SARS-CoV2 Vaccines to Prevent COVID-19

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Outline

- FDA approval process
- Basic technology
- mRNA vaccines
- Adenovirus vector vaccines
- Subunit vaccines
- Frequently asked questions

How a new vaccine is developed, approved and manufactured

The Food and Drug Administration (FDA) sets rules for the three phases of clinical trials to ensure the safety of the volunteers. Researchers test vaccines with adults first.

PHASE 1

20-100 healthy volunteers

- Is this vaccine safe?
- Does this vaccine seem to work?
- Are there any serious side effects?
- How is the size of the dose related to side effects?

PHASE 2

several hundred volunteers

- What are the most common short-term side effects?
- How are the volunteers' immune systems responding to the vaccine?

PHASE 3

hundreds or thousands of volunteers

- How do people who get the vaccine and people who do not get the vaccine compare?
- Is the vaccine safe?
- Is the vaccine effective?
- What are the most common side effects?

FDA licenses the vaccine only if:

- **It's safe and effective**
- **Benefits outweigh risks**

Vaccines are made in batches called lots.

Manufacturers must test all lots to make sure they are safe, pure and potent. The lots can only be released once FDA reviews their safety and quality.

The FDA inspects manufacturing facilities regularly to ensure quality and safety.

FOR MORE INFORMATION, VISIT HTTPS://WWW.FDA.GOV/CBER

Requirements for biologic licensure from the FDA

- The Vaccine and Related Biological Products Advisory Committee (VRBPAC) will evaluate the data on COVID-19 vaccines and advise the FDA

- Section 351 of the Public Health Service Act, 42 USC 262: The Secretary shall approve a biologics license application (BLA) - on the basis of a demonstration that
  - the biological product is safe, pure, and potent; and
  - the facility meets standards designed to assure that the biological product continues to be safe, pure, and potent
  - Minimum 8wks of safety data

- Only those vaccines that are demonstrated to be safe and effective, & that can be manufactured in a consistent manner will be licensed by the FDA

Source: https://www.fda.gov/media/143422/download

Requirements for biologic licensure from the FDA

> FDA will apply the same standards to grant a biologics license for a COVID-19 vaccine as for other preventive vaccines

> " all indications [e.g., prevention of disease] must be supported by substantial evidence of effectiveness."

> Demonstration of effectiveness must be based on adequate and well-controlled clinical studies

Source: https://www.fda.gov/media/143422/download

Requirements for emergency use authorization (EUA)

- Issuance of an EUA for an investigational COVID-19 vaccine would require:
  - adequate manufacturing information to ensure the product's quality and consistency
  - a determination that the benefits outweigh its risks based on data from at least one well-designed Phase 3 clinical trial demonstrating safety and efficacy

- Any assessment regarding an EUA would be made on a case-by-case basis considering the proposed target population, the product characteristics, preclinical and human clinical data, and the totality of the available scientific evidence relevant to the product

Source: https://www.fda.gov/media/143422/download

How a vaccine is added to the U.S. Recommended Immunization Schedule

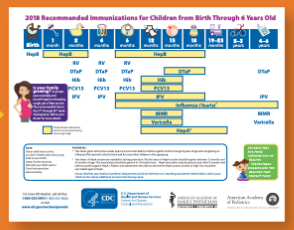
The Advisory Committee on Immunization Practices (ACIP) is a group of medical and public health experts. Members of the American Academy of Pediatrics (AAP) and American Academy of Family Physicians (AAFP) are among some of the groups that also bring related immunization expertise to the committee. This group carefully reviews all available data about the vaccine from clinical trials and other studies to develop recommendations for vaccine use. The ACIP continues to monitor vaccine safety and effectiveness data even after the vaccine's routine use and may change or update recommendations based on that data.

When making recommendations, ACIP considers:

- How safe is the vaccine when given at specific ages?
- How well does the vaccine work at specific ages?
- How serious is the disease this vaccine prevents?
- How many children would get the disease the vaccine prevents if we didn't have the vaccine?

ACIP recommendations are not official until the CDC Director reviews and approves them and they are published. These recommendations then become part of the United States official childhood immunization schedule.

New vaccine to protect your child against a disease is added to the schedule.



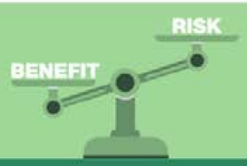
FOR MORE INFORMATION, VISIT HTTPS://WWW.CDC.GOV/VACCINES

Initial ACIP recommendations for COVID-19 vaccine

- In the initial phase of COVID-19 vaccination (phase 1a), the following groups should be prioritized:
  - Healthcare workers
  - Residents of long-term care facilities

Source: MMWR December 3, Vol 69

How a vaccine's safety continues to be monitored



FDA and CDC closely monitor vaccine safety after the public begins using the vaccine.

The purpose of monitoring is to watch for adverse events (possible side effects). Monitoring a vaccine after it is licensed helps ensure that possible risks associated with the vaccine are identified.

Vaccine Adverse Event Reporting System (VAERS)

VAERS collects and analyzes reports of adverse events that happen after vaccination. Anyone can submit a report, including parents, patients and healthcare professionals.

Vaccine Safety Datalink (VSD) and Post-Licensure Rapid Immunization Safety Monitoring (PRISM)

Two networks of healthcare organizations across the U.S.

- **VSD** can analyze healthcare information from over 24 million people.
- **PRISM** can analyze healthcare information from over 190 million people.

Scientists use these systems to actively monitor vaccine safety.

Clinical Immunization Safety Assessment Project (CISA)

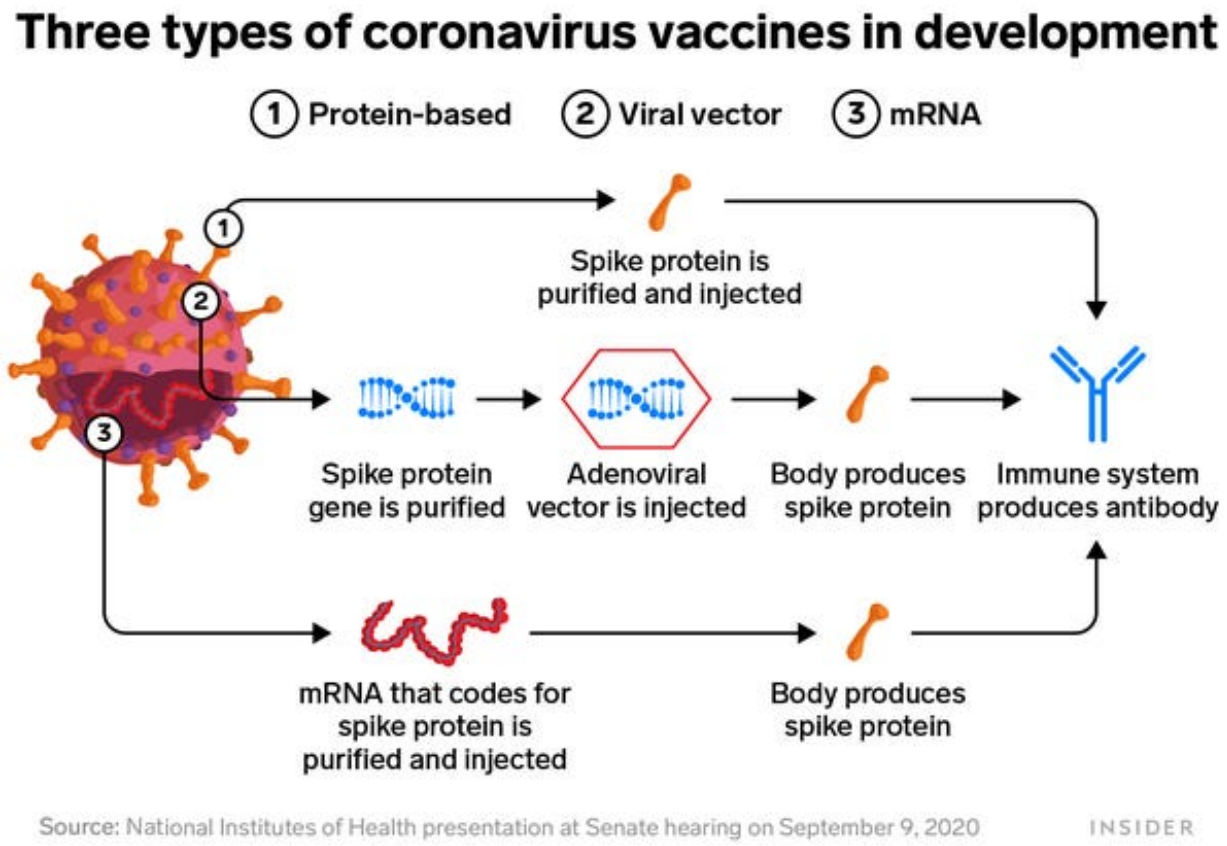
CISA is a collaboration between CDC and 7 medical research centers.

- Vaccine safety experts assist U.S. healthcare providers with complex vaccine safety questions about their patients.
- CISA conducts clinical research studies to better understand vaccine safety and identify prevention strategies for adverse events following immunization.

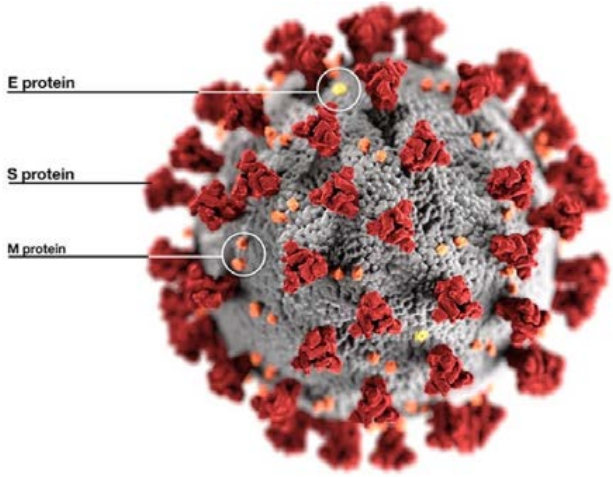
Vaccine recommendations may change if safety monitoring reveals new information on vaccine risks (like if scientists detect a new serious side effect).

FOR MORE INFORMATION, VISIT HTTPS://WWW.CDC.GOV/VACCINESAFETY

Different Types of Vaccines

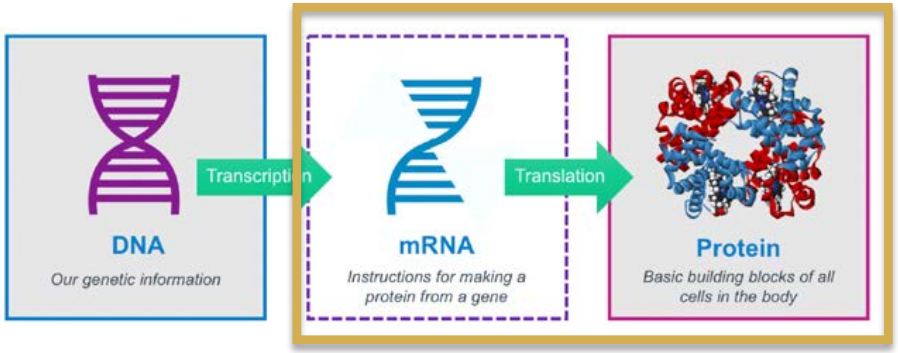


mRNA vaccines



- mRNA vaccines teach our cells how to make proteins that trigger an immune response
  - Think of mRNA as instructions for protein construction
- Instead of injecting a denatured / inactive protein or germ into the body, they inject mRNA, which codes for the COVID-19 spike protein
- Our body then produces antibodies to the COVID-19 spike protein, thus conferring protection against infection

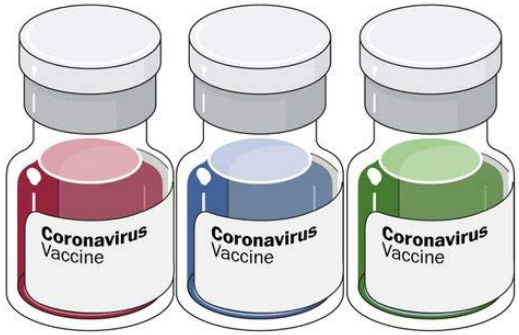
mRNA vaccines



- There are currently no licensed mRNA vaccines in the U.S., but mRNA vaccines have been studied for decades
  - Flu - Zika
  - Rabies - CMV

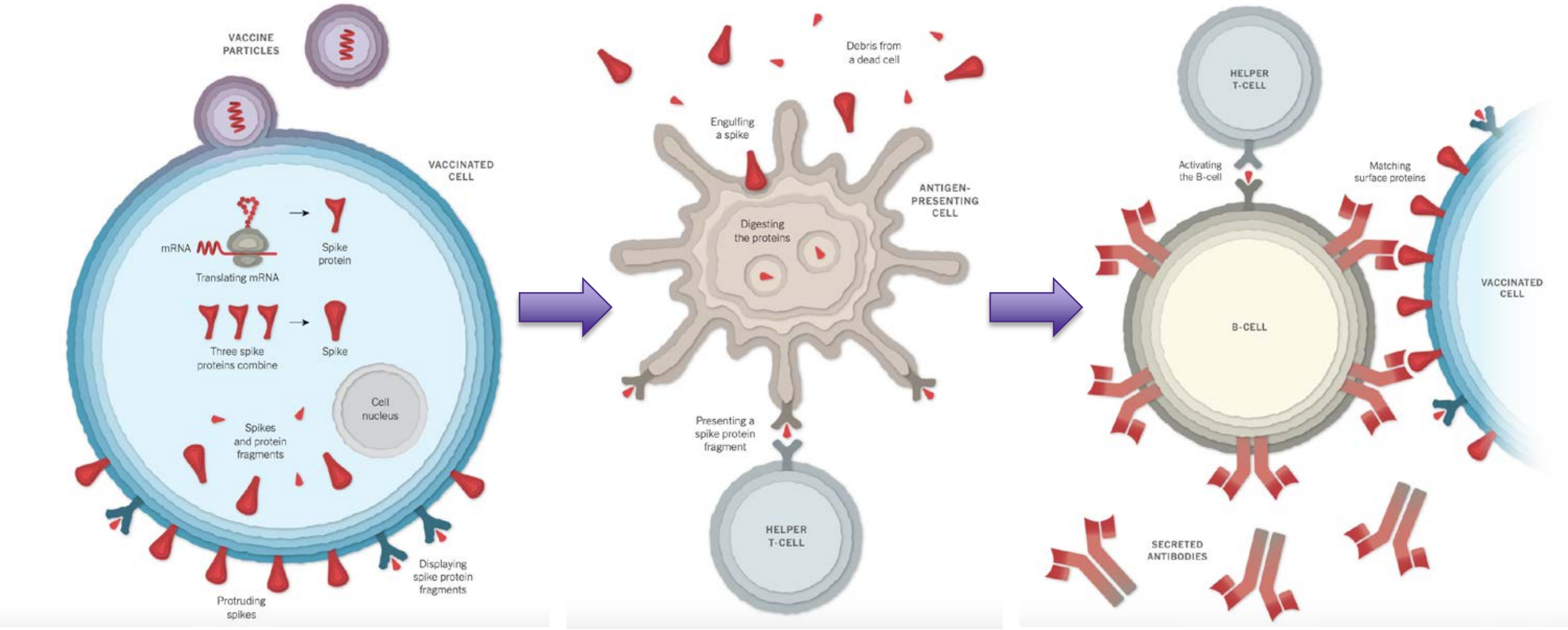
- Interest has grown in this vaccine technology because these vaccines can be developed more quickly in the lab with readily available materials

mRNA vaccines
Pfizer/BioNTech and Moderna



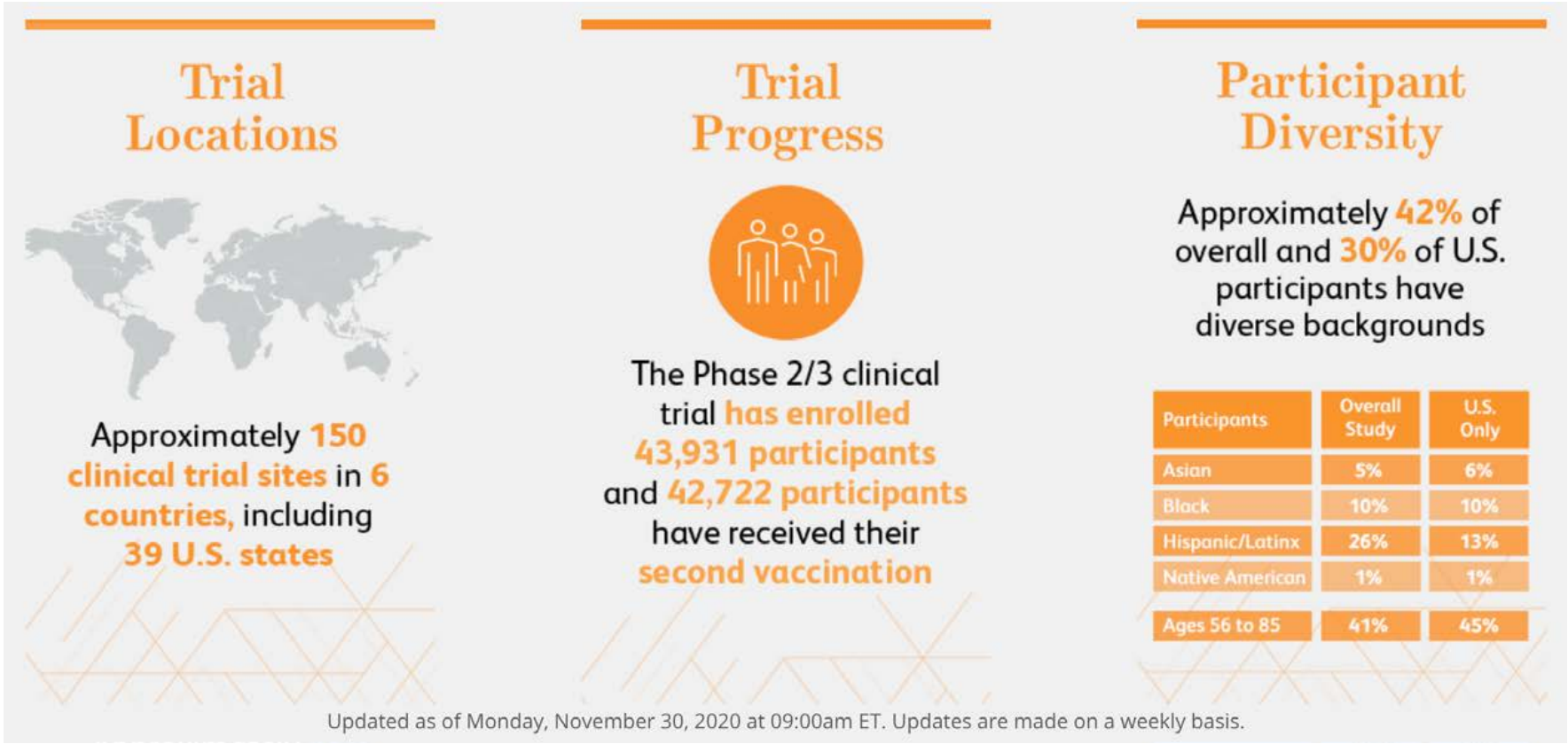
> This vaccine uses mRNA wrapped in lipid nanoparticles to protect the integrity of the mRNA

> After injection, the vaccine particles fuse with cells and release the mRNA, which is then translated into spike proteins.



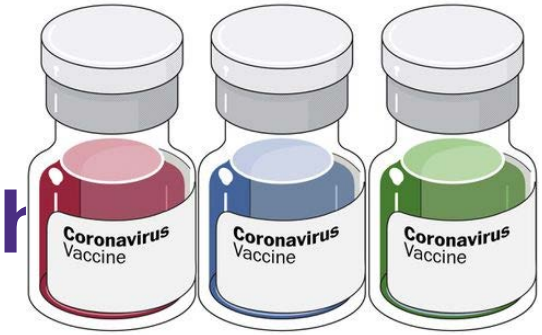
Source: https://www.nytimes.com/interactive/2020/health/pfizer-biontech-covid-19-vaccine.html

mRNA vaccines: Pfizer/BioNTech



Source: https://www.pfizer.com/science/coronavirus/vaccine

mRNA vaccines: Pfizer/BioNTech



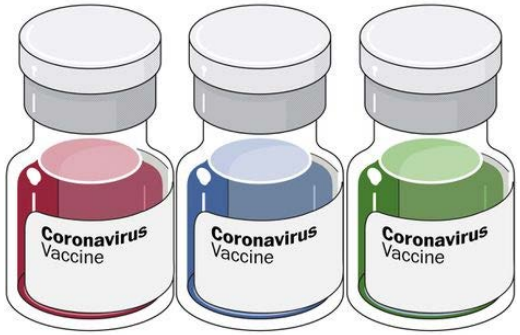
- On Nov. 18th, Pfizer/BioNTech release initial results
- There were 170 cases of COVID-19, 162 in the placebo group and 8 in the vaccine group.
  - Vaccine efficacy = 95%
  - 10 cases of severe COVID-19, 9 in the placebo group and 1 in the vaccine group
- Efficacy was consistent across age, gender, race and ethnicity demographics.
- Observed efficacy in adults >65yrs was 94%
- 3.8% of participants reported fatigue and 2.0% reported headache

Source: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-conclude-phase-3-study-covid-19-vaccine

mRNA vaccines: Pfizer/BioNTech other considerations

- This is a two-dose vaccine given at days 0 and 21. Efficacy endpoints were assessed beginning at day 28.
- mRNA molecules are fragile and will quickly fall apart at room temperature.
- Because of this, vaccine must be transported and stored at -70^{o}C (-94^{o}F).

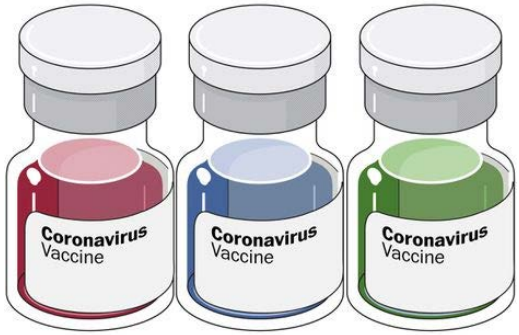
mRNA vaccines: Moderna



- Interim analysis reviewed on Nov. 15th
- Trial enrolled >30,000 participants across 100 sites in the U.S.
- 37% of participants reported to be racial/ethnic minorities
- Trial included 7,000 people over the age of 65 and 5,000 people <65 but with underlying high-risk chronic diseases

Source: https://www.nih.gov/news-events/news-releases/promising-interim-results-clinical-trial-nih-moderna-covid-19-vaccine

mRNA vaccines: Moderna



- 95 cases of symptomatic COVID-19, 90 in the placebo arm and 5 in the vaccine arm.
  - Vaccine efficacy = 94.5%
  - 11 cases of severe COVID-19, all occurring in the placebo arm

- Adverse events: 2.7% injection site pain; 9.7% fatigue; 8.9% myalgias; 5.2% arthralgias; 4.5% headache; 4.1% pain; 2.0% redness at injection site

Source: https://www.nih.gov/news-events/news-releases/promising-interim-results-clinical-trial-nih-moderna-covid-19-vaccine

Source: N Engl J Med. 2020 Sep 29:NEJMoa2028436.

mRNA vaccines: Moderna – other considerations

- This is a two-dose vaccine given at days 0 and 28. Efficacy endpoints were assessed beginning at day 42.
- Like the Pfizer vaccine, the mRNA molecules are fragile and will fall apart at room temperature.
- Due to the composition of the lipid nanoparticle envelope, Moderna's vaccine can be stored at -20^{o}C (typical freezer temp)
  - Can be dethawed and kept in the refrigerator for up to 30 days

mRNA vaccines: Important points about safety

- Like all vaccines, COVID-19 mRNA vaccines have been rigorously tested for safety before being authorized for use in the United States.
- mRNA technology is new, but not unknown. They have been studied for more than a decade.
- mRNA vaccines do not contain a live virus and do not carry a risk of causing disease in the vaccinated person.
- mRNA from the vaccine never enters the nucleus of the cell and does not affect or interact with a person's DNA.

Source: https://www.cdc.gov/vaccines/covid-19/hcp/mrna-vaccine-basics.html

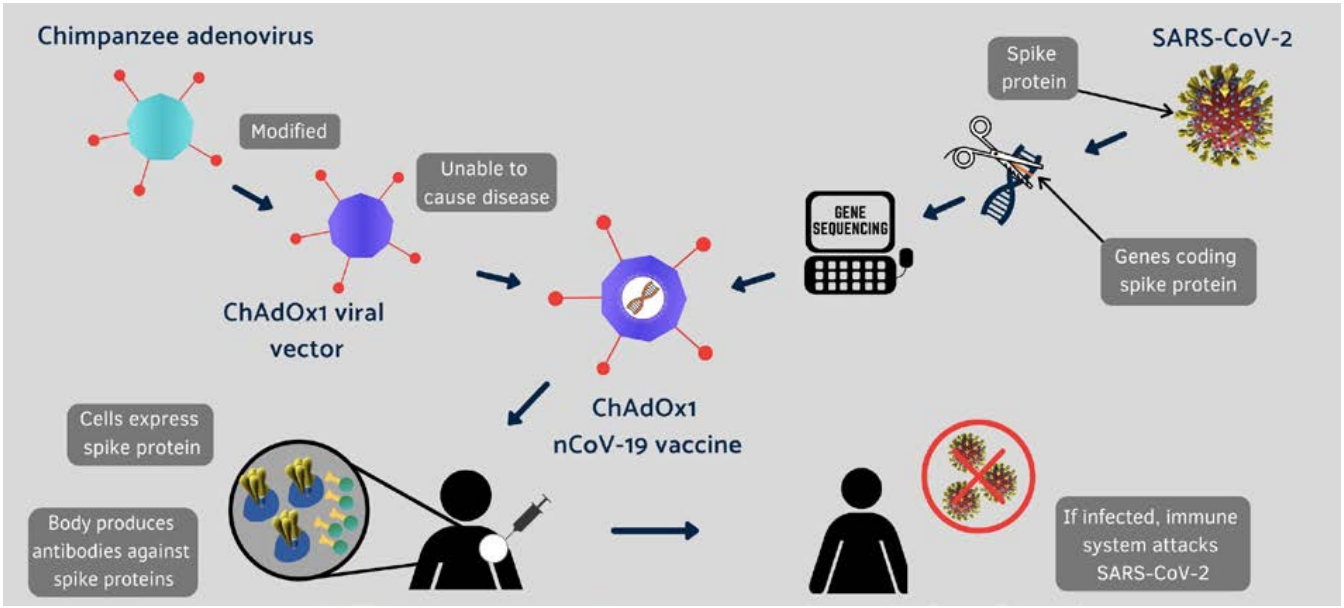
Adenovirus Vector Vaccines

- AstraZeneca/Oxford
- Johnson & Johnson
- Sputnik/Gamaleya Research Institute (Russia)
- CanSino Biological/Beijing Institute of Biotechnology (China)

AstraZeneca (aka Oxford) Vaccine

- Two injections 1 month apart
- Can be stored at routine refrigeration temps
- Uses chimpanzee adenovirus vector
- 200M doses avaibable worldwide by end of 2020
- Cheapest of first round vaccines ($15/dose)
- Adenovirus doesn't cause disease, doesn't replicate and doesn't permanently incorporate into cells

AstraZeneca COVID Vaccine Technology



Source: TheConversation.com

AZ Vaccine Creates Robust Immune Response

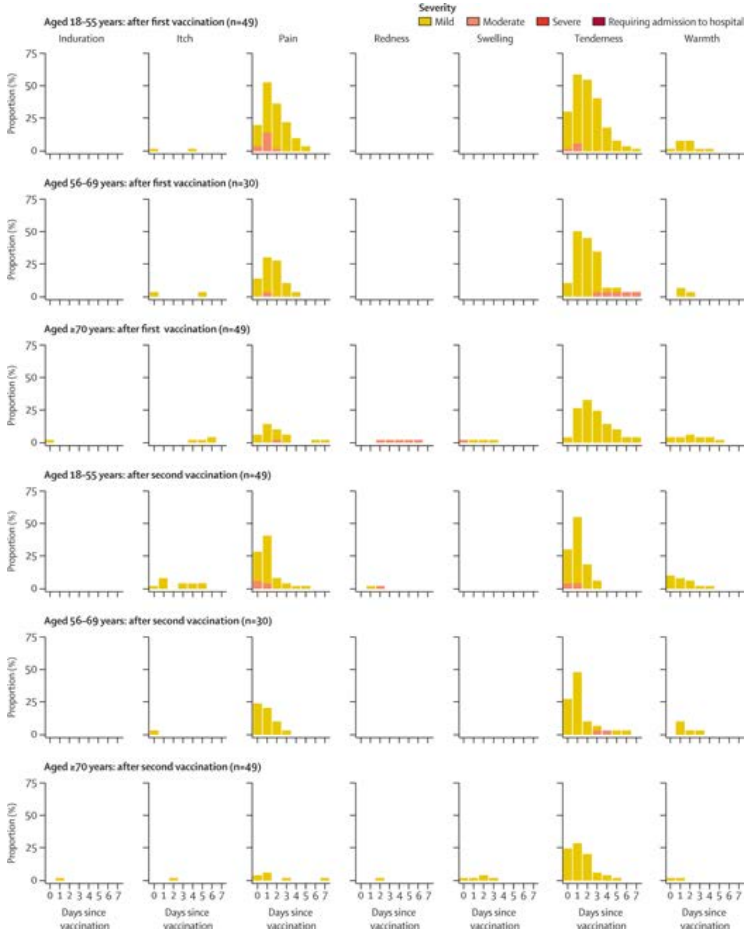
- 560 volunteers enrolled (incl. 160 age 56-69 yo and 240 70+ yo) in UK
- Majority were HCWs, 50% female, 95% white
- Similar antibody titers for all age groups
- >99% had evidence of neutralizing antibodies, 2 wks after second injection

Source: MN Ramasamy, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *The Lancet* 2020; ttps://doi.org/10.1016/ S0140-6736(20)32466-1.

AZ Vaccine is Safe

- Most common reactions are injection site pain and swelling, fatigue, and myalgias
- 3 patients developed transverse myelitis (an inflammation in spinal cord)
  - 1 had pre-existing but undiagnosed multiple sclerosis; 1 had 3 d episode but made full recovery w/ minimal therapy; 1 was in placebo arm

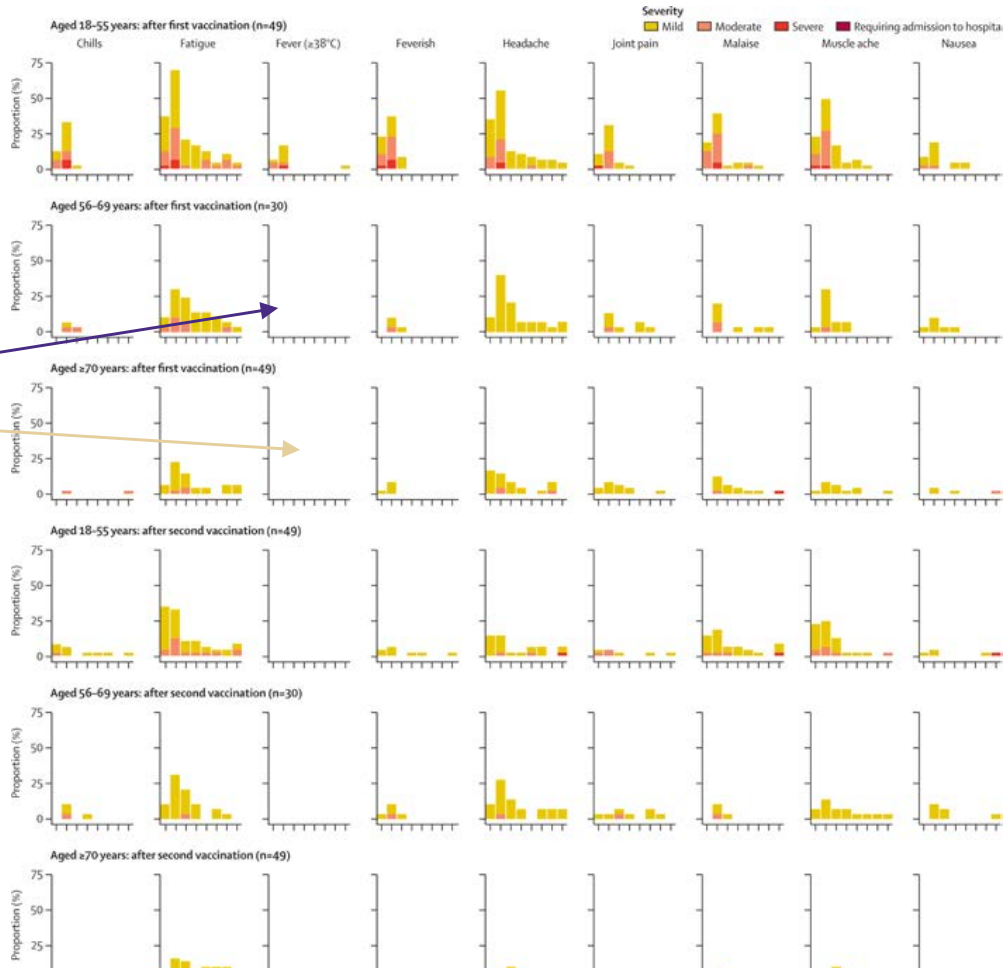
AstraZeneca Vaccine Caused Fewer Inflammatory Reactions in Older Adults



Source: MN Ramasamy, et al. The Lancet 2020; ttps://doi.org/10.1016/ S0140-6736(20)32466-1.

Fever was uncommon in older adults

No cases of fever



Unpublished results on efficacy

- **Brazilian study: 9000 subjects rec'd, both injections were full dose, 62% effective**
- **UK study: 2700 volunteers rec'd, first injection was half dose, second injection full dose, 90% effective**
- **60,000 subjects to be enrolled globally, results to be published soon**

Source: https://www.nature.com/articles/d41586-020-03326-w

Other Adenovirus-Vector Vaccines

- Sputnik, JnJ and CanSino
- Use human adenovirus-5 or -26 vector
- Appear to be efficacious, but unrandomized
- Concern about prior immunity and therefore lower "take"
- Concern about lower immunity in older adults

Source: DY Lagunov, et al. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. The Lancet 2020; https://doi.org/10.1016/ S0140-6736(20)31866-3

Subunit Vaccines

- Theory: immune system protects against foreign AND *dangerous* material
- Organism Subunit + Adjuvent
- Examples:
  - HBV vaccine
  - Purtussis part for TDaP

Subunit Vaccines - Novavax

- coronavirus spike (S) protein antigen
- patented saponin-based Matrix-M™
- 2 IM injections, 21 days apart

Subunit Vaccines - Saponin as an adjuvent

- Plant based
  - Extracted from a South American tree
- Studied > 20 yrs
  - Infections
  - Cancers
  - Alzeihmers
- Not in use due to limited supply
- Only saponin based FDA approved vaccine:
  - **Shingrix**

Subunit Vaccines - Novavax

- Novavax's Current pipeline with this adjuvant
  - Flu vaccine: phase 3
  - RSV vaccine: phase 3

Subunit Vaccines – Novavax Phase 1/2

- complete/published
- 131 healthy adults – 83 received antigen + adjuvant
- Followed 35 days
- 1 dose -> Ab levels equal to asymptomatic infected people
- 2 dose -> Ab levels equal to symptomatically infected people
- No serious adverse effects
- Most minor symptoms resolved within 2 days, all by 7 days

DOI: 10.1056/NEJMoa2026920

Subunit Vaccines – Novavax Phase 1/2

- Fully enrolled for phase 3 trials in UK (15,000 people, includes people >65 (>25 %) and with co-morbidities)
- Fully enrolled phase 2b trial in South Africa (4,422 people, includes people with HIV)
- Enrolling for phase 3 trials in US and Mexico
- Expect interim data in next 3-4 months

FAQs

Q: Can I get COVID from the COVID vaccine?

A: No. None of the vaccines use live or attenuated vaccines.

FAQs

Q: Why should I get a COVID vaccine now? Can't I wait and see how it performs in other people?

A: Getting a vaccine is a personal decision. However, the faster and more people are vaccinated, the faster we can return to normal. That means being able to hug our loved ones, get rid of the masks, have parties, and travel. In addition, health care workers have a duty to protect their patients.

FAQs

Q: Why are nursing home residents prioritized for first phase of vaccinations? Are they being guinea pigs? Is there data in older adults?

A: Nursing home residents are at the highest risk for death from COVID. They represent 1% of total US population but >40% (100,000+) of the deaths in US. They are not guinea pigs but rather have the most to gain from a vaccine. Moreover, the vaccine studies have included thousands of patients >65 yo.

FAQ

Q: Should pregnant or lactating women receive the COVID vaccine?

A: None of the vaccines were tested in pregnant or lactating women, so we don't know. The American College of Obstetrics and Gynecology (ACOG)'s position is that pregnant women should not be excluded from Covid-19 vaccines and should be able to have a risk/benefit discussion with providers. ACOG is working furiously to have information/talking points for providers and patients ready to roll once the EUA is issued.

FAQ

Q: How long will the vaccine protect me against COVID-19?

A: It is likely that we will not know the answer to that question when a vaccine is released. That will take more research. This vaccine may be like the annual flu vaccine, where we may need to have vaccine shots for COVID-19 on a regular basis. More research is needed to know this, and it also depends on whether and how much the virus changes over the coming months to years.

Comparison to other vaccines

Vaccine	# people	Follow-up period
HPV	30,000	7 years
Pneumococcal	35,000	
Moderna	30,000	60 days
Pfizer	44,000	60 days
Johnson&Johnson	60,000	60 days
Novavax	TBD	TBD