COVID Vaccines: Approaches to vaccine trial design

November 4, 2020

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These are my views, and do not represent those of the NIH, DHHS, or the US government.

Plan

- Vaccine research
- Ethical challenges in vaccine trials
- Approaches to testing a SARS CoV-2/COVID-19 vaccine
- Current status/ COVID-19 vaccine landscape

Vaccines

- "With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction…"

- Since 2000-
  - Deaths in children < 5yo reduced (Millennium Development Goals)
  - More children reached than ever before (>100 million in 2005-07)
  - More vaccines available and more lives saved in developing countries
  - More money available through innovative funding mechanisms
  - Most productive decade in history of vaccine development
  - Global vaccine market has tripled, vaccine industry one of fastest growing sectors of industry

WHO, UNICEF, and the World Bank. State of the world's vaccines and immunization, 3rd Ed. Geneva, WHO, 2009

Table 1. Currently Licensed Vaccines

Adenovirus	Meningococcal B
Anthrax	Mumps
Cholera	Pertussis
Dengue	Pneumococcal conjugate
Diphtheria	Pneumococcal polysaccharide
Enterovirus 71	Polio, inactivated
Hemophilus influenzae type b	Polio, live
Hepatitis A	Rabies
Hepatitis B	Rotavirus
Human papilloma virus	Rubella
Influenza, live	Smallpox
Influenza, killed	Tetanus
Japanese encephalitis	Tick-borne Encephalitis
Malaria RTS/S	Varicella
Measles	Yellow fever
Meningococcal A, C, W, Y	Zoster

Plotkin S. Vaccines we Need but Don't Have. *Viral Immunology* 2018

Table 2. Selected Diseases and Infections for Which We Do Not Have Licensed Vaccines or Only Partially Effective Vaccines

Campylobacter	Human immunodeficiency virus
Candida	Influenza, avian
Chikungunya	Influenza, conserved
Chlamydia	Leishmaniasis
Clostridium difficile	Lyme disease
Cryptosporidium	Malaria
Cytomegalovirus	Metapneumovirus
Ebola	Norovirus
Epstein–Barr virus	Parainfluenza
Escherichia coli, toxin producing	Respiratory syncytial virus
Escherichia coli, urine tract	Salmonella paratyphi A
Helicobacter pylori	SARS
Hemophilus influenzae, nontypable+Moraxella for otitis	Shigella
Hepatitis C	Staphylococcus
Hepatitis E	Strep Group A
Herpesvirus 6	Strep Group B
Herpes simplex	Trypanosomiasis
	Tuberculosis
	West Nile

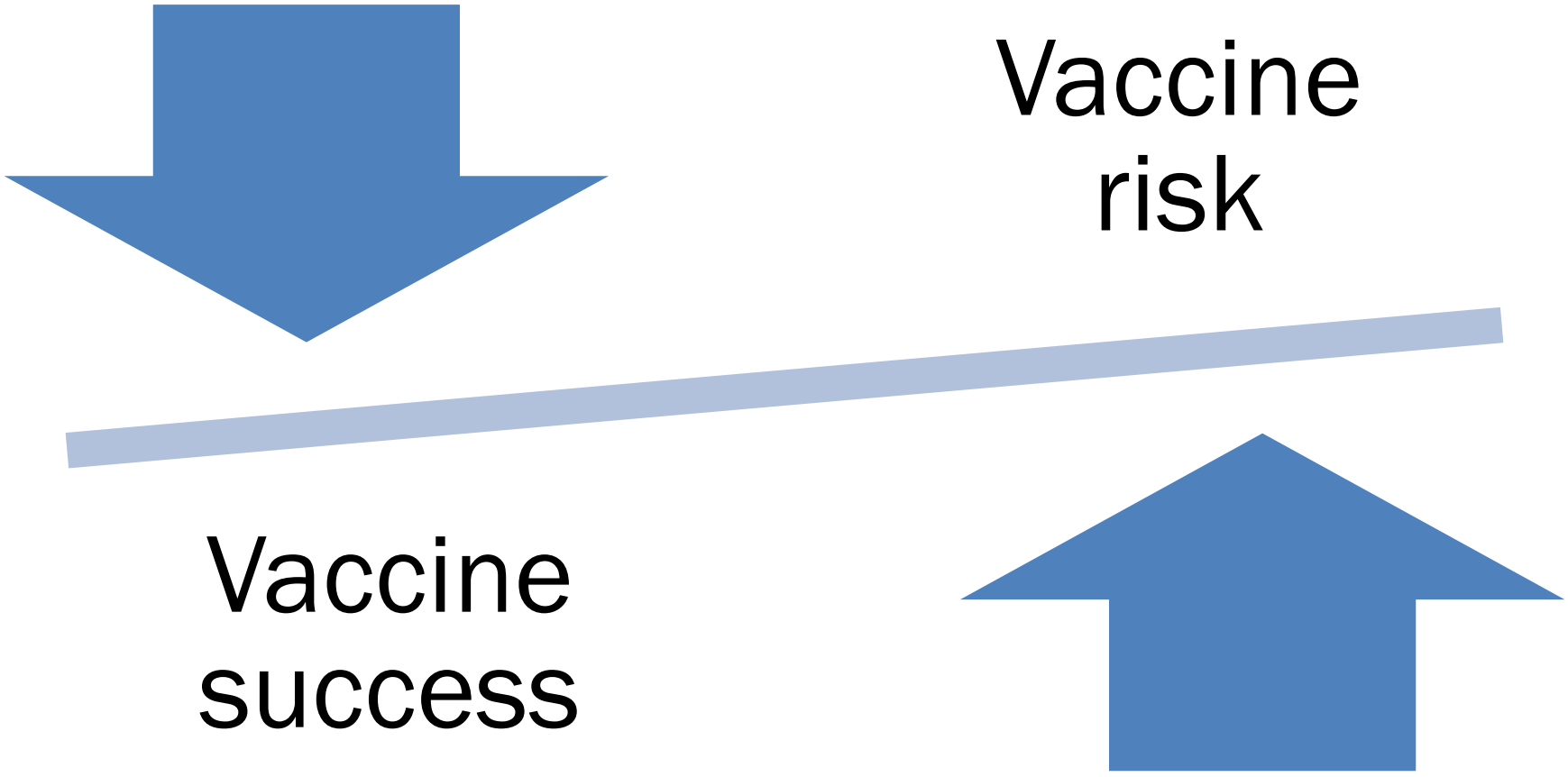
SARS, severe acute respiratory syndrome.

One of the brightest chapters in the history of science is the impact of vaccines on human longevity and health."(S Plotkin, 2014

Vaccines

- Substantial contributions to global public health, but always controversial
  - Disturbing the natural order
  - Safety and untoward effects
  - Public good versus individual rights
  - Uneven access
  - …

The paradox of vaccines



Vaccines

- Many ethical challenges:
  - Development and testing of vaccines
  - Distribution/allocation of vaccines
  - Public health use of vaccines
  - Social acceptability of vaccines
  - Vaccine related injury and compensation
  - Anti- vax movement
  - Etc.

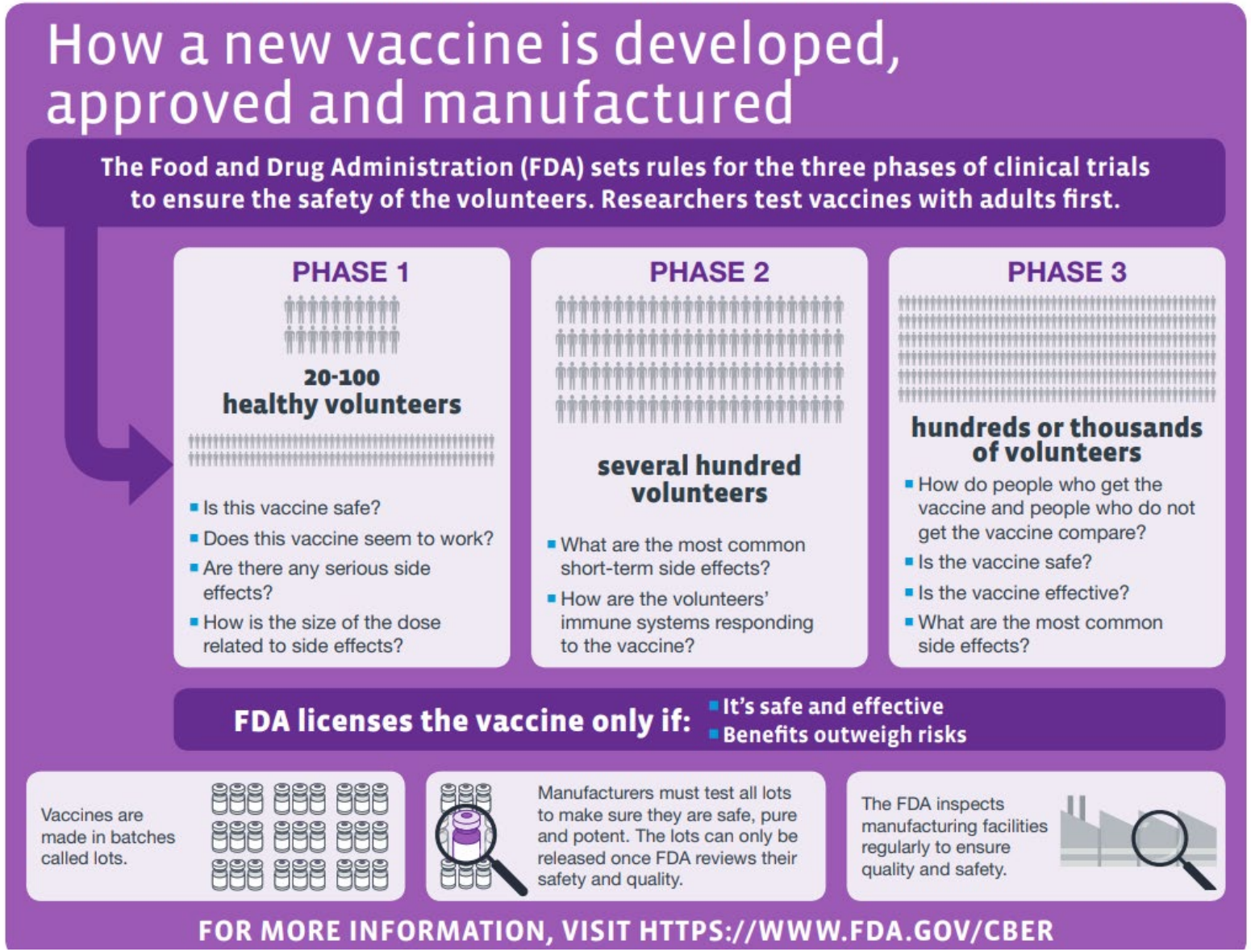
Vaccines

- Many ethical challenges:
  - Development and testing of vaccines
  - Distribution of vaccines
  - Public health use of vaccines
  - Untoward effects
  - Social acceptability of vaccines
  - Allocation
  - Etc.

Vaccine development and testing

- **Basic** research
- **Preclinical** testing
- **Clinical Testing**
  - Phase I - Safety/toxicity
  - Phase II- Safety/immunogenicity
  - Phase III- Safety/efficacy
  - Phase IV- Post-marketing

Before a new vaccine is ever given to people, extensive lab testing is done that can take several years. Once testing in people begins, it can take several more years before clinical studies are complete and the vaccine is licensed.



https://www.cdc.gov/vaccines/parents/infographics/journey-of-child-vaccine.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fparents%2Finfographics%2Fjourney-of-child-vaccine-text.html

Vaccine Development Goals

- SAFE- Reasonably/acceptably safe in a wide range of possible users
- EFFECTIVE in a large percentage of persons who are at risk

- Relatively simple to deliver, store, and administer
- Affordable & Widely available
- Used

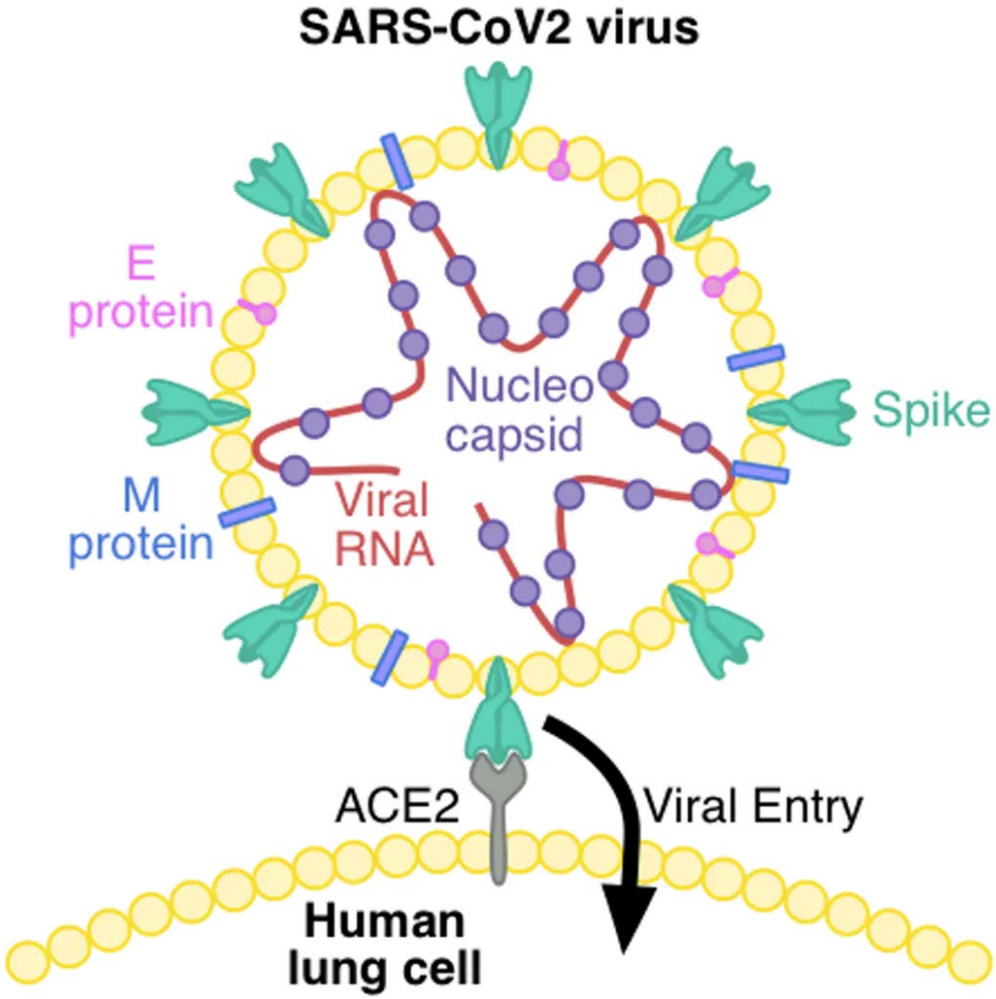
Ethical challenges in phase 3 vaccine research

- Healthy populations (at risk of infection or of disease)
- Large numbers of participants
- Some risk to individuals, conditional individual benefit
- Benefit to community or society

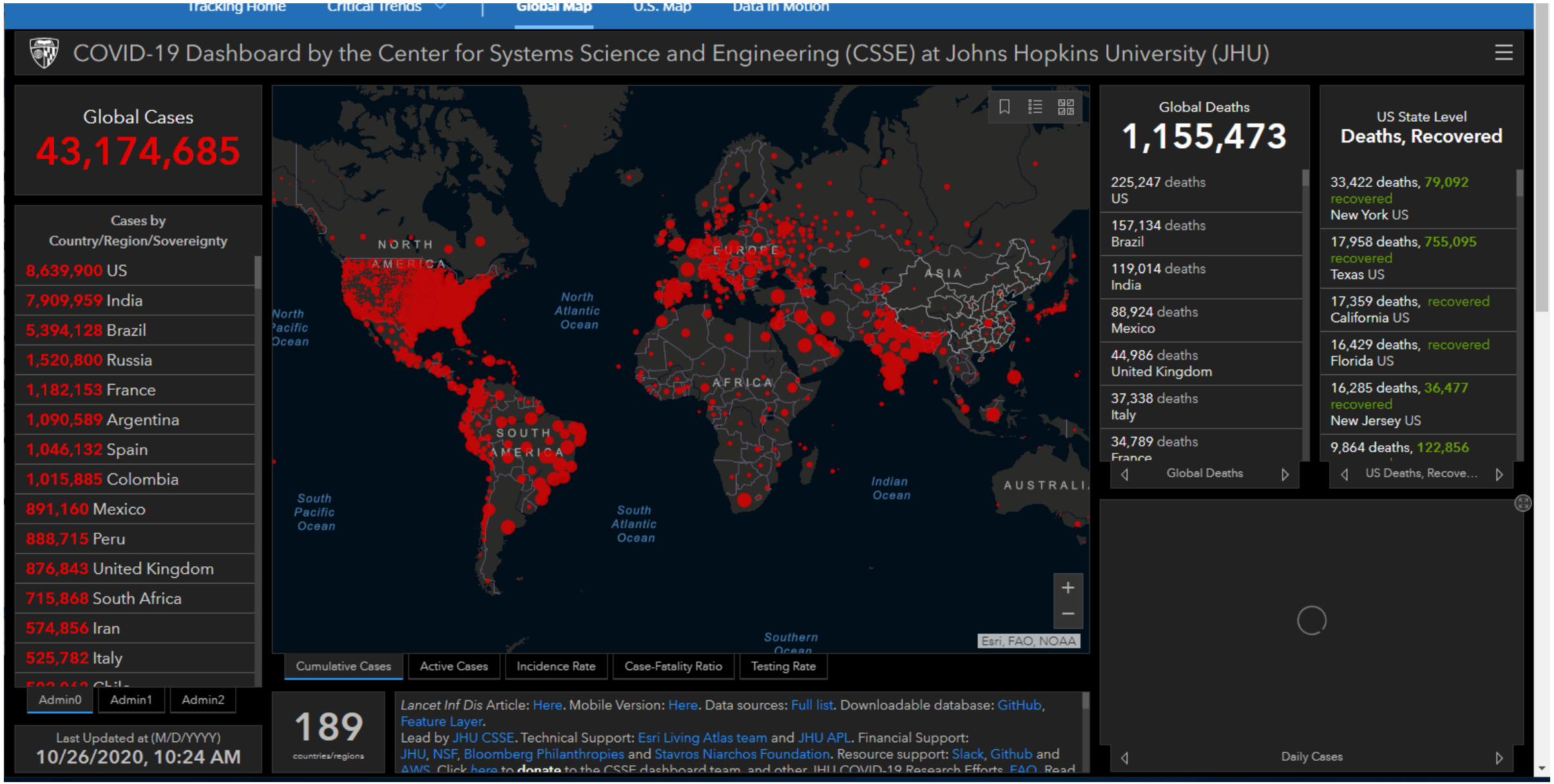
Vaccine benefits to community and society

- Reduced morbidity and mortality
- Herd immunity and protection
  - Herd immunity occurs when the % of persons immune to a disease (the herd) is large enough to reduce the likely spread from person to person. Others in the community, not just those who are immune, are protected.
  - Can protect those who can't receive or sufficiently respond to a vaccine.

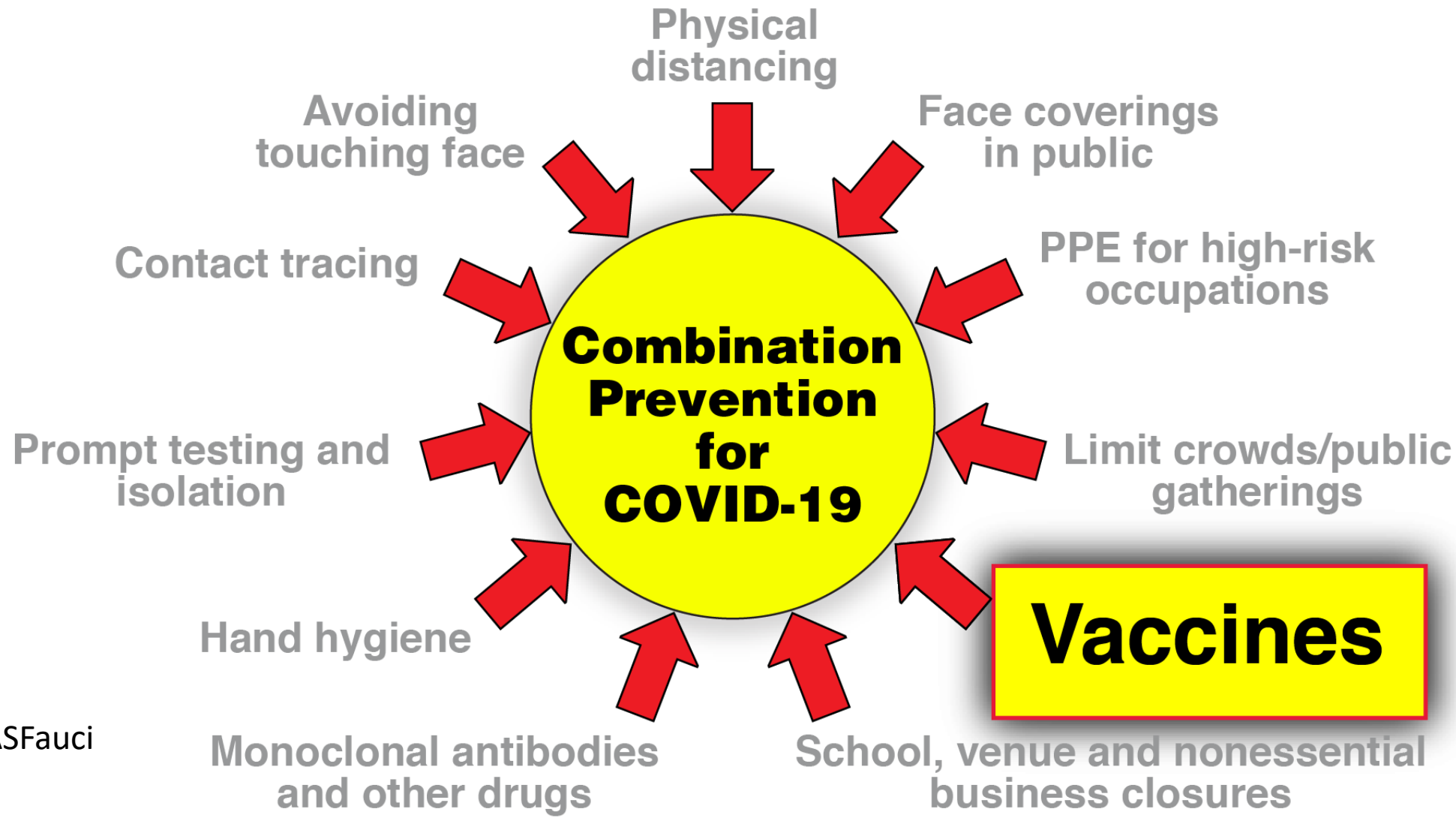
SARS CoV-2


SARS-CoV2 virus
E protein
Nucleo capsid
Spike
M protein
Viral RNA
ACE2
Viral Entry
Human lung cell

SARS CoV-2


Tracking Home
Critical Trends
Global Map
U.S. Map
Data in Motion
COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)
Global Cases
43,174,685
Cases by Country/Region/Sovereignty
8,639,900 US
7,909,959 India
5,394,128 Brazil
1,520,800 Russia
1,182,153 France
1,090,589 Argentina
1,046,132 Spain
1,015,885 Colombia
891,160 Mexico
888,715 Peru
876,843 United Kingdom
715,868 South Africa
574,856 Iran
525,782 Italy
Admin0
Admin1
Admin2
Last Updated at (M/D/YYYY)
10/26/2020, 10:24 AM
NORTH AMERICA
EUROPE
ASIA
AFRICA
SOUTH AMERICA
AUSTRALI
North Pacific Ocean
North Atlantic Ocean
South Pacific Ocean
South Atlantic Ocean
Indian Ocean
Southern Ocean
Esri, FAO, NOAA
Cumulative Cases
Active Cases
Incidence Rate
Case-Fatality Ratio
Testing Rate
189
countries/regions
Lancet Inf Dis Article: Here. Mobile Version: Here. Data sources: Full list. Downloadable database: GitHub, Feature Layer.
Lead by JHU CSSE. Technical Support: Esri Living Atlas team and JHU APL. Financial Support:
JHU, NSF, Bloomberg Philanthropies and Stavros Niarchos Foundation. Resource support: Slack, Github and
Global Deaths
1,155,473
225,247 deaths US
157,134 deaths Brazil
119,014 deaths India
88,924 deaths Mexico
44,986 deaths United Kingdom
37,338 deaths Italy
34,789 deaths
Global Deaths
US State Level
Deaths, Recovered
33,422 deaths, 79,092 recovered New York US
17,958 deaths, 755,095 recovered Texas US
17,359 deaths, recovered California US
16,429 deaths, recovered Florida US
16,285 deaths, 36,477 recovered New Jersey US
9,864 deaths, 122,856
US Deaths, Recove...
Daily Cases

Prevention of COVID-19 with a Highly Effective Vaccine and Widespread Uptake

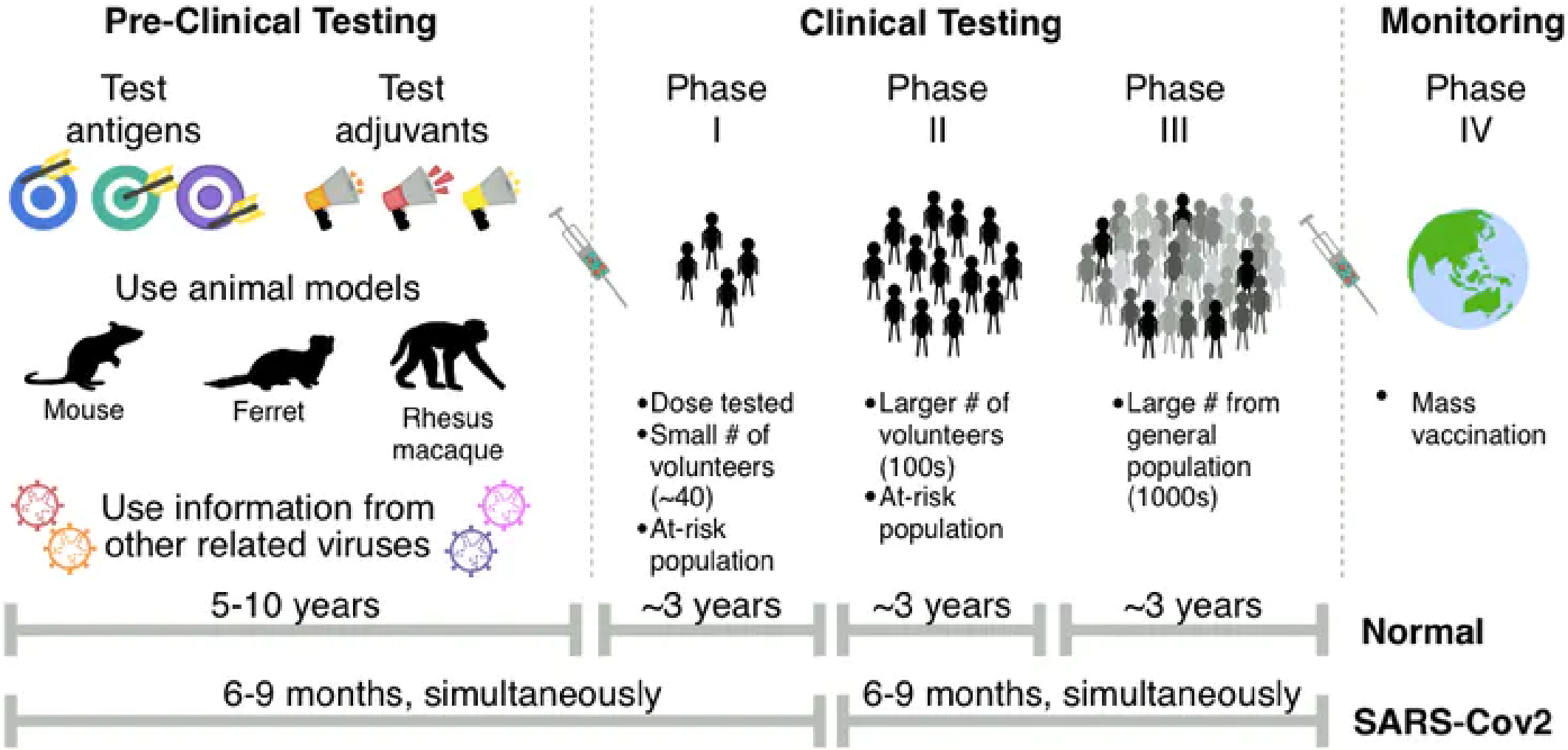


Courtesy of ASFauci

COVID-19 Vaccine Development Goals

- SAFE- Reasonably/acceptably safe in a wide range of possible users
- EFFECTIVE in a large percentage of persons who are at risk

- Relatively simple to deliver, store, and administer
- Affordable & Widely available
- Used
- FAST



https://theconversation.com/where-are-we-at-with-developing-a-vaccine-for-coronavirus-134784

Accelerating SARS CoV-2 vaccines

- “Pandemic” Speed (Coalition for Epidemic Preparedness Innovation- CEPI)
- Operation Warp Speed- (US govt)
  - Produce and deliver 300 million doses of safe and effective vaccines as early as Jan 2021; part of a broader strategy to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics.
  - Partnership among DHHS components, including CDC, NIH, BARDA, ASPR, DoD, and engagement with private firms and other federal agencies
  - Select promising candidates, investing in development and manufacturing.
  - Distribution strategy

Pace of vaccine development

- Vaccine research started within weeks of identifying and sequencing SARS CoV-2
- By October 2020, 200 vaccine candidates in the pipeline

- "Shortcuts in vaccine development and testing might expedite the timeline of scientific progress, *and* could also result in compromising quality, acceptability, and ethics"

Grady C et al. So much at stake: Ethical tradeoffs in accelerating SARS CoV-2 vaccine. *Vaccine* Aug 2020

PUBLIC HEALTH | OPINION

The Risks of Rushing a COVID-19 Vaccine

Telescoping testing time lines and approvals may expose all of us to unnecessary dangers

By William A. Haseltine on June 22, 2020

VIEWPOINT

COVID-19: BEYOND TOMORROW

Adverse Consequences of Rushing a SARS-CoV-2 Vaccine

Implications for Public Trust

Brit Trogen, MD, MS
NYU Langone Health, New York, New York.

David Oshinsky, PhD
NYU Langone Health, New York, New York.

Arthur Caplan, PhD
NYU Langone Health, New York, New York.

Viewpoint
pages 2462, 2458, and 2455

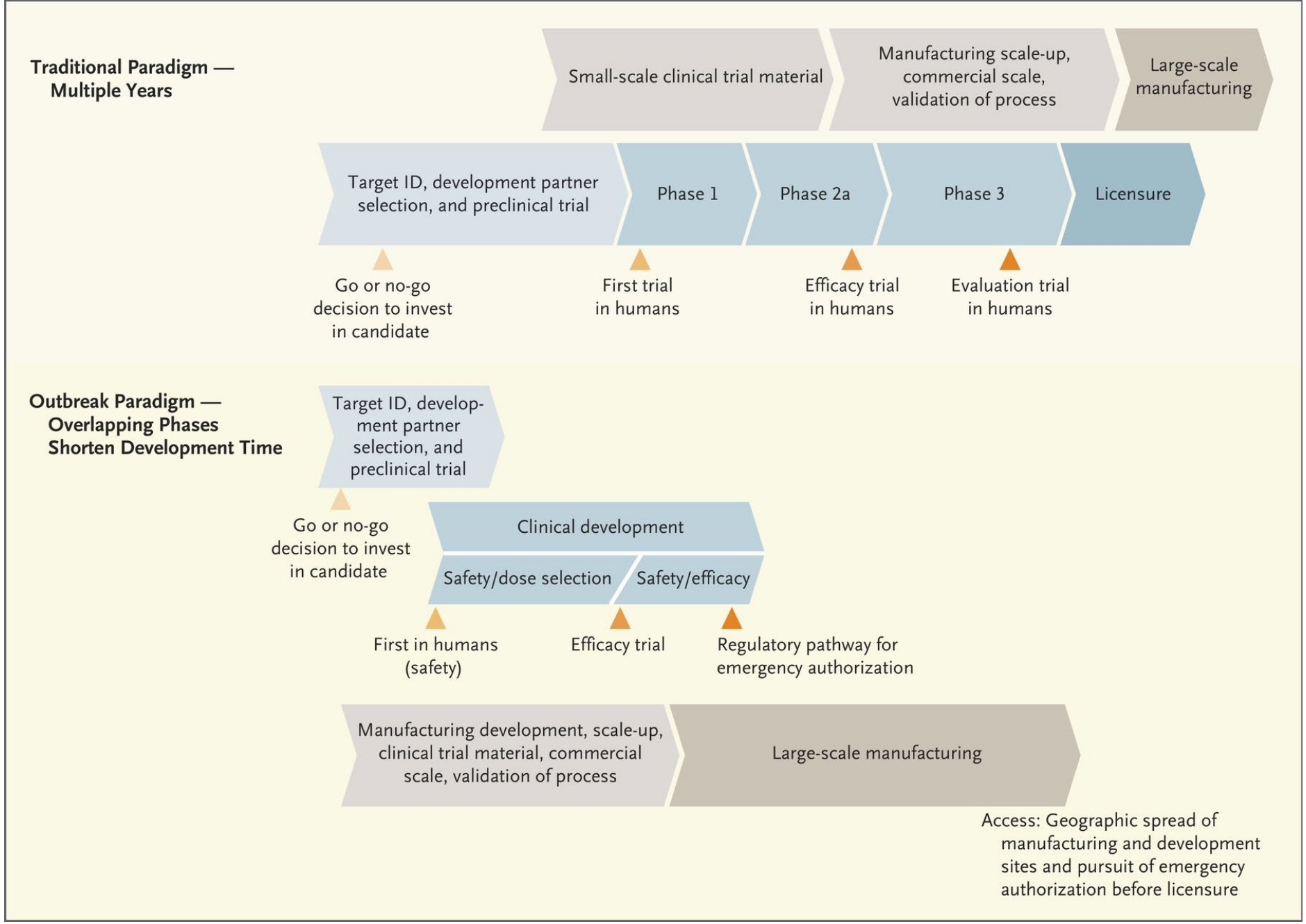
As the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) pandemic persists across the US and the world, the spotlight on vaccine science has never been more intense. Researchers across the globe are working rapidly to produce a potential vaccine, and 7 candidates are already in clinical trials.[1] Operation Warp Speed, the vaccine development project announced by President Trump, has advocated for a vaccine to be made available in the US by the beginning of 2021.[1] But for scientists and physicians, the term "warp speed" should trigger concern. Good science requires rigor, discipline, and deliberate caution. Any medical therapy approved for public use in the absence of extensive safeguards has the potential to cause harm, not only for COVID-19 prevention efforts and vaccine recipients, but also for public trust in vaccination efforts worldwide.

Long before coronavirus disease 2019 (COVID-19), vaccine hesitancy and refusal were increasing.[2] In 2019, the World Health Organization listed vaccine refusal as one of the top 10 global health threats.[3] Pediatricians, in particular, frequently encounter resistance to childhood vaccinations, and as a result, outbreaks of measles

> What cannot and must not be allowed is for desperation to result in the suspension of scientific principles and ethical research values.

activated polio vaccine developed by Jonas Salk was declared "safe, potent, and effective" following the largest public health experiment in the nation's history, involving more than a million schoolchildren.[5] Within weeks, however, the miracle vaccine intended to end the scourge of polio stood accused of causing it. Years in development, the Salk vaccine had been rigorously tested in preparation for the massive trials. But the very success of these trials led to an understandable outcry for the immediate, but premature, public release of the vaccine. Five pharmaceutical companies were given Salk's formula and left to produce the vaccine without significant oversight. As speed took precedence over caution, serious mistakes went unreported.[5] One company, Cutter Laboratories, distributed a vaccine so contaminated with live poliovirus that 70 000 children who received that vaccine developed muscle weakness, 164 were permanently paralyzed, and 10 died.[6] Not surprisingly, that incident forced the federal government to directly intervene. The legacy of this event is a regulatory landscape in which vaccines undergo thousands of tests to ensure their safety and effectiveness.[6]

Yet on rare occasions, this vital evidence-based process of vaccine development and testing has still been ignored. In 1976, concerns about the emergence of a new swine flu strain reminiscent of the lethal 1918 version led President Gerald Ford to convene a panel that recommended a government-backed mass vaccination program.[7]



Lurie N et al. Developing COVID-19 vaccines at Pandemic Speed. NEJM May 2020

Various approaches for testing SARS CoV-2 vaccine

- Randomized controlled trials
- Combined phases
- Variations on RCT design
- Controlled human infection studies
- Approval via an emergency use authorization

Ethical framework: 8 principles

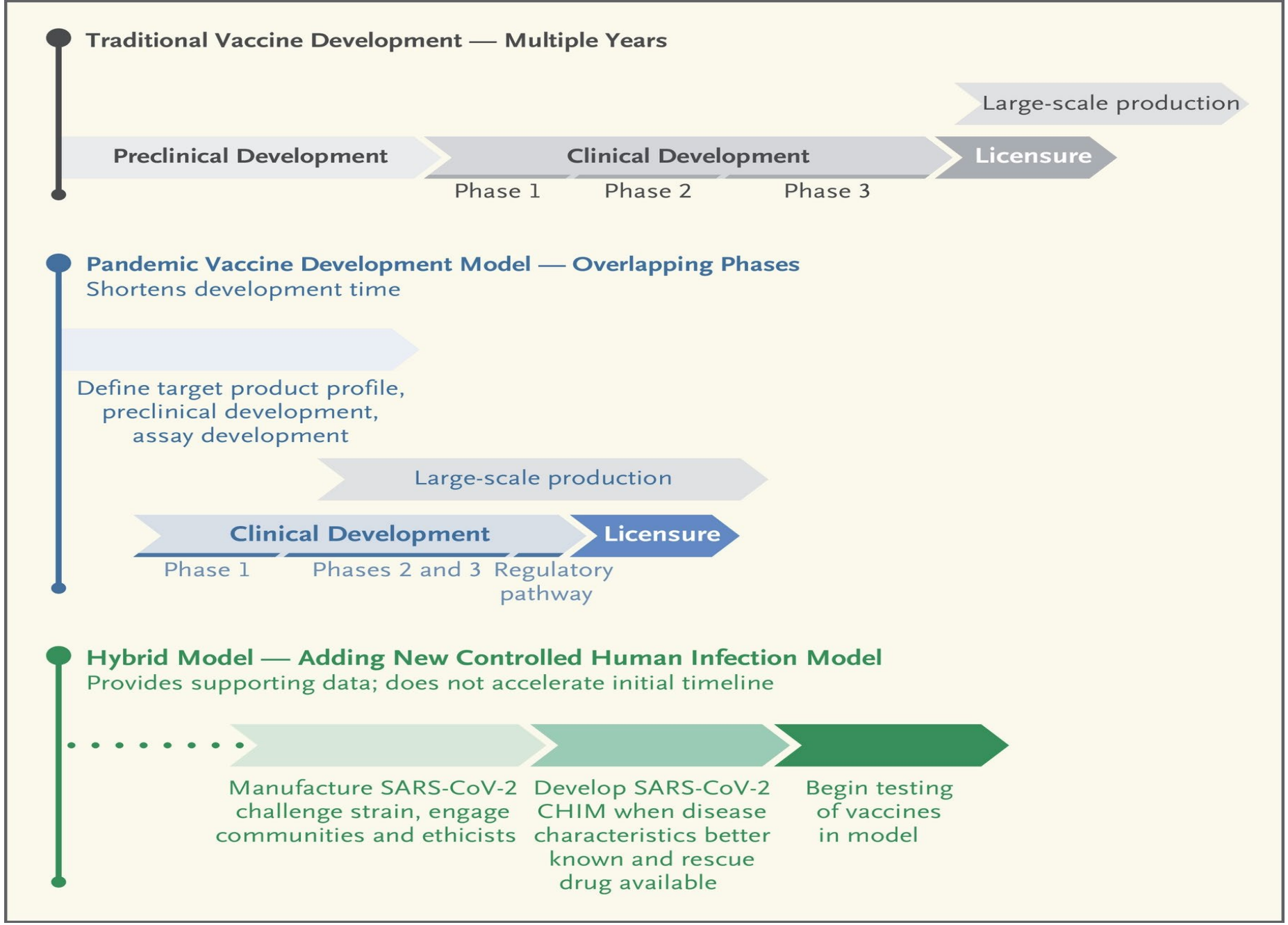
- Collaborative partnership
- **Valuable scientific question**
- **Valid scientific methodology**
- Fair subject selection
- **Favorable risk-benefit**
- Independent review
- Informed consent
- Respect for enrolled subjects

Emanuel E, Wendler D, Grady C. What makes clinical research ethical? *J Am Med Assoc.* 2000; 283(20):2701-11; Chpt 11 Oxford Textbook 2008
Emanuel E, Wendler D, Killen J, Grady C. *J Infect. Diseases* 2004; 189:930-7

Table 1. Selected ethically relevant dimensions affecting social and scientific value in accelerated vaccine development approaches

	Approach	Selected ethically relevant dimensions						
		Speed	Total number of research participants	Risks to participants and vaccinees	Cost	Feasibility - research capacity	Feasibility - pandemic dynamics	Social risks: Distrust or Negative Public Perception
STANDARD	**Consecutive Phase I, II and III Trials**	Years to trial completion	Thousands to tens of thousands	Low and carefully monitored	High	High: existing experience and infrastructure	Showing efficacy depends on sufficient incidence	Usually low; familiar trajectory
ACCELERATED	***Individually randomized RCT Combining Phases II/III***	↓	↓	↔	↓	↔	↔	↔↑
	Cluster randomized RCT in Phase III	↓	↓	↔	↓	↔↑	↔↓	↑
	EUA following Phase I	↓↓	N/A	↑↑	↓	N/A	N/A	↑↑
	CHI study with or without field trial	↓	↓↓	↑	↓	↑	↓	↑↑

Grady et al *Vaccine* 2020



Deming M et al. Accelerating Development of SARS-CoV-2 Vaccines — The Role for Controlled Human Infection Models. *NEJM* Sept 2020

Vaccine RCT considerations

Design:

- Parallel individual randomization
- Cluster randomization
- Alternative design- e.g. ring vaccination, stepped-wedged

Comparator

Randomization

Double Blinded

Sample size

Primary endpoints

/science/coronavirus-vaccine-tracker.html

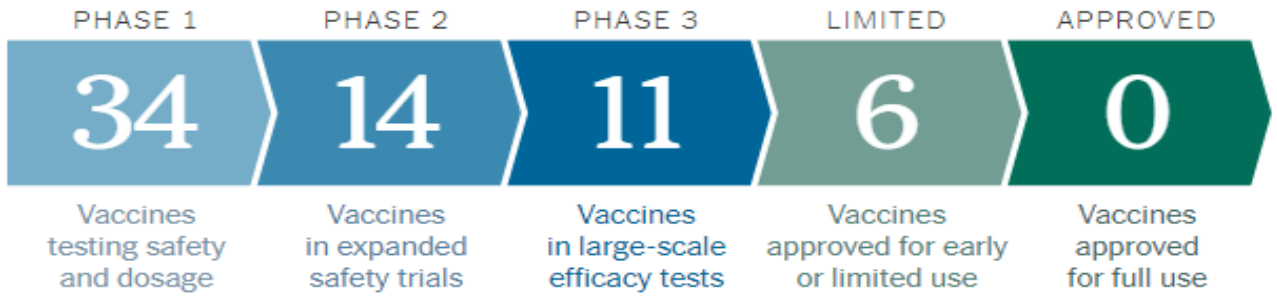
The New York Times

The Road to a Coronavirus Vaccine | Vaccine Tracker | When Can I Get One? | After the First Vaccine | Understanding Long-Term Safety

WORLD | COUNTRIES | U.S.A. | STATES | COLLEGES

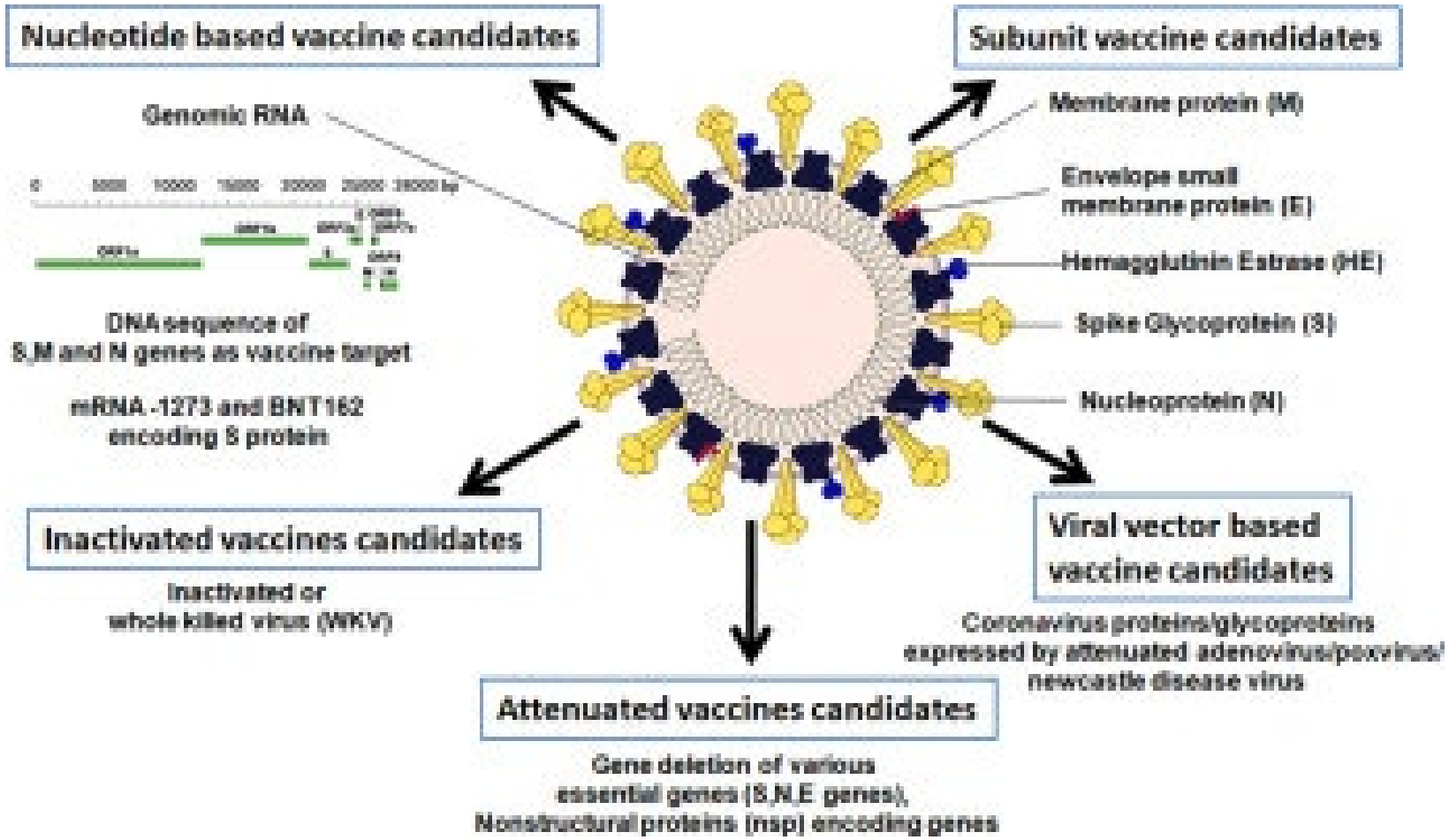
Coronavirus Vaccine Tracker

By Jonathan Corum, Sui-Lee Wee and Carl Zimmer Updated October 26, 2020



Vaccines typically require years of research and testing before reaching the clinic, but scientists are racing to produce a safe and effective coronavirus vaccine by next year. Researchers are testing **48 vaccines** in clinical trials on humans, and at least 88 preclinical vaccines are under active investigation in animals.

https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html



Platforms used by previous vaccines: inactivated, live attenuated, subunit
Newer Platforms: Nucleotide based, viral vector based

Selected COVID-19 Vaccine Candidates

Platform	Developer	Phase 1/2	Phase 2/3
Nucleic acid	moderna	Enrolled	Ongoing
	BIONTECH Pfizer	Enrolled	Ongoing
Viral vector	UNIVERSITY OF OXFORD AstraZeneca	Enrolled	Ongoing
	Janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson	Enrolled	Ongoing
	MERCK	Ongoing	--
Protein subunit	NOVAVAX Creating Tomorrow's Vaccines Today	Ongoing	Ongoing
	gsk SANOFI	Ongoing	--

Courtesy of ASFauci

	Pfizer	Moderna	Astra-Zeneca
Sample size	30,000	30,000	30,000
Participants getting vaccine	15,000	15,000	20,000
Efficacy target	60%	60%	50%
Lower 95% CI efficacy	30%	30%	30%
Number of Events at Completion	164	151	150
Number of Interim Analyses	4	2	1
Alpha-spending function at Interim Analysis for Stopping Rule	Pocock-type	O'Brien-Fleming type	Lan-DeMets
Number of Events at 1st (or only) Interim Analysis	32	53	75

FDA guidance

- US FDA. *Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry,* June 2020. https://www.fda.gov/media/139638/download

- US FDA. *Emergency Use Authorization for Vaccines to Prevent COVID-19: Guidance for Industry,* October 2020. https://www.fda.gov/media/142749/download

COVID-19 Vaccine development

- Scientific challenges
- Ethical challenges
- Practical challenges
- Societal challenges

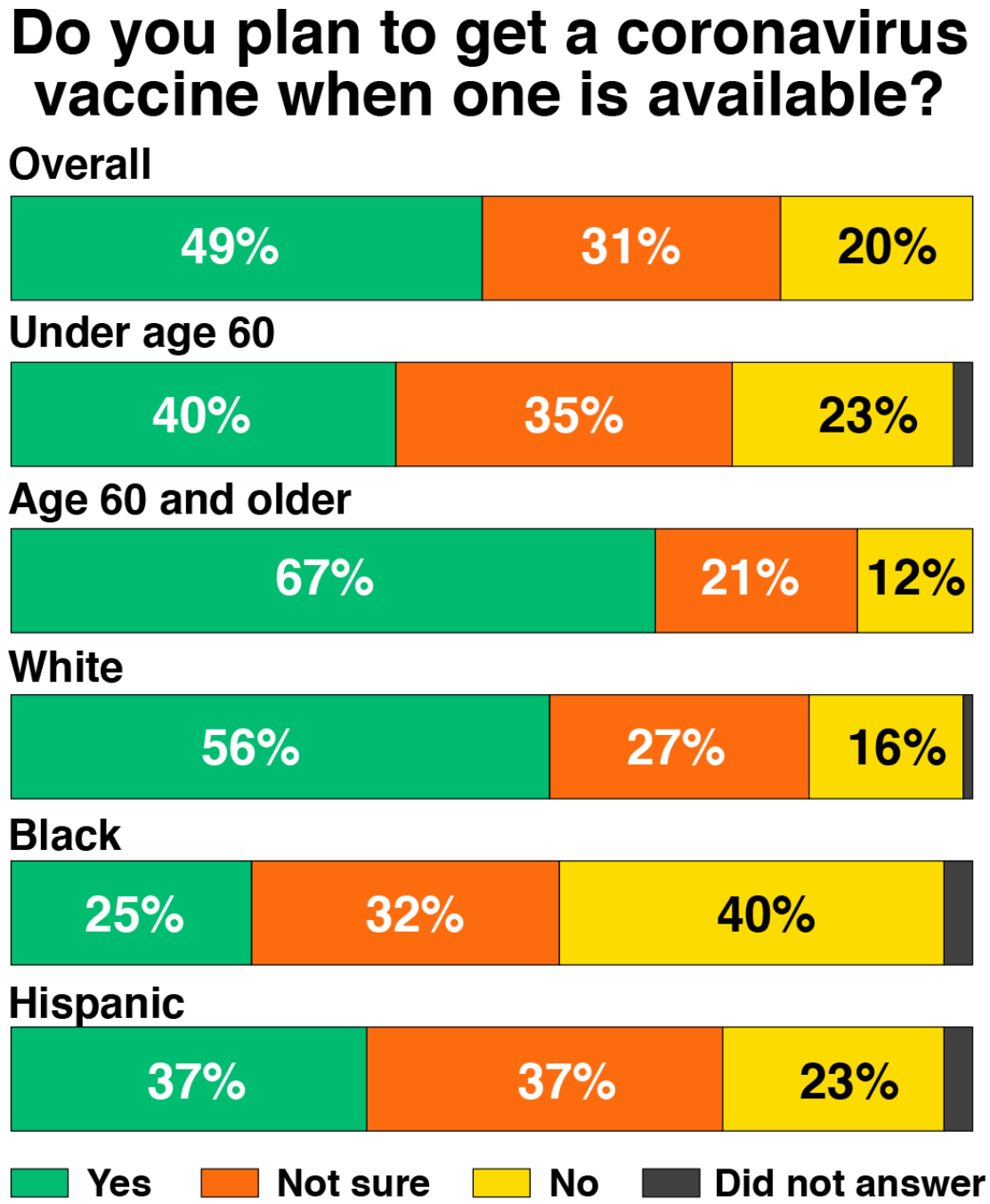
Public trust

- Science literacy
- Trust in science
- Public Trust

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



Courtesy AS Fauci

Willingness to take vaccine

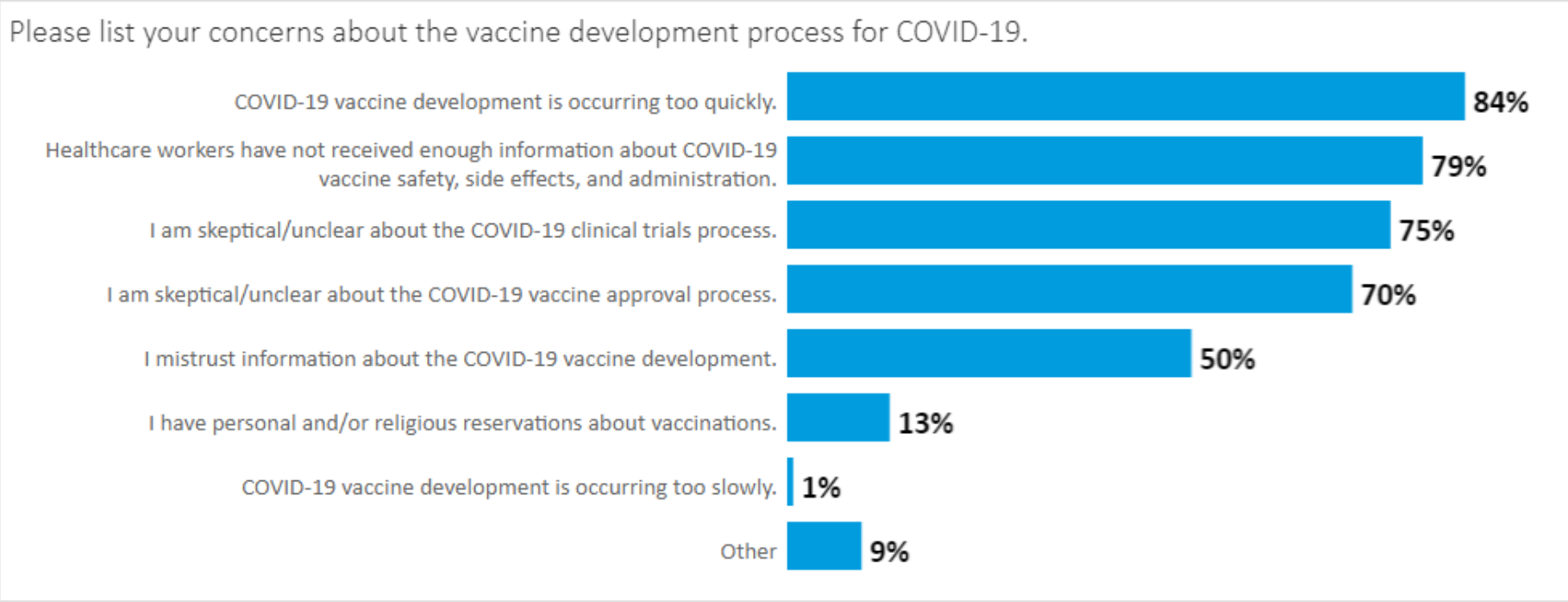
	Accept COVID Vaccine if available?	Accept vaccine if employer recommended?
Completely agree	46.8%	39.1
Somewhat agree	24.7%	29.5
Neutral	14.2 %	20.6
Somewhat disagree	6.1	8.1
Completely disagree	8.1	9.8

A study of potential acceptance of a COVID-19 vaccine in 13,426 randomly selected individuals across 19 countries, most with a high COVID-19 burden.

- High heterogeneity in responses between countries.
- Furthermore, willingness to get vaccinated might not be necessarily a good predictor of acceptance

Lazarus et al *Nature Med* Oct 2020

More data



American Nurses Foundation, Pulse on the Nation's Nurses COVID-19 Survey Series: COVID-19 Vaccine, October 2020. (N=12,939 US nurses)
https://www.nursingworld.org/practice-policy/work-environment/health-safety/disaster-preparedness/coronavirus/what-you-need-to-know/covid-19-vaccine-survey/

COVID-19

Scientists Warn Americans Are Expecting Too Much From a Vaccine

By Liz Szabo and JoNel Aleccia

OCTOBER 28, 2020

Ethical framework: 8 principles

- Collaborative partnership
- Valuable scientific question
- Valid scientific methodology
- Fair subject selection
- Favorable risk-benefit
- Independent review
- Informed consent
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