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# Overview of Vaccine Drug Delivery System

Kiran S. Sale[1], Pallavi M. Chaudhari[2]
[1,2](DepartmentofPharmaceutics,Dr.D.Y.P.CollegeofPharmacy,Akurdi,Pune-411044, Maharashtra,India)
[1]Corresponding Author: kiransale1996@gmail.com

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***Abstract:*** *Until the 20th century, infectious diseases were the leading cause of death and disability worldwide, and this is still the case in much of the developing world. Immunisation has played a central role in radically reducing the incidence of many dangerous diseases, and some diseases have been wiped out entirely (e.g. smallpox). This article presents the World Health Organization's (WHO) recommendations on the use of various vaccines. Vaccines prevent an estimated two –three million deaths worldwide every year. But, a further 2 million lives could be saved annually with better global vaccine coverage. Vaccines prevent an estimated two – three million deaths worldwide every year. But, a further 2 million lives could be saved annually with better global vaccine coverage. The purpose of vaccination is to produce immunity. Vaccines contain the same germs that cause disease. (For example, measles vaccine contains measles virus.) But they have been either killed or weakened. A vaccine provides a conducted exposure to a pathogen, training and encourage the immune system so it can fight that disease quickly and effectively in future. The national Vaccine Injury Compensation Program covers routine vaccines for children (against a total of 16 diseases). Vaccines are safe and effective. Because vaccines are given to millions of wholesome people. Vaccines have one of the greatest impacts on public good health. The prevention of disease has had an enormous impact on commercial development by limiting the costs of curative care and saving billions of dollars in countries where diseases have been well controlled or eliminated.*

***Key Word****: vaccines, immunization, pathogen, vaccine injury compensation program.*

## I. Introduction

The term vaccines and vaccination are derived from Variolae vaccine (small pox of cow) the term derived by Edward Jenner to denote cowpox. [1] The word comes from Latin word vacca meaning cow. Development of first vaccine against small pox (by Edward Jenner in1978) and rabies (by Louis Pasteur in 1880) are landmarks in the history of immunology. Vaccines is used to bacterial toxins or block virus binding, if TH cells are not elicited.[1] Various vaccine performed immune mechanism by which they are efficacious. Immunochemist plays acritical role to build up understanding of protective immune response and designing the vaccine to meet the demand. [2] This article will briefly mention about what is the exact meaning of vaccine, how do they work in the body, value of vaccines. this review article will also concentrate on various types of vaccines, their quality control tests, etc. vaccination has become more common for diseases such as rubella, diphtheria, tetanus, pertussis, Hemophilus influenzae type b (childhood), hepatitis B, measles, polio, and tuberculosis. [3]

It is generally considered as one of the greatest public health achievements in many countries during twenty country, which reduces mobility and morality from a broad range of vaccine preventable diseases.[4] Globally over 5.1 million deaths are prevented annually through vaccination. The vaccine teaches the body how to defend itself against the pathogen by creating immune responses. Preventive vaccines work to protect and individual from infectious or disease by introducing a small component or non-harmful from of the pathogen intro the body. they are administered in Liquid form by

1. oral
2. IM

3.SC routes

They are biological preparation which are prepared from living organism. they produce immunity to a specific disease. Vaccine is the administration of antigenic material to stimulate immune system. Vaccine contain dead or weak microbes and stimulates they body to produce antibodies. [5]

## II. National Vaccination Day

India observes National Vaccination Day on sixteen March every year. Sometime called as National Immunization Day (NID). National Immunization Day was first observed on March 16, 1995 when first dose of Oral OPV was given. Every year, India observes National Immunization Day in January to mark the launch of pulse polio programmed. [6] India has been executing the Pulse Polio Programmed since 1995.India has one of the largest Universal Immunization Programs (UIP) in which large number of vaccines is used. The main aim of this program is to ensure full immunization with all available vaccines for children up to two years and pregnant women. Under this programmed, cost of vaccine is lowered. [7]

## III. Need of Vaccine

A vaccine is introduced into the body to prevent various infections or to control disease due to a certain pathogen. [1] The vaccine fight against many pathogens by producing an immune response. vaccines are preparations of components derived from a pathogen and they a protective effect through 1 to 3 very small doses, In the range of μg to mg. Immunity lasts for a longer period, from 1 year up to lifetime protection. [8]

## IV. How Do The Vaccines Work?

Vaccines contain dead or weakened microbial strains of a particular diseases. When vaccine is introduced in a body it produces specific cells against pathogen which is called antibodies. These antibodies become active when pathogen attack on our body. the body fight and kill them by producing specific set of reaction. These antibodies remain in the body for life long and protect against the body when microbes entre to the body. [10]

## V. Composition of Vaccine

Ingredients provide immunity

***1. Antigen***

Very small amount of weak or dead germs that can cause diseases. They help our immune system and learn how to fight against infections faster and more effectively. [11]

Example: flu virus

***2. Adjuvants***

Helps our immune system to respond strongly to vaccine. This increases immunity against the disease. [12]

Example: Aluminum, paraffin oil, squalene, calcium phosphate hydroxide, IL-1, IL-2, IL-12.

Ingredients keep vaccines safe and long lasting.

a) Preservatives: Protect the vaccine from outside bacterial or fungus. [12]

Example

a) Phenol – Typhoid, Pneumococcal.
b) BenzthoniumCl – Anthrax
c) 2-phenoxy ethanol – Inactive Polio
d) Thimerosal – Influenza
e) Monosodium glutamate – acts as preservative and stabilizer

***3. Stabilizers***

Stabilizer helps the active ingredients in vaccines to continue their work while vaccine is made, stored and moved. They keep the active ingredients from changing. [11]

Example: sugar, gelatin

***Ingredients used during production of vaccines*** *[*13]

***1. Cell culture material***

To help the growth of vaccine antigen

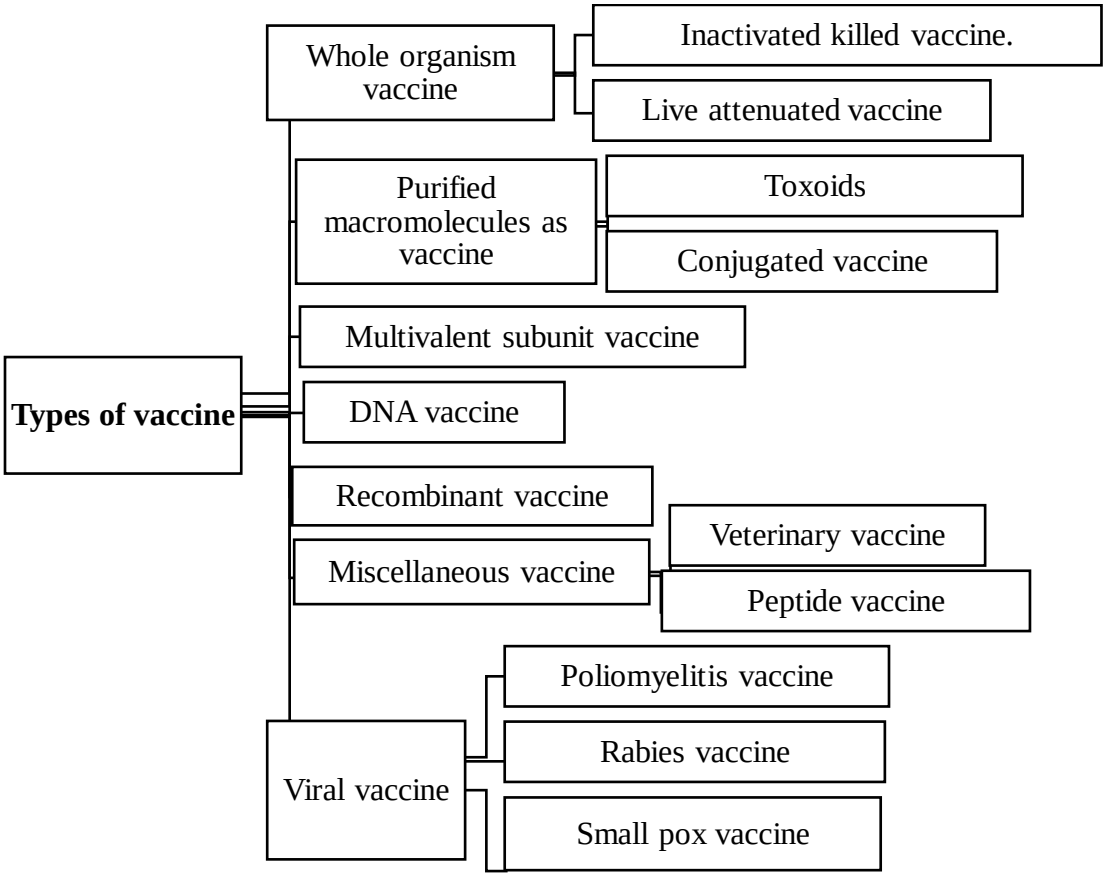
Example: eggs

**2.** ***Inactivating ingredients (Germ killing)*** *[14]*

To weaken or kill viruses, bacteria from growing in the vaccine.

Example: Formaldehyde

**4.** ***Antibiotics:*** **I**t is used to help keep outside germs and bacteria from growing in the vaccine
Example: Neomycin




## VI. Types of Vaccine

***1. Whole organism vaccine*** *[15]*

Vaccine currently in use consists of inactivated (killed) or live but attenuated (avirulent) bacterial cells or viral particles.

***A. Live attenuated vaccine***

They mimic an actual infection as the pathogen reproduces within host cell. The immunity is induced lifelong immunity is achieved without booster immunization. this long-term effectiveness occurs because attenuated viruses replicate in the body. [15]

e.g. TB, BCG, yellow fever, rotavirus, measles

***B. Inactivated killed vaccine***

Use microbes that have been killed by formalin or phenol. they are used against rabies, influenza, polio. They required booster dose.

E.g. whole-cell pertussis, inactivated poliovirus

***2. Purified macromolecules as vaccine*** *[16]*

***A. Toxoids***

It is defined as they modified toxins, detoxified by the use of moderate heat and chemical treatment so that their antigenic properties are retained. Toxoids are toxins whose toxicity has been removed.

The toxin invades the bloodstream and is largely responsible for the symptoms of the disease. The toxin is used in vaccine production and used as the antigen in the vaccine to elicit immunity. To increase the immune response, the toxoid is absorbed to aluminum or calcium salts, which serves as adjuvants.

e.g. tetanus toxoid, staphylococcus toxoid.

***B. Conjugated vaccine***

They deal with the poor immune response of children to vaccines based on capsular polysaccharides. [16]
e.g. Hemophilus influenza type B.

***3. Multivalent subunit vaccine***

Microbes are producing desired antigenic action called as recombination vaccine. [16]
e.g. hepatitis B, Hemophilus influenza type B, pneumonia.

***4. DNA vaccine***

Basics of DNA vaccine is first reported by Ulmer et al in 1993. The injection of DNA into animal does not generate an immune response but that DNA is expressed to yield a protein that can stimulate an immune response. They are composed of bacterial plasmid.
DNA is they introduced in to the tissue cells and that host responds to the antigenic materials the introduced DNA is lost from the recipient cells and antigen releases. [17]
e.g. influenza and herpes, measles. HIV, Ebola etc.

Preparation of DNA vaccine
↓
Insert gene into an expression plasmid
↓
Transform bacterial cells.
↓
Grow bacteria, purify plasmid DNA
↓
Immunize with immunogen expressing plasmid.

***5. Recombinant Vaccine***

The recombinant vaccine is developed through the rDNA technology. These vaccines are produced by the insertion of genetic material which encoding the antigen that stimulates an immune response. Plasmid DNA is used as vaccine which is propagated in bacteria like E. coli and they get isolated and purified into the vaccine.
This method is used to prepare highly pure component vaccine (subunit vaccine). E.g. hepatitis B surface antigen from hepatitis B virus is isolated, sequenced, done by using yeast cell. First recombinant vaccine was developed in India by Shantha Biotechnic Pvt.Ltd. Hyderabad in 1997. In recombinant vaccine genetic manipulation of the antigen itself is possible. [17]
E.g. hepatitis B

***6. Miscellaneous vaccine***

***A. Veterinary vaccine***

These are living or dead preparation of micro-organism used to stimulate active immunity in animals. Vaccine recommended on the basis of kind of exposure, diseases, stress, species and strain of animals. They are classified as killed, Live and subunit vaccine [15]
e.g. anthrax vaccine, Newcastle, foot and mouth diseases.

Table no.1: Veterinary vaccine

| **Vaccine** | **Animal/ Bird vaccinated** | **Dose** |
|---|---|---|
| Anthrax | Cow, sheep, Goats | 0.5 to 1 ml |
| Newcastle | Chicks | 0.5 ml |
| Foot and mouth disease (FMD) | Cow, Buffaloes, sheep | 5 ml |

***B. Peptide vaccine***

The first identification of peptide had vaccine potential was demonstrated in 1963 with a plant virus. Tobacco mosaic virus. (Ander 1963). In this study, a chemically isolated hexapeptide fragment from the virus coat protein was coupled to bovine serum albumin and used to elicit rabbit antibodies which neutralizes infection. This peptide vaccine is now widely used against rabies virus, polio virus, measle virus, influenza virus. Peptides are poor immunogens and this require carrier coupling to enhance immunogenicity. The free peptides are also effective when they are delivered in small, unilamellar liposomes. Peptide vaccines are based in vitro synthesized peptides of 20-30 amino acids. [15] [16]

Advantage:

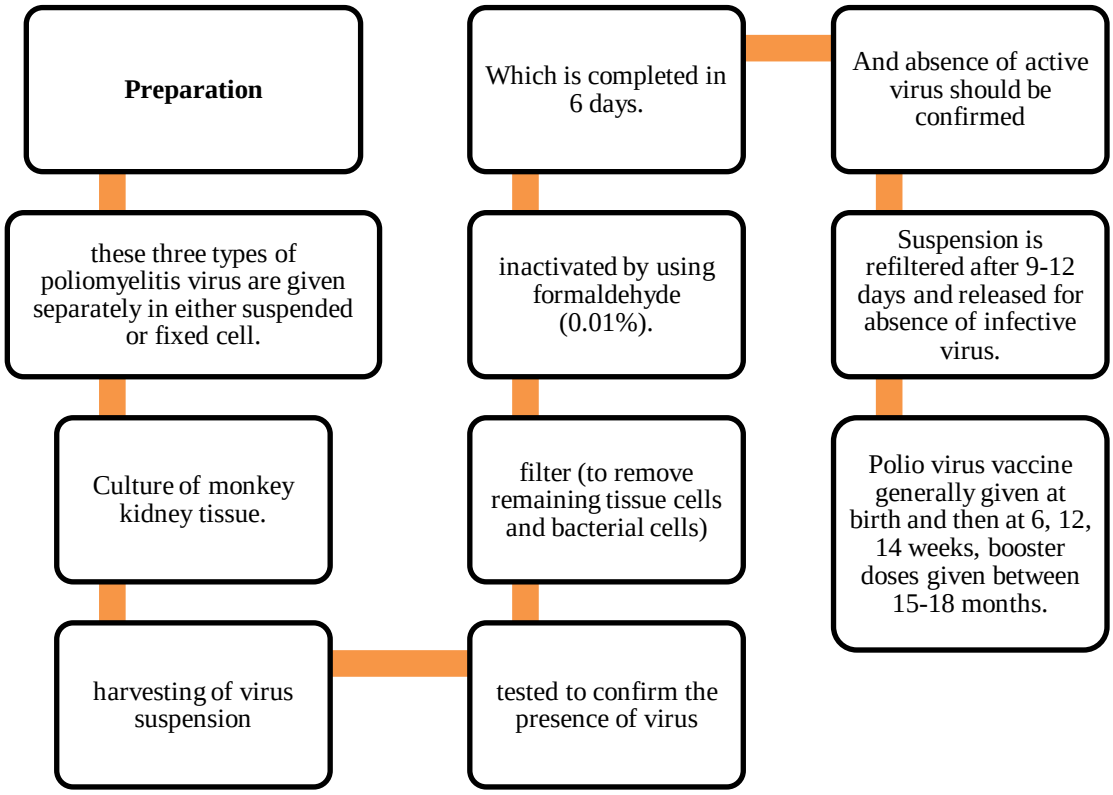
- Easy synthesis with low cost
- Increases stability
- Safety
- They can be designed with self or non-self-antigen to properly balance the immune response.

***7. Viral vaccine***

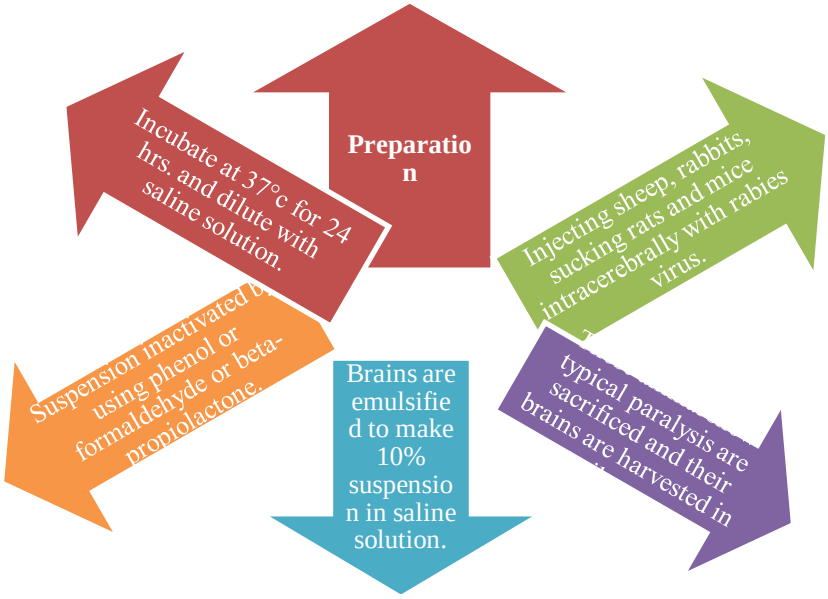
These are suspension of viruses or preparation obtained from tissues or blood of animal or from cultures in fertile eggs, cells, tissue culture. They may be live, inactivated/ killed and may be freeze dried. [15] [18]

***1. Poliomyelitis vaccine***

It is an aqueous suspension of suitable strains of poliomyelitis virus, type 1, 2, 3 grown in suitable culture and inactivated by suitable method. [18]



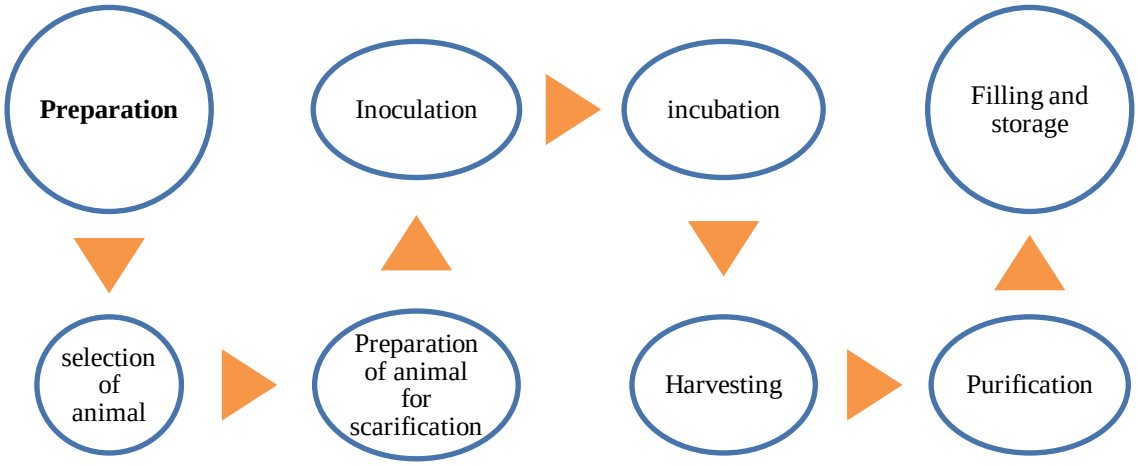
***2. Rabies vaccine*** *It is a suspension of a suitable strain of fixed rabies virus. [18]*




A chick embryo is the most suitable site for growth of rabies virus

***3. Small pox vaccine***

It is a freeze- dried suspension of living virus of vaccine a strain capable of protecting against smallpox. The vaccine virus is grown in the skin of living healthy sheep or in the membrane of chick. [15] [18]

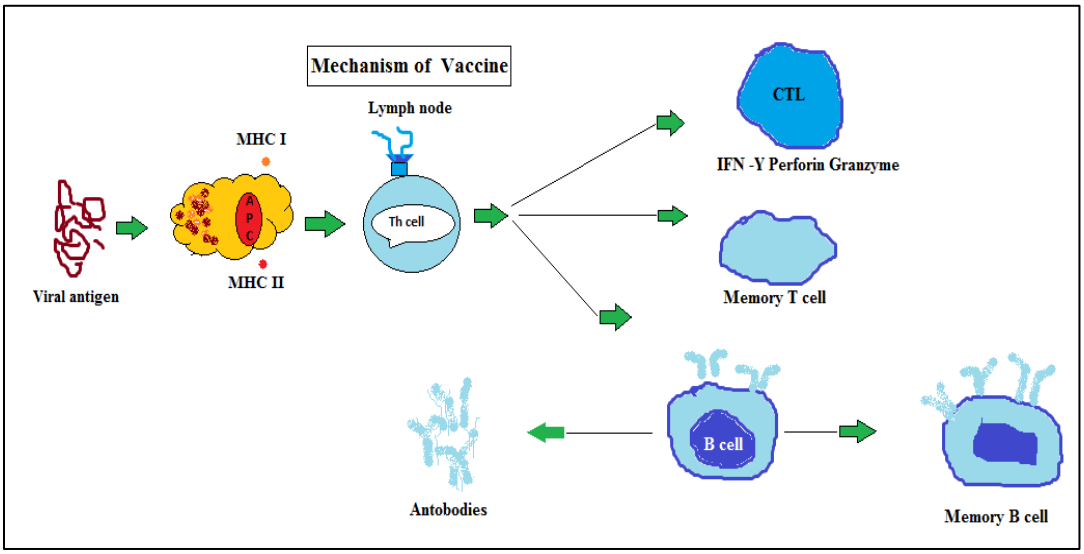



Liquid small pox vaccine retains its potency foe a year at 10°c but at higher reduces its stability.

## VII. Mechanism of Action

To initiate an adaptive immune response a number of signals are required by T Cells. Signal one is the vaccine derived, peptide antigen (Ag) bound to major histocompatibility class-II (MHC) and class-I is displayed on surface of antigen presenting cells (APC's). signal two is also known as costimulation and together with signal one, induces immune response (Fig.1). Signal two involves cross linking of CD28 and other receptors on T cells by costimulatory molecules such as B7-1 (CD80), B7-2 (CD86) and other ligands are expressed by APC. signal 3 is provided by cytokines and is delivered from the APC to the T cell which determines differentiation into on effector cell. Both signal 2 and 3 are provided to T cell by activated cells (DC's). Mature DC's are able to induce T cells clonal expansion and prime immune response. [19]

Fig.1 Mechanism of Vaccine [19] [20]




**Advantage of vaccines** [21]

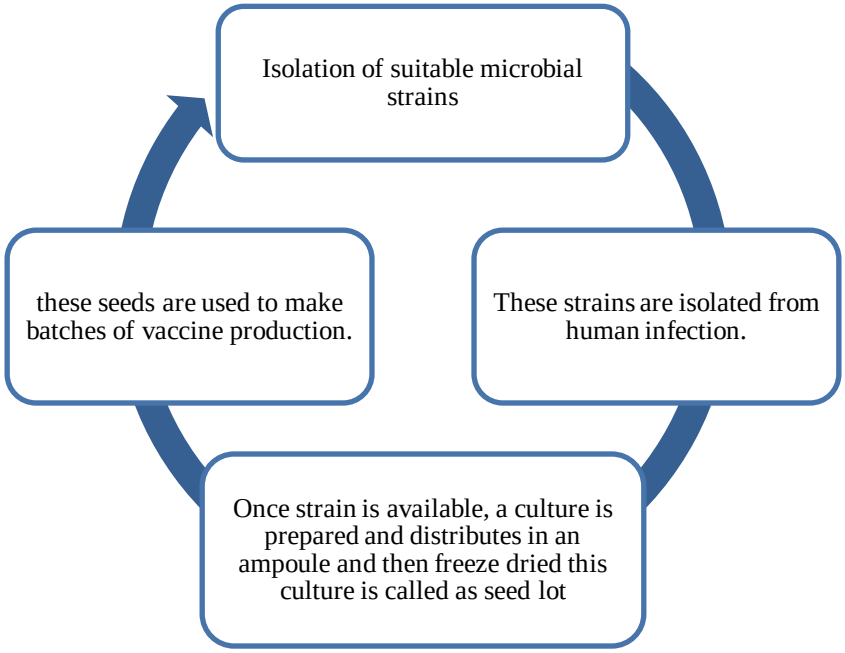
1. Prevents an infected person from spreading disease.
2. Provide immunity to fight against harmful disease.
3. Protect drug against degradation.
4. Virosomes are biodegradable, bio compatible and non-toxic.
5. Enable drug delivery into cytoplasm of target cell.
6. Prevent epidemic and pandemics.
7. Prevent the potential greater cost treating the infected patient.
8. Promote fusion activity in the endolysosomal pathway.
9. No auto immunogenic.
10. No disease transmission risk.

**Disadvantage of vaccines** [21]

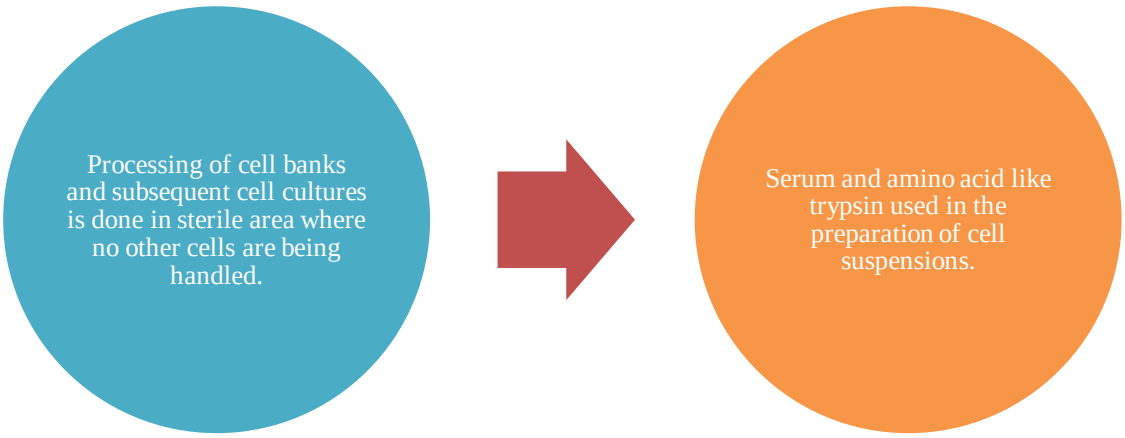
1. Shelf life is too short.
2. Vaccine can cause serious and sometime fetal side effect.
3. Booster injection can be inconvenient.
4. Can be unpleasant or painful.
5. Not guaranteed to work or provide 100% protection.
6. Only humoral immunity can be induced.
7. Inactivation may after antigenicity.

## VIII. General Method of Preparation [21] [22]

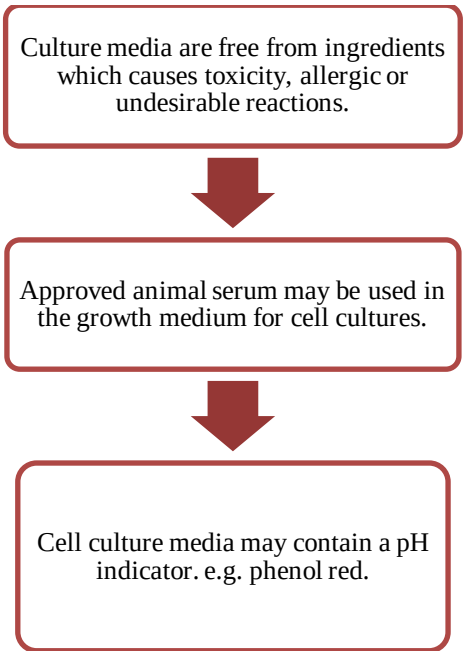
***1 Seed lot system***



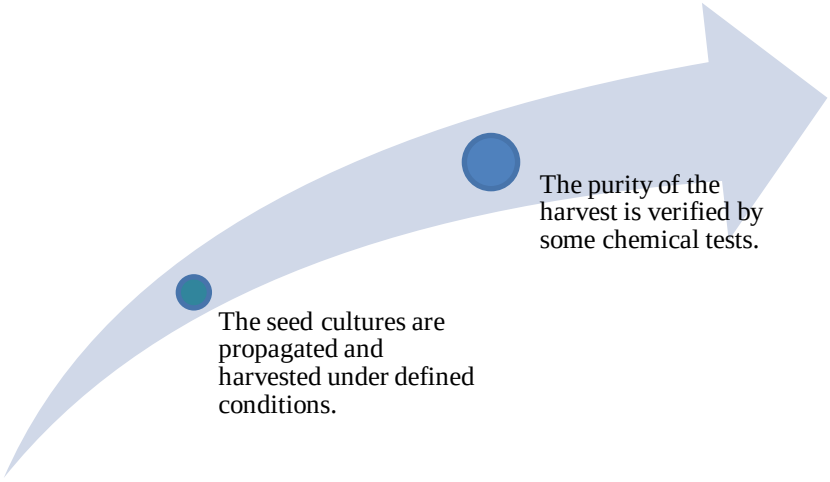

***2.Substrate for Propagation***



***3.Culture Media***




***4.Propagation and Harvest***




Marketed example of vaccine [23]

Table no.2: Example of marketed products

| Sr no | Manufactured by | Vaccine | Marketed preparation | Company founded | Location |
|---|---|---|---|---|---|
| 1 | Lupin Pvt.Ltd | Pneumococcal vaccine | Pneumovax 23 | 1968 | Pune |
| 2 | Panacea Biotech Ltd | Hepatitis B vaccine-<br>Hepatitis B (recombinant) | Ecovac<br><br>Enivac HB | 1984 | New Delhi |
| 3 | Bharat serum and vaccine Ltd | Hepatitis B (recombinant) vaccine | Heppacine B | 1971 | Mumbai |
| 4 | GlaxoSmithKline Pharmaceuticals Ltd | Human papillomavirus vaccine-<br>Hepatitis B vaccine<br>Hepatitis A vaccine | Cervarix<br><br>Engerix<br>Boostrix | 1924 | Mumbai |
| 5 | Serum institute of India | BCG vaccine-<br>Tetanus vaccine I.P<br>Measles and rubella vaccine<br>Poliomyelitis vaccine I.P | Tubervac<br>Tetanus vaccine<br><br>MR-VAC<br><br>Poliovac PFS/SD | 1996 | Pune |
| 6 | Indian immunologicals limited | Porcine cysticercosis vaccine<br>sheep pox vaccine | Cysvax<br><br>Raksha SP | 1983 | Hyderabad |
| 7 | Shantha biotechnics limited | Hepatitis B recombinant vaccine<br>Typhoid vaccine(live) | FUSYS/ shanvac B<br>Shantyph | 1993 | Hyderabad |
| 8 | Merck pharmaceutical | Human papillomavirus (HPV) quadrivalent vaccine<br>rotavirus vaccine<br>Hepatitis A vaccine | GARDASIL<br><br><br>Rota tea<br>VAQTA | 1967 | Mumbai |
| 9 | Haffkin bio pharmaceutical corporation limited | Cholera vaccine<br>Polio vaccine<br><br>Scorpion vaccine | Cholera vaccine Oral<br>polio virus vaccine (OPV)<br>Scorpion venom antiserum | 1956 | Pune |
| 10 | Sanofi Aventis Pharma India | Measles vaccine –<br>Mumps vaccine -<br>Typhoid vaccine – | MoruparMoruparTyphoral | 1956 | Mumbai |

## IX. Technology for Vaccines Delivery

***1.Auto-disable (AD) Syringes And Safety Boxes***

The rationale of Auto-disable syringe is lowest risk of person-to-person transmission of blood borne pathogen because it is designed to prevent reuse. It is the disposable equipment of choice for administering vaccines for mass immunization campaigns. The risk posed to health staff and the general public by contaminated needles and syringes is reduced by the use of puncture-proof containers, known as safety boxes, for the collection and disposal of used disposable and Auto-disable syringes, needles and other materials. The Auto-disable syringes, which is now widely available at low price. [24]

***2.Point-Of-Use Sharps Processing Technologies***

Rationale of Point-of-use sharps processing technology is that the hazards of storing and transporting infected syringes and needles to the point of final disposal can be reduced by de-fanging (i.e. Separating, encapsulating or destroying the needles), disinfection and compaction. After they have been disinfected the possibility of cross-infection is reduced, and after compaction the processes of storage and transportation become more feasible. [24]

A number of technologies which is mentioned below:

- Disinfectants
- Thermoprocessing technology or melting
- Needle destroyer
- Plasma-melting and small-scale incineration Nature of Gating

***3.Thermostable Vaccines And Vaccine Vial Monitors***

Rationale of this technology is that vaccine distribution without a cold chain would significantly simplify the delivery system and make it easier to integrate with drug distribution in progressing countries.

Sugar-glass drying technology allows vaccines to be made which can be stored and transported regularly at tropical room temperatures or in freezing climates. Extremes can be monitored by VVMs (Simonsen 1999, Kane 2000, Stein glass2005). [24]

## X. Single Shot Vaccines

It is a mixture product of prime component antigen with an appropriate adjuvant & a microsphere component that encapsulates antigen & provide booster immunization by delayed delivery of antigen. [25]

**Important aspects of single shot vaccines** [25]

1.biodegradable technology
2. Particle size distribution
3.encapsulation efficiency
4. Preservation of bio activity during formulation and release
5. Scalable production process
6. Effects of combination with various adjuvant
7. Effects of different administration route

The size distribution of a microsphere can be controlled by the shear force applied during emulsification step. The presence of excipient in the starting composition may change the matrix density & encapsulation efficiency to a microsphere product. [26]

E.g. DTap(diptheria-tetanus-pertusis), trivalent IPV (three strains of inactivated polio vaccine), MMR (measles-mumps-rubella), etc.

## XI. Quality Control Test

***1. Sterility Test***

Incubate the media for not less than 14 days at 30" to 37" in the test for detecting bacteria and at 20" to 25" in the test for detecting fungi. However, for live bacterial vaccines growth of the organism from which the vaccine was prepared is permitted. [27]

***2. Safety Test***

Inject at least 2 healthy, susceptible animals. The quantity to be injected in each animal is twice the appropriate vaccinating dose. Observe the animals for not less than 7 days. No animal exhibits an abnormal reaction. [27]

***3. Abnormal Toxicity***

Inject 0.5 ml subcutaneously into each of five mice and 2 ml intraperitoneally into each of two guinea pigs. If the vaccine being examined contains an adjuvant, inject 2 ml of the vaccine subcutaneously into each guinea pig. Observe the animals for 7 days. None of the animals shows significant local or systemic reaction. If one animal dies or shows signs of ill-health during the observation period repeat the test. None of the animals of the second group dies or shows signs of ill health. This test may be omitted if a safety test is carried out on animals of the species for which the vaccine is intended. [27]

***4. Identification Test***

the identities of bacterial vaccines can be checked by precipitation and agglutination reactions. Inactivated viral vaccines are tested by observation of the specific antibody responses in vaccinated animals and live viral vaccines by neutralization of their cytopathic effects by specific antisera. [27]

***5. Phenol Concentration***

Phenol is used as a preservative in different types of vaccines. Its concentration must not 0.5% w/v. [27]

## XII. Combination of Vaccine

The development of combination vaccines for protection against many diseases began with the combination of diphtheria, tetanus, and pertussis (DTP) vaccines into a single product; this combined vaccine was first used to vaccinate infants and children in 1948. Combination vaccines represent 1 solution to the problem of increased numbers of injections. [28]

**Advantages of combination vaccine** [28]

1. Fewer injection.
2. Reduce trauma to the infant.
3. Higher rates of compliance with vaccination schedule.
4. Better vaccine coverage.
5. Timely vaccination.
6. Lower storage space requirements.
7. Allows incorporation of new vaccines into immunization schedules.
8. Reduced administration costs.

## XIII. Contraindication

Contraindications of vaccination were referring to conditions caused by vaccines unsuitable to inject, which might increase the chance or severity of adverse reactions or interfere the immunity of vaccines. The risks associated with vaccine administration need to be considered against the benefits. The judgment of contraindications is mainly based on Specification of Product Characteristics (SPC), also rely on physician's clinical experience in evidence of excess risk. [29]

Table no.3: Example of Contraindication

| **Vaccine** | **Contraindications** | **Precaution** |
|---|---|---|
| Hepatitis B (HepB) | Anaphylaxis<br>Hypersensitivity to yeast | Moderate or severe acute illness<br>Infant weighing less than 4lbs |
| Rotavirus (RV5 [RotaTeq], RV1 [Rotarix]) | Anaphylaxis<br>Severe combined immunodeficiency (SCID) | Moderate or severe acute illness.<br>Altered immunocompetence.<br>Chronic GIT diseases.<br>Bladder exstrophy. |
| Haemophilus influenzae type b (Hib) | Anaphylaxis | Moderate or severe acute illness |

## XIV. Conclusion

It is clear from this article that, from the past few years the whole field of vaccine research has been changed significantly. Immunochemist plays vital role to form more defined and efficacious products. Immunization policy needs to be national in scope. Implementation of Immunization policy must be flexible at the state and local levels. The importance of vaccination to young generation can have long lasting beneficial effects in the population. The childhood Immunization schedule may become more complex over time as scientific progress are made and new vaccines are developed.

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