

# **THE CHALLENGES AND PROMISE OF mRNA IN GLOBAL PUBLIC HEALTH AND MEDICINE**

**Scientific Colloquium on Enhancing mRNA Vaccine Production  
Cape Town, South Africa  
8 July 2022**

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**Professor of Medicine and Microbiology,**  
**Biochemistry, Immunology**  
**Morehouse School of Medicine**  
**Atlanta, GA**

# Disclosures

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- Inventor on vaccine patents for:
  - Coronaviruses
  - Respiratory syncytial virus
  - Influenza virus
  - Nipah and other paramyxoviruses
  - Zika
- Inventor on monoclonal antibody patents for:
  - Ebola
  - SARS-CoV-2 and other coronaviruses

# NIAID Vaccine Research Center

**Commencement Address by President Clinton at Morgan State University, Baltimore, May 18, 1997**

"If America commits to find an AIDS vaccine and we enlist others in our cause, we will do it... **Today I'm pleased to announce the National Institutes of Health will establish a new AIDS vaccine research center dedicated to this crusade.**"



Basic Research



Process Development



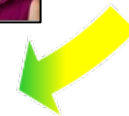
cGMP Manufacturing



GLP Analysis



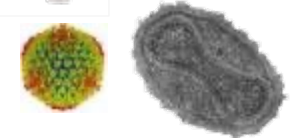
Clinical Trials



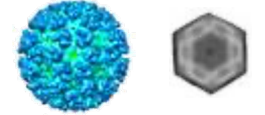
Nucleic acid



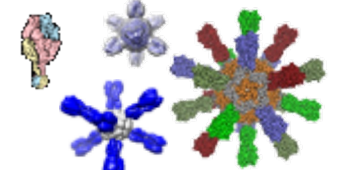
Vectors



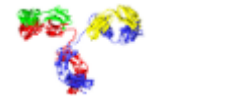
VLPs



Proteins and nanoparticles

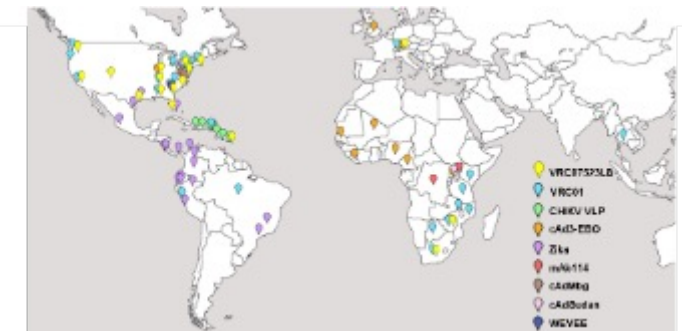


Monoclonal antibodies



- AIDS/HIV
- Influenza
- Ebola/Marburg
- RSV
- Malaria
- Tuberculosis
- EID

- West Nile virus, Zika
- Chikungunya
- W/E/V equine encephalitis viruses
- MERS-CoV, SARS, and other CoV
- Nipah and other paramyxoviruses
- EV-D68 and other picornaviruses
- Smallpox





# Public health burden of re-emerging & emerging viruses

## Vaccine Challenges

- Vaccines for unmet needs
- Emerging viruses
- Improved licensed vaccines



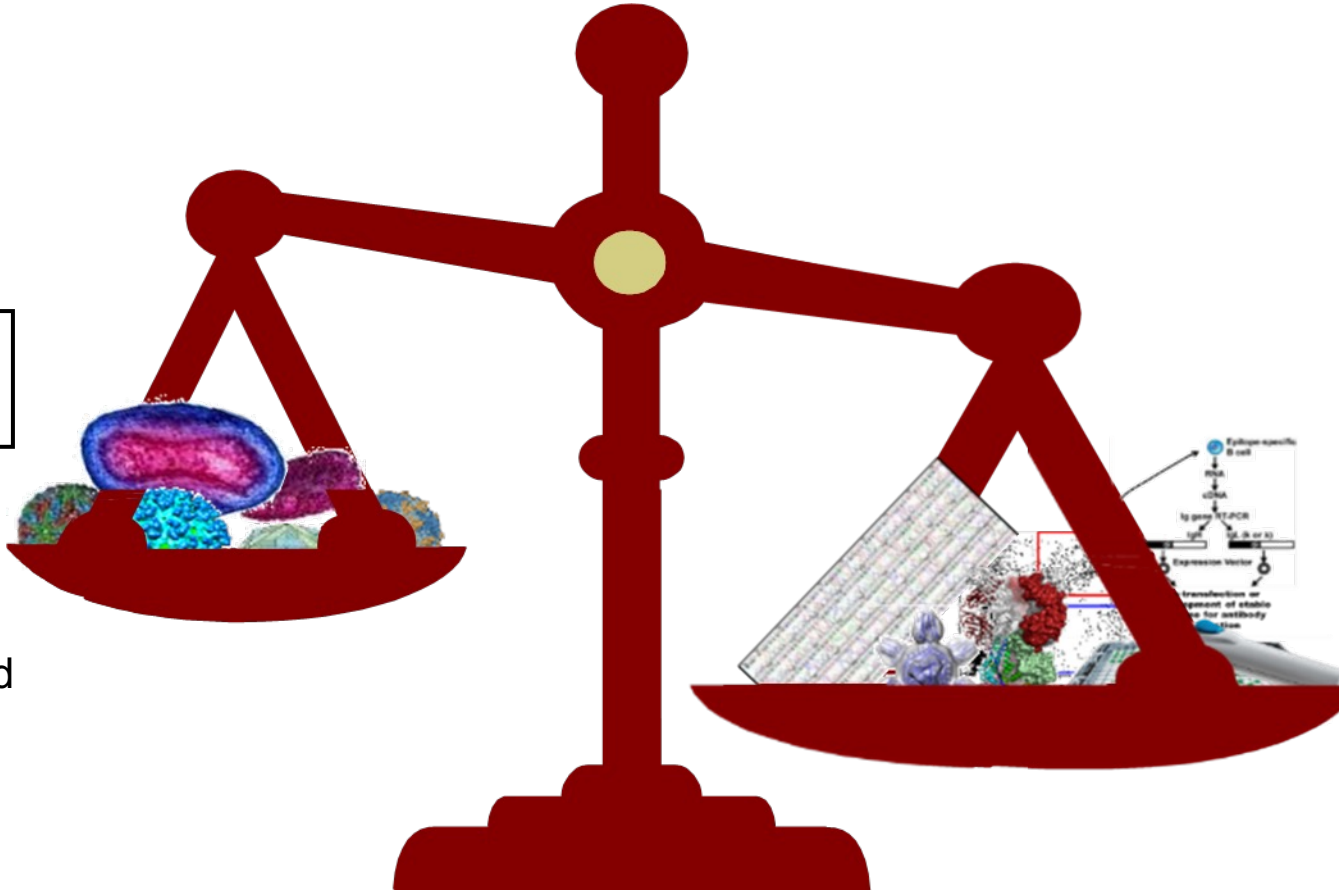
## Traditional Approaches

- Licensed vaccines/antibiotics
- Passive surveillance
- Contact tracing
- Quarantine

# New Technologies Facilitate an Engineering Approach

## Vaccine Challenges

- Vaccines for unmet needs
- Emerging viruses
- Improved licensed vaccines

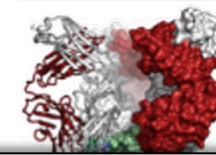


## New Technologies

- Structural biology
- Protein engineering
- Single cell sorting and analysis
- High throughput sequencing
- Rapid isolation of human mAbs
- Antibody lineage analysis
- Rapid diagnostic tools
- Systems biology
- Gene-based delivery
- Rapid gene synthesis
- Platform manufacturing

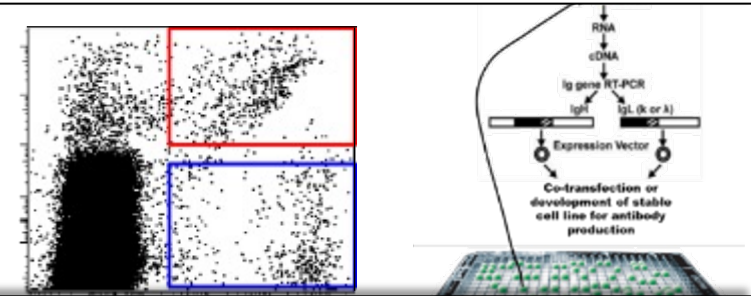
# New Technologies are Transforming Vaccinology

- Structure-based vaccine design
  - Single-cell sorting, sequencing, and bioinformatics
    - Rapid isolation of human mAbs
    - Definition of antibody lineages
    - Analysis of immune responses
  - Protein engineering of self-assembling nanoparticles
- Rapid DNA synthesis
  - Recombinant DNA and genetic engineering technology
    - Rapid cell line development
    - Animal model development
  - Nucleic acid and vector-based delivery of vaccine antigen

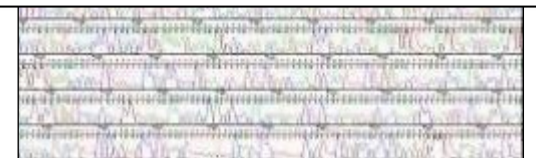


Structural analysis of antigenic sites on viral surface glycoproteins

## Precision



## Speed

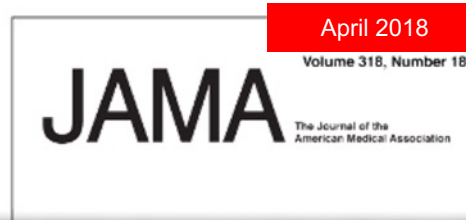


Sequencing B cells to define clonal lineages;  
TCR & BCR-specific transcriptome

# ... and Provide New Options for Pandemic Preparedness and Response



## Preparedness

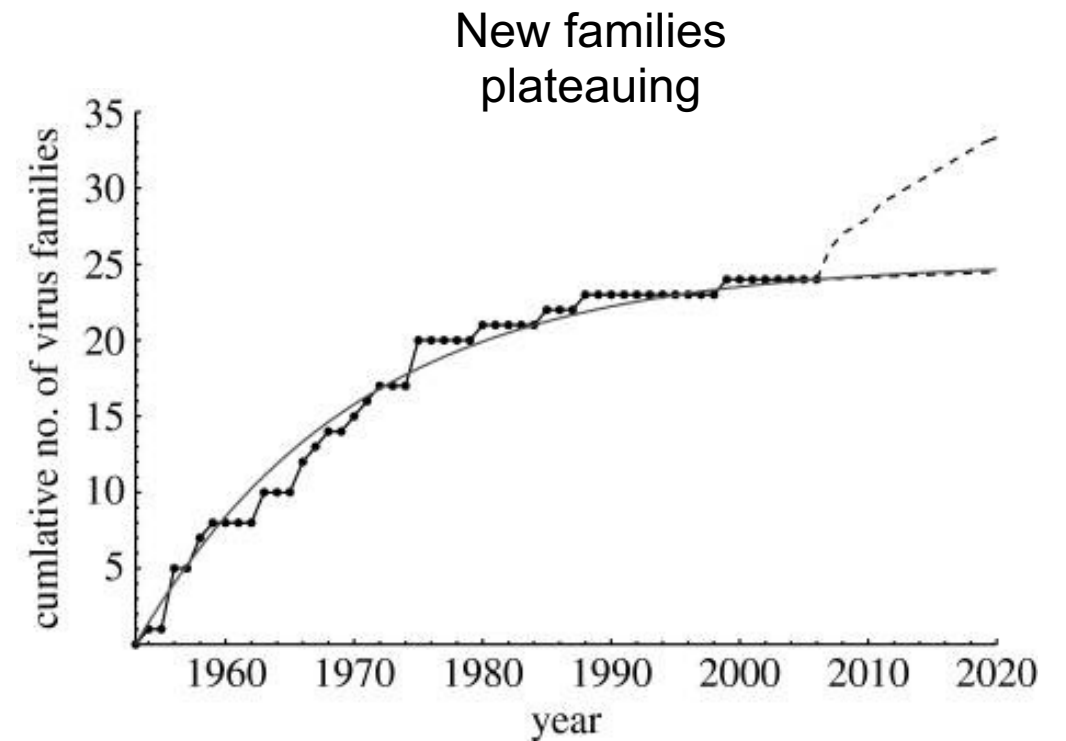
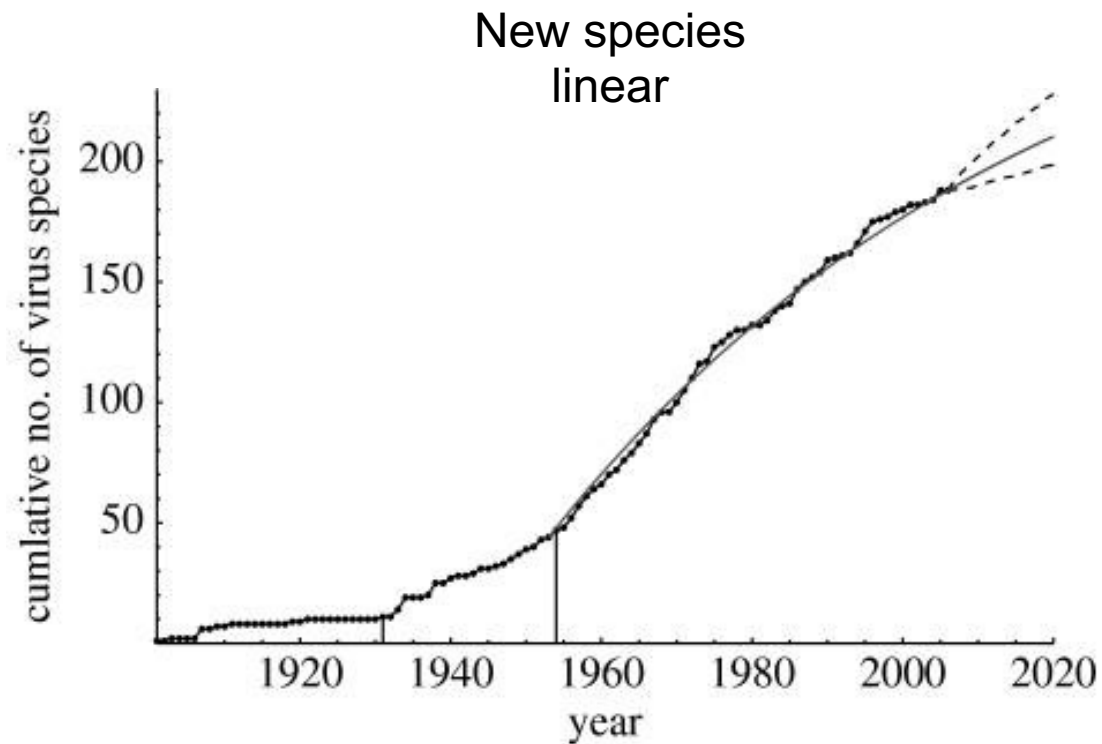


**Novel Vaccine Technologies Essential  
Components of an Adequate Response  
to Emerging Viral Diseases**

BS Graham, JR Mascola, AS Fauci

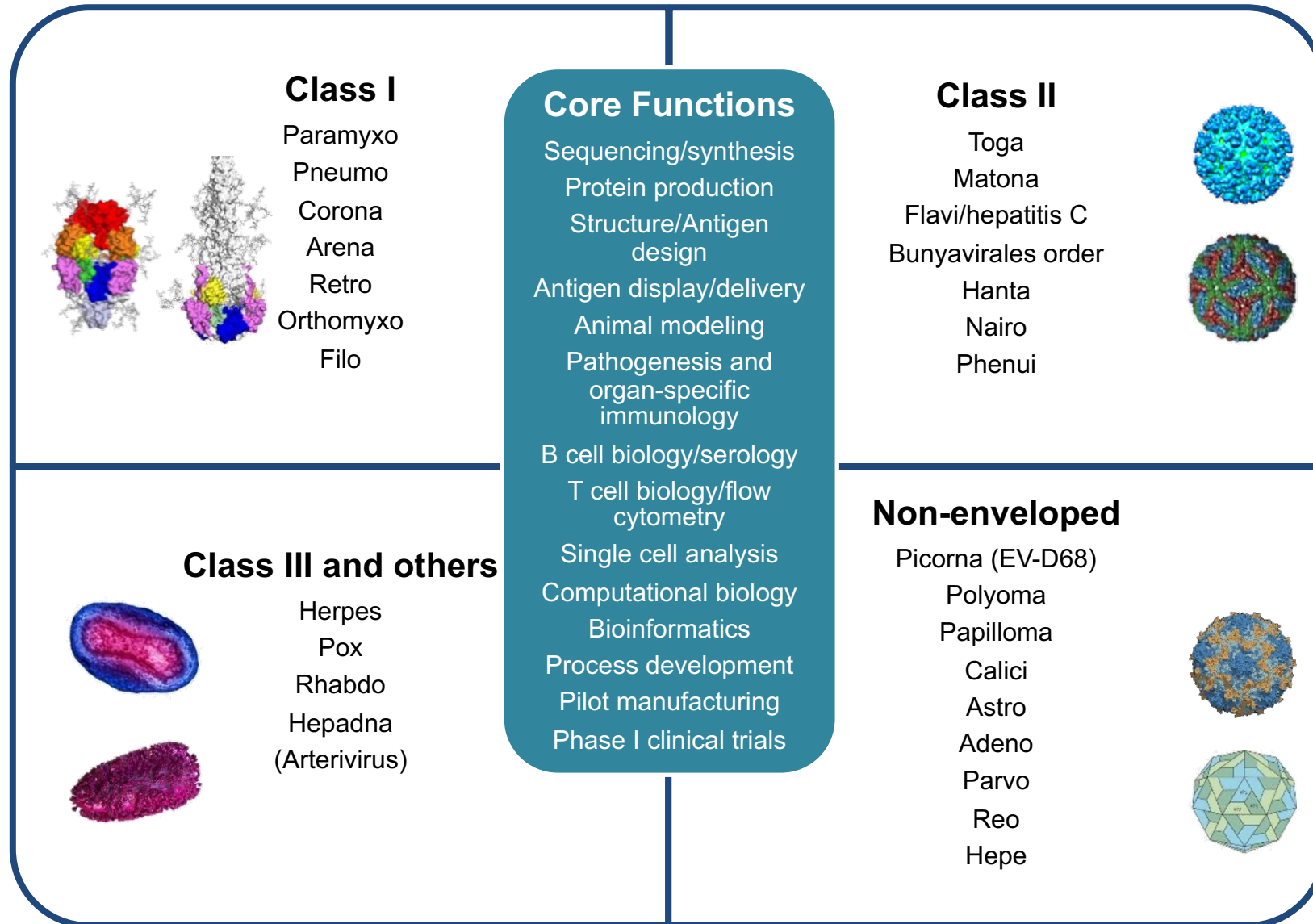
## Response

# New Human Viral Pathogens in the 20<sup>th</sup> Century





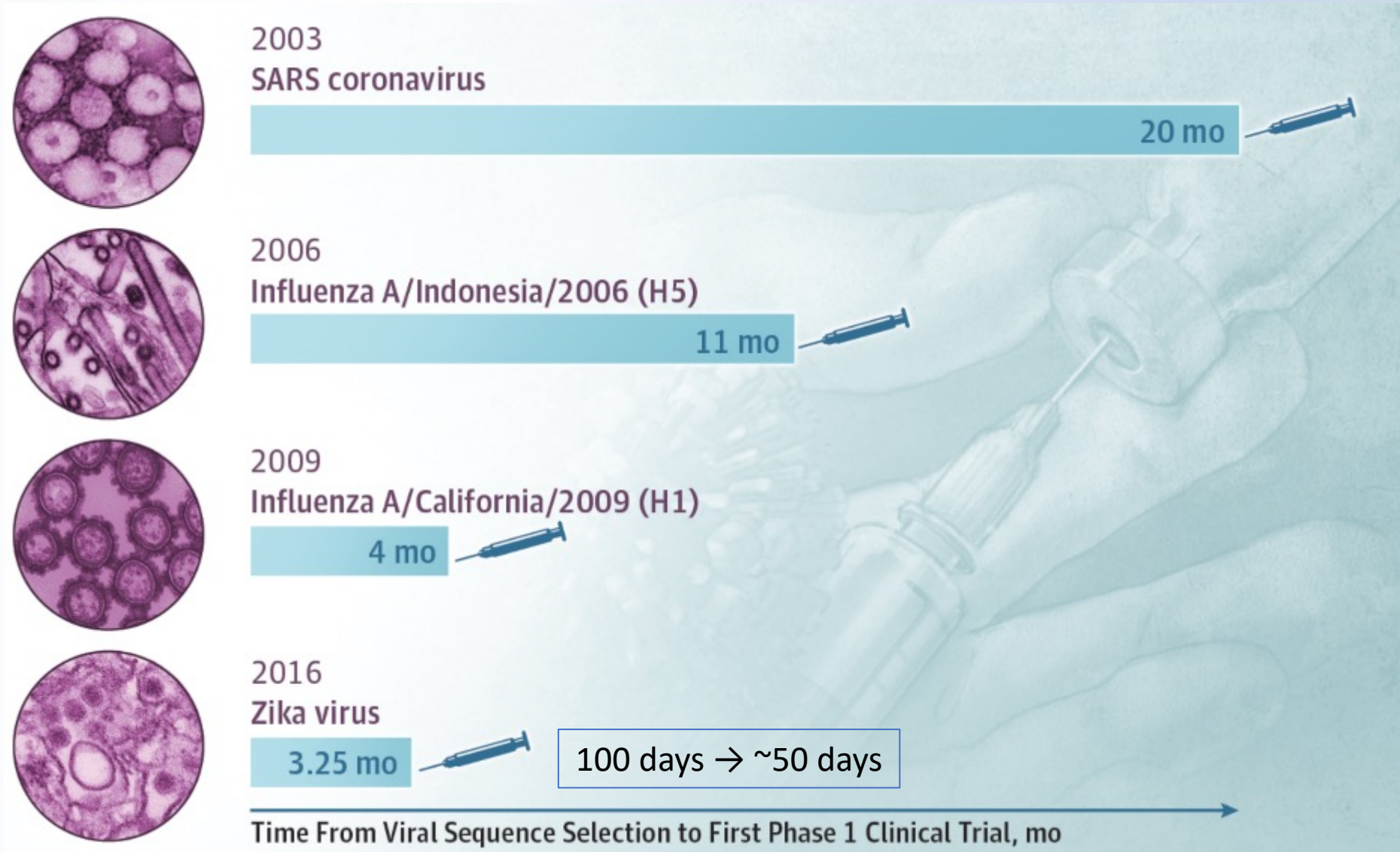
# Prototype Pathogen Approach for Pandemic Preparedness



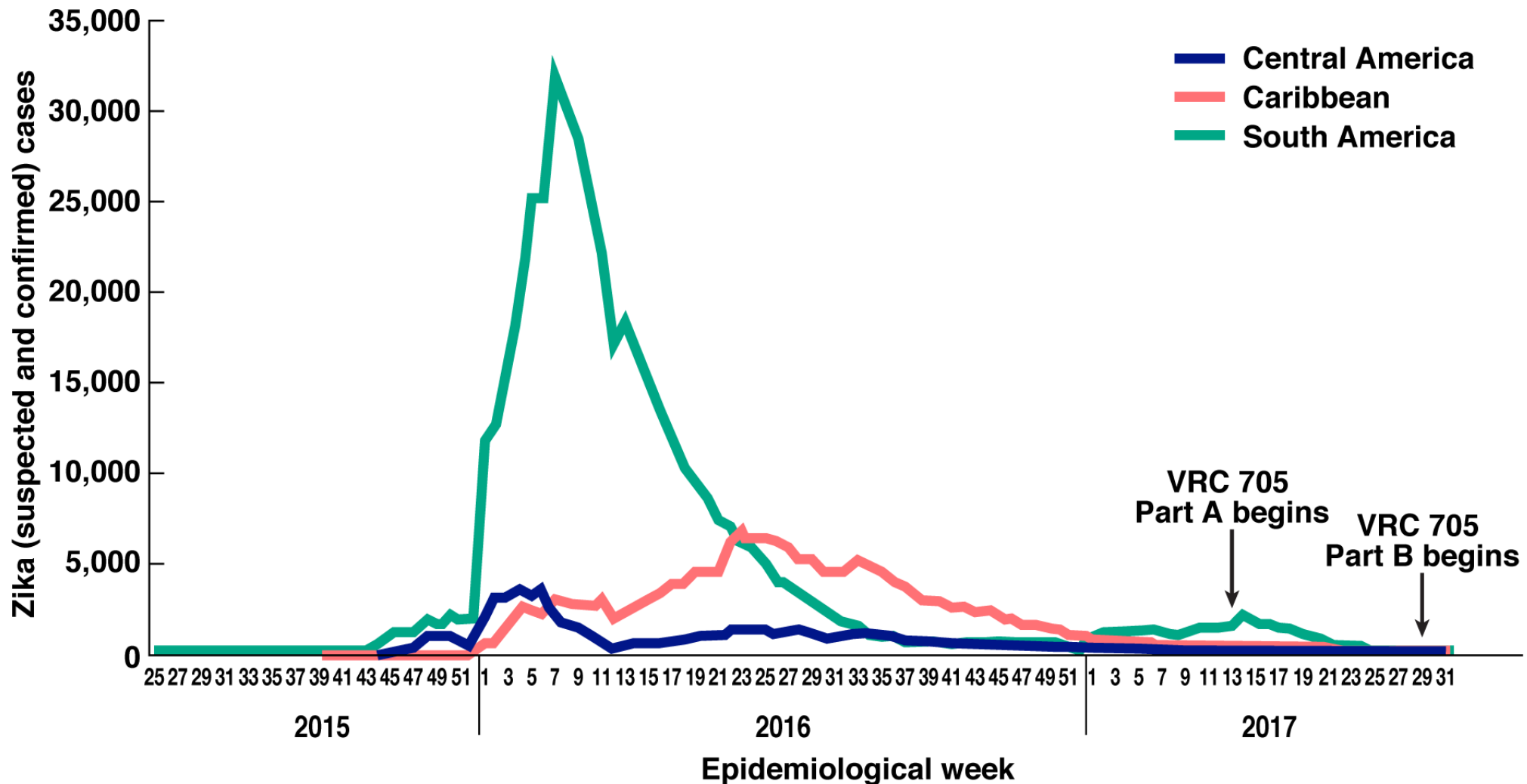
- **~120 viruses from 26 families known to infect humans with potential for increased human-to-human transmission and virulence**
- **Develop vaccines for ~30 prototype viruses through phase 1**
- **Develop vaccine candidates (& reagents) for other ~90 through animal testing**

Graham & Sullivan.  
Nature Immunology 2018

# Platform Technologies Shorten Manufacturing Timelines

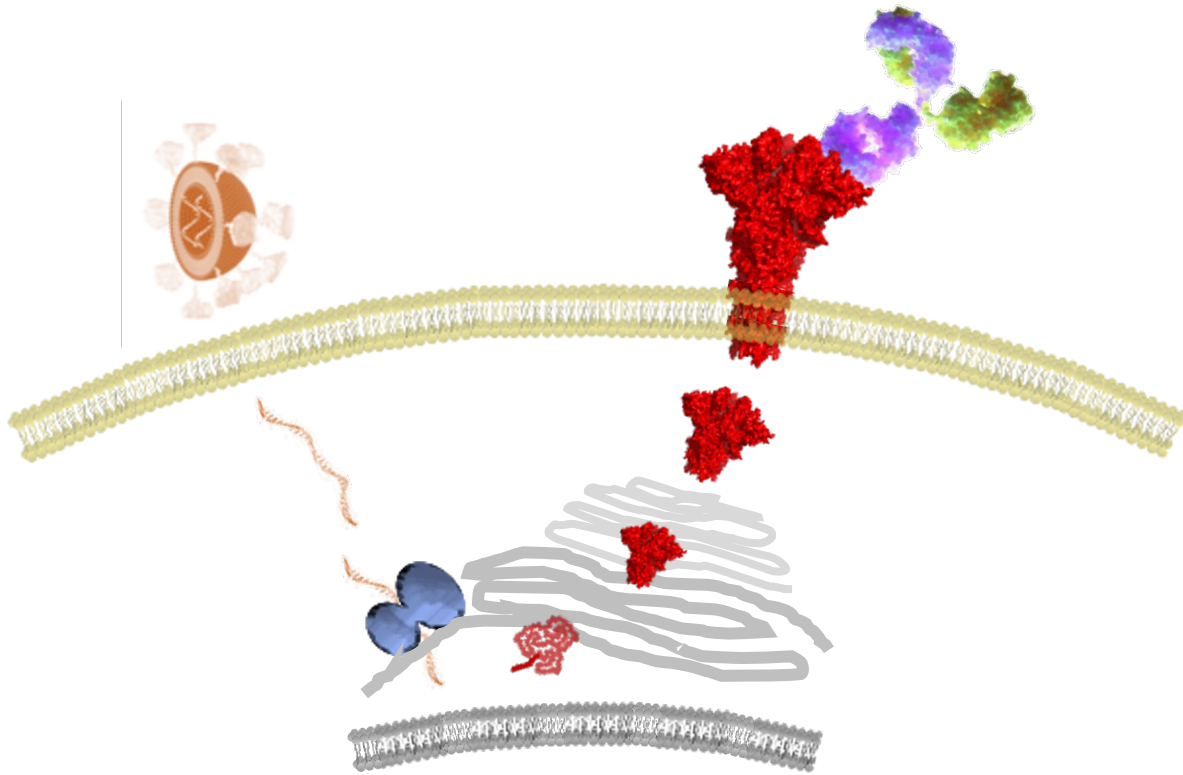


# Suspected and Confirmed Zika Cases in the Americas, 2015-2017



# mRNA immunization strategy

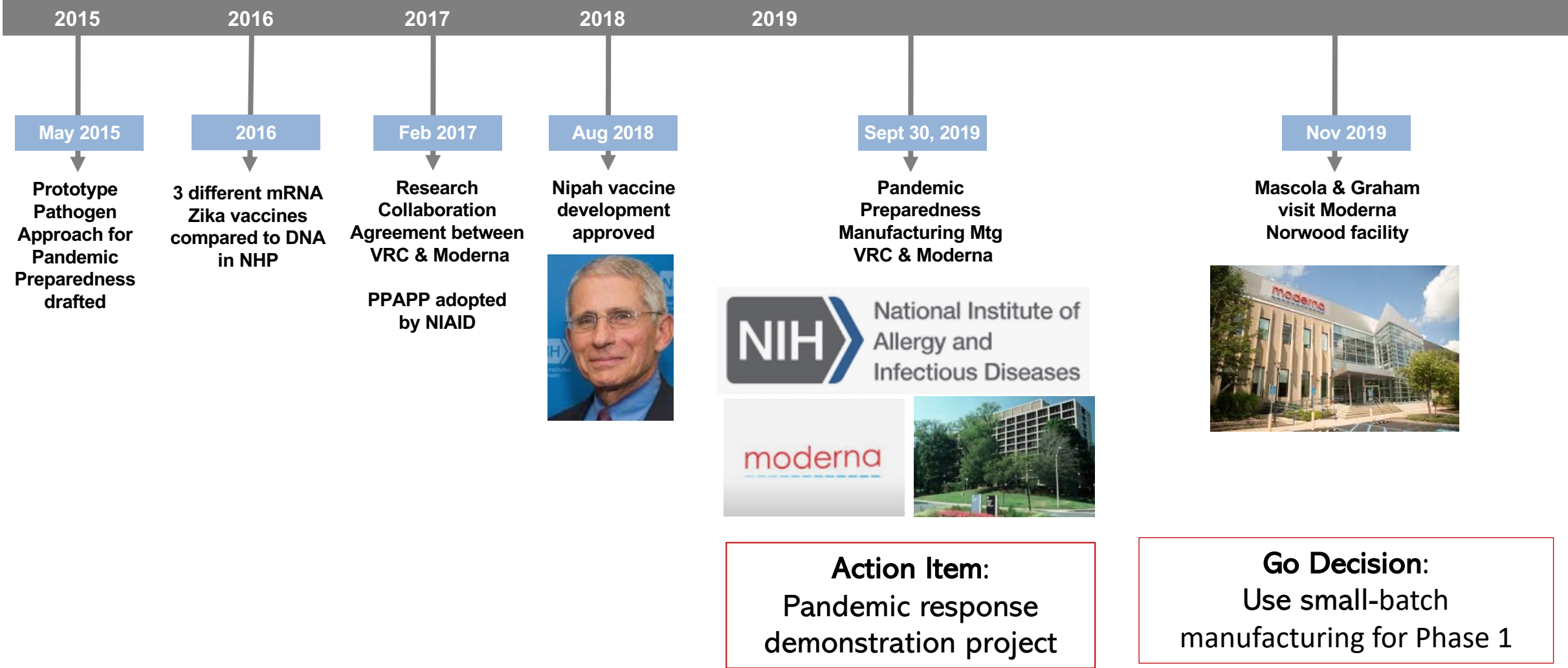
Protein expression affected by mRNA chemistry and manufacturing process



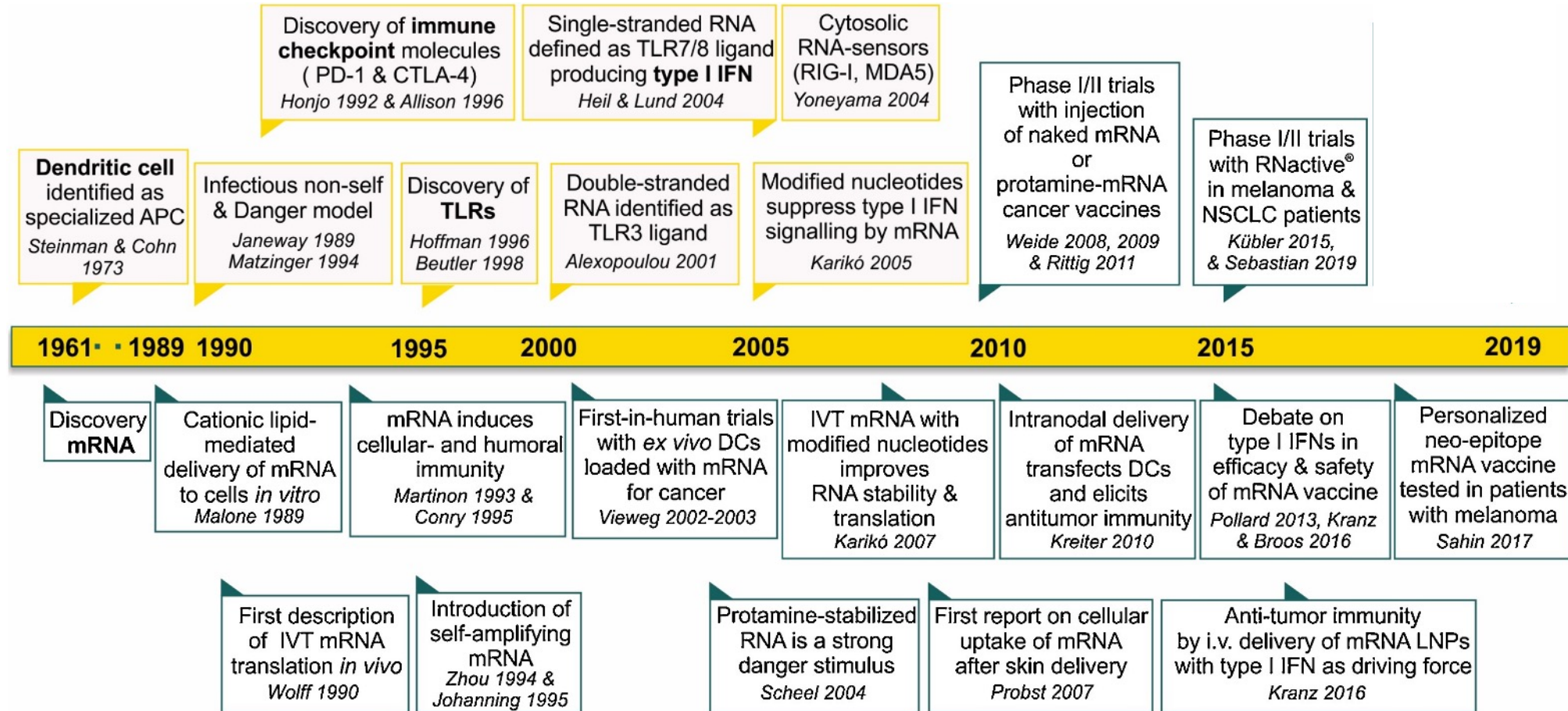
- Authentic antigen presentation
- Induction of both antibody and CD8 T cells
- Th1-biased CD4 T cells
- Vaccine components rapidly degraded
- Only requires entry into cytoplasm
- No anti-vector immunity
- Chemical synthesis, no bioreactor requirement
- Rapid platform manufacturing



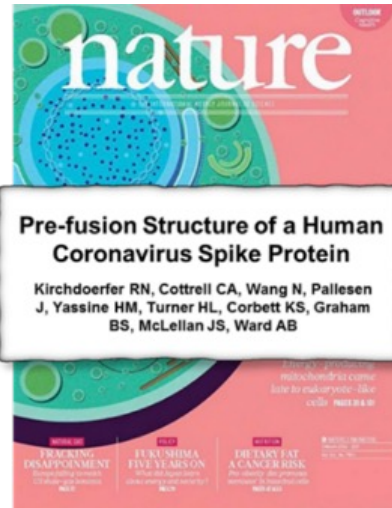
# Pandemic Preparedness Demonstration Project



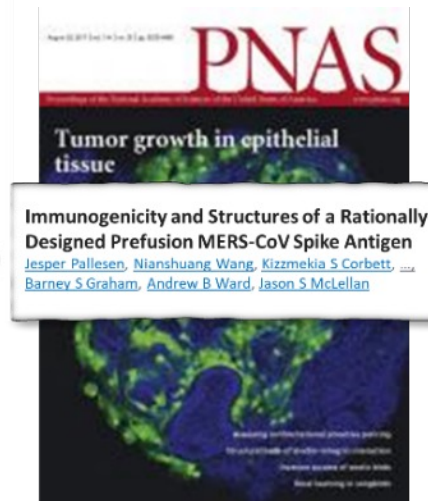
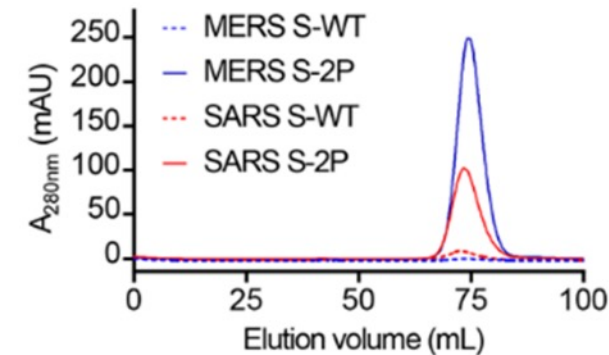
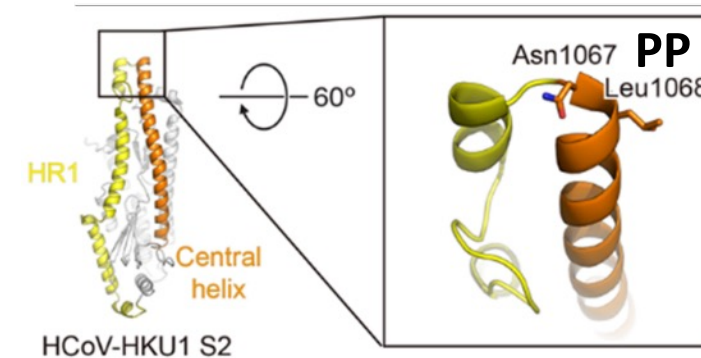
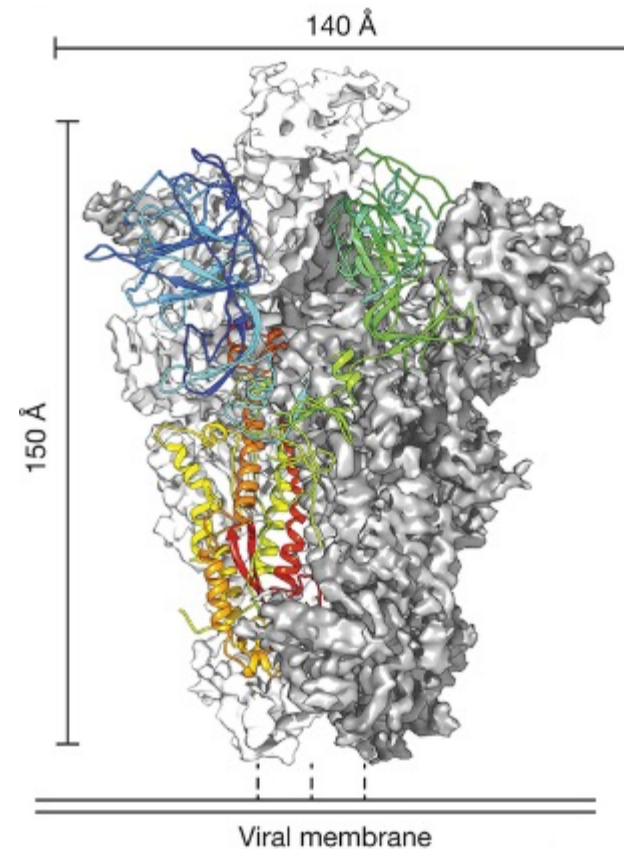
# History of mRNA Therapeutics (Pre-COVID)



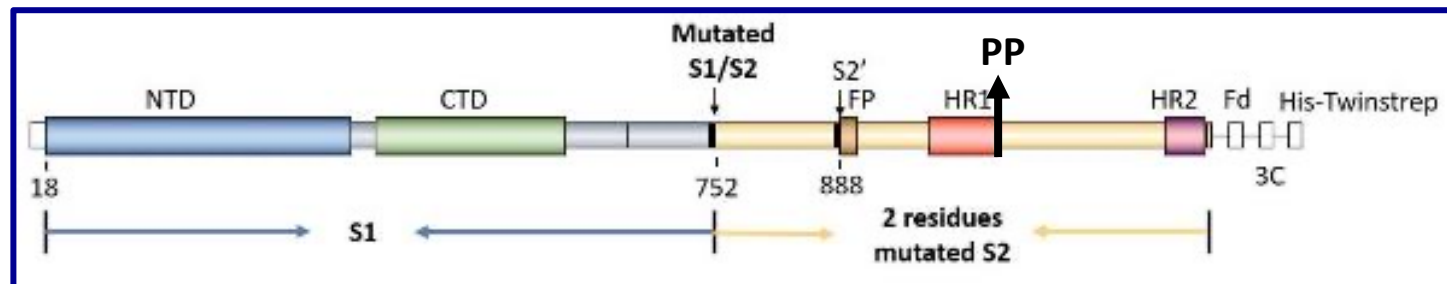
# Structure-guided Stabilization of HKU1 CoV Spike



2016



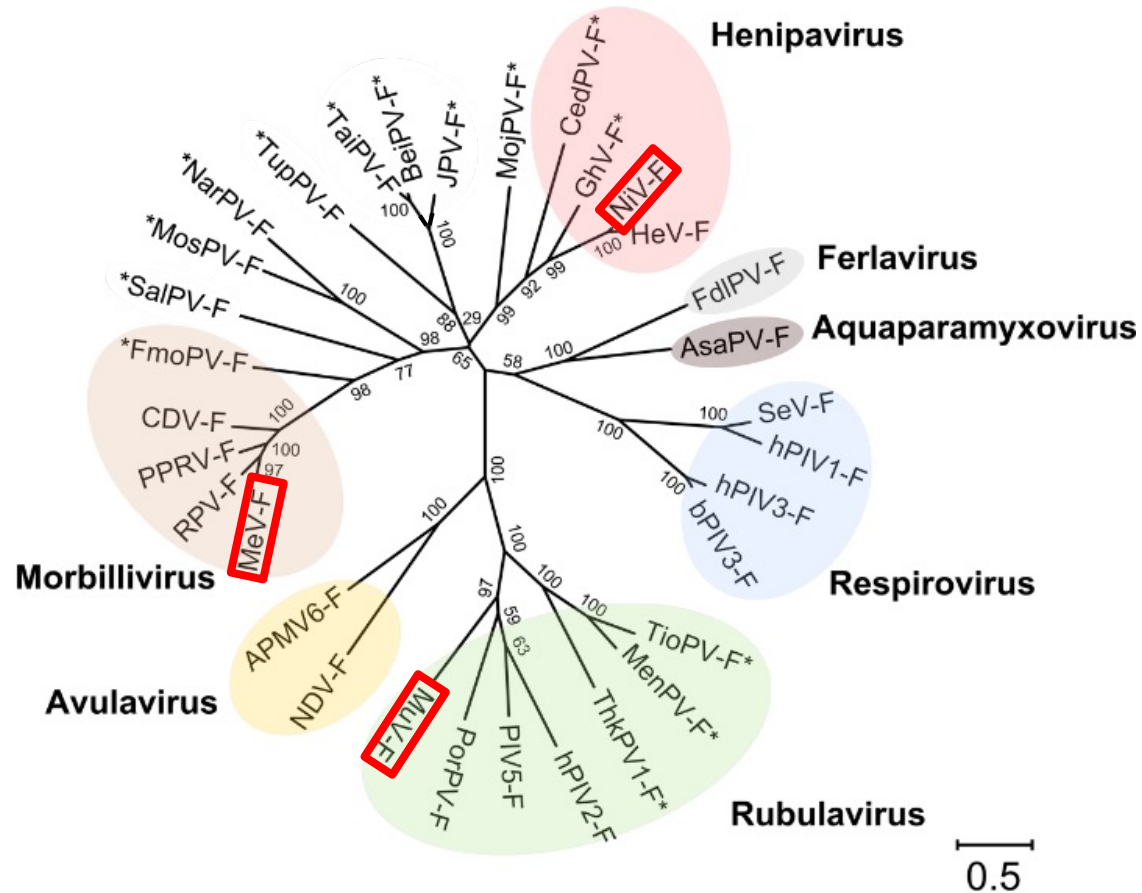
2017



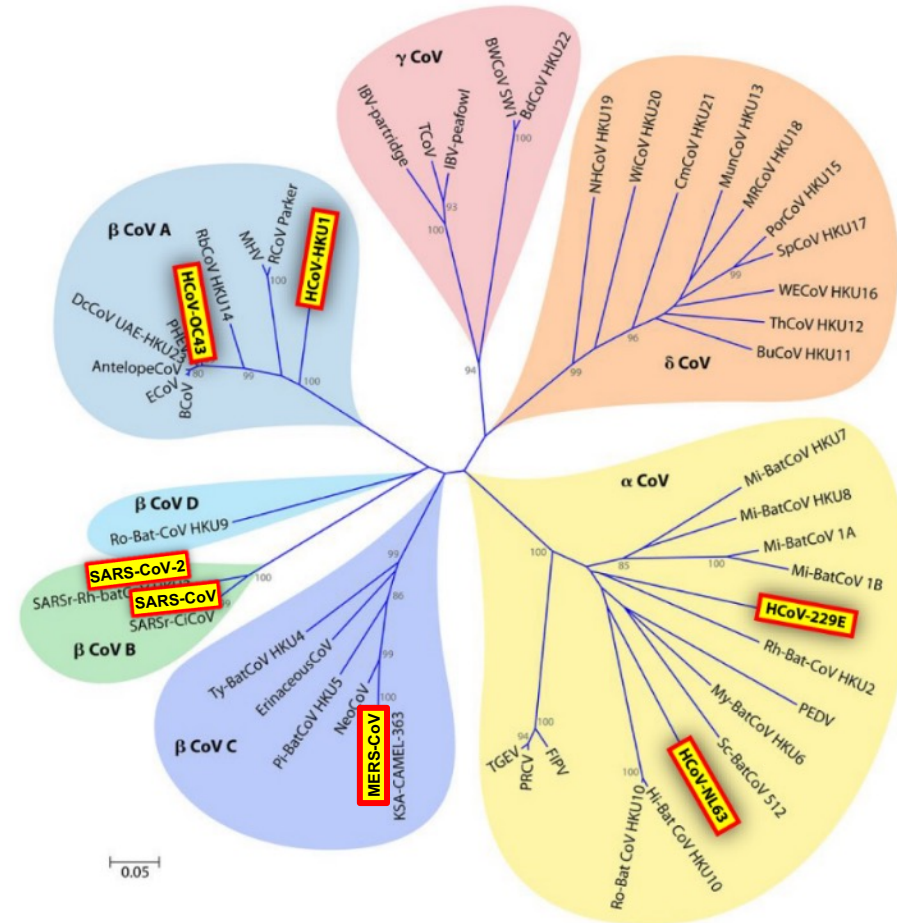


# Two Viral Families with Extensive Zoonotic Reservoirs

## Paramyxoviridae



## Coronaviridae





# COVID-19 mRNA VACCINE DEVELOPMENT

2013-2019

2020

## SARS-CoV-2 Outbreak

Extensive work on MERS, other CoV, and other Fusion proteins

Dec 31, 2019

1<sup>st</sup> report of respiratory virus outbreak in Wuhan, China

Jan 6, 2020

Wuhan outbreak may be CoV

Jan 10, 2020

2019-nCoV sequences published

Jan 31, 2020

VRC makes nCoV spike protein

Feb 1, 2020

First nCoV spike ELISA for cross-reactivity

Feb 3, 2020

UT-Austin solves spike structure

Feb 18, 2020

Immunogenicity confirmed in mice

Mar 16, 2020

Phase 1 Clinical vaccine trial starts

Jul 27, 2020

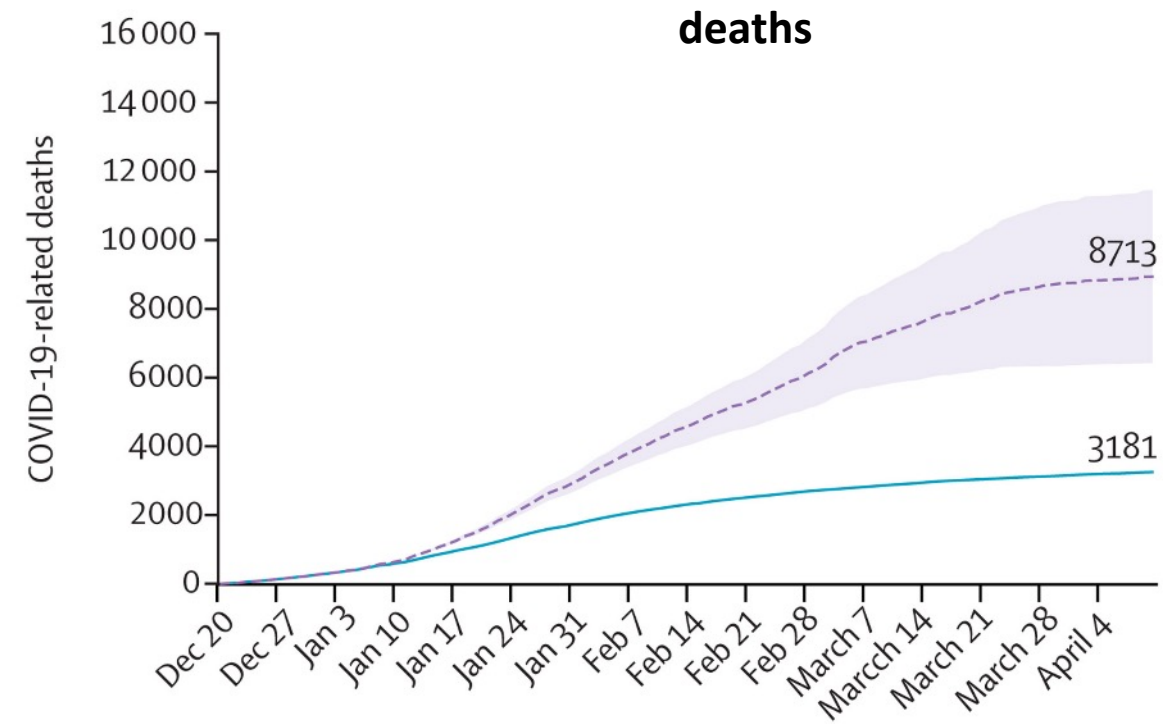
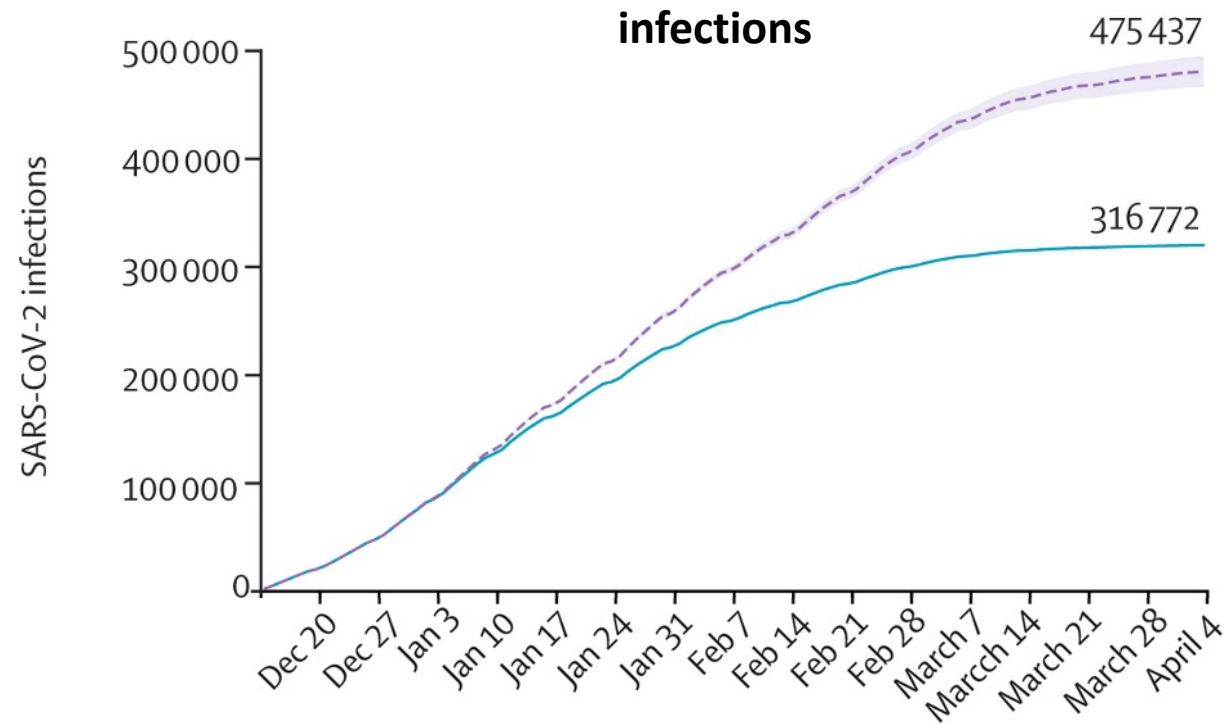
Phase 3 Clinical vaccine trial starts

6.5 months to phase 3

10 months to phase 3 results

11 months to EUA

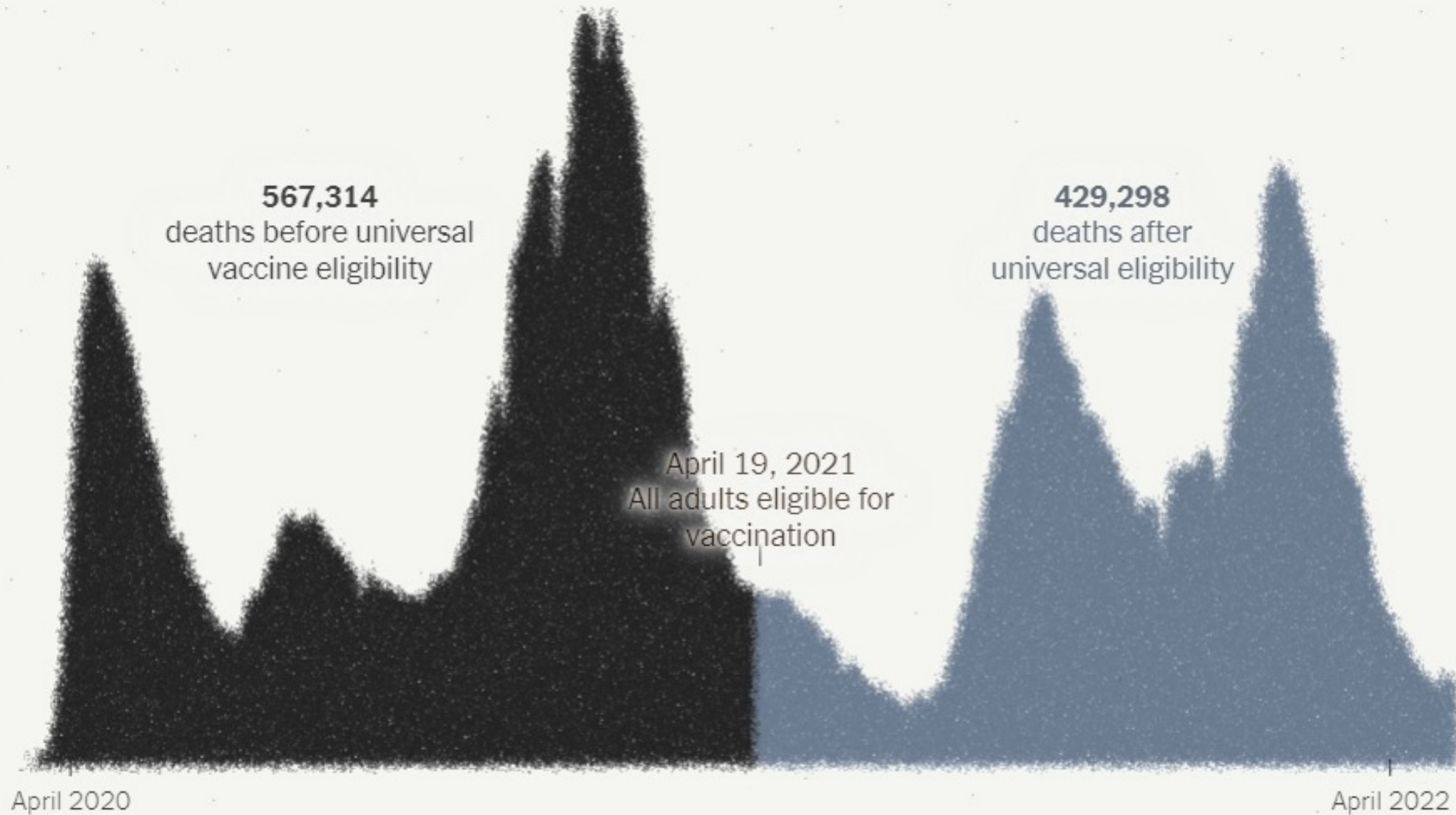
# Real World Effectiveness Estimates from Israel



- Population with BNT162b2 mass vaccination (actual)
- - - Population without BNT162b2 vaccination (estimated)
- Population without BNT162b2 vaccination (estimated, 95% CI)

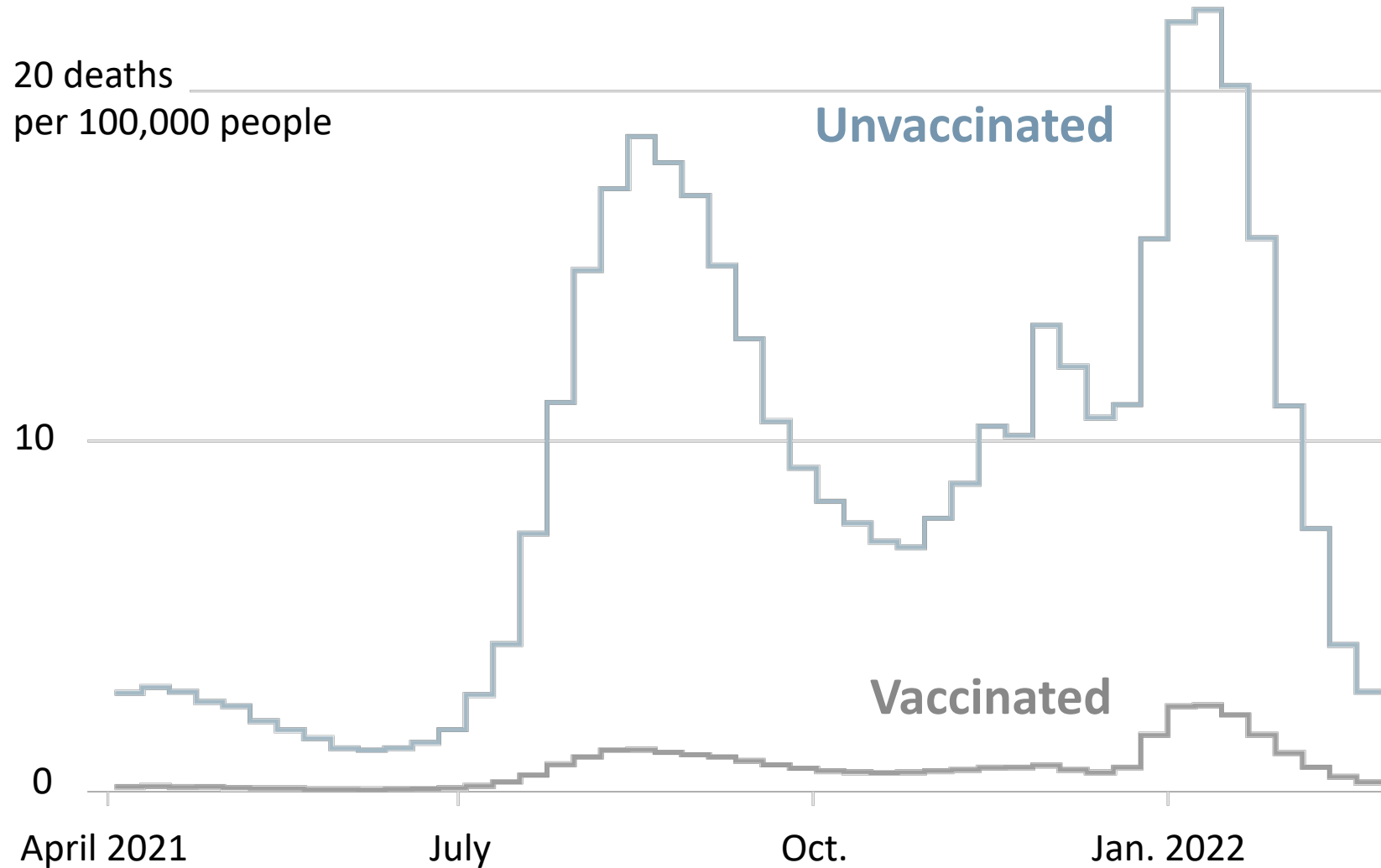
Haas EJ et al. Lancet Infect Dis 2021; 22:S1473-3099 (21)00566-1. doi: 10.1016/S1473-3099(21)00566-1.

# Impact of Vaccination on Mortality in U.S.



Note: Data is weekly. | Source: [C.D.C.](#) published by NYTimes

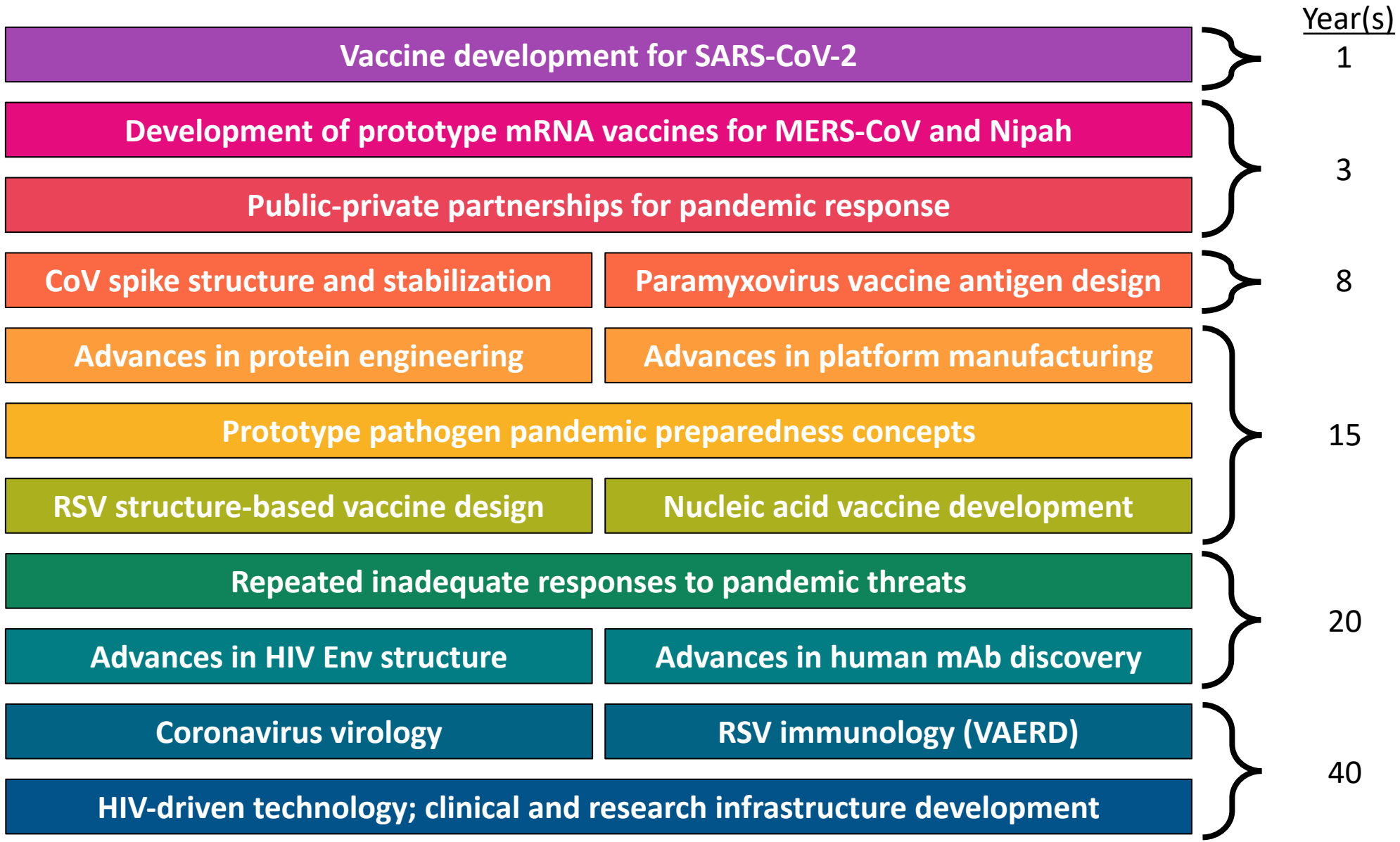
# Death rate for unvaccinated people has been at least nine times that of vaccinated people



Note: Data is weekly. | Source: [C.D.C.](#) published by NYTimes

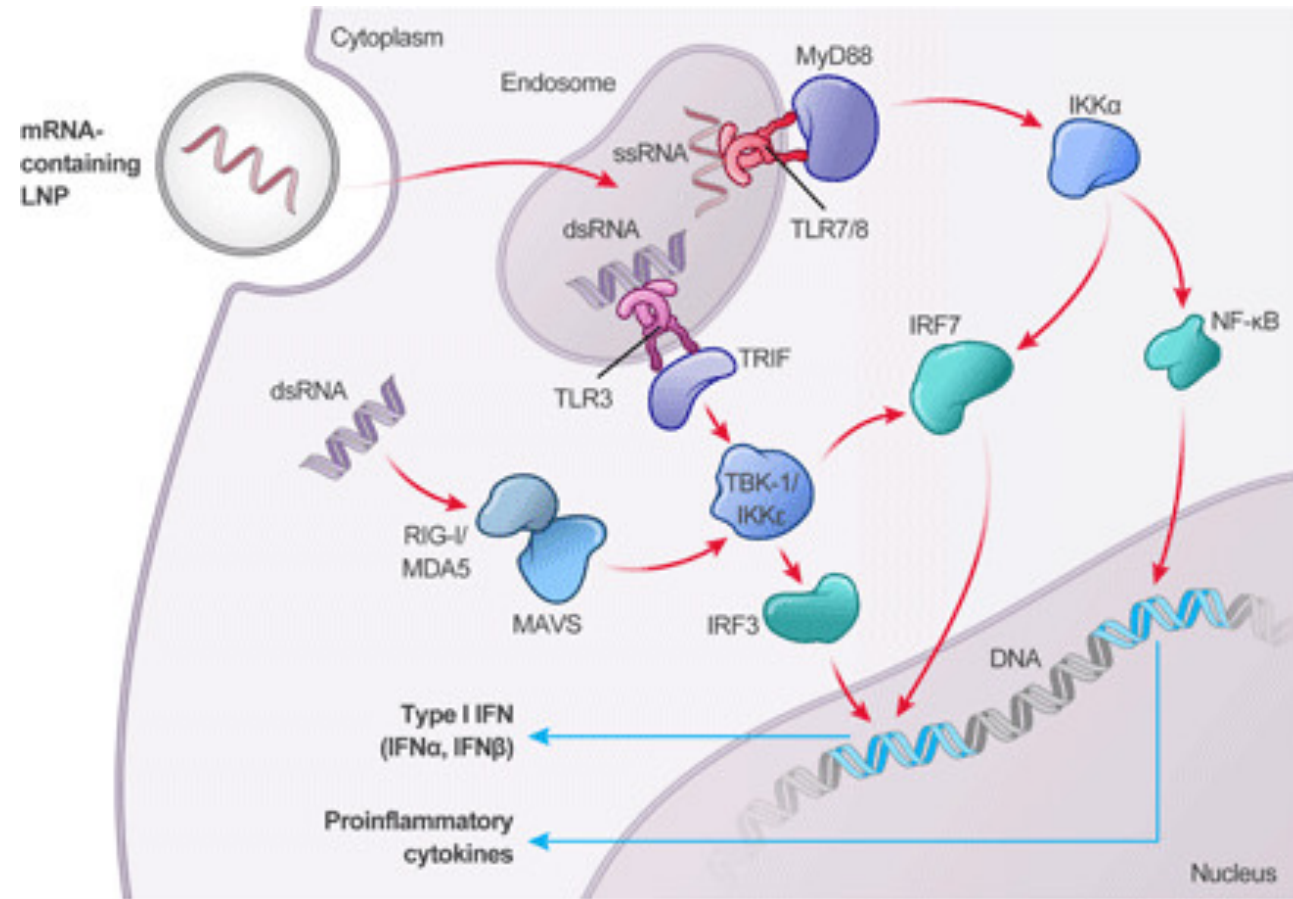


# Foundation for rapid COVID-19 vaccine development



# mRNA immunization strategy

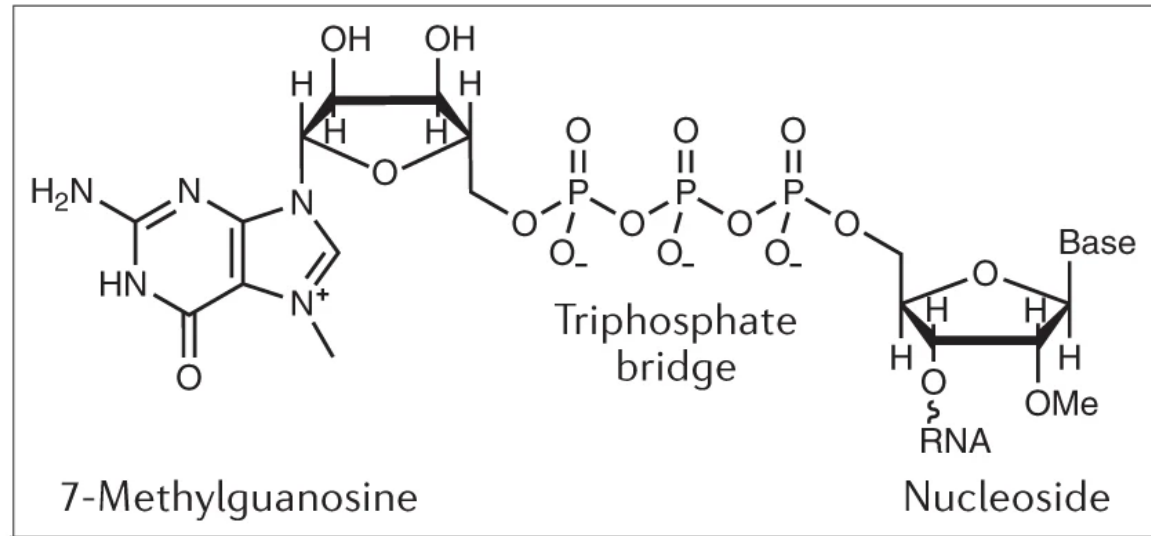
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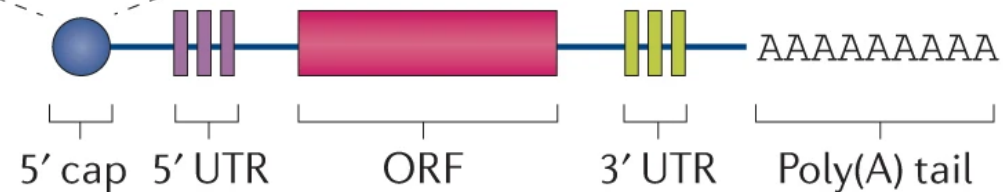
- COVID-19 data indicate mRNA is safe and efficacious
- Stability and supply chain is improving
- Small footprint, small batch manufacturing is well suited for LMICs and rapid iterative design cycles
- mRNA is not magic – antigen design is critical
- Room for improvement in mRNA design and production

Nelson et al. Sci Adv 2020

# Elements of mRNA Design

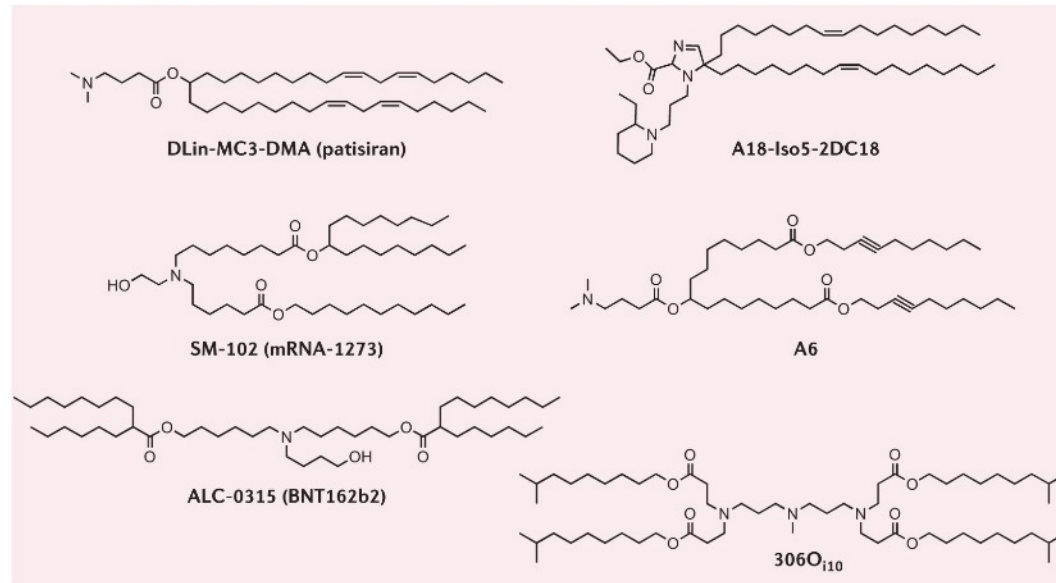


- Nucleotide modifications
- Self amplification
- Codon modification
- Secondary RNA structure
- Downstream processing
- Formulation



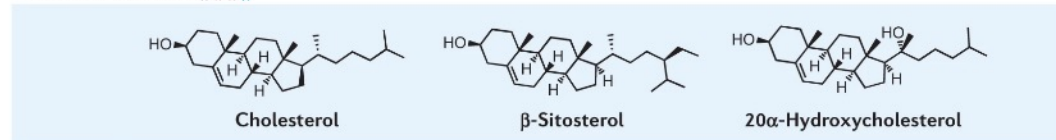
# Lipid Components of LNPs

Ionizable lipid



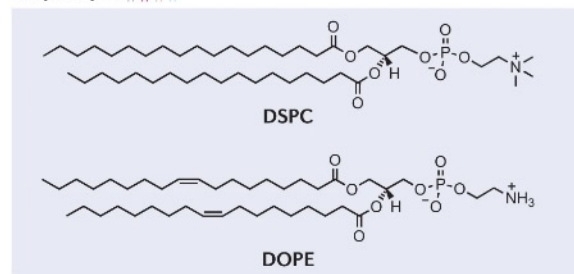
Ionizable cationic lipid

Cholesterol variants



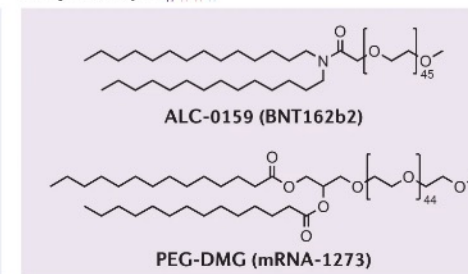
Cholesterol

Helper lipid



Neutral lipid

PEGylated lipid

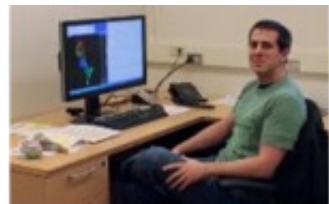


PEGylated lipid



# Conclusions

- mRNA is a safe, effective, and scalable modality for vaccine delivery
- mRNA creates new options for R&D
  - Rapid design cycles
  - Chemical synthesis
  - Small footprint, small batch manufacturing
- mRNA makes the prototype pathogen approach to pandemic preparedness feasible
- Access and uptake



Jason McLellan

The University of Texas at Austin  
Dell Medical School



Ralph Baric



Mark Denison