UNIVERSITY OF
DETROIT MERCY
SCHOOL OF DENTISTRY

Viruses, Vaccines, and Variants...Oh My!
What you need to know about SARS-CoV-2 and Why

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Learning Objectives:

- Explain how viruses enter the body, establish infection and are transmitted to others.
- Describe how SARS-CoV-2 is transmitted and leads to COVID-19.
- Compare and contrast the types and efficacy of the available COVID-19 vaccines.
- Evaluate the benefits and potential risks of receiving a COVID-19 vaccine.
- Describe treatments with potential to decrease likelihood of severe COVID-19

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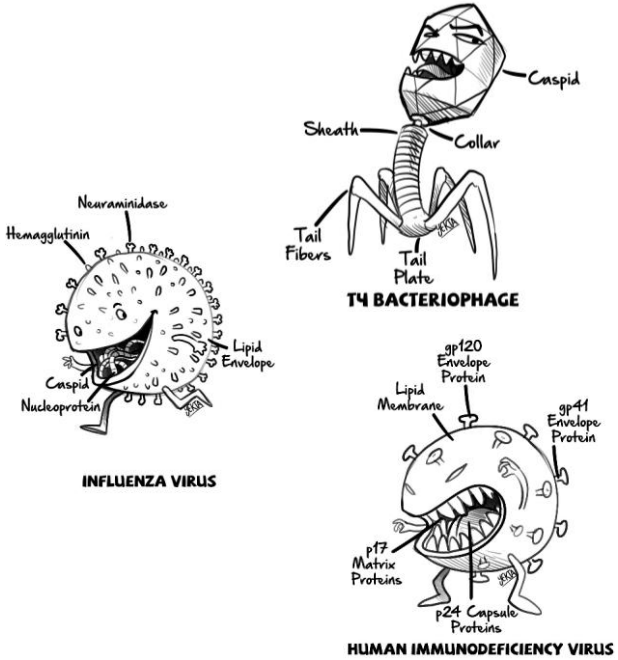
What is a virus?

- **An infectious, obligate intracellular parasite comprising genetic material (DNA or RNA) surrounded by a protein coat and/or a membrane**
  - Capable of directing its own reproduction and spread by "taking over" the machinery inside of the host cell it invades
  - Infectious "recipes"
  - Do not independently fulfill the characteristics of life
    - Are not "alive"
- "Little bags of DNA or RNA"
  - Dental Hygiene student – Class of 2021



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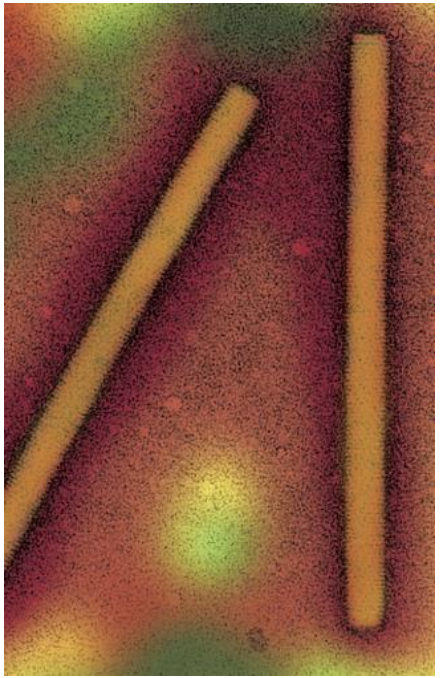
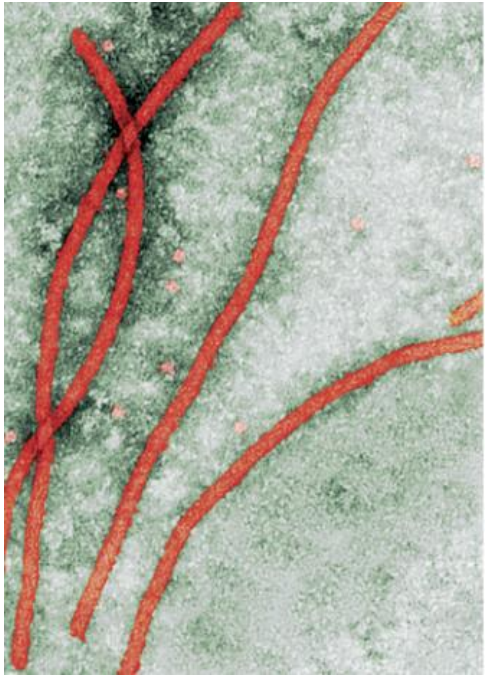
Plant Viruses

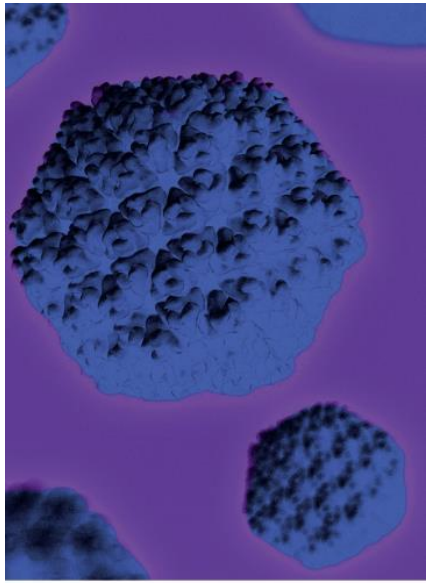
Tobacco Mosaic Virus



Potato Virus Y



Rice Dwarf Virus



Roossinck, Marilyn J. Virus: An Illustrated Guide to 101 Incredible Microbes. 2017. 1st Edition. Princeton University Press. ISBN: 978-0691166964

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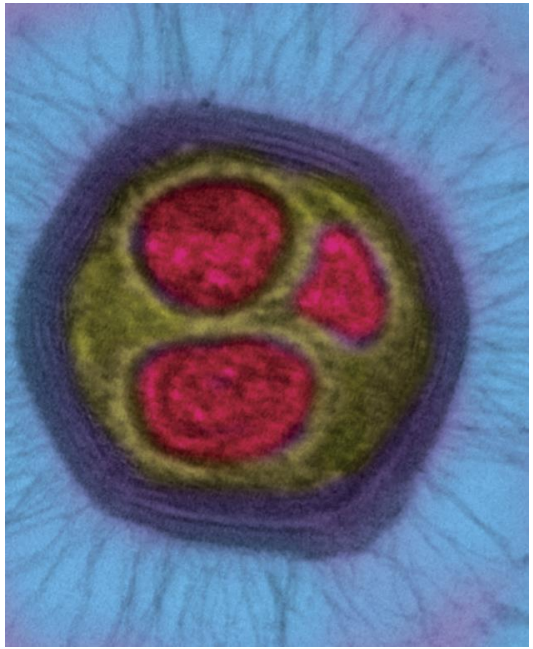
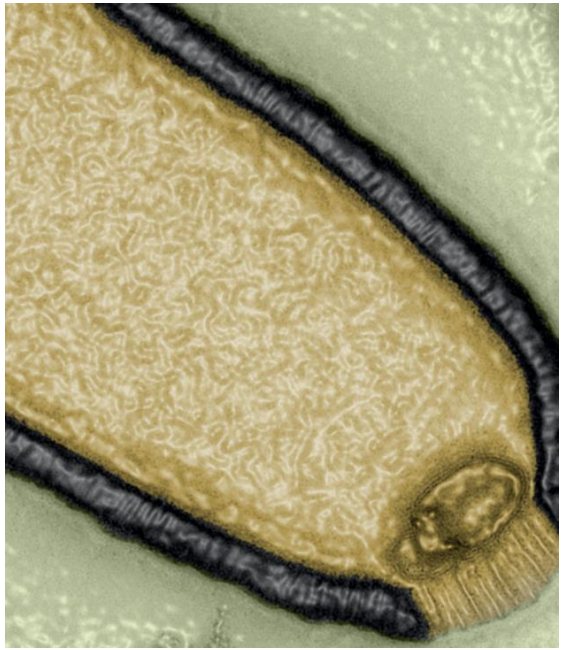
Amoeba Viruses

Mimivirus



Pithovirus



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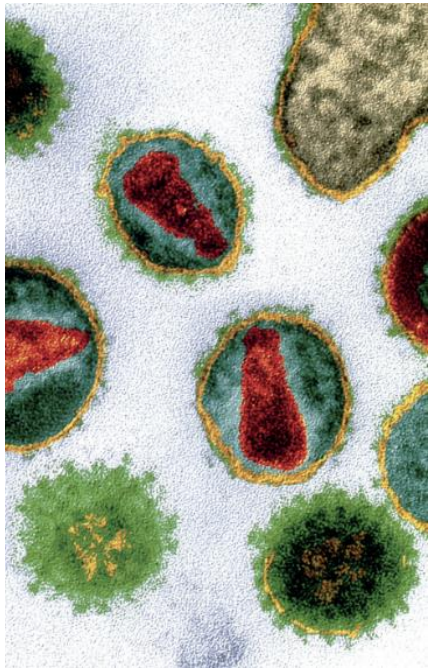
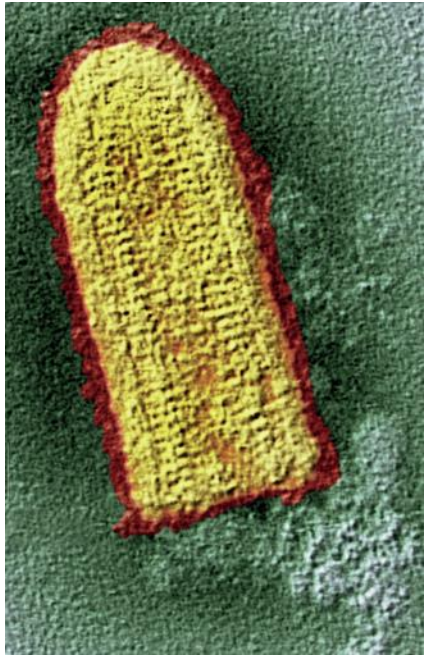
Human Viruses

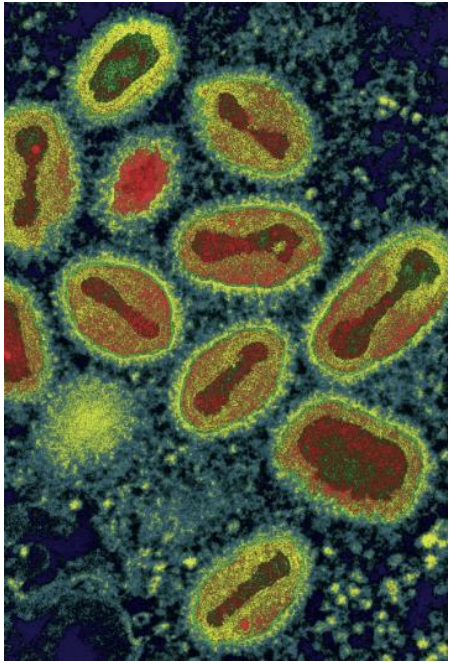
HIV



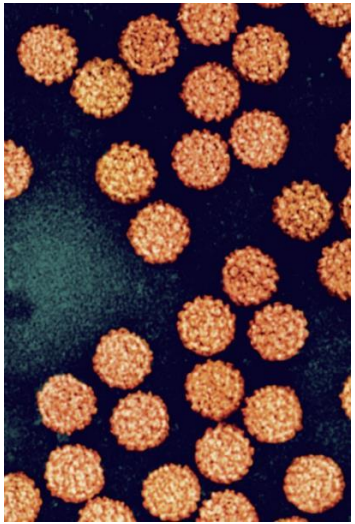
Rabies Virus



Variola Virus



HPV-16



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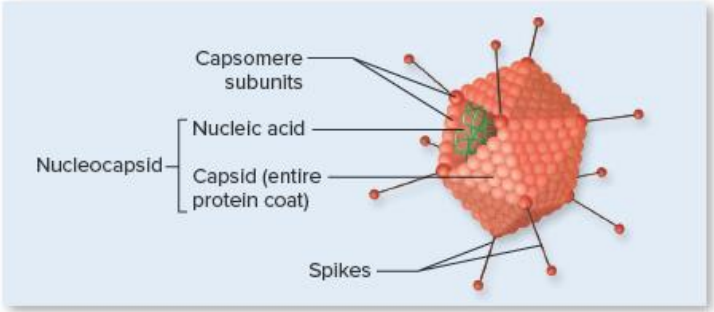
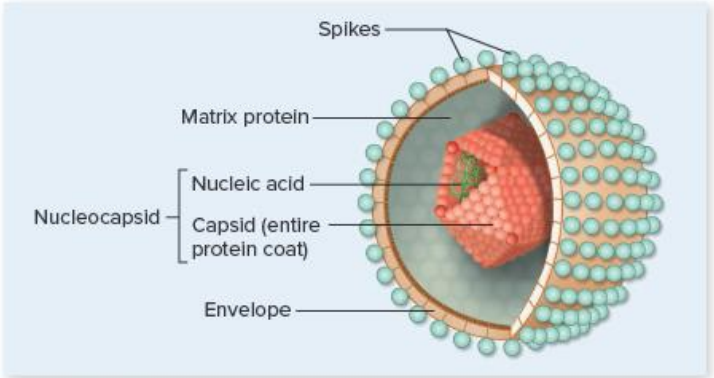
Parts of a Virus

- **Virion** = Entire virus particle, used to refer to something infectious
  - Particle gets used when you cannot determine infectiousness
- **Genome**: DNA or RNA, single or double-stranded (recipe for new viruses)
- **Capsid**: Protein shell, composed of repeated units called capsomeres
  - Can be icosahedral or helical
  - Different than capsule of bacteria and fungi
- **Nucleocapsid = Capsid + Genome**
- **Envelope** (on some): lipid coating on outside, derived from host plasma membrane
- Surface (Envelope or Capsid) contains glycoprotein spikes that serve various functions



(a) Non-enveloped virus



(b) Enveloped virus

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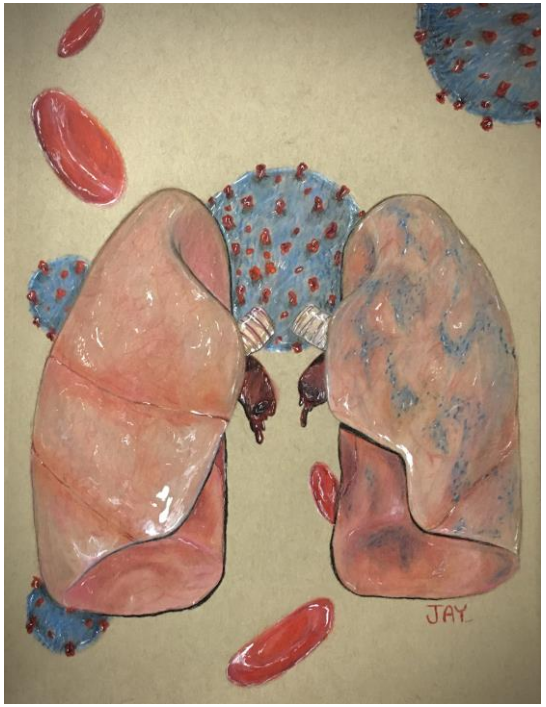
Anderson et al. Nester's Microbiology. 9th ed. McGraw-Hill Higher Education (2019).

Infection vs. Infectious Disease

- **Infection:**
  - Colonization by a pathogen on or within the body
  - Viral infection – Replication within a host cell
  - **Example**: **SARS-CoV-2** infects lung epithelial cells
  - We are infected with viruses all the time without even knowing it
- **Viral Infectious Disease:**
  - When a viral infection prevents the body from functioning normally
  - **Example**: SARS-CoV-2 infects lung epithelial cells leading to signs and symptoms of **COVID-19**
  - Viral infection can result in no symptoms, mild symptoms, severe symptoms or even death



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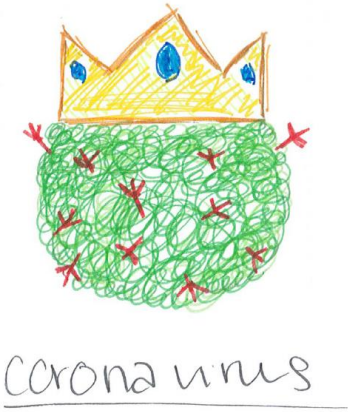
SARS-CoV-2: Virus vs. Disease Nomenclature

- **Virus: SARS-CoV-2**
  - SARS = Severe Acute Respiratory Syndrome
  - CoV = Coronavirus
  - 2 = Related to, but different from the coronavirus responsible for the 2003 SARS outbreak



- **Disease: COVID-19**
  - CO = corona
  - VI = virus
  - D = Disease
  - 19 = first emerged in 2019
- Wide range of symptoms characterized by fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea

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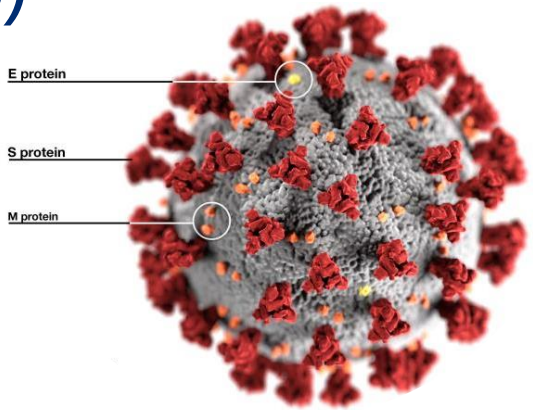
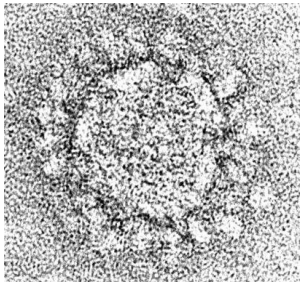
Human Coronaviruses (hCoVs)

- **Family:** *Coronaviridae*
  - "crown" -like glycoprotein spikes on surface
- **Genome:** single-stranded RNA (+)
  - CoVs have the largest genomes of known RNA viruses
  - Have some proofreading ability, slows mutation rate
- **Enveloped**
  - Generally susceptible to desiccation and detergents
- **Asymptomatic infections common**
- **Mild infections common**
  - 229E, NL63, OC43, HKU1 cause about 15% of seasonal colds
- **Coronaviruses can infect animals and humans**
  - Agricultural pathogens: PEDV, TGEV in pigs
  - Bats, cats, rabbits, mice, rats, cattle, poultry, civets, etc.
- **Severe infections can occur when coronaviruses jump from animals to humans**
  - SARS-CoV-1, MERS-CoV, SARS-CoV-2

SARS-CoV-2



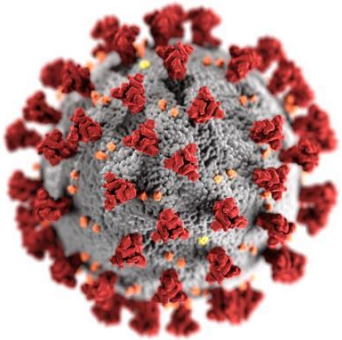
Public Health Image Library ID#: 23313
Alissa Eckert, MSMI; Dan Higgins, MAMS



Public Health Image Library ID#: 23640
Cynthia S. Goldsmith and A. Tamin

Viral Infection

- To cause an infection, a virus must first get into a cell
  - Cannot replicate/grow on its own
- SARS-CoV-2 uses its spike protein to attach to and enter cells
- After the virus enters the cell, it releases its RNA genome
- The virus uses our ribosomes to make new viral proteins from its RNA



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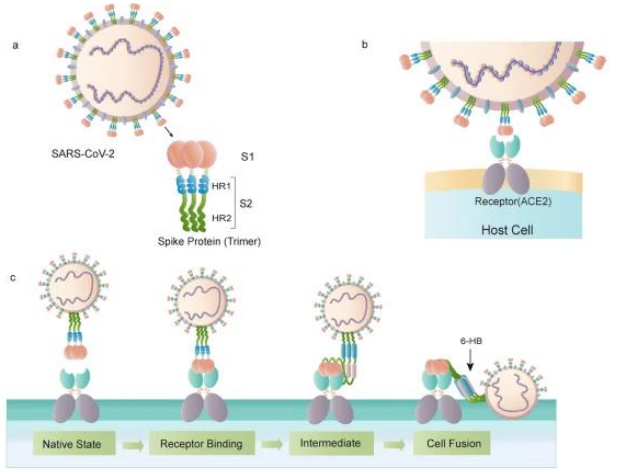
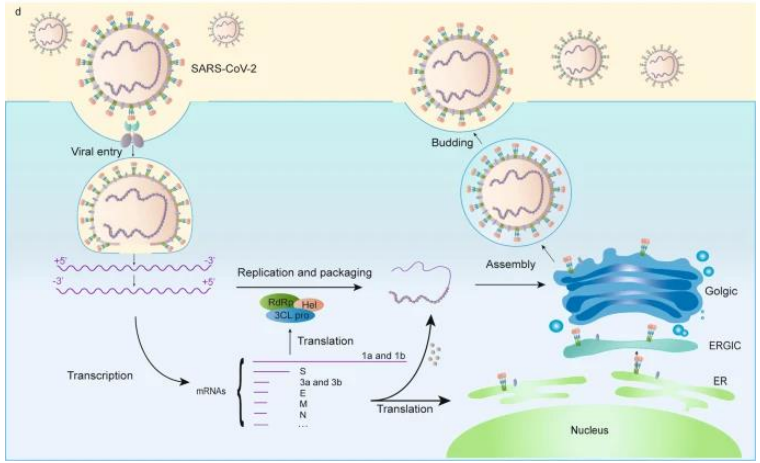
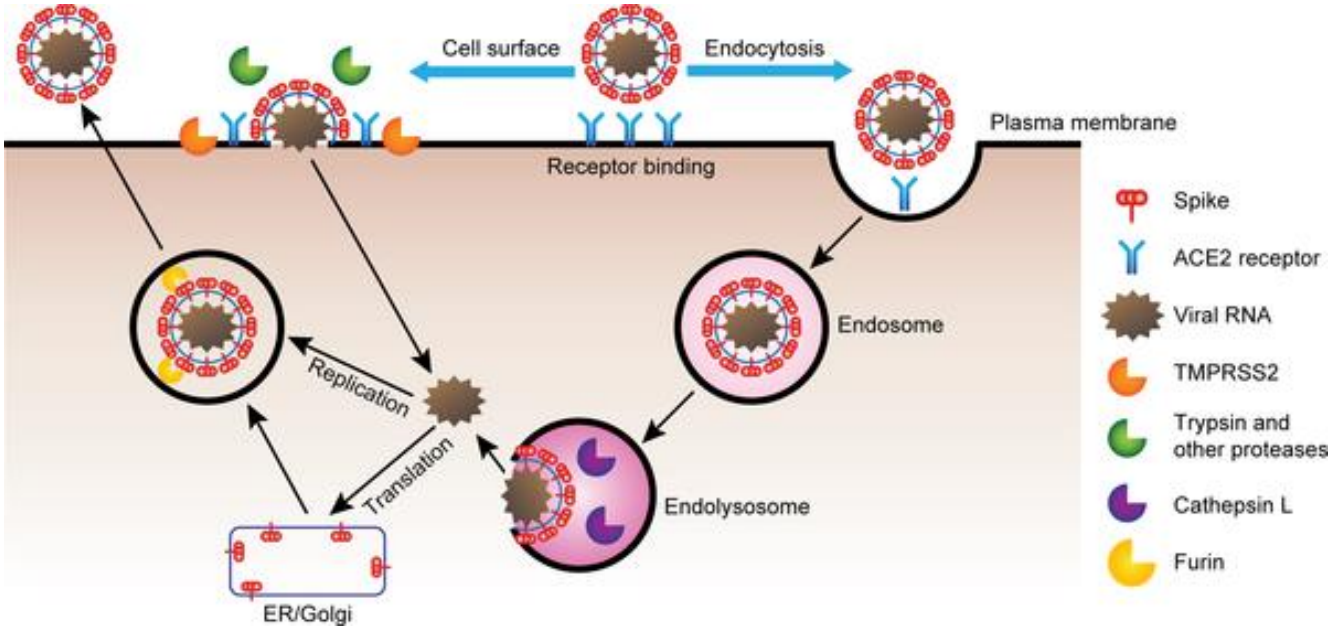




https://www.nature.com/articles/s41401-020-0485-4

Fig 1. SARS-CoV-2 entry mechanisms.



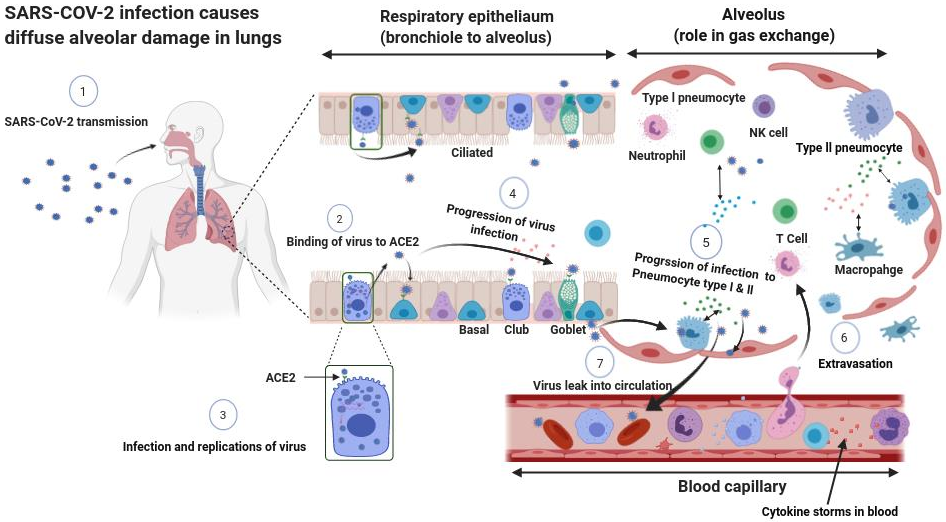
Murgolo N, Therien AG, Howell B, Klein D, Koeplinger K, et al. (2021) SARS-CoV-2 tropism, entry, replication, and propagation: Considerations for drug discovery and development. PLOS Pathogens 17(2): e1009225. https://doi.org/10.1371/journal.ppat.1009225
https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1009225

PLOS PATHOGENS

Viral coat spike protein binds to ACE2, and in some cases, perhaps NRP1, on responsive cells. Virus spike protein is either processed by TMPRSS2 and other serine proteases facilitating cell surface entry or endocytosed into endosomes where spike is processed by CTSL in the lysosome. Viral RNA released from TMPRSS2-mediated entry or endosome release is replicated as partial and complete genome copies and translated in the ER to form new SARS-CoV-2 virions. Processing of spike protein by furin occurs prior to release of new viruses into the extracellular environment. ACE2, angiotensin converting enzyme 2; CTSL, cathepsin L; ER, endoplasmic reticulum; NRP1, Neuropilin 1; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2. show less

COVID-19 Pathophysiology

1. SARS-CoV-2 enters the body and reaches lower respiratory tract
2. SARS-CoV-2 binds ACE2 on airway epithelial cells
3. Virus replicates and is released from airway epithelial cells
4. Virus reaches alveoli and types I & II pneumocytes
5. Neutrophil and macrophage driven innate immune response begin
6. Inflammatory cytokines recruit additional leukocytes to the site of infection, amplifying the inflammatory response
7. Virus leaks into circulation, significant system-wide release of cytokines



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Estimated COVID-19 Infections, Symptomatic Illnesses, and Hospitalizations—United States, Feb – Dec. 2020

- 1 in 1.9 (95% UI* 1.7 - 2.2) COVID-19 hospitalizations were reported
- 1 in 4.2 (95% UI* 3.7 – 4.7) COVID–19 symptomatic illnesses were reported
- 1 in 4.6 (95% UI* 4.0 – 5.4) total COVID–19 infections were reported

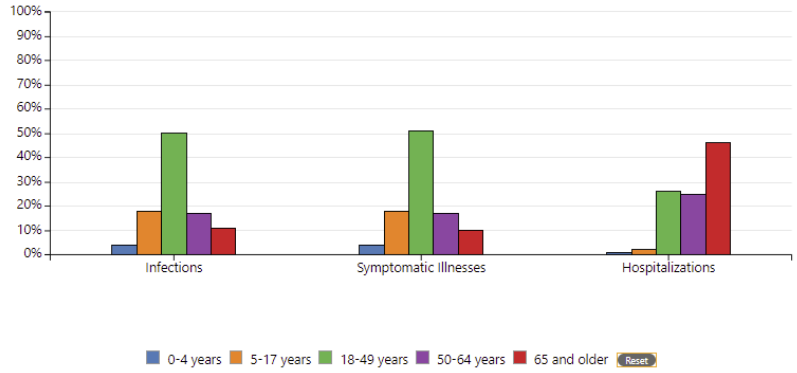
- *Using statistical model previously used for disease burden of influenza, accounting for multiple factors that lead to underreporting

These estimates suggest that during that period, there were approximately:

83.1 Million	70.4 Million	4.1 Million
Estimated Total Infections	Estimated Symptomatic Illnesses	Estimated Hospitalizations

Last Updated*: January 15, 2021

Percentage of COVID-19 infections, symptomatic illness, and hospitalizations by age group



https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html

Estimated SARS-CoV-2 Seroprevalence Among Persons Aged <18 Years — Mississippi, May–September 2020

- Retrospective seroprevalence study of a convenience sample of residual blood specimens of persons aged <18 years in Mississippi
  - 1,603 specimens tested for anti-SARS-CoV-2 antibodies
  - 175 (10.9%) tested positive for SARS-CoV-2 antibodies
  - Non-Hispanic Black and Hispanic young persons were 2.4 and 4.3 times, respectively, the rate among non-Hispanic White persons.
  - After adjustment for race/ethnicity, estimated seroprevalence increased from 2.5% in May to 16.3% in September
- Seroprevalence from banked samples was extrapolated to state population
  - Suggests 113,842 (16.3%) of 698,420 young persons in Mississippi might have been infected by the end of September 2020, similar to known rates in 18-49 years old group
  - During this time only 8,993 confirmed and probable cases of COVID-19
  - **Might be as much as 13x the number of cases in young populations**
    - Under tested, less symptomatic cases, shorter time period of symptoms/positivity by nucleic acid test

DETROIT MERCY DENTAL

Hobbs CV, Drobeniuc J, Kittle T, et al. Estimated SARS-CoV-2 Seroprevalence Among Persons Aged <18 Years — Mississippi, May–September 2020. MMWR Morb Mortal Wkly Rep 2021;70:312–315. DOI: http://dx.doi.org/10.15585/mmwr.mm7009a4

Long Term Complications

- **Post-acute sequelae of COVID-19 (PASC)**
  - Previous terms: Long COVID, Long COVID syndrome, COVID Long Haulers
- **The most commonly reported long-term symptoms include:**
  - Loss of taste and smell, Fatigue, Shortness of breath, Cough, Joint pain, Chest pain
- **Other reported long-term symptoms:**
  - Difficulty with thinking and concentration ("brain fog"), Depression, Muscle pain, Headache, Intermittent fever, heart palpitations
- **More serious long-term complications are less common but can affect different organ systems in the body including:**
  - Cardiovascular: inflammation of the heart muscle (myocarditis)
  - Respiratory: lung function abnormalities
  - Renal: acute kidney injury
  - Dermatologic: rash, hair loss
  - Neurological: smell and taste problems, sleep issues, difficulty with concentration, memory problems
  - Psychiatric: depression, anxiety, changes in mood
- Davis et al 2020 (medrxiv preprint): web survey of 3,762 patients with Long COVID/PASC, 56 countries
  - **78.9% were female**, 8.4% were hospitalized, **27% reported laboratory diagnosis of COVID-19**
  - **Nearly half (45.2%) could not work full time, six months later**
  - **Most frequent symptoms: fatigue (77.7%), post-exertional malaise (72.2%) , cognitive dysfunction (55.4%)**
  - Relapses most commonly triggered by exercise, mental activity, or stress

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https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects.html

https://www.medrxiv.org/content/10.1101/2020.12.24.20248802v2

Long Term Complications in Children

- Buonsenso et al 2021 (medrxiv preprint): **Preliminary Evidence on Long COVID in children**
  - Children <19 years-old with lab confirmed COVID-19 (129, mean age of 11)
    - Classified into asymptomatic vs. symptomatic for acute-phase illness
    - 3 children had Multi-system Inflammatory Syndrome (MIS-C), 2 had myocarditis
  - **53% of children were reported to have one or more symptoms 120 days or more after diagnosis**
    - Insomnia, respiratory symptoms (chest tightness and pain), nasal congestiona, tiredness, difficulty concentrating, muscle pain, headaches, palpitations
    - More prevalent in symptomatic acute COVID-19 cases, but still present in those with asymptomatic COVID-19 acute phase

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https://www.medrxiv.org/content/10.1101/2021.01.23.21250375v1

SARS-CoV-2 Infection of U.S. Pregnant Women

- January 22–June 7: 91,412 women of reproductive age (15–44 years) with known pregnancy status who had positive test results for SARS-CoV-2 (8,207 (9.0%) were pregnant)
  - Hospitalization: pregnant women (31.5%), nonpregnant (5.8%)
  - ICU Admissions: pregnant women (1.5%), nonpregnant (0.9%)
  - Mechanical Ventilation: pregnant women (0.5%), nonpregnant (0.3%)
  - Death rate: pregnant women (0.2%), nonpregnant (0.2%)

- Hispanic and non-Hispanic black pregnant women appear to be disproportionately affected by SARS-CoV-2 infection during pregnancy.

- Among reproductive-age women with SARS-CoV-2 infection, pregnancy was associated with hospitalization and increased risk for intensive care unit admission, and receipt of mechanical ventilation, but not with death.

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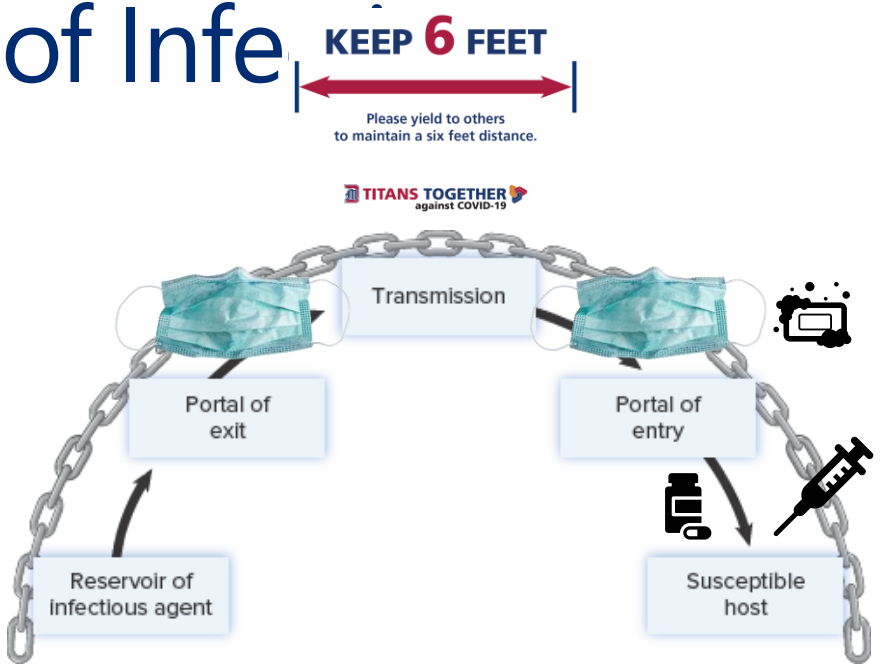
Morbidity and Mortality Weekly Report (MMWR), Weekly / June 26, 2020 / 69(25);769–775

https://www.cdc.gov/mmwr/volumes/69/wr/mm6925a1.htm?s_cid=mm6925a1_e&deliveryName=USCDC_921-DM31373

Breaking the Chain of Infe

- **SARS-CoV-2 can not live/replicate on its own.**
  - Rely on cellular machinery to grow and replicate
  - SARS-CoV-2 needs to infect new cells in the infected person or move on to another susceptible person
- **Chain of Infection:** If any link in this chain is broken, disease transmission is slowed or stopped
  - Avoidance of infection sources, masks, hygiene, immunity from a previous infection, antiviral drugs, vaccination
  - Uncontrolled: 1 person infected with SARS-CoV-2 will infect 2.5-5.7 people



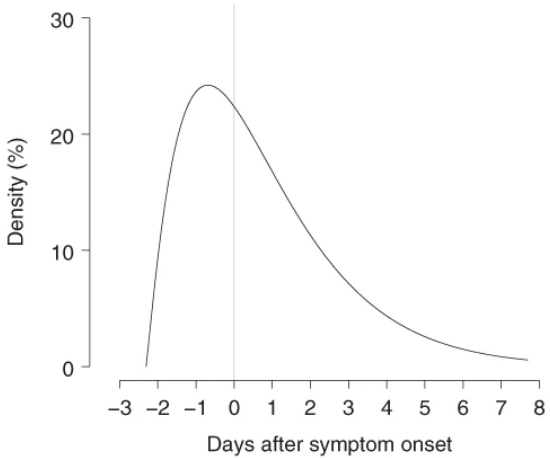
DETROIT MERCY DENTAL

Anderson et al. Nester's Microbiology. 9th ed. McGraw-Hill Higher Education (2019).

Stopping Transmission

- **Avoid infected people**
  - Problem: SARS-CoV-2 is frequently transmitted BEFORE symptoms appear
    - **Infectiousness starts 2.3 days before symptom onset and peaks at 0.7 days before symptom onset**
  - Makes isolation difficult
    - **Estimated that at least half of all transmission occurs during the pre-symptomatic phase**
    - SARS-CoV-1 was only contagious after symptoms appeared
  - **Infectiousness declines rapidly within 7 days**
    - Viral nucleic acid can be detected longer, but this is remnants of dead virus or abortive infections which are not contagious
    - Rationale for symptom-based criteria rather than requiring negative test to return to school or work
      - Criteria: At least 10 days have passed since symptom onset **and** at least 24 hours have passed since resolution of fever without the use of fever-reducing medications **and** other symptoms have improved.
  - Superspreaders:
    - 20% of cases may be responsible for 80% of transmission (Adam, 2020)

SARS-CoV-2 Inferred Infectiousness Profile



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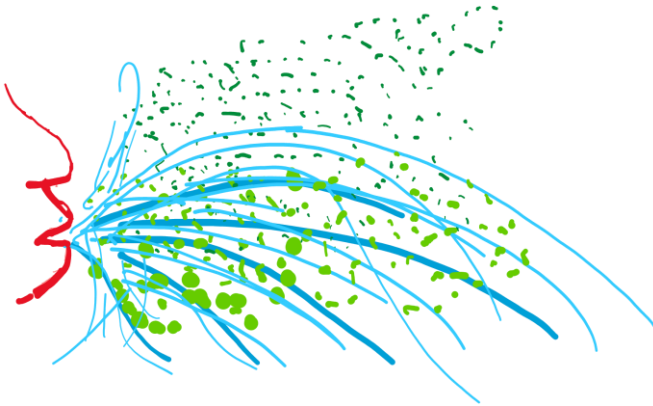
He, X., Lau, E. H., Wu, P., Deng, X., Wang, J., Hao, X., ... & Mo, X. (2020). Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nature medicine*, *26*(5), 672-675.

Lancet **395**, 1054–1062 (2020)

Ferretti et al 2020 – The timing of COVID-19 transmission. Preprint. doi: https://doi.org/10.1101/2020.09.04.20188516
https://www.medrxiv.org/content/10.1101/2020.09.04.20188516v2#:~:text=We%20found%20that%20it%20was,to%202%2D3%20days%20after.

Stopping Transmission

- **PRIMARY ROUTES OF TRANSMISSION: Close Contact and Droplets**
  - **Close contact = being within 6 feet of someone for 15 minutes in a 24-hour period**
  - **Aerosol transmission likely has a much lower infectious dose than surface transmission**
- Breathing, speech, sneezing, coughing and certain medical procedures can produce droplets or aerosols
  - Droplets are larger than aerosols, usually fall to the ground within 3-6 feet (1-2m)
    - Distancing: Large effect at 1m, double the effect at 2m
    - Coughing, sneezing, singing and shouting can project particles further
    - **Talking produces as many droplets as coughing**
    - **Talking loudly increases the number of droplets released and projects them further**



A sneeze captured on high-speed video. After a sneeze, large droplets of saliva and mucus (green) shoot out of the mouth, but fall relatively quickly. A turbulent cloud carries smaller droplets (red) and allows them to drift for up to 8 meters.
L. Bourouiba/The Fluid Dynamics of Disease Transmission Laboratory/MIT

Chu et al., (2020); Meselson (2020); Peters et al., (2020), Asadi et al. (2019)
https://www.cdc.gov/coronavirus/2019-ncov/php/public-health-recommendations.html
https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations

Stopping Transmission

- **Surface transmission = Minor/rare route of transmission**
  - According to the CDC, *"it may be possible that a person can get COVID-19 by touching a surface or object that has the virus on it and then touching their own mouth, nose, or possibly their eyes, but this isn't thought to be the main way the virus spreads."*
    - **Surface transmission likely requires a very high infectious dose.**
  - SARS-COV-2 is efficiently inactivated within 1 minute by 62-71% ethanol, 0.5% hydrogen peroxide, 0.1% sodium hypochlorite

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Stopping Transmission

- Early reports claimed SARS-CoV-2 could be detected hours to days later on copper, cardboard, plastic and stainless steel
  - One study used an amount of virus equivalent to 100 people coughing and sneezing in a concentrated area
- Other reports found SARS-CoV-2 weeks later on the Diamond Princess
- **Detectability does not equal viability**
- **Detectability does not necessarily mean there is enough virus to cause an infection.**
- Real-world studies that detect viral RNA in the environment report very low levels, and few have isolated viable virus

DETROIT MERCY DENTAL

Ann Intern Med. 2020 Sep 17 : M20-5008.

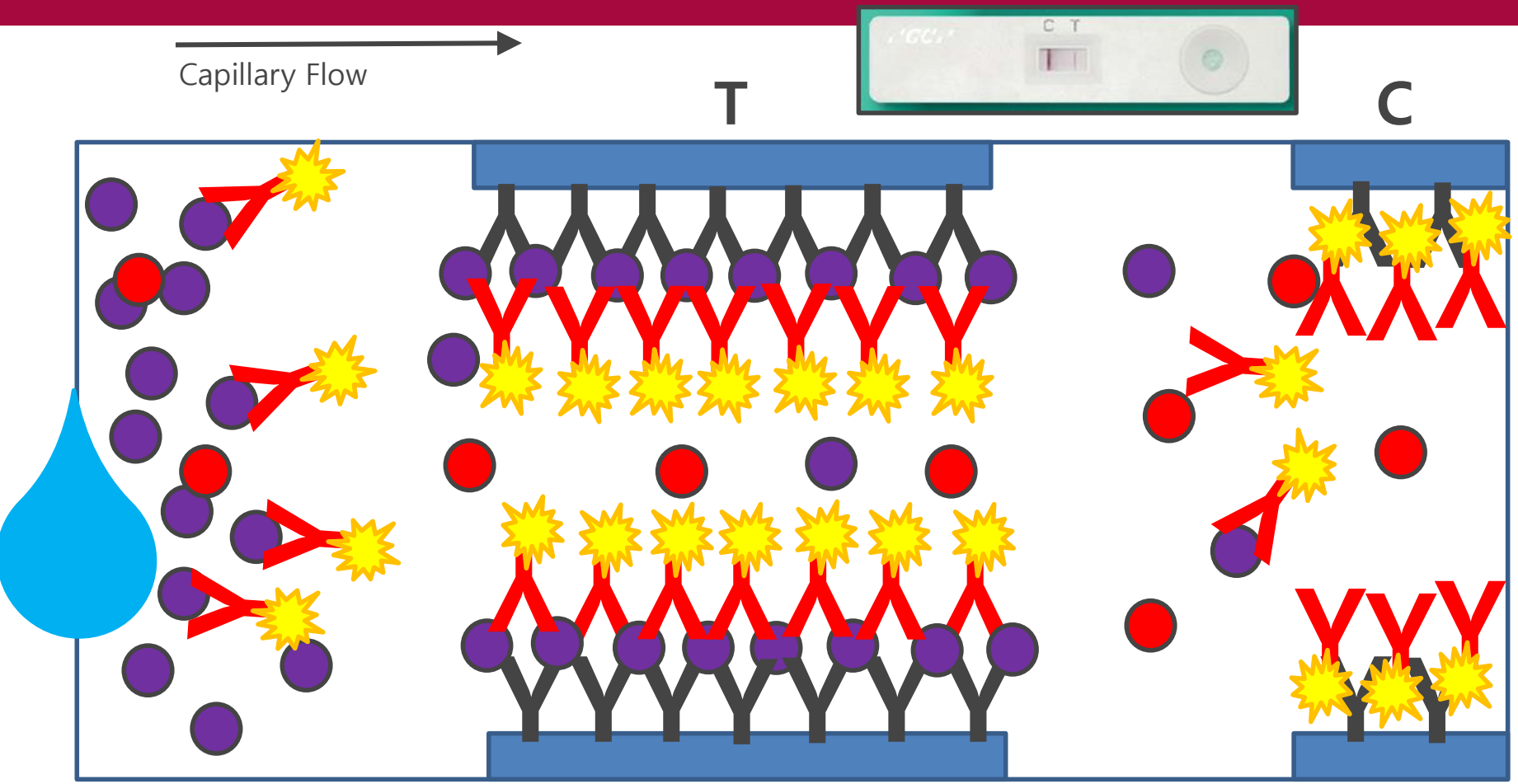
Stopping Transmission

- Identify and isolate infected individuals
- **COVID Testing:**
  - **Molecular testing:**
    - Detects SARS-CoV-2 RNA
    - Highly accurate
    - Takes longer to get results
  - **Antigen testing:**
    - Detects SARS-CoV-2 Protein, better indicator of infectious virus
    - Risk of false negatives, negative tests should be confirmed with PCR testing if a person has a known exposure
    - High confidence in positive tests
    - Rapid results
  - These tests must be taken at an appropriate time
  - **SARS-CoV-2 has a 5-day incubation period**
    - **<u>Testing in the first 4 days after exposure has a very high risk of giving false negatives</u>**
  - **Antibody tests identify previous infection or vaccination**
    - Cannot determine if someone currently has COVID-19

	MOLECULAR TEST	ANTIGEN TEST	ANTIBODY TEST
Also known as...	Diagnostic test, viral test, molecular test, nucleic acid amplification test (NAAT), RT-PCR test, LAMP test	Rapid diagnostic test (Some molecular tests are also rapid tests.)	Serological test, serology, blood test, serology test
How the sample is taken...	Nasal or throat swab (most tests) Saliva (a few tests)	Nasal or throat swab	Finger stick or blood draw
How long it takes to get results...	Same day (some locations) or up to a week	One hour or less	Same day (many locations) or 1-3 days
Is another test needed...	This test is typically highly accurate and usually does not need to be repeated.	Positive results are usually highly accurate but negative results may need to be confirmed with a molecular test.	Sometimes a second antibody test is needed for accurate results.
What it shows...	Diagnoses active coronavirus infection	Diagnoses active coronavirus infection	Shows if you've been infected by coronavirus in the past
What it can't do...	Show if you ever had COVID-19 or were infected with the coronavirus in the past	Definitively rule out active coronavirus infection. Antigen tests are more likely to miss an active coronavirus infection compared to molecular tests. Your health care provider may order a molecular test if your antigen test shows a negative result but you have symptoms of COVID-19.	Diagnose active coronavirus infection at the time of the test or show that you do not have COVID-19

DETROIT MERCY DENTAL

Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., ... & Xing, X. (2020). Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. *New England Journal of Medicine*.
Wiersinga et al., JAMA. 2020;324(8):782-793. doi:10.1001/jama.2020.12839


Capillary Flow
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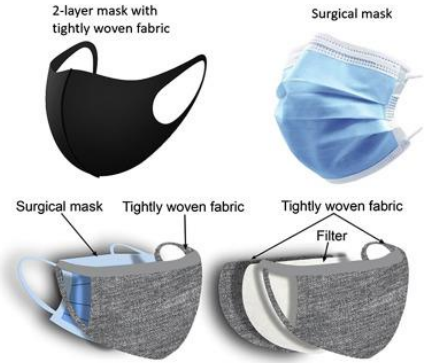
Stopping Transmission

- **Mask Usage**
  - Must cover mouth and nose to be effective
- N95 and KN95 masks offer the most protection
- Combinations in figure have an overall efficiency of >90% for particles of similar size to respiratory droplets
- Surgical masks 60%–70% effective at protecting others and 50% effective at protecting the wearer
- Mask mandate in Germany reduced transmission by 47% in 21 days
- USS Theodore Roosevelt and a retrospective study in Thailand showed 70% reduction in risk
- Masking on flights over 10 hours suggested reduced risk of in-flight transmissions based on absence of infections 14 days after travel
- In Missouri 2 symptomatically ill hair stylists interacted for an average of 15 minutes with each of 139 clients during an 8-day period
  - Both stylists and clients were masked
  - 0 of the 67 clients consented to an interview developed COVID-19



DETROIT MERCY DENTAL

Med DOI: (10.1016/j.medj.2020.12.008), https://www.cdc.gov/coronavirus/2019-ncov/more/masking-science-sars-cov2.html

Stopping Transmission

- Avoid high-risk settings (The Three C's)
  - **Closed spaces with poor ventilation**
    - Probability of getting COVID-19 is estimated to be 18.7 times higher in a closed environment than an open environment
  - **Crowded places**
  - **Close-contact**
    - Within 6 feet of someone for a total of 15 minutes in a 24-hour period
    - Direct physical contact, sharing utensils, etc.
- Friends and family members taking the same transportation, living with each other, being within 6 feet of each other, and eating together are far more likely to spread COVID-19 than brief contacts with non-family
- People who dined at a restaurant were twice as likely to develop COVID-19

DETROIT MERCY DENTAL

https://www.medrxiv.org/content/10.1101/2020.02.28.20029272v2.full.pdf, https://publichealth.sdsu.edu/covid-19/risky-situations/

Stopping Transmission

- **If 6ft. social distancing and mask utilization is enforced:**
  - Being in the same building as an infected person is not a risk factor for COVID-19
  - Being in a large, ventilated room with an infected person is not a risk factor for COVID-19

DETROIT MERCY DENTAL

Antivirals

- Antiviral drugs could reduce the severity of viral disease and lower viral load, leading to less spread
- **There are no available, effective antiviral drugs for COVID-19**
  - In well controlled clinical studies, neither hydroxychloroquine nor remdesivir have been shown to have any benefits at any phase of COVID-19 disease when compared to placebo
- Monoclonal antibody therapies recommended for the treatment of outpatients with mild to moderate COVID-19 who are at high risk of clinical progression as soon as possible after positive test result within 10 days
  - No deaths in treatment arm, 10 in placebo group
  - Hospitalization in 11/518 (2%) treatment arm participants and 36/517 (7%)
  - Require infusion outside of the home
- Oral nucleoside analogue drug, Molnupiravir, showing promise for early treatment
  - Incorporating this into growing RNA causes fatal flaws in sequence and shut down replication
  - Showed reduction in time to virus negativity
  - Phase 3 and Phase 2/3 studies are underway

DETROIT MERCY DENTAL

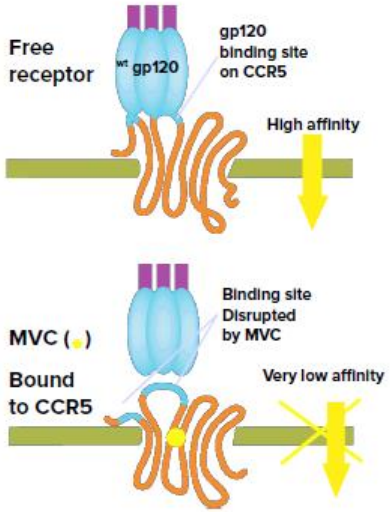
https://jamanetwork.com/journals/jama/fullarticle/2772921,
https://www.nejm.org/doi/full/10.1056/NEJMoa2007764

https://www.covid19treatmentguidelines.nih.gov/
https://www.merck.com/news/ridgeback-biotherapeutics-and-merck-announce-preliminary-findings-from-a-phase-2a-trial-of-investigational-covid-19-therapeutic-molnupiravir/

Antiviral Target: Attachment

Attachment: Interaction of a viral attachment protein with its cell surface receptor

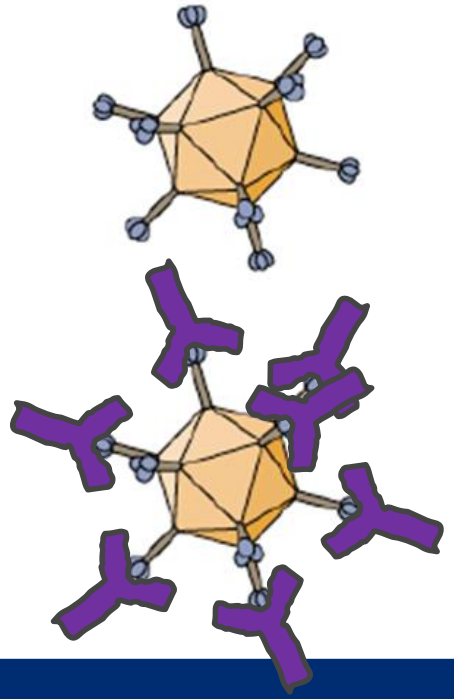
- **Neutralizing antibodies**: Bind and coat the virion
  - HBIG, VZIG, Rabies IG
  - Convalescent Serum
- **Receptor Antagonists:** peptide or sugar analogues of the cell receptor, compete for binding to viral attachment proteins
  - HIV: Maraviroc (Selzentry)
    - CCR5 antagonist – co-receptor for HIV
    - Maraviroc binds CCR5 and changes its conformation, now low binding affinity for gp120
  - Heparan and dextran sulfate (polysaccharides)
    - Suggested for use with HIV,HSV, and others

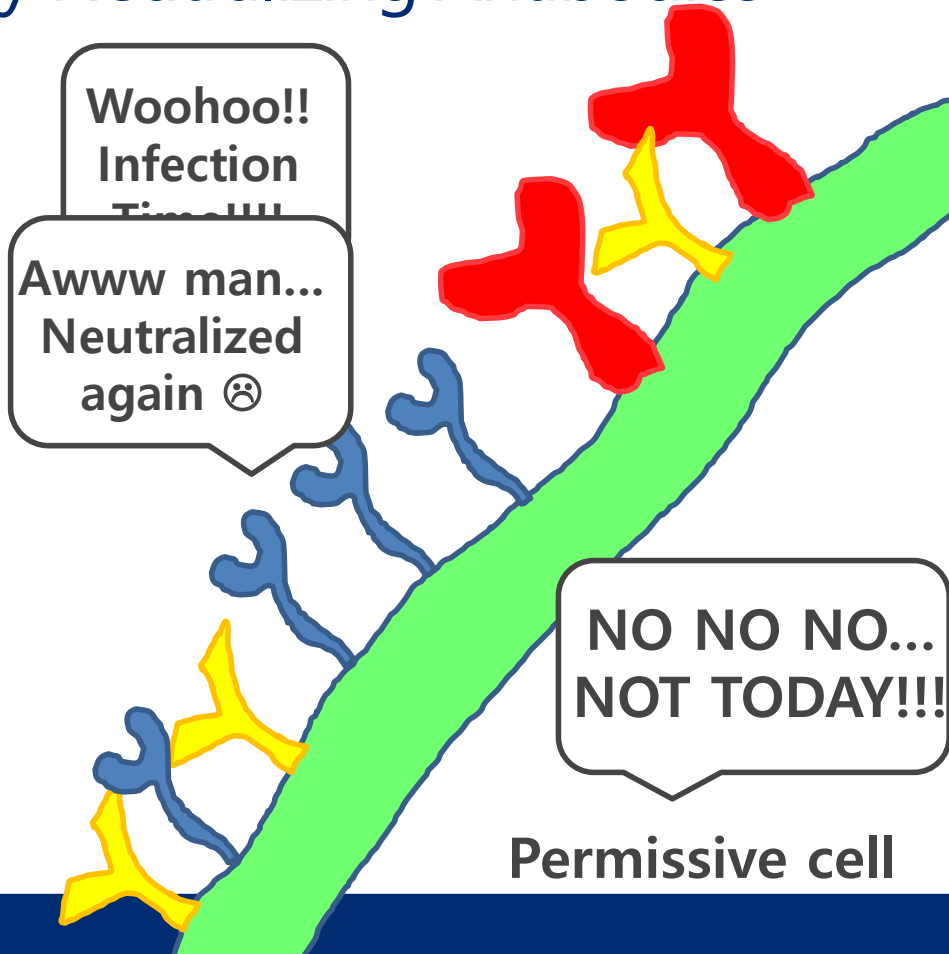


DETROIT MERCY DENTAL

Flint et al., Principles of Virology, 4th ed. ASM Press. (2015)

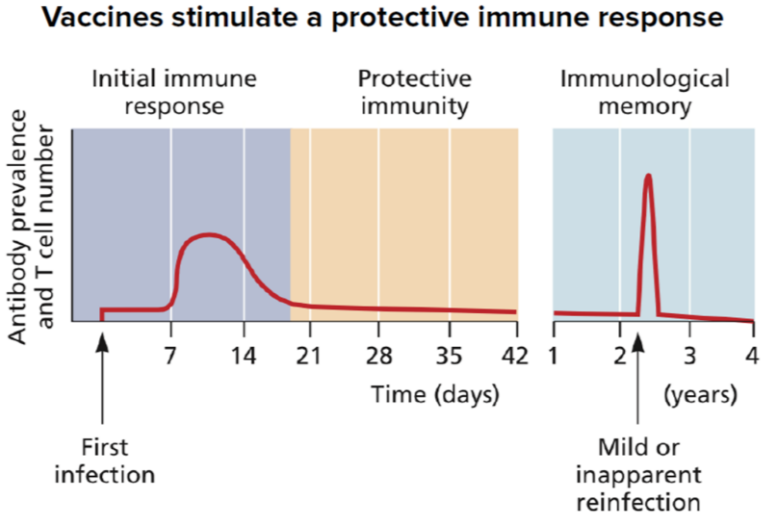
Inhibition of Viral Attachment by Neutralizing Antibodies





Vaccines are our best defense against SARS-CoV-2

- **Vaccination arms the immune system to prevent viral infections**
  - Neutralizing antibodies
  - Immune memory
  - T cell response
- **Why vaccinate?**
  - To prevent severe disease
    - Primary goal
  - To prevent infection entirely
    - Ultimate goal, not always possible
  - To prevent disease entirely
  - To protect those at most severe risk of disease (elderly, those with preexisting conditions, etc.) or exposure (health care workers, first responders)
  - Decrease sources for transmission (population immunity)



DETROIT MERCY DENTAL

Flint et al., Principles of Virology, 4th ed. ASM Press. (2015)

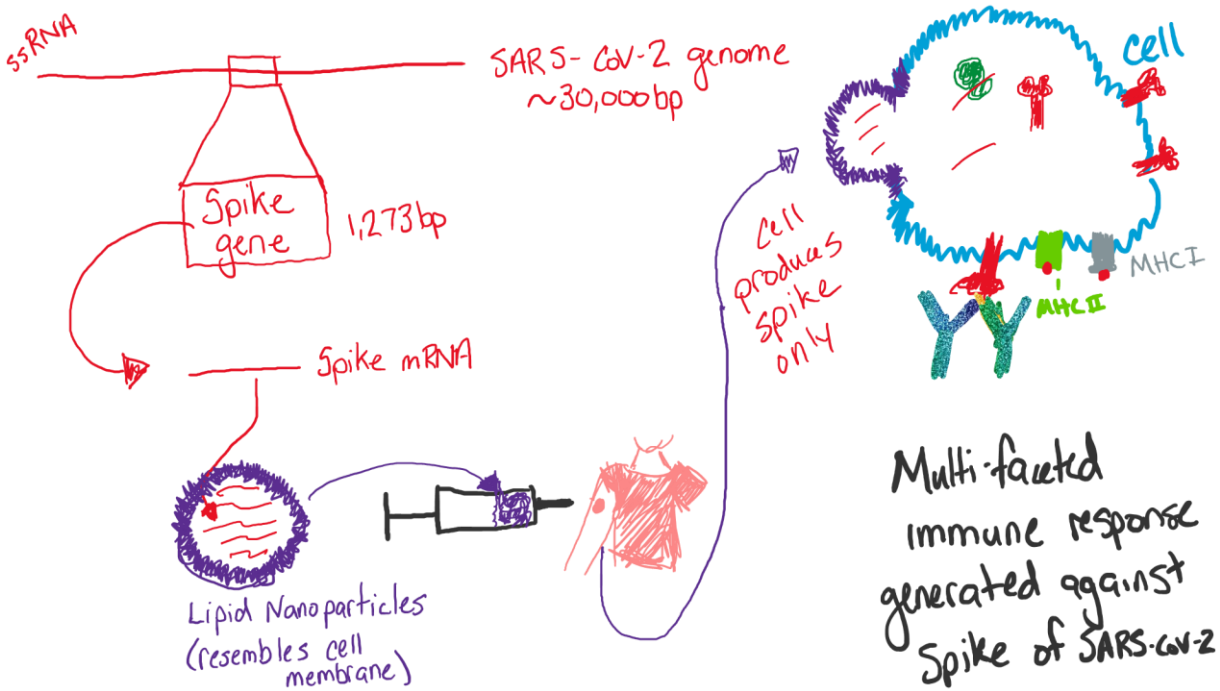
Pfizer & Moderna Vaccines

- **What are the differences between the two vaccines?**
  - Pfizer vaccine for ages 16+, given 21 days apart
  - Moderna vaccine for ages 18+ given 28 days apart
  - **Very similar mRNA platform**
    - Small differences in sequence optimization
    - Proprietary lipid nanoparticle delivery systems
  - **Moderna and Pfizer vaccines have nearly identical efficacy after 2 doses**
    - **Both around 95%**
  - Moderna vaccine may be more effective after first dose
    - Pfizer 52%, Moderna 80%
  - Moderna vaccine may have more side effects, particularly after the second dose
  - Pfizer vaccine more widely available in Michigan

DETROIT MERCY DENTAL

How do the mRNA Vaccines Work?

- Vaccine injected
- mRNA in lipid nanoparticles enter muscle cells
- Cellular ribosomes use mRNA sequence to make spike protein
- Spike protein embeds in cell membrane
- Immune system cells recognize viral protein and induce an immune reaction
- The body makes antibody producing B Cells and helper and killer T Cells
- Person is protected from disease or infection



Why were mRNA vaccines for SARS-CoV-2 available before other, more traditional types of vaccines?

- **Traditional protein-based vaccines:**
  - Require the growth of large amounts of infectious material before purification of antigens
  - Isolation and production of single proteins requires significant optimization
    - Will it grow properly in cells?
    - Will the protein fold properly?
    - Can the protein be purified easily?
    - Will the protein be modified by the cell?
    - Will the protein be stable?
  - Do not always stimulate robust immune responses
    - May need to add adjuvants to increase the immune response
  - Several are in the pipeline

- **mRNA vaccines:**
  - Have been extensively studied for 10+ years
  - Flexible platform, easy to optimize
  - Delivery mechanism in place, platform is ready for new targets
    - Moderna had completed Phase I trials for other vaccines using the mRNA technology
    - Flu, Zika, rabies, cytomegalovirus (CMV), MERS, RSV tested
- **mRNA vaccine production:**
  - Isolate RNA sequence
  - Produce plasmids to generate mRNA
  - Isolate mRNA
  - Package with lipid nanoparticles for delivery
  - Give to the person, body makes viral spike protein from mRNA, immune response begins

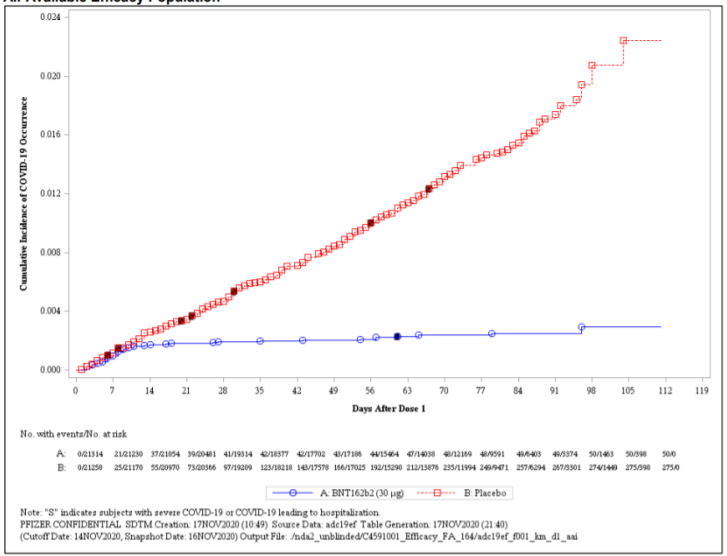
DETROIT MERCY DENTAL

https://www.virology.ws/2021/01/07/rna-in-a-nutshell/

Pfizer & Moderna Vaccines - Efficacy

Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)

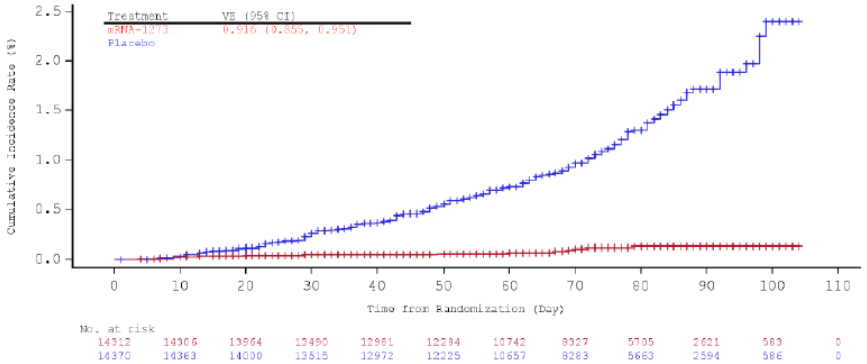
Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Dose 1 All-Available Efficacy Population



Note: "S" indicates subjects with severe COVID-19 or COVID-19 leading to hospitalization.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adc19ef Table Generation: 17NOV2020 (21:40)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: /nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_f001_km_dl_aai

Moderna COVID-19 Vaccine (mRNA-1273)

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Randomization, mITT Set



DETROIT MERCY DENTAL

COVID-19/SARS-CoV-2 Vaccine FAQs

- **Are the Pfizer and Moderna vaccines FDA approved?**
  - **The two available vaccines have not received FULL FDA approval**
  - **The two available vaccines ARE APPROVED for use under an emergency use authorization (EUA)**
- What is an EUA?
  - *"Under an EUA, in an emergency, the FDA makes a product available to the public based on the best available evidence, without waiting for all the evidence that would be needed for FDA approval or clearance."*
  - Substantial evidence vs. available evidence
- Example: Pfizer vaccine evaluated for EUA after 170 of >44,000 recipients of the vaccine of placebo were infected with SARS-CoV-2
  - Efficacy and incidence of adverse events evaluated
  - Approved because benefits were determined to significantly outweigh risks

DETROIT MERCY DENTAL

https://www.nejm.org/doi/full/10.1056/NEJMp2031373
https://www.fda.gov/vaccines-blood-biologics/vaccines/emergency-use-authorization-vaccines-explained

COVID-19/SARS-CoV-2 Vaccine FAQs

- **Both the Pfizer and Moderna vaccines underwent rigorous Phase 3 clinical trials with efficacy and safety testing**
- What happened under the EUA timeline vs standard approval timeline?
  - Fewer animal tests (time/lack of a good animal model)
  - IgM and IgG antibodies measured at 2 months following vaccination rather than 6 months or years following vaccination
  - 2-month vs. 6-month follow-up for adverse medical events

DETROIT MERCY DENTAL

https://www.nejm.org/doi/full/10.1056/NEJMp2031373
https://www.fda.gov/vaccines-blood-biologics/vaccines/emergency-use-authorization-vaccines-explained

COVID-19/SARS-CoV-2 Vaccine FAQs

- **mRNA platform allows quick turnaround**
- **Other factors:**
  - **Urgency**
    - Most vaccines in development are made for pathogens that are non-deadly, rare or slow to cause serious disease, not those causing global pandemics
  - **$$$**
    - $4.1 billion from CARES act alone
  - **Redirection of resources in academia and at pharmaceutical companies**
    - Rare to have a near singular focus on one disease
  - **Clinical trials:**
    - Many people eager to join
      - Rare to get 10's of thousands of people to sign up in weeks!
      - Usually takes several years to find enough volunteers
    - High infectivity of SARS-CoV-2 and high number of SARS-CoV-2 cases circulating made it easier to judge efficacy
      - Usually takes several years to have enough infections to generate statistically sound data

DETROIT MERCY DENTAL

Most commonly reported adverse events to VAERS after COVID-19 vaccines*

Pfizer-BioNTech COVID-19

Adverse event†	N (%)
Headache	2,322 (20.0)
Fatigue	1,801 (15.5)
Dizziness	1,659 (14.3)
Pyrexia	1,551 (13.4)
Chills	1,508 (13.0)
Nausea	1,482 (12.8)
Pain	1,464 (12.6)
SARS-CoV-2 Test Positive	1,002 (8.6)
Injection Site Pain	997 (8.6)
Pain in Extremity	923 (8.0)

Moderna COVID-19 vaccine

Adverse event†	N (%)
Headache	1,353 (23.4)
Pyrexia	1,093 (18.9)
Chills	1,056 (18.3)
Pain	945 (16.3)
Fatigue	888 (15.4)
Nausea	884 (15.3)
Dizziness	792 (13.7)
Injection Site Pain	671 (11.6)
Pain in Extremity	576 (10.0)
Dyspnoea	487 (8.4)

- No empirical Bayesian data mining alerts (EB05 ≥2) detected for any adverse event-COVID-19 vaccine pairs (most recent [Feb 18, 2021] weekly results)

12

* Reports received and processed through Feb 16, 2021; †Adverse events are not mutually exclusive

v-safe after vaccination health checker

	Pfizer-BioNTech	Moderna	Total
People receiving 1 or more doses in the United States*	28,374,410	26,738,383	55,220,364
Registrants completing at least 1 v-safe health check-in†	1,776,960	2,121,022	3,897,982
Pregnancies reported to v-safe	16,039	14,455	30,494

* COVID Data Tracker as of Feb 16, 2021 (107,571 doses with manufacturer not identified)

† V-safe data as of Feb 16, 2021, 5 am ET

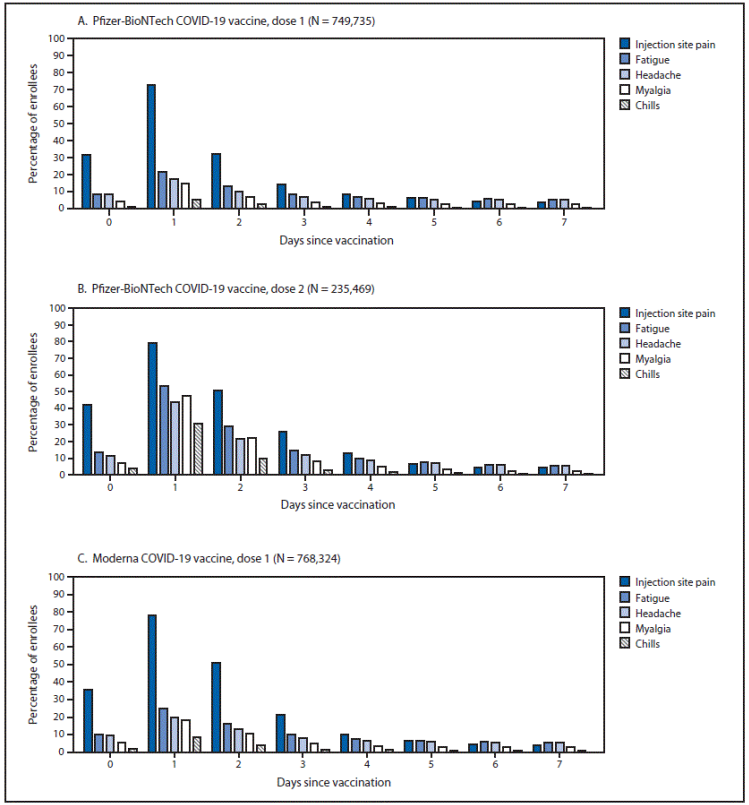


FIGURE. Percentage of enrollees who reported common local and systemic reactions by day after receipt of the first dose of Pfizer BioNTech COVID-19 vaccine (A), second dose of Pfizer BioNTech COVID-19 vaccine (B), and first dose of Moderna COVID-19 vaccine (C) — v-safe, United States, December 14, 2020–January 13, 2021

https://www.fda.gov/media/146269/download

Gee J, Marquez P, Su J, et al. First Month of COVID-19 Vaccine Safety Monitoring — United States, December 14, 2020–January 13, 2021. MMWR Morb Mortal Wkly Rep 2021;70:283–288. DOI: http://dx.doi.org/10.15585/mmwr.mm7008e3

Vaccine Safety in Pregnancy

- Adverse events in pregnant women following COVID-19 vaccine reported to VAERS* (N=154)
  - Miscarriage was most frequent pregnancy-specific adverse event to VAERS, but the number was not concerning considering expected background rate
  - VAERS is not designed to assess causality, but can rapidly detect safety signals

Characteristic	
Maternal age in years, median (range)	33 (16–51)
Gestational age in weeks at time of vaccination when reported, median (range)	13 (2–38)
Trimester of pregnancy at time of vaccination	**n (%)**
First (0-13 weeks)	60/118 (51)
Second (14-27 weeks)	36/118 (31)
Third (28+ weeks)	22/118 (19)
Vaccine	
Pfizer-BioNTech	97 (63)
Moderna	56 (36)
Unreported	1 (0.6)

Adverse events	N (%)
Pregnancy/neonatal specific conditions	**42 (27)**
Spontaneous abortion/miscarriage†	29
Premature rupture of membranes	3
Fetal hydrops	2
Neonatal death in 22-week preterm birth	1
Premature delivery	1
Gestational diabetes	1
Vaginal bleeding	1
Stillbirth	1
Shortened cervix	1
Leakage amniotic fluid	1
Calcified placenta	1
Non-pregnancy specific adverse events (top 10) Headache (31), fatigue (29), chills (21), pain in extremity (17), nausea (15), dizziness (14), pain (14), pyrexia (13), injection site pain (13), injection site erythema (10)	**112 (73)**

† The frequency of clinically recognized early pregnancy loss for women aged 20–30 years is 9–17%, and this rate increases sharply from 20% at age 35 years to 40% at age 40 years and 80% at age 45 years. Reference: ACOG Practice Bulletin No. 200: Early Pregnancy Loss. Obstet Gynecol. 2018132(5):e197-e207.

https://www.fda.gov/media/146269/download

“I’m worried, frankly,” said Francis Collins, director of the National Institutes of Health. “There are stories out there on the Internet about how vaccination can lead to infertility. There’s absolutely nothing to that. But when we look at people who are expressing hesitancy, in many instances those are women of childbearing age.”

https://www.washingtonpost.com/health/2021/02/22/women-vaccine-infertility-disinformation/

COVID-19/SARS-CoV-2 Vaccine FAQs

- **Are there any issues with the vaccine and fertility?**
  - A former Pfizer scientist (left 9 years ago) who argues against vaccines (and claimed the pandemic was over in the UK in November) claims the spike protein resembles a protein involved in placental development and could lead to infertility
    - **<u>If this were true, any person naturally infected would have fertility issues too. No data to support this.</u>**
    - There are only four amino acids that are similar, spike is 1,273 amino acids
      - Antibodies recognize regions that are larger than this
  - Dr. Langel
    - *"Coronavirus spike and the placental protein in question have almost nothing in common, making the vaccine highly unlikely to trigger a reaction to these delicate tissues. The two proteins share only a minuscule stretch of material; mixing them up would be akin to mistaking a rhinoceros for a jaguar because they are wearing the same collar."*
  - SARS-CoV-2 infection can cause systemic inflammation and affect organs including those in the urogenital tract
    - Case studies indicate that COVID-19 can lead to sexual dysfunction, erectile dysfunction and anorgasmia in men

DETROIT MERCY DENTAL

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7545238/ https://www.nytimes.com/2020/12/10/technology/pfizer-vaccine-infertility-disinformation.html

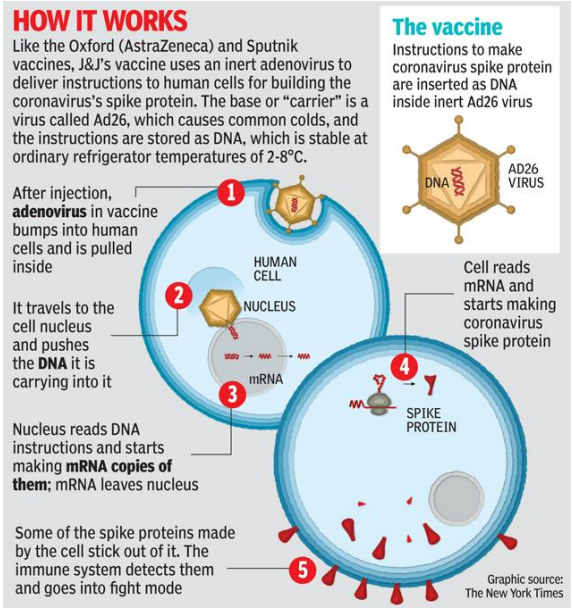
COVID-19/SARS-CoV-2 Vaccine FAQs

- **Are there any issues with the vaccine and fertility?**
  - Moderna FDA Briefing Document:
    - Study participants of childbearing potential were screened for pregnancy prior to each vaccination, with a positive test resulting in exclusion or discontinuation from study vaccination.
    - **The study is collecting outcomes for all reported pregnancies that occur after vaccination, or before vaccination and not detected by pre-vaccination screening tests.**
    - **Thirteen pregnancies were reported through December 2, 2020 (6 vaccine, 7 placebo).**
    - A combined developmental and perinatal/postnatal reproductive toxicity study of mRNA-1273 in rats was submitted to FDA on December 4, 2020. FDA review of this study concluded that mRNA1273 given prior to mating and during gestation periods at dose of 100 µg did not have any adverse effects on female reproduction, fetal/embryonal development, or postnatal developmental except for skeletal variations which are common and typically resolve postnatally without intervention.
  - Pfizer FDA Briefing Document:
    - At the time of the data cutoff in Study C4591001 (14 November 2020), a total of 23 participants had reported pregnancies in the safety database, including 9 participants who withdrew from the study due to pregnancies. These participants continue to be followed for pregnancy outcomes.

DETROIT MERCY DENTAL

Viral Vector Vaccines: Janssen COVID-19 Vaccine

- **Janssen COVID-19 (Johnson and Johnson) Vaccine**
  - 1 dose, does not need ultracold storage
  - Adenovirus vector
    - Adenoviruses can cause common colds and other mild disease
      - Vector modified so it gets into the cell, releases its content, but can't replicate and cause an infection
    - SARS-CoV-2 spike protein genome is reverse engineered from RNA to DNA and is inserted into the adenovirus vector
    - Virus vector delivers spike protein DNA to the cell nucleus
    - Cell transcribes spike DNA to spike mRNA
    - Ribosomes translate spike mRNA to protein
    - Immune response begins



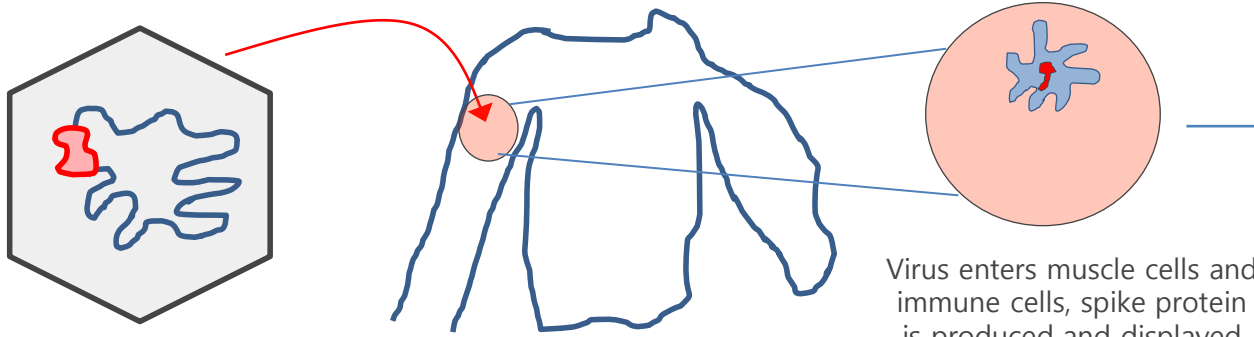
DETROIT MERCY DENTAL

Viral Vector Vaccines: Janssen COVID-19 Vaccine

Modified virus (Adenovirus type 26, Ad26) that delivers a gene from the target pathogen into our own cells to generate an immune response.

Developed by the Janssen Pharmaceutical Companies of Johnson & Johnson

Replication of vector virus (Ad26) in insect cells



Virus genome contains SARS-CoV-2 spike gene to produce stabilized conformation of spike protein

Virus enters muscle cells and immune cells, spike protein is produced and displayed to immune system

Virus replication does not occur

DETROIT MERCY DENTAL

Janssen COVID-19 Vaccine Trial

- Single-dose (0.5 mL) COVID-19 vaccine for use in individuals 18 years of age and older
  - Received FDA Emergency Use Authorization on February 27, 2021
  - The vaccine is estimated to remain stable for two years at -4°F (-20°C), and a maximum of three months at routine refrigeration at temperatures of 36-46°F (2 to 8°C)
- **Phase 3 ENSEMBLE:** randomized, double-blind, placebo-controlled clinical trial
  - **43,783 individuals (21,895 received vaccine)**
    - United States (n=19,302), Brazil (n=7,278), South Africa (n=6,576), Colombia (n=4,248), Argentina (n=2,996), Peru (n=1,771), Chile (n=1,133), Mexico (n=479)
  - Primary Endpoints: preventing **Moderate to Severe/Critical COVID-19**
    - **66.9% effective** across all regions studied after 14 days
    - **66.1% effective** across all regions studied after 28 days
  - Secondary Endpoints: preventing **Severe/Critical COVID-19**
    - **76.7% effective** across all regions studied after 14 days
    - **85.4% effective** across all regions studied after 28 days
  - As of January 22, 2021, there were no COVID-19-related deaths in vaccine group, compared to 5 in placebo group
  - Will be followed for safety and efficacy for up to 24 months

Table 8: Summary of Vaccine Efficacy against Moderate to Severe/Critical and Severe/Critical COVID-19 for Countries With >100 Reported Moderate to Severe/Critical Cases

		Severity	
	Onset	Moderate to Severe/Critical Point estimate (95% CI)	Severe/Critical Point estimate (95% CI)
US	at least **14 days** after vaccination	74.4% (65.0; 81.6)	78.0% (33.1; 94.6)
	at least **28 days** after vaccination	72.0% (58.2;81.7)	85.9% (-9.4; 99.7)
Brazil	at least **14 days** after vaccination	66.2% (51.0; 77.1)	81.9% (17.0; 98.1)
	at least **28 days** after vaccination	68.1% (48.8; 80.7)	87.6% (7.8; 99.7)
South Africa	at least **14 days** after vaccination	52.0% (30.3; 67.4)	73.1% (40.0; 89.4)
	at least **28 days** after vaccination	64.0% (41.2; 78.7)	81.7% (46.2; 95.4)

DETROIT MERCY DENTAL

https://www.jnj.com/johnson-johnson-covid-19-vaccine-authorized-by-u-s-fda-for-emergency-usefirst-single-shot-vaccine-in-fight-against-global-pandemic
https://www.fda.gov/media/146304/download

Janssen COVID-19 Vaccine: Safety

- **Local solicited adverse reactions** with 7 days:
  - Injection site pain (48.6%)
- **Systemic adverse reactions** with 7 days:
  - Headache (38.9%)
  - Fatigue (38.2%)
  - Myalgia (33.2%)
  - Nausea (14.2%)
  - One case of anaphylaxis
- **Unsolicited Adverse Events** (AEs) for 28 days
  - Janssen COVID-19 Vaccine group (13.1%), placebo group (12.0%).
- **Serious Adverse Events** (SAEs) for 8 weeks:
  - Janssen COVID-19 Vaccine group (0.4%), placebo group (0.4%)

- **Additional AEs of interest:**
  - Urticaria, non-serious, 5 Vaccine, 1 Placebo
  - Angioedema of the lips in 1 vaccinated 4 days after vaccine, likely related
  - One SAE of severe pain in injected arm ongoing for 74 days
  - One SAE, severe, generalized weakness, fever, and headache, resolution three days later
- **Vaccine components:**
  - 5×10^{10} virus particles (replication incompetent)
  - citric acid monohydrate (0.14 mg), trisodium citrate dihydrate (2.02 mg), ethanol (2.04 mg), 2-hydroxypropyl-β-cyclodextrin (HBCD) (25.50 mg), polysorbate-80 (0.16 mg), sodium chloride (2.19 mg)
  - Each dose may also contain residual amounts of host cell proteins (≤0.15 mcg) and/or host cell DNA (≤3 ng)
  - Does not contain a preservative

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https://www.fda.gov/media/146304/download

Virus Vector Vaccine: Astrazenca/Oxford

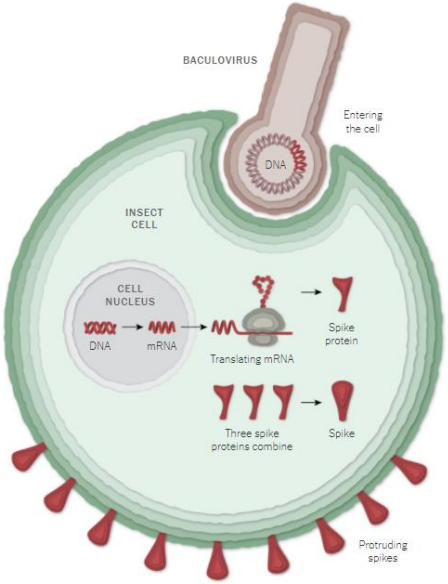
- ***March 25, 2021 Press Release***
  - ***76% vaccine efficacy against symptomatic COVID-19***
  - ***100% efficacy against severe or critical disease and hospitalisation***
  - ***85% efficacy against symptomatic COVID-19 in participants aged 65 years and over***

DETROIT MERCY DENTAL

https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2021/azd1222-us-phase-iii-primary-analysis-confirms-safety-and-efficacy.html

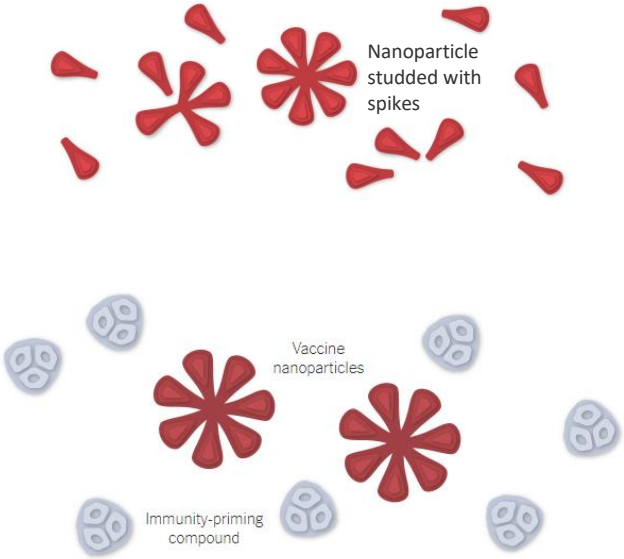
How does the Novavax COVID-19 Vaccine work?

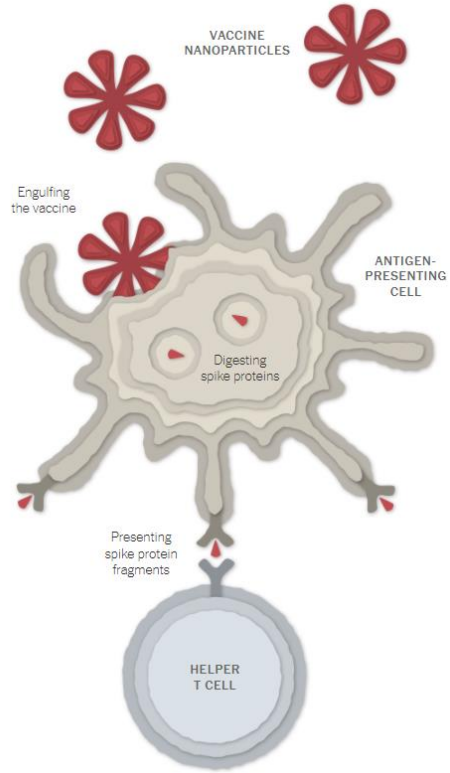
Growing Spike Proteins



A similar method of growing and harvesting virus proteins is already used to make licensed vaccines for diseases including influenza and HPV.

Building Nanoparticles





COVID-19/SARS-CoV-2 Vaccine FAQs

- **Could the Pfizer, Moderna, or J&J vaccines cause a SARS-CoV-2 infection leading to COVID-19?**
  - **NO!**
  - mRNA vaccine and virus vector vaccines only contains the genetic material to make the spike protein of SARS-CoV-2
    - Spike protein allows the virus to get into cells
    - Neutralizing antibodies target this protein and prevent infection
  - SARS-CoV-2 has 29 proteins
    - Need all of these proteins, plus full genetic sequence to establish an infection

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https://cen.acs.org/biological-chemistry/infectious-disease/know-novel-coronaviruss-29-proteins/98/web/2020/04

COVID-19/SARS-CoV-2 Vaccine FAQs

- **If the vaccine can't infection with the virus, why do so many people feel fatigued, have headaches, etc. after being vaccinated?**
  - **<u>An immune reaction is occurring!</u>**
    - The immune response makes the body hostile to pathogens and activates cells of the immune system causing them to grow or change behavior. This process is energy intensive and damaging.
  - When you are sick, you feel the effects of damage caused by the pathogen and the effects of immune system activation.
  - When you are vaccinated, you are feeling the effects of immune activation.
    - **Symptoms of immune activation:**
      - Inflammatory response
        - Pain at the injection site
      - Cytokine and interferon production
        - Fever, aches and pain, malaise
      - The immune response makes the body hostile to the pathogen, but is energy intensive and damaging
        - Fatigue

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Which Vaccine Should I Get?

Monica Gandhi MD, MPH
@MonicaGandhi9

	Company	Platform	Doses	Non-clinical results	# with vaccine (same placebo)	Protection from COVID-19 hospitalization	Protection from COVID severe dz (some at home)	Efficacy against milder COVID
US	moderna	mRNA-1273 mRNA in lipid nanoparticle	2	Neutralizing Abs; Strong Th1 CD4+ protection from challenge (macaques)	~15,000	97% (1 in vaccine arm after 2nd dose hospitalized)	97% (30 cases in placebo arm; 0 in vaccine reported but 1 severe per FDA)	94.1%
US	Pfizer	BNT162b2 mRNA in lipid nanoparticle	2	Neutralizing Abs; Strong Th1 CD4+, CD8+; protection from challenge (macaques)	~18,600	100%	100% (9 cases in placebo arm; 0 in vaccine- 1 initially severe but not)	95%
US	Johnson & Johnson	JNJ-78436725 Non-replicating human adenovirus/DNA	1	Neutralizing Abs; Strong Th1 CD4+ > Th2; CD8+; challenge protection (macaque)	~22,000 US, Latin America, S. Africa	100%	85.4% across 3 sites (7 deaths, 16 hospitalizations, all in placebo arm)	72% US; 61% Latin America; 64% S. Africa (95% B1.351)
US: not completed	AstraZeneca	AZD 1222 Non-replicating Chimp Adenovirus-DNA	2	Neutralizing Abs; Strong Th1 CD4+ > Th2; CD8+; protection from challenge (macaques)	~28,588 (UK, SA, US/Peru/ Chili)	100%	100% (UK, 15 placebo arm hospitalized, 0 in vaccine; US, 8 severe in placebo, 0 vaccine)	76% US (85% in >65 yrs); 70% UK; S. Africa halted for mild
	NOVAVAX Creating Tomorrow's Vaccines Today	NVX-CoV2373 Spike protein/RBD + Matrix M adjuvant	2	Neutralizing Abs; Strong Th1 CD4 > Th2; macaque challenge protection	~8833 (Phase 3 UK; 2b SA)	100%	100% (10 severe in placebo in UK/SA; 0 in vaccine)	96.4% UK; 89% B117 UK; 55% SA (94% B1351)

Which Vaccine Should I Get?

- Difficult to make direct comparisons as each vaccine was tested individually against placebo, not against each other
- Notes:
  - Timing: more variants had emerged by the time the J&J vaccine had reached clinical trials
  - J&J had used a lower threshold for the definition of severe disease

- **BOTTOM LINE:**
  - **All 3 vaccines are very effective in preventing mild disease**
  - **All 3 vaccines significantly reduce the chance of developing severe illness**
  - **All 3 vaccines offer complete protection against hospitalization and death**

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Which Vaccine Should I Get?

THE BEST COVID-19 VACCINE IS THE ONE YOU CAN GET, AS SOON AS YOU CAN GET IT!

https://tenor.com/view/hamilton-gif-9021862

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Will vaccines prevent asymptomatic infection?

Studies to date that showed COVID-19 vaccines reduce asymptomatic infection (transmission)		
Setting	Finding of xx% reduction in asymptomatic or infections including asymptomatic	Reference
Healthcare workers in England	**86%**	Hall SSRN, **February 22, 2021**
Healthcare workers in Israel	**75%**	Amit, Lancet, **March 6, 2021**
Patients in Mayo Clinic health system	**88.7%**	Pawlowski medRxiv, **February 27, 2021**
Israel Ministry of Health (nationwide) Israel general population (Pfizer)	**94%** **90%**	**Pfizer press release, March 11, 2021** Dagan NEJM, **February 24, 2021**
Pre-surgical patients in Mayo Clinic system swabbed asymptomatically	**80%**	Tande Clin Inf Dis, **March 10, 2021**
Healthcare workers in Cambridge University Hospitals	**75%**	Weekes Authorea, **February 24, 2021**
Nasal viral load values are most important determinant of transmissibility (Lancet study); Nasal viral loads from post-vaccination exposures are low and likely noninfectious per CT values (use rapid antigen tests after vaccination if want to test symptomatic)		

Monica Gandhi MD, MPH
@MonicaGandhi9

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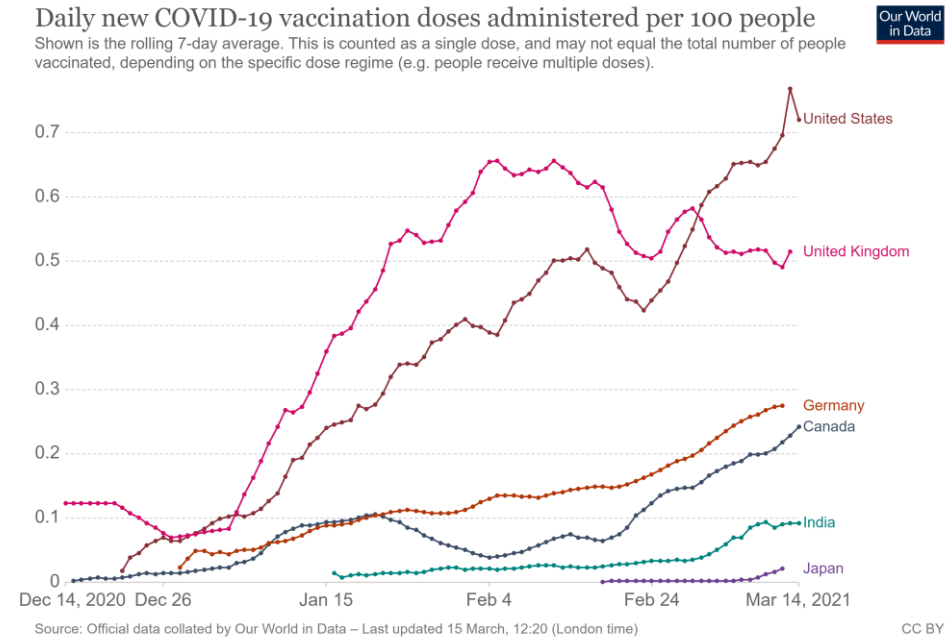
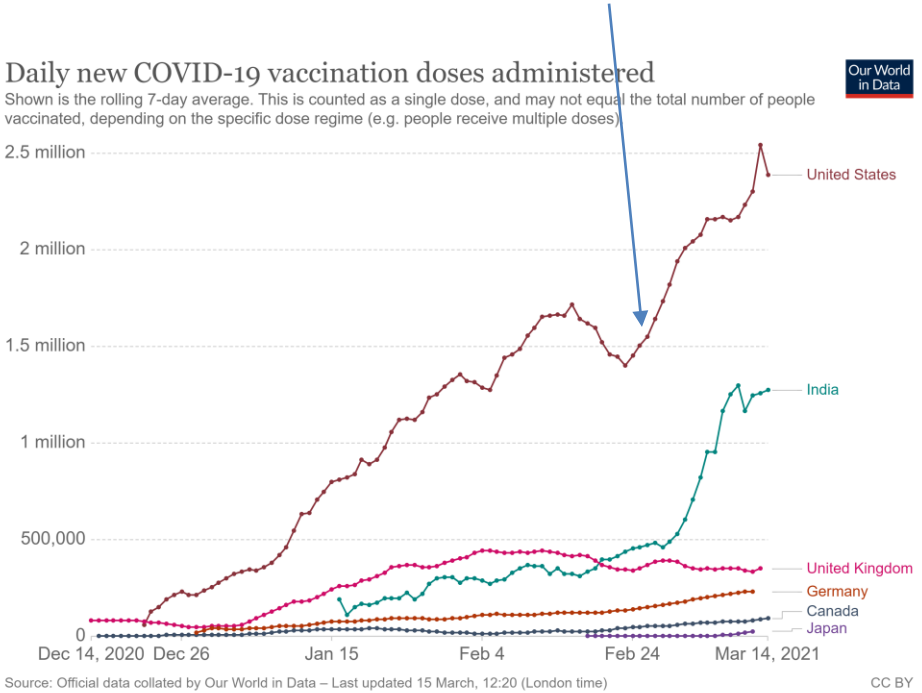
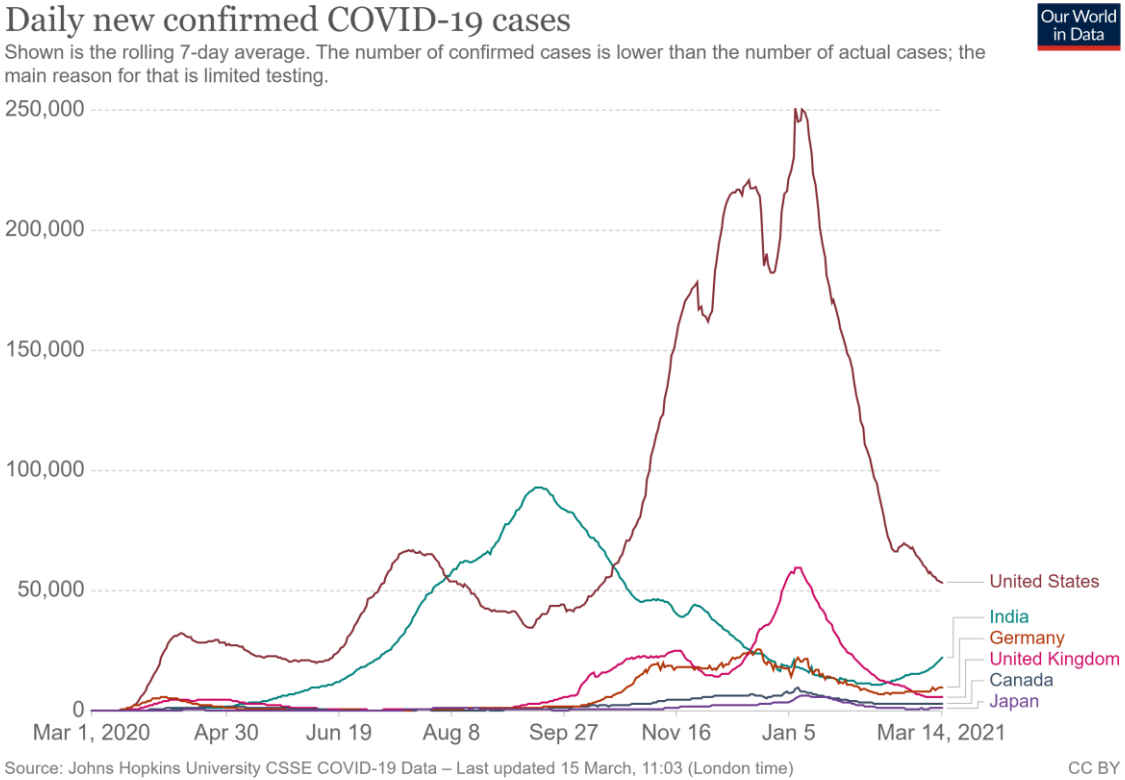
Vaccination Rollout

Janssen J&J Vaccine: EUA Feb. 27





https://ourworldindata.org/covid-overview



https://ourworldindata.org/covid-overview

How are the vaccines performing in the real world?

- **Evaluation of the Pfizer/BioNTech mRNA vaccine in Israel**
  - 1:1 match of vaccinated vs. unvaccinated from Dec. 20, 2020 to Feb. 1, 2021, each with 596,618 persons
  - Study Outcomes: vaccine effectiveness at interval (A) days 14-20 after first dose and (B) ≥7 days after dose 2
    - SARS-CoV-2 infection without documented symptoms: (A) 46% and (B) 92%
    - Symptomatic COVID-19: (A) 57% and (B) 94%
    - Hospitalization: (A) 74% and (B) 87%
    - Severe COVID-19: (A) 62% and (B) 92%

- Levine-Tiefenbrun et al 2021 (medrxiv preprint)
  - Analyzed SARS-CoV-2 positive RT-qPCR tests in patients 12-28 days following first dose
  - Found 4-fold reduction in viral genome copies in vaccinated individuals
  - Might indicate reduced viral replication and potential for transmission

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Dagan, N., Barda, N., Kepten, E., Miron, O., Perchik, S., Katz, M. A., ... & Balicer, R. D. (2021). BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *New England Journal of Medicine*. DOI: 10.1056/NEJMoa2101765

Levine-Tiefenbrun, M., Yelin, I., Katz, R., Herzel, E., Golan, Z., Schreiber, L., ... & Kishony, R. (2021). Decreased SARS-CoV-2 viral load following vaccination. *medRxiv*.

Vaccines and Long-COVID

- Improvement in symptoms of “long haulers” after vaccination
  - Anecdotal and experimental evidence showing reduction in symptoms of post-acute sequelae of COVID-19 (PASC) or Long-COVID
  - Poll of a 400 members of Facebook group of Long-haulers
    - 36% reported improvement of symptoms (mild to complete resolution) after vaccination
    - Dr. Daniel Griffin, an infectious disease physician at Columbia University, said about 40 percent of the long Covid patients he’s been treating cite symptom improvement after the vaccine. “They notice, ‘Hey, over the days, I’m feeling better. The fatigue isn’t so bad, maybe smell is coming back,’” Dr. Griffin said. (NY Times)
    - Arnold et al 2021 (preprint): Vaccine recipients in this British study showed increase in symptom resolution compared to unvaccinated matched recipients

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https://www.nytimes.com/2021/03/17/health/coronavirus-patients-and-vaccine-effects.html

Arnold, D. T., Milne, A., Stadon, L., Maskell, N. A., & Hamilton, F. W. (2021). Are vaccines safe in patients with Long COVID? A prospective observational study. *medRxiv*.

Variants

- **B.1.1.7 variant** (23 mutations with 17 amino acid changes) was first described in the United Kingdom on December 14, 2020
  - B.1.1.7 variant showed a modest decrease in neutralization activity, by a factor of 1.5
- **501Y.V2 variant** (23 mutations with 17 amino acid changes) was initially reported in South Africa on December 18, 2020
  - 501Y.V2 variant showed complete escape from neutralizing antibodies in 48% of convalescent serum samples (21 of 44) obtained from patients who had previously had Covid-19
  - In serum from Pfizer recipients, neutralization was 2/3 lower than the US isolates tested
  - Moderna study was 6-fold lower neutralizing titer
- **P.1 variant** (approximately 35 mutations with 17 amino acid changes) was reported in Brazil on January 12, 2021
- All three variants have the N501Y mutation, which changes the amino acid asparagine (N) to tyrosine (Y) at position 501 in the receptor-binding domain of the spike protein
- **501Y.V2 and P.1 variants** both have two additional receptor-binding–domain mutations, K417N/T and E484K

- "Even with a 6-fold decrease, serum can still effectively neutralize the virus", Mascola, Graham, Fauci (https://jamanetwork.com/journals/jama/fullarticle/2776542)
- Moderna Announces it has Shipped Variant-Specific Vaccine Candidate, mRNA-1273.351, to NIH for Clinical Study
  - https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-it-has-shipped-variant-specific-vaccine

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https://www.nejm.org/doi/full/10.1056/NEJMc2100362 *https://jamanetwork.com/journals/jama/fullarticle/2777785*

Variants:

- Recent publication shows strong T cell response to variants of concern in vaccine recipients
  - Don't forget the T cells!
  - Help to limit viral replication, spread of infection, and duration of infectiousness even if you are not protected from infection
  - Reduction in hospitalization and death even if you are not protected from infection

- Tarke et al 2021 (preprint): "sequences of the vast majority of SARS-CoV-2 **T cell epitopes are not affected by the mutations found in the variants analyzed**. Overall, the results demonstrate that CD4+ and CD8+ T cell responses in convalescent COVID-19 subjects or COVID-19 mRNA vaccinees are **not substantially affected by mutations found in the SARS-CoV-2 variants**."

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Tarke, A., Sidney, J., Methot, N., Zhang, Y., Dan, J. M., Goodwin, B., ... & Sette, A. (2021). Negligible impact of SARS-CoV-2 variants on CD4+ and CD8+ T cell reactivity in COVID-19 exposed donors and vaccinees. *bioRxiv*. *https://www.biorxiv.org/content/10.1101/2021.02.27.433180v1*

COVID-19/SARS-CoV-2 Vaccine FAQs

- **Will the vaccine elicit protection against the new variants?**
  - Viruses, particularly RNA viruses will mutate over time
  - SARS-CoV-2 mutates slower than other RNA viruses
    - Biologically meaningful mutations occur infrequently
  - Some variant viruses may be more transmissible as they bind ACE2 more efficiently
  - Concerns that variants will escape neutralizing antibodies
    - Note: antibodies target multiple areas of the spike protein – mutations in one area will not prevent antibodies from binding in other areas
    - Pfizer vaccine still neutralizes UK variant
      - https://www.biorxiv.org/content/10.1101/2021.01.07.425740v1
    - Waiting on data for South African variant
    - mRNA vaccines could be adapted to variants in 4 weeks

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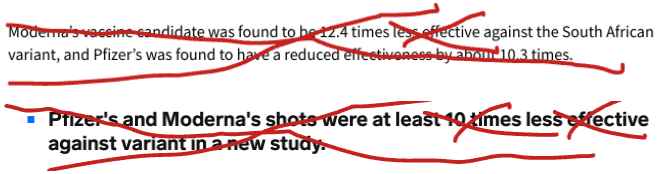
https://www.nature.com/articles/d41586-021-00031-0

Things to Monitor

- Length of immune response
  - Strong protection from natural infection and vaccination at 8 months
    - https://science.sciencemag.org/content/371/6529/eabf4063
  - Data extrapolated from a preliminary study suggests vaccine protection may last 10 years or more
    - https://assets.researchsquare.com/files/rs-310773/v1_stamped.pdf
- Variants
  - Some indication that the current vaccines may not produce as many antibodies towards the variant strains
    - BUT: Still strong enough to neutralize, just not as powerful as a reaction as against the original variants
    - Antibodies bind multiple areas of the receptor binding site
    - T Cells play a role as well
    - mRNA vaccines could be adapted to new variants as quickly as 4 weeks
  - Cases/hospitalizations/deaths not rising even with increased prevalence of variants in some areas



@zeynep

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When do we see this coming to an end?

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What are the most effective ways to educate individuals and the public on vaccine safety and efficacy? Do you have suggestions for educational strategies for combatting vaccine hesitancy?

- Stories and experiences
  - People respond to stories and anecdotes, not facts
    - They remember their own experiences or the stories from someone they know
  - If your mother/loved one got vaccinated and over the next three days was more ill-looking than you had ever seen them, and then they were hospitalized, would you line up to get the vaccine?
  - Get information out there, you never know who you will reach

DETROIT MERCY DENTAL

Just try…communicate…try again…

Josh Thomson
December 3 at 3:34 PM ·

I wanted to try and offer some information about the new coronavirus vaccines. It is not everything, but I hope you feel like reading so that you too can become an advocate for information rather than misinformation. This is difficult because I am doing my best to give what I know and what I teach, rather than sound preachy. I have been fortunate to learn and study these concepts and all I wish to do is share for the benefit of public health. Feel free to ask questions in the comments if you would like or if I missed something you would like me to address.

There is a lot of misinformation out there. I have been receiving questions regarding vaccines containing nonhuman DNA, altering our DNA, and causing COVID-19. I would like to address these and offer some background on the vaccines in production.

You cannot be infected with SARS-CoV-2 or get COVID-19 from the vaccines. The reason for this is that the vaccines do not contain the virus. They contain the code to make a protein of the virus or just a protein of the virus. However, when you get the vaccine you are likely develop a fever, headache, soreness at the injection area or other symptoms that seem like you are getting sick. This is not COVID-19, this is your immune system reacting to the vaccine and immune responses lead to those symptoms. This is sometimes difficult to understand because these symptoms can be identical to a viral infection, but in the case of these vaccines---they are not an infection just response to a part of the virus.

Now for some info on the leading vaccine candidates:

Moderna and Pfizer vaccines: These two vaccines are called "mRNA" vaccines.

Our genes (chromosomes, the recipes for us) are made of DNA which gets turned into mRNA and the mRNA gets made into the proteins that make up the cells and do the processes in our body. I like to use a particular analogy for this process. Our genes are like a recipe for a cake that you got from your Polish grandmother but it is written in Polish (DNA). So you go to someone that can first transcribe this information into English (mRNA). Then you can add all the ingredients (proteins) to make the cake (human).
The mRNA in the vaccines do not produce any of our own proteins, but they will go into our cells and make one protein of the coronavirus. This protein is a really important protein for the virus to infect us. Our cells will use this mRNA for a short period of time and produce this coronavirus protein so that our immune system will react to it (The mRNA will break down quickly after it is used to make protein). This is great because our immune system has never seen it before and this vaccine will prepare it and provide a memory to the immune system to react to the virus if we ever see it to clear it out of our body much much faster than if we got infected without it.

The mRNA for the vaccines are produced from a sequence of DNA in a test tube in a laboratory and then the DNA is removed from the test tube. There is no non-human DNA in these vaccines. Another claim that is made about the mRNA vaccines is that they may alter our DNA. This is also false. RNA does not interact with DNA in that way and will not alter our DNA.

AstraZeneca/Oxford Vaccine and Johnson and Johnson Vaccines: These are called virus vector vaccines.

These vaccines have the genes for the same coronavirus protein I mentioned above. However, the genes are incorporated into an adenovirus. Adenoviruses are viruses that cause common colds and we are exposed to them all the time, but these ones are modified so they cannot replicate and make new viruses in us. The virus vector allows it to get into our cells like a normal virus would and then it forces that cell to produce the coronavirus protein but no viruses. Like above this production stimulates our immune system to identify the coronavirus protein and protect us from natural infection.

The non-human DNA in this vaccine is the DNA from the adenovirus vector and the coronavirus gene. There is nothing abnormal about this.

Other types of vaccines:

Recombinant protein vaccines: Recombinant protein vaccines are usually made by putting the coronavirus gene into yeast cells and growing the yeast in huge tanks where they make tons of protein. Then the protein is purified from and the cells and the content and the protein is what is injected for a vaccine. This type of vaccine is being tested elsewhere in the world right now, but is not a frontrunner in the US.

Non-human DNA is not in this type of vaccine. Non-human DNA here would be the yeast DNA during production, but it is removed before vaccination.

Cell-culture vaccines (e.g. FluBlok for influenza):

These types of vaccines are made similar to the yeast production method but use other types of cells (human or otherwise). FluBlok is an example of this type of vaccine and is for Influenza vaccination in certain cases, especially if people have egg allergies. This vaccine has an influenza gene that is put into an insect virus. The insect virus infects insect cells and so it is cultured in these cells and forces the insect cells to make the protein, which is then harvested and purified.

Non-human DNA is not in this type of vaccine either. The proteins are purified from the cultures and the protein is what is injected.

Again, please feel free to ask any questions.

Stacie Thomson, Paul Thomson and 82 others 87 Comments 127 Shares

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Questions

- The remaining slides are a list of frequently asked questions about COVID-19 vaccines

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What in your opinion are the biggest barriers to slowing/ending the spread of COVID-19 and ending the global pandemic? How can we overcome those barriers?

- **Masking, masking, masking**, vaccines, vaccines, vaccines
- Barriers:
  - Misinformation and political barriers
    - People are using every angle of this as a political argument
    - Masks are political, vaccines are political
  - Distribution of vaccines to lower income countries
  - Slow rollout of vaccines

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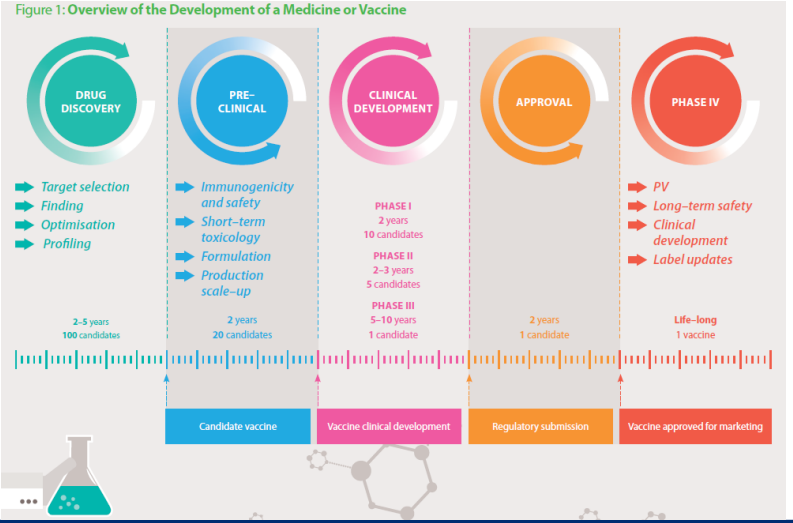
COVID-19/SARS-CoV-2 Vaccine FAQs

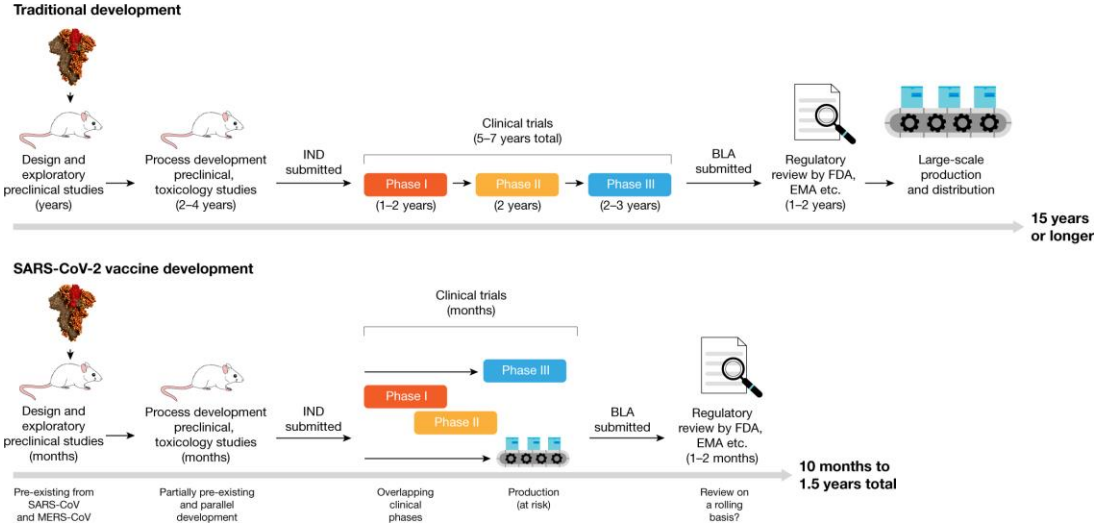
- How come this vaccine was developed so quickly in comparison to others?
- Will a vaccine cause me to test positive for COVID-19?
- Will the components of the vaccine alter my DNA?
- How long will the vaccine protect me? Will one course of vaccination be enough?
- One dose or two?
- I already had COVID-19. Should I still get vaccinated?
- I am pregnant or breastfeeding - Should I still get vaccinated?
- Do the vaccines cause fertility issues?
- Do either of the vaccine formulations contain aborted fetal tissues or cells?
- How long until we achieve herd immunity? When will things go back to normal?
- Will the vaccine protect against the variants that have emerged?

DETROIT MERCY DENTAL

COVID-19/SARS-CoV-2 Vaccine FAQs

- Timeframe:
  - Usual development process is approximately 10 years
  - SARS-CoV-2 vaccines developed in 1 year. How?





COVID-19/SARS-CoV-2 Vaccine FAQs

- **Will a vaccine cause me to test positive for COVID-19?**
- **Antigen tests:**
  - **No**
    - mRNA encased in lipid nanoparticles will enter cells near the injection site
    - No way for mRNA to travel to the respiratory tract
      - mRNA is fragile
        - Exists for a short time period inside the cell, does not leave
        - We have RNases on every surface of our body and in our extracellular spaces
          - Part of antiviral defense
          - Break down material from dead or damaged cells
    - This mRNA will not replicate and would not be able to get to high enough levels to detect anywhere other than the injection site
- **Antibody tests:**
  - **I sure hope so!**
  - Anti-SARS-CoV-2 IgM and IgG antibodies should be detectable beginning 7-14 days after the first dose

First test dose of Moderna Vaccine
3/31/2020
AP PHOTO/TED S. WARREN

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5964141/

COVID-19/SARS-CoV-2 Vaccine FAQs

- **Can the mRNA in the SARS-CoV-2 get into my DNA and alter it?**
  - **NO!**
    - Central dogma: DNA→RNA→Protein
    - "There is no reasonable possibility based on the totality of our knowledge of cell biology, reverse transcriptases, human genetics, and the immune system that mRNA vaccines can affect your DNA."
    - mRNA in the vaccine will stay outside of the nucleus and produce proteins there, RNA does not go from the cytoplasm to the nucleus
- **But what about HIV and other viruses that have reverse transcriptase or alter DNA?**
  - HIV and HBV have reverse transcriptases which convert RNA into DNA in the cytoplasm
  - HIV also has specific enzymes that direct that transport the newly made viral DNA into the nucleus and insert it into the genome
  - For all of these the, reverse transcriptase needs to be primed to begin making DNA from RNA
  - Reverse transcriptases are not capable of picking up any random RNA and generating a DNA from it

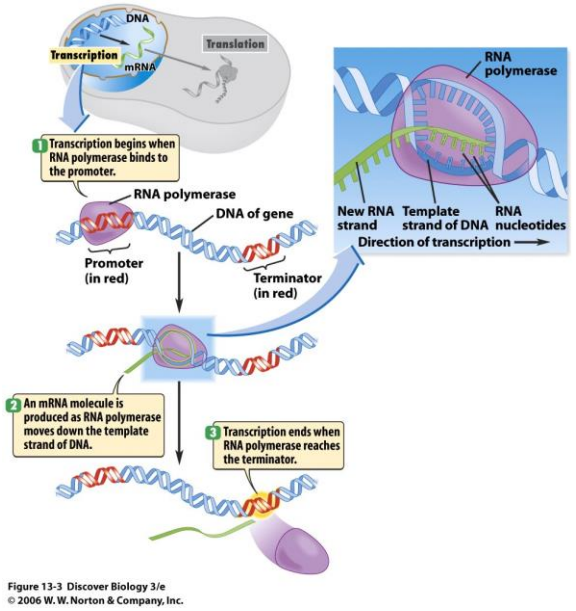

Figure 13-3 Discover Biology 3/e
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For further information regarding the chances with endogenous retroviruses, telomerase, etc.:
https://www.deplatformdisease.com/blog/no-really-mrna-vaccines-are-not-going-to-affect-your-dna

COVID-19/SARS-CoV-2 Vaccine FAQs

- **How long will the vaccine protect me? Will one course of vaccination be enough?**
  - **Too soon to tell**
    - Only a few months of vaccine data, only 14 months from natural infection
    - Not enough re-exposures to naturally occurring infections
  - Immunity from natural SARS-CoV-2 infection lasts at least 6 months (Dan, 2020)
    - IgG to the Spike protein was relatively stable over 6+ months.
    - Spike-specific memory B cells were more abundant at 6 months than at 1 month post symptom onset.
    - SARS-CoV-2-specific $CD4^+$ T cells and $CD8^+$ T cells declined with a half-life of 3-5 months.
  - Immunity to the four seasonal coronaviruses is short-lived (Eldridge, 2020)
    - People can be re-infected within one year of the initial infection
  - Memory cells specific for SARS-CoV-1 can be found 17 years later

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https://doi.org/10.1101/2020.11.15.383323 https://science.sciencemag.org/content/early/2021/01/06/science.abf4063
https://www.nature.com/articles/s41591-020-1083-1?utm_medium=affiliate&utm_source=commission_junction&utm_campaign=3_nsn6445_deeplink_PID100052172&utm_content=deeplink

COVID-19/SARS-CoV-2 Vaccine FAQs

- **How long will the vaccine protect me? Will one course of vaccination be enough?**
  - **Too soon to tell**
  - Antibody titers will decline over time
    - This is true for all antibodies to ANY infection
    - Threshold of protection is unknown at this time
    - Booster shots may be needed
      - State Health Department is developing plans for distributing vaccines on 1-, 2- and 5-year cycles
  - Role of memory T Cells still being examined
  - If immunity wanes, we may not be completely protected from reinfection, but reinfection may be less serious (like a seasonal cold)
- **One dose or two doses?**
  - **Follow current 2-dose guidelines**
  - First dose 80-90% effective – some countries are considering only giving one dose to stretch supplies
  - Unknown when efficacy from first shot wanes
    - Additive vs multiplicative effects?
    - Lower peak antibody titers?
    - Shorter length of immunity?
    - Less affinity maturation and memory cell development?

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https://www.nature.com/articles/s41591-020-1083-1?utm_medium=affiliate&utm_source=commission_junction&utm_campaign=3_nsn6445_deeplink_PID100052172&utm_content=deeplink

COVID-19/SARS-CoV-2 Vaccine FAQs

- **I already had COVID-19. Should I still get vaccinated?**
  - **Yes**
    - We do not know how long immunity lasts
    - Vaccine would boost the strength and duration of existing antibody protection and may improve immune memory
  - CDC Guidelines:
    - https://www.cdc.gov/coronavirus/2019-ncov/vaccines/faq.html
    - Vaccination should be offered regardless of a previous COVID-19 infection
    - Antibody tests should not be required
    - If you are currently ill, you should wait to be vaccinated until you have met the criteria to discontinue isolation
    - Since immunity has been shown to last at least 3 months, individuals with a previous infection may chose to wait until the end of the 90-day period before being vaccinated

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COVID-19/SARS-CoV-2 Vaccine FAQs

- **I am pregnant or breastfeeding. Should I still get vaccinated?**
  - **Consult your physician and pediatrician**
  - No indications of adverse pregnancy outcomes during natural infection
  - Vaccination would allow the mother to transfer antibodies to the developing fetus through the placenta or to a nursing infant via breastfeeding
  - **There have been no clinical trials done in pregnant or lactating women, however there is no reason to expect vaccination with one of the EUA vaccines would harm a developing fetus or nursing infant**
    - *Viral-vector versions of the vaccine that are under development will likely not be recommended for pregnant women*
    - Interim animal study data from Moderna and Pfizer show no concerning signs
  - **The American College of Obstetricians and Gynecologists supports the vaccination of pregnant and lactating women with either the Moderna or Pfizer vaccine.**
    - https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/12/vaccinating-pregnant-and-lactating-patients-against-covid-19
  - Video from Stephanie Langel, Ph.D., Coronavirus and Maternal/Fetal/Infant/Breastmilk Immunity expert, Duke Human Vaccine Institute and new mother:
    - https://www.youtube.com/watch?fbclid=IwAR1GDK8fPh-hXlNsYttlQovzjxte6H6jhN2JmioA53SzmP3JX3M-9omyW1c&v=EmV5YdWLlYM&feature=youtu.be

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COVID-19/SARS-CoV-2 Vaccine FAQs

- **Do either of the vaccine formulations contain aborted fetal tissues or cells?**
  - **NO**
    - The Pfizer and Moderna vaccines are produced in cell-free systems
      - The vaccines do not contain any human DNA or RNA, cells or tissues
  - Note: Some laboratory testing for safety and efficacy was done in HEK-293 cells, a commonly used laboratory cells descended from tissue taken from a 1973 elective abortion that took place in the Netherlands.
    - From the Vatican's Congregation for the Doctrine of the Faith:
      - *"When alternative vaccines are not available, it is morally acceptable to receive COVID-19 vaccines developed or tested using cell lines originating from aborted fetuses."*

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https://www.nebraskamed.com/COVID/you-asked-we-answered-do-the-covid-19-vaccines-contain-aborted-fetal-cells
https://www.catholicnews.com/vatican-without-alternatives-current-covid-19-vaccines-are-morally-acceptable/

COVID-19/SARS-CoV-2 Vaccine FAQs

- **How long until we achieve herd immunity? When will things go back to normal?**
  - Depends on how long immunity lasts
  - Depends on if the vaccine will prevent a person from transmitting the virus
    - Some promising data from Moderna
  - Depends on the efficacy of vaccine distribution
  - Depends on how many people get vaccinated
    - Up to 39-54% of adult Americans say they are not willing to be vaccinated
  - **Estimated percentage of people protected from natural infection or vaccination to achieve herd immunity – 55-82%**
    - US: About 1% vaccinated, about 6%* with confirmed infection
      - Asymptomatic cases and cases that occurred when testing was not available mean this number is probably higher
    - Michigan DHHS expects wide distribution by late Spring

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Immunological Memory to SARS-CoV-2

- Study of 254 samples from 188 COVID-19 cases, 43 at 6-8 months post-infection
  - 51 subjects provided longitudinal blood samples
- ~95% of subjects retained immune memory ~6 months after infection
  - Antibodies against SARS-CoV-2 spike decline moderately over 8 months
  - Memory B cells increase from 1 to 8 months
  - Memory CD8+ T Cells declined with an initial half-life of 3 to 5 months (~50% possessed detectable levels by 6 to 8 months)
  - Memory CD4+ T Cells remained high from 1 to 8 months (92%)
- Circulating antibodies were not predictive of T Cell Memory (serological tests do not reflect the entirety of immune memory)

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Dan, J. M., Mateus, J., Kato, Y., Hastie, K. M., Yu, E. D., Faliti, C. E., ... & Crotty, S. (2021). Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. *Science*. DOI: 10.1126/science.abf4063