TEACHING OBJECTIVES:

    1.   Know the distinction between passive and active immunization and their examples
    2.   Distinguish between artificial and natural means of immunization
    3.   Know the applications and problems of artificial passive immunization
    4.   Know the applications and problems of artificial active immunization
    5.   Know the modern approaches to immunization

READING:

    Male, Brostoff, Roth and Roitt: Immunology. 7th ed., chapter 18

Immunization is the means of providing specific protection against most common and damaging pathogens. The mechanism of immunity depends on the site of the pathogen and also the mechanism of it pathogenesis. Thus, if the mechanism of pathogenesis involves exotoxins, the only immune mechanism effective against it would be neutralizing antibodies that would prevent its binding to the appropriate receptor and promoting its clearance and degradation by phagocytes. Alternatively, if the pathogen produces disease by other means, the antibody will have to react with the organism and eliminate by complement-mediated lysis or phagocytosis and intracellular killing. However, if the organism is localized intracellularly, it will not be accessible to antibodies while it remains inside and the cell harboring it will have to be destroyed and, only then antibody can have any effect. Most viral infections and intracellular bacteria and protozoa are examples of such pathogens. In this case, the harboring cells can be destroyed by elements of cell mediated immunity or if they cause the infected cell to express unique antigens recognizable by antibody, antibody-dependent and complement mediated killing can expose the organism to elements of humoral immunity. Alternatively, cells harboring intracellular pathogen themselves can be activated to kill the organism. Such is the case with pathogens that have the capability of surviving within phagocytic cells.

Specific immunity can result from either passive or active immunization and both modes of immunization can occur by natural or artificial processes (Figure 1).
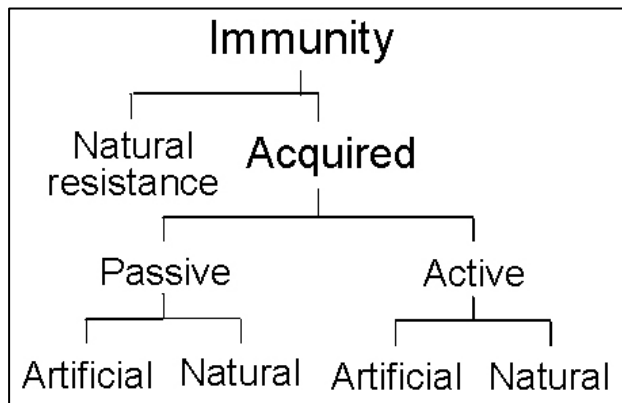

Figure 1 Different modes of acquiring immunity

Passive Immunity:

Immunity can be gained, without the immune system being challenged with an antigen, by transfer of serum or gamma globulins from an immune donor to a non-immune individual. Alternatively, immune cells from an immunized individual may be used to transfer immunity. Passive immunity may be acquired naturally or artificially.

Naturally acquired passive immunity: Immunity is transferred from mother to fetus through placental transfer of IgG or colostral transfer of IgA.

Artificially acquired passive immunity: Immunity is often artificially transferred by injection with gamma globulin from other individuals or from an immune animal. Passive transfer of immunity with immune globulin or gamma globulin is practiced in numerous acute infections (diphtheria, tetanus, measles, rabies, etc.), poisoning (insect-, reptile-bites, botulism), and as a prophylactic measure (**hypogammaglobulinemia**). In these situations, gamma globulin of human origin is preferable although specific antibodies raised in other species (usually horse) are effective and used in some cases (*e*.g., poisoning, diphtheria, tetanus, gas gangrene, botulism, *etc*.). While this form of immunization has the advantage of providing immediate protection, it is effective for a short duration only and often results in pathological complications, such as **serum sickness** characterized by rash, fever, arthralgia, vasculitis, nephritis, *etc*., and anaphylaxis. Homologous immunoglobulin may carry the risk of transmitting hepatitis and HIV and other blood borne diseases.

Passive transfer of cell-mediated immunity (immunity that is transferred by cells and not by antibody) can also be accomplished in certain diseases (cancer, immunodeficiency). However, it is difficult to find histocompatible (matched) donors and there is severe risk of graft versus host disease.

Active Immunity:

This refers to immunity produced by the body following exposure to antigens.

Naturally acquired active immunity: Exposure to different pathogens leads to sub clinical or clinical infections, which normally result in a protective immune response against these pathogens.

Artificially acquired active immunity: Immunization may be achieved by administering live or dead pathogens or their components. Vaccines used for active immunization consist of live (attenuated: capable of producing very mild or no symptoms) organism, killed whole organism, microbial components or secreted, detoxified toxins (toxoid).

Live vaccines: Live organisms are used for immunization against a number of viral infections. Live vaccines for measles, mumps, rubella and chicken pox (varicella) are used routinely. A live bacterial vaccine consisting of a strain of *Mycobacterium bovis*, Bacillus Calmet Geurin (BCG) is used against tuberculosis in many African, European and Asian countries but not many others.

Whereas many studies have shown the efficacy of BCG vaccine, a number of studies also cast doubt on its benefits.

Live vaccines normally produce self-limiting non-clinical infections and lead to subsequent immunity, both humoral and cell-mediated, the latter being essential for intracellular pathogens. However, they carry a serious risk of **causing overt disease in immunocompromised individuals**. Furthermore, since live vaccines are often attenuated (made less pathogenic) by passage in animal or thermal mutation, they can revert to their pathogenic form and cause serious illness. It is for this reason, polio live (Sabin) vaccine, which was used for many years, has been replaced in many countries by the inactivated (Salk) vaccine.

Killed vaccines: These consist of whole organisms inactivated by heat, chemicals or UV irradiation treatment. Many killed viral and bacterial vaccines are available. Some of these are used to immunize people at risks (*e.g.* influenza, hepatitis A, etc.) while others are used to immunize travelers to different countries (*e.g.* cholera, typhoid *etc*.). Pertussis (whooping cough) whole bacterial vaccine was used routinely until a few years ago, but due to its serious side effect, it has been replaced by a formulation of acellular components.

Sub-unit vaccines: Some vaccines consist of subcomponents of the pathogenic organisms, usually proteins or polysaccharides. Since polysaccharides are relatively weak T-independent antigens, and produce only IgM responses without immunologic memory, they are made more immunogenic and T-dependent by conjugation with proteins (*e.g.*, haemophilus, meningococcus, pneumococcus, etc.). Hepatitis-B, rabies vaccines consist of antigenic proteins cloned into a suitable vector (*e.g.*, yeast). These subunit vaccines are designed to reduce the problems of toxicity and risk of infection. When the pathogenic mechanism of an agent involves a toxin, a modified form of the toxin (toxoid) is used as vaccine (*e.g.*, diphtheria, tetanus, *etc*.). Toxoids, although lose their toxicity, they remains immunogenic.

Other novel vaccines: A number of novel approaches to active immunization are in the investigative stage and are used only experimentally. These include anti-idiotype antibodies, DNA vaccines and immunodominant peptides (recognized by the MHC molecules) and may be available in the future. Anti-idiotype antibodies against polysaccharide antibody produce long lasting immune responses with immunologic memory. Viral peptide genes cloned into vectors, when injected transfect host cells and consequently produce a response similar to that produced against live-attenuated viruses (both cell-mediated and humoral). Immunodominant peptides are simple and easy to prepare and, when incorporated into MHC polymers, can provoke both humoral and cell mediated responses.

Adjuvants: Weaker antigens may be rendered more immunogenic by the addition of other chemicals. Such chemicals are known as **adjuvants**. There are many biological and chemical substances that have been used in experimental conditions (Table 1). However, only Aluminum salts (alum) are approved for human use and it is incorporated in DTP vaccine. Furthermore, pertussis itself has adjuvant effects. Adjuvants used experimentally include mixtures of oil and detergents, with (Freund's complete adjuvant) or without certain bacteria (Freund's incomplete adjuvant). Bacteria most often used in an adjuvant are Mycobacteria (BCG) and *Nocardia*. In some instance sub-cellular fractions of these bacteria can also be used effectively as adjuvants.

Newer adjuvant formulations include synthetic polymers and oligonucleotides. Most adjuvants recognize TOLL-like receptors thus activating mononuclear phagocytes and inducing selective cytokines that can enhance Th1 or Th2 responses, depending on the nature of the adjuvant.

Table 1. Selected adjuvants in clinical or experimental use

Adjuvant type	human use	Experimental only
Salts:		
aluminum hydroxide,	Yes	Slow release of antigen, TLR interaction and cytokine induction
aluminum phosphate-	Yes	
calcium phosphate		
Beryllium hydroxide	No	
Synthetic particles:		
Liposomes, ISCOMs,	No	Slow release of antigen
polylactates	No	
Polynucleotides:	No*	TLR interaction and cytokine induction
CpG and others		
Bacterial products:	Yes	TLR interaction and cytokine induction
B.pertussis	No	
M. bovis (BCG and others)	No	Antigen depot
Mineral oils		
Cytokines:	No*	Activation and differentiation of T- and B cells and APC.
IL-1, IL-2, IL12, IFN-γ, *etc*.		

*Experimental use in human malignancies

The protective immunity conferred by a vaccine may be life-long (measles, mumps, rubella, small pox, tuberculosis, yellow fever, etc.) or may last as little as a few months (cholera). The primary immunization may be given at the age of 2-3 months (diphtheria, pertussis, tetanus,
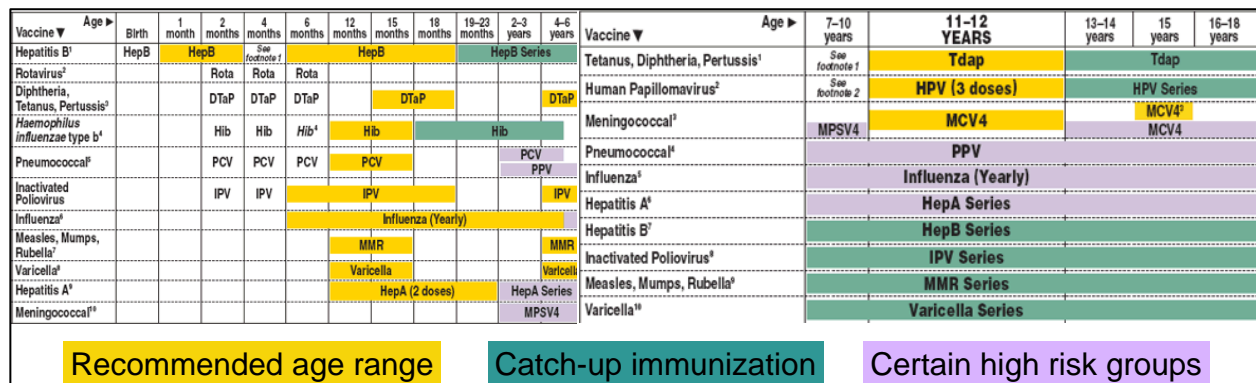

Figure 2. Recommended immunization schedule, United States, 2007 (MMWR, 55: Jan 5, 2007)

polio), or 13-15 months (mumps, measles, rubella). The currently recommended schedule of routine immunization in the USA (recommended by CDC and AIP) is summarized in Figure 2. This schedule is revised on yearly basis or as need by the CDC Advisory Committee on Immunization Practice (AICP).

Prophylactic versus therapeutic immunization: Most vaccines are given prophylactic ally, *i.e.*, prior to exposure to the pathogen. However, some vaccines can be administered therapeutically , *i.e.*, post exposure (*e.g.*, rabies virus). The effectiveness of this mode of immunization depends on the rate of replication of the pathogen, incubation period and pathogenic mechanism. For this reason, only a booster shot with tetanus is sufficient if the exposure to the pathogen is within less than 10 years and if the exposure is minimal (wounds are relative superficial). In a situation where pathogen has a short incubation period, the pathogenic mechanism is such that only a small amount of pathogenic molecules could be fatal (*e.g.*, tetanus and diphtheria) and/or bolus of infection is relatively large, both passive and active post exposure immunization are essential. Passive prophylactic immunization is also normal in cases of defects in the immune system, such as hypogammaglobulinemias.

Adverse effects of immunization: Active immunization may cause fever, malaise and discomfort. Some vaccine may also cause joint pains or arthritis (rubella), convulsions, sometimes fatal (pertussis), or neurological disorders (influenza). Allergies to egg may develop as a consequence of viral vaccines produced in egg (measles, mumps, influenza, yellow fever). Booster shots result in more pronounced inflammatory effects than the primary immunization. The noticeable and serious side effects documented have been those following the DTP vaccine (Table 2). Most of these were attributable to the whole pertussis component of the vaccine and have been eliminated since the use of the acellular pertussis preparation.

Table 2. Approximate rates of adverse event occurring
within 48 hours DTP vaccination

Event	Frequency
Local:	
redness, swelling, pain	1 in 2-3 doses
Mild/moderate systemic:	
fever, drowsiness, fretfulness	1 in 2-3 doses
vomiting, anorexia	1 in 5-15 doses
More serious systemic:	
persistent crying, fever	1 in 100-300 doses
collapse, convulsions	1 in 1750 doses
acute encephalopathy	1 in 100,000 doses
permanent neurological deficit	1 in 300,000 doses