular)	None (1x)[c] None (2x)[c]	Partial (1x)[c] Complete (2x)[c]	Rhesus macaques
Janssen[41]	Ad26COVS1 (non-replicating AdV)	1 x 10^{11} VP (i.m.)	1:100 range[d]	—	Low	10^5 $TCID_{50}$ (i.n, i.t.)	Complete in S.PP group[c]	Complete in S.PP group[c]	Rhesus macaques
Moderna[57]	mRNA-1273 (mRNA via LNPs)	2x 10–100 µg (i.m.)	ND[e]	1:501–1:3,481 range[d]	Yes, CD4, T_{FH}	7.5 x 10^5 $TCID_{50}$ (i.n., i.t.)	None (10 µg)[c] Partial (100 µg)[c]	Partial (10 µg)[c] Complete (10 µg)[c]	Rhesus macaques
Novavax[83]	NVX CoV2373 (spike protein + Matrix-M)	2x 2.5–25 µg	—	17,920–23,040 range[a]	ND	10^4 (i.n., i.t.)[f]	Partial (low dose)[c] Complete (higher doses)[c]	Complete[c]	Cynomolgus macaques

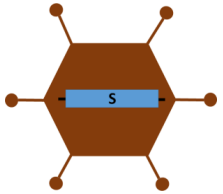
Data from Phase I/II trials

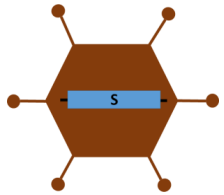
Company (reference)	Vaccine (type)	Dose range (route)	Neut. titre after prime	Neut. titre after boost	T cell response	Trial registration number
Sinovac[35]	CoronaVac (inactivated SARS-CoV-2 + aluminium hydroxide)	3–6 µg (i.m.) 2x	ND	1:30–1:60 range[a]	ND	NCT04352608
Sinopharm	Inactivated whole virus COVID-19 vaccine (inactivated SARS-CoV-2 + aluminium hydroxide)	2.5, 5 or 10 µg (i.m.) 3x (0/28/56 or 0/28) 5ug (i.m.) 2x (0/14 or 0/21)	Not reported in detail	1:316 (2.5 ug, 0/28/58)[c] 1:206 (5 ug, 0/28/58)[c] 1:297 (10 ug, 0/28/58)[c] 1:121 (5ug, 0/14)[c] 1:247 (5 ug, 0/21)[c]	ND	ChiCTR2000031809
CanSino[46]	Ad5 nCoV (non-replicating AdV5 expressing spike protein)	5 x 10^{10}, 10^{11} VP (i.m.)	1:18.3–1:19.5 range[b]	—	Yes	NCT04341389
AstraZeneca[47]	ChAdOx1nCOV-19 (non-replicating chimpanzee AdV expressing spike protein)	5 x 10^{10} VP 1 x or 2´ (i.m.)	Median 1:218[c] Median 1:51[d] Median 1:4–1:16[e]	Median 1:136[d] Median 1:29 [d]	Yes	NCT04324606
Moderna[59]	mRNA-1273 (mRNA)	2x 25, **100**, 250 µg (i.m.)	Low	1:112.3 (25 µg)[f] 1:343.8 (100 µg)[f] 1:332.2 (250 µg)[f] 1:339.7 (25 µg)[g] 1:654.3 (100 µg)[g]	Good $CD4^+$ and low $CD8^+$ response	NCT04283461
Pfizer[60]	BNT162b1 (mRNA)	2x 10, 30, 100 µg (i.m.)	Low	1:180 (10 µg)[h] 1:437 (30 µg)[h]	ND	NCT04368728
Pfizer[84]	BNT162b1 (mRNA) and **BNT162b2** (mRNA)	2x 10, 20, **30** µg	Low	Day 28[h] BNT126b1 (18–55 years): 1:168 (10 µg) 1:267 (30 µg) BNT126b1 (65–85 years): 1:37 (10 µg) 1:179 (20 µg) 1:101 (30 µg) BNT126b2 (18–55 years): 1:157 (10 µg) 1:363 (20 µg) 1:361 (30 µg) BNT126b2 (65–85 years): 1:84 (20 µg) 1:147 (30 µg)	ND	NCT04368728
Novavax[90]	NVX CoV2373 (Matrix-M) Spike protein 'rosettes'	2 x 2.5–25 µg (i.m. ± Matrix-M) 1x 25 µg (i.m. + Matrix-M)	1:128 (25 µg + Matrix-M)[i]	1:3,906 (5 µg + Matrix-M)[i] 1:3,305 (25 µg + Matrix-M)[i] 1:41 (25 µg unadjuvanted)[i]	$CD4^+$	NCT04368988

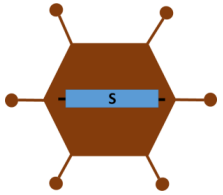
Vaccines in Phase III

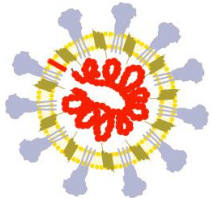
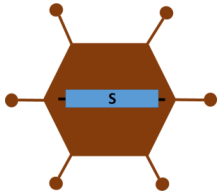
- Moderna ✓ 

- Pfizer ✓ 

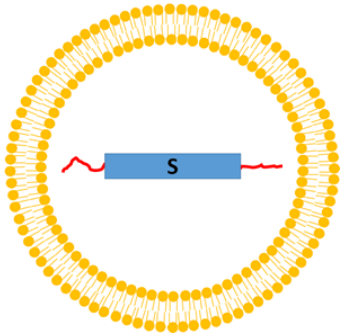
- AstraZeneca IR 

- Janssen 

- Novavax
- Gamaleya IR 

- Sinovac/Sinopharm (3x) IR 
- Cansino 

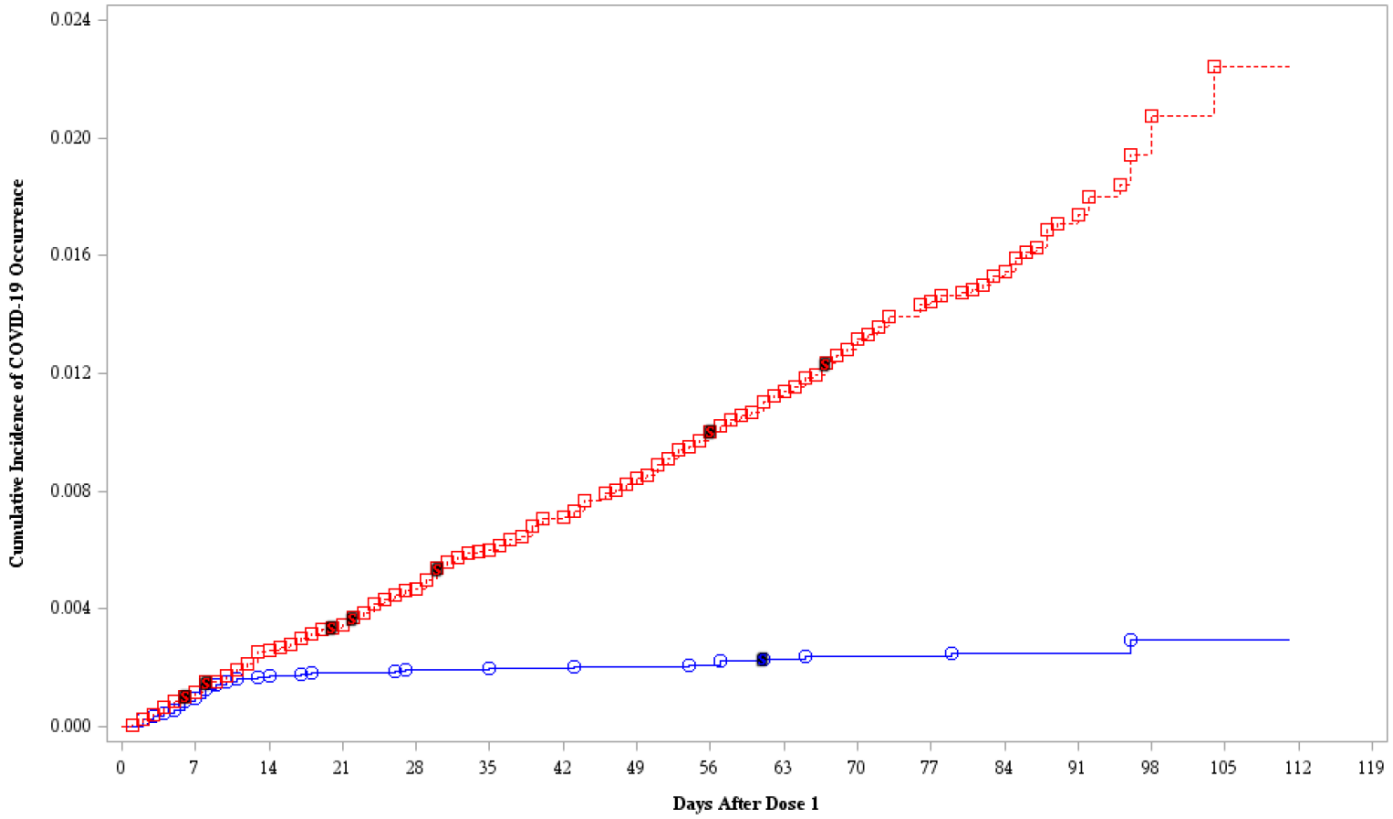
What do the Pfizer results mean?



- 43,538 individuals are in the study
- 170 COVID-19 cases were recorded
  - 162 in the placebo group (9 severe)
  - 8 in the vaccine group (1 severe)
- 95% efficacy (they start measuring this 7 days post dose 2)
- 94% efficacy in the 65-85 year old group
- No significant safety concerns

- The vaccine received different degrees of approval in Bahrain, the UK, Mexico, Canada, Saudi Arabia, the EU, the US etc.

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Dose 1 All-Available Efficacy Population



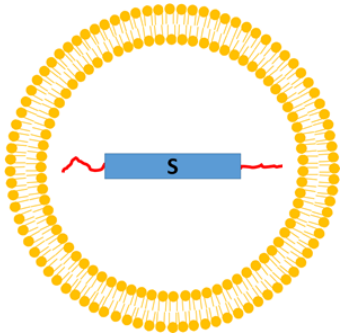
No. with events/No. at risk

A:	0/21314	21/21230	37/21054	39/20481	41/19314	42/18377	42/17702	43/17186	44/15464	47/14038	48/12169	48/9591	49/6403	49/3374	50/1463	50/398	50/0
B:	0/21258	25/21170	55/20970	73/20366	97/19209	123/18218	143/17578	166/17025	192/15290	212/13876	235/11994	249/9471	257/6294	267/3301	274/1449	275/398	275/0

Note: "S" indicates subjects with severe COVID-19 or COVID-19 leading to hospitalization.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adc19ef Table Generation: 17NOV2020 (21:40)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_f001_km_d1_aai

https://www.fda.gov/media/144245/download accessed 8Dec20

What do the Moderna results mean?

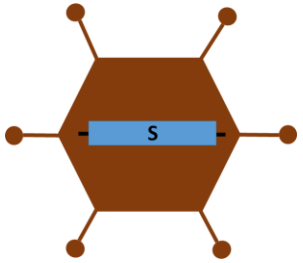


- 30,000 individuals are in the study
- 196 COVID-19 cases were recorded (33 in older/65+ adults)
  - 185 in the placebo group (30 severe cases, one death)
  - 11 in the vaccinated group (no severe cases)
- 94.1% efficacy (they start measuring this 14 days post dose 2)
- No significant safety concerns
- Some indication of reduction of asymptomatic infections

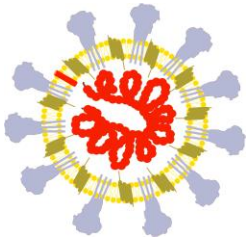
- The vaccine received different degrees of approval in the EU, the US etc.

Other vaccine (interim) results

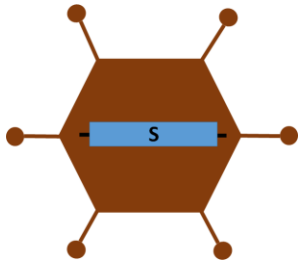
- AstraZeneca
  - Two studies (they start measuring this 14 days post dose 2)
    - 62% efficacy in Brazil (n=11,636)
    - 90% efficacy in the UK (n=2,741)
  - 131 COVID-19 cases
  - It turned out the UK group got only a half-dose as first shot due to an error…..
  - We don't know how well this vaccine works, but it works



- Sinovac
  - Trial with 31,000 individuals
  - 86% efficacy (no data available)
  - Licensed in the UAE



- Gamaleya
  - Sputnik V
  - 95% efficacy (no data available)

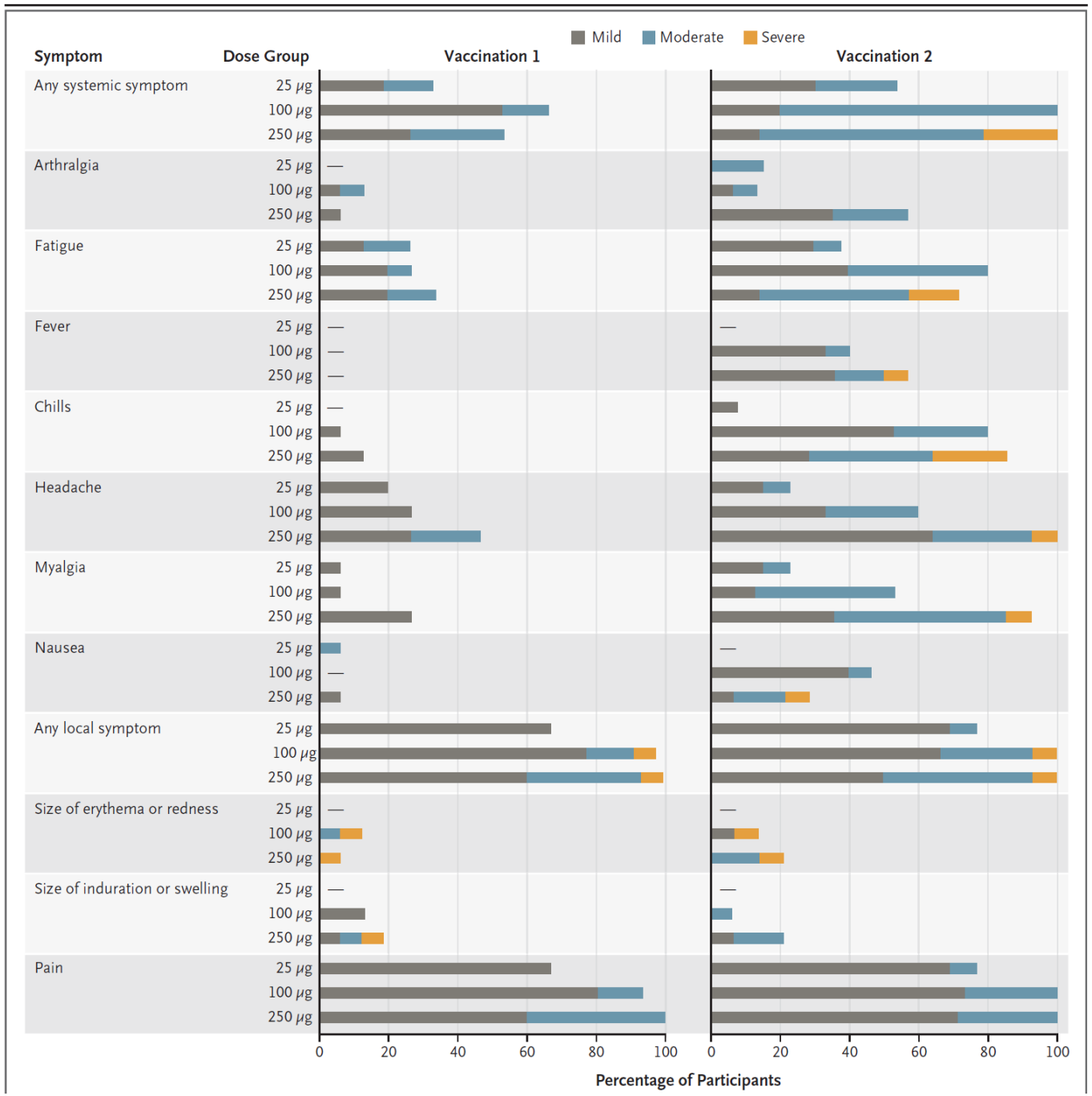


Reactogenicity

- Injection site pain
- Headache
- Fatigue
- Elevated temperature
- Myalgia
- Mild flu-like symptoms

→unpleasant, but not dangerous

AdV>mRNA>recombinant protein>inactivated vaccine



Moderna/VRC mRNA 1273 via LNPs

Allergic reactions

- Some people have severe allergic reactions to vaccines
  - These people were excluded from the Pfizer trial
  - Regular ‘allergic’ individuals were not excluded

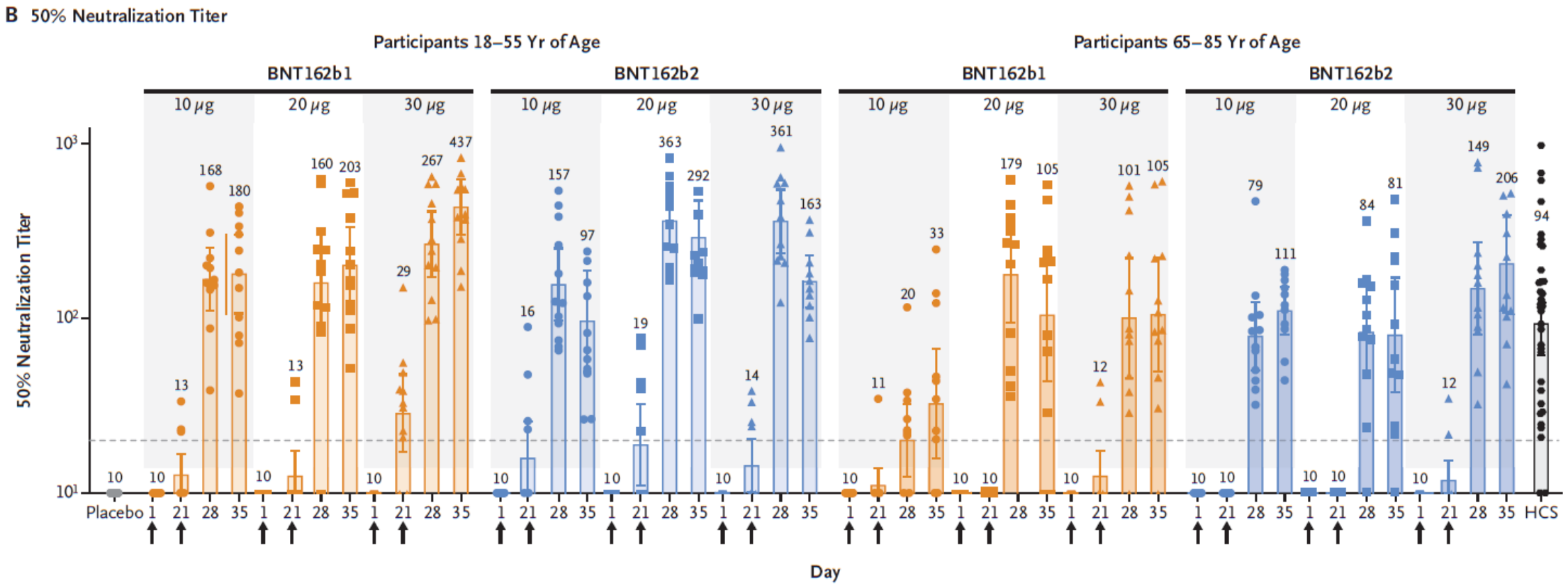
- The rate is approximately 11 reactions per 1 million vaccinated individuals (CDC)

The vaccines seem to be working better in younger people

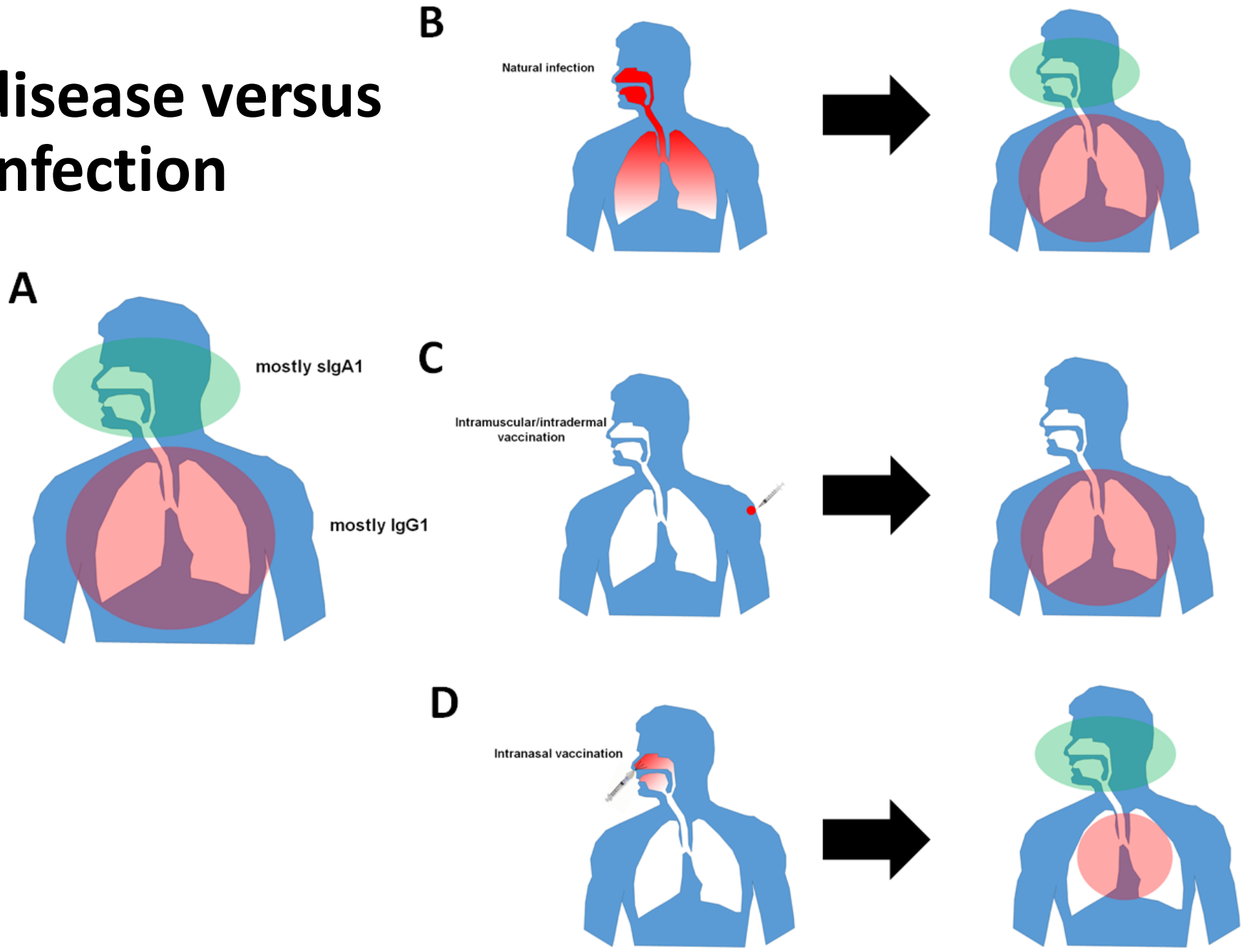
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates



Protection from disease versus protection from infection



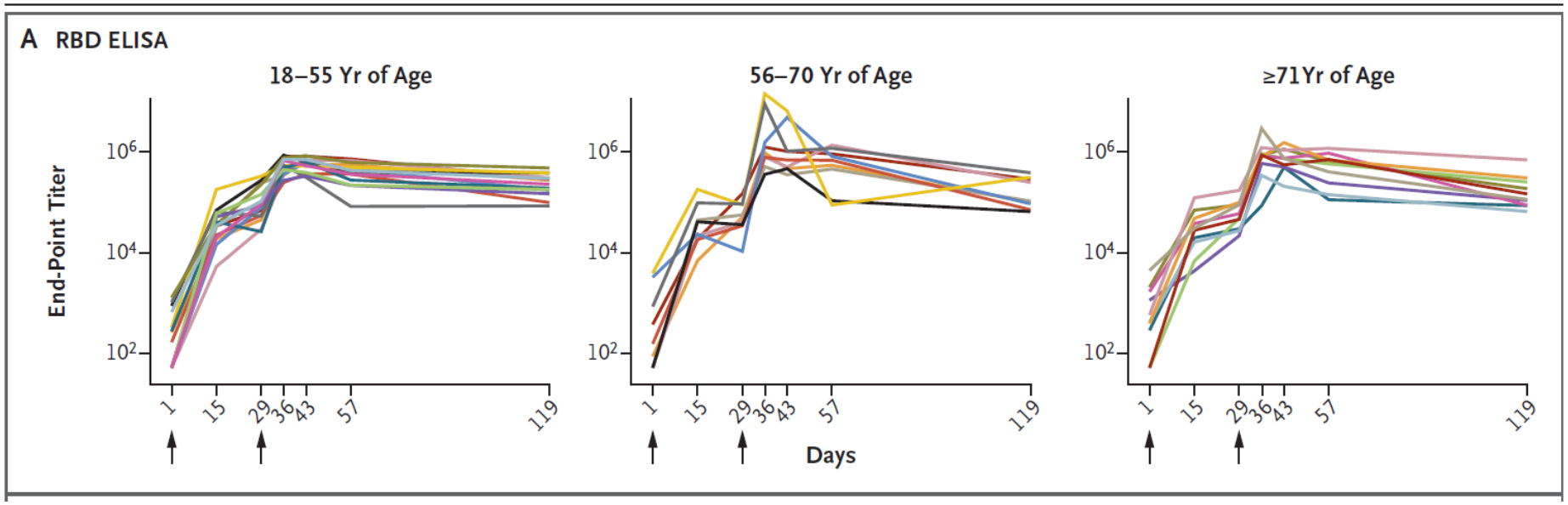
The NEW ENGLAND JOURNAL of MEDICINE

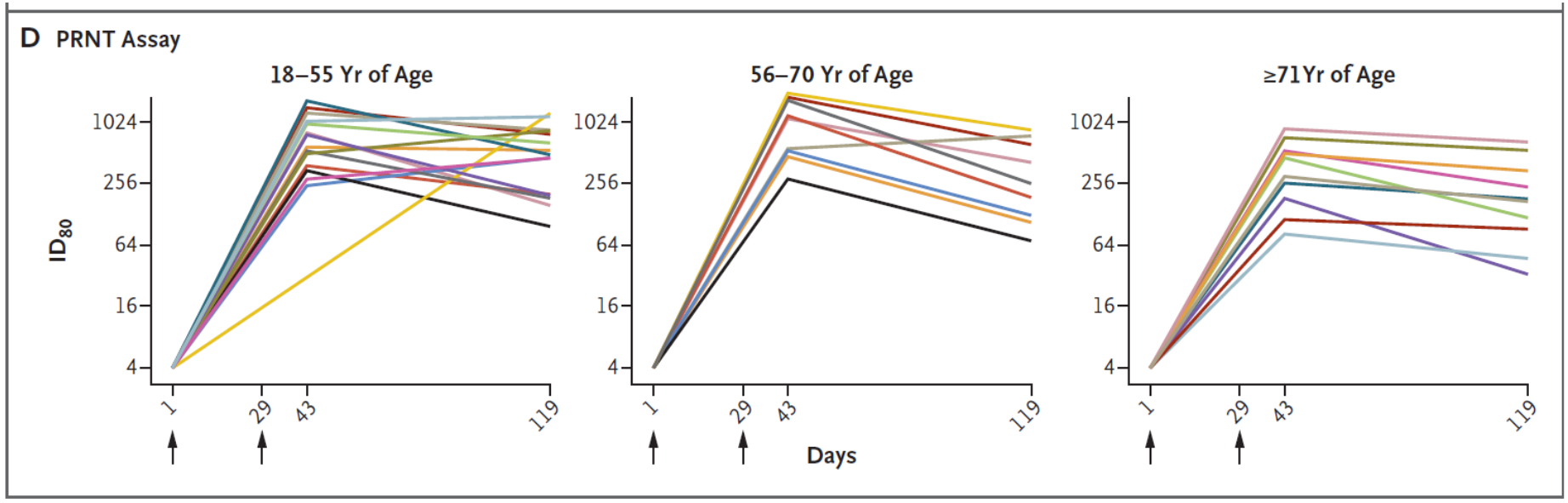
CORRESPONDENCE

Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination

Longevity of protection

The immune response to the mRNA vaccines looks pretty normal





Global rollout

Country	No. of doses administered ▼	Per 100 people	Last updated
Global total	*15,905,118*	–	*Jan. 06*
U.S.	5,455,685	1.66	Jan. 06
China	4,500,000	0.32	Dec. 31
Israel	1,490,000	16.46	Jan. 06
U.K. +	1,300,000	1.95	Jan. 05
U.A.E.	826,301	7.69	Jan. 05
Russia*	800,000	0.55	Jan. 02
Germany	367,331	0.44	Jan. 06
Italy	260,948	0.43	Jan. 06
Canada +	172,083	0.46	Jan. 06
Spain	139,339	0.30	Jan. 06
Saudi Arabia	100,000	0.29	Jan. 06
Poland	92,220	0.24	Jan. 05
Bahrain	63,893	4.31	Jan. 05
Denmark	63,312	1.09	Jan. 06
Mexico	48,236	0.04	Jan. 06
Portugal	42,035	0.41	Jan. 06
Argentina	32,013	0.07	Dec. 31
Romania	25,508	0.13	Jan. 04
Hungary	21,000	0.21	Jan. 06
Czech Republic	13,000	0.12	Jan. 05
Oman	10,728	0.26	Jan. 05
Slovenia	9,750	0.47	Dec. 29
Greece	9,528	0.09	Jan. 04
Chile	9,254	0.05	Jan. 05
Croatia	7,864	0.19	Dec. 30
Slovakia	7,201	0.13	Jan. 04
Austria	6,000	0.07	Dec. 30
Bulgaria	5,448	0.08	Jan. 06
Finland	5,445	0.10	Jan. 05
Norway	4,036	0.08	Jan. 06
Ireland	4,000	0.08	Jan. 05
Estonia	2,535	0.19	Jan. 04
Kuwait	2,500	0.05	Dec. 29
Costa Rica	2,455	0.05	Jan. 03
Lithuania	2,270	0.08	Dec. 28
France	2,000	0.00	Jan. 05
Luxembourg	1,200	0.20	Dec. 30

https://www.bloomberg.com/graphics/covid-vaccine-tracker-global-distribution/

Conclusions - Vaccines

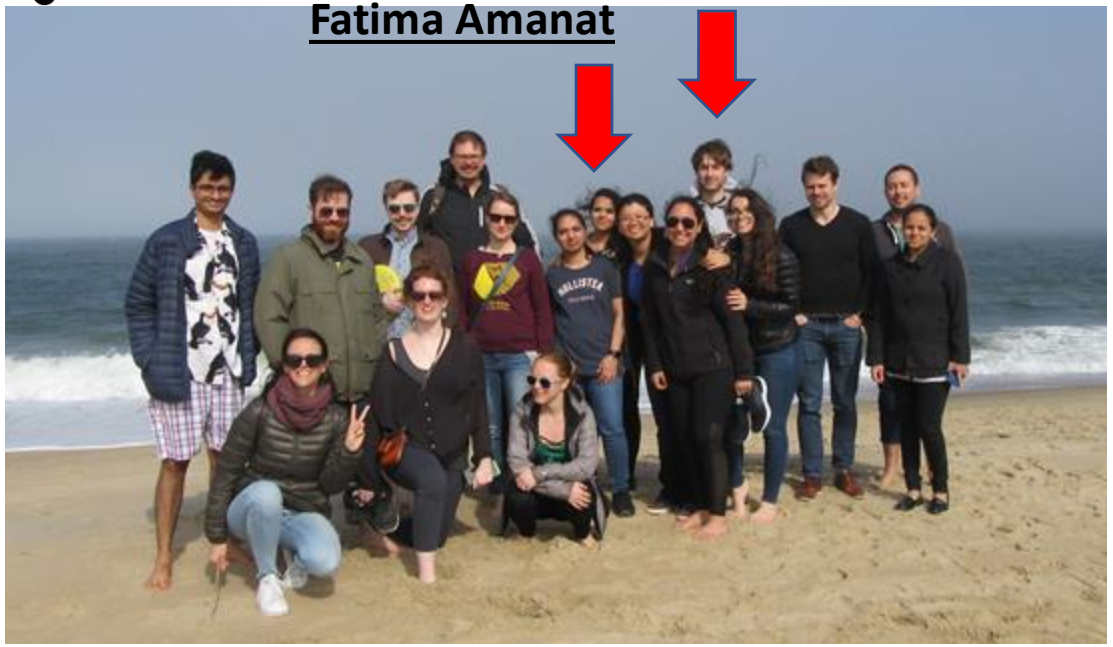
- Several candidates induce strong neutralizing antibody responses in non-human primates and in humans
- Protection from lower respiratory tract infection (disease) in non-human primate models seems solid
- Protection from upper respiratory infection is often partial
  - None of the vaccines in clinical trials is designed to induce a mucosal immune response
- Pfizer and Moderna Phase III results look really good!
- The Pfizer and Moderna vaccines are already licensed in several countries, the AstraZeneca vaccine is licensed in the UK

Acknowledgements

Krammer Laboratory

Daniel Stadlbauer

Fatima Amanat



florian.krammer@mssm.edu
http://labs.icahn.mssm.edu/krammerlab/
Twitter: @florian_krammer

Department of Microbiology/
Icahn School of Medicine at Mount Sinai
Peter Palese

Viviana Simon

Maria Bermudez-Gonzalez
Denise Jurczyszak
Matt Hernandez

Kantaro

CIVICs
Collaborative Influenza Vaccine Innovation Centers

CEIRS
NIAID Centers of Excellence for Influenza Research and Surveillance

Ania Wajnberg
(Mount Sinai Hospital)

Carlos Cordon-Cardo
Adolfo Firpo
(Mount Sinai Hospital)

Harm van Bakel
(ISMMS)

Mia Sordillo
David Rich
Judy Aberg
(Mount Sinai Hospital)

Adolfo García-Sastre
Lisa Miorin
Teresa Aydillo

Tom Moran

Katherine Kedzierska (U Melbourne)
Jussi Hepojoki (U Helsinki)
Olli Vapalahti (U Helsinki)