VACCINES

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CONTENTS

INTRODUCTION

- Vaccines are one of the greatest achievements of public health of the last century.
- A Vaccine is developed to prevent or cure a disease, and elicits an appropriate immune response towards development of immunological memory to combat infections on future exposures.
- A better understanding of disease process along with knowledge of mode of action, benefits, risks, and potential real-life impact health of vaccines has greatly helped in the development immunizations for various diseases.

VACCINE

- The term Vaccine was coined by Louis Pasteur.
- It is a biological preparation containing an agent which is similar to the disease causing organism that provides active acquired immunity against a particular disease.
- Vaccines are generally prepared from Live attenuated/ killed microbes that cause infection. Sometimes the chemically ineffective toxin or one of the surface antigenic proteins are also used.
- Vaccines can be
  - **Prophylactic** ie., may prevent the effect of future infection by any wild or natural antigen.
  - **Therapeutic** eg., vaccines against cancer

VACCINATION

- Vaccination is the administration of antigenic material ie., a vaccine to an individual to elicit an adaptive immune response to a pathogen and create immunological memory towards prevention of future infections

IMMUNIZATION

- Immunization is a process of making a person immune or resistance to a disease causing organism, typically through scheduled administration of vaccine.

VACCINATIONS

- Vaccinations involve the administration of one or more of vaccines to an individual.
- Vaccination results in development of an adaptive immune response and formation of memory cells without development of disease.
- When the vaccinated individual is later exposed to the live pathogens in the environment, their immune system, can destroy them before they can cause disease.

HOW DO VACCINES WORK?

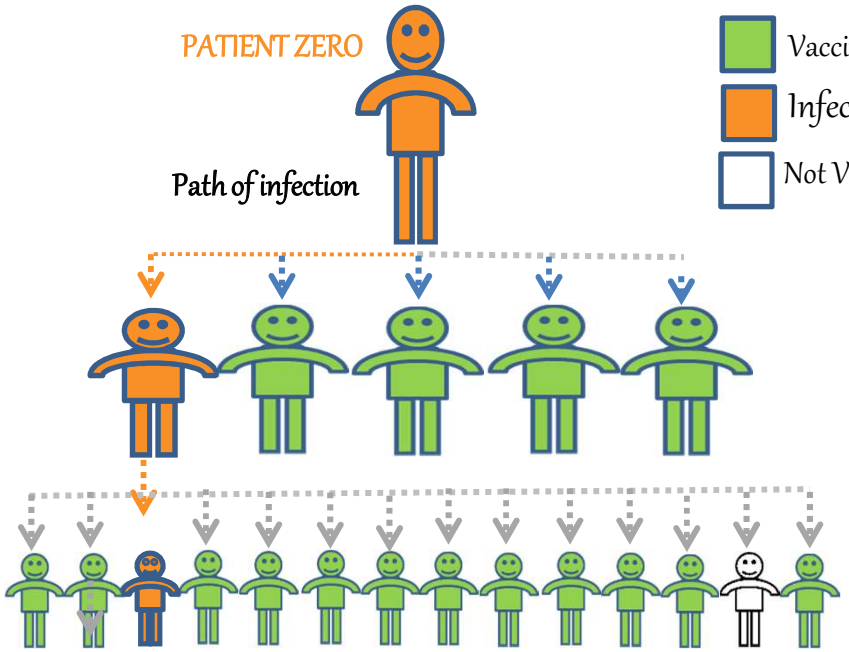
- Innate immunity provides the first line of defence against invading pathogens.
- It is quick and nonspecific and its activation of innate immunity is necessary towards development adaptive immune response.
- Adaptive immunity is the second line of defence and develops relatively later than innate response, and varied clones of lymphocytes and antibodies are produced to recognize and combat almost all antigens.
- A vaccine is immunogenic and results in induction of cell-mediated and humoral immunity. This is the basis of long-term protection.
- Vaccination is often highlighted by
  - the generation and production of antibodies and
  - the formation of memory cells which can quickly get activated upon subsequent exposure to the same antigen.

HOW DO VACCINES WORK? HERD IMMUNITY

- Vaccines protect the vaccinated population as well as the unvaccinated population by decreasing the transmission of infection from one person to another and in this way only limited individuals are at risk.
- This sort of unintended decrease in the risk factor is termed as HERD OR COMMUNITY PROTECTION.
- Herd or Community Protection to be successful necessitates that
  - a majority of the population (75–95%)
  - Vaccination of particular group playing a key role in spread of disease.
- For any vaccination program to be successful it is necessary to develop Herd protection example for measles.

HERD IMMUNITY

HERD IMMUNITY



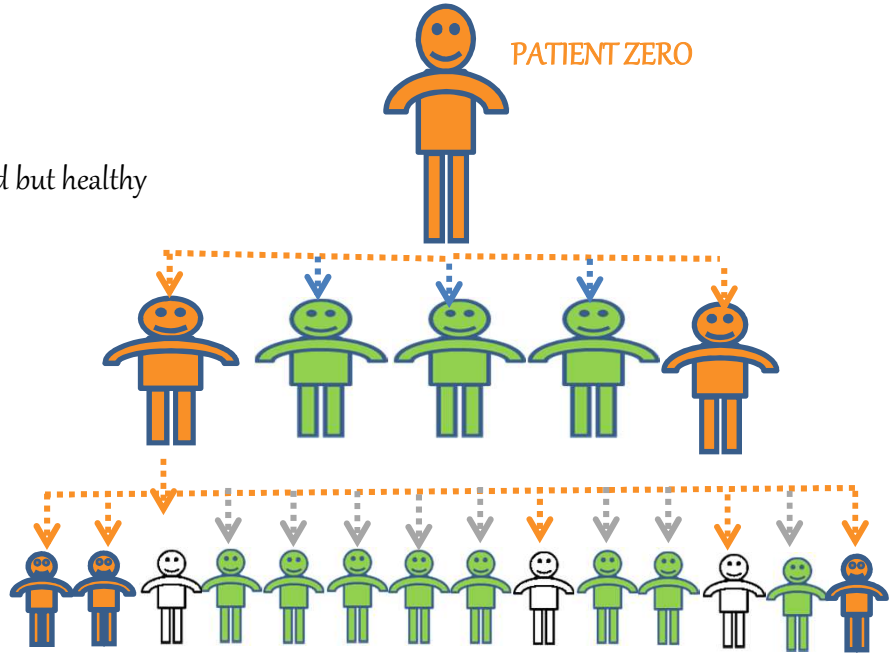
Vaccinated

Infected

Not Vaccinated but healthy

VACCINATED PEOPLE PREVENT SPREAD OF INFECTION. THEY ACT AS BARRIER OF INFECTION

NO HERD IMMUNITY



WHEN THERE ARE LESS VACCINATED PEOPLE, THE INFECTION SPREADS RAPIDLY.

HISTORY OF VACCINE DEVELOPMENT

In 7th century India Buddhist monks used to drank snake venom in order to develop immunity against snake bites.

Variolation, the practice of inoculating the dried pustules of smallpox into a healthy individual, to prevent the in Central Asia in the second millennium. Which then spread east to China and West to Turkey, Africa, and Europe.

In 1798, in England, Edward Jenner inoculated the cowpox virus, Variolae vaccinae, to prevent smallpox in humans.

At the end of the 19th century, Louis Pasteur demonstrated of disease-causing organisms could be weakened (or attenuated) in the laboratory. He first demonstrated the effectiveness of vaccines against chicken cholera and anthrax in animals, and developed vaccine against rabies for use in humans in 1885.

In 1886, in the US, Daniel Elmer Salmon and Theobald Smith demonstrated that vaccines could be produced also from killed disease-causing organisms.

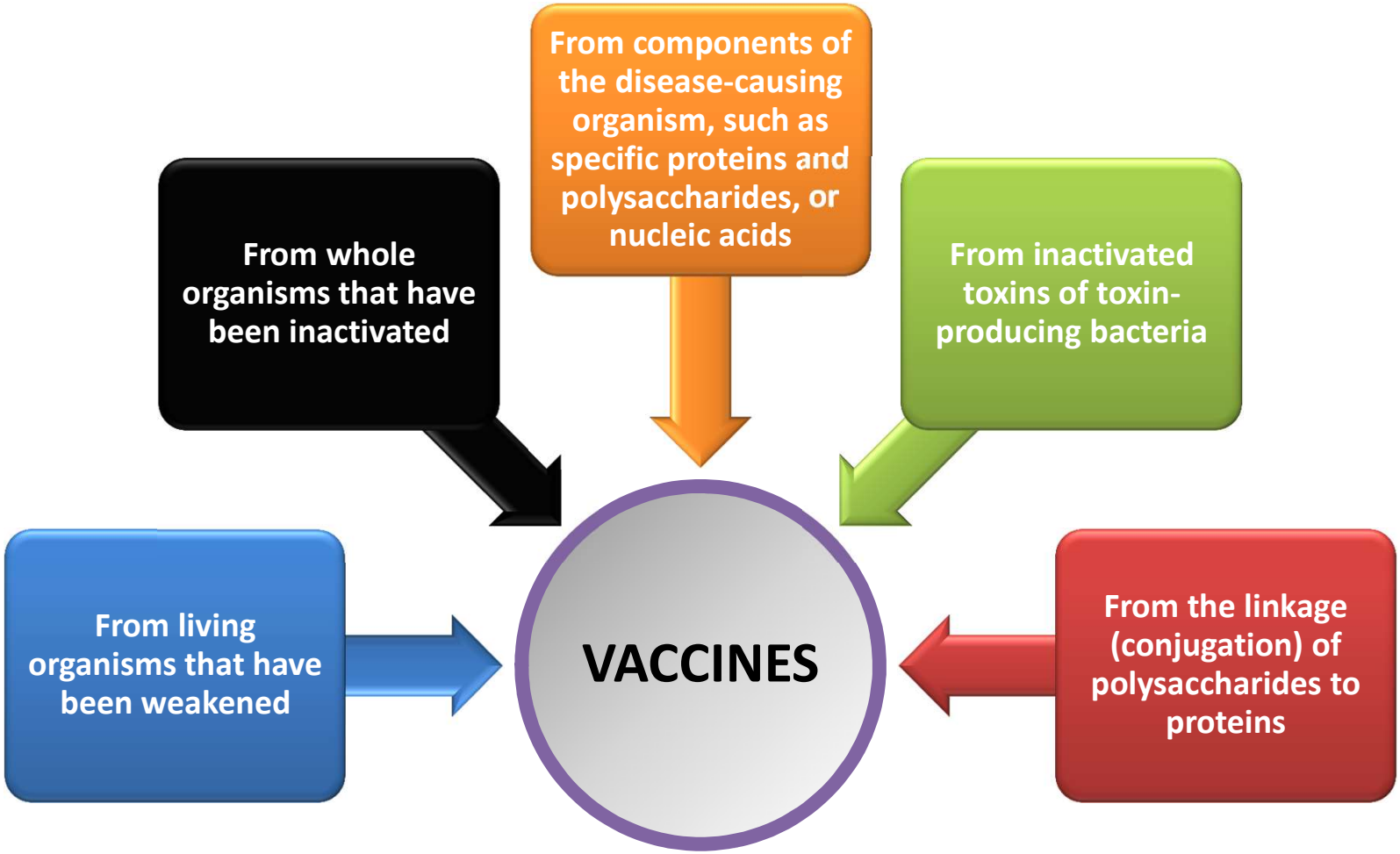
In the early 20th century inactivated toxins were developed as vaccines (toxoids).

By the end of the 20th century several new methods of producing vaccines including by recombinant organisms, by conjugation of polysaccharides to carrier proteins, and by the assembly of virus-like particles.

ACTIVE AND PASSIVE IMMUNIZATION

- Active immunization involves the administration of an immunogen to render the host more responsive to a subsequent encounter.
- Passive immunization involves the transfer of immune components, such as antibodies or lymphocytes, or of immune-cell-producing tissues.

VACCINES ARE COMPOSED OF EITHER THE ENTIRE DISEASE-CAUSING MICROORGANISM OR SOME OF ITS COMPONENTS.



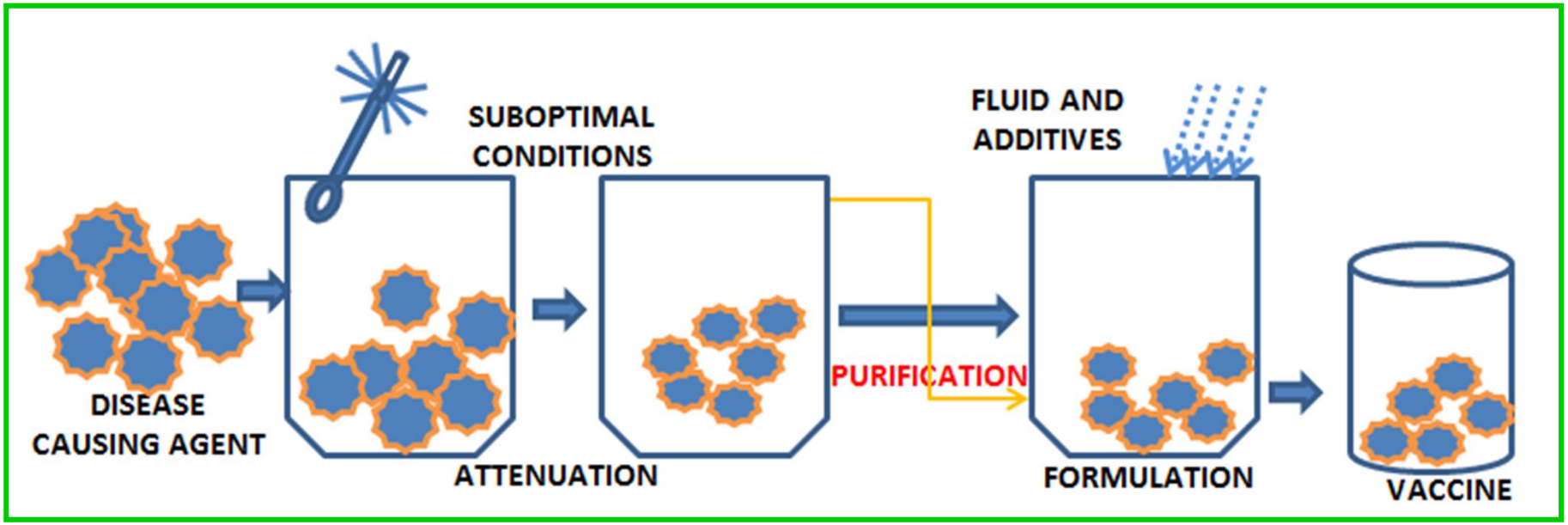
S.NO.	TYPE OF VACCINE	EXAMPLE
1.	LIVE, ATTENUATED VACCINES	BCG , Oral Polio Vaccine, Measles, Rotavirus, Yellow Fever
2.	KILLED OR INACTIVATED VACCINES	Whole Cell Pertusis, Inactivated Polio Virus.
3.	TOXOIDS/ TOXOID VACCINES	Tetanus Toxoid, Diphtheria Toxoid.
4.	SUBUNIT VACCINES	Acellular pertussis vaccine and influenza vaccine the human papillomavirus (HPV) vaccine, Hepatitis B vaccines
5.	POLYSACCHARIDE VACCINES	Meningococcal disease caused by Neisseria meningitidis groups A, C, W135 and Y, as well as Pneumococcal disease.
6.	CONJUGATE SUBUNIT VACCINES	Meningococcus, Haemophilus influenzae type b (Hib)
7.	PLANT BASED VACCINES	Avian influenza vaccine in transgenic tobacco (Medicago), and Ebola Vaccine in transgenic tobacco (under trails)
8.	DNA VACCINES	Melanoma, HIV,CMV, Cancer, HBV (uder trail)
9.	DENDRITIC CELL (DCS) VACCINES	Sipuleucel-T designed for the treatment of prostate cancer

LIVE, ATTENUATED VACCINES

- Live attenuated vaccines are often modified forms a disease-producing (virulent) virus or bacterium.
- Small dose of these vaccines are required to develop an appropriate immune response.
- Conditions such as light and heat which can damages the live organism or inhibits the division of the organism in the body (antibodies)can make the vaccine ineffective.

ATTENUATED VACCINES CONTD....

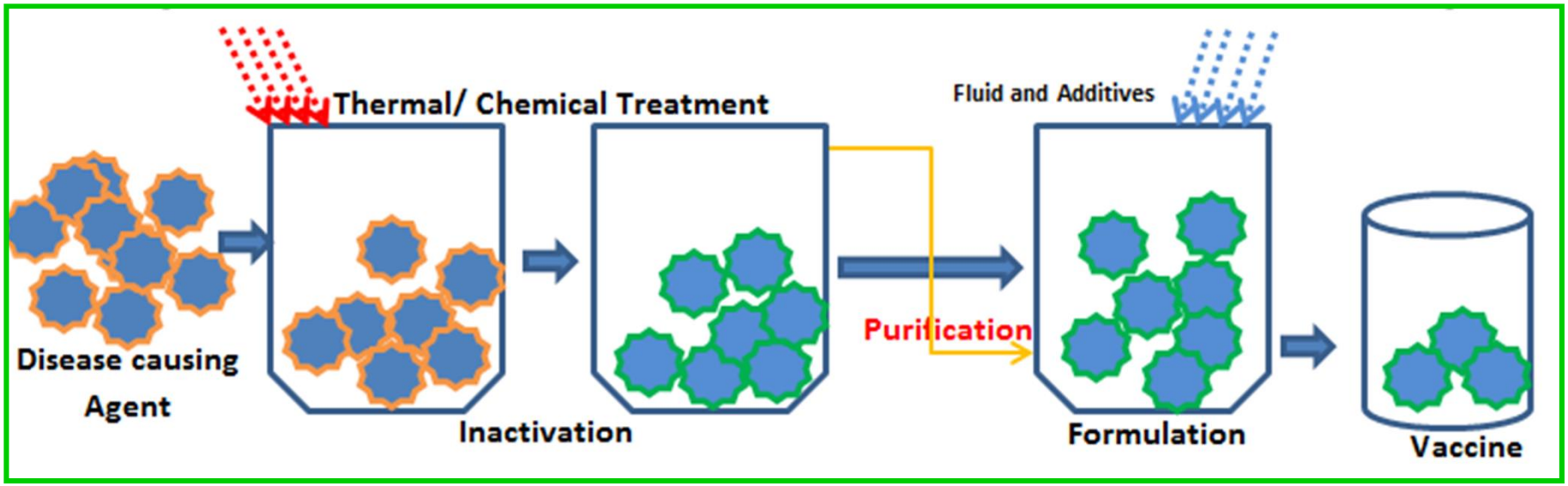
- The most common method used for attenuation of viruses involves growing them in a series of cell cultures or animal embryos (mostly chick embryos).
- With each passage in different embryos, the virus starts replicating with better efficiency in the chick cells than in human cells.
- This form of the virus is still immunogenic in humans, suitable to be used



LIVE ATTENUATED VACCINES	
BENEFITS	Immune response is similar to natural infection Not recommended for use in immune-compromised individuals and pregnant women. • Activate both humoral and cell-mediated immunity. • Life-long immunity possible after 1 or 2 doses
LIMITATIONS	• Have low storage life and heat labile • May revert to natural form(e.g. poliovirus)
EXAMPLES	Vaccines for Measles, mumps, rubella, varicella, rotavirus, herpes zoster, influenza, oral poliovirus (OPV), yellow fever .

KILLED OR INACTIVATED VACCINES

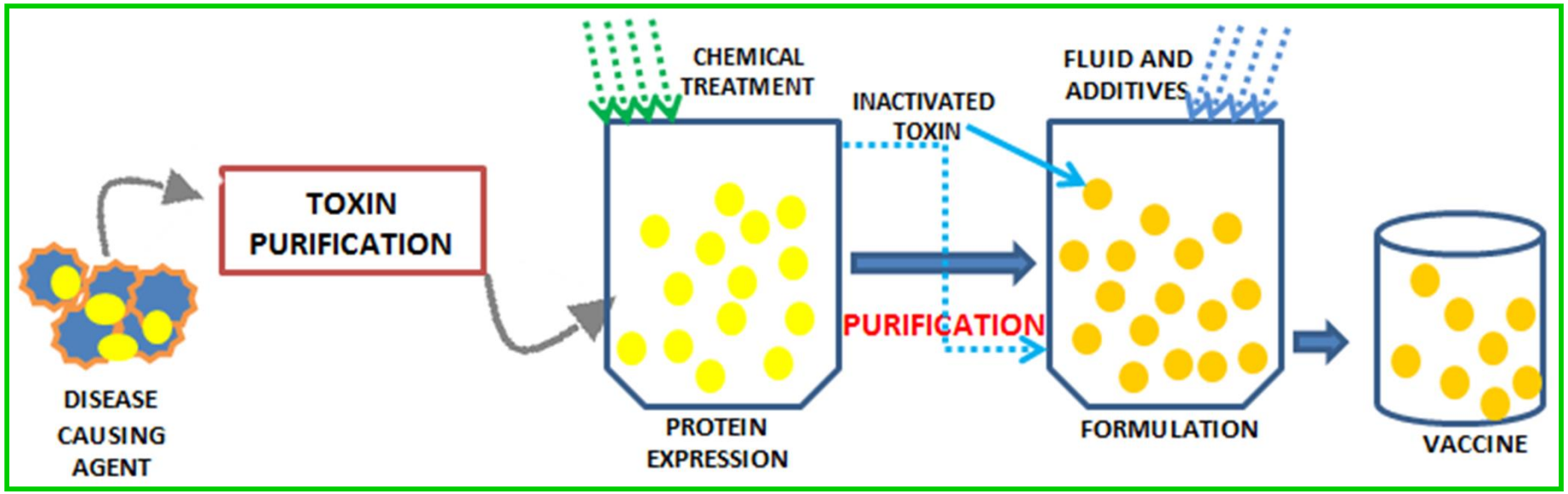
- These contain killed or inactivated pathogen.
- The inactivation is done by using heat or chemicals such as formaldehyde or formalin
- During inactivation the infectious agent remains immunogenic but loses its ability to replicate.
- These inactivated strains can't revert to a more virulent form capable of causing disease.
- These vaccines generate only shorter length of protection as compared to live vaccines, usually require boosters for inducing long-term immunity.
- Examples: inactivated polio vaccine and influenza vaccine (in shot form).



INACTIVATED VACCINES	
BENEFITS	These are highly stable Impact on carriage There is no replication of the inactivated pathogen Safe for use in immunocompromised individuals and pregnant women
LIMITATIONS	• Limited immunogenicity, adjuvants may be required • Multiple primary and booster doses required to obtain long-term protection
EXAMPLES	Whole-cell pertussis , hepatitis A , rabies, Japanese encephalitis , cholera

TOXOIDS

- Some bacterial diseases are caused by toxins produced by the bacterium and vaccines made from inactivated toxins are called toxoids.
- Toxoids contain an inactivated toxin of bacteria.
- Inactivation is accomplished by treatment formalin, or by using heat or other methods.
- Example is tetanus: which is caused by a neurotoxin (tetanospasmin) produced by **Clostridium** *tetani*..



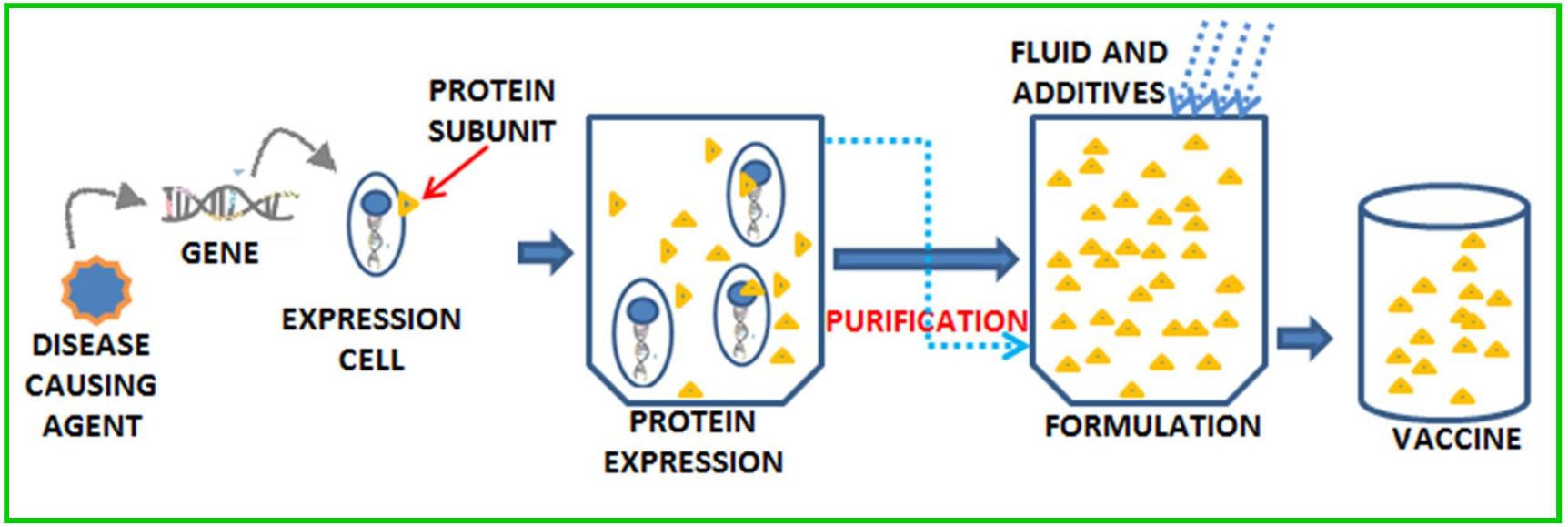
TOXOID VACCINES	
BENEFITS	Vast experience as mature technology Non-infectious Used as carrier proteins due to good immunogenicity
LIMITATIONS	• Toxoids can target the toxin not the the pathogen • No herd protection • Priming and boosting necessary
EXAMPLES	Tetanus, diphtheria, acellular pertussis (as part of DTaP combination vaccines Boostrix, Infanrix, Adacel, etc.)

SUBUNIT VACCINES

- Only a specific protein from a pathogen is isolated and presented as antigen on its own to provoke an immune response. Examples : **acellular pertussis vaccine** and **influenza vaccine** are examples of such subunit vaccines.
- Sub unit vaccines can also be made by genetic engineering e.g., **the human papillomavirus (HPV) vaccine.**
- There are two types of HPV vaccine one against two strains of HPV and the other against four.
- From these two strains , a single viral protein is isolated, expressed, and finally packaged as virus-like particles (**VLPs**) .
- As these VLPs are devoid of genetic material they can't cause illness, but are immunogenic. This is the basis of future protection against HPV.

SUBUNIT VACCINE VIA GENETIC ENGINEERING

- A gene that codes for a viral antigenic protein is inserted into a carrier virus, or into producer cells in culture.
- The viral antigenic protein is produced in the carrier virus as it divides, or in the metabolizing producer cell.
- The results in a recombinant vaccine: the expressed protein will be immunogenic and will activate immune response towards future protection against the target virus.
- Example of recombinant subunit vaccine is the Hepatitis B vaccine.



SPLIT AND SUBUNIT PROTEIN VACCINES (NATURAL OR RECOMBINANT)	
BENEFITS	• Non-infectious • Low reactogenicity
LIMITATIONS	• Non-infectious • No or limited innate defence triggers • Less immunogenic than whole pathogen vaccines • For vaccines with low immunogenicity often adjuvants are required.
EXAMPLES	Influenza, acellular pertussis, hepatitis B, human papillomavirus , meningococcal B malaria , herpes zoster .

POLYSACCHARIDE VACCINES

- Some bacteria are protected by a polysaccharide capsule that helps the organism evade the human defence systems especially in infants and young children.
- Polysaccharide vaccines create a response against the molecules in the pathogen's capsule.
- These molecules are small, and often not very immunogenic. As a consequence they tend to not be effective in infants and young children (under 18–24 months),
- Induce only short-term immunity (slow immune response, slow rise of antibody levels, no immune memory).
- Examples of polysaccharide vaccines include Meningococcal disease caused by Neisseria meningitidis groups A, C, W135 and Y, as well as Pneumococcal disease.

POLYSACCHARIDE VACCINES	
BENEFITS	• target can be easily identified.
LIMITATIONS	• Weak immunogens, activate only a transient antibody response thus provide protection for limited period. • Limited immunogenicity in infants • There is a decrease in response after succesive doses, • There is almost no impact on carriage
EXAMPLES	Pneumococcal polysaccharide vaccine, meningococcal polysaccharide vaccine .

CONJUGATE VACCINES

- Conjugate vaccines are similar to recombinant vaccines and are made by combination of two different components.
- Coats of bacteria which have been chemically linked to a carrier protein is used as a vaccine.
- The piece of bacterial coat combined with a carrier protein can generate immunity against future infection.
- Examples are vaccines for pneumococcal bacterial infections for use in children are made using this technique.

POLYSACCHARIDE CONJUGATE VACCINES	
BENEFITS	Increased immune response leading to more protection in kids. Provide longer duration of protection as compared to polysaccharide vaccines due to B-Cell and T-cell responses. Impact on carriage and transmission.
LIMITATIONS	• Boosters doses may be required to produce long term protection.
EXAMPLES	Meningococcal C , ACWY, pneumococcal conjugate vaccine , Haemophilus influenzae type b.

PLANT BASED VACCINES

- These vaccines are produced in a plant through genetic engineering and have a higher therapeutic value to treat many human and animal diseases.
- The target sequence of the selected antigen is integrated with the vector before being transferred into the expression system.
- The transgene is then expressed in the plants either through a stable transformation system or through transient transformation system, depending on the location where the transgene has been inserted in the cells.
- These genes are engineered in such a way that plants can handle the downstream processing of these antigenic proteins.
- These proteins maintain their activity and efficacy, thus contributing to their viability as subunit vaccines.

PLANT-BASED VACCINES CONTD.....

- Although many plant-based vaccines such as Avian influenza vaccine in transgenic tobacco (Medicago), and Ebola Vaccine in transgenic tobacco have been produced but these are still under clinical trials [L. Faye and V. Gomord, 2010; M. McCarthy, 2014.].
- Till today, there is no plant made vaccine that has been approved to be marketed for human consumption.
- Generally, three main challenges in production and usage of these vaccines are
  - the selection of antigen and plant expression host,
  - consistency of dosage, and
  - manufacturing of vaccines according to Good Manufacturing Practice (GMP) procedures.

DNA VACCINES

- DNA vaccines use DNA sequences coding for a particular antigen.
- These DNA sequences are directly inject in the muscle of the individual being vaccinated.
- The DNA after binds itself into the host cells results in the production of the antigen from the infectious agent. This antigen being foreign elicits an immune response.
- These vaccines can be easily produced, as the DNA is highly stable and easy to make copies.
- Till date no DNA-based vaccines have been shown to elicit substantial immune response required to prevent infection.
- DNA vaccines may be good candidates vaccines against parasitic diseases such as malaria. However, currently, there is no human vaccine in use against a parasite.

DNA VACCINES

Advantages

- Defined composition
- Non-replicating platform capable of inducing T-cell immunity
- Potential application in development of therapeutic vaccines
- Construct may code for multiple epitopes and also inducers of innate immune responses

Disadvantages

- Poor immunogenicity in humans
- Concerns/issues regarding potential for construct to integrate with
- host genome

DENDRITIC CELL (DCs) VACCINES

- Monocytes from the blood (in most cases from the individual who will receive the vaccine) are used to produce immature DCs in vitro.
- The monocytes are loaded with antigen and induced to mature into APCs and then infused back into the patient.
- The first DC vaccine, designed for the treatment of prostate cancer, was licensed in 2010 (Sipuleucel-T).
- DC vaccines offer an personalized approach towards development of therapeutic vaccine and represent a specialised method of vaccination that is currently limited to aggressive cancers, and the treatment of serious, intractable infections.

ADVANTAGES AND DISADVANTAGES OF DC VACCINES

Advantages :

- Individualised approach to therapeutic vaccine development
- Can induce potent T-cell responses
- Clinical responses can be achieved

Disadvantages:

- Expensive (these vaccines typically use autologous DCs) with
- sophisticated logistics
- Mature DCs rapidly lose viability and function after injection
- Difficult to achieve clinically sufficient levels of circulating antigen-specific Tcells.

COMPONENTS OF A VACCINE

- Vaccines include a variety of ingredients including antigens, stabilizers, adjuvants, antibiotics, and preservatives.
- They may also contain residual by-products from the production process.
- Knowing the precise composition of each vaccine can be helpful when investigating adverse events following immunization (AEFIs) and for selecting alternative products persons with allergies or who have had an adverse event known or suspected to be related to a vaccine component.

COMPONENTS OF A VACCINE

- ANTIGENS are the components derived from the structure of disease-causing organisms, which are recognized as 'foreign' by the immune system and trigger a protective immune response to the vaccine.
- STABILIZERS are used to help the vaccine maintain its effectiveness during storage. Stabilizing agents include $MgCl_2$ (for OPV), $MgSO_4$ (for measles), lactose-sorbitol and sorbitol-gelatine.
- ANTIBIOTICS Trace amounts appear in vaccines, for example, MMR vaccine and IPV each contain less than 25 micrograms of neomycin per dose (less than 0.000025 g). Persons who are known to be allergic to neomycin should be closely observed after vaccination so that any allergic reaction can treated at once.

COMPONENTS OF A VACCINE contd...

- PRESERVATIVES are added to multidose vaccines to prevent bacterial and fungal growth for example Thiomersal, Formaldehyde, or Phenol derivatives
- ADJUVANTS are a highly heterogeneous group of compounds which enhance the immune response. There are several hundred different types of adjuvants that are being used or studied in vaccine technology

EXAMPLES OF ADJUVANTED VACCINES

S.No.	Adjuvanted Vaccine	Type of Adjuvant
1.	Hepatitis A	Aluminium salt
2.	Hepatitis B	Aluminium salt
3.	Diptheria, Tetanus, acellular Pertusis, combinations (DTap or Tdap)	Aluminium salt
4.	Haemophilus influenza type b (Hib)	Aluminium salt
5.	Human Papilloma Virus	Aluminium salt or ASO4 (aluminium salt and monophospholipid A).
6.	Pneumococcal conjugate	Aluminium salt
7.	Japanese encepphalitis	Aluminium salt
8.	H1N1 influenzae	MF 59 (oil in water emulsion)

From VACCINE FACT BOOK 2012

AN IDEAL VACCINE SHOULD BE ....

GOOD IMMUNE RESPONSE

- Both Cell Mediated Immunity and antibody responses.
- Immunity is long lived
- Single dose

SAFETY

- Danger of reversion to virulence, or Severe disease in immuno-comprised

STABILITY

- Organisms in the vaccine must remain viable in order to infect and replicate in the host
- Vaccine preparations are therefore very sensitive to adverse storage conditions

EXPENSE

- Cheap to prepare

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To be continued.....