This information was presented by Steven Chamow, PhD on Tuesday, June 30 2020 during the educational webinar, "Technologies for New Vaccines for COVID-19”

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Steven Chamow, Ph.D.

Technologies for New Vaccines for COVID-19

San Mateo, CA USA | +1 650-345-1878 | info@chamowassociates.com

CHAMOW & Associates
Biopharmaceutical Product Development

Webinar Series
Two sessions

	Date*	Topic
Session 1	Tuesday 23 June	What does it take to develop a new drug for COVID-19?
Session 2	Tuesday 30 June	Technologies for new vaccines for COVID-19

*Both sessions via Zoom at 5:00-6:30 pm PDT

Overview

- Lessons from the 1918 flu pandemic
  - How bad was it?
  - How did it end?
- Vaccination
  - The immune system and vaccination
- Designing a vaccine for SARS-CoV-2
  - The importance of spike glycoprotein as a protective vaccine target
  - How a vaccine creates immunity
- Types of vaccines
- How are vaccines made?
  - Technologies used to create and manufacture vaccines
  - Biologic vs. chemically synthesized
- Leading COVID-19 vaccine programs

Pre-readings

“How the Horrific 1918 Flu Spread Across America”, by John Barry, published in the Nov 2017 issue of Smithsonian Magazine.

https://www.smithsonianmag.com/history/journal-plague-year-180965222/

“How the COVID-19 Pandemic Could End”, by Lydia Denworth, appears in the Jun 2020 issue of Scientific American Magazine.

https://www.scientificamerican.com/article/how-the-covid-19-pandemic-could-end1/

“Pandemic I: The First Modern Pandemic”, a 2020 essay by Bill Gates

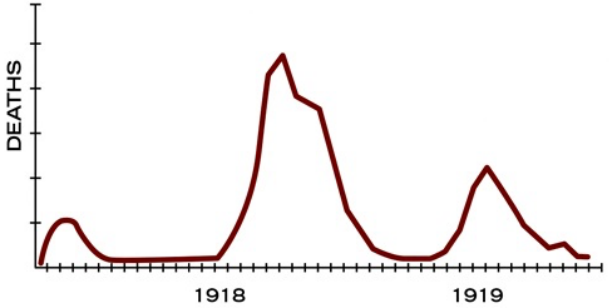
https://www.gatesnotes.com/Health/Pandemic-Innovation

Lessons from the 1918 flu pandemic

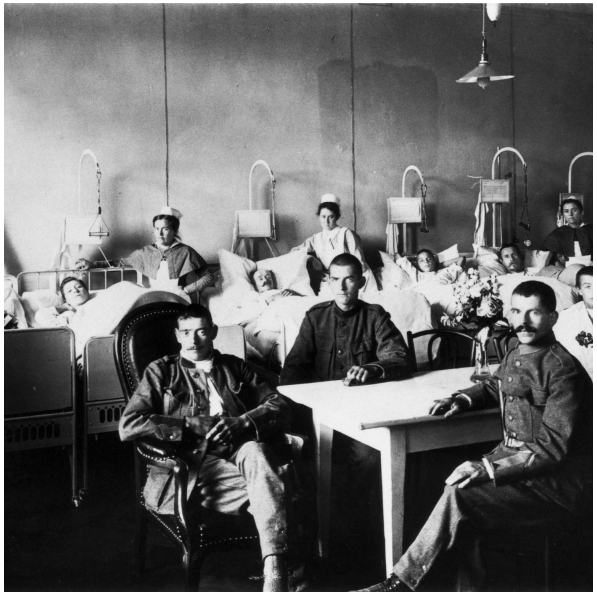
Influenza pandemic

H1N1 influenza in 1918-1919

- Three waves of infection, starting in March 1918 and subsiding by spring 1919
- Wave 1-Spring 1918
  - Began in Kansas
  - “3-day fever” with few deaths, victims recovered after a few days
- Wave 2-Fall 1918
  - Far more severe
  - Affected elderly, young adults and children
  - Victims died within hours, lungs filled with fluid and they suffocated to death
  - Shortages of medical personnel throughout the US due to WWI
- Wave 3-Winter 1918



Influenza pandemic (cont'd.)



- Worldwide 500 million (1/3 population) infected, 50-100 million died
- US 26 million infected (1/4 population) 675,000 died (2.6%)
- So many deaths in 1918 that the total US population decreased for the only time in the 20th century
- Ended after Wave 3
- Circulated for another 40 years as a seasonal virus

What causes a pandemic to end?

Three reasons

1. Genetic mutations in virus reduce virulence which slows or stops disease spread

2. Infection spreads to the point at which the population reaches herd immunity
   - 30-80% of population (varies with R0 for each virus)
   - Not enough uninfected individuals to sustain further spread

3. Development of vaccine
   - Enables population to achieve herd immunity without spread of viral disease

Vaccination

Infection vs. vaccination

"Tricking" the immune system to reach immunity

INFECTION

Virus → Human → Virus stimulates immune system to make antibodies. → Disease. Antibodies neutralize virus to prevent re-infection = IMMUNITY

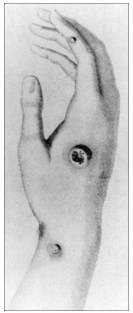
VACCINATION

Vaccine → Human → "Immunogen" stimulates immune system to make antibodies. The immunogen can be a virus or parts of a virus. → No disease. Antibodies neutralize virus to prevent infection = IMMUNITY

Discovery of vaccination

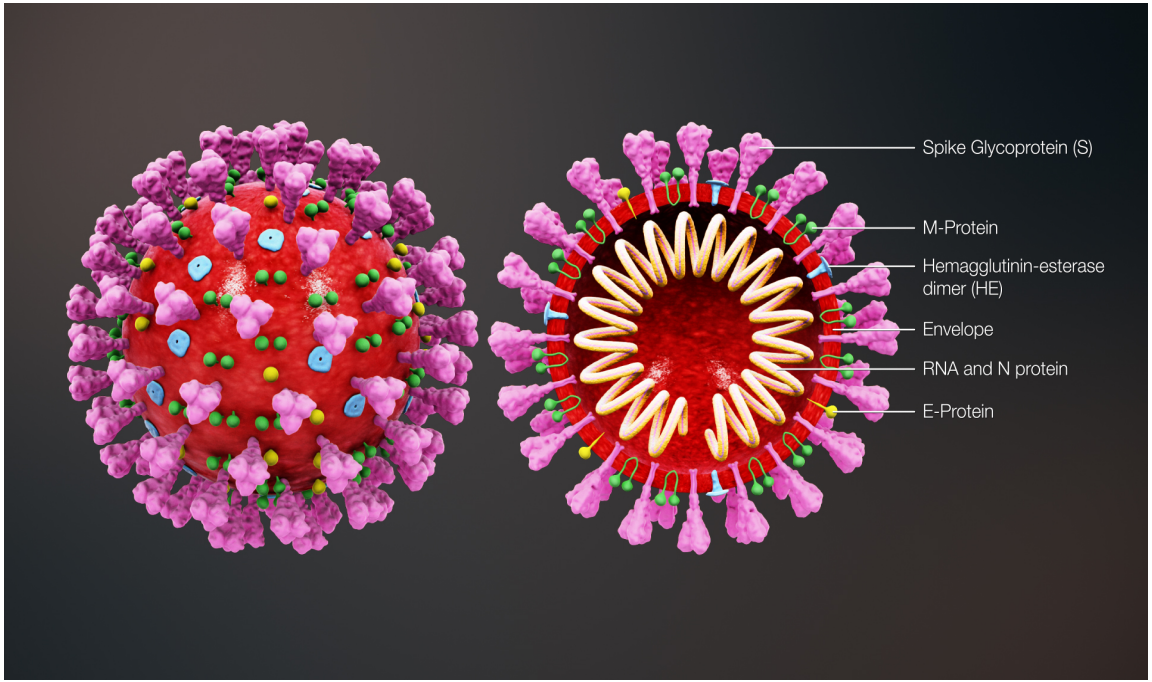
Dr. Edward Jenner and milkmaids

- In the 18th century, it was commonly known that survivors of smallpox became immune to the disease
- In 1762, as an apprentice at 13 to a country surgeon in England, Jenner learned that milkmaids were in some way protected from smallpox
  - Milkmaids suffered from cowpox, a related pox virus of cows that passed to them from udders of infected cows
  - Cowpox caused a mild form of disease
- In 1796, Jenner sampled cowpox lesions from a dairymaid and inoculated an 8-year-old boy, James Phipps, who fell ill
  - Two months after Phipps recovered, Jenner inoculated him again with smallpox
  - No disease developed
- He published in 1798 that infection with cowpox protects against subsequent infection with smallpox; the practice spread rapidly throughout Europe

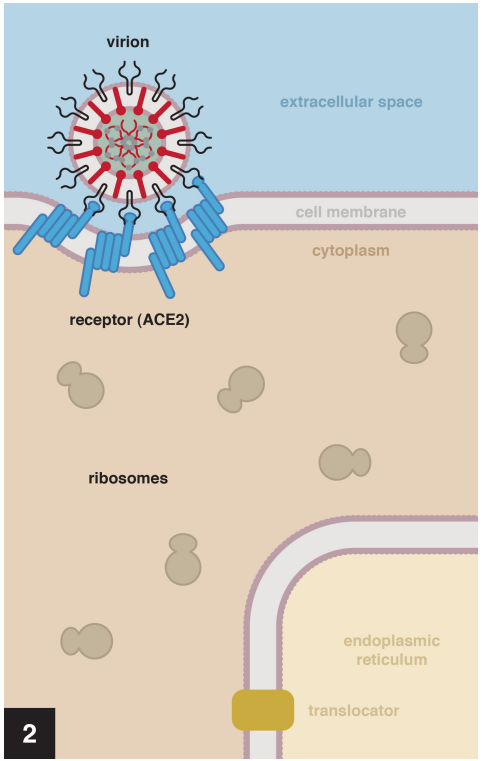


Designing a vaccine for SARS-CoV-2

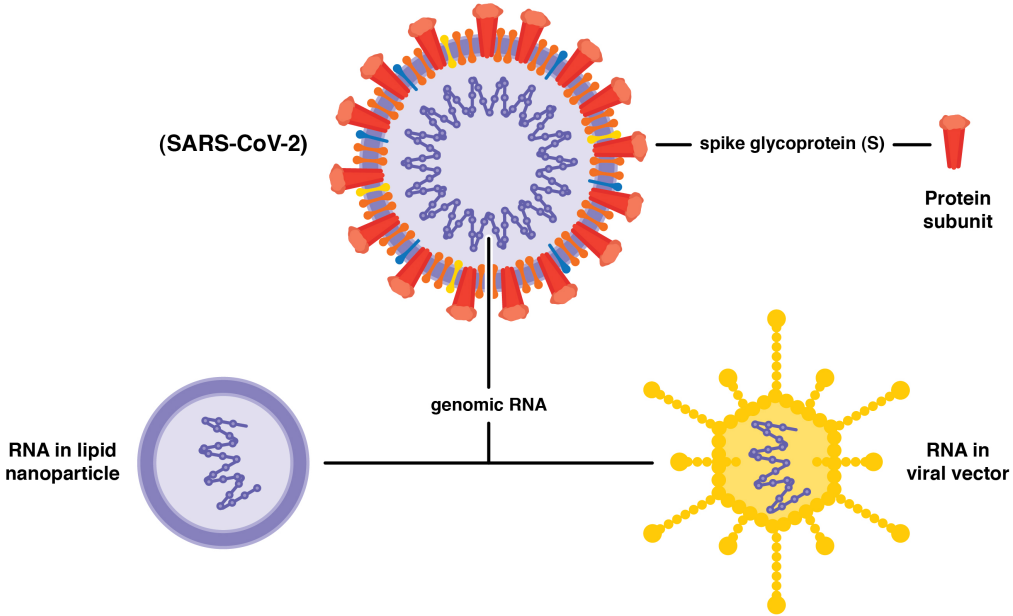
SARS-CoV-2


Spike Glycoprotein (S)
M-Protein
Hemagglutinin-esterase dimer (HE)
Envelope
RNA and N protein
E-Protein

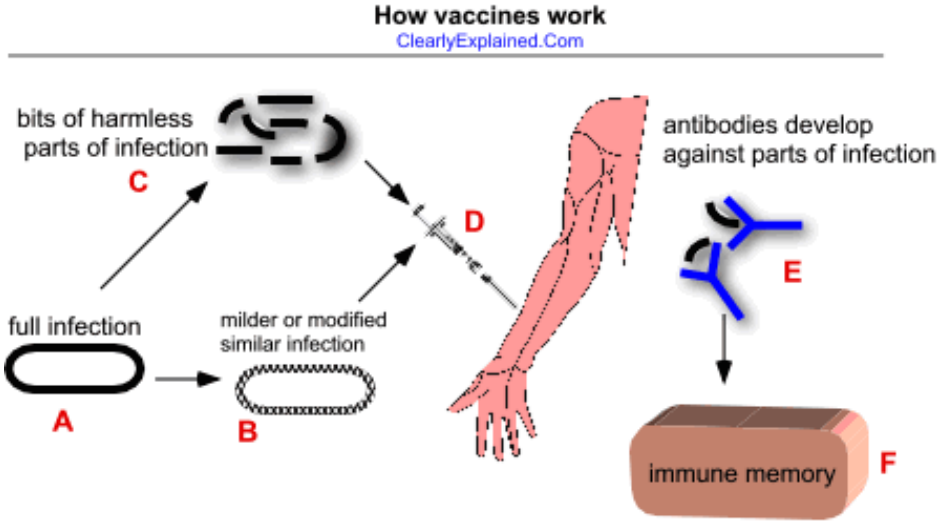
Spike glycoprotein is critical for viral infection of lung cells



SARS-CoV-2 or its parts can be used as immunogens

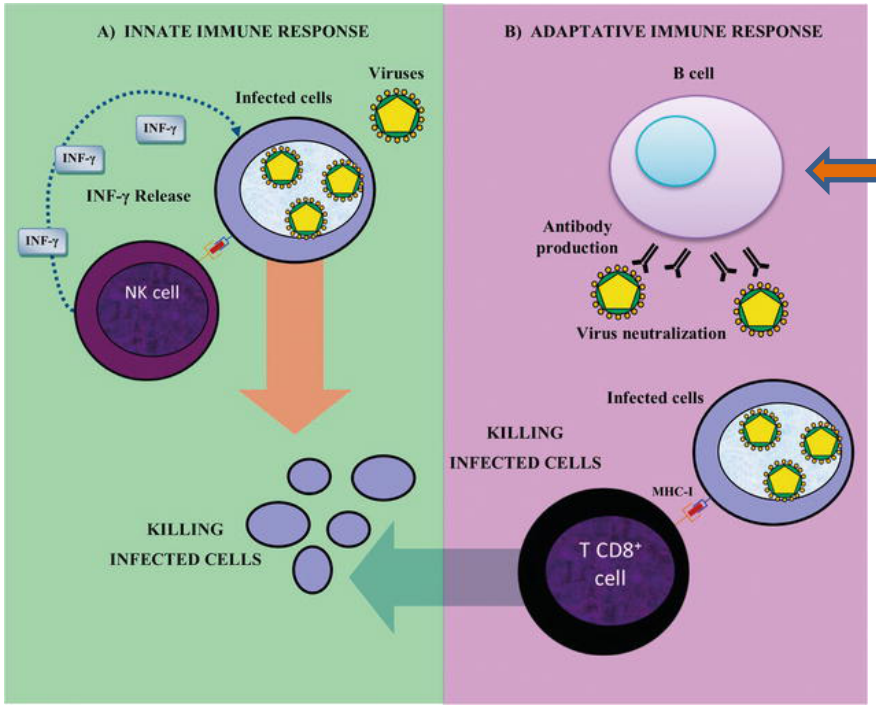


How a vaccine creates antibodies which are the key to protection



- The immunogen (A, B, C) can be a whole virus or its parts
- The immunogen is injected (D) into the individual, where it stimulates the immune system to create antibodies (E) that interfere with the virus' ability to recognize lung cells
- Long term protection is achieved by immune memory (F)

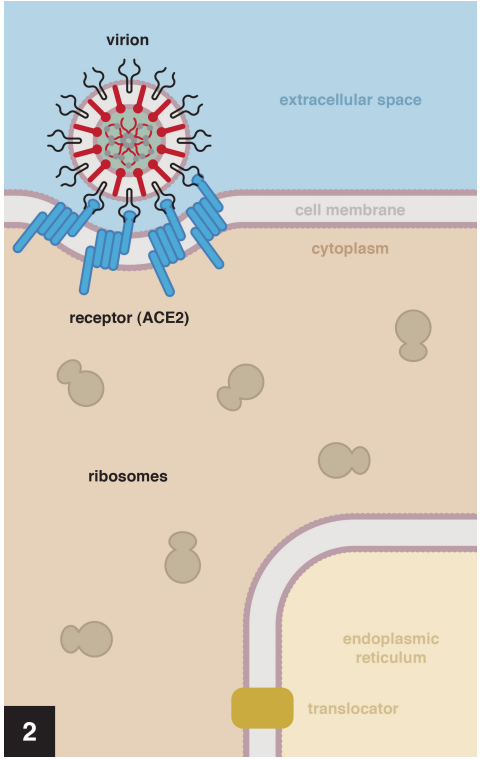
Immunity results from the immune response



Immune mechanisms inactivate or kill virus

- Virus or parts of virus induce B cells to produce antibodies
- Virus is neutralized by antibodies
- Cells infected with virus are killed by CD8+ T cells and NK cells
- B cells are long lived and are the source of immune memory

Antibodies must interfere with spike glycoprotein to be protective



The goal is to prevent recognition and binding of virus to lung cells

Types of Vaccines

Three types of vaccines

Vaccine type	Immunogen type	What is it?	Examples	Number under development for COVID-19
Whole virus vaccine	Live attenuated virus	Virus weakened by extensive passage in cells to be not infectious	Smallpox, rabies, polio, measles, mumps, rubella, yellow fever	3
Subunit vaccine	Protein subunit	Proteins isolated from virus itself and manufactured separately	Hepatitis C, shingles	9
Nucleic acid vaccine	Viral vector	Unrelated virus engineered to contain SARS-Cov-2 genes but be non-infectious	First approved in 2019 for vaccine against Ebola (rVSV-ZEBOV)	13
	DNA or RNA-based	DNA or RNA isolated from virus itself and manufactured separately	Technology developed in the 2010s. Potentially the fastest development time.	12

Why wouldn't we always use whole virus vaccines?

Live attenuated virus

- Advantages
  - Immune response is robust and long lived
  - Development does not require detailed knowledge of the virus
- Disadvantages
  - Virus may not replicate efficiently in cell culture (e.g., HCV)
  - Potential to revert to virulent strain (HIV, rabies)

Subunit vaccine

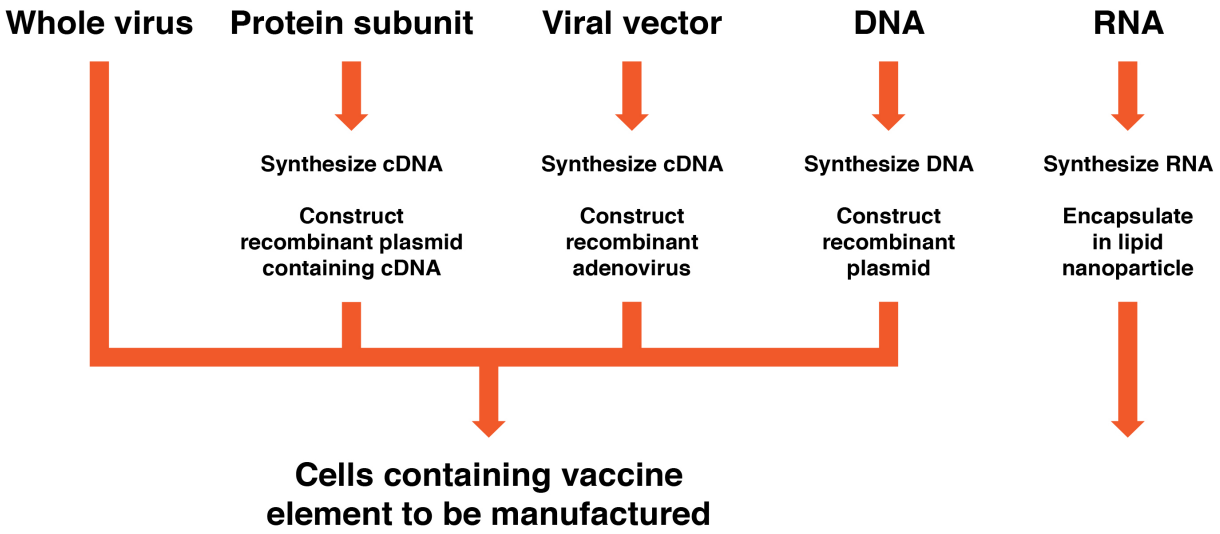
- Virus protein produced artificially using genetic engineering technology
- Typically co-administered with an adjuvant to enhance immune response
- Advantages
  - Safe-no living organism
  - Focuses the immune system on critical protein components of a virus
- Disadvantages
  - Protection may be short-lived

Nucleic acid vaccine

- Combines the positive attributes of live attenuated and subunit vaccines
- Types
  - Viral vector
  - DNA
  - RNA
- Advantages
  - Safe-no living organism
  - Effective-mimic live infection by expressing antigen after immunization.
  - Focused-immune response is directed toward only selected antigen of pathogen
  - Adaptable-platform manufacturing technology amenable to rapid response
- Disadvantages
  - Uncertain whether protection will be long-lived

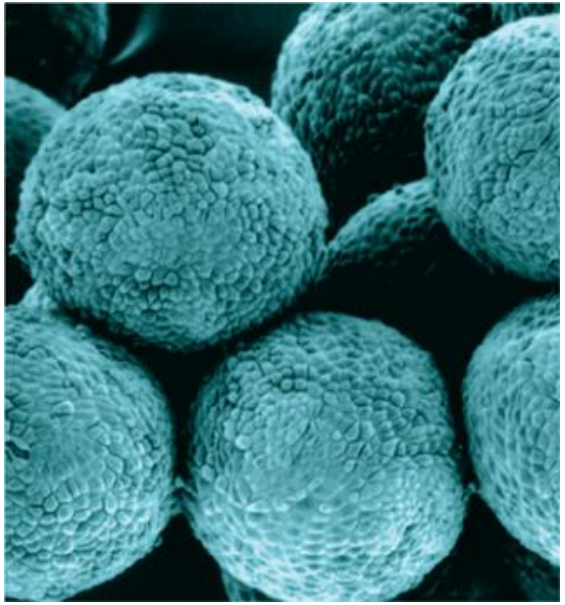
How are Vaccines Made?

Producing vaccines

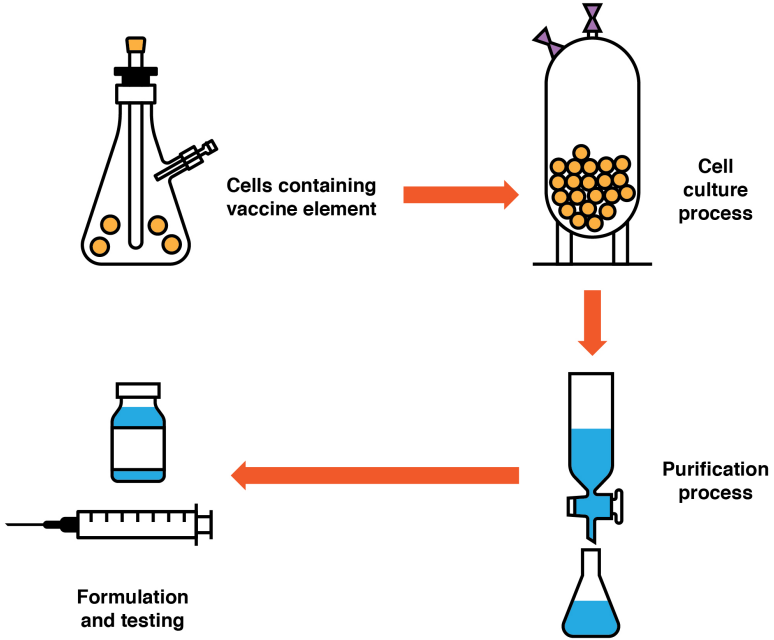


Cells containing vaccine elements

Human, insect and microbial cell lines, e.g., PER.C6, HEK293, sf9, *E. coli*



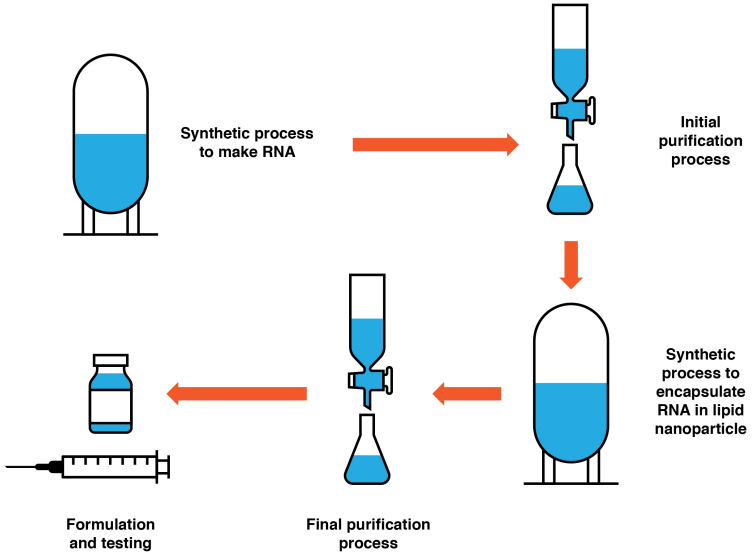
The cell-based process for vaccine manufacture is complex and time consuming



Whole virus, protein subunit, viral vector, DNA

RNA vaccines are manufacturing using a completely synthetic process

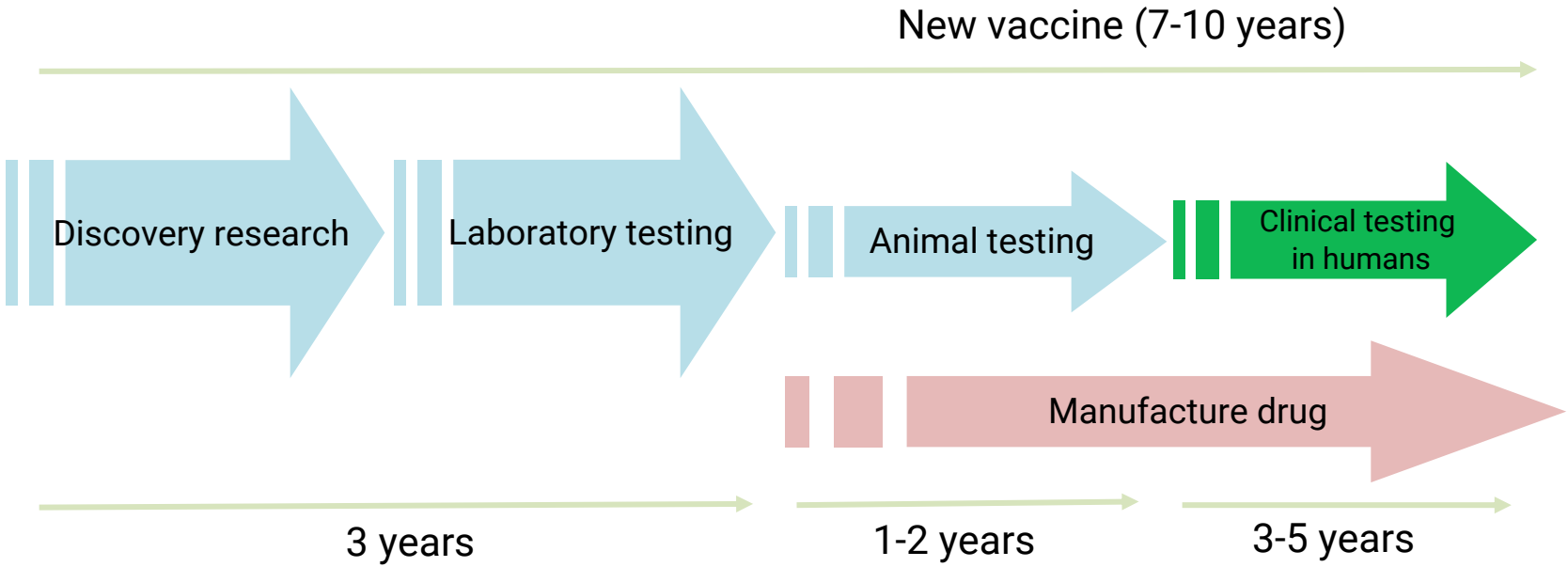
- Platform technology-enables rapid manufacturing
- Moderna-42 days from sequence selection to shipping first manufactured batch of clinical drug product



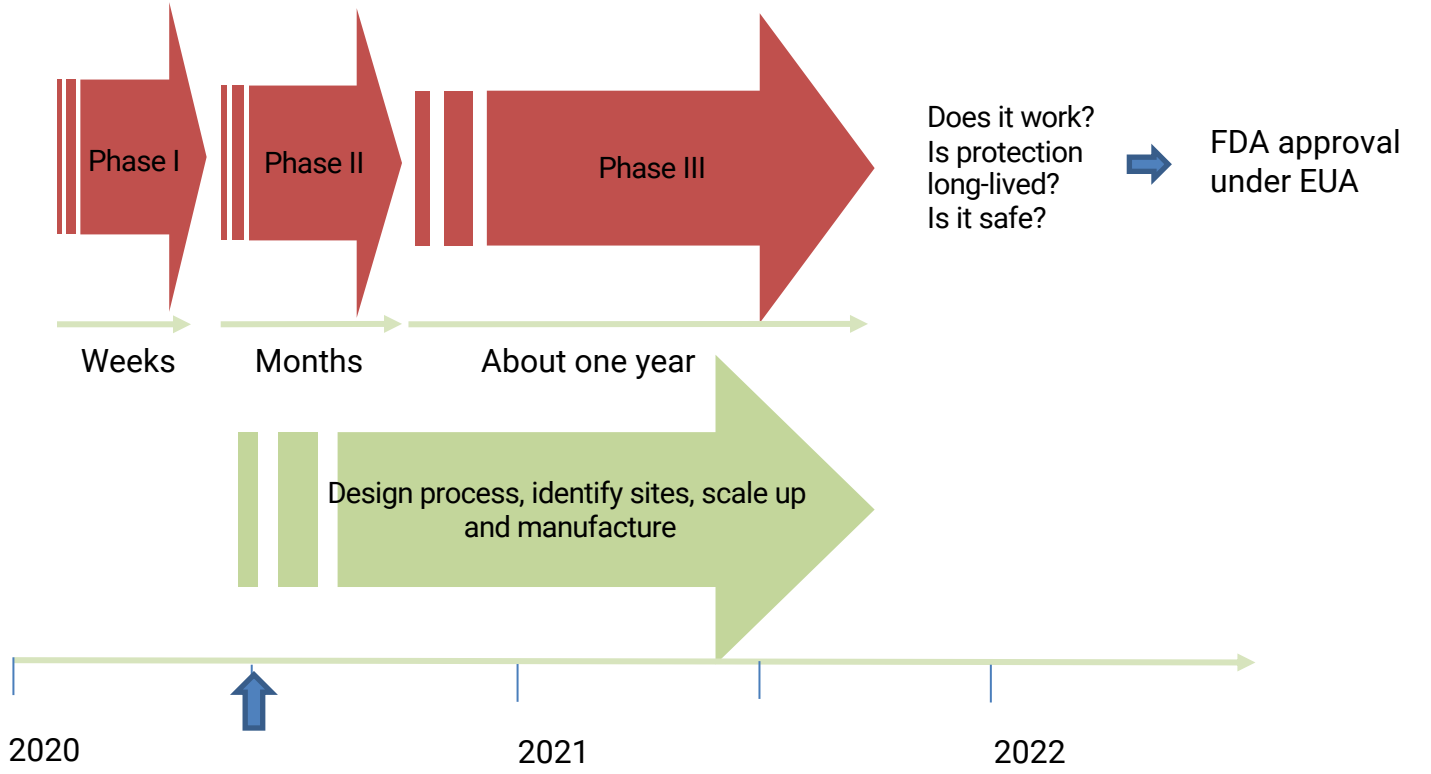
Leading Vaccine Programs

Vaccine development occurs in stages

In normal circumstances, the 4 stages take a long time to complete and drug manufacture is not scaled up until there is clear clinical evidence that the vaccine is effective.



Clinical testing and manufacture of a vaccine at pandemic pace



Leading vaccine candidates

Vaccine	Type	What is it?	Sponsor and status
mRNA-1273	RNA-based	Lipid nanoparticle-encapsulated mRNA encoding S protein	Moderna and NIH; Phase I in Seattle underway
INO-4800	DNA-based	Plasmid delivered to cells by electroporation upon intramuscular injection	Inovio, CEPI, Beijing Advaccine; Phase I underway in US with preliminary data this month
Ad26	Viral vector	Adenovirus engineered to express S protein and produced in PER.C6 cells	Janssen Pharmaceutical/Johnson & Johnson/BARDA, animal studies underway, Phase I/IIa to begin in Jul in US and Belgium
ADZ1222	Viral vector	Adenovirus vector that expresses S protein	University of Oxford, AstraZeneca; Phase I in UK underway
SCB-2019	Protein subunit + adjuvant	Genetically engineered, purified S protein formulated with synthetic adjuvant	Clover Biotechnologies/GSK/Dynavax; Phase I began this month in Australia w/ preliminary data in Aug

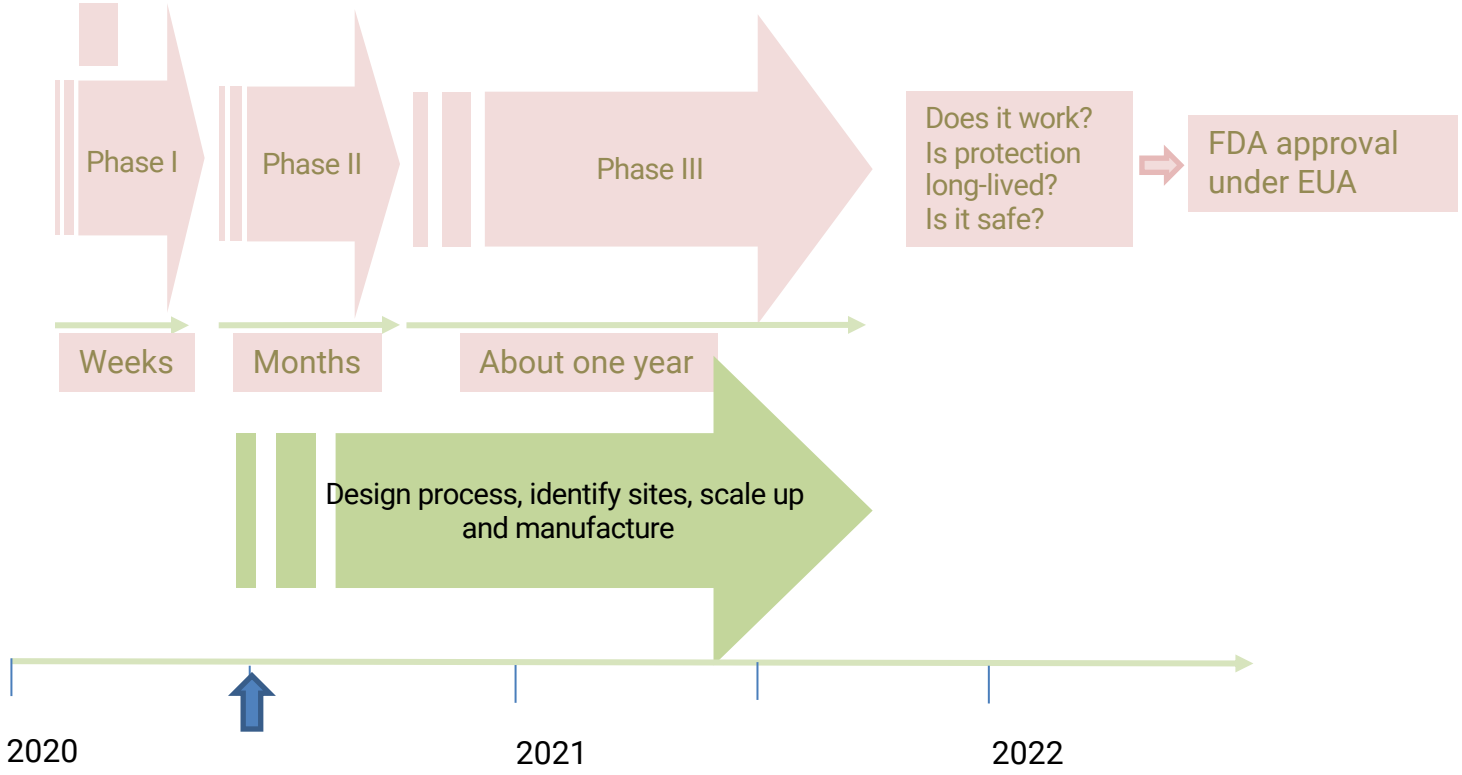
Worldwide, 78 confirmed vaccine projects are in early stages of development (according to WHO)

News on Moderna/NIH trial of mRNA-1273

- Animal data
  - Studies in a mouse disease model demonstrated that the vaccine kept the virus from replicating in the lungs of mice
- Phase 1 human clinical trial results reported 18 May
  - Three dose levels in several dozen volunteers ages 18-55
    - Anti-virus antibodies were detected in eight of them
    - All eight developed neutralizing antibodies to the virus at levels reaching or exceeding the levels seen in people who've naturally recovered from COVID-19
- Phase II begun on 29 May-two doses selected
  - 600 patients
  - 2 injections, 4 weeks apart
- Phase III planned to begin in Jul
  - 30,000 volunteers

moderna

Scale-up of production is being done completely at risk



Vaccine manufacturing deals for front runners

Vaccine	Sponsor	Manufacturing partnerships
mRNA-1273	Moderna/NIH/BARDA	• 1M doses annually to be manufactured by Lonza in 10-year supply agreement • BARDA to pay $483M to enable large-scale production
Ad26.COV2-S	Johnson & Johnson/Janssen Pharmaceutical//BARDA	• $135M production deal with Emergent Biosolutions and Catalent in US • Plans to manufacture 1B doses with first batches available for EUA early 2021 • $456M committed by BARDA toward supporting development
ADZ1222	AstraZeneca, University of Oxford	• $87M production deal with Emergent Biosolutions in US • $750M agreement with Vaccine Alliance to distribute 300M doses • Serum Institute of India to supply 1B doses to low-and middle-income countries, 400M in 2020

Vaccine makers face the biggest medical manufacturing challenge in history

“Developing a COVID-19 vaccine in record time will be tough. Producing enough to end the pandemic will be the biggest medical manufacturing feat in history.”

J Steenhuysen, K Kelland
Reuters, 25 June 2020

Summary

- SARS-CoV-2 (COVID-19) is an RNA virus
- An effective vaccine will be based on whole virus or individual parts of the virus
- Whole virus vaccines generate long-lasting protection and are the gold standard for vaccine efficacy
- Newer platform technologies based on genetic engineering can create vaccine candidates more quickly
- A new vaccine will require more than a year to complete the key stages of development

Questions and Discussion