

Ask an Immunologist about mRNA COVID vaccines

Angelina Crans Yoon, M.D.

Allergy/Immunology

Woodland Clinic Medical Group

1/4/2021



Dignity Health
Medical FoundationTM

Outline

- Basics of cell biology
- How the mRNA COVID vaccines works
- Common questions
- Myths
- Q&A

Cells: how do they work?

- Cells are the basic building blocks of all living things.
- The human body is composed of trillions of cells.
- They provide structure for the body, take in nutrients from food, convert those nutrients into energy, and carry out specialized functions.
- Cells also contain the body's hereditary material and can make copies of themselves.

scanning electron micrograph of a SARS-CoV-2 infected cell

Cytoplasm

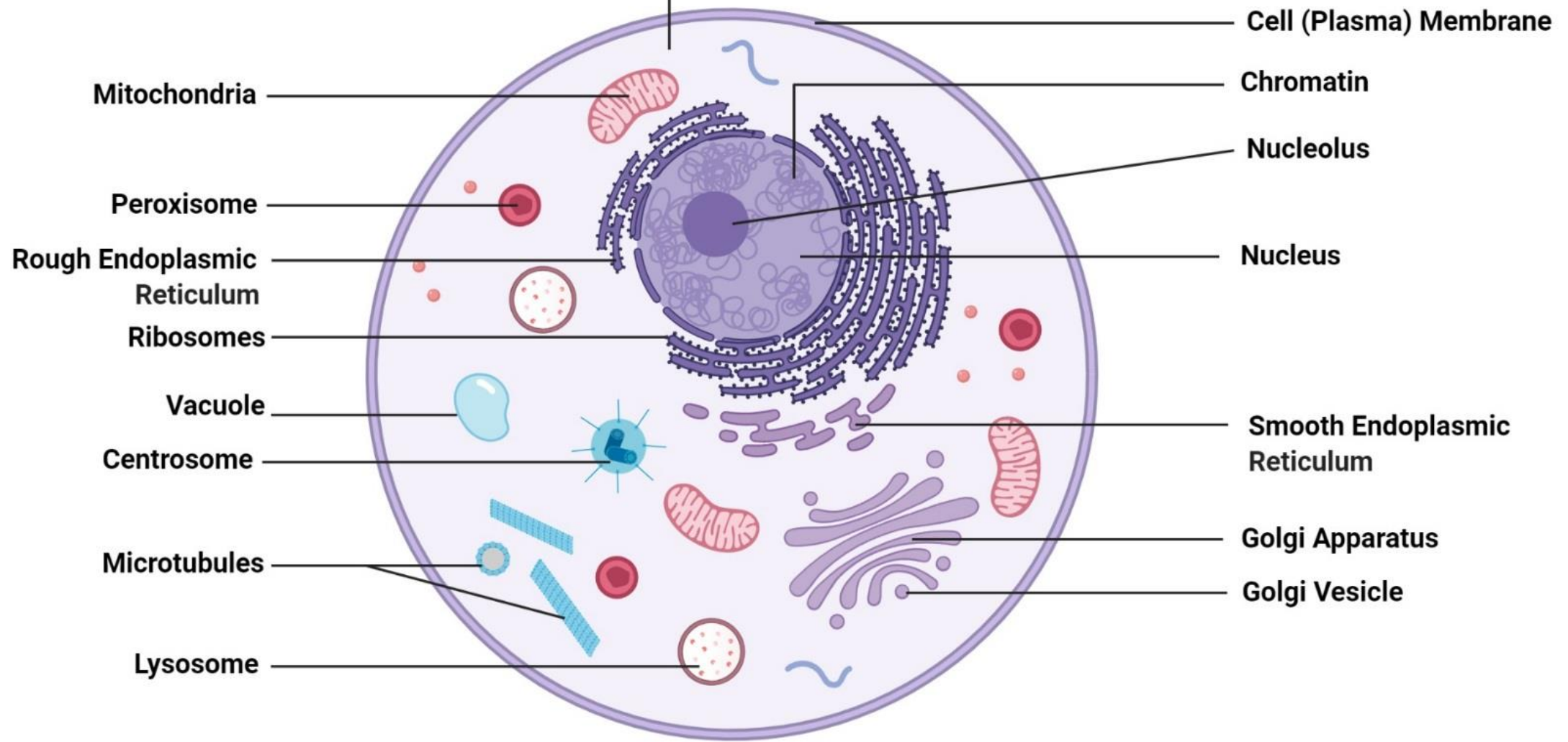


Figure: Animal Cell Structure with Cytoplasm, Image Copyright © Sagar Aryal, www.microbenotes.com

Cytoplasm

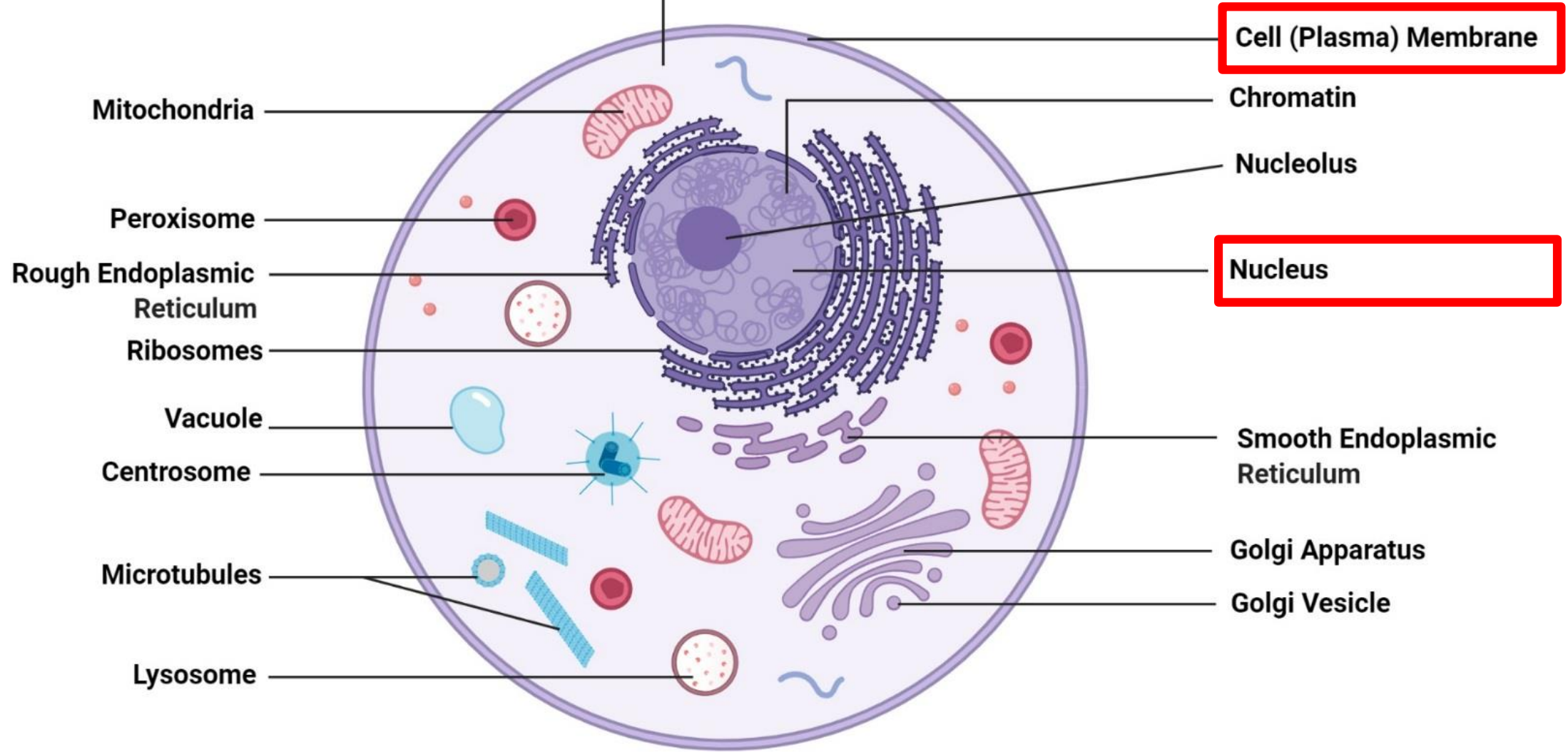


Figure: Animal Cell Structure with Cytoplasm, Image Copyright © Sagar Aryal, www.microbenotes.com

Cytoplasm

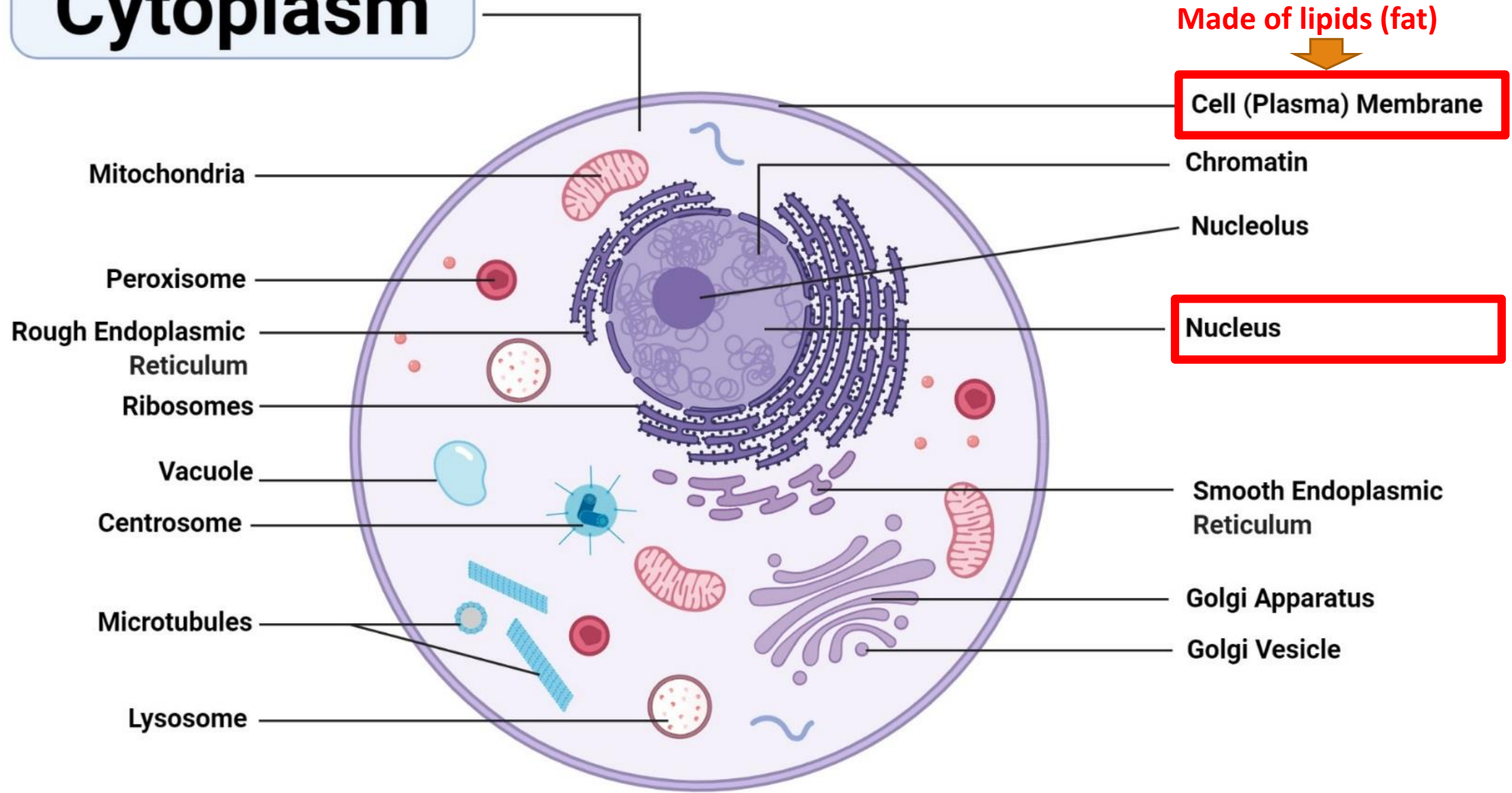
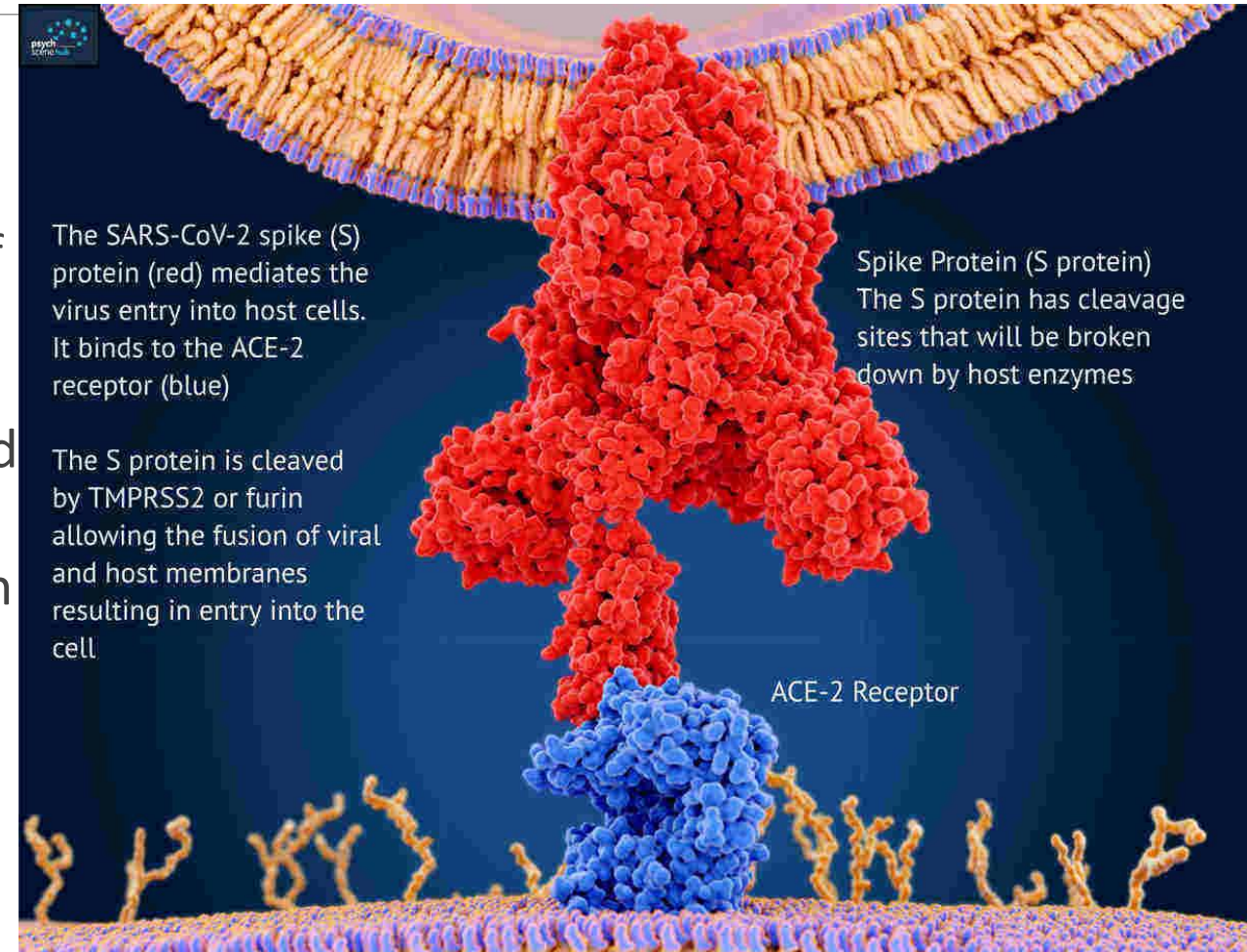


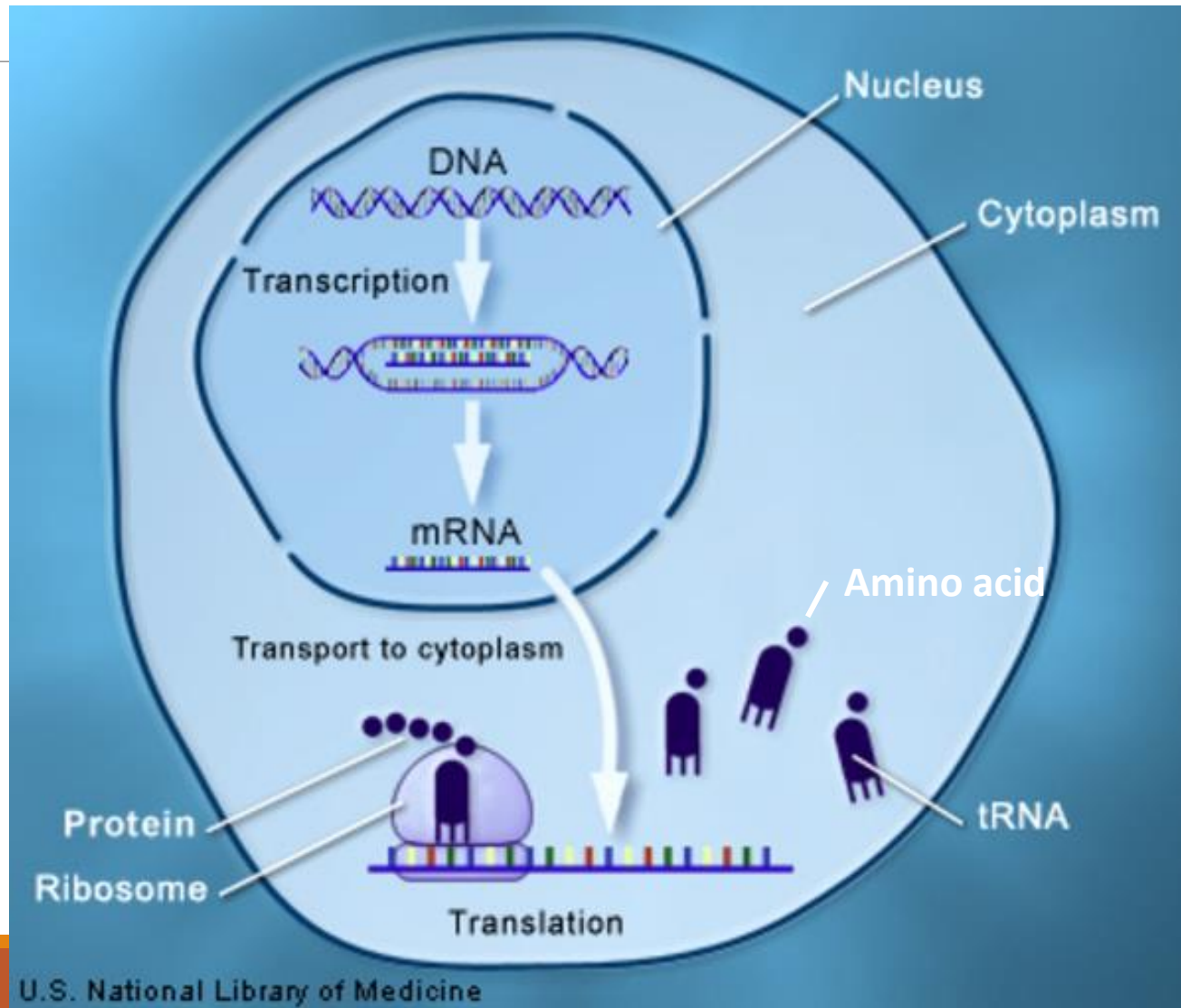
Figure: Animal Cell Structure with Cytoplasm, Image Copyright © Sagar Aryal, www.microbenotes.com

What are proteins and what do they do?

- Proteins are large, complex molecules that play many critical roles in the body.
- They do most of the work in cells
 - required for the structure, function, and regulation of the body's tissues and organs.
- Proteins are made up of hundreds or thousands of smaller units called amino acids, which are attached to one another in long chains.
- There are 20 different types of amino acids that can be combined to make a protein.
- The sequence of amino acids determines each protein's unique 3-dimensional structure and its specific function.



How does a cell make a protein?



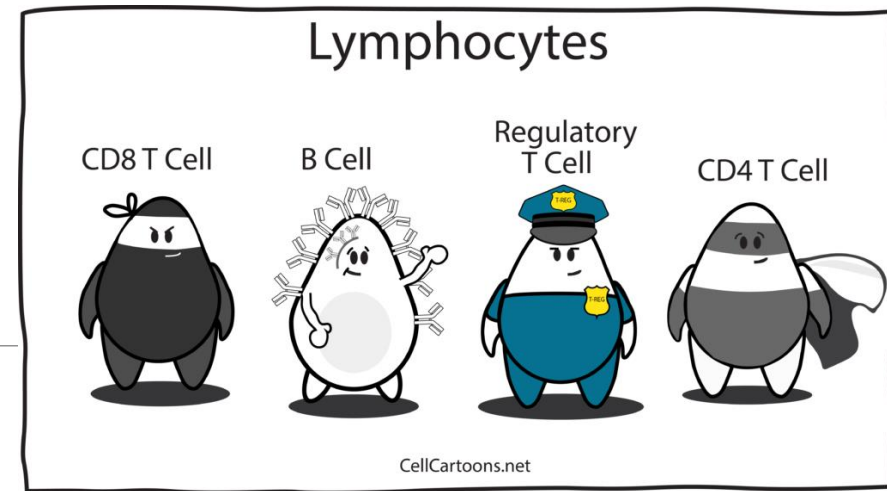
Your Immune System

Innate:

- Barriers: skin, mucosal surface (eyes, nose, mouth)
- Defense mechanisms: mucus, gastric acid
- Immediate: circulating proteins and cells in the body which directly attack invaders (complement system, macrophages)-no memory

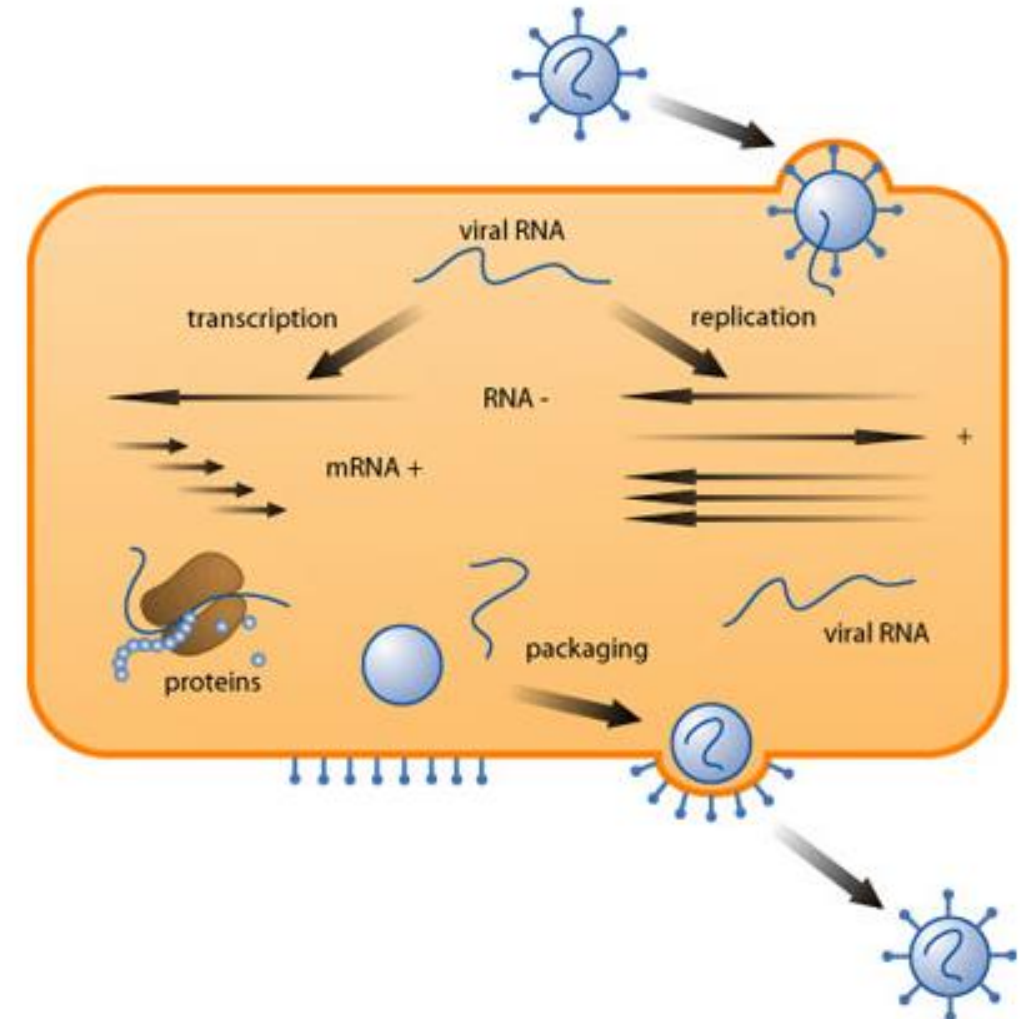
Adaptive:

- Has memory, is able to learn
- T-cells: helper (CD4) and killer (CD8) T cells: sound the alarm and kill infected cells
- B-cells: make antibodies which circulate and bind to antigens, inactivating them and tagging them for destruction
- **Vaccines use your natural adaptive immune response**



What happens during a viral infection?

- Virus enters your body and the viral particle attaches to a cell
- The virus opens up and its genetic information (usually RNA) enters your cell
- Your cell's machinery reads the RNA and makes the proteins
- These viral proteins assemble into new viruses
- Once enough viruses assemble, the cell dies and over 10,000 new viruses are released into the body to infect other cells
- The immune system recognizes the viral proteins on the cell surface and sounds the alarm, and tries to kill the virus infected cells before it releases all the viruses.
- SARS-CoV-2 also has other proteins it which help it to evade the immune system and cause many of the other symptoms



What are Vaccines?

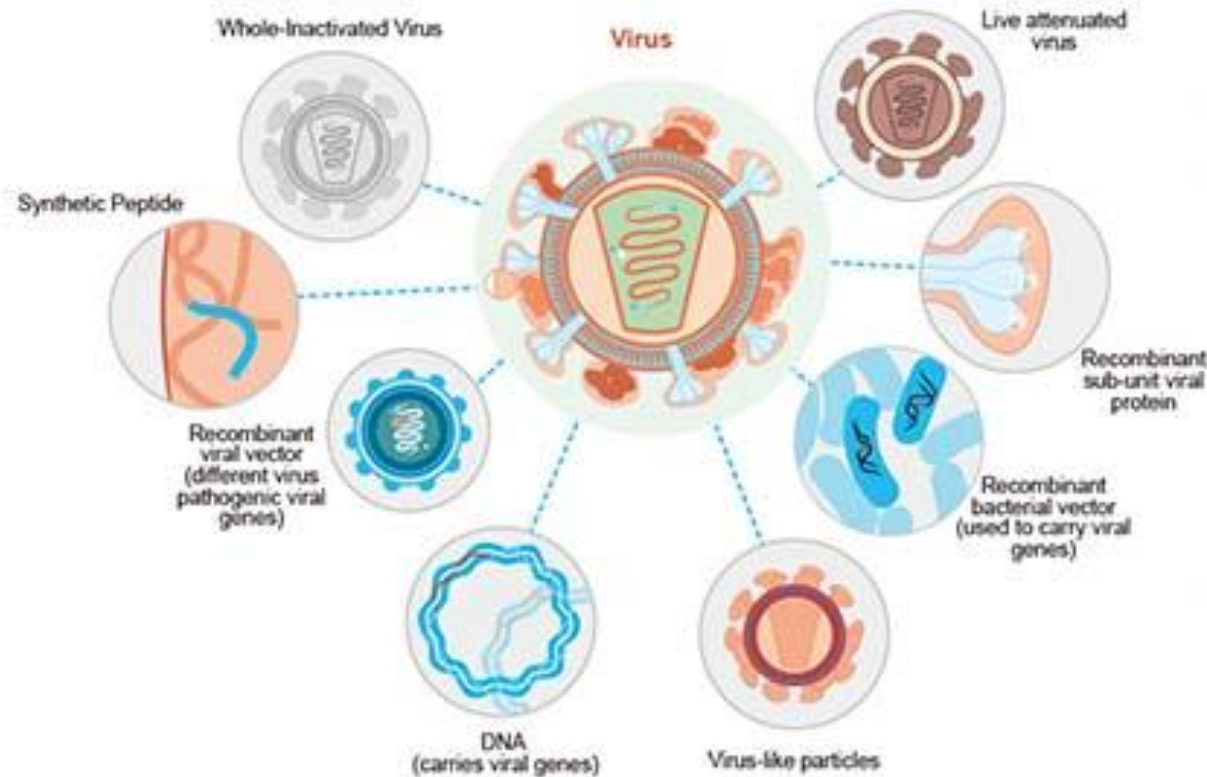
- Vaccines contain the same germs that cause disease
 - but killed or weakened to the point that they don't make you sick.
- Some vaccines contain only a *part* of the disease germ.
- A vaccine stimulates your immune system to produce antibodies, exactly like it would if you were exposed to the disease. After getting vaccinated, you develop immunity to that disease, without having to get the disease first.
- This is what makes vaccines such powerful medicine. Unlike most medicines, which treat or cure diseases, vaccines *prevent* them.

Edward Jenner: first vaccine 1796



The Cow-Pock — or — the Wonderful Effects of the New Inoculation! — vide. the Publications of the Anti-Vaccine Society.

Types of Vaccines



Live attenuated (LAV)

- Tuberculosis (BCG)
- Oral polio vaccine (OPV)
- Measles
- Rotavirus
- Yellow fever
- Influenza

Inactivated (killed antigen)

- Whole-cell pertussis (wP)
- Inactivated polio virus (IPV)

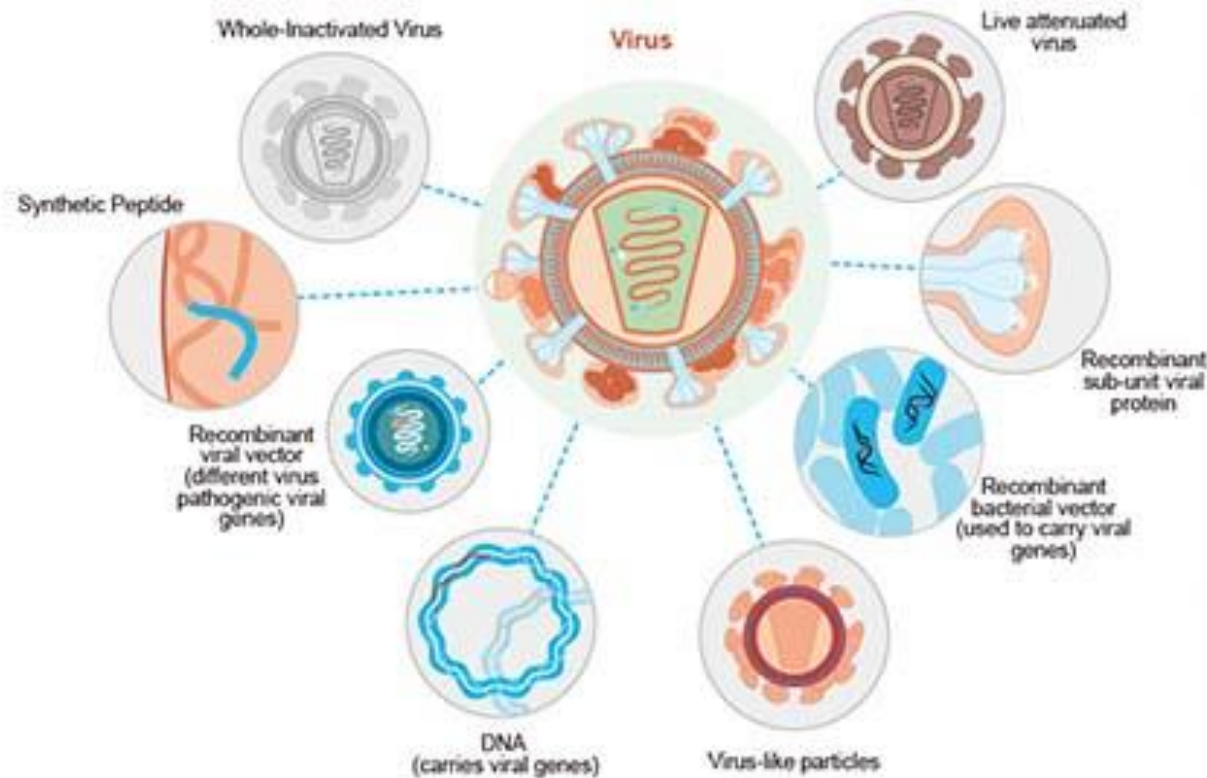
Subunit (purified antigen)

- Acellular pertussis (aP).
- *Haemophilus influenzae* type B (Hib).
- Pneumococcal (PCV-7, PCV-10, PCV-13)
- Hepatitis B (HepB)

Toxoid (inactivated toxins)

- Tetanus toxoid (TT).
- Diphtheria toxoid

Types of Vaccines



Live attenuated (LAV)

- Tuberculosis (BCG)
- Oral polio vaccine (OPV)
- Measles
- Rotavirus
- Yellow fever
- Influenza

Inactivated (killed antigen)

- Whole-cell pertussis (wP)
- Inactivated polio virus (IPV)

Subunit (purified antigen)

- Acellular pertussis (aP).
- *Haemophilus influenzae* type B (Hib).
- Pneumococcal (PCV-7, PCV-10, PCV-13)
- Hepatitis B (HepB)

Toxoid (inactivated toxins)

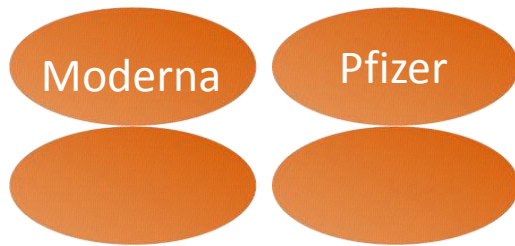
- Tetanus toxoid (TT).
- Diphtheria toxoid

mRNA

Six COVID-19 Vaccines

<http://www.dhmf.org/vaccintrial>

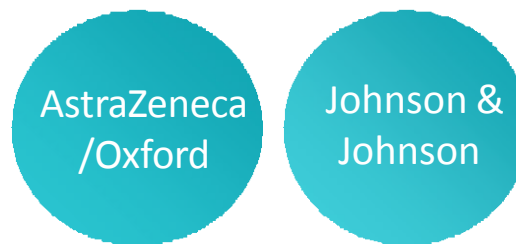
mRNA Vaccine



- 30,000 Participants
- Phase III started July
- (37% ethnically diverse, 42% high risk pop)
- FDA 12/17

- 44,000 Participants
- Phase III started July
- (30% ethnically diverse, 45% 56-85 years old) U.S. participants
- FDA 12/10
- Canada and Britain EUA

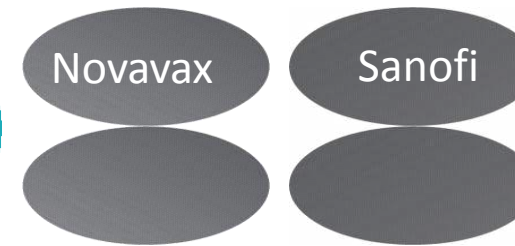
Viral Vector Vaccine



- Chimp adenovirus
- Phase III started August
- Halted September 6th ...Resumed October 23rd
- Promising results in young and older adults

- 60,000 participants
- Phase III started September
- Halted October 13th
- Resumed October 24th
- November 16th launching second phase III trial to observe effects of two doses

Protein-Based Vaccine



- Phase III in UK with 10,000 participants
- Phase III Oct/Nov with 30,000 U.S. participants

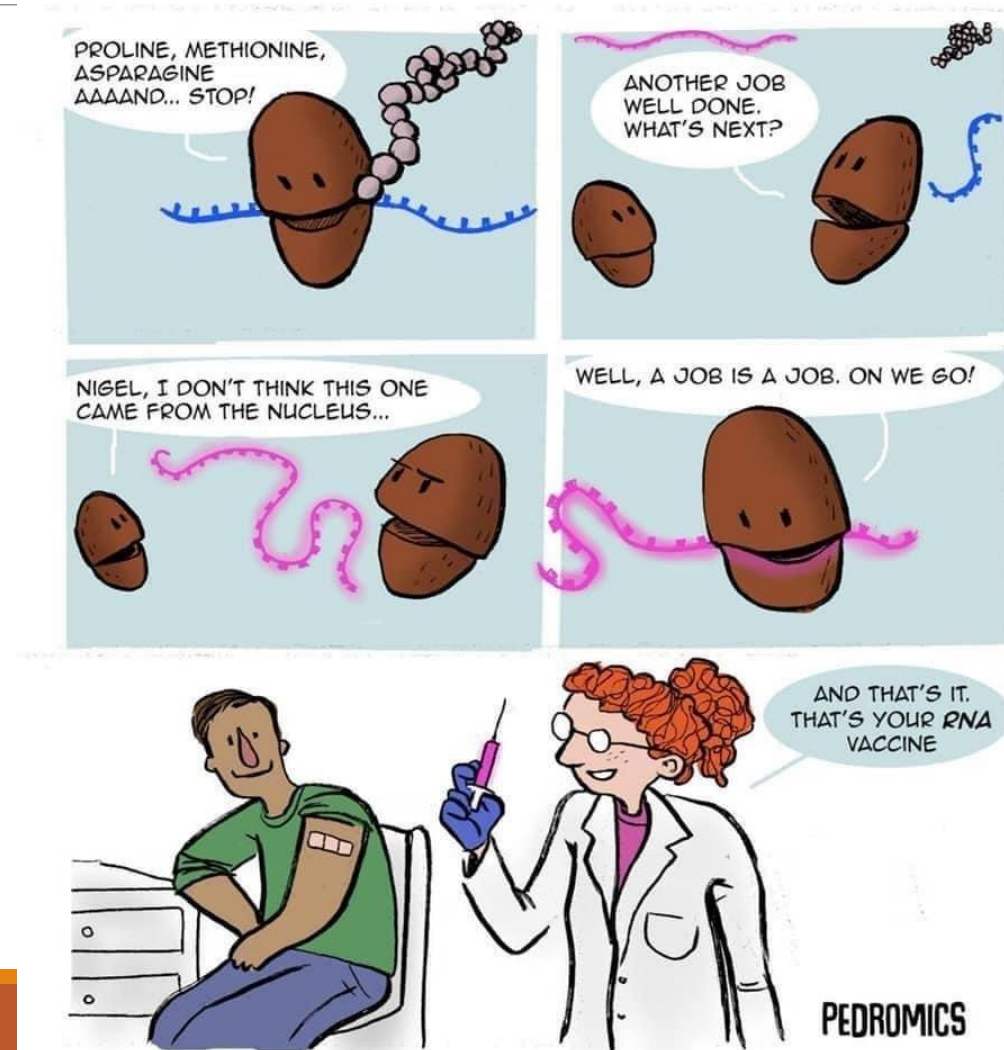
- Flublok technology
- Dec 2020: Phase III abandoned. Less response in older people
- New phase 2 in Feb with different formulation

- carry the **genetic instructions** for the host's cells to make the antigen, which more closely mimics a natural infection

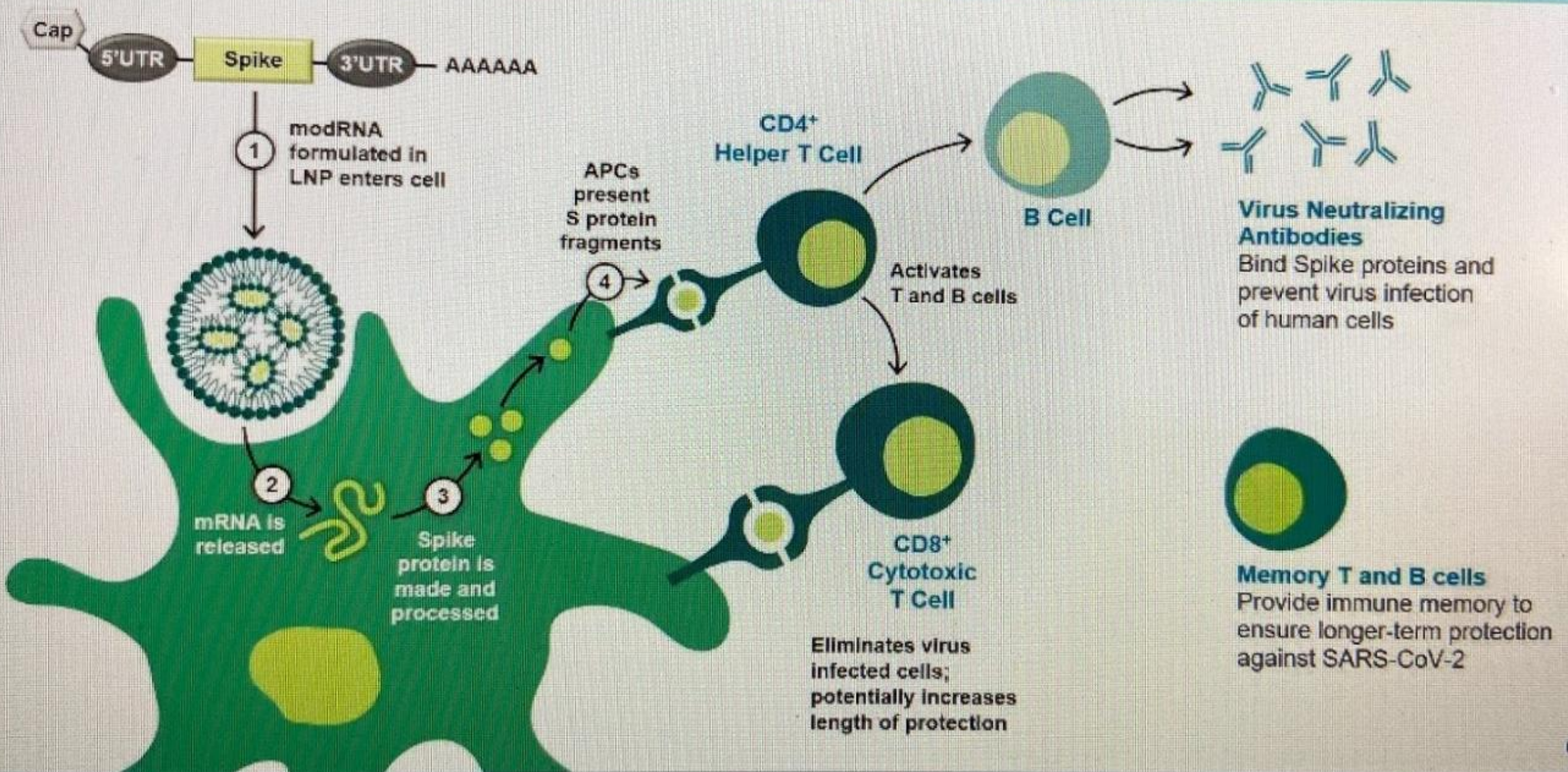
- Subunit vaccine, more traditional approach

How does an mRNA vaccine work?

- Delivery of mRNA-coded genetic information as blueprint for vaccine into cells
- mRNA uptake into muscle and local immune cells results in protein synthesis
- mRNA stimulates immune system of vaccinated individual, generating immune response to the viral protein
- mRNA is then degraded quickly by the cell (minutes to hours). It is gone by 24 hours
- The spike protein peaks at 48 hours and is gone by 72 hours in the body
- “Snapchat” for the immune system



Mode of Action of the BNT162 Vaccine Candidates



How effective are these vaccines?

Every vaccine trial has 2 groups- one who gets the vaccine and one who doesn't (they get a placebo). Then they count up who gets sick

Pfizer:

18,000 people RECEIVED the vaccine: **8** got Covid

18,000 people DIDN'T GET the vaccine: **162** got Covid

Moderna:

14,000 people RECEIVED the vaccine: **11** got Covid

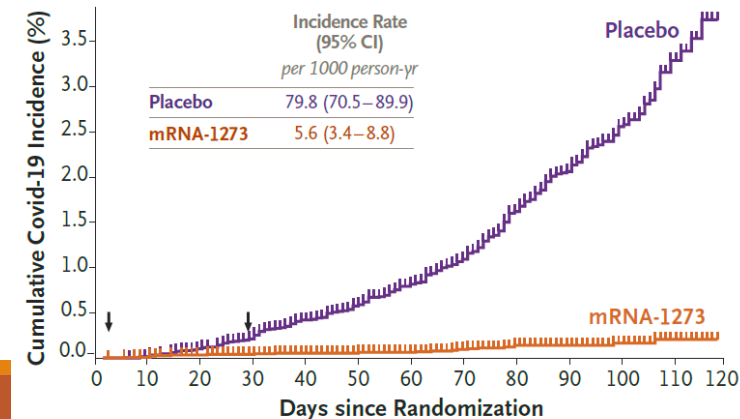
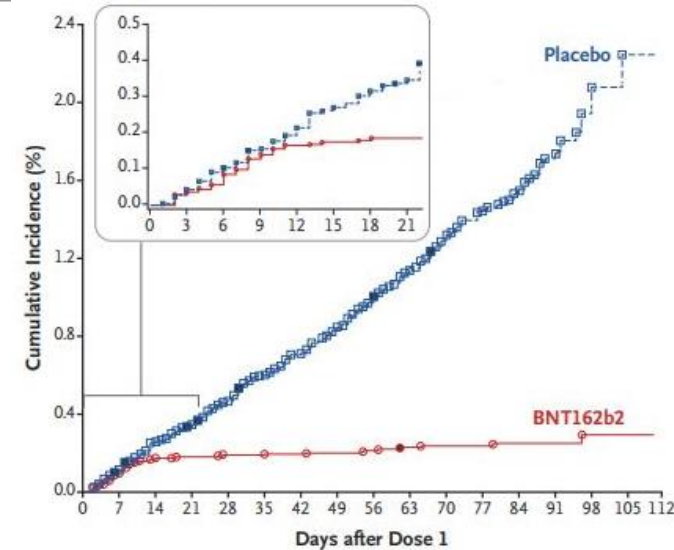
14,000 people DIDN'T GET the vaccine: **185** got Covid

So in total:

32,000 people RECEIVED the vaccine: **19** got Covid

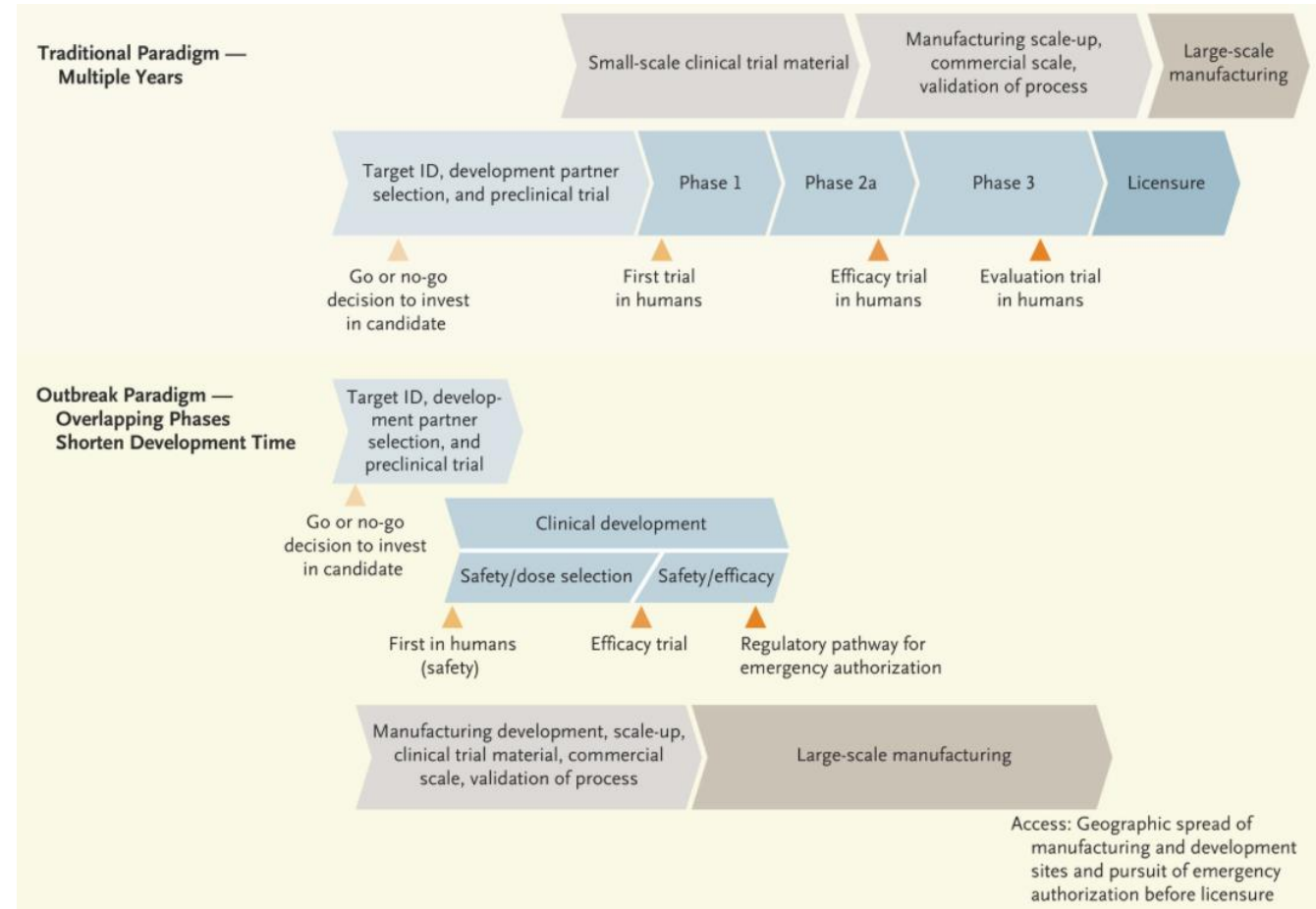
32,000 people DIDN'T GET the vaccine: **347** got Covid

— adds up to **>94% effectiveness** — it's unbelievably fantastic, SPECTACULARLY good.



Was it rushed?

- This is the fastest vaccine development in the history of the world because a bunch of science went on for years before this and then a bunch of good stuff happened all at once.
- Our knowledge about genetic sequencing is way better than it was even a few years ago
- They figured out SARS-CoV-2's whole genetic code within days
- Scientists have been studying other coronaviruses behind the scenes for years;
- Scientists have been studying mRNA vaccines behind the scenes for years
- Researchers have figured out how to do really good vaccine trials
- There was so much coronavirus around and it's so contagious that trials could finish up quickly
- The government, industry, and a bunch of charities poured buckets of money into this research
- The government paid for vaccines to be manufactured before the studies were done and sped all their processes up
- They've been working on vaccine distribution for months
- **Because if you spend a ton of money miracles can happen.**



How long will it take to work?

- You won't get the full protection from the mRNA vaccines until about **a week after the *second* dose**
- the vaccine's protection starts about ten days after the first dose, but only about 50% percent efficacy
- A week after the second dose, the efficacy rose to 95 percent
- =Get both doses

Will it hurt? What are the side effects?

- >35,000 people have already received the vaccines, and none of them have reported any serious health problems.
 - Started in July
 - Side effects if related should be apparent within 2 months from vaccine
- The side effects, which can resemble the symptoms of Covid-19, last about a day and appear more likely after the second dose.
 - fatigue, headaches, fever, chills and muscle pain
 - Not nasal congestion, cough (if you have these, test for COVID)
- While these experiences aren't pleasant, they are a **good sign** that your own immune system is mounting a potent response to the vaccine that will provide long-lasting immunity.

Side Effect Comparison

Pfizer/BioNTech:

Moderna:

Less reported side effects compared to Moderna

- Fatigue 3.8%
- Headache 2%
- High fever 39–40 C (102F) <2%

- Fatigue almost 10%
- Muscle pain 9%
- Joint pain 5%
- Headache 4.5%
- High fever <2%

All higher than most influenza vaccine side effects

How do I know it's safe?

- Each company's application to the F.D.A. includes two months of follow-up safety data from Phase 3 of clinical trials conducted by universities and other independent bodies.
 - Some people got their shots in July and they have been followed ever since (six months) with no new side effects during that time.
- In Phase 3, tens of thousands of volunteers got a vaccine and waited to see if they became infected, compared with others who received a placebo.
- By September, Pfizer's trial had 44,000 participants; no serious safety concerns have been reported.
- Similarly, Moderna had 30,000 participants
- They kept close track of the short-term reactions (sore arm, fatigue, etc) and saw they didn't change over time and didn't last.
- As a rule with viruses you just don't see side effects or reactions more than few weeks after getting a vaccine

Has this technology been used before?

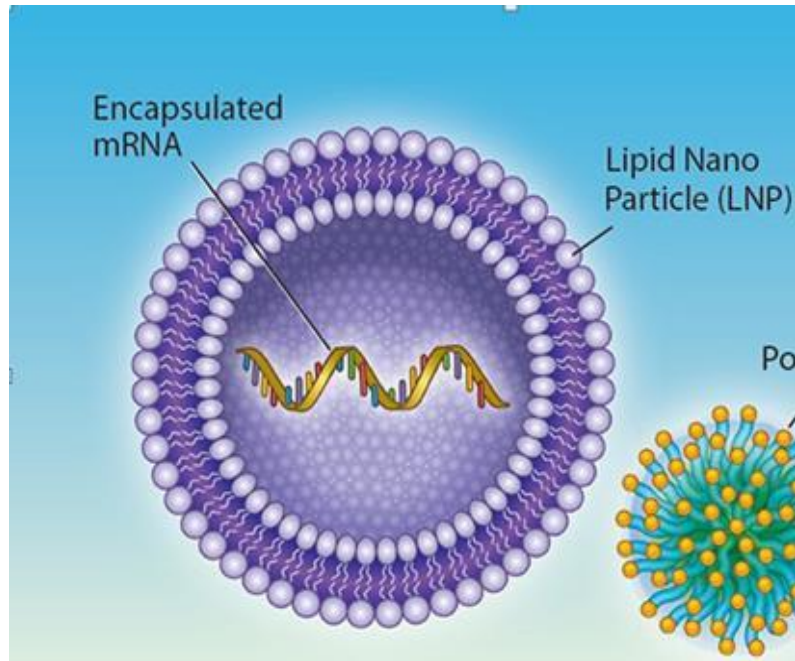
YES

- **Has been in development for over 15 years, using the past 50 years of immunology and cell biology research**
- **Personalized cancer immunotherapy research**
 - Some cancers express specific proteins that the body can recognize as foreign
 - Decoding the mRNA of those proteins to produce tumor vaccines
 - mRNA tumor vaccines either alone or in conjunction with immunotherapy or adjuvant chemotherapy
 - Dozens of clinical trials are underway or completed
 - Metastatic prostate, ovarian, malignant melanoma, small cell lung, brain and breast cancers
- **Preventing other infectious diseases**
 - A vaccine against rabies is currently in clinical trials
 - Vaccines against influenza, HIV or tuberculosis are at the research stage.

If I have allergies, should I be concerned?

- People with severe allergies who have experienced anaphylaxis in the past should talk to their doctor
 - it should be fine
- Fewer than one in a million recipients of other vaccines a year in the U.S. have an anaphylactic reaction (1 in 1.31 million)
- Among those who participated in the Pfizer trials, a very small number of people had allergic reactions.
 - 0.63% of participants who received the vaccine reported potential allergic reactions, compared to 0.51% of people who received a placebo.
 - In Pfizer's late-stage clinical trial, one of the 18,801 participants who received the vaccine had an anaphylactic reaction, according to safety data published by the F.D.A. None in the placebo group did.
- In Moderna trials, the only reported allergic reactions were seen in people with history of dermal fillers in their face who developed face swelling.

Reaction to the vaccine



- mRNA is packaged in lipid particles in order to help it cross the cell membrane
- Lipid nanoparticles can cause fever and other short-term reactions without the mRNA
- Short-term, less than 12 hours high fever was reported in participants
- Since increased vaccinations of health care workers, increasing reports of possible allergic reactions (about 12 reported in > 4,563,260 doses given to HCW in past 2.5 weeks as of 1/4/2021 9:00am ET)
- May be related to polyethylene glycol
- Check tryptase in blood to determine if allergic reaction or not (within 4 hours of reaction)
- Treatable!
- Report!



**Get vaccinated.
Get your smartphone.
Get started with v-safe.**

V-safe is a smartphone-based tool that checks in on you after your COVID-19 vaccination. Your participation helps keep COVID-19 vaccines safe — for you and for everyone.

If you got vaccinated in the last 6 weeks, you can participate in v-safe!

It takes just a few minutes to register and get started. All you need is your smartphone and information about the COVID-19 vaccine you received. This information can be found on your vaccination record card. If you cannot find your card, please contact your healthcare provider.

https://vsafe.cdc.gov/?fbclid=IwAR2lsXTU1hqxrT_BhVU8Oh22oUYh5MI mJtA3eiFsSCxl9amqA5_TIR7k3Ak

What will happen if serious side effects crop up after the vaccine is rolled out?

- Once a vaccine starts to reach large numbers of people, it's possible (and not uncommon) for a small number of severe "adverse events" to occur.
- Many existing vaccines, including the flu shot, also can cause rare complications, including Guillain-Barré syndrome or seizures
- While this sounds frightening, the risk is minuscule when considered over the millions of people who are safely vaccinated each year, and most of these complications are more often triggered by the virus itself.
- Health officials will investigate each event to see if it's simply coincidence — or if it could have been caused by the vaccine. While everyone should be prepared to hear about these reports, they should not be a cause for worry or prompt you to delay getting the vaccine.
- **Your risk of severe complications from Covid-19 is far higher than your risk of complications from the vaccine.**

I had Covid-19 already. Do I need the vaccine?

Yes.

- It's safe, and probably even beneficial, for anyone who has had Covid to get the vaccine at some point
- Although people who have contracted the virus do have immunity, it seems to vary in how long it lasts. So for now, it makes sense for them to get the shot. The question is when.
- Some members of the C.D.C. advisory committee have suggested people who have had Covid in the past 90 days should be toward the back of the line.
- Current recommendation is to get it once you've recovered/out of isolation/feeling better
- Don't need to check antibodies before vaccination
- Vaccination won't cause positive COVID viral tests
 - Should cause positive spike protein IgG, while natural infection will also have positive nucleocapsid IgG

Will it work on older people?

Yes.

- All the evidence we have so far suggests that the answer is yes.
- The clinical trials for the two mRNA vaccines have shown that they work about the same in older people as younger people.

Will it work on this “new variant”?

Yes.

- No indication that this “new variant”, which has a few small mutations, would decrease efficacy
 - It is not a new “strain”
 - Unclear if it is truly more contagious in humans
 - current data is speculative based on increased amount of virus RNA detected
 - Timing of increased spread is likely more related to holiday gatherings/winter
- Your body is making many different types of anti-spike protein antibody with the vaccine, so one small amino acid change in the virus spike protein will not be a problem
- Should I be worried about this variant?
 - YES! Just as much as you have been worried about COVID in the past year
- With mRNA technology, even if a significant mutation occurred, a new vaccine could be available to test in as little as 6 weeks.

I'm young and at low risk. Why not take my chances with Covid-19 rather than get a vaccine?

Get a vaccine.

- Covid-19 is by far the more dangerous option.
- Although people who are older, obese or have other health problems are at highest risk for complications from Covid-19, younger people can become severely ill, too.
 - In a study of more than 3,000 people ages 18 to 34 who were hospitalized for Covid, 20 percent required intensive care and 3 percent died.
- As many as one in three people who recover from Covid have chronic complaints, including exhaustion, a racing heart and worse for months afterward.
- Covid vaccines, in contrast, carry little known risk.
- Will likely decrease transmission to family/friends/essential workers

What about Children?

- Typically, childhood vaccines are approved after being tested and showing promise in adults
- Most of the trials were on non-pregnant adults
 - Pfizer now studying children 12 years and above
 - Moderna planning to follow suit
 - AztraZeneca vaccine has been tested on children down to age 5
- Children will need to be vaccinated
 - Children can still suffer and be hospitalized from this virus – though less frequently than adults
 - Children can asymptotically or symptomatically transmit this virus to other people
- There could be a vaccine available for children by mid-to-late 2021.
- No reason these vaccines would not work in children

What about women who are pregnant or breastfeeding?

- Pregnant and breastfeeding women should consult with their obstetricians and pediatricians about whether to get the vaccine.
- The Pfizer vaccine has not been tested in pregnant women or in those who were breastfeeding, and federal health officials have not issued any specific guidance, other than allowing these women to be vaccinated if they choose. (The American College of Obstetricians and Gynecologists issued practice guidelines to help women and their doctors talk about vaccination.)
- In the initial rollout, it will be mostly pregnant health care workers who must weigh the benefits and possible risks. By the time the vaccine is available to pregnant essential workers or to women in the general population, there should be a lot more data available.
- Some experts said the virus itself poses greater risks to pregnant women than the new vaccine. Since the 1960s, pregnant women have been urged to receive vaccines against influenza and other diseases. These women are generally cautioned against live vaccines, which contain weakened pathogens — but the Pfizer or Moderna vaccines do not contain live virus.

What if I'm Immunocompromised?

- It is safe and recommended.
- Both Phase 3 trials excluded people who were on long term immunosuppression.
- No reason to think there would be any increase in adverse events, but might not work as well.
- Further study ongoing regarding efficacy.

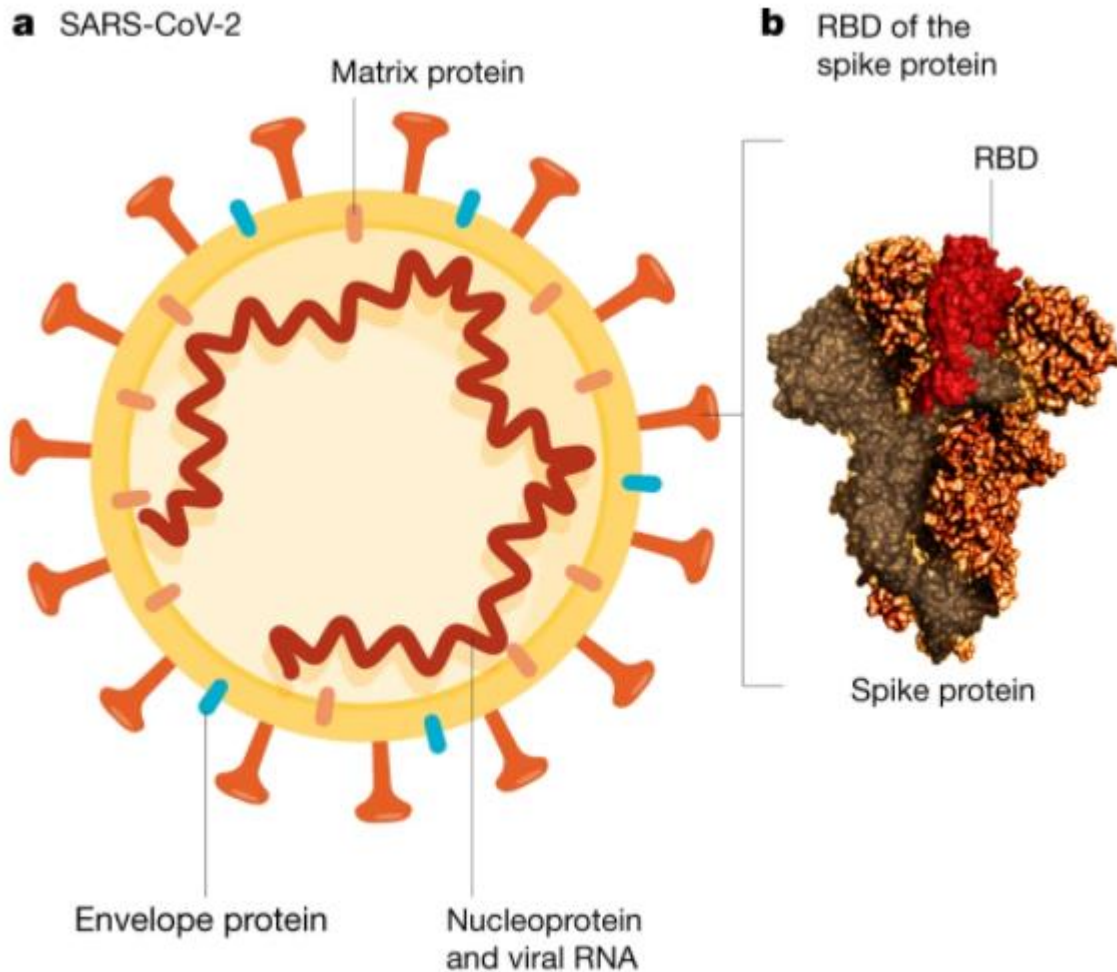
Myth: mRNA alone causes the side effects. Not true.

- mRNA molecules are highly unstable
- That is part of the reasons why it needs very cold refrigeration
- Human blood contain nucleases (enzymes) that rapidly degrade free-floating/unprotected RNA in minutes
- Only possible concern is that the mRNA might not be doing the job in the cell as expected

Myth: mRNA changes your DNA. Not true.

- mRNA does not affect recipients DNA
 - This is because in order to do so, the mRNA must convert into DNA, enter the nucleus, and integrate into the cell's DNA. (A reversal of normal function)
- RNA vaccines do NOT change your DNA, as it does not enter the nucleus.
 - This is a complex multiple-step process requiring action of several enzymes that the cell doesn't have.
- It's like you have a book that represents the genetic code. You then scan that book in a copy machine, and now you have a bunch of papers that are an image of the original book. The copy does not change the original book. It can't.
- On the other hand the cells have plenty of enzymes that can readily destroy the mRNA, so the mRNA is usually degraded after the protein is made.
- "Snapchat" for your cell

Myth: mRNA vaccine will give me COVID. Not true.



- The mRNA fragment causes just one part of the virus to be produced and shown to the immune system from your cells – the Spike-protein.
- That protein induces an immune response, but it is a tiny part of the virus.
 - It cannot reproduce.
 - It cannot cause disease.
 - It cannot be spread.
- The Spike-protein is useless without the rest of the virus, except to induce an immune response. That's it.
- There are no live, attenuated, or dead viruses in the mRNA vaccines.
- **You cannot contract COVID-19 from this vaccine.**

Myth: mRNA vaccine will harm the fetus during pregnancy. Not true.

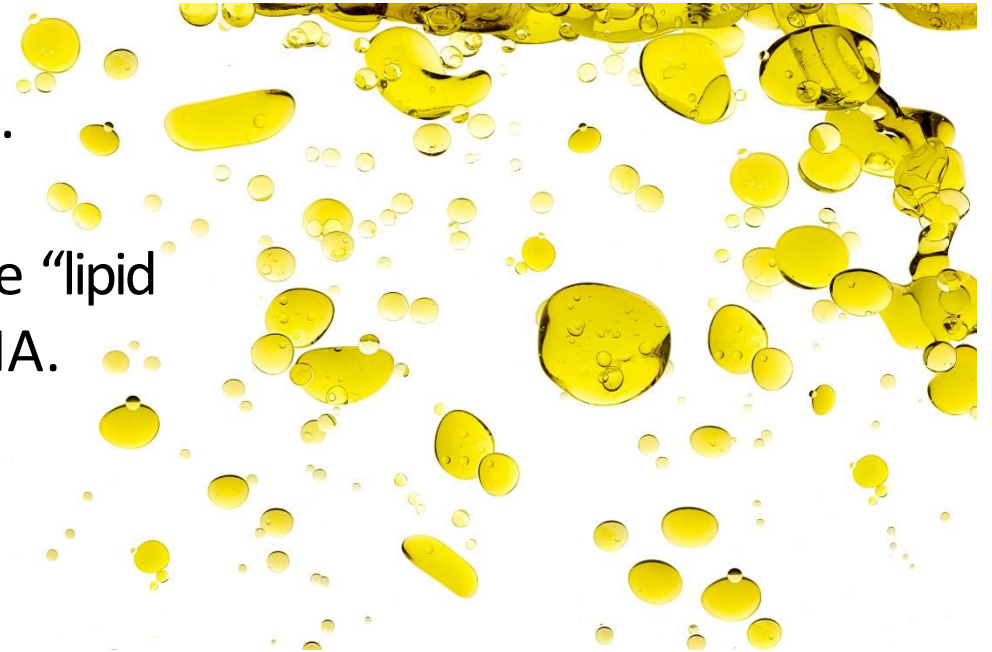
- The cell biology of the fetus is similar to the ones in fully grown adults – the mRNA fragment is probably not going to cross the blood-placenta barrier.
- If it does, it's still not going to enter the nucleus of the cell and change the fetal DNA.
- The mRNA functions exactly the same in the fetus and adult.

Myth: mRNA vaccine will cause infertility. Not true.

- Basically, the claim is that there is a protein subunit on the spike protein that is "homologous" or similar to the syncytin-1 protein that facilitates the development of the placenta.
 - There is simply no evidence that there is some immune cross-reactivity between the spike protein and syncytin-1.
- Also not plausible that one small part of those two proteins would induce some sort of cross-reactivity.
- The sequence is too short for the immune system to meaningfully confuse it with placental proteins
- Women have contracted COVID-19, and there aren't reports of sudden infertility risks or increased miscarriages.
- It is also false to say there are different gender-specific COVID-19 vaccines.

Myth: mRNA vaccines are using hydrogel nanotechnology to introduce microchips into the human body. Not true.

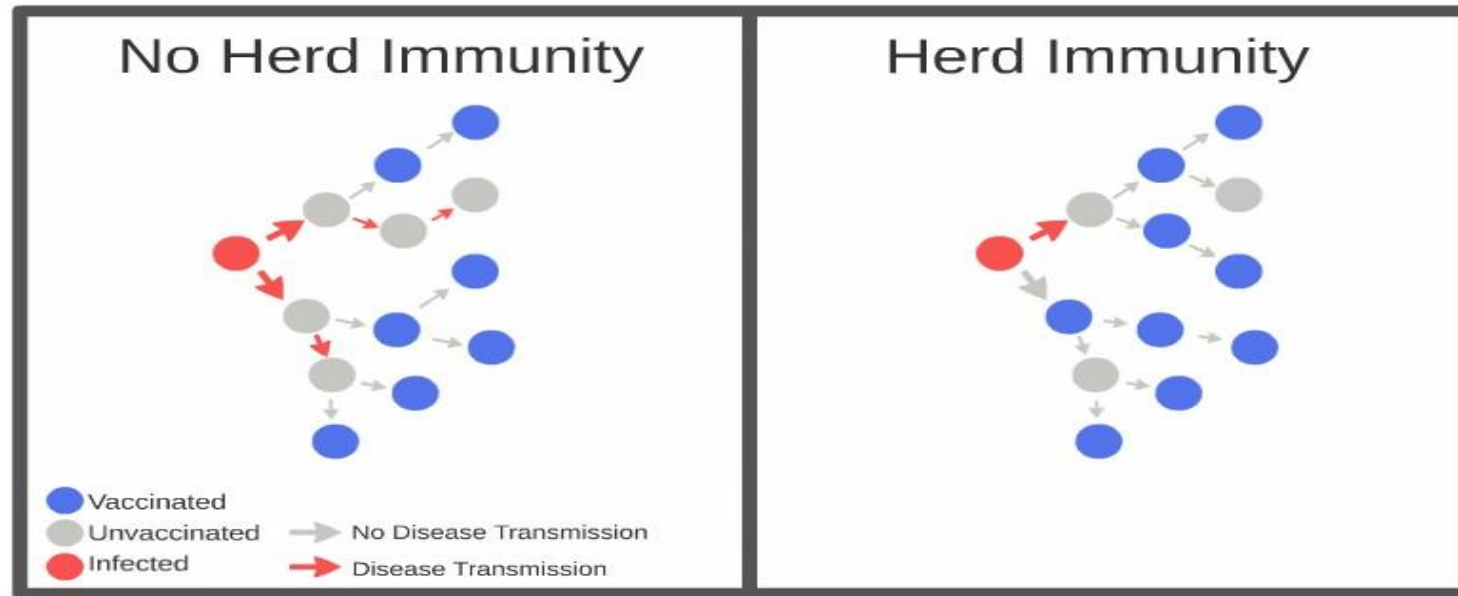
- No microchips are present in vaccines.
- Hydrogel nanotechnology refers to the “lipid nanoparticles” which encase the mRNA.
 - Lipid=fat
 - Nano=very very small
 - Particle=small sphere
- The microchips would have to be so small they wouldn't work. It is impossible.



If I've been vaccinated, will I still need to wear a mask?

- **Yes, but not forever.**
- The vaccine appears to be enough protection to keep the vaccinated person from getting ill. But what's not clear is whether it's possible for the virus to bloom in the nose — and be sneezed or breathed out to infect others — even as antibodies elsewhere in the body have mobilized to prevent the vaccinated person from getting sick.
- The vaccine clinical trials were designed to determine whether vaccinated people are protected from illness — not to find out whether they could still spread the coronavirus.
- Based on studies of flu vaccine and even patients infected with Covid-19, researchers have reason to be hopeful that vaccinated people won't spread the virus, but more research is needed.
 - Moderna data looks encouraging, but very preliminary
- In the meantime, everyone — even vaccinated people — will need to think of themselves as possible silent spreaders and keep wearing a mask.

Community Immunity



- When enough people in a community are vaccinated, the whole community, including the individuals that were not vaccinated, is protected against the disease. This is herd immunity.
- Herd immunity is important because not everyone can be vaccinated.
- However, the number of vaccinated individuals must be great enough for community protection to occur.
- We don't yet know this number for Covid-19 with certainty.

A Successful Example of Community Immunity



- Polio was once one of the most feared diseases in the U.S.
- In the early 1950s, before polio vaccines were available, polio outbreaks caused more than 15,000 cases of paralysis each year.
- Following introduction of vaccines—specifically, trivalent inactivated poliovirus vaccine (IPV) in 1955 and trivalent oral poliovirus vaccine (OPV) in 1963—the number of polio cases fell rapidly to less than 100 in the 1960s and fewer than 10 in the 1970s.
- **Thanks to a successful vaccination program, the United States has been polio-free since 1979.**



mRNA Vaccines: the choice is up to you

mRNA Covid vaccines appear to be incredibly safe and effective

- Unknown long term serious side effects (if any)
- Intermediate data shows no significant major side effect at least up to 2 months
- The two vaccine trials consisted of about 74,000 participants
- FDA/CDC will continue to monitor safety

Must weigh risk versus benefits



mRNA Vaccines: the choice is up to you

mRNA Covid vaccines appear to be incredibly safe and effective

- Unknown long term serious side effects (if any)
- Intermediate data shows no significant major side effect at least up to 2 months
- The two vaccine trials consisted of about 74,000 participants
- FDA/CDC will continue to monitor safety

BUT

- Global Covid cases more than 80 million, 1.77 million deaths
- Economic, social and mental health loss of historic proportions
- Millions of lost jobs, extended unemployment, education disrupted, increase in chronic illness
- A successful and widely adopted vaccine is our best chance for a better future

Must weigh risk versus benefits



mRNA Vaccines: the choice is up to you

mRNA Covid vaccines appear to be incredibly safe and effective

BUT

- Unknown long term effects (if any)
- Intermediate data show significant major side effects at least up to 2 months
- The two vaccine trials involved about 74,000 participants
- FDA/CDC will continue to monitor safety



Over 1 million Covid cases more than 80,000 deaths, 1.77 million deaths

Economic, social and mental health impacts, loss of historic proportions

Millions of lost jobs, extended unemployment, education disruption, increase in chronic diseases

Vaccines are successful and widely adopted. This is our best chance for a better future

Must weigh risk versus benefits

