

COVID-19 Vaccines: Progress and Priorities

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**National Institute of Allergy and Infectious
Diseases**

National Institutes of Health

December 10, 2020



NIH Research on Coronavirus Disease 2019 (COVID-19)

Therapeutics



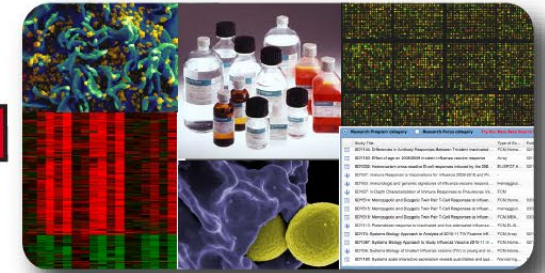
Vaccines



Diagnostics



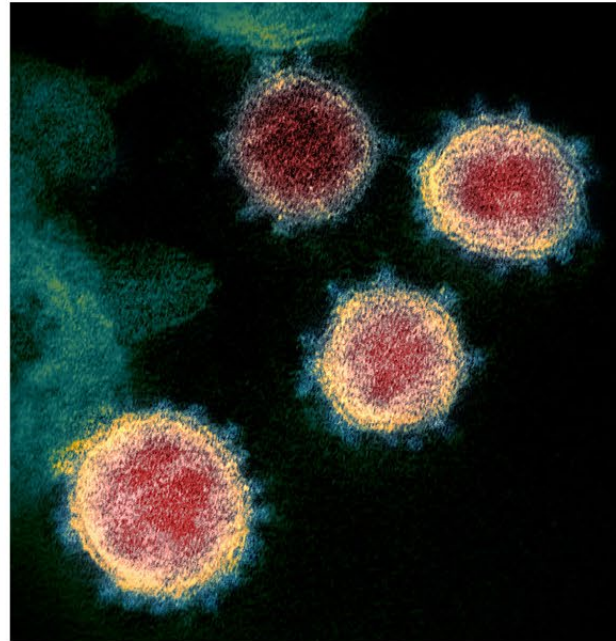
Research Resources



Natural History



Basic Research

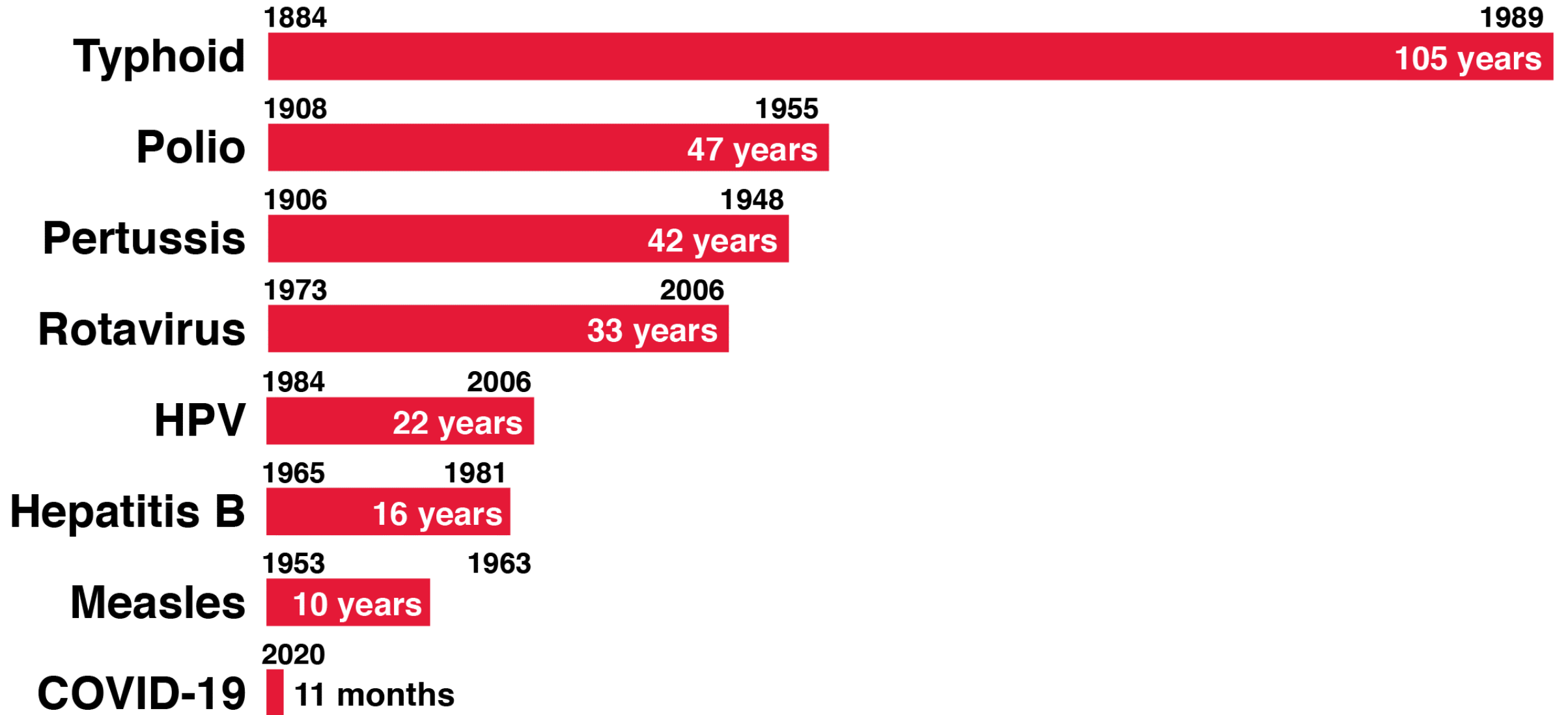


NIH Research on Coronavirus Disease 2019 (COVID-19)

Vaccines



Time to Develop a Vaccine



Duration between discovery of microbiologic cause of selected infectious diseases and development of a vaccine.

Adapted from AVAC

Primary USG Vaccine Development Stakeholders



NIAID

- Basic and clinical research on vaccine candidates



- Basic and clinical research on vaccine candidates
- Limited manufacturing and advanced development for



- Advanced clinical development and manufacturing support via contracts
- ASPR oversees Strategic National Stockpile

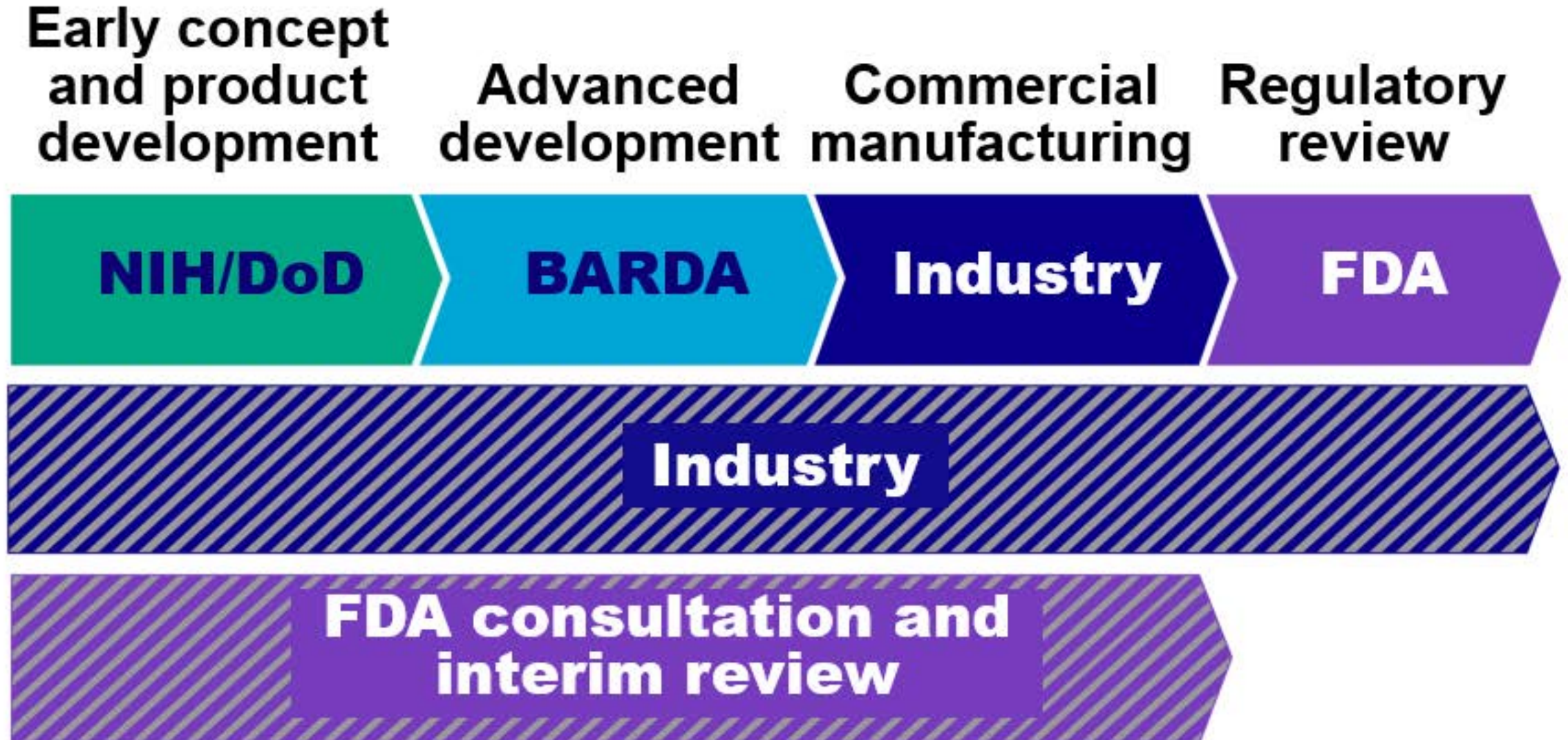


- Advises on data requirements each stage of vaccine development
- Reviews preclinical and clinical data packages for potential authorization of licensure



- Via Advisory Committee on Immunization Practices, recommends who is vaccinated, when and with what vaccine
- Shapes prioritization for immunization when quantities are scarce

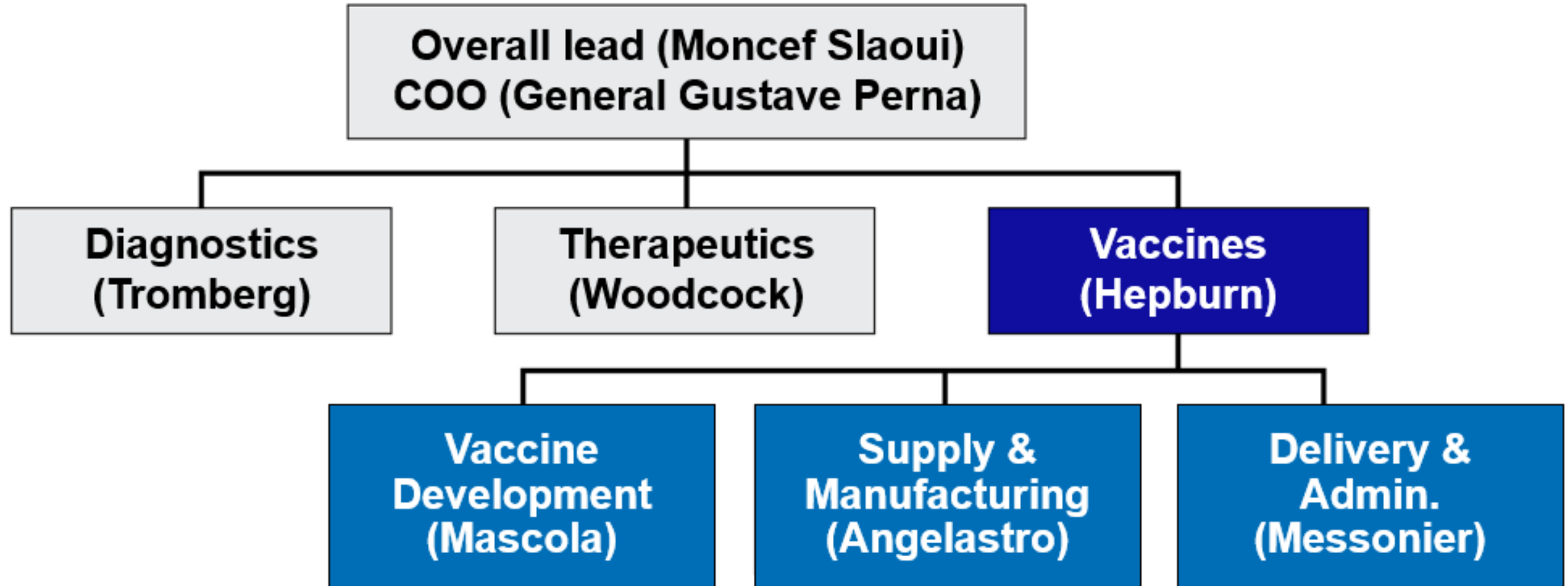
Pre-COVID-19 USG Vaccine Development Model



Operation Warp Speed



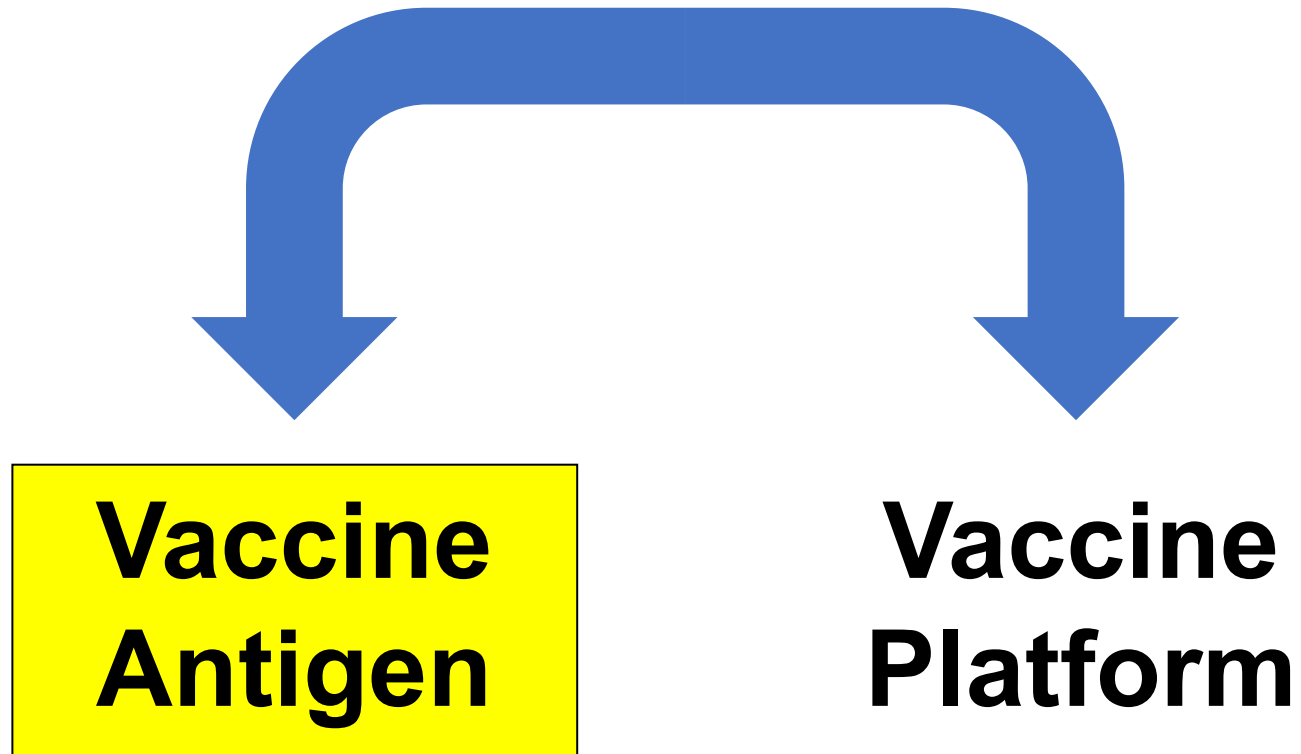
Operation Warp Speed Organizational Structure



Core Components of Vaccine Development and Delivery

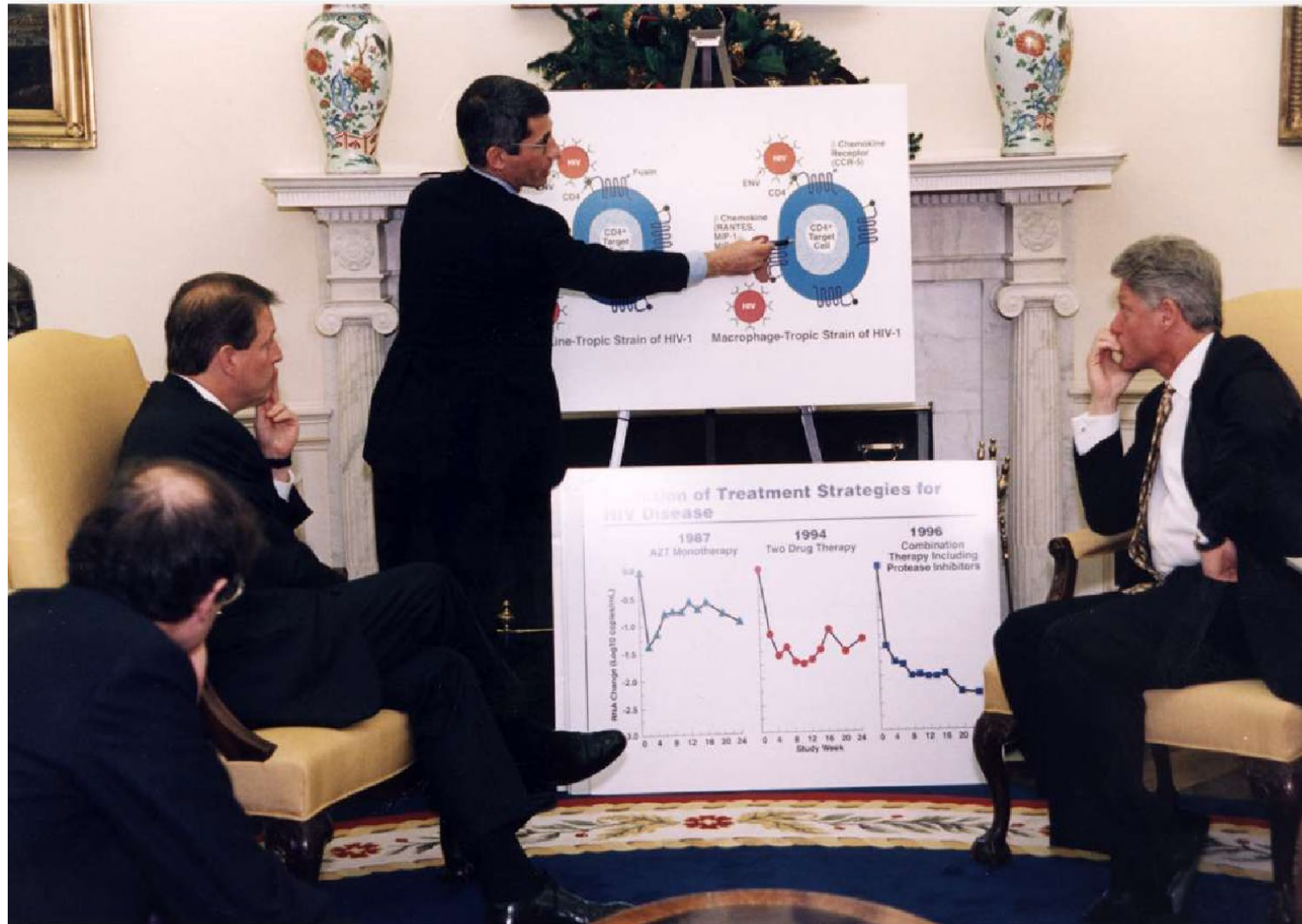
- **Developing vaccine construct – antigen and platform**
- **Manufacturing**
- **Clinical Trials**
- **Regulatory review and immunization policy**
- **Distribution and vaccinations**

Vaccine Construct



History of the NIAID Vaccine Research Center

Meeting at the White House to Discuss AIDS Research, Dec. 3, 1996



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.”



NIAID Vaccine Research Center



VRC Senior Investigators

Basic Research



Clinical Trials

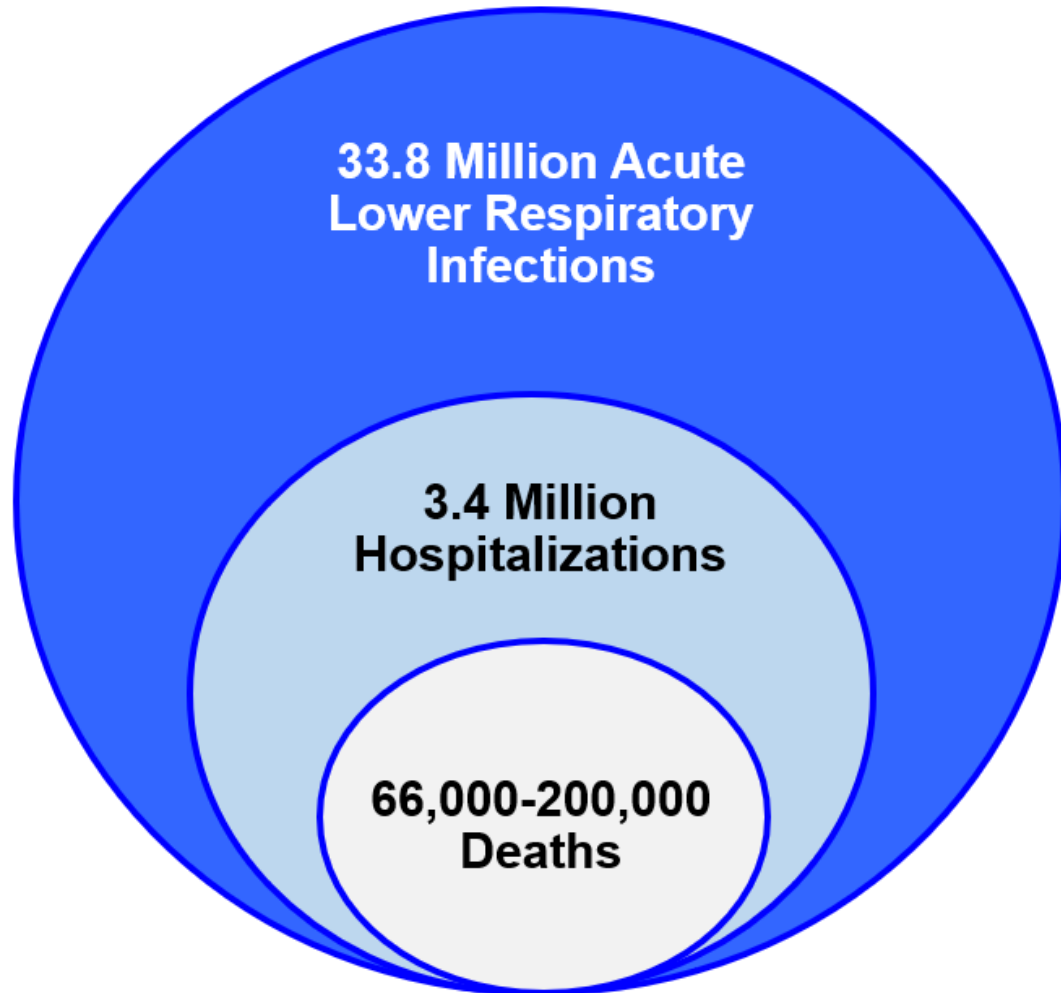
VRC Research: From HIV to Zika



- HIV
- West Nile virus
- Chikungunya
- Ebola/Marburg
- Influenza
- Malaria
- Coronaviruses
- **RSV**
- Tuberculosis
- Venezuelan, Eastern, and Western equine encephalitis viruses
- Zika

Global Respiratory Syncytial Virus (RSV) Mortality and Morbidity

Global Annual Burden of Disease



- Causes 6.7 percent of deaths in children aged 1 month-1 year
- Nearly $\frac{1}{4}$ of children under age one hospitalized with RSV will develop asthma

NIAID Vaccine Research Center



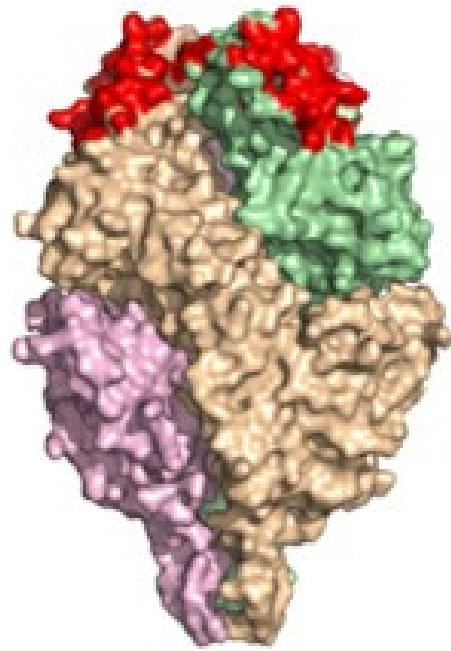
VRC Senior Investigators

Basic Research

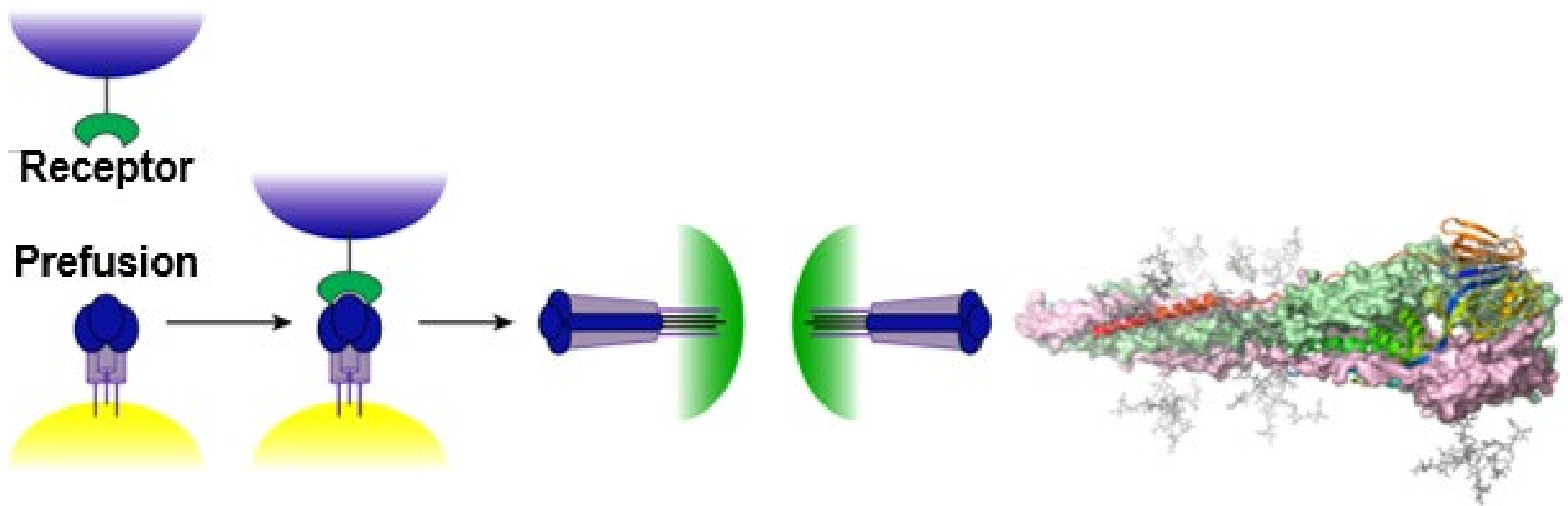


Clinical Trials

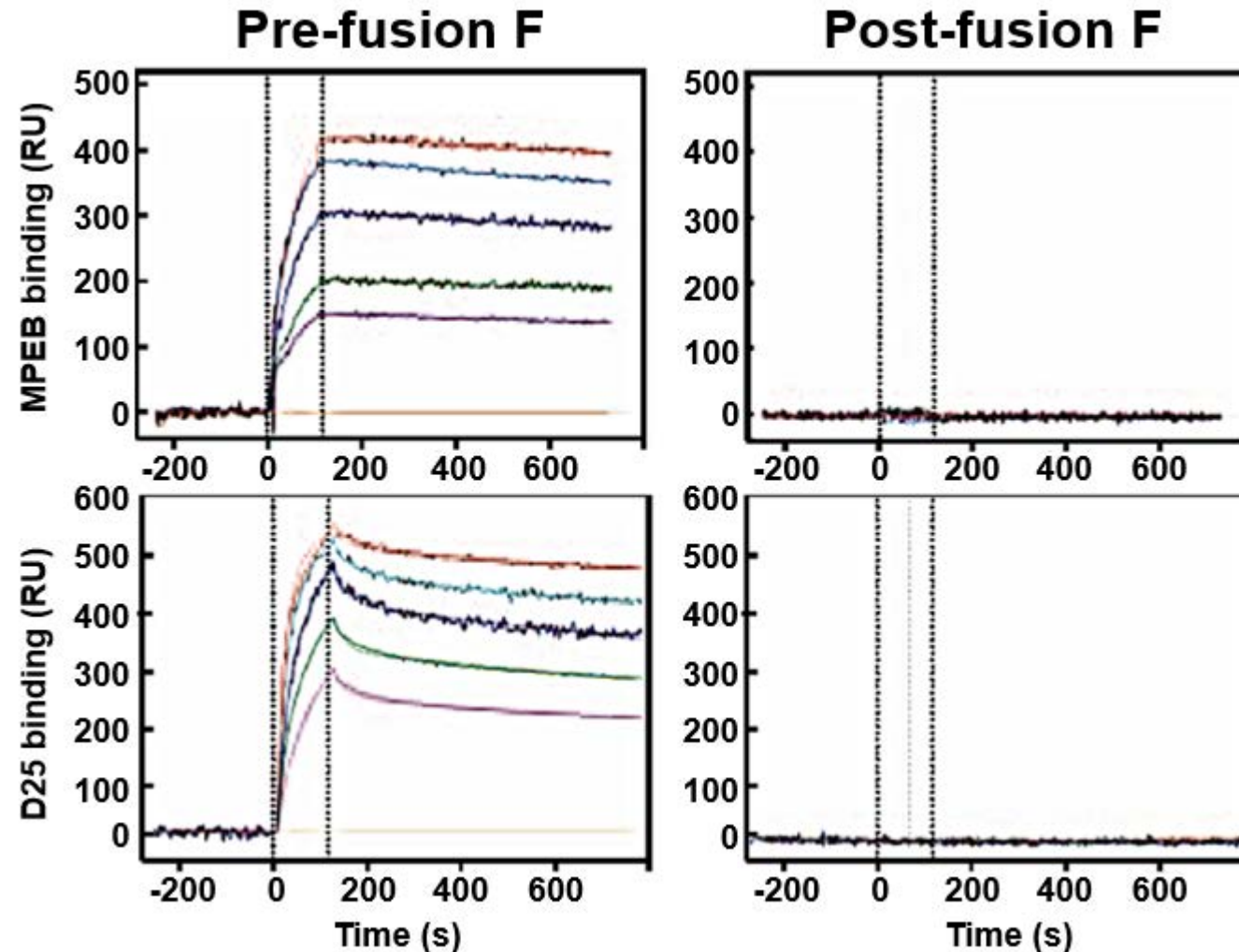
F Protein Adopts Two Primary Conformations: Pre- and Post-Fusion



**Pre-Fusion
(Unstable)**

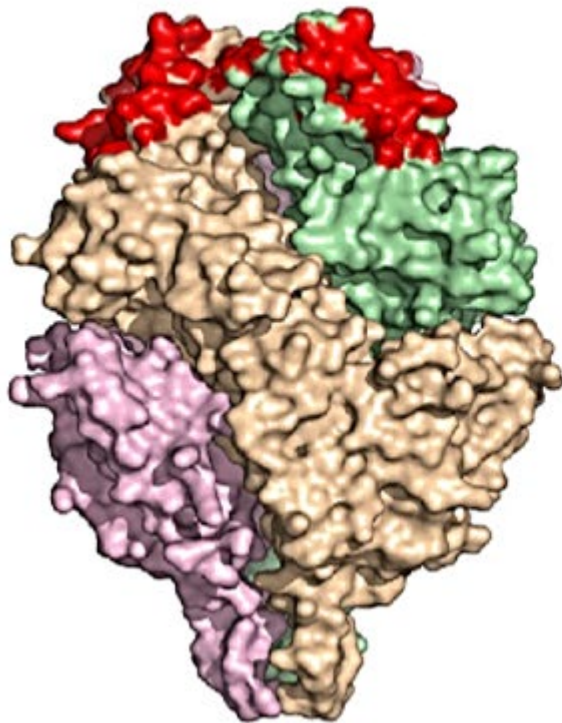


Broadly Neutralizing Antibodies Bind More Readily to the Pre-Fusion Form



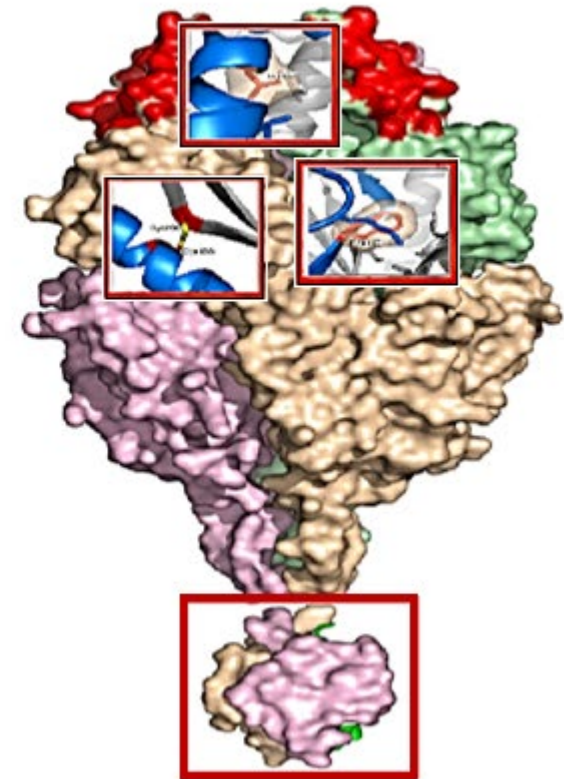
Pre-Fusion F Protein Stabilized Using Structure-Based Vaccine Design

Pre-Fusion F Protein



Stabilization

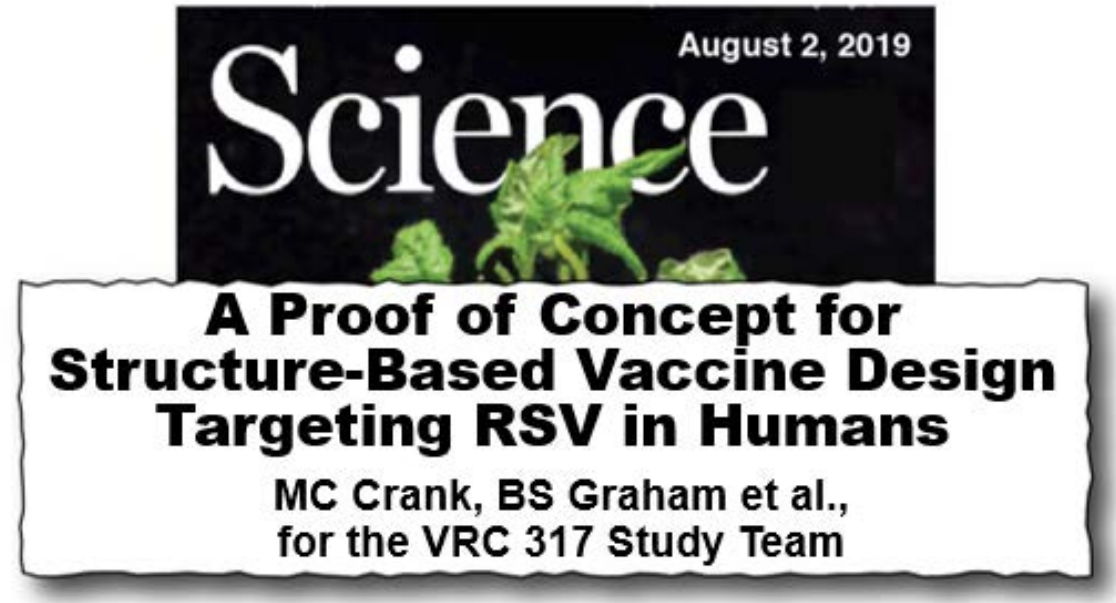
Vaccine immunogen



Source: McLellan JS, Chen M, et al. *Science* 342(6158), 2013.

Structure-Based RSV Vaccine Shows Promise in Phase 1 Trial – “Precision Vaccinology”

- RSV fusion glycoprotein stabilized in prefusion conformation (DS-Cav1) used as immunogen



- 1 dose of DS-Cav1 induced large increase in RSV-neutralizing antibodies that were sustained for several months

VRC Research: From HIV to Zika



- HIV
- West Nile virus
- Chikungunya
- Ebola/Marburg
- Influenza
- Malaria
- **Coronaviruses**
- RSV
- Tuberculosis
- Venezuelan, Eastern, and Western equine encephalitis viruses
- Zika

Structure-based Design of MERS Vaccine

August 29, 2017

PNAS

Proceedings of the National Academy of Sciences of the United States of America

Immunogenicity and Structures of a Rationally Designed Prefusion MERS-CoV Spike Antigen

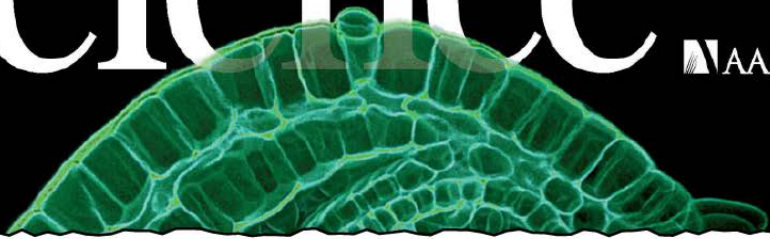
Jesper Pallesen, Nianshuang Wang, Kizzmekia S Corbett, Daniel Wrapp, Robert N Kirchdoerfer, Hannah L Turner, Christopher A Cottrell, Michelle M Becker, Lingshu Wang, Wei Shi, Wing-Pui Kong, Erica L Andres, Arminja N Kettenbach, Mark R Denison, James D Chappell, Barney S Graham, Andrew B Ward, Jason S McLellan.

January 3, 2020
Volume 367
Issue 6473

Science

sciencemag.org

AAAS



Novel Human Virus? Pneumonia Cases Linked to Seafood Market in China Stir Concern

By Dennis Normile

Convoluted shapes
from simple rules pp. 24 & 91

January 11, 2020

Science

NEWS

Chinese Researchers Reveal Draft Genome of Virus Implicated in Wuhan Pneumonia Outbreak

Jon Cohen

NIAID Vaccine Research Center

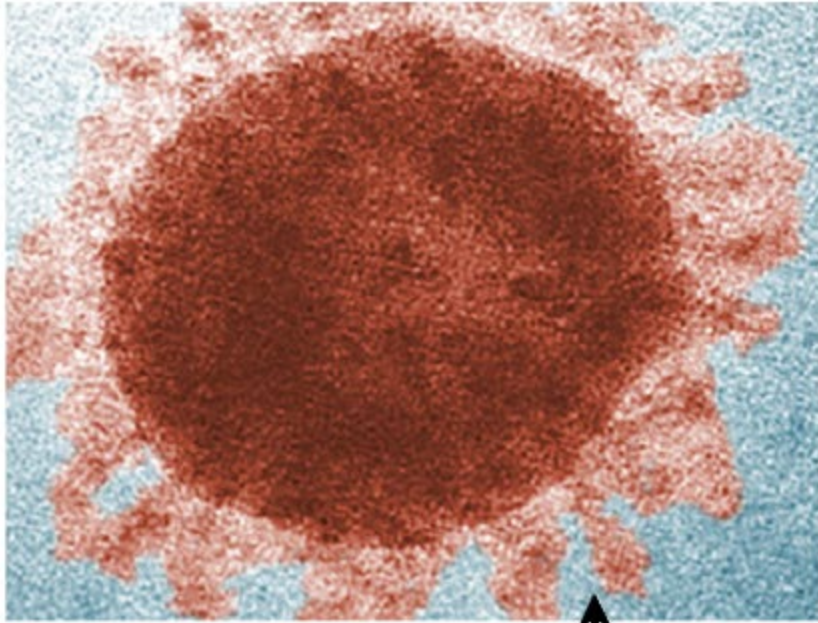


VRC Senior Investigators

Basic Research

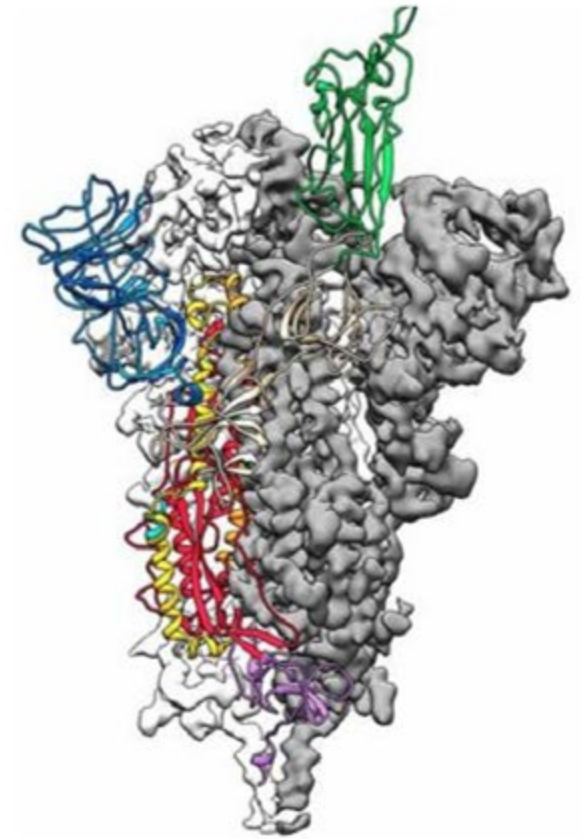


Clinical Trials



**SARS-CoV-2
Spike protein
Pre-fusion form
(Unstable)**

Mutations



**SARS-CoV-2
Spike protein
Pre-fusion form
(Stable)**

Imagining the future at the
Sundance Film Festival p. 1188

Shrinking Colorado River
flow pp. 1192 & 1252

Structure of a key SARS-CoV-2
protein p. 1260

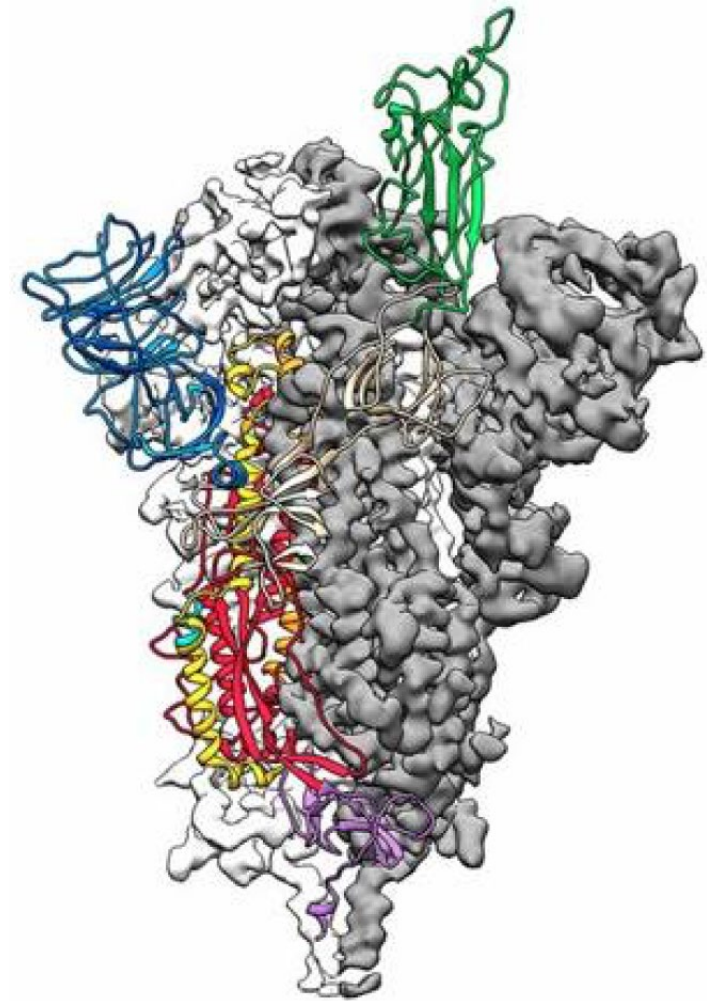
March 13, 2020
Vol. 367 Issue 6483

Science

AAAS

Cryo-EM Structure of the 2019-nCoV Spike in the Prefusion Conformation

D Wrapp, N Wang, KS Corbett, JA Goldsmith,
C-L Hsieh, O Abiona, BS Graham, JS McLellan



Viral membrane

**Atomic-level structure of SARS-CoV-2
spike protein, Receptor binding
domain is colored green.**

published online August 5, 2020

nature

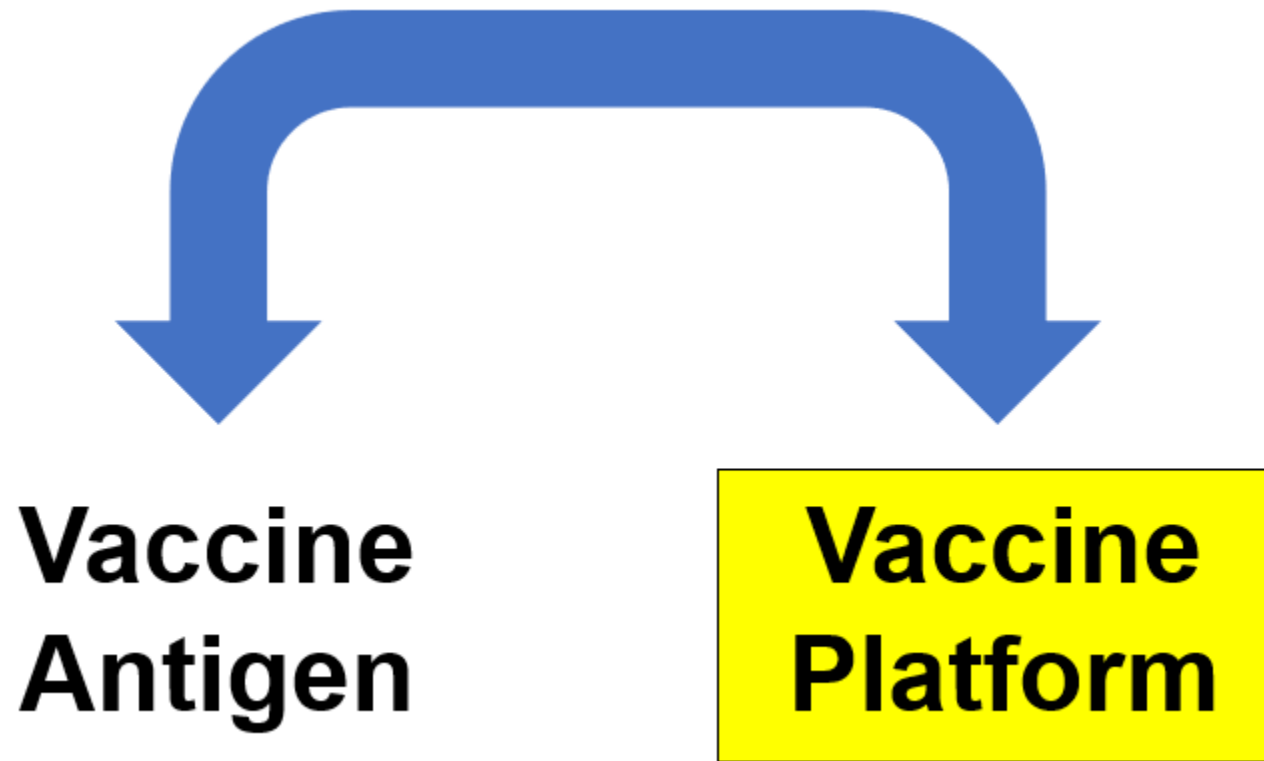
International weekly journal of science

SARS-CoV-2 mRNA Vaccine Design Enabled by Prototype Pathogen Preparedness

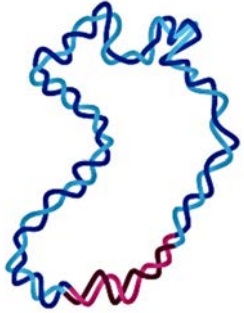
KS Corbett, BS Graham et al.

- Using established immunogen design, the release of SARS-CoV-2 sequences triggered immediate rapid manufacturing of an mRNA vaccine expressing the prefusion-stabilized SARS-CoV-2 spike trimer.

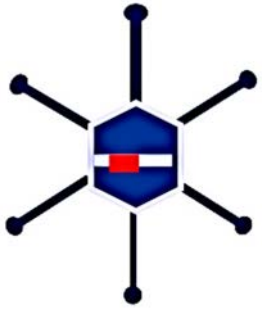
Vaccine Construct



Vaccine Platform Technologies



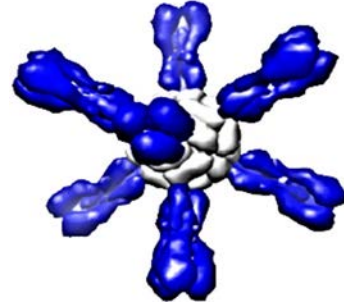
Genetic immunization
(DNA and RNA vaccines)
**SARS, MERS, West Nile,
Zika, RSV**



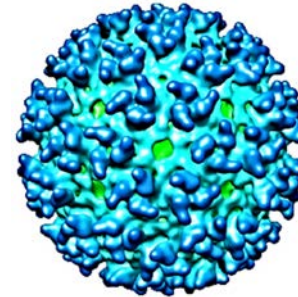
Viral vector
(e.g., VSV, adenovirus)
Ebola, Marburg, Zika



Recombinant protein
Influenza, RSV



Nanoparticles
(viral protein on particle)
Influenza, Malaria, RSV






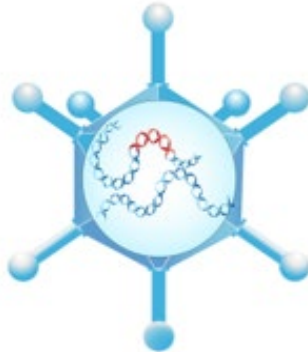

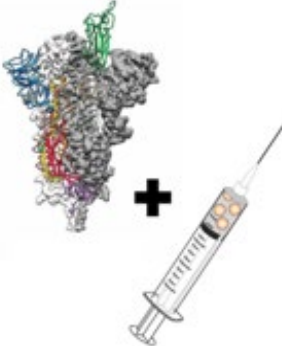
Virus-like particle (VLP)
(no RNA or DNA;
non-infectious)
**Chikungunya, Zika,
WEVEE**



Adjuvants
(e.g., AS01, MF59)

Selected Examples

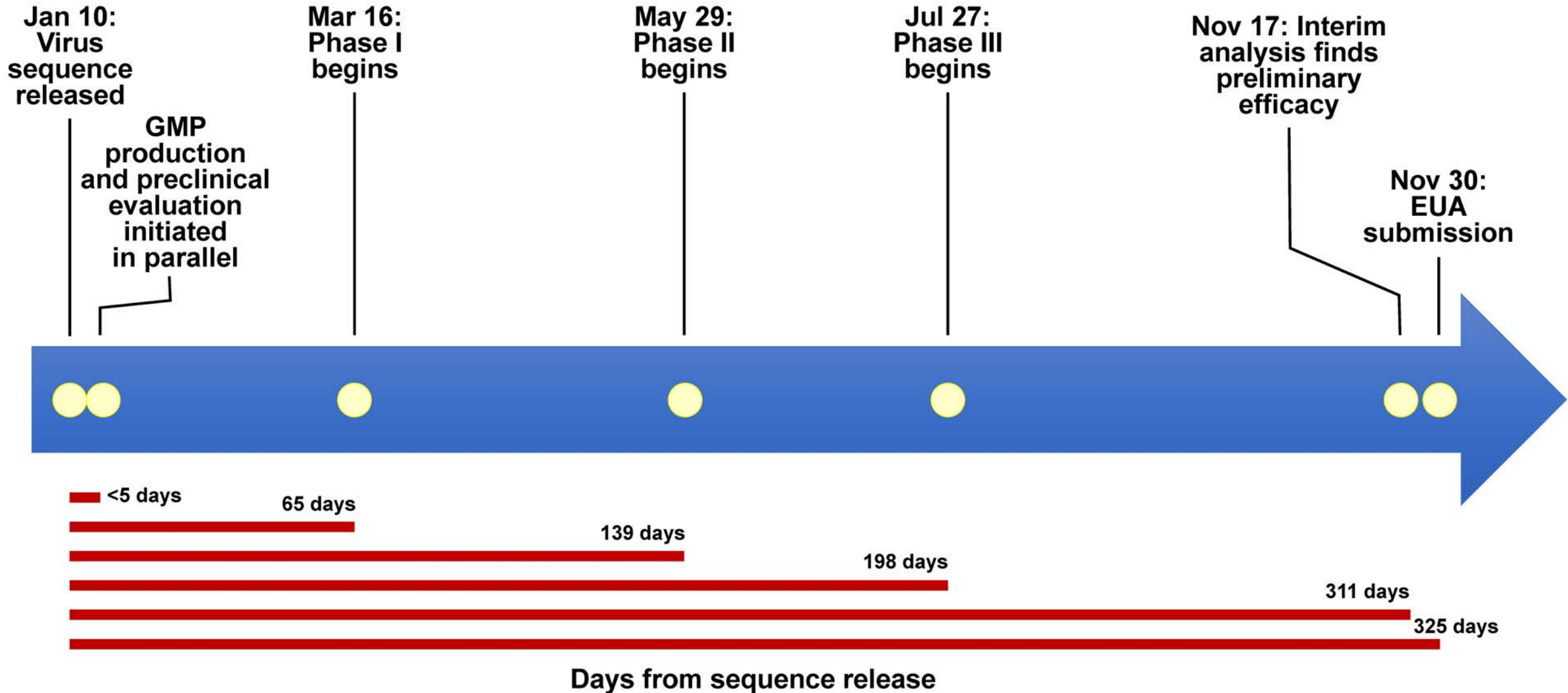
COVID-19 Vaccines in Operation Warp Speed Development

	<p>mRNA mRNA</p>		<ul style="list-style-type: none"> ■ mRNA: Rapid manufacturing facilitating efficient move to clinic, highly immunogenic
	<p>Adenovirus vector Adenovirus vector</p>		<ul style="list-style-type: none"> ■ Adenovirus: Rapid manufacturing facilitating efficient move to clinic, vaccine using this platform is approved in Europe
	<p>Recombinant protein + adjuvant Recombinant protein + adjuvant</p>		<ul style="list-style-type: none"> ■ Adjuvanted recombinant protein: not as fast to manufacture but scalable, several approved vaccines use this approach







Core Components of Vaccine Development and Delivery

- **Developing vaccine construct – antigen and platform**
- **Manufacturing**
- **Clinical Trials**
- **Regulatory review and immunization policy**
- **Distribution and vaccinations**

SARS-CoV-2 Vaccine Development: mRNA-1273



Selected COVID-19 Vaccine Candidates

Platform	Developer	Phase 1/2	Phase 2/3
Nucleic acid		Enrolled	Enrolled
		Enrolled	Enrolled
Viral vector		Enrolled	Ongoing
		Enrolled	Ongoing
Protein subunit		Enrolled	Ongoing
		Enrolled	- -



A Strategic Approach to COVID-19 Vaccine R&D

L Corey, JR Mascola, AS Fauci & FS Collins

- **Unprecedented collaboration and resources will be required to research and develop safe and effective vaccines for COVID-19 that can be manufactured and delivered in the scale of billions of doses to people globally.**

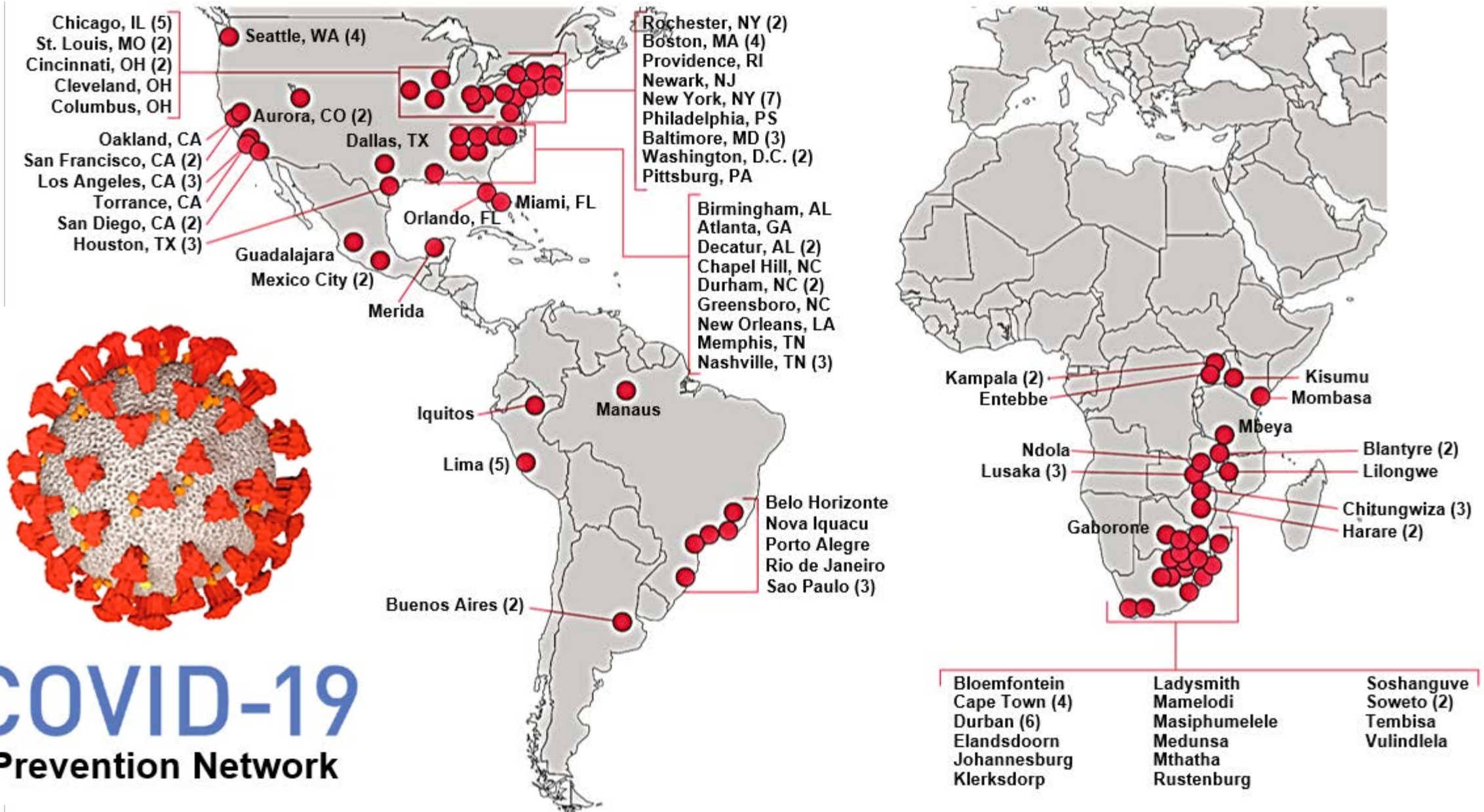
Elements of OWS Harmonized Protocols

- **Harmonized endpoints**
- **Collaborating clinical trials networks**
- **Shared immune assays**
- **Common Data and Safety Monitoring Board**
- **Shared statistical plan for immune correlates of protection**

OWS Phase 3 Design Overview

- **Randomized, Placebo-Controlled Efficacy Trial: 1:1 or 2:1**
- **Sample size: 30,000 to 60,000 volunteers**
 - **A primary efficacy endpoint estimate of $\geq 60\%$**
 - **The lower bound of the confidence interval $>30\%$**
- **Study Population: age ≥ 18 years, at risk of acquisition, targeting subset at higher risk of severe disease, diverse populations**
 - **The Pfizer trial, which is independently conducted, is now enrolling down to age 12**
- **Primary Endpoint: Prevention of symptomatic COVID-19 disease (PCR confirmed)**
 - **All identified cases are assessed for severity and followed to resolution**
 - **Unblinded clinical case data are submitted to shared biostatistical group**

NIAID COVID-19 Prevention Network



COVID-19
Prevention Network



Press Release

November 30, 2020

Moderna Announces Primary Efficacy Analysis in Phase 3 COVE Study for Its COVID-19 Vaccine Candidate and Filing Today with U.S. FDA for Emergency Use Authorization

- **Vaccine efficacy against COVID-19 was 94%;
vaccine efficacy against severe COVID-19 was 100%**



News Release

Friday, November 20, 2020

Pfizer and BioNTech to Submit Emergency Use Authorization Request Today to the U.S. FDA for COVID-19 Vaccine

- **Vaccine efficacy rate of 95%, with no serious safety concerns observed to date**

Core Components of Vaccine Development and Delivery

- **Developing vaccine construct – antigen and platform**
- **Manufacturing**
- **Clinical Trials**
- **Regulatory review and immunization policy**
- **Distribution and vaccinations**



REUTERS

December 2, 2020

In World First, UK Approves Pfizer-BioNTech COVID-19 Vaccine



Vaccines and Related Biological Products Advisory Committee Meetings

DECEMBER 2020

SUN	MON	TUE	WED	THU	FRI	SAT
		1	2	3	4	5
6	7	8	9	10 Pfizer	11	12
13	14	15	16	17 Moderna	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

**Vaccine distribution plan awaiting
recommendations from CDC after
consultation with the Advisory
Committee on Immunization
Practices (ACIP) and the National
Academy of Medicine**

Advisory Committee on Immunization Practices Proposed Vaccine Prioritization – Phase 1

Phase 1a

Healthcare Personnel

Long-term Care Facilities

Phase 1b

Essential workers

**(examples: Education Sector, Food & Agriculture, Utilities,
Police, Firefighters, Corrections Officers, Transportation)**

Phase 1c

Adults with high-risk medical conditions

Adults 65+

Core Components of Vaccine Development and Delivery

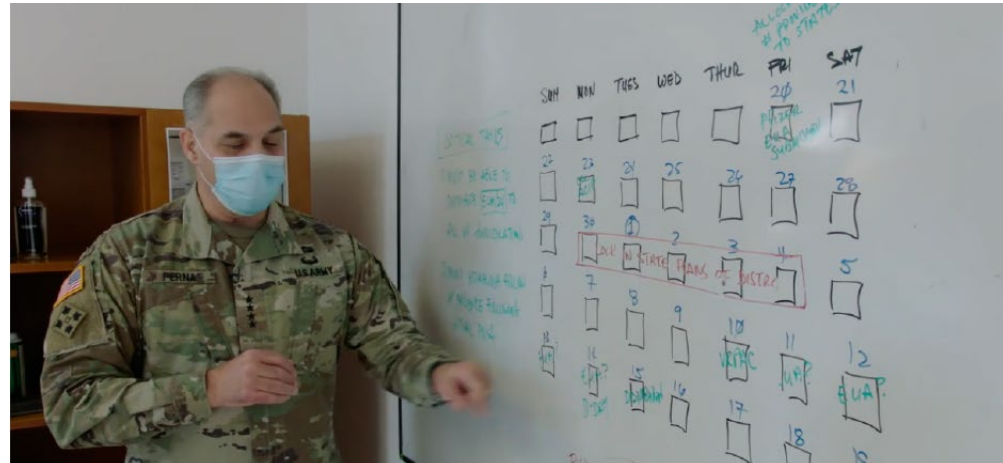
- **Developing vaccine construct – antigen and platform**
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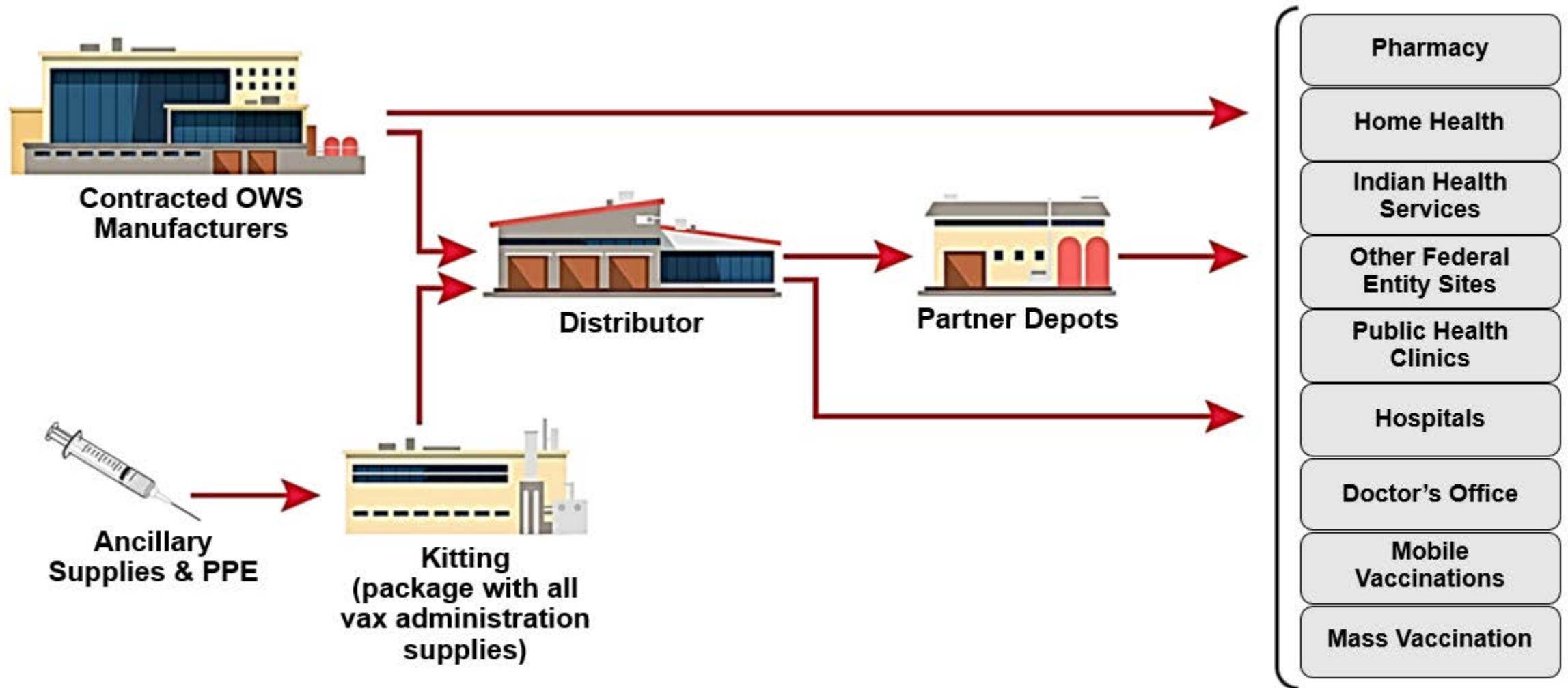
November 24, 2020

General: COVID-19 Vaccines Will Be Ready for Delivery 24 Hours After FDA Authorization

Operation Warp Speed has a delivery plan in place.



OWS Overview of Distribution and Administration



Vaccine Administration Sites

Walgreens



Efficacy

Versus

Effectiveness

June 30, 2020

Science

**Just 50% of
Americans Plan to
Get a COVID-19
Vaccine.
Here's How to Win
Over the Rest**

W Cornwall

Do you plan to get a coronavirus vaccine when one is available?

Overall



Under age 60



Age 60 and older



White



Black



Hispanic



Yes Not sure No Did not answer

November 17, 2020
Vol 324 No. 19

JAMA
The Journal of the
American Medical Association

Preventing the Spread of SARS-CoV-2 With Masks and Other “Low-tech” Interventions

AM Lerner, GK Folkers and AS Fauci

“While results of phase 3 trials for multiple candidate vaccines are on the near horizon, “low-tech” tools to prevent the spread of SARS-CoV-2 are essential, and it must be emphasized that these interventions will still be needed after a vaccine is initially available.”

Published May 28, 2020



Universal Coronavirus Vaccines: The Time to Start Is Now

LT Giurgea, A Han and MJ Memoli