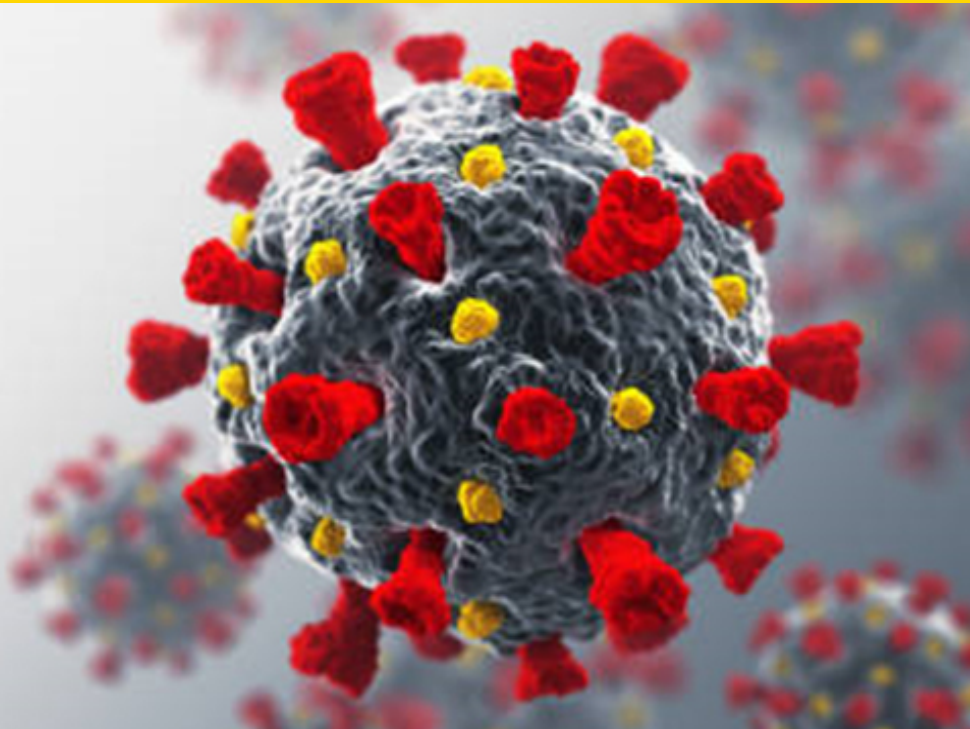
CVD·GLOBAL HEALTH

CENTER FOR VACCINE DEVELOPMENT AND GLOBAL HEALTH

CORONAVIRUS Vaccines

Kathleen Neuzil, MD, MPH

24 June 2020

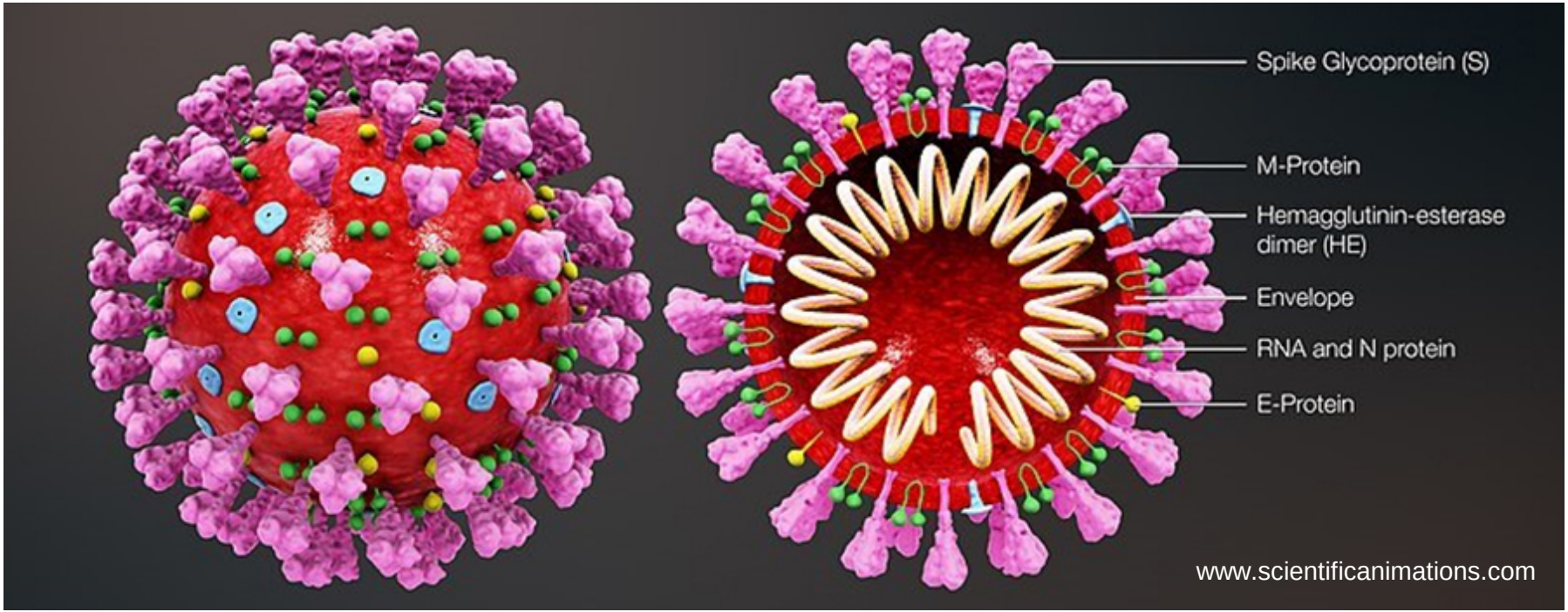


UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE
CENTER FOR VACCINE DEVELOPMENT
AND GLOBAL HEALTH

Outline

- Our Target: SARS-CoV-2
- The Complexity of Vaccine Development
- Vaccines for SARS-CoV-2
  - Vaccine platforms and attributes
  - Candidates in development
  - Upcoming trials

What do we know about the pathogen and immunity?

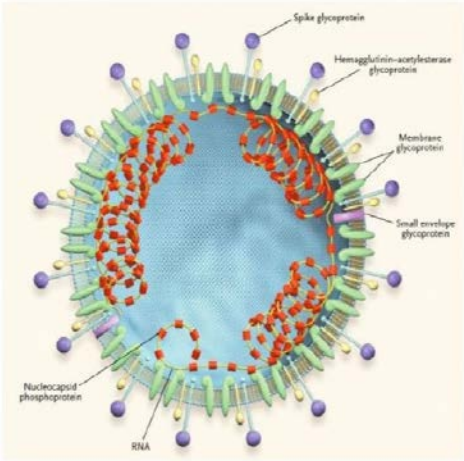


Single stranded, positive RNA with 4 major structural proteins:

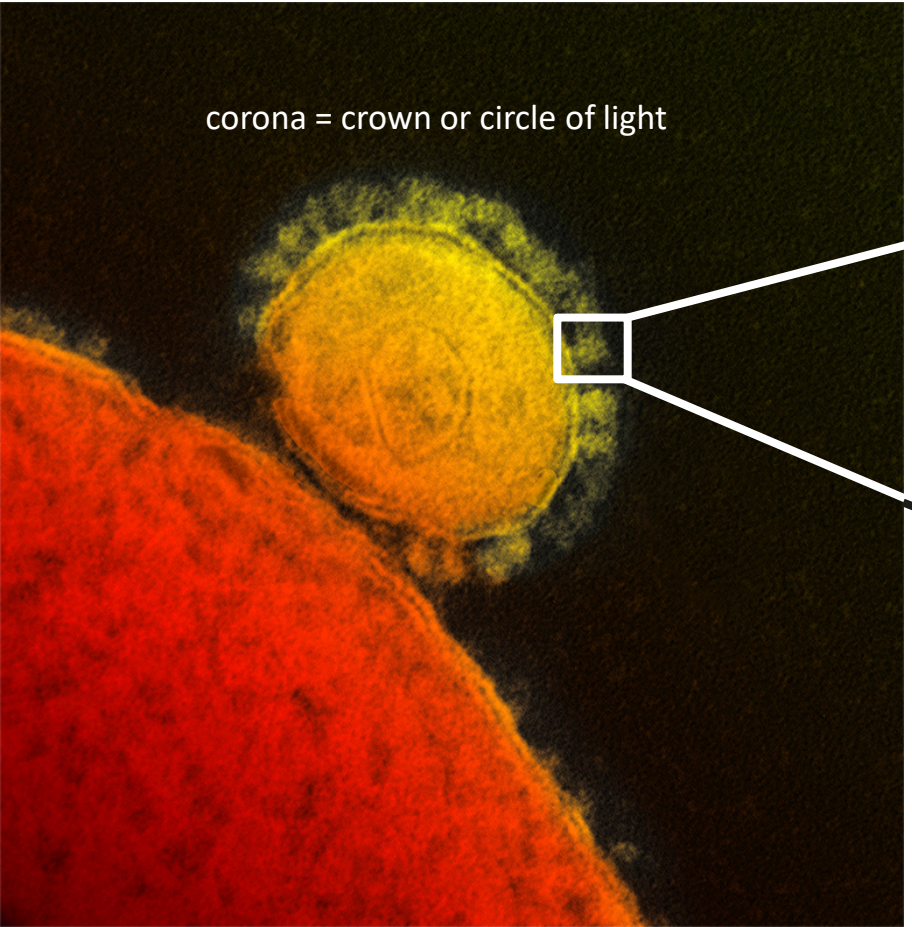
- Spike Protein (S) ⟶ Contains receptor binding domain
- M Protein
- Envelope (E) Protein
- Nucleocapsid (N) Protein

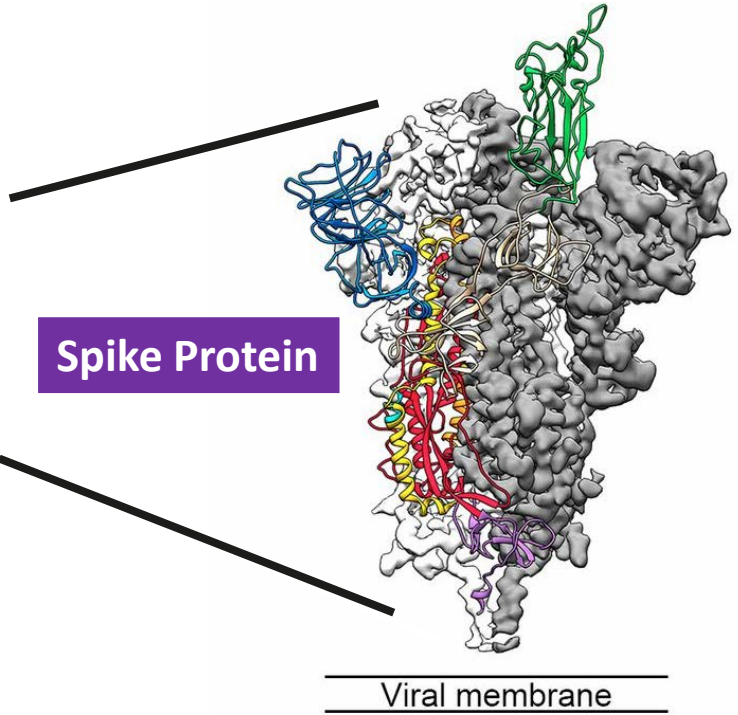
Vaccine Development Lessons from Other Coronaviruses

- Sequence comparison Spike S protein
  - MERS spike S protein 30% homologous
  - SARS Spike S protein is 80% homologous
- Good vaccine responses to several vaccine constructs in animals for SARS, MERS
- Phase 1 human trials in SARS, MERS
  - Broadly neutralizing antibodies
  - MERS development continues
  - SARS investments re-allocated



SARS-CoV-2 Spike Protein: Viral Entry

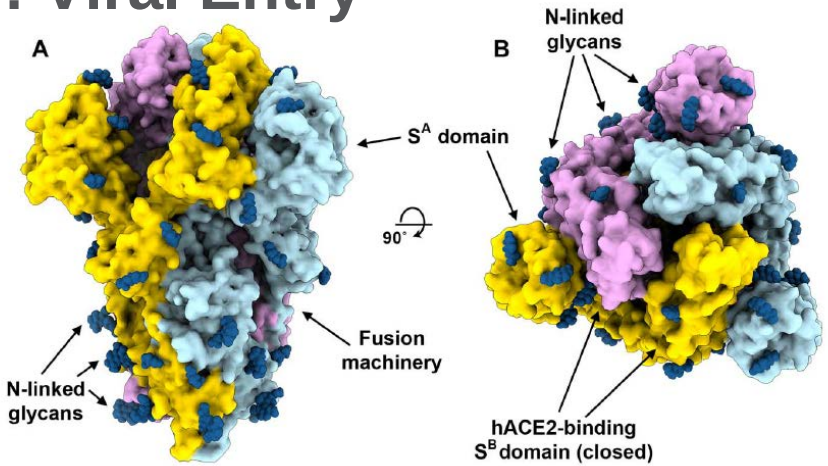


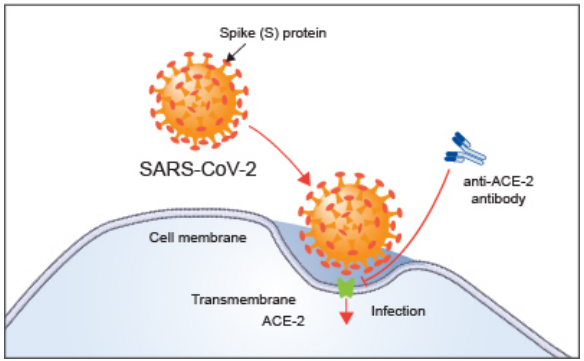


Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020 Feb 19:eabb2507. doi: 10.1126/science.abb2507.

SARS-CoV-2 Spike Protein: Viral Entry

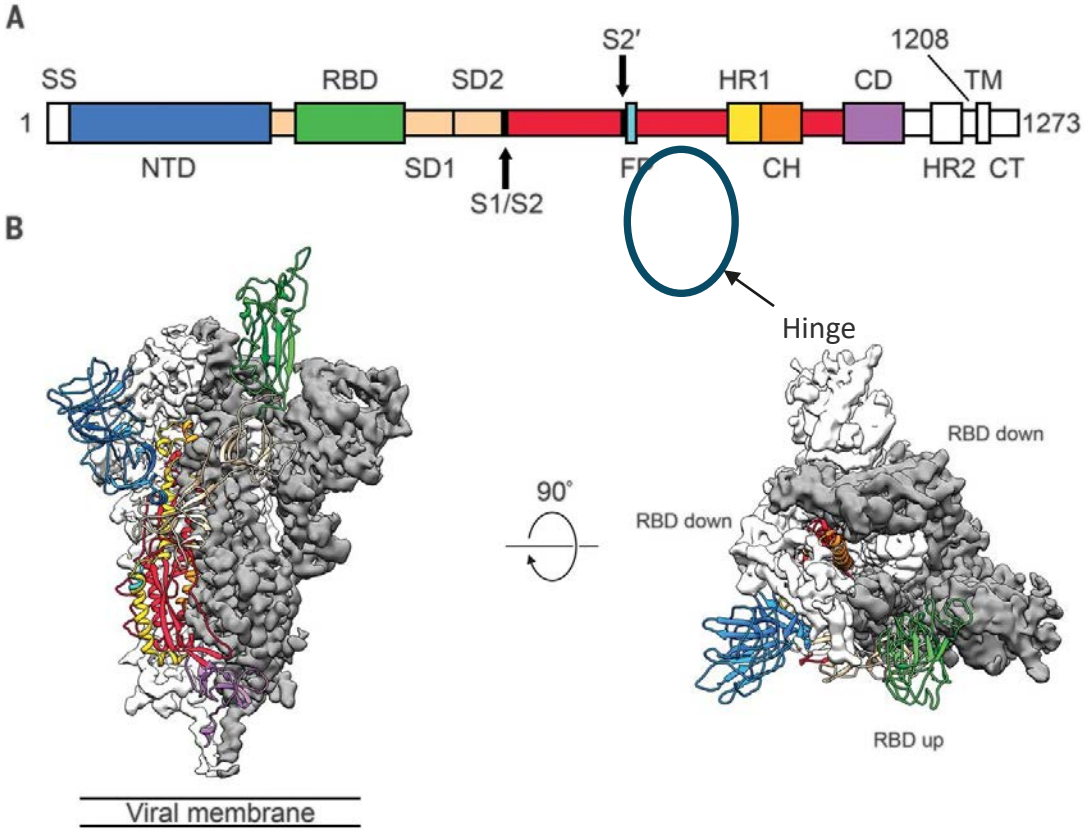
- Trimeric fusion protein
- Metastable prefusion conformation
- Undergoes substantial structural rearrangement to fuse the viral membrane with the host cell membrane
- Process triggered when S1 subunit binds to host cell receptor – S2 engages cell with fusion peptide
- Shedding of S1 subunit and transition of S2 subunit to stable postfusion conformation





bioRxiv https://doi.org/10.1101/2020.02.19.956581, Feb. 20, 2020

Conformationally Correct Protein

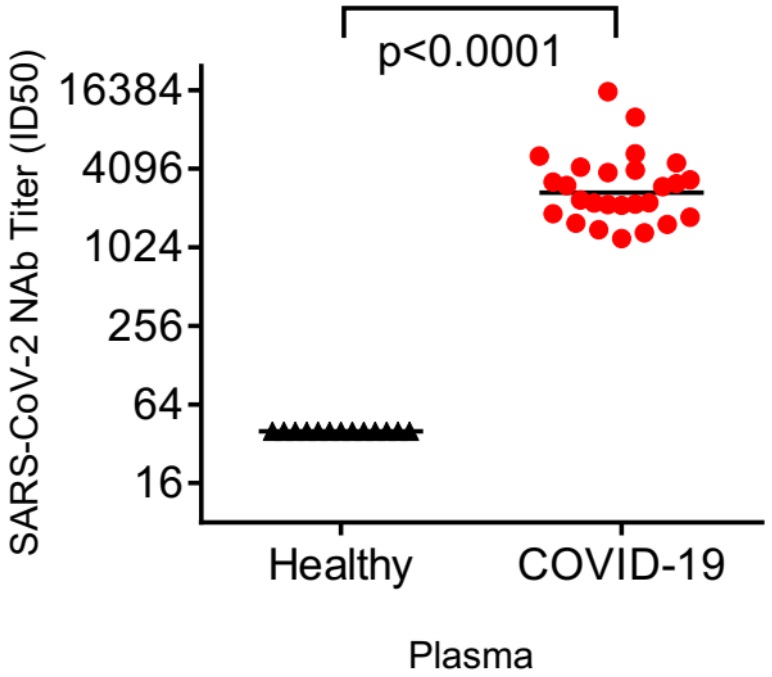


Receptor-binding domain of S1 undergoes hinge-like conformational movements that transiently hide or exposure determinants of receptor binding. Two stabilizing proline mutations effective for other betacoronaviruses applied to SARS-CoV-2.

Science 13 Mar 2020:Vol. 367, Issue 6483, pp. 1260-1263

What Do We Know About Immunity in Humans?

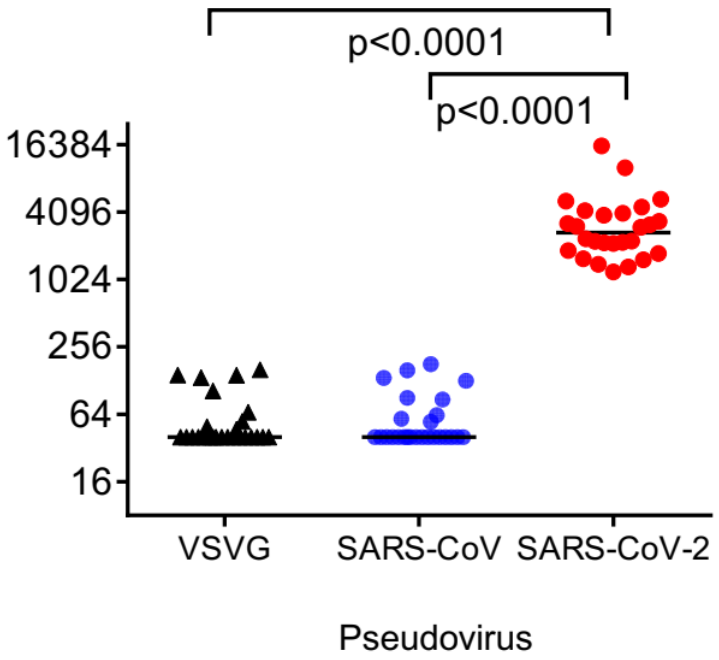
- Immune response post-infection to spike protein
- Neutralizing responses



medRxiv preprint doi: https://doi.org/10.1101/2020.03.30.20047365.

What Do We Know About Immunity in Humans?

- Immune response post-infection to spike protein
- Neutralizing responses
  - Don’t cross-react with SARS virus
- Level of antibody needed to prevent re-infection?
- Duration of protection from natural immunity?
- Importance of T cell immunity?



medRxiv preprint doi: https://doi.org/10.1101/2020.03.30.20047365.

Does Infection with SARS-CoV-2 Protect Upon Re-Exposure?

Science

RESEARCH ARTICLES

Cite as: A. Chandrashekar *et al.*, *Science*
10.1126/science.abc4776 (2020).

SARS-CoV-2 infection protects against rechallenge in rhesus macaques

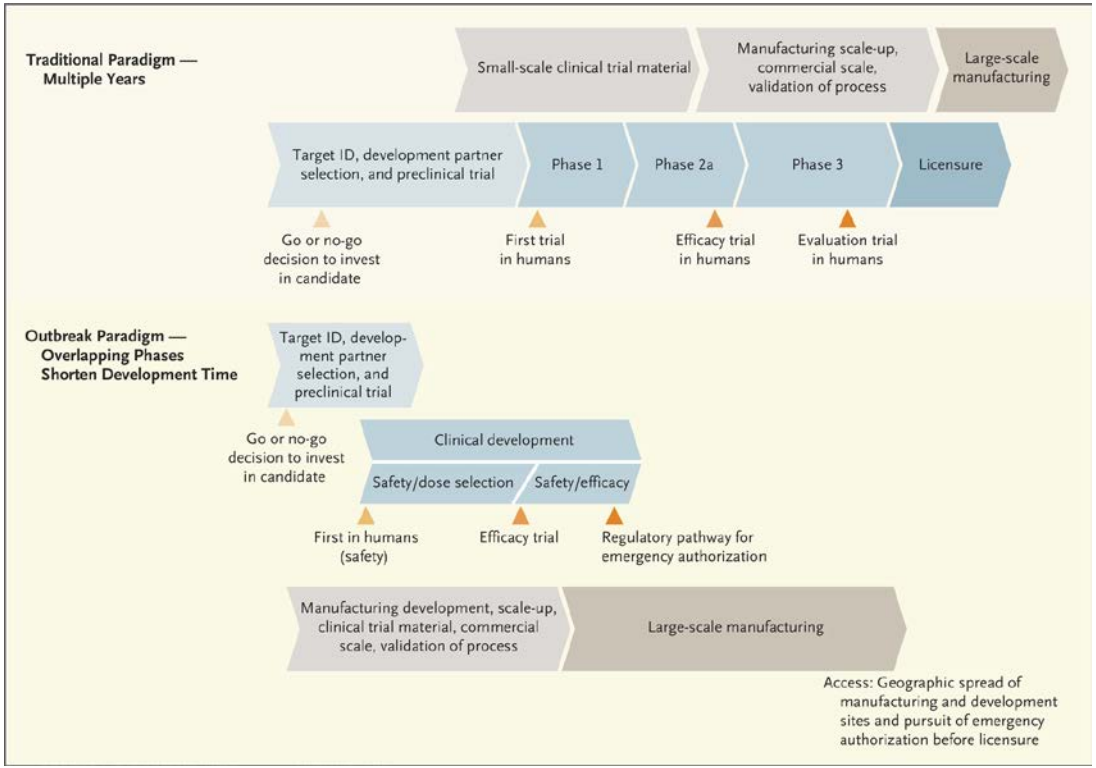
Abishek Chandrashekar[1]*, Jinyan Liu[1]*, Amanda J. Martinot[1,2]*, Katherine McMahan[1]*,

1 **Lack of Reinfection in Rhesus Macaques Infected with SARS-CoV-2**

2

3 Linlin Bao[†,1], Wei Deng[†,1], Hong Gao[†,1], Chong Xiao[†,1], Jiayi Liu[†,2], Jing Xue[†,1], Qi

Vaccine Development:
A Lengthy, Risky and Expensive Process



15-20 years

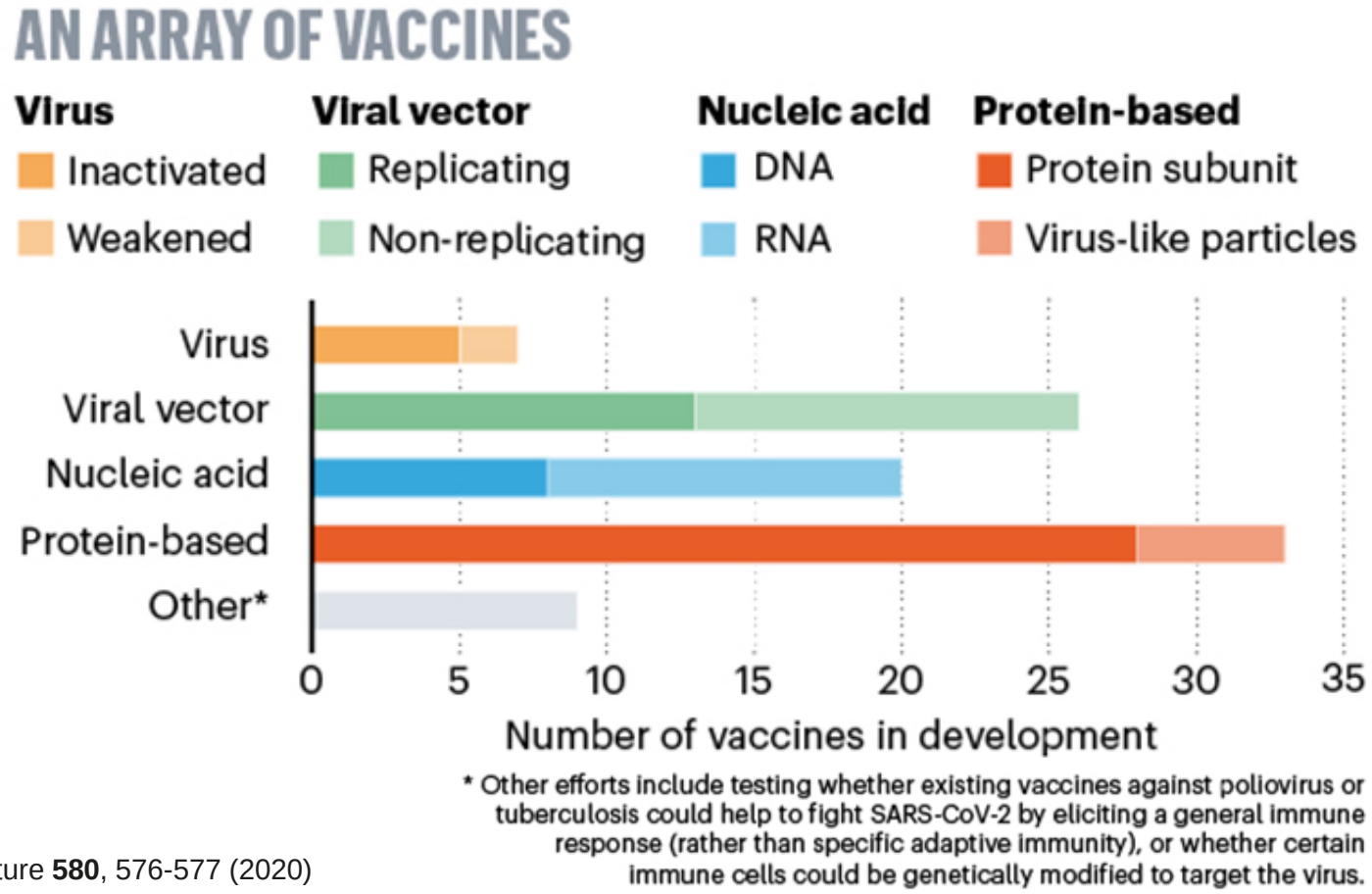
12-18 months

N Engl J Med 2020; 382:1969-1973 **DOI: 10.1056/NEJMp2005630**

Vaccine Platforms and Attributes

	Single Dose	Licensed Platform	Speed	Scale
DNA	No	No	Fast	Medium
RNA	No	No	Fast	Low to medium
Nonreplicating vector	Possibly	No	Medium	High
Replicating viral vector	Possibly	Yes	Medium	High
Protein subunit	No	Yes	Medium	High
Inactivated	No	Yes	Medium	Medium to high
Live attenuated	Yes	Yes	Slow	High

Vaccine Approach: Strategies

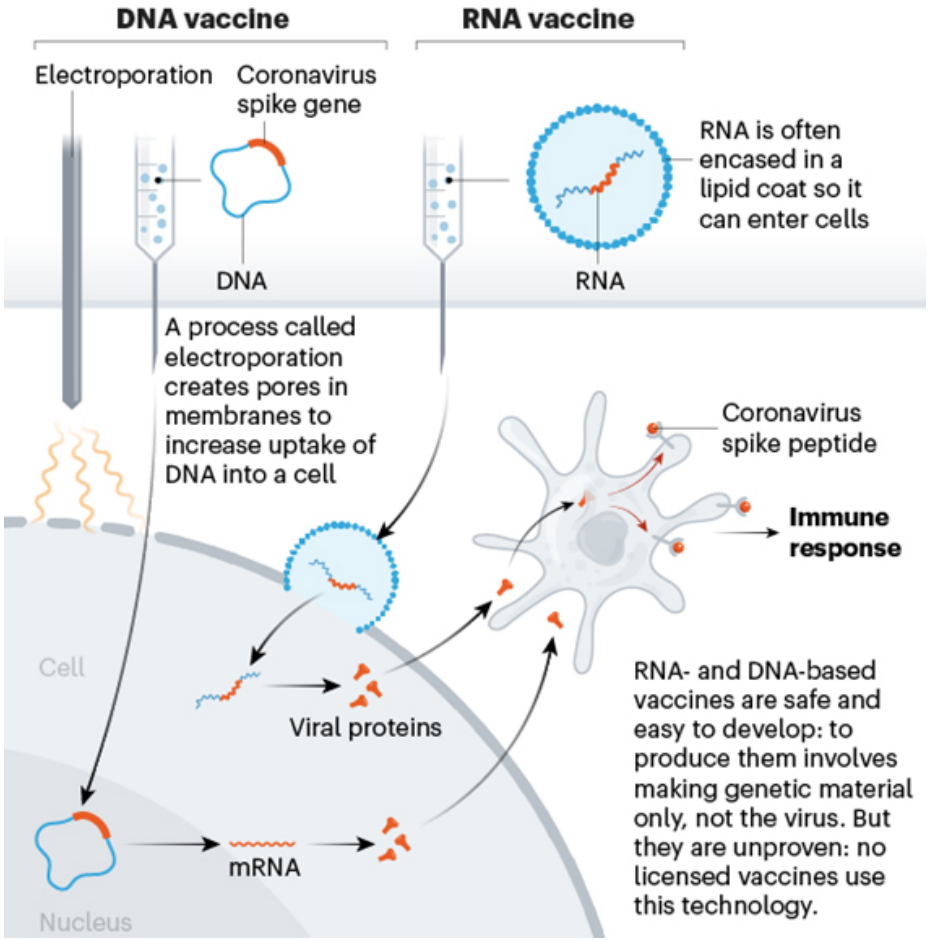


Nature **580**, 576-577 (2020)

COVID-19 Vaccine Candidates in Clinical Evaluation

Platform	Type	Developer	Phase	Same Platform
Non-replicating viral vector	ChAdOx1-S	Oxford/AZ	1/2	MERS, influenza, TB, Chik, Zika
Non-replicating viral vector	Ad Type 5	CanSino Biol Inc	2	Ebola
RNA	LNP-mRNA	Moderna/NIAID	2	Influenza, Zika, Chik
Inactivated	Inactivated +/- alum	Multiple Chinese developers	1/2	
Protein subunit	Recombinant GP nanoparticle/matrix M	Novavax	1/2	RSV; CCHF, HPV, VZV, Ebola
RNA	3 LNP-mRNAs	Pfizer/BioNTech	1/2	
DNA	DNA plasmid/electroporation	Inovio Pharm.	1	Multiple

Vaccine Approach: Nucleic Acid – DNA and RNA



Nature **580**, 576-577 (2020)

moderna

Moderna Announces Positive Interim Phase 1 Data for its mRNA Vaccine (mRNA-1273) Against Novel Coronavirus

May 18, 2020

After two doses all participants evaluated to date across the 25 µg and 100 µg dose cohorts seroconverted with binding antibody levels at or above levels seen in convalescent sera

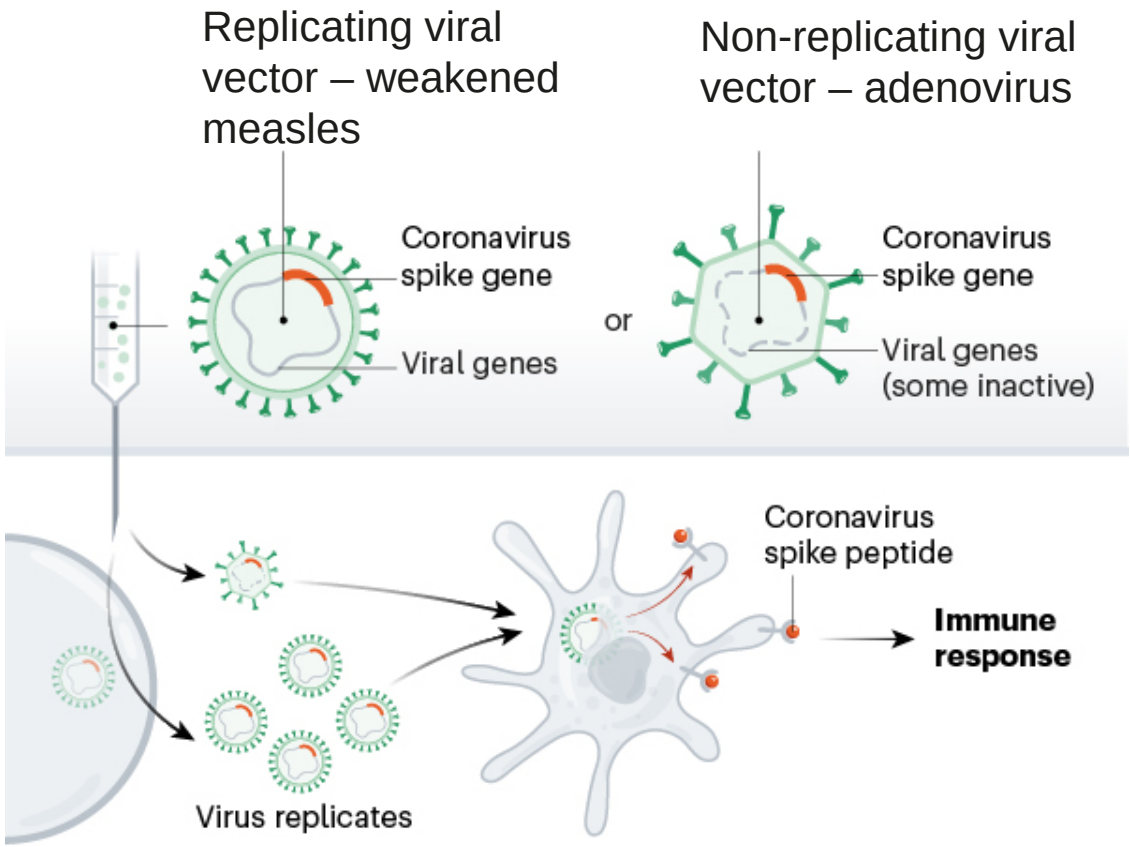
mRNA-1273 elicited neutralizing antibody titer levels in all eight initial participants across the 25 µg and 100 µg dose cohorts, reaching or exceeding neutralizing antibody titers generally seen in convalescent sera

mRNA-1273 was generally safe and well tolerated

mRNA-1273 provided full protection against viral replication in the lungs in a mouse challenge model

Anticipated dose for Phase 3 study between 25 µg and 100 µg; expected to start in July

Vaccine Approach: Viral Vectored Vaccine



Nature **580**, 576-577 (2020)

Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial

Feng-Cai Zhu, Yu-Hua Li*, Xu-Hua Guan, Li-Hua Hou, Wen-Juan Wang, Jing-Xin Li, Shi-Po Wu, Bu-Sen Wang, Zhao Wang, Lei Wang, Si-Yue Jia, Hu-Dachuan Jiang, Ling Wang, Tao Jiang, Yi Hu, Jin-Bo Gou, Sha-Bei Xu, Jun-Jie Xu, Xue-Wen Wang, Wei Wang, Wei Chen*

www.thelancet.com **Published online May 22, 2020 https://doi.org/10.1016/S0140-6736(20)31208-3**

Adverse Reactions to Ad5 Vectored COVID-19 Vaccine

	Low dose group (n=36)	Middle dose group (n=36)	High dose group (n=36)	Total (N=108)
All adverse reactions within 0–7 days				
Any	30 (83%)	30 (83%)	27 (75%)	87 (81%)
Grade 3	2 (6%)	2 (6%)	6 (17%)	10 (9%)
Injection site adverse reactions within 0–7 days				
Pain	17 (47%)	20 (56%)	21 (58%)	58 (54%)
Induration	2 (6%)	1 (3%)	1 (3%)	4 (4%)
Redness	2 (6%)	1 (3%)	1 (3%)	4 (4%)
Swelling	4 (11%)	4 (11%)	0	8 (7%)
Itch	2 (6%)	3 (8%)	0	5 (5%)
Muscular weakness	0	0	1 (3%)	1 (1%)
Systemic adverse reactions within 0–7 days				
Fever	15 (42%)	15 (42%)	20 (56%)	50 (46%)
Grade 3 fever	2 (6%)	2 (6%)	5 (14%)	9 (8%)
Headache	14 (39%)	11 (31%)	17 (47%)	42 (39%)
Fatigue	17 (47%)	14 (39%)	16 (44%)	47 (44%)

ELISA Antibody Responses to the RBD and Neutralizing Antibodies

	Day 14				Day 28			
	Low dose group (n=36)	Middle dose group (n=36)	High dose group (n=36)	p value	Low dose group (n=36)	Middle dose group (n=36)	High dose group (n=36)	p value
ELISA antibodies to the receptor binding domain								
GMT	76·5 (44·3–132·0)	91·2 (55·9–148·7)	132·6 (80·7–218·0)	0·29	615·8 (405·4–935·5)	806·0 (528·2–1229·9)	1445·8 (935·5–2234·5)	0·016
≥4-fold increase	16 (44%)	18 (50%)	22 (61%)	0·35	35 (97%)	34 (94%)	36 (100%)	0·77
Neutralising antibodies to live SARS-CoV-2								
GMT	8·2 (5·8–11·5)	9·6 (6·6–14·1)	12·7 (8·5–19·0)	0·24	14·5 (9·6–21·8)	16·2 (10·4–25·2)	34·0 (22·6–50·1)	0·0082
≥4-fold increase	10 (28%)	11 (31%)	15 (42%)	0·42	18 (50%)	18 (50%)	27 (75%)	0·046

- Dose-dependent antibody response
- High pre-existing Ad5 neutralizing antibody responses compromised neutralizing antibody post-vaccination, regardless of vaccine dose

Science

PERSPECTIVES

Cite as: B. S. Graham *et al.*, *Science* 10.1126/science.abb8923 (2020).

Rapid COVID-19 vaccine development

By **Barney S. Graham**

Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. Email: bgraham@mail.nih.gov

Finding the fastest pathway to vaccine availability includes the avoidance of safety pitfalls

Potential risks associated with vaccine development for COVID-19

Antibodies that bind virus without neutralizing infectivity can cause disease through increased viral replication or formation of immune complexes that deposit in tissue and activate complement pathways associated with inflammation. T helper 2 cell (T_H2)–biased responses have also been associated with ineffective vaccines that lead to enhanced disease after subsequent infection. Antibody-dependent enhancement (ADE) of viral replication has occurred in viruses with innate macrophage tropism. Virus-antibody immune complexes and T_H2-biased responses can both occur in vaccine-associated enhanced respiratory disease (VAERD).

	Antibody-mediated		T cell–mediated
	ADE	**VAERD**	**VAERD**
Mechanism	Fc-mediated increase in viral entry	Immune complex formation and complement deposition	T_H2-biased immune response
Effectors	Macrophage activation and inflammatory cytokines	Complement activation and inflammatory cytokines	Allergic inflammation and T_H2 cytokines
Mitigation	Conformationally correct antigens and high-quality neutralizing antibody		T_H1-biasing immunization and $CD8^+$ T cells

Summary

- Safe and effective vaccines that is accessible, affordable and globally available is needed for COVID-19
- Robust pipeline of promising candidates in clinical development
  - We need multiple wins
  - Many challenges – New disease, poorly understood immunity, uncertain trajectory of outbreak
  - Vaccine safety will be meticulously assessed
  - If enhanced disease occurs it will be carefully assessed and immune mechanisms investigated

Thank You

Center for Vaccine Development and Global Health
University of Maryland School of Medicine

685 West Baltimore Street, Room 480
Baltimore MD 21201

TEL: +1 410 706 5328 FAX: +1 410 706 6205

Visit us online at www.medschool.umaryland.edu/cvd

UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE
CENTER FOR VACCINE DEVELOPMENT
AND GLOBAL HEALTH