ANTI-VIRAL

3rd Year Pharmacology and Toxicology-
Biomedical Sciences
School of Health Sciences

Andrew M Bambala
bambalaandrew@gmail.com

Viruses

- Viruses are made up of core genome of nucleic acid contained in a protein shell called Capsid
- Surrounded by lipoprotein membrane called envelope (Genome + Capsid + Envelope = Virion)
- Viruses are obligate intracellular parasite ie. do not have a metabolic machinery of their own –uses host enzymes
- Certain viruses multiply in the cytoplasm but others do in the nucleus
- Some viruses have unique enzymes for DNA/RNA synthesis or protein cutting in virus assembly.
- Most multiplication take place before diagnosis is made

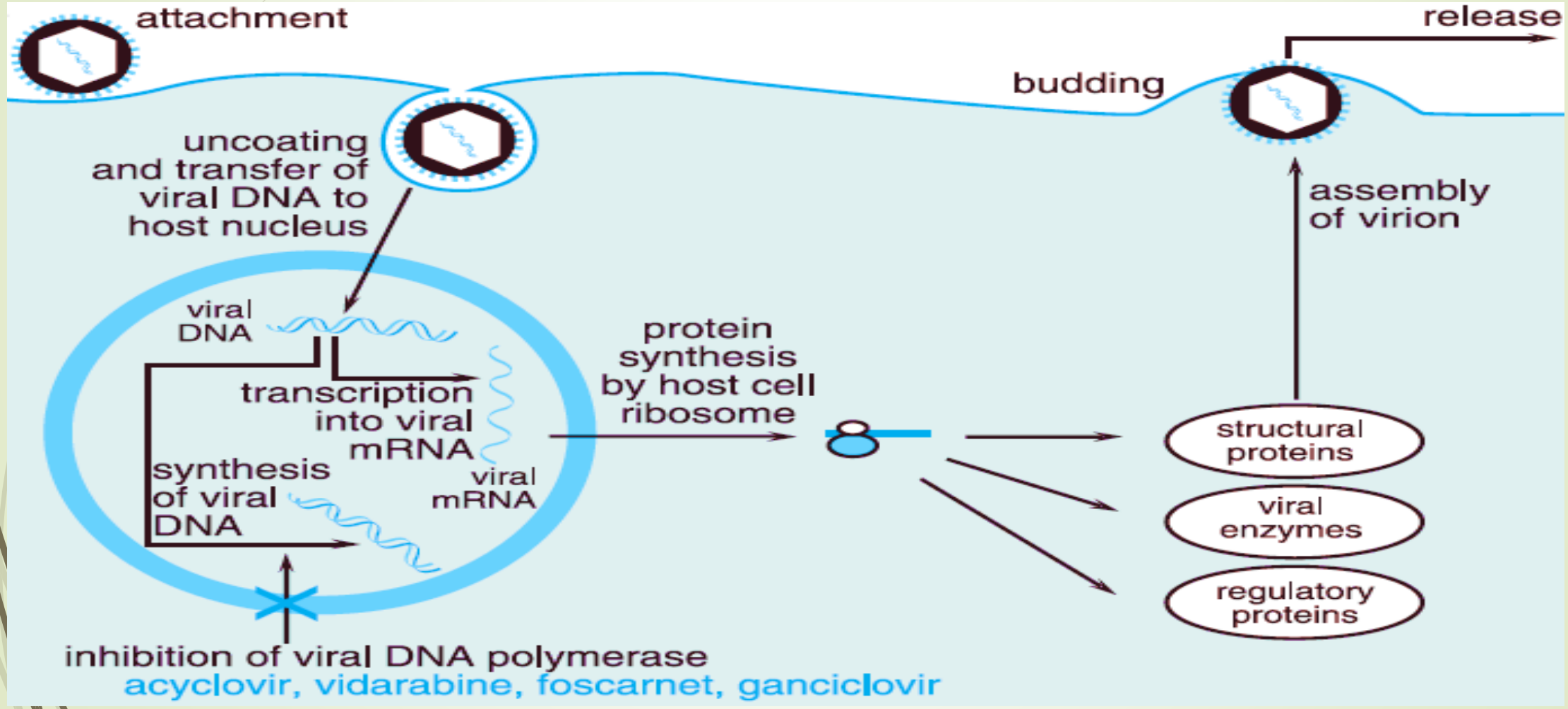
Types of Viruses

- DNA viruses
  - Adenoviruses (upper respiratory infections)
  - Herpes simplex (genital herpes)
  - Hepadnavirus (hepatitis B)
  - Cytomegalovirus (CMV)
  - Varicella (chickenpox) and varicella-zoster
  - Smallpox
- RNA viruses : Influenza A and B
- RNA retroviruses :Human immunodeficiency virus (HIV)

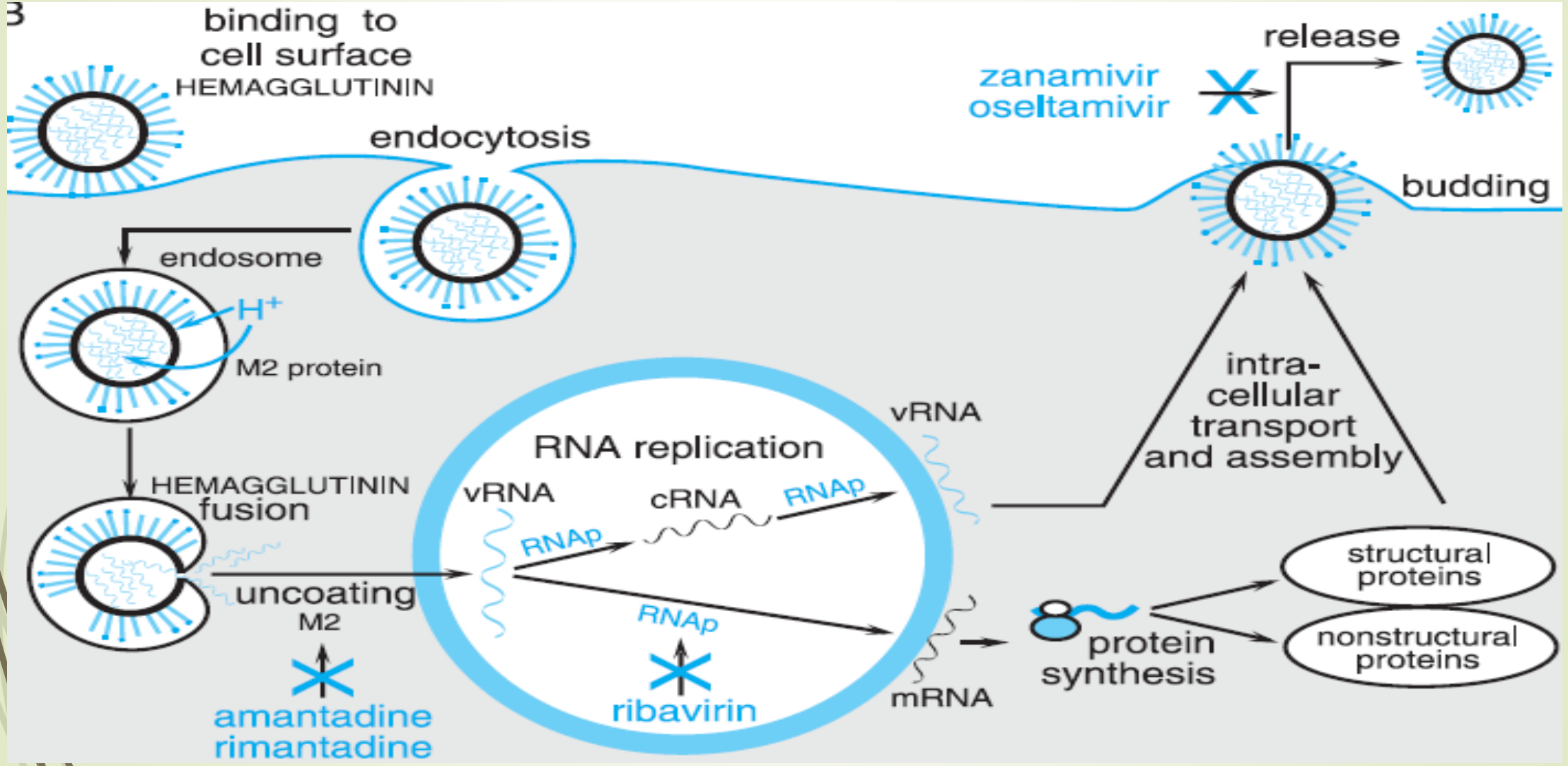
Viral Replication

- Adsorption to and penetration of susceptible cells.
- Synthesis of early, nonstructural proteins.
- Synthesis of RNA or DNA.
- Synthesis of late, structural proteins
- Assembly of viral particles and release

DNA -Viral Replication Cycle



RNA- Viral Replication Cycle



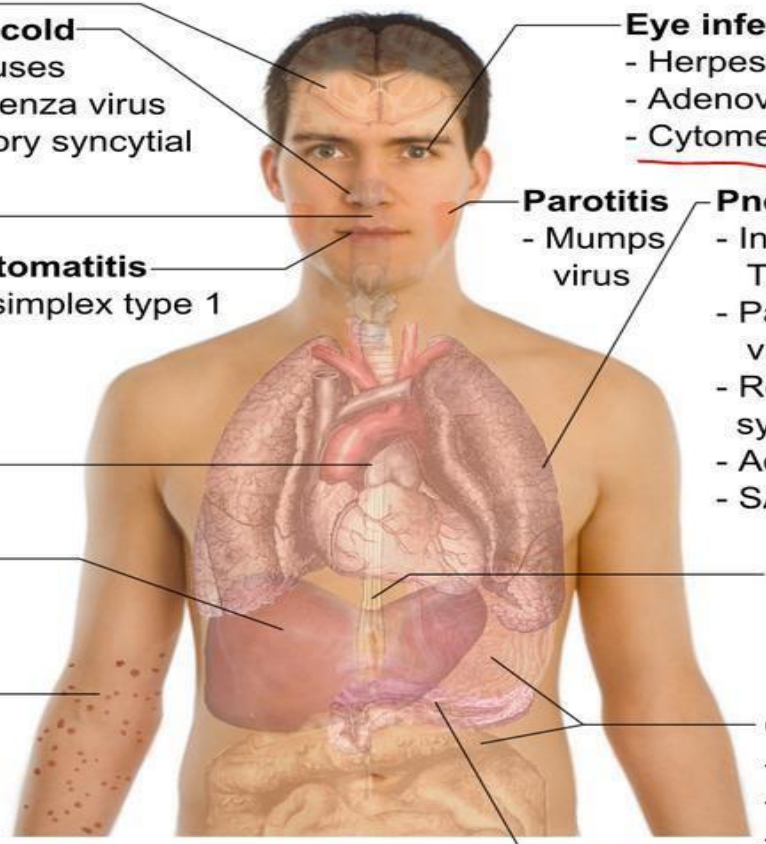
Targets for antivirals

- Viral uncoating
- Nucleoside analogs
- Non-nucleoside polymerase inhibitors
- Non-nucleoside reverse transcriptase inhibitors
- Protease inhibitors
- Neuraminidase inhibitors

Anti-Viral Drugs

- Many antiviral drugs are Purine or Pyrimidine analogs.
- Many antiviral drugs are Prodrugs.
  - They must be phosphorylated by viral or cellular enzymes in order to become active.
- Anti-viral agents inhibits active replication
- The viral growth resumes after drug removal
- Current anti-viral agents do not eliminate non-replicating or latent virus
- Effective host immune response remains essential for the recovery from the viral infection
- Clinical efficacy depends on achieving inhibitory conc. at the site of infection within the infected cells

Viral infections



Encephalitis/ meningitis
- JC virus
- Measles
- LCM virus
- Arbovirus
- Rabies

Common cold
- Rhinoviruses
- Parainfluenza virus
- Respiratory syncytial virus

Eye infections
- Herpes simplex virus
- Adenovirus
- Cytomegalovirus

Parotitis
- Mumps virus

Pneumonia
- Influenza virus, Types A and B
- Parainfluenza virus
- Respiratory syncytial virus
- Adenovirus
- SARS coronavirus

Pharyngitis
- Adenovirus
- Epstein-Barr virus
- Cytomegalovirus

Gingivostomatitis
- Herpes simplex type 1

Cardiovascular
- Coxsackie B virus

Hepatitis
- Hepatitis virus types A, B, C, D, E

Myelitis
- Poliovirus
- HTLV-I

Skin infections
- Varicella zoster virus
- Human herpesvirus 6
- Smallpox
- Molluscum contagiosum
- Human papillomavirus
- Parvovirus B19
- Rubella
- Measles
- Coxsackie A virus

Gastroenteritis
- Adenovirus
- Rotavirus
- Norovirus
- Astrovirus
- Coronavirus

Sexually transmitted diseases
- Herpes simplex type 2
- Human papillomavirus
- HIV

Pancreatitis
- Coxsackie B virus

Respiratory Viral Infections

- Immunization against influenza A is the preferred approach.
- However, antiviral agents are used when patients are allergic to the vaccine or
- When the outbreak is due to an immunologic variant of the virus not covered by vaccines (for example, H1N1), or
- When outbreaks occur among unvaccinated individuals who are at risk and in closed settings (for example, elderly homes).

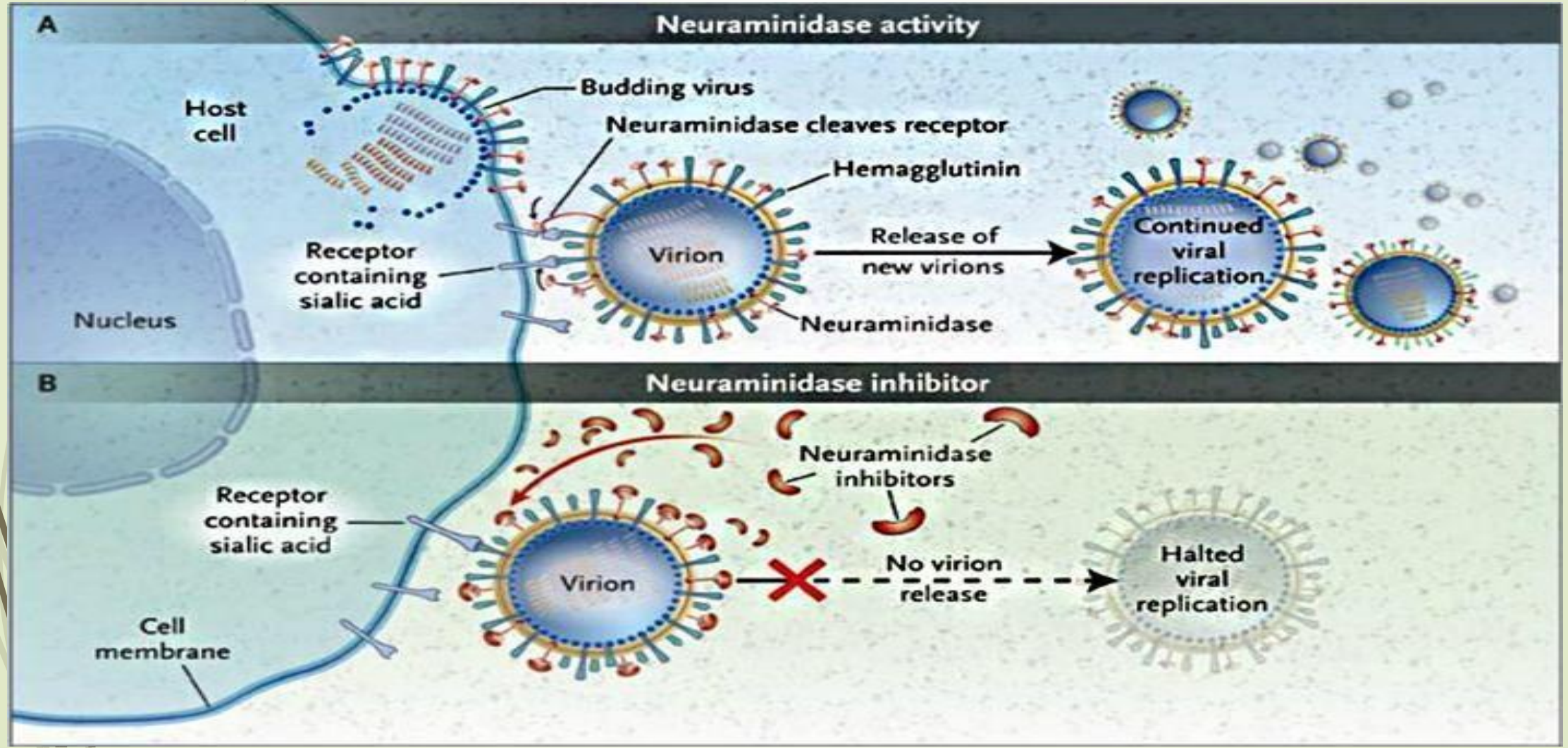
Neuraminidase Inhibitors

- Orthomyxo viruses that cause influenza contain the enzyme neuraminidase, which is essential to the life cycle of the virus.
- Viral neuraminidase can be selectively inhibited by the sialic acid analogs, such as:-

Oseltamivir and zanamivir.

- These drugs prevent the release of new virions and their spread from cell to cell.
- They do not interfere with the immune response to influenza A vaccine.
- Administered prior to exposure, neuraminidase inhibitors prevent infection, and, when administered within the first 24 to 48 hours after the onset of infection, they have a modest effect on the intensity and duration of symptoms.

Neuraminidase Inhibitors mode of action



Pharmacokinetics

- Pharmacokinetics: Oseltamivir is an orally active prodrug that is rapidly hydrolyzed by the liver to its active form.
- Zanamivir, on the other hand, is not active orally and is either inhaled or administered intranasally
- Both drugs are eliminated unchanged in the urine.

Adverse Effects

- The most common side effects of **oseltamivir** are gastrointestinal (GI) discomfort and nausea, which can be alleviated by taking the drug with food.
- Irritation of the respiratory tract does occur, however.
- **Zanamivir** should be avoided in individuals with severe reactive asthma or chronic obstructive respiratory disease, because bronchospasm may occur with the risk of fatality.
- Neither drug has been reported to have clinically significant drug interactions.

Inhibitors of viral uncoating
Adamantan derivatives

- Amantadine and rimantadine is limited to influenza A infections, for which the drugs have been shown to be equally effective in both treatment and prevention.
- For example, these drugs are 70 to 90 percent effective in preventing infection if treatment is begun at the time of, or prior to, exposure to the virus.
- Also, both drugs reduce the duration and severity of systemic symptoms if started within the first 48 hours after exposure to the virus.
- Amantadine is also effective in the treatment of some cases of parkinson disease.a weak antagonist of the NMDA-type glutamate receptor, increases dopamine release, and blocks dopamine reuptake.

Amantadine mode of action

- The primary antiviral mechanism of amantadine and rimantadine is to block the viral membrane matrix protein, M2, which functions as a channel for hydrogen ions.
- This channel is required for the fusion of the viral membrane with the cell membrane that ultimately forms the endosome(created when the virus is internalized by endocytosis).
- Note: The acidic environment of the endosome is required for viral uncoating.
- These drugs may also interfere with the release of new virions.

Pharmacokinetics

- Both drugs are well absorbed orally.
- Amantadine distributes throughout the body and readily penetrates into the CNS whereas Rimantadine does not cross the blood-brain barrier to the same extent.
- Amantadine is not extensively metabolized. It is excreted into the urine and may accumulate to toxic levels in patients with renal failure.
- On the other hand, rimantadine is extensively metabolized by the liver, and both the metabolites and the parent drug are eliminated by the kidney

Adverse Effects

- The side effects of **amantadine** are mainly associated with the CNS.
- Minor neurologic symptoms include insomnia, dizziness, and ataxia.
- More serious side effects have been reported (for example, hallucinations and seizures).
- The drug should be employed cautiously in patients with psychiatric problems, cerebral atherosclerosis, renal impairment, or epilepsy.
- **Rimantadine** causes fewer CNS reactions, because it does not efficiently cross the blood-brain barrier.
- Both drugs cause GI intolerance. **Amantadine and rimantadine** should be used with caution in pregnant and nursing mothers, because they have been found to be embryotoxic and teratogenic in rats.

Treatment of hepatic Viral Infection

- The hepatitis viruses thus far identified (A, B, C, D, and E) each have a pathogenesis specifically involving replication in and destruction of hepatocytes.
- Of this group, hepatitis B and hepatitis C are the most common causes of chronic hepatitis, cirrhosis, and hepatocellular carcinoma
- Note: Hepatitis A is a commonly encountered infection, but it is not a chronic disease.
- Chronic hepatitis B may be treated with eg interferon-a-2a, which is injected subcutaneously once weekly

Treatment of hepatic Viral Infection

- Oral therapy includes lamivudine, adefovir, entecavir, tenofovir, or telbivudine.
- Combination therapy of an interferon plus lamivudine is no more effective than monotherapy with lamivudine.
- Patients with acquired immunodeficiency syndrome (AIDS) who are co-infected with hepatitis B are usually poor responders to interferon therapy.
- Peg interferon-a-2a or peg interferon-a-2b plus ribavirin is treatment choice for chronic HERP C.

Interferon

- Interferon is a family of naturally occurring, inducible glycoproteins that interfere with the ability of viruses to infect cells.
- The interferons are synthesized by recombinant DNA technology. At least three types of interferons exist, α, β, and γ .
- In so-called —'pegylated' formulations, bis-monomethoxy polyethylene glycol has been covalently attached to either interferon-α-2a or -α-2b to increase the size of the molecule.
- The larger molecular size delays absorption from the injection site, lengthens the duration of action of the drug, and also decreases its clearance.

Adverse effects

- Adverse effects include flu-like symptoms on injection, such as fever, chills, myalgias, arthralgias, and GI disturbances.
- Neurotoxicity characterized by somnolence and behavioral disturbances;
- severe fatigue and weight loss; autoimmune disorders
- Interferon interferes with hepatic drug metabolism, and toxic accumulations of theophylline have been reported.
- Interferon may also potentiate the myelo suppression caused by other bone marrow–depressing agents such as idovudine

Lamivudine

- This cytosine analog is an inhibitor of both hepatitis B virus (HBV) DNA polymerase and human immunodeficiency virus (HIV) reverse tran-scriptase.
- Lamivudine must be phosphorylated by host cellular enzymes to the triphosphate(active) form.
- As with many nucleotide analogs, the intracellular half-life of the triphosphate is many hours longer than its plasma half-life. Lamivudine is well absorbed orally and is widely distributed. Its plasma half-life is about 9 hours.
- 70% is excreted unchanged in urine. Dose reductions are necessary when there is moderate renal insufficiency (creatinine clearance less than 50 mL/min).
- Lamivudine is well tolerated, with rare occurrences of headache and dizziness

Treatment of Herpes viruses Infections

- Herpes viruses are associated with a broad spectrum of diseases, for example, cold sores, viral encephalitis, and genital infections (the latter being a hazard to the newborn during parturition).
- The drugs that are effective against these viruses exert their actions during the acute phase of viral infections and are without effect during the latent phase.
- Except for foscarnet and fomivirsen, all are purine or pyrimidine analogs that inhibit viral DNA synthesis.

Acyclovir

- Acyclovir (acycloguanosine) is the prototypic antiherpetic therapeutic agent.
- It has a greater specificity than vidarabine against herpesviruses.
- Herpes simplex virus (HSV) Types 1 and 2, varicella-zoster virus (VZV), and some Epstein-Barr virus–mediated infections are sensitive to acyclovir.
- It is the treatment of choice in HSV encephalitis and is more efficacious than vidarabine at increasing the rate of survival.
- The most common use of acyclovir is in therapy for genital herpes infections.
- It is also given prophylactically to seropositive patients before bone marrow and after heart transplants to protect such individuals during post transplant immunosuppressive treatments

Pharmacokinetics

- Administration of acyclovir can be by an intravenous (IV), oral, or topical route.
- The drug distributes well throughout the body, including the cerebrospinal fluid (CSF).
- Acyclovir is partially metabolized to an inactive product. Excretion into the urine occurs both by glomerular filtration and by tubular secretion
- Acyclovir accumulates in patients with renal failure.
- Valacyclovir has greater oral bioavailability than acyclovir.
- This ester is rapidly hydrolyzed to acyclovir and achieves levels of the latter comparable to those from IV acyclovir administration.

Adverse Effects

- Side effects of acyclovir treatment depend on the route of administration.
- For example, local irritation may occur from topical application; headache, diarrhea, nausea, and vomiting may result after oral administration.
- Transient renal dysfunction may occur at high doses or in a dehydrated patient receiving the drug IV.
- High-dose valacyclovir can cause GI problems

Foscarnet

- Unlike most of the antiviral agents, is not a purine or pyrimidine analog. Instead, it is a phosphonoformate (a pyrophosphate derivative) and does not require activation by viral (or human) kinases.
- Foscarnet has broad in vitro antiviral activity. It is approved for
- CMV retinitis in immunocompromised hosts and for acyclovir-resistant
- HSV and herpes zoster infections.

Ganciclovir

- Ganciclovir is an analog of acyclovir that has 8 to 20 times greater activity against CMV, which is the only viral infection for which it is approved.
- It is currently available for treatment of CMV retinitis inmmunocompromised patients and for CMV prophylaxis in transplant patients

Drug Treatment of HIV Infection

- Antiretroviral therapy (ART) is now recommended for nearly all patients.
- Highly active antiretroviral therapy (HAART) is a medication regimen used to manage and treat human immunodeficiency virus primarily virus type 1 (HIV-1)
- HAART may also be called antiretroviral therapy (ART) or combination antiretroviral therapy (cART)
- ART aim;
  - Reduce the plasma HIV RNA level to undetectable (ie, < 20 to 50 copies/mL)
  - Restore the CD4 count to a normal level (immune restoration or reconstitution)
  - ART can usually achieve its goals if patients take their drugs > 95% of the time.
- If treatment fails, drug susceptibility (resistance) assays can determine the susceptibility of the dominant HIV strain to all available drugs. Genotype assays may also be helpful.

Goals of HAART in Patients with HIV Infections

- Reduce morbidity and mortality (AIDS and non-AIDS associated causes)
- Improve the quality of life
- Reduce plasma viral RNA load
- Prevent transmission to others (sex partners, needle-sharing partners, mother to infant)
- Prevent drug resistance
- Improve immune function

Mechanism of Action

- There are six main classes of HAART agents that target different stages in the viral lifecycle.
- A fundamental cornerstone of HAART is the co-administration of different drugs that inhibit HIV replication by several mechanisms so that the propagation of a virus with resistance to a single agent is inhibited by the action of the other two agents.
- Some agents may be co-formulated to increase ease of patient compliance with these medications.

HHART

1.Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs),

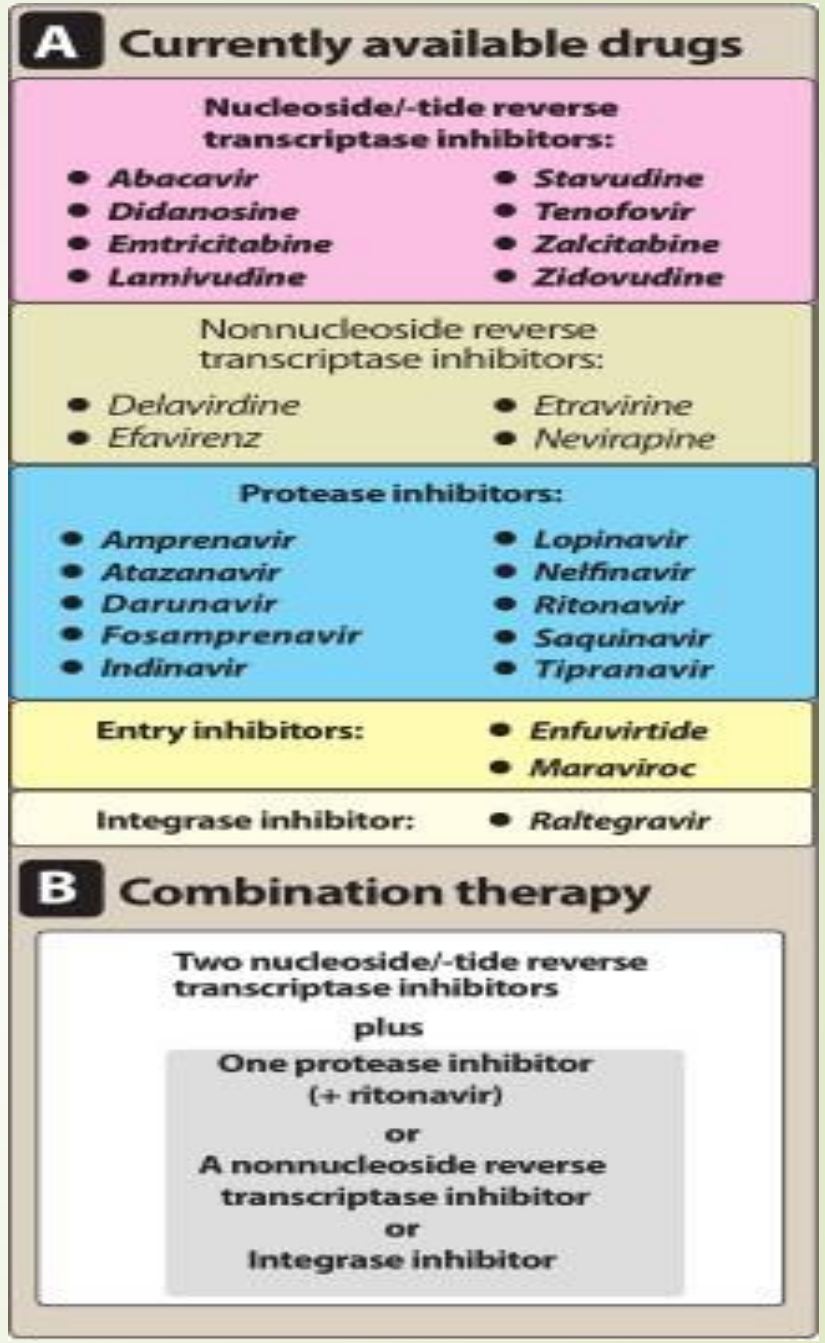
2.Nonnucleosidereverse transcriptase inhibitors (NNRTIs),

3.Protease inhibitors,

4. Entry/Fussioninhibitors, and

5. Integraseinhibitors.

6. CCR5 co-receptor antagonists



1. Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

- NRTIs require intracellular phosphorylation via host enzymes before they can inhibit viral replication. These agents are nucleoside or nucleotide analogs with an absent hydroxyl at the 3' end that are incorporated into the growing viral DNA strand.
- They competitively bind to reverse transcriptase and cause premature DNA chain termination as they inhibit 3' to 5' phosphodiester bond formation.
- Examples include: abacavir, didanosine, lamivudine, stavudine, tenofovir, and zidovudine

2. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- NNRTIs bind to HIV reverse transcriptase at an allosteric, hydrophobic site. These agents cause a stereochemical change within reverse transcriptase, thus inhibiting nucleoside binding and inhibition of DNA polymerase.
- competitively inhibit the HIV reverse transcriptase enzyme, as do NRTIs, but do not require initial phosphorylation.
- Examples include delavirdine, efavirenz, nevirapine, and rilpivirine.

3. Protease inhibitors (PIs) –

- PIs competitively inhibit the proteolytic cleavage of the gag/pol polyproteins in HIV-infected cells. These agents result in immature, non-infectious virions. PIs are generally used in patients who fail their initial HAART regimen and should be administered with boosting agents such as ritonavir or cobicistat.
- Drug interactions are a common problem for all protease inhibitors, because they are not only substrates but also potent inhibitors of CYP isozymes.

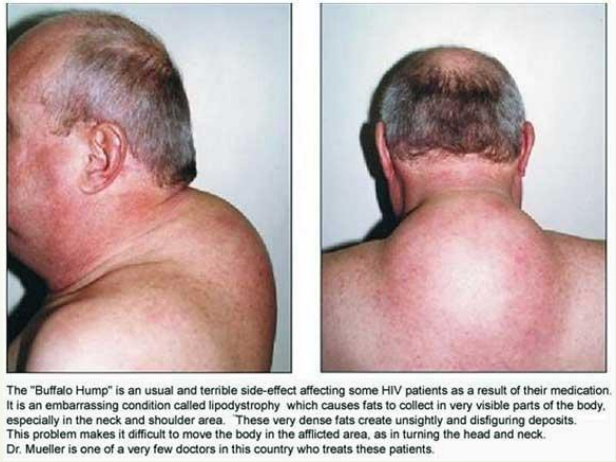
Examples include atazanavir, Loponavir, darunavir, indinavir.

4. Integrase Strand Transfer Inhibitors (INSTIs)- Integrase inhibitors bind viral integrase and prevent viral DNA from being incorporated into the host cell chromosome.

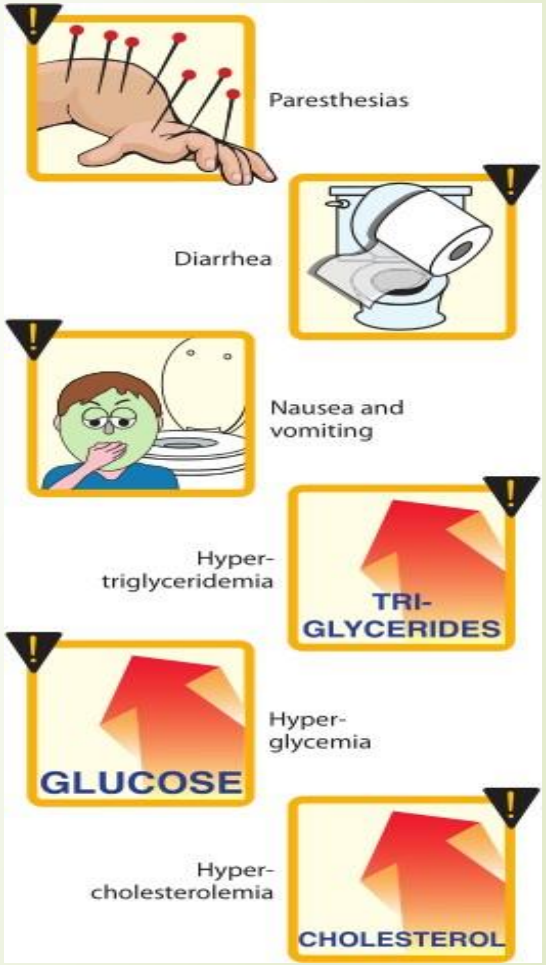
Examples include: dolutegravir, elvitegravir, raltegravir

Protease inhibitors Adverse Effects

- Paresthesias,
- Nausea
- Vomiting
- Diarrhea
- Hypertriglyceridemia, and
- Hypercholesterolemia
- Buffalo hump



The "Buffalo Hump" is an usual and terrible side-effect affecting some HIV patients as a result of their medication. It is an embarrassing condition called lipodystrophy which causes fats to collect in very visible parts of the body, especially in the neck and shoulder area. These very dense fats create unsightly and disfiguring deposits. This problem makes it difficult to move the body in the afflicted area, as in turning the head and neck. Dr. Mueller is one of a very few doctors in this country who treats these patients.



Examples include: dolutegravir, elvitegravir, raltegravir

5. Fusion inhibitors (FIs)-Fusion inhibitors bind to the envelope glycoprotein gp41 and prevent viral fusion to the CD4 T-cells.

Examples include enfuvirtide.

6. Chemokine Receptor Antagonists (CCR5 Antagonists) CCR5 antagonists selectively and reversibly block entry into the CD4 T-cells by preventing interaction between CD4 cells and the gp120 subunit of the viral envelope glycoprotein.

Examples include maraviroc.

Antiretroviral regimens

- Combinations of 2, 3, or 4 drugs from different classes are usually necessary to fully suppress replication of wild-type HIV.
- The specific drugs are chosen based on the following:
  - Anticipated adverse effects
  - Simplicity of regimen
  - Concomitant conditions (eg, hepatic or renal dysfunction)
  - Other drugs being taken (to avoid drug interactions)
- To maximize adherence, clinicians should choose an affordable, well-tolerated regimen that uses once/day (preferable) or twice-a-day dosing.

POSSIBLE TREATMENT OPTIONS FOR COVID-19

- Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus.
- Most people infected with the virus will experience mild to moderate respiratory illness and recover without requiring special treatment
- immune responses includes a sudden release of an enormous number of definite cytokines into circulation. This phenomenon is known **as 'cytokine storm,'** which can cause a severe systemic inflammatory syndrome. The main pro-inflammatory cytokines that are found in COVID-19 patients is IL-6

POSSIBLE TREATMENT OPTIONS FOR COVID-19

- Some drugs have demonstrated to be helpful for COVID-19 patients based on immune basic and its antiviral properties of the disease.
- Previous studies have been indicated that deterioration of COVID-19 condition is associated with a weaker immune system.
- Vaccines prompt your cells to produce a harmless version of the spike protein, thereby stimulating immune system to produce antibodies to fight off the potential threat.
- Most of these therapies impact on the immune system and immune cells.
- Some drugs **vitamin-D, zinc, remdesivir, Lopinavir-Ritonavir, hydroxychloroquine or chloroquine, colchine, ,azithromycin, dexamethasone, amantadine, aspirin**, Monoclonal antibody (mAb) **Baricitinib or tocilizumab**

POSSIBLE TREATMENT OPTIONS FOR COVID-19

Monoclonal antibody (mAb) treatments:

- An antibody is a protein that adheres to another specific protein, the antigen, in order to become part of the immune system and destroy tumour cells. Similarly, monoclonal antibodies are artificial proteins that help in neutralizing pathogenic agents.
- Therefore, mAb are therapeutic mechanisms that, by binding to the viral spike protein and angiotensin-converting enzyme 2 (ACE2) receptors, impede viral invasion in SARS-COV-2
- The mAb treatment helps boost your body's ability to fight COVID-19.

POSSIBLE TREATMENT OPTIONS FOR COVID-19

Monoclonal antibody (mAb) treatments:

- The mAb treatment helps boost your body's ability to fight COVID-19.
- The mAb treatment can block the SARS-CoV-2 virus from entry, limiting the multiplication of the virus
- Assist the immune system to recognize and respond more effectively to the virus.
- first defenses against getting infected.
- The treatment is for people who are at a high risk for developing serious symptoms of COVID-19 and needs to be given within the first 7 days of when symptoms appear.
- Examples : **Baricitinib or tocilizumab**

POSSIBLE TREATMENT OPTIONS FOR COVID-19

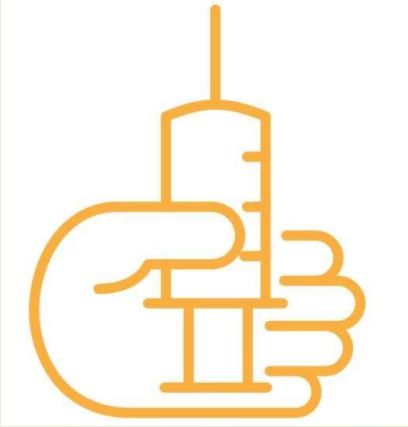
Antiviral:

- Antivirals - *they make it harder for viruses to make more virus within the body. They may also make it harder for viruses to get into your cells*
- Remdesivir -was developed for treatment of hepatitis C virus infection, and was also studied in Ebola and Marburg virus
- Remdesivir is a nucleoside drug. Its mechanism of action involves chain termination, the drug is incorporated preferentially to the endogenous adenosine nucleoside by the SARS-CoV-2 polymerase during replication of the RNA genome
- **Remdesivir** inhibits SARS-CoV-2 replication, reduces viral load, and exerts protective effects in SARS-CoV-2 infected animals. Remdesivir also reduces the pathological process, alleviates mild symptoms, and improves pulmonary lesions in SARS-CoV-2-infecetd animals. Remdesivir has been used as a **compassionate drug** for treating COVID-19 patients.

Why we use vaccines

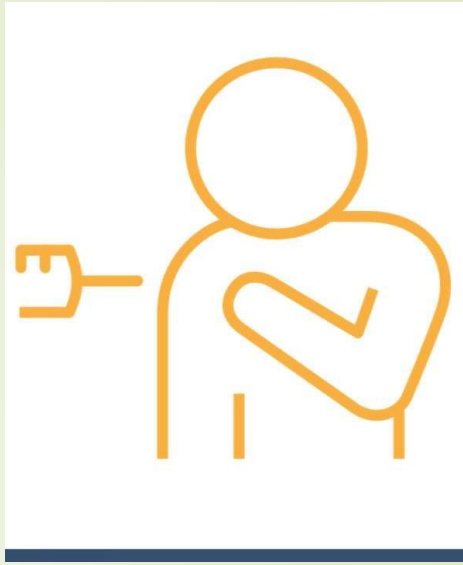
- **Vaccines can prevent infectious diseases.** Examples of vaccine-preventable diseases are: measles, polio, hepatitis B, influenza and many others.
- When most people in a community are vaccinated against a disease, the ability of the pathogen to spread is limited. This is called 'herd' or 'indirect' or 'population' immunity.
- When many people have immunity, this also indirectly protects people who cannot be vaccinated, such as very young babies and those who have compromised immune systems.

How vaccines work



- Vaccines greatly reduce the risk of infection by training the immune system to recognize and fight pathogens such as viruses or bacteria
- Vaccines safely deliver an **immunogen** which is a *specific type of antigen that elicits an immune response*, to train the immune system to recognize the pathogen when it is encountered naturally.

How vaccines are delivered



- A vaccine can be administered through different routes, for example injection in the muscle or under the skin or via the oral route.
- Vaccines sometimes require **more than one dose** to:
  - build complete immunity
  - give a 'booster' dose when immunity wears off
  - immunize people against viruses causing disease that may be different from season to season, for example, the yearly flu vaccine

Immunogens used to develop viral vaccines

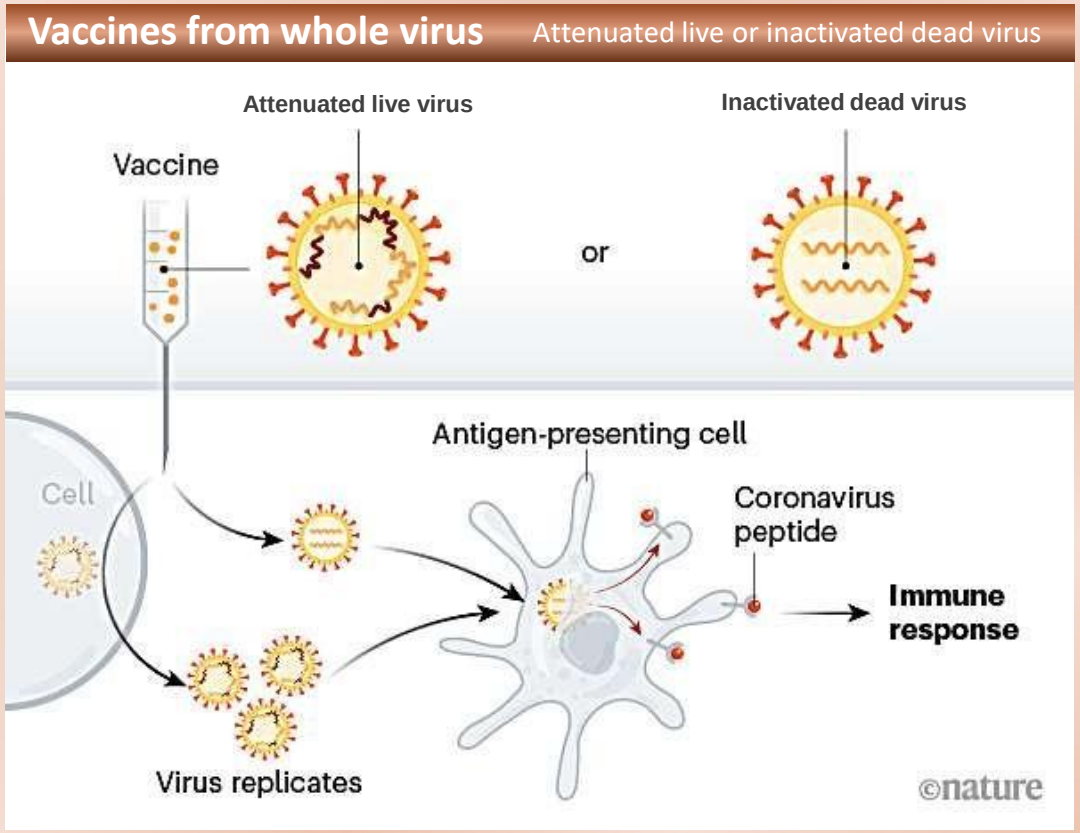
- Vaccines are being developed with different technologies — some well-known and others completely new for human vaccines, such as peptide and nucleic acid technologies

IMMUNOGEN	HOW IT WORKS	ADVANTAGE	DISADVANTAGE	EXAMPLE of vaccines
Attenuated live virus	Live virus but doesn't cause disease	Induces same response as natural infection	Not recommended for pregnant women and immunocompromised persons	Measles, rubella, mumps, yellow fever, smallpox (vaccinia)
Whole inactivated virus	Inactivated dead virus	Induces strong antibody response	Requires large quantities of virus	Influenza, rabies hepatitis A
Protein subunit	A protein derived from a pathogen	May have fewer side effects than whole virus (redness, swelling at injection site)	May be poorly immunogenic; complex process	Influenza
Recombinant	Host cell is used to express an antigen	No need to produce the whole virus	May be poorly immunogenic; High cost	Hepatitis B
Peptides	Synthetic produced fragment of an antigen	Rapid development	Poorly immunogenic; High cost	*COVID-19 vaccines in development*
Replicating or non-replicating viral vector	Viral pathogen expressed on a safe virus that doesn't cause disease	Rapid development	Prior exposure to vector virus (eg. adenovirus) may reduce immunogenicity	Ebola
Nucleic acid	DNA or RNA coding for a viral protein	Strong cellular immunity; rapid development	Relatively low antibody response	*COVID-19 vaccines in development*

Virus vaccines

- **Virus is selected, modified (weakened) or completely inactivated** so that it will not cause disease

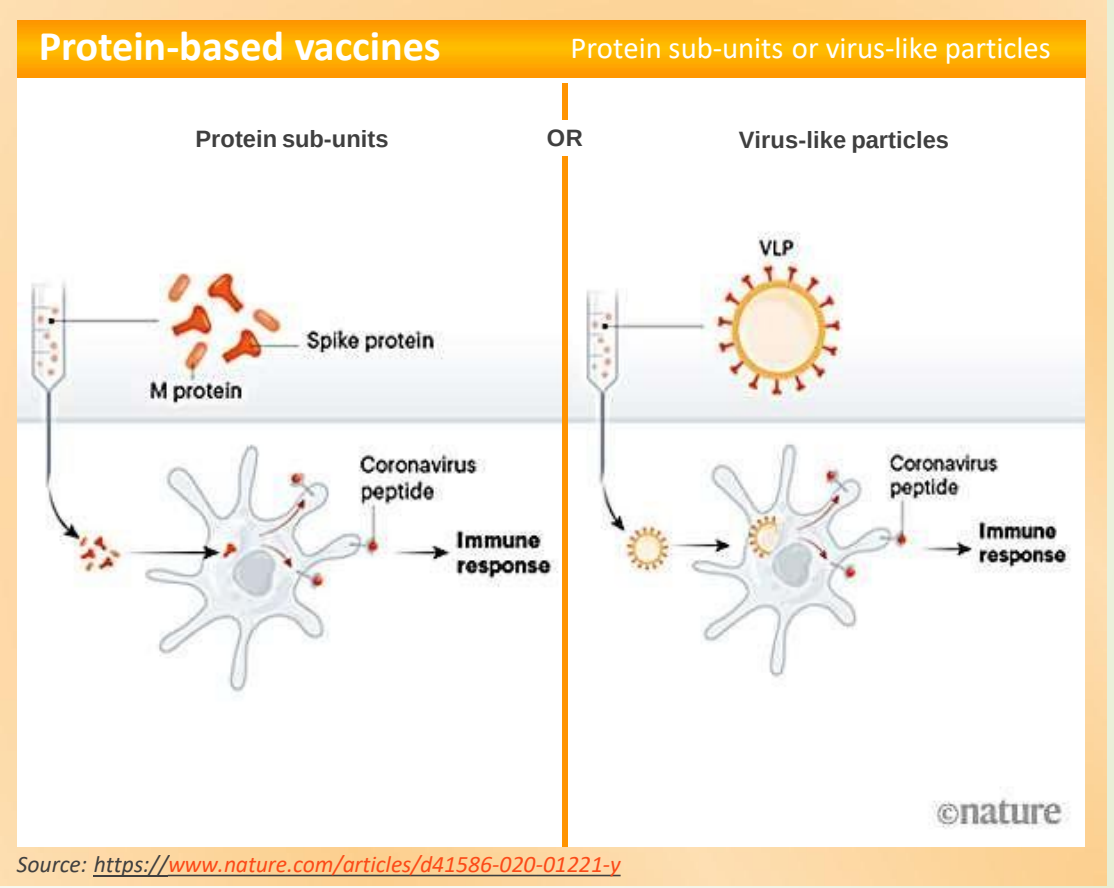
Note:
This illustration shows injectable vaccines. Some vaccines in this category are administered orally



Source: https://www.nature.com/articles/d41586-020-01221-y

Protein-based vaccines

- **A protein is extracted from the virus** (alive or inactivated), purified, and injected as a vaccine
- For coronavirus, this is most commonly the spike protein
- Virus-like particles work in the same way

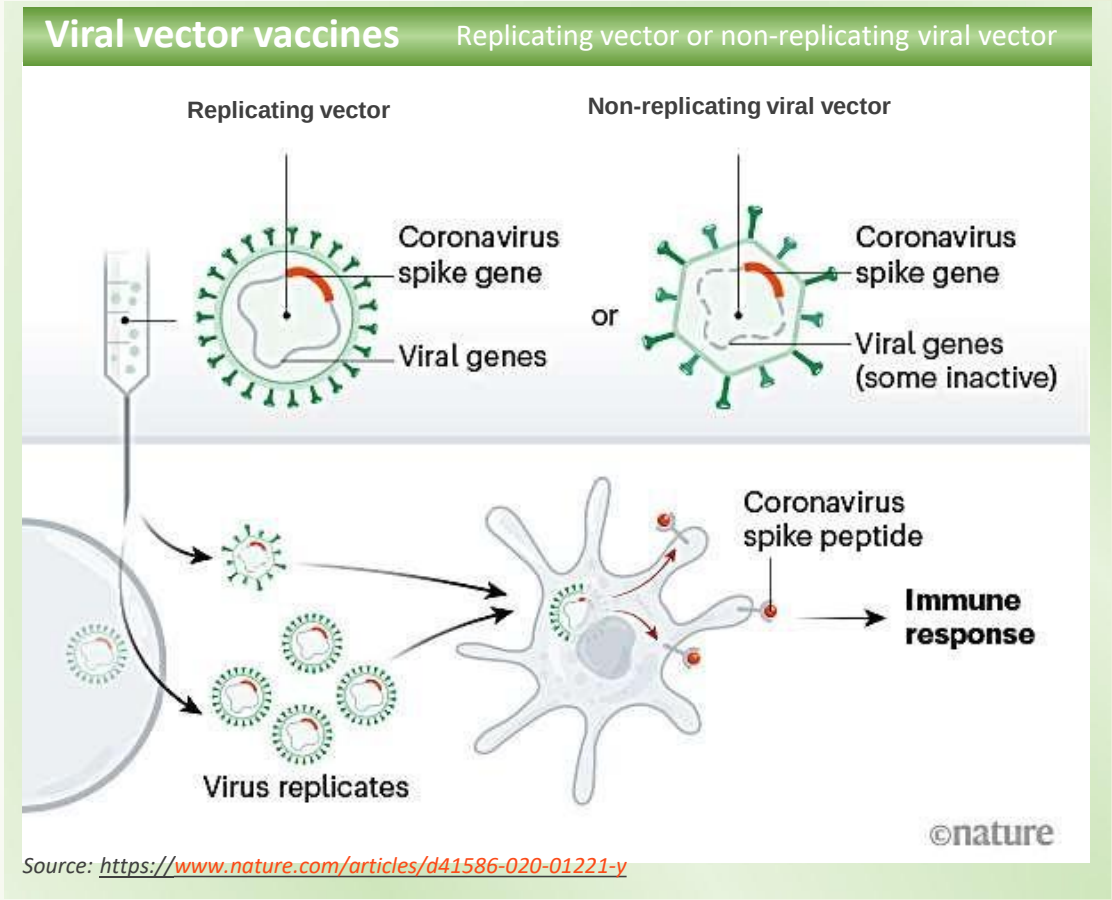


Source: https://www.nature.com/articles/d41586-020-01221-y

Viral vector vaccines

VACCINE DEVELOPMENT — Mechanism of action for types of vaccines

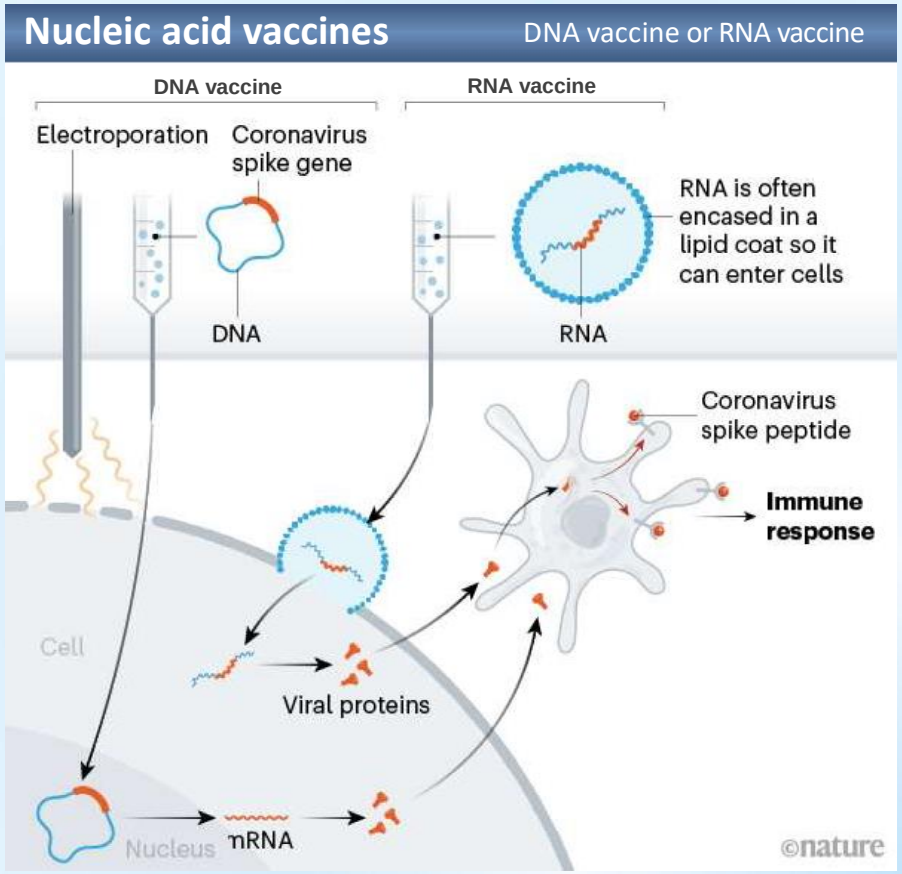
- The gene for a pathogen protein is inserted into a different virus that can infect someone without causing disease
- The safe virus serves as a 'platform' or 'vector' to deliver the protein that triggers an immune response
- The safe virus is then injected as a vaccine
- Some replicate (reproduce) in the body and some do not



Source: https://www.nature.com/articles/d41586-020-01221-y

Nucleic acid vaccines

- Instead of a virus, a protein antigen, or a virus expressing the protein, **nucleic acid coding for the antigen is injected**
- DNA plasmid: enters nucleus, translated to mRNA for expression of protein
- Or mRNA can be injected. More direct (no translation required) but less stable than DNA
- This is new technology – no other vaccines for human use have used this



Source: https://www.nature.com/articles/d41586-020-01221-y

Steps in vaccine development

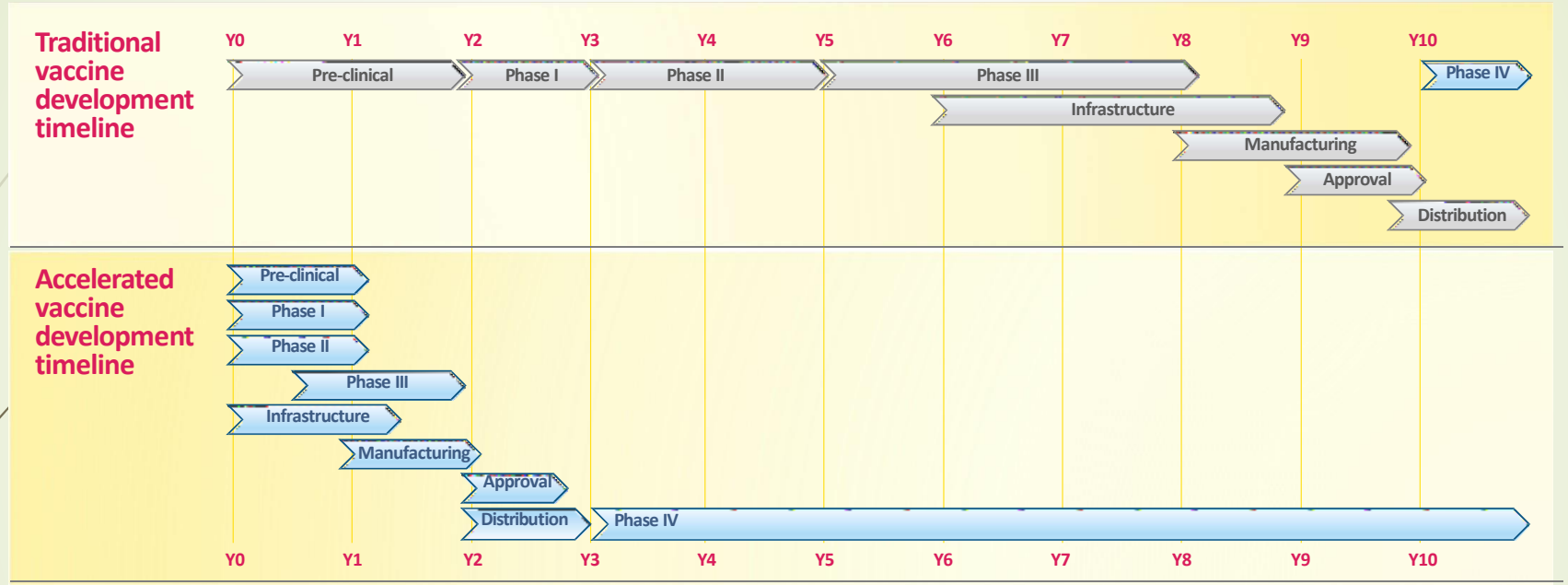
Actions taken to ensure a new vaccine is safe and works well

- **Pre-clinical studies**
  Vaccine is tested in animal studies for efficacy and safety, including challenge studies
- **Phase I clinical trial**
  Small groups of healthy adult volunteers receive the vaccine to test for safety
- **Phase II clinical trial**
  Vaccine is given to people who have characteristics (such as age and physical health) similar to those for whom the new vaccine is intended
- **Phase III clinical trial**
  Vaccine is given to thousands of people and tested for efficacy and safety
- **Phase IV post marketing surveillance**
  Ongoing studies after the vaccine is approved and licensed, to monitor adverse events and to study long-term effects of the vaccine in the population
- **Human challenge studies**
  Studies in which a vaccine is given followed by the pathogen against which the vaccine is designed to protect. Such trials are uncommon in people as they present considerable ethical challenges

Why there are so many COVID-19 vaccines in development

- There are many different COVID-19 vaccines in development because it is not yet known which ones will be effective and safe
- Based on experience, **roughly 7% of vaccines in preclinical studies** succeed. Candidates that reach **clinical trials have about a 20% chance of succeeding.**
- Different vaccine types may be needed for different population groups
- For example, some vaccines may work in older persons and some may not, as the immune system weakens with older age

COVID-19 vaccine accelerated development



- Normal vaccine development performs each step in sequence
- To accelerate COVID-19 vaccine development, **steps are done in parallel**
- All usual safety and efficacy monitoring mechanisms remain in place; such as adverse event surveillance, safety data monitoring & long-term follow-up
- **Phase IV post-marketing surveillance** for side effects is critical and essential

Covid-19 Vaccines in currently in Use

- As of 12 January 2022, the following vaccines have obtained approve

- The Pfizer/BioNTech Comirnaty vaccine, 31 December 2020.
- The SII/COVISHIELD and AstraZeneca/AZD1222 vaccines, 16 February 2021.
- The Janssen/Ad26.COV 2.S vaccine developed by Johnson & Johnson, 12 March 2021.
- The Moderna COVID-19 vaccine (mRNA 1273), 30 April 2021.
- The Sinopharm COVID-19 vaccine, 7 May 2021.
- The Sinovac-CoronaVac vaccine, 1 June 2021.
- The Bharat Biotech BBV152 COVAXIN vaccine, 3 November 2021.
- The Covovax (NVX-CoV2373) vaccine, 17 December 2021.
- The Nuvaxovid (NVX-CoV2373) vaccine, 20 December 2021
-