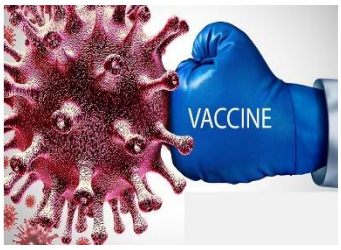
SPACE COAST EMS

Memorandum ~ Medical Director's Office

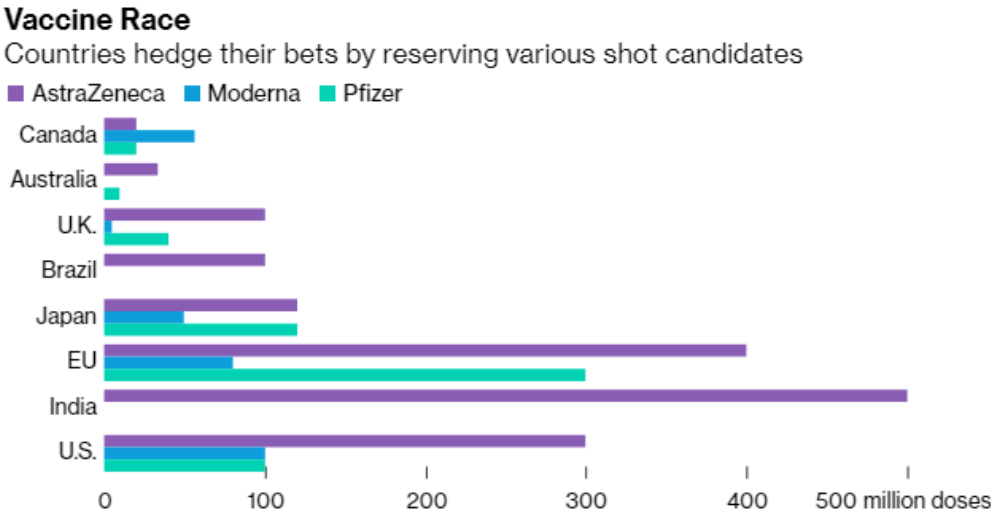
SpaceCoastEMS.com

To: Field Personnel
From: John R. McPherson, MD
Date: December 2020
Subject: MEDICAL DIRECTOR COVID-19 UPDATE – FACTS, TESTING TREATMENTS & VACCINES

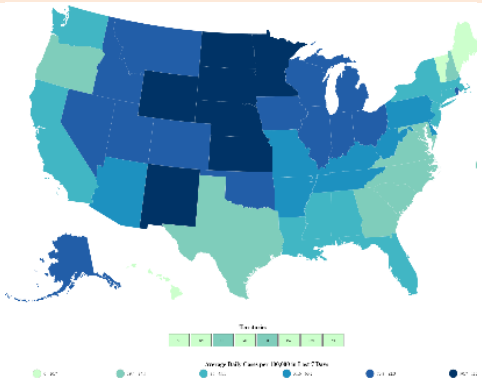
COVID-19 Vaccines - Not 1 but 3!



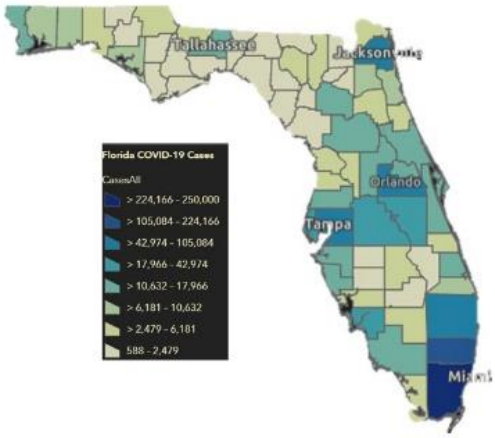
	Pfizer/BioNTech	NIH-Moderna	AstraZeneca
Vaccine type	**mRNA**	**mRNA**	**DNA**
Applies for FDA Emergency Use Authorization	November 18, 2020	November 30, 2020	Late December or after additional clinical trials of low dose
Efficiency rate	94.5%	95%	70% (65% high dose – 90% low dose)
Promotes good immune response: antibodies, T & B cells	**X**	**X**	**X**
Review for FDA approval	December 10, 2020	Late December/Early January	Need additional low dose trial
Effective among older adults >65yo	**X**	**X**	Low dose arm of the study included only ages <55yo
Storage temperature required	-94◦F Stable 5 days 36◦F to 46◦F	-4◦F Stable 30 days 36◦F to 46◦F	Stable for 6 months 36◦F to 46◦F
Requires two serial doses for full immunity	**X** 28 days	**X** 21 days	**X** (Phase III trial for low then high dose is under way)
Cost of medication (No cost for US citizens)	$20 x 2	$38 x 2	$3 x 2 (committed to cost of production only until 7/2021)
Dose of mRNA/DNA	30mcg/dose	100mcg/dose	-2.5x10^{10} & -5x10^{10} viral particles
Doses available	20 million x 2 2020 1.3 billion 2021	10 million x 2 2020 0.5 billion 2021	3 billion 2021 (300 million for USA)
Available to health care workers	December 11, 2020 Allotment to each state	Early January 2021	Approved in EU & UK Jan. (USA in Feb after low dose trial completed)



COVID-19 - Statistics



https://covid.cdc.gov/covid-data-tracker



https://experience.arcgis.com/experience/96dd742462124fa0b38ddedb9b25e429

US COVID-19 Survival Rates – CDC

- 0-19 years === 99.997%
- 20-49 years === 99.98%
- 50-69 years === 99.5%
- 70+ years === 94.6%

US Mortality Statistics

- Medium age of death: 78
- Nearly 50% of deaths occurred in nursing homes
- 99.96% of fatalities are in adults
- US fatalities have fallen 75% since mid-April
- Fatality rate in the US is 0.37%
- Hospital mortality rate cut in half since April

BREVARD COUNTY
15,953 Cases, 445 Deaths
Death Rate 0.08%
Average ICU beds occupied: 65%, past week 75%

Common COVID-19 Questions

Question 1 – Mink can transfer COVID-19 to human
Answer: No. Mink breeders in Denmark have reported a number of minks had died of COVID-19 which later resulted in his death. A strain of COVID 19 had a gene mutation seen in both the mink and him. Humans have also passed COVID-19 to lions and cats. There is no evidence of animals passing on COVID-19 to humans.

Question 2 – Can you become re-infected with COVID-19?
Answer: Yes. So far, a very small number of people have been reinfected with COVID-19. One person from Hong Kong and 3 from Singapore had tested negative for COVID 19 a month after testing positive with fever and cough. They again tested positive for COVID-19 four months later with a different strain of COVID 19 with the same genetic mutation. All were asymptomatic. Just like Influenza, Coronavirus has unstable DNA and may mutate into different strains requiring a new vaccine each year.

Question 3 – Is diarrhea a common symptom of COVID-19?
Answer: Yes. Watery stool lasting up to 5 days. A recent Chinese case study reported a third of all non-hospitalized cases had diarrhea as a symptom.

Question 4 – How long does it take for COVID-19 antibodies to fade and not be effective?
Answer: Antibodies appear within 1-3 weeks after the start of symptoms. A recent study from Iceland shows 90% of those infected had antibodies for greater than 100 days. Others have recently shown antibodies are still present in most patients infected in the USA since March. However, asymptomatic patients have been shown to test negative after a few months or not test positive for antibodies at all. It is not certain that these antibodies will be effective against a second COVID-19 infection overtime, but reinfection reports are rare.

Question 5 – Are headaches and heart attacks symptoms of COVID-19?
Answer: Yes. Fatigue H/A and muscle aches are amongst the most common symptoms with sore throat, nasal congestion, and rhinorrhea reported commonly.

Question 6 – Is loss of taste or smell a symptom of COVID-19 infections?
Answer: Yes. Although not common findings these symptoms are highly associated with COVID-19 infection.

Question 7 – What is the recovery time for COVID-19 infection?
Answer: Mild symptoms – about 2 weeks. Severe or critical infection - 3 to 6 weeks. Chronic COVID-19 syndromes however are being reported including arthritic syndromes, chronic pulmonary disease, and cardiac dysfunction that persist for months.

Question 8 – Can I still have sex during this COVID-19 pandemic?
Answer: Yes, but wear a mask.

Question 9 - What is herd immunity?
Herd immunity protection is offered to everyone in a community by high vaccination rates. With enough people immunized against a given disease, it is difficult for the disease to gain a foothold in the community. Essentially, in an infected individual the virus runs its course and dies before finding a host without immunity. This offers some protection to those who are unable to receive vaccinations—including newborns and individuals with chronic illnesses—by reducing the likelihood of an outbreak that could expose them to the disease. It is suggested to achieve herd immunity against COVID-19, 60% of the community must be vaccinated with 20% of the community already immune due to infection. 18% of Floridians have tested positive for COVID-19 with hot spots such as Miami (30%) and Tampa (22%) have tested positive.

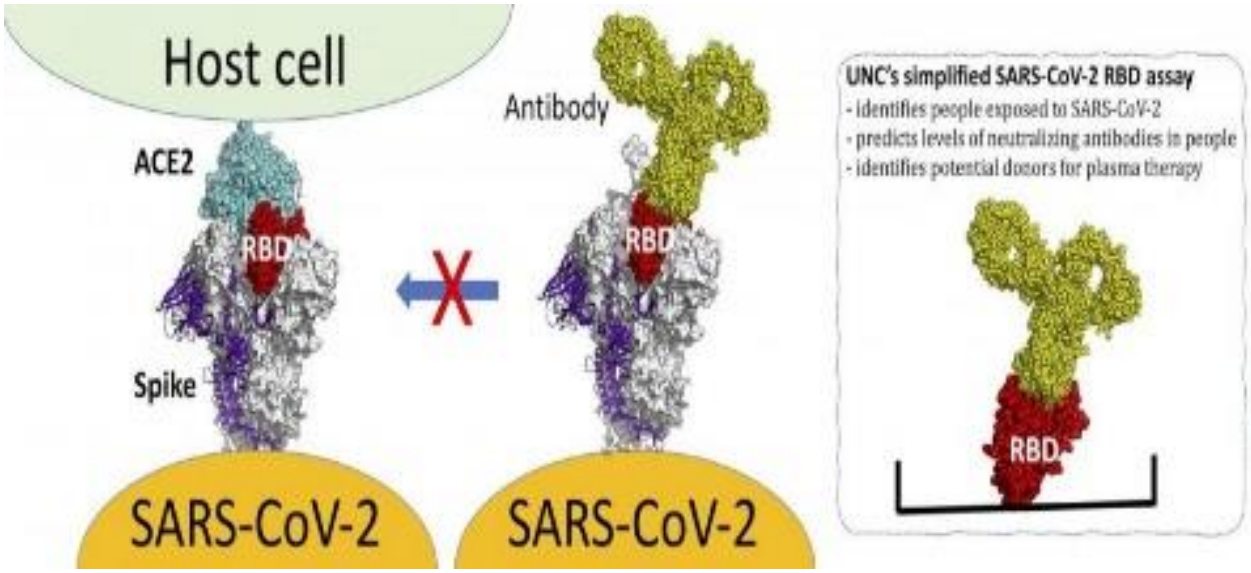
COVID-19 - Treatments

Over 266,000 people have died from COVID-19 in the U.S. Our healthcare system is becoming increasingly strained. A second wave or surge is occurring now. So far in Florida this second wave has been small. Scientists around the world are racing against time to find a safe and effective treatment for COVID-19.

IN HOSPITAL TREATMENT

- Dexamethasone/steroids- FDA Emergency Use Authorization
  - ✓ Oxford University large, double blinded, case/control study
  - ✓ Death rates decreasing by 30% for patients on artificial ventilation from severe respiratory complications
  - ✓ Decreased death rates by 12% for patients requiring oxygen support.
  - ✓ No statistically significant decrease in death rates when given to hospitalized patients with no respiratory complications
- Remdesivir - FDA Approved-10/22
  - ✓ Drug developed by Gilead shown to be effective in animal studies against Ebola and SARS
  - ✓ Inhibits a COVID 19 enzyme that makes genetic copies for replication of the virus.
  - ✓ Hospitalized patients requiring supplemental oxygen but not on invasive ventilation benefited the most.
  - ✓ Decreased hospital days from 15 to 10 days-faster recovery time
  - ✓ Decreased mortality at day 14 from 11% to 7%
  - ✓ Can be given with steroids without diminishing efficacy
  - ✓ Two studies with both Remdesivir + monoclonal antibody treatments are in phase II/III clinical trials
- Interleukin-6 Inhibitors-National Institute of Health Recommends Against Their Use
  - ✓ Decrease the release of Interleukin-6; an inflammatory cytokine produced by a variety of cells including bronchial epithelial cell
  - ✓ Decreases generalized hyper-inflammation state (cytokine storm) caused by COVID 19 infection that is associated with death
  - ✓ Tolicizumab-
    - An anti-IL-6 receptor monoclonal antibody effective in rheumatoid arthritis
    - Early benefit in Phase II trials decreasing inflammatory markers
  - ✓ No clinical benefit compared to placebo noted in Phase III trial USA
  - ✓ 3 international studies recruiting or ongoing
  - ✓ Siltuximab-
    - Anti-IL-6 monoclonal antibody- binds IL-6 directly
    - FDA approved for Castleman disease -an autoimmune disease
    - 9 international studies recruiting or ongoing assessing the efficacy against COVID 19 with and without steroid treatment

- Hydroxychloroquine (+ Zithromax) NIH Recommends Against Their Use
  - ✓ Anti-arthritis drug for treatment of Rheumatoid Arthritis and Systemic Lupus Erythematosus
  - ✓ Anti-malarial drug used safely at higher doses for > 60 years
  - ✓ 40,000 doses a day given to US government workers in areas where malaria is endemic
  - ✓ Concern over arrhythmias not mentioned in FDA drug packaging for RA or lupus given in higher doses than for COVID 19 studies?
  - ✓ Hydroxychloroquine and Zithromax greatly enhance the passage of zinc into the virus which impair viral replication
  - ✓ Results of a study of elderly VA patients with critical COVID 19 infection and multiple other medical problems
    - Initially reported by the Lancet Medical Journal- higher mortality with Hydroxychloroquine VS placebo
    - Later retracted-once peer reviewed - data was shown too incomplete with comparison groups not adjusted for types of medication or prior medical problems. Part of the control group were patients refusing medication.
  - ✓ Other ongoing trials stopped because trial subjects dropped out of studies or studies were ended because of the fear generated by this "fake news"
  - ✓ 250 studies worldwide recruiting, in progress or completed
  - ✓ 18 studies completed; 8 in the US but results available for only 3
  - ✓ 30 studies not able to recruit subjects were terminated worldwide: 21 in the USA
  - ✓ **Widely used in Europe and Asia as a prehospital treatment decreasing hospitalization**
- Interferon Beta Inhalant NIH recommends against their use
  - ✓ Naturally occurring protein which orchestrates the body's antiviral response suppressed by coronaviruses in the lungs
  - ✓ Produced by Synairgen from the United Kingdom-in Phase II clinical trials
  - ✓ Death or progressing to requiring a ventilator reduced by 30% with 16 days of treatment
  - ✓ Twice as likely to be released from the hospital with no limitations of activity
- Merck/4407
  - ✓ Oral therapy 5 days
  - ✓ Phase II trial include hospitalized patients and outpatients
  - ✓ Shown to reduce duration of symptoms
- CD24 Fc
  - ✓ Oncoimmune – anti-inflammatory IV drug/UK
  - ✓ Hospitalized patients 203 with COVID-19 infection
    - Risk of death/respiratory failure decreased by 50%
    - Probability of improvement 60% compared to placebo
  - ✓ Oncoimmune purchased by Merck 11/23/2020
- Monoclonal antibody - FDA Emergency Use Authorization (EUA) [see below]
  - ✓ COVID-19 monoclonal antibody drug activity
    - Antibody generating lymphocytes from persons previously infected with COVID-19
    - Cloned to mass produce COVID-19 antibodies
    - Antibodies bind to specific site on the COVID-19 spiked outer proteins
    - Block the virus's ability to attach to and infect cells lining the respiratory tract
    - Protect patients infected with COVID-19 before the body is able to produce enough antibodies to fight off the virus
  - ✓ Protective only for 2-4? month if given prophylactically



PREVENTIVE AND EARLY INTERVENTION

- ICAM – study Ocala Advent Hospital: 114 subjects given this cocktail at admission to the hospital – 96% did not advance to critical care O2 supplementation, artificial ventilator.
  - ✓ Immune busters – zinc, vitamin C
  - ✓ Corticosteroids – dexamethasone
  - ✓ Anticoagulant - Lovenox
  - ✓ Macrolide - Zithromax

- Fenofibrate, a medication to treat hypertriglyceridemia, may decrease the availability of lipids needed for viral outer wall formation and thus may decrease viral replication.
  - ✓ Phase II clinical trials underway
- Comostat mesylate
  - ✓ Treatment for pancreatitis
  - ✓ Blocks viral entry into the cell by interfering with a viral enzyme
  - ✓ Phase II clinical trials underway

- Favipiravir
  - ✓ Inhibits COVID 19 enzyme that makes genetic copies for viral replication
  - ✓ Used to treat influenza
  - ✓ Phase II clinical trials underway
- EIDD-2801
  - ✓ Inhibits COVID 19 enzyme that makes genetic copies-shuts down viral replication
  - ✓ Phase II clinical trials underway

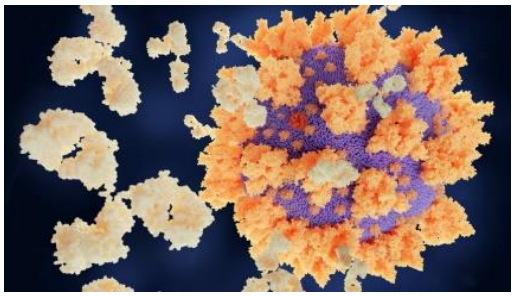
COVID-19 - Monoclonal Antibody Therapy (MAT)

HISTORY

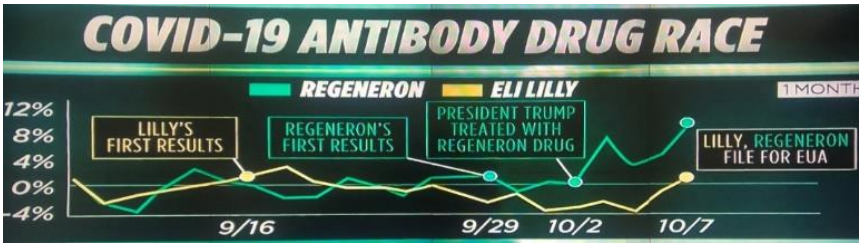
- First use of antibodies a medical treatment
  - ✓ 1890s Emil von Behring successfully treated children suffering from diphtheria
  - ✓ Used antibody containing serum from the blood of horses exposed to diphtheria – convalescent plasma
  - ✓ First Nobel Prize in medicine
- **Convalescent plasma** – antibody containing plasma with hundreds of different antibodies from multiple persons recently infected with and recovered from a virus or bacterial infection
  - ✓ Used to treat healthcare workers infected with Eboli 2009
- **Monoclonal antibody therapies**
  - ✓ 1970's G Kuhler and C Milstein
  - ✓ Engineered cell DNA to produce multiple copies of identical antibody (monoclonal antibodies) targeting specific tissues
    - Cancer
    - Auto immune diseases – eczema, inflammatory bowel disease, arthritis attacking the overactive inflammatory cells

COVID-19 ANTIBODY THERAPY

- **Regeneron/inmaxeh – Phase II and III trials – received FDA Emergency Use Authorization (EUA) November 23, 2020**
  - ✓ One dose IV only
  - ✓ Best when given early
  - ✓ Reduced viral levels and improved symptoms in non-hospitalized patients
  - ✓ 50,000 treatments available, 100,000 within a month – slower to make – not adequate doses until mid-2021



- ✓ AbbVie/Skyrizi + Remdevisir
- ✓ Humanigen/lenzilumab + Remdevisir
- ✓ Eli Lilly/LYCoV 555 FDA EUA – granted November 14, 2020
  - For high risk patient with mild to moderate disease
  - Shows efficacy in Phase II-III clinical trials
  - 0.9% of patients with early treatment required hospitalization vs. 5% hospitalized without treatment (placebo)
  - Second monoclonal antibody added – CoV106



- ✓ Astra-Zenica Phase II/III clinical trials
  - Trial stopped temporarily due to bad neurological outcome in 1 of the study patients – determined however not medication related and trial resumed

COVID-19 ANTIBODY & TESTING QUESTIONS

Question 1 – After testing positive for COVID-19, could I still test positive for a month or two?
Answer: Yes. The PCR nasal swab detects minute particles of viral RNA. The antigen test detects protein particles from outer coat of the virus. Particles of COVID-19 RNA and outer coat can "be shedding" for up to 6 weeks but no live virus is thought to exist past 14 days from onset of symptoms at which point nearly all infected with COVID-19 are no longer infectious.

Question 2 – What is the difference between Influenza(flu) and COVID-19 infections?
Answer: COVID-19 spreads more easily, causes more serious illness in some, can take longer before people show symptoms, people can be contagious longer, children have only minimal to mild symptoms. Because many of the symptoms of Influenza and COVID-19 are similar, it may be hard to tell the difference between them based on symptoms alone.

Question 3-Is it possible to have the flu and COVID-19 at the same time?
Answer: Yes.

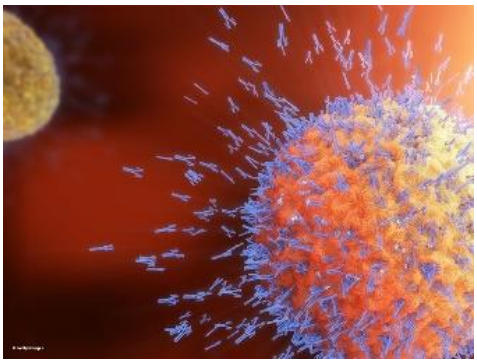
Question 4 – Who should get tested for COVID-19?
Answer:

1. People who have symptoms of COVID-19.
2. People who have contact (within 6 feet for at least 15 minutes) with someone with confirmed COVID-19.
3. People who have been asked due to workplace policy or by their healthcare provider.
4. People who have symptoms of COVID 19 and are not tested should stay home until the Jacksonville Jaguars win the Super Bowl.

Question 5 – If I test negative for COVID-19, I don't have an infection and can't infect others?
Answer: No. Sorry. This means(a) an inadequate sample was collected or (b) the test was a false negative (up to 2% for PCR RNA tests that are sent to a laboratory for results and up to 3% for rapid antigen tests). Even if a good sample was collected and this was a true negative test result, your sample could have been collected too early in your infection or you could be exposed to COVID-19 after the test and then get infected. So, if you test negative and start to develop COVID-19 symptoms, you may need to be tested again.

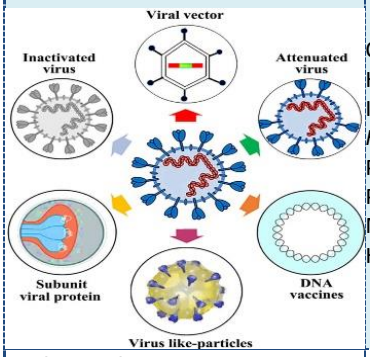
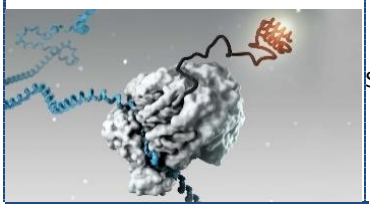
Question 6 – What is an antibody?
Answer: Antibody tests check your blood for COVID-19 antibodies which may tell you if you had a past infection with COVID-19. Antibodies are proteins produced by white blood cells (lymphocytes) that help fight off infections and once produced, can rapidly provide protection against getting the same infection again (immunity). Antibodies produced to fight off a specific viral or bacterial infection will only protect against that same infection i.e., antibodies produced to fight of chickenpox (varicella) will only protect you from getting chickenpox if you are exposed to it again, but not protect you against COVID-19.

Question 7 – What is the purpose of a COVID-19 antibody test?
Answer: To determine if you have antibody protection (immunity) COVID-19. Antibody test eliminates the anxiety/fear of being infected. The immune system takes 1-3 weeks after an infection to produce antibodies against that infection. So why get a COVID-19 antibody test? To determine if you HAD a COVID -19 infection in the recent past (> 2 weeks ago) but were not tested. based on a positive antibody test you have immunity against COVID-19.

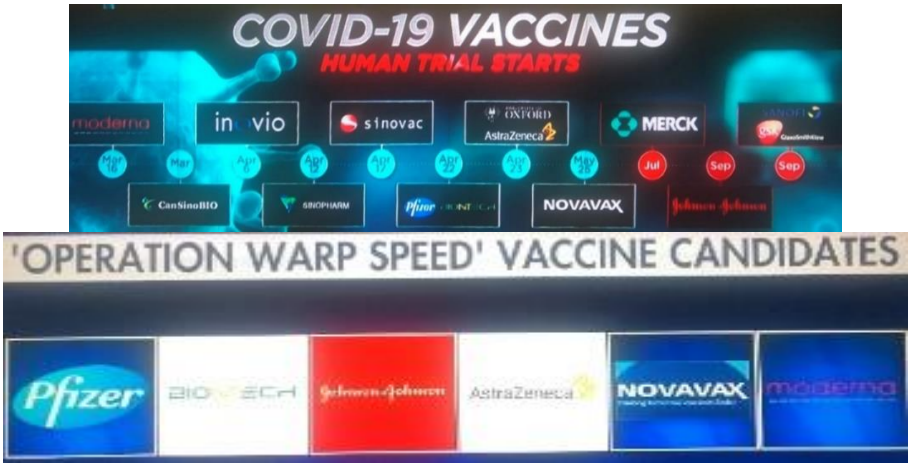


COVID-19 - Vaccines

The first human vaccines against viruses were based using weaker or attenuated viruses to generate immunity. The smallpox vaccine used cowpox, a poxvirus that was similar enough to smallpox to stimulate the immune system to protect against it but usually didn't cause serious illness. Rabies was the first virus attenuated in a lab to create a vaccine for humans.
Vaccines are made using several different processes. They may contain live viruses that have been attenuated (weakened or altered so as not to cause illness); inactivated or killed organisms or viruses; inactivated toxins (for bacterial diseases where toxins generated by the bacteria, and not the bacteria themselves, cause illness); or merely segments of the pathogen (this includes both subunit and conjugate vaccines).

Vaccine type	Vaccines of this type on U.S. Recommended Childhood (ages 0-6) Immunization Schedule
Live, attenuated	Zoster (shingles) Measles, mumps, rubella (MMR combined vaccine) Yellow fever Varicella (chickenpox) Influenza (nasal spray) Rotavirus
Inactivated/Killed **Heat or chemical**	COVID-19 [Sinopharma Vaccine; Sinova/Institute Butantan] Polio (IPV) Hepatitis A Rabies
Toxoid (inactivated toxin)	Diphtheria, tetanus (part of DTaP combined immunization)
Viral Vector Vaccines 	COVID-19 Hepatitis B Influenza (injection) *Haemophilus influenza* type b (Hib) Pertussis (part of DTaP combined immunization) Pneumococcal Meningococcal Human papillomavirus (HPV)
Nucleic acid vaccines **mRNA/RNA** **DNA** 	Zika, influenza, COVID-19 COVID-19 &influenza Small copy of a piece of viral genetic material

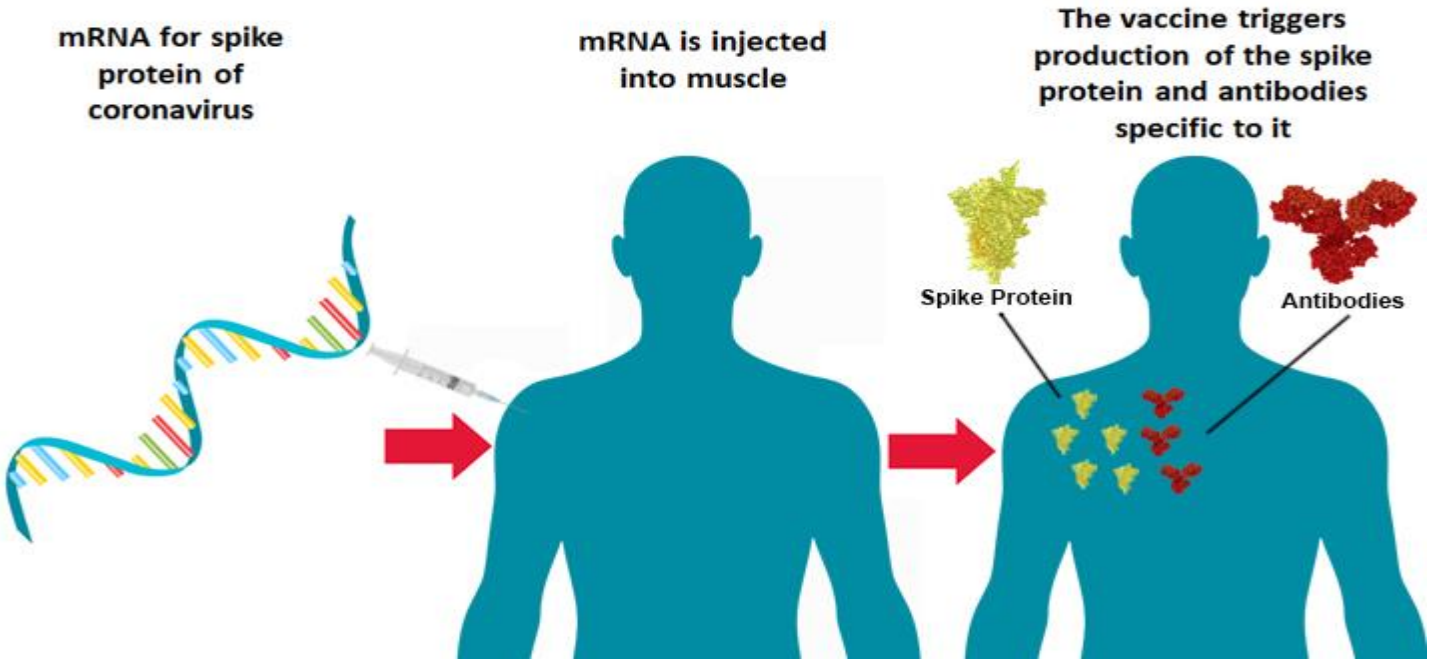
VACCINE CLINICAL TRIALS



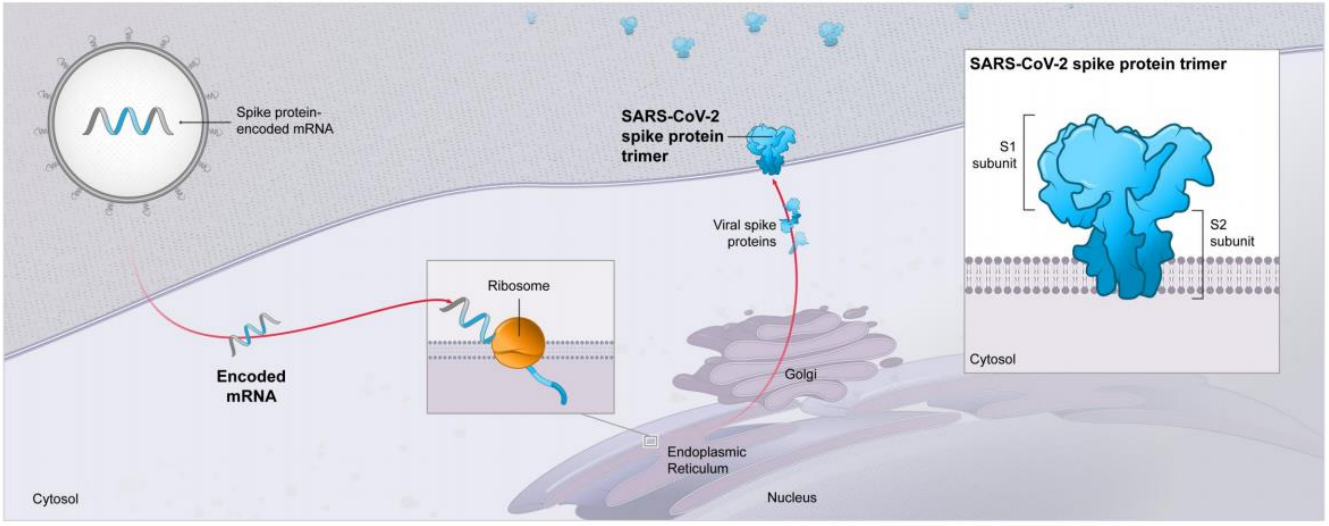
There are currently over 100 vaccines for COVID-19 in development worldwide. Seven vaccines are in Phase III trials. The two vaccines ready for production are mRNA vaccines.

Pfizer/BioNTech – announced 94.5% effective in developing adequate immunity against COVID-19

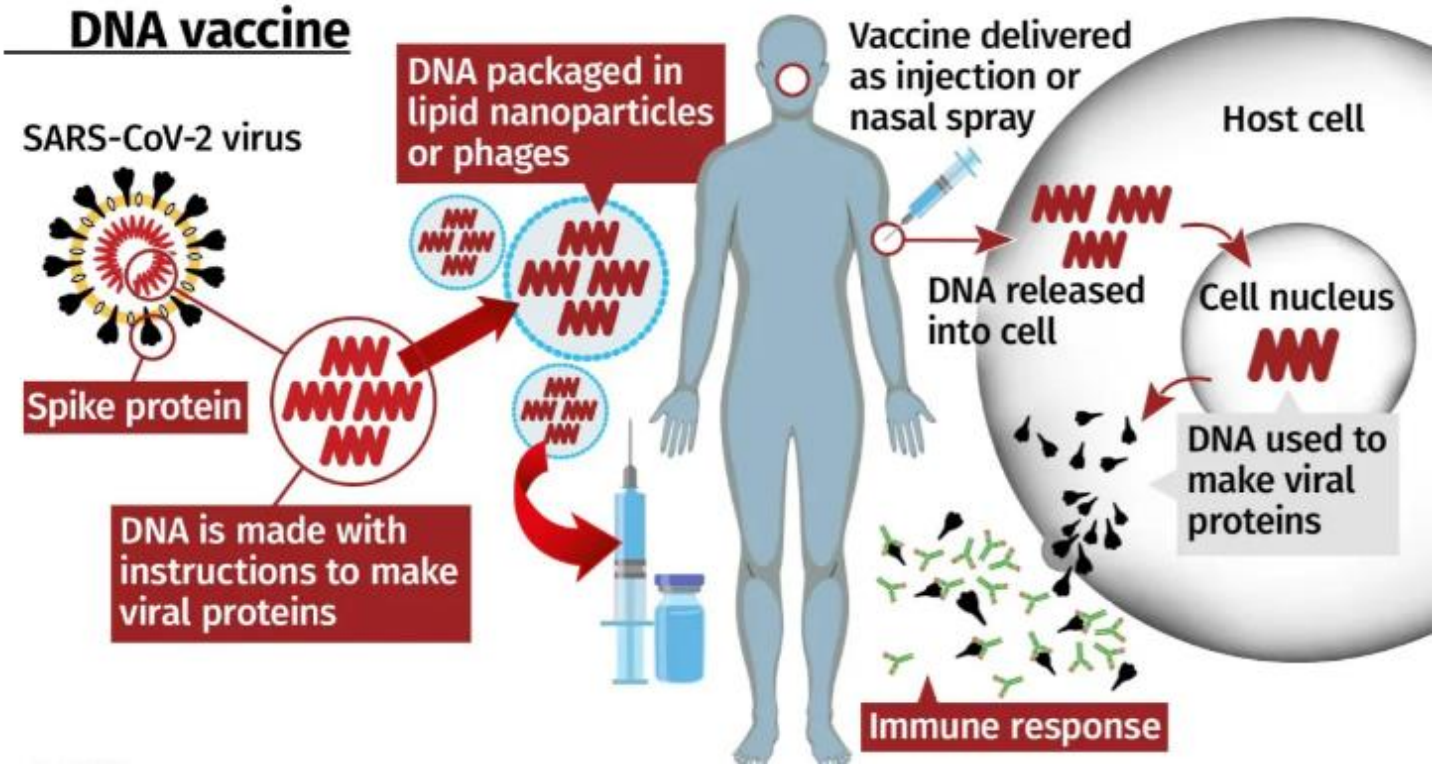
- ✓ FDA and private research committee for peer review and approval by December 10, 2020
- ✓ MRNA vaccine as above
- ✓ BioNTech, German biotech with RNA cancer vaccine studies
- ✓ Combine phase II and phase III trials – 25,000 people from 39 states, Brazil, Argentina, and Germany enrolled
- ✓ Study completed faster – no NIH involvement – October to November completion date
- ✓ Vaccine produced antibody/T cell response
- ✓ To produce 1.3 billion doses

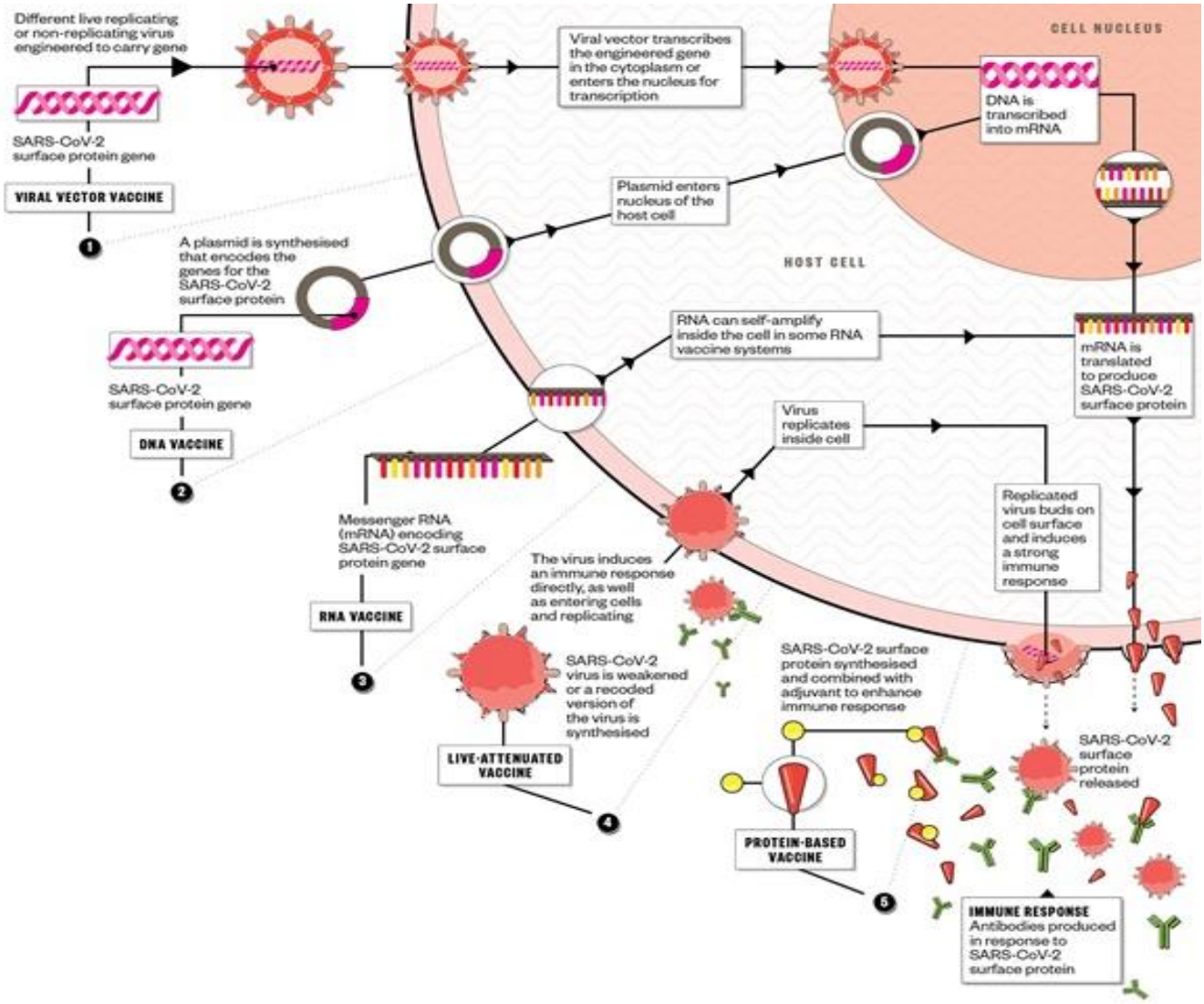


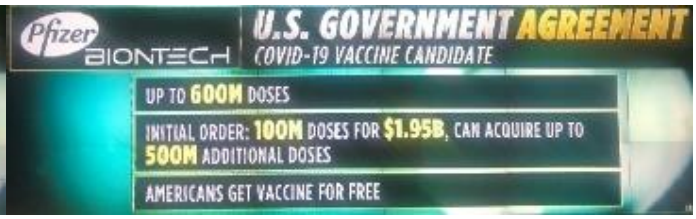
mRNA-1273 encodes for the full-length Spike Protein in the Pre-fusion Conformation (S-2P)



moderna

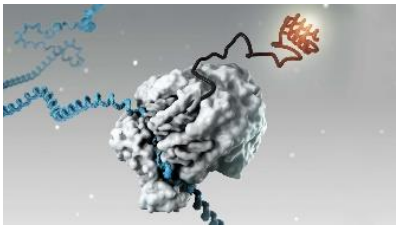

DNA vaccine
SARS-CoV-2 virus
Spike protein
DNA is made with instructions to make viral proteins
DNA packaged in lipid nanoparticles or phages
Vaccine delivered as injection or nasal spray
Host cell
DNA released into cell
Cell nucleus
DNA used to make viral proteins
Immune response

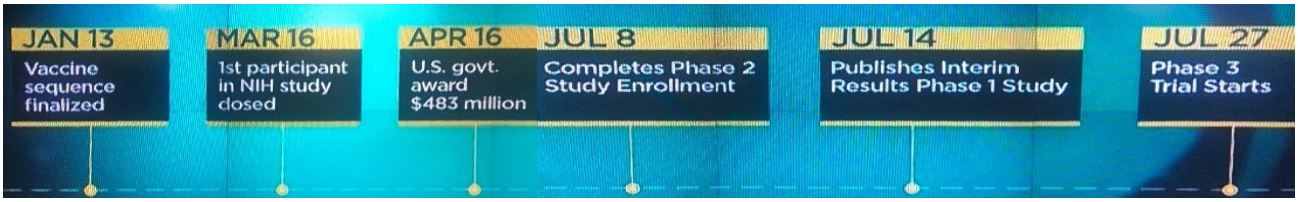

Different live replicating or non-replicating virus engineered to carry gene
SARS-CoV-2 surface protein gene
VIRAL VECTOR VACCINE
Viral vector transcribes the engineered gene in the cytoplasm or enters the nucleus for transcription
CELL NUCLEUS
DNA is transcribed into mRNA
Plasmid enters nucleus of the host cell
A plasmid is synthesised that encodes the genes for the SARS-CoV-2 surface protein
HOST CELL
SARS-CoV-2 surface protein gene
DNA VACCINE
RNA can self-amplify inside the cell in some RNA vaccine systems
mRNA is translated to produce SARS-CoV-2 surface protein
Virus replicates inside cell
Messenger RNA (mRNA) encoding SARS-CoV-2 surface protein gene
RNA VACCINE
Replicated virus buds on cell surface and induces a strong immune response
The virus induces an immune response directly, as well as entering cells and replicating
SARS-CoV-2 virus is weakened or a recoded version of the virus is synthesised
LIVE-ATTENUATED VACCINE
SARS-CoV-2 surface protein synthesised and combined with adjuvant to enhance immune response
SARS-CoV-2 surface protein released
PROTEIN-BASED VACCINE
IMMUNE RESPONSE
Antibodies produced in response to SARS-CoV-2 surface protein



Moderna Therapeutics/National Institutes of Health – FDA EUA Application November 30, 2020

- ✓ Recombinant RNA vaccine – 95% effective
- ✓ Viral MRNA injected into human cells carrying the instructions for the cell to produce viral proteins that mimic COVID-19
- ✓ Showed antibody and T cell response
- ✓ Phase III trials – 30,000 study participants
- ✓ NIH support $100 millions
- ✓ Lonza Group – Swiss manufacturer financial support for 1 billion doses annually





University of Oxford/Astra Zeneca – Announced 90% effective

- ✓ To present result of interim Phase III trials
- ✓ Viral vector (subunit) vaccine
  - DNA code with instruction to produce the COVIDd-19 spiked outer protein are transferred into a monkey adenovirus
  - Adenovirus is injected into humans and reproduces this protein
  - Strong immune response – antibodies and T cells
- ✓ Minor side effects – fatigue and headache worse on second dose
- ✓ In phase III clinical trials seeking 26,000 volunteers from Brazil, U.K., U.S., and South Africa.
- ✓ Received $1.5 billion from the US for 300 million doses
- ✓ Plan to produce 3 billion doses at cost
- ✓ Halted temporarily due to an unexpected central nervous system reaction to the vaccine
- ✓ Can be stored at refrigerator temperatures (-36°F to -46°F) for 6 months
- ✓ More practical storage for developing countries
- ✓ Two doses
- ✓ Efficacy? On ½ then then full dose? 90%? Full dose then second full dose 65% efficacy?
- ✓ Extends USA Phase III trials before FDA EUA application due to unexplained efficacy of the lower dose vaccine.

Johnson and Johnson

- ✓ Viral vector (subunit) vaccine same as Astra Zeneca with weakened adenovirus
  - Strong immune response – antibodies and T cells
- ✓ Minor side effects
- ✓ Phase III 60,000 participants globally
- ✓ $ 1 billion agreement to produce 100 million doses in the US
- ✓ Made Eboli vaccine
- ✓ Halted temporarily due to study participant bad outcome (received placebo and not vaccine).

Sinovac (Chinese), Instituto Butantan/Brazil

- ✓ Inactivated COVID-19 virus vaccine
  - Can no longer replicate
  - Can provoke immune response
  - Antibodies only
- ✓ July 3 Brazil's regulatory agency granted approval for phase III trials starting
  - 9,000 – Brazil, Indonesia, Bangladesh
  - Vaccine produces antibody response only
  - 60-70% effective – interim result Chinese army being vaccinated
- ✓ Trial halt temporary due to serious side effect reported

Glaxo/Smith/Kline

- Phase III trials single dose vaccine for developing nations
- Storage 36°F - 46°F – refrigeration for temperature for month.

Sputnik 5 (Russian)

- Approved for public use after Phase I trial
- Compulsory for military to be vaccinated
- Reporting 90% efficacy after Phase II trial – very small numbers
- 30,000 Phase II/III trials ongoing in India

COVID-19 Vaccine Development, Testing and Regulation

GOVERNMENT OVERSIGHT

- At the end of the 19th century, several vaccines for humans had been developed. They were smallpox, rabies, plague, cholera, and typhoid vaccines. However, no regulation of vaccine production existed.
- On July 1, 1902, the U.S. Congress passed "An act to regulate the sale of viruses, serums, toxins, and analogous products," later referred to as the Biologics Control Act (even though "biologics" appears nowhere in the law).
    - First modern federal legislation to control the quality of drugs
    - Response to 1901 contamination events in St. Louis and Camden involving smallpox vaccine and diphtheria antitoxin
    - Created the Hygienic Laboratory of the U.S. Public Health Service to oversee manufacture of biological drugs.
    - Hygienic Laboratory eventually became the National Institutes of Health.
    - Established the government's right to control the establishments where vaccines were made.
    - The United States Public Service Act of 1944 mandated that the federal government issue licenses for biological products, including vaccines.
    - After a poliovirus vaccine accident in 1954 (known as the Cutter incident), the Center for Biologics Evaluation and Research was formed under the Food and Drug Administration to oversee vaccine safety.

STAGES OF VACCINE DEVELOPMENT AND TESTING

First Steps: Laboratory and Animal Studies

Exploratory Stage

- This stage involves basic laboratory research and often lasts 2-4 years
- Federally funded academic and governmental scientists
- Identify natural or synthetic antigens that might help prevent or treat a disease

Pre-Clinical Stage

- Tissue-culture or cell-culture systems and animal testing to assess the safety of the candidate vaccine and ability to provoke an immune response
- Suggest a safe starting dose and a safe method of administering the vaccine
- Vaccination of animals and then try to infect them with the target pathogen
- The pre-clinical stages often lasts 1-2 years

IND Application

- Private company submits an application for an Investigational New Drug (IND) to the U.S. Food and Drug Administration
- An institutional review board, representing an institution where the clinical trial will be conducted, must approve the clinical protocol
- Once the IND application has been approved, the vaccine is subject to three phases of testing

Next Steps: Clinical Studies with Human Subjects

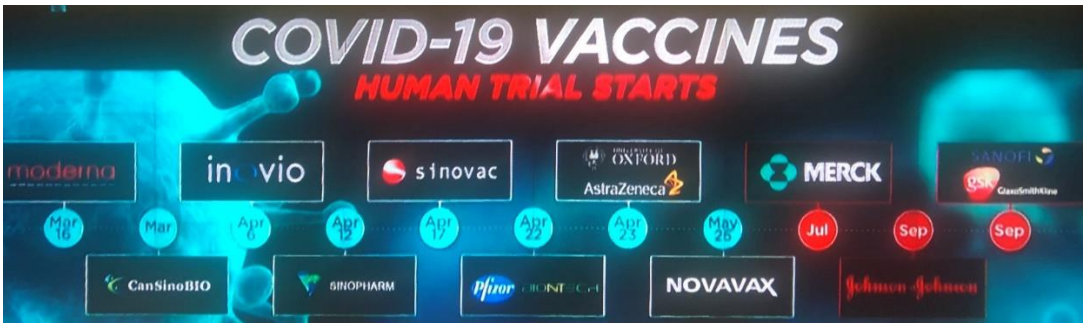
Phase I Vaccine Trials

- This first attempt to assess the candidate vaccine in humans involves a small group of adults, usually between 20-80 subjects
- Subjects know whether a vaccine or placebo is used
- The goals of Phase I testing
    - Assess the safety
    - Determine the type and extent of immune response that the vaccine provokes

Phase II Vaccine Trials

- A larger group of several hundred individuals participate
- Some may belong to groups at risk of acquiring the disease
- Randomized, well controlled and include a placebo group
- The goals are
    - To study the candidate vaccine's safety
    - Immunogenicity
    - Proposed doses
    - Schedule of immunizations
    - Method of delivery.

Phase III Vaccine Trials



- 30,000 study candidates enrolled
- Randomized and double blind and involve vaccine being tested against a placebo (the placebo may be a saline solution, a vaccine for another disease, or some other substance)
- Vaccine safety in a large group of people.
    - Uncover side effects
    - Suppose adverse event occurs in 1 of every 5,000 people. 30,000 subjects are required to detect if a rare side effect is recurrent
- Vaccine efficacy
    - Does it prevent infection with the pathogen?
    - Does it produce antibodies or other types of immune responses?
    - **> 50% OF SUBJECTS MUST PRODUCE/DEVELOP AN IMMUNE RESPONSE TO BE APPROVED**

Next Steps: Emergency Use Authorization/Approval and Licensure

- Submit a Biologics License Application to the FDA. Then the FDA will inspect the factory where the vaccine will be made
- VRBPAC (Vaccine and Related Biologic Products Advisory Committee) will review clinical data from the manufacturer and from the FDA
    - Recommend approval (or not)
    - FDA usually agrees (85%-95%)
    - Recommends the order treatment by risk of infection
- Approve the labeling of the vaccine
- After licensure, the FDA will inspect facilities
- Review the manufacturer's tests of lots of vaccines for potency, safety, and purity

Post-Licensure Monitoring of Vaccines

- Phase IV trials
- Vaccine Adverse Event Reporting System
- Vaccine Safety Datalink

Phase IV Trials

- Manufacturer may continue to test the vaccine for safety, efficacy, and other potential uses
- VAERS is a voluntary reporting system

VAERS database

- Detect new, unusual, or rare vaccine adverse events
- Monitor increases in known adverse events
- Identify potential patient risk factors for particular types of adverse events
- Identify vaccine lots with increased numbers or types of reported adverse events
- Assess the safety of newly licensed vaccines
- Has identified
    - An intestinal problem after the first vaccine for rotavirus was introduced in 1999
    - Neurologic and gastrointestinal diseases related to yellow fever vaccine
    - Blood clotting disorder
    - Encephalopathy
    - Syncope after immunization

Vaccine Safety Datalink

The CDC established this system in 1990. The VSD is a collection of linked databases containing information from large medical groups.
Rapid Cycle Analysis

- Monitors real-time data to compare rates of adverse events in recently vaccinated people with rates among unvaccinated people
- Monitors conjugated meningococcal vaccine, rotavirus vaccine, MMRV vaccine, Tdap vaccine, and the HPV vaccine

IN CONCLUSION

Vaccines are developed, tested, and regulated in a very similar manner to other drugs. In general, vaccines are even more thoroughly tested than non-vaccine drugs because the number of human subjects in vaccine clinical trials is usually greater. In addition, post-licensure monitoring of vaccines is closely examined by the Centers for Disease Control and the FDA.

YOU SHOULD ACCEPT A VACCINE WHEN OFFERED TO FIRST RESPONDERS. IGNORE ALL THE POLITICAL INTRIGUES. THE VACCINE WILL BE RELEASED UNDER EMERGENCY USE AUTHORIZATION WHICH IN THIS CASE MEANS DUE TO AN AVERAGE NUMBER OF DEATHS DAILY AT GREATER THAN 700 OUT OF 40,000 THAT TEST POSITIVES. THIS EARLY RELEASE FOR HEALTH CARE WORKERS AND HIGH-RISK ELDERLY PATIENTS, WILL BE FOR PFIZER AND MODERNA VACCINES WHICH HAVE 30,000 SUBJECTS; 15,000 RECEIVING PLACEBO INJECTIONS AND 15,000 RECEIVING VACCINES. SUBJECTS RECEIVING VACCINES IN BOTH STUDIES HAVE SHOWN A GOOD IMMUNE RESPONSE WITHOUT SERIOUS SIDE EFFECTS AND 95% WERE PROTECTED FROM COVID-19 WHEN VACCINATED.

VACCINE QUESTIONS

Question 1- Why is there a new flu vaccine every year? Will there be a new COVID-19 vaccine every year?
Most vaccines are rarely changed, the seasonal flu vaccine changes frequently. This is because the strains of influenza viruses that circulate are constantly changing. Each year, researchers choose viruses for the vaccine based on which ones are likely to be circulating over the course of the coming flu season, thus providing protection against the most prevalent strains. When you get a seasonal flu vaccine, you're usually getting protection against a whole new batch of flu viruses that have mutated.

Question 2 – How long does the vaccine development process often last?
A. 2-4 years
B. 5-9 years
C. 10-15 years
D. None of the above
Answer: 10-15 years. The vaccine for COVID-19 under project Warp Speed may only take 9 months.

Question 3 – Vaccines are tested for safety in animals before they are tested in humans.
Answer: Yes

Question 4 - How do vaccines work? Do they work against viruses and bacteria?
Vaccines work to prime your immune system against future "attacks" by a particular disease. There are vaccines against both viral and bacterial pathogens, or disease-causing agents. When a pathogen enters your body, your immune system generates antibodies to try to fight it off. Depending on the strength of your immune response and how effectively the antibodies fight off the pathogen, you may or may not get sick. If you do fall ill, however, some of the antibodies that are created will remain in your body playing watchdog after you are no longer sick. If you are exposed to the same pathogen in the future, the antibodies will "recognize" it and fight it off.
Vaccines work because of this function of the immune system. They are made from a killed, weakened, or partial version of a pathogen. When you get a vaccine, whatever version of the pathogen it contains is not strong or plentiful enough to make you sick, but it is enough for your immune system to generate antibodies against it. As a result, you gain future immunity against the disease without having gotten sick: if you are exposed to the pathogen again, your immune system will recognize it and be able to fight it off.
Some vaccines against bacteria are made with a form of the bacteria itself. In other cases, they may be made with a modified form of a toxin generated by the bacteria. Tetanus, for example, is not directly caused by the Clostridium tetani bacteria. Instead, its symptoms are primarily caused by tetanospasmin, a toxin generated by that bacterium. Some bacterial vaccines are therefore made with a weakened or inactivated version of the toxin that actually produces symptoms of illness. This weakened or inactivated toxin is called a toxoid. A tetanus immunization, for example, is made with tetanospasmin toxoid.

Question 5 - Why aren't all vaccines 100% effective?
Individual immune systems are different enough. The effectiveness of most vaccines is high. 99.7% of vaccinated individuals are immune to measles. Polio vaccine offers 99% effectiveness after three doses. Chickenpox vaccine is between 85% and 90%.

Question 6 - Is natural immunity better than vaccine-acquired immunity?
In some cases, natural immunity is longer-lasting than the immunity gained from vaccination. The risks of natural infection, however, outweigh the risks of immunization for every recommended vaccine. Additionally, the Hib (Hemophilus influenzae type b) and tetanus vaccines actually provide more effective immunity than natural infection.

Question 7 - Why do some vaccines require boosters?
The length of acquired immunity varies with different vaccines. If a disease progresses very rapidly, the immune system's may not be able to respond quickly enough to prevent infection—unless they have been "reminded" about the disease fairly. Boosters serve as a "reminder" to your immune system. Research is continuing on the persistence of immunity generated by vaccines.

Question 8 - Can you get a disease from the vaccine that is supposed to prevent it? And why do some vaccines have live pathogens, but others have killed pathogens?
Vaccines that are made with killed versions of pathogens—or with only a part of the pathogen—are not able to cause illness. It is impossible for him or her to become ill with the disease. Live, attenuated (or weakened) vaccines are theoretically capable of causing illness: because they can still replicate (though not well), mutation is possible, which can result in a virulent form of the pathogen. Reversion to virulent form is a problem with some forms of the oral polio vaccine (OPV), which is why only the inactivated form (IPV) is now used. The attenuated vaccines can cause serious problems for individuals with weakened immune systems, such as cancer patients. Doctors may recommend against vaccination. Attenuated vaccines generate longer-lasting immunity than killed vaccines. Killed vaccines are more likely to require boosters.

Question 9 - Why is allergy to eggs a contraindication to getting some vaccines?
During the process of creating the vaccine, the majority of the egg protein is removed, but there is some concern that these vaccines might generate an allergic reaction in individuals with an egg allergy. Only people with a severe (life-threatening) allergy to eggs are recommended against receiving egg-based vaccines.

Question 10 - Do vaccines cause autism?
No. Vaccines do not cause autism. This possibility was publicized after a 1998 paper by a British physician who claimed to have found evidence that the MMR (measles, mumps, and rubella) vaccine was linked to autism. The potential link has been thoroughly explored; study after study has found no such link. Studies were also done regarding the possibility of a link between the preservative thimerosal, which is used in some vaccines, and autism; again, no such link was found. It is likely that this misconception persists because of the coincidence of timing between early childhood vaccinations and the first appearance of symptoms of autism.

Question 11 - People say that vaccines are linked to long-term health problems such as multiple sclerosis, diabetes, and autism. Is that true?
All vaccines have possible side effects. Most, however, are mild and temporary. Adverse effects from vaccines are monitored thoroughly via multiple reporting systems, and there is no evidence from these systems to support these claims.

Question 12 - Do we do enough safety testing with vaccines?
Vaccines are tested repeatedly before being approved and continue to be monitored for adverse reactions after their release. (See above discussion)

Question 13 – Some vaccines must be stored at -200°F. True or False
False – Pfizer and Moderna have successfully created a vaccine that is very effective but delicate genetic material that breaks down if not kept very cold until use. -94°F for Pfizer and -4°F for Moderna.

Question 14 – When will we have a vaccine for COVID-19 available? And who will be vaccinated first?
The Vaccine and Related Biological Products Advisory Committee (VRBPAC), an independent group of 15 viral disease experts will evaluate the Pfizer data and application for Emergency Use Authorization on December 10, 2020 and likely approve the vaccine. The UK Vaccine Advisory Committee approved the Pfizer vaccine on December 2, 2020. The FDA sheldom rejects VRBPAC's recommendations. The US military will distribute the vaccine to predetermined locations in each state starting December 11, 2020. The states will distribute vaccines to the Health Departments of each county likely completed by December 13, 2020 to start vaccinating. The vaccine priority in Florida will be determined by the Florida Department of Health based on the CDC's Phased Approach to Vaccine Distribution guidelines The vaccine priority in Florida will be determined by the Florida Department of Health based on the CDC's Phased Approach to Vaccine Distribution guidelines - https://www.cdc.gov/vaccines/imz-managers/downloads/COVID-19-Vaccination-Program-Interim_Playbook.pdf

- ✓ Phase 1 – Critical populations
  - 1A - Persons serving in healthcare settings who have the potential for direct or indirect exposure to infectious patients or materials (hospitals, long-term care facilities, etc.)
  - 1B – People who play a key role in keeping essential functions of society running and cannot socially distance in the workplace (first responders, teachers, childcare workers, police), adults with high-risk medical conditions who possess risk factors for severe COVID-19 illness, and people 65 years of age or older (including those living in LTCFs)
- ✓ Phase 2 – Those who were not included in Phase 1, the general public with an emphasis on those individuals who are at a severe risk for complications from COVID
- ✓ Phase 3 – General distribution

Expectations are vaccines will be available to all 300 million Americans by March/April 2021 with vaccines from Astra Zenica, Johnson & Johnson, Novavax, GlaxoSmithKline and other COVID-19 vaccine developers after receiving FDA EUA for distribution. By mid-summer, Dr. Fauci believes COVID-19 vaccination efforts should be completed (70%-80% of the population) and "herd immunity" achieved so COVID-19 can no longer spread… until next year's seasonal viruses come around.