Historical overview of vaccine development:

The first recorded attempts to deliberately induce immunity were performed by the Chinese and Turks in the fifteenth century. They were attempting to prevent smallpox, a disease that is fatal in about 30% of cases and that leaves survivors disfigured for life. Reports suggest that the dried crusts derived from smallpox pustules were either inhaled or inserted into small cuts in the skin (a technique called *variolation*) in order to prevent this dreaded disease.

1718- Lady Mary Wortley Montagu, the wife of the British ambassador in Constantinople, observed the positive effects of *variolation* on the native Turkish population and had the technique performed on her own children.

1798- Edward Jenner observed milkmaids who had contracted the mild disease cowpox were subsequently immune to the much more severe smallpox, Jenner reasoned that introducing fluid from a cowpox pustule into people might protect them from smallpox. To test this idea, he inoculated an eight-year-old boy with fluid from a cowpox pustule and later intentionally infected the child with smallpox. As predicted, the child did not develop smallpox. However, this method is ethically incorrect.

1870- Louis Pasteur had succeeded in growing the bacterium that causes fowl cholera in culture, and confirmed this by injecting it into chickens that then developed fatal cholera.

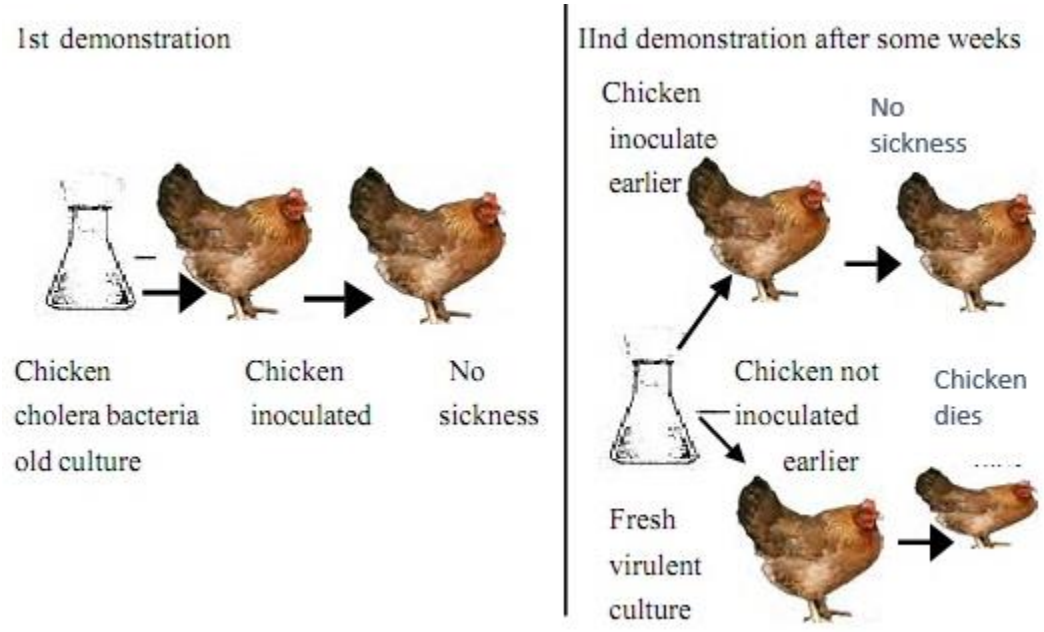

Figure 1- After returning from a summer vacation, he and colleagues resumed their experiments. 1st set of experiments involved old cholera bacterial culture, which caused the chickens to develop the disease on inoculation (inject) with the bacterial culture. However, the chickens recovered from the disease. In the second set of experiment, the chickens were inoculated with a new culture. The chickens who had been inoculated earlier and had survived the first set of experiment survived this stage as well. However, those chickens that were not inoculated earlier, developed the disease and died.

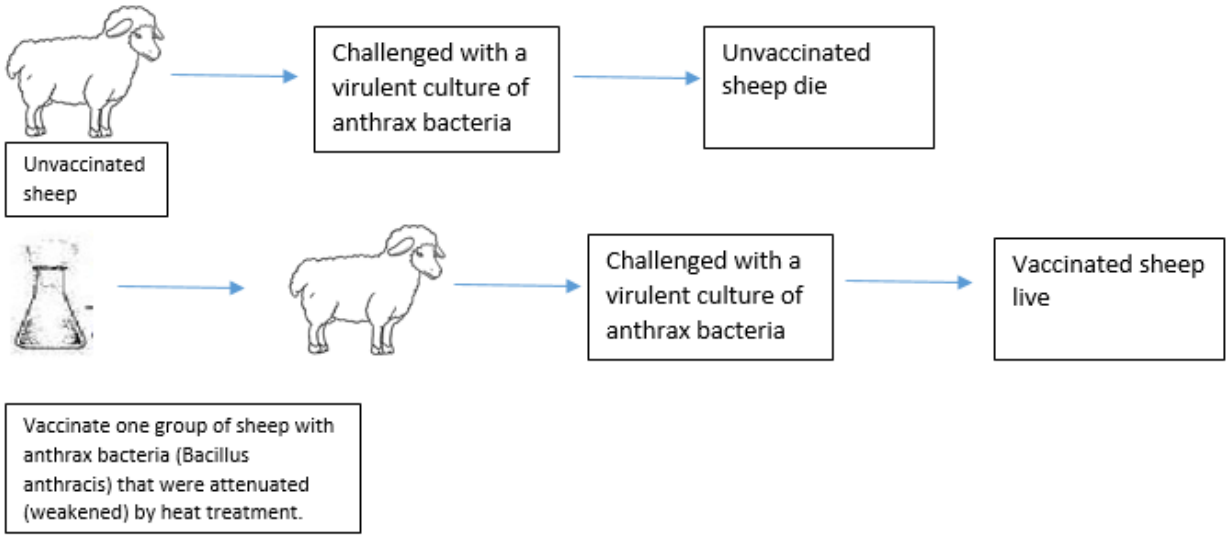

Figure 2- Pasteur extended these findings to other diseases, demonstrating that it was possible to attenuate a pathogen and administer the attenuated strain as a vaccine. In a now classic experiment performed in the small village of Pouilly-le-Fort in 1881, which marked the beginnings of the discipline of immunology.

In 1885, Pasteur administered his first vaccine to a human, a young boy who had been bitten repeatedly by a rabid dog. The boy, Joseph Meister, was inoculated with a series of attenuated (weakened) rabies virus preparations. The rabies vaccine is one of very few that can be successful when administered shortly after exposure. Joseph lived, and later became a caretaker at the Pasteur Institute, which was opened in 1887 to treat the many rabies victims that began to flood in when word of Pasteur's success spread; it remains to this day an institute dedicated to the prevention and treatment of infectious disease.

Introduction:

A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and keep a record of it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

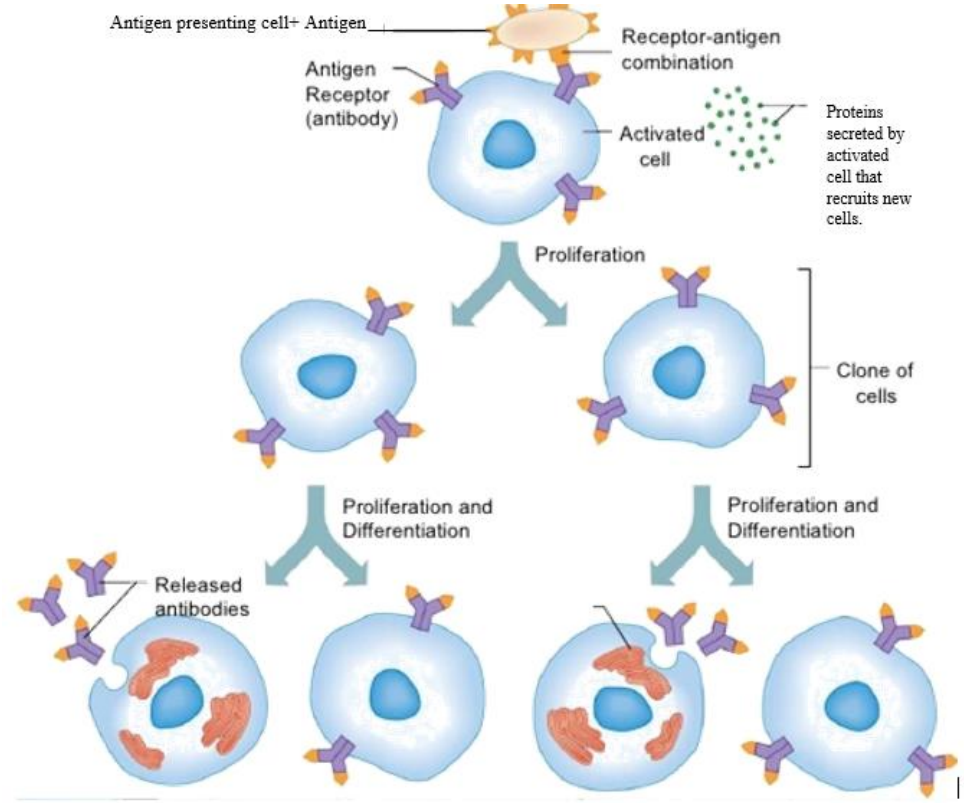

Figure 3- Cascade of immune reactions. On contact with an antigen, the Antigen presenting cell (APC) present the antigen to an effector cell. The effector cell recognizes the antigen that the APC holds at its cell surface and releases proteins that calls more immune cells to destroy the antigen. The effector cell has a second function of division (proliferation)

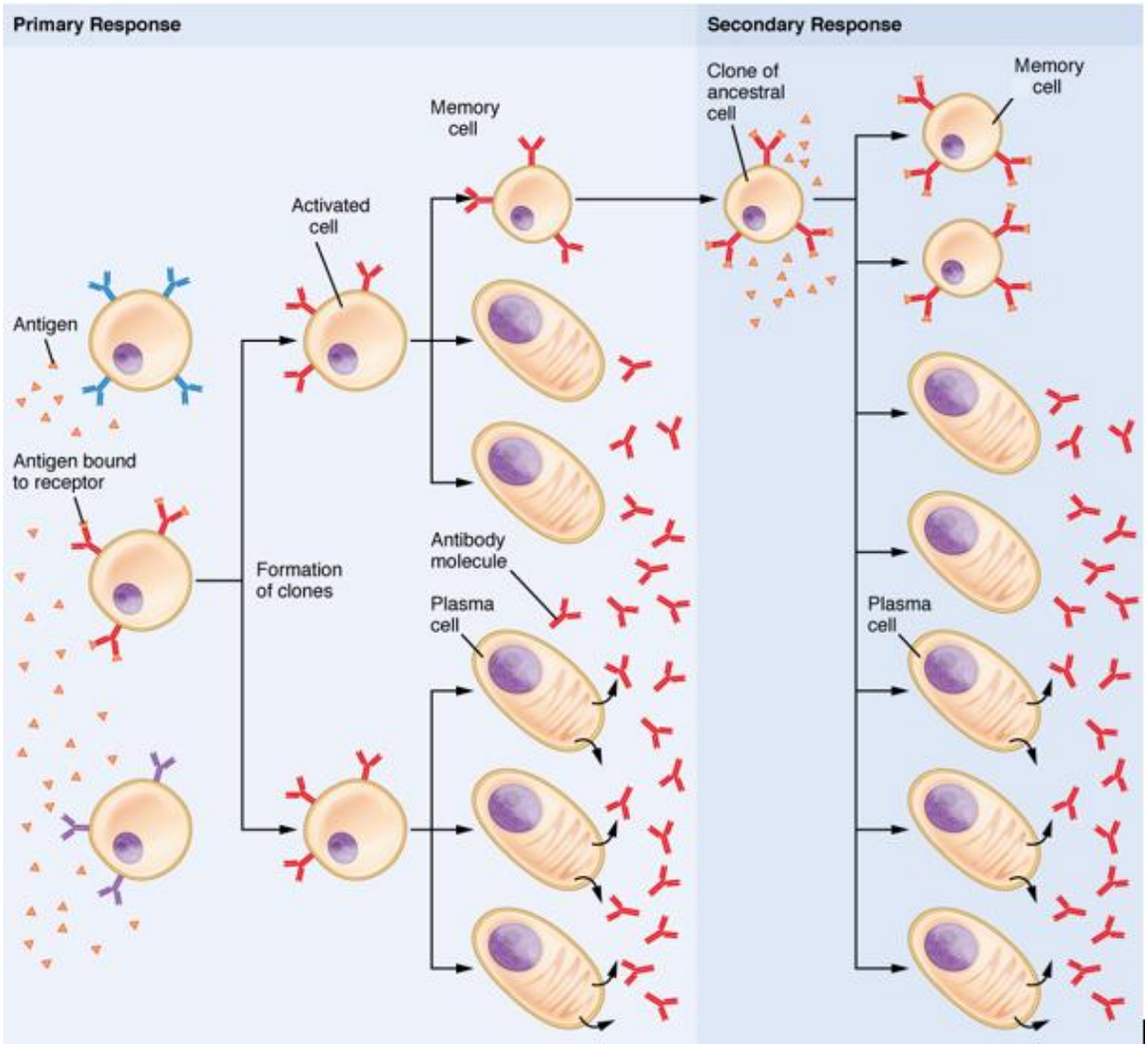

Figure 4- Primary response- When an antigen is encountered by the immune system for the first time, the body takes more time to recruit and activate all the cells and destroy the antigen. The result of primary response is destruction of the antigen and memory cells. Memory cells remember the properties of the antigen and in case of a second attack by the same antigen, cause a more rapid and more vigorous response. This is called the secondary response.

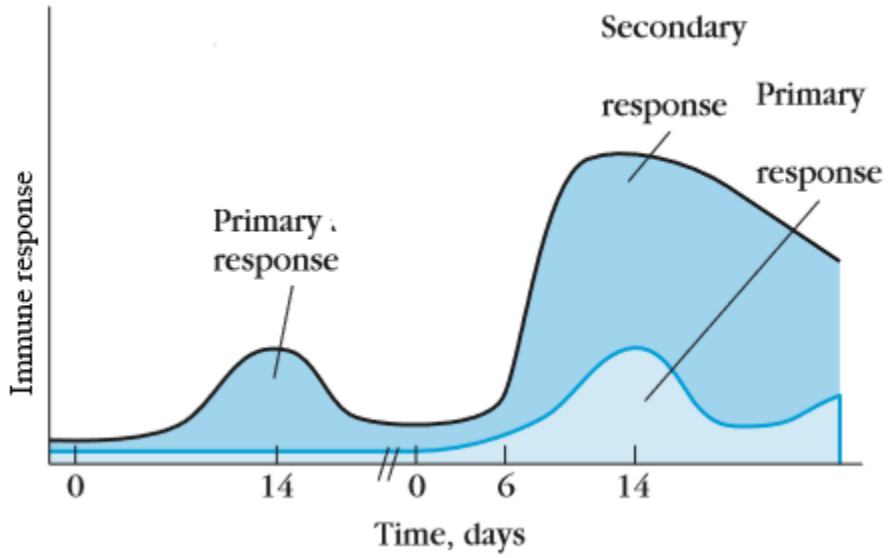

Figure 5- Primary response of antigen indicated in blue line. Primary and secondary response to antigens indicated by black line

Vaccine mode of action:

Immunization is the process of eliciting a long-lived state of protective immunity against a disease-causing pathogen. Exposure to the live pathogen followed by recovery is one route to immunization. Vaccination, or intentional exposure to forms of a pathogen that do not cause disease (a **vaccine**), is another. In an ideal world, both engage antigen-specific cells and result in the generation of memory cells, providing long-lived protection. However, vaccination does not ensure immunity, and a state of immune protection can be achieved by vaccination.

A state of immunity can be induced by passive or active immunization. Short-term passive immunization is induced by the transfer of preformed antibodies. Natural infection or vaccination can induce active immunization and lead to long-term immunity.

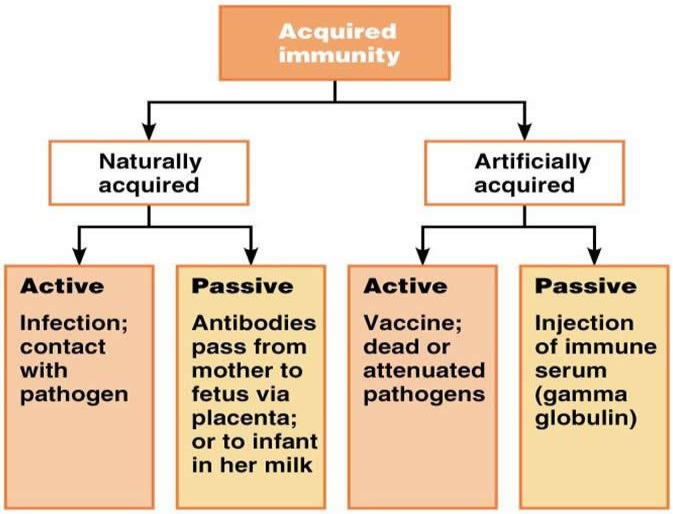

Figure 6- Immunity can be gained by passive or active way

Types of vaccines:

Five types of vaccines are currently used or under experimental consideration in humans: live, attenuated (avirulent) microorganisms; inactivated (killed) microorganisms and purified macromolecules (subunits).

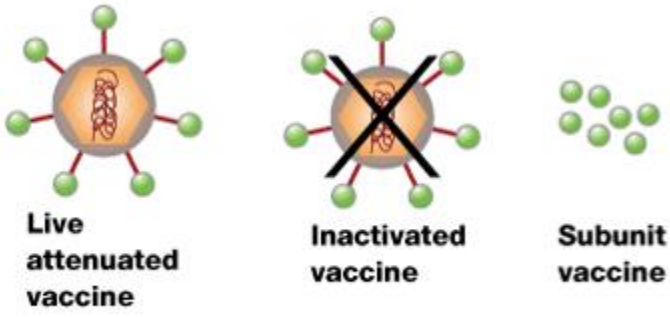

Figure 7- Types of vaccines

Live vaccines have the advantage of inducing both humoral and cell-mediated immunity, and can produce more effective overall protective immunity. However, live, attenuated vaccines carry the risk of reversion, which is not an issue with recombinant forms.

Scientists produce inactivated vaccines by killing the disease-causing microbe with chemicals, heat, or radiation. Such vaccines are more stable and safer than live vaccines: The dead microbes can't mutate back to their disease-causing state. Inactivated vaccines usually don't require refrigeration, and they can be easily stored and transported in a freeze-dried form, which makes them accessible to people in developing countries.

Isolated protein components of pathogens expressed in cell culture can be used to create effective vaccines, especially when the toxic effects of the pathogen are due to discrete protein

products. Polysaccharide and other less immunogenic vaccines may be conjugated to more immunogenic proteins to enhance or maximize the immune response.

Some vaccines show effect on a pathogen, however this effect is lost in the offsprings of the pathogen: Example of influenza vaccines

The virions are surrounded by an outer envelope, Inserted into the envelope are two glycoproteins, hemagglutinin (HA) and neuraminidase (NA).

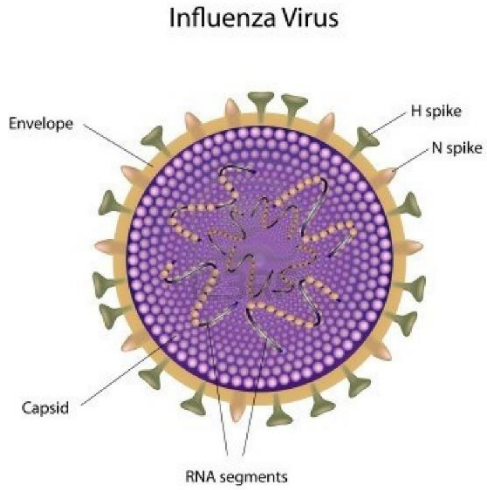

Figure 8- Influenza virus particle.

The first time a human influenza virus was isolated was in 1934; this virus was given the subtype designation H0N1 (where H is hemagglutinin and N is neuraminidase). The hemagglutinin trimer binds to sialic acid groups on host-cell glycoproteins and glycolipids. Neuraminidase, as its name indicates, cleaves N-acetylneuraminic (sialic) acid from nascent viral glycoproteins and host-cell membrane glycoproteins, an activity that presumably facilitates viral budding from the infected host cell.

A number of vaccines have been designed that target hemagglutinin and neuraminidase. However, the virus still is capable of surviving against the vaccines because of two processes that the virus is capable of:

1. Producing a series of spontaneous point mutations that occur gradually, resulting in minor changes in HA and NA.
2. Producing sudden emergence of a new subtype of influenza, who's HA and possibly also NA are considerably different from that of the virus present in a preceding epidemic.

Evolution of the immune system:

The innate immune system acts as the first line of defense and exists to provide early defense against pathogen attack, and to alert the adaptive immune system to the fact that pathogen invasion has begun. Many attributes of the innate immune system cells like macrophage cells are very similar to the movement of the most primitive organism amoeba. However, at such a basic level of organism, a stronger defense mechanism is not present. Innate immunity in eukaryotes can be thought of as arising from the need of a unicellular microorganism such as an amoeba to

discriminate between food and other amoebas. Innate immunity in eukaryotes allows the initial recognition of a foreign pathogen. However, this initial defense system does not provide the memory response required to identify a second round of attack by the pathogen. Therefore, a vaccine cannot be designed for such an organism that can only raise the innate response.

Genomic analysis of plants and animals provides evidence that a sophisticated mechanism of host defense was in existence by the time the ancestors of plants and animals diverged.

It has been known for at least 50 years that all jawed fish can mount an adaptive immune response. On the other hand, hagfish and lampreys, which are jawless vertebrates, lack all signs of an adaptive immune system: they do not have organized lymphoid tissue, they lack primary immune responses, and most importantly, they do not exhibit immunological memory. It was only in 1998 that the answers to these questions began to become apparent.

Adaptive immune system is the second line of defense of the immune system. In jawed fish and all 'higher' vertebrates, adaptive immunity is possible because a transposable element invaded a stretch of DNA, presumably a gene that was similar to an immunoglobulin gene. On the other hand, hagfish and lampreys, which are jawless vertebrates, lack all signs of an adaptive immune system: they do not have immune organs, they lack primary immune responses, and most importantly, they do not exhibit immunological memory. By contrast, even cartilaginous fish, the earliest jawed fish to survive to the present day, have organized immune organs, albeit primitive, and the ability to mount adaptive immune responses.

Thus the ability of mounting an adaptive immune response allows the organism to enlist cells for clearing out the invading pathogen and most important, produce memory cells for the specific pathogen (launch a secondary immune response). Such organisms which can mount an adaptive immune response and a secondary immune response can be vaccinated.