Vaccines

Microbiology V

Introduction

- The modern era of vaccines and vaccination began in 1798 with Edward Jenner's use of cowpox as a vaccine against smallpox. [Latin *vacca,* cow]
- **Vaccine** is a preparation from an infectious agent that is administered to humans and other animals to induce protective immunity.

- **Vaccination** (Active immunization) is the protection of susceptible humans and domestic animals from communicable diseases by the administration of vaccines.
- It is used to induce immunity artificially.
- The vaccines induce active immunity whereas immunoglobulins and antisera are used for passive immunity.

Vaccines types:

- Whole organisms:
  - Killed (inactivated) microorganisms
  - Attenuated microorganisms (living and weakened virus/bacteria)
- Toxoids - inactivated bacterial toxins
- Purified macromolecules
- Recombinant vectors - modified polio vaccine
- DNA vaccines
- Multivalent subunit vaccines

Currently Available Vaccines

Table 81–1. Diseases against which vaccines are currently available

Bacterial		*Viral*	
Attenuated	*Inactivated*	*Attenuated*	*Inactivated*
Tuberculosis	Typhoid fever*	Poliomyelitis	Poliomyelitis
Typhoid fever	Pertussis	Measles	Rabies
	Cholera	Mumps	JE
	Tetanus**	Rubella	Hepatitis B
	Diphtheria**	Yellow fever	Influenza
	Plague		Hepatitis A
	H. influenzae type b*		
	Pneumococcal infections*		
	Meningococcus A,C* + Tetravalent		

* Capsular polysaccharides; ** Toxoids

Whole-Organism Vaccines

- Many of the current vaccines in use for humans that are effective against viral and bacterial diseases consist of whole microorganisms.
- They are of two types:
- Inactivated (killed)
- Attenutaed (live but avirulent)

Attenuated vaccines

- Microorganisms can be attenuated so that they lose their ability to cause significant disease.
- but retain their capacity for transient growth within an inoculated host.
- Attenuation often can be achieved by **growing a pathogenic bacterium or virus** for **prolonged periods** under abnormal culture conditions.
- This procedure selects mutants that are better suited to growth in the abnormal culture conditions
- and are therefore less capable of growth in the natural host.

- **Bacillus Calmette-Guerin (BCG)**
- Is an example of attenuated strain of *Mycobacterium bovis.*
- 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 a vaccine for tuberculosis.

- **Sabin polio vaccine:**
- Consist of attenuated viral strain.
- The poliovirus used in the Sabin vaccine was attenuated by growth in monkey kidney epithelial cells.
- The Sabin polio vaccine consists of three attenuated strains of poliovirus
- it is administered orally to children on a sugar cube or in sugar liquid.
- The attenuated viruses colonize the intestine and induce protective immunity to all three strains of virulent poliovirus.
- Sabin vaccine in the intestines induces production of secretory IgA which serves as an important defense against naturally acquired poliovirus.
- The vaccine also induces IgM and IgG classes of antibody.

- Sabin polio vaccine requires boosters, other attenuated vaccines require single immunizing dose.
- Because the three strains of attenuated poliovirus in the vaccine interfere with each other's replication in the intestine.
- First immunization - one strain will predominate in its growth, inducing immunity to that strain.
- Second immunization - the immunity generated by the previous immunization will limit the growth of the previously predominant strain in the vaccine, enabling one of the two remaining strains to predominate and induce immunity
- Third immunization - immunity to all three strains is achieved.

- **Salk polio vaccine:**
- is produced by inactivation by chemical treatment using formaldehyde.

A Comparison of Inactivated (Killed) and Attenuated (Live) Vaccines

Major Characteristic	Inactivated Vaccine	Attenuated Vaccine
Booster shots	Multiple boosters required	Only a single booster
Production	Virulent microorganism inactivated by chemicals or irradiation	Virulent microorganism grown under adverse conditions or passed through different hosts until avirulent
Reversion tendency	None	May revert to a virulent form
Stability	Very stable, even where refrigeration is unavailable	Less stable
Type of immunity induced	Humoral	Humoral and cell-mediated

Disadvantages

- Whole-organism vaccines fail to protect against some diseases
- Attenuated vaccines can also cause illness in individuals whose immune system is compromised.
- Ex. AIDS patients, cancer patients undergoing chemotherapy, the elderly.

- These same individuals may also contract the disease from healthy people who have been vaccinated recently.

- Attenuated viruses can at times mutate and restore virulence.
- They contain molecules that can trigger allergic or other disruptive reactions.

Toxoids

- Toxoids are the inactivated and purified form of toxins prepared from the bacterial pathogen and used as vaccines.
- Some pathogens produce exotoxins, that causes diseases like **diphtheria and tetanus**.
- In diphtheria and tetanus, the toxoid vaccine can be prepared by purifying the bacterial exotoxin and then inactivating the toxin with formaldehyde to form a **toxoid**.
- Vaccination with the toxoid induces anti-toxoid antibodies, which are also capable of binding to the toxin and neutralizing its effects.

- The toxoid vaccine is made by detoxification without excessive modification of the epitope structure.
- Cloning the exotoxins genes & expression in a host can produce toxoid vaccine.
- Exotoxins can be purified, inactivated & produced in large amounts.

Toxoids:	
Diphtheria	Inactivated exotoxin
Tetanus	Inactivated exotoxin

Subunit Vaccines

- They contain only specific, purified macromolecules derived from pathogenic microorganisms.

- Forms of **subunit vaccines:**

  1. capsular polysaccharides
  2. recombinant surface antigens

Subunit vaccine

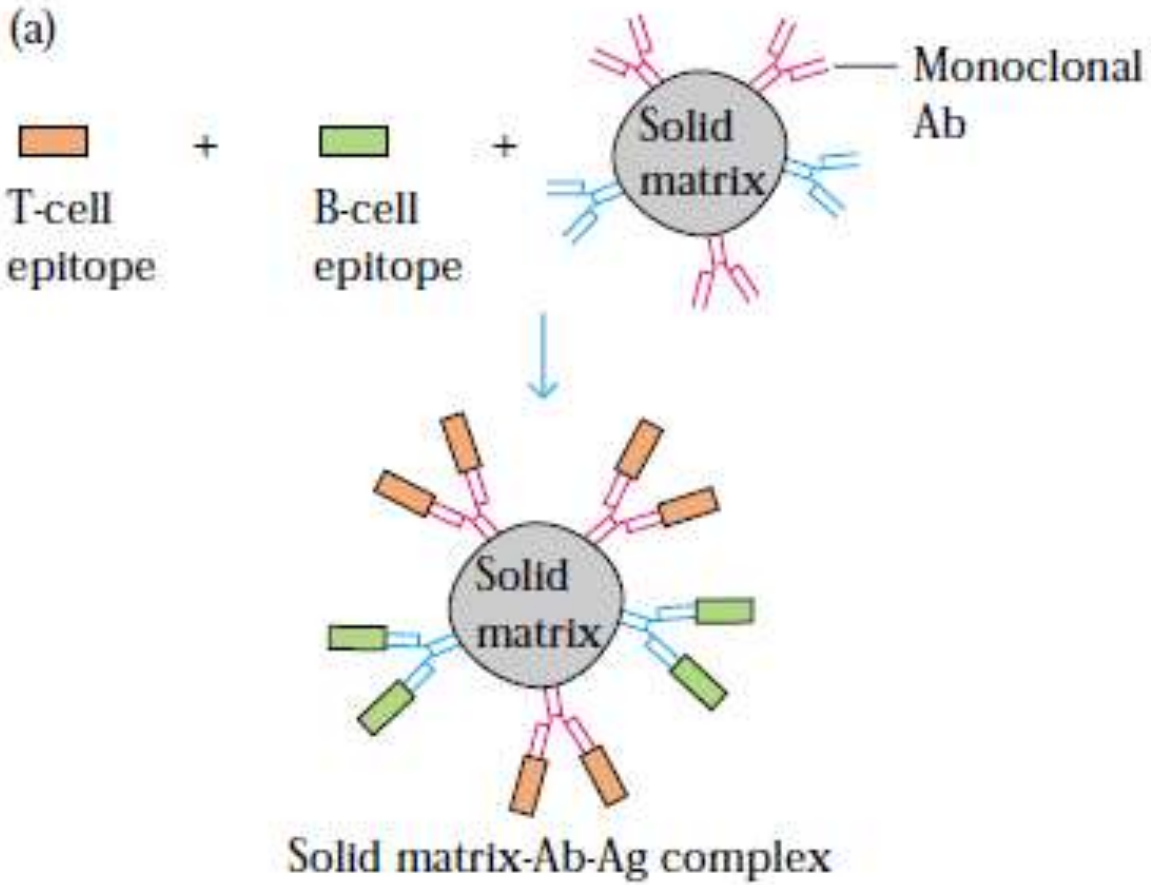
Type of Purified Macromolecule (Disease or Microorganism)	Form of Vaccine
1. Capsular polysaccharide:	
Haemophilus influenzae type b	Polysaccharide-protein conjugate
	(HbCV) or bacterial polysaccharide (HbPV)
Neisseria meningitidis	Polysaccharides of serotypes
	A/C/Y/W-135
Streptococcus pneumoniae	23 distinct capsular polysaccharides
2. Surface antigen:	
Hepatitis B	Recombinant surface antigen (HbsAg)

Subunit vaccine preparation:

- These are synthetic peptide vaccines that contain both immunodominant B-cell and T-cell epitopes.
- The multivalent subunit vaccines present multiple copies of a given peptide or a mixture of peptides to the immune system.
- Solid matrix Ab-Ag (SMAA) complexes
- Protein micelles, liposomes, and immunostimulating complexes (ISCOMs)

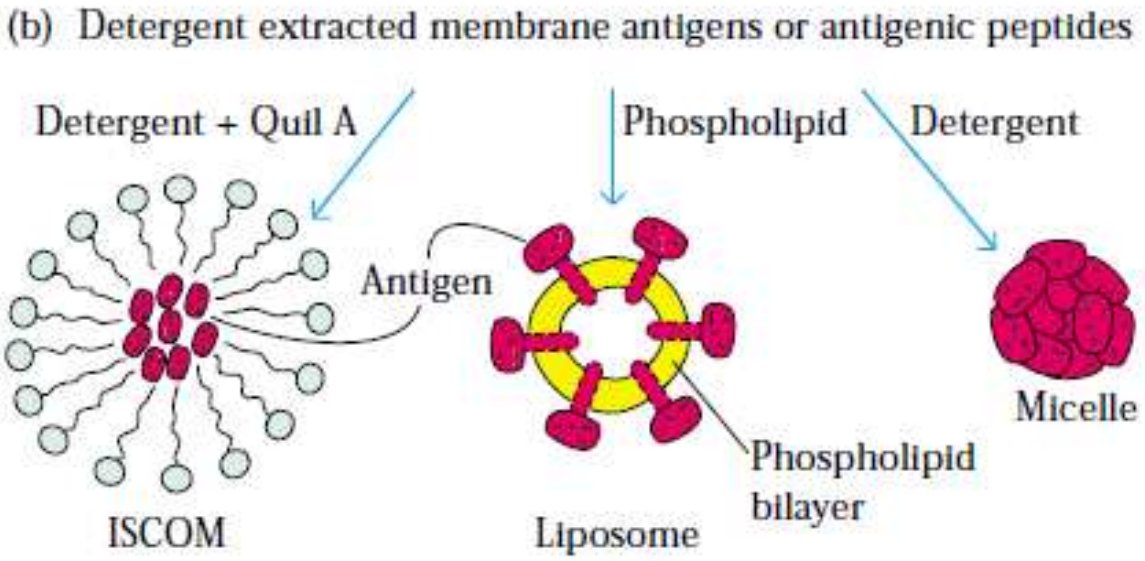
Solid Matrix–Antibody Antigen (SMAA) Complexes

- SMAA complexes are prepared by attaching monoclonal antibodies to particulate solid matrices and then saturating the antibody with the desired antigen.
- The resulting complexes are then used as vaccines.
- By attaching different monoclonal antibodies to the solid matrix, it is possible to bind a mixture of peptides or proteins, composing immunodominant epitopes for both T cells and B cells.
- These multivalent complexes have been shown to induce vigorous humoral and cell-mediated responses.
- Their particulate nature contributes to their increased immunogenicity by facilitating phagocytosis by phagocytic cells.


(a)
T-cell epitope
+
B-cell epitope
+
Solid matrix
Monoclonal Ab
Solid matrix
Solid matrix-Ab-Ag complex

Protein micelles, liposomes or ISCOMs

- Another means of producing a multivalent vaccine is to use detergent to incorporate protein antigens into
  - protein micelles,
  - lipid vesicles (called liposomes), or
  - immunostimulating (ISCOMs) complexes.



- **Protein micelles:**
- Mixing proteins in detergent and then removing the detergent forms micelles.
- The individual proteins orient themselves with their hydrophilic residues toward the aqueous environment and the hydrophobic residues at the center so as to exclude their interaction with the aqueous environment.

- **Liposomes:**
- liposomes containing protein antigens are prepared by mixing the proteins with a suspension of phospholipids under conditions that form vesicles bounded by a bilayer.
- The proteins are incorporated into the bilayer with the hydrophilic residues exposed.

- **Immunostimulating complexes (ISCOMs):**
- These are lipid carriers prepared by mixing protein with detergent and a glycoside called Quil A.

- Membrane proteins from various pathogens, including influenza virus, measles virus, hepatitis B virus, and HIV have been incorporated into micelles, liposomes, and ISCOMs
- They are currently being assessed as potential vaccines.
- In addition to their increased immunogenicity,
- liposomes and ISCOMs appear to fuse with the plasma membrane to deliver the antigen intracellularly,
- where it can be processed by the cytosolic pathway and thus induce a cell-mediated response.

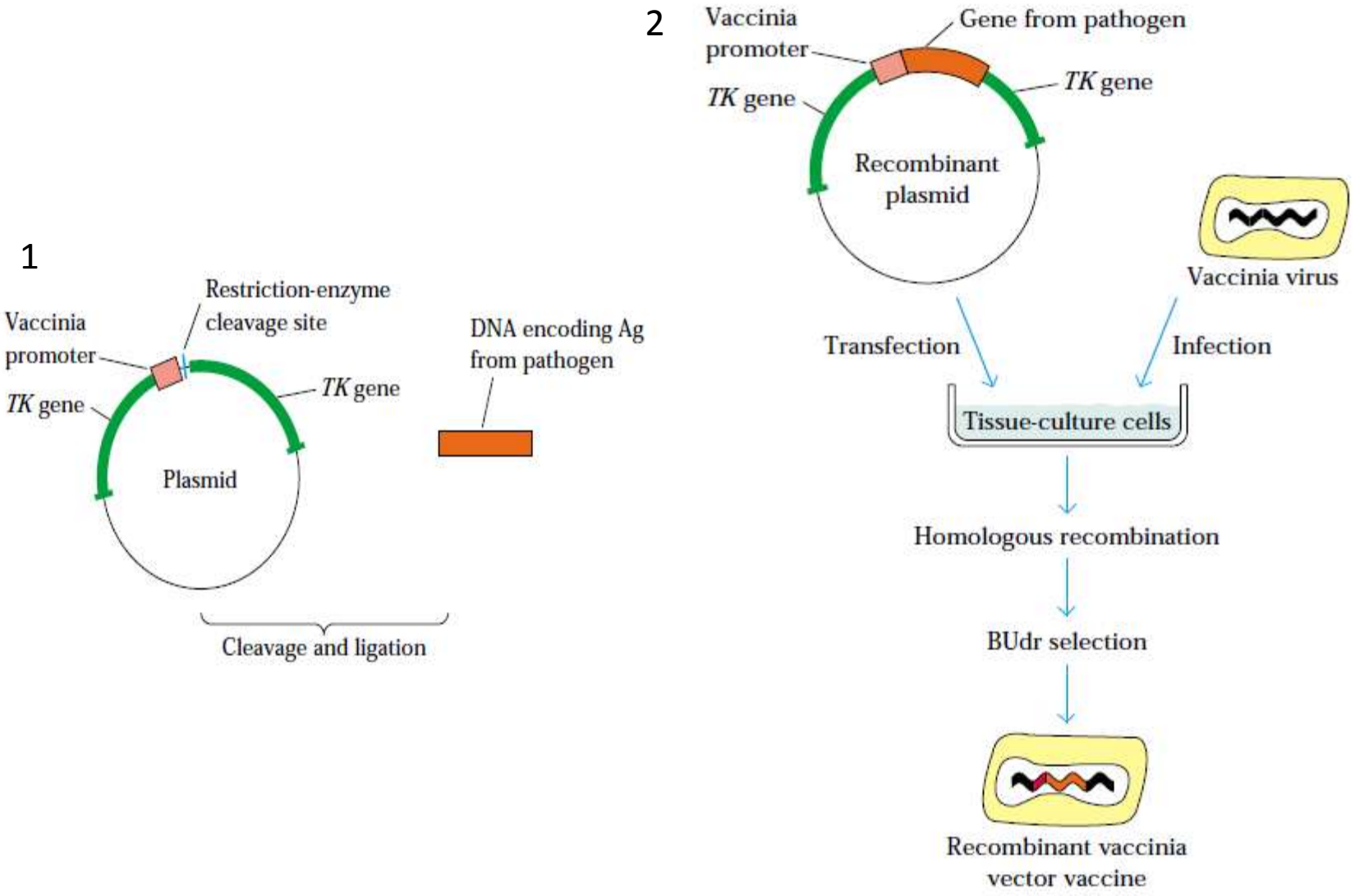
Recombinant-Vector Vaccines

- Genetic vaccines are quite different in structure from whole organism vaccines.
- The isolated genes that encode major antigens from a pathogen is inserted into nonvirulent viruses or bacteria.
- The vaccines are usually delivered by needle injection or by a device called a gene gun.

- Vector:
- The attenuated microorganism serves as a vector,
- It replicates within the host and
- expresses the gene product of the pathogen–encoded antigenic proteins.
- The antigens can elicit humoral immunity when they escape from the vector
- They elicit cellular immunity when they are broken down and properly displayed on the cell surface

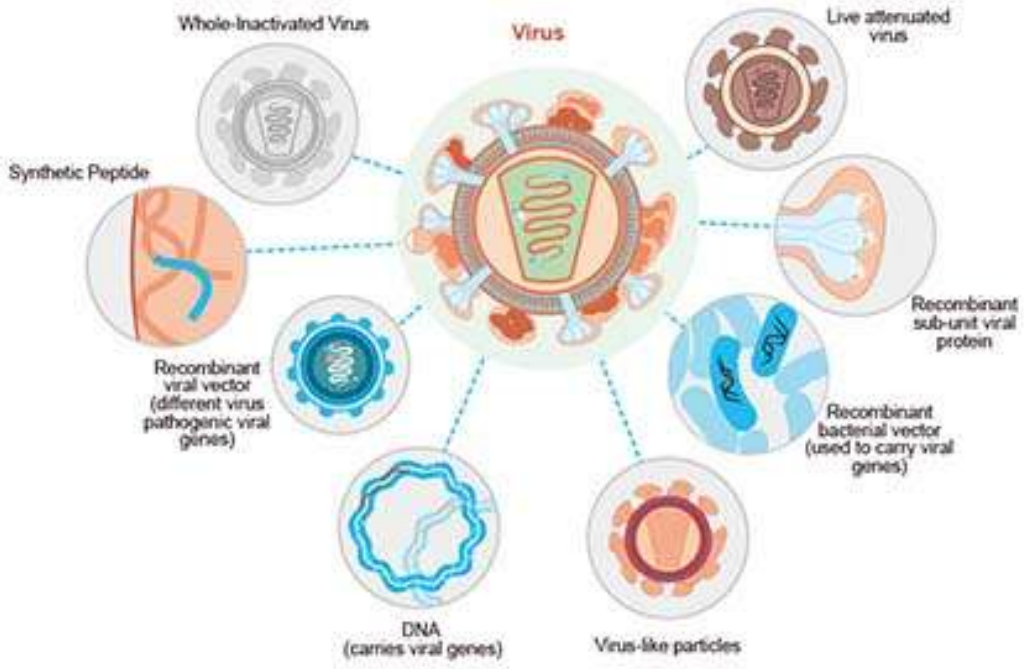
- Ex. **Vaccinia virus**: the attenuated vaccine used to eradicate **smallpox**, has been widely employed as a vector vaccine
- The large genome (200 genes) is engineered to carry several foreign genes
- without impairing its capacity to infect host cells and replicate.
- The genetically engineered vaccinia expresses **high levels** of the inserted gene product
- which serve as a potent immunogen in an inoculated host.

Recombinant-vector vaccine: Vaccinia virus



- Production of vaccinia vector vaccine.
- The gene that encodes the desired antigen is inserted into a plasmid vector adjacent to a vaccinia promoter
- and flanked on either side by the vaccinia thymidine kinase (*TK*) gene.
- When tissue culture cells are incubated simultaneously with vaccinia virus and the recombinant plasmid,
- the antigen gene and promoter are inserted into the vaccinia virus genome by homologous recombination
- at the site of the nonessential *TK* gene, resulting in a TK^- recombinant virus.
- Cells containing the recombinant vaccinia virus are selected
- by addition of bromodeoxyuridine (BUdr), which kills TK cells

Types of Vaccines



Live attenuated (LAV)

- Tuberculosis (BCG)
- Oral polio vaccine (OPV)
- Measles
- Rotavirus
- Yellow fever

Inactivated (killed antigen)

- Whole-cell pertussis (wP)
- Inactivated polio virus (IPV)

Subunit (purified antigen)

- Acellular pertussis (aP),
- *Haemophilius influenzae* type B (Hib),
- Pneumococcal (PCV-7, PCV-10, PCV-13)
- Hepatitis B (HepB)

Toxoid (inactivated toxins)

- Tetanus toxoid (TT),
- Diphteria toxoid

Whole-inactivated virus,
live attenuated virus,
recombinant subunit viral protein,
recombinant bacterial vector,
Recombinant viral vector,