



VACCINES

T-cell memory is very important for long-lasting immunity, because T-cells control both humoral and cell mediated immunity. When the immune system recognizes a foreign antigen for the first time, an immune response is produced. When T cells are involved, immunological T-cell memory is produced. When the body encounters same antigen subsequently, a stronger immune response is produced. This is because of existing immunological memory against that antigen. Further antigenic stimulus increases the immune response. First antigenic stimulus is “priming” whereas subsequent stimuli are “booster”. This is the principle of active immunization.

The term “vaccine” was coined by Louis Pasteur to commemorate first successful immunization against small pox by Edward Jenner. The term vaccine was derived from “vacca”, meaning cow, since Edward Jenner used cowpox virus (*Vaccinia*) to prevent smallpox infection. Vaccination involves deliberate exposure to antigen under conditions where disease should not result. Vaccination is aimed at inducing active immunity in an individual, so that subsequent contact with the microorganism following natural infection induces strong protective immune response. The protective immunity may involve secretion of neutralizing antibodies or production of memory CTL or Th1 cells. The use of vaccines is now being extended to immunize against tumors or to block fertilization (contraceptive vaccines). A vaccine is a suspension of whole (live or inactivated) or fractionated bacteria or viruses that have been rendered nonpathogenic, and is given to induce an immune response and prevent disease. Even though no vaccine is entirely safe or completely effective, their use is strongly supported by their benefit-to-risk ratio.

Properties of ideal vaccine:

- Provide long lasting immunity.
- Should induce both humoral and cellular immunity.
- Should not induce autoimmunity or hypersensitivity.
- Should be inexpensive to produce, easy to store and administer.
- Vaccines must also be perceived to be safe.

The vaccine vial may contain relevant antigen, adjuvant (usually alum), preservatives and/or traces of protein derived from the cells in which the vaccine agent was cultured e.g. egg protein

Types of vaccines:

A. KILLED VACCINES:

When it is unsafe to use live microorganisms to prepare vaccines, they are killed or inactivated. These are preparations of the normal (wild type) infectious, pathogenic microorganisms that have been rendered non-pathogenic, usually by treatment with using heat, formaldehyde or gamma irradiation so that they cannot replicate at all. Such killed vaccines vary greatly in their efficacy.

Microorganism	Vaccine	Method	Route
<i>Salmonella typhi</i>	TAB	Heat, Phenol, Acetone	SC
<i>Vibrio cholerae</i>		Phenol	SC or ID
<i>Yersinia pestis</i>	Haffkine	Formalin	SC
<i>Bordetella pertussis</i>	-	Merthiolate	IM
Poliomyelitis	Salk	Formalin	IM
JE virus	Nakayama Strain	Formalin	IM
Rabies virus	Semple	Phenol	SC
	BPL	BPL	SC
	HDCV	BPL	IM or SC
	DEV	BPL	IM or SC
Influenza virus	-	Formalin	IM
Hepatitis A	HM175	Formalin	IM

Advantages:

- Safe to use and can be given to immunodeficient and pregnant individuals.
- Cheaper than live attenuated vaccine
- Storage not as critical as live vaccine

Disadvantages:

- Since the microorganisms cannot multiply, a large number are required to stimulate immunity.
- Periodic boosters must be given to maintain immunity.
- Only humoral immunity can be induced.
- Most killed vaccines have to be injected.
- Some vaccines such as *Bordetella pertussis* induce ill effects like postvaccinal encephalomyelitis. Anaphylactic reaction to neomycin or streptomycin may occur in (Inactivated Polio Vaccine) recipients. Anaphylactic hypersensitivity to eggs may occur in recipients of influenza vaccine.
- Inactivation, such as by formaldehyde in the case of the Salk vaccine, may alter antigenicity.
- Presence of some un-inactivated microbes can lead to vaccine-associated disease.

B. LIVE ATTENUATED VACCINE:

These vaccines are composed of live, attenuated microorganisms that cause a limited infection in their hosts sufficient to induce an immune response, but insufficient to cause disease. To make an attenuated vaccine, the pathogen is grown in foreign host such as animals, embryonated eggs or tissue culture, under conditions that make it less virulent. The strains are altered to a non-pathogenic form; for example, its tropism has been altered so that it no longer grows at a site that can cause disease. Some mutants will be selected that have a better ability to grow in the foreign host. These tend to be less virulent for the original host. These vaccines may be given by injection or by the oral route. A major advantage of live virus vaccines is that because they cause infection, the vaccine very closely reproduces the natural stimulus to the immune system.

Bacteria/virus	Vaccine	Method	Route
Vibrio	CVD103Hgr	Genetically modified	Oral
Salmonella	Ty21a	Genetically modified	Oral
Mycobacterium	BCG	Prolonged subculture	ID
Polio	Sabin	Passage in MK cells	Oral
JE	SA 14-14-2	Passage in weanling mice	IM
Yellow Fever	17D	Passage in chick embryo cells	SC
Influenza	-	Temperature sensitive mutant	IN
Mesales, Mumps, Rubella	MMR Rubella (Wistar RA 27/3)	Passage in fibroblasts cells	SC
Chicken pox	Oka/Merck	Human diploid cell cultures	SC
Small pox	Vaccinia virus	Naturally avirulent	ID

The influenza vaccine contains cold-adapted vaccine strains of the influenza virus that have been grown in tissue culture at progressively lower temperatures. After a dozen or more of these passages, the virus grows well only at around 25° C and in vivo growth is restricted to the upper respiratory tract.

Advantages:

- Infectious microbes can stimulate generation of memory cellular as well as humoral immune responses.
- Since these can multiply in the host, fewer quantities must be injected to induce protection.
- A single administration of vaccine often has a high efficacy in producing long-lived immunity. Multiple booster doses may not be required.
- Whole microbes stimulate response to antigens in their natural conformation. They raise immune response to all protective antigens.
- Some live vaccines can be given orally; such vaccines induce mucosal immunity and IgA synthesis, which gives more protection at the normal site of entry.
- Oral preparations are less expensive than giving injections.
- They can lead to elimination of wild type virus from the community

Disadvantages:

- May very rarely revert to its virulent form and cause disease.
- Live vaccines cannot be given safely to immunosuppressed individuals. Administration of live attenuated vaccines to people with impaired immune function can cause serious illness or death in the vaccine recipient.
- Since they are live and because their activity depends on their viability, proper storage is critical.
- Spread to contacts of vaccinee who have not consented to be vaccinated. In some cases, it turns out to be an advantage.

C. SUBUNIT VACCINES:

Subunit vaccines contain purified antigens instead of whole organisms. Such a preparation consists of only those antigens that elicit protective immunity. Subunit vaccines are composed of toxoids, subcellular fragments, or surface antigens. Administration of whole organism, as in case of pertussis was found unfavorable immune reactions resulting in severe side effects. The effectiveness of subunit vaccines is increased by giving them in adjuvants. Adjuvants slow antigen release for a more sustained immune stimulation.

Antigen	Vaccine	Microorganism	Route
Cell wall polysaccharide	Hib	<i>Hemophilus influenzae b</i>	IM
	ACW-135 Y	<i>Nisseria meningitides</i>	IM
	23 Valent	<i>Streptococcus pneumoniae</i>	IM
	-	Group B Streptococcus	IM
	Vi (Typhim)	<i>Salmonella typhi</i>	IM
Toxoid	Tetanus	<i>Clostridium tetani</i>	IM
	Diphtheria	<i>Corynebacterium diphtheriae</i>	IM
Membrane proteins	-	Influenza virus	IM
	HbsAg	Hepatitis B	IM
Microbial proteins	Acellular DTP	Bordetella pertussis	IM

Advantages:

- They can safely be given to immunosuppressed people
- They are less likely to induce side effects.

Disadvantages:

- Antigens may not retain their native conformation, so that antibodies produced against the subunit may not recognize the same protein on the pathogen surface.
- Isolated protein does not stimulate the immune system as well as a whole organism vaccine.

Peptide vaccines: Peptide vaccine consists of those peptides from the microbial antigen that stimulates protective immunity. Synthetic peptides are produced by automated machines rather than by microorganisms. Peptide immunogenicity can be increased by giving them in ISCOMS, lipid micelles that transport the peptides directly into the cytoplasm of dendritic cells for presentation on Class I MHC. Injected peptides, which are much smaller than the original virus protein, induce an IgG response. Example: spf66 anti-malarial vaccine

Advantages:

- If the peptide that induces protective immunity is identified, it can be synthesized easily on a large scale.
- It is safe and can be administered to immunodeficient and pregnant individuals.

Disadvantage:

- Poor antigenicity. Peptide fragments do not stimulate the immune system as well as a whole organism vaccine.
- Since peptides are closely associated with HLA alleles, some peptides may not be universally effective at inducing protective immunity.

D. CONJUGATE VACCINES:

Conjugate vaccines are primarily developed against capsulated bacteria. While the purified capsular antigen can act as subunit vaccine, they stimulate only humoral immunity. Polysaccharide antigens are T independent, they

generate short-lived immunity. Immunity to these organisms requires opsonizing antibodies. Infants cannot mount good T-independent responses to polysaccharide antigens. By covalently linking the polysaccharides to protein carriers, they are converted into T-dependent antigens and protective immunity is induced.

Examples: *Haemophilus influenzae* HiB polysaccharide is complexed with diphtheria toxoid. Tetramune vaccine, which combines the tetanus and diphtheria toxoids, whole-cell pertussis vaccine, and *H. influenzae* type b conjugate vaccine.

E. RECOMBINANT VACCINES:

The vaccines are produced using recombinant DNA technology or genetic engineering. Recombinant vaccines are those in which genes for desired antigens of a microbe are inserted into a vector. Different strategies are:

- Using the engineered vector (e.g., Vaccinia virus) that is expressing desired antigen as a vaccine
- The engineered vector (e.g., yeast) is made to express the antigen, such as vector is grown and the antigen is purified and injected as a subunit vaccine. Other expression vectors include the bacteria *Escherichia coli*, mutant *Salmonella* spp., and BCG.
- Introduction of a mutation by deleting a portion of DNA such that they are unlikely to revert can create an attenuated live vaccine.
- Live attenuated vaccines can also be produced by reassortment of genomes of virulent and avirulent strains.
- Genes coding for significant antigens are introduced into plants, such that the fruits produced bear foreign antigens. This is edible vaccine and is still in experimental stage.

Examples:

- Hepatitis B Virus (HBV) vaccine is a recombinant subunit vaccine. Hepatitis B surface antigen is produced from a gene transfected into yeast (*Saccharomyces cerevisiae*) cells and purified for injection.
- Vaccinia virus may be engineered to express protein antigens of HIV, rabies etc. Foreign genes cloned into the viral genome are expressed on the surface of infected cells in association with class I MHC molecules. The antigen-MHC complex induces a Tc cell response.
- B subunit of cholera toxin, the B subunit of heat-labile *E. coli* enterotoxin (LT), and one of the glycoprotein membrane antigens of the malarial parasite are being developed using this technique.
- *Salmonella typhimurium* engineered to express antigens of *Vibrio cholerae*.
- Bacille Calmette-Guérin vaccine strain engineered to express genes of HIV-1.
- Reassortment of genomes between human and avian strains to create Influenza vaccine. Human and swine strains to create Rotavirus vaccine.

Advantages:

- Those vectors that are not only safe but also easy to grow and store can be chosen.
- Antigens which do not elicit protective immunity or which elicit damaging responses can be eliminated from the vaccine. Example Cholera toxin A can be safely removed from cholera toxin.

Disadvantages:

- Since the genes for the desired antigens must be located, cloned, and expressed efficiently in the new vector, the cost of production is high.
- When engineered vaccinia virus is used to vaccinate, care must be taken to spare immunodeficient individuals.

F. DNA VACCINES:

These vaccines are still in experimental stage. Like recombinant vaccines, genes for the desired antigens are located and cloned. The DNA is injected into the muscle of the animal being vaccinated, usually with a "gene gun" that uses compressed gas to blow the DNA into the muscle cells. DNA can be introduced into tissues by bombarding the skin with DNA-coated gold particles. It is also possible to introduce DNA into nasal tissue in nose drops. Some muscle cells express the pathogen DNA to stimulate the immune system. DNA vaccines have induced both humoral and cellular immunity.

Advantages:

- DNA is very stable, it resists extreme temperature and hence storage and transport are easy.
- A DNA sequence can be changed easily in the laboratory.
- The inserted DNA does not replicate and encodes only the proteins of interest.

- There is no protein component and so there will be no immune response against the vector itself.
- Because of the way the antigen is presented, there is a cell-mediated response that may be directed against any antigen in the pathogen.

Disadvantages:

- Potential integration of DNA into host genome leading to insertional mutagenesis.
- Induction of autoimmune responses: anti-DNA antibodies may be produced against introduced DNA.
- Induction of immunologic tolerance: The expression of the antigen in the host may lead to specific non-responsiveness to that antigen.

G. ANTI-IDIOTYPIC VACCINE:

An antigen binding site in an antibody (paratope) is a reflection of the three-dimensional structure of part of the antigen (epitope). This unique amino acid structure in the antibody is known as the idiotype, which can be considered as a mirror of the epitope in the antigen. Antibodies can be raised against the idiotype by injecting the antibody into another animal. This anti-idiotypic antibody mimics part of the three dimensional structure of the antigen. This can be used as a vaccine. When the anti-idiotypic antibody is injected into a vaccinee, antibodies (anti-anti-idiotypic antibodies) are formed that recognize a structure similar to part of the virus and might potentially neutralize the virus.

Advantage:

Antibodies against potentially significant antigen can be produced.

Disadvantage:

Only humoral immunity is produced. There is no cellular immunity and poor memory. Identification and preparation of idiotypes is labor intensive and difficult.