DC CTSA Spring Regulatory Update & Hot Topics in Clinical and Translational Research

Moving Swiftly to Combat the COVID-19 Global Health Crisis

Keynote Address

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George Washington University School of Medicine & Health Sciences

Moderator: Rebecca Eberle, MSHS, CIP
Interim Director, Office of Human Research
George Washington University

9:45 - 10:30 AM EST

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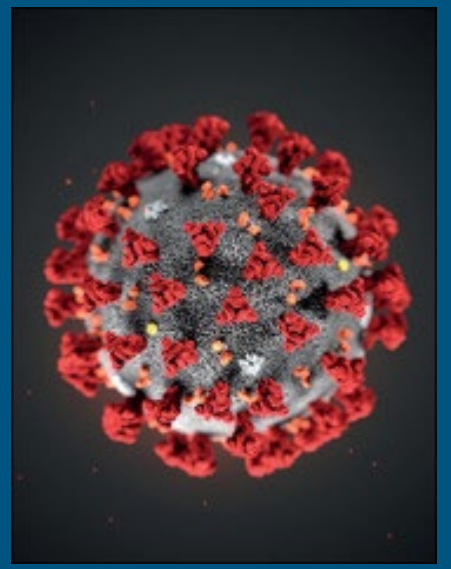
COVID-19 Vaccine Development:

The GW Experience



David Diemert, MD

Professor of Medicine & Microbiology, Immunology and Tropical Medicine

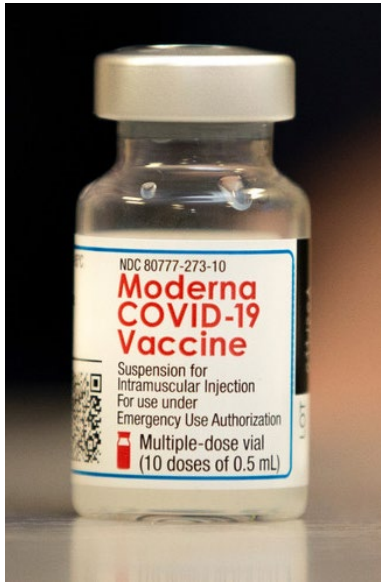
GW SMHS

23 Apr2021

smhs.gwu.edu

Disclosures

- Exhausted, but…
- Relieved & hopeful

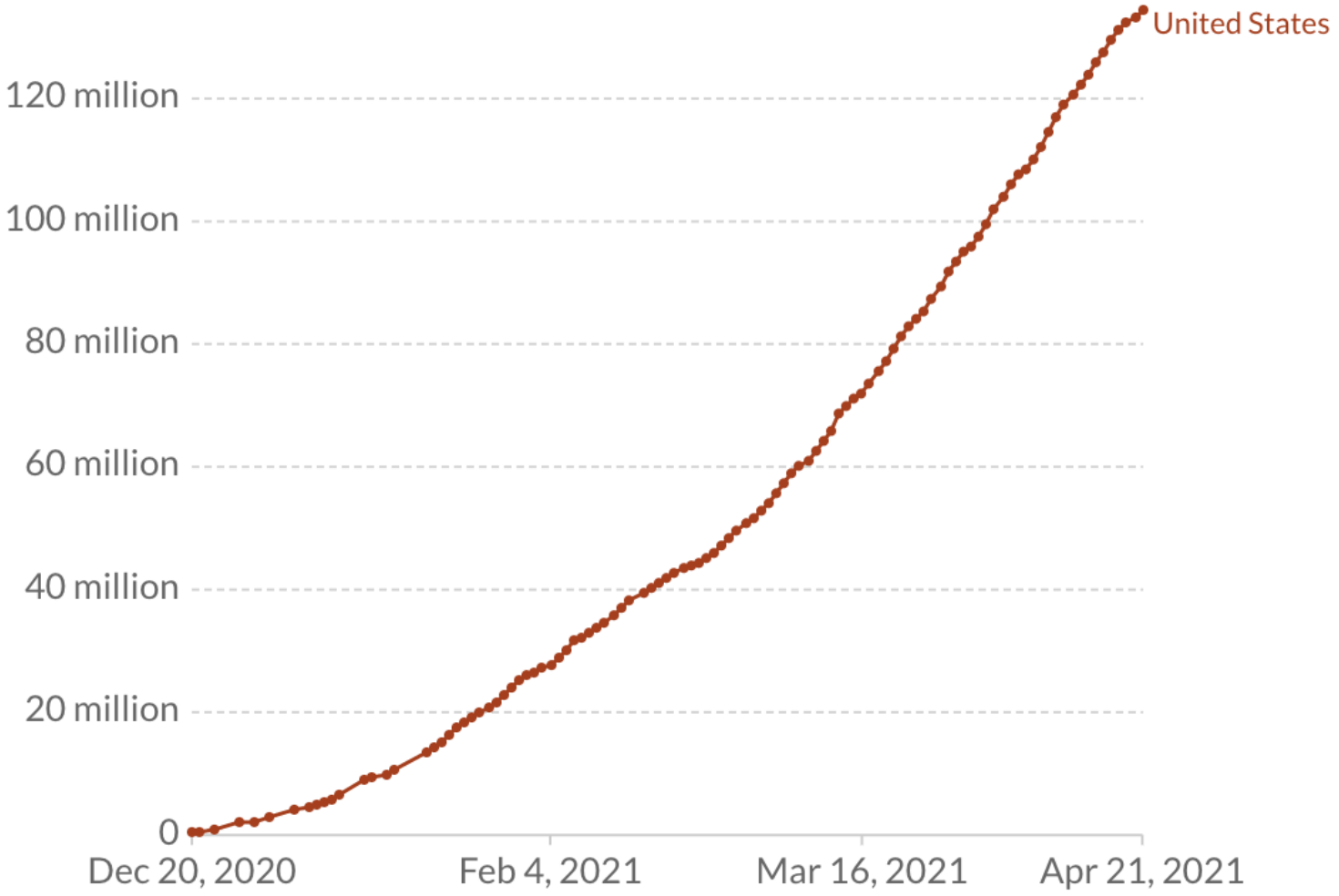


Number of people who received at least one dose of COVID-19 vaccine

Our World in Data

Total number of people who received at least one vaccine dose. This may not equal the number of people that are fully vaccinated if the vaccine requires two doses.

LINEAR | LOG



Source: Official data collated by Our World in Data

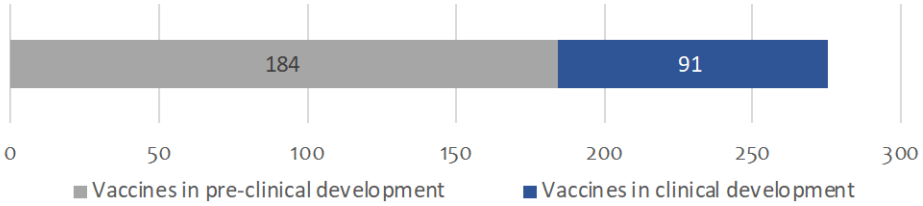
In US, 3 EUA vaccines:

- Pfizer
- Moderna
- Janssen/J&J

COVID-19 Vaccines in Clinical Trials

Summary Information on Vaccine Products in Clinical Development

1. - Number of vaccines in clinical development	**91**
2. - Number of vaccines in pre-clinical development	**184**

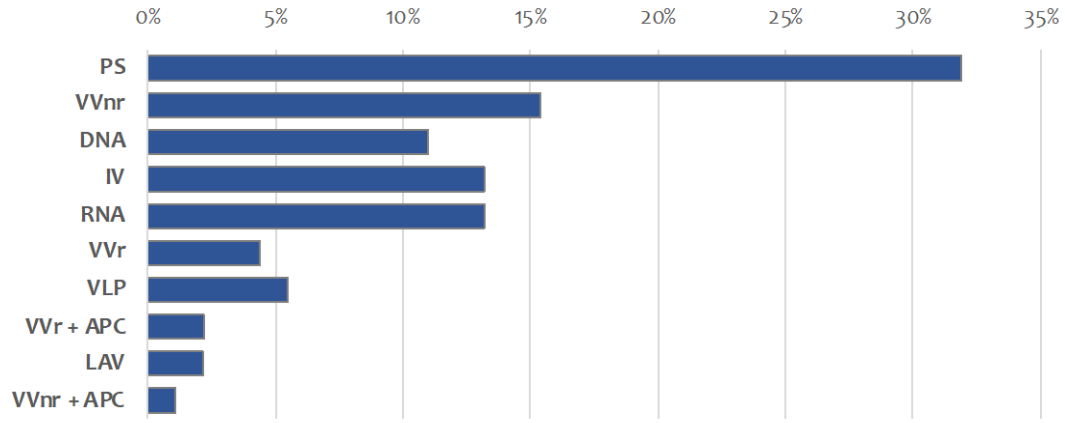


3. - Candidates in clinical phase

Filter: All

Select phase of development (default is all)

Platform		Candidate vaccines (no. and %)	
PS	Protein subunit	29	32%
VVnr	Viral Vector (non-replicating)	14	15%
DNA	DNA	10	11%
IV	Inactivated Virus	12	13%
RNA	RNA	12	13%
VVr	Viral Vector (replicating)	4	4%
VLP	Virus Like Particle	5	5%
VVr + APC	VVr + Antigen Presenting Cell	2	2%
LAV	Live Attenuated Virus	2	2%
VVnr + APC	VVnr + Antigen Presenting Cell	1	1%
		91	

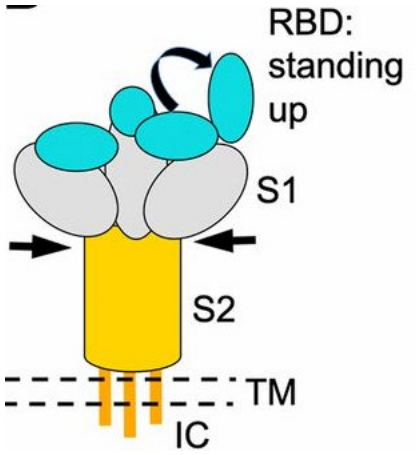


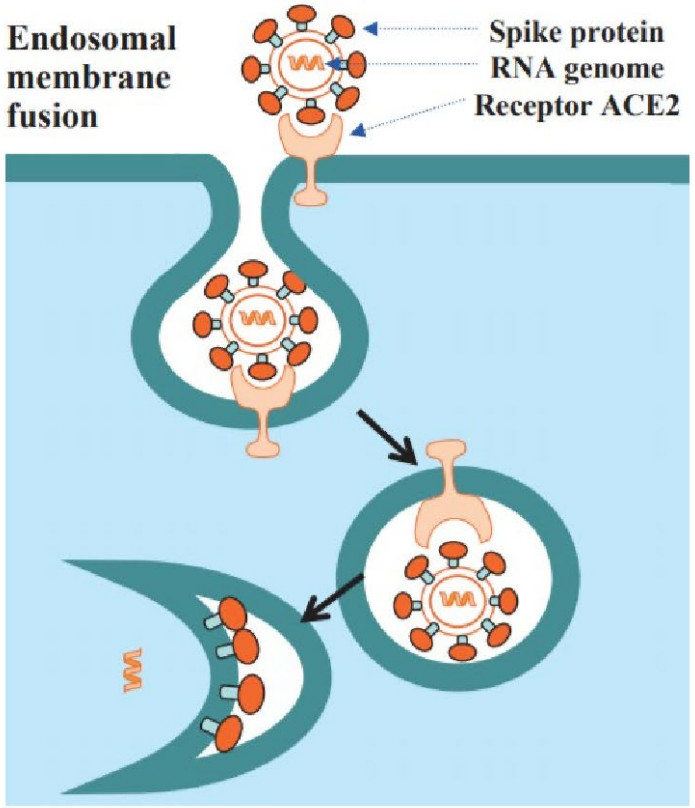
Source: WHO, 20APR2021

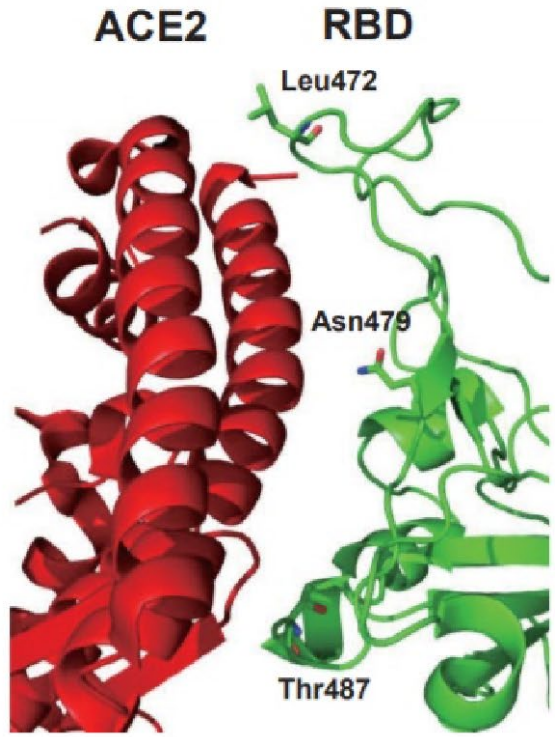
SARS-CoV-2 infects human cells via ACE2 for efficient viral entry

Mechanism of target cell entry

- Spike protein binds to ACE2 receptor via receptor binding domain (RBD)
- Endocytosis into vesicle
- Spike cleaved by endosomal proteases
- Fuses with endosomal membrane

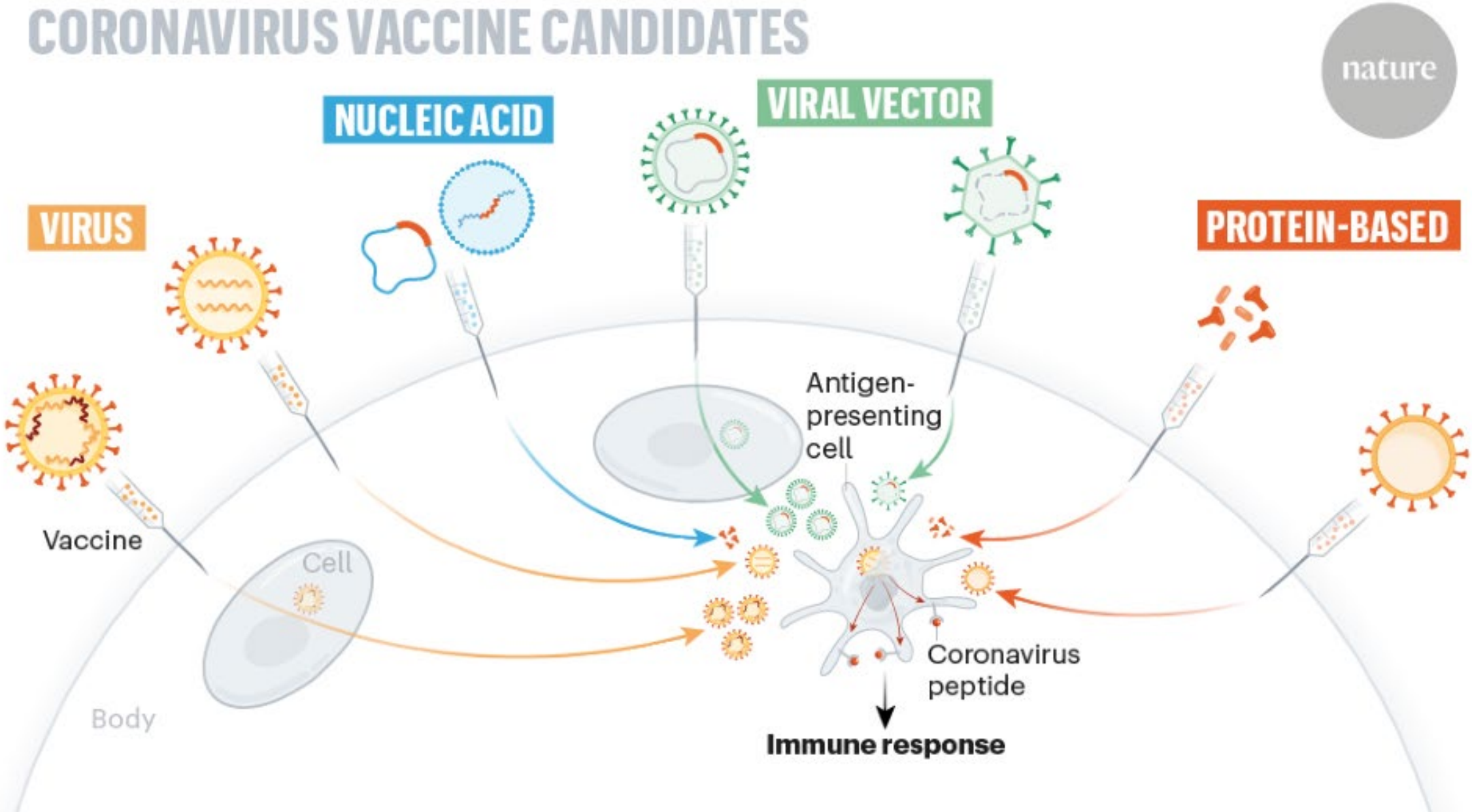






Zhu X, Liu Q, Du L, et al. Receptor-binding domain as a target for developing SARS vaccines. J Thorac Dis 2013;5(S2):S142-S148

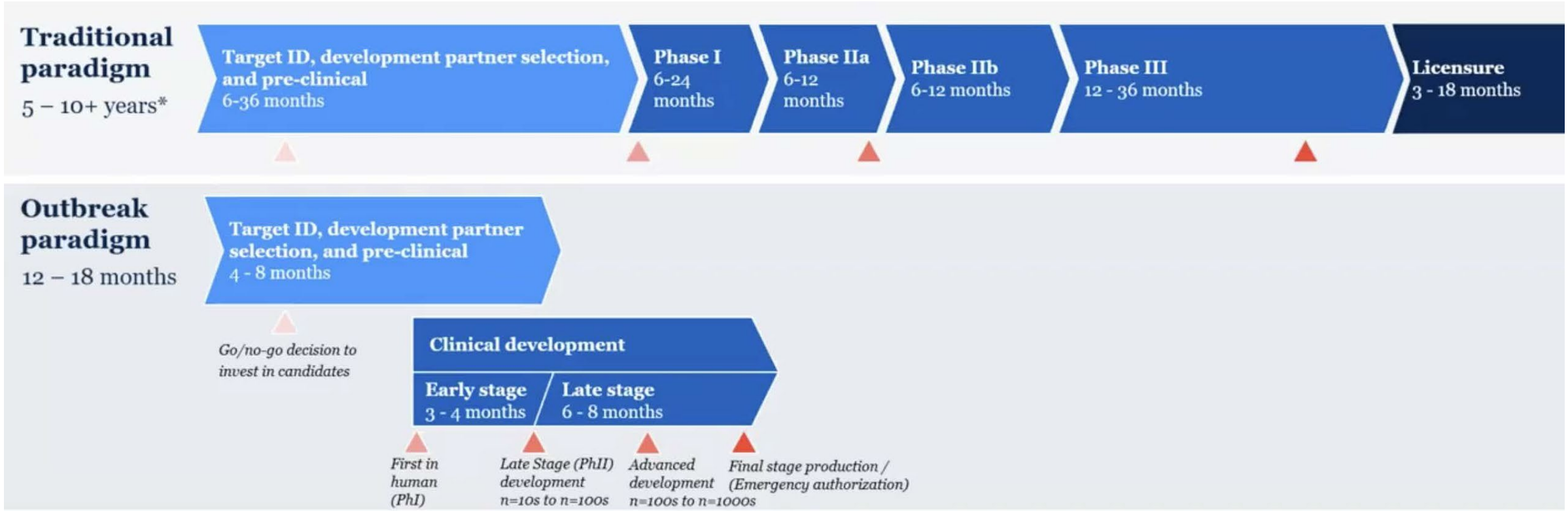
CORONAVIRUS VACCINE CANDIDATES



US Gov't-Supported COVID-19 Vaccine Candidates

moderna	mRNA
AstraZeneca	Replication Incompetent Adenovirus (ChAdOx1)
janssen (Johnson & Johnson)	Replication Incompetent Adenovirus (Ad26)
SANOFI	Adjuvanted protein subunit
MERCK iavi	Replication-competent Vesicular Stomatitis Vector (VSV)
NOVAVAX	Adjuvanted protein subunit
Pfizer	mRNA

Speed Requires a Paradigm Shift



Source: CEPI

mRNA Vaccine Approach

National Institute of Allergy and Infectious Diseases

March 16, 2020

News Release

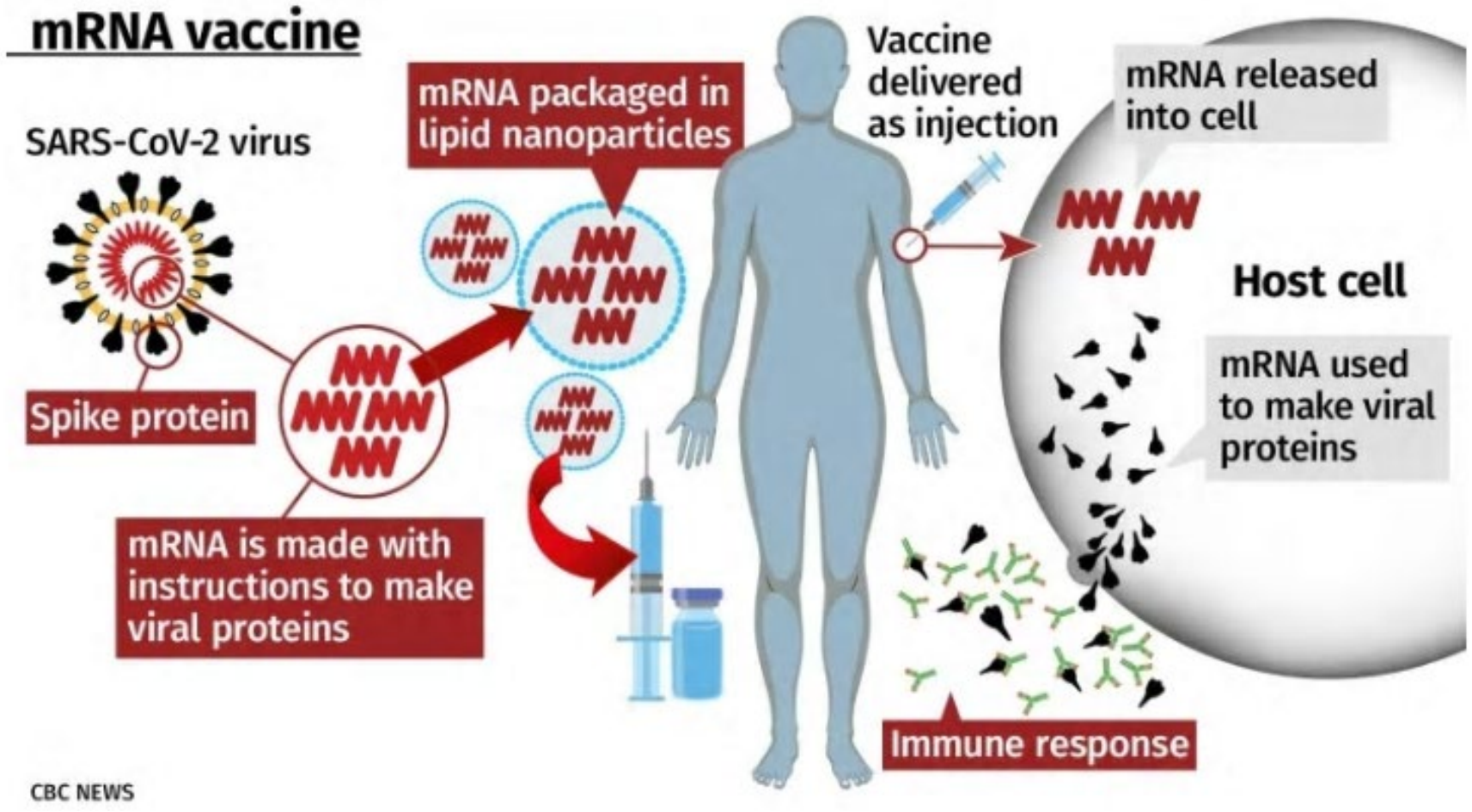
NIH Clinical Trial of Investigational Vaccine for COVID-19 Begins

Study Enrolling Seattle-Based Healthy Adult Volunteers

- Trial of vaccine candidate mRNA-1273 will enroll 45 healthy adult volunteers ages 18 to 55 years over approximately 6 weeks

Photo: AP

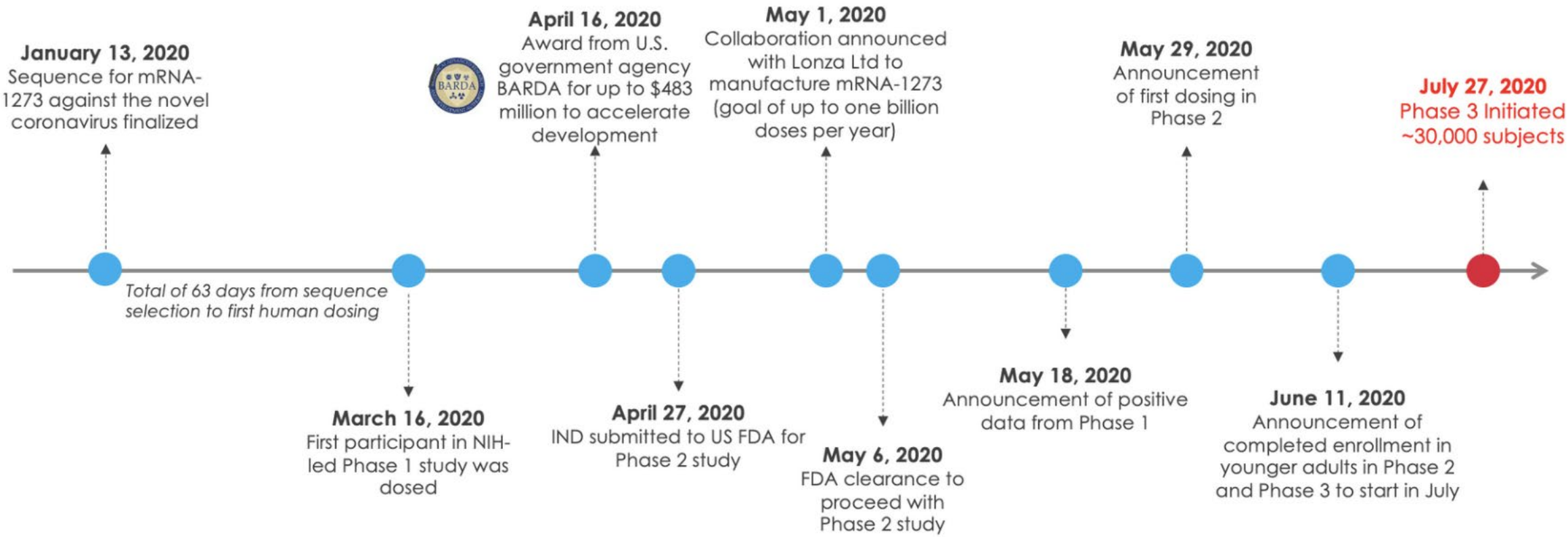
COVID-19 mRNA Vaccine Design



Wang F. Med Sci Monit 2020

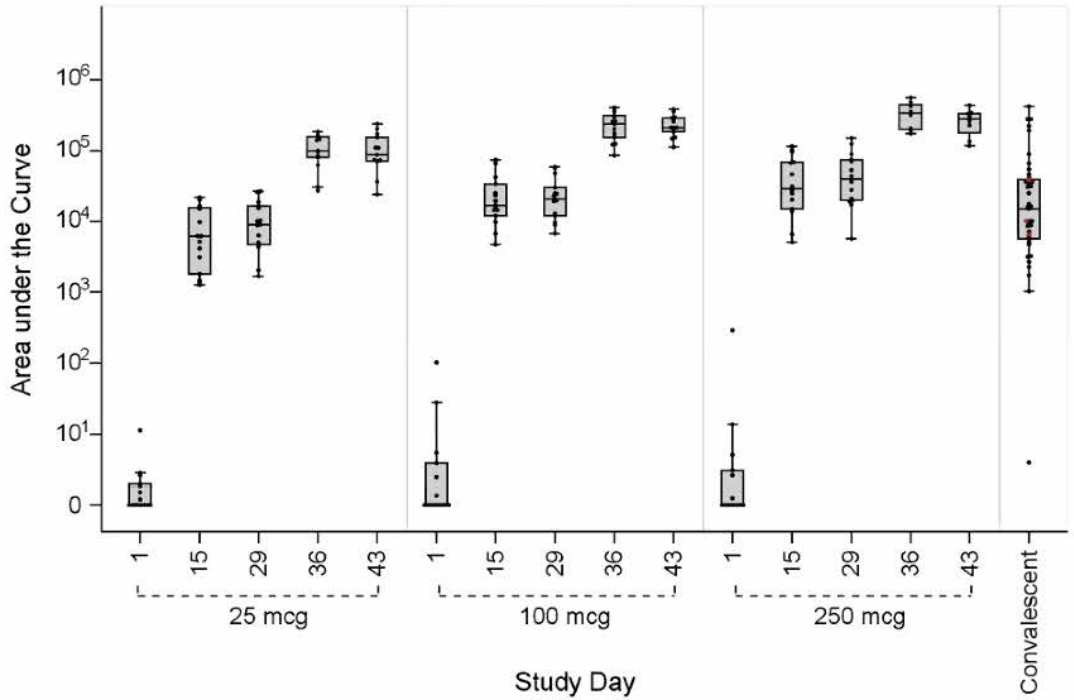
mRNA-1273 program timeline

mRNA-1273 timeline: Research and development of SARS-CoV-2 vaccine

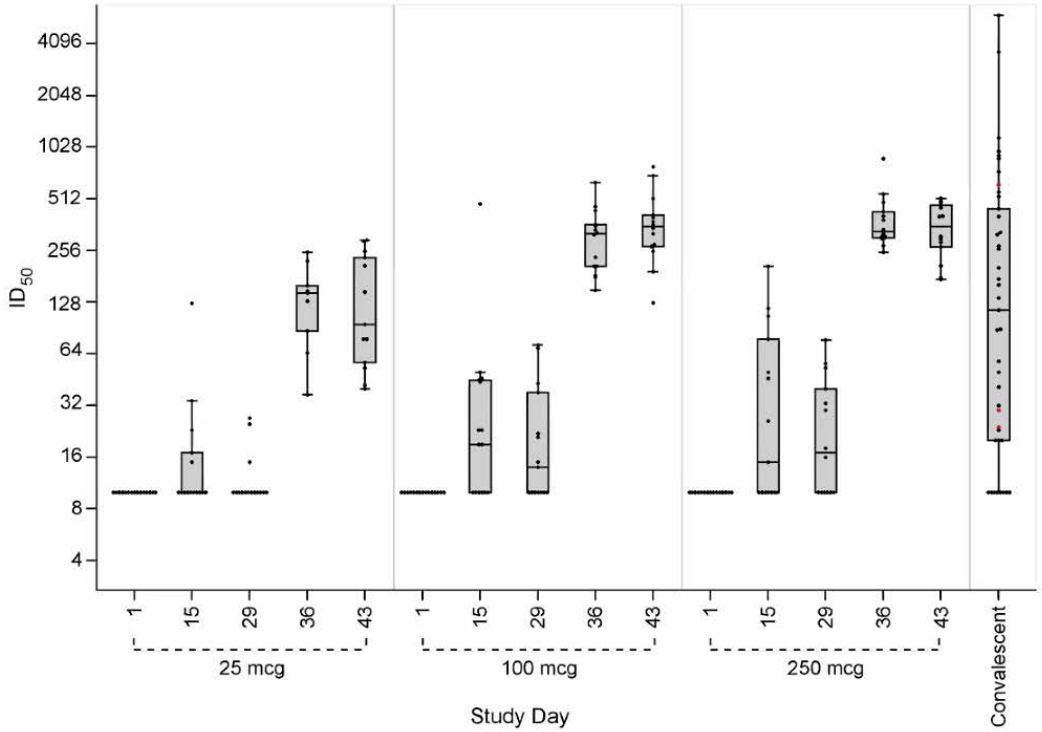


Moderna COVID-19 Vaccine: IgG Responses to S Protein

Binding Ab (ELISA)



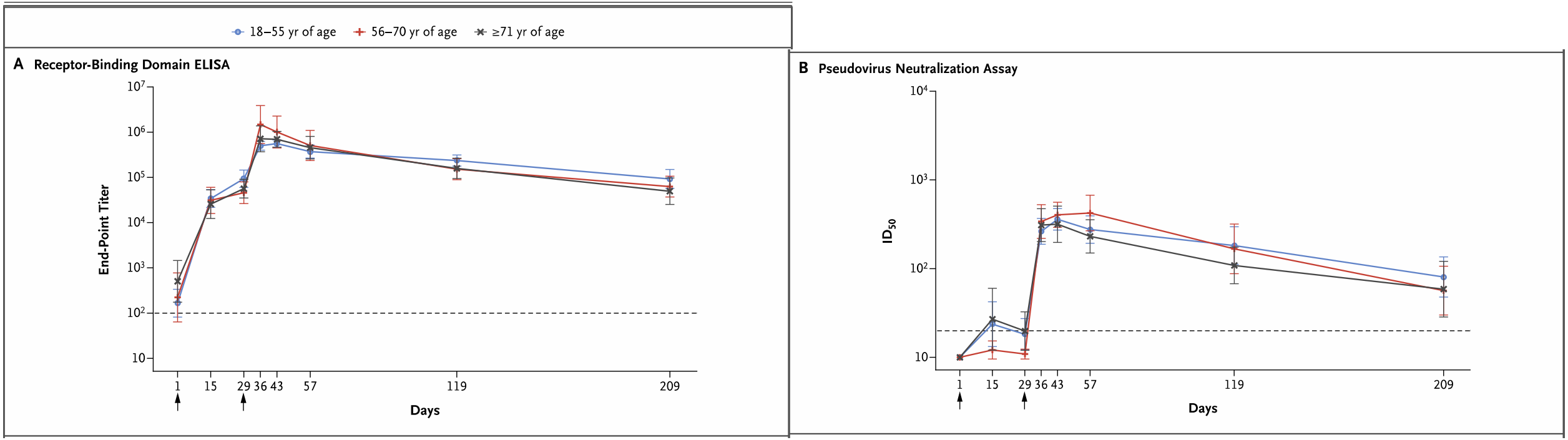
Neutralizing Ab (Pseudovirus)



Phase 1 Trial (<55 years old)

Jackson L et al, NEJM, ePub 14Jul2020

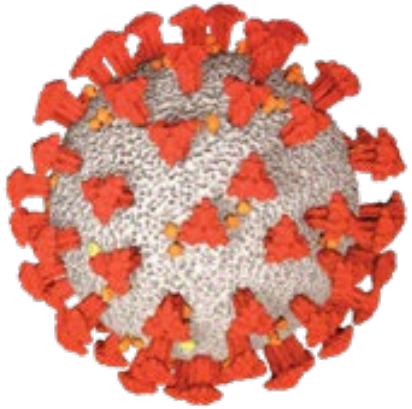
Moderna mRNA-1273 IgG Durability



Phase 1 Trial

Doria-Rose et al, NEJM, 06pr2021

Phase 3 COVID-19 Prevention Trial Network



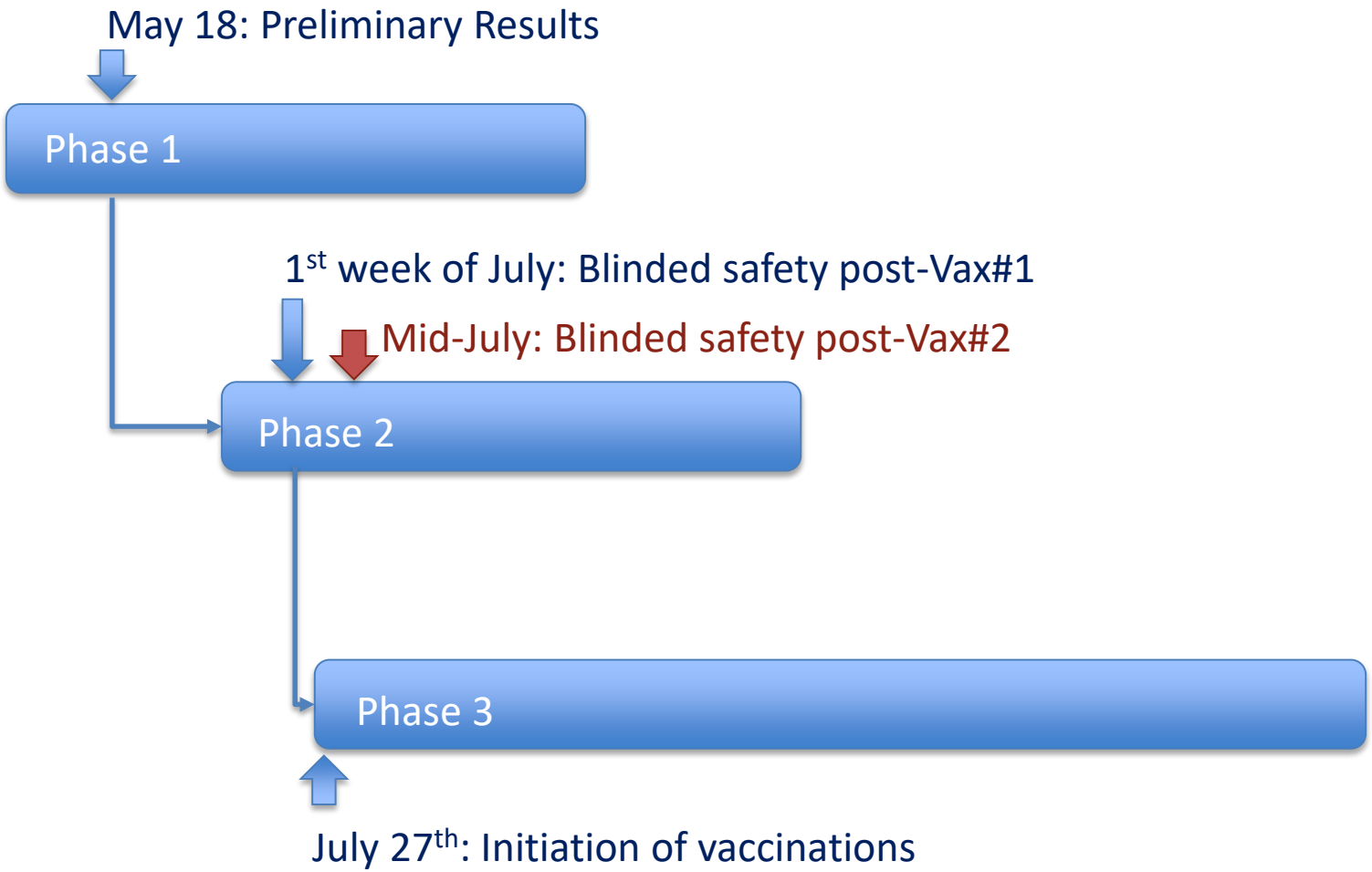
COVID-19
Prevention Network

- NIAID-led consortium

Goals:

- Enroll 5 Phase 3 trials by mid-2021
  - *30,000 participants/trial*
- Harmonized protocol design
  - *Similar definitions of primary and main secondary endpoints*
- Central laboratories
- Common DSMB

Moderna mRNA vaccine Accelerated Clinical Development



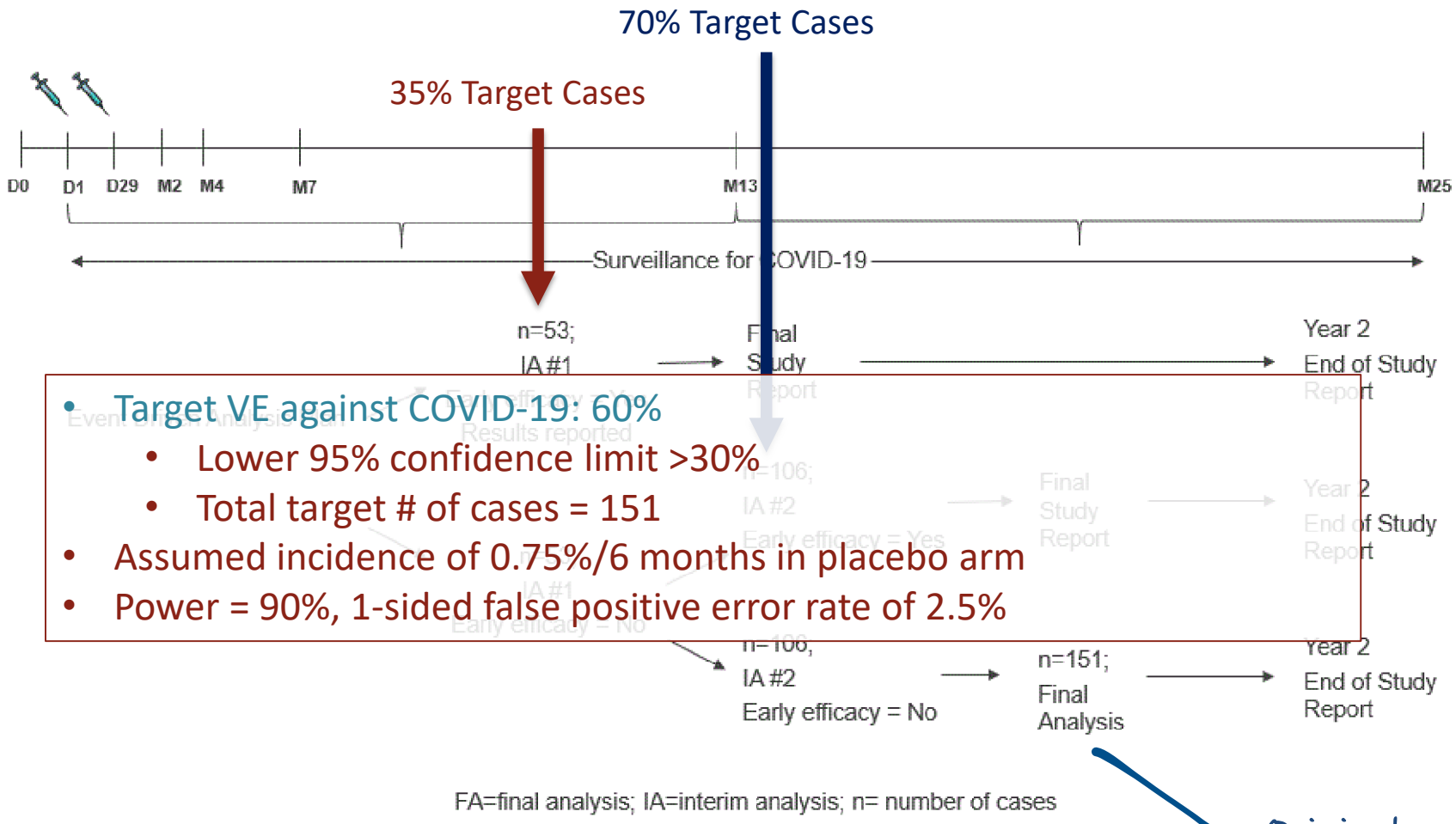
Moderna mRNA COVID-19 Phase 3 Trial Design

- Randomized, placebo-controlled, observer blind
- 100 µg mRNA-1273-P301 *vs*. saline placebo (1:1), IM

<u>Primary Efficacy Endpoint</u>:

- ≥2 of fever, chills, myalgia, headache, sore throat, new olfactory/taste disorder, OR
- ≥1 of cough, SOB/dyspnea, OR clinical/radiologic evidence of pneumonia, AND
- NP, nasal or saliva sample + for SARS-CoV-2 by RT-PCR

Moderna mRNA COVID-19 Phase 3 Trial Design



- Target VE against COVID-19: 60%
  - Lower 95% confidence limit >30%
  - Total target # of cases = 151
- Assumed incidence of 0.75%/6 months in placebo arm
- Power = 90%, 1-sided false positive error rate of 2.5%

Original estimate: July 2021
Actual: Nov 2020

Moderna mRNA COVID-19 Phase 3 Trial Demographics

- Enrollment closed on Oct 23, 2020: n=30,420 (n=349 at GW)

Table 1. Demographic and Clinical Characteristics at Baseline.*

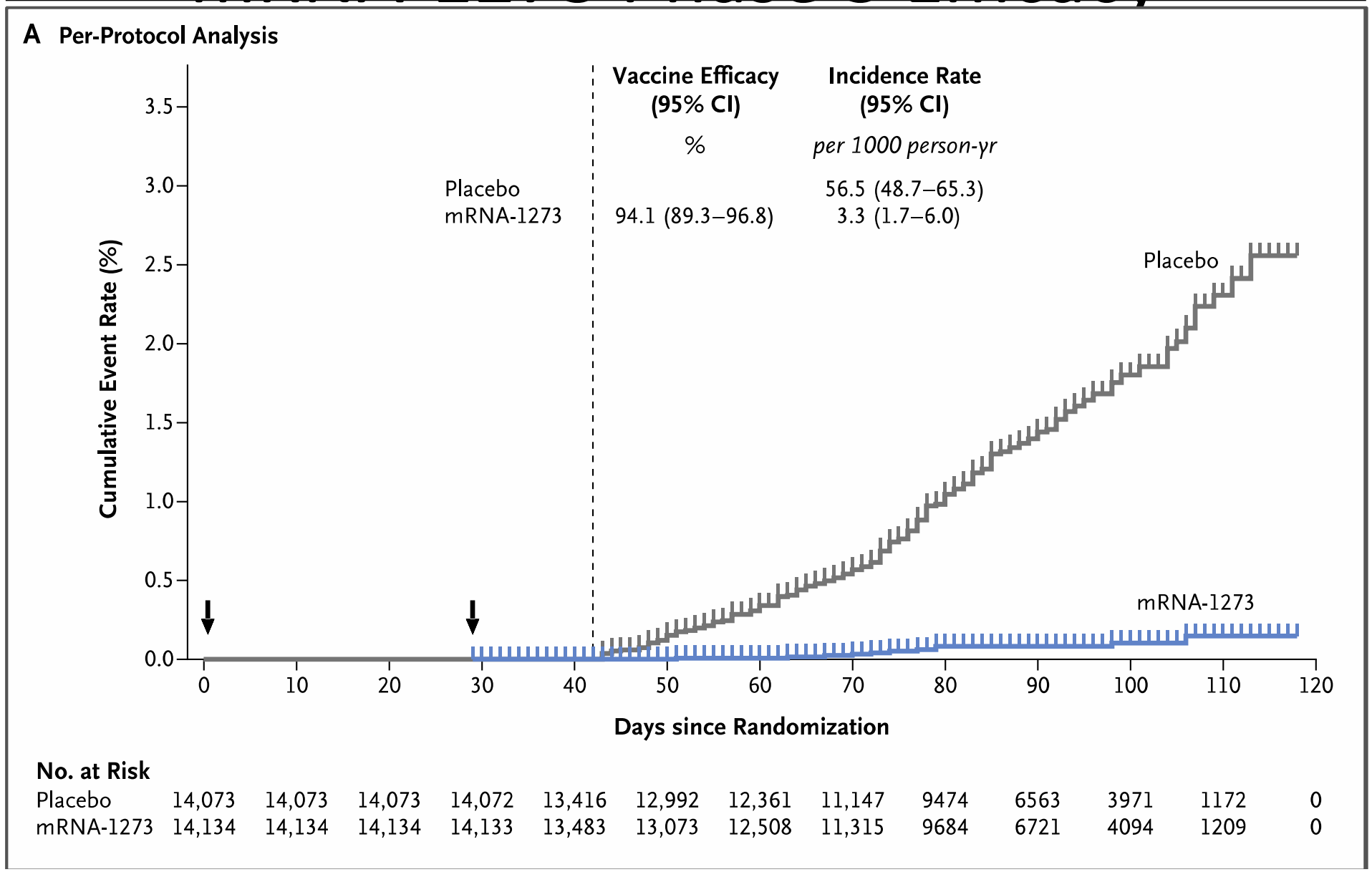
Characteristics	Placebo (N=15,170)	mRNA-1273 (N=15,181)	Total (N=30,351)
Sex — no. of participants (%)			
Male	8,062 (53.1)	7,923 (52.2)	15,985 (52.7)
Female	7,108 (46.9)	7,258 (47.8)	14,366 (47.3)
Mean age (range) — yr	51.3 (18–95)	51.4 (18–95)	51.4 (18–95)
Age category and risk for severe Covid-19 — no. of participants (%)†			
18 to <65 yr, not at risk	8,886 (58.6)	8,888 (58.5)	17,774 (58.6)
18 to <65 yr, at risk	2,535 (16.7)	2,530 (16.7)	5,065 (16.7)
≥65 yr	3,749 (24.7)	3,763 (24.8)	7,512 (24.8)
Hispanic or Latino ethnicity — no. of participants (%)‡			
Hispanic or Latino	3,114 (20.5)	3,121 (20.6)	6,235 (20.5)
Not Hispanic or Latino	11,917 (78.6)	11,918 (78.5)	23,835 (78.5)
Not reported and unknown	139 (0.9)	142 (0.9)	281 (0.9)
Race or ethnic group — no. of participants (%)‡			
White	11,995 (79.1)	12,029 (79.2)	24,024 (79.2)
Black or African American	1,527 (10.1)	1,563 (10.3)	3,090 (10.2)
Asian	731 (4.8)	651 (4.3)	1,382 (4.6)
American Indian or Alaska Native	121 (0.8)	112 (0.7)	233 (0.8)
Native Hawaiian or Other Pacific Islander	32 (0.2)	35 (0.2)	67 (0.2)
Multiracial	321 (2.1)	315 (2.1)	636 (2.1)
Other	316 (2.1)	321 (2.1)	637 (2.1)
Not reported and unknown	127 (0.8)	155 (1.0)	282 (0.9)

Baden et al, NEJM, 30Dec2020

Moderna mRNA COVID-19 Phase 3 Trial Results

- Final analysis: reported on Nov 30, 2020
  - 196 cases: 185 in placebo arm, 11 in vaccine arm
    - **VE = 94.1%, p<0.0001**
  - 30 severe cases (1 death): all in placebo arm
  - Similar efficacy across age groups, racial/ethnic groups, co-morbidities
- EUA application filed with FDA on Nov 30, 2020
  - FDA external advisory committee meeting: Dec 17, 2020
  - EUA issued on Dec 18, 2020

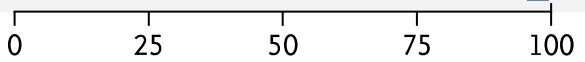
mRNA-1273 Phase 3 Efficacy



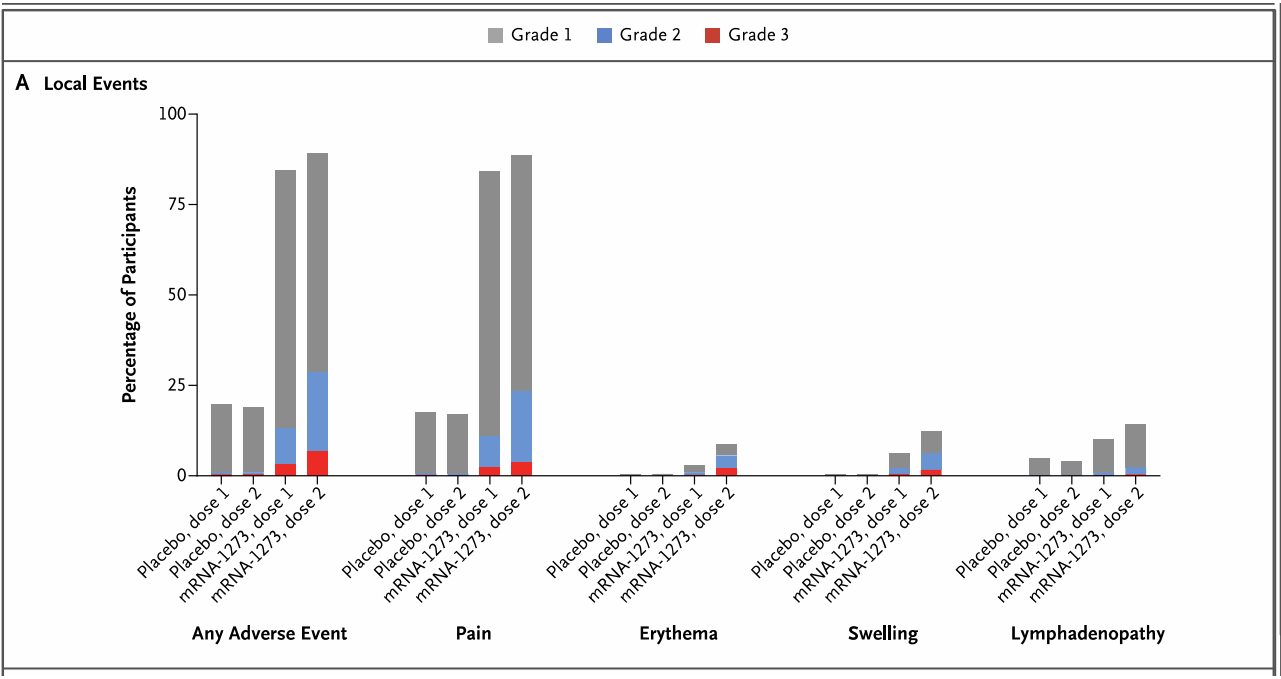
Baden et al, NEJM, 30Dec2020

mRNA-1273 Vaccine Efficacy by Subgroup

Subgroup	Placebo (N=14,073)	mRNA-1273 (N=14,134)	Vaccine Efficacy (95% CI)
	no. of events/total no.		
All patients	185/14,073	11/14,134	94.1 (89.3–96.8)
Age			
≥18 to <65 yr	156/10,521	7/10,551	95.6 (90.6–97.9)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Age, risk for severe Covid-19			
18 to <65 yr, not at risk	121/8403	5/8396	95.9 (90.0–98.3)
18 to <65 yr, at risk	35/2118	2/2155	94.4 (76.9–98.7)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Sex			
Male	87/7462	4/7366	95.4 (87.4–98.3)
Female	98/6611	7/6768	93.1 (85.2–96.8)
At risk for severe Covid-19			
Yes	43/3167	4/3206	90.9 (74.7–96.7)
No	142/10,906	7/10,928	95.1 (89.6–97.7)
Race and ethnic group			
White	144/8916	10/9023	93.2 (87.1–96.4)
Communities of color	41/5132	1/5088	97.5 (82.2–99.7)



mRNA-1273 Phase 3 Trial: Safety



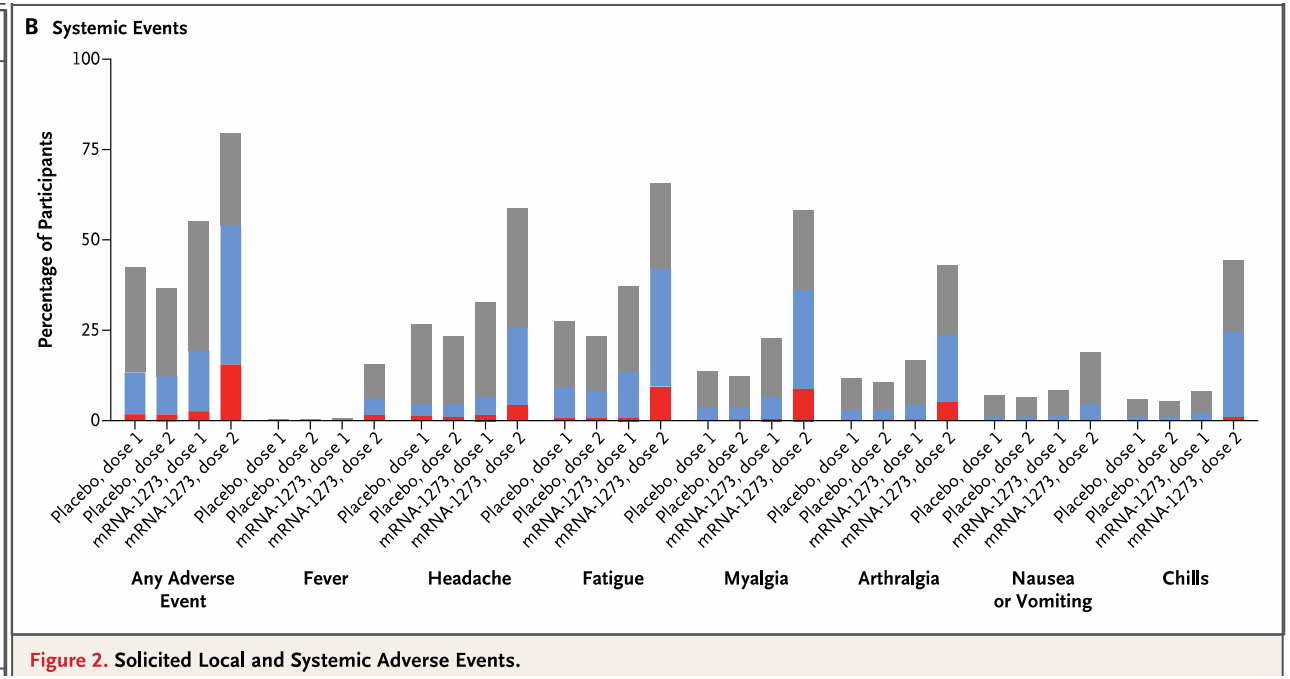


Figure 2. Solicited Local and Systemic Adverse Events.

mRNA-1273-P301 – Safety

- Allergic Reactions
  - 3 anaphylaxis cases, all unrelated (>10 days post-vax)
- Bell's Palsy
  - 3 cases in mRNA-1273, 1 in placebo
  - All deemed unrelated to vaccine
  - FDA: not more than background rate
- Dermal Filler Reactions
  - 3 cases of facial/lip swelling in mRNA-1273 recipients

mRNA-1273: Unanswered Questions

- Pregnancy
  - 13 pregnancies through December 2, 2020 (6 vaccine, 7 placebo). Vaccination occurred:
    - 1 spontaneous abortion, 1 elective abortion, both in the placebo
    - Pregnancy outcomes are otherwise unknown at this time
- Pediatrics
- Asymptomatic Transmission

- ½ Dose?
  - Phase 2 trial included 50µg arm: immunogenicity MAY be equivalent
- Delayed 2nd dose?

Moderna Phase 3 Plans: Unblinding

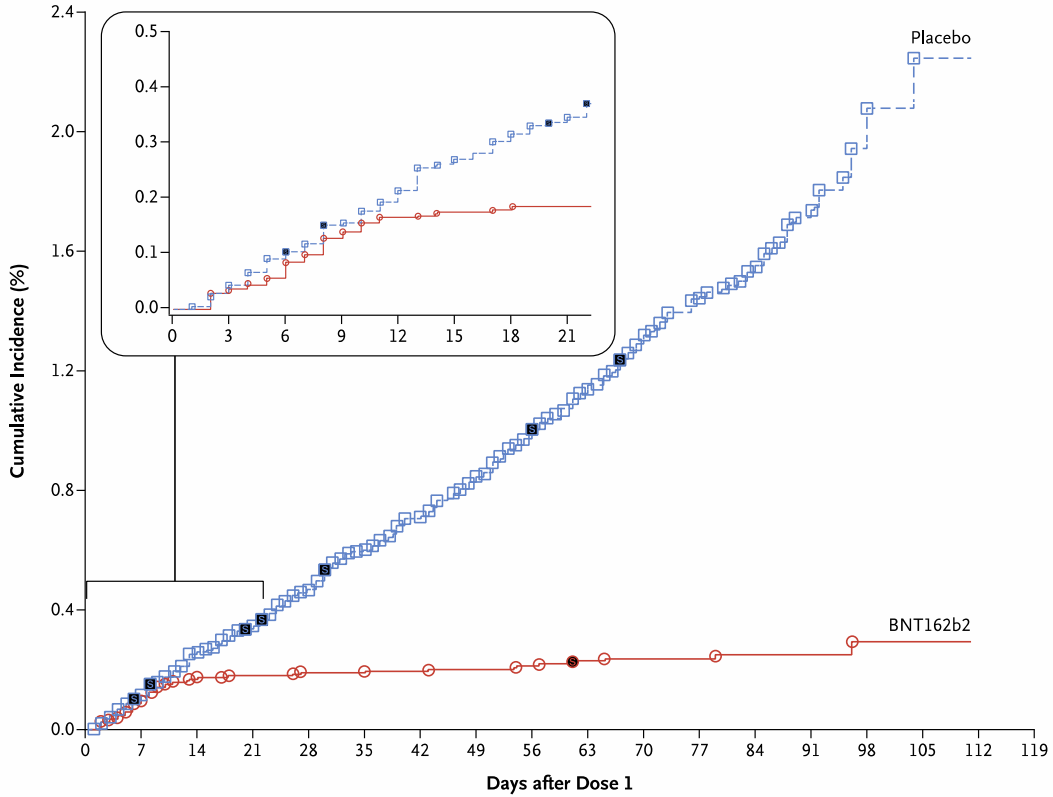
- <u>All participants</u> invited for “Decision Visit” to unblind
  - Started at GW on Dec 30th, 2020
  - All Decision Visits completed at GW on Mar 15th, 2021

- Placebo recipients offered vaccine

Pfizer/BioNTech BNT162b2 mRNA Vaccine

- Phase 3 Trial: 40,277 participants
- VE = 95.0% (90.3 – 97.6)
- Similar safety profile to Moderna

- EUA – Dec 12th, 2020
  - Approved for ≥16 y/o



Polack et al, NEJM, 31Dec2020

AZD1222 (ChAdOx1 nCoV-19) Candidate Vaccine

- University of Oxford/AstraZeneca
- Replication-deficient chimpanzee adenovirus vector expressing the full-length SARS-CoV-2 spike protein
- ChAdOx1 vector used to develop investigational vaccines against other pathogens:
  - Malaria, MERS, tuberculosis, influenza and chikungunya virus (Phase 1/2)

- Clinical development (Phase 1) initiated in April 2020
- Phase 2/3 in the UK
- Phase 3 in Brazil

- CoVPN Phase 3 fully enrolled (US & International)

SARS-CoV-2 Vaccine Development:

Viral Vectored Vaccine Construct

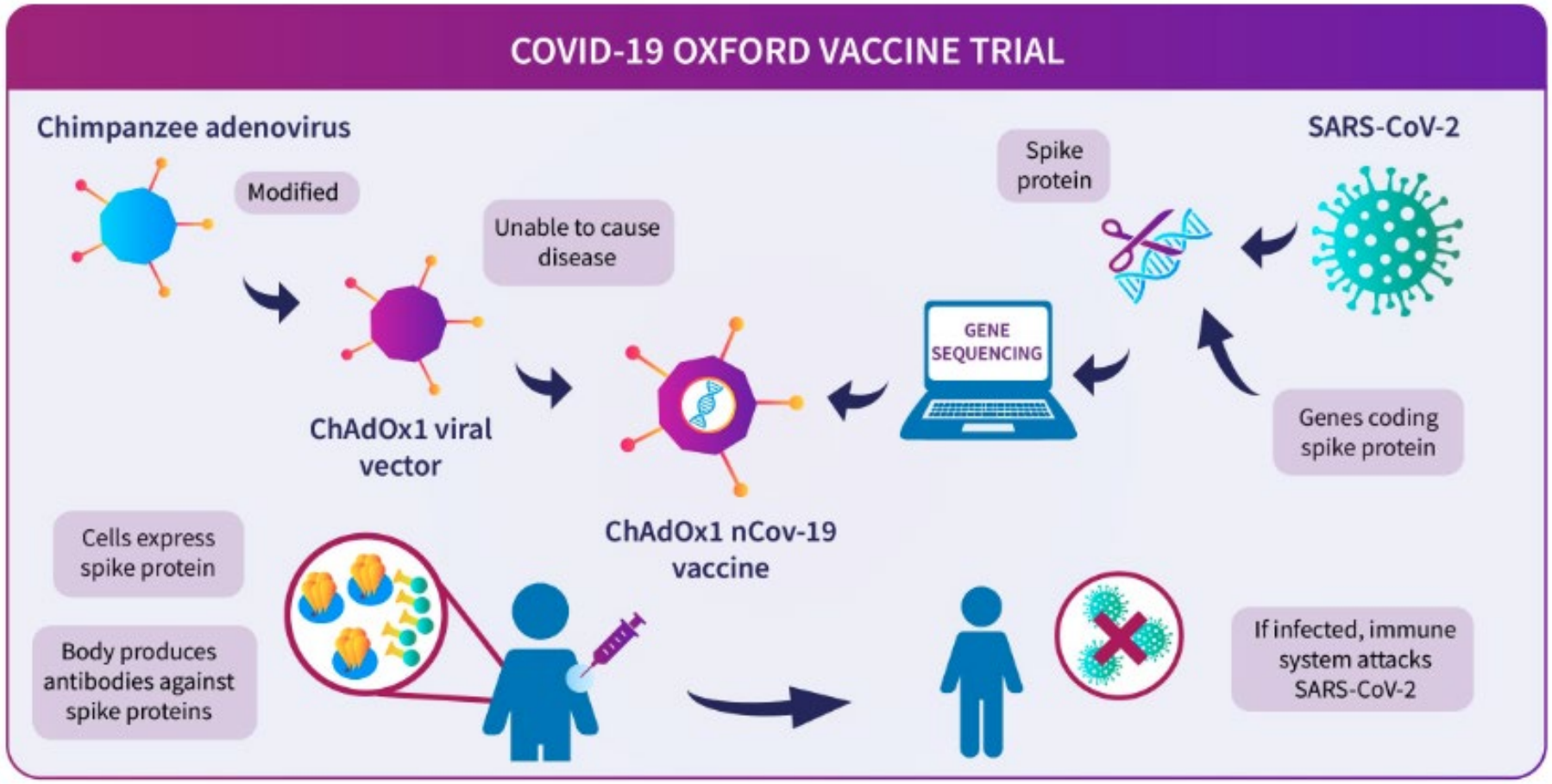


Table 2 COVID-19 Vaccine AstraZeneca efficacy against COVID-19

Population	COVID-19 Vaccine AstraZeneca		Control		Vaccine efficacy % (CI)
	N	Number of COVID-19 cases, n (%)	N	Number of COVID-19 cases, n (%)	
Primary (see above)	**5,807**		**5,829**		
COVID-19 cases		30 (0.52)		101 (1.73)	70.42 (58.84, 80.63)[a]
Hospitalisations[b]		0		5 (0.09)	-
Severe disease[c]		0		1 (0.02)	-
Any dose	**10,014**		**10,000**		
COVID-19 cases after dose 1		108 (1.08)		227 (2.27)	52.69 (40.52, 62.37)[d]
Hospitalisations after dose 1[b]		2 (0.02)[e]		16 (0.16)	-
Severe disease after dose 1[c]		0		2 (0.02)	

- **Primary Analysis included 1367 LD/SD and 4440 SD/SD**
- **94% < 65 years old**

AZ/Oxford Vaccine – Phase 3 Efficacy

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	
All LD/SD and SD/SD recipients	131	30/5807 (0·5%)	44·1 (248 299)	101/5829 (1·7%)	149·2 (247 228)	70·4% (54·8 to 80·6)†
COV002 (UK)	86	18/3744 (0·5%)	38·6 (170 369)	68/3804 (1·8%)	145·7 (170 448)	73·5% (55·5 to 84·2)
LD/SD recipients	33	3/1367 (0·2%)	14·9 (73 313)	30/1374 (2·2%)	150·2 (72 949)	90·0% (67·4 to 97·0)‡§
SD/SD recipients	53	15/2377 (0·6%)	56·4 (97 056)	38/2430 (1·6%)	142·4 (97 499)	60·3% (28·0 to 78·2)
COV003 (Brazil; all SD/SD)	45	12/2063 (0·6%)	56·2 (77 930)	33/2025 (1·6%)	157·0 (76 780)	64·2% (30·7 to 81·5)‡
All SD/SD recipients	98	27/4440 (0·6%)	56·4 (174 986)	71/4455 (1·6%)	148·8 (174 279)	62·1% (41·0 to 75·7)

Voysey et al, Lancet, 09JAN2021

AZ/Oxford Vaccine: CoVPN Phase 3 Trial

- Overall efficacy 79% at preventing symptomatic COVID-19
- 100% efficacy against severe or critical disease and hospitalisation

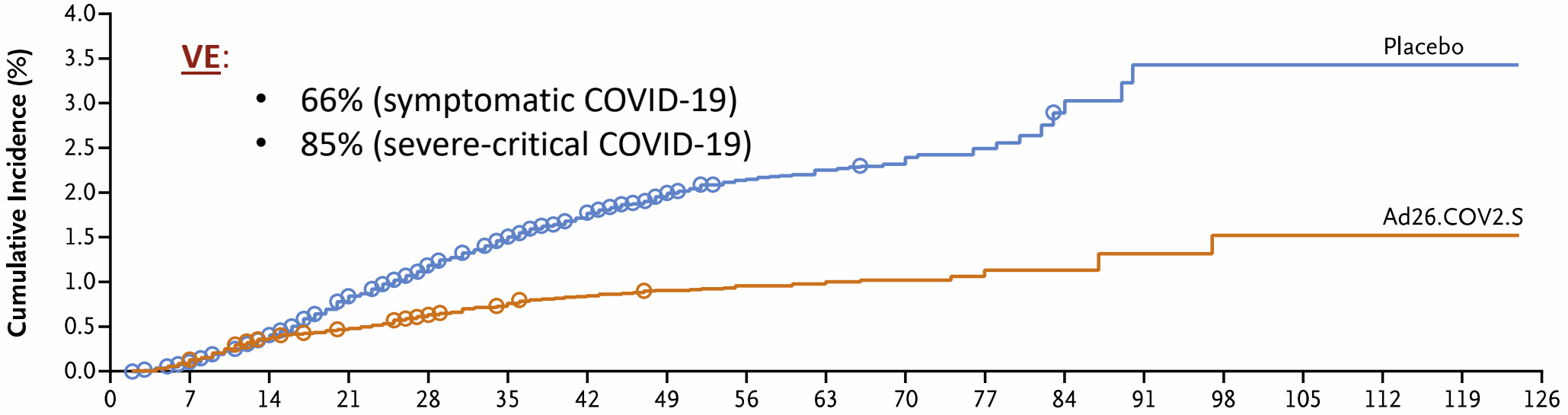
- Comparable efficacy result across ethnicity and age
  - 80% efficacy in participants aged ≥65 years

Source: AZ

CoVPN: What's Next?

Janssen/J&J COVID-19 Vaccine

A Moderate to Severe–Critical Cases of Covid-19



No. at Risk																			
Placebo	19,822	19,804	19,745	19,652	19,579	19,488	18,411	14,814	10,823	7740	3876	1439	708	485	482	480	133	27	0
Ad26.COV2.S	19,744	19,725	19,669	19,642	19,612	19,578	18,541	14,909	10,930	7831	3998	1468	713	484	483	482	142	31	0
No. of Cases																			
Placebo	0	22	81	168	237	299	351	387	407	416	423	425	430	432	432	432	432	432	432
Ad26.COV2.S	0	27	76	96	126	151	168	178	184	188	189	191	191	192	193	193	193	193	193

Sadoff et al, NEJM, 22APR2021

COVID-19 Vaccine Trials at GW

FROM MODERNA TO SANOFI….

Sanofi-Pasteur Phase I/II VAT00001 Study

- Same technology used to produce recombinant influenza vaccine
- SARS-CoV-2 Spike protein + adjuvant
- Sept 2020, US, 440 ppts
- Good antibody response in younger people but lower levels in older individuals
  - Seroconversion 85% in >50 yo, 62.5% in > 60 yo

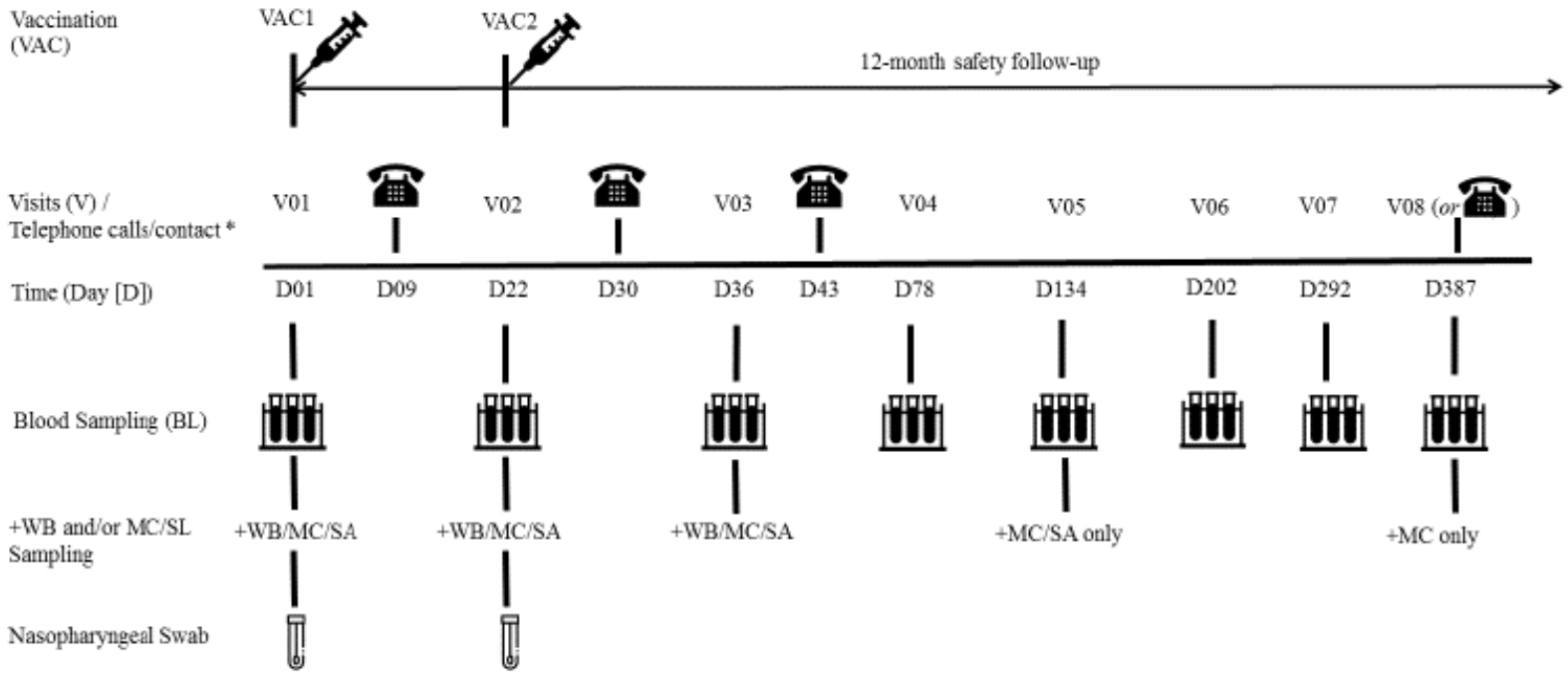
- Led Sanofi to optimize the vaccine dose & formulation

VAT00002 Study at GW

- US Phase II: US, 720 ppts, ≥18 yo (50% ≥ 60 yo)
- Higher doses and greater purity of protein from VAT00001 study
- 3 different SARS-CoV-2 Spike protein doses (5, 10 and 15 mcg) with AS03 adjuvant (GSK)
- 2 injections (21 days apart), randomized 1:1:1
  - No placebo
- Participants randomized based on prior SARS-CoV-2 infection as naïve and non-naïve

- Enrollment 24FEB2021 – 09MAR2021
  - 44 enrolled at GW
  - Vaccinations completed on 26MAR2021

VAT00002 Study at GW



COVID-19 Vaccine Trials at GW

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GW COVID-19 Vaccine Trials Team

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