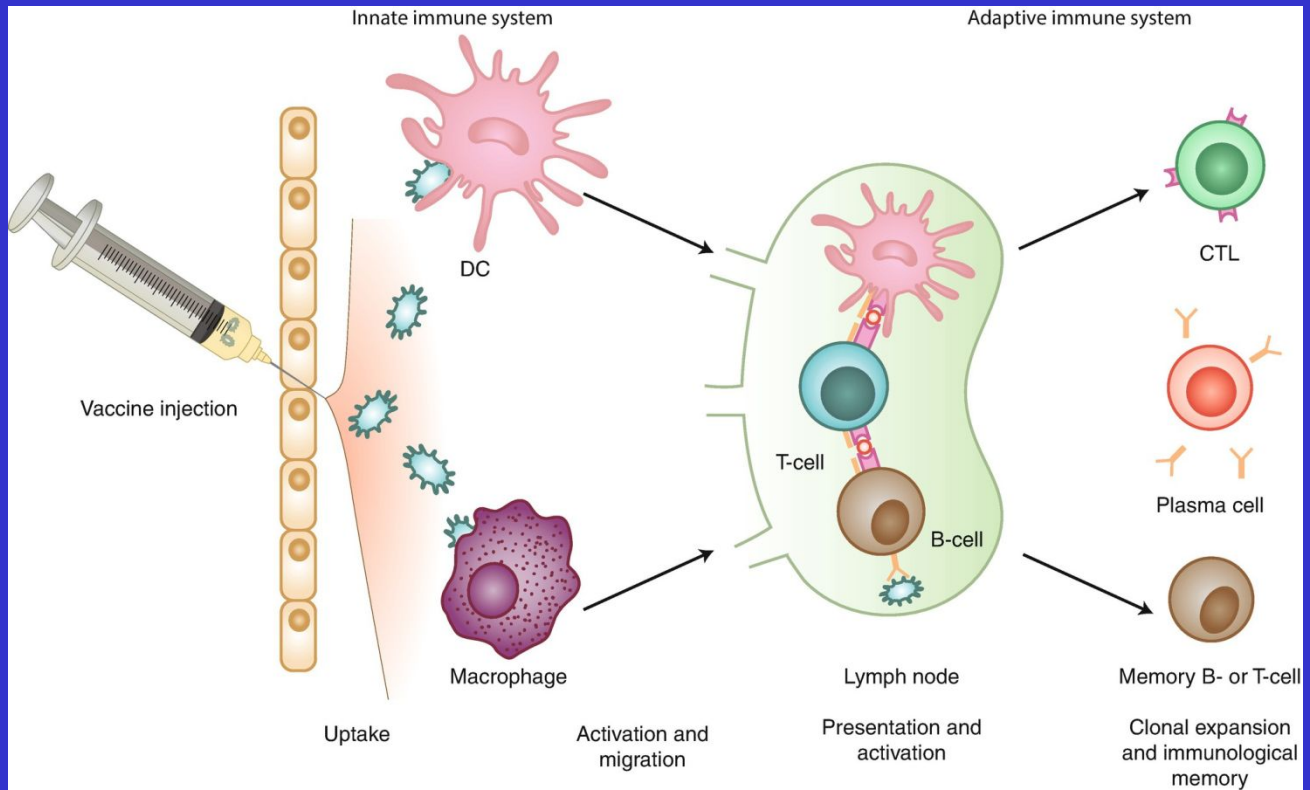
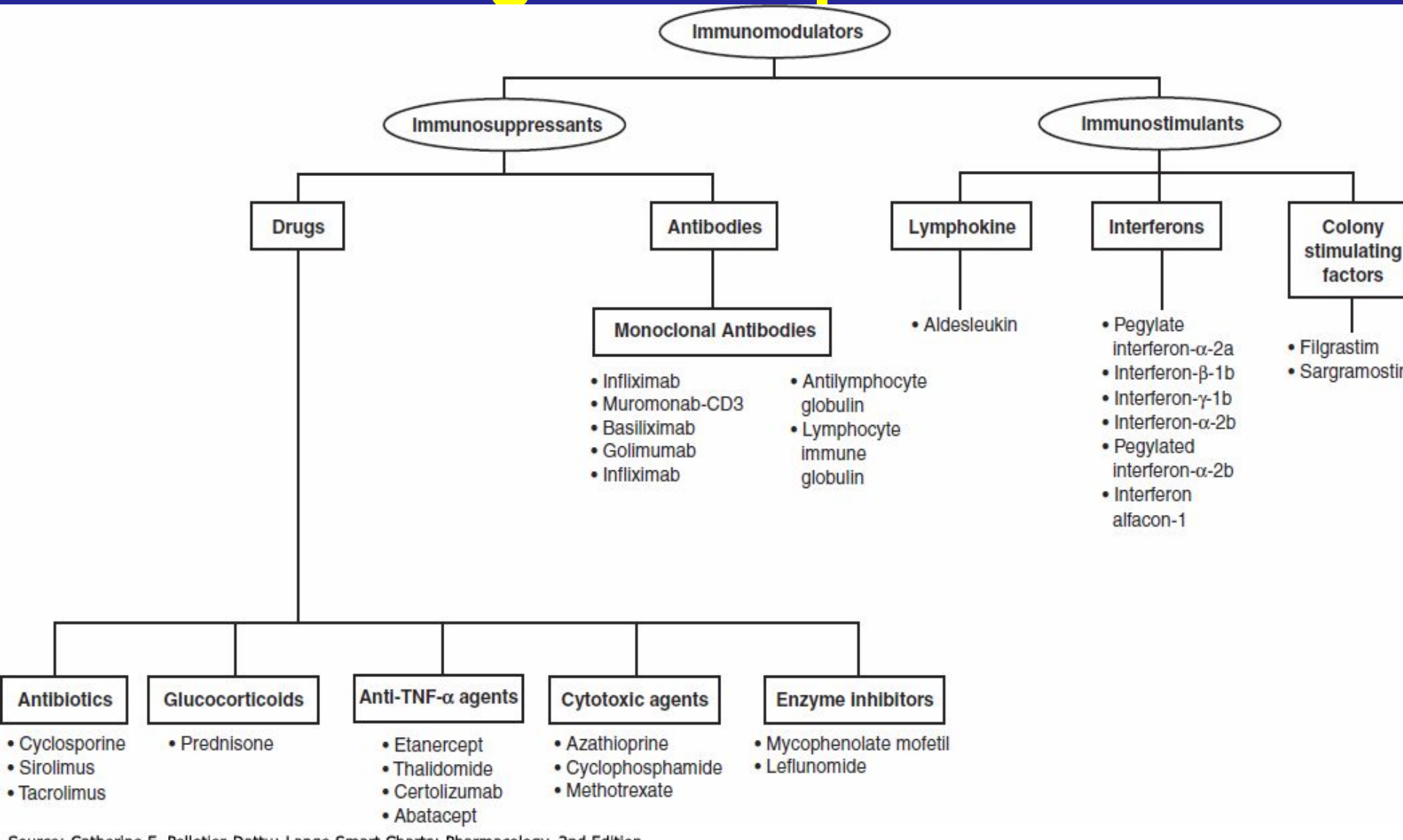
Lecture 8
Immunological preparations in Immunotherapy& Immunoprophylaxis



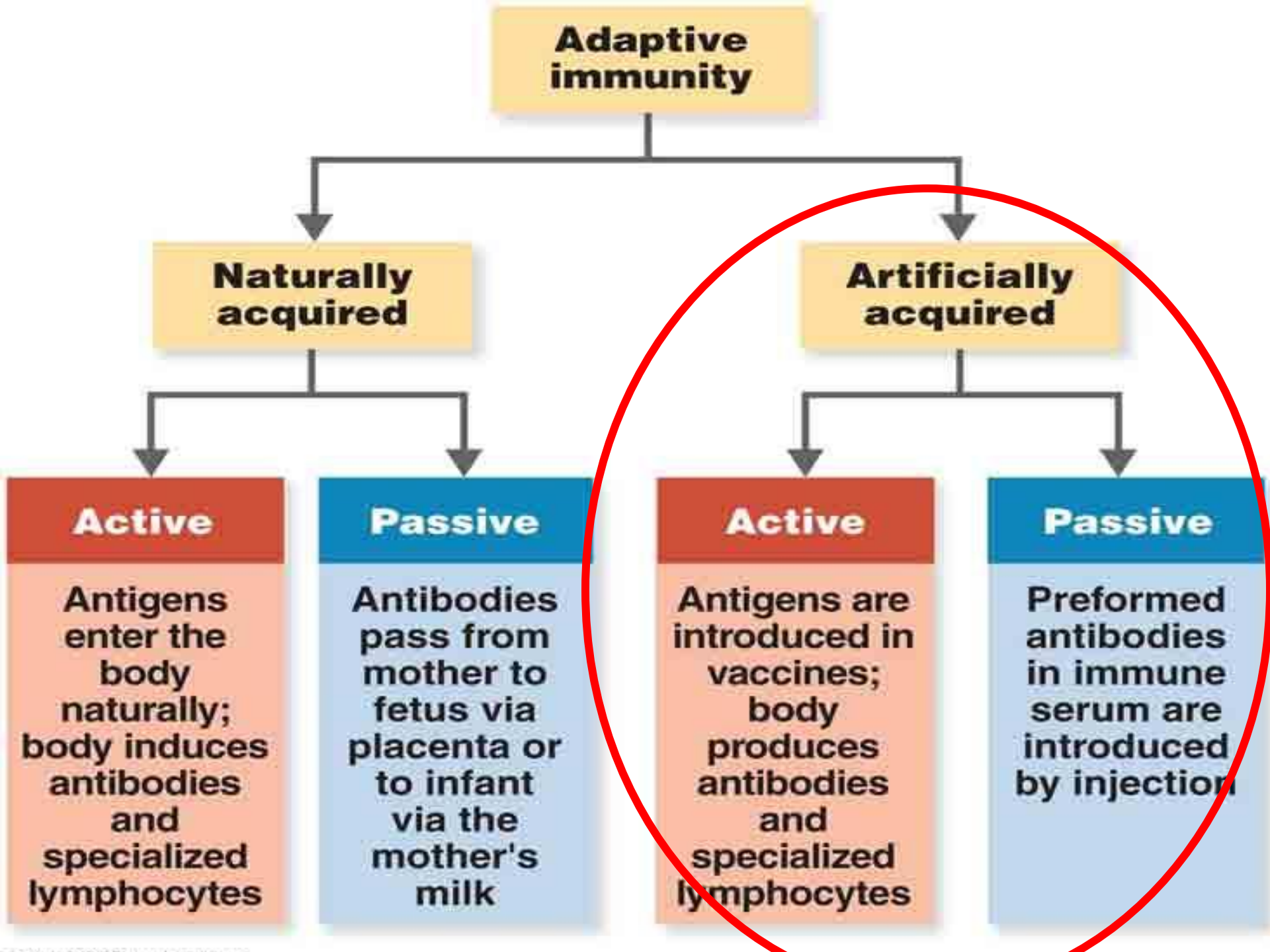
Immunological preparations: antigen-independent



Immunological preparations: antigen dependent

-Vaccines (antigens)

-Immune sera or Immunoglobulins


Adaptive immunity
Naturally acquired
Artificially acquired
Active
Passive
Active
Passive
Antigens enter the body naturally; body induces antibodies and specialized lymphocytes
Antibodies pass from mother to fetus via placenta or to infant via the mother's milk
Antigens are introduced in vaccines; body produces antibodies and specialized lymphocytes
Preformed antibodies in immune serum are introduced by injection

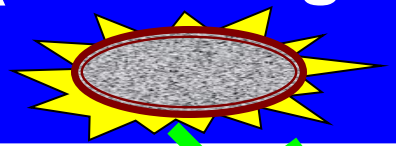
Immunization is the method of controlling infections

Immune responses to immunization or immuno-therapy can block the spread of a bacterium, bacterial toxin, or virus to the target organ.

The immunization of population stops the spread of the infectious agent among a community by reducing the number of susceptible to this infection individuals. Such immunization develops **herd immunity** (national and international levels).

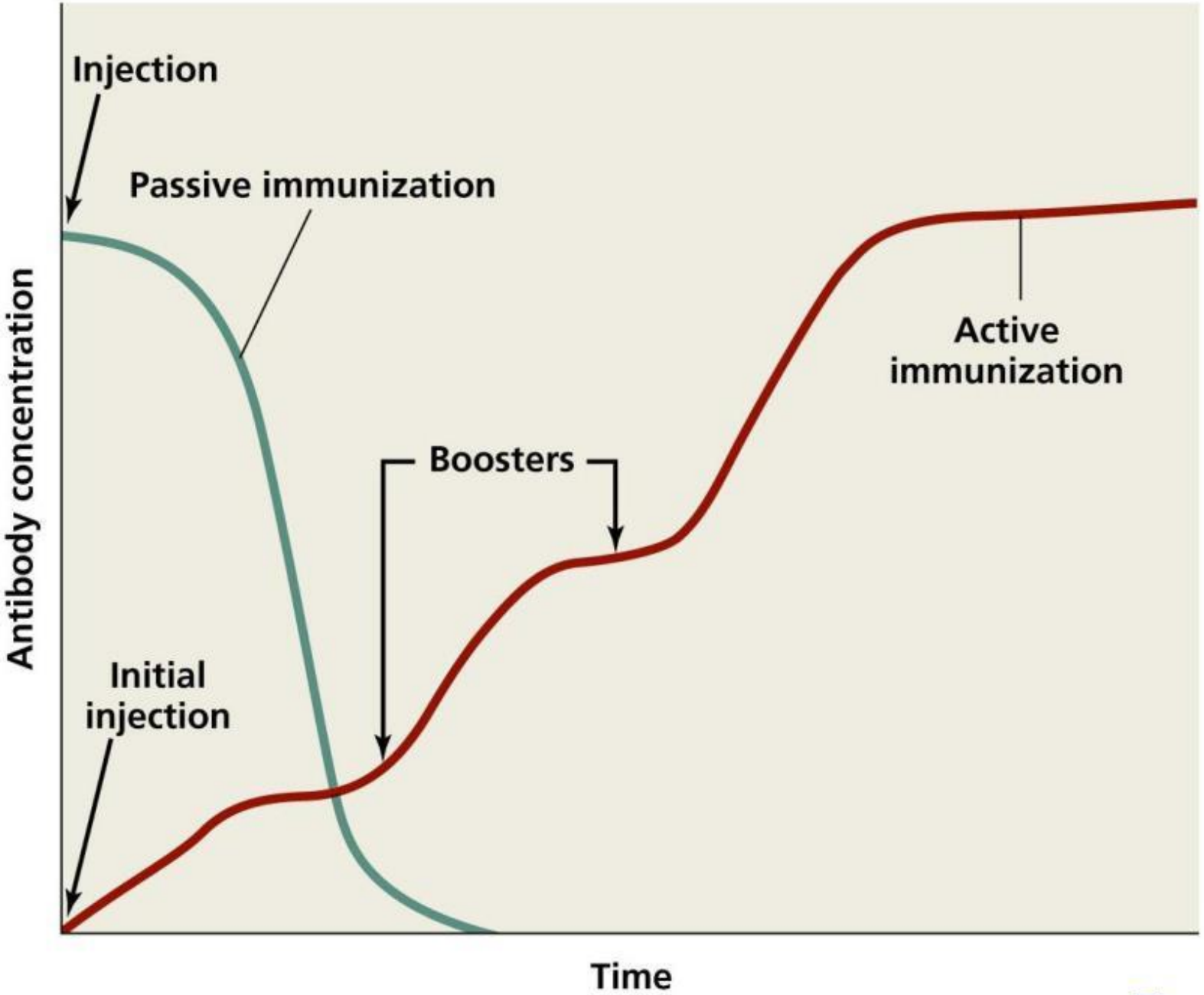
Immunization has succeeded in protecting of popu-lation from the symptoms of *pertussis*, *diphtheria*, *tetanus*; in controlling the spread of *measles*, *mumps*, *rubella*, and in eliminating *smallpox* in the whole world and *poliomyelitis* in

Types of immunization

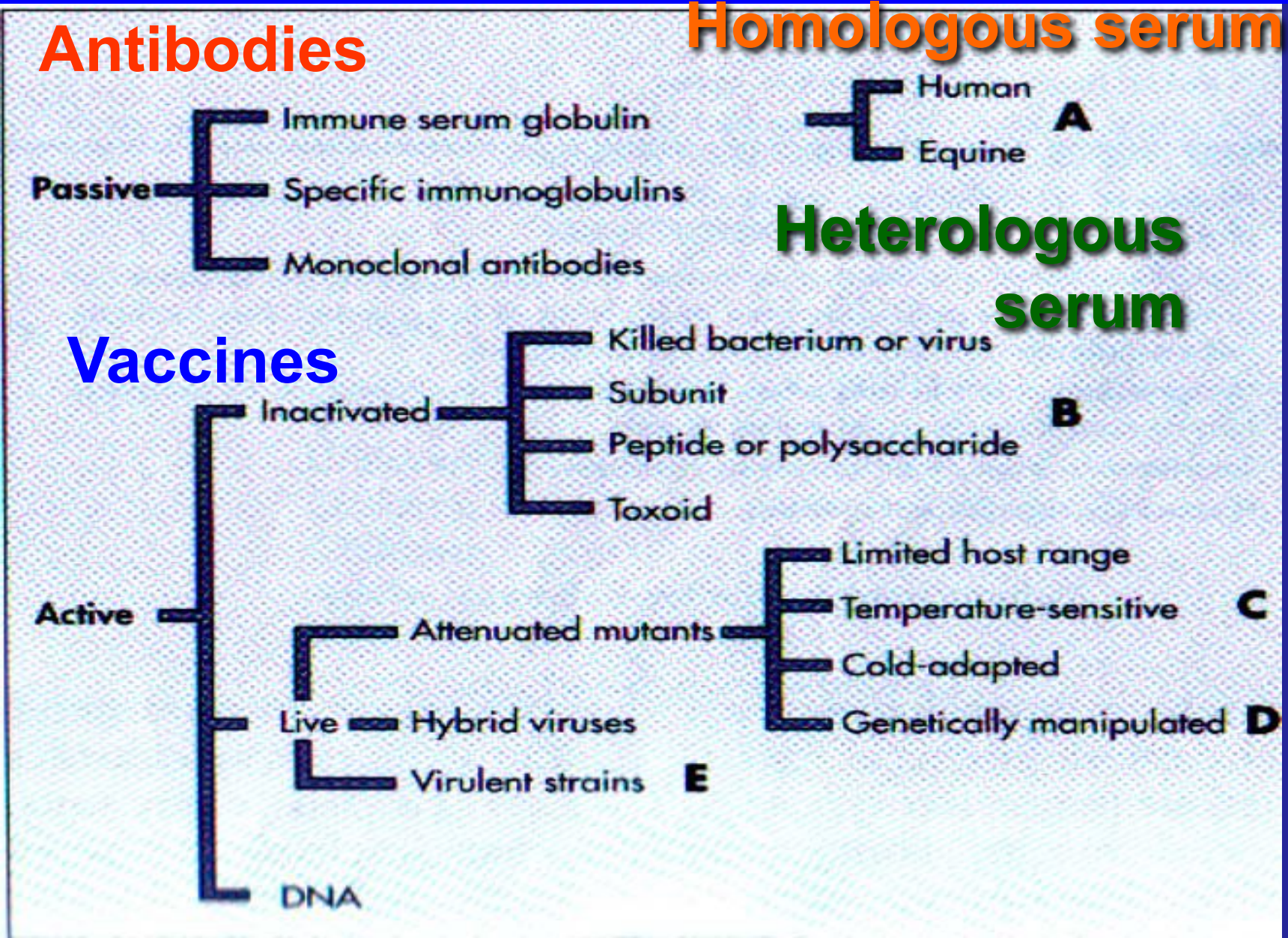
Type	Method	Goal
Active	Challenge with an **antigen** (immunogen) 	**Immune response** and **immunological memory**
Passive	Administration of exogenously produced **antibodies**	**Rapid temporary treatment** or **prevention** of infectious diseases

Combined: active + passive

Passive vs. Active Immunization



Active and Passive immunization



Artificial passive immunization (API)

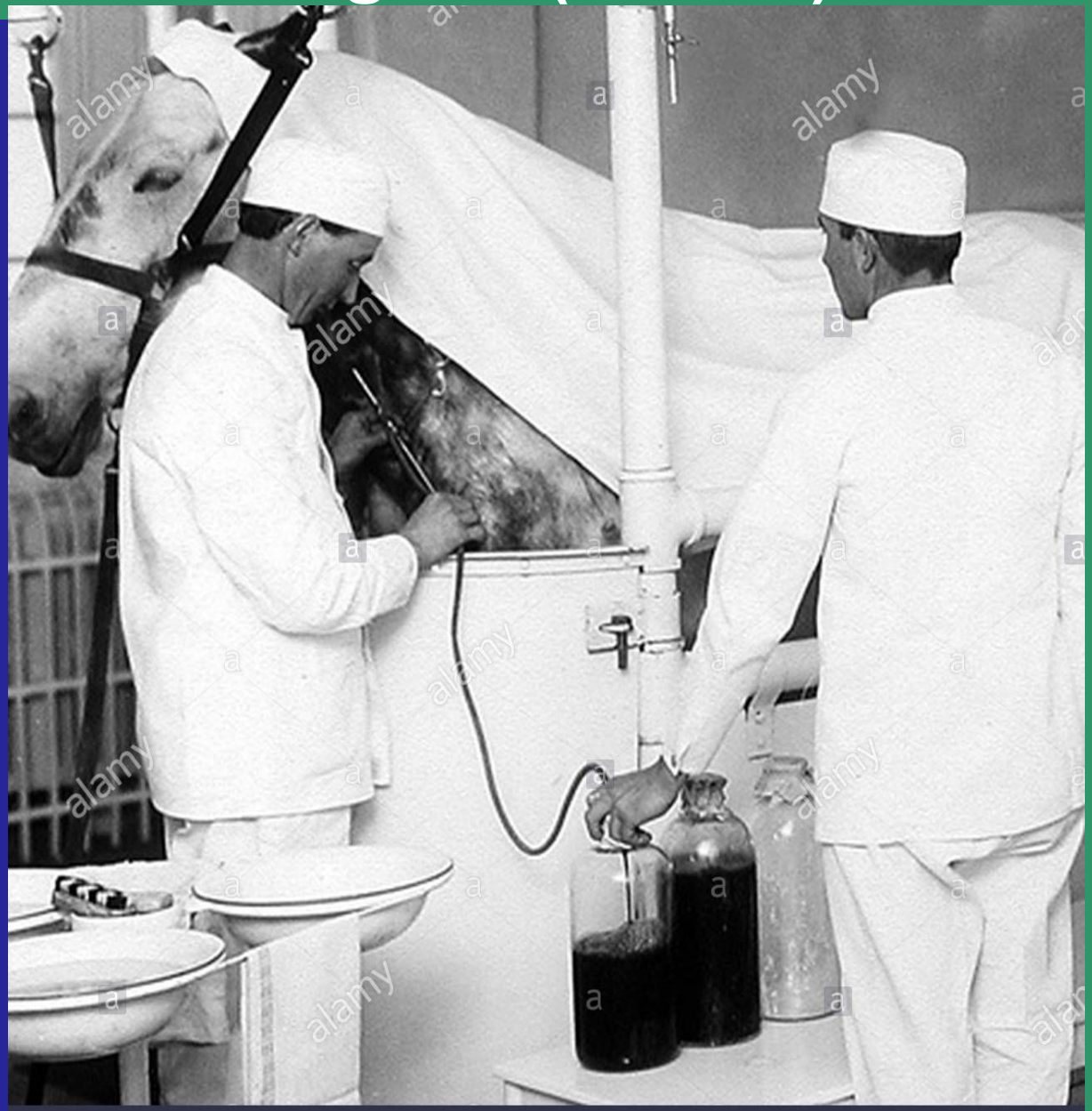
API may be used:

1) To prevent disease **after a known exposure** (needle stick injury with *HBV*-contaminated blood);
2) To protect **immunosuppressed patients**;
3) To **ameliorate the symptoms** of an ongoing disease (*chicken pox* or *measles*);
4) To **block the action of** bacterial **toxins** and pre-vent the disease they cause (*tetanus*, *diphtheria*).

Sources of antibodies:

- Seropositive individuals – donors (homologous);
- Animals, hyperimmunised with antigens (heterologous).

Heterologous (animal) serum: Complications



- ***Hypersensitivity reactions*** **(type I or type III)**

To prevent **these reactions the serum can be given*:***

(1) <u>by portions</u> with 10-15 minutes intervals

(2) <u>i/m</u> (not i/v) to prevent platelets aggregation and complement activation.

Passive immunization: The preparations

Prepara-tion	Manufacture	Source	Prophylaxis of *disease*
Immune serum globulin	**Antitoxins** -hyperimmu-nization with *toxoids*	(1) Equine, human (2) Equine (3) Equine	(1) *Tetanus* (Tlg), (HTIG) (2) *Botulism* (3) *Diphtheria*
	High titer Im-munoglobulin for viruses (pooled plasma from seropositive)	(1) Human (2) Human (3) Equine, human	(1) *Hepatitis B* (HBIG) (2) *Varicella zoster* (VZIG) (3) *Rabies* (Rlg), (HRIG)

Passive immunization: The preparations (1)

Preparation	Manufacture	*Prophylaxis of disease* / Patients
Human serum gamma-globulin 	**Pooled plasma:** normal repertoire of antibodies in an adult; *without hyperimmuni-zation*	•***Common infections*** Immunocompromised •***Chicken pox*** or ***Measles*** Premature infants, Children with malnutrition · ***Hepatitis A*** Post exposure prophylaxis

Passive immunization: The preparations (3)

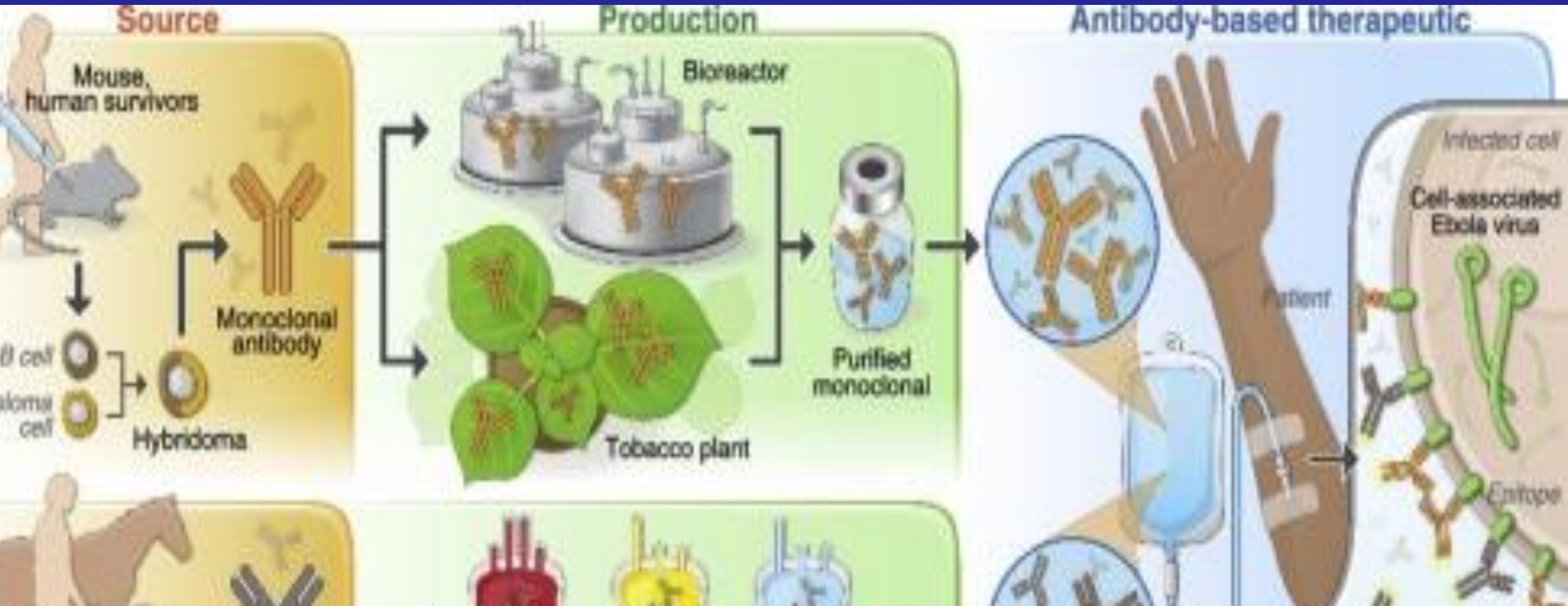
Preparation	Manufacture	*Disease*
Monoclonal antibodies (MCABs)	**Hybrido-ma**	**Cancer** **Viral** **Bacterial** **Hypersensitivity**
Immuno-toxins (ITs) 	**MCAB to tumor-specific antigen (TAg) is *conjugated* with a toxin (*diphtherial*)**	**Tumor:** **(1) The IT *binds with* the TAg on the malignant cell.** **(2) The IT *is uptaken* by the cell and then *released* into cytoplasm.** **(3) Free toxin *blocks protein synthesis* and *causes* the cell death.**

Evolution of Immunoglobulin therapy

Prior to 2014, only convalescent blood products from EHF survivors had been administered to newly infected individuals as a form of treatment.

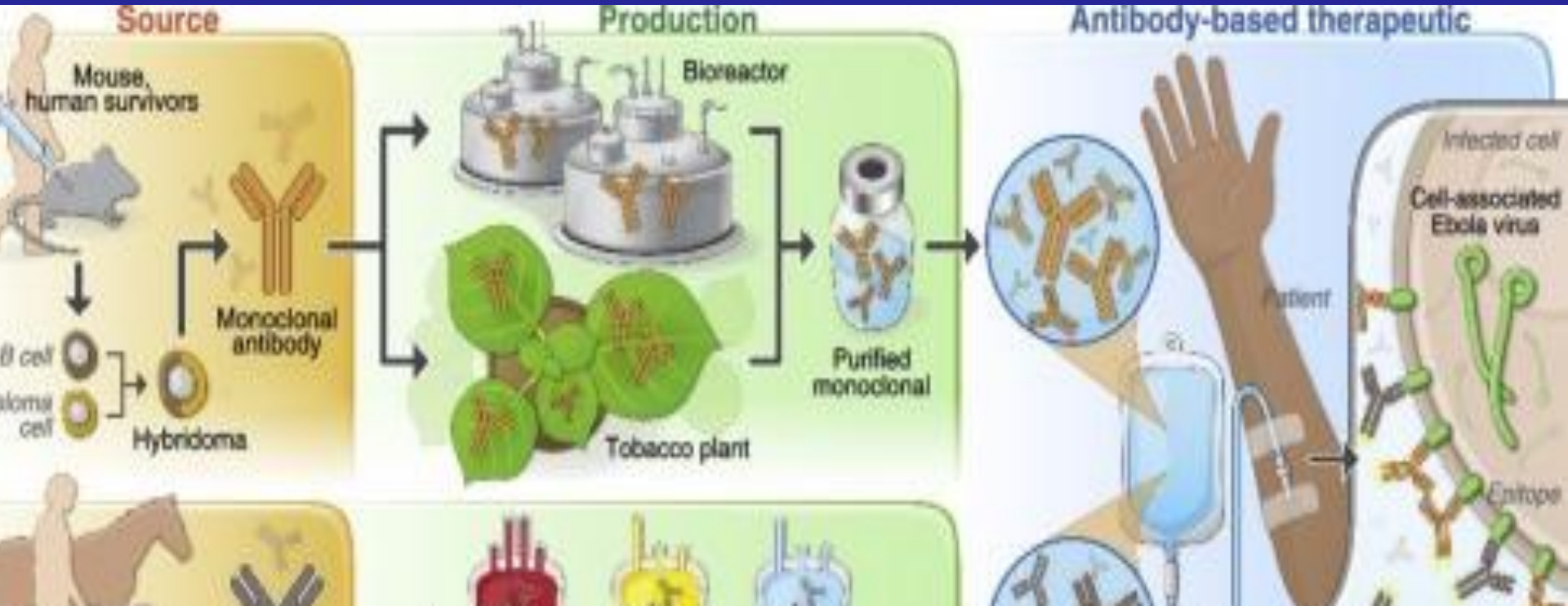
Evolution of Immunoglobulin therapy

The 2014-2016 Ebola virus outbreak in West Africa was the deadliest in history, prompting the evaluation of various drug candidates, including McAb-based therapeutics for the treatment of Ebola hemorrhagic fever (EHF).



Evolution of Immunoglobulin therapy

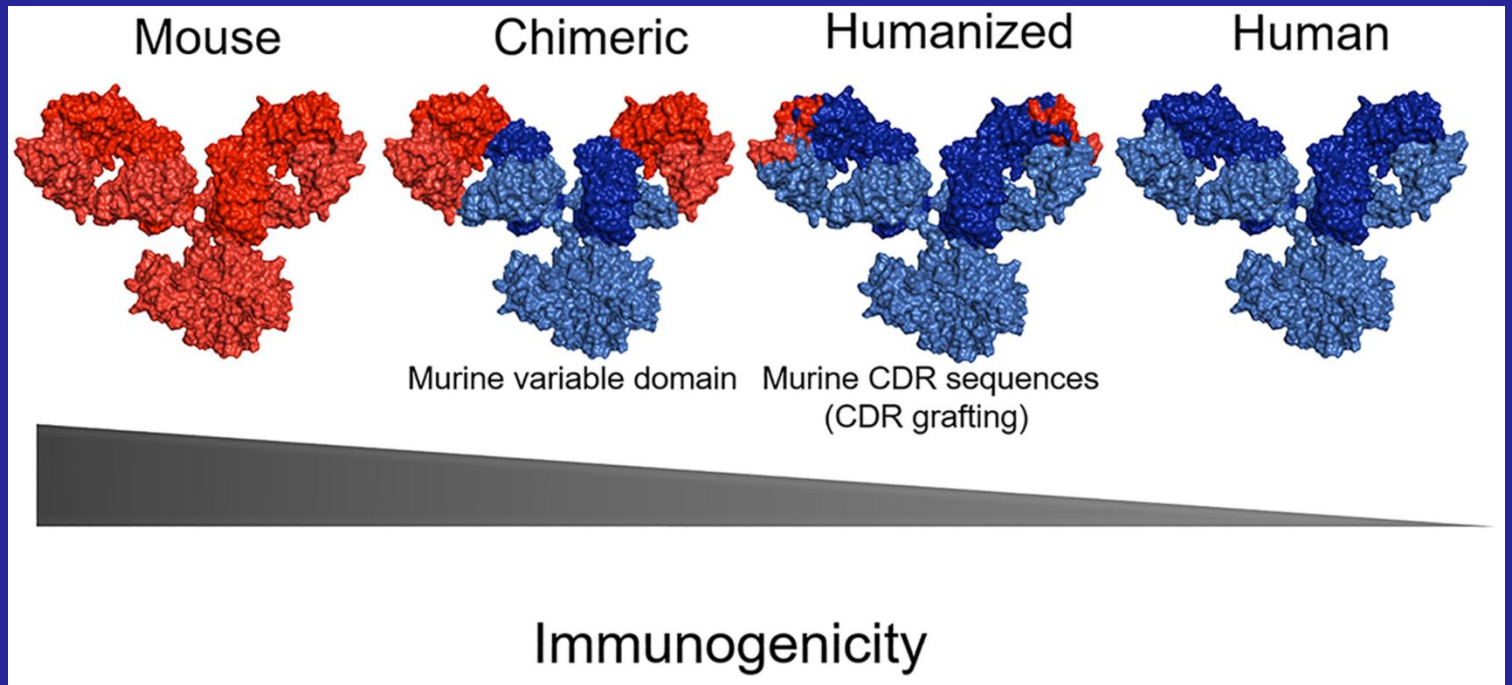
the genes encoding for the antibodies were extracted from the hybridomas, genetically engineered to replace mouse components with human components, and transfected into tobacco plants.



Schematic overview of antibody humanization

- **a** The murine McAb
- **b** The chimeric McAb : variable regions are of murine origin, and the rest of the chains are of human origin.
- **c** Humanized McAb : only includes the hypervariable segments of murine origin.

  d Human monoclonal.



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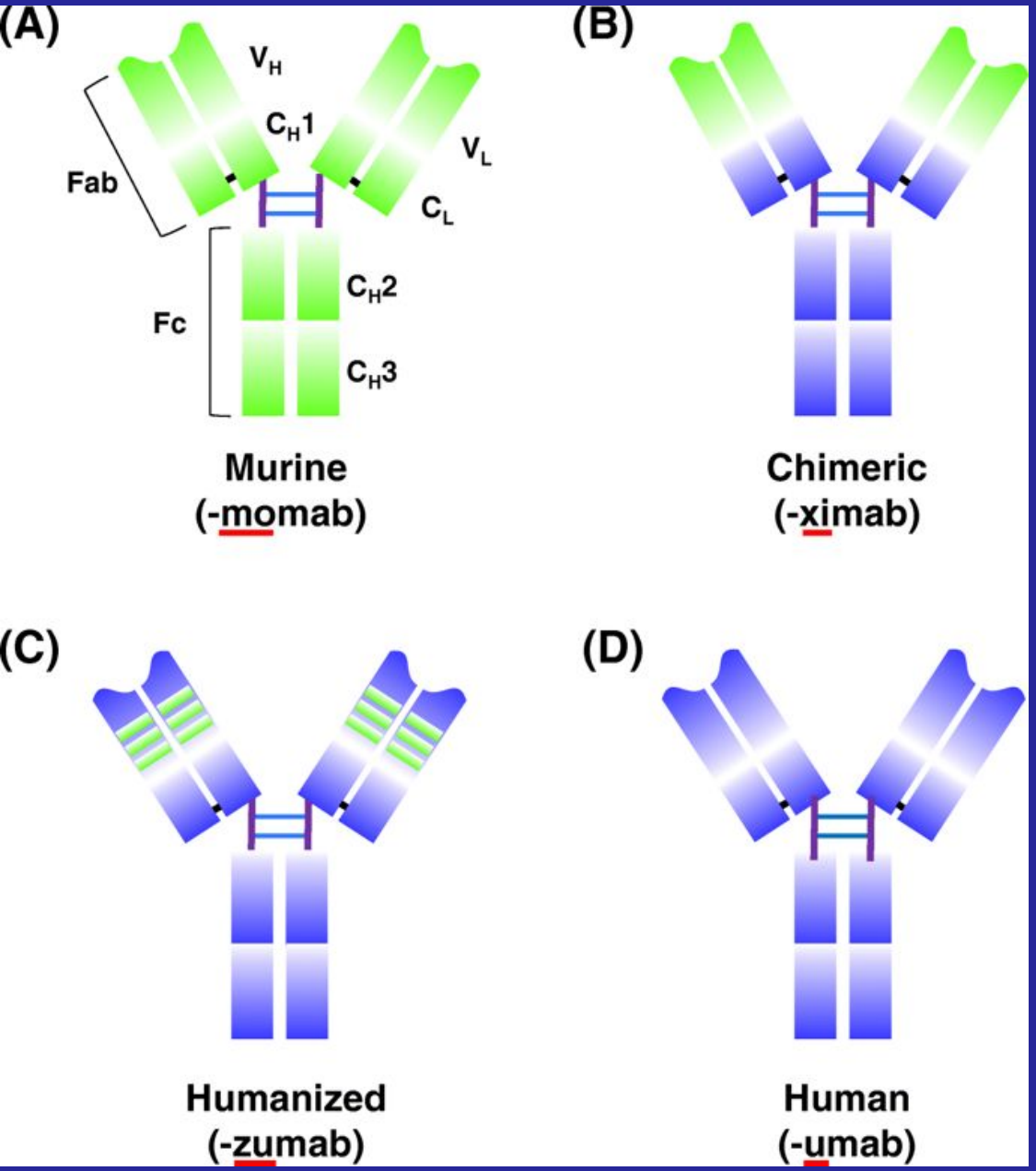


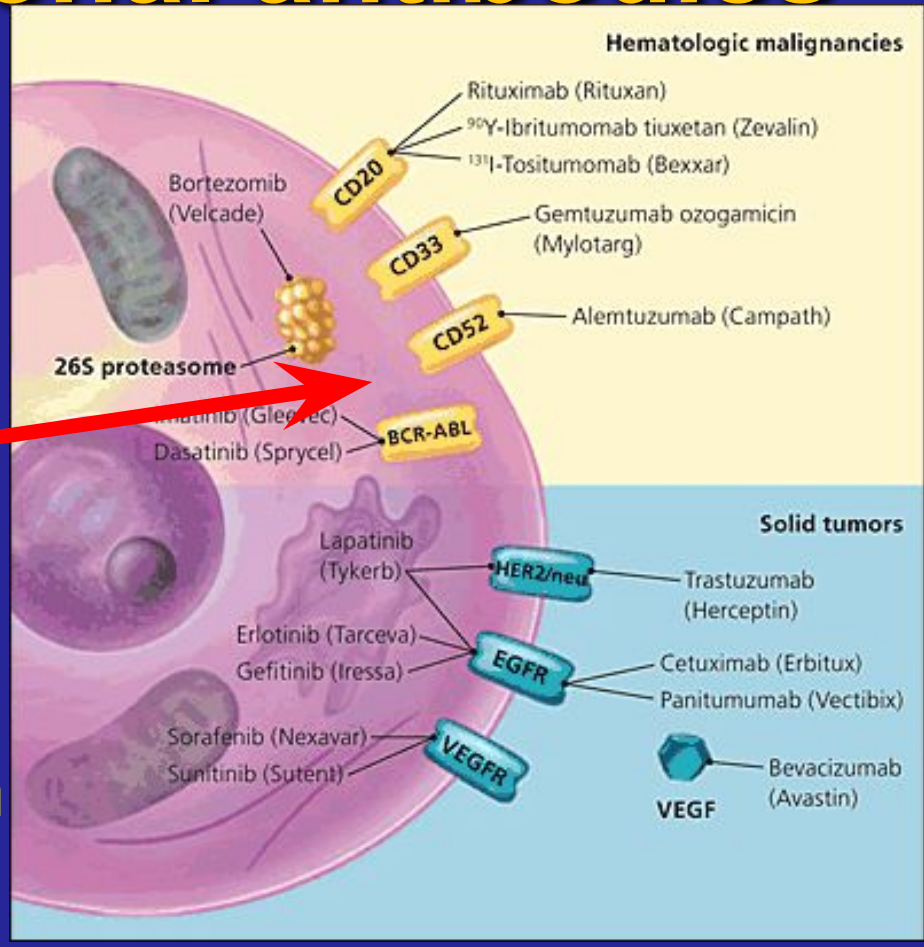
- **a** The murine McAb
- **b** The chimeric McAb variable regions are o murine origin, and the rest of the chains are of human origin.
- **c** Humanized McAb : only includes the hypervariable segments of murine origin.

  d Human monoclonal.

Types of monoclonal antibodies

Naked mAbs are antibodies are the most common type of mAbs used to treat cancer. Examples:

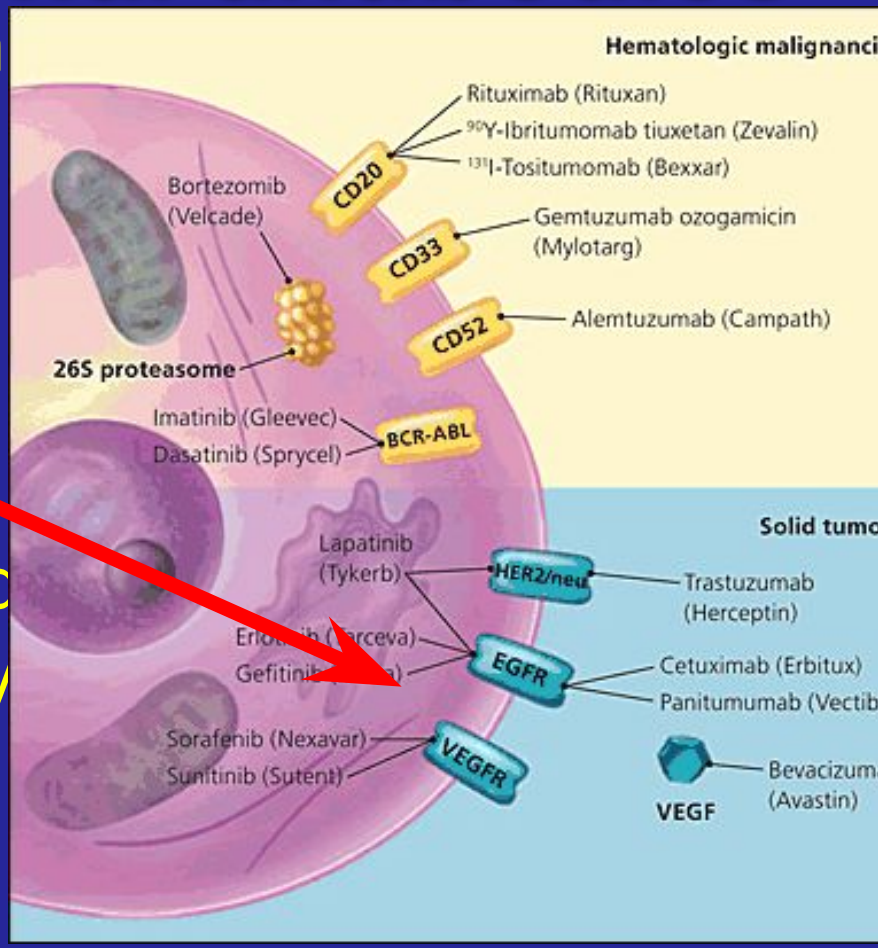
- **Alemtuzumab** - chronic lymphocytic leukemia(CLL). They binds to the CD52 antigen, which is found on *lymphocytes* (which include the leukemia cells). The antibody cause a first-dose cytokine release syndrome (TNF-α, IL-6 and interferon-γ) and ADCC



Types of monoclonal antibodies

Bevacizumab (Avastin®) is an mAb that targets a protein called **Vascular** *EGF* that affects tumor blood vessel growth. It can cause side effects such as high blood pressure, bleeding, poor wound healing, blood clots, and kidney damage.

Cetuximab targets a cell protein *EpidermalGFR*, which is found on normal skin cells (as well as some types of cancer cells and cause serious rashes.



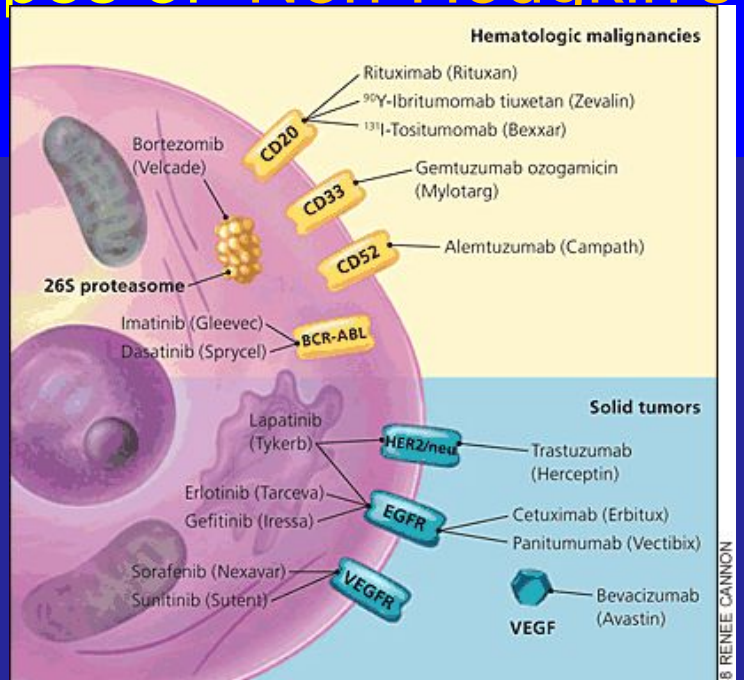
Monoclonal antibodies in cancer therapy

Name of drug	Type of cancer used to treat
Alemtuzumab (Campath)	Chronic lymphocytic leukemia.
Bevacizumab (Avastin)	Breast cancer. Colon cancer. Lung cancer.
Cetuximab (Erbitux)	Colon cancer. Head and neck cancers.
Gemtuzumab (Mylotarg)	Acute myelogenous leukemia.
Ibritumomab (Zevalin)	Non-Hodgkin's lymphoma. Chronic lymphocytic leukemia.
Panitumumab (Vectibix	Colon cancer.
Rituximab (Rituxan)	Non-Hodgkin's lymphoma.
Tositumomab (Bexxar)	Non-Hodgkin's lymphoma
Trastuzumab (Herceptin	Breast cancer

Conjugated Mabs (Immunotoxins)

Mabs that have been attached to a specific toxic agent.

Ibritumomab tiuxetan (Zevalin®) is an example of a radiolabeled mAb. This is an antibody against the CD20 antigen, which is found on B lymphocytes. The antibody delivers radioactivity directly to cancerous B cells and can be used to treat some types of Non-Hodgkin's lymphoma.

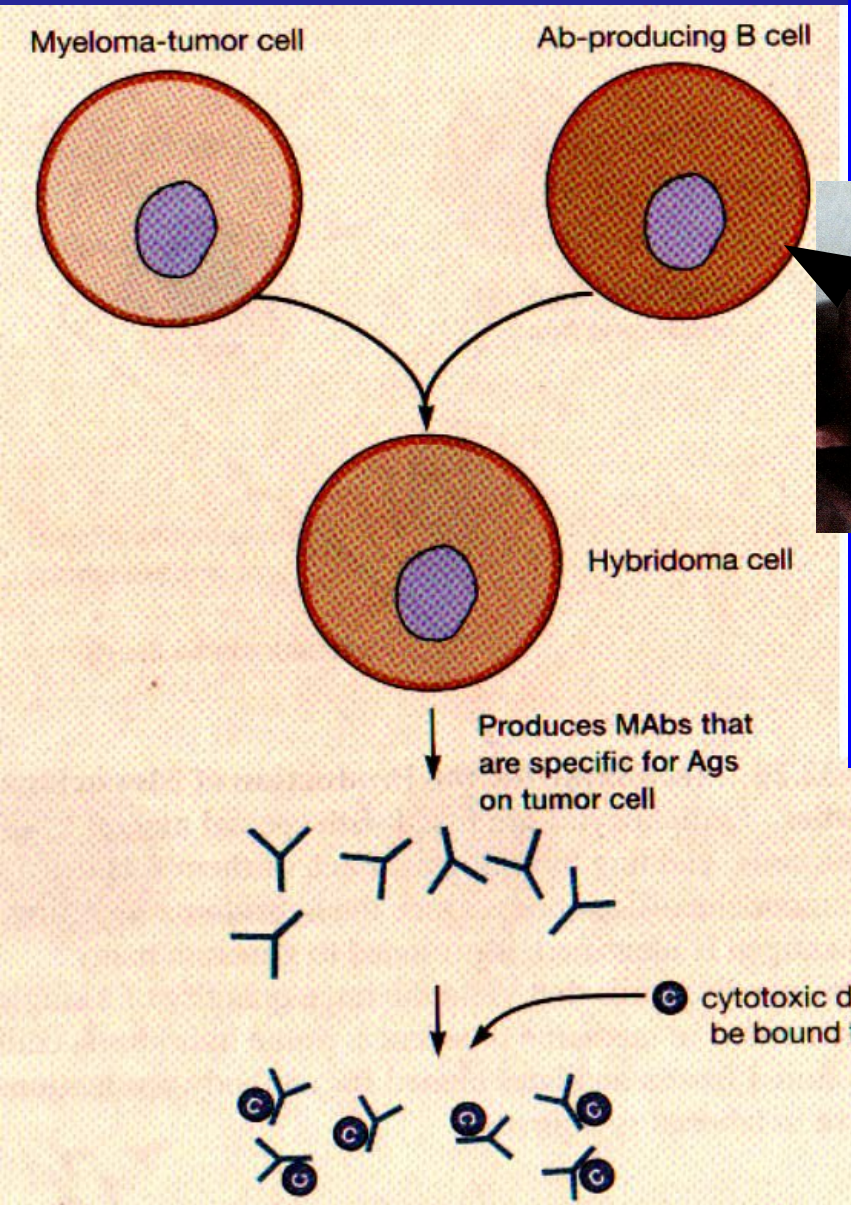


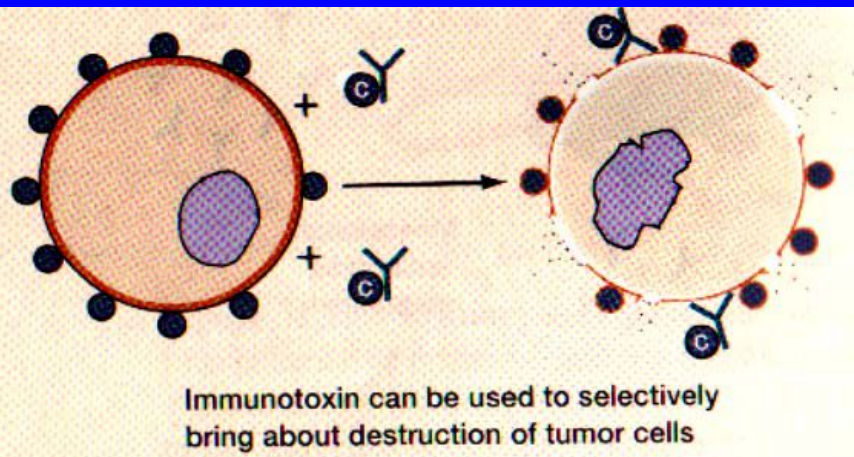
Immunotoxins

are monoclonal antibodies that have been attached to a specific toxic agent.

The antibody binds specifically to a target (tumor) cell and the attached toxin affects the target cell, but not other cells.

This is a promising approach in the treatment of certain types of cancer.





The use of the Artificial Passive Immunization

Goal	Examples	Preparations
(1)To prevent disease after a known exposure (post exposure prophylaxis)	Hepatitis B (needle stick injury with HBV-contaminated blood)	Human immunoglobulin preparation for hepatitis B virus (HBIG)
	Hepatitis A	Human serum gamma-globulin

The use of the Artificial Passive Immunization

Goal	Examples	Preparations
(2) *To protect* Immunosup-pressed patients	Common infections	Human serum gamma-globulin
(3) *To ameliorate the symptoms* of an ongoing disease	·Chicken pox ·Measles	Human serum gamma-globulin (*premature* infants, children with *malnutrition*)

The use of the Artificial Passive Immunization

Goal	Examples	Preparations
(4) *To block the action* of bacterial toxins and *prevent the disease* they cause	·Tetanus ·Diphtheria	Immune serum globulin preparations: · *Tetanus* antitoxin (equine), · *Diphtheria* antitoxin (equine)

Active immunization

is the induction of an

(1) **immune response** and

(2) **immunological memory**

in response to a challenge with an **antigen (immunogen).**

Immunization occurs after <u>exposure to</u>:

(1) microbes or their antigens in <u>vaccines</u> to prevent the disease (artificial active immunization) or

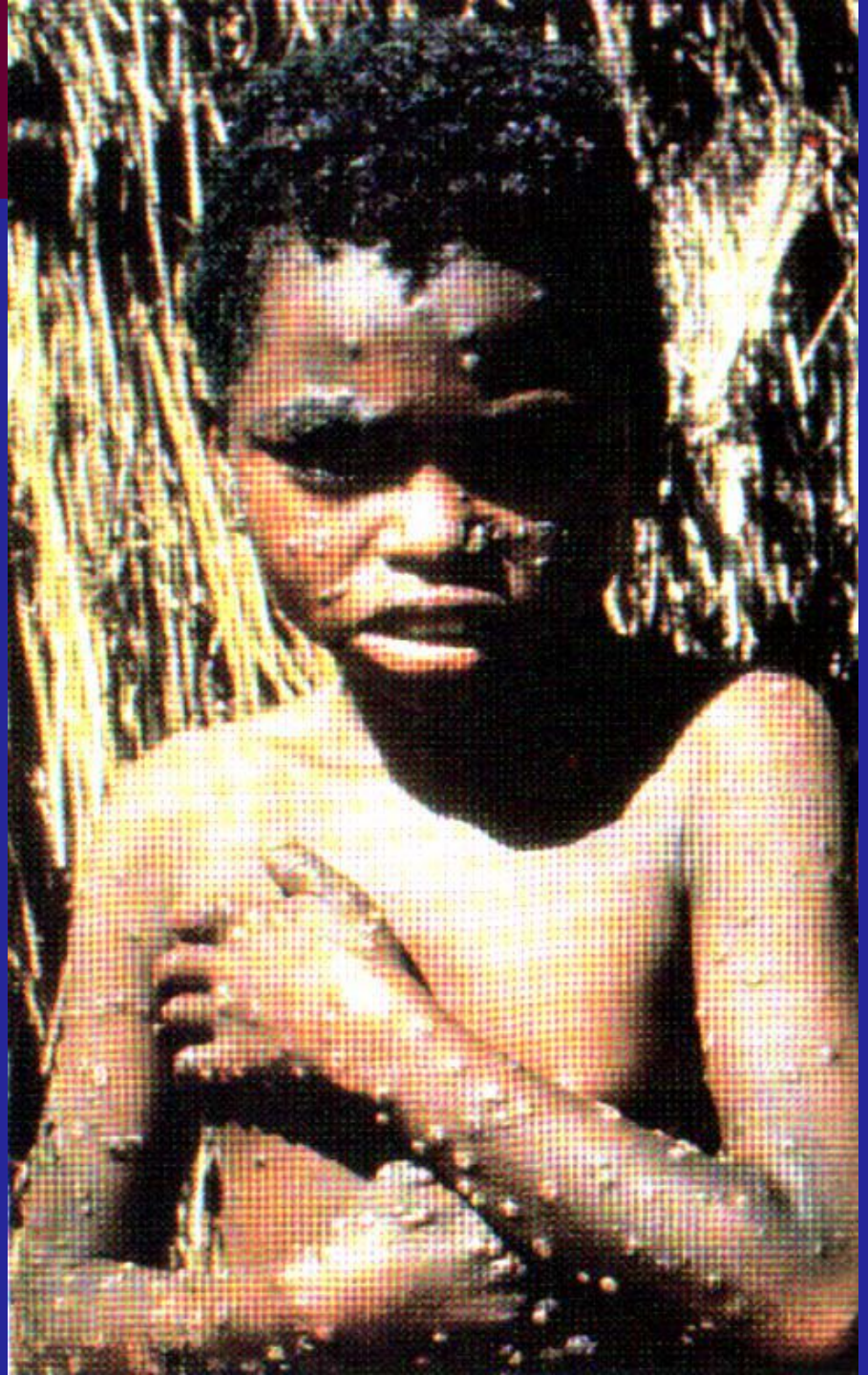
(2) an <u>infectious agent</u> (natural active immunization) .

The term ‘vaccine’ (*Latin ‘vacca’*, cow)

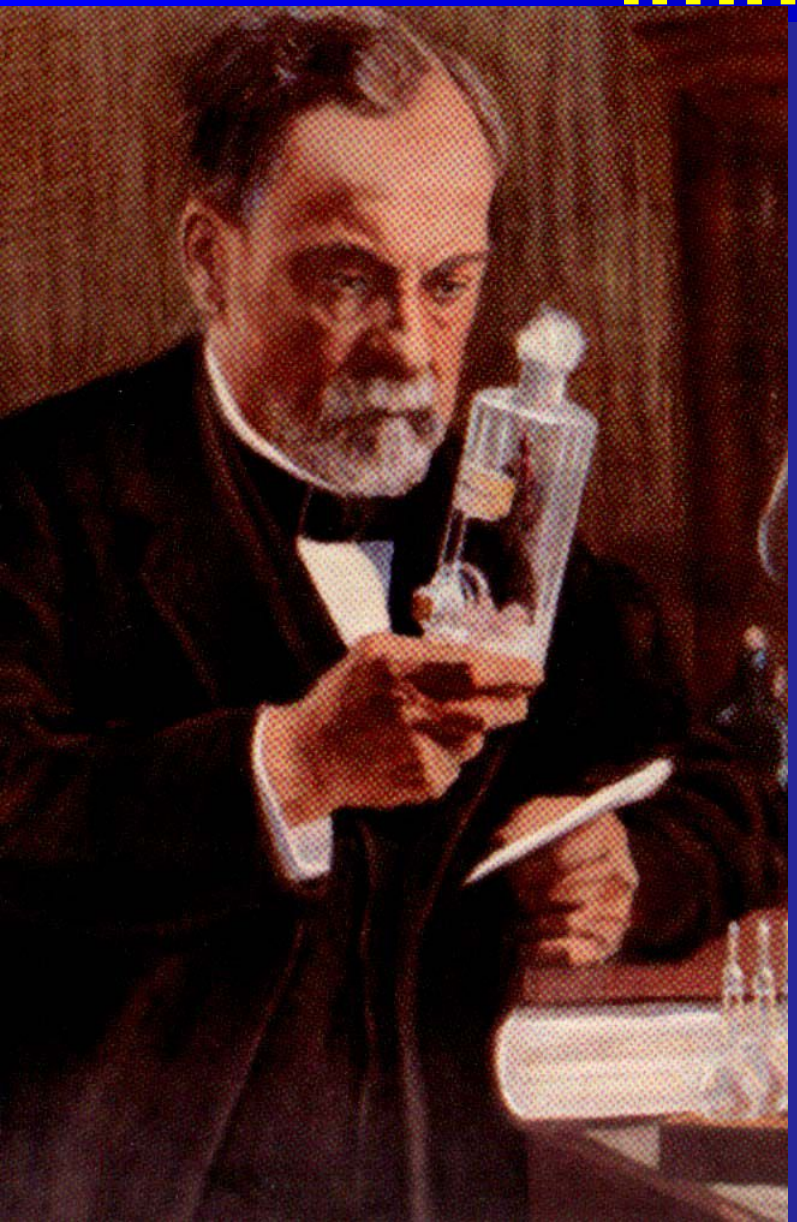
Caricature in a British magazine

This term comes from the **first successful immunization against smallpox** by cowpox pustule’s material performed by ***Edward Jenner*** in 1798 .

Smallpox



Vaccination is the artificial active immunization



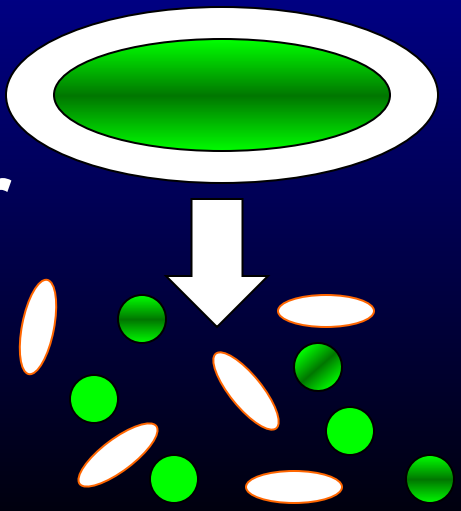
Louis Pasteur introduced this term recognizing the relevance of Jenner's research work for his own experiments and for vaccinology as a field of knowledge.

An immunizing agent derived from microorganism is called vaccine

- A vaccine consists either of *whole organism* or *microbial extracts* and *products*.
- Broadly, vaccines can be subdivided into *two groups* on the base

(1) whether they *infect the person* (live vaccines) or

(2) whether they *do not* (inactivated vaccines).



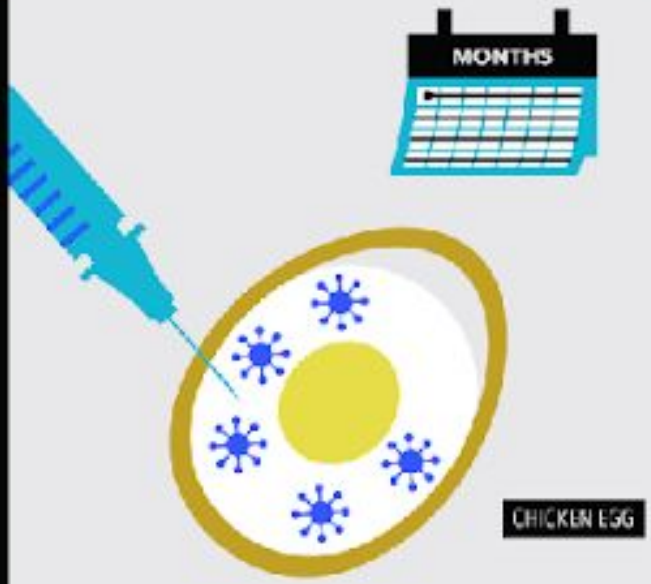
- Conventional vaccines - usually contain inactivated disease-causing organisms or proteins made by the pathogen (antigens), which work by mimicking the infectious agent. They stimulate the body's immune response, so it is primed to respond more rapidly and effectively if exposed to the infectious agent in the future;

- Advanced vaccines - RNA vaccines use a different : RNA vaccine consists of an mRNA strand that codes for a disease-specific antigen. Once the mRNA strand in the vaccine is inside the body's cells, the cells use the genetic information to produce the antigen. This antigen is then displayed on the cell surface, where it is recognized by the immune system.

PRODUCTION TIME

CONVENTIONAL VACCINES

Most vaccines against viral diseases are made from viruses grown in chicken eggs or mammalian cells. The process of collecting the viruses, adapting them to grow in the lab, and shipping them around the world can take months and is complex. For newly emerging viruses like SARS-CoV-2, for which a new vaccine is needed as quickly as possible, these steps may slow down development.



RNA VACCINES

The RNA (which encodes an antigen of the infectious agent) is made from a DNA template in the lab. The DNA can be synthesized from an electronic sequence that can be sent across the world in an instant by computer. Currently it takes about a week to generate an experimental batch of an RNA vaccine.

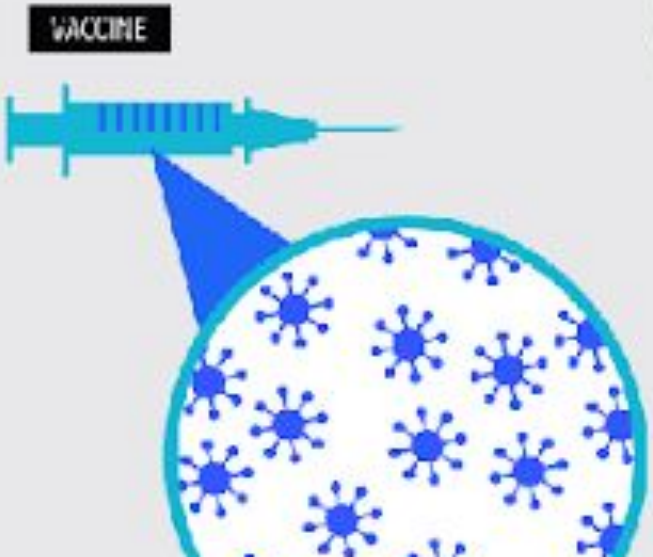
BIOSAFETY

CONVENTIONAL VACCINES

Growing large quantities of virus to make each batch of vaccine creates potential hazards.

RNA VACCINES

No virus is needed to make a batch of an RNA vaccine. Only small quantities of virus are used for gene sequencing and vaccine testing.



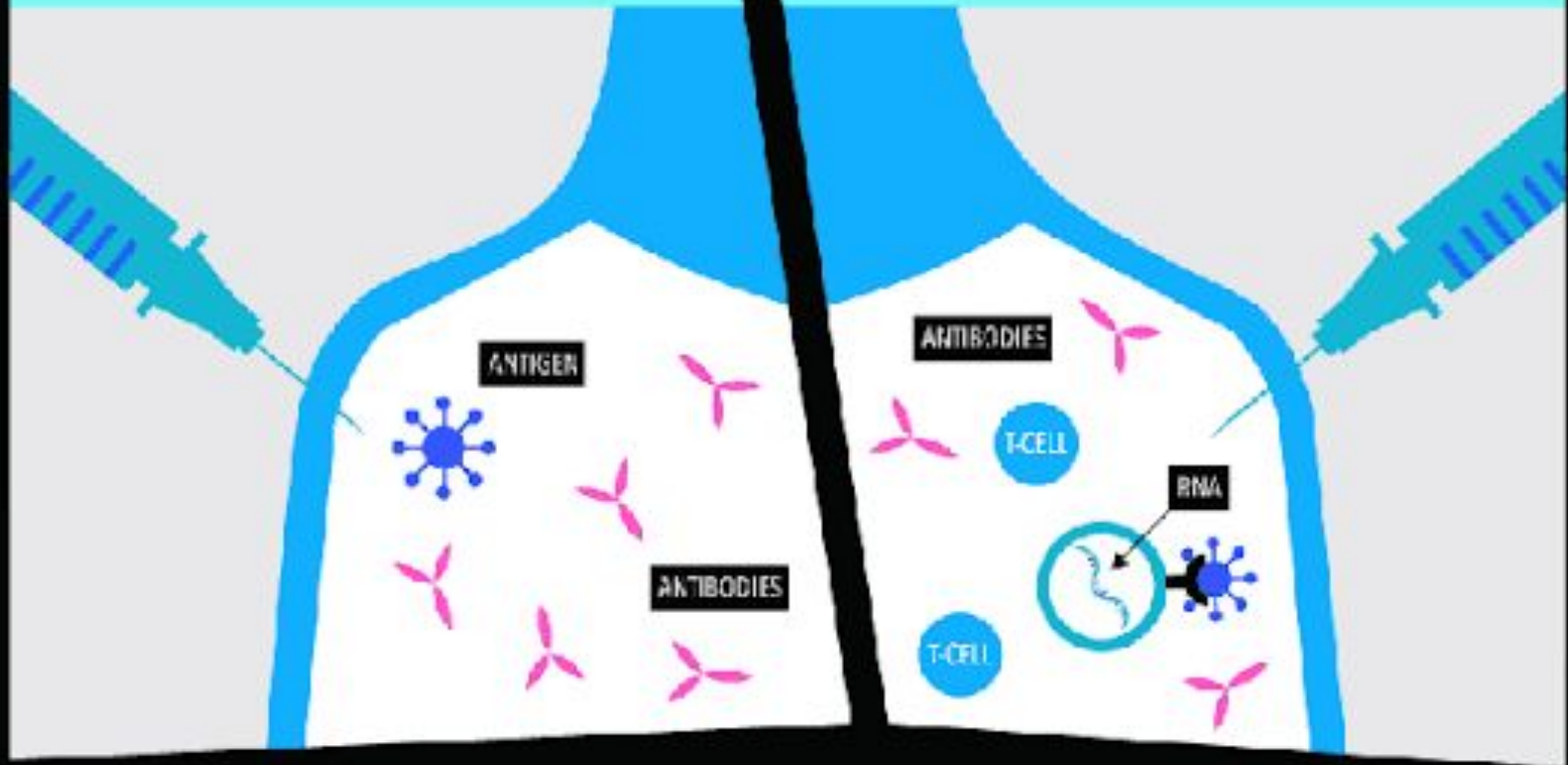
IMMUNE RESPONSE

CONVENTIONAL VACCINES

The antigen (a piece of the virus) is injected into the body. Upon recognizing the antigen, the immune system produces specific antibodies in preparation for the next time the body encounters the pathogen.

RNA VACCINES

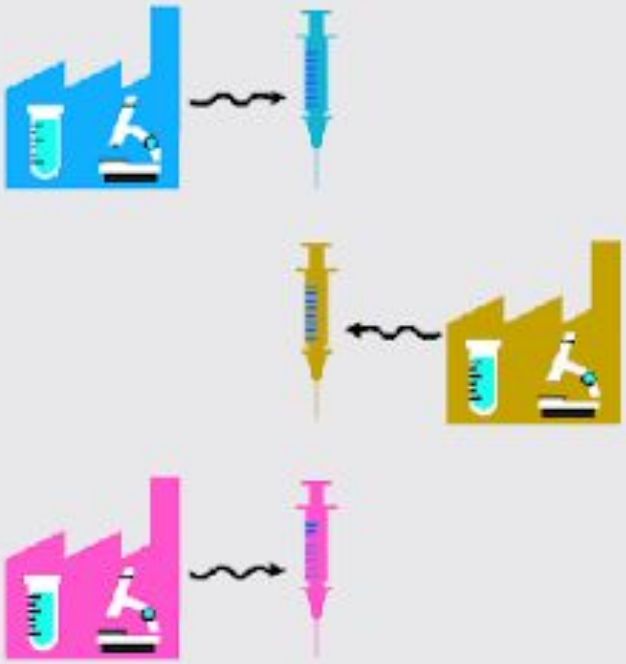
The RNA is injected into the body and enters cells, where it provides instructions to produce antigens. The cell then presents the antigens to the immune system, prompting T-cell and antibody responses that can fight the disease.



FLEXIBILITY

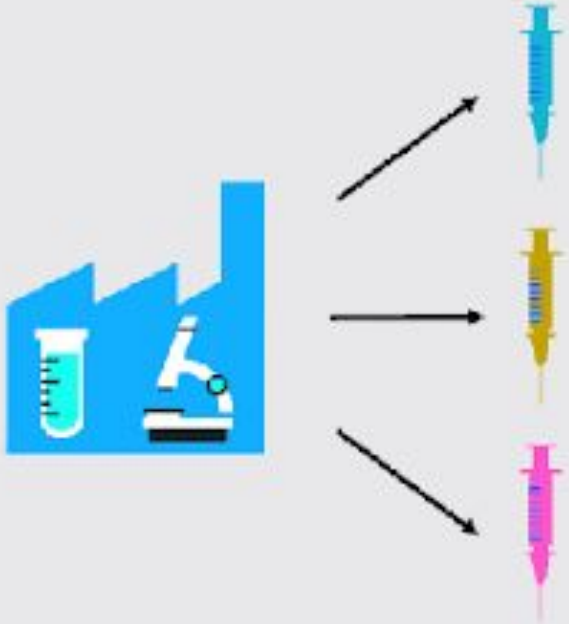
CONVENTIONAL VACCINES

Each new vaccine requires a bespoke production process, including complex purification and testing.



RNA VACCINES

We anticipate that the production process for RNA vaccines may be able to be scaled and standardized; potentially enabling replacement of the sequence encoding the target protein of interest for a new vaccine, with minimal changes to the vaccine production process.



Types of Live Vaccines (LVNs)

- LVNs are prepared with organisms limited in the ability to cause disease (avirulent or attenuated).
- These organism mimic the natural behavior of the 'wild' microbe without causing severe disease.
- LVNs may consist of the following types of organisms:

(1) Attenuated (weakened) wild type bacteria or viruses.

(2) Virulent microorganisms from other species that share antigens with human pathogens (Divergent VNs).

(3) Hybrid vaccines that can be used for those pathogens that cannot be properly attenuated.

Live vaccines (1): Attenuated vaccines

They are the **wild type bacteria or viruses *weakened* by modifying conditions** under which the organisms grow or by other approaches:

(1) Growing under Nonphysiological Temperature.

(2) Passage in Non-Susceptible Hosts. The **mutant organisms do *not replicate* well *in* any *human cells*** (host range mutant of **rabies virus**), or can replicate at a benign site but ***do not replicate in the target tissues*** characteristically affected by the disease (**polio virus** replicates in the GIT but does not reach or infect the **brain**, as wild type does).

(3) Genetically modified vaccines may be created by **genetically engineering mutations** that **inactivate or delete a virulent gene** instead of randomly attenuating the virus through passages.

Live vaccines (2): Attenuated vaccines

Generally attenuation can be achieved by modify-ing conditions under which the organism grows.

The organism can be grown at nonphysiological temperature:

1) Higher temperature (and anaerobic conditions) - *chicken cholera bacillus* and *anthrax bacil-lus* (42,5°C) were cultured by Louis Pasteur ;

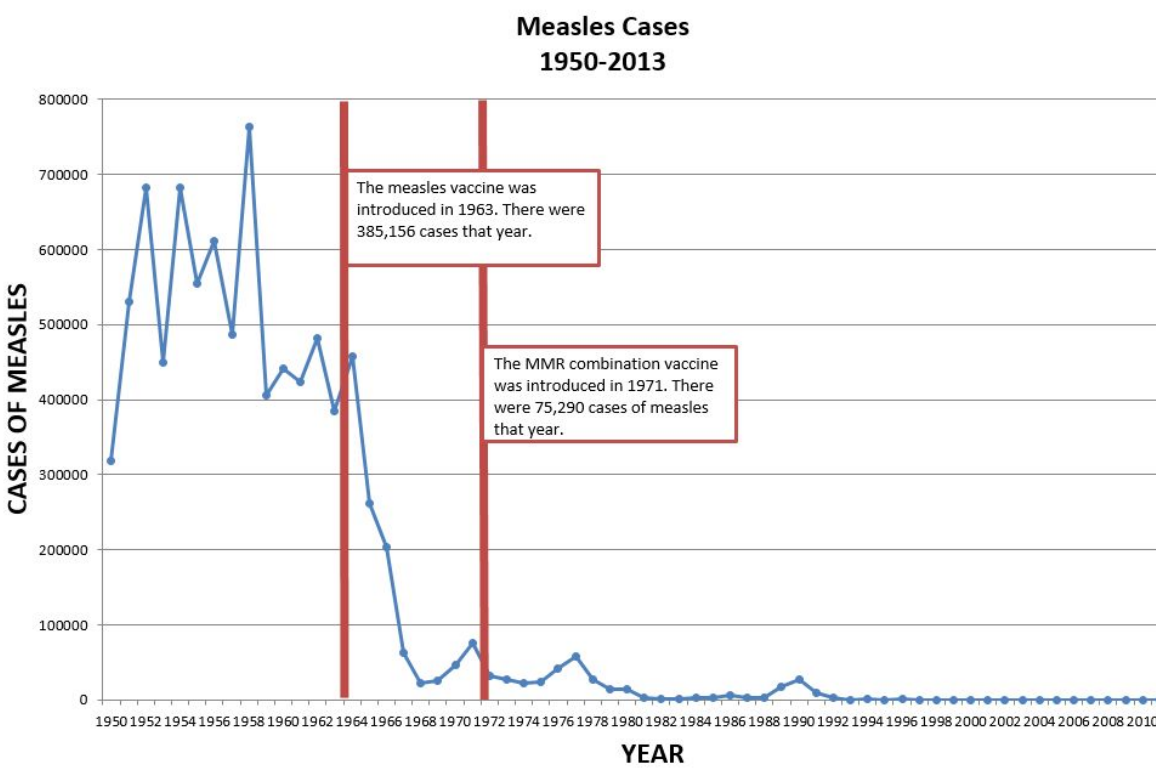
(2) Low temperature (32^0-34^0C) selects for the growth in embryonated chicken eggs or tissue culture cells of less virulent mutant strains that grow poorly at 37^0C, and fail to replicate in low respiratory tract (*measles*, *influenza vaccines*)

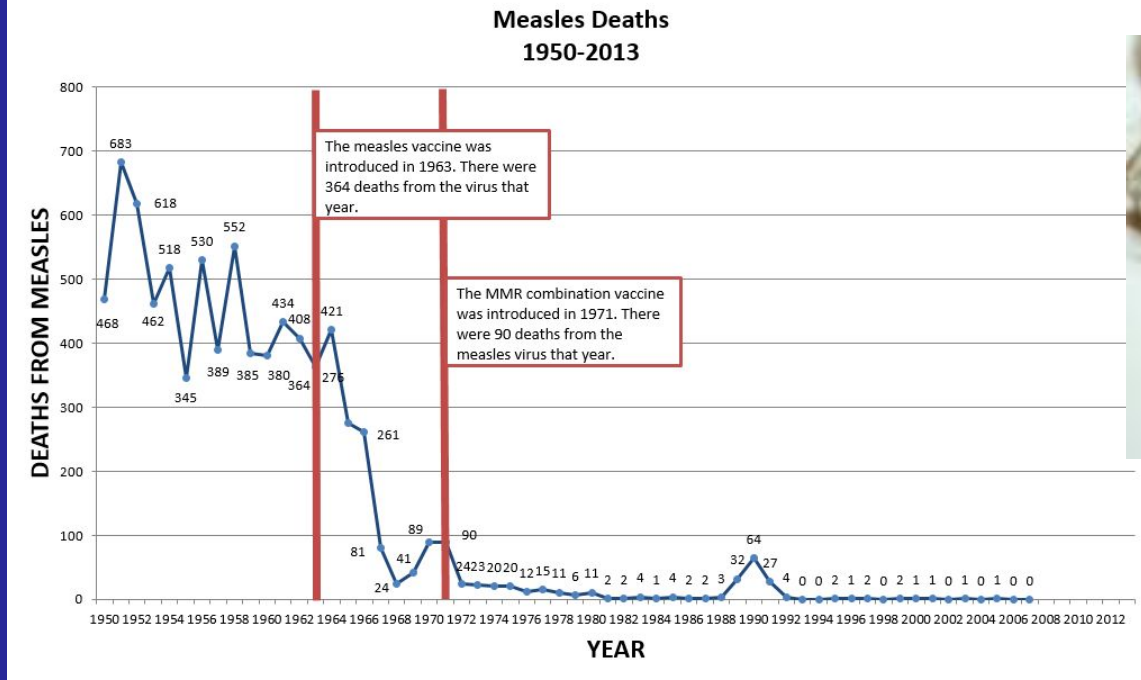
Live viral vaccines (LVVNs): Immune responses

Immunization with a LVVNs resembles natural infection and *elicits both humoral* and *cell-mediated* immune responses.

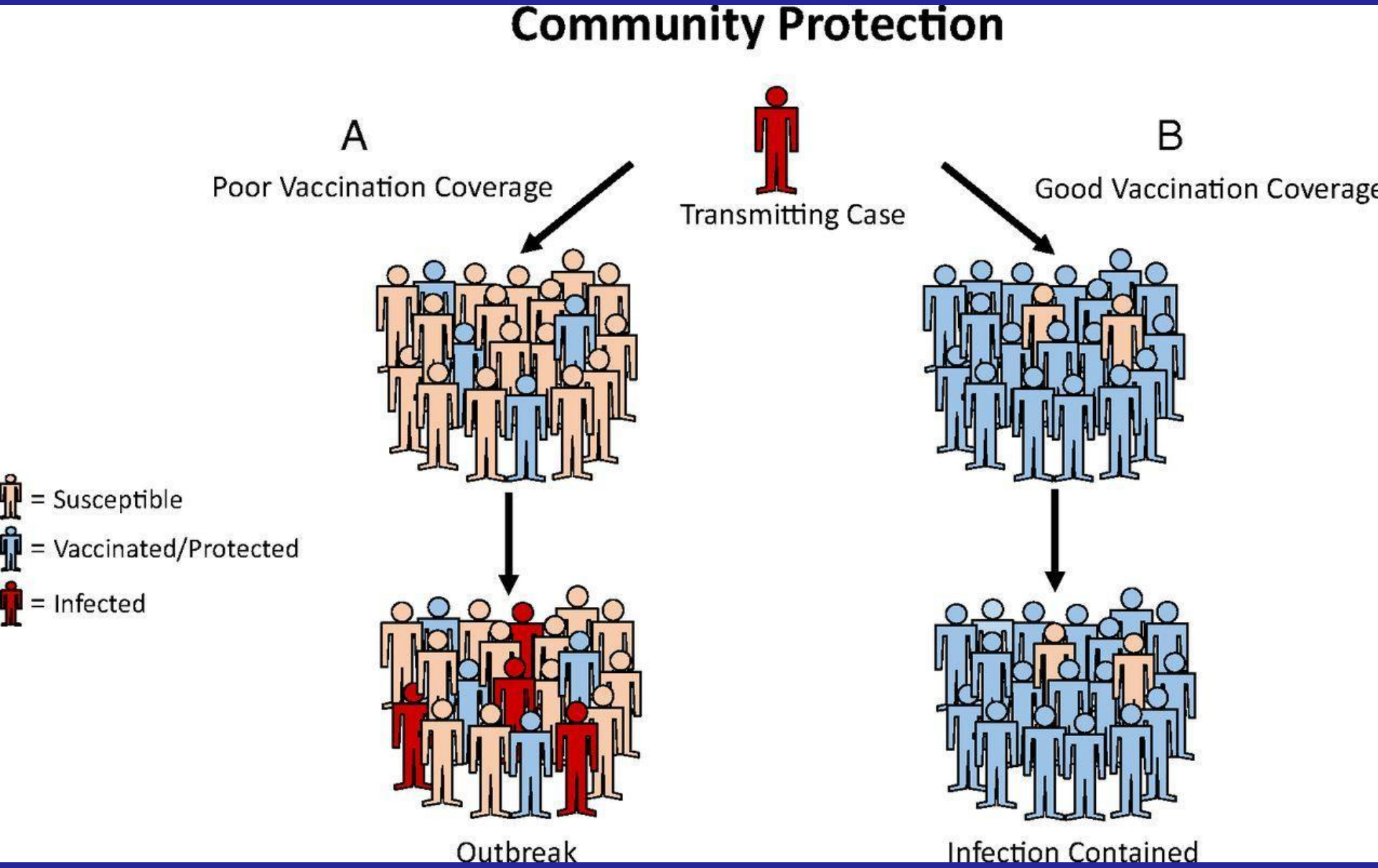
Most LVVNs designed to protect people against viral diseases, for which the *cellular* immune response is required for the infection to resolve. These are *measles*, *mumps*, *polio*, *rubella*, *chickenpox*, *adenovirus*, *yellow fever*.

Effect of vaccination

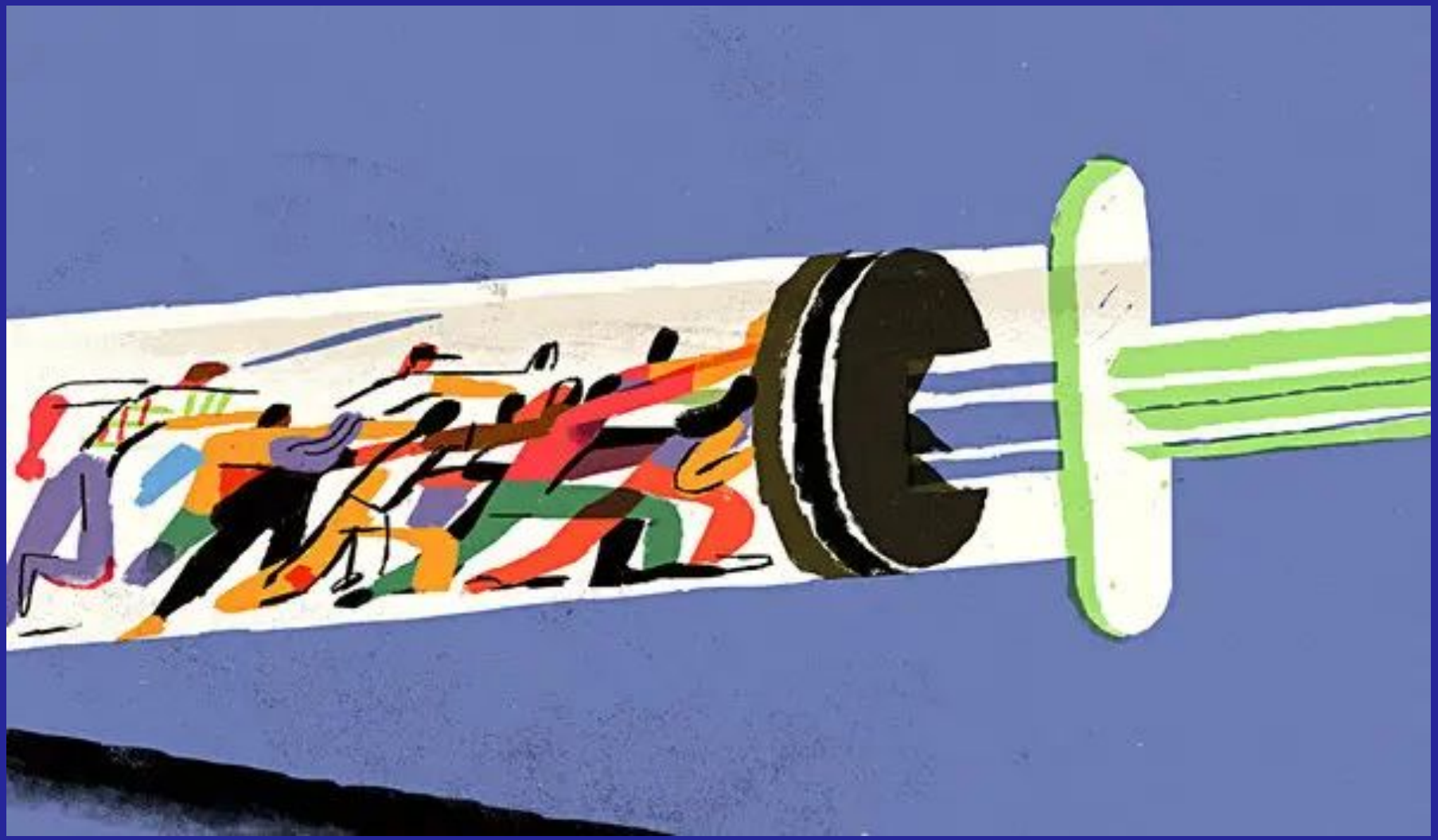




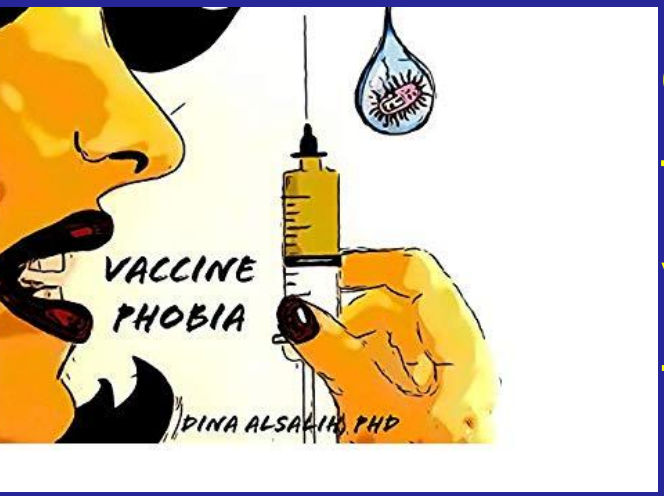
Effect of vaccination



The Anti-vaccination Movement: A Regression in Modern Medicine



The Anti-vaccination Movement: A Regression in Modern Medicine



There have been recent trends of parents in Western countries refusing to vaccinate their children due to numerous reasons and fears. While opposition to vaccines is as old as the vaccines themselves, there has been a recent surge in the opposition to vaccines in general, specifically against the MMR (measles, mumps, and rubella) vaccine.

The Anti-vaccination Movement: A Regression in Modern Medicine

Almost incredibly, the trigger for what would become a worldwide controversy over vaccine safety was a single scientific research paper published in a medical journal – the Lancet – in February 1998, written by a then-41-year-old academic researcher, Andrew Wakefield, and co-authored by a dozen associates.

The Anti-vaccination Movement: A Regression in Modern Medicine

It reported on the cases of 12 anonymous children with apparent brain disorders who had been admitted to a paediatric bowel unit at the Royal Free hospital in Hampstead, north London, between July 1996 and February 1997. The prime cause of the alarm was findings in the paper claiming that the parents of two thirds of the 12 children blamed MMR for the sudden onset of what was described as a combination of both an inflammatory bowel disease and what Wakefield called “regressive autism”.

Live divergent vaccines: (2) Virulent micro-organisms from other species

that share antigens with human pathogens:

(1) *cowpox virus* – first vaccine developed against smallpox.

(2) vaccines consisting of *bovine* or *simian rotavirus* have shown the initial success in *protecting infants* against human rotavirus in *clinical trials*.

(3) *Adenovirus vaccines* may consist a virulent strains used for oral/GIT administra-tion to induce immunity in

Newborn baby Rotaviruses vaccine immunization

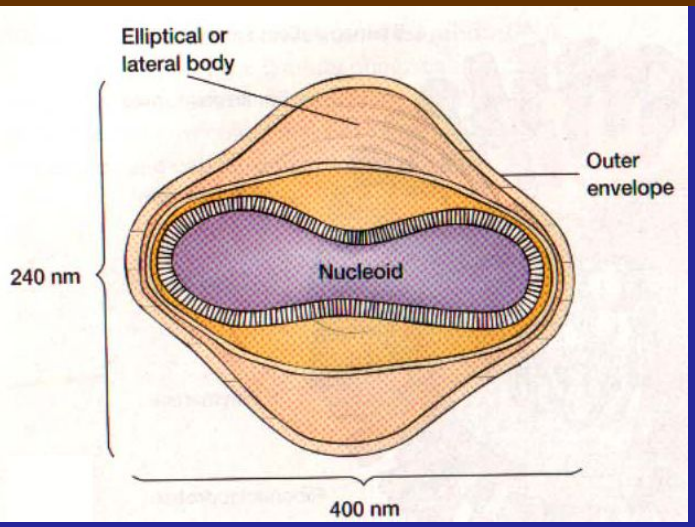
Rotavirus is a virus that causes diarrhea, mostly in babies and young children. The diarrhea can be severe, and lead to dehydration. Vomiting and fever are also common in babies with rotavirus.

Two rotavirus vaccines are currently licensed for use in infants in the United States:

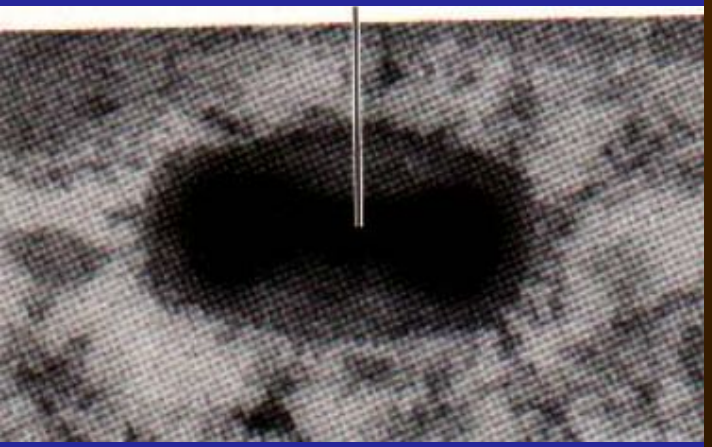
RotaTeq® (RV5) is given in 3 doses at ages 2 months, 4 months, and 6 months

Rotarix® (RV1) is given in 2 doses at ages 2 months and 4 months

Live vector vaccines:(3)Hybrid vaccines

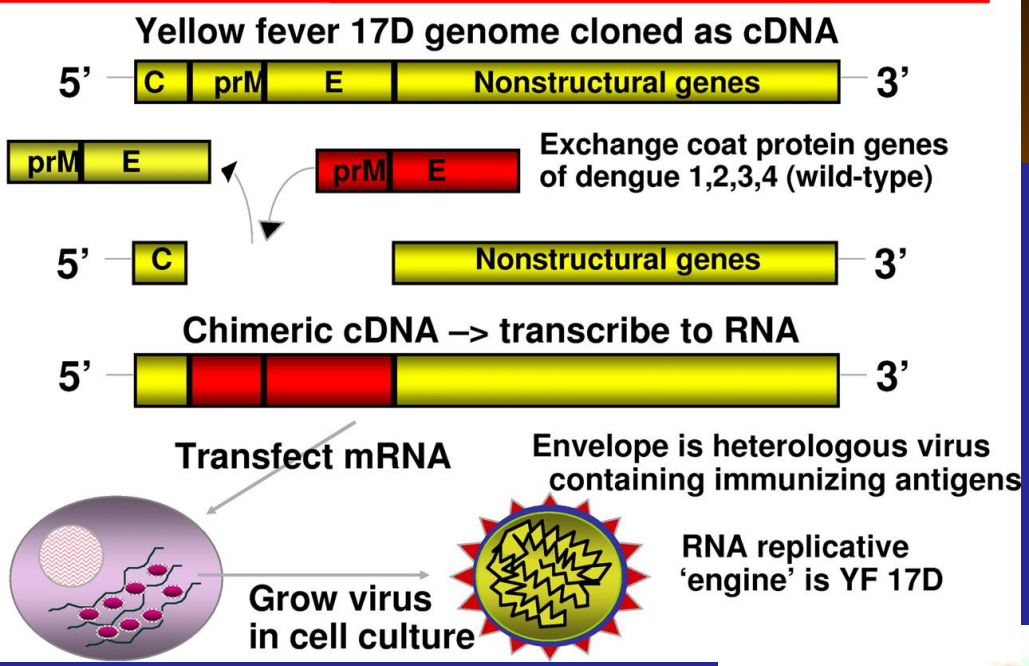


Nucleoid



- These VNs can be used for those pathogens that cannot be properly attenuated.
- Genes from them can be inserted into safe virus (vaccinia) to form a polyvalent vaccine to many agents in a single, safe, inexpensive, and reliable vector.
- On infection, the hybrid virus *exp-resses* and *initiates immune res-ponse* to itself and the inserted antigens.
- The *vaccinia, herpes simplex virus, and adenoviruses* have been used in several *experimental vaccines*.

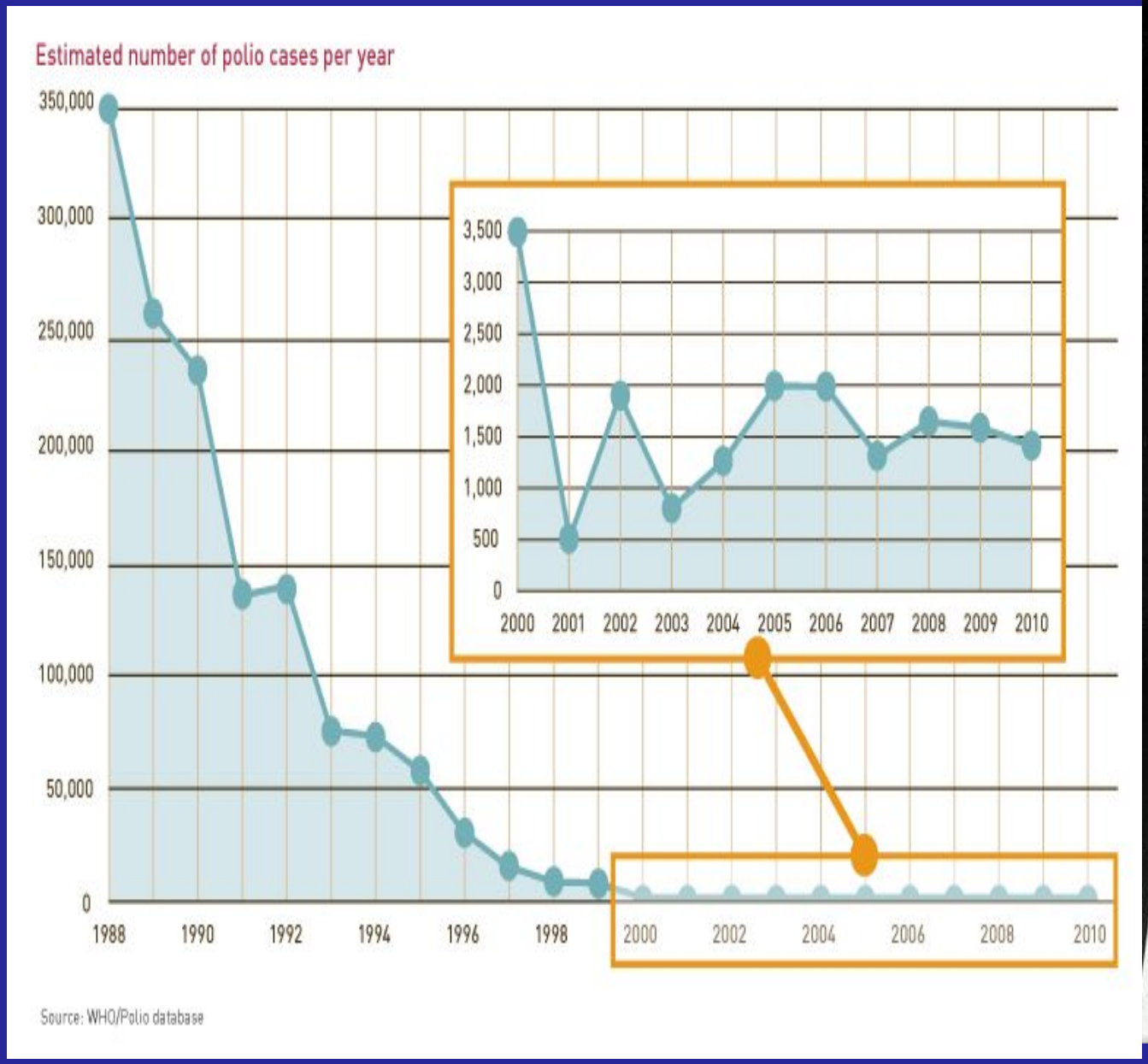
ChimeriVax Technology

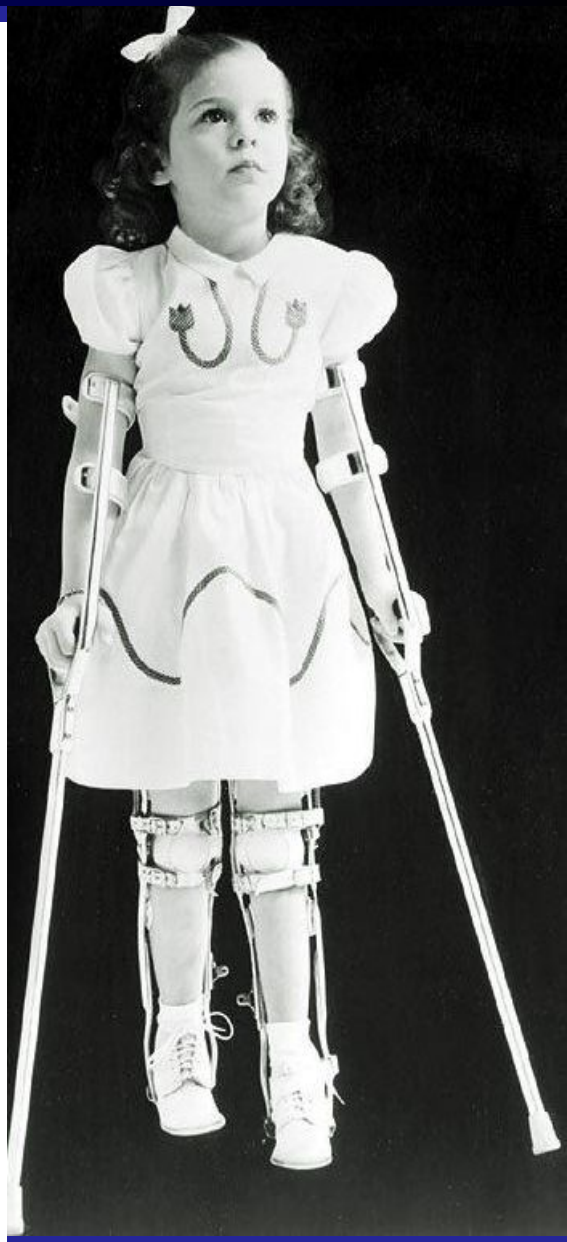


CYD-TDV "Dengvaxia®"

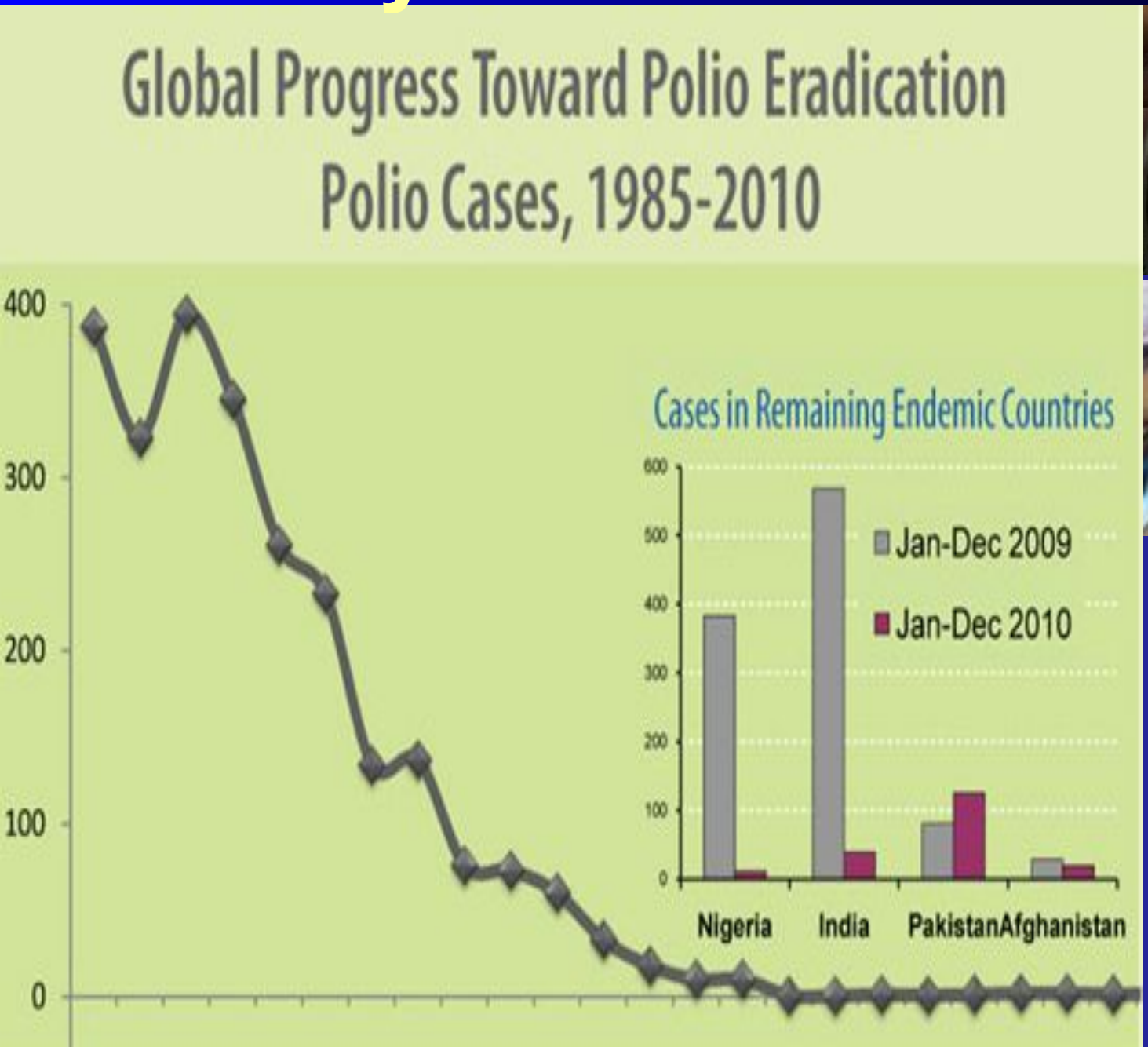
- 17D Yellow fever vaccine backbone
- Pre-membrane (preM) and envelope (E) structural genes replaced with those from each of 4 dengue serotypes (DENV1-4)
- 3 doses – given at 0, 6, and 12 months

Poliomyelitis: Effect of vaccination





Poliomyelitis: Effect of vaccination



Live bacterial vaccines (LBVNs): Immune responses

LBVNs include attenuated strains *Salmonella typhi* (typhoid fever), BCG for tuberculosis made from attenuated strain of *Mycobacte-rium bovis*, and attenuated tularemia vaccine.

A LBVN may be required to elicit protection against infections such as these because both *humoral* and *cellular* responses are important to confer protection against intracellular parasites.

Live vaccines: The advantages

(1) The **immunity is long live**, and mimics the normal immune responses.

(2) When vaccine is administrated orally, **SIgA** is secreted in the **gut** and **oropharynx** ***to protect*** **the mucous** (oral polio vaccine, OPV).

This ***prevents*** the establishing of **carrier state** and ***facilitates*** the near **eradication** of the **wild** type **virus** from the community.

(3) Live vaccines are administrated in **low doses**. Basically **one single administration** is enough for protection because **organisms multiply** in a body.

Live vaccines: The disadvantages

(1) they may cause disease in immunosuppressed individuals and should be replaced by the other type of vaccine (OPV can be replaced by IPV);

(2) the vaccine may revert to virulent form.

Inactivated vaccines (IVNs)

- IVNs provide safe antigen for immunization and are used to confer protection against most bacteria and viruses that may be *too virulent* to be attenuated or may be *oncogenic*.
- IVNs can be produced by chemical modification with formalin, by heating of the organism or its products (bacterial toxins), by purification of the bacterial or viral components.

IVNs can be of tree major types:

(1) whole killed (for bacteria) or inactivated (for viruses);

(2) capsule (for bacteria) or subunit (for viruses);

(3) toxoid (for bacterial toxins).

Whole killed & Inactivated viral vaccines

Whole killed	Inactiva-ted (viral)	Advan-tages	Disadvantages
Pertus-sis, *Chole-ra*, *Anth-rax*, *Plague*	Influenza, Polio Salk, HepatitisA Rabies, Japanese and Tick-born e Encepha-li tis	Could not revert to virulent strain	Less immunogenic (compare with live vaccines), administrated with *adjuvants* (*alum*)
		Could not cause infection in immuno-c ompro-mi sed	Requires booster shots and a larger dose
			The immunity is not lifelong
			Does not elicit local SIgA
			Can cause adverse side effects: *allergic reactions*

Capsule vaccines for bacteria and subunit vacines for viruses

They can be developed after identification of the microbial components, that elicit a protec-tive immune response–protective antigens.

Immunogenic component may be isolated from bacterium or viruses:

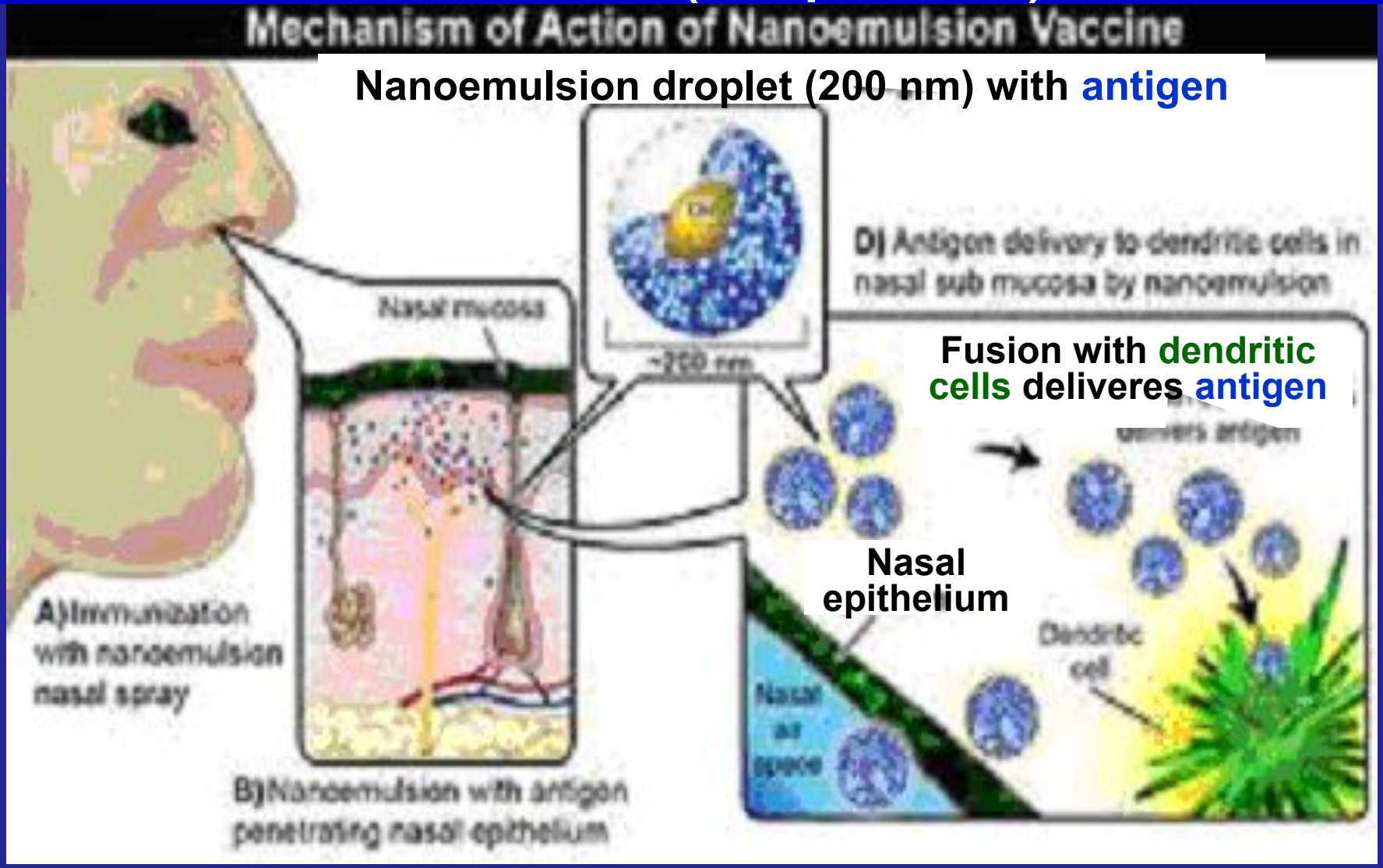
(1) by biochemical means (*chemical vaccines*) or

(2) by genetic engineering (*recombinant vaccines*) involving the expression of cloned viral genes in bacteria or eukariotic cell

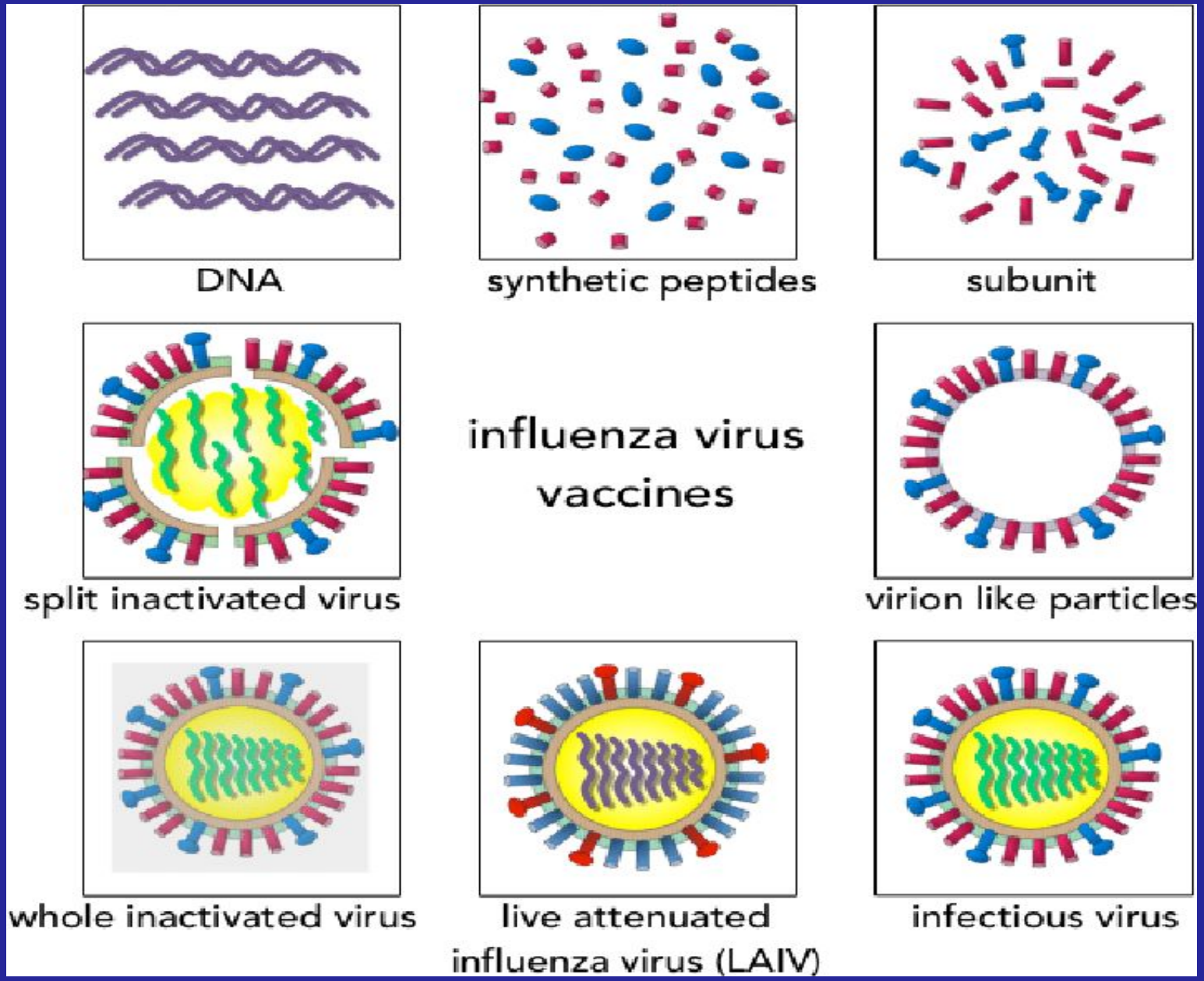
Capsule & Subunit vaccines (VNs)

Capsule (bacteria)	Subunit (viruses)	Disadvantages
Surface polysac-charides (PSs): **Meningococcal** (PSs of 4 serotypes), **Pneumococcal** (from 23 serotypes), **Haemophilus influenza** VCN (PS serotype B), **Recombinant Lyme disease** (recombinant OspA-outer surface	Isolated Purified surface envelope proteins. **Influenza** VN (hemagglutinin and neuraminidase glycoproteis), **Hepatitis B** VN (HB_S antigen from the **human sera** of carriers or recombinant antigen from **yeasts** expressing the gene for HB_S)	The polysaccharide VNs are poor immu-nogenic and can be chemically conjuga-ted with carrier proteins to enhance immunogenicity.
		Subunit VNs are poor immunogens and need to be admi-nistered with **adju-vants** or inside small lipid membrane ve-sicles -

Mucosal Synthetic Conjugated Vaccine (Peptides)



Influenza vacccines



Toxoids (TDs)

TDs are exotoxins converted to non-toxigenic but still immunogenic form.

Immunization with the TD provokes the formation of protective antibodies which neutralize the toxin and facilitate the toxin removal by phagocytosis.

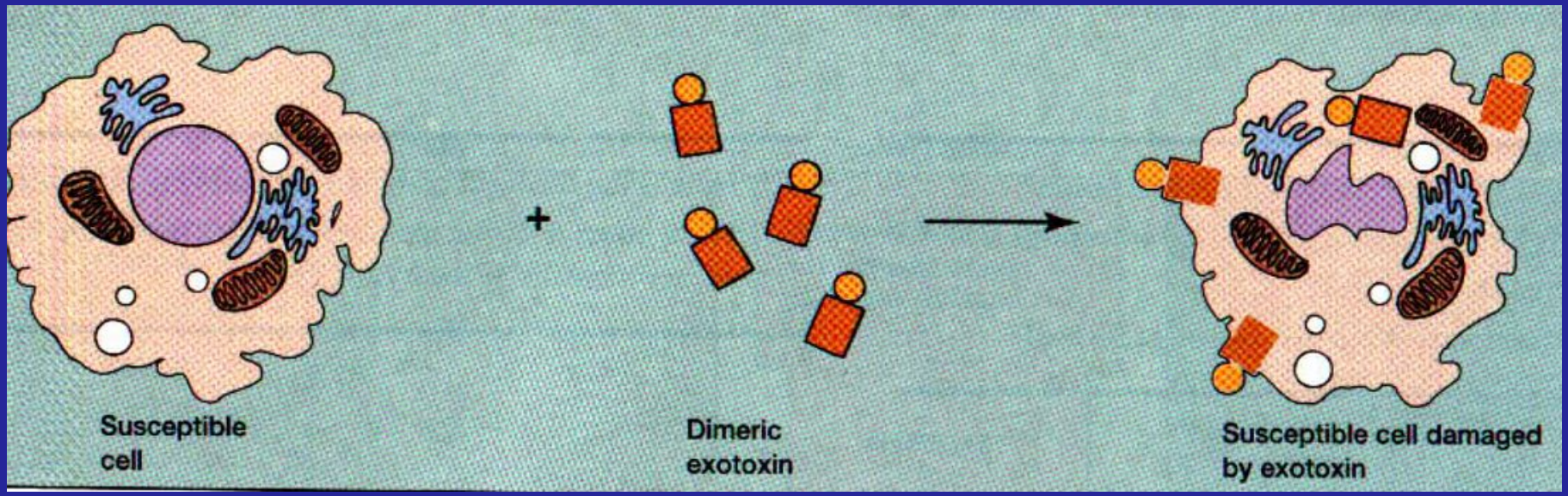
TDs are poor immunogenic and should be adminis-trated with adjuvants (alum - $Al(OH)_3$ or $Al(PO_4)$) or can be covalently attached to a protein antigen.

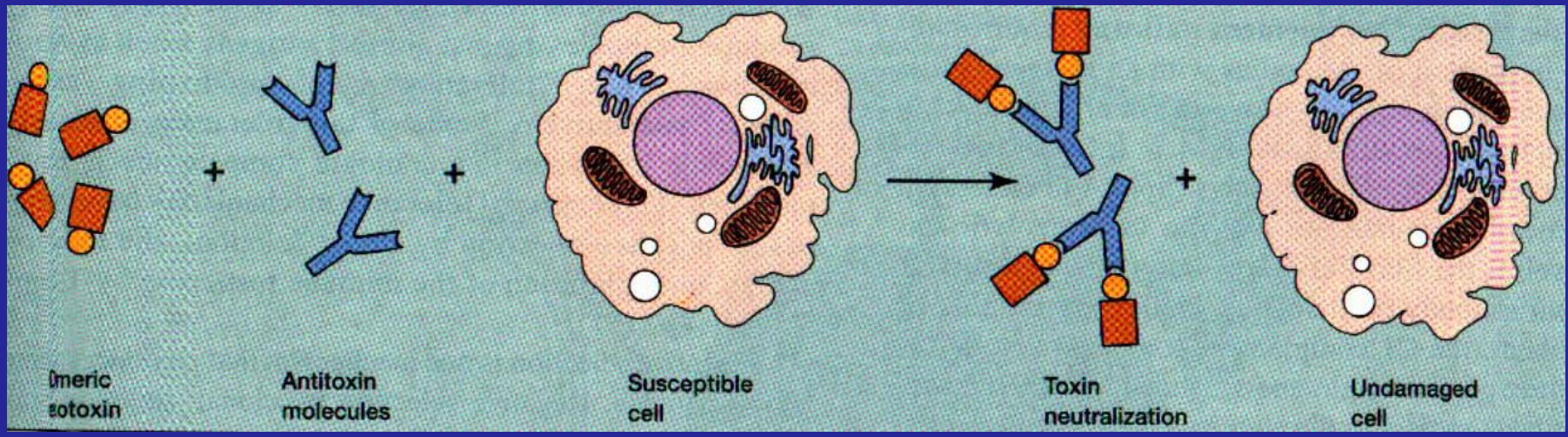
TDs need booster shots to conform protection.

Vaccines that contain toxoids are for *tetanus, diphtheria, cholera, botulism*.

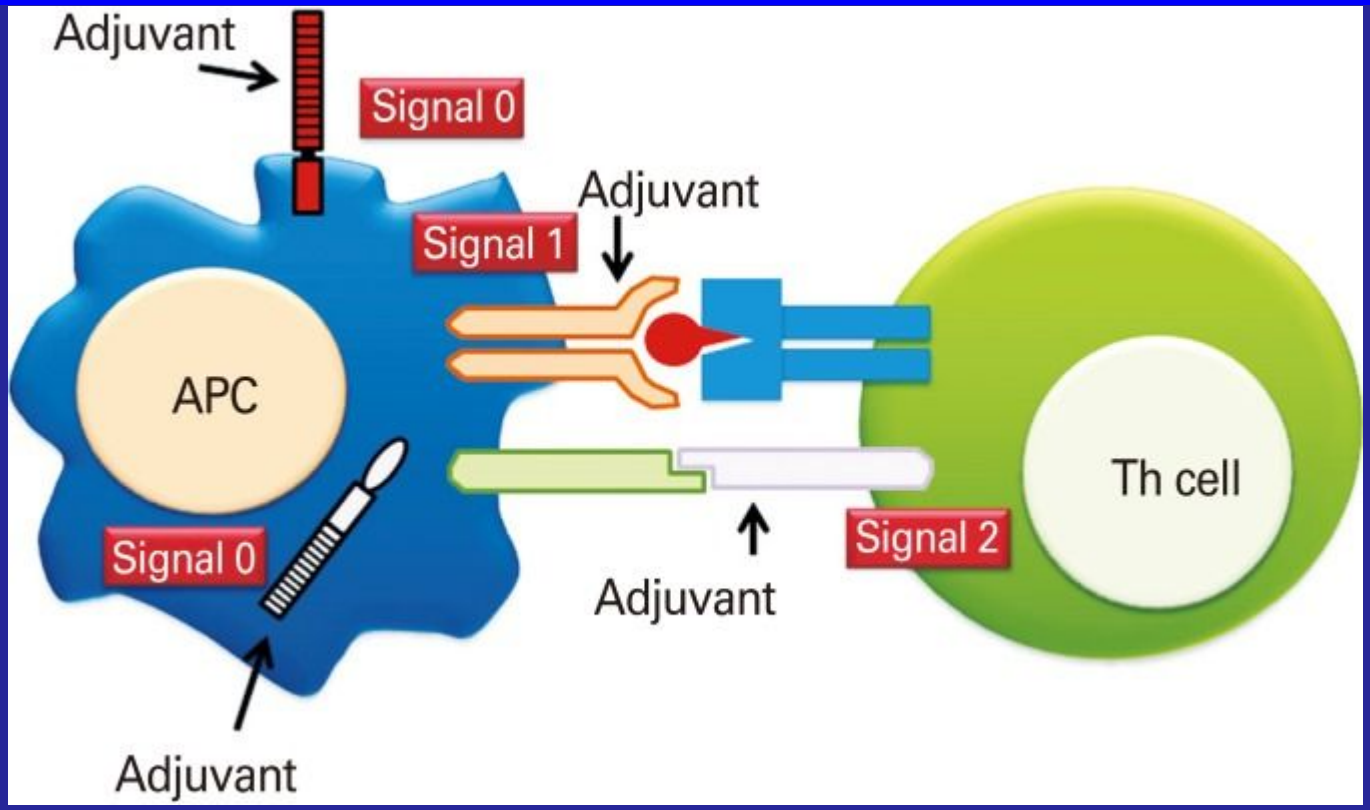
Composite vaccine DPT contains *2 toxoids* absor-bed on alum – *diphtheria* and *tetanus* – and whole killed pertussis cells.

Toxoids: Induction of antitoxins



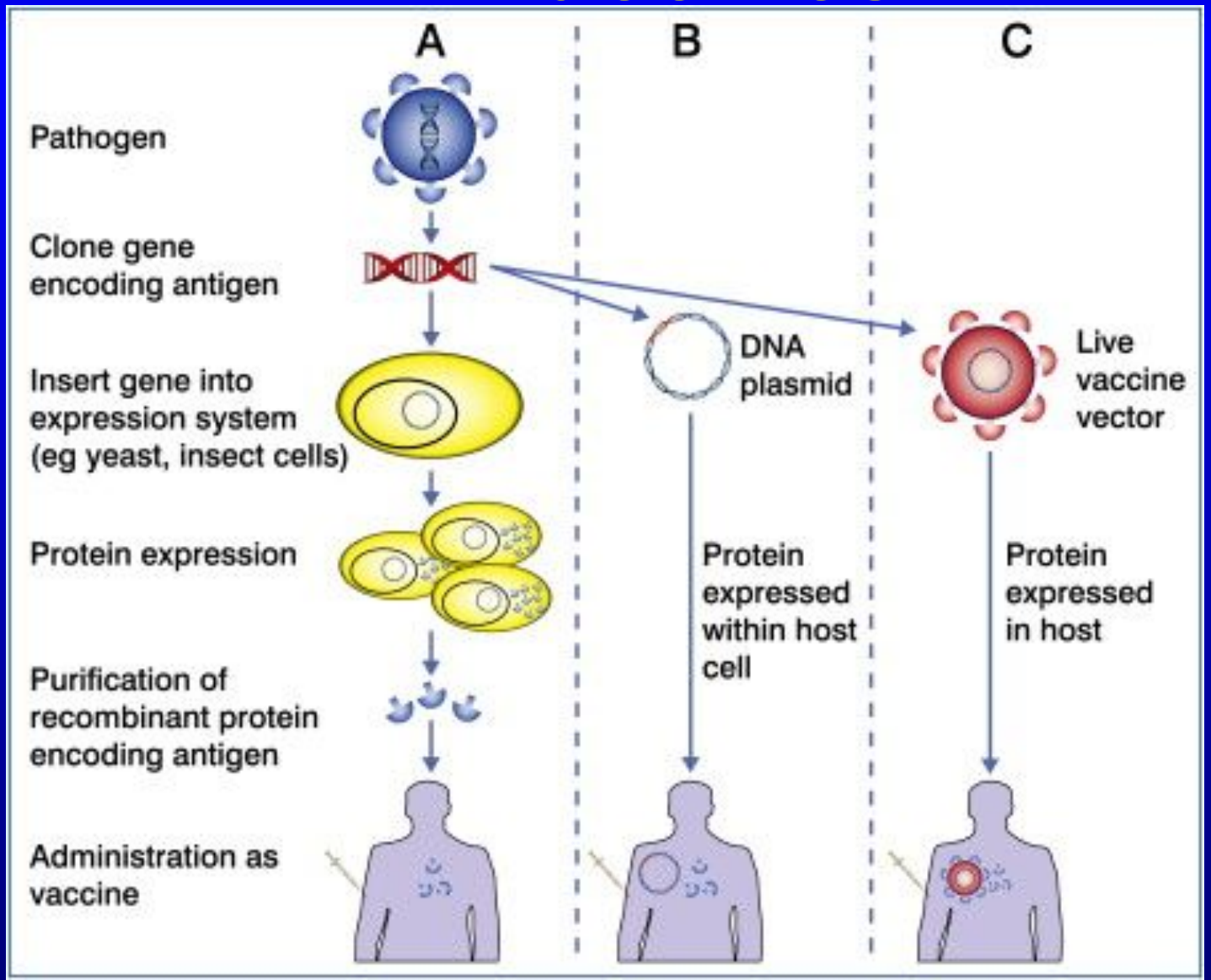


Adjuvants



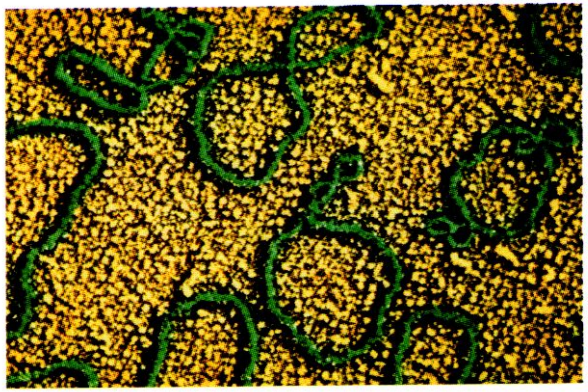
The target site of vaccine adjuvants. Most of the recently developed specific adjuvants, such as pattern recognition receptor (PRR) ligands act on signal 0 (antigen recognition and antigen-presenting cells [APCs] activation), and indirectly on signal 2 (co-stimulation). In addition, PRR ligands can act on signal 1 (efficient presentation of the co-administered antigen).

Recombinant/DNA approaches in vaccines



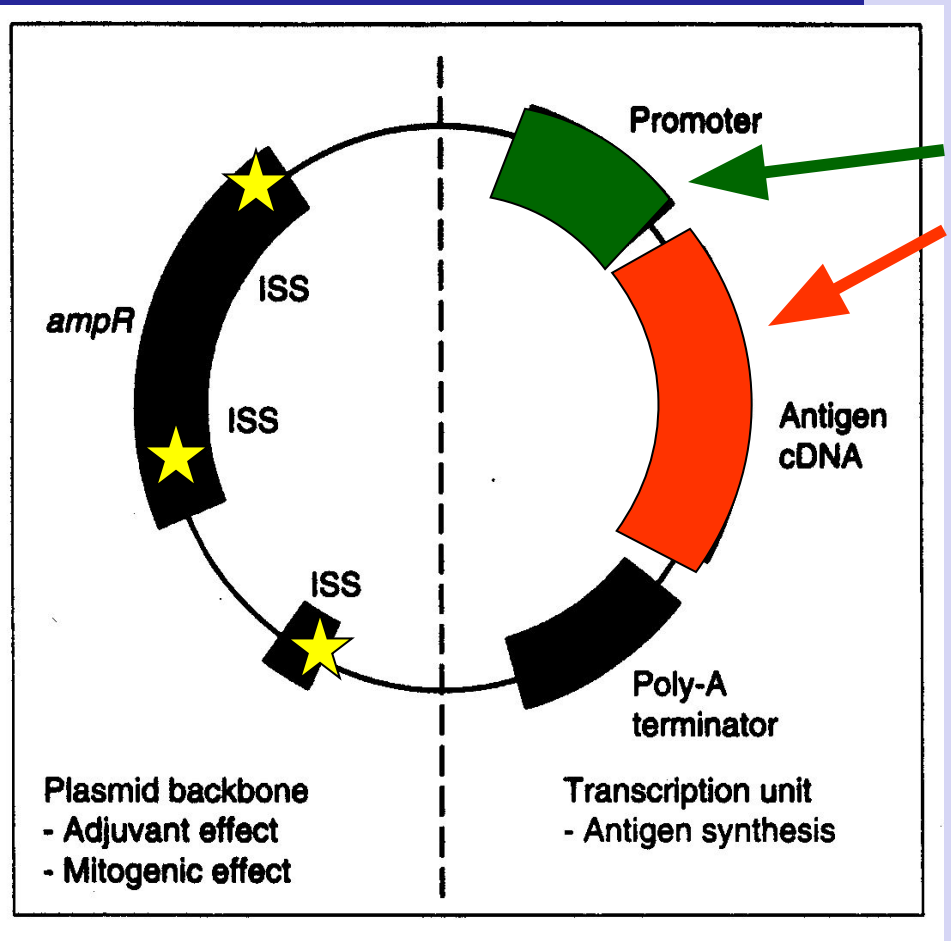
DNA vaccines

- DNA vaccines consist of naked DNA code for a gene for vaccinal protective antigen. This construct is produced by cloning gene, code for protective antigen, into a bacterial plasmid.



- The use of DNA vaccines makes possible developing vaccines against infectious agents such as HIV, herpes virus, malaria, and others, which require not only *humoral* but also *cellular* immune responses for protection.

Plasmid DNA for gene vaccination



has two major units:

(1) A transcription unit comprising promoter, an antigen cDNA, and poly-adenylation (A) addition sequence, which together direct protein synthesis.

(2) A plasmid backbone deli-vers adjuvant and mitoge-nic activity via immuno-stimulatory seq★ences (ISS). ISS are located within the ampicillin antibiotic resistance gene (ampR). ISS are the noncoding region of the plasmid.

Immune responses elicited by DNA vaccines

The DNA plasmid is injected into the muscle cell or skin of the vaccine recipient.

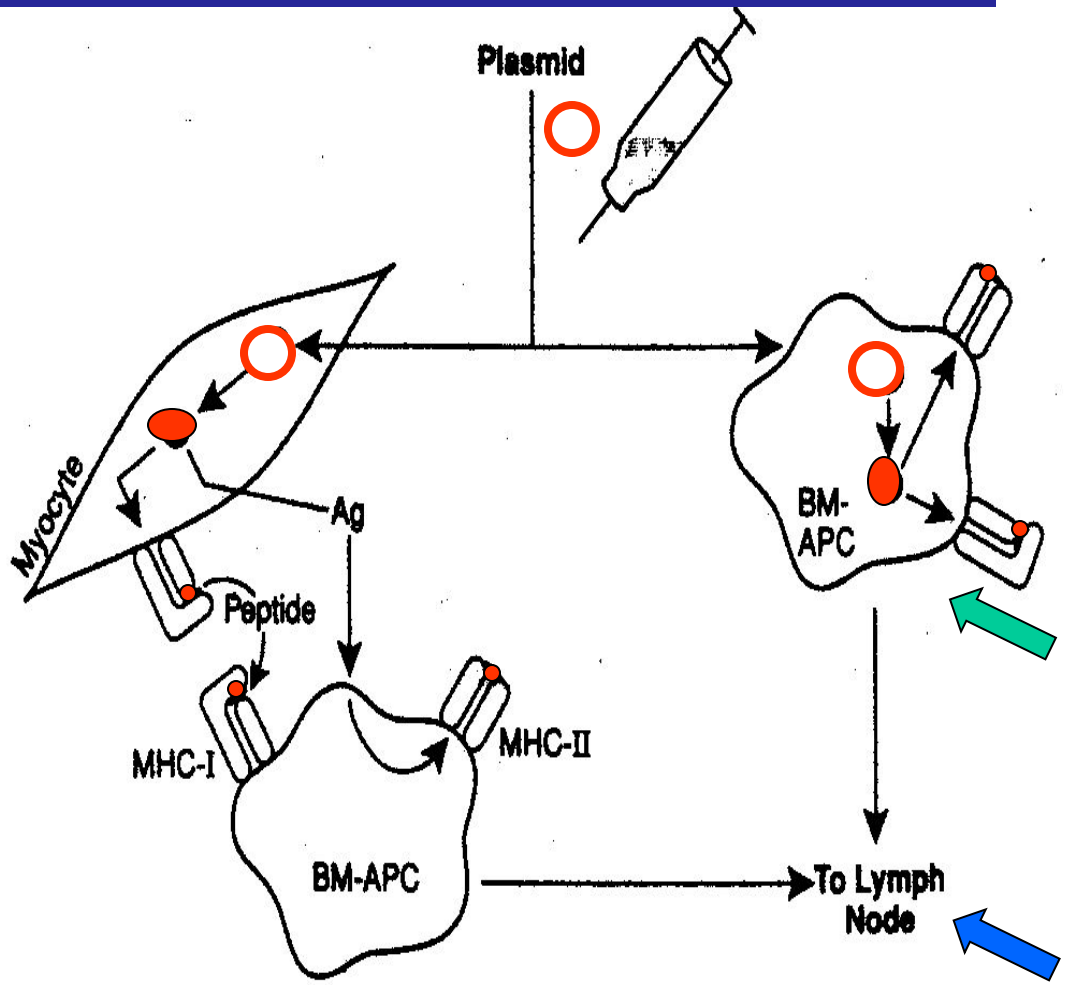
The plasmid can be uptaken by both muscle cell and antigen-presenting cell (APC).

The *gene for the antigen* (Ag) will be *expressed in muscle cell* and this antigen will be produced by the recipient muscle cells in large amounts.

(1) When uptaken by APC, the Ag can be presented on the APC together with class MHC-II to activate T helper cells to mediate humoral immunity.

(2) When the Ag is produced and presented as endogenous Ag together with class MHC-I on the surface of the muscle cell, it can elicit TH1 cell-mediated immune response.

Transfection of host cells with plasmid DNA



Plasmid (O) is taken up by host cells (actively or passively).

Antigen (Ag) produced by transfected myocytes is taken up by bone mar-row (BM)–derived antigen presenting cells (APCs).

BM-APCs can be trans-fected directly also.

Ag-bearing APC then can process and present anti-genic peptides com-plexed with MHC-molecu-les to the immune system after

DNA Vaccines

At present, several different DNA- based vaccines are on clinical trails against *malaria*, *HIV*, *influenza*, *hepatitis B*, and others. There is a special device for delivery – the gene gun.

2020 Recommended Immunizations for Children from Birth Through 6 Years Old

Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
HepB	HepB			HepB						
		RV	RV	RV						
		DTaP	DTaP	DTaP		DTaP				DTaP
		Hib	Hib	Hib	Hib					
		PCV13	PCV13	PCV13	PCV13					
		IPV	IPV		IPV					IPV
					Influenza (Yearly)*					
					MMR					MMR
					Varicella					Varicella
					HepA§					

Is your family growing? To protect your new baby against whooping cough, get a Tdap vaccine. The recommended time is the 27th through 36th week of pregnancy. Talk to your doctor for more details.

Shaded boxes indicate the vaccine can be given during shown age range

NOTE:
If your child misses a shot, you don't need to start over. Just go back to your child's doctor for the next shot. Talk with your child's doctor

FOOTNOTES:

* Two doses given at least four weeks apart are recommended for children age 6 months through 8 years of age who are getting an influenza (flu) vaccine for the first time and for some other children in this age group.

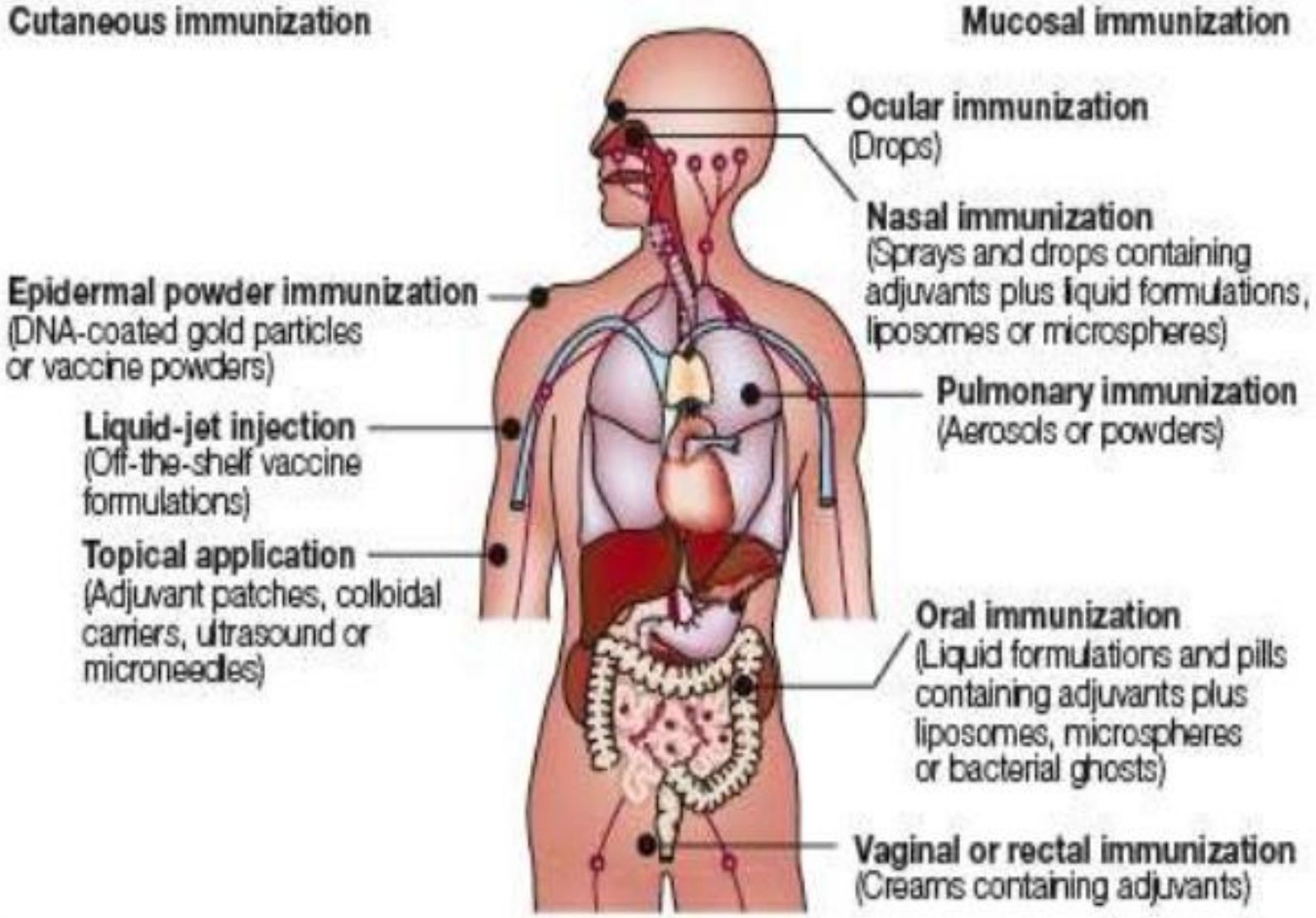
§ Two doses of HepA vaccine are needed for lasting protection. The first dose of HepA vaccine should be given between 12 months and 23 months of age. The second dose should be given 6 months after the first dose. All children and adolescents over 24 months of age who have not been vaccinated should also receive 2 doses of HepA vaccine.

See back page for more information on vaccine-preventable diseases and the

НАЦИОНАЛЬНЫЙ КАЛЕНДАРЬ ПРОФИЛАКТИЧЕСКИХ ПРИВИВОК В РОССИИ

Возраст ребенка	Вакцины
Первый день жизни	Против вирусного гепатита В (1-я вакцинация)
3 - 7-й день	Против туберкулеза
1 месяц	Против вирусного гепатита В (2-я вакцинация)
2 месяца	Против пневмококковой инфекции (1-я вакцинация)
3 месяца	Против дифтерии, коклюша, столбняка (1-я вакцинация); против полиомиелита (1-я вакцинация)
4,5 месяца	Против дифтерии, коклюша, столбняка (2-я вакцинация); против полиомиелита (2-я вакцинация); против пневмококковой инфекции (2-я вакцинация)
6 месяцев	Против дифтерии, коклюша, столбняка (3-я вакцинация); против вирусного гепатита В (3-я вакцинация); против полиомиелита (3-я вакцинация)
12 месяцев	Против кори, краснухи, паротита
15 месяцев	Против пневмококковой инфекции (ревакцинация)
18 месяцев	Против полиомиелита (1-я ревакцинация); против дифтерии, коклюша, столбняка (1-я ревакцинация)
20 месяцев	Против полиомиелита (2-я ревакцинация)
6 лет	Против кори, краснухи, паротита (ревакцинация)
6 - 7 лет	Против дифтерии, столбняка (2-я ревакцинация); против туберкулеза (ревакцинация)
14 лет	Против дифтерии, столбняка (3-я ревакцинация); против полиомиелита (3-я ревакцинация)

Дмитрий ПОЛУХИН


Cutaneous immunization
Mucosal immunization
Ocular immunization
(Drops)
Nasal immunization
(Sprays and drops containing adjuvants plus liquid formulations, liposomes or microspheres)
Epidermal powder immunization
(DNA-coated gold particles or vaccine powders)
Pulmonary immunization
(Aerosols or powders)
Liquid-jet injection
(Off-the-shelf vaccine formulations)
Topical application
(Adjuvant patches, colloidal carriers, ultrasound or microneedles)
Oral immunization
(Liquid formulations and pills containing adjuvants plus liposomes, microspheres or bacterial ghosts)
Vaginal or rectal immunization
(Creams containing adjuvants)

1. Non-viral gene delivery using lipoplexes. DNA is complexed with cationic liposomes and is internalized through receptor mediated