Vaccine Development: The Case of COVID-19

October 27, 2021

Christine Grady
Department of Bioethics
Clinical Center | National Institutes of Health

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

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

Vaccines

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

- Many ethical challenges:
  - Development and testing of vaccines
  - Distribution/allocation of vaccines
  - Public health use and social acceptability of vaccines

Paradox of vaccines

- As vaccines prove to be successful, public acceptance can wane
  - Vaccines successful in preventing disease
  - Decreased appreciation of the severity of the disease
  - Decreased tolerance for any vaccine side effects

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
  - …

Vaccines

- Many ethical challenges:
  - Development and testing of vaccines
  - Distribution/allocation of vaccines
  - Public health use and social acceptability of vaccines

Vaccine Development Goals

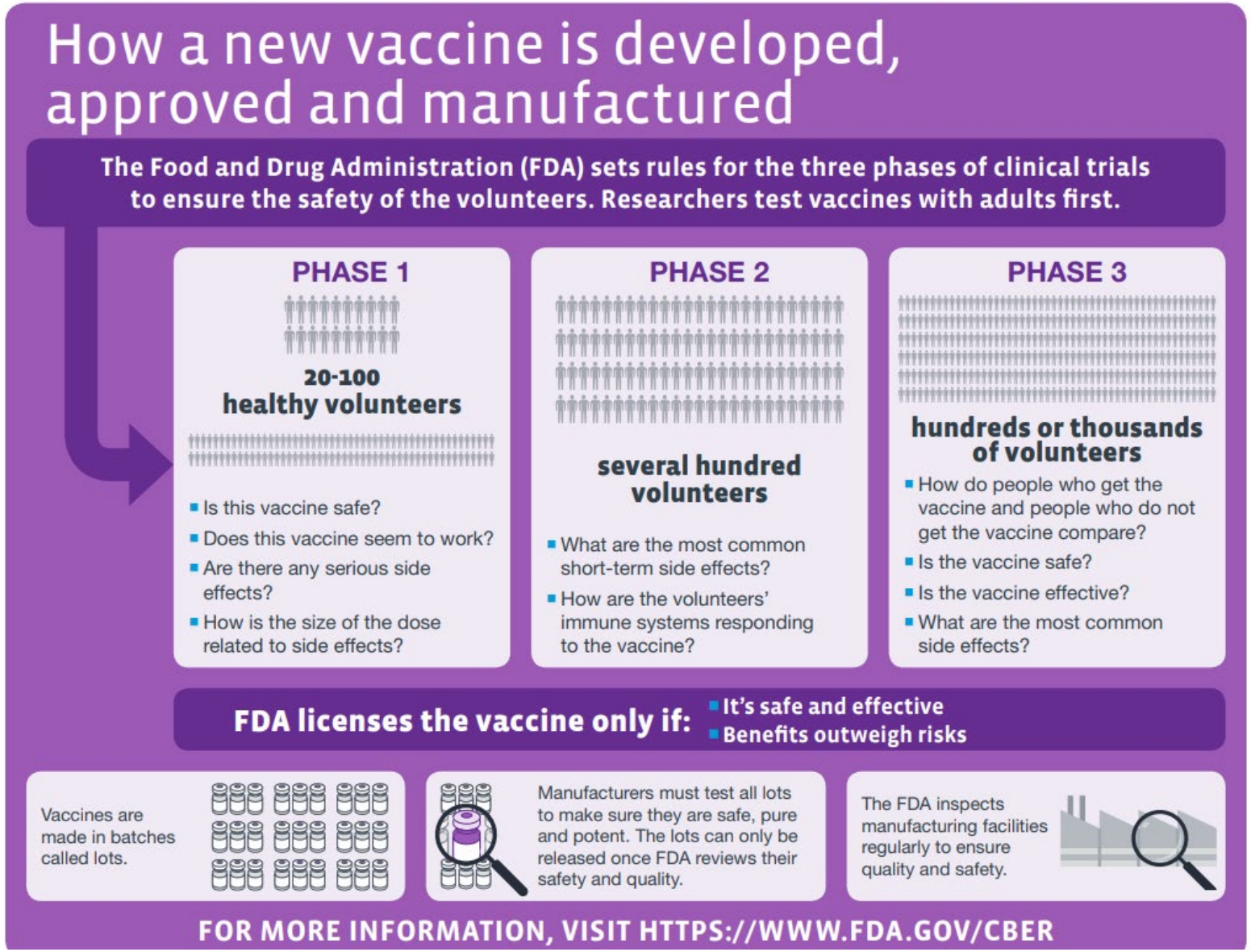
- SAFE- Reasonably/acceptably safe in a wide range of possible users
- EFFECTIVE in a large percentage of persons who are at risk

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

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

Ethical challenges in phase 3 vaccine research

- Healthy populations (at risk of infection or of disease)
- Large numbers of participants
- Individuals accept some risk, small chance of individual benefit
- Benefit to community or society

Vaccine development and testing

- Multiple scientific and ethical decision points along the trajectory of scientific discovery and testing
  - Microbe, natural immunity, what to test, research design, primary endpoints, how measured, who to include, for how long, etc.

- Was (how was) COVID-19 vaccine research unique? (4 Ps)

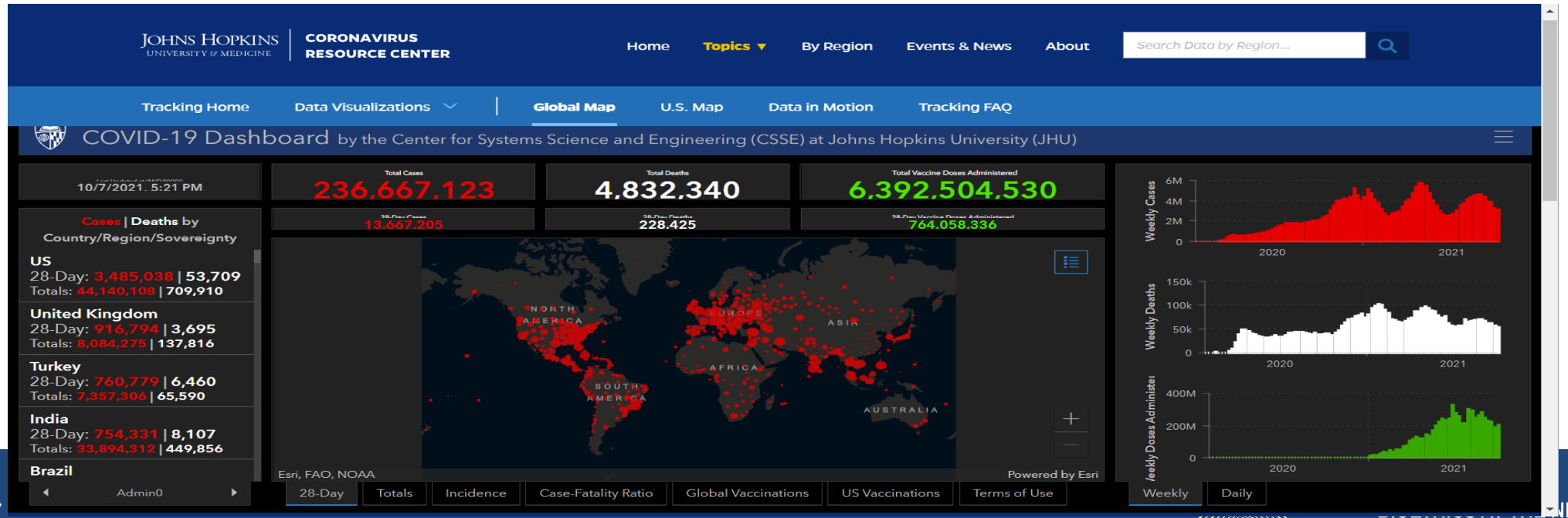
COVID-19 Vaccine development

- Pandemic
- Platform
- Pace
- Politicization/Public views

Pandemic Research

- Urgency and Uncertainty

- Research is essential to address both



Pandemic Research Ethics

Urgency, complexity  rigor, trustworthiness

- Avoid compromising ethics or science
- Learning and doing
- Evaluate trade-offs
- Rapidly & accurately communicate with public

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]

Ethical tradeoffs: Vaccine research

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

- Compared standard RCTs, Accelerated RCTs, CHIM, Early authorization without efficacy data on 5 ethically relevant dimensions: 1) confidence in and generalizability of data, 2) feasibility, 3) speed and cost, 4) participant risks, and 5) social risks.

- Accelerated RCTs more likely than other approaches to enhance social value without compromising ethics or science.

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

Ethical framework

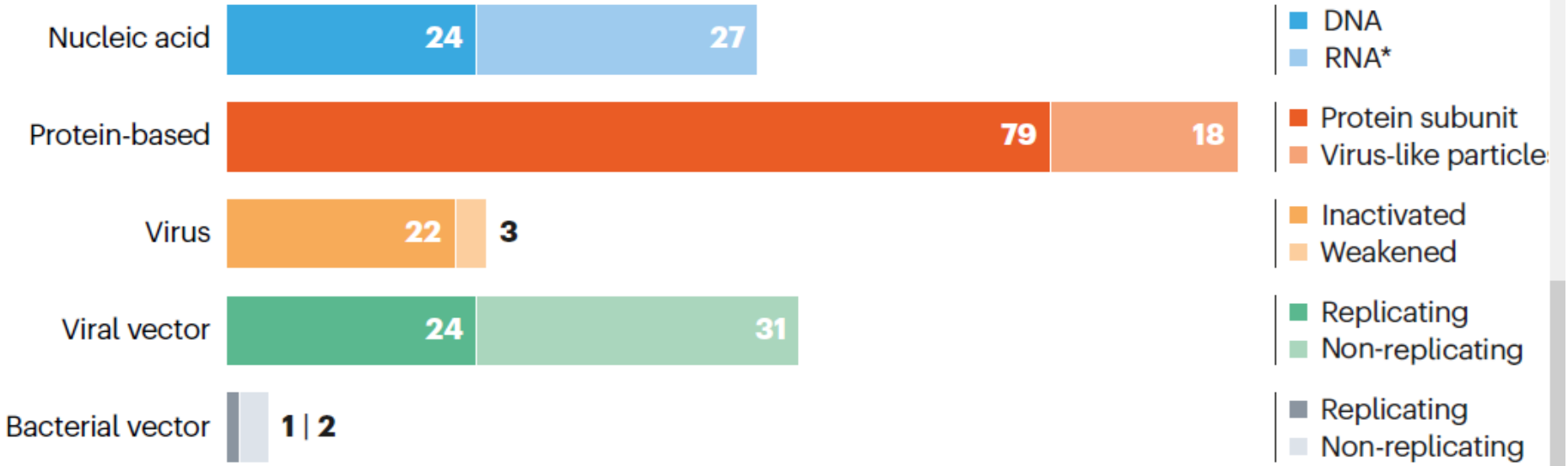
- Collaborative partnership
- **Valuable scientific question**
- **Valid scientific methodology**
- Fair subject selection
- **Favorable risk-benefit**
- Independent review
- Informed consent
- Respect for enrolled subjects

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

PLATFORM

NEXT-GENERATION VACCINES

About 230 COVID-19 vaccines are in development whose trial enrolment could be affected by the authorization of first-generation shots. About 60 of them are already being tested in humans.



Virus vaccines contain either inactivated or weakened forms of the coronavirus. Viral- and bacterial-vector vaccines contain genetically modified versions o viruses (such as adenoviruses) or bacteria (such as *Salmonella*) that can produce coronavirus proteins while replicating or not. Nucleic acid vaccines contain eithe DNA or RNA instructions that, when injected, produce coronavirus proteins. Protein-based vaccines contain proteins from coronaviruses that are injected directl

*Pfizer and BioNTech's RNA vaccine, a first-generation vaccine, is included in these numbers because the firm is currently recruiting for a trial in China

Vaccine development

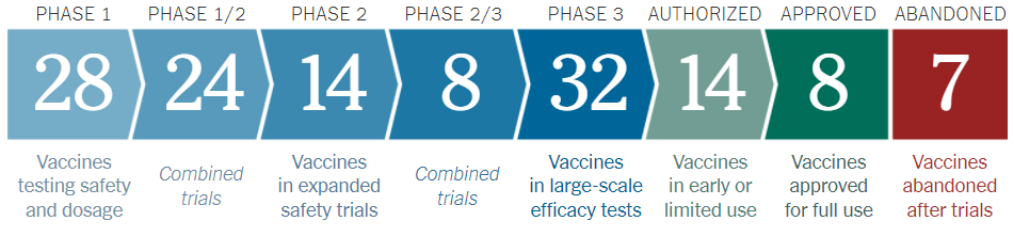
The New York Times

The Coronavirus Pandemic › | LIVE Covid-19 Updates | Coronavirus Map and Cases | World Vaccination Tracker | Vaccine FAQ

Coronavirus Vaccine Tracker

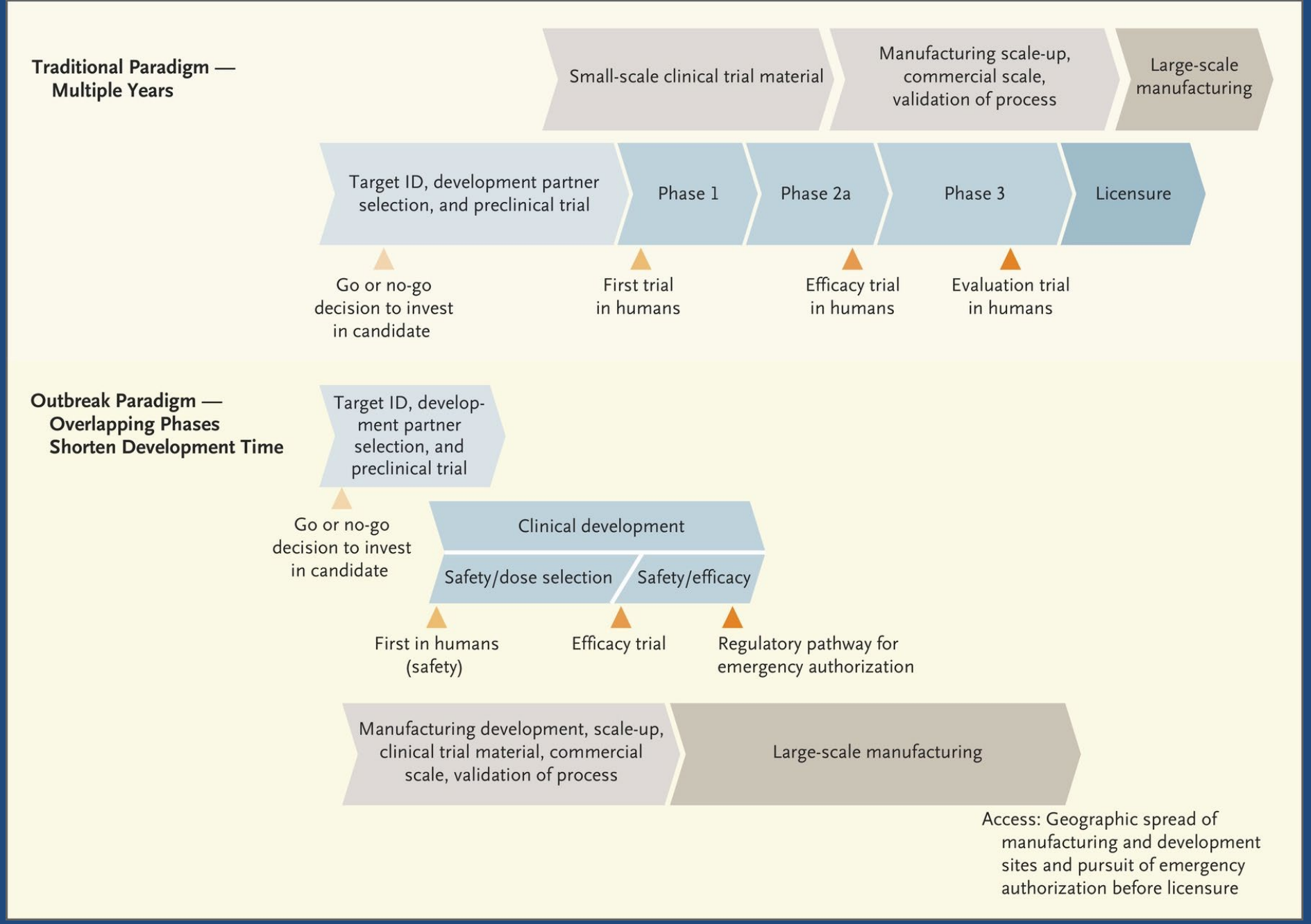
By Carl Zimmer, Jonathan Corum and Sui-Lee Wee Updated Oct. 19, 2021

U.S.A. | World | Health

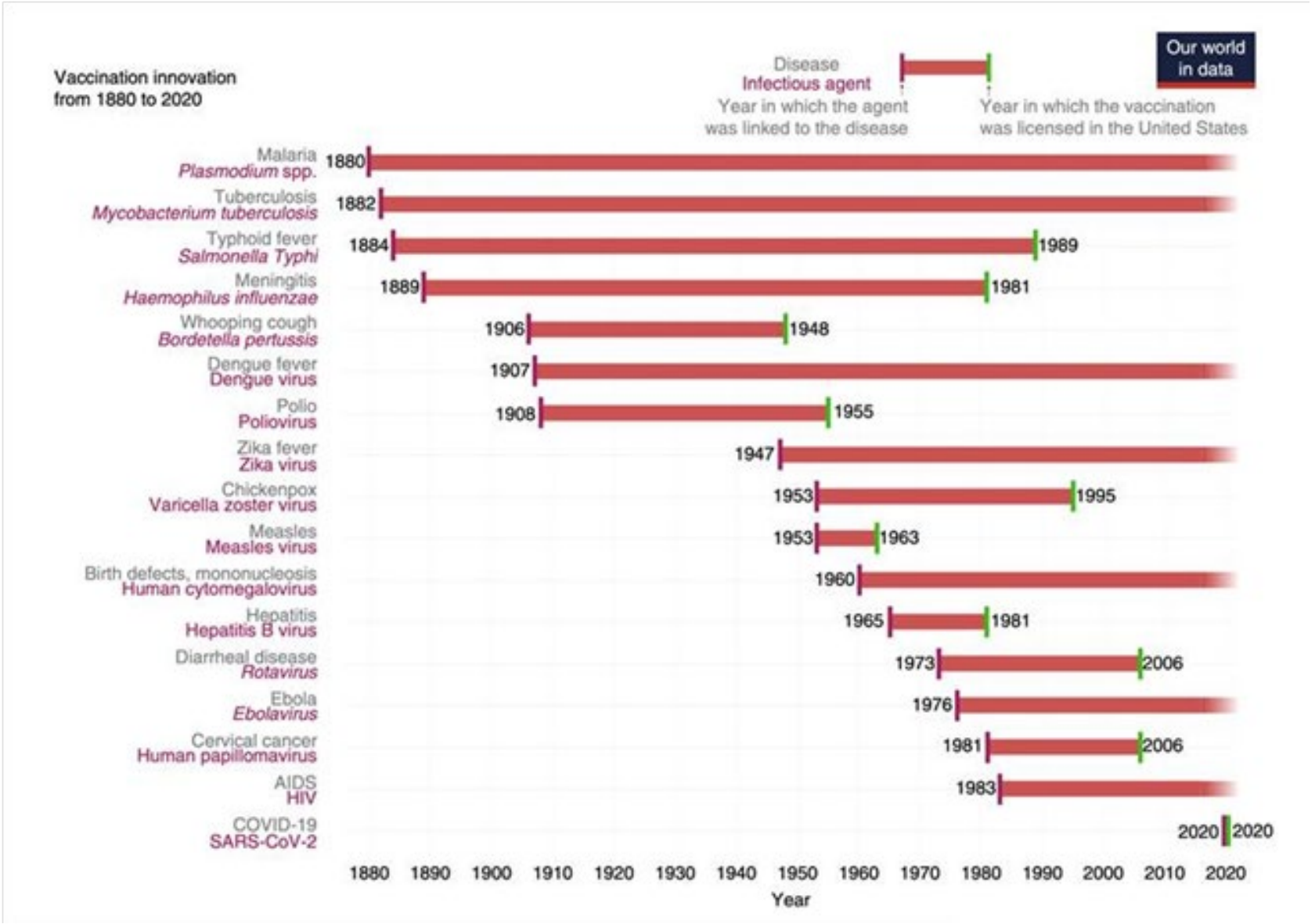


Vaccines typically require years of research and testing before

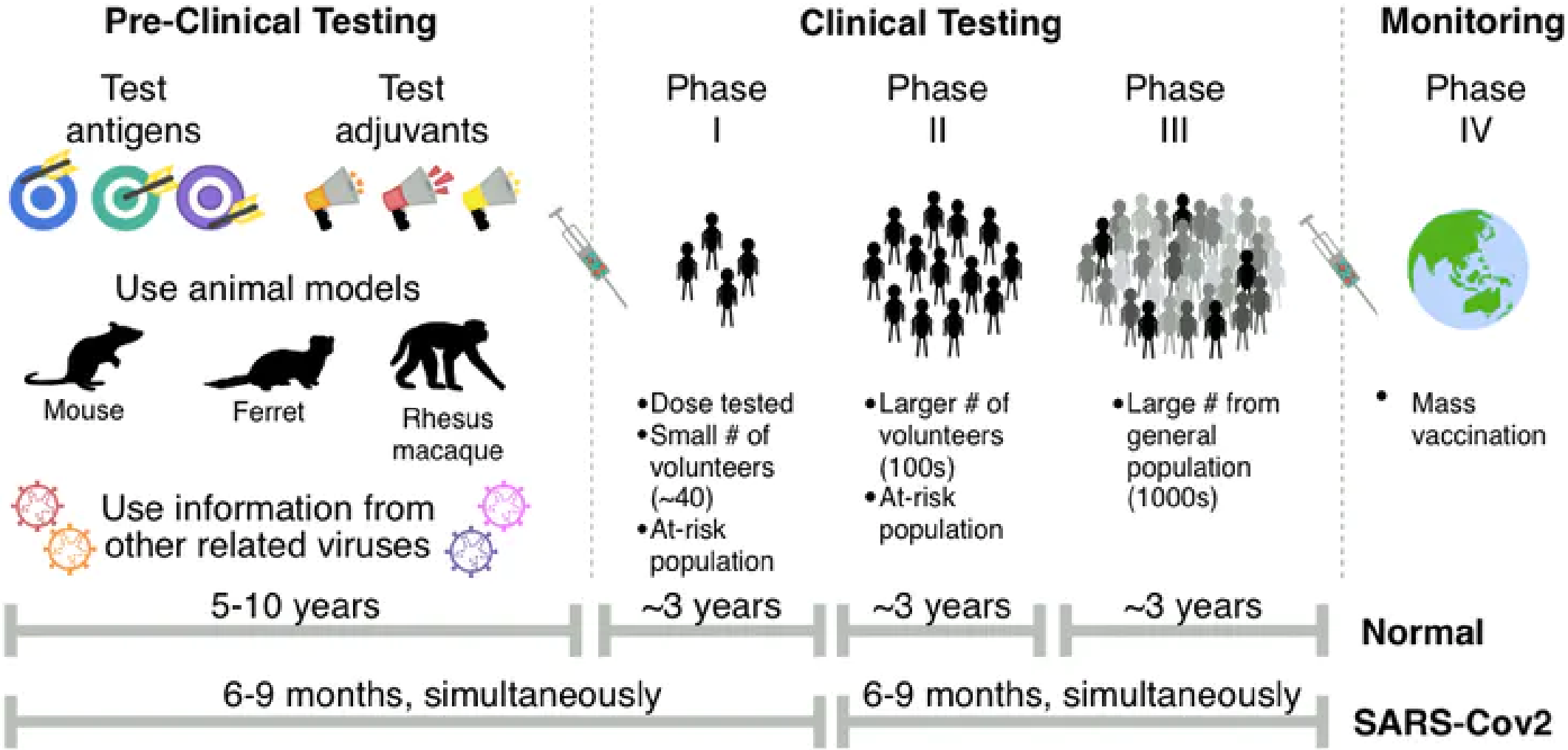
https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html



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



Mathieu J et al. Nature Human Behaviour | May 10, 2021
www.nature.com/nathumbehav



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

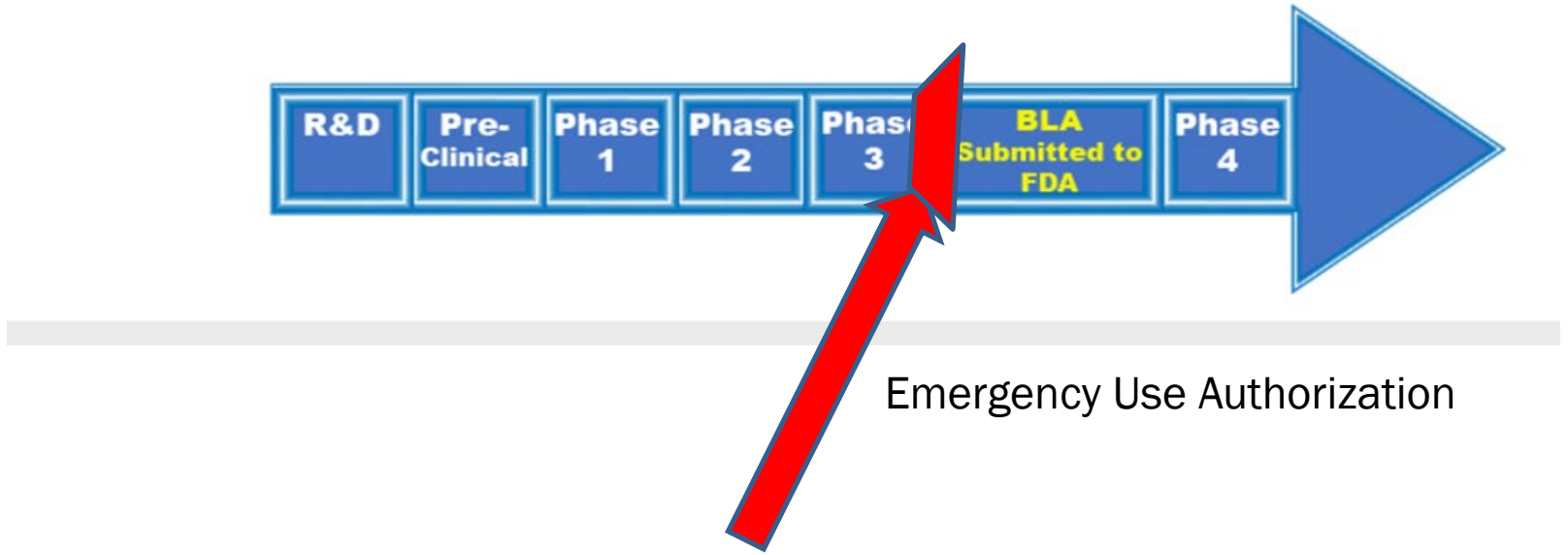
Pace

- Vaccine research started within weeks of identifying and sequencing SARS CoV-2
- Built on scientific progress and opportunity.
- Clinical trials rapidly enrolled. Several vaccines found safe and efficacious in less than a year (Operation Warp Speed)
- U.S. – one COVID vaccine licensed, two others authorized under an Emergency Use Authorization.
- By October 2021, (about 20 months after viral sequence), ~400 million doses administered in the US, and 3.6 billion in the world.

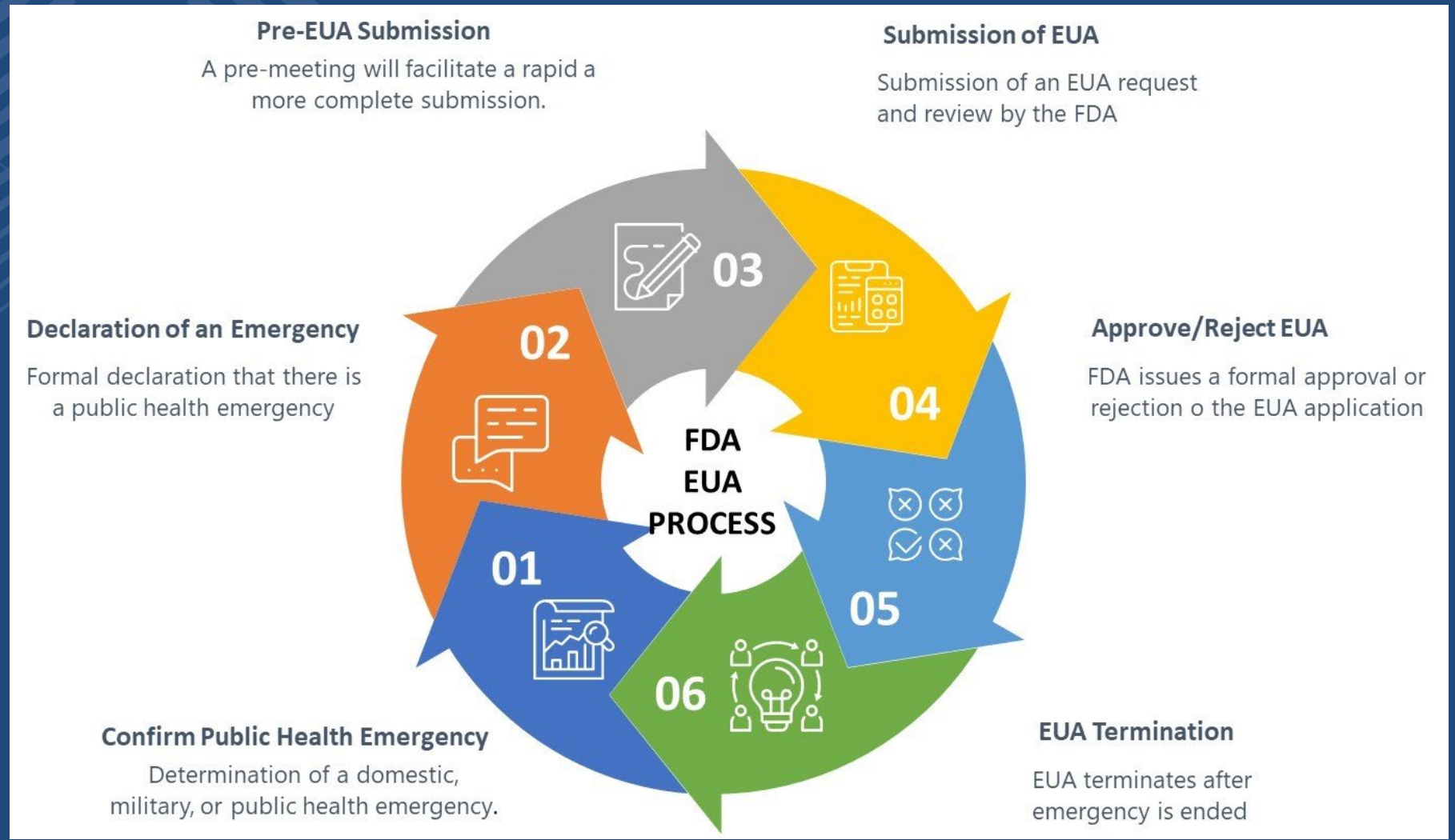
US Emergency Use Authorization/Approval

- Dec. 2020 Two mRNA vaccines (Pfizer and Moderna), each >90% efficacious in preventing symptomatic COVID authorized for emergency use (EUA).
- Feb 2021 EUA for J & J - Adenovirus viral vector vaccine (single dose).
- May 2021- authorized Pfizer for 12-16 year olds
- August 2021- Approved BLA for Pfizer/BioNTech
- Sept 2021 Booster (additional dose) authorized for Pfizer
- October 2021- Boosters authorized for Moderna and J&J.

https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/vaccine-development-101



US FDA. *COVID-19 Vaccines*. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines
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


Pre-EUA Submission
A pre-meeting will facilitate a rapid a more complete submission.
Submission of EUA
Submission of an EUA request and review by the FDA
Declaration of an Emergency
Formal declaration that there is a public health emergency
Approve/Reject EUA
FDA issues a formal approval or rejection o the EUA application
FDA EUA PROCESS
01
02
03
04
05
06
Confirm Public Health Emergency
Determination of a domestic, military, or public health emergency.
EUA Termination
EUA terminates after emergency is ended

Politicization

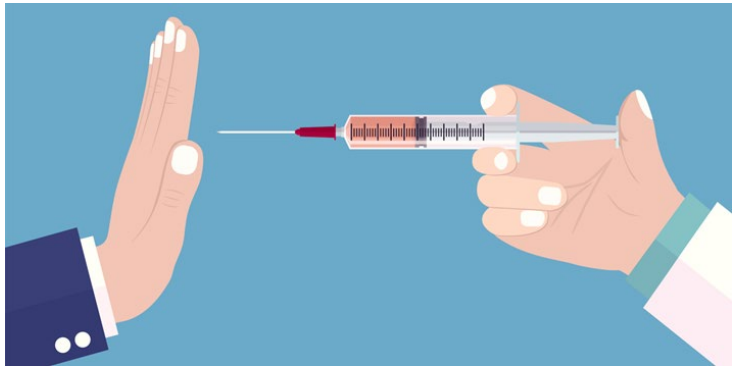
"The politicization of vaccines, not just in the case of COVID-19 … is a key problem of public health" Saad B. Omer, Yale News, Oct 2020

Washington Post 2/21/2021

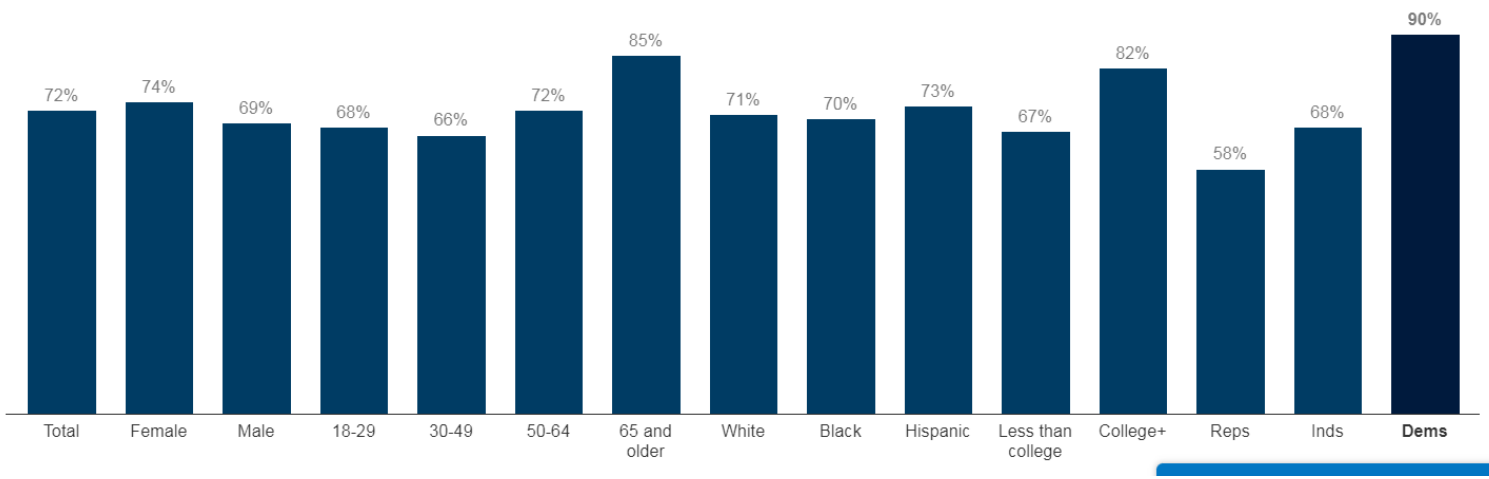
Disparate Public views-COVID vaccines

Vaccine acceptance

- Fast process
- Confusion about data
- Fear of side effects
- Politicization
- Misinformation and disinformation
- Lack of trust



Already got vaccinated | ASAP | Wait and see | Only if required | Definitely not



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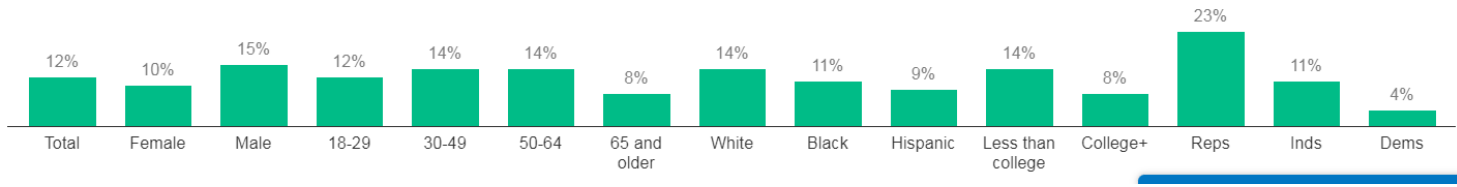


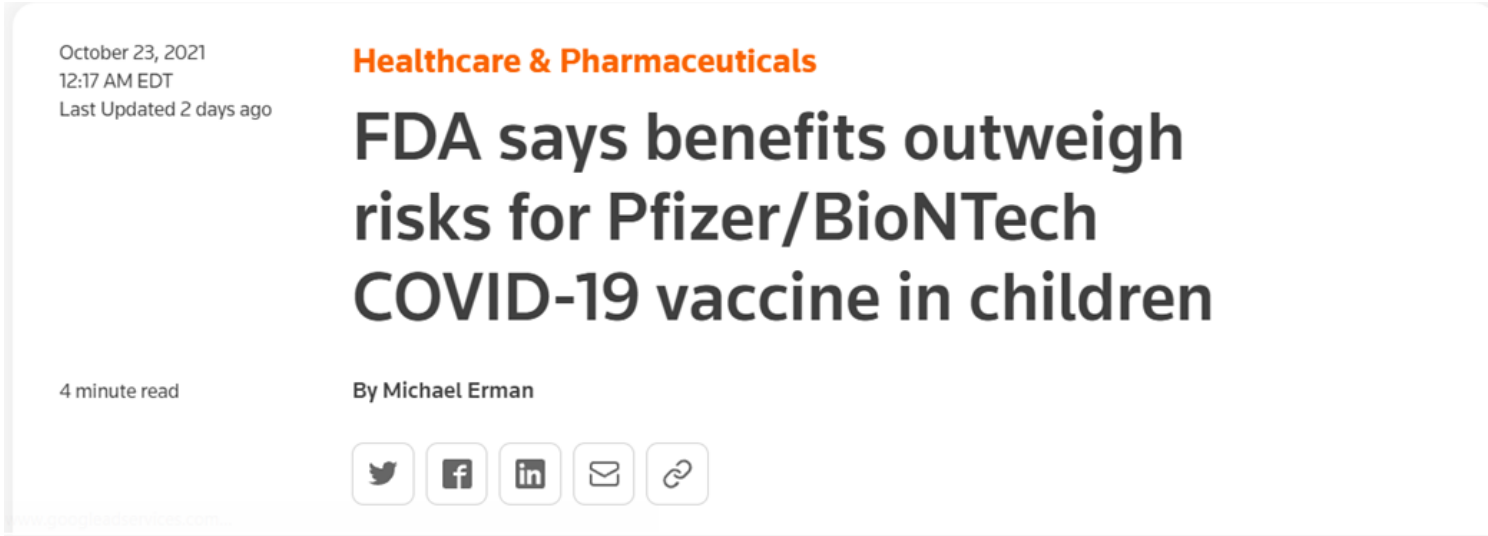

THE CONVERSATION
Academic rigor, journalistic flair
Search analysis, research, academics...
COVID-19
Arts + Culture
Economy + Business
Education
Environment + Energy
Ethics + Religion
Health
Politics + Society
Science + Technology
At my hospital, over 95% of COVID-19 patients share one thing in common: They're unvaccinated
September 2, 2021 8.22am EDT

Why should more people be vaccinated?

- Individual benefit
- Public Health Benefit
- Workplace benefit
- Social benefit

Pediatrics

- Pfizer submitted data that vaccine is safe and 90.7% effective against symptomatic Covid-19 in children ages 5 to 11.



October 23, 2021
12:17 AM EDT
Last Updated 2 days ago

Healthcare & Pharmaceuticals

FDA says benefits outweigh risks for Pfizer/BioNTech COVID-19 vaccine in children

4 minute read

By Michael Erman

Reuters 10/23/21

Vaccine Trials

Vaccine trials goals? design? public engagement?

Ethical framework

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

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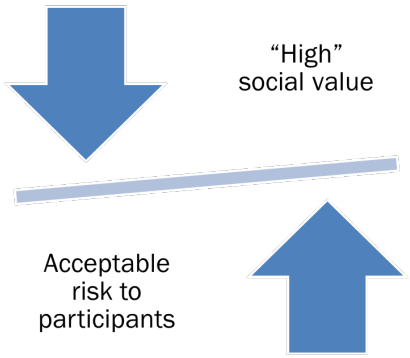
Vaccine trials

- Social value:
  - Duration
  - Reactogenicity/ adverse effects
  - Practicality
  - Special populations
  - Response to variants
  - Other?



- Does (when does) the value of answering these questions justify:
  - Risk to participants?
  - A placebo controlled trial or different trial design?

Wendler et al. *Science* 2020

Future vaccine trials

- Placebo-controlled studies?
- Non-equivalence studies?
- Alternative design- e.g. ring vaccination, stepped-wedged
- Open label extensions?
- Challenge studies?
- Smaller immuno-bridging studies?
- Other?

Decisions about: Sample size, Primary endpoints, populations, length of follow up

Public engagement

- How research is done and safeguards in place
- Details about vaccines, including
  - How vaccines work, how these work
  - Safety, reactogenicity
  - How vaccines are studied
  - “Authorized” vaccines
  - Why we need more vaccines, more research

Vaccines

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

- Many ethical challenges:
  - Development and testing of vaccines
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