"How did we get here so fast?"

Development, clinical trial process and manufacturing of the COVID-19 vaccines

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Disclosure Statement

No faculty, Provider or planning committee member in a position to influence or control the content of this presentation has any relevant financial relationships to disclose.

Learning Objectives

By the end of this activity, participants will be able to:

1. Discuss how vaccination provides immunity to SARS-CoV-2
2. Describe how an mRNA vaccine works
3. Outline the factors that led to the expedited approval of COVID vaccines
4. Know the basics of the 2 approved COVID vaccines

Outline

- COVID-19 Timeline
- SARS-CoV-2 background
- Purpose of Vaccination
- Factors that lead to the expedited vaccine production & approval
- Approved COVID Vaccines
- Vaccination hurdles

COVID-19 Timeline

December 31, 2019: Wuhan Municipal Health Commission in Wuhan City, Hubei province, China, reported a cluster of pneumonia cases of unknown etiology

- Common link to Wuhan's Huanan Seafood Wholesale Market

2020

- January 9: WHO Announces Coronavirus-Related Pneumonia in Wuhan, China
  - 59 cases
  - China’s CDC reported cause as novel coronavirus - later named SARS-CoV-2
- January 21: CDC Confirms First US Coronavirus Case
  - Washington state resident who returned from Wuhan on January 15

COVID-19 Timeline

2020

- January 31: WHO Issues Global Health Emergency
  - Worldwide death toll jumps to more than 200 with more than 9800 cases
  - Spreading to United States, Germany, Japan, Vietnam, and Taiwan
- February 3: US Declares Public Health Emergency
- February 10: China’s COVID-19 Deaths Exceed Those of SARS Crisis
- March 11: WHO Declares COVID-19 a Pandemic

COVID-19 Timeline

2020

- August 17: COVID-19 Third-Leading Cause of Death in the US
- September 28: Global COVID-19 Deaths Surpass 1 Million
- December 11 & 18: FDA Agrees to Emergency Use Authorization (EUA) for 2 COVID-19 Vaccines
  - Pfizer/BioNTech and Moderna/NIH
  - Shipments begin & vaccinations of health care workers begin within days

Fastest vaccine development ever

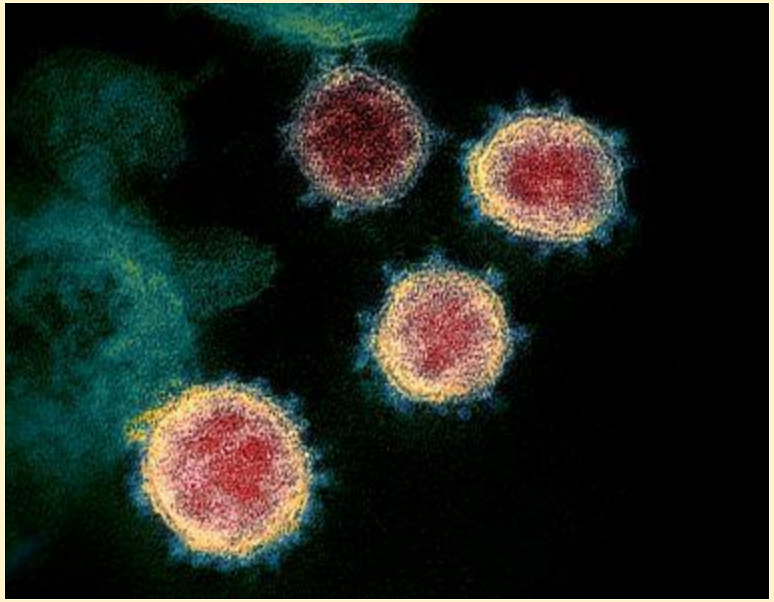
- **Approved vaccine within about a year of virus discovery**
- Development to deployment: Mumps vaccine in the 1960s
  - About four years
- 1983 HIV virus was isolated and identified
  - No vaccine yet

https://www.historyofvaccines.org/content/articles/mumps

So……..“How DID we get here so fast?”

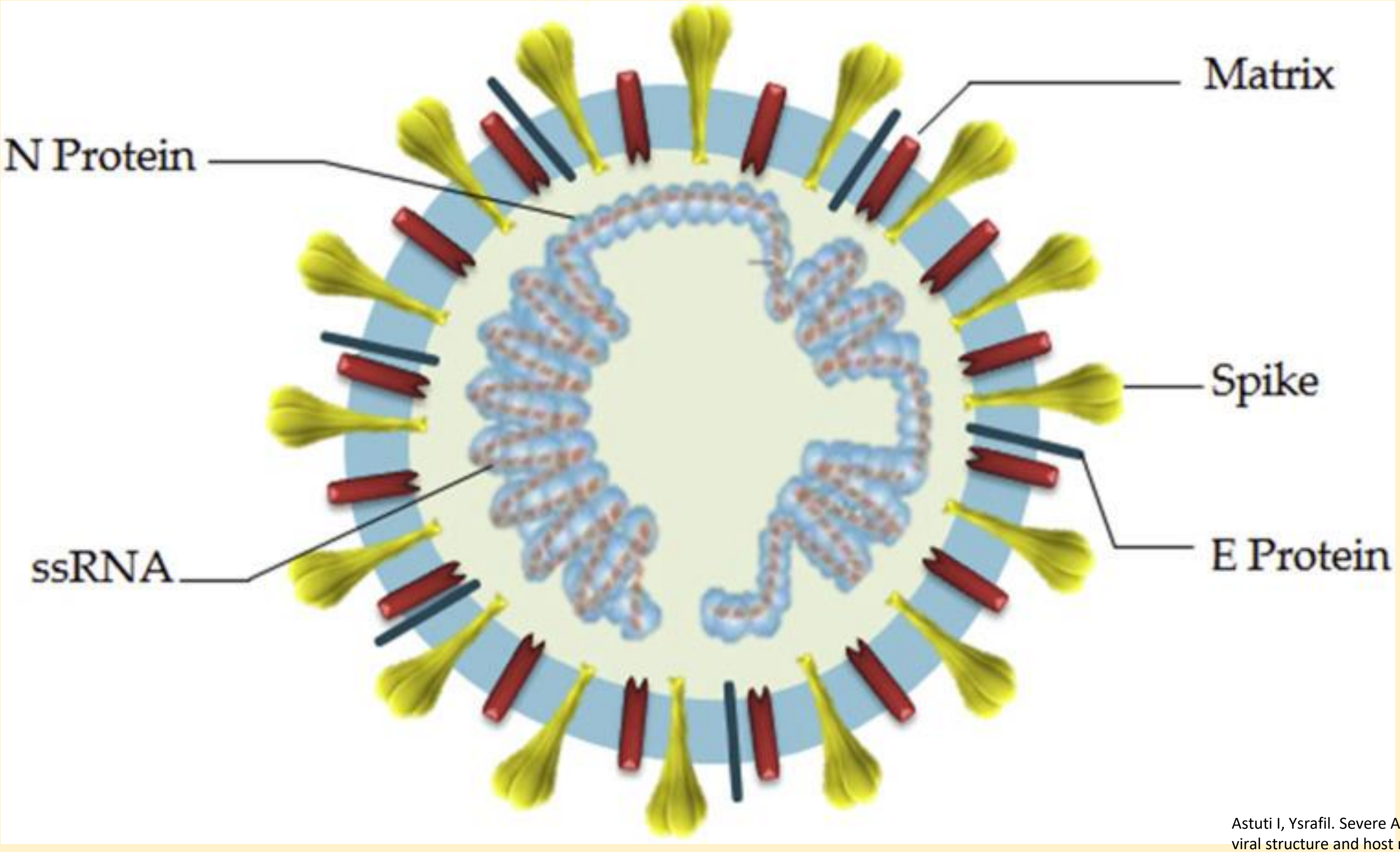
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

- Coronavirus disease 2019 (COVID-19)
- Related to SARS-CoV and MERS-CoV
  - Pulmonary failure, fatal respiratory tract infection
  - Outbreaks in Guandong, China and Saudi Arabia
- β-coronavirus
  - Broadly distributed in humans and other mammals
  - Enveloped
  - Crown-like spikes on the outer surface
  - Positive sense RNA virus



https://www.nih.gov/news-events/nih-research-matters/novel-coronavirus-structure-reveals-targets-vaccines-treatments

SARS-CoV-2

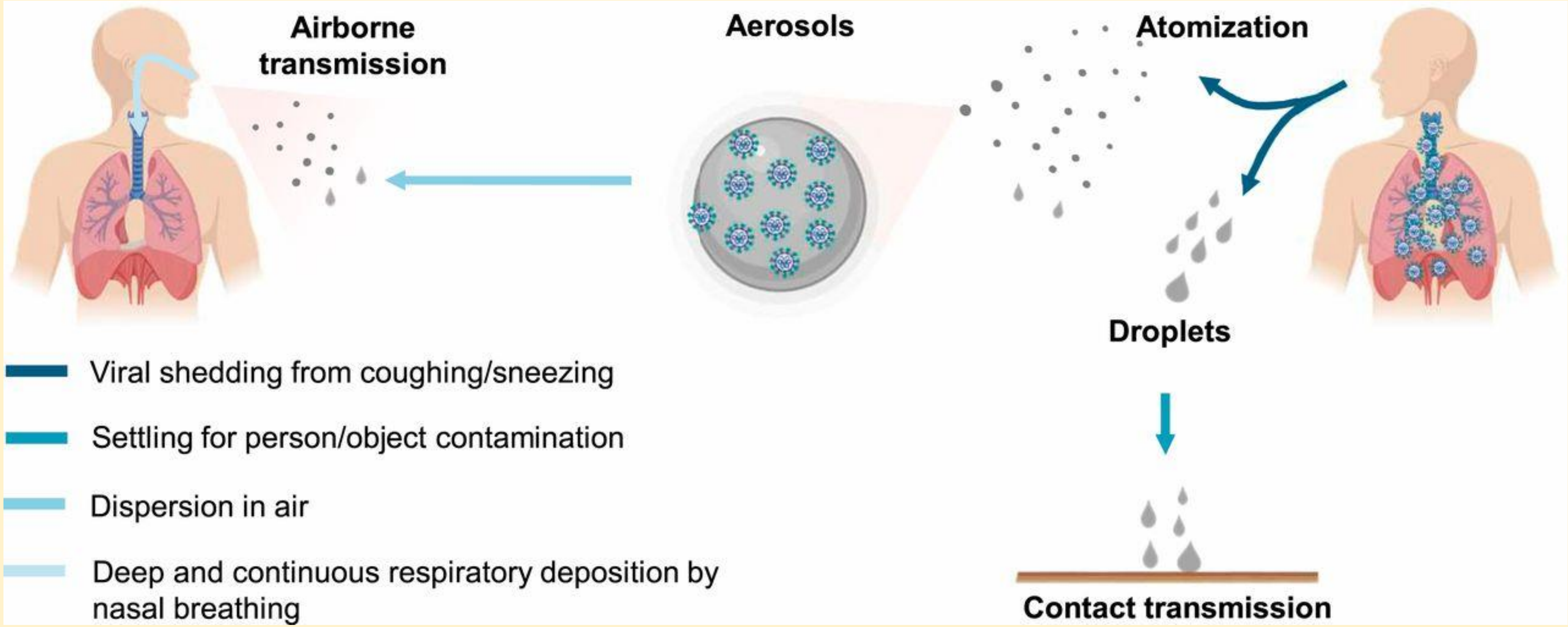


Viral Spike protein binds to host cell Angiotensin converting enzyme 2 (ACE2):

- Type II alveolar cells in lungs, upper esophagus & stratified epithelial cells
- Absorptive enterocytes in ileum & colon
- Cholangiocytes
- Myocardial cells
- Kidney proximal tubule cells
- Bladder urothelial cells

Astuti I, Ysrafil. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. Diabetes Metab Syndr. 2020;14(4):407-412. doi:10.1016/j.dsx.2020.04.020

SARS-CoV-2



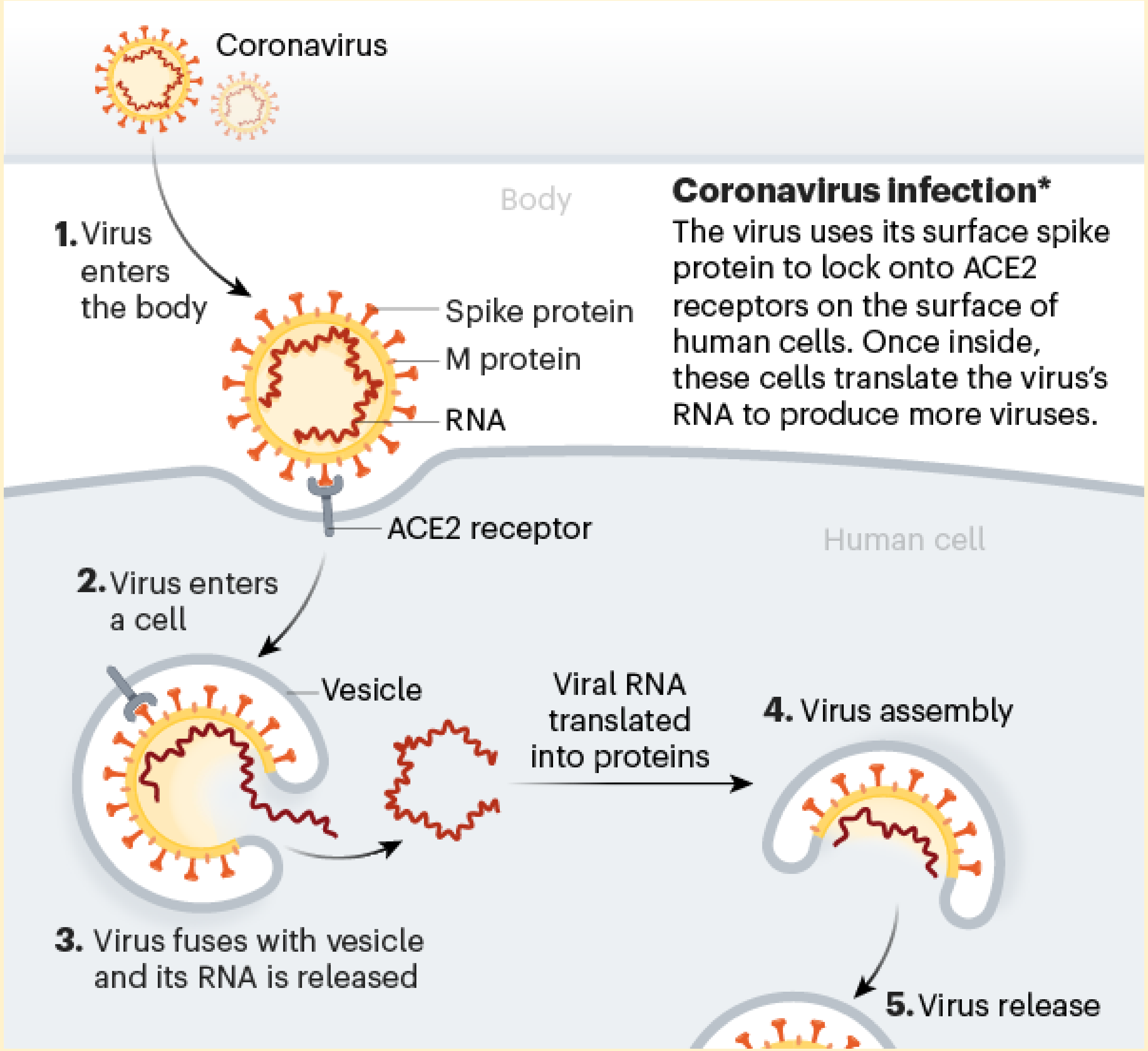
https://www.pnas.org/content/117/26/14857

COVID-19

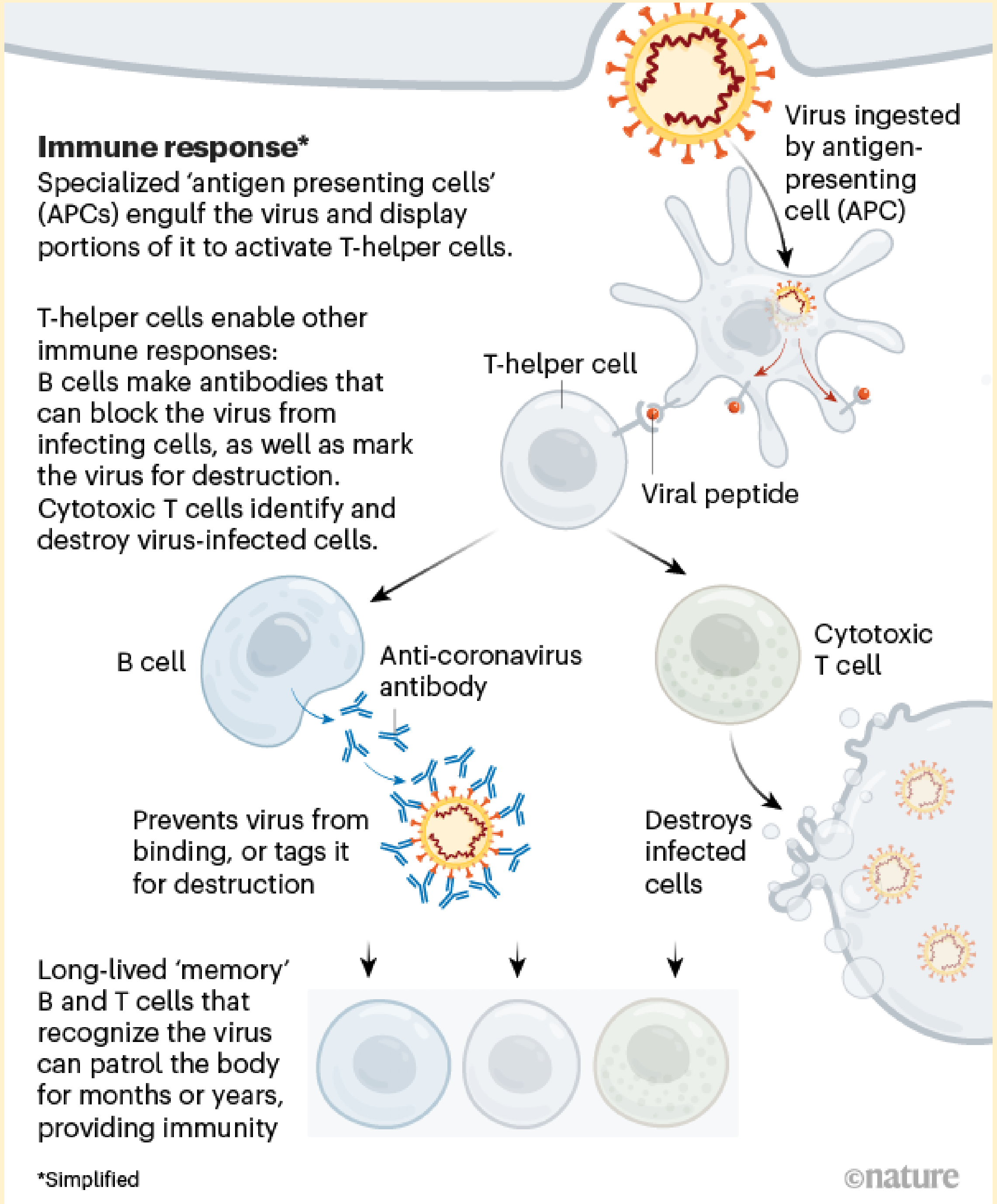
- Symptoms
  - Fever
  - Cough
  - Tiredness
  - Loss of taste or smell
  - Shortness of breath or difficulty breathing
  - Muscle aches
  - Chills
  - Sore throat
  - Runny nose
  - Headache
  - Chest pain
  - Conjunctivitis

- Severe Disease
  - Progressive respiratory failure
  - Acute respiratory distress syndrome (ARDS)
  - Lymphopenia
  - Thromboembolic complications
  - Disorders of the central or peripheral nervous system
  - Acute cardiac, kidney, and liver injury
  - Shock
  - Death

- Long-Term sequela - Long Haulers



https://www.nature.com/articles/d41586-020-01221-y



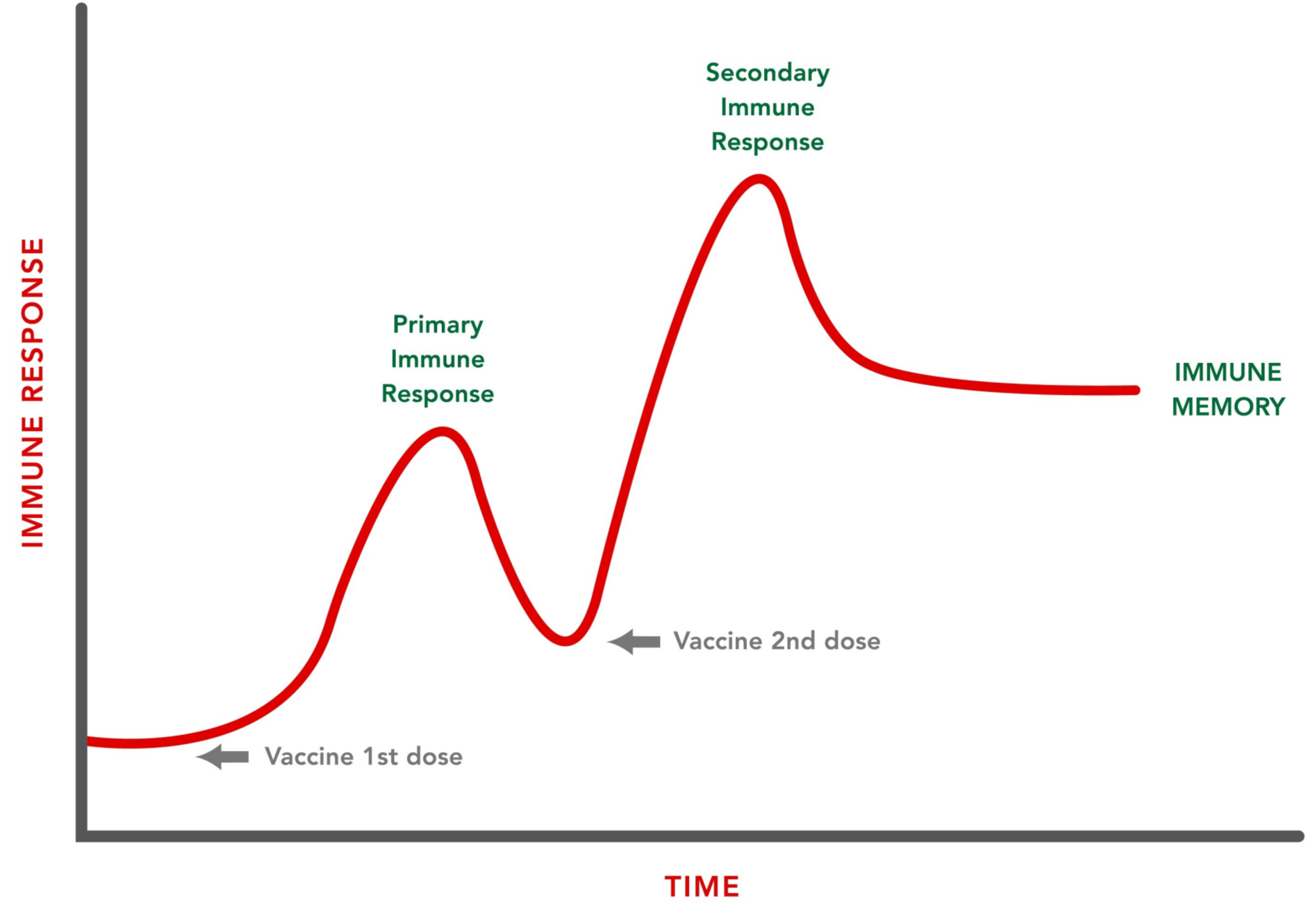
https://www.nature.com/articles/d41586-020-01221-y

Native Immunity to SARS-CoV-2

- Infection SARS-CoV-2 does illicit an immune response
  - Quality/Quality varies substantially
    - Protective antibodies can wane over time (4 months)
    - SARS-CoV-1: humoral immunity last up to 2 - 3 years; antigen-specific T cells about 11 years
  - Limited cross-reacting immunity from seasonal coronaviruses

Purpose of Vaccination

- Reduce the unprecedented morbidity, mortality, and economic disruption
- To produce immunity and prevent severe disease
  - Stimulate the **host's** immune system
    - Prevent infection by this pathogen
    - Reduce severity of disease
  - Short-term, long-term, sometimes life-long immunity?
- **Without needing to get the disease first**



https://www.usacs.com/covid-19-vaccine

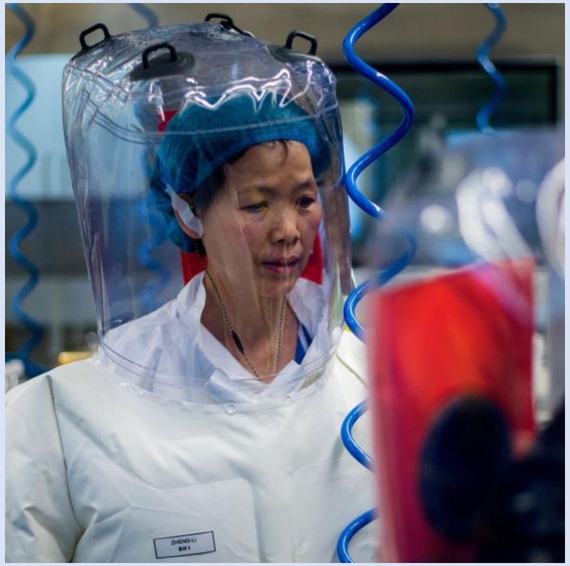
Purpose of Vaccination

- Community immunity – "Herd immunity"
  - High vaccination rates within a population
  - Offers protection to those unable to receive vaccinations
    - Newborns
    - Individuals with chronic illnesses
    - People with allergies to vaccine components
    - Individuals who may not have been fully immunized
  - Pathogen spread efficiency determines % immunized
    - R0 - average # of people an infected person goes on to infect

Disease	R0	% Population Immunized
Measles	12-18	94%
Polio	5-7	80-86%
COVID-19	1.5-3.5	70-85%

Ok………“How DID we get here so fast?”

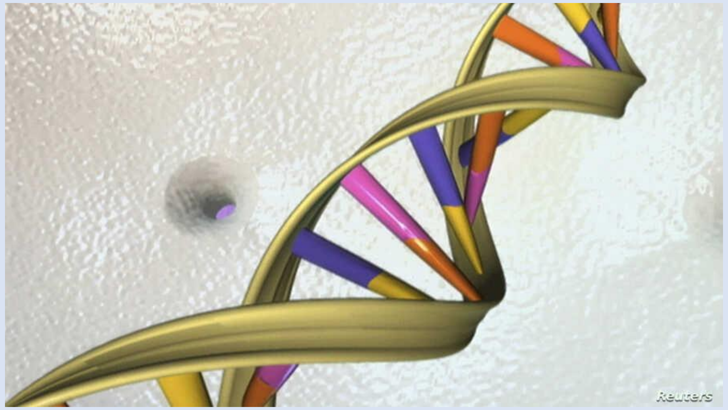
Why so fast?



- **Etiological agent identification**
- After China’s SARS response in 2002
  - Improved reporting to health officials, quarantine and isolation measures, hygiene precautions, and protections for healthcare workers
  - Mitigation strategies in place
- Robust Case Identification and Large-Scale Surveillance
- Wuhan Institute of Virology, Chinese Academy of Sciences
  - 2003 – BSL-4 facility
  - World leader in coronavirus research

https://www.wsj.com/articles/chinas-bats-expert-says-her-wuhan-lab-wasnt-source-of-new-coronavirus-11587463204

Why so fast?

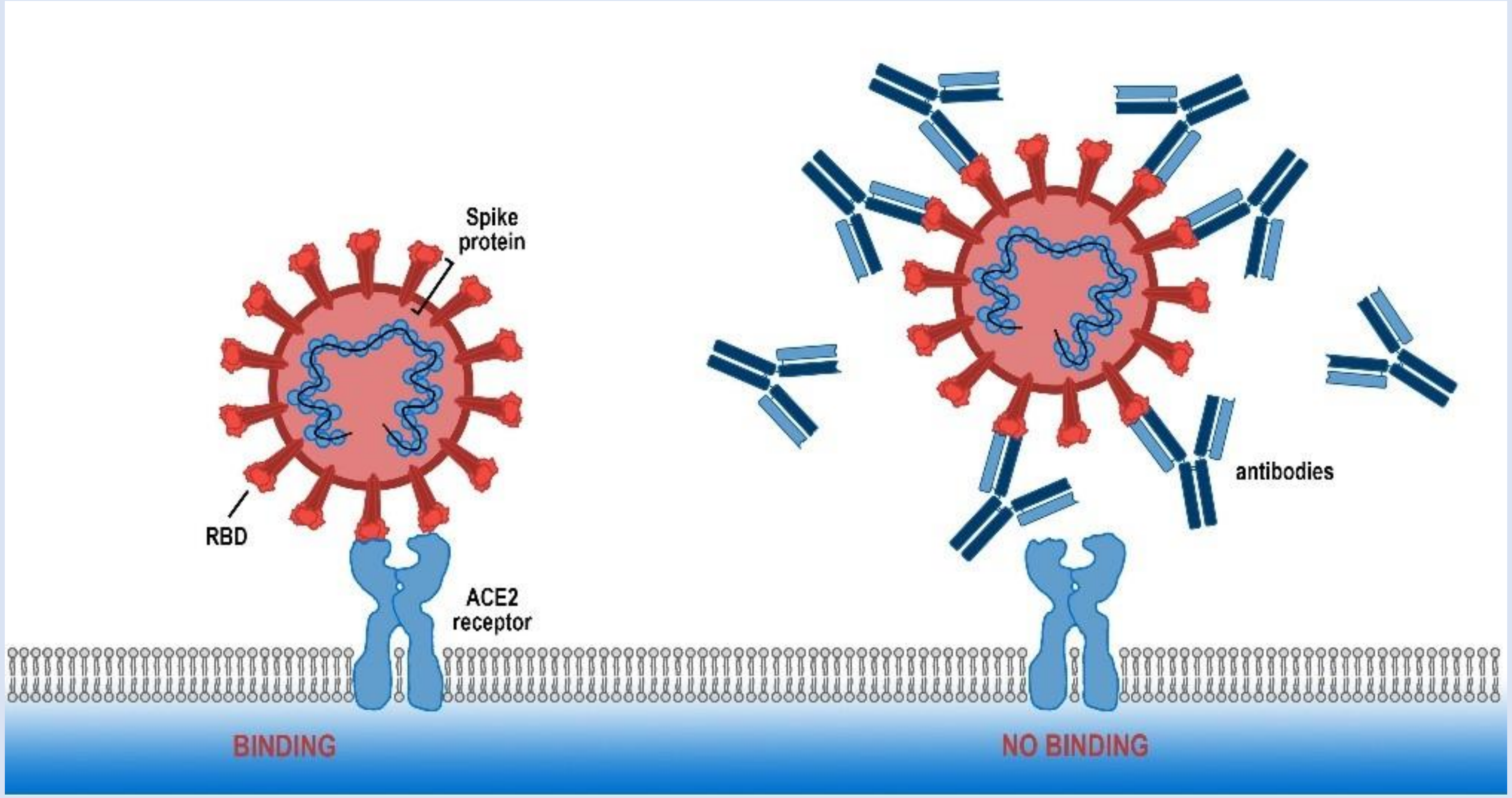


- **Efficient viral genome sequencing and sharing**
- Genetic sequencing faster and cheaper than ever
    - Human genome project in 1990: $2.7 billion in 12 years
    - Today: $1000 in less than 1 day
- January 10, 2020 - novel coronavirus genome sequence was made publicly available
    - Chinese Center for Disease Control and Prevention
    - GenBank database (accession number MN908947)
    - Uploaded to the Global Initiative on Sharing All Influenza Data (GISAID)
- Also the basis for genetic testing for viral infection

FILE - DNA double helix is seen in an undated artist's illustration released by the National Human Genome Research Institute.

Why so fast?

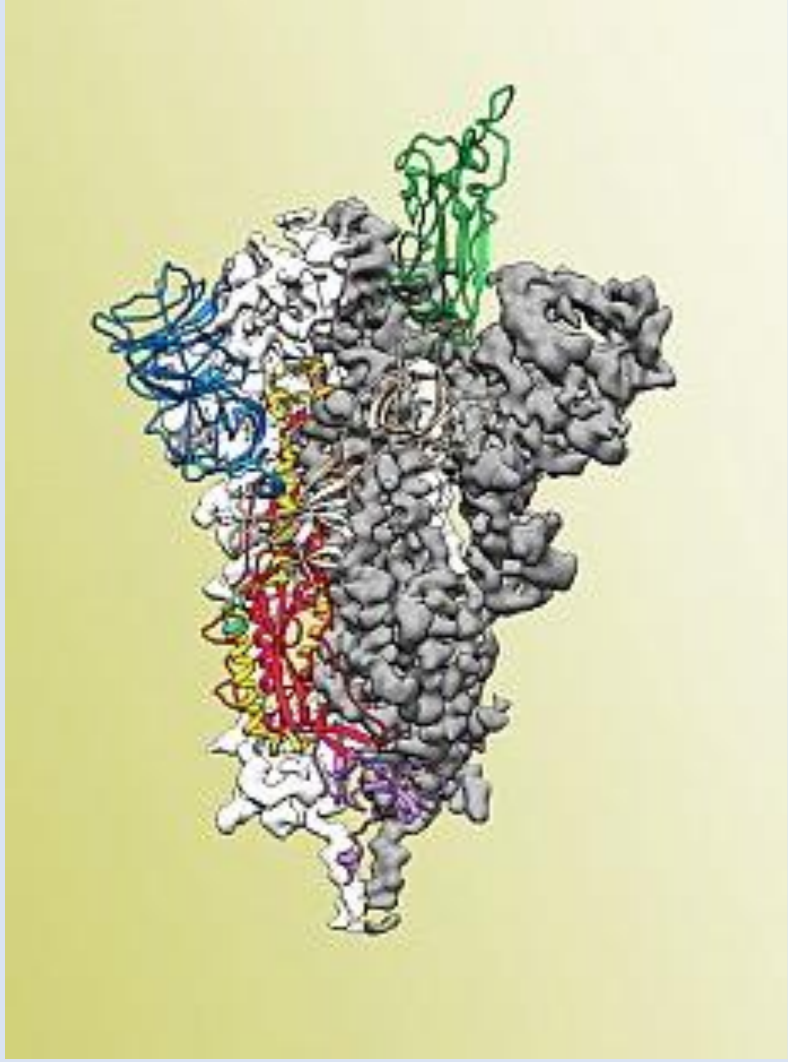
- **Good idea of effective vaccine targets**
  - Vaccines for SARS-CoV-1
    - Similarities in sequence and structure of spikes
    - 3 different 2002 SARS vaccines did not bind to SARS-CoV-2 spike protein



https://www.fluidic.com/resources/solution-phase-affinity-profiling-of-a-SARS-CoV-2/

Why so fast?

- **New technology**
- Cryo-electron microscopy of spike protein
  - Uses stream of high-energy electrons to create tens of thousands of images that are then combined to yield a detailed 3D view
- SARS-CoV-2 spike 10 - 20 X more likely to bind ACE2 than the SARS-CoV-1 spike
  - Higher person to person spread

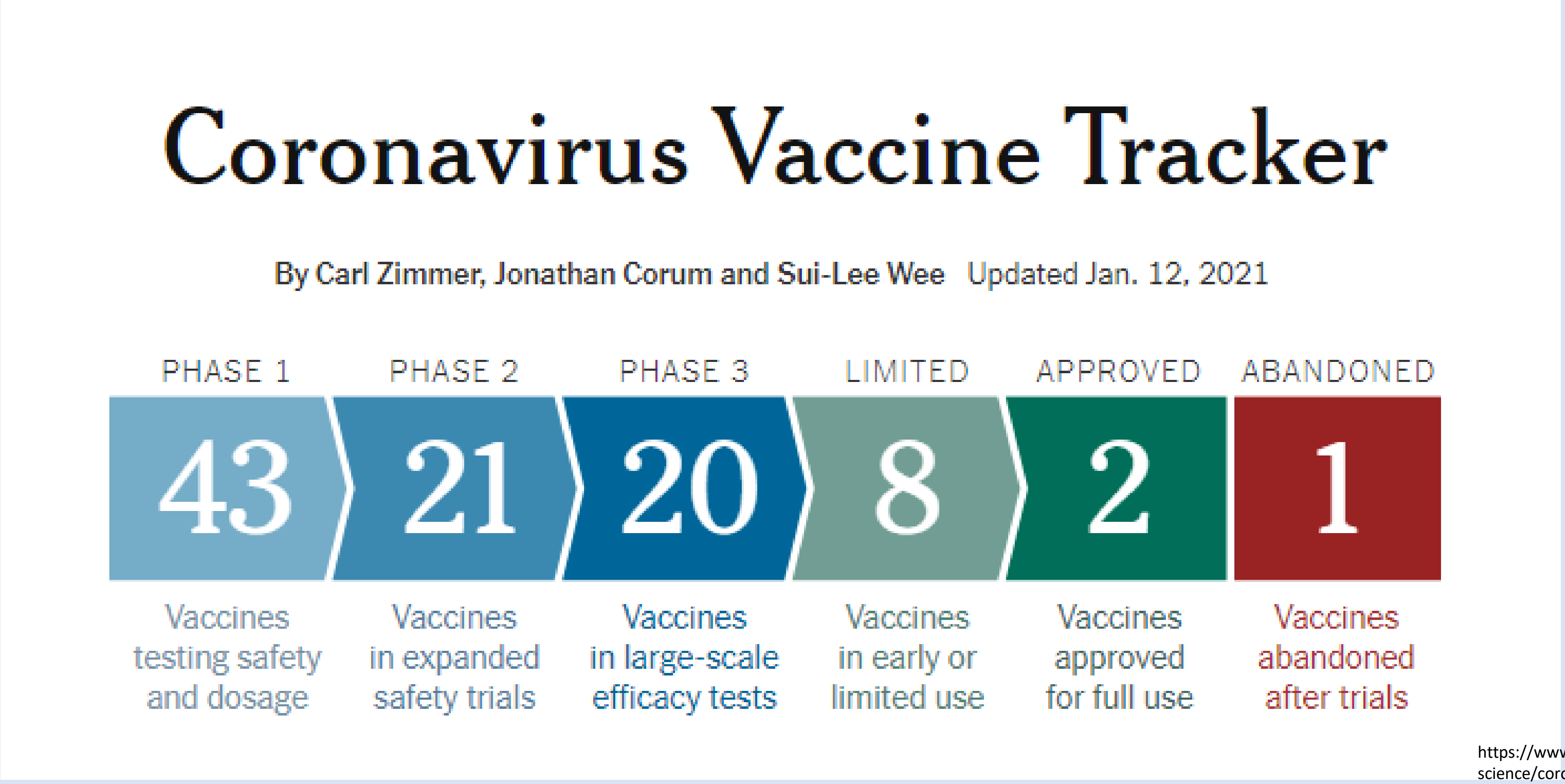


Atomic-level structure of the SARS-CoV-2 spike protein. The receptor binding domain is colored green. UT Austin, McLellan Lab

https://www.nih.gov/news-events/nih-research-matters/novel-coronavirus-structure-reveals-targets-vaccines-treatments

Why so fast?

- **Shear Number of Vaccines in Development**



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

Why so fast?

- **Advances in Vaccine platforms**

Vaccine History

- 17th century Buddhist monks:
  - Drank snake venom
  - Smeared their skin with cowpox to prevent smallpox
- 1796-1798 - Edward Jenner developed smallpox vaccine using cowpox (vaccinia virus)
  - Global eradication of smallpox in 1979
- 1897 – 1904 – Louis Pasteur developed vaccines using live, attenuated cholera and anthrax
- 1908 – 1921 - Albert Calmette and Camille Guérin developed Bacille Calmette-Guérin (BCG) against tuberculosis (TB)

https://uk.finance.yahoo.com/news/the-history-of-vaccines-who-is-edward-jenner-054200087.html?guccounter=1&guce_referrer=aHR0cHM6Ly93d3cuZ29vZ2xlLmNvbS8&guce_referrer_sig=AQAAAIp8xrPXfamOdbrHHOAfGH3JtmukvkvPacWrMkMTm0MeQpoKlzvWxfWQQGjUEfQMOV7tZW1ixdSg0HUaigZgcCanz0-i1kbYo0l-7ZDhfMb_zt-qXv4X7piVRpjGpLHjtb2tidz22skRHJig25Emjtakj09JzjUv3Zw65favnjjA

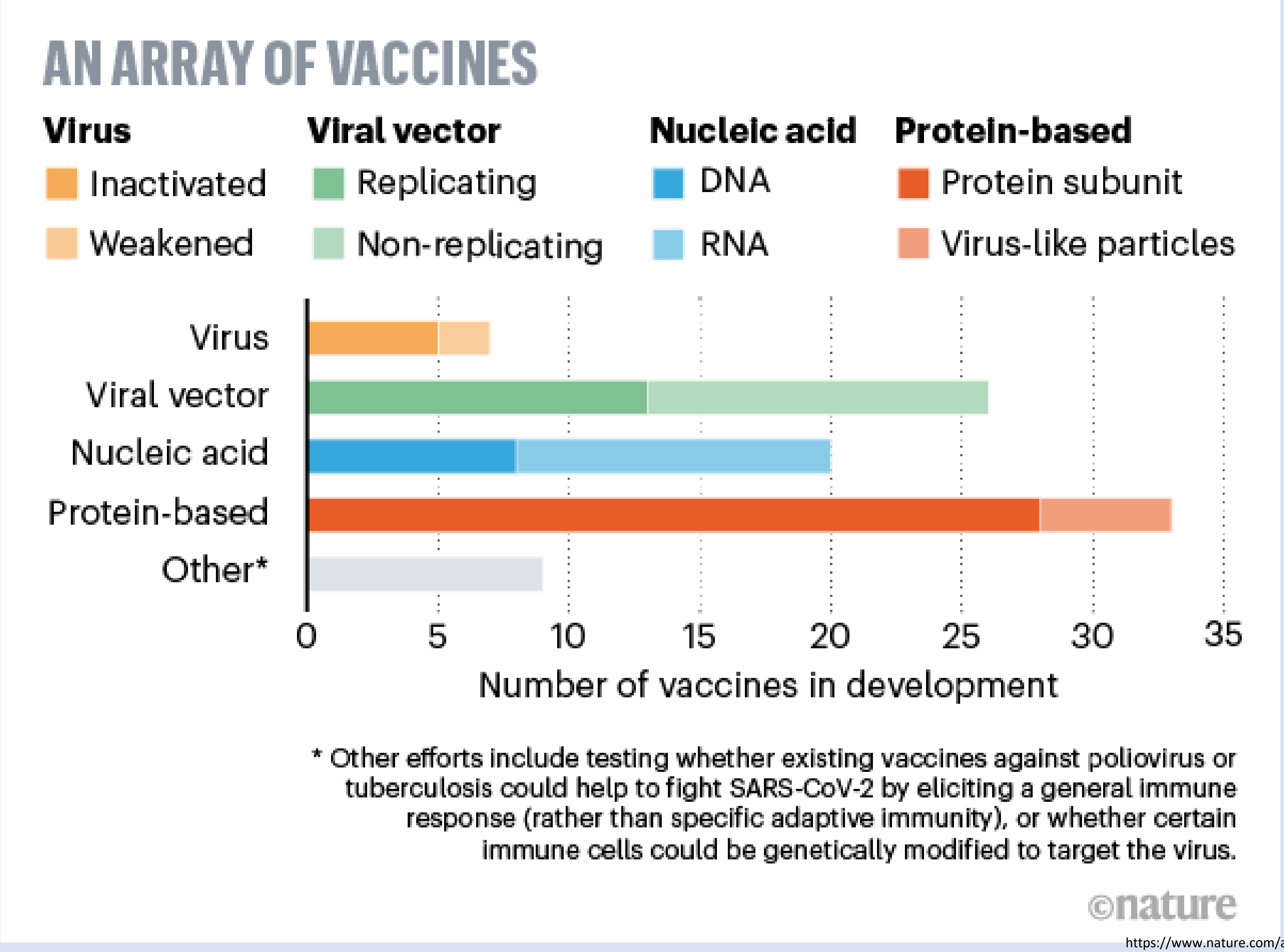
Vaccine History

- 1923 – Alexander Glenny developed formaldehyde inactivation & vaccine for tetanus toxin
  - 1926 – Diphtheria vaccine
  - 1948 – Pertussis vaccine
- 1950's - Jonas Salk inactivated polio vaccine and Albert Sabin live attenuated oral polio vaccine

Peters' Atlas of Tropical Medicine and Parasitology, 3, 165-243

Types of Vaccines

- Live
- Live-attenuated:
  - Reduce virulence or replication
  - Heat, chemicals
  - Could revert
- Killed:
  - By physical or chemical treatment
  - No guarantee all organisms dead
- Extract/Particle:
  - Not whole pathogen but material from disrupted/lysed organism
  - Viral-like particle
- Recombinant:
  - Genetically altered organism with impaired virulence/or replication
  - Could revert
- DNA/RNA:
  - No whole pathogen
  - Only gene products which can produce isolated pathogen protein/s



https://www.nature.com/articles/d41586-020-01221-y

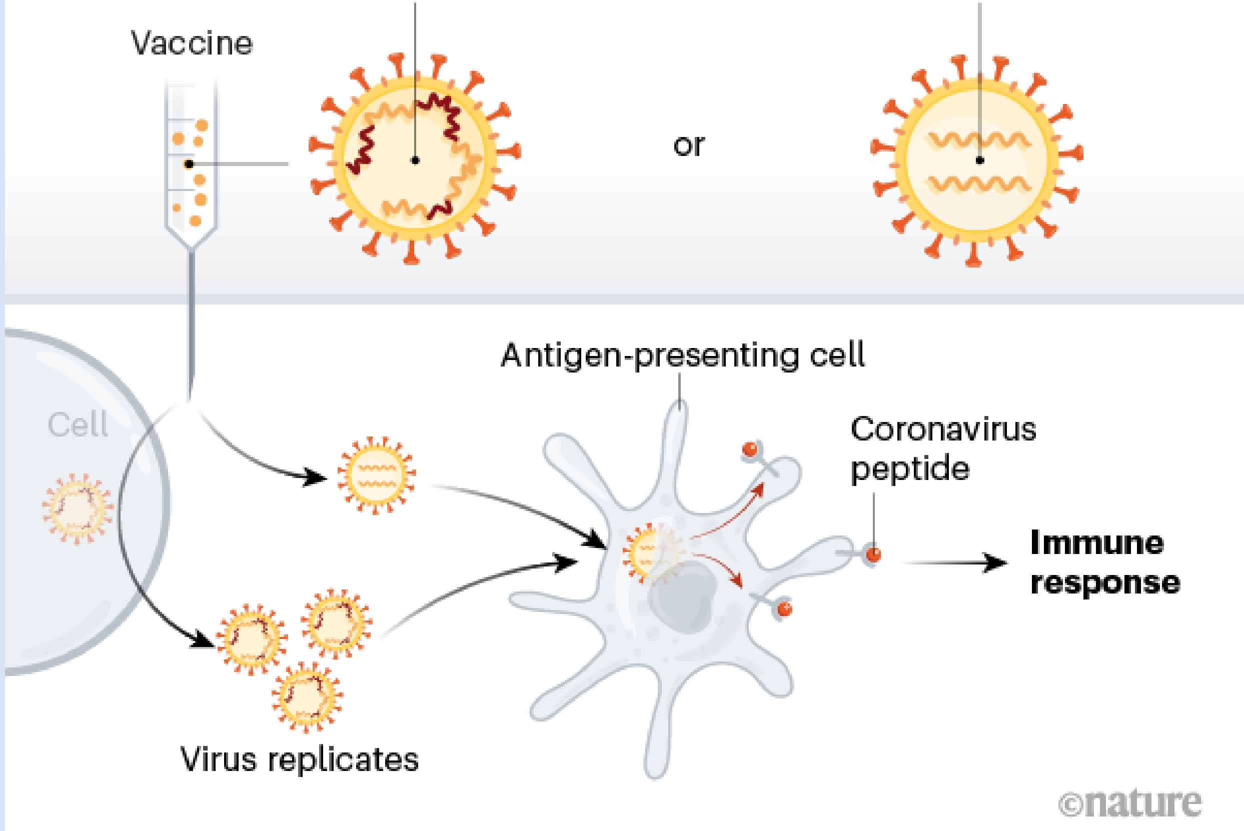
VIRUS VACCINES

Weakened virus

A virus is conventionally weakened for a vaccine by being passed through animal or human cells until it picks up mutations that make it less able to cause disease. Codagenix in Farmingdale, New York, is working with the Serum Institute of India, a vaccine manufacturer in Pune, to weaken SARS-CoV-2 by altering its genetic code so that viral proteins are produced less efficiently.

Inactivated virus

In these vaccines, the virus is rendered uninfectious using chemicals, such as formaldehyde, or heat. Making them, however, requires starting with large quantities of infectious virus.

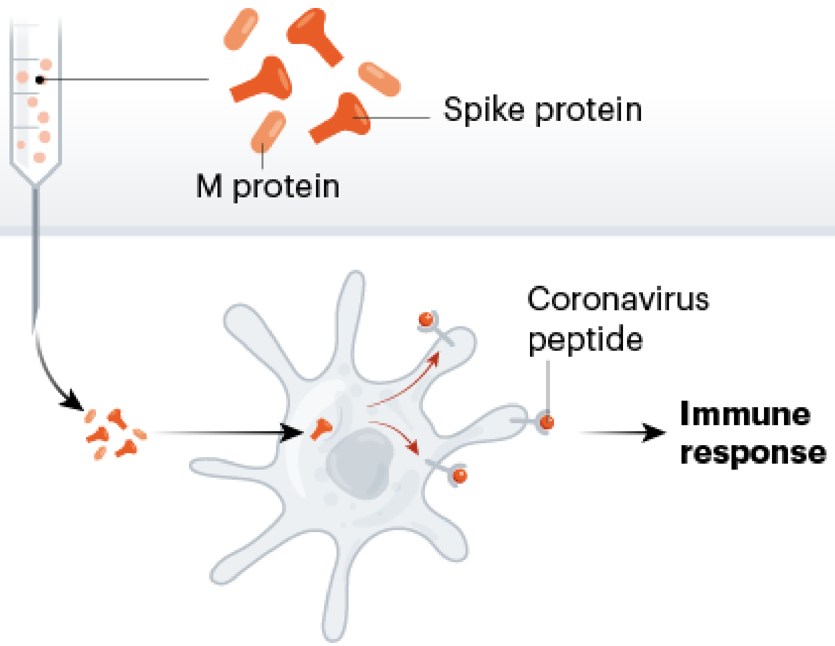


https://www.nature.com/articles/d41586-020-01221-y

PROTEIN-BASED VACCINES

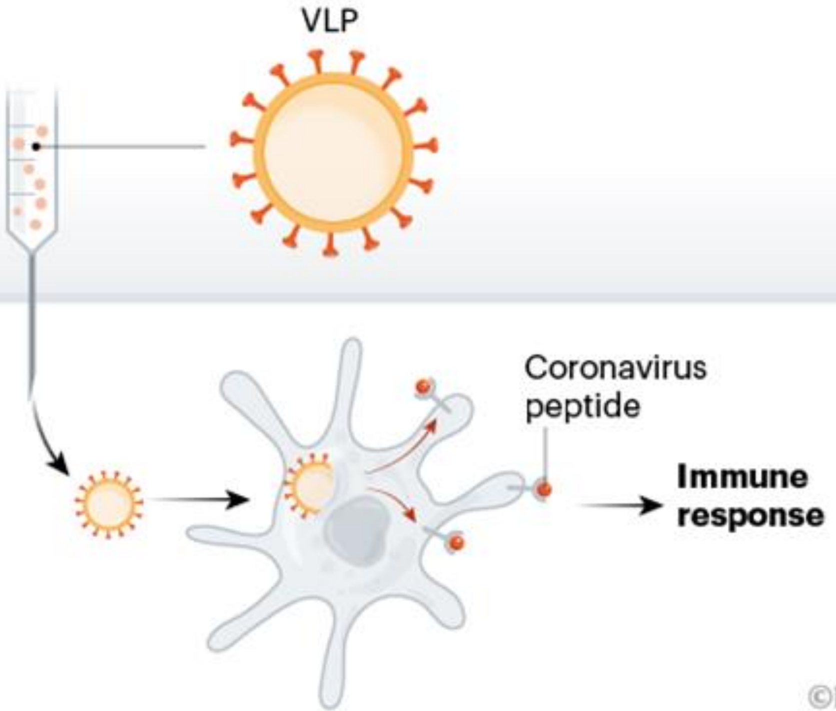
Protein subunits

Twenty-eight teams are working on vaccines with viral protein subunits — most are focusing on the virus's spike protein or a key part of it called the receptor binding domain. Similar vaccines against the SARS virus protected monkeys against infection but haven't been tested in people. To work, these vaccines might require adjuvants — immune-stimulating molecules delivered alongside the vaccine — as well as multiple doses.



Virus-like particles

Empty virus shells mimic the coronavirus structure, but aren't infectious because they lack genetic material. Five teams are working on 'virus-like particle' (VLP) vaccines, which can trigger a strong immune response, but can be difficult to manufacture.



https://www.nature.com/articles/d41586-020-01221-y

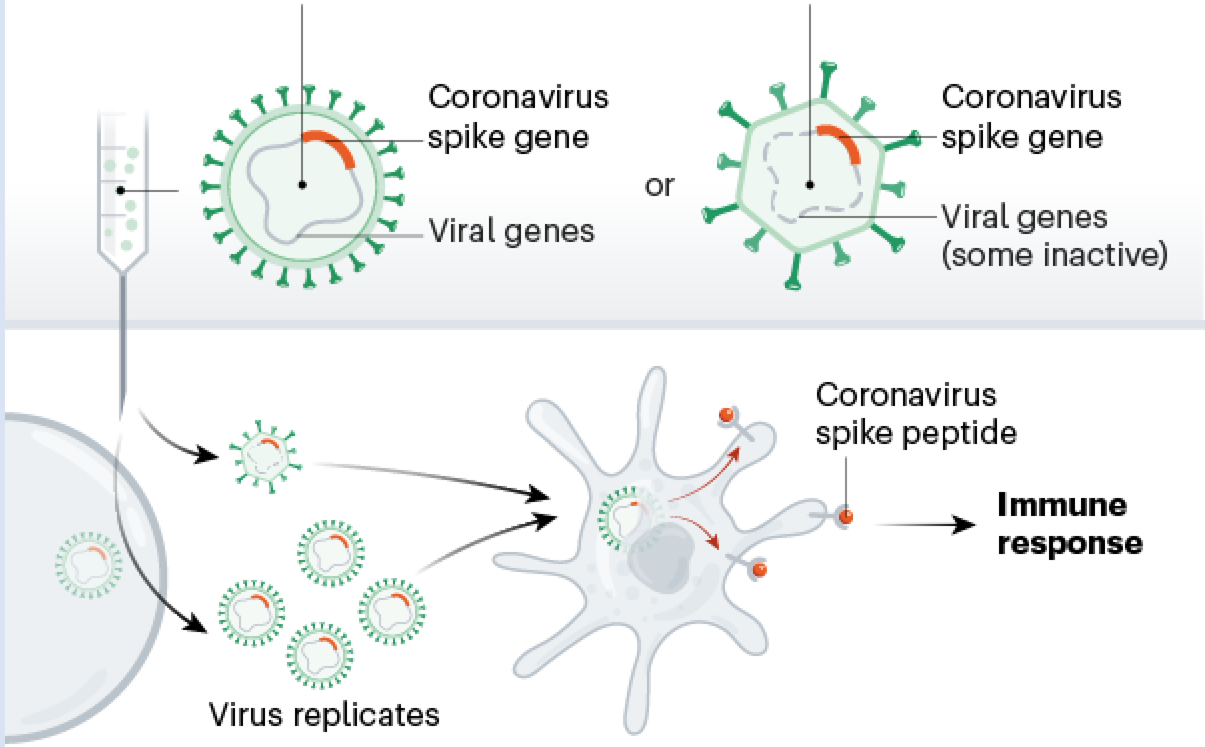
VIRAL-VECTOR VACCINES

Replicating viral vector (such as weakened measles)

The newly approved Ebola vaccine is an example of a viral-vector vaccine that replicates within cells. Such vaccines tend to be safe and provoke a strong immune response. Existing immunity to the vector could blunt the vaccine's effectiveness, however.

Non-replicating viral vector (such as adenovirus)

No licensed vaccines use this method, but they have a long history in gene therapy. Booster shots can be needed to induce long-lasting immunity. US-based drug giant Johnson & Johnson is working on this approach.

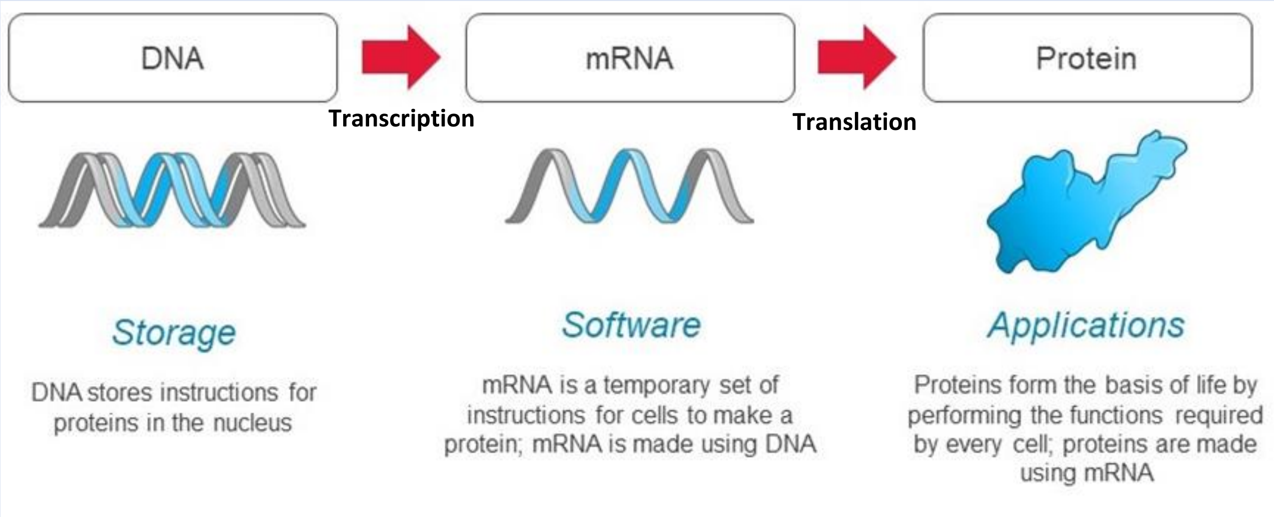


https://www.nature.com/articles/d41586-020-01221-y

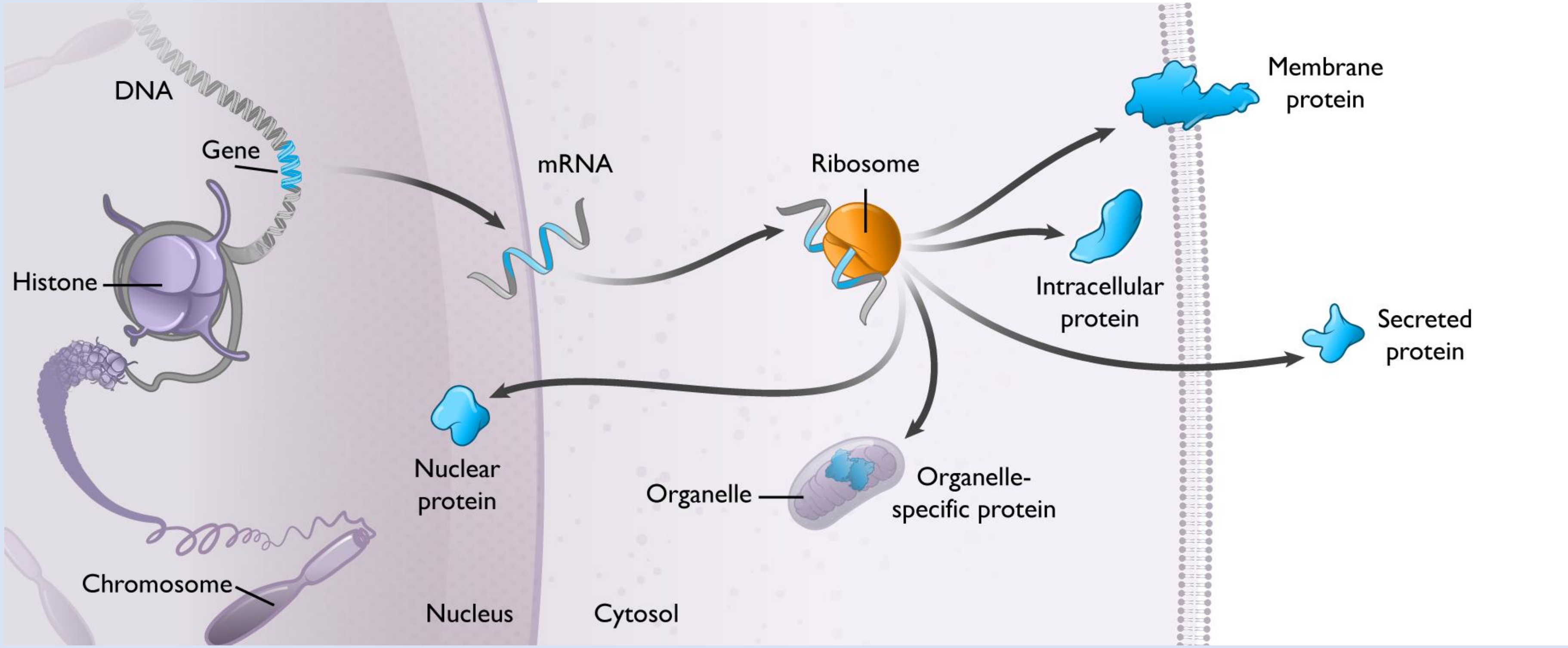
mRNA Vaccines

- Advantages:
  - Non-infectious
  - Non-integrating/no insertional mutagenesis
  - Degraded by normal cellular processes
  - Really easy to make in laboratory!
    - Rapid, inexpensive, scalable manufacturing
- Technology first published in 1990
  - Reporter gene mRNA injected into mouse – protein product detected
- Recently overcome important challenges
  - mRNA instability
  - High innate antigenicity
  - Inefficient in vivo delivery

mRNA Basics



https://www.sec.gov/Archives/edgar/data/1682852/000168285220000006/moderna10-k12312019.htm



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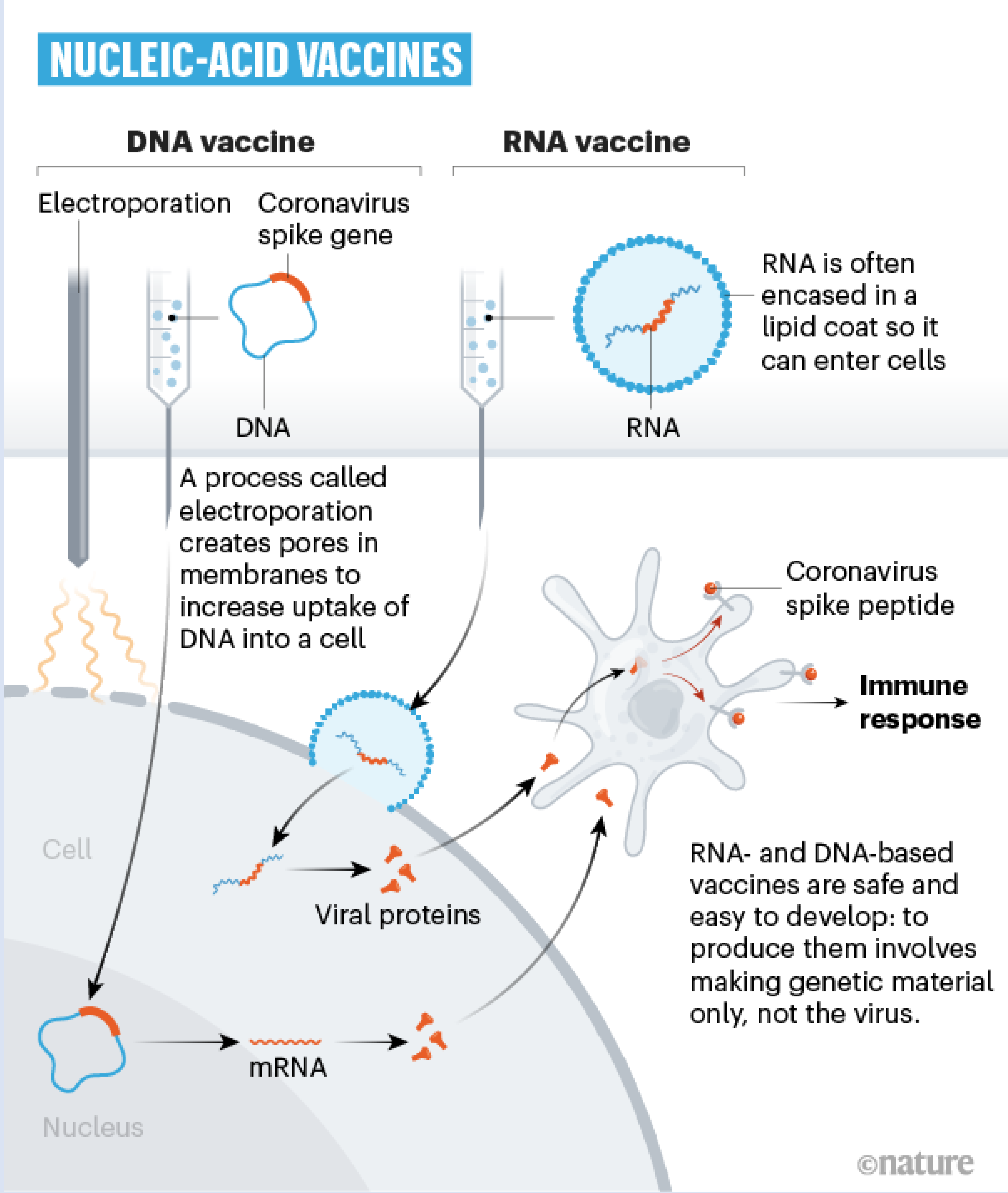


https://www.nature.com/articles/d41586-020-01221-y

Why so fast?

- **Resources – Money!**
- Operation Warp Speed
  - $10 billion
  - Vaccine and therapeutic development, manufacturing, distribution
  - Department of Health and Human Services (HHS), Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), the Biomedical Advanced Research and Development Authority (BARDA), the Department of Defense (DoD)

https://www.defense.gov/Explore/Spotlight/Coronavirus/Operation-Warp-Speed/

Why so fast?

- **Resources – Money!**
- COVAX
  - Coordinated by Gavi, the Vaccine Alliance, the Coalition for Epidemic Preparedness Innovations (CEPI), and WHO
  - One pillar of Access to COVID-19 Tools (ACT) Accelerator
  - Governments, global health organizations, manufacturers, scientists, private sector, civil society, and philanthropy
- Private donations

Why so fast?

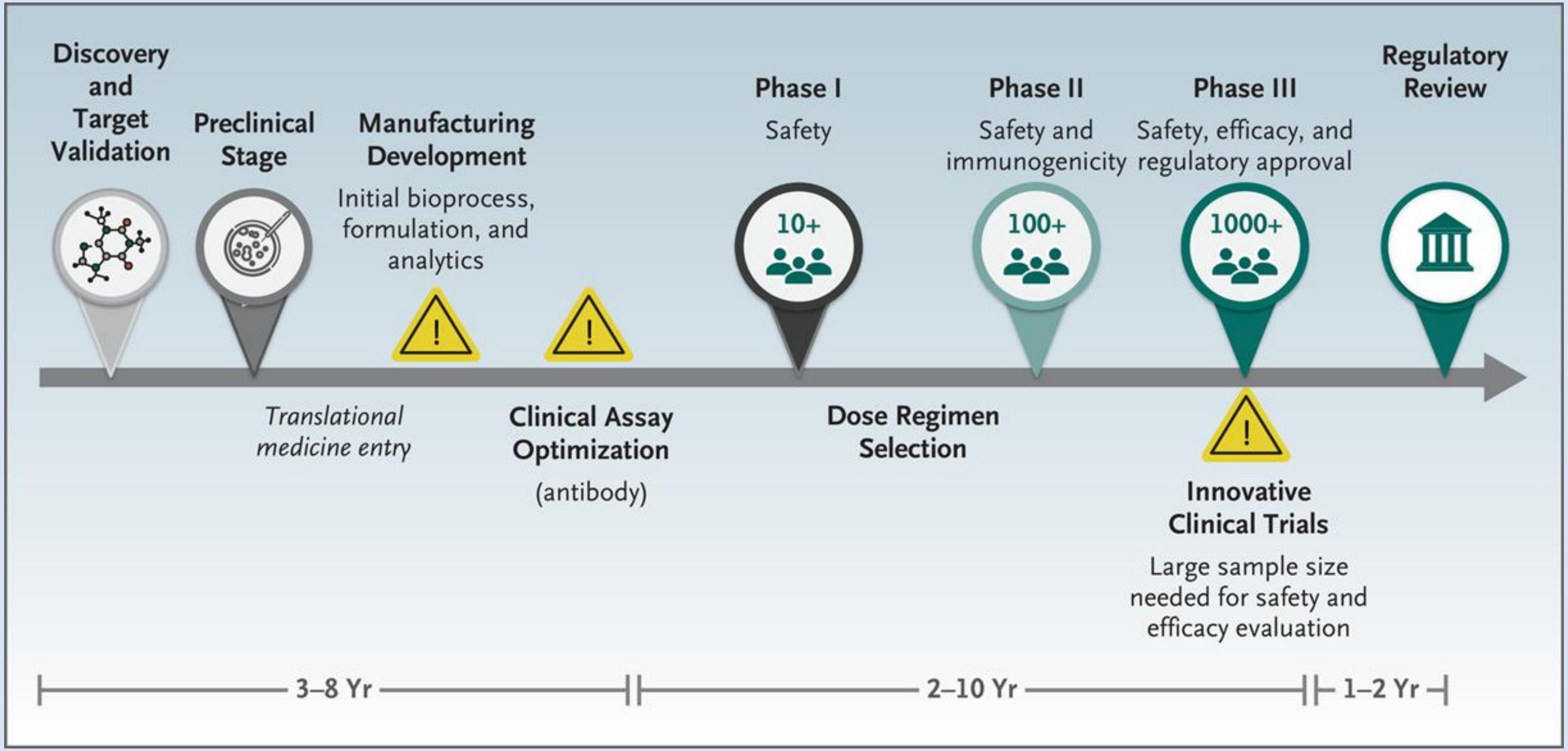
- **Resources – Hands!**
- Scientists shifted their focus
  - Study all aspects – basic virology, immunology, pharmacology, epidemiology, vaccines
  - Intersection between COVID-19 and their specialty
  - Capitalizing on their unique expertise

https://www.hvtn.org/en/community/community-compass/vol20-issue1/facing-down-pandemics.html

https://www.fredhutch.org/en/news/releases/2020/11/fred-hutch-begins-experimental-covid-19-vaccine-efficacy-trial.html

Why so fast?

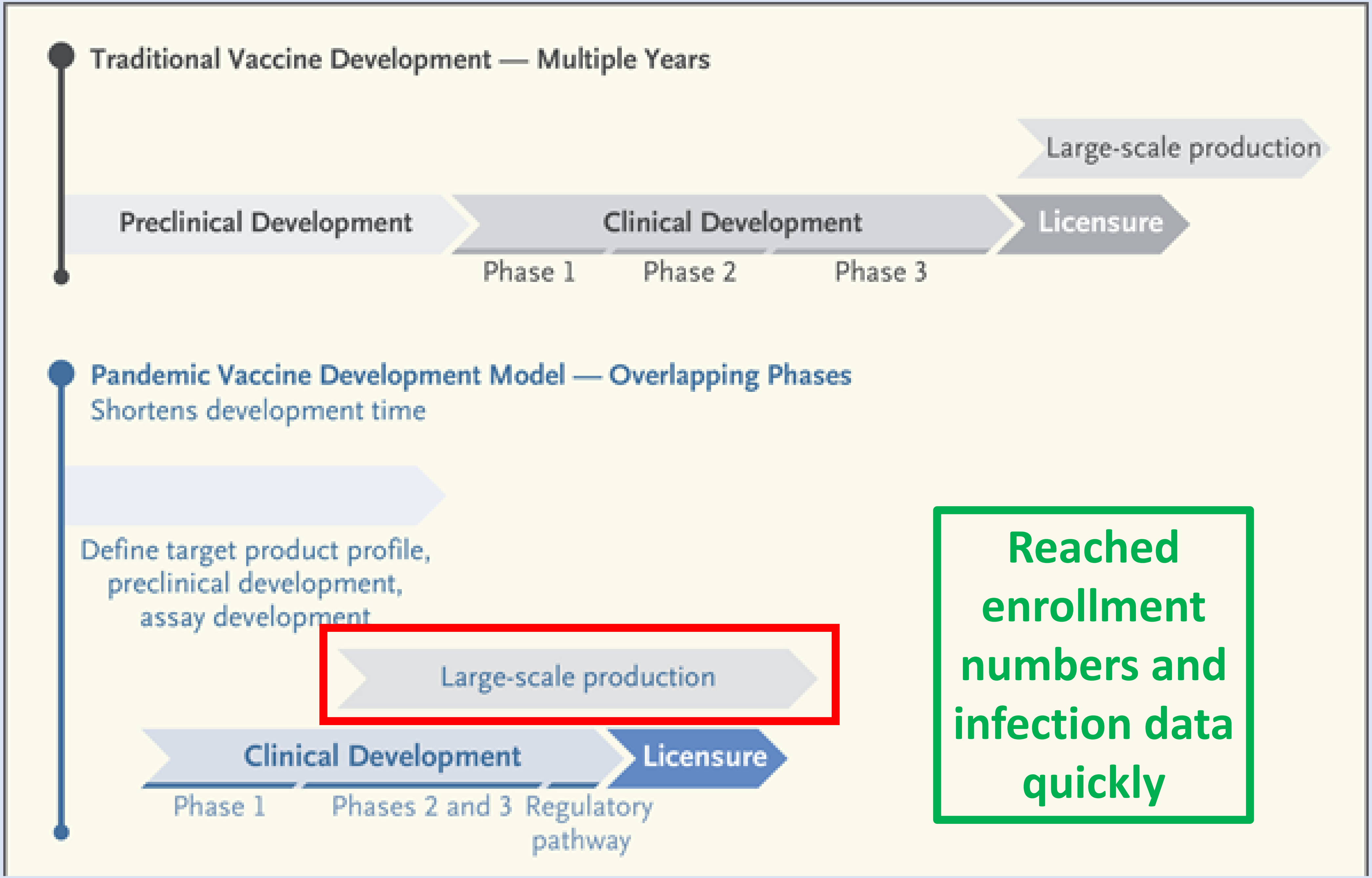
- **Compression of clinical trial process**



https://www.nejm.org/doi/full/10.1056/NEJMe2025111

Safety data gathered

- Phase 1: Vaccine given to small # people
  - Healthy people
  - Increasing doses
- Phase 2: Given to hundreds of people
  - Varying health statuses and different demographic groups
  - Various dosages
  - Common short-term side effects, adverse effects, and risks
  - Initial information regarding the effectiveness of the vaccine
- Phase 3: Thousands to 10’s of thousands of people
  - Broad demographic groups - population intended for use of the vaccine
  - Randomized, controlled studies
    - Control placebo group
    - Compare outcomes (infection rate), side effects, adverse effects

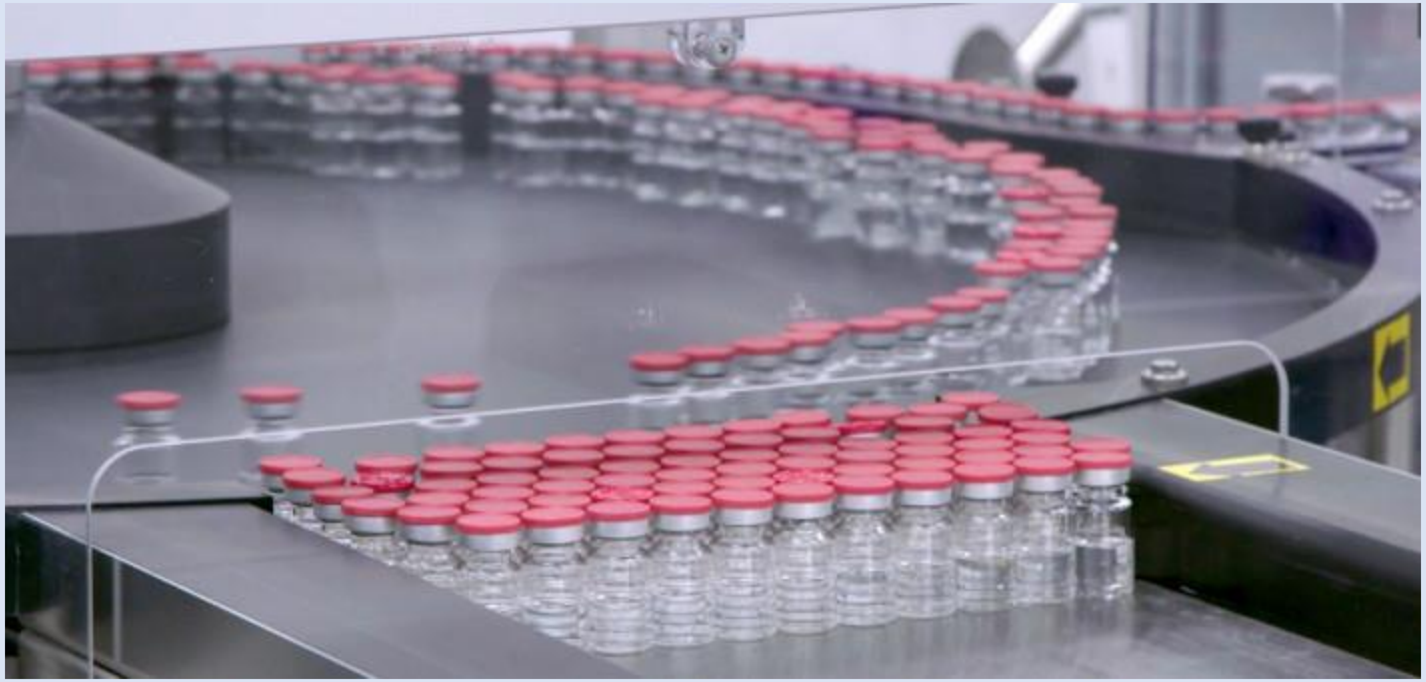


Reached enrollment numbers and infection data quickly

https://www.nejm.org/doi/full/10.1056/NEJMp2020076

Why so fast?

- **Resources – Production!**
- Exchange of technical information about manufacturing processes and platforms



https://www.covidhealth.com/article/third-covid19-vaccine-90-effective

Why so fast?

- **Emergency Use Authorization (EUA)**
- Mechanism to facilitate the availability and use of medical countermeasures during public health emergencies
  - Requires:
    - All safety data from Phase 1 and 2 studies
    - Safety data from Phase 3 for at least 60 days after 50% got their last dose
      - Over 95% of long-term adverse vaccine effects happen between 30-45 days
    - Manufacturing information to ensure quality and consistency
  - Reviewed by:
    - FDA career scientists and physicians
    - Vaccines and Related Biological Products Advisory Committee made up of external scientific and public health experts

2 COVID-19 Vaccines

https://www.medpagetoday.com/infectiousdisease/covid19/88222

https://www.pharmaceutical-technology.com/comment/covid-19-mrna-based-vaccine/

Pfizer BNT162b2

- Collaboration of Pfizer (New York) and BioNTeck (Germany)
- mRNA based - Spike (S) protein
- Funded by Pfizer and German Government
- 95% efficacy after studying 44,000 participants - 16 years and older
- 2-doses given 21 days apart
- Storage conditions (-70°C ±10°C)
- Well-tolerated and good safety
    - Adverse events: mild to moderate pain at the injection site, fatigue and headache
    - Severe reactions: fewer than 2% of vaccine recipients
    - Serious adverse events: similar between vaccine and placebo groups (0.6% and 0.5%)

Moderna Therapeutics mRNA-1273

- Collaboration Moderna (Massachusetts) and NIH
- mRNA based - Spike (S) protein
- Funded by BARDA (Warp Speed)
- 94.1% efficacy after studying 30,000 participants - 18 years and older
- 2-doses, given 28 days apart
- Storage conditions (-25 to -15^{o}C)
- Well-tolerated and good safety
  - Adverse events: mild to moderate pain at the injection site, fatigue and headache
  - Severe reactions: fewer than 2% of vaccine recipients
  - Serious adverse events: similar between vaccine and placebo groups (1% and 1%)

Moderna Therapeutics mRNA-1273

Early Timeline:

- January 11 - Chinese authorities shared genetic sequence of SARS-CoV-2
- January 13 - NIH and Moderna research team finalized sequence for mRNA-1273
  - Disclosed intent to run a Phase 1 study
- February 7 - first clinical batch of vaccine was completed
  - **25 days from sequence selection to vaccine manufacture!**
- February 24 - Clinical batch was shipped
- March 4 - FDA completes Investigational New Drug (IND) application review
- March 16 - first participant in Phase 1 study dosed
  - **63 days from sequence selection to first human dosing!**

https://www.sec.gov/Archives/edgar/data/1682852/000119312520074867/d884510dex991.htm

Vaccination Hurdles

- 1986 – National Vaccine Injury Compensation program
  - Deal with vaccine litigation
  - Opened the door for companies to take on risky vaccine development

- 1998 - Andrew Wakefield and 12 colleagues publish case series in the Lancet suggesting MMR vaccine was linked to autism
  - Later found guilty of deliberate fraud and falsifying facts

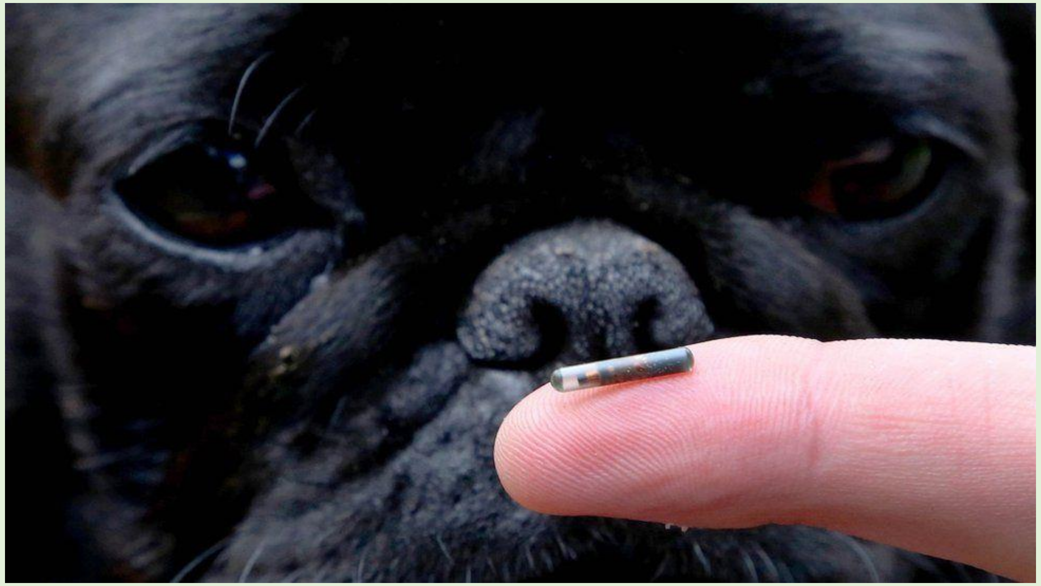
Vaccination Hurdles

- COVID-19 Vaccine Ingredients:
  - mRNA
  - Lipids
    - (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
    - 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
    - 1,2-Distearoyl-sn-glycero-3- phosphocholine
    - Cholesterol
  - Ingredients to maintain pH & Stability
    - Potassium chloride
    - Monobasic potassium phosphate
    - Sodium chloride
    - Dibasic sodium phosphate dehydrate
    - Sucrose

https://www.technologyreview.com/2020/12/09/1013538
/what-are-the-ingredients-of-pfizers-covid-19-vaccine/

Vaccination Hurdles

- COVID-19 Vaccine DO NOT contain:
  - Aluminum or Mercury
  - Preservatives
  - Fetal cells or tissue
    - Did use HEK 293 in early efficacy experiments
      - Descended from tissue taken from a 1973 elective abortion in the Netherlands
  - Microchips



https://www.bbc.com/news/uk-35972480

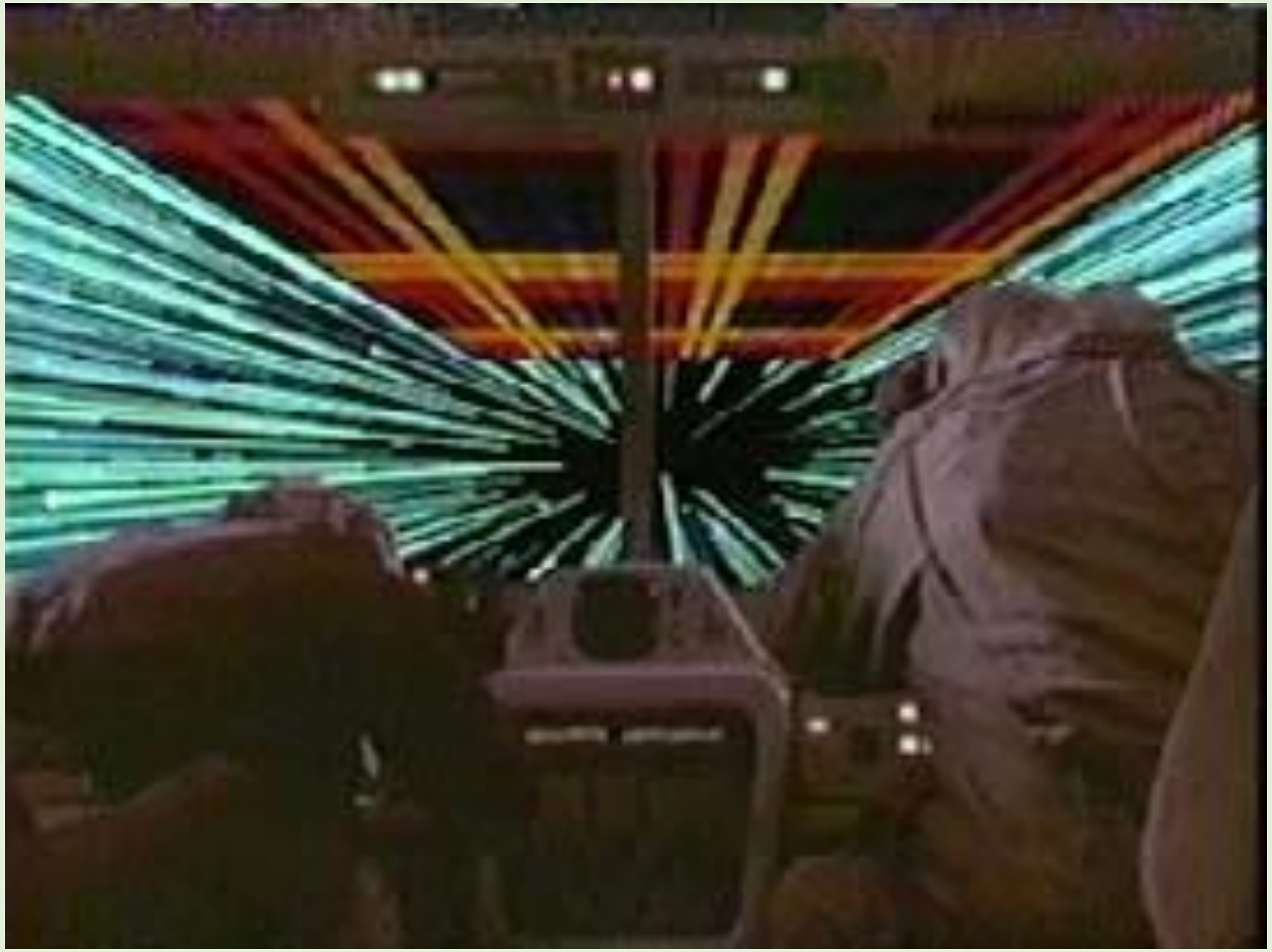
Vaccination Hurdles

COVID-19 Vaccine Events

- Anaphylaxis
  - 21 cases after 1,893,360 first doses of the Pfizer-BioNTech COVID-19 vaccine
    - 11.1 cases per million doses
    - 71% of these occurred within 15 minutes
    - Screening recipients for contraindications and precautions
- Bell's palsy
  - Rate the similar to general population
    - 0.01% of Americans normally
    - 0.009% of Pfizer participants – 4 total, all in vaccine group
    - 0.013% of Moderna participants – 3 total, 1 in the placebo group

Vaccination Hurdles

- "We got here too fast"
- "Skip safety measures"
- "First to receive vaccine are Guinea pigs"



Questions?