A Brief Introduction to Covid-19 Vaccines

Khusro Arastu, MD

skarastu@aol.com

December 2020

Types of possible Covid-19 Vaccines

- **Active Immunity** (Vaccination)
  - **DNA Vaccine** (Inovio)
  - **RNA Vaccine** (Moderna, Pfizer)
  - **Viral Vector** (Oxford/AstraZeneca, Janssen, Gamalaya-Sputnik)
  - **Viral Subunit** (Novavax, AdaptVac, Clover Biopharma)
  - **Live Attenuated** (Codagenix, Indian Immunologicals Ltd.)
  - **Inactivated Virus** (SinoVac, SinoPharm, Bharat Biotech)
  - **VPL (Virus Like Particles)**
  - **Split Virus Vaccines** (e.g. Flu Vaccines)
  - RNP (Ribonucleoprotein) Vaccine.
- **Passive Immunity** (Antibody Administration)
  - Antibodies
    - Monoclonal Antibodies (e.g. Bamlanivimab)
    - Polyclonal Antibodies (e.g. Regeneron)
  - Convalescent Plasma
  - **mRNA Induced Antibody** (M.I.T.)

Vaccines in US (Phase 3)

Moderna*
Pfizer*
AstraZeneca*
Janssen
Novavax

** Completed Phase 3*

Types of Covid-19 Vaccines in the Pipeline

NUCLEIC ACID VACCINES	Company	Mechanism	Current Examples
DNA Vaccines	Inovio	Gene that codes for Viral proteins	*None currently*
RNA Vaccines	BioNTech/Pfizer; Moderna	mRNA templete for Viral proteins	*None Currently*
Viral Vector Vaccines	AztraZeneca; CanSino, Janssen, Gamalaya	A harmless Virus transports Virus gene	Ebola, Zika, Dengue
RNA Induced Antibody	M.I.T (Mass Institute of Technology)	mRNA thats translated into Antibodies	*None currently*
PROTEIN VACCINES			
Viral Sub-Unit Vaccines	Novavax; AdaptVac, Clover Pharma	Virus Surface Protiens / subunits	Zoster, Hepatitis B, HPV, DPT
Split Virus Vaccine	*None currently*	Cut Pieces of the actual virus	Flu Vaccines
VLP Vaccines	*None Currently*	Virus Like Particles simulate virus	*None Currently*
VIRAL VACCINES			
Live Attenuated Vaccines	Codagenix, Indian Immunologicals	Weakened Actual Virus	MMR, Chickenpox, Polio, TB
Inactivated Vaccines	SinoVac; SinoPharm	Virus killed by heat/chemicals	Polio

Status of the Vaccines

Company	Type	Doses (days)	Route	Trials	Status
Sinovac	Inactivated	**2 (0,14)**	IM	Phase 3	
SinoPharma	Inactivated	**2 (0,21)**	IM	Phase 3	
Bharat Biotech	Inactivated	**2 (0,28)**	IM	Phase 3	
Oxford/AstraZeneca	Viral Vector (Non-replicating)	**2 (0,28)**	IM	Phase 3	**Complete**
CanSino	Viral Vector (Non-replicating)	**1**	IM	Phase 3	
Gamaleya-Sputnik	Viral Vector (Non-replicating)	**2 (0,21)**	IM	Phase 3	**Complete**
Janssen (J & J)	Viral Vector (Non-replicating)	**2 (0,21)**	IM	Phase 3	
Novavax	Protein Sub-Unit	**2 (0,21)**	IM	Phase 3	
Moderna	Lipid Nanoparticle-**mRNA**	**2 (0,28)**	IM	Phase 3	**Complete**
BioNTech / Pfizer	Lipid Nanoparticle-**mRNA**	**2 (0,28)**	IM	Phase 3	**Complete**
Wantai - Xiamen	Viral Vector (Replicating)	**1**	**Nasal spray**	*Phase 2*	
Inovio	**DNA** Vaccine	**2 (0.28)**	**Intra Dermal**	*Phase 2*	

- *Most of the vaccines are intra-muscular (IM), but some are intranasal (Nasal spray), intra-dermal, subcutaneous or even oral (capsules)*

Why Multiple Vaccines ?

- A variety of COVID-19 vaccines are being developed around the world.
- According to WHO, as of November 12th 2020, there are **48 vaccines in Clinical Trials** and 164 candidate vaccines in Pre-clinical evaluations.
- All of them share one thing in common: they all stimulate a primary immune response so that the body can develop memory B and T cells against the SARS-CoV-2 virus.
- The development of immune memory by vaccines is what will protect the person against subsequent COVID-19 infection.
- Each COVID-19 vaccine has distinct advantages and disadvantages, but the development of different COVID-19 vaccines provides some redundancy and overlap.
- In case a vaccine is unsafe in humans or fails to protect people against COVID-19, the world has other COVID-19 vaccines that it can trial and produce.
- It is this pursuit of multiple vaccines that will allow the global population to be immunized sooner, allowing COVID-19 to be eliminated so that the world can start to recover from the pandemic!!

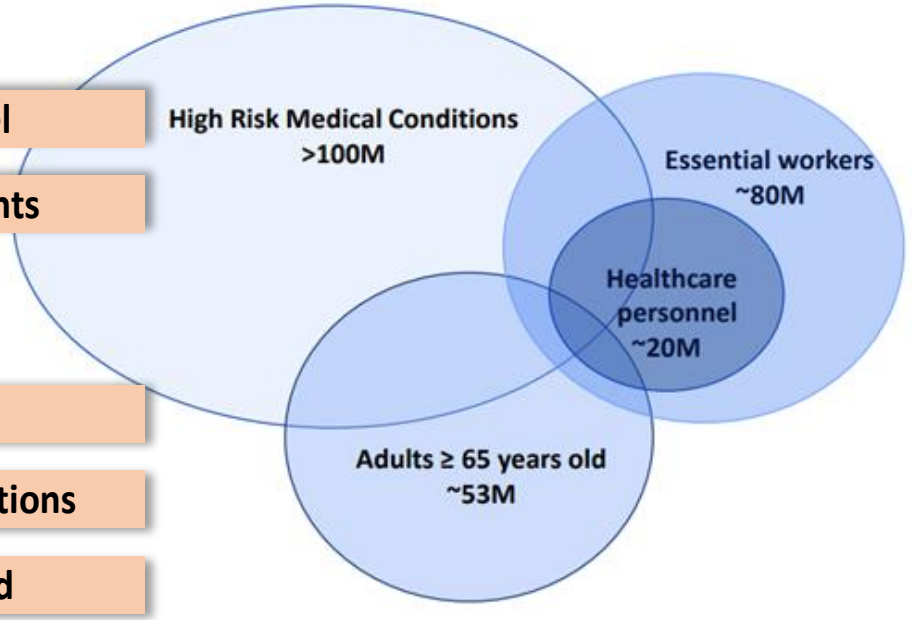
CDC Phase 1 Vaccine Rollout Plans:

PHASE 1a

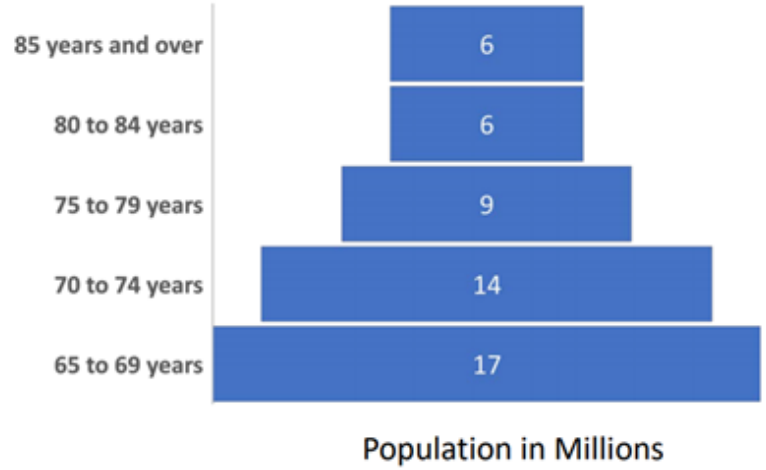
21 million	Health Care Personel
3 Million	Nursing Home Residents

PHASE 1b

87 Million	Essential Workers
100 Million	High Risk Medical Conditions
53 Million	Adults > 65 Years Old



Adults 65 years and older



Healthcare personnel

- All paid and unpaid persons serving in healthcare settings who have the potential for direct or indirect exposure to patients or infectious materials
- Includes persons not directly involved in patient care but potentially exposed to infectious agents while working in a healthcare setting

Estimated Population ~17-20M

Examples:

- Hospitals
- Long term care facilities (assisted living facilities & skilled nursing facilities)
- Outpatient
- Home health care
- Pharmacies
- EMS
- Public health

Essential Workers (non-Healthcare)

- Workers who are essential to continue critical infrastructure and maintain the services and functions Americans depend on daily
- Workers who cannot perform their duties remotely and must work in close proximity to others should be been prioritized
- Sub-categories of essential workers may be prioritized differently in different jurisdictions depending on local needs

Estimated Population ~60M

Examples:

- Food & Agriculture
- Transportation
- Education
- Energy
- Water and Wastewater
- Law Enforcement

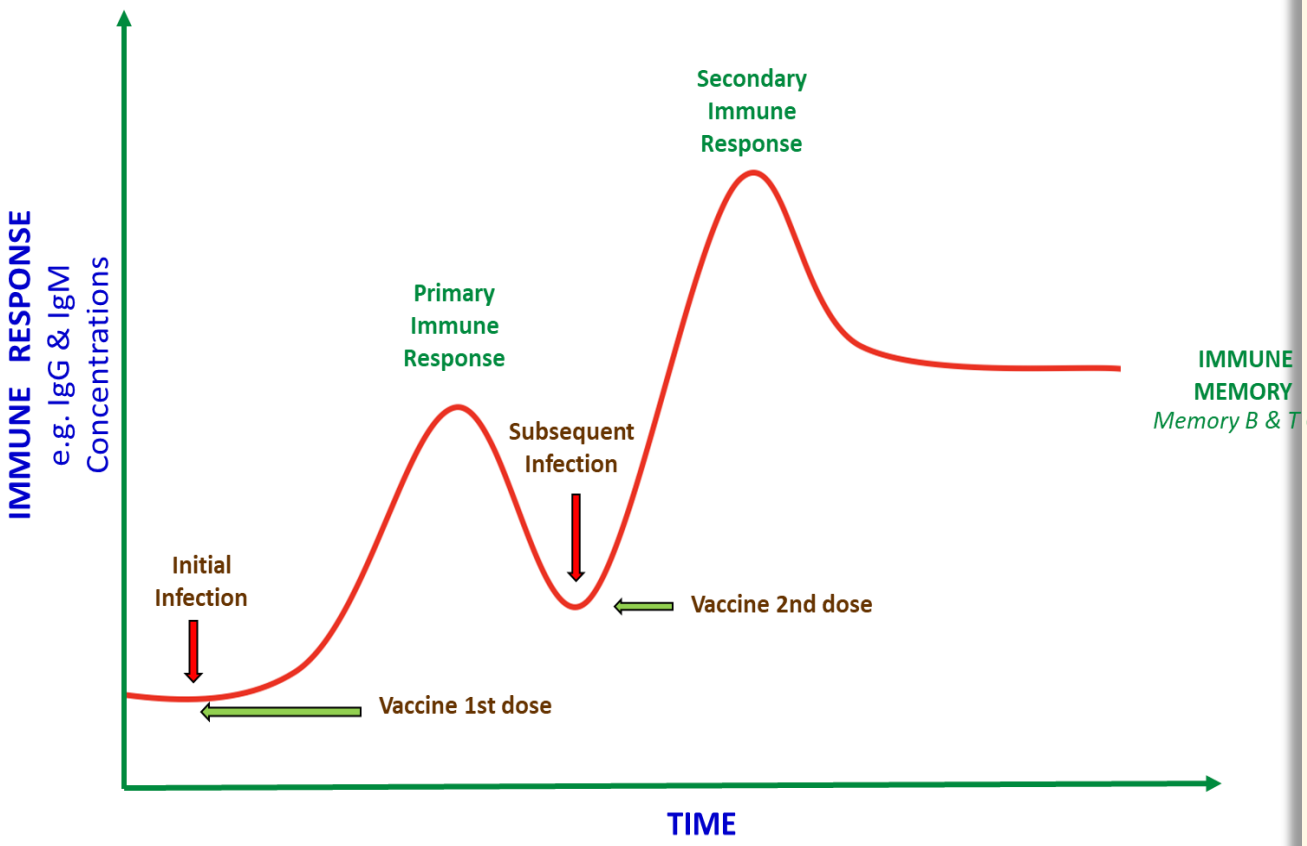
Adults with medical conditions at higher risk for severe COVID-19*

- Cancer
- Chronic kidney disease
- Chronic obstructive pulmonary disease (COPD)
- Immunocompromised state from solid organ transplant
- Obesity (BMI of 30 or greater)
- Serious heart conditions (heart failure, coronary artery disease or cardiomyopathies)
- Sickle cell disease
- Type 2 diabetes mellitus

Estimated Population >100M

Examples‡	% Population
Obesity	31%
Diabetes	11%
COPD	7%
Heart Condition	7%
Chronic kidney	3%

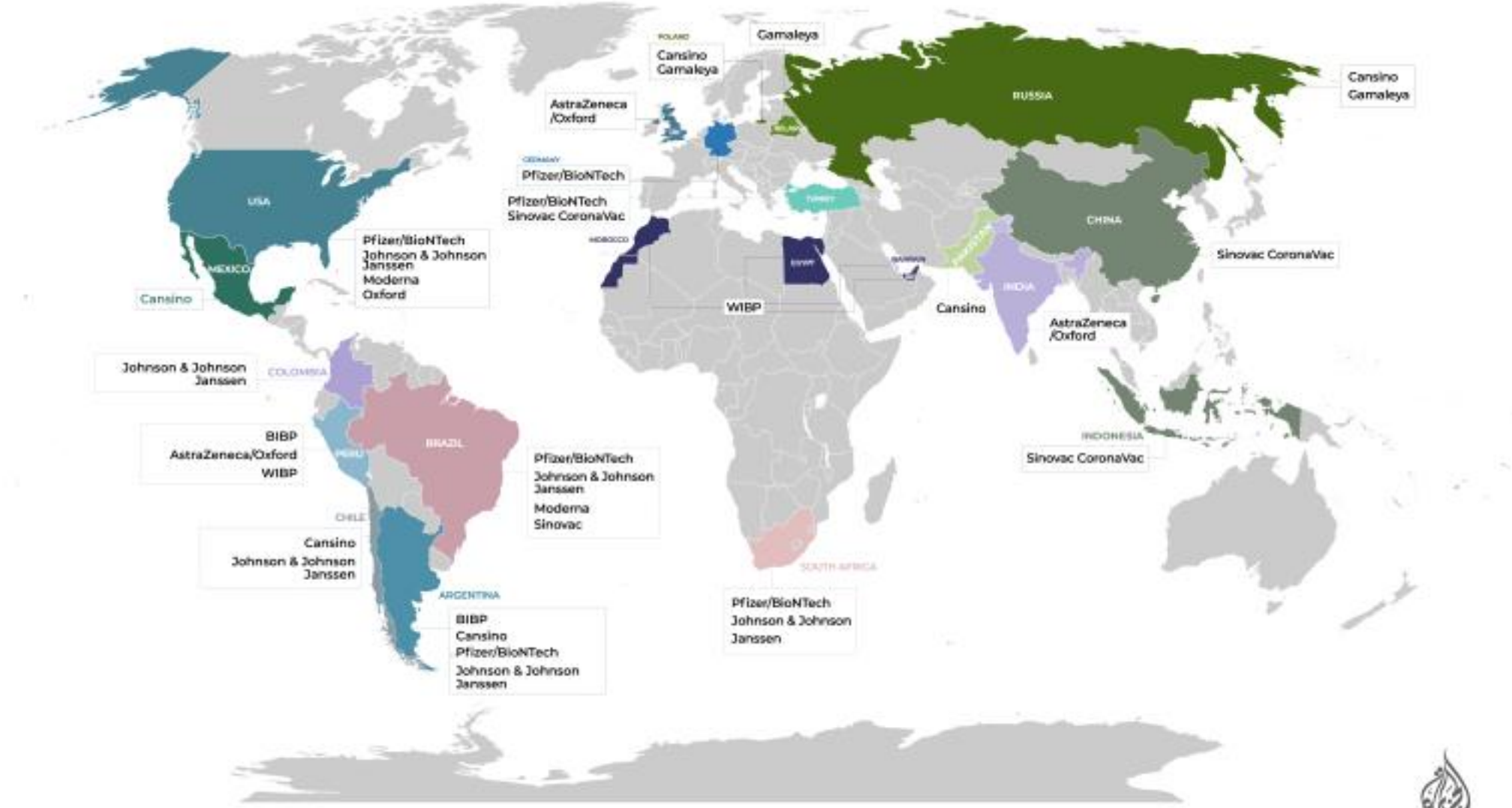
Why Two Doses ?



- Depending on how many times the body is exposed to the virus or vaccinated, the body can generate two types of immune responses.
- The body generates a **primary immune response** when exposed to the SARS-CoV-2 virus for the first time or gets the 1st dose of the vaccine. The primary immune response is slow and weak as it takes days for the body to generate enough antibodies and T cells to eliminate the virus.
- However, the body generates long-lasting memory B and T cells that "remember" the SARS-CoV-2 virus, generating **immune memory**.
- When the virus enters the body for the second time or the 2nd dose of the vaccine is given, the body develop a **secondary immune response**. The secondary immune response is stronger and quicker than the primary immune response as memory B and T cells are rapidly activated.
- This results in higher antibody concentrations and T cell counts around the body to eliminate the virus more quickly, reducing the symptoms and severity of COVID-19.
- In addition, more memory B and T cells are produced after infection which strengthens memory of the SARS-CoV-2 virus.
- It is the development of immune memory that is key to how a vaccine works!!

The Global Picture

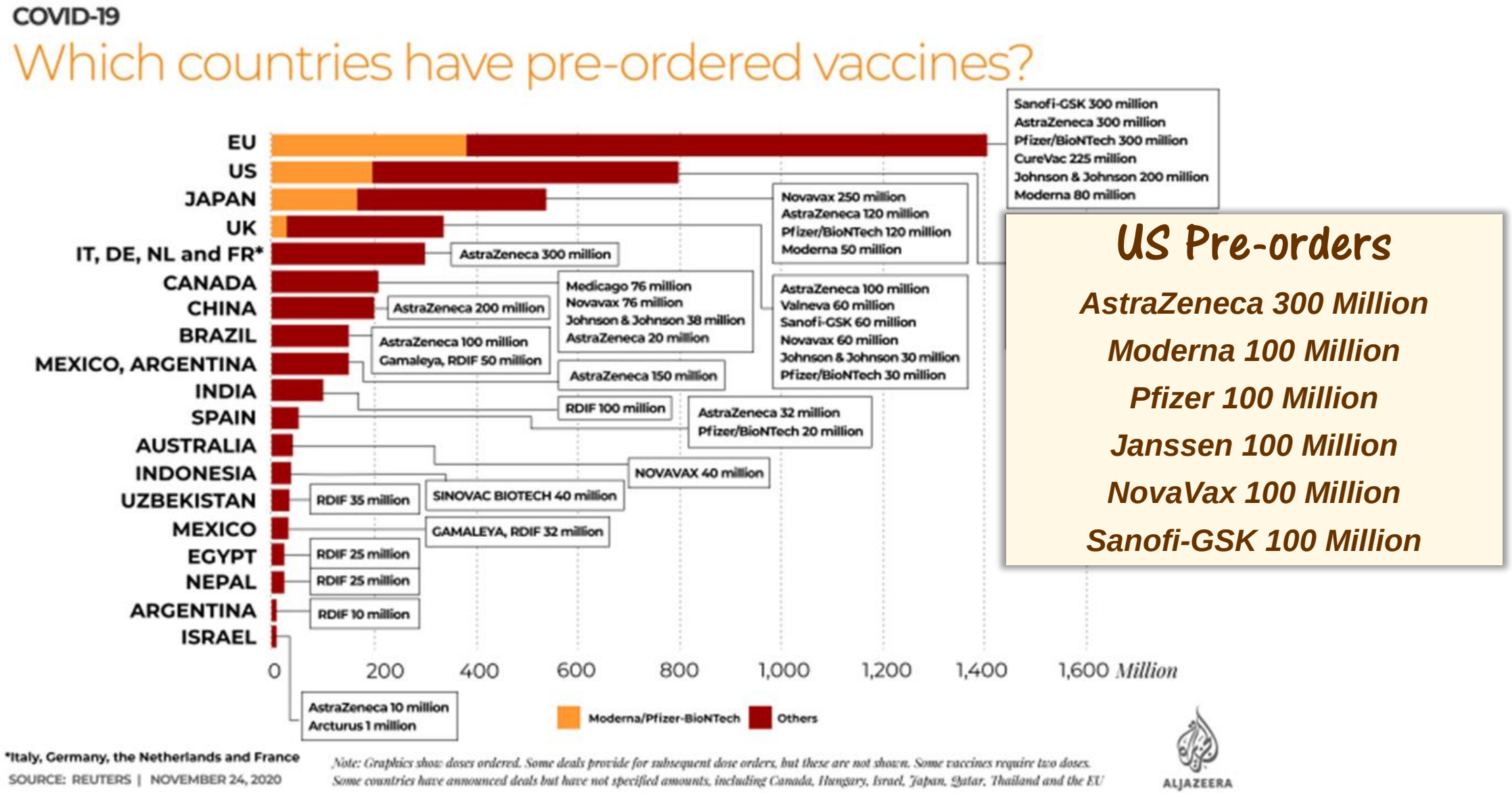
Which countries have active vaccine trials?



SOURCE: LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE | NOVEMBER 24, 2020

ALJAZEERA

Vaccine Pre-orders:



US Pre-orders

AstraZeneca 300 Million

Moderna 100 Million

Pfizer 100 Million

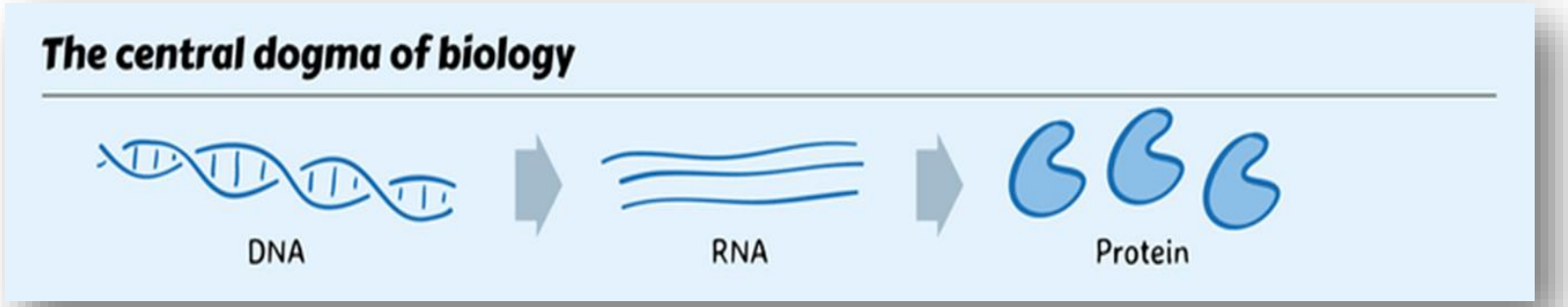
Janssen 100 Million

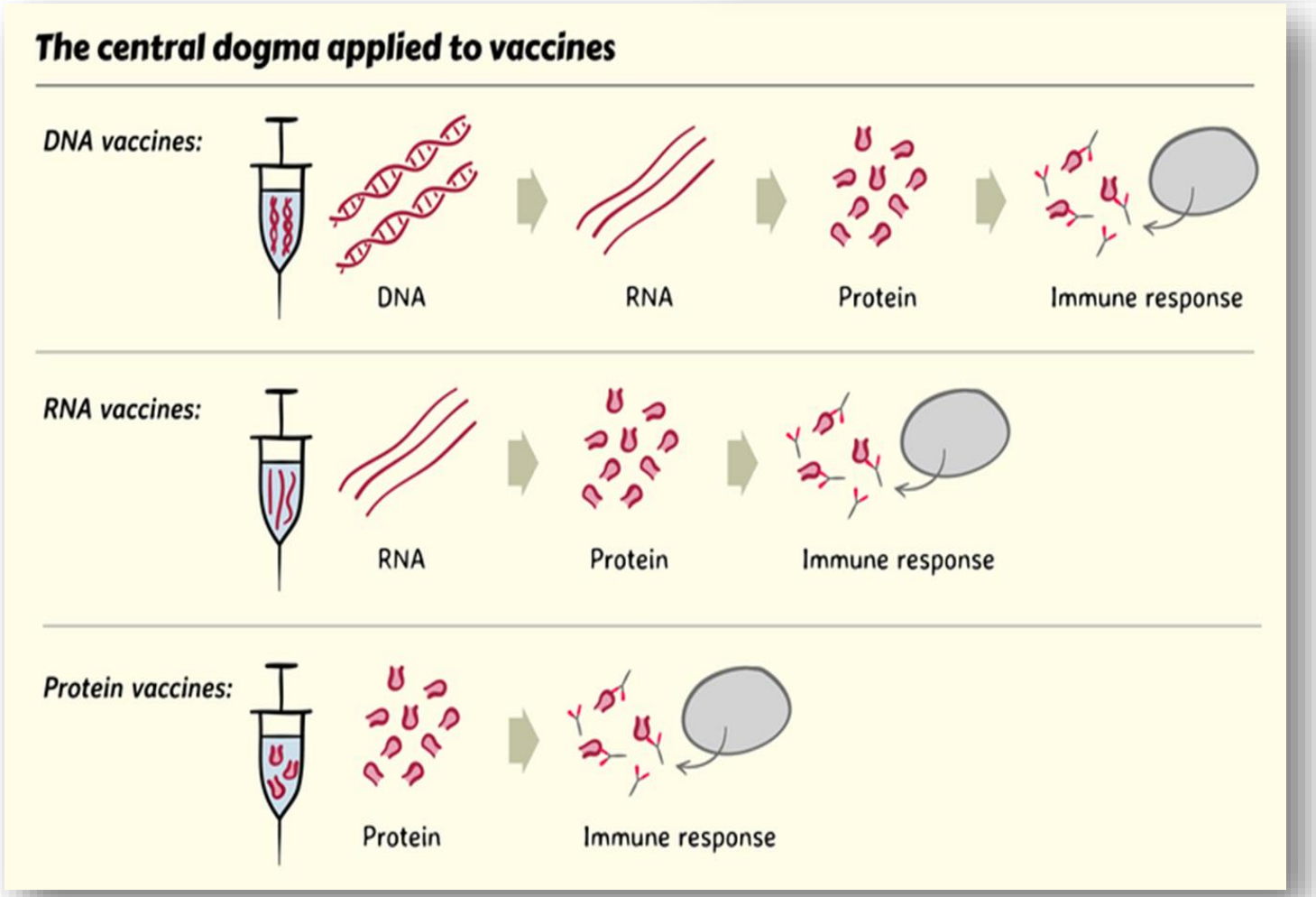
NovaVax 100 Million

Sanofi-GSK 100 Million

The Different Kinds of Vaccines Explained

Types of Vaccines

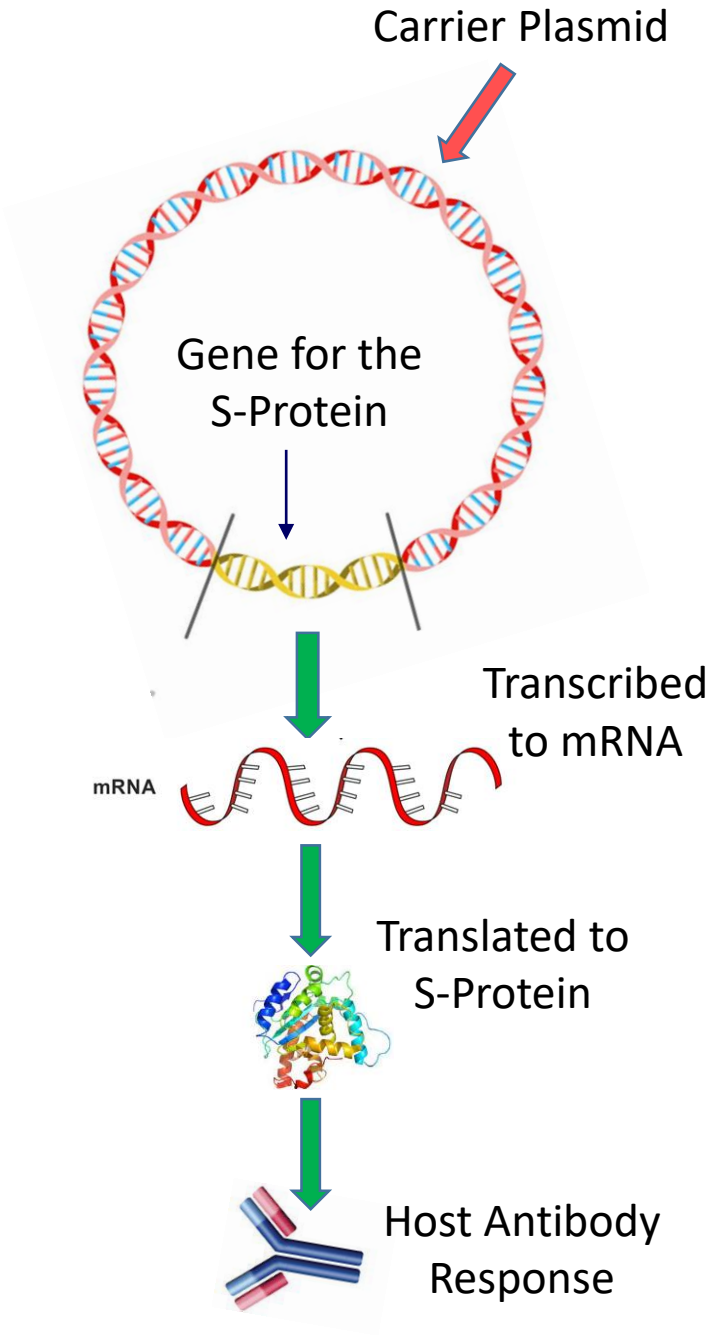




- The SARS-CoV-2 outbreak has prompted the rapid expansion of several technology platforms, including DNA and RNA vaccines, never before clinically tested in humans.
- DNA or RNA Vaccines direct our cells to make parts of viral proteins that do not cause disease, but provoke the immune system, and the immune system then makes antibodies the same as it would had the protein been injected directly.
- Today, rapid production of DNA or RNA in large amounts only requires the sequence of the virus's genetic material. The sequence of SARS-CoV-2 was identified and published by Chinese researchers on *January 11th, 2020*.
- Also other novel vaccines are being developed like the Protein Sub-unit Vaccine and Split virus vaccines. There is also development of synthetic substances called the Virus-Like Particles (VLPs) and the development of mRNAs making Antibodies (Ig) directly instead of the antigen.

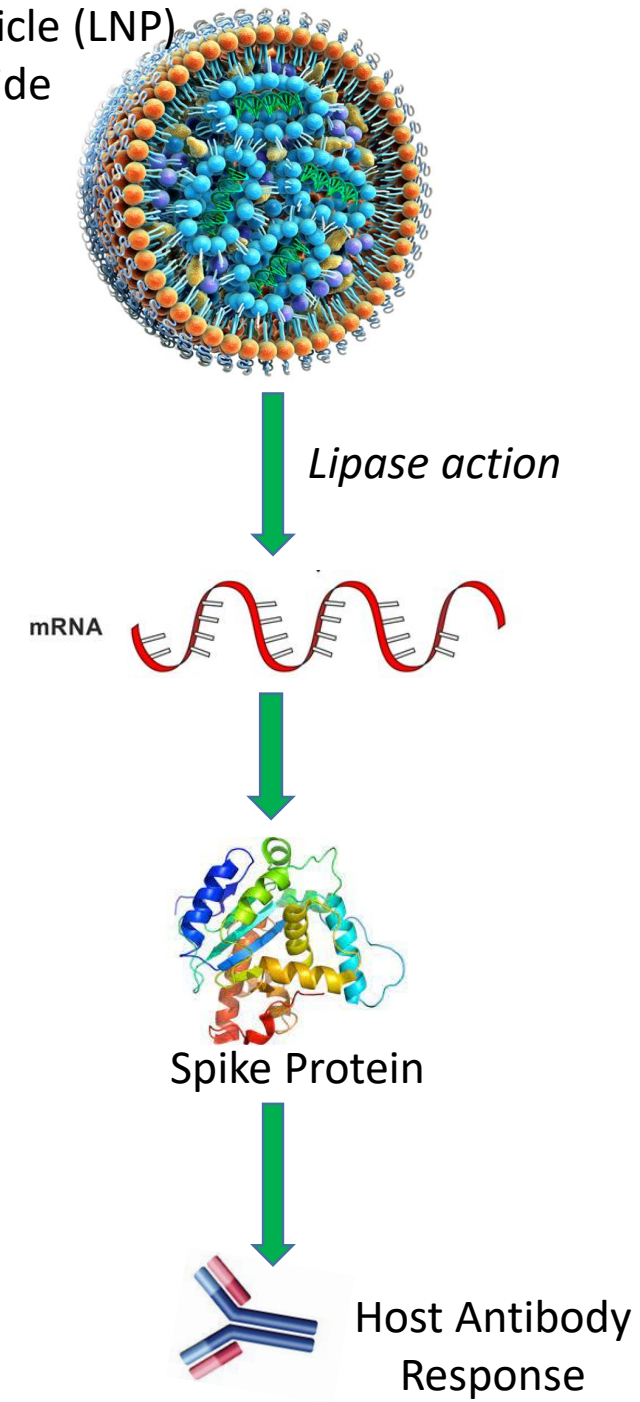
DNA Vaccines

- DNA vaccines are made up of small strands of DNA. Actually the gene encoding the antigen of interest (in this case the Spike Protein or S-Protein, of the Covid-19 Coronavirus).
- The gene is attached to a plasmid for delivery into the body. The Plasmid is used so that the body does not degrade the foreign gene before it can provoke an immune response.
- Once administered the DNA are taken up by host cells which produce the S-Protein, and then reflect the antigen (S-Protein) on its cell surface, thus stimulating an antibody and T cell response.
- ***Inovio Pharma*** (USA) is developing the DNA vaccine INO-4800.
- DNA Vaccines need a special delivery system, and the Inovio vaccine is Intra-Dermal (ID).



mRNA Vaccines

- RNA vaccines consist of an mRNA encoding the antigen of interest (The Corona Virus Spike protein or the S-Protein).
- This is placed in a Lipid Nanoparticle (LNP) vehicle. The LNP prevent the mRNA degradation by the host until it is taken up by the cell. Once administered the RNA are taken up by host cells. The intra-cellular lipases degrade the LNP exposing the mRNA.
- The mRNA is then translated into the S-protein, which is then reflected on the cell surface, stimulating an antibody and T cell response.
- ***Moderna*** has developed the mRNA-encapsulated in a lipid nanoparticle vaccine. The RNA used is the viral RNA, Isolated and spliced to give the exact gene.
- ***Pfizer/BioNTech***, RNA Vaccine uses an mRNA that is genetically engineered in the Lab from the sequenced viral genome. It is also enclosed in Lipid Nanoparticles.
- The gene being packaged is for the S protein.



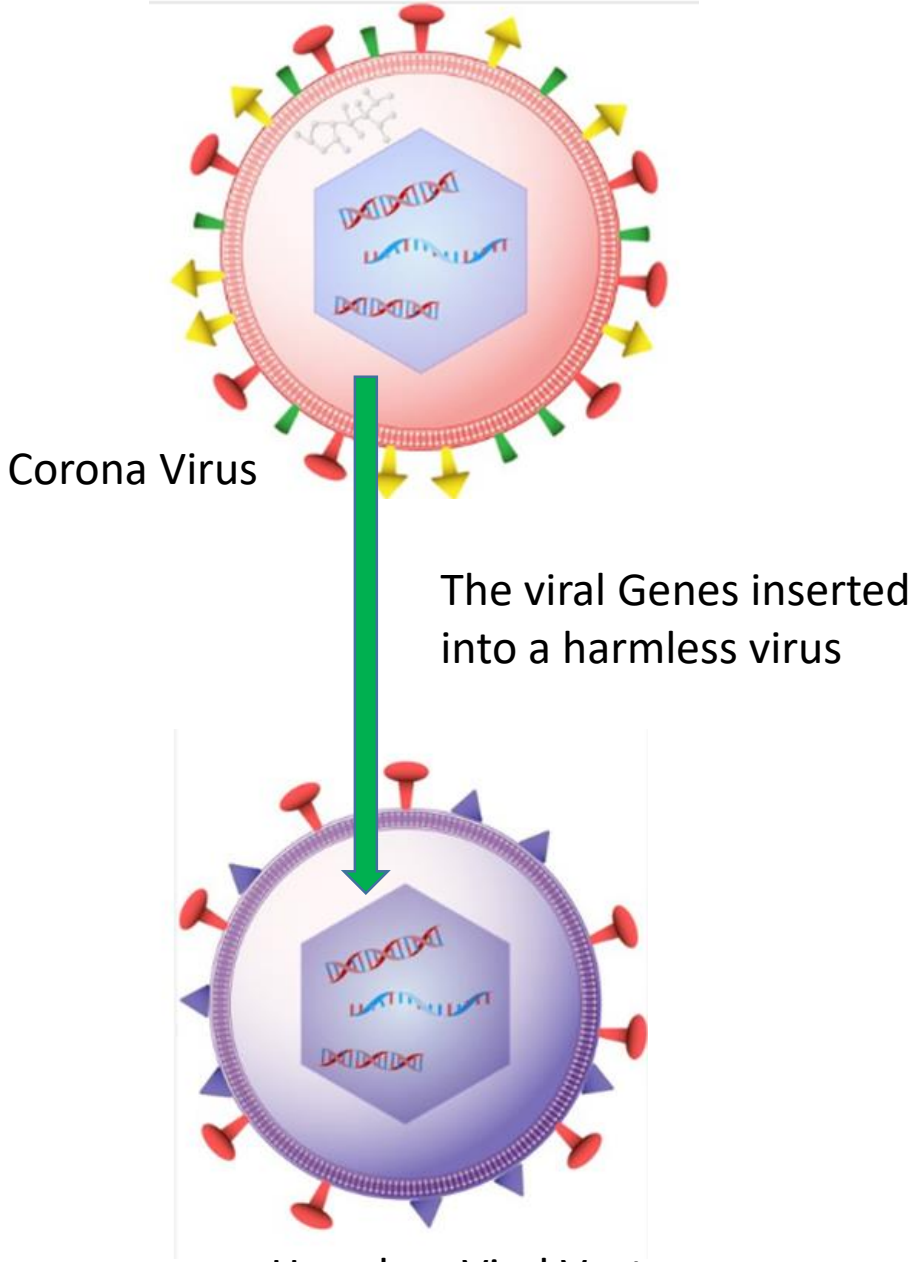
RNA & DNA Vaccines

- DNA and RNA vaccines strike the balance between generating effective immune responses and ease of production.
- DNA and RNA vaccines can induce strong cell-mediated and antibody immune responses as once the DNA or RNA is taken up by the cell, the cell can produce and show the protein on the cell surface to stimulate an immune response.
- the same time, DNA and RNA vaccines are cheaper to produce as genetic material is easy to mass produce.
- They are also safe to administer on immunosuppressed or immunocompromised people as no pathogenic or infectious components are injected, eliminating the risk of infection.

- DNA and RNA vaccines, however, present some challenges. As there are currently no approved DNA or RNA vaccines, it is unclear how effective they will be in vaccinating a population against COVID-19 or how quickly they can be scaled up.
- In addition, naked genetic material alone is unlikely to produce strong immune responses and memory as they can be quickly degraded outside cells and need to cross cell membranes to produce and shuttle the antigen on the cell surface.
- There are also safety concerns that DNA or RNA vaccines can persist in the body for a long period of time and may incorporate into the host's genome. This can mutate cells, leading to the development of tumor cells or malignancies.

Vector Vaccines

- **Viral vector vaccines** are similar to live-attenuated vaccines in that they use a harmless virus known as a vector, to carry a gene encoding the antigen of interest (S-Protein).
- When the vector virus infects a cell, they administer this foreign gene into the cell.
- The cell then transcribes and translates the gene to produces the antigen (s-protein), which is then displayed on the cell surface to stimulate an immune response.
- The infected cell may also slowly reproduce the virus which allows more cells to become infected and produce more antigen, thus amplifying the effect.
- The Oxford/**AstraZeneca**, **Gamalaya**-Sputnik and the **Janssen** vaccines are all Vector Vaccines. They use a harmless adenovirus as a vector for gene delivery.



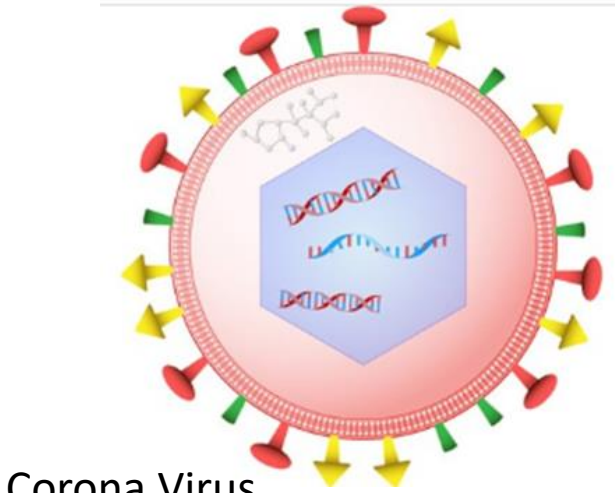
Vector Vaccines

- Viral vector vaccines are a new vaccine technology with only one vaccine of this type currently approved for clinical use. Dengvaxia is a dengue vaccine that consists of two genes from the dengue virus being expressed in an attenuated yellow fever 17D viral strain. The vaccine is only given to people who were previously infected with dengue as it has been shown to cause severe complications and dengue infection among uninfected people.
- Two well-known COVID-19 vaccine candidates are viral vectors, both of them possessing the foreign gene for the S protein.
- AZD1222, developed by Oxford University, in partnership with AstraZeneca contains a gene for the whole S protein that is expressed in a non-replicating chimpanzee adenovirus.
- Gam COVID Vac (Sputnik) is another COVID-19 viral vector vaccine that is developed by Gamaleya Research Institute, Russia. The vaccine consists of the gene for the whole S protein that is contained in two different recombinant human adenoviruses administered separately.

- Similar to live-attenuated vaccines, viral vector vaccines can stimulate strong antibody and T cell responses as the virus is able to (slowly) infect cells to produce and display the S protein on the cell surface.
- This allows both B and T cells to be activated, producing strong immune responses and memory.
- There are some obstacles, though, in approving viral vector vaccines for use in humans. Like live-attenuated vaccines, viral vector vaccines cannot be used in immunocompromised or immunosuppressed people as the immune system is unable to contain the slow replication of the viral vector.
- The viral vector vaccine may also be less effective in people with pre-existing antibodies against the viral vector, preventing it from infecting cells to generate immune memory against the SARS-CoV-2 virus.
- Viral vector vaccines are quite complicated to produce. They require specialized facilities to produce the viral vector vaccine and maintain its purity.
- The Vectors with the inserted gene are considered a genetically modified organism (GMO) that carries a potential risk to the environment, it is also subject to strict environmental regulation and risk management.

Live Attenuated Vaccines

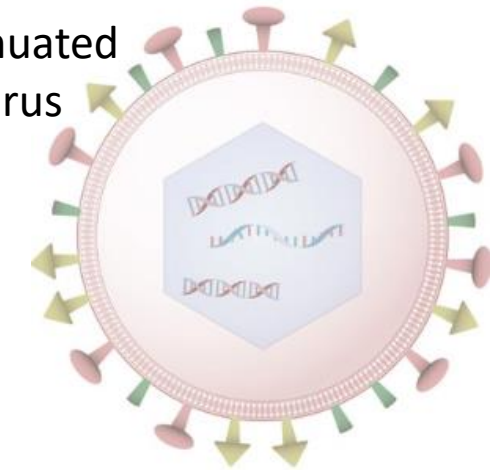
- **Live attenuated vaccines** contain a live but less infective form of the same virus. These vaccines have all the components of the original pathogen, but they possess mutations that reduce their ability to replicate inside the body, so they will not reproduce natural infection.
- It is a proven vaccine technology used to vaccinate people against many infections such as polio, chickenpox and tuberculosis.
- As of the beginning of September 2020; however, only three COVID-19 vaccines are live attenuated vaccines with none entering clinical trials in the U.S.
- One of these is being developed in Griffith University, where parts of the SARS-CoV-2 genome are mutated to reduce but not abolish the ability of the SARS-CoV-2 virus to replicate in human cells.
- Codagenix and Indian Immunological Ltd are developing Live Attenuated Vaccines which are also not yet in clinical trials.



Corona Virus

Virus is alive but rendered less infective but still able to provoke a robust immune response

Live Attenuated Corona Virus



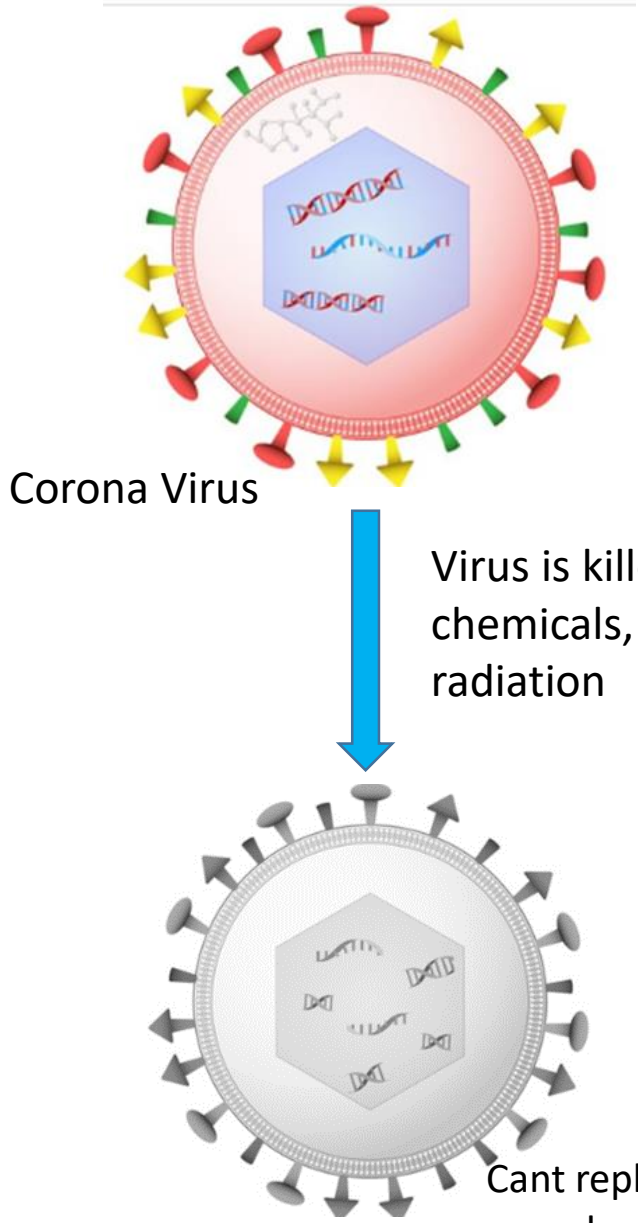
Live Attenuated Vaccines: Advantages & Disadvantages

- Live-attenuated vaccines present some advantages to combating COVID-19.
- A single dose of the vaccine is sufficient to protect the person against COVID-19 as it has all the components of the original SARS-CoV-2 virus to generate strong antibody and T cell responses.
- This generates long-lasting immunity to COVID-19 due to the mass proliferation of memory B and T cells.
- At the same time, a live attenuated COVID-19 vaccine, once approved, can be quickly produced at scale as existing methods and facilities are available to produce live attenuated vaccines.

- There are also disadvantages associated with a live attenuated COVID-19 vaccine. The production of live attenuated vaccines requires biosafety-level facilities to safely produce the vaccine.
- Cold storage facilities are also required to maintain stability of a live attenuated COVID-19 vaccine, limiting the global distribution of the vaccine.
- Also, a live attenuated COVID-19 vaccine cannot be given to immunocompromised or immunosuppressed patients as the attenuated SARS-CoV-2 virus can slowly replicate, exceeding the immune system's ability to contain the pathogen.
- Lastly, there is the risk that the attenuated SARS-CoV-2 virus can accumulate mutations while it replicates to revert back to its infective form, reproducing infection. This is the case for the oral polio vaccine. As it accumulates mutations inside the body, the vaccine can become pathogenic to humans. causing vaccine-derived polio.

Inactivated Vaccines

- Evolving from live-attenuated vaccines that are able to (slowly) replicate in the body, **inactivated vaccines** contain a whole virus that is killed or inactivated by chemical, heat or radiation.
- This eliminates the possibility of the pathogen replicating and possibly causing infection, yet the vaccine still has all the components of the original pathogen to induce a memory response.
- Various inactivated vaccines are available to vaccinate people against infections such as cholera and hepatitis A.
- Following in these footsteps is the CoronaVac, produced by **SinoVac** R&D Co, **SinoPharm** vaccine, and the vaccine from **Bharat Biotech** (Hyderabad, India)
- CoronaVac contains the inactivated SARS-CoV-2 virus that is combined with alum (aluminium salt). Alum acts as an adjuvant to stimulate immune responses against the vaccine.



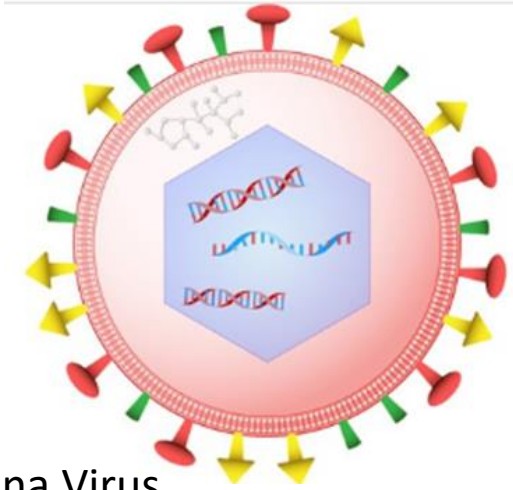
Inactivated Vaccines: Pros & Cons

- Inactivated vaccines are considered safer to use than live-attenuated vaccines with fewer side effects.
- This is because the vaccine components cannot replicate inside the body, eliminating the possibility of infection.
- Inactivated vaccines can also be stored at room temperature as the pathogen is dead and non-replicative. This eliminates the need for refrigeration, allowing the vaccine to be distributed to more remote areas of the world.

- On the other hand, as the inactivated pathogen cannot replicate inside the body, more than one dose of the inactivated vaccine is required to give the body time to develop immune memory against the SARS-CoV-2 virus.
- In addition, specialized biosafety-level facilities are needed to firstly grow the pathogen and then inactivate it at scale.
- Lastly, inactivation of the pathogen may alter the shape of the antigens which may be different from the original version. Hence, the body may not generate the correct immune memory response against the original SARS-CoV-2 virus.

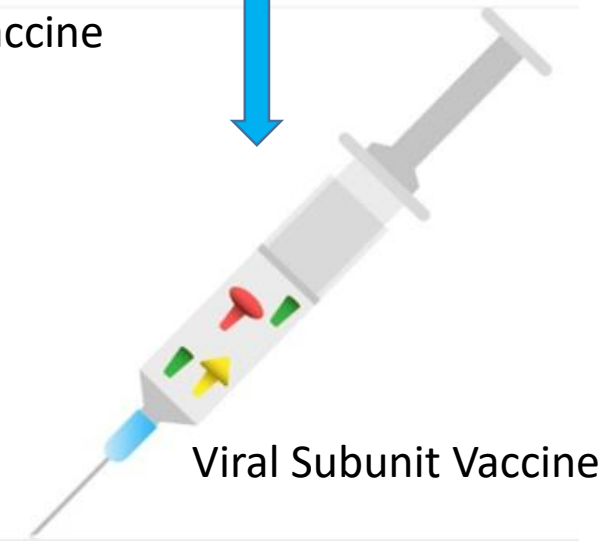
Viral Subunit Vaccines

- **Subunit vaccines** take parts of the Virus (antigens) that simulate an immune response and inject them into the body.
- Most subunit vaccines consist of proteins from the pathogen (such as the SARS-CoV-2 S protein, but they can also be fragments of bacterial toxins (toxoids) or pathogenic components such as the cell wall.
- Two of the COVID-19 vaccine candidates are subunit vaccines: NVX-CoV2373 developed by ***Novavax*** and SCB-2019 developed by ***Clover Biopharma***.
- Both vaccines contain the whole S protein of the SARS-CoV-2 virus combined with an adjuvant, a chemical that enhances the immune response to the vaccine.
- Subunit vaccines produce strong antibody responses as the antigens are collected, processed and presented to B cells to stimulate antibody production.
- Nevertheless, they are safe to administer as the whole pathogen is not injected, so it will not cause infection.
- Lastly, they are simpler and cheaper to produce as only parts of the pathogen need to be produced.



Corona Virus

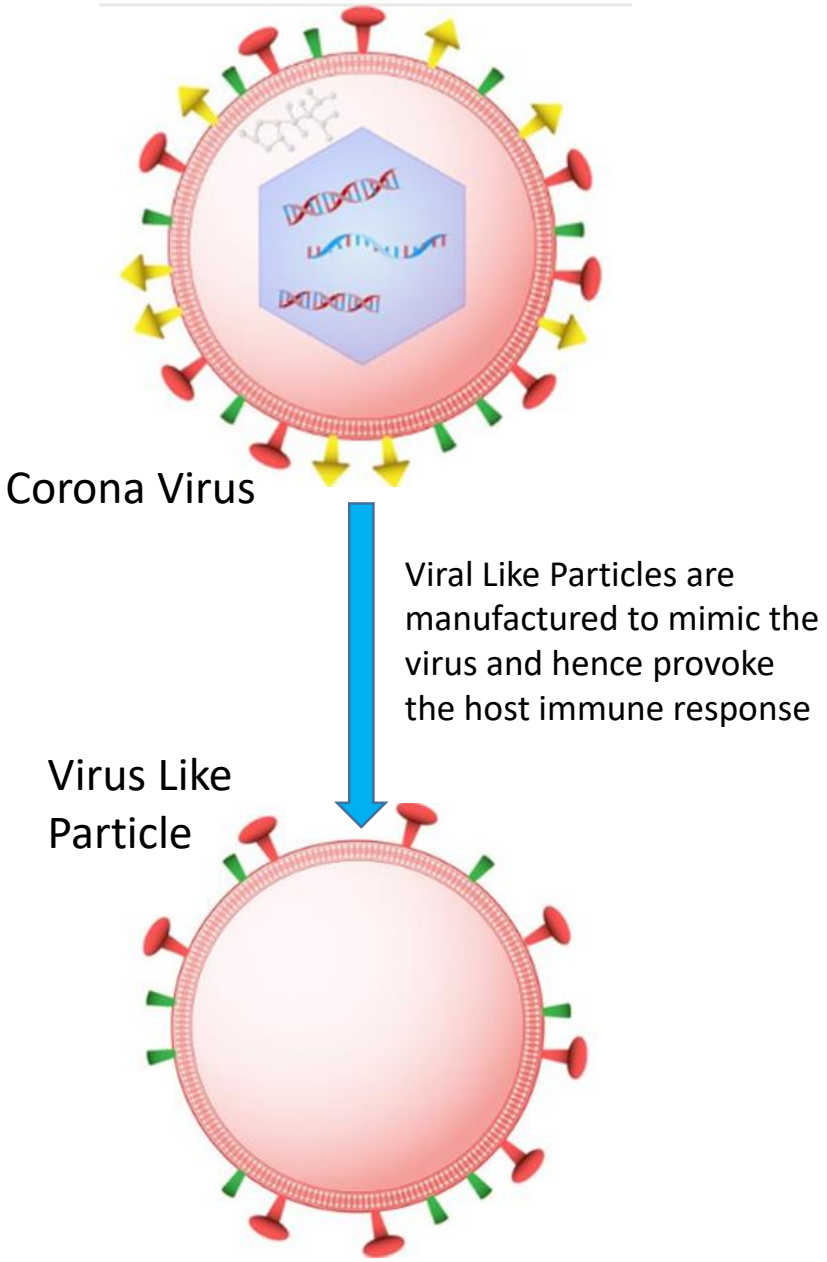
Viral proteins particularly the spike proteins are extracted and made into a vaccine



Viral Subunit Vaccine

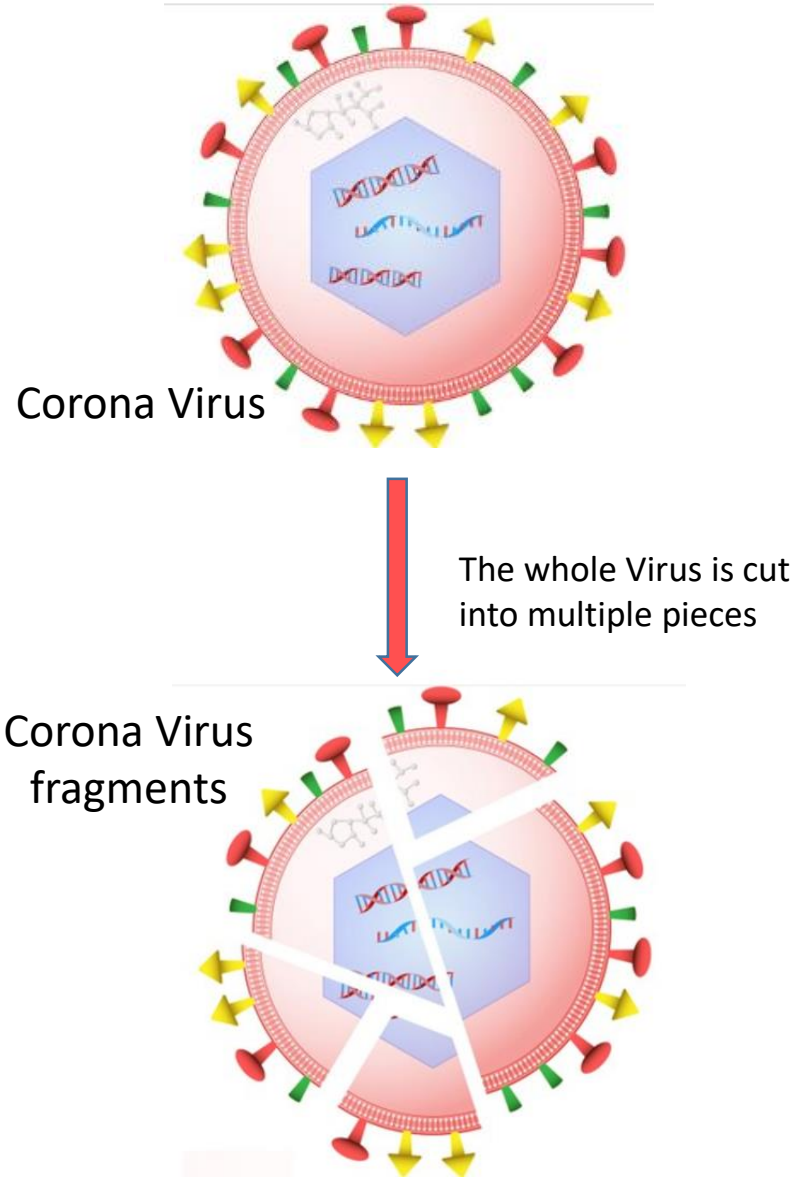
VLP Vaccines (Virus Like Particles)

- **Virus-like particle:** This type of vaccine contains molecules that mimic the virus but are not infectious and, therefore, not a danger. VLP has been an effective way of creating vaccines against diseases such as human papillomavirus (HPV), hepatitis and malaria.
- Virus-like particles (VLPs) are synthetic nanostructures, like Lipid-Nanoparticles, Dendrimers or Fullerenes. They are made to resemble the Virus Antigen and trick the immune system.
- They are composed of structural proteins that can be arranged in several layers and can also contain a lipid outer envelope.
- VLPs trigger a high humoral and cellular immune response due to their repetitive structures.
- A key factor regarding VLP safety is the lack of viral genomic material, which enhances safety during both manufacture and administration.



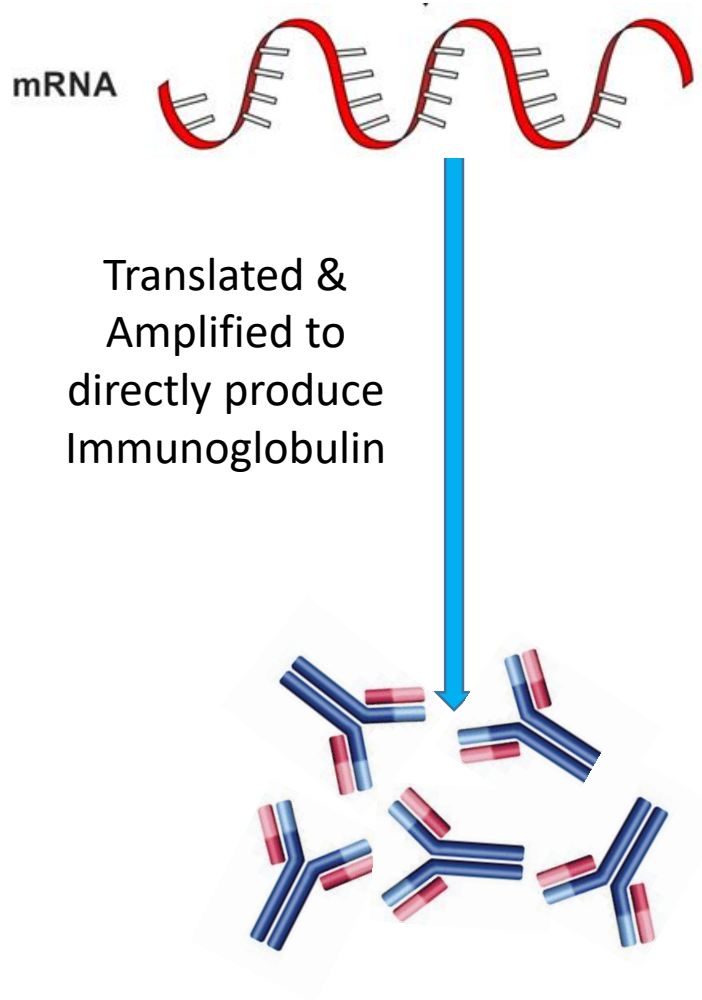
Split-Virus Vaccines

- The vaccine is made by cutting the virus into several pieces.
- All the fragment of the virus are present but in a random mixture. So they cannot cause the disease but provoke an immune response.
- No company is currently working on the split Virus Vaccine technology for the coronavirus
- The advantage of this type of vaccine is the virus is inactive, while all viral elements are present to produce a strong immune response.
- It is difficult to determine the right dose though and moreover, this type of vaccine is not easy to produce.
- The only current example of this kind of vaccine is the *influenza vaccine (Flu vaccine)*.



mRNA Induced Antibody

- This is another novel vaccine concept being explored by **M.I.T.**
- The mRNA here is not coding for the antigen of interest (e.g. the viral S-protein), instead it codes for the actual antibody against the S-protein.
- The mRNA enters the host cell and makes multiple copies of the antibody or the specific Immunoglobulin (against the Virus s-protein).
- This process bypasses several steps of the host immune response by directly making the antibodies of interest and start the fight against the virus.
- Risks and benefits are similar to the other RNA vaccines except that it behaves like passive immunity (by producing the antibody itself) and may have a much faster response time!



Risks, Response and Ease of production:

NUCLEIC ACID	Risks	Immune Response	Manufacture
DNA Vaccine	Risk of integration/Mutation	Medium	Special Facility
RNA Vaccines	Safe	Strong	Easy to produce
Viral Vector	Risk of integration/Mutation	Strong	Easy to produce
VIRUS / PROTEIN	**Risks**	**Immune Response**	**Manufacture**
Live Attenuated	Risk of infection	Robust response	Easy to produce
Inactivated	Safe	Strong	Special Facilities
Viral Sub-Units	Safe	Strong	Easy to produce

The Pipeline: Clinical Trials to Distribution

- Vaccine development moves through established pipelines that require rigorous safety and efficacy testing before public availability. After identification of a vaccine candidate, **pre-clinical studies** in cultured cells and animals ensure the vaccine elicits an effective immune response without being toxic, before clinical trials begin in humans. At this point, the FDA recognizes the vaccine as an **Investigational New Drug** (IND).
- The **Phase 1 Clinical Trial** assesses risk factors or adverse effects, what dose is required, whether this dose is the same for different individuals, and if the vaccine promotes healthy immune systems to make antibodies. The Phase 1 trial for the Moderna vaccine began in record time, just two months after the sequence of the virus was published.
- If there are no risk factors or adverse effects in Phase 1 trials, **Phase 2** and **Phase 3** trials expand to more volunteers, increasing statistical power. Each phase has built-in objectives and endpoints and volunteers are monitored for months. After Phase 3, the vaccine must receive FDA approval before licensing and distribution.
- Then, **Phase 4 Clinical Trials** is the last phase and includes ongoing studies of risk and side effects after the vaccine is distributed.

- Once available, vaccine distribution follows guidelines recommended by the **CDC** (Centers for Disease Control) and developed by the Advisory Committee on Immunization Practices (**ACIP**).
- Vaccine distribution areas include the 50 states, District of Columbia, and eight US territories. During the H1N1 pandemic in 2009, doses were distributed according to population in each distribution area.
- The CDC recommends vaccinating the highest-risk populations first. A priority list is then phased out.
- Before a vaccine is widely available, **Compassionate Use Authorizations** (CUA), **Emergency Use Authorizations** (EUAs) and **the strategic national stockpile** are designed to streamline responses during a crisis and mitigate the most severe cases.
- **BARDA** (Biomedical Advance Research & Development Authority), a government agency, provides national funding for companies and programs dedicated to developing drugs, vaccines and antivirals.
- The **FDA** (Federal Drug Administration) issued EUAs authorizing use without trials and testing for healthcare professionals to test patients for antiviral drugs.