COVID-19 Vaccine Development Considerations: A Summary of ACIP Meeting 7/29/20

CAPT THOMAS WEISER, MD, MPH
MEDICAL EPIDEMIOLOGIST,
PORTLAND AREA INDIAN HEALTH SERVICE

Overview

- Current status of COVID-19 Pandemic and brief summary of emerging epidemiology
- Introduction to Operation Warp Speed (OWS)
- COVID-19 Vaccine Safety Considerations
- FDA update on licensure and EUA
- Preparing for COVID-19 Vaccine Implementation
- COVID-19 vaccine prioritization

Current Status of COVID-19 Pandemic in the US – 8/2/2020

USA

4,601,526

TOTAL CASES

CDC | Updated: Aug 2 2020 12:15PM

USA

154,002

TOTAL DEATHS

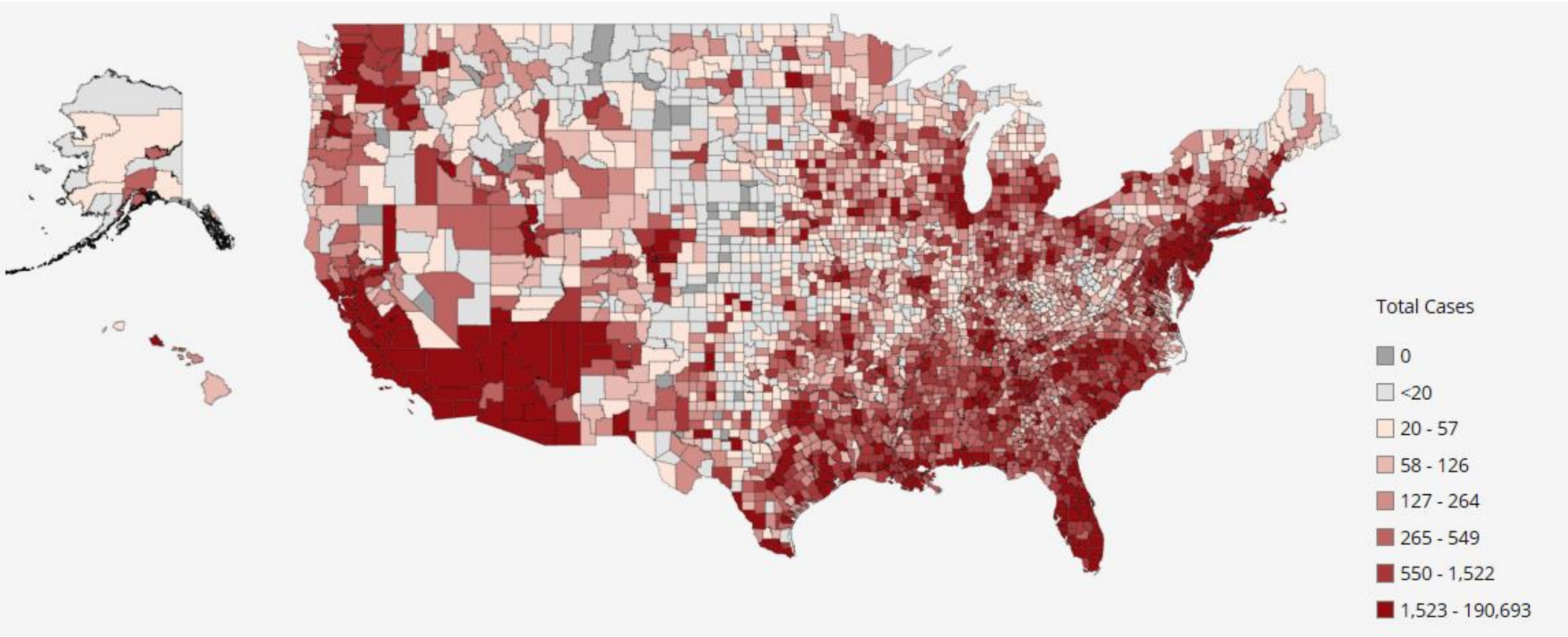
CDC | Updated: Aug 2 2020 12:15PM

USA

1,404

Cases per 100,000 People

CDC | Updated: Aug 2 2020 12:15PM



https://www.cdc.gov/covid-data-tracker/index.html#cases

Epi Summary

- Over 4 million cases of COVID-19 diagnosed in the United States through July
- Information on occupation for COVID-19 cases has not been systematically collected and reported
- Many occupations appear to have increased risk for COVID-19, including healthcare personnel and staff at long term care facilities, correctional and detention facilities, and food/agricultural settings
- Surveillance/projects ongoing to identify risk factors for COVID-19

OPERATION WARP SPEED:

Overview of COVID Vaccine Efficacy Trials

JULY 29, 2020

Julie Ledgerwood, DO
Deputy Director,
Chief Medical Officer,
Vaccine Research Center
National Institute of Allergy and Infectious Diseases
National Institutes of Health

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

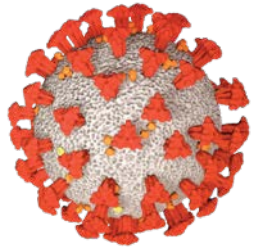
Three Entities with Distinct Roles in COVID-19 Response

Operation Warp Speed

USG body responsible for strategic approach, coordination and resource allocation

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)

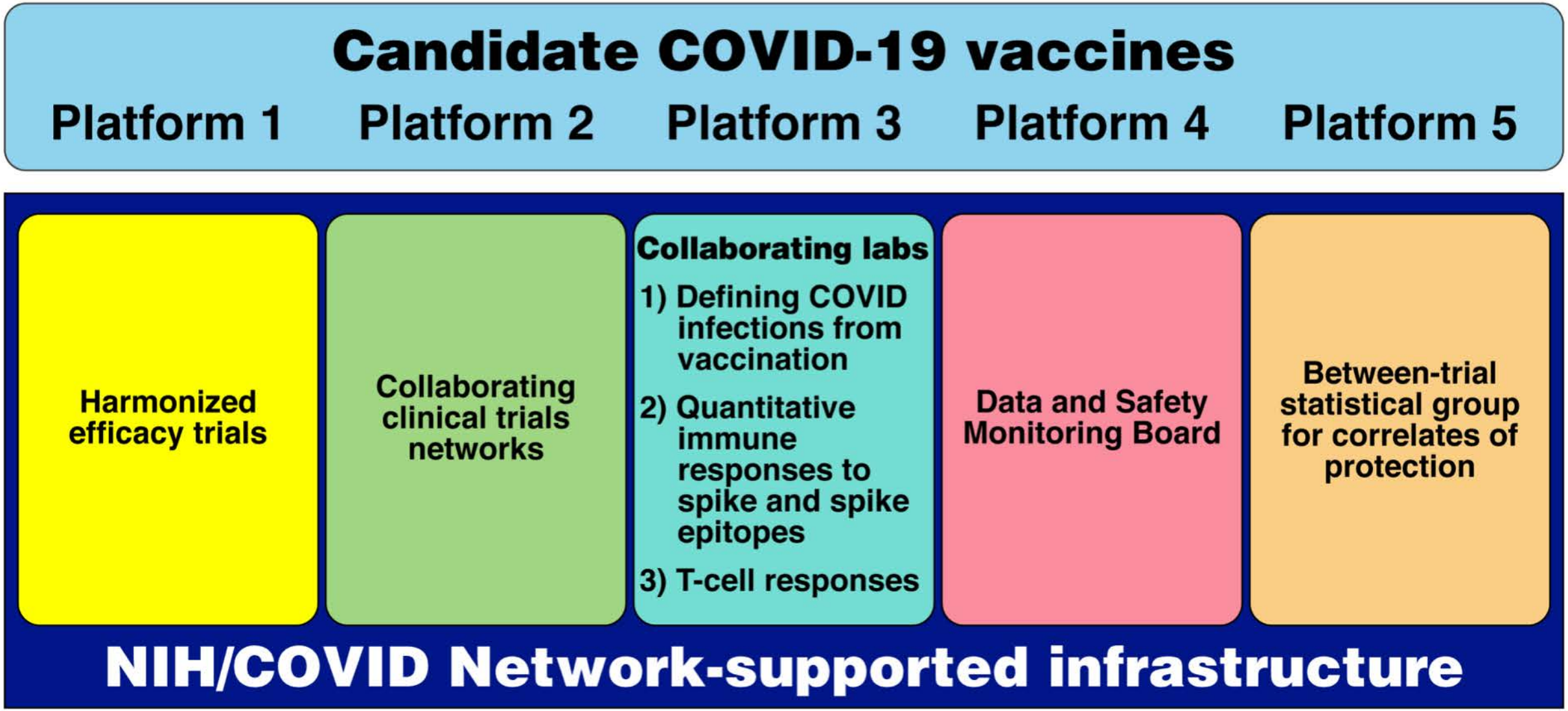
NIH established Public-private partnership for coordinating COVID-19 response



COVID-19 Prevention Network

NIH Funded networks - Phase 3 trial execution

Semi-Independent Harmonized Trials



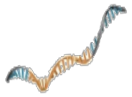
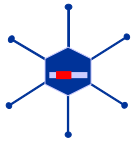
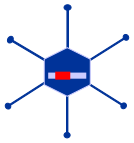
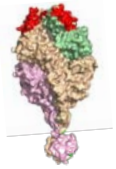
AS Fauci/NIAID

OWS Phase 3 Efficacy Trial Principles

- Randomized, Placebo-Controlled Efficacy Trial
- Sample size: approximately 30,000 volunteers
- Study Population: age ≥ 18 years, targeting subset at higher risk of severe disease, diverse populations
- Primary Endpoint: Prevention of symptomatic COVID-19 disease (virologically confirmed)
  - The primary efficacy endpoint point-estimate at least 50%
  - the statistical success criterion should be lower bound of the CI confidence around the point estimate is >30%.*
- Harmonized OWS immunogenicity assays and correlates analysis
- Common DSMB (NIAID Managed)

*Consistent with FDA guidance, June 2020

COVID-19 Vaccines in OWS Development

Vaccine companies Participating in OWS Led BARDA & NIH Funded Phase 3 Efficacy Trials			Phase 3 Open to Accrual (projected as of July 29, 2020)
moderna	mRNA		July 27, 2020
AstraZeneca	Ad Vector		TBD
janssen	Ad Vector		September 2020 (projected)
NOVAVAX Creating Tomorrow's Vaccines Today	Recombinant Protein+adjuvant		October 2020 (projected)

COVID-19 vaccines in human clinical trials – United States*

Candidate	Manufacturer	Type	Phase	Trial characteristics	Trial #
mRNA-1273	Moderna TX, Inc.	mRNA	II	• 2 doses (0, 28d) • IM administration • 18-55, 56+ years • Phase III: July 2020	NCT04283461 NCT04405076
mRNA-BNT162	Pfizer, Inc./BioNTech	mRNA	I/II	• Single or 2 doses • IM administration • 18-85 years	NCT04368728
INO-4800	Inovio Pharmaceuticals, Inc.	DNA plasmid	I/II	• 2 doses (0, 4w) • SC administration/ electroporation • ≥18 years	NCT04336410
KBP-COVID-19	Kentucky BioProcessing, Inc.	Protein subunit	I/II	• 2 doses (1,22d) • IM administration • 18-49, 50-70	NCT04473690

*As of July 23, 2020; trials have commenced or are approved to commence.
Sources: https://milkeninstitute.org/covid-19-tracker; https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines; https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/

COVID-19 Vaccine Safety Considerations

Kathryn M. Edwards MD
Sarah H. Sell and Cornelius Vanderbilt Professor
Division of Infectious Diseases
Department of Pediatrics
Vanderbilt University Medical Center

Mechanisms of Vaccine-Enhanced Disease

Immune response	Antibody		T cell
Syndrome	Antibody-dependent enhancement (ADE)	Vaccine-associated enhanced respiratory disease (VAERD)	
Mechanism	Fc-mediated increase in viral entry	Immune complex formation Complement deposition	T_H2-biased immune response
Effectors	Macrophage activation Inflammatory cytokines	Complement activation Inflammatory cytokines	Allergic inflammation T_H2 cytokines
Mitigation	Conformationally correct antigens High quality neutralizing antibody		T_H1-biasing immunization $CD8^+$ T cells

Rapid COVID-19 Vaccine Development: Finding the fastest pathway to vaccine availability includes the avoidance of safety pitfalls . Science 2020

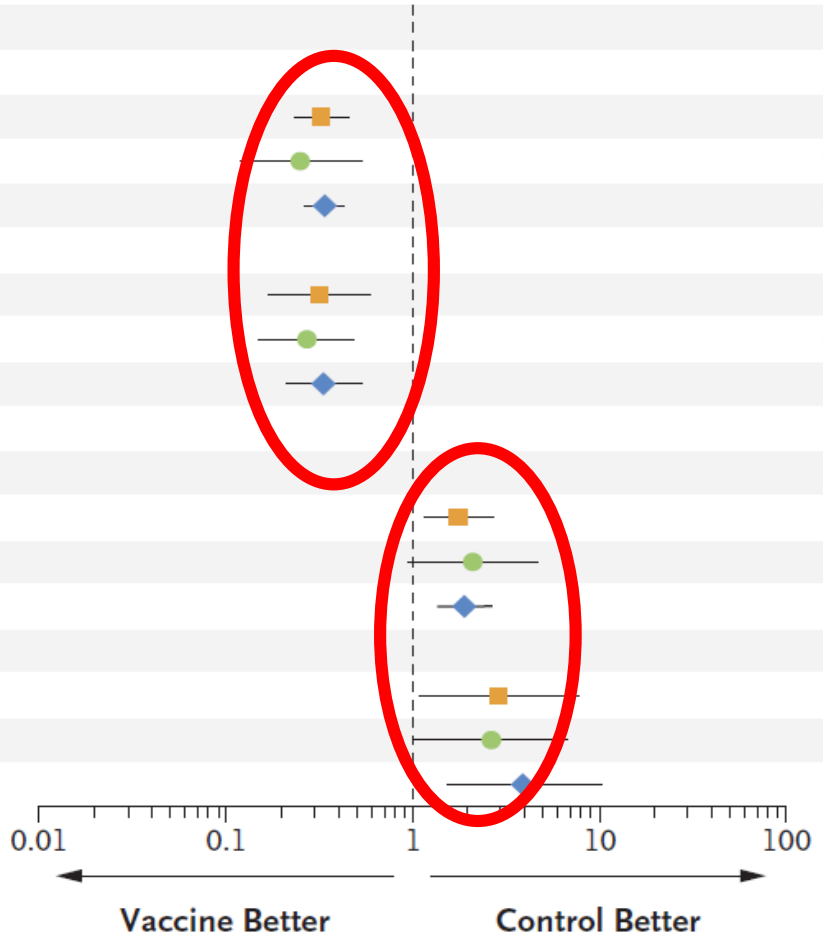
RS virus infection and serious illness in comparable groups of infants receiving one or more injections of inactivated RS and parainfluenza vaccines

Vaccine	Category of infants	No. and age of infants during designated time period of RS virus prevalence				
		1965–1966		1966–1967		Total No. infants
		No. infants	Age§ (mo.)	No. infants	Age§ (mo.)	
RS lot 100	At risk*	20	5.1	25‡	12.7	31
	RS infection†	5		15		20 (65%)‖
	Hospitalized	4		12		16 (80%)¶
Para 1 lot 23	At risk*	20	5.0	17‡	15.8	20
	RS infection†	2		10		12 (60%)‖
	Hospitalized			1		1 (8%)¶

Risk of Hospitalization for Virologically Confirmed Dengue (VCD) and of Severe VCD

B 2–16 Yr of Age

Serostatus, End Point, and Method	Vaccine Group	Control Group	Relative Risk or Hazard Ratio (95% CI)
	no./total no.		
Seropositive			
Hospitalization for VCD			
MI, month 0 onward	152.4/1816.1	227.5/886.2	0.32 (0.23–0.45)
TMLE, month 0 onward	99.2/1742.3	199.5/846.7	0.25 (0.12–0.53)
NS1, T9, month 13 onward	124/1750	175/822	0.34 (0.26–0.43)
Severe VCD			
MI, month 0 onward	35.1/1816.1	53.4/886.2	0.31 (0.17–0.58)
TMLE, month 0 onward	28.2/1742.3	49.9/846.7	0.27 (0.15–0.48)
NS1, T9, month 13 onward	31/1750	44/822	0.33 (0.21–0.53)
Seronegative			
Hospitalization for VCD			
MI, month 0 onward	201.6/567.9	62.5/307.8	1.75 (1.14–2.70)
TMLE, month 0 onward	244.0/547.2	65.5/296.8	2.10 (0.94–4.70)
NS1, T9, month 13 onward	187/512	53/272	1.89 (1.35–2.65)
Severe VCD			
MI, month 0 onward	44.9/567.9	8.6/307.8	2.87 (1.09–7.61)
TMLE, month 0 onward	44.6/547.2	9.3/296.8	2.62 (1.03–6.70)
NS1, T9, month 13 onward	37/512	5/272	3.93 (1.53–10.10)



Enhanced Disease in Animal Models after SARS-Cov1 Vaccines

Table 1
Evidence of enhanced disease in SARS-CoV-1 vaccine candidates.

Animal Model	Vaccine	Adjuvant	Immunopathology	Reference
Murine[1]	VEE Replicon Particles expressing N protein	–	YES	Deming 2006
Murine[2]	Recombinant Vaccinia virus expressing N protein	–	YES	Yasui 2008
Murine[3]	Inactivated Whole Virus	Alum	YES	Bolles 2011
		–	YES	
Murine[4]	Replicon Particles expressing S protein	–	YES	Sheahan 2011
Murine[5]	Inactivated Whole Virus and S protein vaccines	Alum	YES	Tseng 2012
		–	YES	
Ferret[6]	Recombinant Modified Vaccinia Virus Ankara (rMVA) expressing S protein	–	YES[†]	Weingartl 2004
NHP[7]	Modified Vaccinia Ankara (MVA) virus encoding full-length S protein	–	YES	Liu 2019
	Passive anti-S sera	N/A	YES	
NHP[7]	Inactivated Whole Virus	–	YES	Wang 2016/2020
	Passive Human SARS Antiserum	N/A	YES	

[1] Young and senescent female BALB/c mice.
[2] BALB/c mice.
[3] Aged BALB/c mice.
[4] Young and aged BALB/c mice.
[5] Female BALB/c mice.
[6] *Mustela putorius furo*, castrated males.
[7] Chinese rhesus macaque.
[†] Acute hepatitis.

CEPI/Brighton Collaboration Consensus Meeting

Concluding remarks

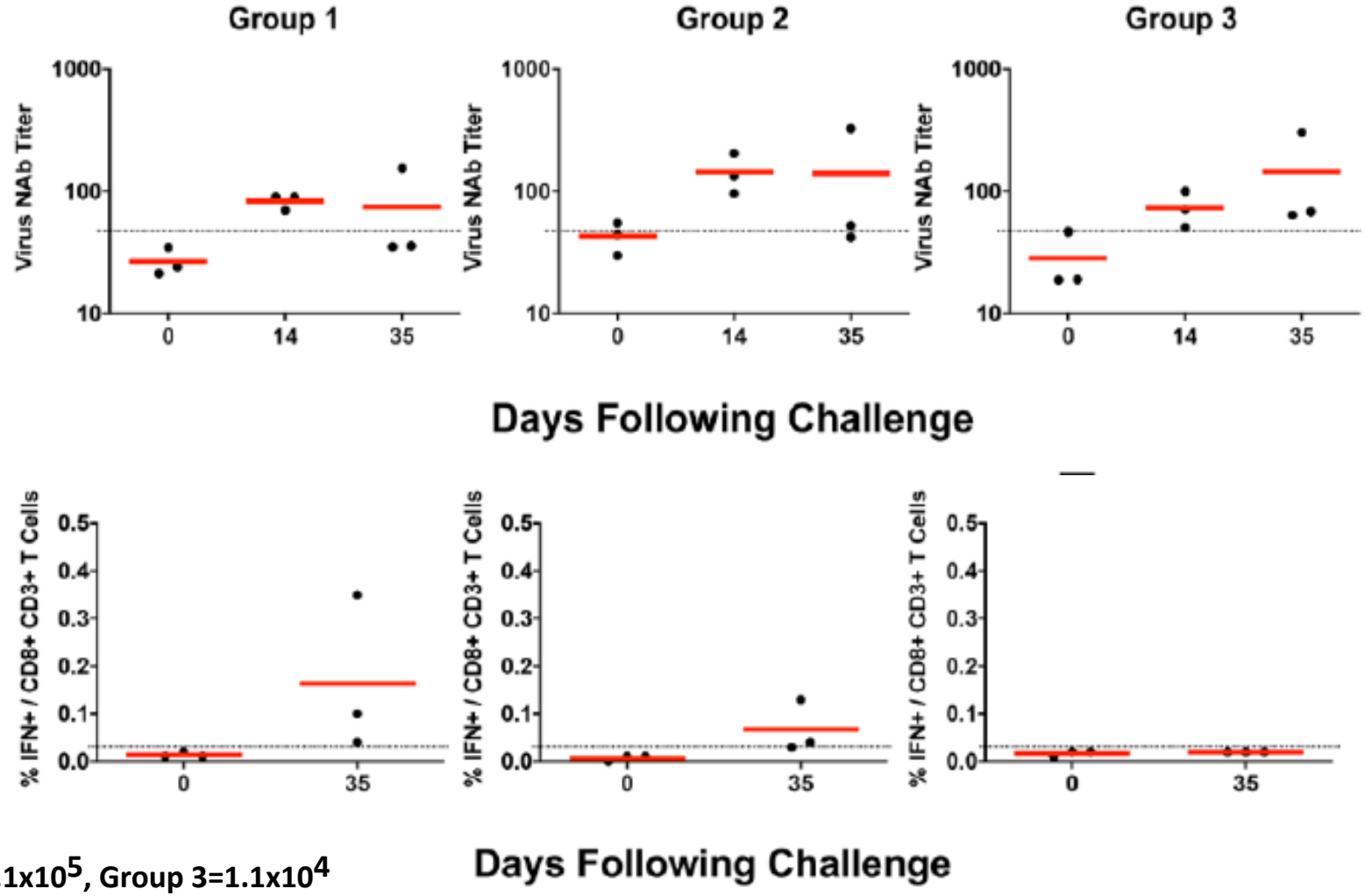
- The group of Experts considers that the demonstration of some disease enhancement with any candidate vaccine after viral challenge in animal models should not necessarily represent a no-go signal for deciding whether to progress into early trials in clinical development of a COVID-19 vaccine.
- Continuous monitoring of this risk during clinical trials in an epidemic context will be needed.
- Each observed effect should be discussed by the developers with their regulators who will ultimately define the actual requirements for clinical studies.

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

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

Neutralizing Antibody

Th1 response



Group 1=1.1x10^6 Group 2=1.1x10^5, Group 3=1.1x10^4

Control Animals

Immunized Animals

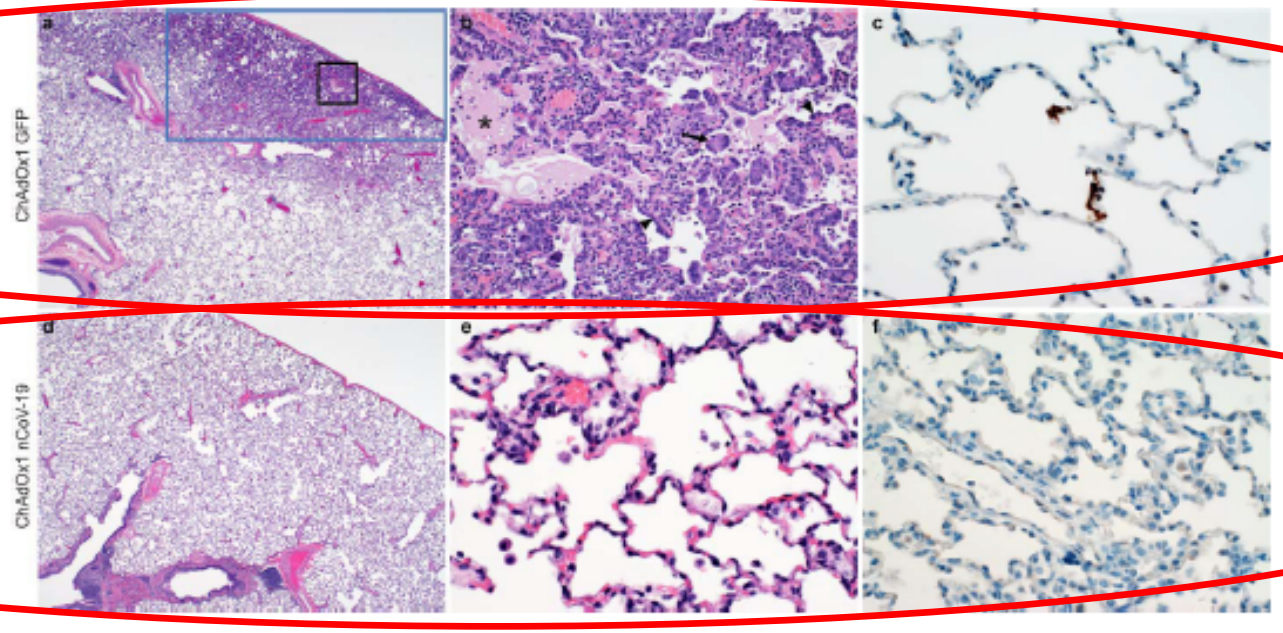


Figure 4. Histological changes in lungs of rhesus macaques on 7 dpi. a) Focal interstitial pneumonia in lungs of a control animal (blue box). The area in the black box is magnified in panel b. b) Interstitial pneumonia with edema (asterisk), type II pneumocyte hyperplasia (arrowhead) and syncytial cells (arrow) in control animals. c) SARS-CoV-2 antigen (visible as red-brown staining) was detected by immunohistochemistry in type I and type II pneumocytes in the lungs of control animals. d) No histological changes were observed in the lungs of ChadOx1 nCoV-19-vaccinated animals. e) Higher magnification of lung tissue in panel d. No evidence of pneumonia or immune-enhanced inflammation is observed. f) No SARS-CoV-2 antigen was detected by immunohistochemistry in the lungs of vaccinated animals. Magnification: panels a, d 40x; panels b, c, e, f 400x.

bioRxiv preprint doi: https://doi.org/10.1101/2020.05.13.093195.

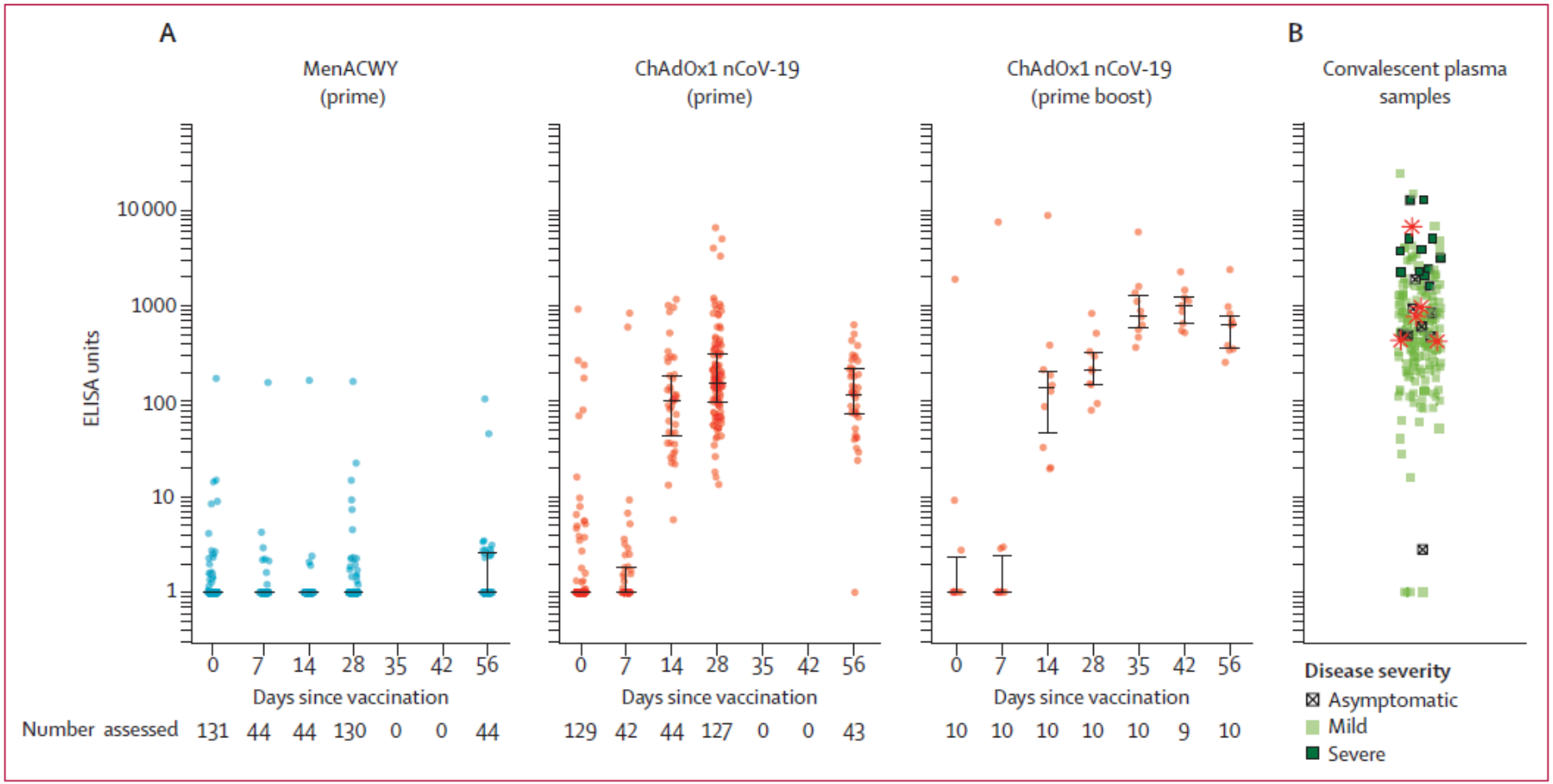


Figure 3: **SARS-CoV-2 IgG response by standardised ELISA to spike protein in trial participants (A) and in 180 convalescent plasma samples from 172 patients with PCR-confirmed COVID-19 and eight asymptomatic health-care workers (B)**

Error bars show median (IQR). Participants in the prime boost group received their second dose at day 28. Lower limit of quantification is 1 ELISA unit. Red stars in panel B show five samples also tested on the Marburg VN assay (see figure 4). MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Safety Assessment

- Standardized comprehensive safety assessments of local and systemic reactions.
- Recommended measuring biomarkers of vaccine-enhanced disease
  - Ratios of neutralizing and non-neutralizing antibodies
  - Antibody isotypes and affinities
  - Proinflammatory cytokine levels
  - Polarity of T cell responses

Conclusions

- An effective vaccine will likely be achieved with at least one of the vaccine approaches
- Vaccine safety will be meticulously assessed
- If enhanced disease occurs it will be carefully assessed and immune mechanisms investigated
- A safe and effective vaccine that is widely available would likely induce herd immunity
- Herd immunity to SARS 2 would allow us to resume normal activities

Considerations for FDA Licensure vs. Emergency Use Authorization of COVID-19 Vaccines

Doran Fink, MD, PhD
FDA/CBER Office of Vaccines Research and Review

ACIP COVID-19 Meeting
July 29, 2020

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA Licensure

- **Requirement for demonstration of vaccine safety, effectiveness and controlled/consistent manufacturing to ensure continued safety and effectiveness of the licensed vaccine**

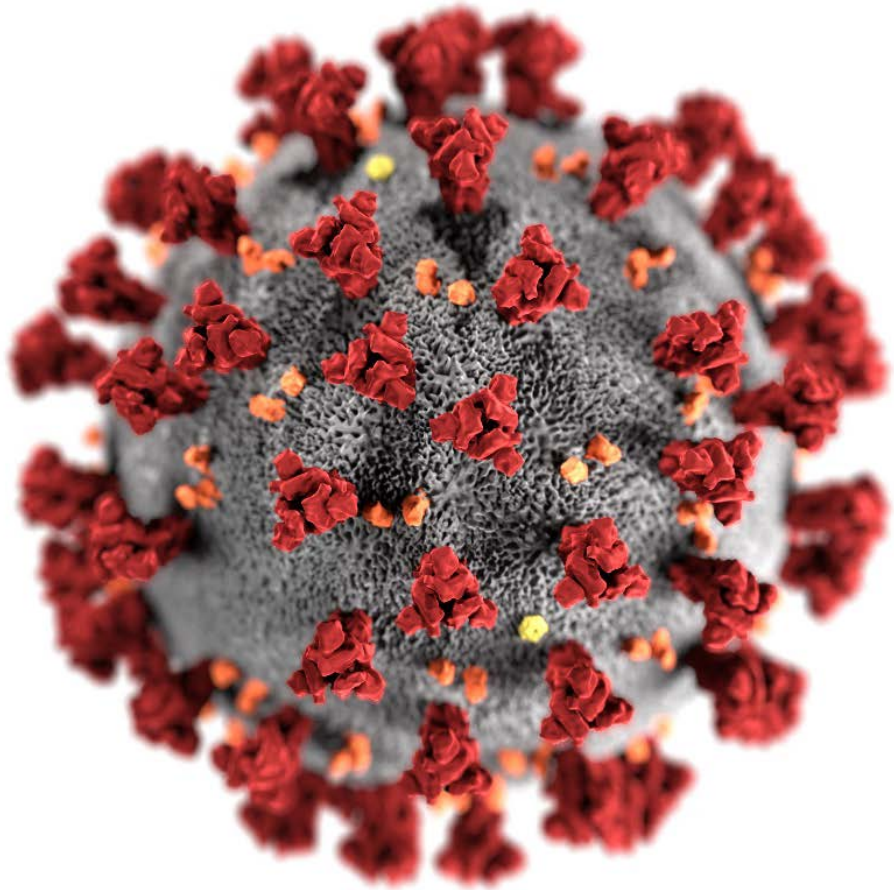
- **“Traditional” approval pathway for COVID-19 vaccines**
  - Substantial evidence of effectiveness to support licensure could be demonstrated in clinical disease endpoint efficacy trials

- **Other FDA licensure pathways (accelerated approval, “animal rule”) would not apply to COVID-19 vaccines at this time, given:**
  - Sufficient COVID-19 incidence to allow for clinical disease endpoint efficacy trials
  - Limited understanding of SARS-CoV-2 immunology and immune response biomarkers that might predict protection against COVID-19

Considerations for EUA

- **FDA Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19 (June 2020):**
  - Issuance of an EUA based on very preliminary safety and efficacy data from randomized, controlled trials could reduce the ability to demonstrate effectiveness and assess benefits vs. risks of the vaccine to support licensure
  - For a vaccine for which there is adequate manufacturing information, issuance of an EUA may be appropriate once studies have demonstrated the safety and effectiveness of the vaccine but before the manufacturer has submitted and/or FDA has completed its formal review of the biologics license application
  - Any assessment regarding an EUA would be made on a case by case basis considering the target population, characteristics of the product, preclinical and human clinical study data, and the totality of available relevant scientific evidence

ACIP COVID-19 Vaccines Work Group



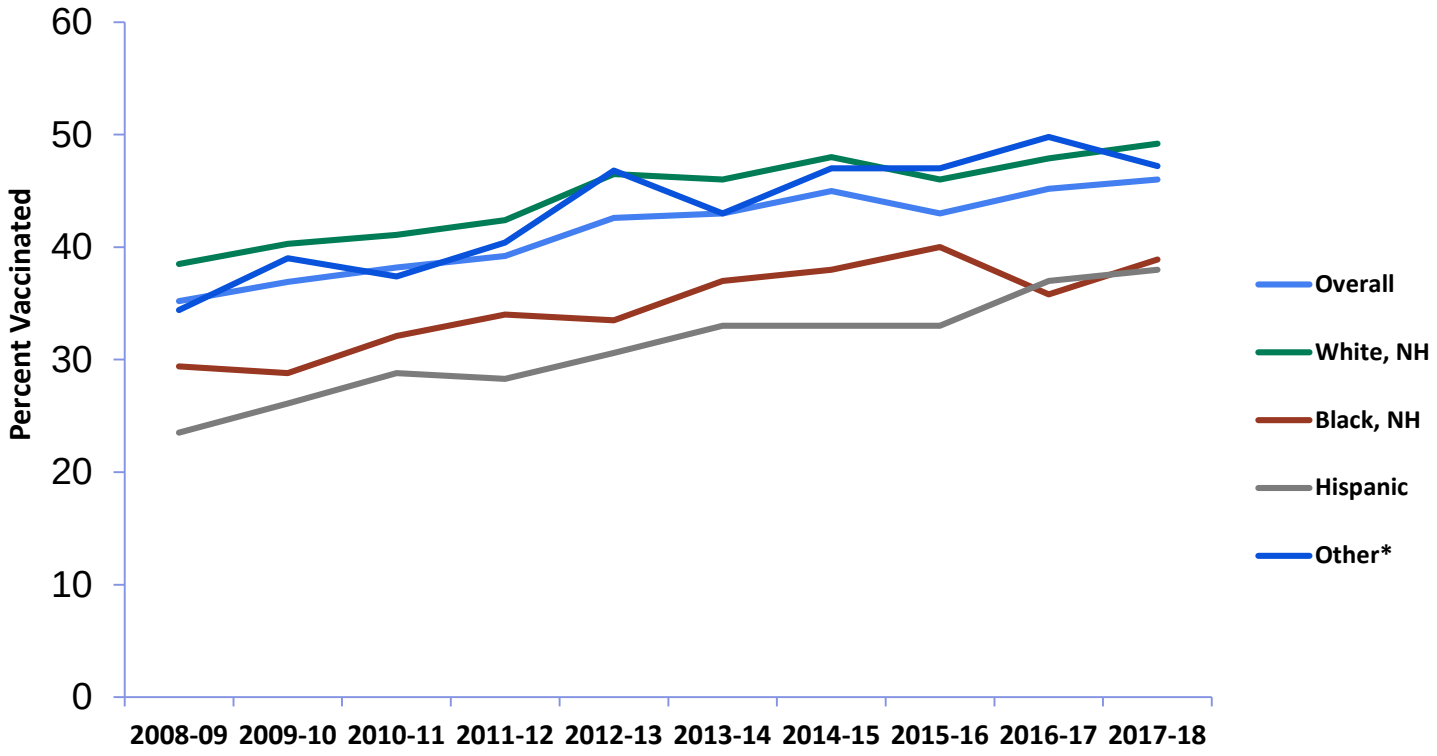
COVID-19 vaccine implementation

Nancy Messonnier, MD

July 29, 2020

Rising to the challenge to achieve high coverage with COVID-19 vaccines

Influenza Vaccination Coverage, ≥18 years, by Race/Ethnicity: 2008-09 – 2017-18



*Other includes Asian, American Indian/Alaska Native, and multiple race.

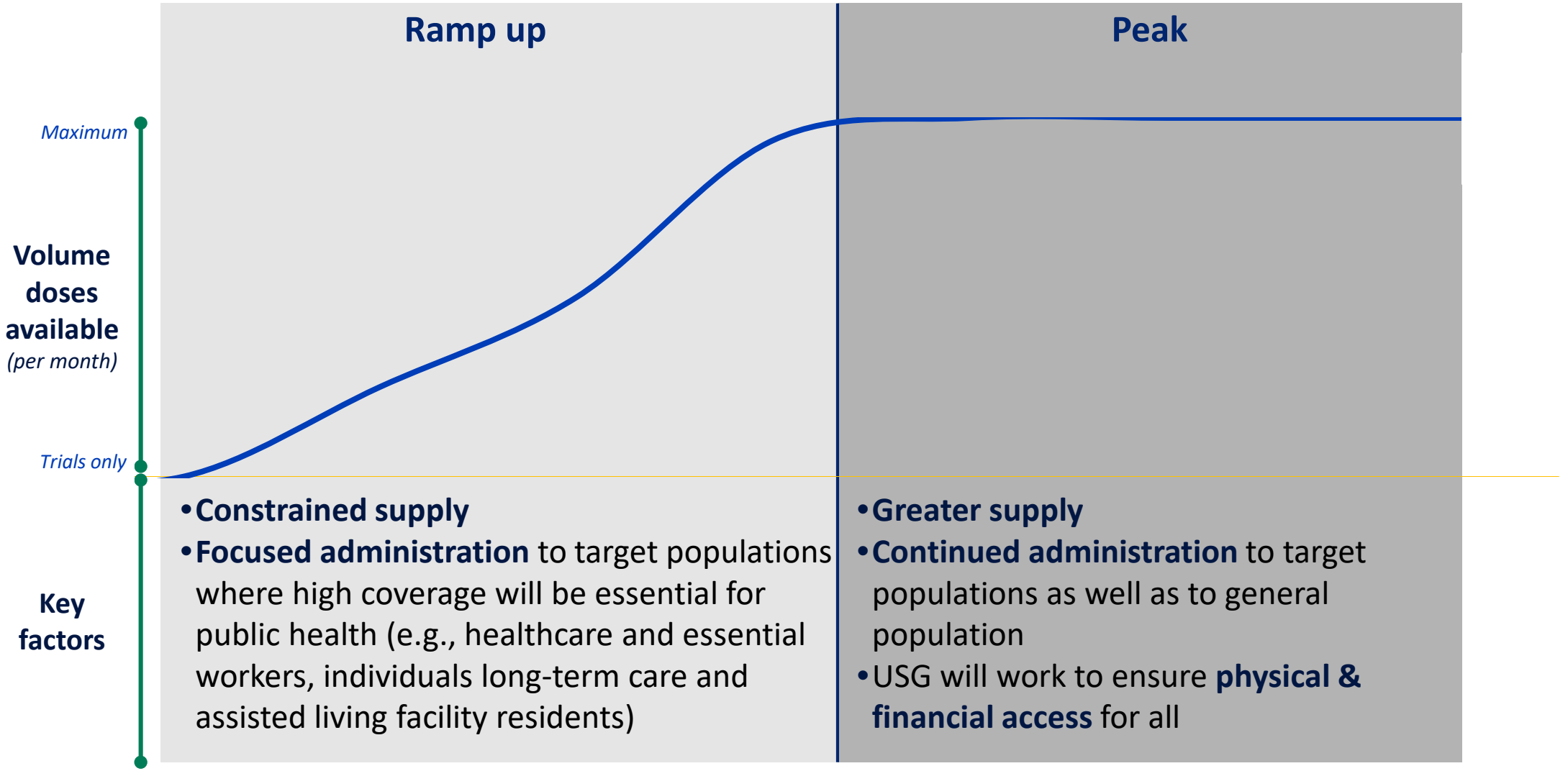
- Vaccination coverage of racial and ethnic minorities is consistently lower than that of white populations
- **We need novel and more robust strategies to increase uptake of COVID-19 vaccine, once one becomes available**

Source: Vaccination Coverage among Adults in the United States, National Health Interview Survey, CDC, 2017. NH = Non-Hispanic. Vaccinations included in this assessment include influenza, pneumococcal, Td, Tdap, Zoster, HepA, HepB, and HPV.

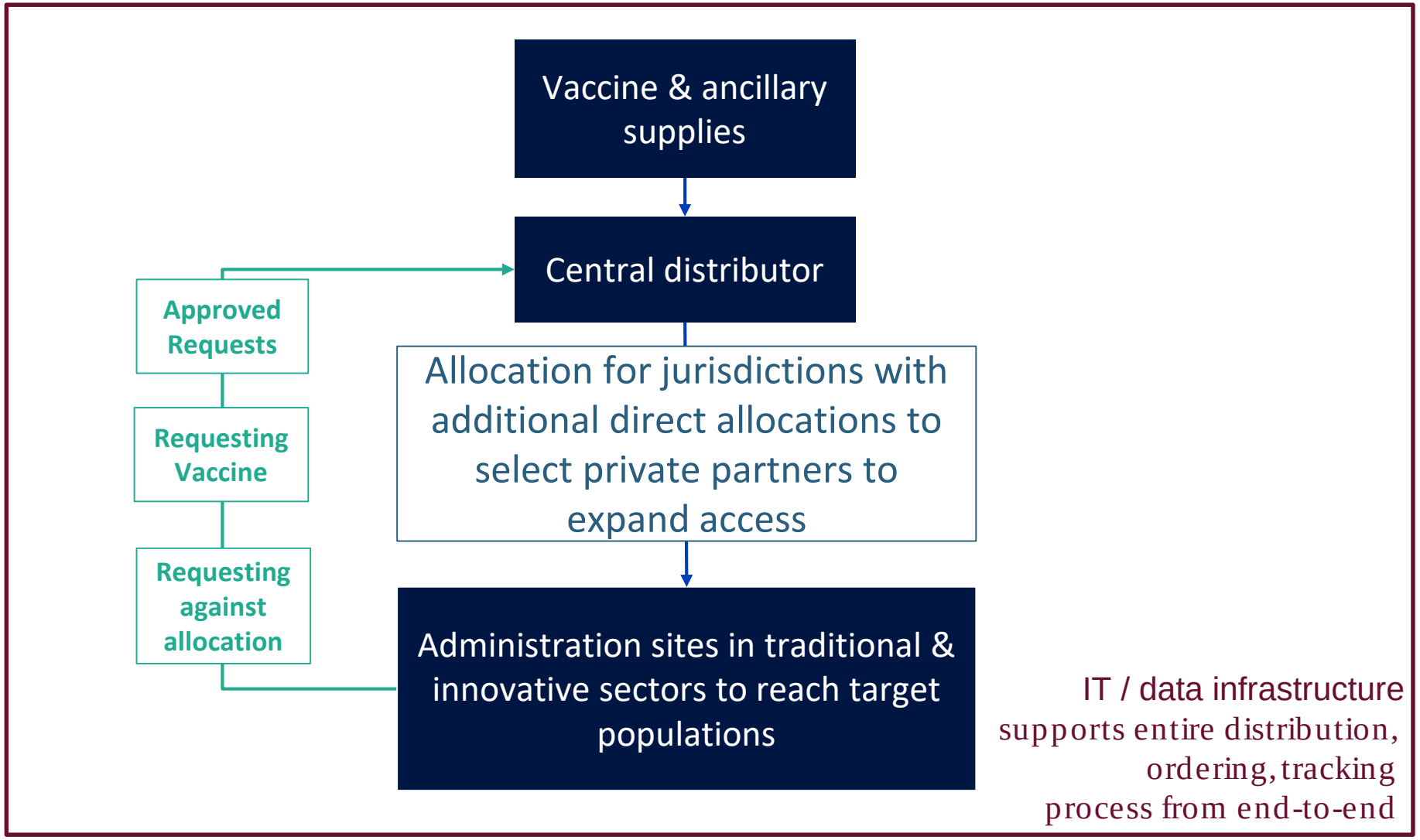
Complex and evolving landscape for COVID-19 vaccine

- One vs. two dose series, products not interchangeable
- Varying presentations
- Vaccine efficacy and adverse event profile in different populations
- Varying cold-chain requirements
- Use in children and pregnant women
- Need for socially distanced vaccination practices
- Communication and education
- High-risk groups for COVID-19 may distrust public health

As volume of doses available increases, we will be able to vaccinate broader populations

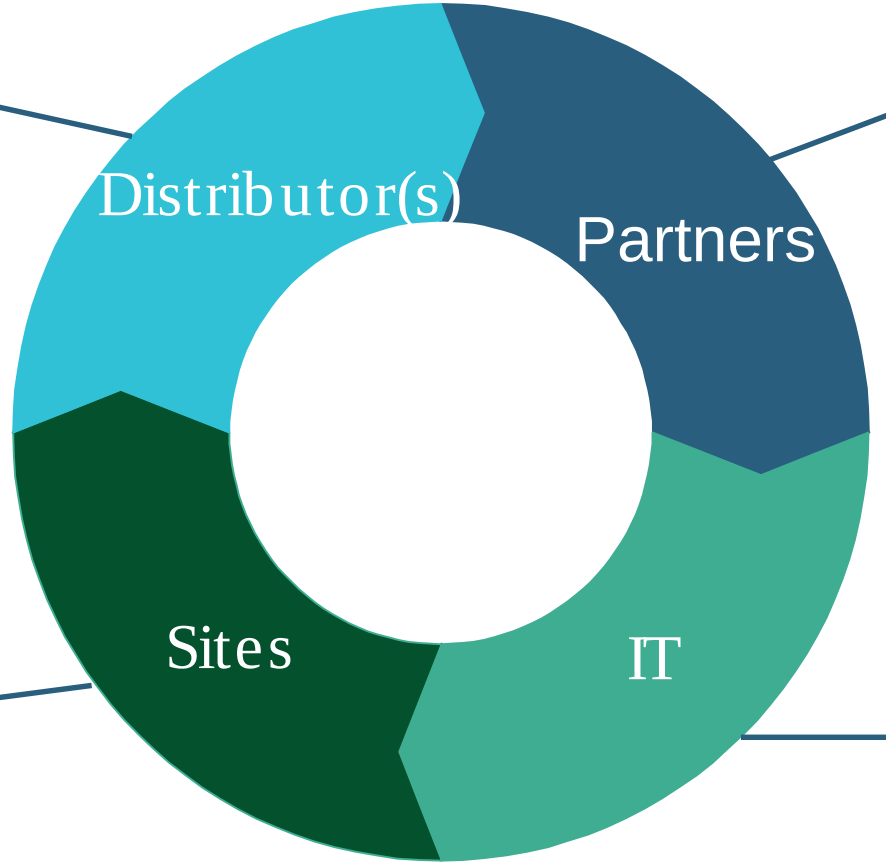


Approach to COVID-19 vaccination



To distribute and administer a COVID-19 vaccine, we will leverage many opportunities to ensure success

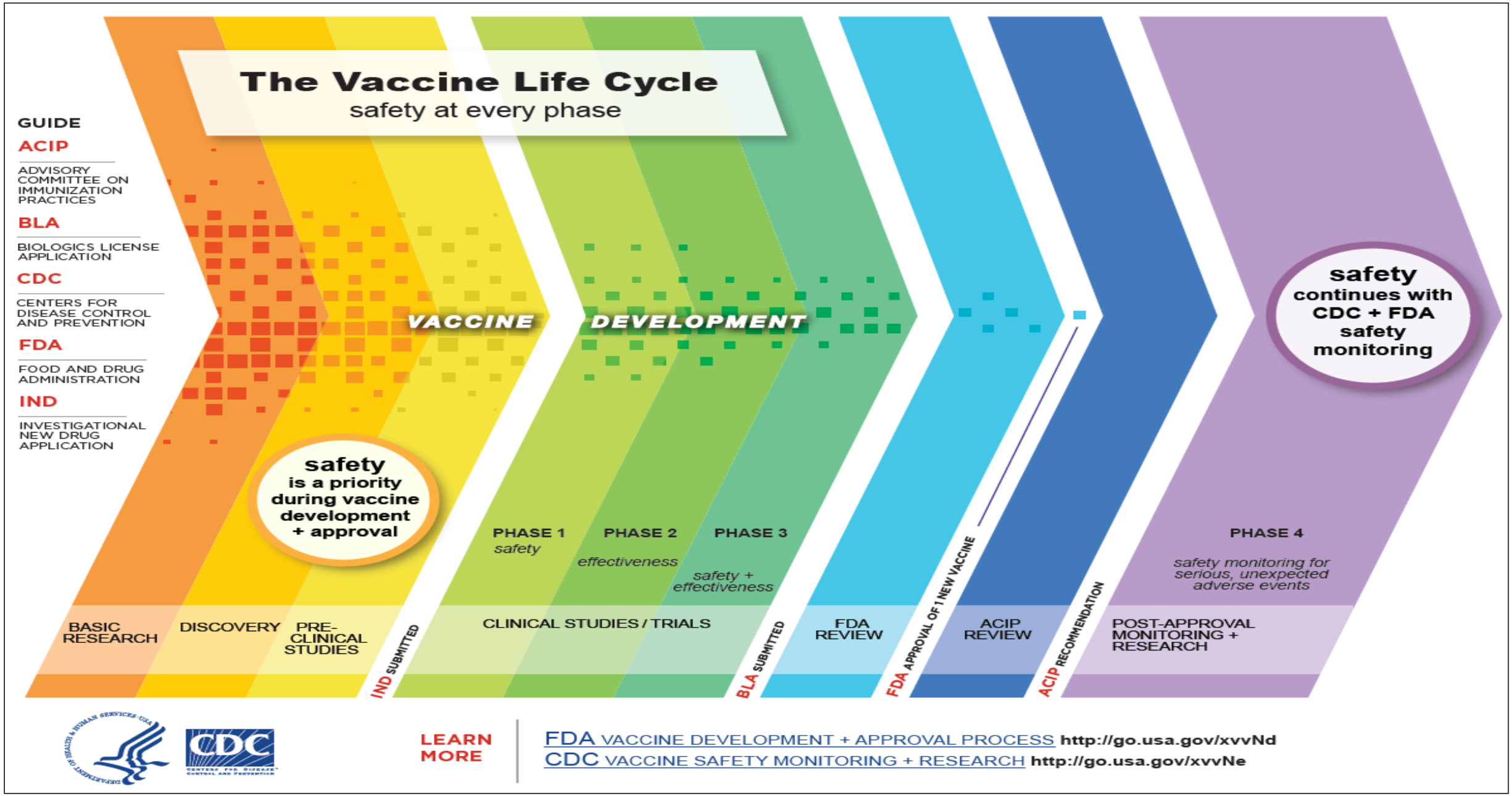
Partnerships with distributor(s) will ensure the vaccine is readily and efficiently distributed across the country



State, local, and community partners will be instrumental in planning for widespread vaccination

Diverse administration sites (pharmacies, doctor's offices, mobile clinics, etc.) will ensure all individuals have physical access to the vaccine

IT infrastructure will support the entire vaccine ordering, distribution, and tracking process from end-to-end


The Vaccine Life Cycle
safety at every phase
GUIDE
ACIP
ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
BLA
BIOLOGICS LICENSE APPLICATION
CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION
FDA
FOOD AND DRUG ADMINISTRATION
IND
INVESTIGATIONAL NEW DRUG APPLICATION
VACCINE DEVELOPMENT
safety is a priority during vaccine development + approval
safety continues with CDC + FDA safety monitoring
PHASE 1
safety
PHASE 2
effectiveness
PHASE 3
safety + effectiveness
PHASE 4
safety monitoring for serious, unexpected adverse events
BASIC RESEARCH
DISCOVERY
PRE-CLINICAL STUDIES
IND SUBMITTED
CLINICAL STUDIES / TRIALS
BLA SUBMITTED
FDA REVIEW
FDA APPROVAL OF 1 NEW VACCINE
ACIP REVIEW
ACIP RECOMMENDATION
POST-APPROVAL MONITORING + RESEARCH
LEARN MORE
FDA VACCINE DEVELOPMENT + APPROVAL PROCESS http://go.usa.gov/xvvNd
CDC VACCINE SAFETY MONITORING + RESEARCH http://go.usa.gov/xvvNe

Vaccinate with **Confidence**

CDC's strategic framework for strengthening vaccine confidence and preventing outbreaks of vaccine preventable diseases.

Protect **communities**

Strategy: Protect communities at risk from under-vaccination

- ✓ Leverage immunization data to find and respond to communities at risk
- ✓ Work with trusted local partners to reach at-risk communities before outbreaks
- ✓ Ensure vaccines are available, affordable, and easy-to-get in every community

Empower **families**

Strategy: Get providers and parents effective information resources

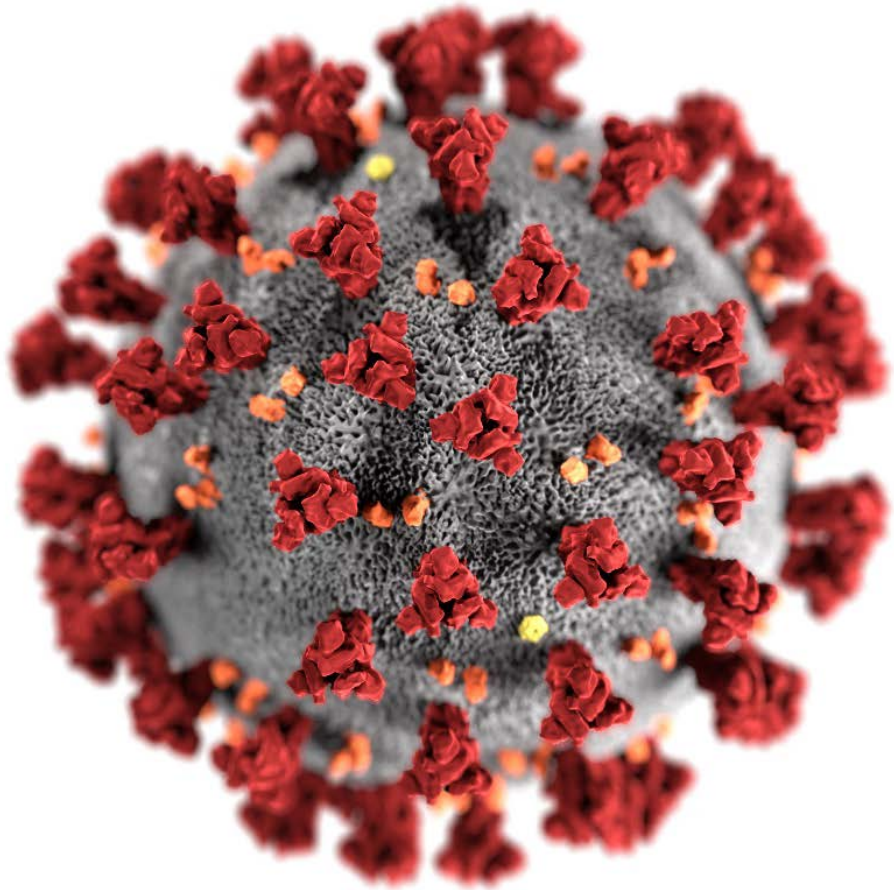
- ✓ Expand resources for health care professionals to help them have effective vaccine conversations with parents
- ✓ Work with partners to start conversations before the first vaccine appointment
- ✓ Help providers foster a culture of immunization in their practices

Stop **myths**

Strategy: Stop misinformation from eroding public trust in vaccines

- ✓ Work with local partners and trusted messengers to improve confidence in vaccines among key, at-risk groups
- ✓ Establish partnerships to contain the spread of misinformation
- ✓ Educate key new stakeholders (e.g., state policy makers) about vaccines

ACIP COVID-19 Vaccines Work Group



COVID-19 vaccine prioritization: Work Group considerations

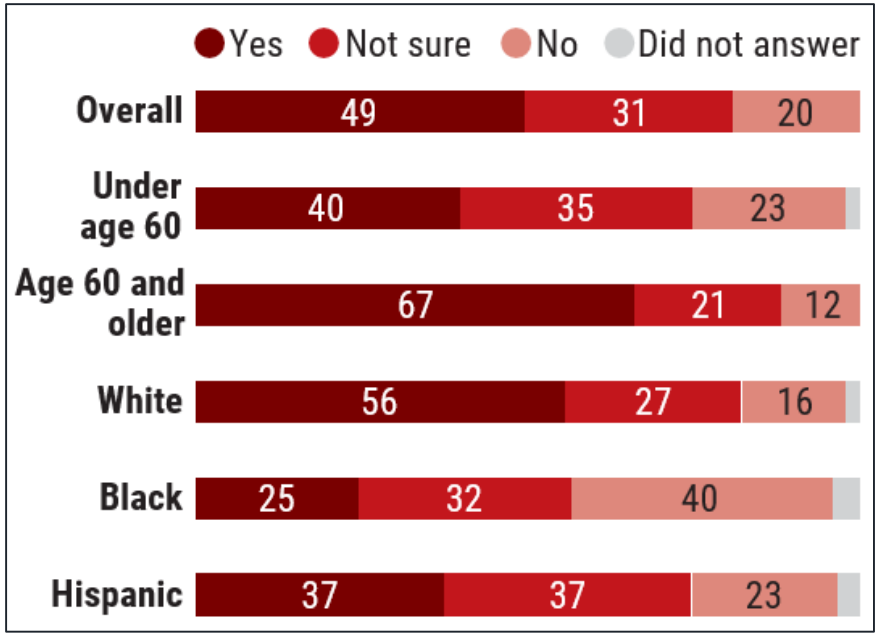
Sarah Mbaeyi, MD MPH

July 29, 2020

Acceptance of COVID-19 vaccines likely varies in the general population

- 49-72% of consumer survey respondents express vaccination intention (May-June 2020)
  - Differences in methodology and framing of question likely accounts for some variation
- Substantial variation in population views towards vaccination
- Limited information available in healthcare personnel and other essential workers

"If a coronavirus vaccine becomes available, do you plan to get vaccinated?"

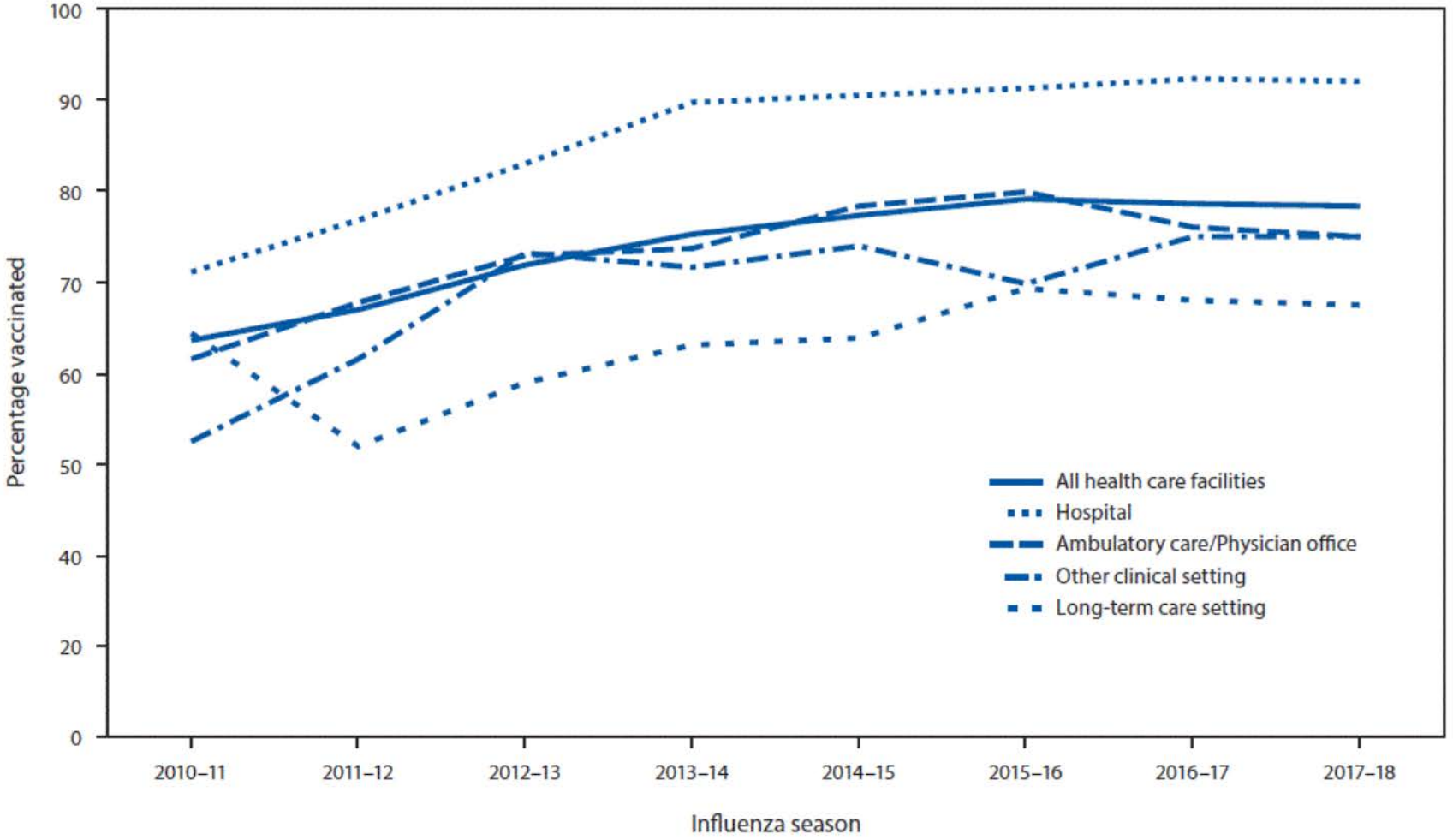


Source: AP/NORC, survey among 1,056 people (May 14-18, 2020)

Washington Post/ABC: https://context-cdn.washingtonpost.com/notes/prod/default/documents/0ed77132-0add-4232-b50f-637bd08dbe15/note/6acfa6e9-e416-4f22-8401-fd871d2ba456
AP/NORC: https://apnews.com/dacdc8bc428dd4df6511bfa259cfec44
Pew: https://www.pewresearch.org/fact-tank/2020/05/21/most-americans-expect-a-covid-19-vaccine-within-a-year-72-say-they-would-get-vaccinated/
ICF: https://www.icf.com/insights/health/covid-19-survey-americans-hesitant-vaccine
IPSOS: https://www.ipsos.com/sites/default/files/ct/news/documents/2020-05/writeup_reuters_2020_coronavirus_vaccine_05_21_2020.pdf
CNN: http://cdn.cnn.com/cnn/2020/images/05/12/rel5b.-.economy.and.reopening.pdf

Influenza vaccination coverage among healthcare personnel

Insight into potential acceptance of COVID-19 vaccines



- **78%** overall coverage in 2017-2018 season
  - Higher than general adult population coverage of 37%
- Workplace vaccination requirement: greatest predictor of coverage
- Lowest coverage in long-term care facility workers

Black CL, et. al. MMWR Morb Mortal Wkly Rep 2018;67:1050–1054.
https://www.cdc.gov/flu/fluvaxview/coverage-1819estimates.htm

Work Group summary: COVID-19 vaccination of essential workers, including healthcare personnel

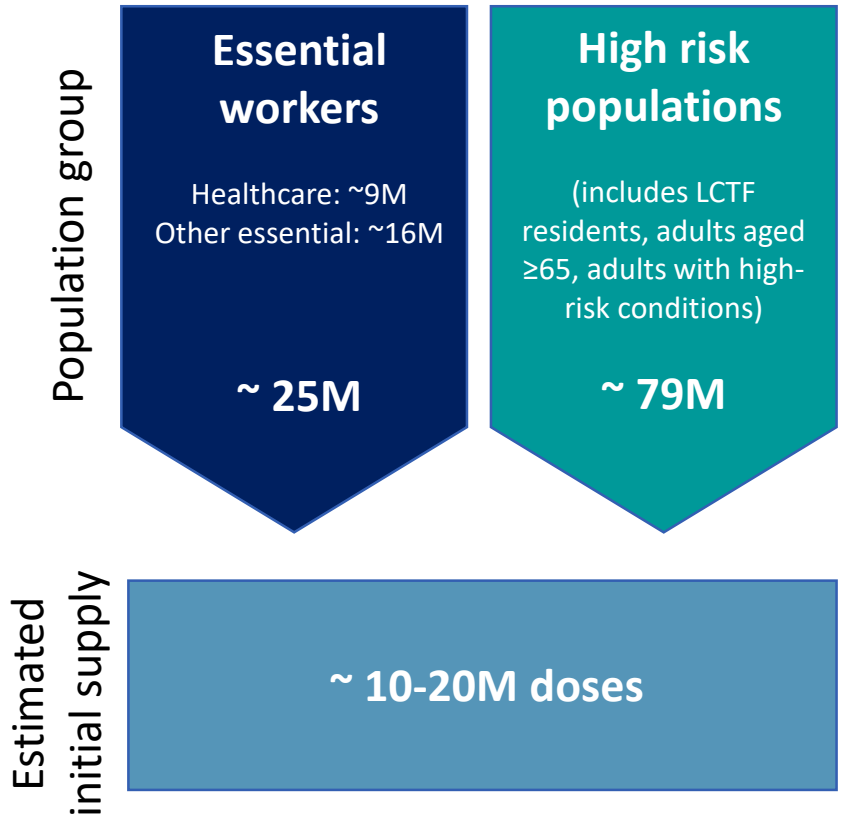
- Protection of the healthcare infrastructure an important consideration
- Health equity a consideration in vaccination of healthcare and other essential workers
  - High proportion of minority, lower income, or medically high-risk populations in some sectors
- Likely broad public support for the prioritization of these groups for COVID-19 vaccine
- Although implementation will likely have challenges, vaccination of these occupational groups likely more feasible than the general public

Work Group considerations: When COVID-19 vaccines become available, should essential workers (including healthcare personnel) be among the initial priority group?

Domain	Criteria	Work Group Interpretation
Problem	• Is the problem of public health importance?	Yes
Values and preferences	• Does the target population feel that the desirable effects are large relative to undesirable effects? • Is there important uncertainty about or variability in how much people value the main outcomes?	Probably yes Yes
Acceptability	• Is the intervention acceptable to key stakeholders?	Probably yes
Feasibility	• Is the intervention feasible to implement?	Probably yes

Overall Work Group interpretation: Initial priority group for COVID-19 vaccination should include healthcare and other essential workers

Work Group considerations: vaccine prioritization during a period of initial limited supply



- Work Group consensus that both essential workers and high risk populations are important groups for early vaccination
  - Given anticipated initial supply, sub-prioritization necessary
- Work Group does not agree that priority group should be limited to only healthcare and other essential workers:
  - Work Group and ACIP largely comprised of healthcare personnel; concern about appearing biased towards this group
  - Groups at highest risk of death would not be included
- **Overall interpretation:** Work Group in agreement that essential workers (including healthcare personnel) should be included as one of the priority groups for early vaccination

* Estimated numbers based on updates to both occupational categories and denominators from 2018 pandemic influenza guidance (https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2020-06/COVID-08-Mbaey-508.pdf). Numbers are preliminary, are currently being updated, and will likely change.

Work Group proposed criteria for sub-prioritization of essential workers for COVID-19 vaccination

Categories of essential workers

- Healthcare personnel
- Homeland and national security
- Other essential workers

Proposed criteria

- Risk of exposure, infection, and severe disease
  - Occupational and community risk
- Protection of the healthcare infrastructure and other societal functions
- Reduce risk of transmission to vulnerable populations
- Equity considerations
- Implementation considerations

* ACIP makes vaccine recommendations for the U.S. civilian population