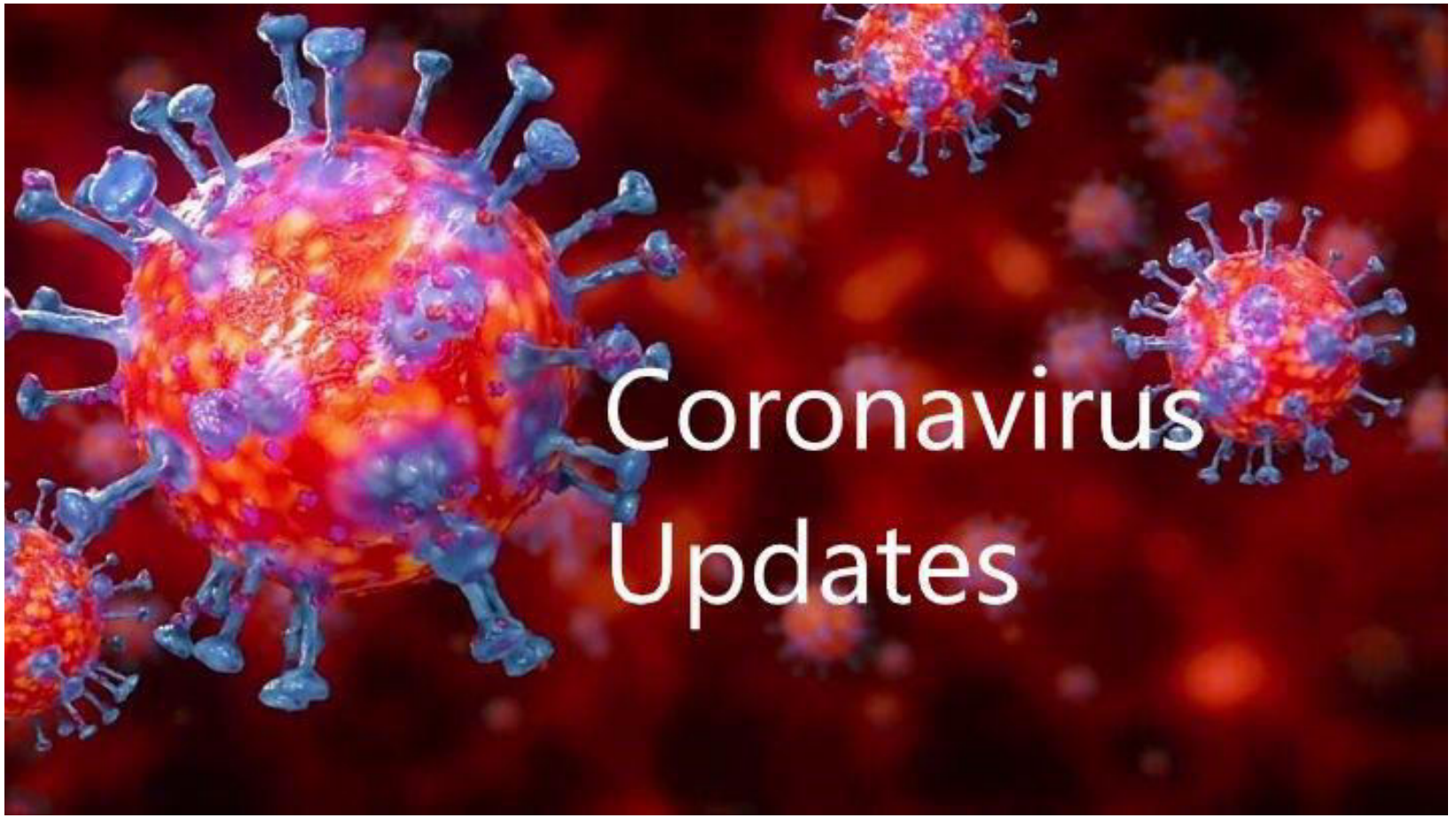

SWAGATHAM

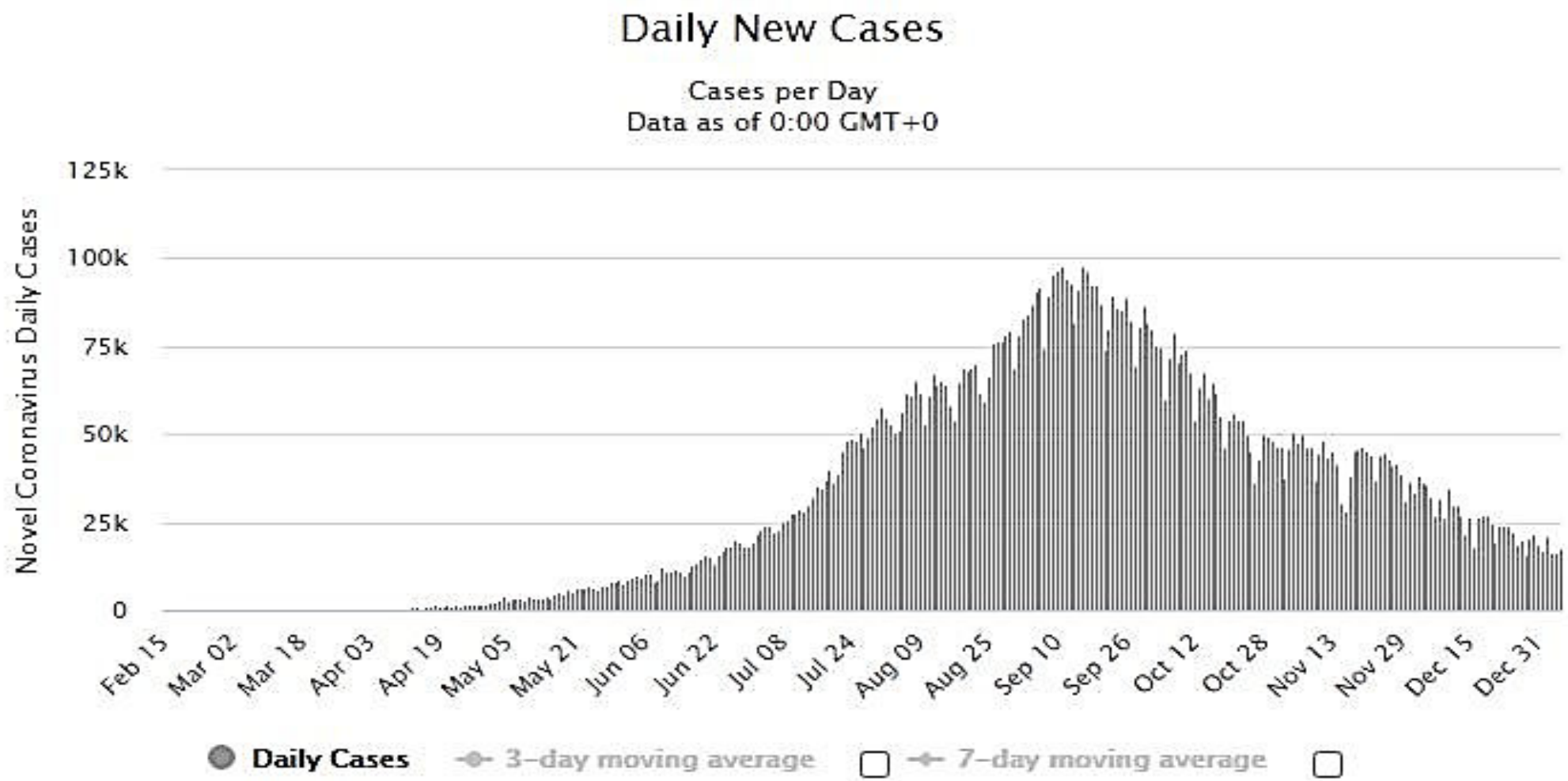
Some public health events of January

- Poliomyelitis was eliminated. The last case on, 13 Jan, 2011. India was officially declared free from polio in 2014, 3 years later. Currently cases of polio occur in only 2 countries, Afghanistan & Pakistan
- World Leprosy Day on last Sunday of January every year since 1954. Coincides with the death anniversary of mahatma Gandhi.

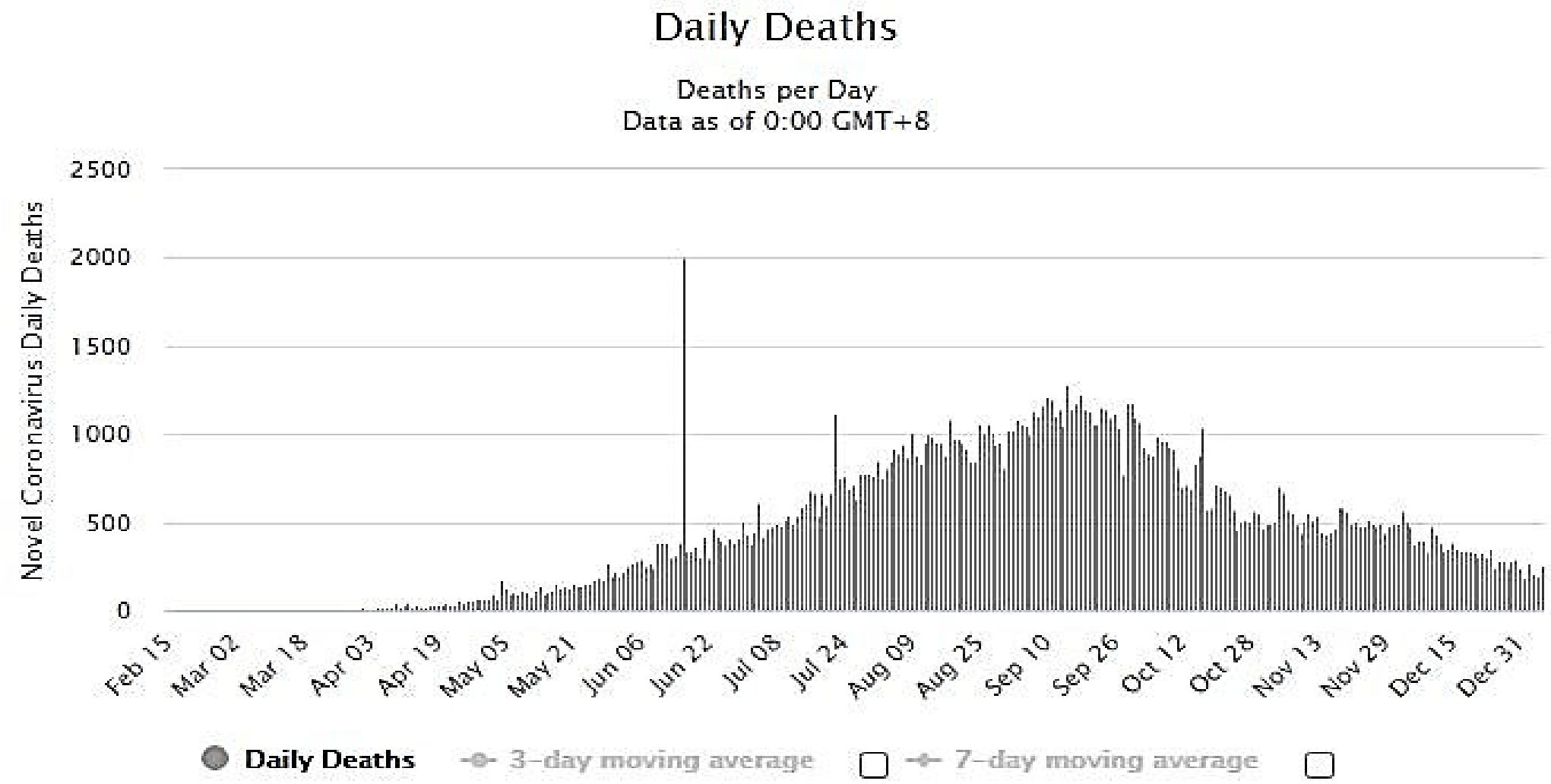
Public Health Point of view



Daily New Cases in India



Daily New Deaths in India



Mutations, Variants

- Multiple mutations occur. 23 in UK; 3 in S.Africa
- 19 variants with escape mutations, circulating in India
- Convalescent plasma may cause mutations
- Cases in world: 86.84 million or 11,141/million
- Deaths in world: 17.8 lakhs or 241/million
- Cases in India: 10.4 million or 7481/million
- Deaths in India: 150,151 or 108/million
- Italy reported nearly 1263 deaths/million out of 60.4 mill pop

Key Points

- Surveillance required till 2024
- Mask, hand wash and social distance. Greet by “namasthe”
- Two types of clots, white clots and red clots
- Raising D Dimer, reducing platelets and LDL are markers of thrombosis
- CRP is a marker of inflammation; Keep it <1 always
- 2 types fever: Viral fever due to IL-6 and pyroptosis fever due to IL-1β
- The Ct value for the new UK variant is lower
- Loss of smell and taste are important symptoms of COVID-19.
- RT PCR

Important facts

- Masking is THE prevention
- RT PCR Ct is THE test for diagnosis
- Zinc is THE Vitamin
- Day 5 is THE day in COVID phase for mortality prevention
- Day 90 is THE day after which the word COVID ends
- Home Isolation is THE modality of Treatment
- 12 years is THE age when the mortality starts
- CRP is THE lab test for seriousness
- Loss of Smell is THE symptom equal to RT PCR test
- 15 minutes is THE time to get the infection.

Pandemic Fatigue (WHO/Europe)

- Demotivation to follow precautions, mask, social distance & hand washing
- Pandemic fatigue evolves gradually over time and is affected by the cultural, social, structural and legislative environment.
- Understand people: collect and use evidence for targeted, tailored and effective policies, interventions and communication.
- Engage people as part of the solution.
- Help people to reduce risk while doing the things that make them happy.
- Acknowledge and address the hardship people experience, and the profound impact the pandemic has had on their lives.

Vaccines

- 30 crores: 1 crore HCWs, 2 crore FLWs & 27 crore prioritized groups
- 2 to 3 doses are required at 3 to 4 week intervals
- Intramuscular injections, 1st dose in the deltoid
- 2nd dose in lateral vastus
- Need -20 to -70 degrees Celsius
- Can be stored between +2 and +8 degrees Celsius
- Efficacy varies between 60% to 70%
- Recovered patients also need it
- VVM, date expiry may not be present

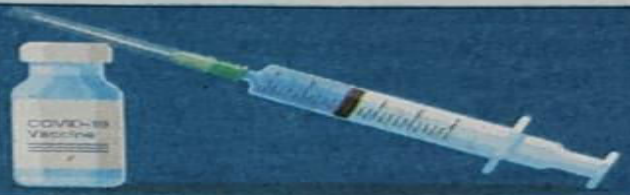
New Strain, **VOC-202012/01**, also known as **lineage B.1.1.7**

- New strain does not seem to be more fatal, reports a preliminary study by Public Health England *(eMediNexus, 30 December 2020)*
- UK variant has unusually large no of mutations, 60% new infections
- Can spread more easily, can cause more milder or severe disease, can evade detection, vaccine may not work, protocols of management need to change

COVID – 19 VACCINES

Inoculation campaign

A look at a select list of COVID-19 vaccines that have been approved for full/emergency use in different countries



Manufacturer	Efficacy	Storage	Status
Oxford University-AstraZeneca	Upto 90%	2-8 degree Celsius	Approved for restricted emergency use in India and emergency use in U.K.
Bharat Biotech-ICMR	Unknown	2-8 °C	Approved for restricted use in emergency situation in India
Pfizer-BioNTech	95%	-70 °C	Approved for full use/emergency use in several countries
Moderna	94.50%	-20 °C	Approved in Canada; emergency use in U.S.
Gamaleya Research Center	91.40%	-18 °C	Early use in Russia, emergency use in Belarus and Argentina
CanSino Biologics	Unknown	2-8 °C	Limited use in China
Vector Institute	Unknown	2-8 °C	Early use in Russia
Beijing Institute of Biological Products	79.34%	2-8 °C	Limited use in China
Sinovac Biotech	>50%	2-8 °C	Limited use in China
Sinopharm	Unknown	2-8 °C	Approved in China, U.A.E. and Bahrain

Types of Covid-19 Vaccines

- Active Immunity (Vaccination)
  - **DNA Vaccine** (Inovio)
  - **RNA Vaccine** (Moderna, Pfizer)
  - **Viral Vector** (Oxford/AstraZeneca, CanSino Biologics, Janssen (J &
  - **Viral Subunit** (Novavax, AdaptVac, Clover Biopharma)
  - **Live Attenuated** (Codagenix, Indian Immunologicals Ltd.)
  - **Inactivated Virus** (SinoVac, SinoParm)
  - **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*

Status of the Vaccines

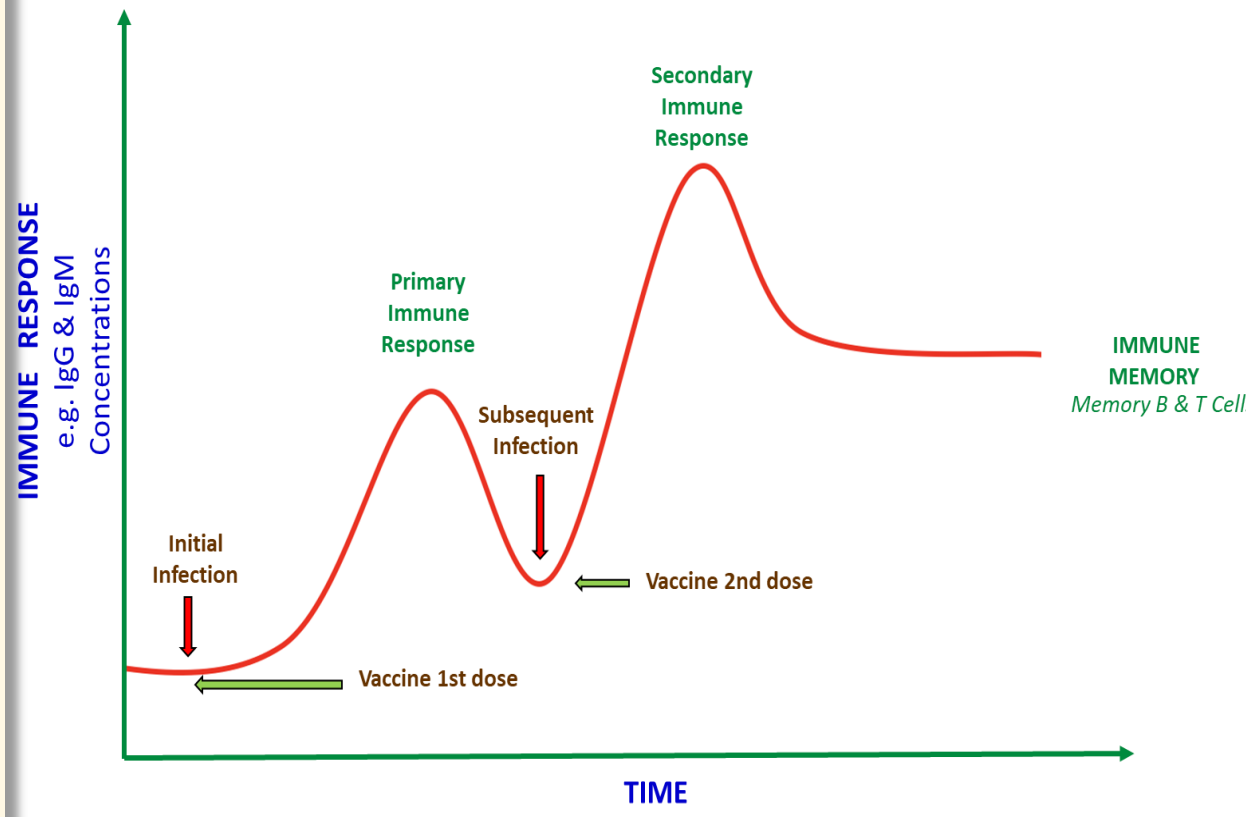
Company	Type	Doses (days)	Route	Trials	Status
Sinovac	Inactivated	2 (0,14)	IM	Phase 3	
SinoPharma	Inactivated	2 (0,21)	IM	Phase 3	
Bharat Biotech	Inactivated	2 (0,28)	IM	Phase 3	
Oxford/AstraZeneca	Viral Vector (Non-replicating)	2 (0,28)	IM	Phase 3	Complete
CanSino	Viral Vector (Non-replicating)	1 dose!	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	LNP-**mRNA**	2 (0,28)	IM	Phase 3	Complete
BioNTech / Pfizer	3LNP-**mRNAs**	2 (0,28)	IM	Phase 3	Complete
Wantai - Xiamen	Viral Vector (Replicating)	1 dose!	Intra-Nasal	Phase 2	
Inovio	**DNA** Vaccine	2 (0.28)	Intra Dermal	Phase 2	

Why Multiple Vaccines?

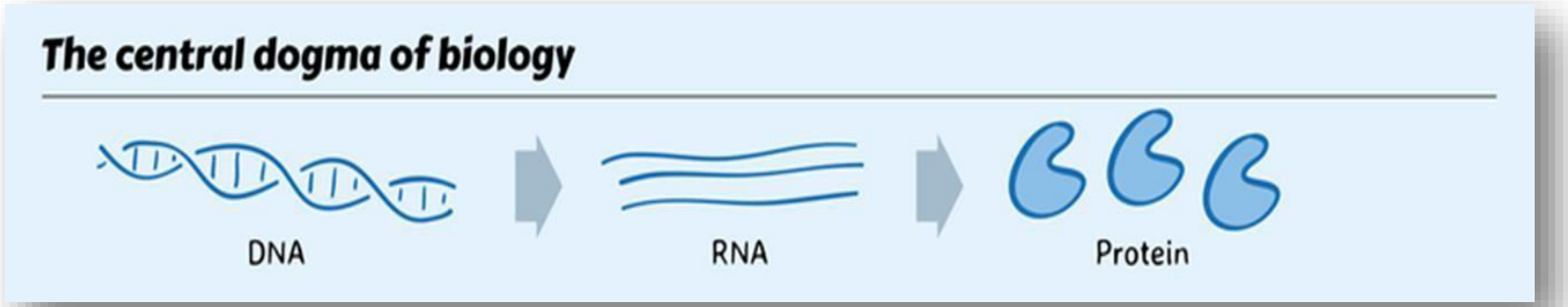
- A variety of COVID-19 vaccines are being developed around the world.
- According to WHO, as of November 12th 2020, there are **48 vaccines in Clinical Trials** and 164 candidate vaccines in Pre-clinical evaluations.
- All of them share one thing in common: they all stimulate a primary immune response 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!!

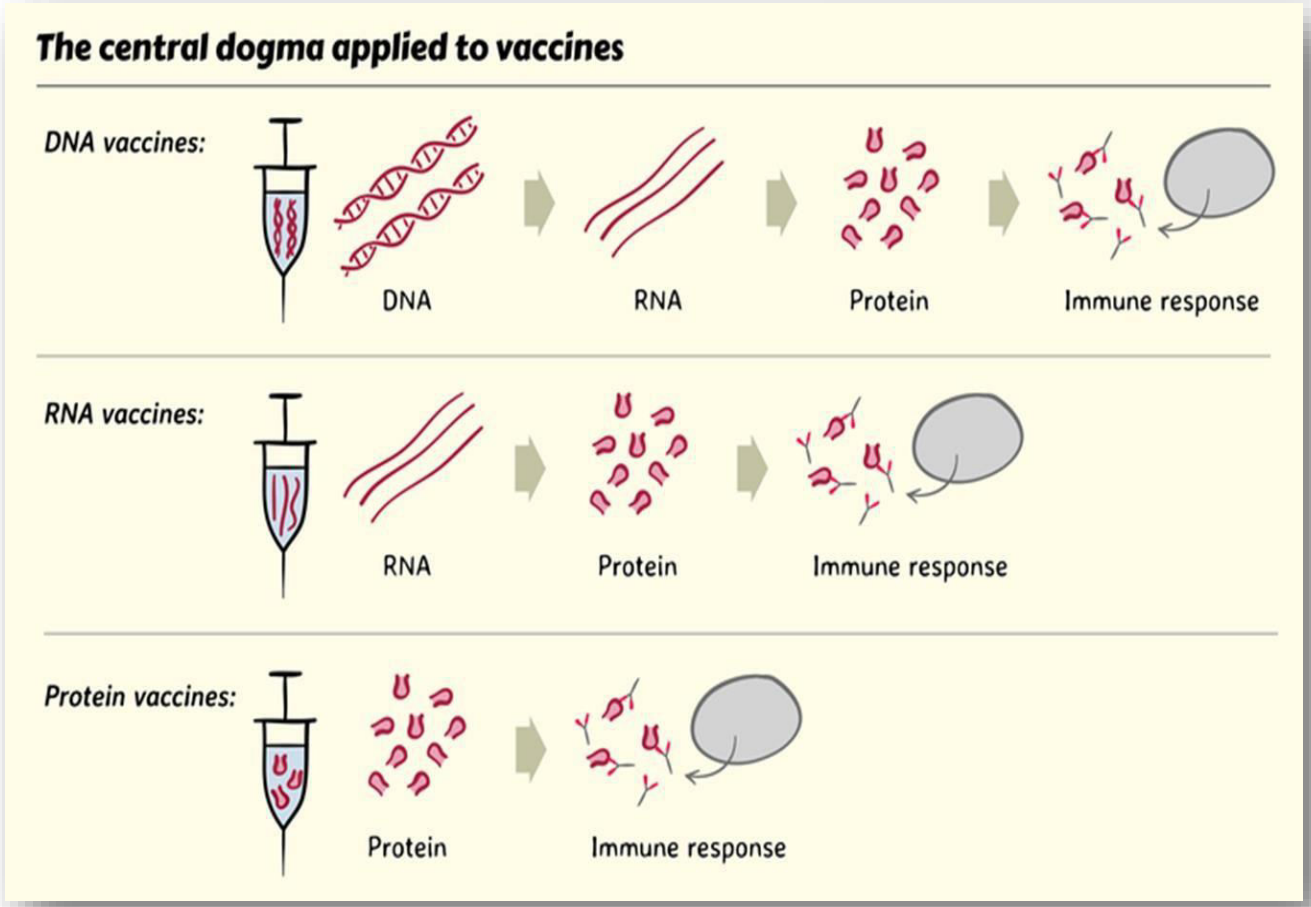
Why two doses ?

- 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!!



Types Vaccines

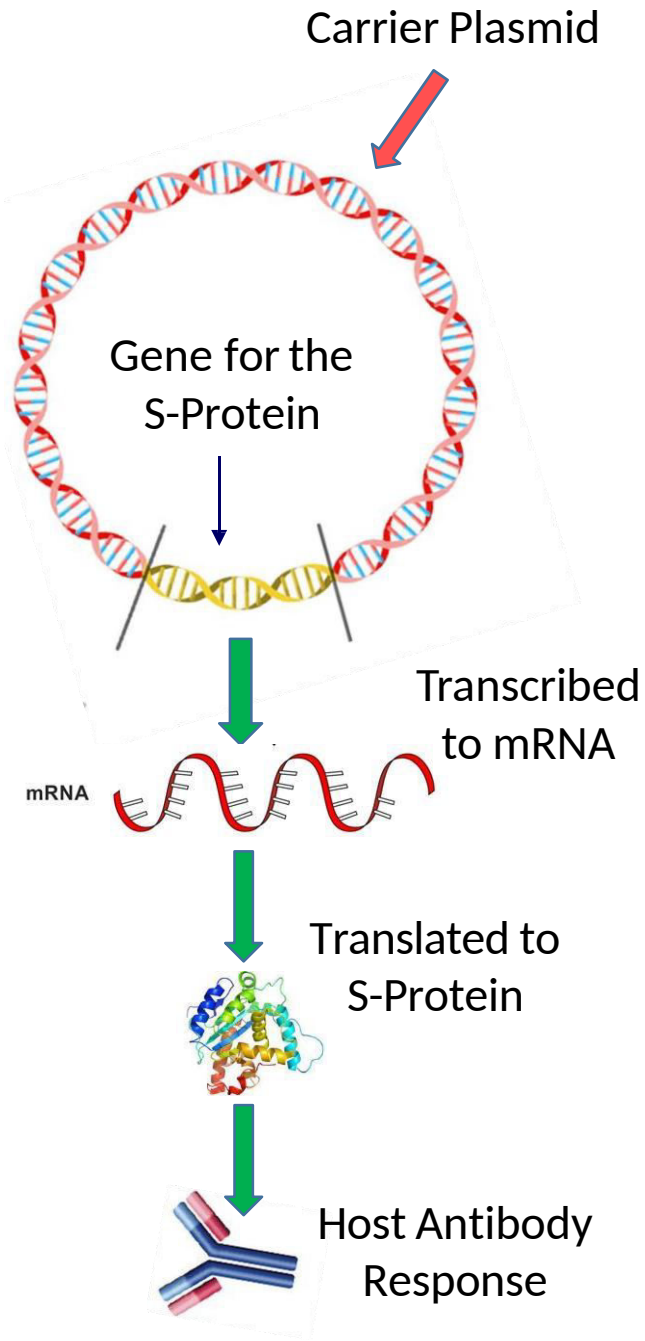




- The SARS-CoV-2 outbreak has prompted the rapid expansion of several technology platforms, including DNA and RNA vaccines, never before clinically tested in humans.
- Rather than producing a viral protein in a lab, delivered DNA or RNA directs our cells to make parts of viral proteins that do not cause disease, 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 novel vaccines are being developed like the Protein Sub-unit Vaccine and Split virus vaccines. Production of Virus-Like Particles to mRNAs making Antibodies directly.

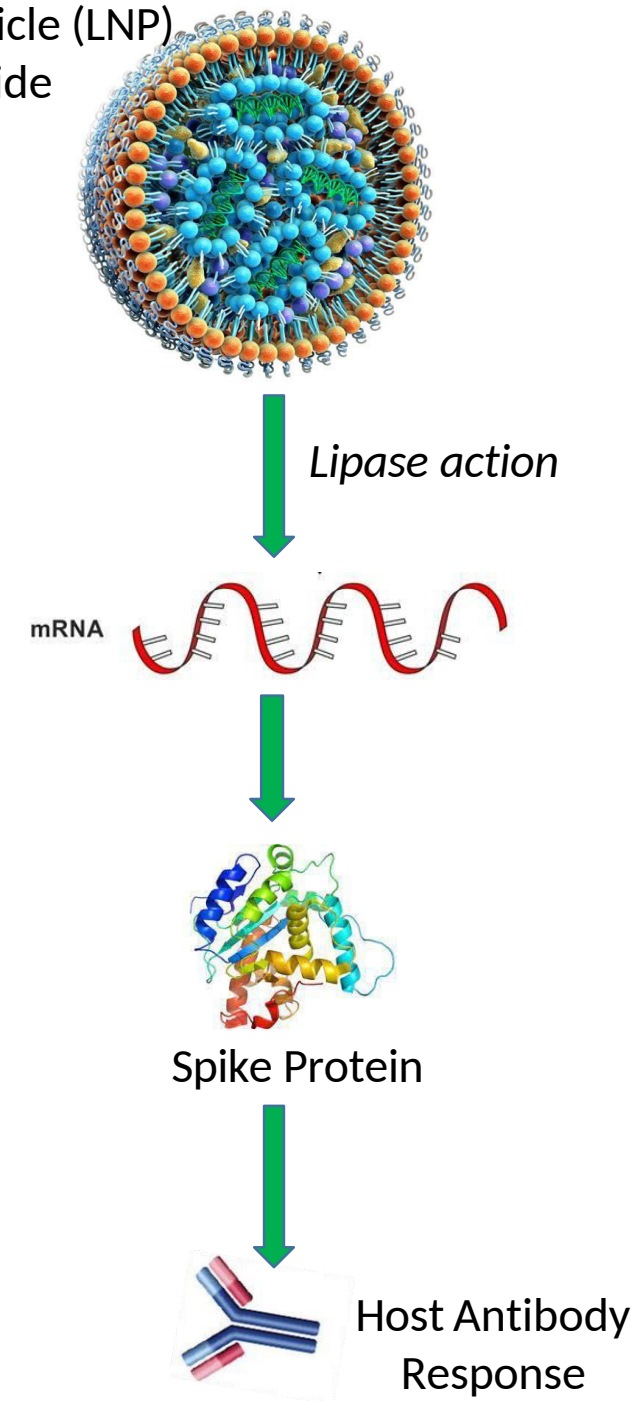
DNA Vaccines

- DNA vaccines are made up of small strands of DNA, a gene, encoding the antigen of interest (in this case 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 show 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.



mRNA Vaccines

- RNA vaccines consist of an mRNA encoding the antigen of interest (The SARS-CoV-2 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, and is on its cell surface, stimulating an antibody and T cell response.
- ***Moderna*** has developed the RNA vaccine mRNA-1273 encapsulated in a lipid nanoparticle. 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.
- Both vaccines carry the foreign gene for whole S protein.



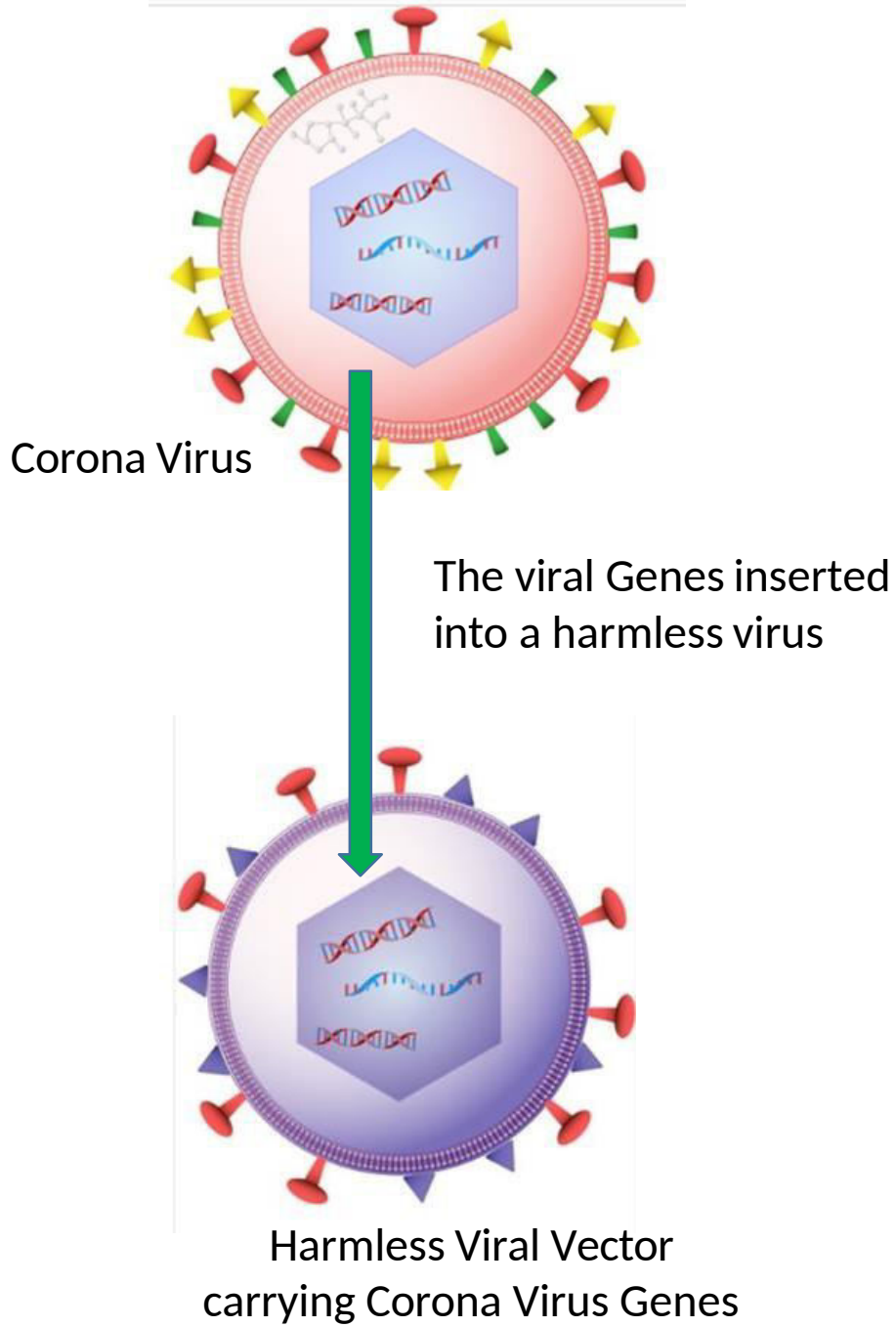
RNA & DNA Vaccines

- 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.

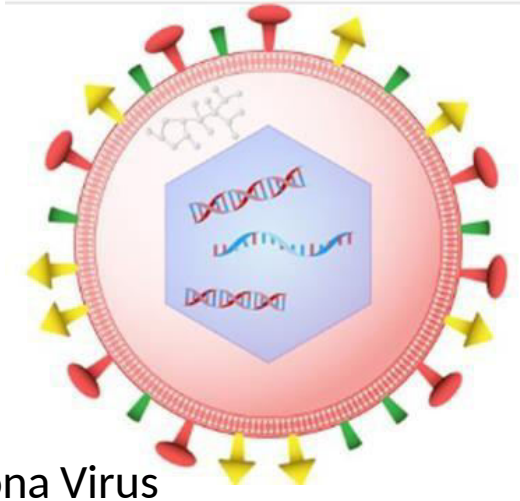
Vector Vaccines

- **Viral vector vaccines** are similar to live-attenuated vaccines in that they use a harmless virus or an attenuated virus known as a vector.
- However, the attenuated virus carries a foreign gene in their genome representing the antigen of interest. For example the Spike Protein in SARS-Cov2.
- When the virus infects a cell, they administer this foreign gene into the cell. The cell then transcribes and translates the gene to produces the antigen, and display the antigen 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 display the antigen on its surface.
- The Oxford/**AstraZeneca**, **Gamalaya**-Sputnik and the **Janssen** vaccines are all Vector Vaccines.



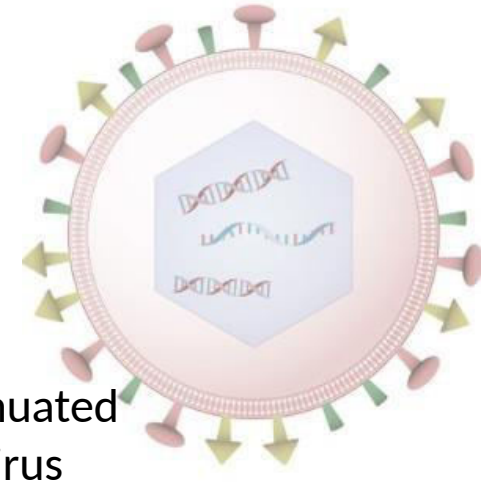
Live Attenuated Vaccines

- **Live attenuated vaccines** contain a live but less infective form of the pathogen. 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, tuberculosis and chicken pox.
- 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 in clinical trials.



Corona Virus

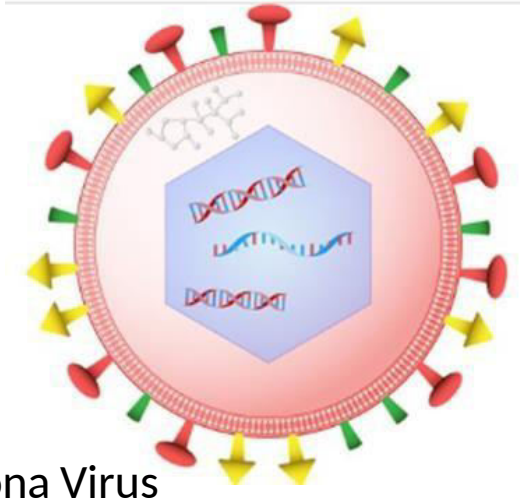
Virus is alive but rendered less infective but still able to provoke a robust immune response



Live Attenuated Corona Virus

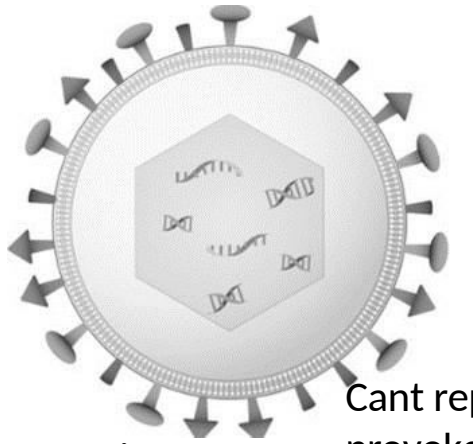
Inactivated Vaccines

- Evolving from live-attenuated vaccines that are able to (slowly) replicate in the body, **inactivated vaccines** contain a whole pathogen 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 **CoronaVac**, produced by **Sinovac** R&D Co.
- 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.



Corona Virus

Virus is killed/ inactivated by chemicals , heat or radiation

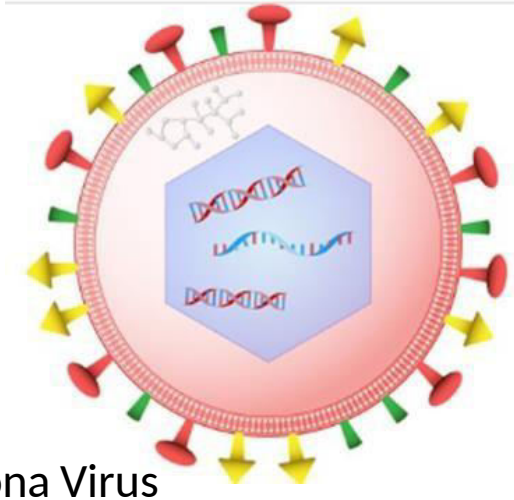


Dead Corona Virus

Cant replicate but provoke a host immune response

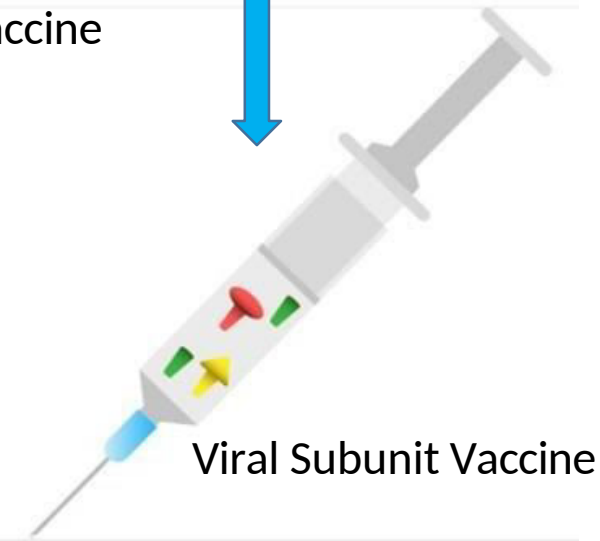
Viral Subunit Vaccines

- **Subunit vaccines** take parts of the pathogen (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

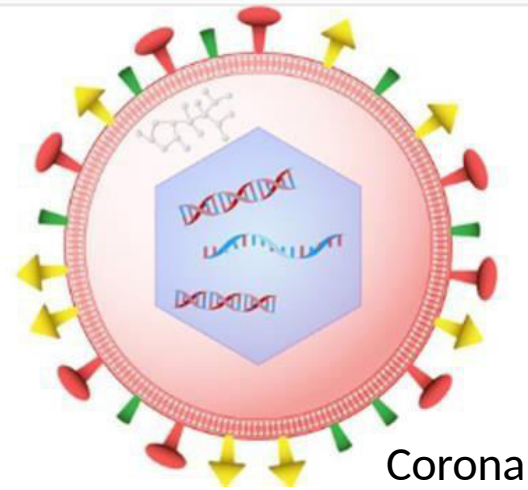
Viral proteins particularly the spike proteins are extracted and made into a vaccine



Viral Subunit Vaccine

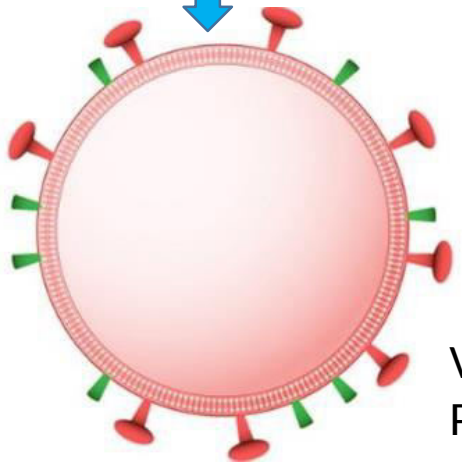
VLP (Virus Like Particle) vaccines

- **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 nanostructures (lipids NPs, dendrimers and fullerenes) that resemble the structures of viruses.
- They are composed of one or more 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.
- Contemporary VLP production may take advantage of several systems, including bacterial, yeast, insect and mammalian cells.



Corona Virus

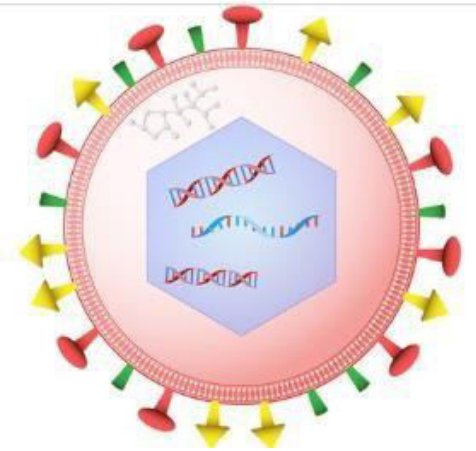
Viral Like Particles are synthetically manufactured to mimic the virus and hence provoke the host immune response



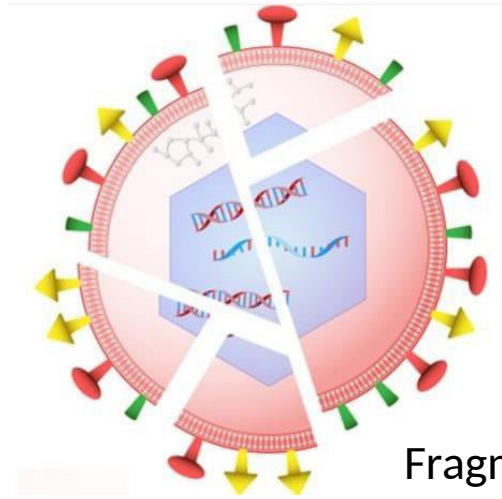
Virus Like Particle

Split-Virus Vaccines

- The vaccine is made by cutting the virus into several pieces.
- All the pieces of the virus are present, but they can't cause disease.
- The only example of this kind of vaccine is the *flu vaccine*.
- No company is currently working on the split Virus Vaccine technology for the coronavirus
- Advantage: the virus is inactive, while all elements remain present
- Disadvantage: it's difficult to determine the right dose. Moreover, this type of vaccine is not easy to produce



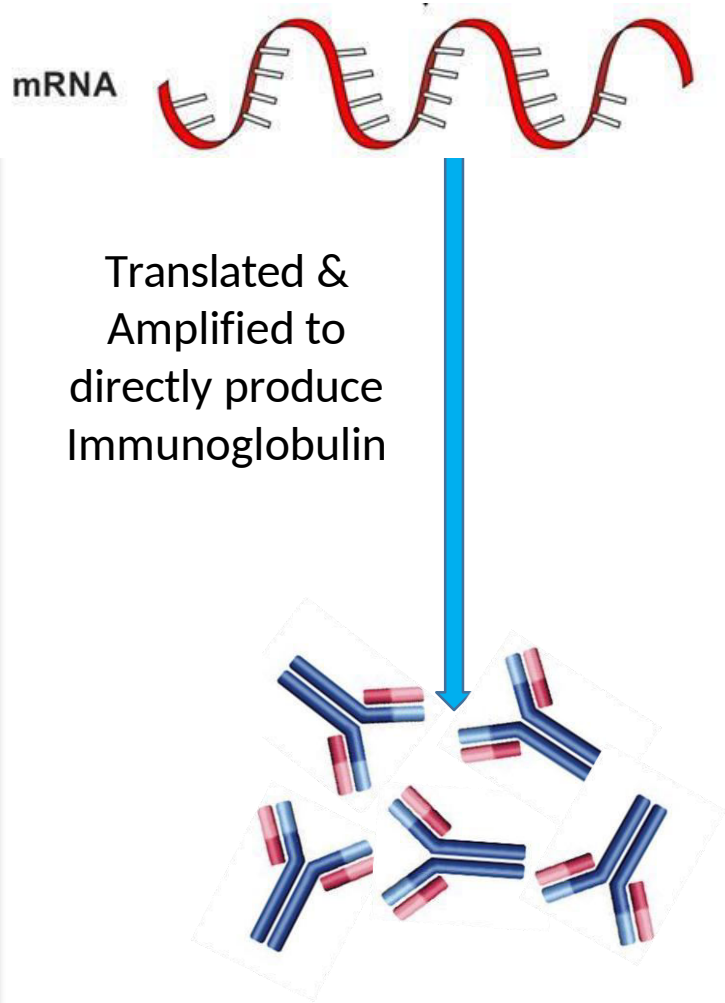
The whole Virus is cut into multiple pieces



Fragmented Corona Virus

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 Spike Protein), instead it codes for the actual antibody.
- The mRNA enters the host cell and makes multiple copies of the antibody (against the Virus).
- This process bypasses several steps of the immune response and makes the antibodies directly for the host.
- 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 faster response.



Thank you!