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Update on COVID-19 Vaccines

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MASSACHUSETTS
GENERAL HOSPITAL

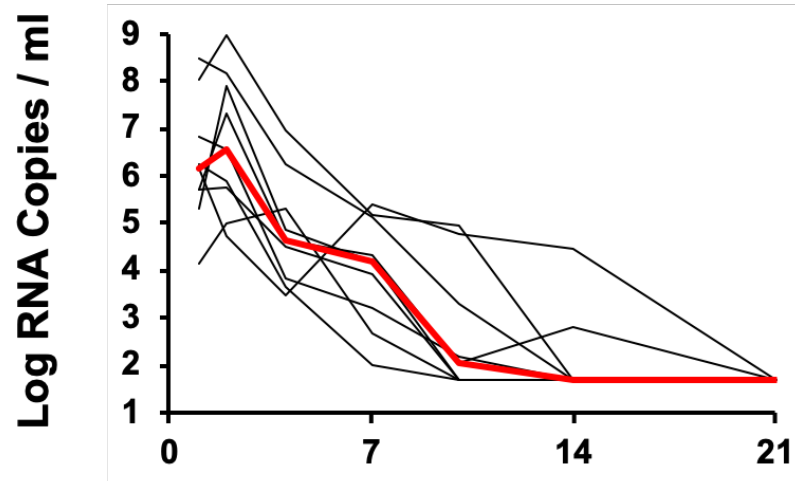
DEPARTMENT OF MEDICINE



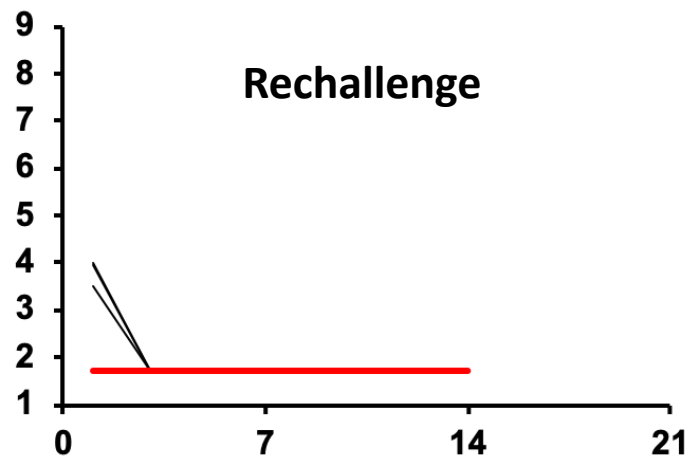
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Seropositive: Protection from future infection?

Primary Challenge

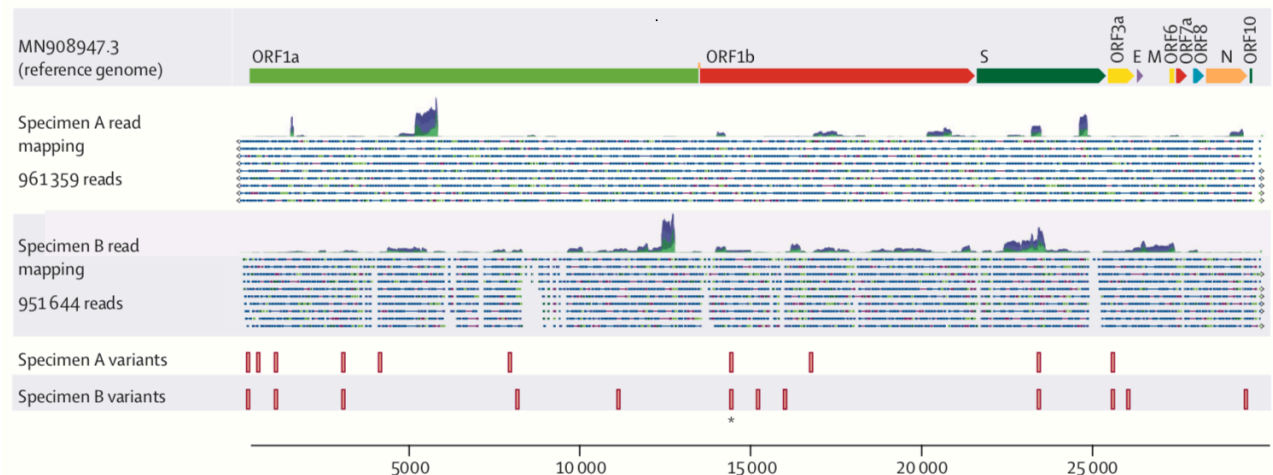
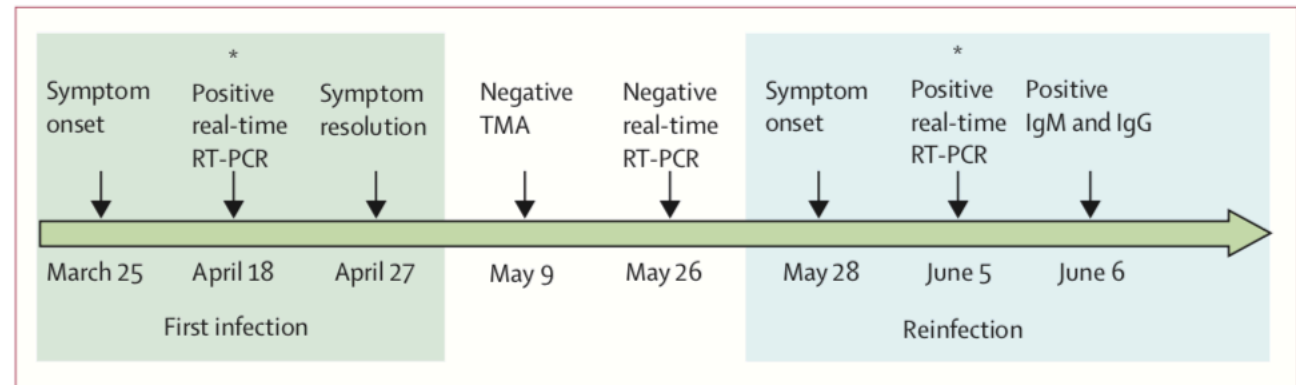


Rechallenge

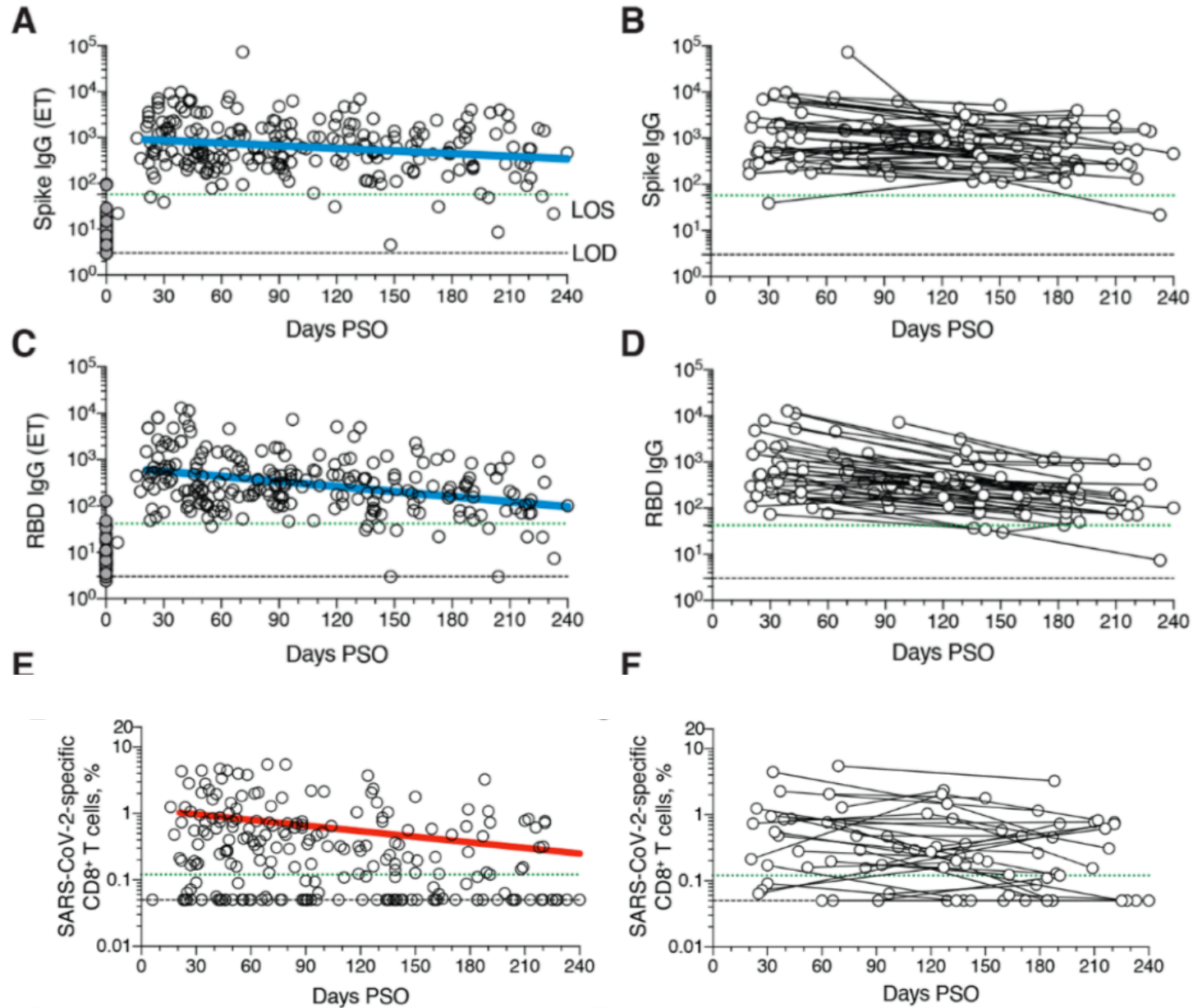


Days following challenge

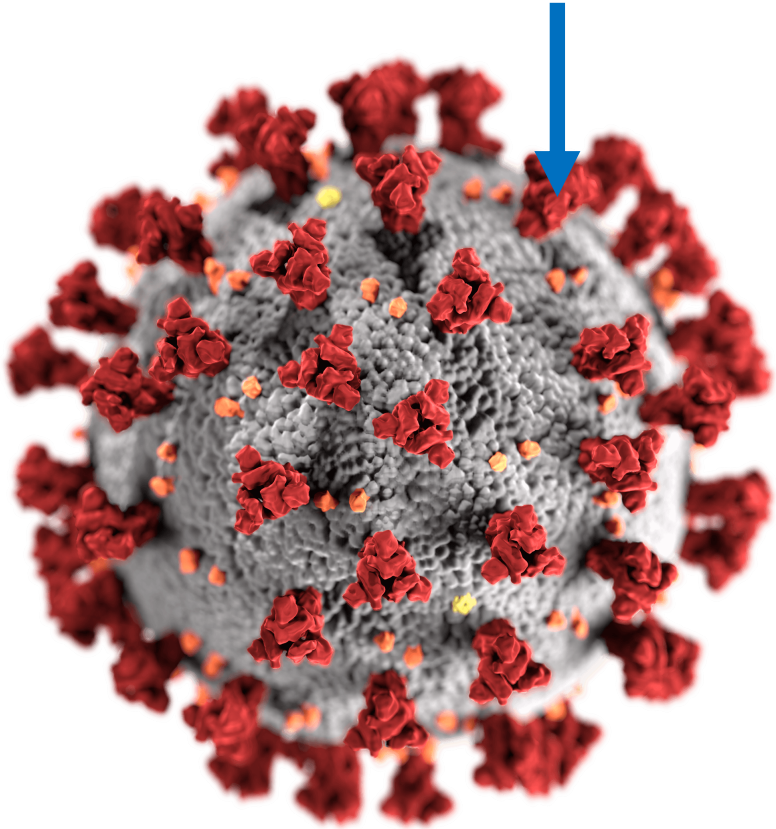
Re-infection?



Antibodies and CD8+ T-cells to SARS-CoV-2 over time



Spike
Protein



SARS-CoV-2 Vaccine

Many concepts: mRNA, DNA, viral vectors (ad5, ad26, VSV, ChAd.....), inactivated/attenuated virus, protein subunit

40+ vaccine candidates in clinical testing, 150+ in preclinical stages

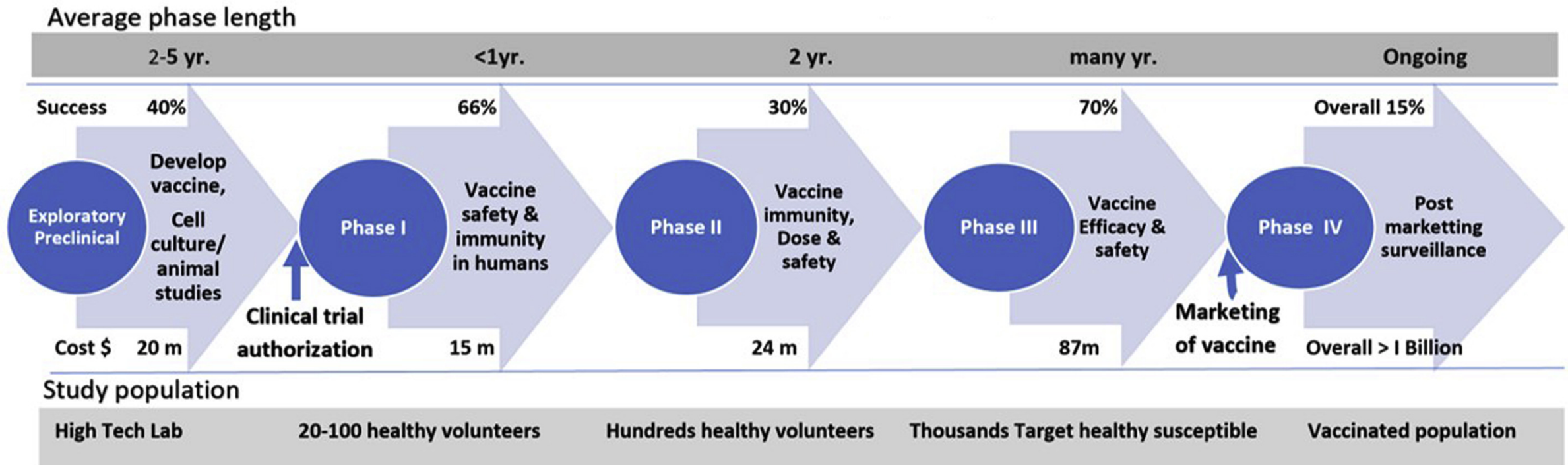
Inducing Herd Immunity

- Dependent on two factors: R_0 and vaccine efficacy.
- $R_0 - 1/R_0$ divided by percent vaccine efficacy.
- For example, if R_0 is 2.0 and vaccine efficacy is 75 percent then $2 - 1$ divided by $2 = 0.5$ divided by $.75$ equals $.67$. Therefore, about 67 percent of the population would need to be vaccinated to stop spread.
- If vaccine efficacy was 100 percent, then 50 percent of the population would need to be immunized; if vaccine efficacy was 50 percent, then 100 percent of the population would need to be immunized.

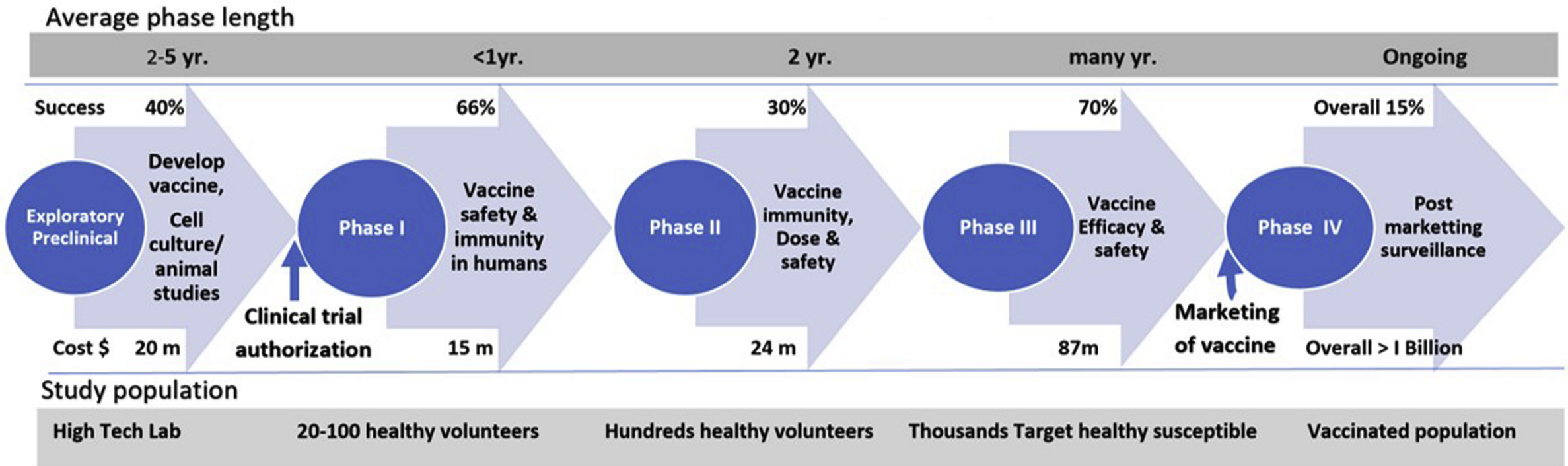
Operation Warp Speed

- Public-private partnership (lead by HHS and DoD; Moncef Slaoui and Gen. G. Perna)
- Goal of delivering 300 million doses of a safe, effective vaccine by January 2021
- Currently 8 companies selected: Moderna, AstraZeneca-University of Oxford, Janssen Pharmaceutical (J&J), Pfizer-BioNTech, Merck, Vaxart, Inovio, and Novavax
- COVID prevention network (CoVPN) is coordinating studies
- FDA: vaccines must be at least 50 percent effective to be approved (across age groups)
- Other large trials operated by WHO, CEPI, or the EU

Typical Vaccine Development Timelines



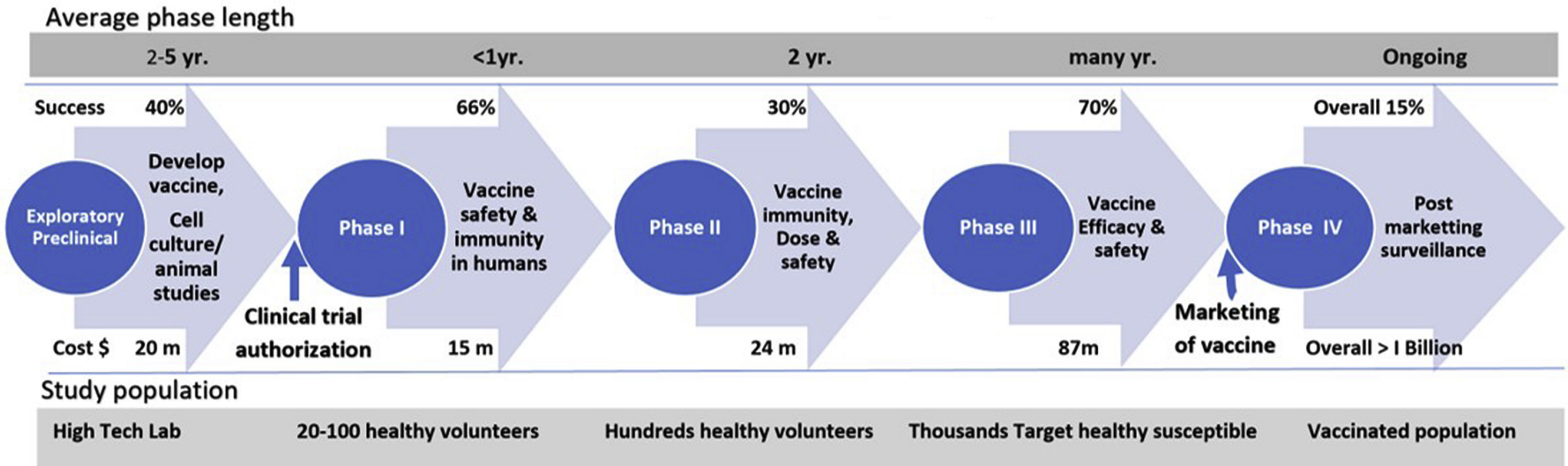
Typical Vaccine Development Timelines



COVID-19:

Spike-sequence published in Jan 2020 -> First phase 1 studies in spring 2020 -> Moderna phase 3 in July 2020 -> First vaccination with Pfizer/BioNtech on 8 December 2020 in UK -> EUA for Pfizer/BioNtech vaccine in US on 12/11/2020

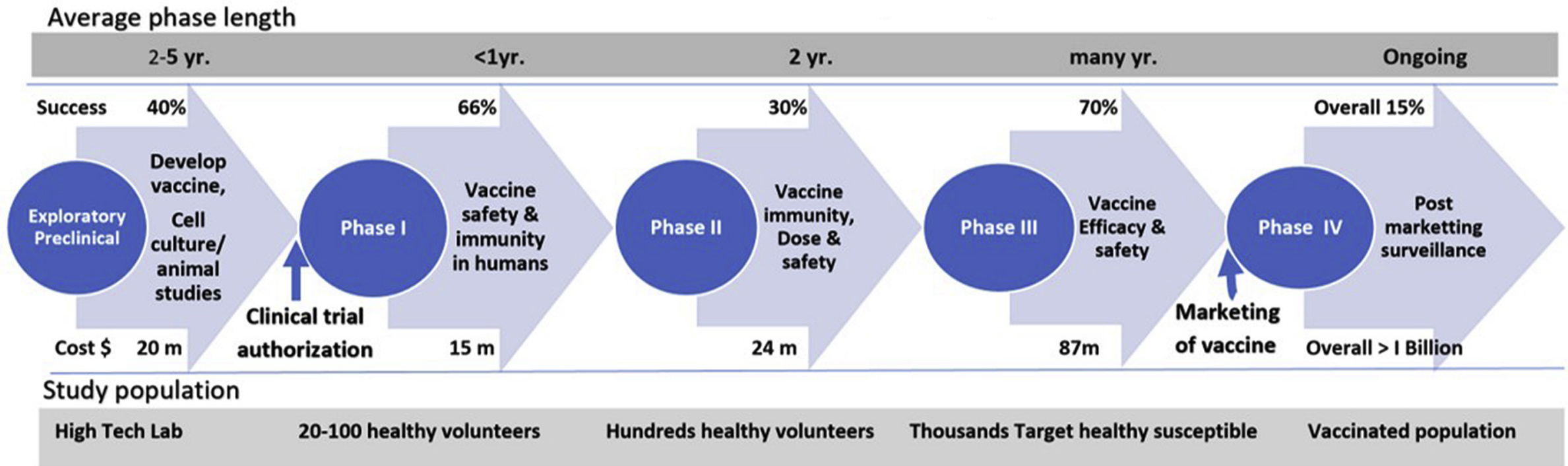
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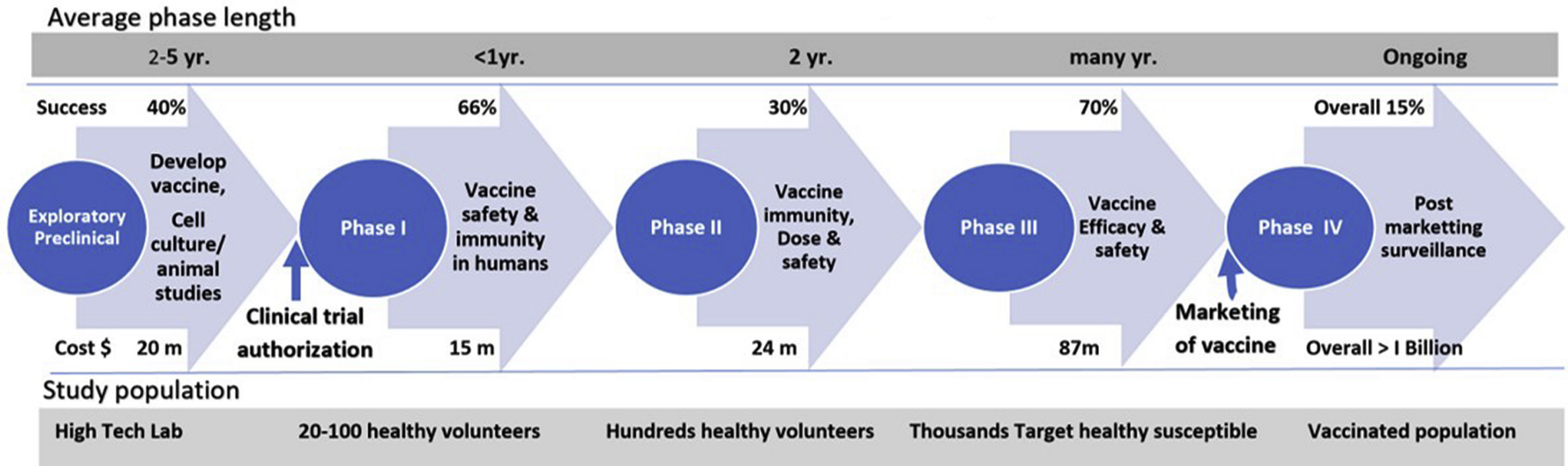
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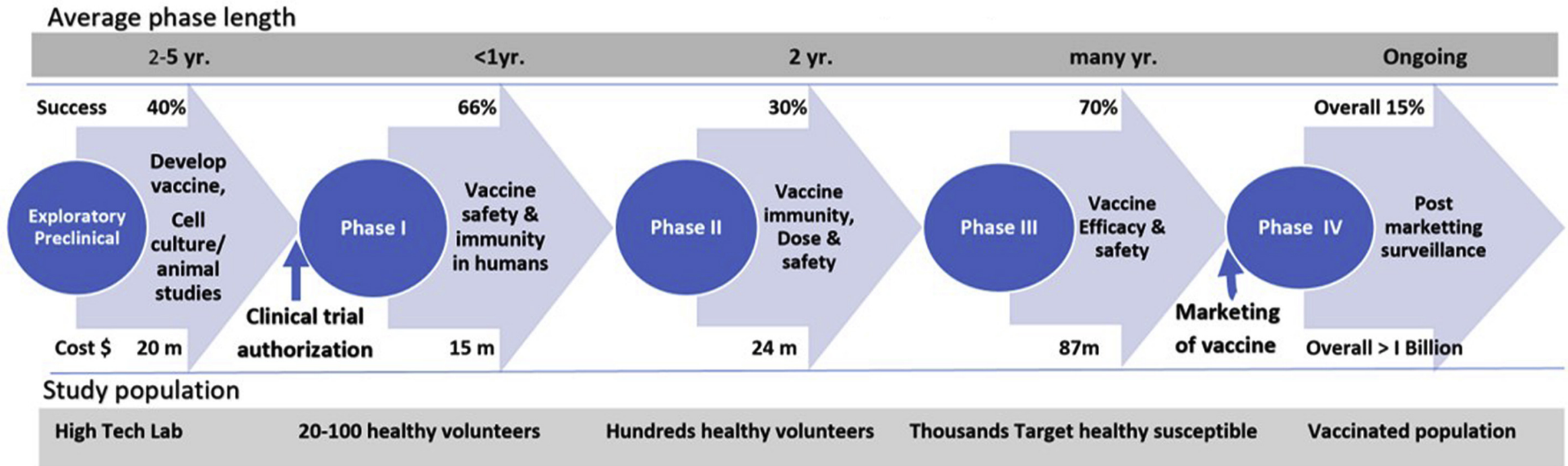
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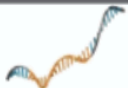

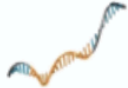

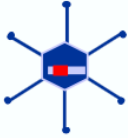

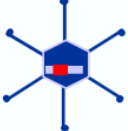




Typical Vaccine Development Timelines



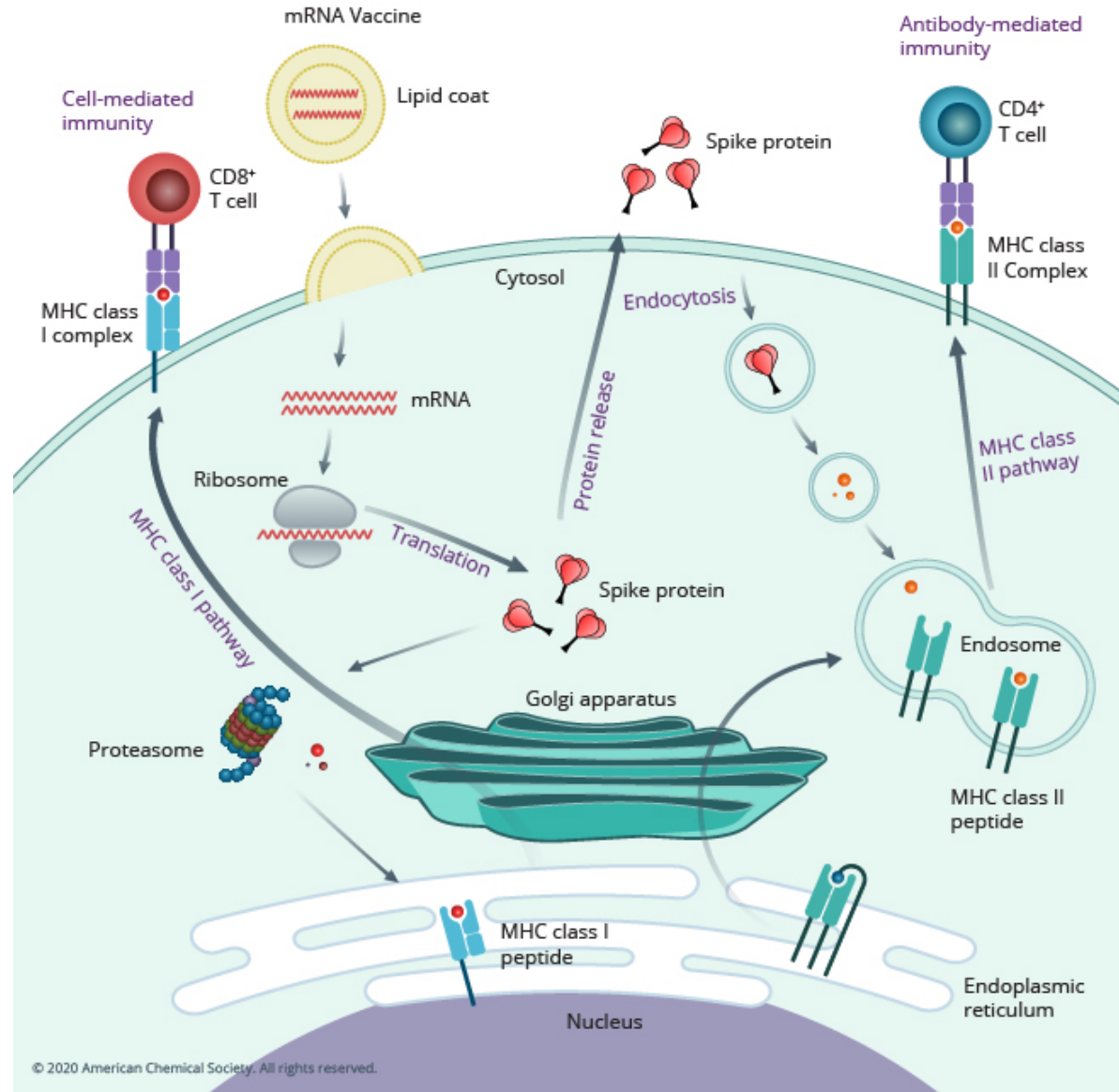
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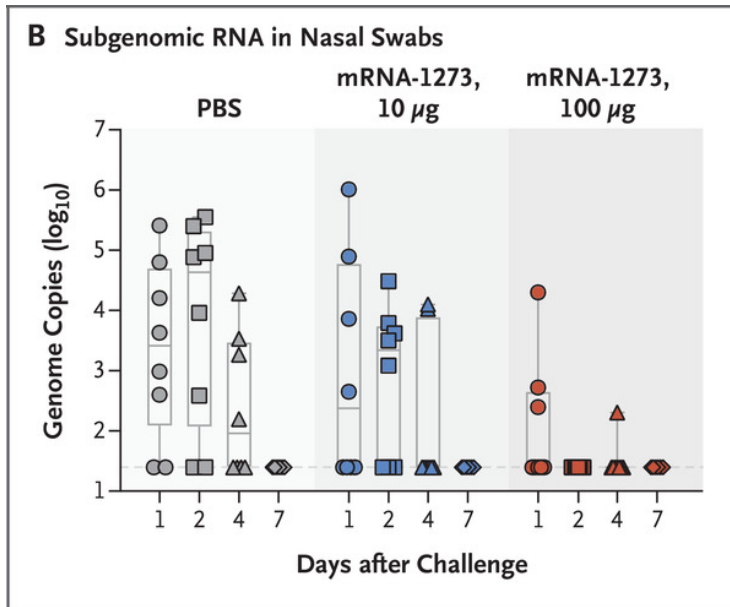
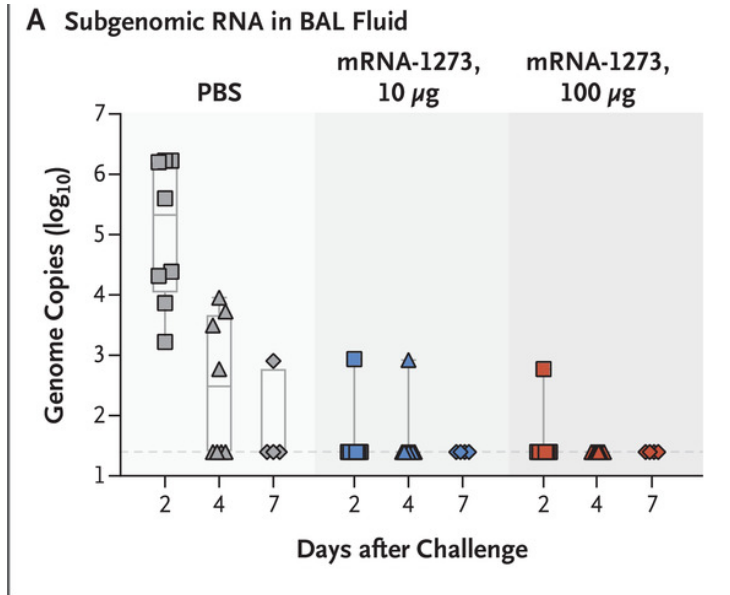
Overview of OWS* CoVID-19 Vaccine Candidates

Company		Platform	Product	Vaccination dose/schedule	Phase 3 Approx. Start
		mRNA	mRNA: encodes 2P-stabilized Spike, TM, FI	2 doses at 100 µg (0, 28 days)	Ongoing
		mRNA	mRNA: encodes stabilized SARS-CoV-2 Spike	2 doses at 30µg (0, 21 days)	Ongoing
		Ad Vector	Replication incompetent ChAdOx1 wild type Spike; ΔF; TM	2 doses at 5×10^{10} vp, (0, 28 days)	Ongoing
		Ad Vector	Replication Incompetent Ad26; stabilized Spike; ΔF; TM	1 dose at 5×10^{10} vp	Ongoing
		Recombinant protein Adjuvanted	Baculovirus Expressed trimeric Stabilized Spike, ΔF; TM; trimerization domain; Matrix M	2 doses at 5 µg with Matrix M (0, 21 days)	12/2020
		Recombinant protein Adjuvanted	Baculovirus Expressed trimeric Stabilized Spike, ΔF; TM; trimerization domain; AS03	5/15 µg +AS03 (0, 21 days)	Requires phase 2b

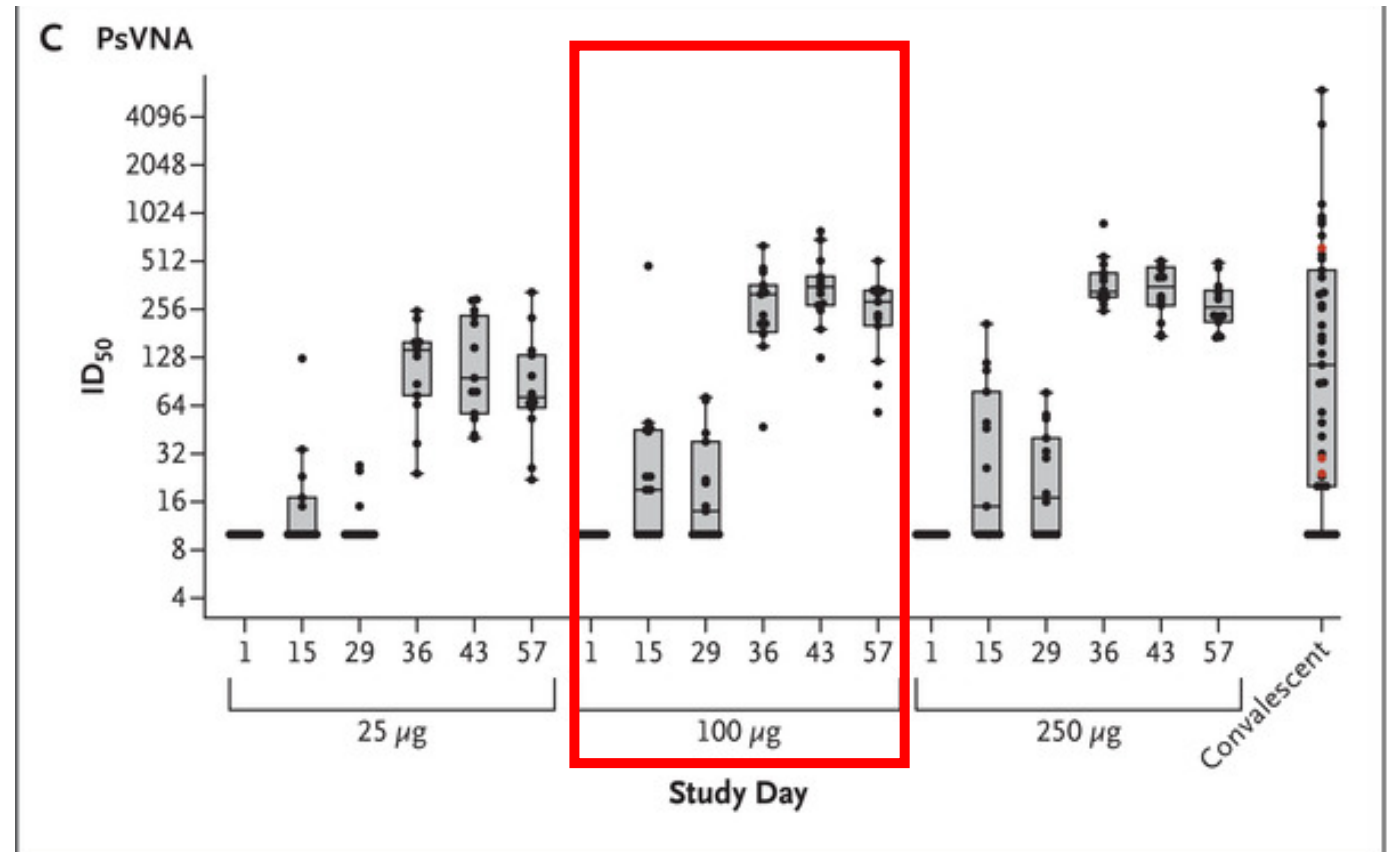
Mechanism: mRNA vaccines



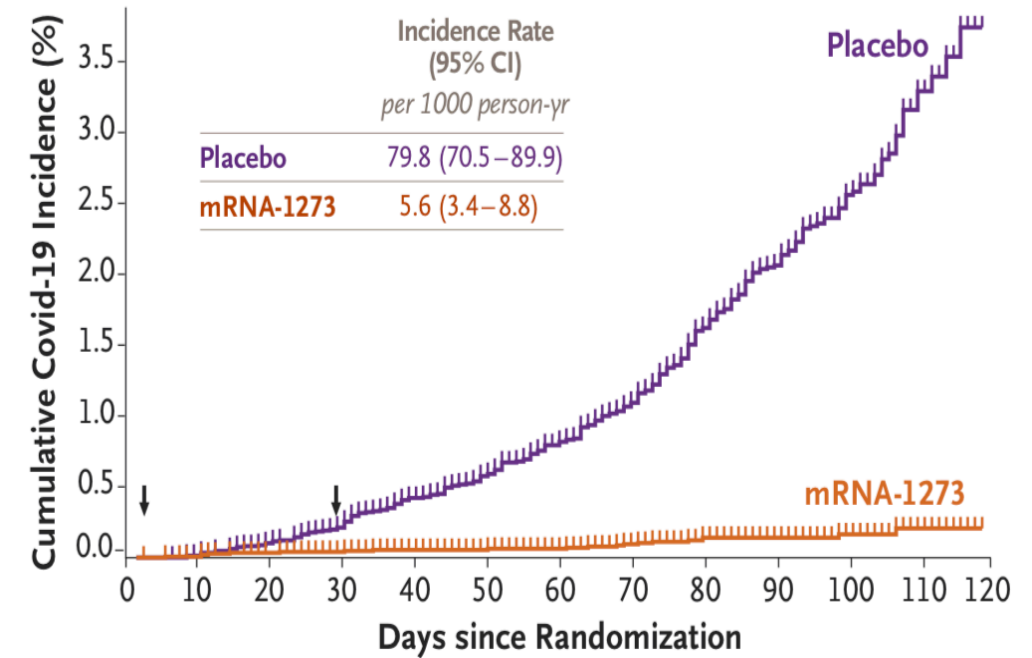
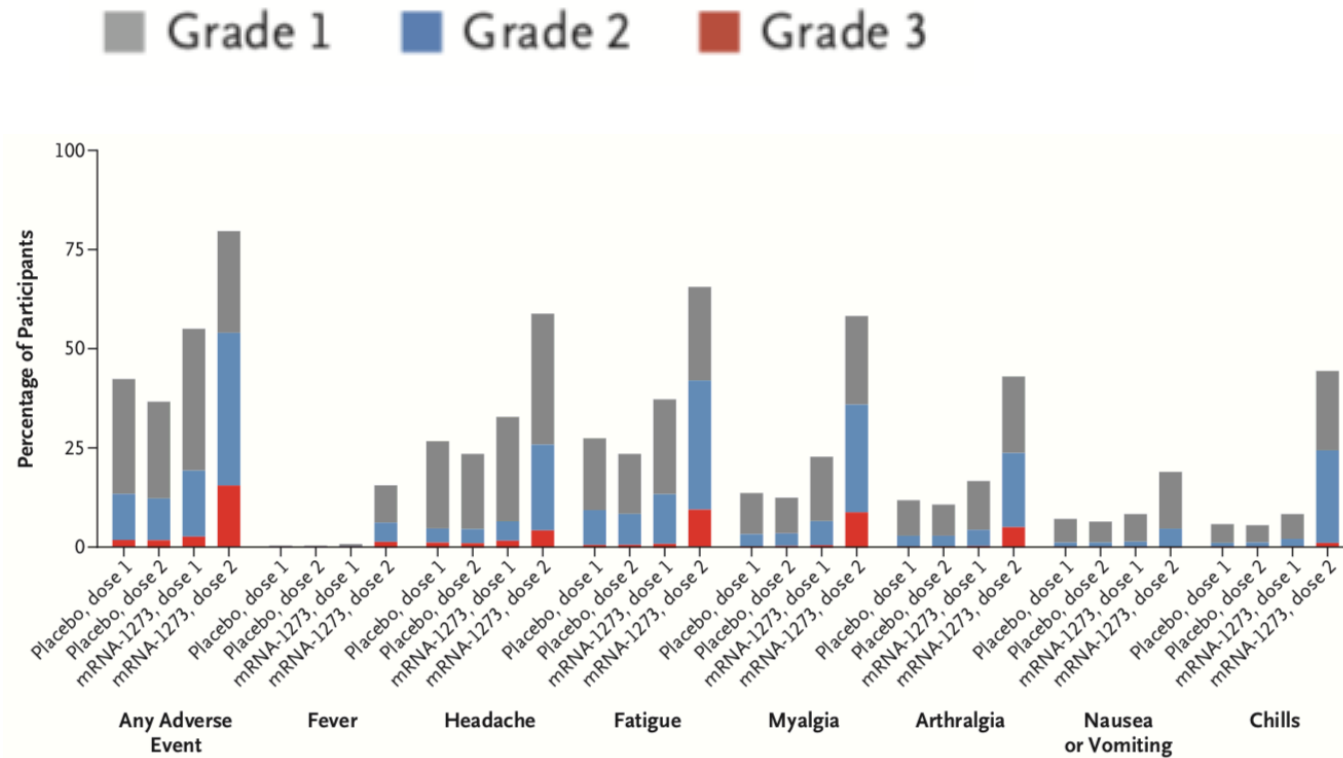
Macaques



Moderna: mRNA-1273



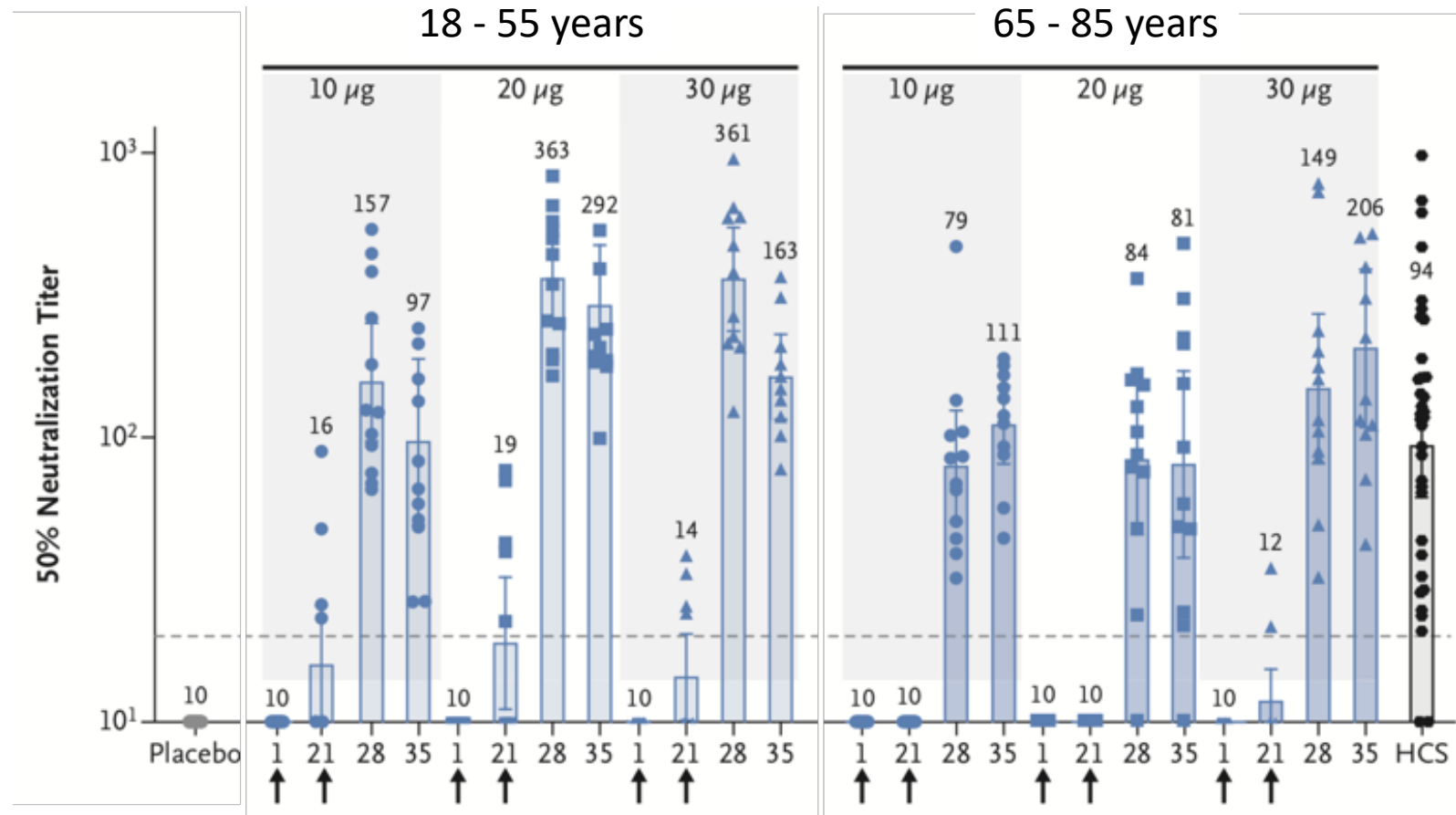
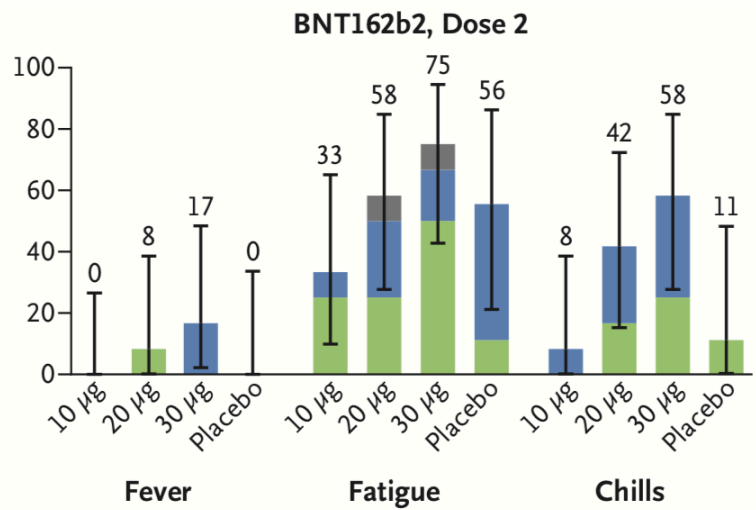
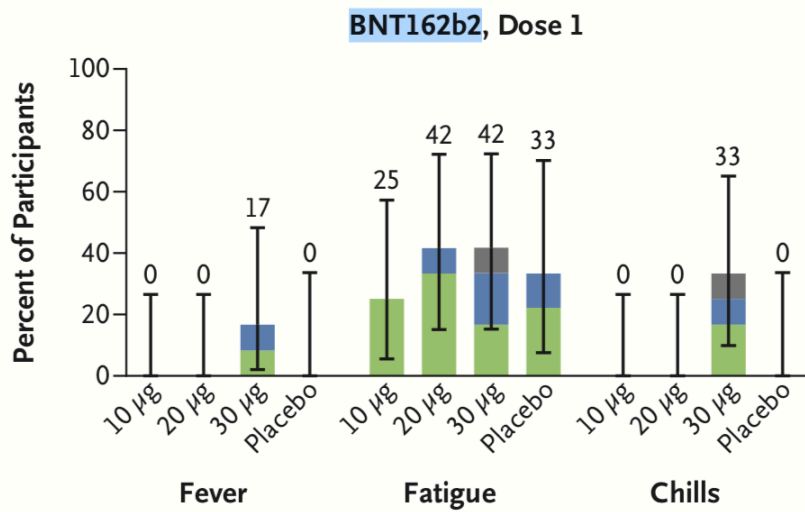
Moderna: mRNA-1273



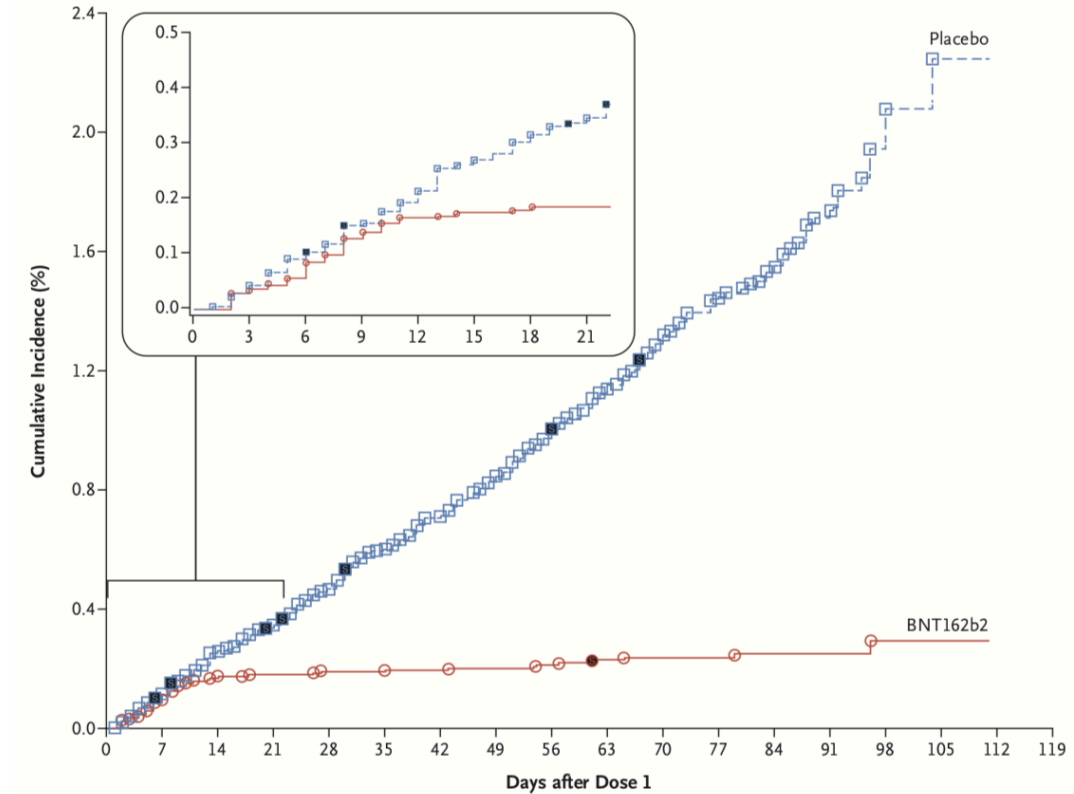
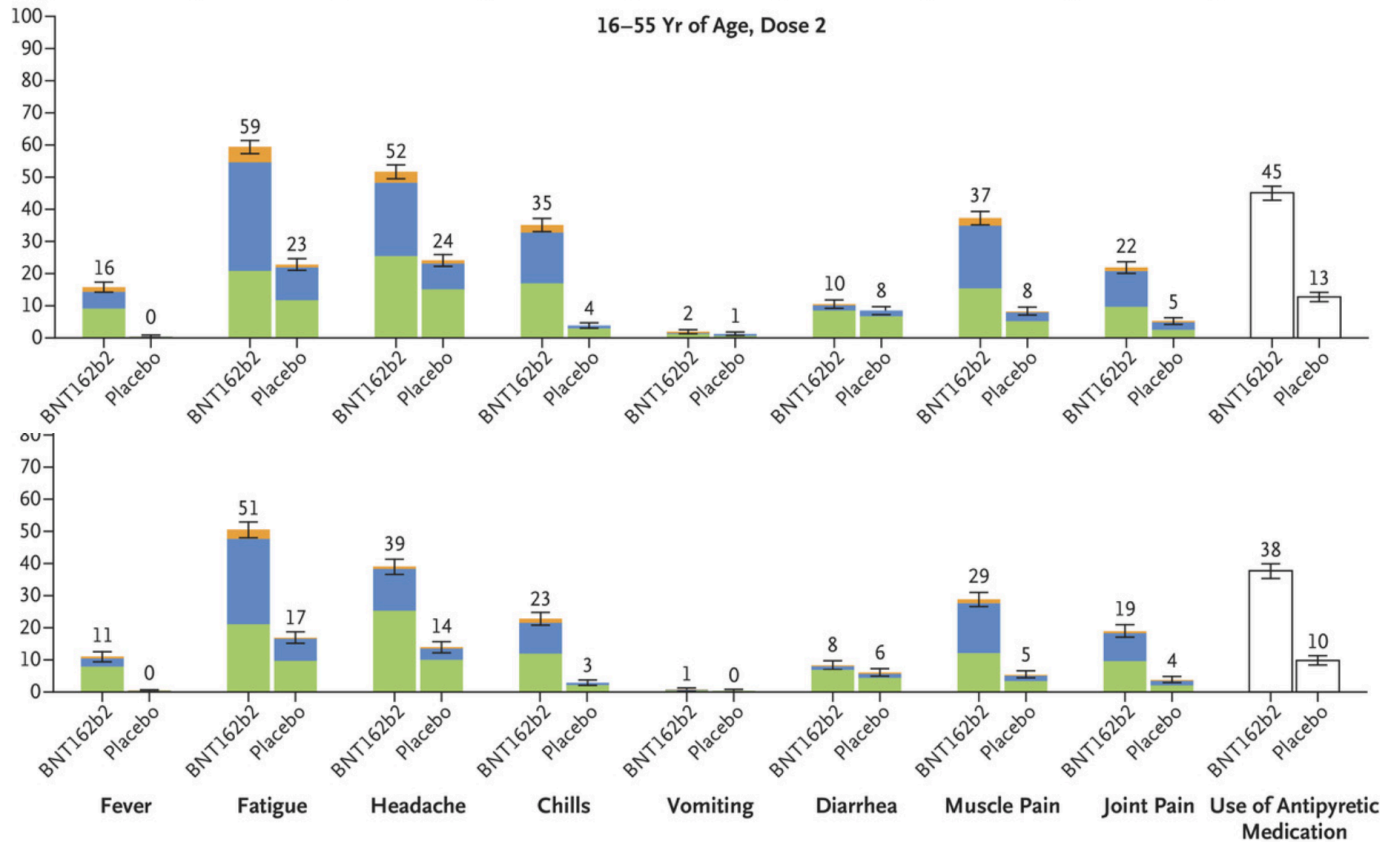
	mRNA-1273 Vaccine N=14,550	Placebo N=14,598
Symptomatic Covid-19	11	185
Severe Covid-19	0	30

Vaccine efficacy of 94.1% (95% CI, 89.3–96.8%; P<0.001)

Pfizer/BioNTech: BNT162b2 (RNA)

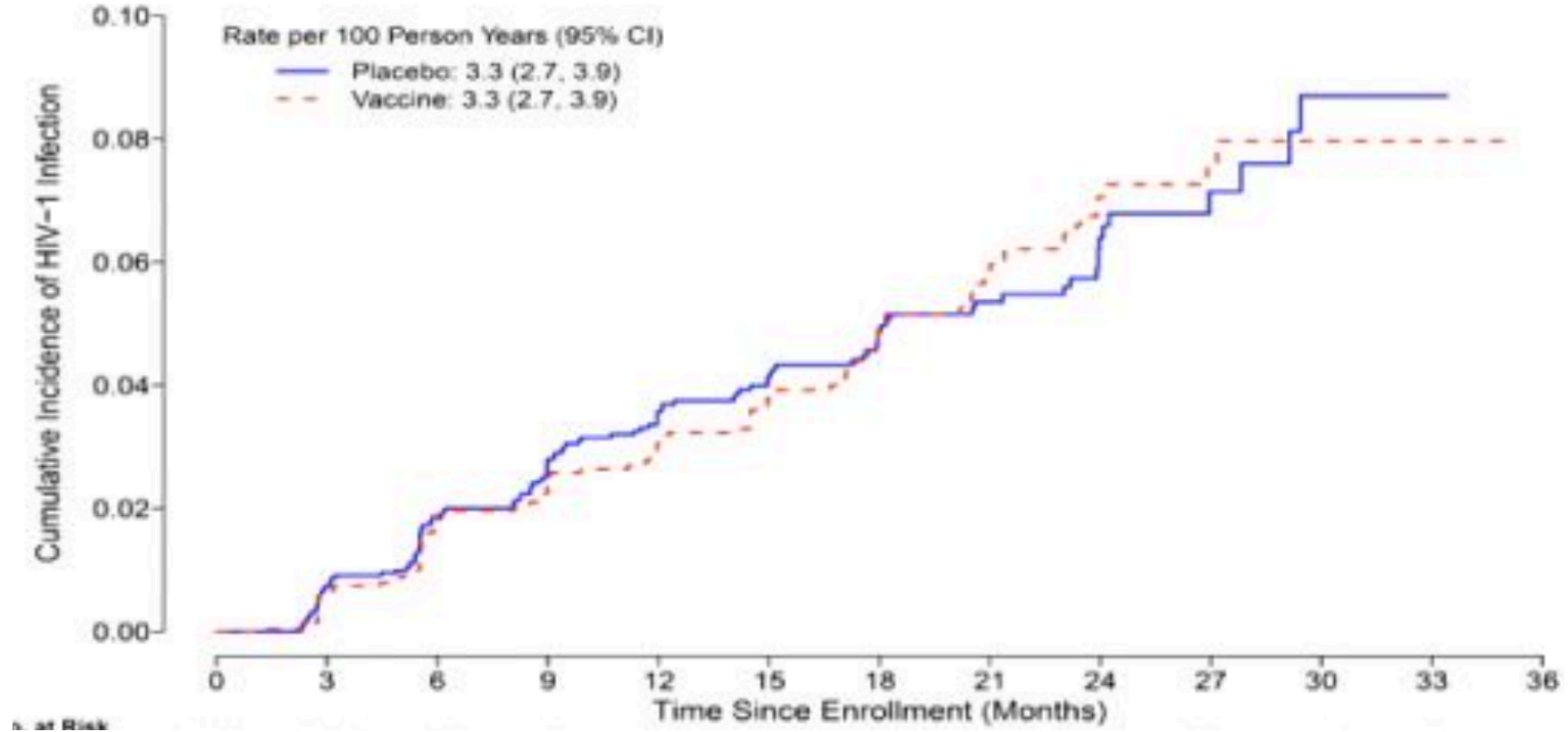


Pfizer/BioNTech: BNT162b2 (RNA)

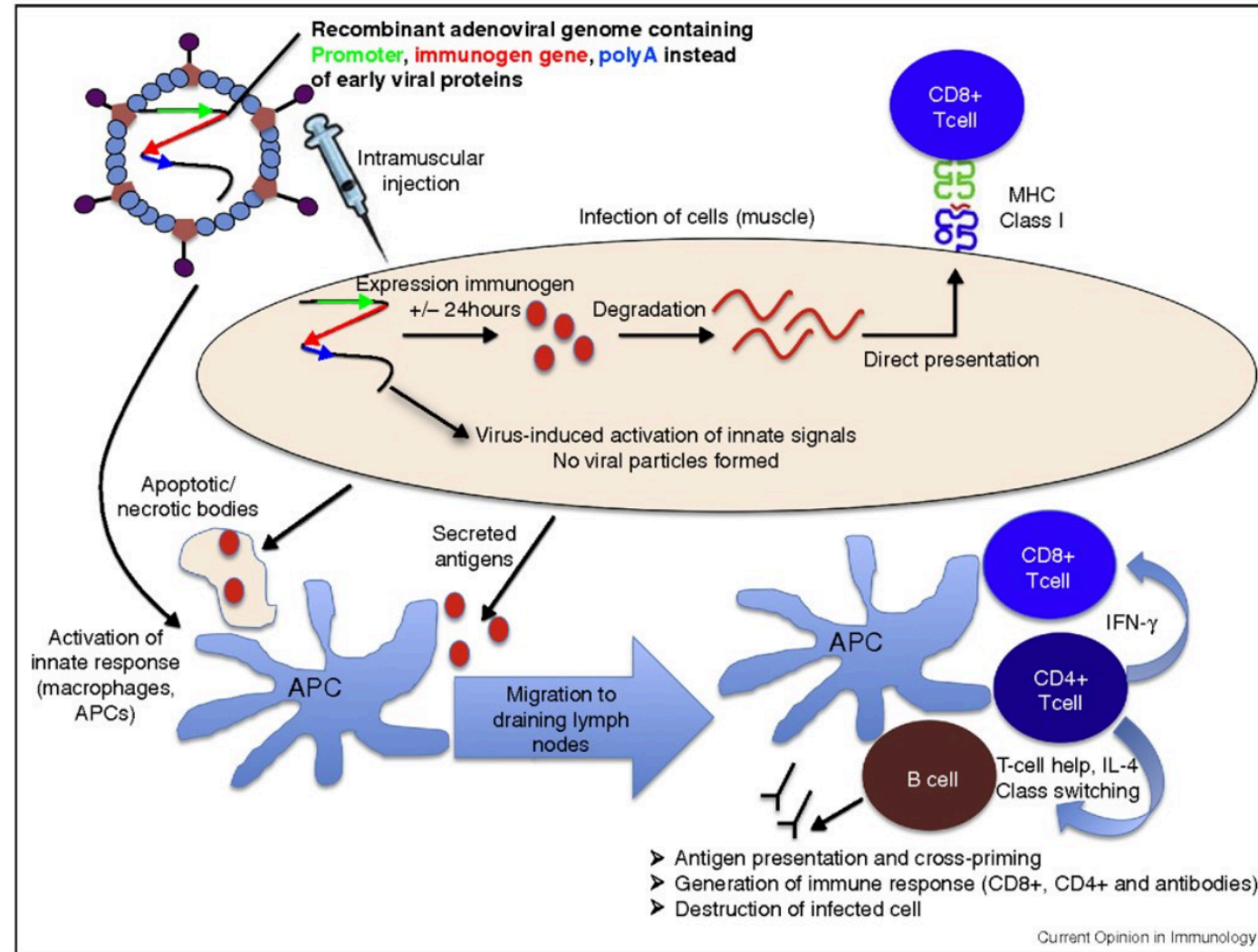


Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time	No. of participants	Surveillance time	percent
		person-yr (no. at risk)		person-yr (no. at risk)	
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (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)

Just a quick reminder: HVTN 702



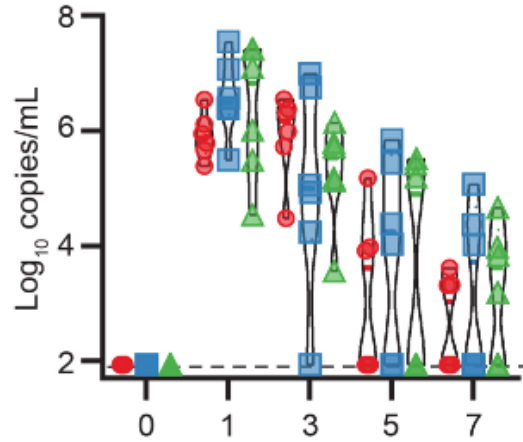
Mechanism: vectors to deliver immunogen



Developer	Vaccine	Phase 1	Phase 2	Phase 3
Non Replicating Viral Vectors				
Oxford -AZ	ChadOx-S	✓	✓	✓
CanSino- Beijing	Adeno 5	✓	✓	✓
Gamaleya Inst	Ad26-S + Ad5-S	✓	✓	✓
Janssen	Ad26-S1	✓	✓	✓
ReiThera/LEUKOCARE	Replic defic Simian Adeno- S	✓		
Acad military Med PLA-China	Ad5-nCoV	✓		
Vaxart	Ad5- ORAL	✓		
Replicating Viral Vector				
Inst Pasteur- Merck	Measles	✓		
Beijing Wanati-Xiamen University	Intranasal Influenza	✓		

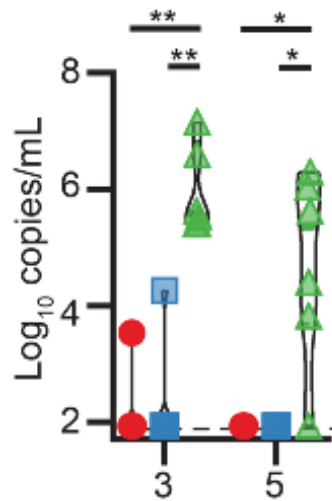
Macaques

Nasal swabs (gRNA)

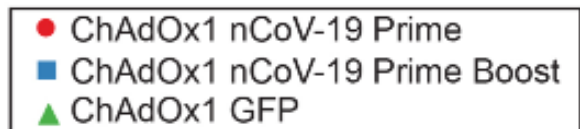


Days post inoculation

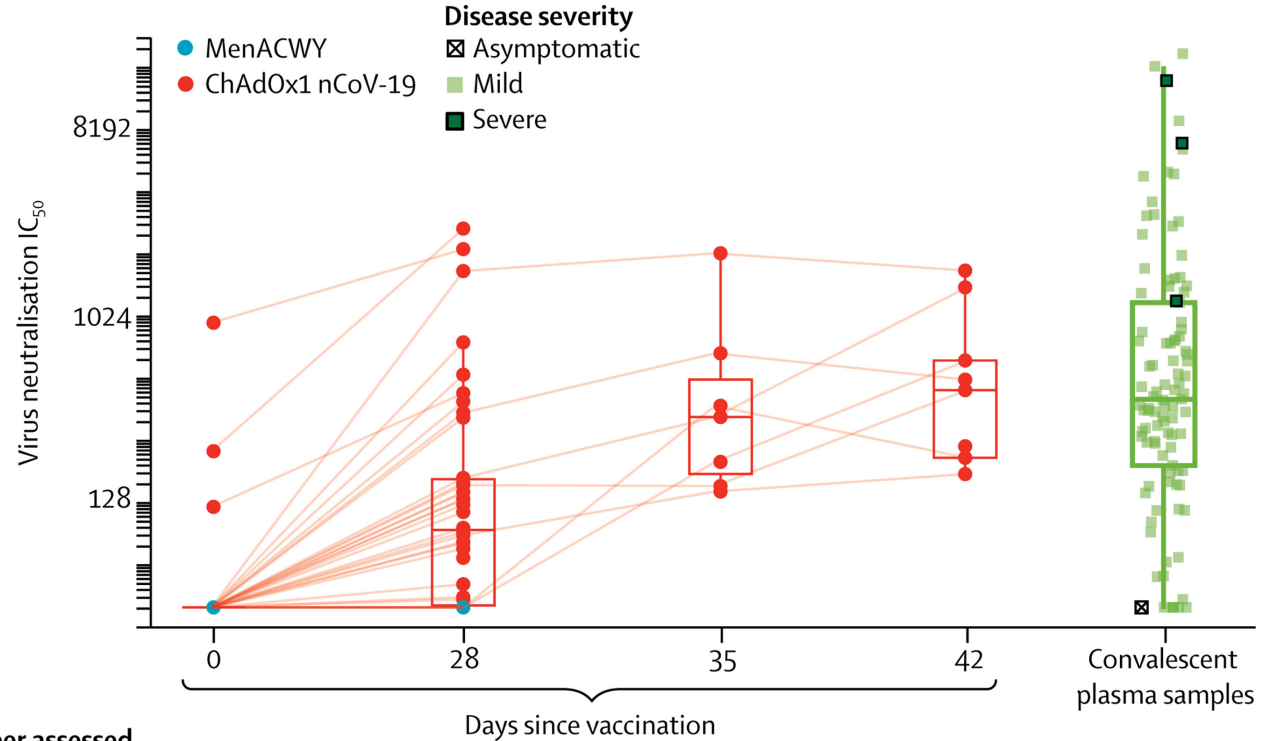
BAL fluid (gRNA)



Days post inoculation



AstraZeneca: ChAdOx1 nCoV-19



Number assessed
ChAdOx1 nCoV-19 39
MenACWY 30

Days since vaccination

0	28	35	42
39	38	10	9
30	30	0	0

Phase 3: ongoing

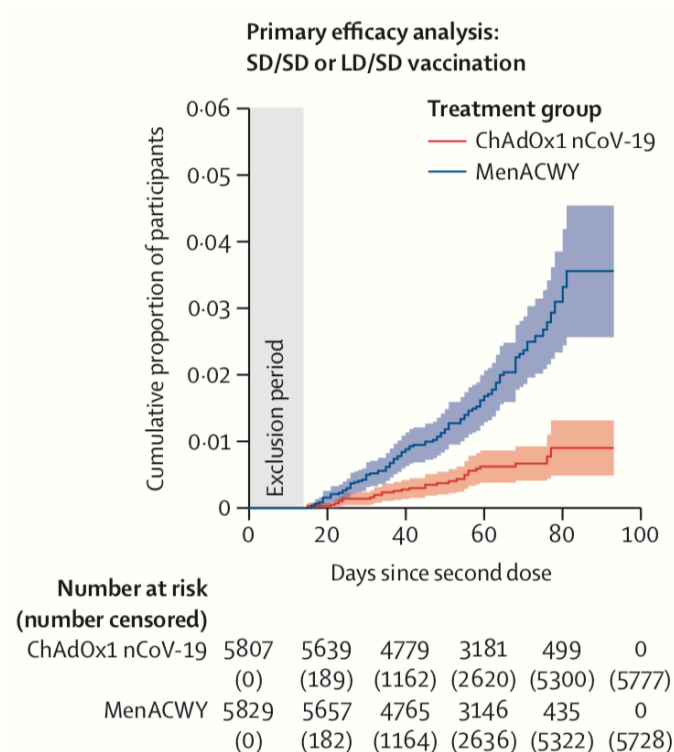
AstraZeneca: ChAdOx1 nCoV-19

COV002 (UK; LD/SD; N=2741)		COV002 (UK; SD/SD; N=4807)		COV003 (Brazil; all SD/SD; N=4088)	
ChAdOx1 nCoV-19 (n=1367)	MenACWY (n=1374)	ChAdOx1 nCoV-19 (n=2377)	MenACWY (n=2430)	ChAdOx1 nCoV-19 (n=2063)	MenACWY plus saline (n=2025)

VE = 90.0% (67.4 to 97.0)

VE = 60.3% (28.0 to 78.2)

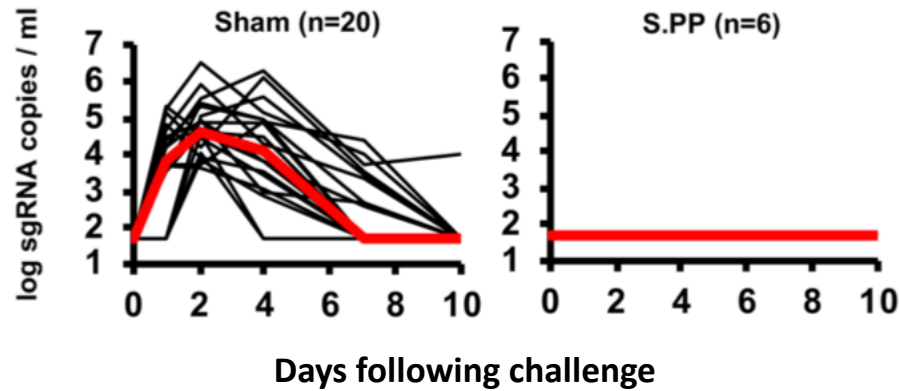
VE = 64.2% (30.7 to 81.5)



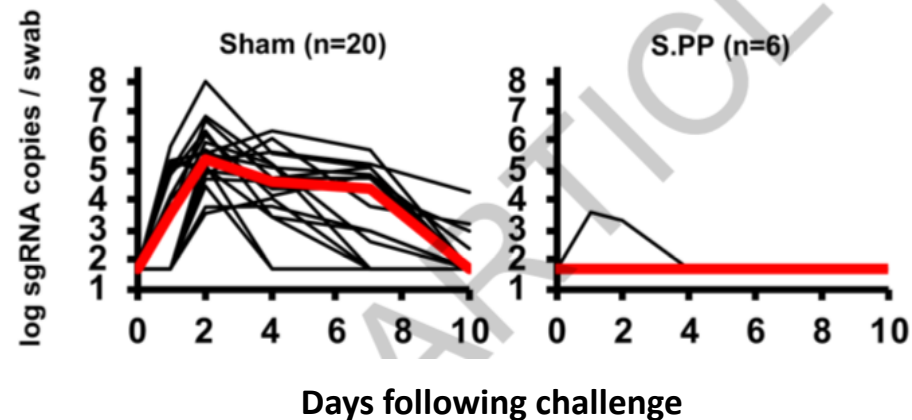
Combined VE = 70.4% (54.8 to 80.6)

Macaques

BAL fluid

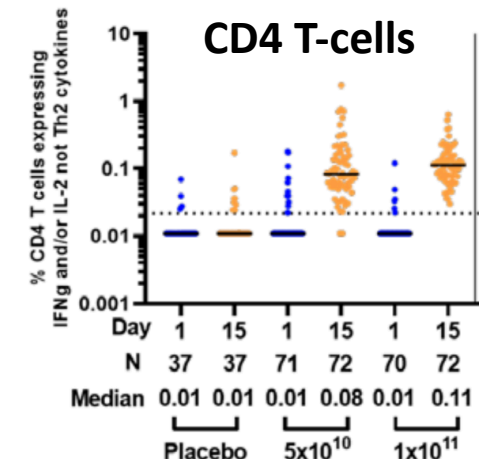
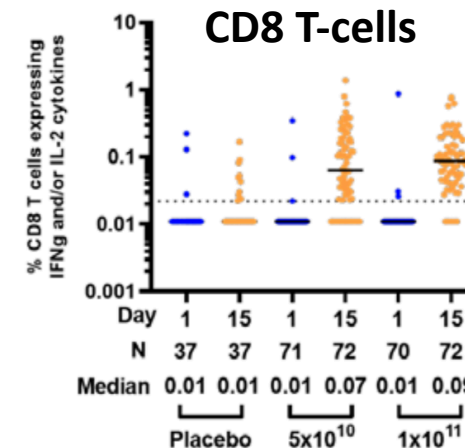
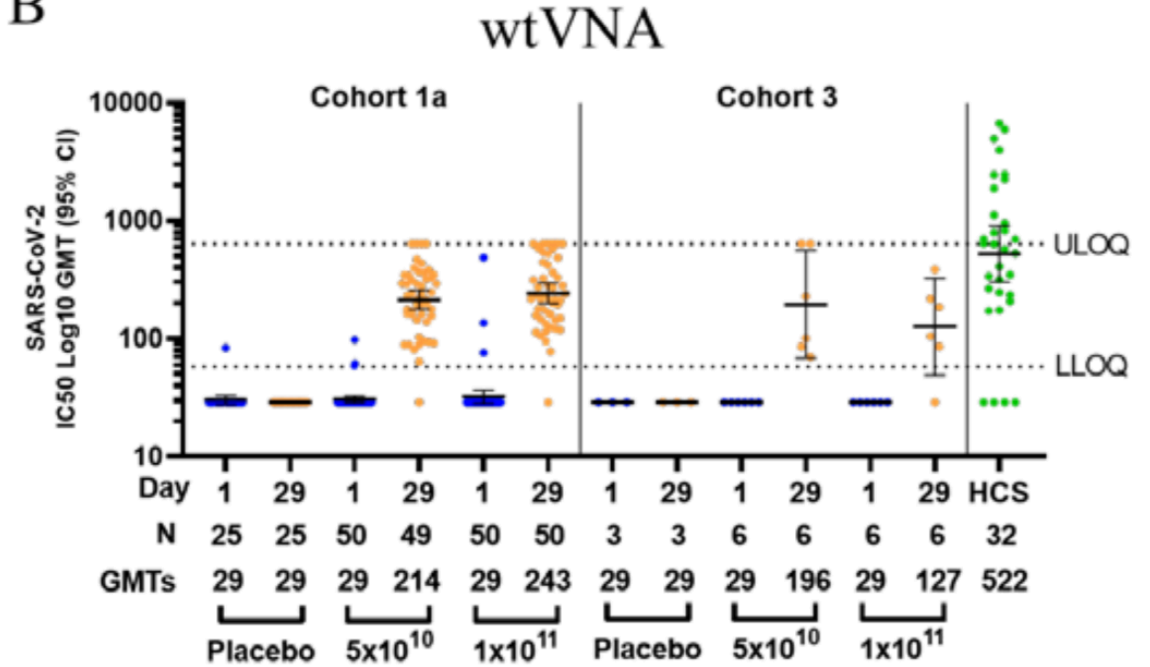


Nasal swab



Janssen (J&J): Ad26.COVS.S

B



Janssen (J&J): Ad26.COV2.S

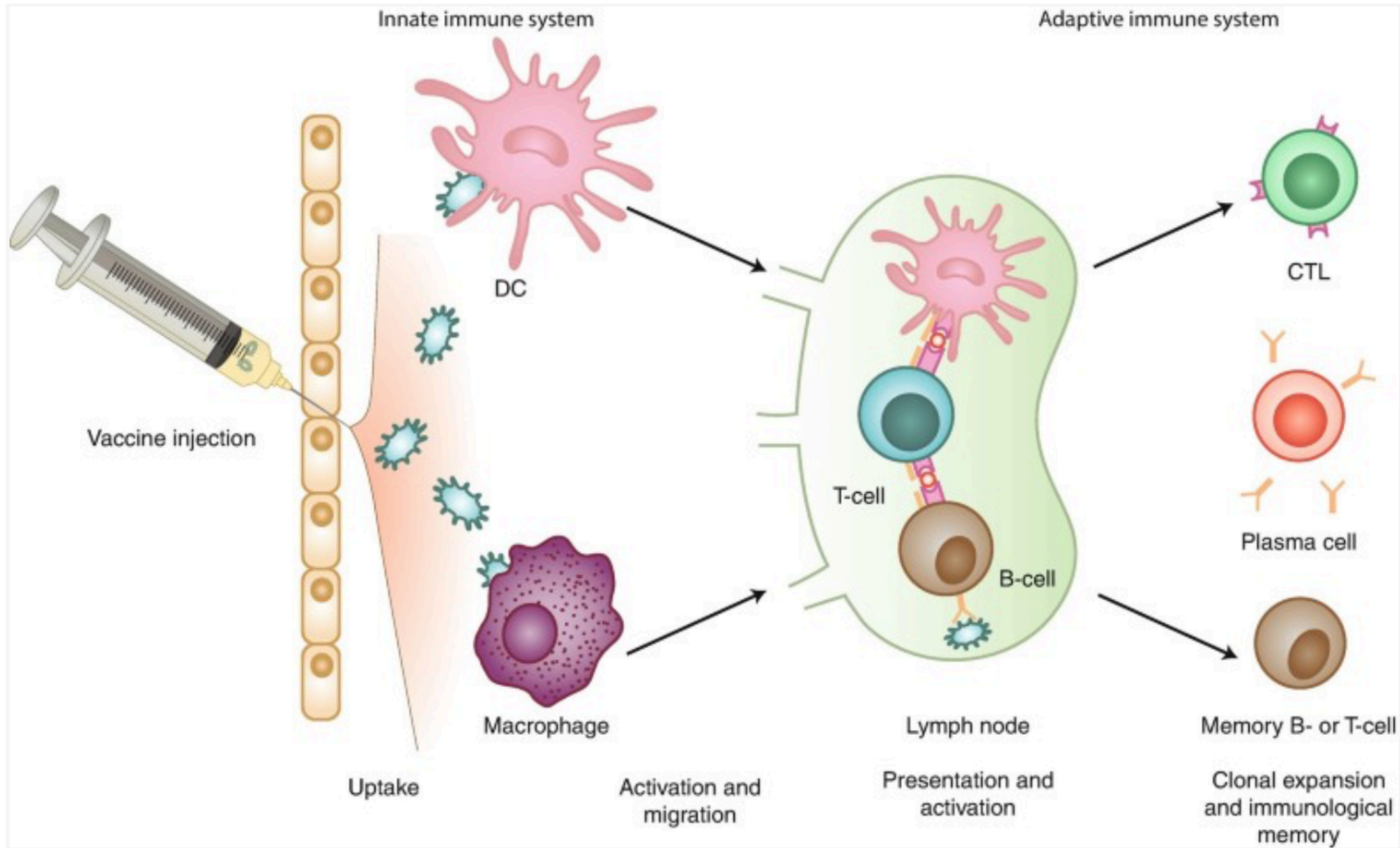


VAC31518COV3001: A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older

VAC31518COV3009: A Study of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults

 Efficacy data expected end of January

Mechanism: protein/subunit vaccines



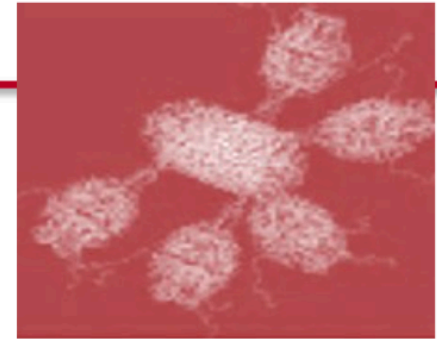
Novavax NVX-CoV2373

- rS (5 ug): Trimers are formulated into a stable detergent/protein nanoparticle
- Adjuvant (50ug): Matrix-M™ (derived from *Quillaja saponaria* saponins), immunogenic with other nanoparticle vaccines (flu HA, RSV))

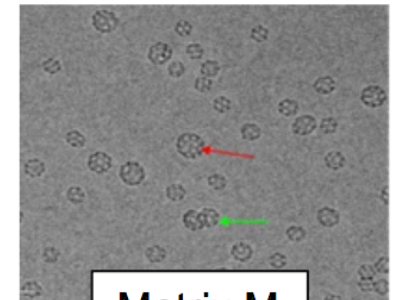
Similar constructs in clinical development

- **NanoFlu™** - quadrivalent influenza nanoparticle vaccine
- **ResVax™** - RSV vaccine for infants via maternal immunization (Madhi S NEJM 2020)

Nanoparticle



Soapbark tree
(*Quillaja Saponaria*)



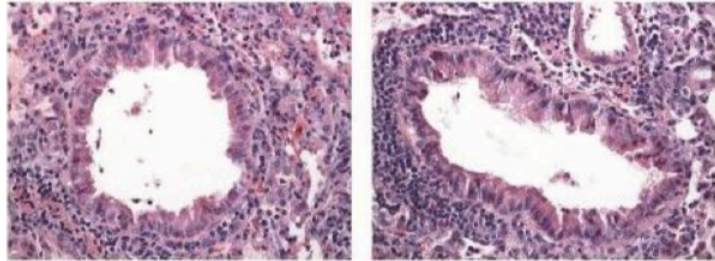
Matrix M

Ad/CMV/hACE2 transduced mice
challenged with SARS-CoV-2

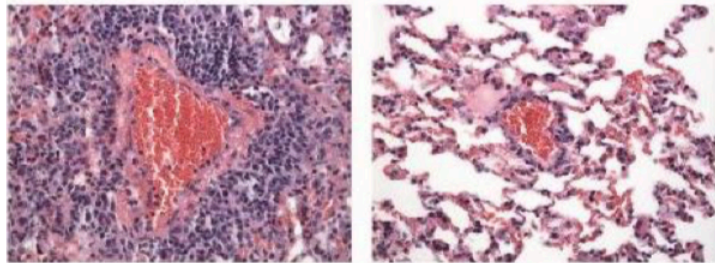
Novavax: NVX-CoV2373

Placebo 10 μ g NVX-CoV2373
+ 5 μ g Matrix-M

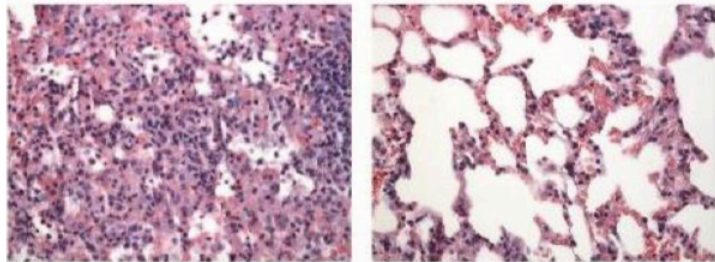
Bronchial



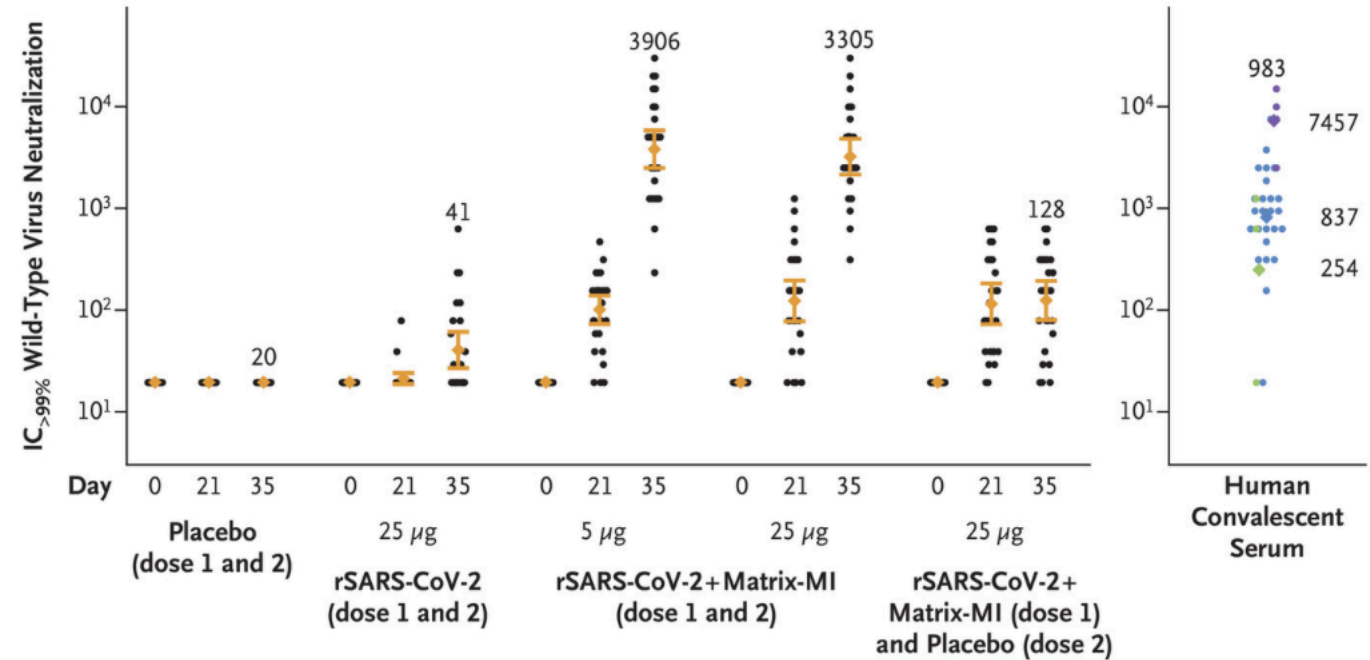
Vascular



Alveoli



7 Days Post Infection












Phase 3 now enrolling

Sanofi/GSK: S-protein + AS03

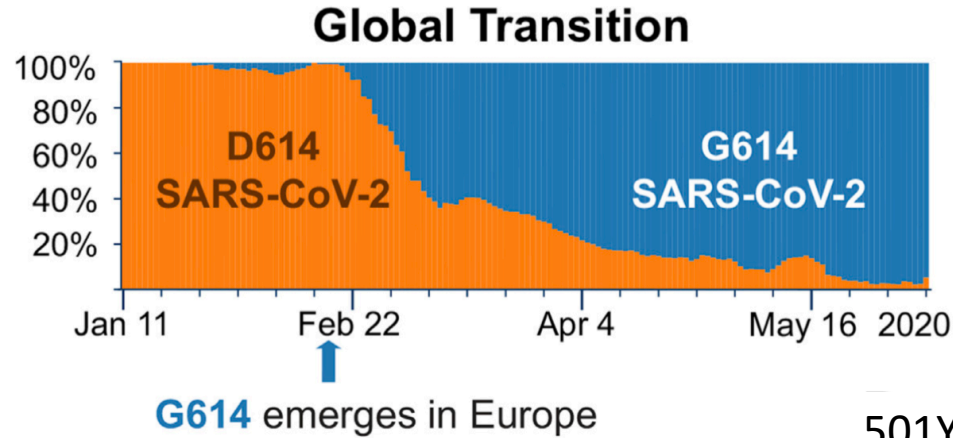
- Phase 1/2 interim results showed an immune response comparable to patients who recovered from COVID-19 in adults aged 18 to 49 years
- Insufficient response in older adults demonstrates the need to refine the concentration of antigen in order to provide high-level immune response across all age groups
- Companies plan a Phase 2b study with an improved antigen formulation in Q1/2021

How do some vaccines compare

Company	Type	Doses	How effective*	Storage	Cost per dose
 Oxford Uni-AstraZeneca	Viral vector (genetically modified virus)	x2 	62-90%	Regular fridge temperature	£3 (\$4)
 Moderna	RNA (part of virus genetic code)	x2 	95%	-20C up to 6 months	£25 (\$33)
  Pfizer-BioNTech	RNA	x2 	95%	-70C	£15 (\$20)
 Gamaleya (Sputnik V)	Viral vector	x2 	92%	Regular fridge temperature (in dry form)	£7.50 (\$10)

Consequences of novel viral variants

D614G mutation in the spike glycoprotein



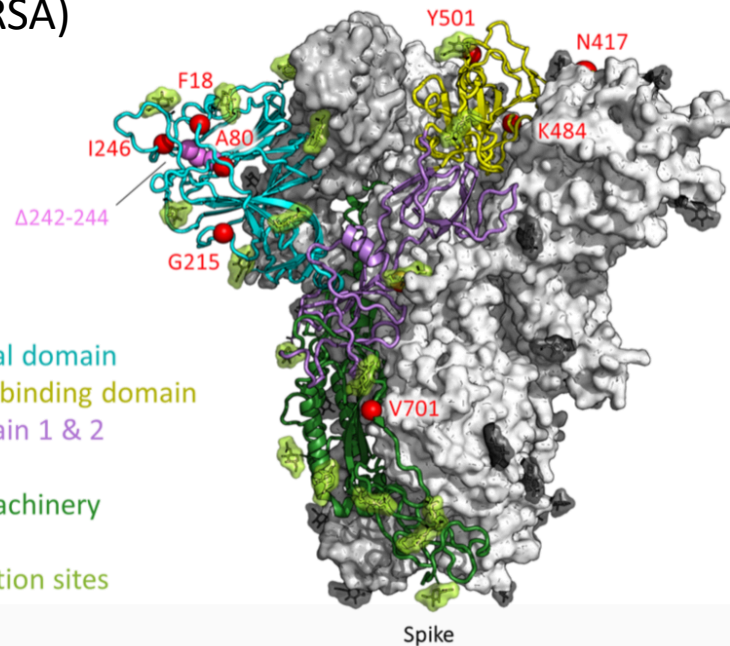
B.1.1.7 lineage (UK)

501Y.V2. (RSA)

S1 N-terminal domain
Receptor binding domain
Sub-domain 1 & 2

S2 Fusion machinery

Glycosylation sites



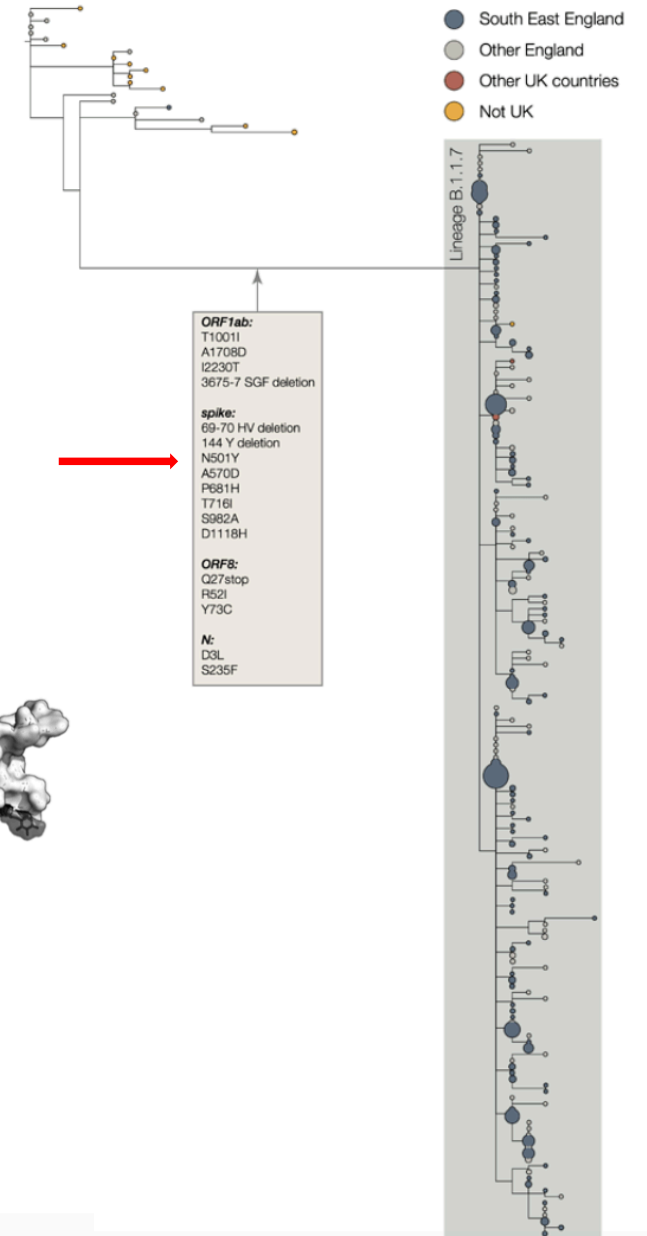
N501Y

ORF1ab:
T1001I
A1708D
I2230T
3675-7 SGF deletion

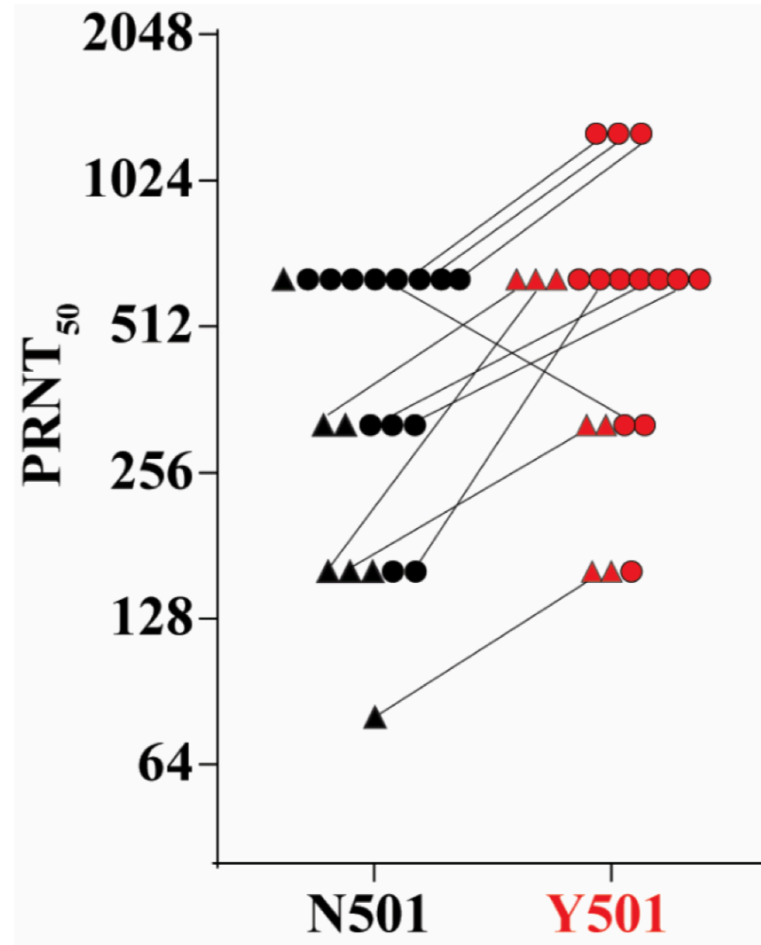
spike:
69-70 HV deletion
144 Y deletion
N501Y
A570D
P681H
T716I
S982A
D1118H

ORF8:
Q27stop
R52I
Y73C

N:
D3L
S235F



Equivalent neutralizing titers to the N501 and Y501 viruses in BNT162b2 recipients



Vaccine acceptance

- Survey (in summer 2020) in 19 countries that have 55% of the world population.
- 71.5% reported that they would be very or somewhat likely to take a COVID-19 vaccine.
- Rates ranged from almost 90% (in China) to less than 55% (in Russia)
- Acceptance in the US was ~75%

<i>n</i>	13,426
Gender (%)	
Female	7,172 (53.5)
Male	6,129 (45.8)
Other	94 (0.7)
Gapminder income level (%)	
<US\$ 2 per day	447 (3.3)
\$2-\$8 per day	840 (6.3)
\$8-\$32 per day	3,011 (22.4)
\$32+ per day	8,498 (63.3)
Did not answer	630 (4.7)
Education level (%)	
Less than high school	3,830 (28.6)
High school or some college	4,692 (35.0)
Bachelor's degree	3,694 (27.6)
Postgraduate degree	1,179 (8.8)
Age group in years (%)	
18-24	2,057 (15.4)
25-54	8,360 (62.4)
55-64	1,493 (11.1)
65+	1,485 (11.1)
Accept COVID-19 vaccine if generally available (%)	
Completely agree	6,288 (46.8)
Somewhat agree	3,316 (24.7)
Neutral/no opinion	1,912 (14.2)
Somewhat disagree	819 (6.1)
Completely disagree	1,091 (8.1)

Inequality

Wealthy countries representing 14 per cent of the world's population have bought up 53 per cent of all the most promising vaccines so far

70 resource limited countries might only be able to vaccinate one in 10 people against COVID-19 in 2021

Efforts to fund and provide vaccine through COVAX, Co-led by Gavi, the Coalition for Epidemic Preparedness Innovations (CEPI) and WHO

Questions to be answered

- Level of vaccine efficacy (VE) (studies are only testing prevention in COVID-19; not prevention of SARS-CoV-2 infection)
- Durability of the different vaccine concepts? In diff. age groups?
- Effects of viral mutations on VE?
- Community acceptance?
- Effects of EUA on ongoing/future trials?