The Vaccine

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.

Passive immunization, in which preformed antibodies are transferred to a recipient, occurs naturally when maternal IgG crosses the placenta to the developing fetus. Maternal antibodies to diphtheria, tetanus, streptococci, rubeola, rubella, mumps, and poliovirus all afford passively acquired protection to the developing fetus. Later, maternal antibodies present in breast milk can also provide passive immunity to the infant in the form of maternally produced IgA.

Passive immunization can also be achieved by injecting a recipient with preformed antibodies, called antiserum, from immune individuals. Before vaccines and antibiotics became available, passive immunization was the only effective therapy for some otherwise fatal diseases, such as diphtheria, providing much needed humoral defense active immunization is to trigger the adaptive immune response in a way that will elicit protective immunity and immunologic memory.

active immunization is, a subsequent exposure to the pathogenic agent elicits a secondary immune response that successfully eliminates the pathogen or prevents disease mediated by its products.

Active immunization can be achieved by natural infection with a microorganism, or it can be acquired artificially by administration of a vaccine. In active immunization, as the name implies, the immune system plays an active role—proliferation of antigen-reactive T and B cells is induced and results in the formation of protective memory cells. This is the primary goal of vaccination. Active immunization with various types of vaccines has played an important role in the reduction of deaths from infectious diseases, especially among children.

Types of vaccines:

Live, Attenuated Vaccines

In some cases, microorganisms can be attenuated or disabled so that they lose their ability to cause significant disease (pathogenicity) but retain their capacity for transient growth within an inoculated host. Some agents are naturally attenuated by virtue of their inability to cause disease in a given host, although they can immunize these individuals.

Attenuation can often be achieved by growing a pathogenic bacterium or virus for prolonged periods under abnormal culture conditions. This selects mutants that are better suited for growth in the abnormal culture conditions than in the natural host.

For example, an attenuated strain of Mycobacterium bovis called **Bacillus Calmette- Guérin(BCG)** was developed by growing M. bovis on a medium containing increasing concentrations of bile. After 13 years, this strain had adapted to growth in strong bile and had become sufficiently attenuated that it was suitable as vaccine for tuberculosis.

The Sabin form of the polio vaccine and the measles vaccine both consist of attenuated viral strains.

Attenuated vaccines have advantages and disadvantages. advantages:

- Because of their capacity for transient growth, such vaccines provide prolonged immune system exposure to the individual epitopes on the attenuated organisms and more closely mimic the growth patterns of the "real" pathogen, resulting in increased immunogenicity and efficient production of memory cells.
- these vaccines often require only a single immunization
- The ability of many attenuated vaccines to replicate within host cells makes them particularly suitable for inducing cell-mediated responses. The oral polio vaccine (OPV) designed by Albert Sabin, consisting of three attenuated strains of poliovirus, is administered orally to children.
- The attenuated viruses colonize the intestine and induce production of secretory IgA, an important defense against naturally acquired poliovirus.
- The vaccine also induces IgM and IgG classes of antibody and ultimately protective immunity to all three strains of virulent poliovirus.

A **major disadvantage of attenuated vaccines:**

- is that these live forms may mutate and revert to virulent forms in vivo, resulting in paralytic disease in the vaccinated individual and serving as a source of pathogen transmission. Attenuated vaccines also may be associated with complications similar to those seen in the natural disease.

In addition to culturing methods, genetic engineering provides a way to attenuate a virus irreversibly, by selectively removing genes that are necessary for virulence or for growth in the vaccine.

Inactivated or "Killed" Vaccines

Another common means to make a pathogen safe for use in a vaccine is by treatment with heat or chemicals. This kills the pathogen, making it incapable of replication, but still allows it to induce an immune response to at least some of the antigens contained within the organism. It is critically important to maintain the structure of epitopes on surface antigens during inactivation. Heat inactivation is often unsatisfactory because it causes extensive denaturation of proteins; thus, any epitopes that depend on higher orders of protein structure are likely to be altered significantly. Chemical inactivation with formaldehyde or various alkylating agents has been successful.

The Salk polio vaccine is produced by formaldehyde inactivation of the poliovirus. Although live attenuated vaccines generally require only one dose to induce long-lasting immunity, killed vaccines often require repeated boosters to achieve a protective immune status. Because they do not replicate in the host, killed vaccines typically induce a predominantly humoral antibody response and are less effective than attenuated vaccines in inducing cell-mediated immunity or in eliciting a secretory IgA response, key components of an ideal protective and mucosally based response.

Subunit Vaccines

Many of the risks associated with attenuated or killed whole-organism vaccines can be avoided with a strategy that uses only specific, purified macromolecules derived from the pathogen. The three most common applications of this strategy, referred to as a subunit vaccine, are inactivated exotoxins or toxoids, capsular polysaccharides or surface glycoproteins, and key recombinant protein antigens

One limitation of some subunit vaccines, especially polysaccharide vaccines, is their inability to activate T cells. Instead, they activate B cells in a thymus- independent type2 (TI-2) manner, resulting in IgM production but little class switching, no affinity maturation, and little, if any, development of memory cells. However, vaccines that conjugate a polysaccharide antigen to a protein carrier can alleviate this problem by inducing TH cell responses.

Some bacterial pathogens, including those that cause diphtheria and tetanus, produce exotoxins that account for all or most of the disease symptoms resulting from infection. Diphtheria and tetanus vaccines have been made by purifying the bacterial exotoxin and then inactivating it with formaldehyde to form a toxoid.

Vaccination with the toxoid induces antitoxoid antibodies, which are capable of binding to the toxin and neutralizing its effects.

The virulence of some pathogenic bacteria depends primarily on the antiphagocytic properties of their hydrophilic polysaccharide capsule. Coating the capsule with antibodies and/or complement greatly increases the ability of macrophages and neutrophils to phagocytose such pathogens.

These findings provide the rationale for vaccines consisting of purified capsular polysaccharides.

The current vaccine for Streptococcus pneumoniae (the organism which causes pneumococcal pneumonia) consists of 13 antigenically distinct capsular polysaccharides (PCV13). The vaccine induces formation of opsonizing antibodies and is vaccines recommended for all infants

The vaccine for Neisseria meningitidis , a common cause of bacterial meningitis, also consists of purified capsular polysaccharides.

The gene encoding any immunogenic protein can be cloned and expressed in cultured cells using recombinant DNA technology, and this technique has been applied widely in the design of many types of subunit vaccines.
For example, the safest way to produce sufficient quantities of the purified toxins that go into the generation of toxoid vaccines involves cloning the exotoxin genes from pathogenic organisms into easily cultured host cells. A number of genes encoding surface antigens from viral, bacterial, and protozoan pathogens have also been successfully cloned into cellular expression systems for use in vaccine development.

Recombinant Vector Vaccines

Recombinant vectors maintain the advantages of live attenuated vaccines while avoiding this major disadvantage.
Individual genes that encode key antigens of especially virulent pathogens can be introduced into attenuated viruses or bacteria.
The attenuated organism serves as a vector, replicating within the vaccinated host and expressing the gene product of the pathogen. However, since most of the genome of the pathogen is missing, reversion potential is virtually eliminate.
A very recent example of this is the yellow fever vaccine that was engineered to express antigens of WNV. A number of organisms have been used as the vector in such preparations, including vaccinia virus, the canarypox virus, attenuated poliovirus, adenoviruses, attenuated strains of Salmonella, the BCG strain of Mycobacterium bovis, and certain strains of Streptococcus that normally exist in the oral cavity.

DNA Vaccines

A more recent vaccination strategy, called a DNA vaccine, utilizes plasmid DNA encoding antigenic proteins that are injected directly into the muscle of the recipient. This strategy relies on the host cells to take up the DNA and produce the immunogenic protein in vivo, thus directing the antigen through endogenous MHC class I presentation pathways, helping to activate better CTL responses.
The DNA appears either to integrate into the chromosomal DNA or to be maintained for long periods in an episomal form, and is often taken up by dendritic cells or muscle cells in the injection area. Since muscle cells express low levels of class I MHC molecules and do not express costimulatory molecules, delivery to local dendritic cells may be crucial to the development of antigenic responses to DNA vaccines.
DNA vaccines offer some potential advantages over many of the existing vaccine approaches. Since the encoded protein is expressed in the host in its natural form—there is no denaturation or modification—the immune response is directed to the antigen exactly as it is expressed by the pathogen, inducing both humoral and cell-mediated immunity. To stimulate both arms of the adaptive immune response with

non-DNA vaccines normally requires immunization with a live attenuated preparation, which incurs additional risk.

DNA vaccines also induce prolonged expression of the antigen, enhancing the induction of immunological memory.

DNA vaccines present important practical advantages. No refrigeration of the plasmid DNA is required, eliminating long term storage challenges.

In addition, the same plasmid vector can be custom tailored to insert DNA encoding a variety of proteins, which allows the simultaneous manufacture of a variety of DNA vaccines for different pathogens, saving time and money.

An improved method for administering DNA vaccines entails coating gold microscopic beads with the plasmid DNA and delivery of the coated particles through the skin into the underlying muscle with an air gun (called a gene gun). This allows rapid delivery of vaccine to large populations without the need for huge numbers of needles and syringes, improving both safety and cost.

Human trials are underway with several different DNA vaccines, including those for malaria, HIV, influenza, Ebola, and herpesvirus, along with several vaccines aimed at cancer therapy