

## COVID-19 Vaccines

**Kathryn Stephenson, MD, MPH**

*Beth Israel Deaconess Medical Center, Boston, MA, USA*

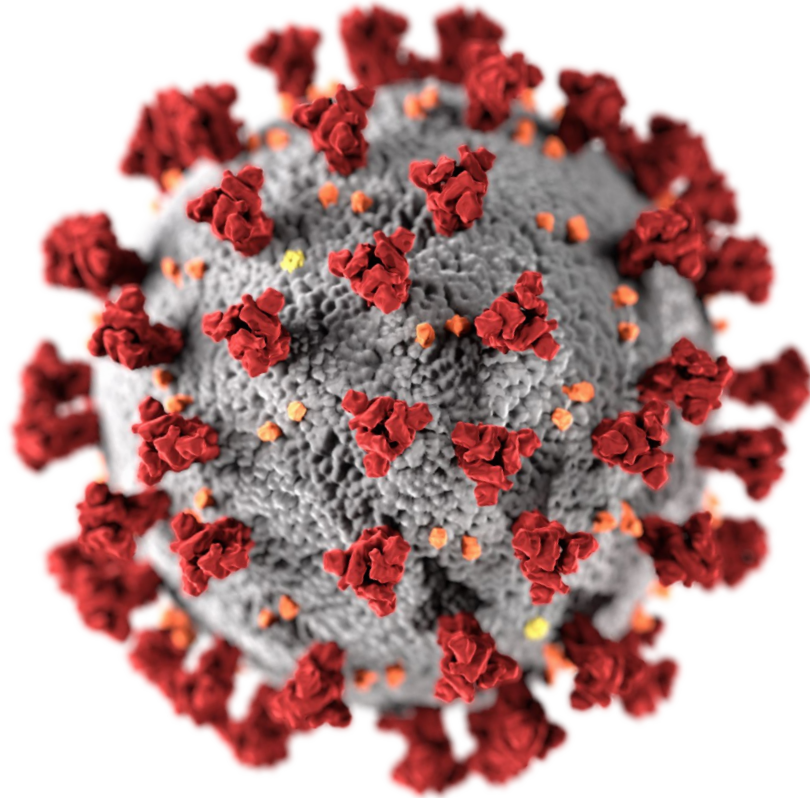


# Conflicts of interest

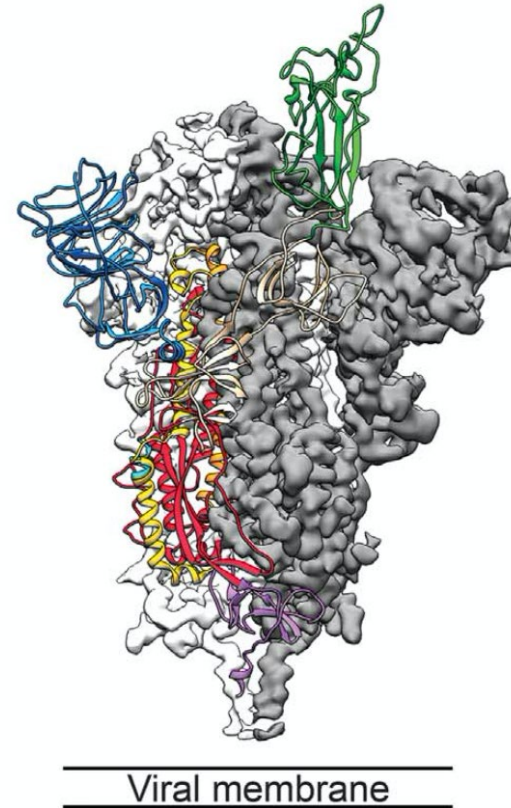
- I have no conflicts of interest to disclose

# SARS-CoV-2

## Viral Particle



## Spike Protein

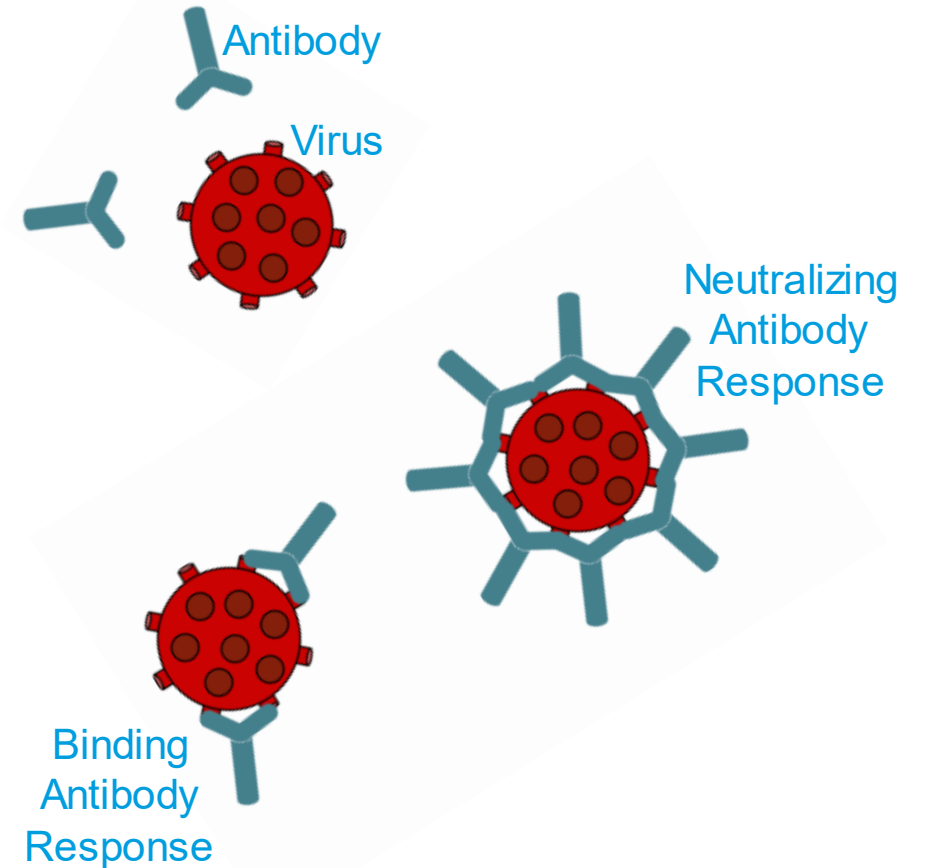


Viral membrane

Wrapp *et al.* Science 2020: Mar 13

# Types of Protective Immune Responses

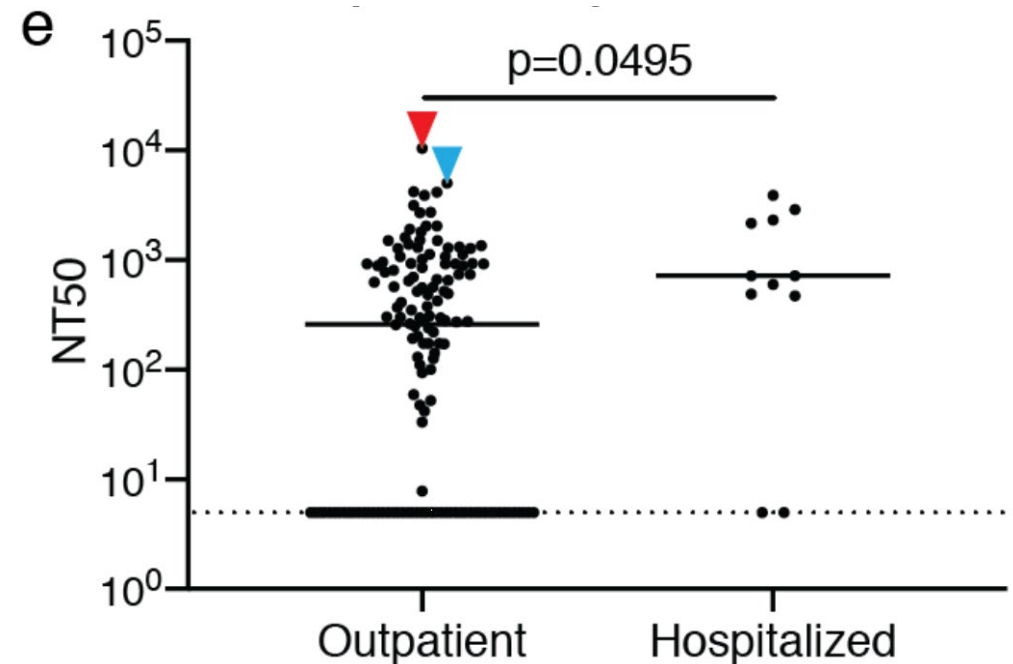
- Neutralizing antibodies
  - Antibodies bind and inactivate virus
  - Prevent viral entry into cells
  - Promote viral clearance
- Binding antibodies
- Non-neutralizing antibodies with other effector functions
- Cellular immune responses



# Natural Immune Responses to SARS-CoV-2

- 149 individuals who had recovered from COVID-19
- Wide range in neutralizing antibody titers
  - 1/3 of people had titers <50, but rare individuals with titers >5000
  - Geometric mean titer = 121
- Antibodies from different individuals were very similar, targeting same epitopes on Spike
- Even at low levels, potent neutralizing antibodies were found in all individuals
- Supports the concept that a vaccine could work in a broad spectrum of individuals

## Neutralizing Antibody Titers in Recovered Individuals

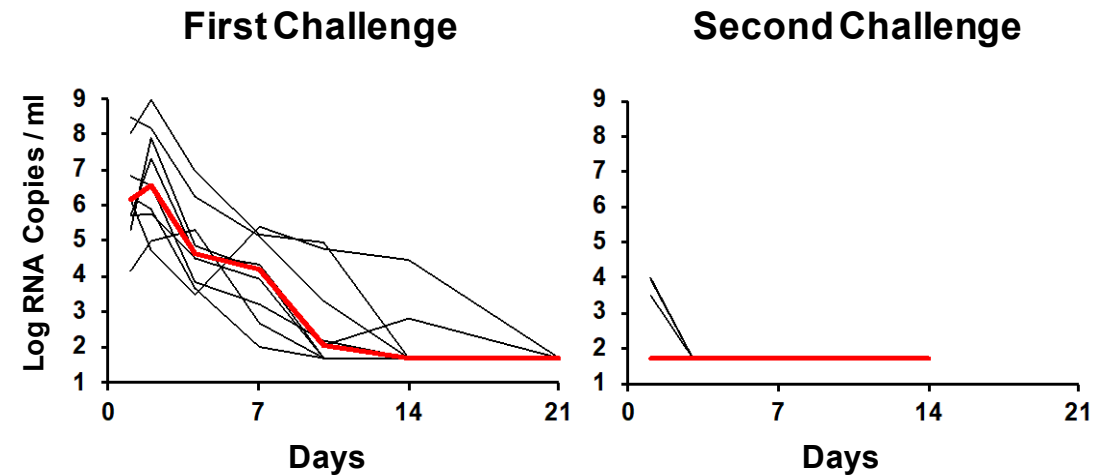


Robbiani *et al.* Nature 2020: Jun 18

# Natural Immunity in Non-Human Primates

- 9 rhesus macaques were infected with SARS-CoV-2 via upper airway
- All animals had high viral load in BAL
- Median NAb titers ~**100**
- At day 35, animals were re-challenged via upper airway again
- 3 animals had low viral load in BAL on day 1, with no recoverable live virus
- No viral RNA was detected in BAL at any other time-points
- All animals had a rapid boost in immune responses, showing robust immune memory

## Viral Load in Bronchoalveolar Lavage

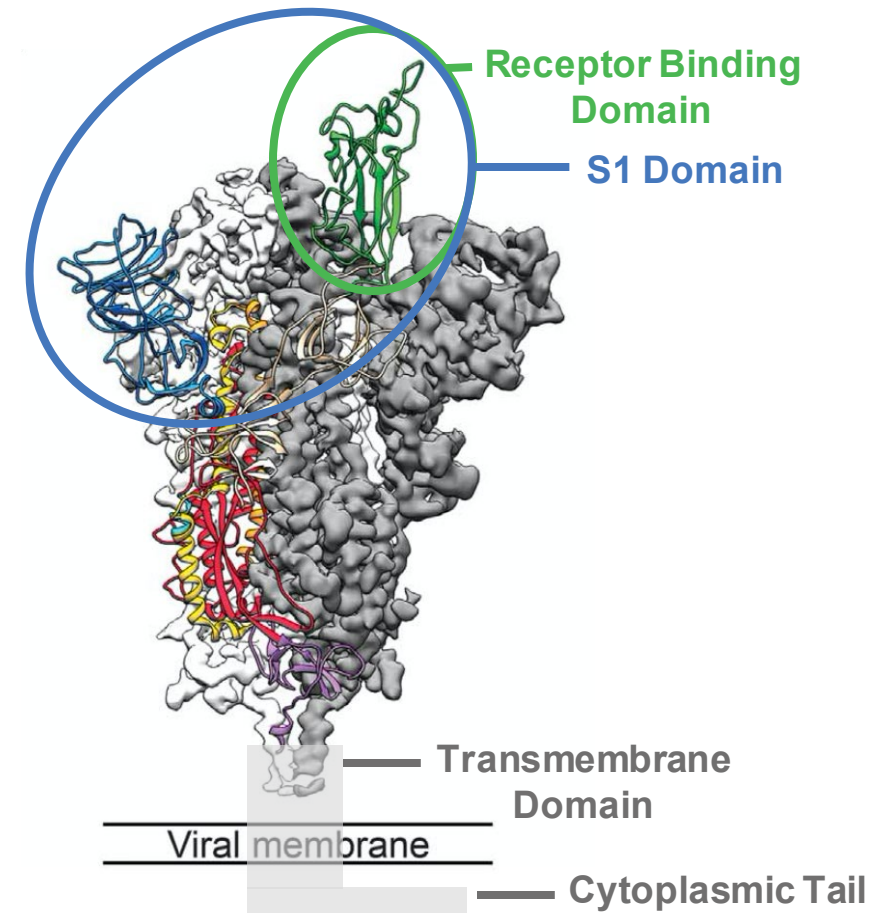


Chandrashekar *et al.* Science 2020: May 20

# Vaccine-Induced Immunity in Non-Human Primates

## DNA Vaccine Experiment: Example and Lessons

	DNA Vaccine Design
S	Full-length spike
S.dCT	Spike with cytoplasmic tail deleted
S.dTM	Spike with transmembrane domain and cytoplasmic tail deleted
S1	Spike S1 domain only
RBD	Spike receptor binding domain only
S.dTM.PP	Spike with transmembrane domain and cytoplasmic tail deleted, plus proline mutations



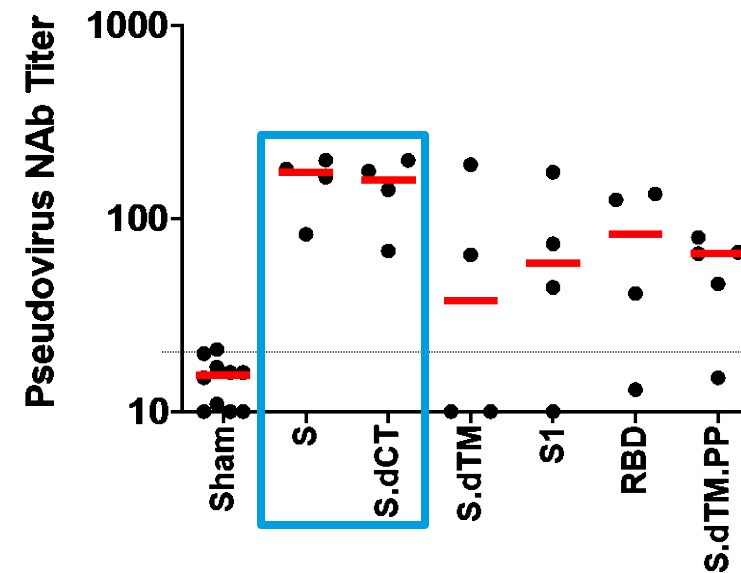
Yu *et al.* Science 2020: May 20; Wrapp *et al.* Science 2020: Mar 13

# Vaccine-Induced Immunity in Non-Human Primates

## DNA Vaccine Experiment: Example and Lessons

- Two of the DNA vaccines elicited neutralizing antibody titers >100
  - Full-length spike protein
  - Spike protein with cytoplasmic tail deleted
- Four of the DNA vaccines were poorly immunogenic
- Spike-specific and RBD-specific antibodies were generated

### Neutralizing Antibody Responses in Monkeys



Yu *et al.* Science 2020: May 20

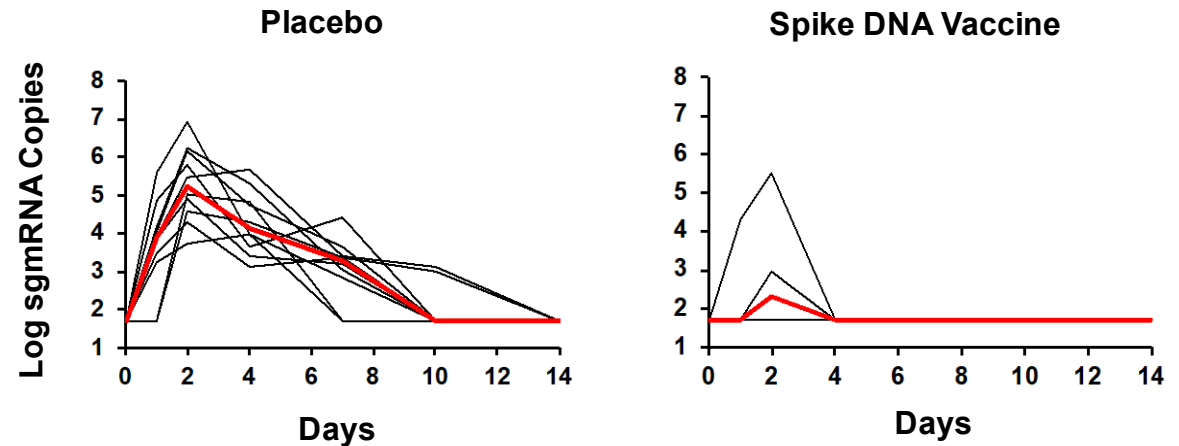


# Vaccine-Induced Immunity in Non-Human Primates

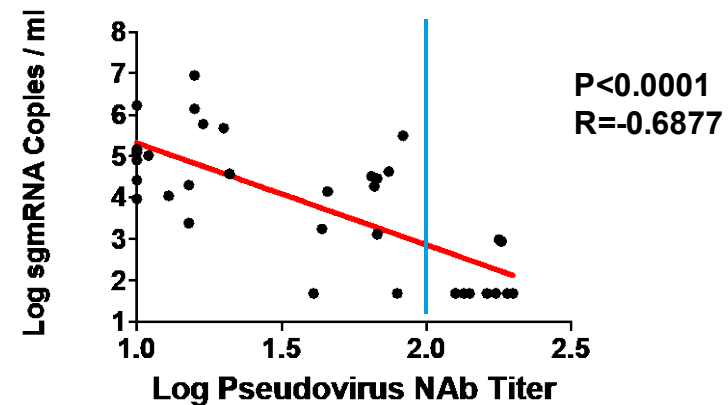
## DNA Vaccine Experiment: Example and Lessons

- At week 6, all animals were challenged via upper airway
- S-vaccinated monkeys had 3 log decrease in RNA in BAL
- 8 of 25 animals had no detectable sub-genomic RNA
- Vaccine-elicited serum NAb titers inversely correlated with protection

### Viral Load in Bronchoalveolar Lavage in Monkeys



### NAbs vs. Viral Load



Yu *et al.* Science 2020: May 20

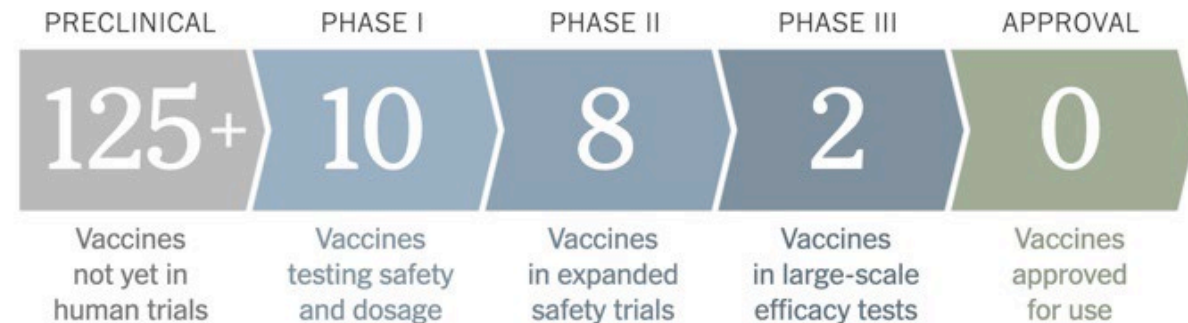
# Types of COVID-19 Vaccines

## Same Spike Protein, Different Mechanisms of Delivery

- Inactivated SARS-CoV-2
- Soluble Spike protein
- Genetic code for Spike introduced into host cells
  - DNA
  - mRNA
  - Viral vector

## Coronavirus Vaccine Tracker

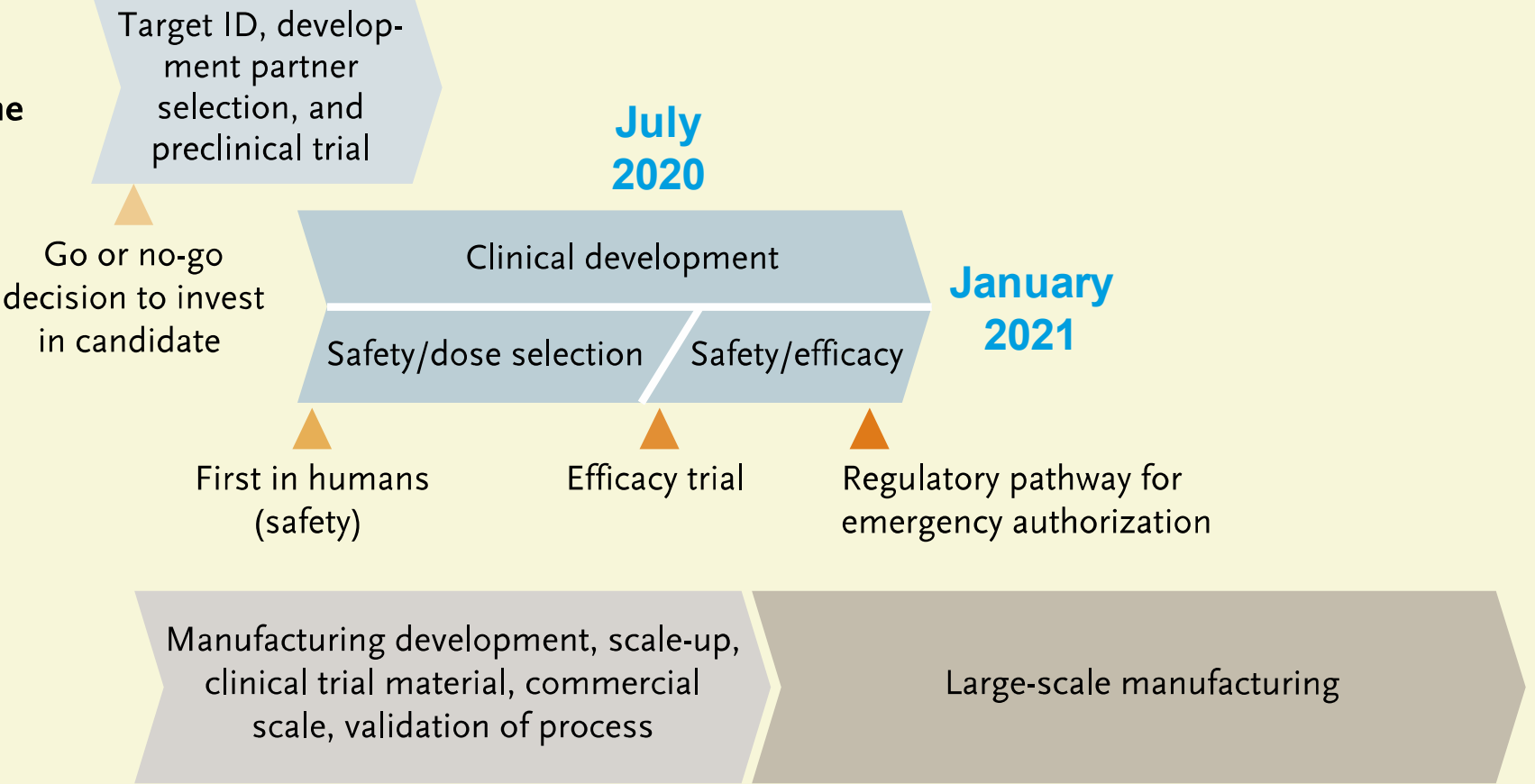
By Jonathan Corum, Denise Grady and Carl Zimmer Updated June 19, 2020



The New York Times

# Outbreak Paradigm for Vaccine Development

**Outbreak Paradigm —  
Overlapping Phases  
Shorten Development Time**

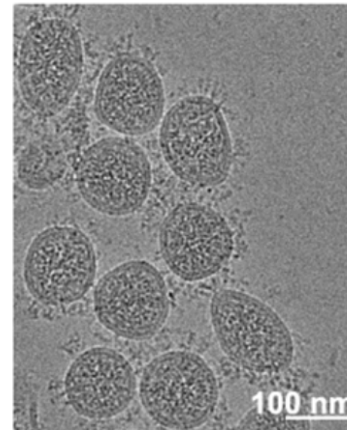


Lurie *et al.* NEJM 2020

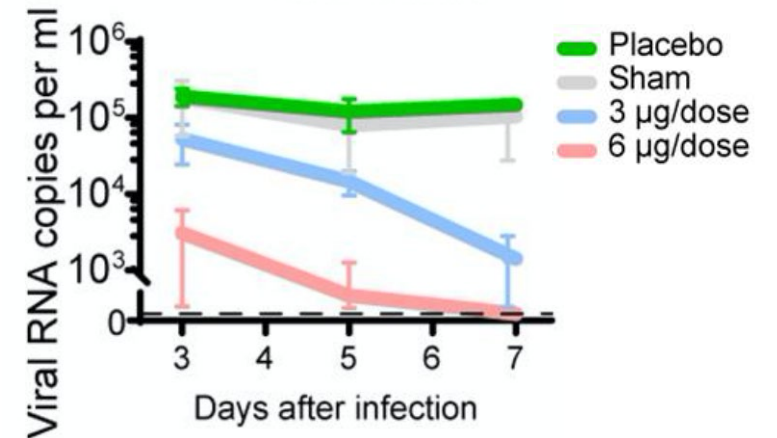
# sinovac Inactivated Virus Vaccine

- Purified inactivated SARS-CoV-2 virus
- Non-human primate study
  - NAb titers ~100
  - Significant reduction in viral RNA and lung pathology
  - No antibody-dependent enhancement
- Phase 1/2 trial launched April 16 (N=744)
  - Induced NAbs in “>90%” – **per media**
  - No safety issues – **per media**
- Phase 3 planning underway

Inactivated  
Virus



Throat Viral Load  
in Monkeys



Gao *et al.* Science 2020: May 6

- Open-label, dose escalation clinical trial of 108 participants in Wuhan, China
  - Replication-defective Ad5 expressing spike
  - Single injection, follow up to day 28
- Vaccine elicited low-moderate immune responses
  - High dose significantly higher titers, but **not well-tolerated**
  - Low and middle dose **NAb titer ~15**
  - Immune responses hampered by pre-existing Ad5 immunity
- Phase 2 trials in progress, but high dose dropped due to poor tolerability

## Neutralizing Antibody Titers in Humans

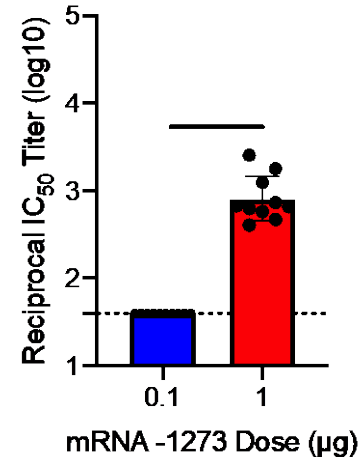
	Day 28		
	Low dose group (n=36)	Middle dose group (n=36)	High dose group (n=36)
GMT	14.5 (9.6–21.8)	16.2 (10.4–25.2)	34.0 (22.6–50.1)
≥4-fold increase	18 (50%)	18 (50%)	27 (75%)

Zhu *et al.* Lancet 2020: May 22

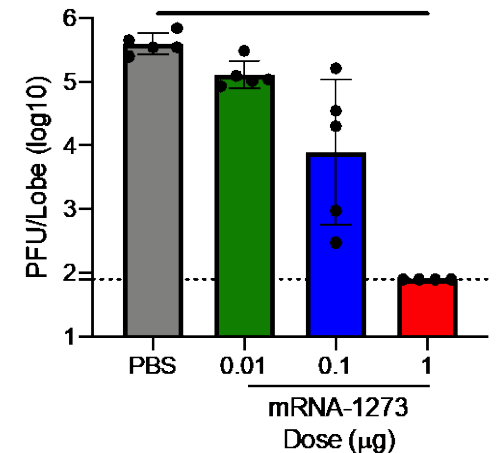
# moderna mRNA Vaccine

- mRNA-1273
  - Lipid nanoparticle encapsulating mRNA
  - Encodes for full-length spike protein
- Mouse study, pre-print only
  - Viral loads in lung reduced (nasal, less so)
  - No disease enhancement
- Phase 1 trial, (N=155), dose-ranging
  - Prelim report (N=8), NAb titers ‘similar to convalescent humans’ – **per media**
  - 250 mcg was not well tolerated – **per media**
- Phase 2 trial, launched May 29 (N=600)

## Neutralizing Antibody Titers in Mice



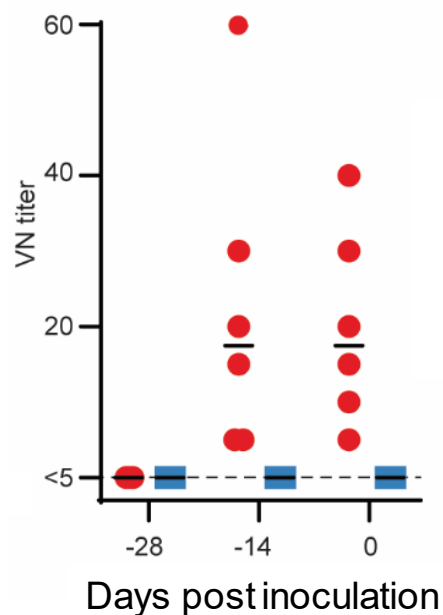
## Lung Viral Load in after Challenge in Mice



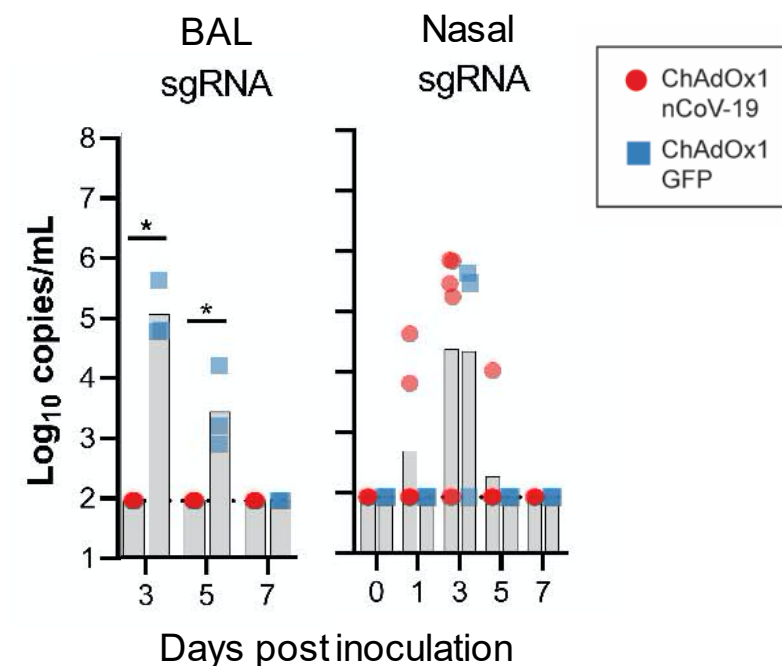
Preprint – Corbett *et al.* bioRxiv 2020: June 11

- ChAdOx1 nCoV-19
  - Chimpanzee adeno vector
  - Encodes for full-length spike protein
- Non-human primate study (N=6)
  - Vaccine prevented lung damage
  - Viral loads in BAL reduced
  - No reduction in nasal virus
  - No disease enhancement
- Phase 1/2 launched April 23 (N=1090)
  - 1 vs. 2 doses
- Phase 2/3 (N=10,000), pending

Neutralizing Antibody Titers in Monkeys



Viral Load in Monkeys



Preprint – Doremalen *et al.* bioRxiv 2020: May 13

# Summary (1)

- COVID-19 leads to neutralizing antibody responses in humans
  - There is a wide range in titers (GMT ~100), likely related to severity of illness
  - NAbs target Spike protein
  - It is unknown if NAbs are protective in humans
  - Convalescent NAbs *are* protective in monkeys
- Nearly all COVID-19 vaccines use Spike protein
  - Only the delivery mechanism is different



## Summary (2)

- Preclinical studies suggest that a successful COVID-19 vaccine is possible
  - Vaccinated animals have reduced symptoms, lung pathology, and viral RNA
  - Sterilizing immunity is *not* seen; rather it is immune-mediated viral clearance
- There is a new ‘outbreak paradigm’ for vaccines
  - Multiple candidates tested at once
  - Global scale manufacturing is occurring simultaneously with trials
- A successful COVID-19 vaccine will need to be **safe, effective, and deployable**

# Thank You and Questions

