# COVID-19 Vaccine Development: The Role of the NIH

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National Institute of Allergy and Infectious Diseases

National Institutes of Health

October 22, 2020

# Vaccines and Related Biological Products Advisory Committee October 22, 2020 Meeting Presentation

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- **Moving From Preparedness to Response**
- **Evaluating Safety and Efficacy – Harmonized Clinical Trials**
- **Key Priorities and Future Directions**

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January 11, 2020

Science

NEWS

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

Jon Cohen

August 29, 2017 | vol. 114 | no. 35

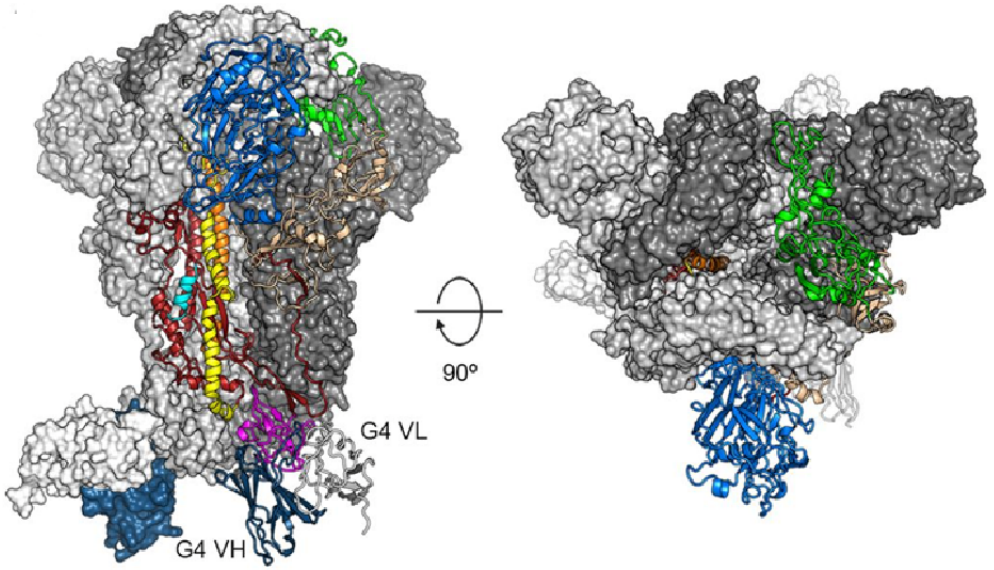
PNAS

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

RESEARCH ARTICLE

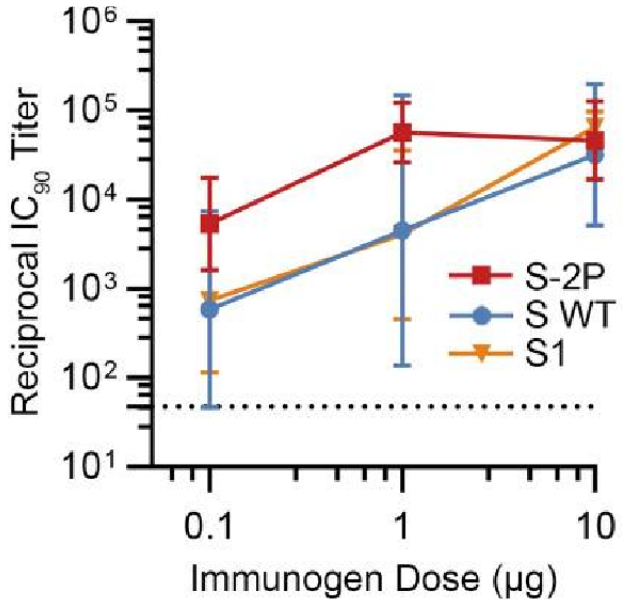
# Immunogenicity and Structures of a Rationally Designed Prefusion MERS-CoV Spike Antigen

J Pallesen, JS McLellan et al.




**Spike with stabilizing mutations bound to MERS-CoV neutralizing Ab G4**

**Stabilized Spike Elicits More Neutralization than WT Spike or S1 Monomer in Mice**



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.**

# COVID-19 Vaccines in Operation Warp Speed Development

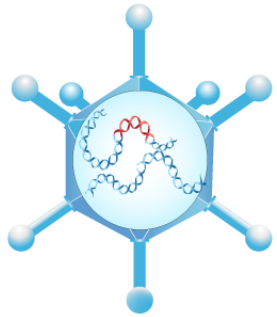
moderna — mRNA

BIONTECH Pfizer — mRNA

- **mRNA:** rapid manufacturing facilitating efficient move to clinic, highly immunogenic

AstraZeneca — Adenovirus vector

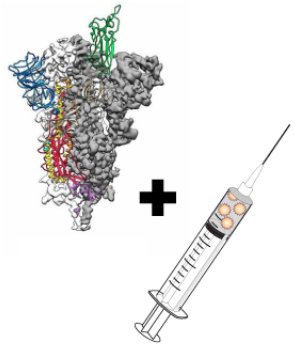
Janssen Pharmaceutical Companies of Johnson & Johnson — Adenovirus vector



- **Adenovirus:** rapid manufacturing facilitating efficient move to clinic, vaccine using this platform is approved in Europe

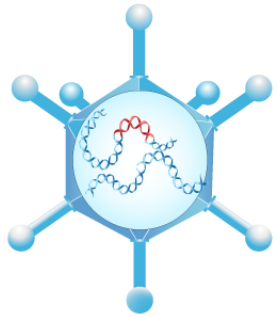
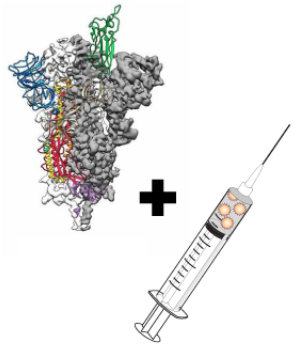
NOVAVAX Creating Tomorrow's Vaccines Today — Recombinant protein + adjuvant

gsk SANOFI — Recombinant protein + adjuvant



- **Adjuvanted recombinant protein:** not as fast to manufacture but scalable, several approved vaccines use this approach

# COVID-19 Vaccines in Operation Warp Speed Development

| | | |
|---|---|---|
| moderna | mRNA |  |
| BIONTECH Pfizer | mRNA | |
| AstraZeneca | Adenovirus vector |  |
| janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson | Adenovirus vector | |
| NOVAVAX Creating Tomorrow's Vaccines Today | Recombinant protein + adjuvant |  |
| gsk SANOFI | Recombinant protein + adjuvant | |

- Initial COVID phase 1 trials launched in March 2020
- Initial evaluation for safety and immune responses in Phase 1 and 2 trials
- To date, COVID vaccines are immunogenic and well tolerated overall
- Binding antibody and viral neutralization titers comparable to human convalescent sera

- Moving From Preparedness to Response
- **Evaluating Safety and Efficacy – Harmonized Clinical Trials**
- Key Priorities and Future Directions

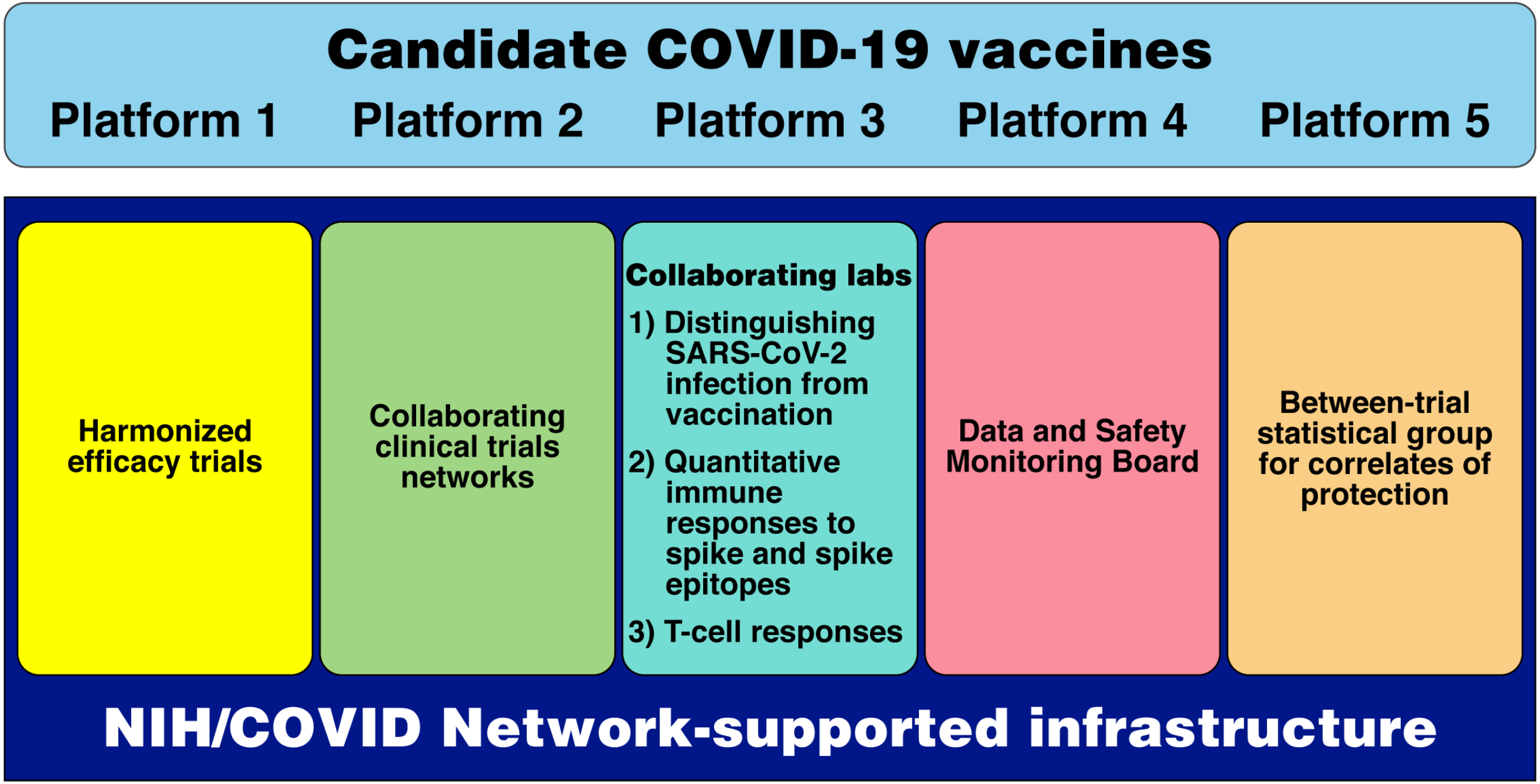
Published online May 11, 2020

Science

# A Strategic Approach to COVID-19 Vaccine R&D

L Corey, JR Mascola, AS Fauci & FS Collins

***The full development pathway for an effective vaccine for SARS-CoV2 will require that industry, government, and academia collaborate in unprecedented ways, each adding their individual strengths. . . .We further discuss a collaborative platform for conducting harmonized, randomized controlled vaccine efficacy trials. This mechanism aims to generate essential safety and efficacy data for several candidate vaccines in parallel, so as to accelerate the licensure and distribution of multiple vaccine platforms and vaccines to protect against COVID-19***

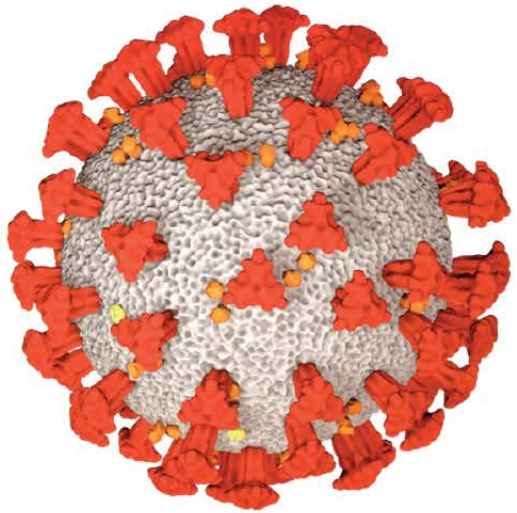



Adapted from Corey et al. *Science* 2020

HIV VACCINE TRIALS NETWORK

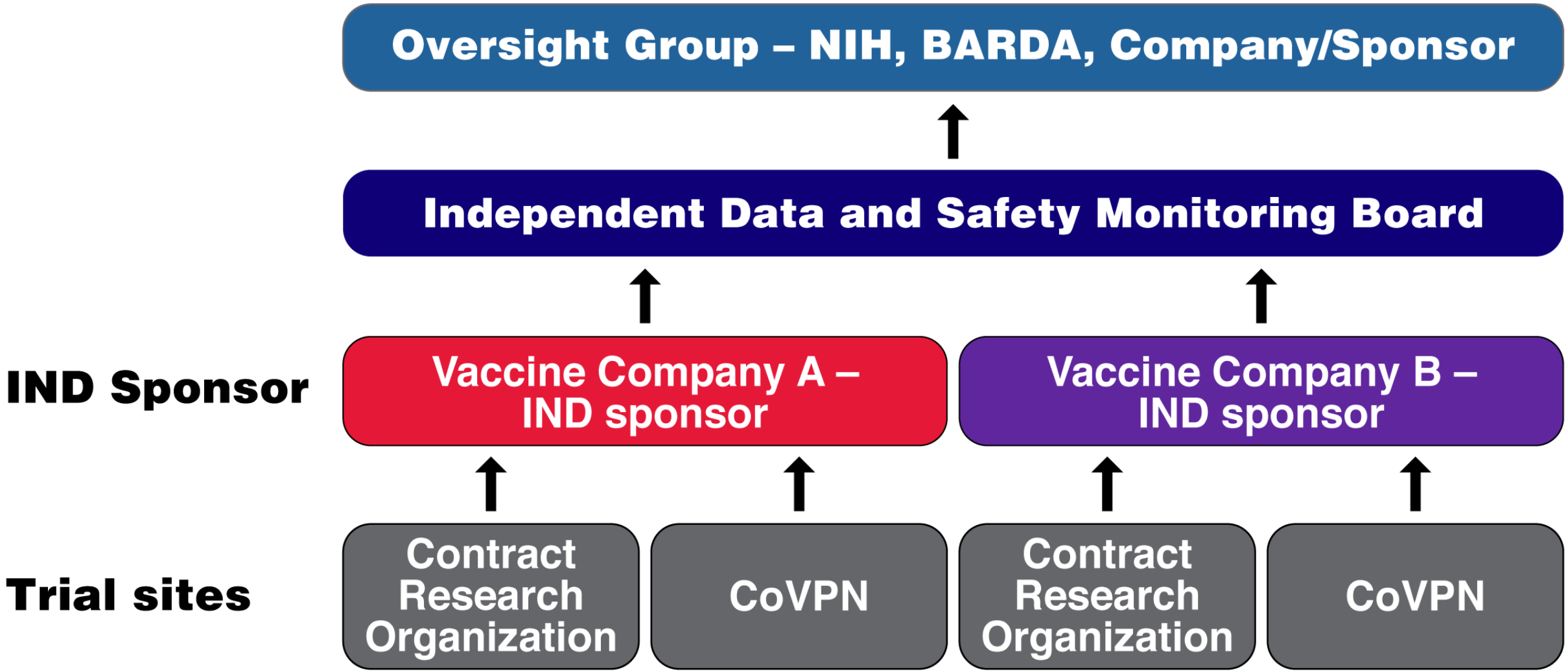
IDCRC
Infectious Diseases Clinical Research Consortium

HPTN
HIV Prevention Trials Network



# COVID-19
## Prevention Network

# Operation Warp Speed/NIH Trial Oversight Structure



# Trial Oversight Structure: The NIH Role

- The company is the regulatory sponsor under 21 CFR 312 and holds the IND for the trials
- Phase 3 trials are designed in collaboration with the NIH-led ACTIV Partnership, OWS, CoVPN and conform to FDA guidance*
- Trials are overseen by an independent Data and Safety Monitoring Board, for which NIH serves as the secretariat**
- NIH CoVPN trial sites support all OWS Phase 3 trials; network investigators are Co-PIs
- NIH, BARDA and the company all participate in the trial Oversight Group (which receives all recommendations from the DSMB)

*https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19
**Exception is Pfizer which is running its trial independent of this structure

# 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 point estimate of ≥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

# Safety Considerations

**Primary Safety Objective: evaluate safety and reactogenicity**

**Safety endpoints:**

- **Solicited local/systemic adverse reactions through 7 days**
- **Unsolicited adverse events through 28 days**
- **Medically attended adverse events, adverse events of special interest and severe adverse events any time (2 yr follow up)**

***All adverse events are reviewed by a dedicated safety team and reviewed in an unblinded fashion by DSMB; for severe AEs, a thorough review is conducted by DSMB.***

***DSMB also reviews for imbalances in severe COVID cases between study arms.***

- Moving From Preparedness to Response
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# Safeguarding volunteers:

# Developing Vaccines in a Public Health Emergency - Financial Risks are Taken (e.g., with respect to manufacturing), Scientific Integrity and Volunteer Safety Are Not Compromised

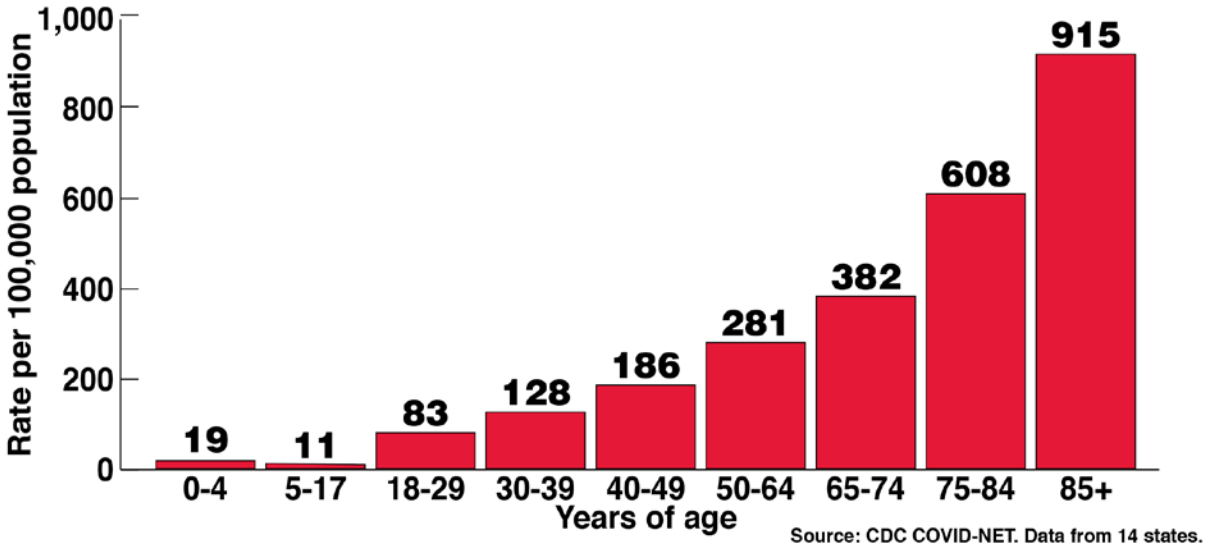
# Safety Pauses and Holds

- **Adverse events (AE):**
  - **Occur in both vaccine and placebo groups in clinical trials**
  - **Monitored and graded by severity using standard procedures**
  - **Regularly reviewed by study clinicians, monitors and protocol safety teams to ensure proper interpretation and reporting if needed**
- **There are multiple layers of safety oversight, including company pharmacovigilance, the NIH-led Protocol Safety Review Team, the DSMB itself and the FDA. <u>These are in place to protect volunteers.</u>**
- ***The recent regulatory hold for AstraZeneca and the clinical pause for Janssen are signs that the system is working as expected***

**Enrolling those at highest risk of infection and severe disease:**

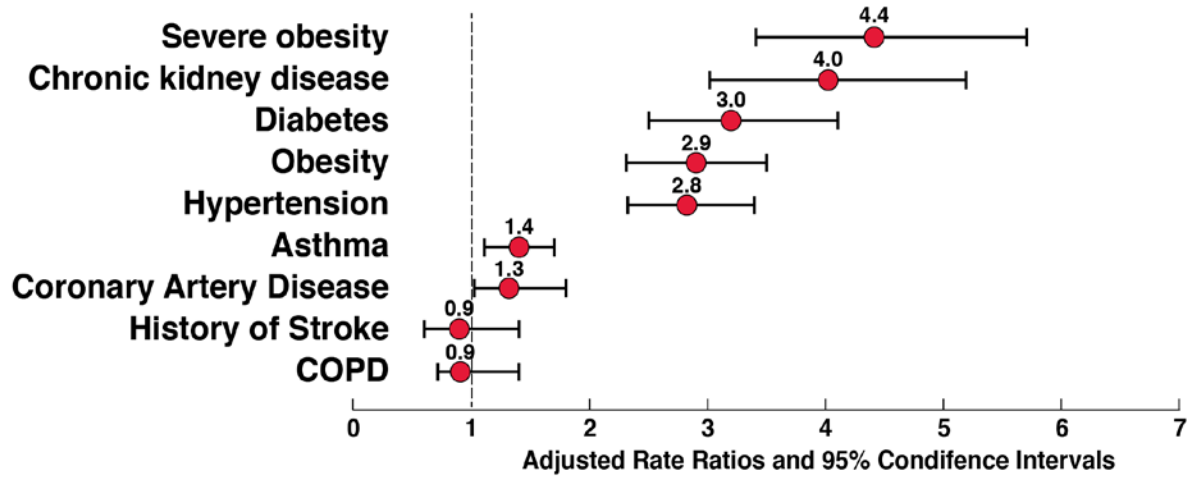
**It is critical that we assess safety and efficacy in those hardest hit by the pandemic.**

## Cumulative Rates of Laboratory-Confirmed COVID-19-Associated Hospitalizations by Age, United States, March 1 – October 10, 2020



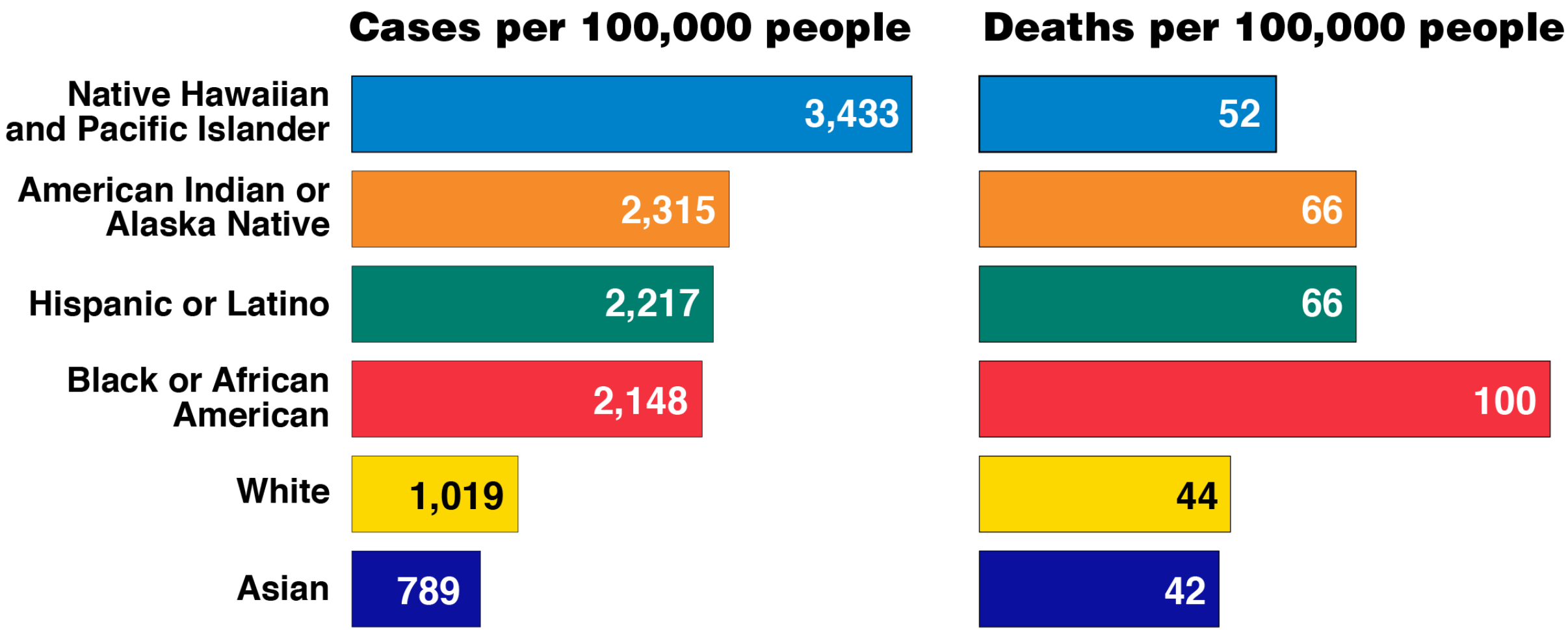

Source: CDC COVID-NET. Data from 14 states.

## Individuals with Underlying Medical Conditions Are at Increased Risk for Severe COVID-19




Source: COVID-net ACIP Presentation 8-26-20

# COVID-19 Cases and Deaths by Race/Ethnicity, United States, 2020

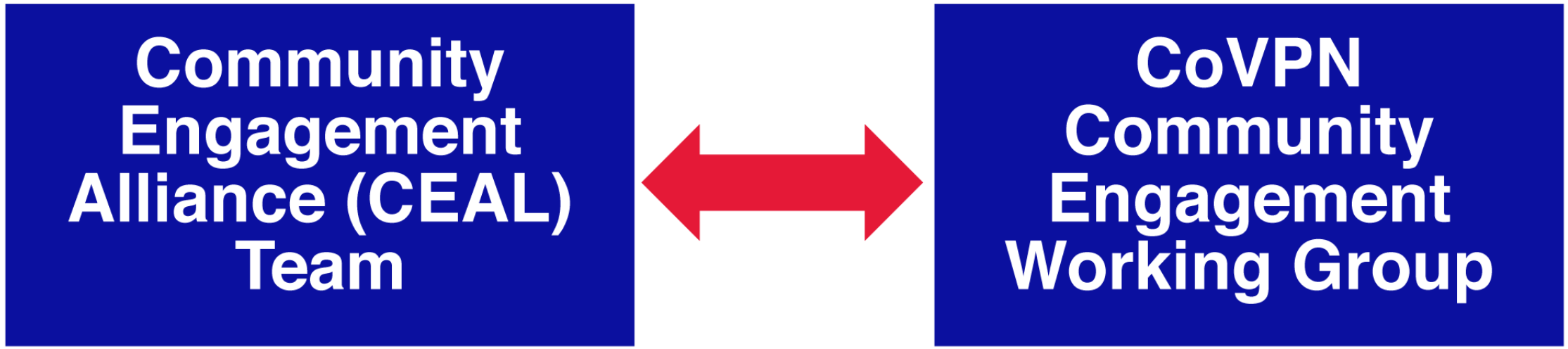



Source: COVID Tracking Project. Data through 10/16/2020.

- **Trials have explicit parameters for enrollment of volunteers with individual risk factors (e.g., ≥65 years of age, comorbidities) and race/ethnicity**
- **Proactive community engagement activities, especially with underserved minorities, are a top priority for NIH and partners**

**These measures are critical to the success of the trials themselves.**

**They will allow assessment of safety and efficacy populations at highest risk, supporting future acceptability**




**Pan-NIH entity leveraging longstanding clinical trial network community engagement**

**CoVPN-led group building on HIV trial expertise; led by health equity experts**

# Community Outreach and Partnership

- Expert Advisory Panels: Scientists from and working with priority populations
  - Modeled after NIH review committees
  - Convene and discuss each protocol
- Convening Community Working Groups with research familiarity
- Stakeholder Outreach – national organizations, local town halls, faith-based and grassroots organizations

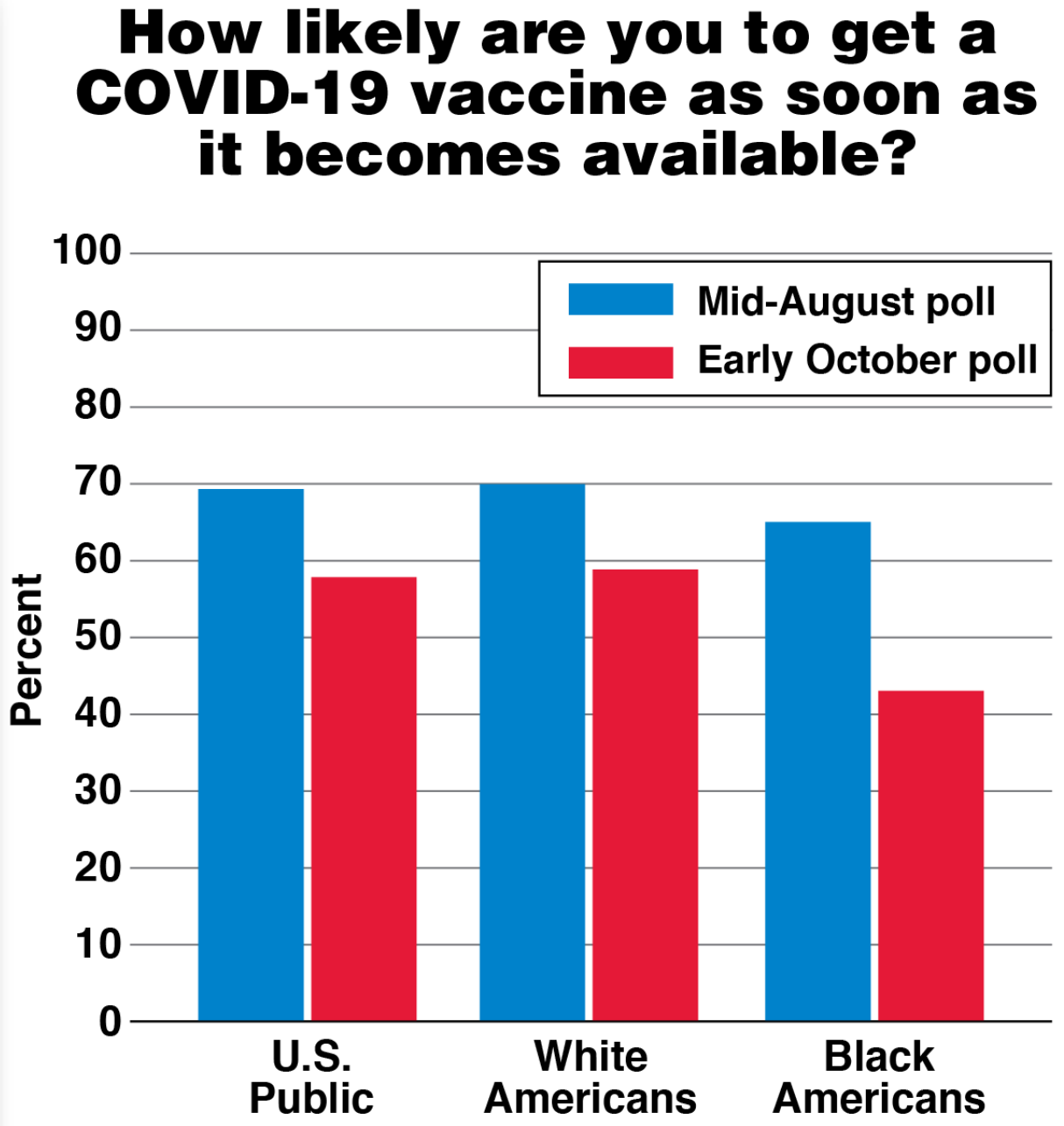
**Generating and maintaining trust in the trials and in the products (if successful):**

**Vaccines can only be effective if uptake is widespread.**

October 19, 2020

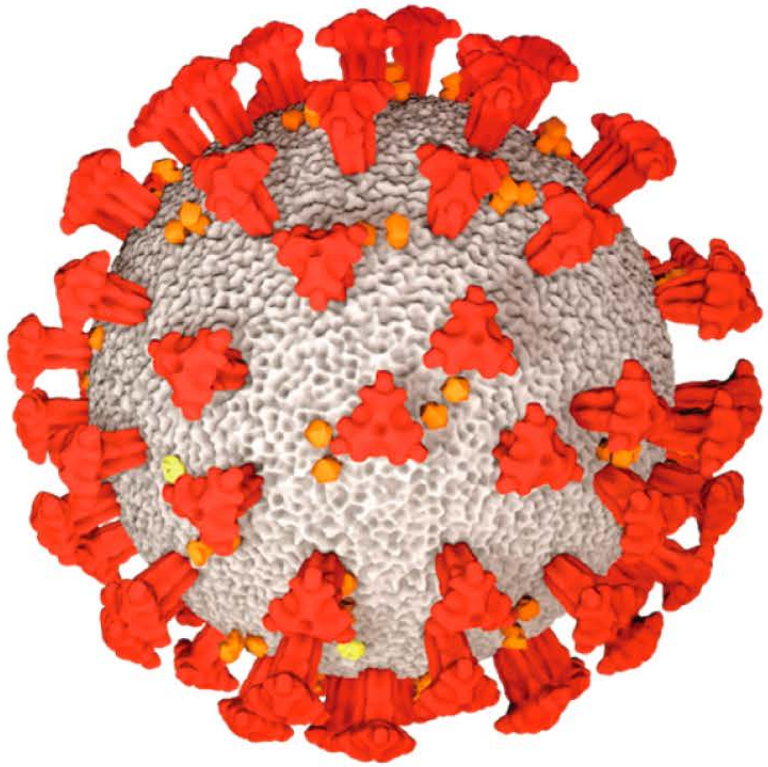
STAT

# STAT-Harris Poll: The Share of Americans Interested in Getting COVID-19 Vaccine as Soon as Possible is Dropping



# Specific Efforts to Improve Confidence in Vaccine Trials

- Maintaining safeguards for volunteers and for study conduct
- Engaging directly with stakeholders including those from underserved minorities hardest hit by the pandemic
- Communicating the roles that entities like the NIH, oversight groups and regulatory bodies play (e.g., NIH and BARDA in oversight of trials, DSMB in monitoring unblinded data and adverse events)
- Committing to transparency – companies have posted final protocols and shared enrollment data (including enrollment by race/ethnicity); prompt sharing of results will also be critical



# COVID-19

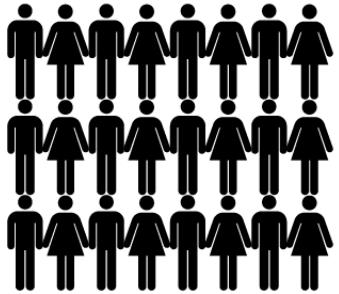
## Prevention Network

**www.preventcovid.org**

# BACKUP

# Randomized, Placebo Controlled, Phase 3 COVID Vaccine Efficacy Trial Explained

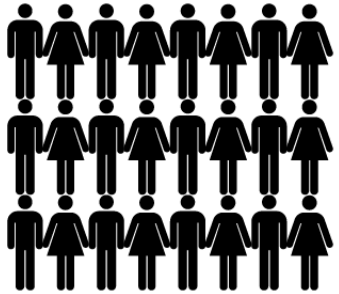
Vaccine Group



?

Volunteers don't know if they receive vaccine or placebo

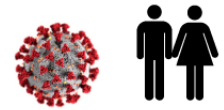
Placebo Group



Volunteers are closely monitored as they go about their lives

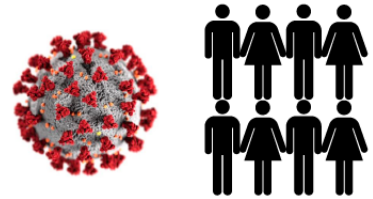
Symptomatic COVID-19 cases are diagnosed by study team (PCR+)

Vaccine Group



Vaccine Efficacy (VE) = %reduction disease incidence in vaccine group vs control group

Placebo Group



*Total number of volunteers range from 30,000 to 60,000 per trial*

*Asymptomatic COVID cases will be defined by retrospective analysis.*

# Comparison of Launched US Phase 3 Trials

| | moderna | BIONTECH Pfizer | AstraZeneca | Janssen Pharmaceutical Companies of Johnson & Johnson |
|---|---|---|---|---|
| Type | mRNA | mRNA | ChAdOx1 | rAd26 |
| n= | 30,000 (1:1) | 44,000 (1:1) | 30,000 (2:1) | 60,000 (1:1) |
| Opening and Status | July 2020 Enrolling | July 2020 Enrolling | Aug 2020 Enrolling (hold) | September 2020 Enrolling |
| Efficacy Target per Protocol (lower 95% CI Efficacy) | 60% (30%) | 60% (30%) | 60% (30%) | 60% (30%) |
| Target number of cases* | 151 | 164 | 150 | 154 |

NOVAVAX Creating Tomorrow's Vaccines Today — Projected to open Nov 2020

gsk SANOFI — Projected to open Dec 2020

*defined as meeting primary endpoint, exact case definitions vary but all information captured in case report forms

Source: Clinicaltrials.gov and respective company protocol public postings

# Nationwide Collaborative Network of COVID-19 Vaccine Clinical Trial Sites