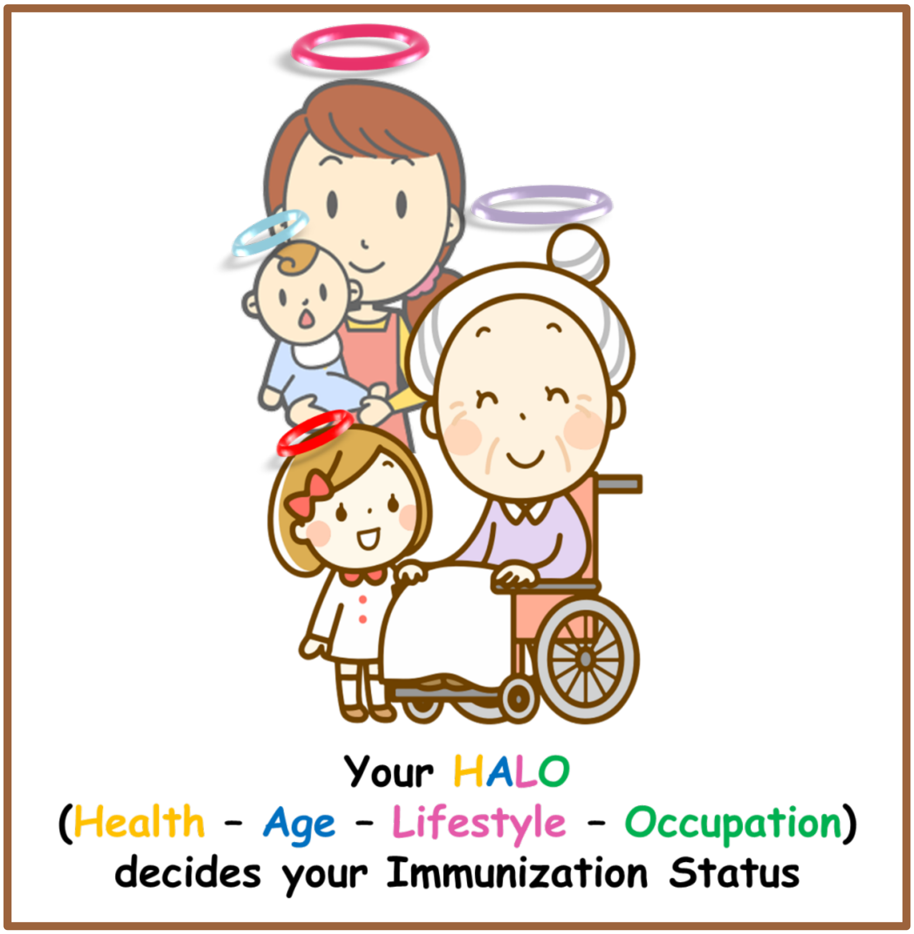
A child-centric microbiology education framework

Why do vaccines not always provide complete protection?

Granny: You must have the flu jab to protect you this winter!
No Darling; you should have it but it does not work for Granny.



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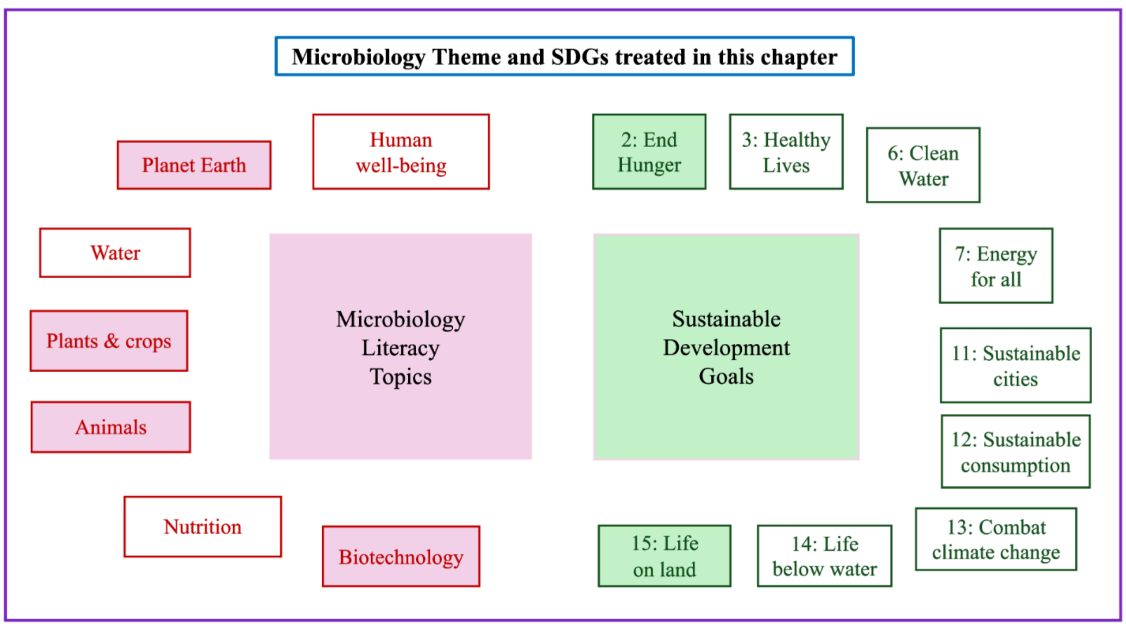
Why vaccines do not always protect?

Storyline

Vaccination is one of the most effective public health interventions for preventing, controlling, and, in some cases, eradicating infectious diseases. However, no vaccine provides complete protection in every individual. This teaching framework introduces the principles of vaccination and immunization, describes the major types of vaccines, and explains why vaccine-induced protection varies among individuals. It discusses host-, vaccine-, and environment-related factors that influence vaccine effectiveness, including antigenic drift and antigenic shift in influenza viruses, which necessitate periodic updates of influenza vaccines.

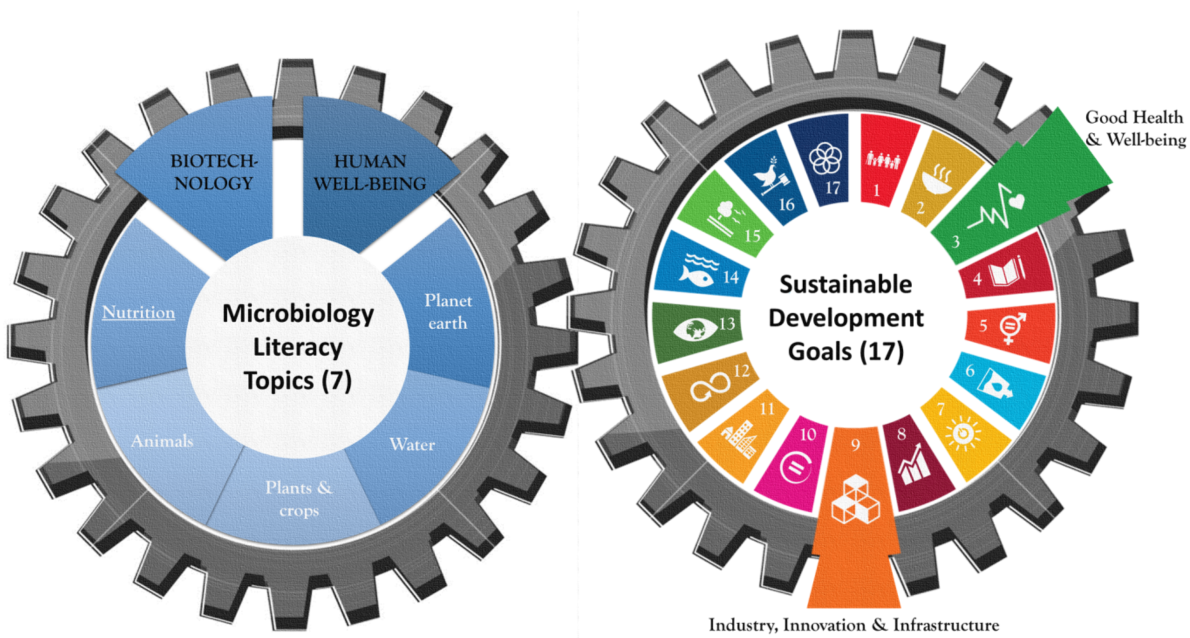


The Microbiology and Societal Context

Protecting human health across all age groups is fundamental to sustainable development and to attain global economic stability.

Goal 3: "Good Health and Well-being" - This Sustainable Development Goal (SDG) laid by the United Nations directly includes wider vaccination coverage for all. It has been precisely defined that by 2030, the goal is "To achieve universal health coverage including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all." This implies an assurance that the healthcare be accessible to even the most disadvantaged/ underprivileged population. The ultimate aim of this SDG is to achieve full childhood vaccination coverage which in turn will markedly influence the overall morbidity and mortality associated with vaccine-preventable infectious diseases to promote overall human well-being.

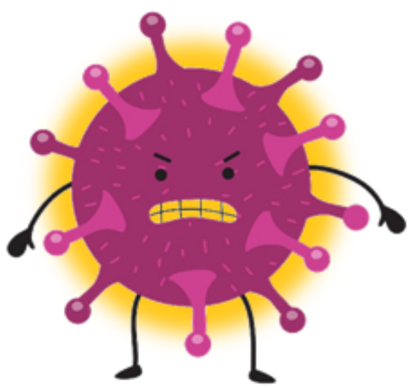
Goal 9: "Industrial and infrastructure innovation" – This SDG is chiefly related to the development and production of newer vaccines. This is because the world is observing an ever growing need for preventive vaccines against cancer, Zika virus, Herpes Simplex Virus (HSV), Human Immunodeficiency Virus (HIV) and other infectious diseases which are burdening the healthcare system worldwide.



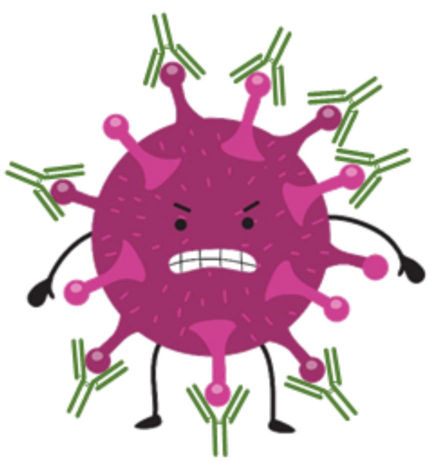
The Microbiological Context

<u>What are vaccines?</u>

A vaccine is a biological preparation containing inactivated or weakened microorganisms , their components, or their products that stimulates the immune system to develop protective immunity without causing the disease.



ACTIVE VIRUS



NEUTRALIZED VIRUS

What is an Antigen?

An antigen is a foreign molecule, usually a protein or polysaccharide, that is recognized by the immune system and triggers an immune response after entering the human body by specifically activating body's infection fighting white blood cells (Lymphocytes).

What are Antibodies?

Antibodies (aka Immunoglobulin) are Y-shaped glycoproteins which are produced by a specific type of White Blood Cells, called B-cells or Plasma cells that recognizes unique antigen on pathogen surface to neutralize it, thereby protecting our body from infection.

<u>Vaccination vs Immunization</u>

The process of administering a vaccine to elicit an immune response is defined as vaccination. For example, Oral Polio Vaccine (OPV) is administered as oral drops, while Inj. BCG

(Bacillus-Calmette-Guerin) is given into the skin as intradermal injection and Hepatitis B vaccine is injected into the muscles as intramuscular injection.

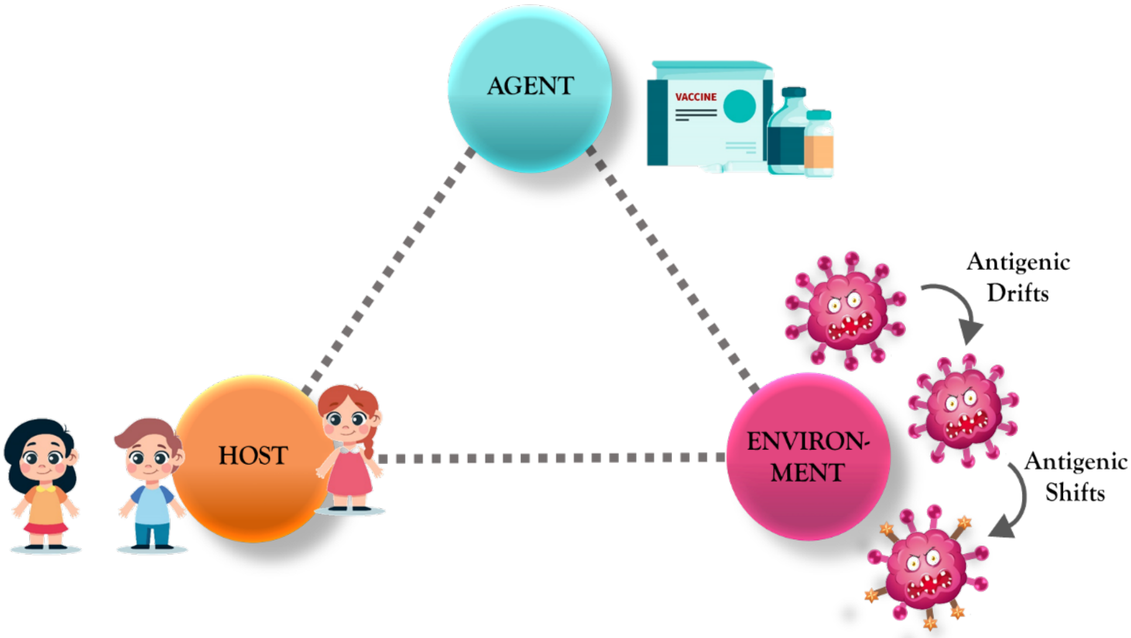
Immunization is the process by which an individual develops protective immunity following vaccination or passive administration of antibodies. It can be classified as *Active Immunity* and *Passive Immunity*.

- ***Active Immunity***: It is when live attenuated/ killed or part of micro-organism is administered prior to natural exposure to induce acquired immunity.
- **P*assive Immunity*:** Passive immunity is obtained when the antibodies formed exogenously are administered either before exposure to the pathogen or immediately after an exposure, so that the disease caused by micro-organisms can be suppressed.

Factors affecting Immunization

The age-old saying "Prevention is better than cure" still holds true even in modern day context. There are some pathogenic (disease-causing) microbes which are harmful and attack human body leading to various diseases. Some diseases can be prevented by following hygienic practices like washing hands with soap before eating, consumption of pure water and home-cooked fresh food can protect us from diarrheal illnesses (Acute Watery Diarrhea, Dysentery, Cholera) or infection from the novel *Coronavirus* can be prevented by wearing mask, social distancing and following hand-hygiene practices.

For some infectious diseases, caused by harmful microbes, there are vaccines which prepares our immune system to fight with the disease-causing germs whenever they attack, thereby protecting vaccinated person from complications of disease. And such diseases are called as Vaccine-Preventable Diseases (VPDs) like Diphtheria, Tetanus, Pertussis, Measles, Poliomyelitis, Mumps, Hemophilus influenzae type b (Hib). Vaccination substantially reduces the risk of infection and severe disease caused by vaccine-preventable pathogens. However, it does not guarantee 100% protection from the disease-causing micro-organisms as multiple factors play role in determining protective efficacy of vaccine. These includes classical triad of – *Agent (Vaccine)*, *Host* and *Environmental factors*.



The triad of factors affecting the immunization status of an individual

A. HOST FACTORS

These are important individual characteristics that affects acquisition of immune response in human body against infectious pathogens.

1. ***Age:*** Age is one of the important factors that affect immune response following vaccination. The various limitations of immunization at a very young age includes-

   i. Immaturity of the neonatal immune system.

   ii. Persistence of maternally derived antibodies that may interfere with vaccine responses during early infancy. (Transferred trans-placentally which declines overtime postnatally, thereby protecting newborns for first 6 months of life)

   iii. During the first 2 years of age, antibody response to polysaccharide vaccine antigens are generally not observed.

These are the major factors that are responsible for age-dependent limitation of vaccine use. However, in many developing countries it has been documented that most of the infectious diseases during childhood may either lead to morbidity or even mortality. Therefore, it becomes imperative to adopt certain measures to counter these limitations. These may include –

i. Use of Adjuvants, thereby minimizing the vaccine dose.
ii. Use of boosters at later age to boost adequate immune response.
iii. Increasing doses of vaccine antigens (Example: Hepatitis A and Measles vaccine)

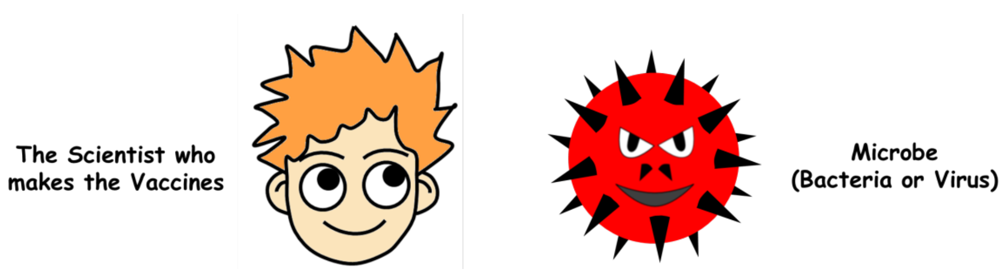
2. ***Inherited or Acquired Immunodeficiency States*:** Individuals with inherited or acquired immunodeficiency may be unable to mount adequate immune responses following vaccination. Consequently, live attenuated vaccines are generally contraindicated in severely immunocompromised individuals because they may cause disease.

3. ***Allergies to Egg/ Egg proteins*:** Certain vaccines, including influenza and yellow fever vaccines, are produced using embryonated chicken eggs and may contain residual egg proteins. Individuals with severe egg allergy should be evaluated according to current vaccination guidelines before receiving these vaccines.

B. AGENT FACTORS

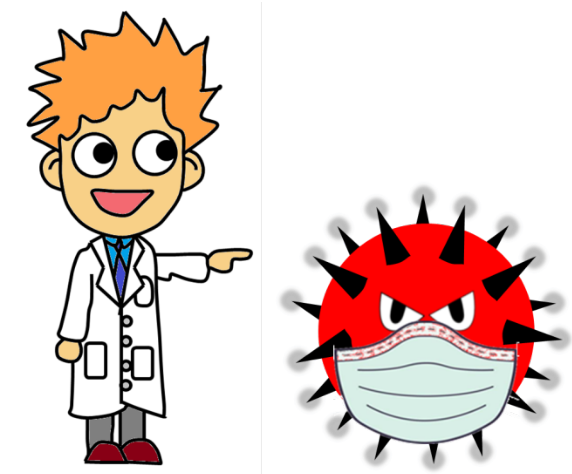
When it comes to immunization, agent is the vaccine that is administered and host is the individual getting the vaccine. So, there are numerous vaccine characteristics that affects the protection provided by the vaccine against disease causing micro-organisms. These includes-

1. ***Type of vaccine*:** As already discussed, there are four major types of vaccines.

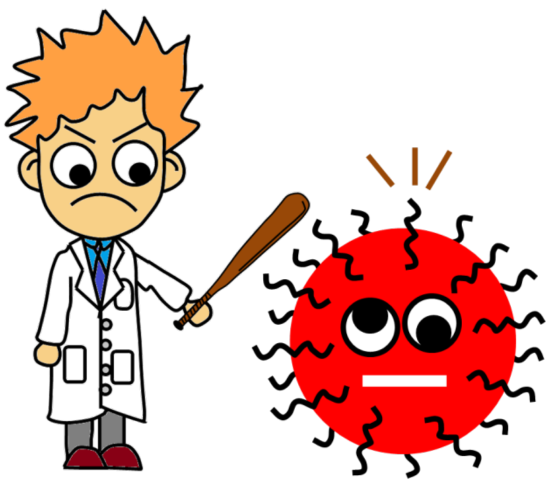


1. Live Attenuated Vaccines

Live attenuated vaccines contain weakened microorganisms that replicate to a limited extend within the host. This mimics natural infection and induces strong, long-lasting immune immune responses without actually causing the disease in healthy individuals. Usually, multiple doses are not required. Very rarely, weakened microbes can revert back to their virulent form and might lead to development of disease in the vaccinated person.



The Microbe gets a tough beating from the scientist but is still strong enough to be effective



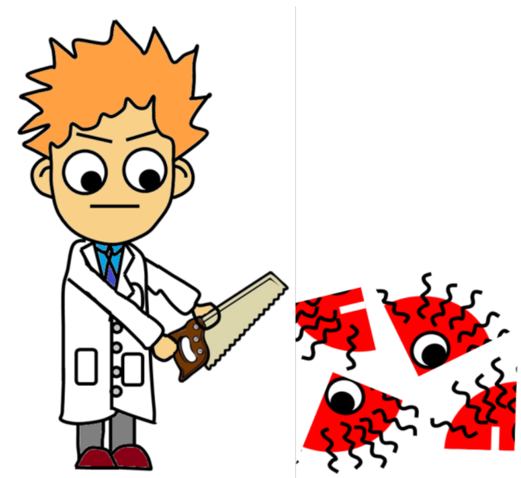
The Microbe is killed dead.
It is no more alive to be effective

2. Killed Vaccines

The preparation of these vaccines involves two steps. Firstly, a culture of the disease-causing micro-organisms is grown in a suitable media and thereafter they are killed either by heat or chemical inactivation methods to obtain a “killed vaccine”. Because they cannot replicate within the host, they are safe but immunity is not permanent and multiple doses as well as booster doses and booster vaccinations are required.

3. Subunit Vaccine

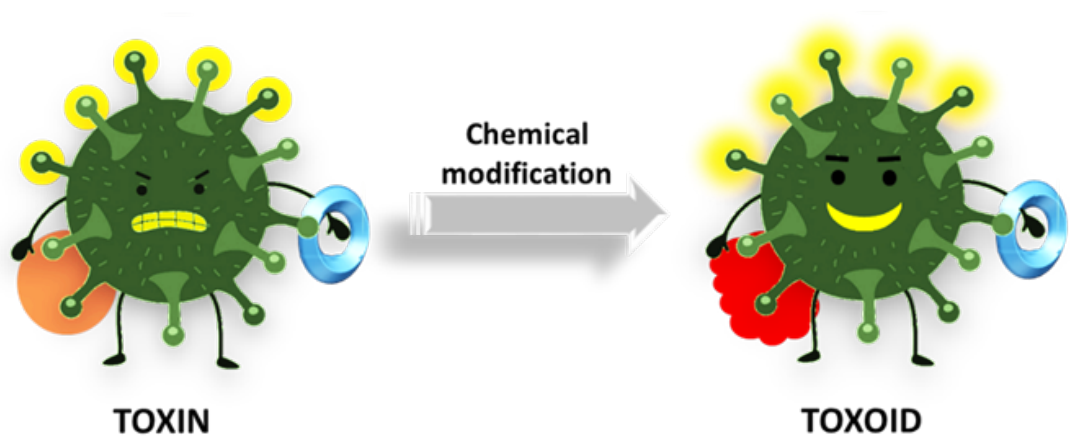
Subunit vaccines contain purified components of pathogens, such as proteins or polysaccharides, rather than the entire microorganism. They are safe but may require adjuvants or booster doses to enhance immune responses. For example, Capsular Polysaccharide Antigen (carbohydrate antigen) in Pneumococcal polysaccharide vaccine which can be given in individuals more than 2 years of age only.



The Microbe is cut into pieces which is then used to make a vaccine

4. Toxoids

Toxoid vaccines contain chemically inactivated bacterial toxins that retain their antigenicity but have lost their toxicity. They stimulate protective antibody responses against toxin-mediated diseases and usually require booster doses to maintain immunity.



5. ***Efficacy of Vaccine:*** Efficacy of a vaccine is defined as the protection conferred to a person from the pathogenic microorganism following administration of a vaccine. It is calculated as follows:

$$\frac{(Attack\ rate\ in\ unvaccinated) - (Attack\ rate\ in\ vaccinated)}{Attack\ rate\ in\ unvaccinated} \times 100$$

No vaccine provides 100% efficacy in protecting a vaccinated individual from disease-causing organism, but they do decrease the chance of disease when attacked by harmful pathogen and even this partial protection is useful in preventing serious disease complications.

6. ***Vaccine Safety:*** Vaccines are relatively safe with very rare serious adverse effects. Though some children might have anaphylactic reaction which becomes contraindication for subsequent doses. But, as a whole, benefits of vaccine outweigh the associated risks. Examples of some serious adverse effects includes – Encephalopathy occurring within 7 days of pertussis vaccine; Vaccine-associated Paralytic Poliomyelitis (VAPP) following Oral Polio Vaccine.

7. ***Vaccine storage and handling:*** Vaccines and toxoids are made up of proteins, polysaccharides which should be stored within a recommended range of temperatures. If vaccines are placed outside the recommended temperature range, they may lose their effectiveness or may get completely destroyed. So, it is necessary to maintain the recommended range of temperature right from the point of vaccine manufacturing till it is administered. For example- BCG, OPV and Measles vaccines are heat and light sensitive, therefore cold chain must be maintained during their storage and transportation at a recommended temperature of +2 C to +8C.

8. ***Adjuvants:*** Derived from a Latin word "*adjuvare*" meaning "to help", adjuvants are the agents that are added to a vaccine to boost the immune response. They increase vaccine

immunogenicity, reduce the amount of antigen required, and often promote longer-lasting protection.

C. ENVIRONMENTAL FACTORS

Environmental factors such as disease epidemiology, population immunity, pathogen evolution and vaccination coverage also influence vaccine effectiveness.

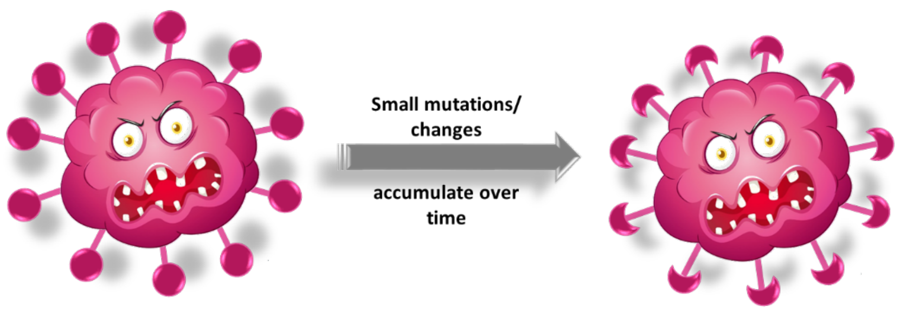
1. ***Disease Epidemiology and Prevalence*:** The frequency of a disease in human beings can be studied based on two parameters including its distribution and its specific determinants. This study indicates the epidemiology of that disease. Age-related prevalence of diseases also varies like Invasive Pneumococcal disease have highest rates in children less than 2 years of age, elderly and immunocompromised individuals; *Hemophilus influenzae* type b causes invasive diseases like pneumonia, meningitis, cellulitis, osteomyelitis, septic arthritis in children < 2 years of age. Therefore, in accordance with the standard recommendations, the suitable age of vaccination is dependent on the age during which the disease is more prevalent.

2. ***Epidemiologic Shift*:** It occurs due to partial vaccination, which leads to upward shift in the age of infection or disease acquisition. Hence, it can also be stated that as the presence of the pathogen declines from an environment, an inversely proportional change is observed in the age of acquisition of its infection. The natural circulation of pathogen decreases and age of acquisition of infection advances. It is important for the diseases where severity worsens with advancing age like with diseases such as Rubella, Varicella and Hepatitis A.

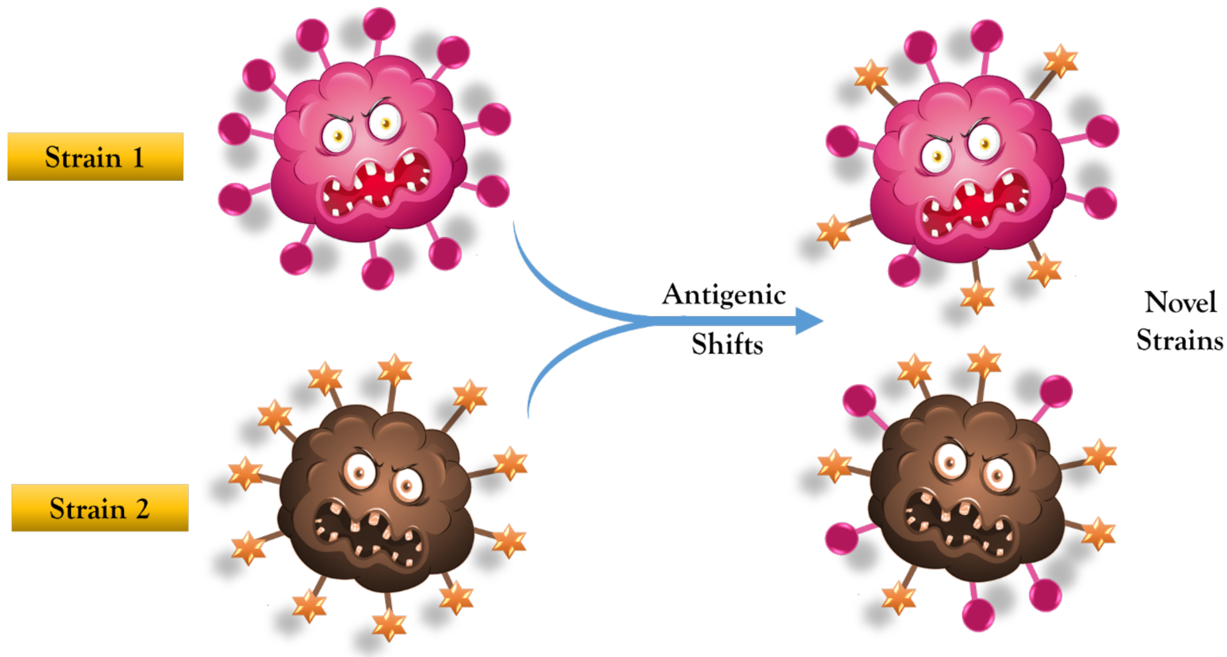
3. ***Antigenic Drift & Shift:*** These are two closely related terms which should not be confused with each other. There are certain genetic mutations leading to changes in surface proteins of virus (especially *Influenza* viruses that are constantly changing). These surface proteins- Hemagglutinin and Neuraminidase act as “viral antigens” i.e. they are recognized

by the immune system and trigger immune responses in form of antibody production, thereby blocking the infection and protecting us from the Flu. These small changes take place continuously with each replication and results in closely related viruses that display similar antigenic properties. However, in due course of time, such small changes that accompany antigenic drift may accumulate and generate viruses presenting a completely different set of antigens. Thus, these altered antigens then may not be recognized by the body's immune system which in turn would result in failure to prevent sickness due to this newer influenza virus. This is the reason why we tend to be prone to Flu infection again and again, as pre-existing antibodies won't be able to recognize the changed/ newer viral antigen. Hence, Flu vaccine composition must be reviewed frequently to keep up with the evolving *Influenza* virus.

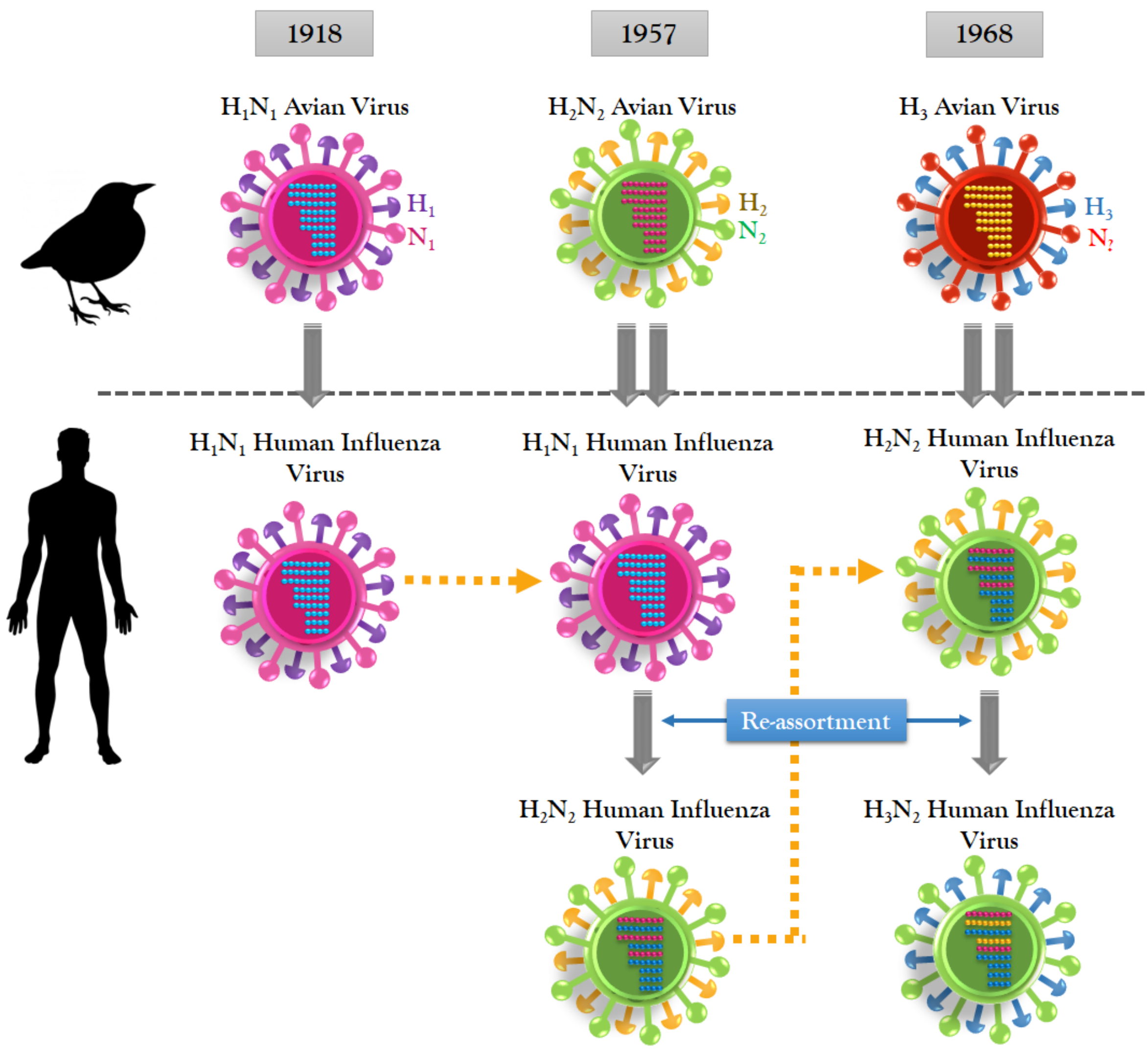
Antigenic drift in influenza viruses resulting from the gradual accumulation of mutations in viral surface antigens.



Whereas, *antigenic shift* in an Influenza A virus involves a sudden and major change at the genetic level, that results in new surface proteins (hemagglutinin and neuraminidase antigen) when two or more different viruses or their strains combine to form a new subtype. Therefore, antigenic shift results in new subtype of Influenza A virus. Similarly, Influenza virus infecting animals can also undergo antigenic shift and gains ability to infect human beings. Such newer viruses which differs from already existing human subtypes, and hence humans do not have protective antibodies against them are called as Novel viruses. For example, Swine Flu caused by H1N1 subtype and resulted in pandemic in 2009; novel coronavirus (COVID19) ongoing pandemic in 2019-2020.



Antigenic shift resulting from genetic assortment between influenza viruses, producing novel viral strains.



Antigenic Shift & Drift in Influenza virus

Table 1: Various types of vaccines

S.No.	Type of Vaccine	Vaccines
1.	**Live- attenuated Vaccines**	BCG, OPV, Measles, MMR, Varicella, Rotavirus, Yellow fever, oral typhoid vaccine
2.	**Killed Vaccines**	DTwP, Hepatitis A, Rabies, Inactivated Polio Vaccine (IPV), whole cell killed typhoid vaccine, Influenza (whole virion)
3.	**Toxoids**	Diphtheria toxoid and Tetanus toxoid
4.	**Subunit Vaccines**	Acellular pertussis, Recombinant Hepatitis B, Influenza (Split subunit), *Salmonella typhi* (Vi) capsular polysaccharide, Hib, Meningococcal, Pneumococcal vaccine

The Evidence Base, Further Reading and Teaching Aids

- Advisory Committee on Vaccines; Immunization Practices (ACVIP). IAP Guidebook on Immunization 2018-2019, 3rd ed. New Delhi: Jaypee Brothers Medical Publishers; 2020.
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- https://www.freepik.com/vectors/character
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Glossary

Antibody (=Immunoglobulin): Y-shaped protective proteins which are produced by lymphocytes in response to foreign antigens

Antigen: A surface molecule on pathogen which induces an immune response in the body following exposure to an infectious micro-organism or after vaccination

Active Immunity: Protective response mounted by body's immune system

Adjuvant: Substances which are unrelated to organism but when it is added to vaccine, increases its ability to mount immune response

Attenuation: Alteration of an infectious agent to make it harmless or less virulent

Booster doses: Re-exposure to an immunizing agent (antigen) in a previously vaccinated person to maintain a functional pool of "antibody-producing memory cells" which decline over time after primary immunization

Epidemiology: The study and analysis of the distribution, pattern and determinants of health and disease conditions in a defined population

Immunization: A process to make a person immune or resistant to an infectious agent by administration of vaccine which mounts a protective immune response

Pandemic: A pandemic is a disease outbreak that spreads across countries or continents preformed animal or human antibodies into the body

Pathogen (=infectious agent/germ): Any micro-organism that is capable of causing disease

Prevalence: At a given time, the number of cases of a disease observed in a particular population

Vaccination: Administration of a vaccine to elicit an immune response in the body

Vaccine: A biological preparation containing antigens that stimulate protective immune responses against infectious diseases