BIOLOGICALS AND IMMUNOPROPHYLAXIS

INTRODUCTION- BIOLOGICALS AND IMMUNOLOGICALS

- Edward Jenner in 1796 observed that dairymaids contracted with cowpox seemed to be protected against small pox.
- He injected fluid from blister of cowpox into 8 years old boy and observed protection against small pox. This technique ofintroducing immunity became known as vaccination (Vacca in Latin means cow).
- Small pox was controlled and eventually the disease was eliminated.
- *Vaccination* is a procedure of introducing a safe antigen (vaccine) into a host to induce immunity against infection. In general *vaccine* is a suspension of living or inactivated organisms used as antigen to provide immunity against infection. Several developments have come to produce safe and effective vaccines and also in delivering the vaccine.
- *Immune Response* is the reaction of the body to foreign substances resulting in the formation of antibodies and lymphokines. When an antigen or infection enters in a body, it invokes a series of reaction leading to either succumb to infection or provide immunity. The immunity can be acquired by active or passive ways by introducing a safe and potent antigen (vaccine) into a body.
- *Active immunity* is produced when the host reacts to an antigen and produce antibody. The immunity develops slowly and persists for a long time. Active immunity may be acquired by two different ways
    - *Natural:* When produced due to natural infection by infectious organisms
    - *Artificial:* This is produced by the host's body in response to inoculation of an antigen.
- *Passive immunity:* The antibody is prepared elsewhere and subsequently introduced into host's body. The immunity is rapidly established but persists for short duration. Passive immunity is also acquired by two different ways: a) Natural: Maternal antibody from mother to foetus (Transplacental transfer) or colostrum antibody through milk from mother to neonates.b) Artificial: By injection of immune serum or by transfer of lymphocyte or immune cells.

TYPES OF VACCINE

Type of vaccine	Example
1. First generation vaccines (conventional vaccines)	• Live attenuated vaccines • Inactivated (killed) vaccines • Toxoid vaccines • Bacterins
2. Second generation vaccines	• Subunit vaccines • Peptides vaccines • Conjugate vaccines • Anti – idiotypic vaccines.
3. Third generation vaccines	• Recombinant subunit vaccines
(all recombinant vaccines and nucleic acid vaccines)	• Recombinant synthetic peptide vaccines • Marker vaccines • Deletion mutant vaccines

LIVE ATTENUATED VACCINES

- The virulence of the pathogen is reduced and immunogenicity is maintained by adapting the pathogen in an unfavourablecondition and the organism still replicates.
- Attenuation is achieved by growing the pathogens in an unnatural host, by passaging in non-homologous host (host/cell culture) for repeated period of time (i.e. 70-80 times) or in

different physiological conditions or in different environment.

- Attenuation may also be done by adapting the virus to grow in a temperature lower than the normal called cold adapted virus and the process is called cold adaption.
- Thermo stable vaccine strain grows at elevated temperature.
- Temperature sensitive mutants cannot grow at slightly elevated temperature.
- The process of reducing the virulence and retaining the immunogenicity is called as attenuation so that the pathogenchanges its habit of growing.

- Advantages
  - Replication provides large quantities of immunogen
  - There is no need for adjuvant
  - Single dose often produces long lasting immunity
  - Whole organism has both T and B epitopes
  - The vaccine is cost effective and often does not require booster vaccination
  - Can be effective against intracellular pathogens
- Disadvantages
  - Chance of reversion to virulence
  - There may be shedding of virus
  - Can induce transient immunosupression
  - Cold chain required for transport
  - Possible contamination with other animal viruses
  - There may be side effects due to unwanted parts of the vaccines.

INACTIVATED/KILLED VACCINE

- Inactivated vaccine is prepared by physical or chemical treatment to the pathogen so that the organisms become inactive(loses replication capability) but maintains its immunogenicity.
- The procedure should not disturb the immunogenic structures or epitopes, but should remove the replication or virulence of the organisms. This vaccine is usually prepared with a virulent strain and the vaccine is more immunogenic.
- In general these kinds of vaccine are used when attenuated vaccines are not available or for an outbreak where characterization of the organism is not determined and pathogenicity have not been assessed.
- Examples of chemical inactivating agents are formaldehyde, glutaraldehyde, beta propiolactone etc., they change the structural conformation or cross link the structures and ultimately inactivate the organisms.
- The physical inactivating agents are gamma irradiation, U-V irradiation etc. which are going to change the structuralconformation or cross – linking structures.
- In general, inactivated vaccine requires an adjuvant to increase the potency of the vaccine.
- Advantages
  - No possibility of reversion
  - No shedding and contamination of environment
  - Quite stable, thus less need for cold chain
  - More immunogenic
  - Whole organism has both T and B epitopes.
- Disadvantages
  - Cannot replicate so antigen is limited
  - Require, multiple doses, adjuvants and boosters vaccination
  - If not properly inactivated, it may cause disease outbreaks
  - Increased risk of allergic reactions due to large amounts of antigen involved
  - Costly
  - May be ineffective against intracellular organisms.

ADJUVANTS

- Adjuvants provide depots effect to an antigen at the site of administration which allows persistence and slow release of antigen over an extended period of time resulting in higher and prolonged immune response.
- Adjuvants increase immunogenicity of weak antigens.
- It helps in stimulation of cell-mediated immune response.
- Addition of adjuvant reduces the cost and dose of an antigen.
- *Examples*, mineral oils (Aluminium hydroxide, Liquid paraffin etc.) Vegetable oils

(Ground Nut oil, Montanide etc.), Mycobacterial products (Freund's adjuvant) etc.

- Some other delivery systems are ISCOM (Immunostimulating complex), Nanoparticles etc.

TOXOID VACCINES

- Both gram negative and gram-positive bacteria produce exotoxins. Exotoxins can be inactivated by formaldehyde, iodine,other chemical or heat treatment and form toxoid.
- Toxoid is immunogenic without toxic effects. Toxoid vaccines have been used for tetanus, anthrax etc.
- Some veterinary vaccines combine both toxoid and killed bacteria by formalinizing whole culture and this is called anaculture. These types of vaccines are available for clostridial diseases. Trypsinization of anaculture makes it more immunogenic.
- *Advantage:* The exotoxin is immunogenic and whole organism can be avoided.
- *Disadvantage:* Only effective if diseases caused solely by bacterial exotoxins.

Bacterins

- Bacterins are the vaccines containing killed bacteria. This is usually done with formal dehyde and adjuvant like aluminiamhydroxide or alum is added to increase its immunogenicity.
- Autogenous vaccines are prepared using the organism from the infected animal itself or from other infected animals in thesame farm after inactivation with formal dehyde and found successful to control diseases. For example fowl cholera vaccine.

- *Advantages:*
  - Easy to prepare
  - No reversion to virulence
- *Disadvantages:*
  - Immunity is short lasting (usually less than six months)

SUBUNIT VACCINES/CONJUGATE VACCINES

- It is possible to identify the peptide sites encompassing the major antigenic sites of viral antigens, from which highly purified subunit vaccines can be produced. But increasing purification may lead to loss of immunogenicity, and this may necessitate coupling to an immunogenic carrier protein or adjuvant.
- *Example* of a purified subunit vaccine is HA vaccines for influenza A and B. Bacterial capsular polysaccharides areimmunogenic but incapable of evoking T cell responses.
- Vaccines efficacy can be greatly increased by conjugating the capsular polysaccharide to a protein carrier capable of supply of T cell epitopes called a conjugate vaccine.
- Advantages
  - Avoids use of whole organism

- Side effects due to undesired part of the organism is reduced
- Supplies multiple epitopes.

- Disadvantages
  - Possible alteration of pathogen protein conformation during purification may decreases immunogenicity
  - Can be laboured intensive and costly to purify immunogens
  - May require cold chain
  - Sometimes too large to fit into the vaccine delivery systems.

PEPTIDE VACCINES

- Once the immunogenic sites of an organism are identified, immunogenic peptides can be synthesized or can be purifiedfrom natural sources.
- Several methods have been used to prepare it.
- Synthetic peptide vaccines would have many advantages. Their antigens are precisely defined and free from unnecessary components which may be associated with side effects.
- They are stable and relatively cheap to manufacture.
- *Example,* foot and mouth disease peptide vaccine where protection was achieved by immunizing animals with a linearsequence of 20 amino acids (141 to 160) of VP1.
- Synthetic peptides do not readily stimulate T cells and require coupling to a protein carrier which is recognized by T-cells.
- Advantages
  - Avoids use of whole organism
  - Side effects due to undesired part of the organism is reduced
  - Small enough to fit into most the antigen delivery vehicles
  - Quite stable
- Disadvantages
  - May be perceived as haptens if not conjugated to carriers
  - Rapidly dissipated in tissues, thus requires highly effective adjuvants or effective delivery vehicles.
  - May be costly or difficult to identify and purify.

ANTI-IDIOTYPIC ANTIBODY VACCINE

- Antibodies formed against an antigen will have a structural image of that antigen at the antigen combining site (idiotype)and antibodies to antibody (anti-idiotype) will have antigen combining site that is structurally similar to that of antigen. Thus the secondary antibody mimics the structure of antigen and can be used as vaccine to produce antibody.
- *Example:* Human hepatitis B vaccine.
- *Advantages:* Avoids risk of exposure to a pathogen.
- *Disadvantages:*
  - Relatively complex and costly
  - Not very effective

RECOMBINANT DNA VACCINE

- The immune dominant part of a pathogen is cloned into a vector and pathogen DNA is transcribed and translated withinthe cells of vaccinated animals.
- Virus proteins have been expressed in bacteria, yeast, mammalian cells, and viruses.
- *E. coli* cells were first to be used for this purpose but the expressed proteins were not glycosylated, which was a majordrawback since many of the immunogenic proteins of viruses such as the envelope glycoproteins, were glycosylated.
- An alternative application of recombinant DNA technology is the production of hybrid virus vaccines. Recombinant technology made some useful safe virus vectors for the expression of protective antigens from potentially harmful infectious agents.
- Compared to the subunit vaccines the vectored vaccines produce good immune responses against various pathogens.
- Poxviruses, adenoviruses, herpes viruses are commonly used as vectors for vaccines.Examples of vector basedrecombinant vaccine, ND virus in fowl pox virus, Rabies virus in vaccinia virus etc..
- Recombinant hepatitis B vaccine is a licensed vaccine.
- Advantages
  - Use of pathogens can be avoided
  - Unwanted reaction is reduced
  - High immune response.

- Hybrid virus vaccines are stable and stimulate both cellular and humoral immunity.
- They are relatively cheap and simple to produce.

- Disadvantages
  - Replication of vector may induce side effects
  - Primary immune responses mounted against vector proteins may generate anti – vector antibodies that blocksbooster immunization.

DIVA/MARKER VACCINES

- Vaccination employing conventional vaccines interferes with the serological detection of infection with the pathogens and thus in the assessment of prevalence and incidence of diseases.
- This necessitates the development of DIVA vaccines that are capable of distinguishing between antibody responses resulting due to vaccination and infection (DIVA-Differentiating infected from vaccinated individuals) or marker vaccines**.**
- A marker vaccine (live or inactivated) is either based on deletion mutant or isolating antigenic proteins that allows thedistinction between vaccinated and infected animals on the basis of identifiable differences in antibody responses.
- A marker vaccine is used in conjuction with a test that detects antibodies against protein that is lacking in the vaccinestrain.
- DIVA vaccine was useful to control avian influenza in Italy.

VETERINARY VACCINES

Bacterial Vaccines

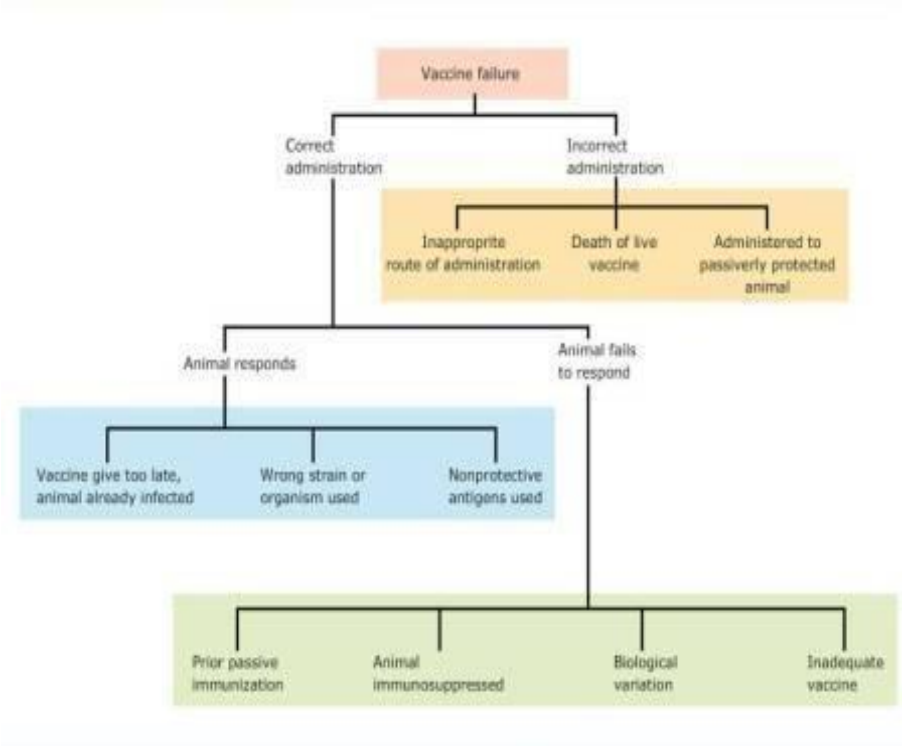
- Anthrax spore vaccine (Sterne strain of *B.anthracis* suspended in glycerin and adjuvanted with saponin), BQ vaccine (Alum precipitated and formalin inactivated *Cl. Chauvoei),* HS vaccine (Alum precipitated and formalin inactivated *Pasteurella multocida),* Fowl cholera vaccine (Formalin inactivated and Aluminium hydroxide adjuvanted *Pasteurella multocida* etc.

Viral Vaccines

- Newcastle disease (ND) virus live attenuated vaccines (RDVF, LaSota, RDVK, R2B), PPR virus vaccine (Live attenuated), Fowl Pox virus vaccine (Live attenuated), Sheep pox virus vaccine (Live attenuated), Inactivated vaccine for ND, Inactivated vaccine for IBD etc.

STRATEGIES TO AVOID VACCINATION FAILURE

- The following points are important to avoid vaccination failure
  - Live vaccines should be stored at recommended refrigeration temperature and carried to the field following coldchain
  - Vaccination interval should not be too short
  - Optimum dose of vaccines should be incorporated
  - Vaccine should be reconstituted with proper diluent
  - Vaccine should be given to healthy animals(should not be immunocompromised).
  - The causes can be as mentioned below.



VACCINATION SCHEDULE FOR LIVESTOCK ANIMALS ANDPOULTRY

Vaccination schedule for livestock animals

Name of the vaccine	Species	Age at first vaccination	Booster Vaccination
Foot and Mouth	Cattle, buffalo, sheep and goat	5 months	Annual vaccination
PPR	Sheep and goat	3 months	Annual vaccination
Sheep pox	Sheep	3 months	For every 6 months
Anthrax spore	Cattle, sheep and goat	6 months	Annual vaccination
Black quarter Alum precipitated	Cattle and sheep	6 months	Annual vaccination
Haemorrhagic Septicemia oil adjuvant	Cattle, buffalo, sheep and goat	6 months	Annual vaccination
Enterotoxemia	Sheep	3 months	For every 6 months

Vaccination schedule for poultry

Age	Type of Vaccine	Broiler	Layer
1st day	Marek's disease vaccine	+	+
5th day	RDVF	+	+
14-21 days	IBD / IBV	+	+
28th day	RDV Lasota/ IBD	+	+
6th week	Fowl Pox Vaccine	-	+
8th Week	RDVK/IBV	-	+
16th Week	Fowl pox vaccine (Booster)	-	+
16th-18th Week	RDV/IBV(Booster)		
Every 30-90 days	RDV/IBV(Booster)		+