MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
STATE BIOTECHNOLOGICAL UNIVERSITY
Institute of Veterinary Medicine and Animal Husbandry
Faculty of Veterinary Medicine
Department of Epizootology and Microbiology

Vaccinology in veterinary medicine

Lecture course

Methodological recommendations for students of 2-3 courses of specialty 211- Veterinary medicine of the second (master's) level

Kharkiv – 2022

UDC 619:616.98:615.371:578/579
Methodological recommendations for students of the 2nd-3rd year of the FVM specialty 211- "Veterinary Medicine" of the second (master's) level - Mala Danylivka, 2022 - 151 slides.

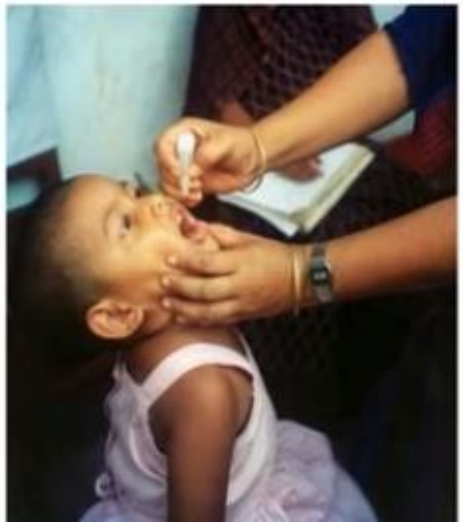
The outlined recommendations are intended for mastering theoretical knowledge (skills) during the study of the course "Vaccinology in Veterinary Medicine". The scope of the discipline according to the curriculum is 90 hours, of which 14 hours are lectures, 16 hours of laboratory classes and 60 hours of independent classes. The recommendations contain the main provisions of the lectures .

Compilers: Haragulya H.I., Basko S.O.

Approved by the Scientific and Methodological Commission of the Faculty of Veterinary Medicine of the State Biotechnological University "22" on December 22, 2022. (protocol No. 61)

Responsible for graduation,
head of the department,
associate professor R.V. Severin

Lecture 1-2.



Vaccinology

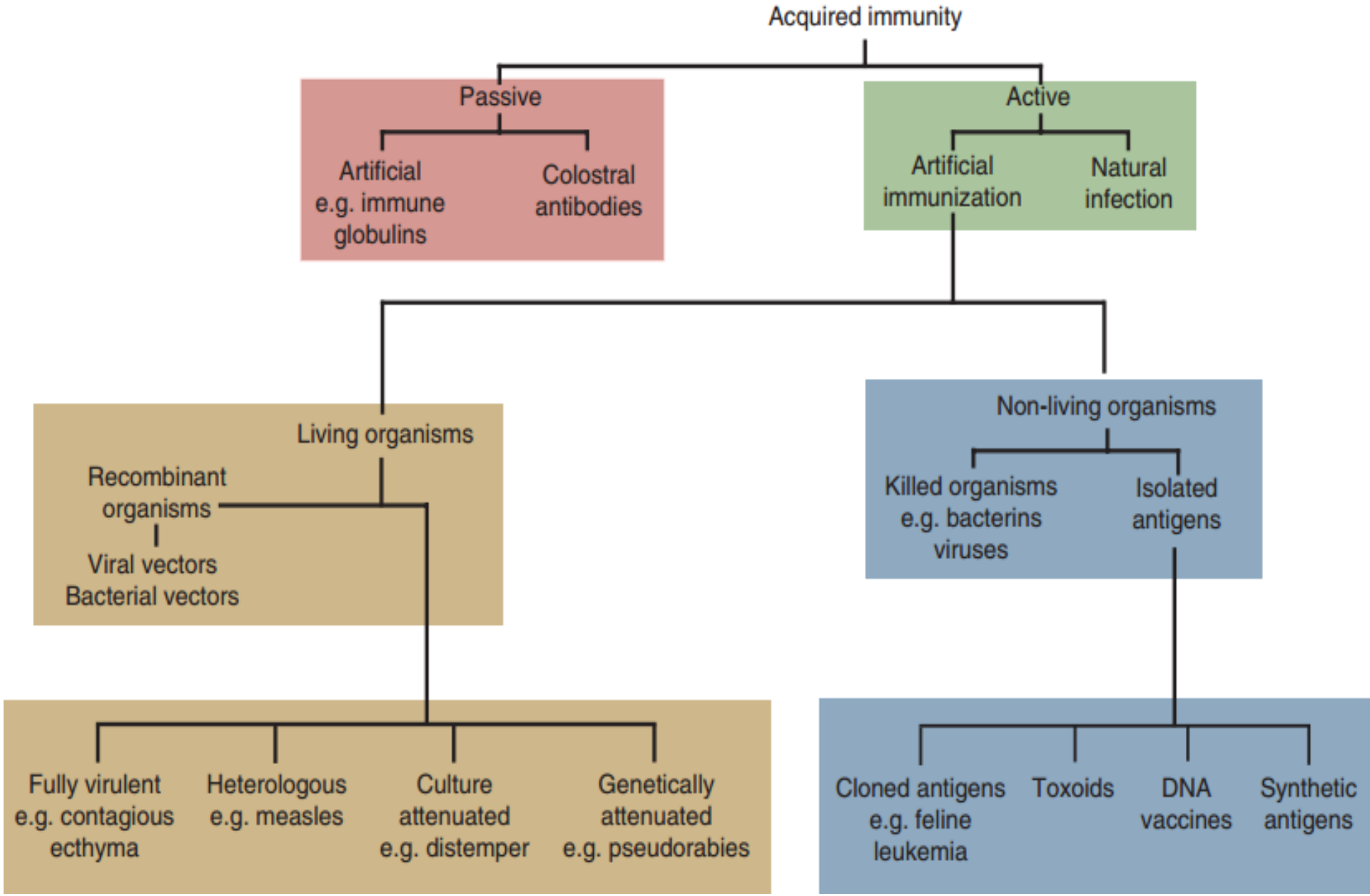
1. Introduction into vaccinoligy.
2. Vaccine antigens.

2022

Immunization - the administration of an antigen to an individual in order to confer immunity.

- There are two basic methods by which any animal may be made immune to an infectious disease: passive and active immunization.
- Passive immunization produces temporary immunity by transferring antibodies from a resistant to a susceptible animal. These passively transferred antibodies give immediate protection, but since they are gradually catabolized, this protection wanes, and the recipient eventually becomes susceptible again.
- Active immunization using vaccines containing live or dead organisms produces slowly developing but long-lasting immunity.

A classification of the different types of adaptive immunity and of the methods employed to induce protection.



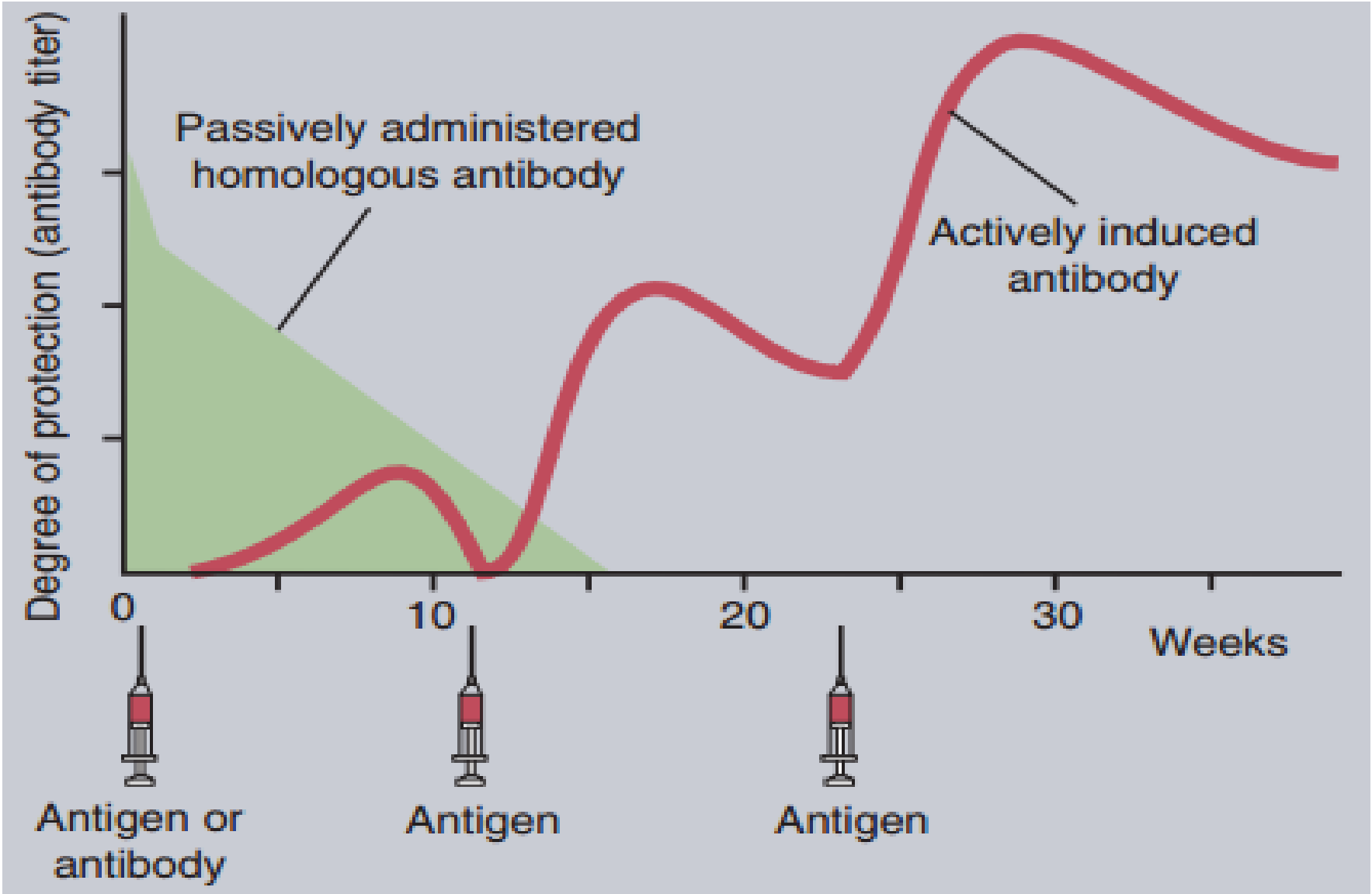
Passive immunization

- Passive immunization requires that antibodies be produced in donor animals by active immunization and that these antibodies be given to susceptible animals to confer immediate protection.
- Serum containing these antibodies (antisera) may be produced against a wide variety of pathogens. For instance, they can be produced in cattle against anthrax, in dogs against distemper, in cats against panleukopenia, and in humans against measles.
- They are most effective protecting animals against toxigenic organisms such as *Clostridium tetani* or *Clostridium perfringens*, using antisera raised in horses. Antisera made in this way are called immune globulins and are commonly produced in young horses by a series of immunizing injections.
- The clostridial toxins are proteins that can be denatured and made nontoxic by treatment with formaldehyde.

Passive immunization

- Although immune globulins give immediate protection, some problems are associated with their use. For instance, when horse tetanus immune globulin is given to a cow or dog, the horse proteins will be perceived as foreign, elicit an immune response, and be rapidly eliminated.
- To reduce antigenicity, immune globulins are usually treated with pepsin to destroy their Fc region and leave intact only the portion of the immunoglobulin molecule required for toxin neutralization — the F(ab)′2 fragment

The levels of serum antibody (and hence the degree of protection) conferred by active and passive methods of immunization.



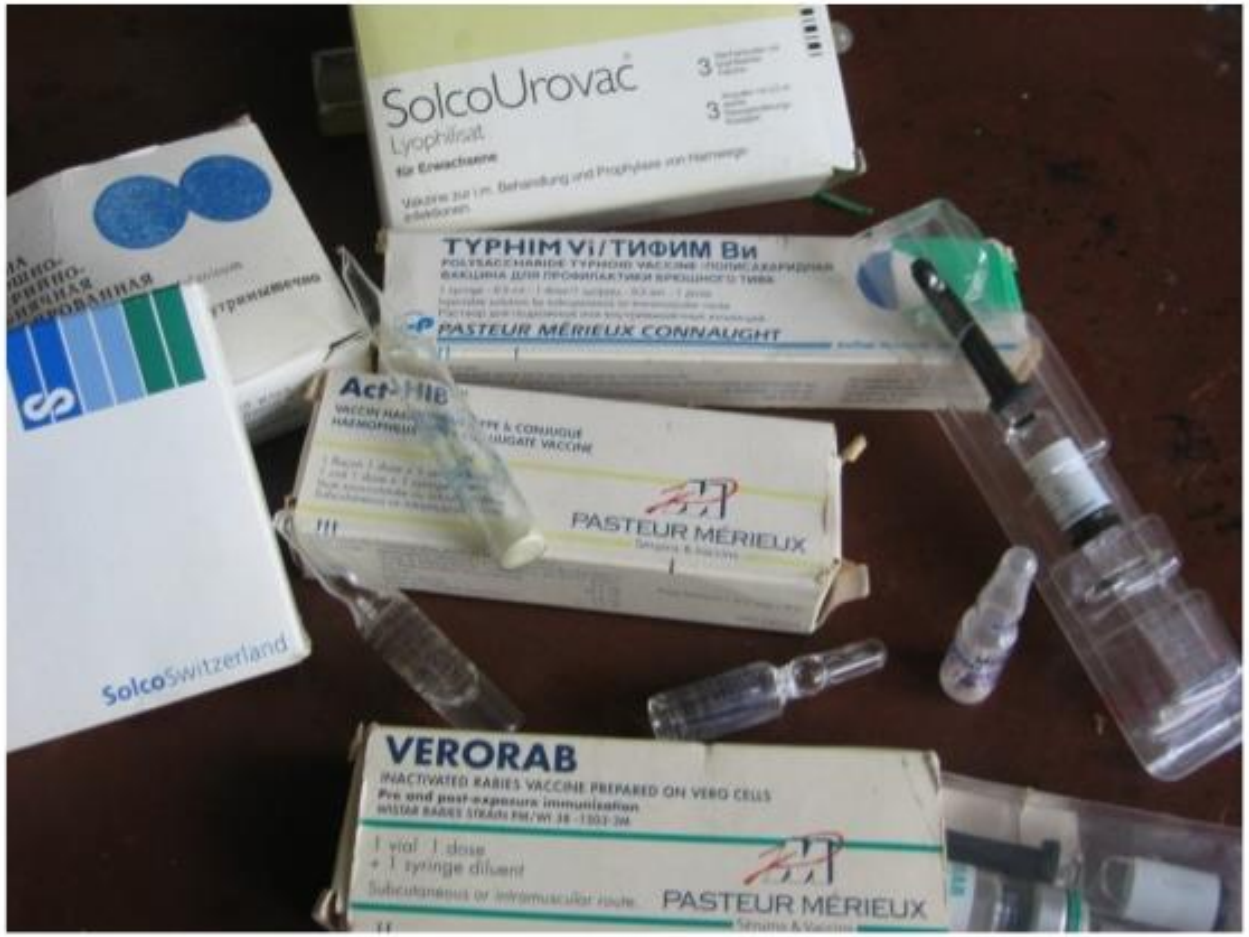
Primary vs. Secondary Immune Responses

Differences between the primary and secondary immune responses	
Primary response	**Secondary response**
Small number of pathogen-specific cells respond at the start	Large number of pathogen-specific cells respond immediately
Delay before pathogen-specific antibodies are produced	Pathogen-specific antibodies already present
Non-isotype-switched antibody having a mixture of affinities for the pathogen is produced at the start	Antibodies are isotype-switched and have high affinity for the pathogen
High threshold of activation	Lower threshold of activation
Delay before effector T cells are generated and are able to enter infected tissues	Effector T cells are present and can enter infected tissue immediately
Innate immunity works alone until an adaptive response is generated	Close cooperation between innate and adaptive immunity from the start

Parham Figure 11.13

https://www.youtube.com/watch?v=Uw8i-n8Uclo

VACCINES



'Prevention is better than cure'

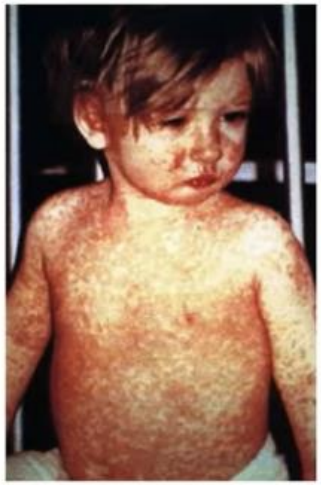
VACCINES

- **Vaccine is a preparation of microbes or toxoids that can no longer induce disease but can still stimulate active immunity against the corresponding pathogen or its toxin**
- *Vaccine is any preparation intended for active immunological prophylaxis, preparation of killed microbes of virulent strains or living microbes of attenuated (variant or mutant) strains, or microbial, plant, metazoan or products*

  [Stedman's Concise Medical Dictionary]
- It is an **antigen**
- Vaccine can induce **antibacterial**, **antiviral** or **antitoxic** immunity, or immunity against **parasites**
- Vaccine (*latin "vacca" = cow, vaccinus=relating to a cow*)

The numbers of deaths vaccines avert is remarkable, especially in lower and middle income countries.

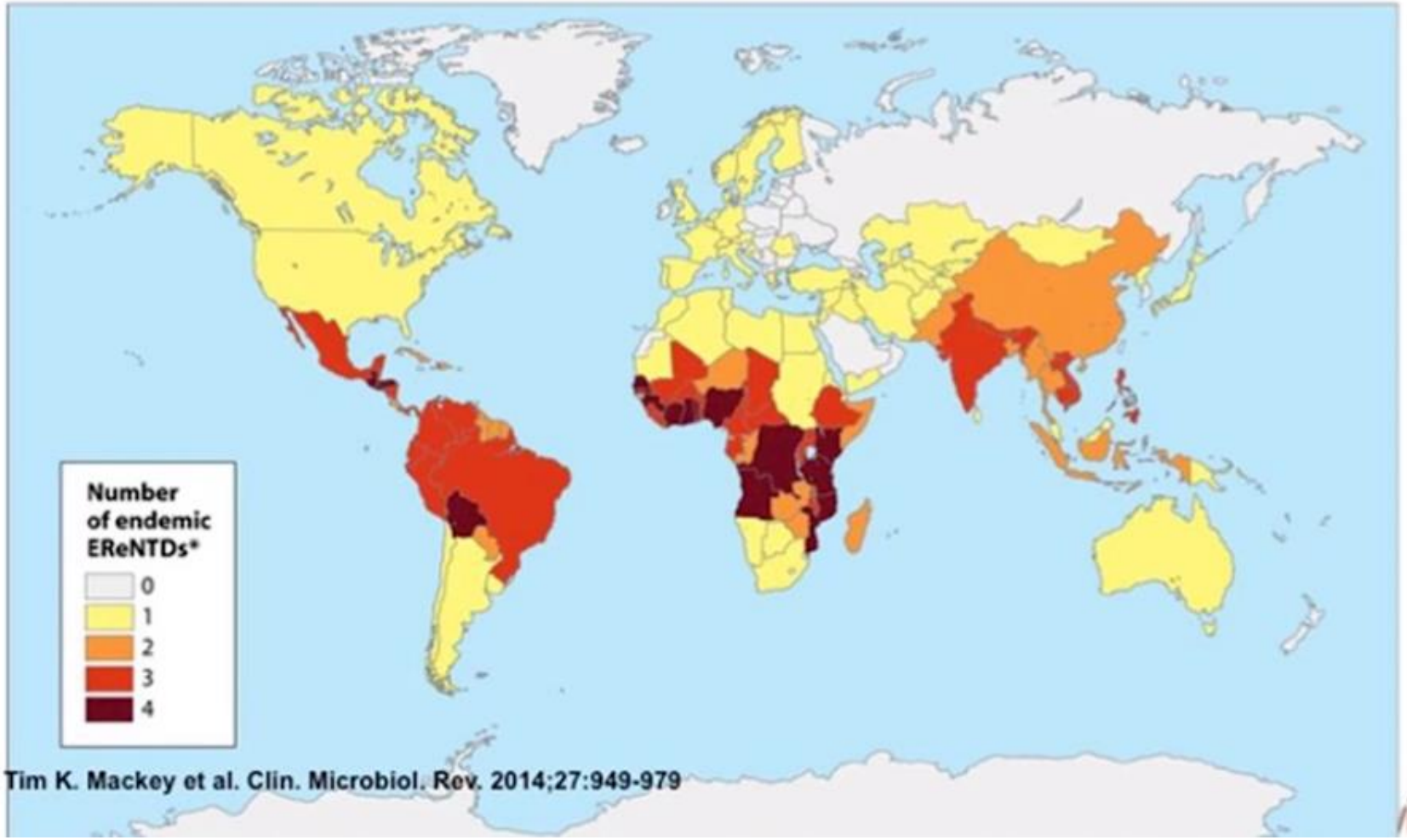
- Recent estimate effect of vaccination against ten pathogens globally:
- Averted 37 million deaths between 2000 and 2019.
- Among children under 5 years, a 57% reduction, most notably from measles.
- *Xiang Li et al Lancet 2021.*



Juliene Harneis/ UNICEF/ CDC

https://www.gresham.ac.uk/watch-now/vaccination

Global intensity map of five major emerging and re-emerging diseases (dengue, rabies, cysticercosis, Chagas' disease, trypanosomiasis)



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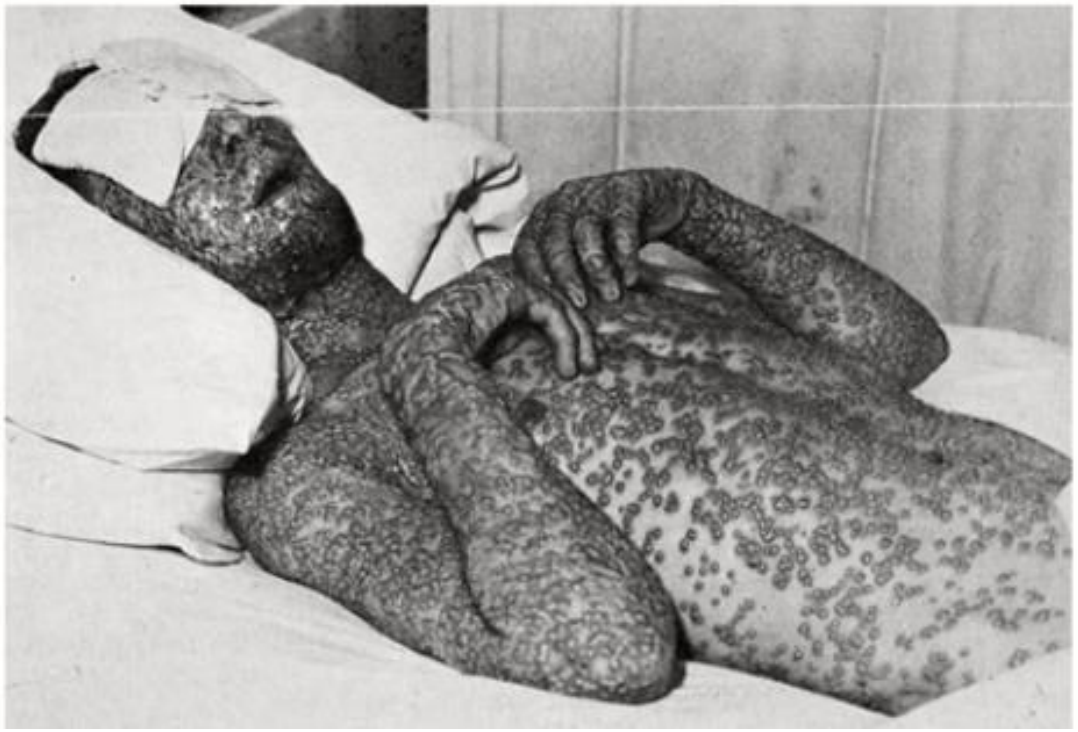


Smallpox

- The mortality of the severe form of smallpox – *variola major* – was very high without vaccination, up to 35% in some outbreaks.
- The **smallpox vaccine** is the first vaccine to be developed against a contagious disease.

- A method of inducing immunity known as inoculation ("variolation") was practiced before the development of a modern vaccine and likely occurred in Africa and China well before the practice arrived in Europe.
- In China, powdered smallpox scabs were blown up the noses of the healthy. The patients would then develop a mild case of the disease and from then on were immune to it. The technique did have a 0.5–2.0% mortality rate, but that was considerably less than the 20–30% mortality rate of the disease itself.

Smallpox vaccine

- In 1796, the British doctor Edward Jenner demonstrated that an infection with the relatively mild cowpox virus conferred immunity against the deadly smallpox virus.
- Cowpox served as a natural vaccine until the modern smallpox vaccine emerged in the 20th century.

Dr Edward Jenner performing his first vaccination on James Phipps, a boy of age 8. 14 May 1796. Painting by Ernest Board (early 20th century).

Smallpox vaccine

An 1802 caricature by James Gillray depicting the early controversy surrounding Jenner's vaccination theory

Dr. Jenner's legacy.

- Many of the most feared diseases largely gone- where vaccines are available.
- Substantial protection against multiple childhood infections.
- New and relatively rapid approaches for responding to epidemics.
- Major drops in adult disease continuing, including cancers.
- Vaccine science advancing rapidly.

Edward Jenner, 1749-1823

https://www.gresham.ac.uk/watch-now/vaccination

This observation by Jenner is important. Many vaccines are not all-or-none. And may need revaccination.

Vaccines can:

- Prevent infection.
- Prevent significant disease if infected.
- Prevent death even in significant disease.

Many vaccines reduce severity of disease even if not able to stop infection.

Effects may wane with time.

Two 13 year old boys, one vaccinated, infected same source. Dr Allan Warner, Leicester 1901.

https://www.gresham.ac.uk/watch-now/vaccination

Eradication of smallpox

- From 1958 to 1977, the World Health Organization (WHO) conducted a global vaccination campaign that eradicated smallpox, making it the only human disease to be eradicated.
- Although routine smallpox vaccination is no longer performed on the general public, the vaccine is still being produced to guard against bioterrorism, biological warfare, and monkeypox.
- By 1984, the only known stocks were kept at the CDC in the U.S. and the State Research Center of Virology and Biotechnology (VECTOR) in Koltsovo, Russia. These states report that their repositories are for possible anti-bioweaponry research and insurance if some obscure reservoir of natural smallpox is discovered in the future.

Live vaccinia vaccine led to smallpox eradication by 1980.

1967

1975

1976-7

- Eradication attempt agreed by World Health Assembly 1959, when 2m a year dying; declared 1980.
- Last continuous case – Somalia October 1977 (last case from lab in Birmingham, 1978).
- Estimated over 300 million deaths during the 20th century.

https://www.gresham.ac.uk/watch-now/vaccination

Monkeypox

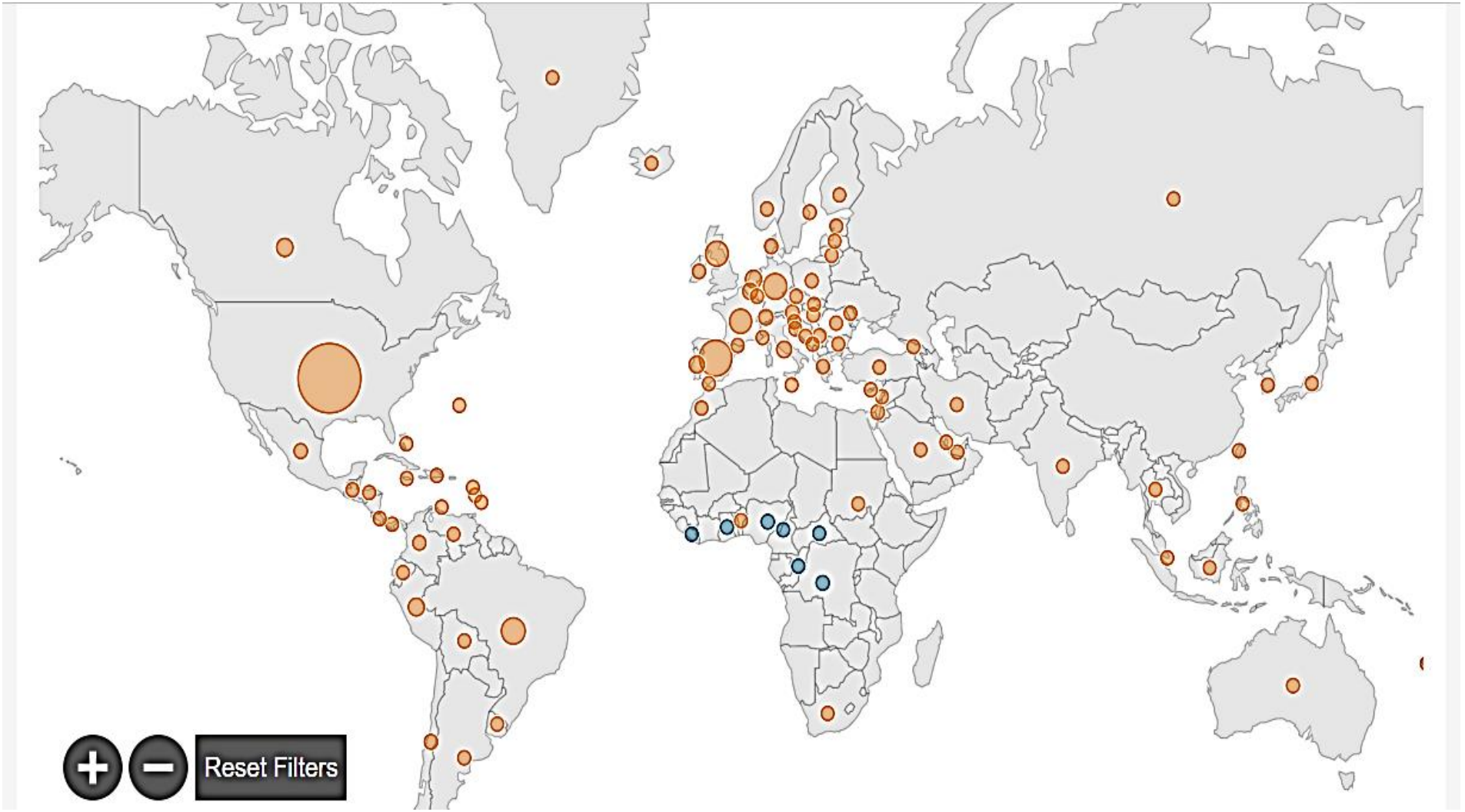
- Monkeypox is a viral zoonotic disease that occurs primarily in tropical rainforest areas of central and west Africa and is occasionally exported to other regions.
- Monkeypox is transmitted to humans through close contact with an infected person or animal, or with material contaminated with the virus.
- **Monkeypox is less contagious than smallpox and causes less severe illness.**
- Vaccines used during the smallpox eradication programme also provided protection against monkeypox. Newer vaccines have been developed of which one has been approved for prevention of monkeypox.
- An antiviral agent developed for the treatment of smallpox has also been licensed for the treatment of monkeypox.

Monkeypox

- Human monkeypox was first identified in humans in 1970 in the Democratic Republic of the Congo.
- Since 2017, Nigeria has experienced a large outbreak, with over 500 suspected cases and over 200 confirmed cases and a case fatality ratio of approximately 3%. Cases continue to be reported until today.
- Vaccination against smallpox was demonstrated through several observational studies to be about 85% effective in preventing monkeypox. Thus, prior smallpox vaccination may result in milder illness.
- Scientific studies are now underway to assess the feasibility and appropriateness of vaccination for the prevention and control of monkeypox.

Monkey pox: WHO has declared a global emergency

Locations with cases



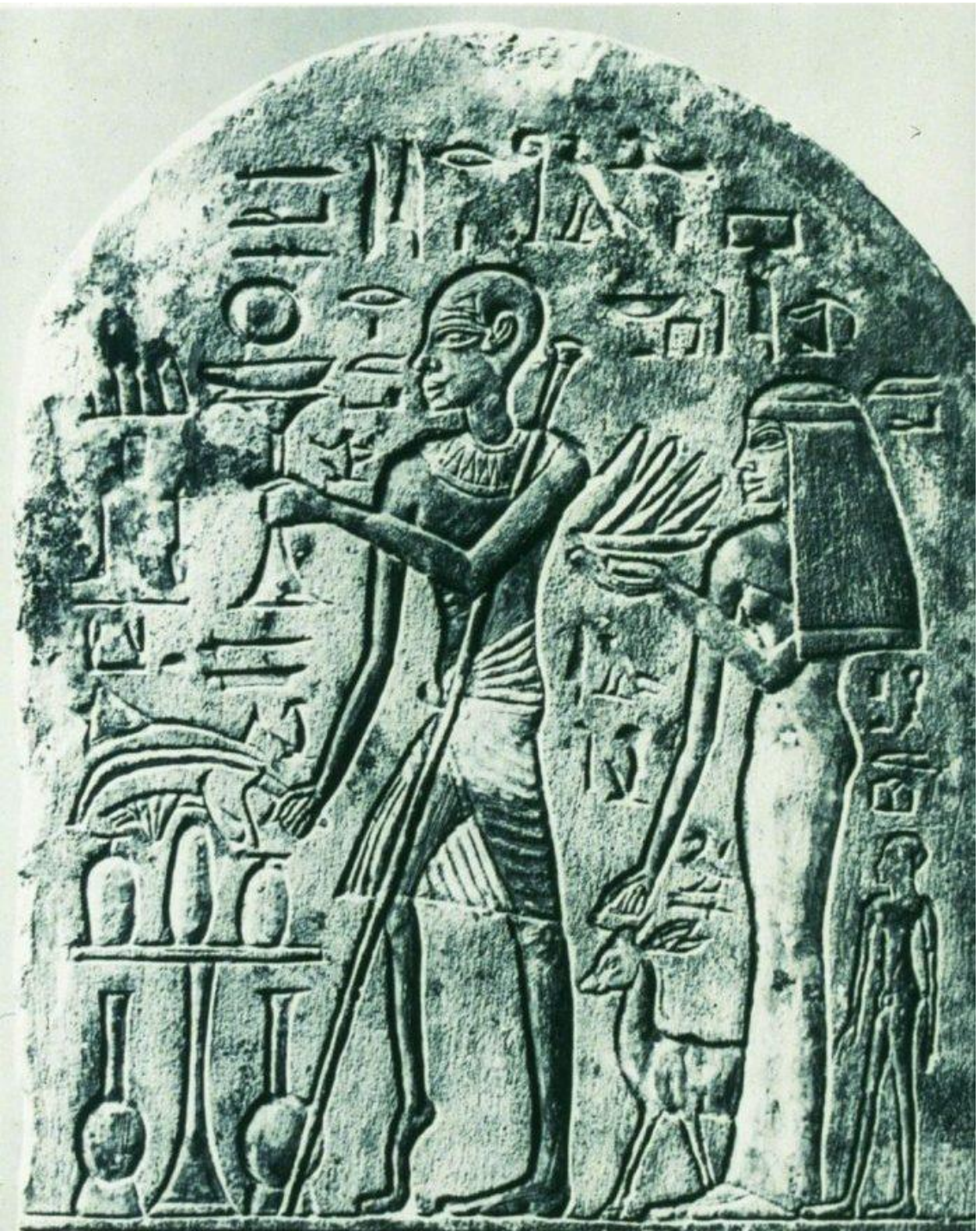
https://www.bbc.com/ukrainian/news-62279874

Rabies

Inactivated rabies vaccine 1885 (Pasteur and Roux).

- Up to 99% of human cases from dog bites. Globally up to 59,000 cases a year (WHO).
- Death within 10 days of symptoms is virtually inevitable. A terrible disease.
- Initial vaccine from infected rabbit spinal cord after infection.
- Has got steadily safer. Now used pre-infection.
- Vaccination of dogs and foxes.
- The map of human rabies is steadily shrinking.

https://www.gresham.ac.uk/watch-now/vaccination



Polio

An Egyptian stele portrays a priest with a withered leg, suggesting that **polio** has existed for thousands of years

https://polioeradication.org/polio-today/history-of-polio/

Polio

Poliomyelitis remains threat in many countries. This undated photo shows polio patients are in Sierra Leone.

https://www.cbsnews.com/news/poliomyelitis-strain-spreads-to-china-is-us-at-risk/

Polio

Children and a teacher with polio participate in a class at Saint Marys Hospital.

https://www.mayoclinic.org/coronavirus-covid-19/history-disease-outbreaks-vaccine-timeline/polio

Polio

Two polio vaccines- attenuated oral and inactivated injection.

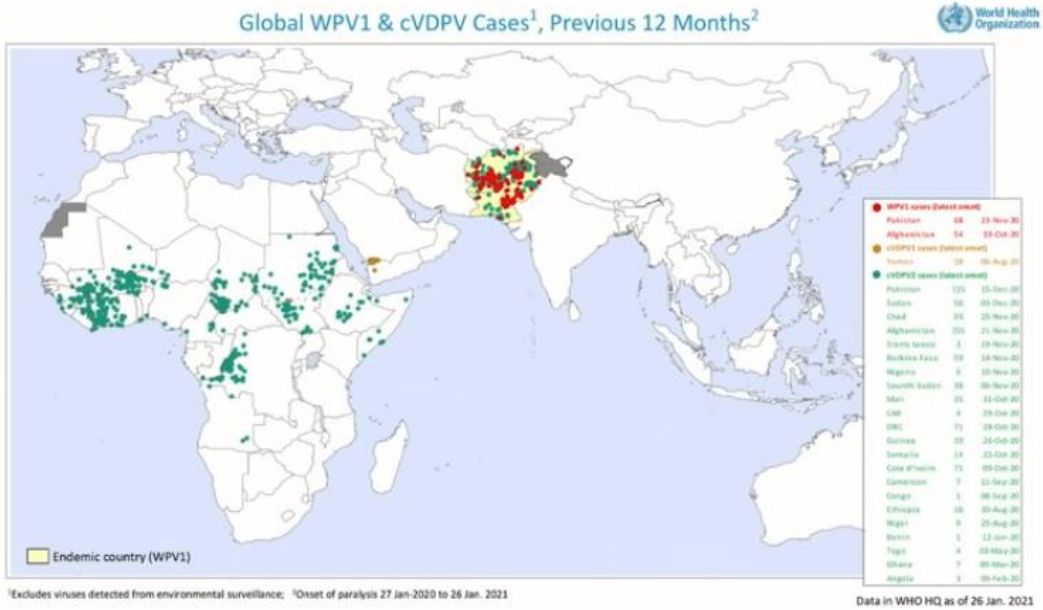
- Polio a paralysing disease. Was very common.
- Jonas Salk inactivated vaccine- 1950s.
- Albert Sabin oral attenuated to the 3 polio strains. Replicates in the gut, but not nerves.
- Pro oral: easy to give, acceptable, good immunity, some spread possible.
- Con oral: very rarely (about three per million doses) can cause paralysis.

Children's Hospital, Boston, Mass.
RareHistoricalPhotographs.com

https://www.gresham.ac.uk/watch-now/vaccination

Polio

350,000 wild cases in 1988; 140 in 2020 (WHO).
Eradication tantalisingly close.



1988

140WPV 99cVDPV

https://www.gresham.ac.uk/watch-now/vaccination

Tetanus

Tetanus, a terrible disease caused by toxin produced by *C. tetani*.

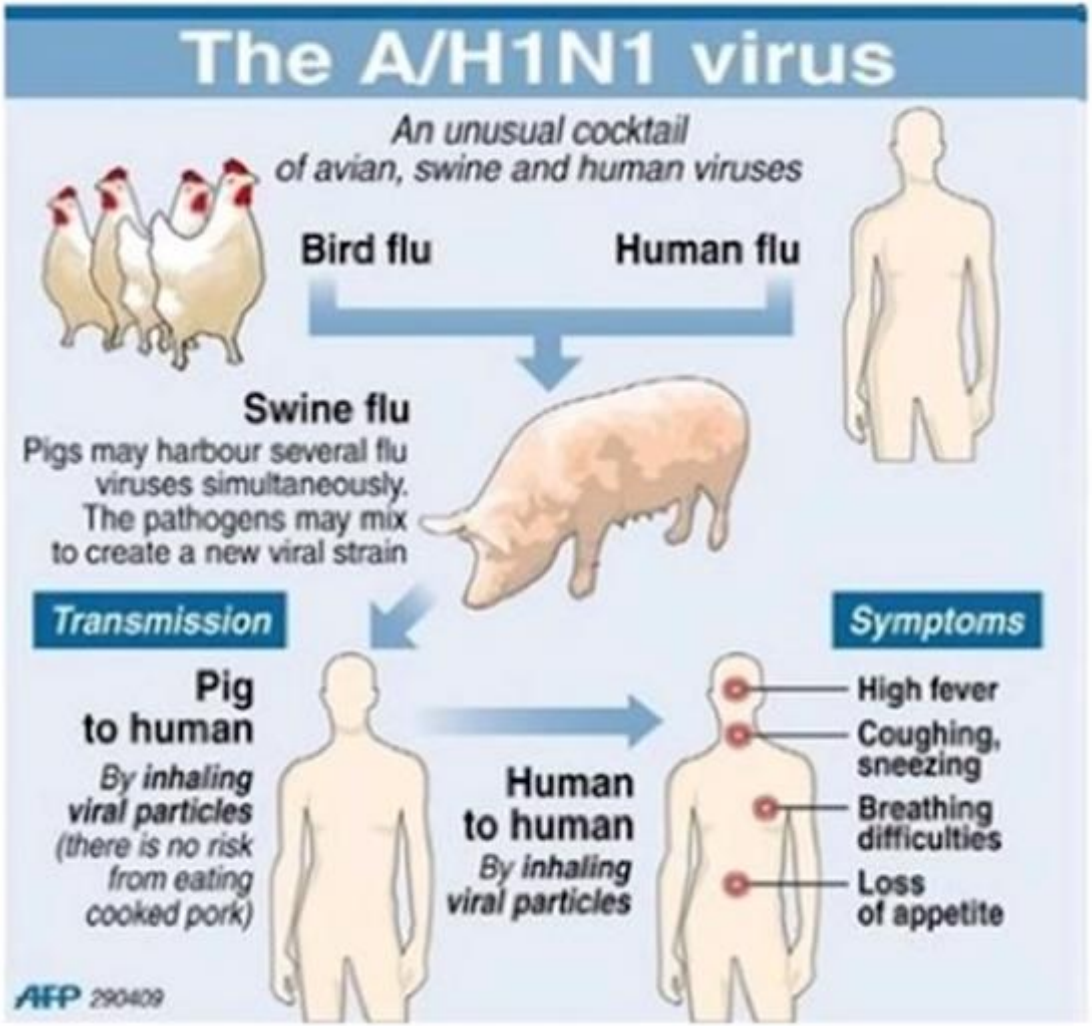
- In rural communities without expert midwifery high infant mortality- up to 50% recorded.
- In some settings tetanus can be the majority of these. Mortality in newborns almost 100%.
- In adults high mortality, exceptionally painful.
- The toxin is inactivated (*toxoid*), and then adsorbed. Developed 1938, introduced widely in 1950s.
- Vaccine is highly effective.
- Does not stop infection- but stops toxin.
- No herd effect.

St Kilda 1880s

https://www.gresham.ac.uk/watch-now/vaccination

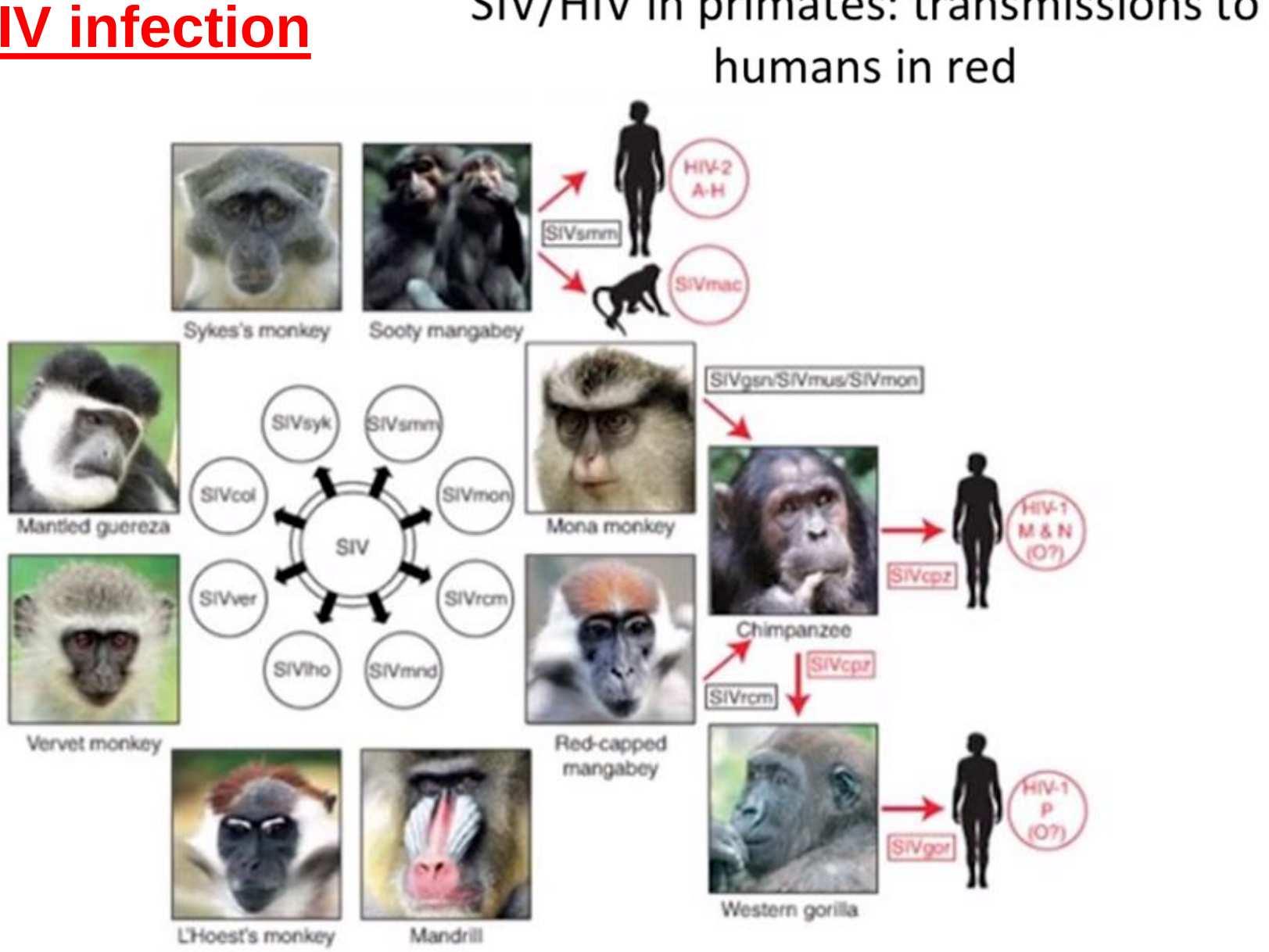
Swine flu

Swine flu viruses are recombinants between three viruses



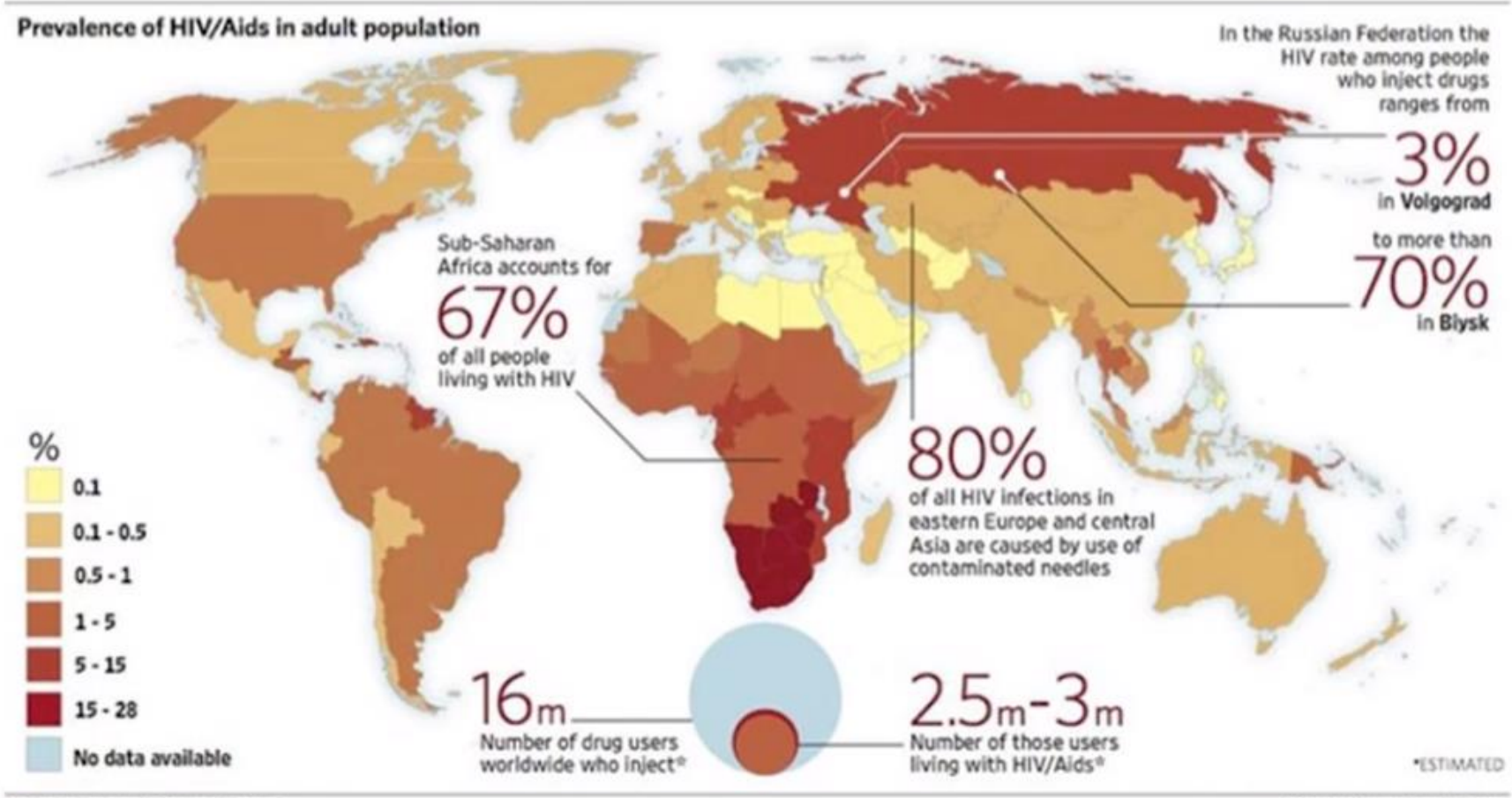
https://www.youtube.com/watch?v=zfHno163zRo

HIV infection



https://www.youtube.com/watch?v=zfHno163zRo

A global view of HIV infection in 2013



35 million people living with HIV

https://www.youtube.com/watch?v=zfHno163zRo

Vaccines and epidemics.

- Known vaccines against known infections- eg Yellow Fever.
- Adapted vaccines against adapted infectious threats- pandemic flu.
- New vaccines against newly emerging threats. Ebola.
- And new threats- COVID-19.
- Epidemics we might get a vaccine- Zika.
- Epidemics we have struggled to get a vaccine- HIV.

Ebola assay, Army technicians.

https://www.gresham.ac.uk/watch-now/vaccination

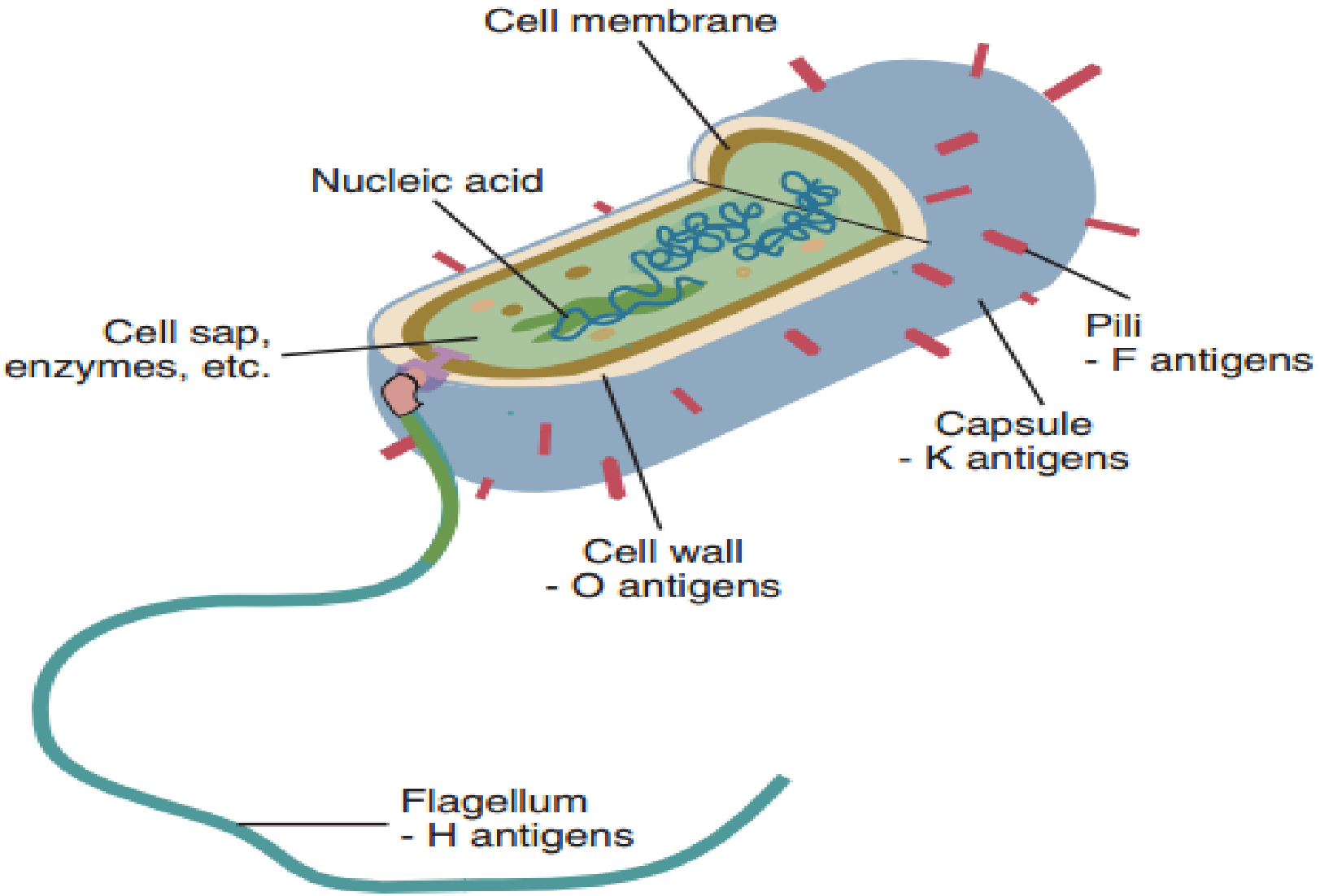
Antigens: Triggers of Adaptive Immunity

- The adaptive immune system is optimized to recognize microbial macromolecules.
- The best antigens are therefore large, complex, stable, foreign proteins.
- Small molecules of less than 10.000 Da are usually poor antigens.
- Small molecules may be made antigenic by linking them to large proteins. Small molecules used as antigens in this way are called haptens.
- The cells of the adaptive immune system use receptors that can recognize specific areas on the surface of foreign molecules. These areas are called antigenic determinants or epitopes.

Bacterial Antigens

- The major components of the bacterial surface thus include the cell wall and its associated protein structures, the capsule, the pili, and the flagella. Many bacteria are classified according to this antigenic structure.
- Bacterial capsules consist mainly of polysaccharides that are usually good antigens. Capsular antigens are collectively called K antigens.
- Pili and fimbriae are short projections that cover the surfaces of some Gram-negative bacteria; they are classified as F antigens.
- Flagella antigens are collectively called H antigens.
- Exotoxins are highly immunogenic proteins and stimulate the production of antibodies called antitoxins.

The antigenic structure of a typical bacterium and the location of its most important antigens.

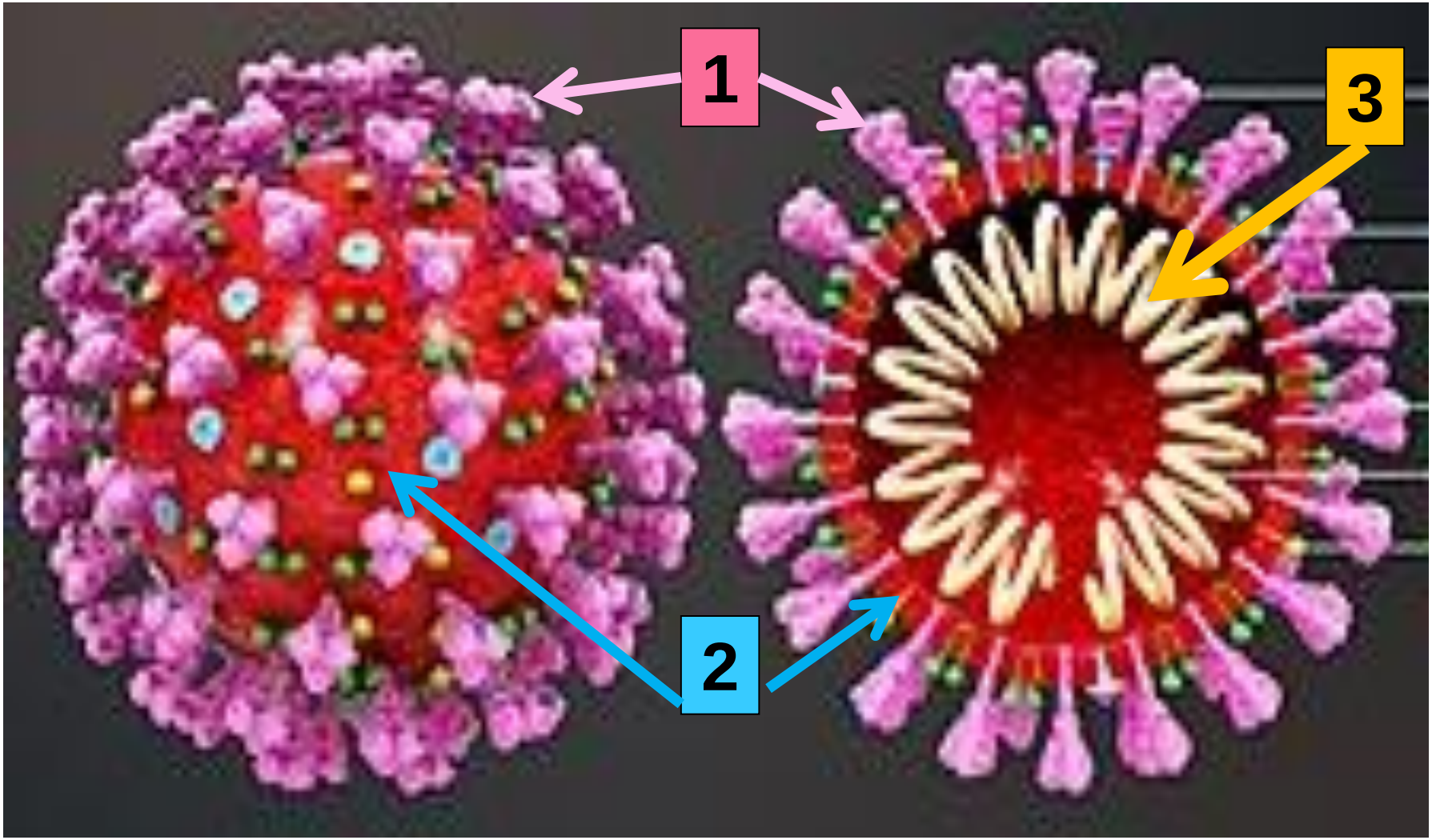


Viral Antigens

- Viruses are very small noncellular organisms that can grow only inside living cells. They are thus “obligate,” intracellular parasites.
- Viruses usually have a relatively simple structure consisting of a nucleic acid core surrounded by a protein layer.
- A complete viral particle is called a virion.
- Capsid proteins are good antigens, highly capable of stimulating antibody formation.
- Some viruses may also be surrounded by an envelope containing lipoproteins and glycoproteins.

The antigenic structure of a coronavirus:

1 – surface glycoproteins, 2 – surface proteins, 3 – RNA



Antigens and epitopes

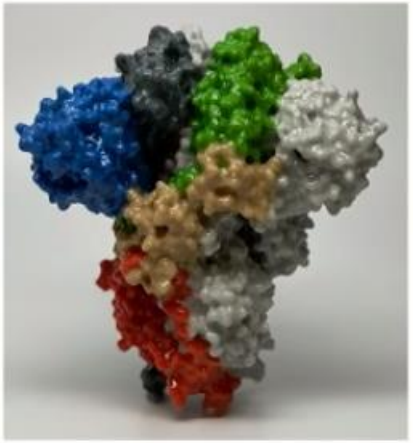
Most target the spike protein the virus uses to enter the cell.

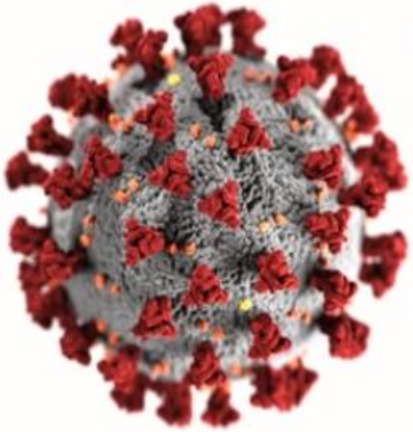
Relatively conventional:

- Whole inactivated virus and adjuvant. Example Valneva.
- Protein and adjuvant. Example Novavax.

More recent technology:

- Virus-vectored. Examples Oxford-AZ, J&J-Jannsen.
- RNA vaccines. Examples Pfizer-BioNTech, Moderna.

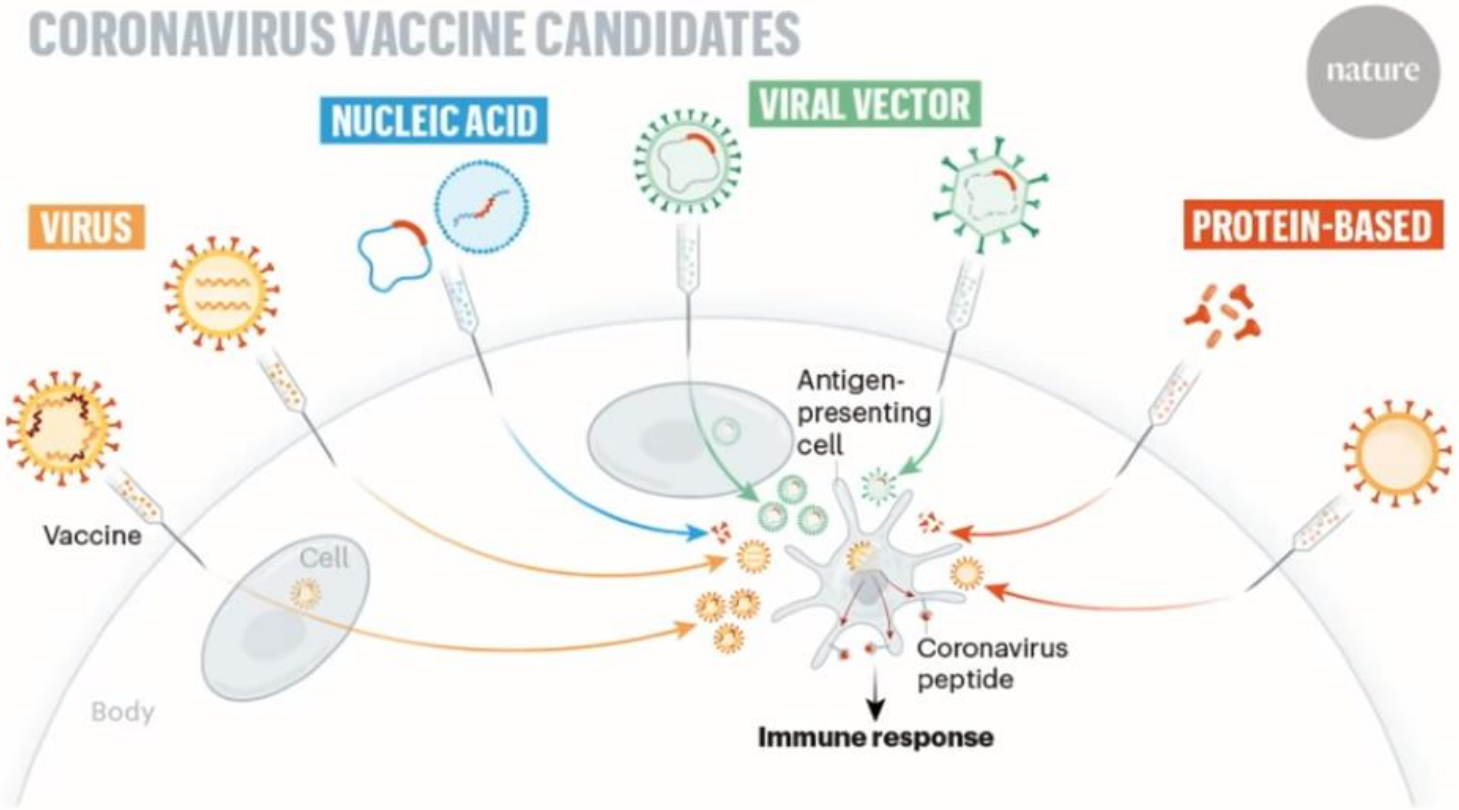




NIH,

https://www.gresham.ac.uk/watch-now/vaccination

COVID-19 has seen the fastest development of vaccines ever. Old and relatively new technologies all produced in a year.

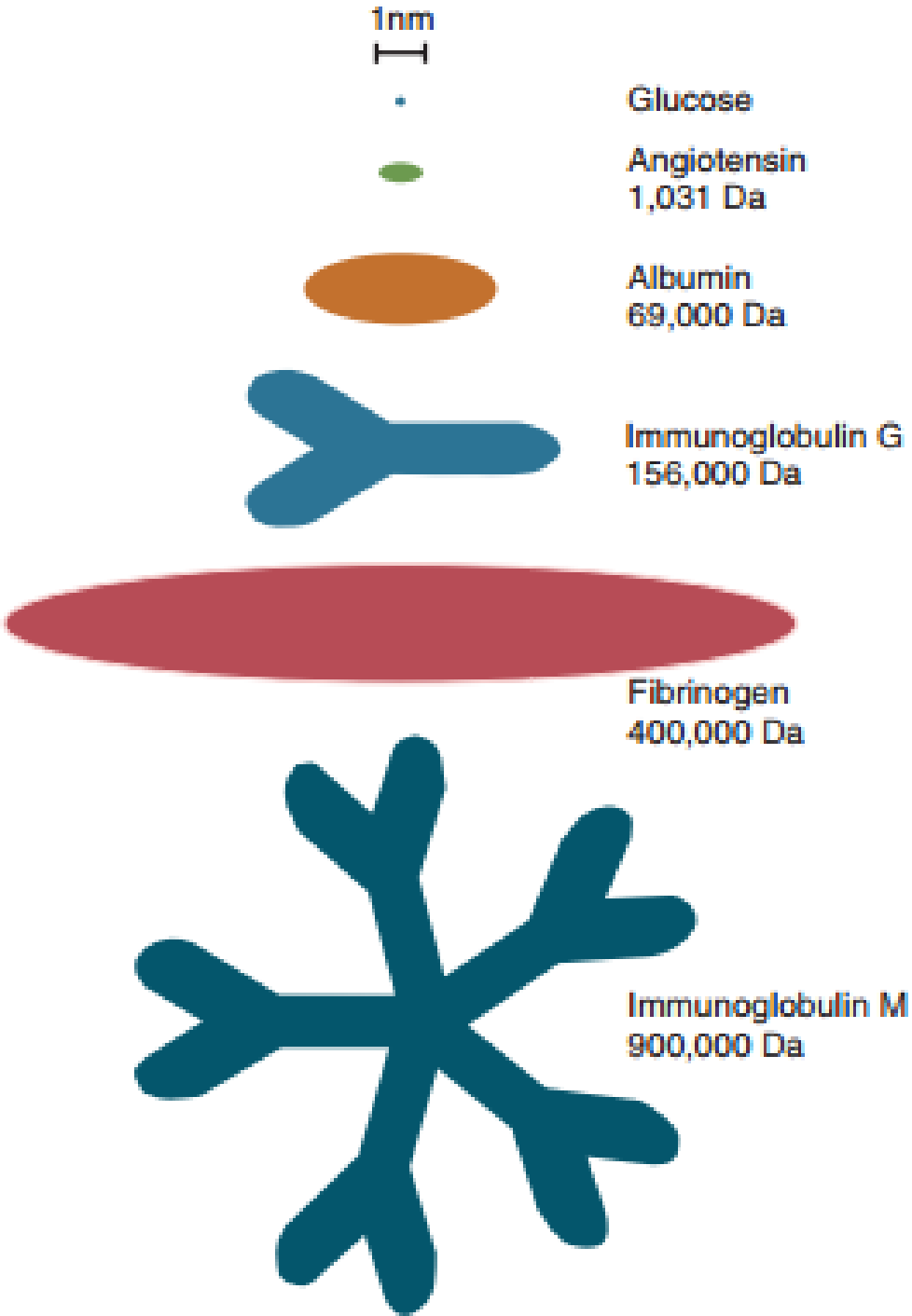


Nature 2020

https://www.gresham.ac.uk/watch-now/vaccination

What Makes a Good Antigen?

- Molecules vary in their ability to act as antigens (their antigenicity). In general, foreign proteins make the best antigens, especially if they are big (greater than 1000 Da is best).
- Simple polysaccharides, such as starch or glycogen, are not good antigens simply. More complex carbohydrates may be effective antigens, especially if bound to proteins.
- Lipids tend to be poor antigens. Nevertheless, when linked to proteins or polysaccharides, lipids can trigger immune responses.
- Mammalian nucleic acids are very poor antigens because of their relative simplicity and flexibility and because they are very rapidly degraded.
- Proteins are the most effective antigens because they have properties that best trigger an immune response.



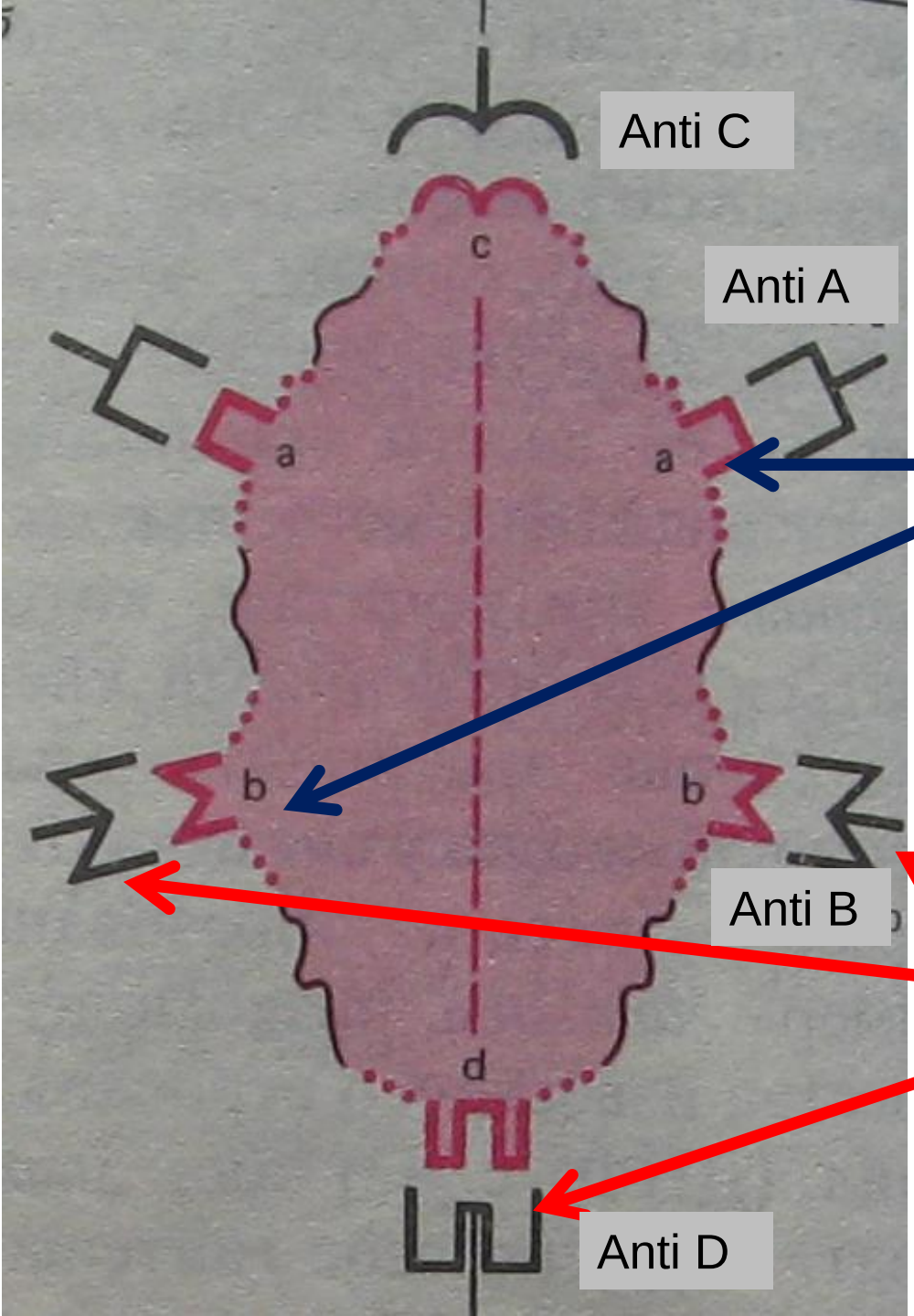
The relative sizes of several significant antigens.

Size does matter! Big molecules are generally much more antigenic than small molecules. Molecules as small as angiotensin are poor antigens.

Epitopes

- Foreign particles, such as bacteria, nucleated cells, and red blood cells, are a complex mixture of proteins, glycoproteins, polysaccharides, lipopolysaccharides, lipids, and nucleoproteins.
- Large molecules have specific regions against which immune responses are directed. These regions, usually on the surface of the molecule, are called epitopes, or antigenic determinants.
- In a large, complex protein molecule, many different epitopes may be recognized by the immune system. The cells of the immune system recognize and respond to these foreign epitopes.

The structure of the antigen molecule



Epitope (antigenic determinants)

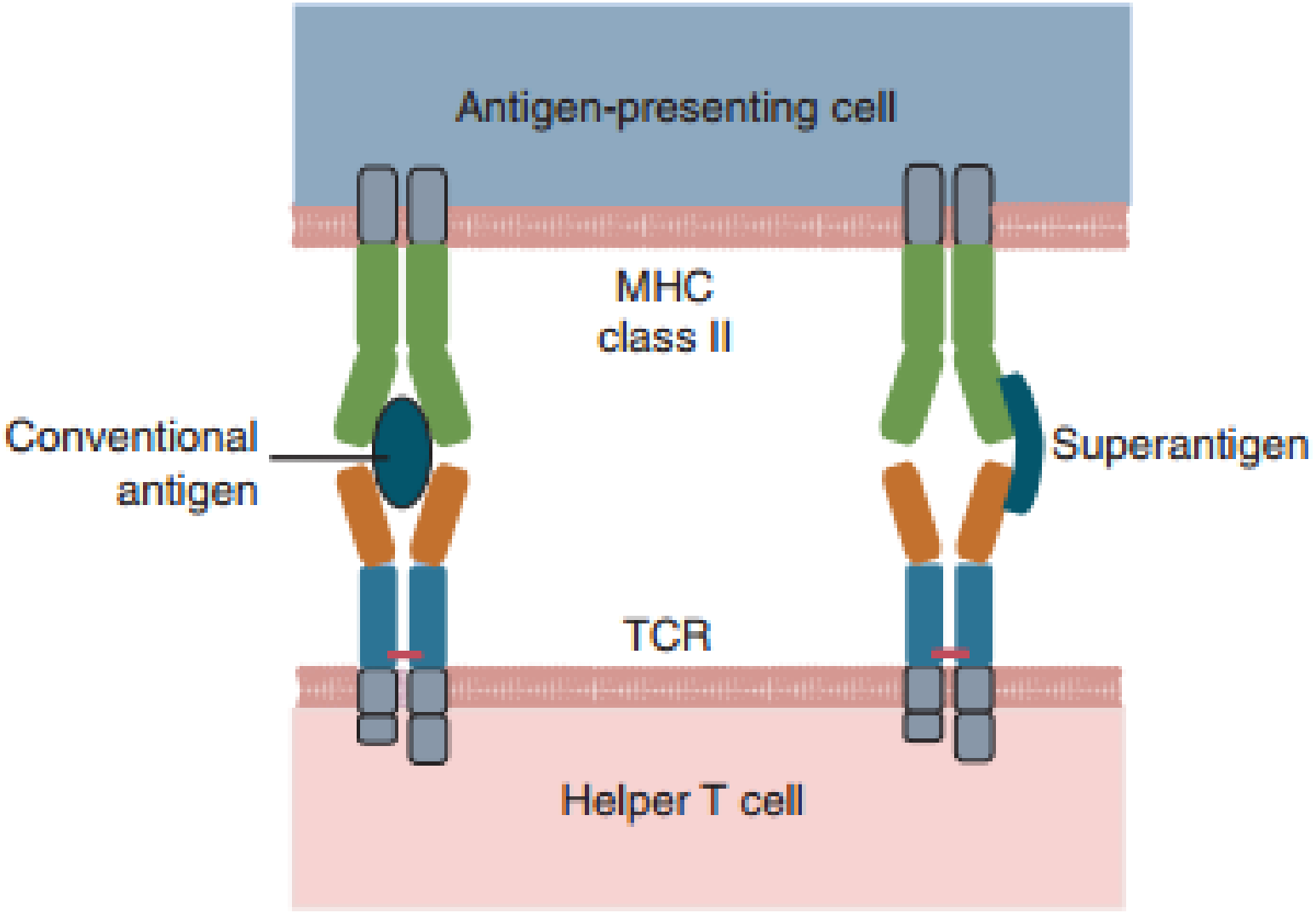
Antibodies (different types)

Haptens

- Small molecules such as many drugs or hormones of less than 1000 Da are far too small to be appropriately processed and presented to the immune system. As a result, they are not immunogenic.
- If, however, these small molecules are chemically linked to a large protein molecule, new epitopes will be formed on the surface of the larger molecule.
- Small molecules that can function as epitopes only when bound to other larger molecules are called haptens (in Greek, *haptein* means “to grasp or fasten”).
- The antigenic molecule to which the haptens are attached is called the carrier.
- Many drug allergies occur because the drug molecules, although small, can bind covalently to normal body proteins and so act as haptens.

SUPERANTIGEN

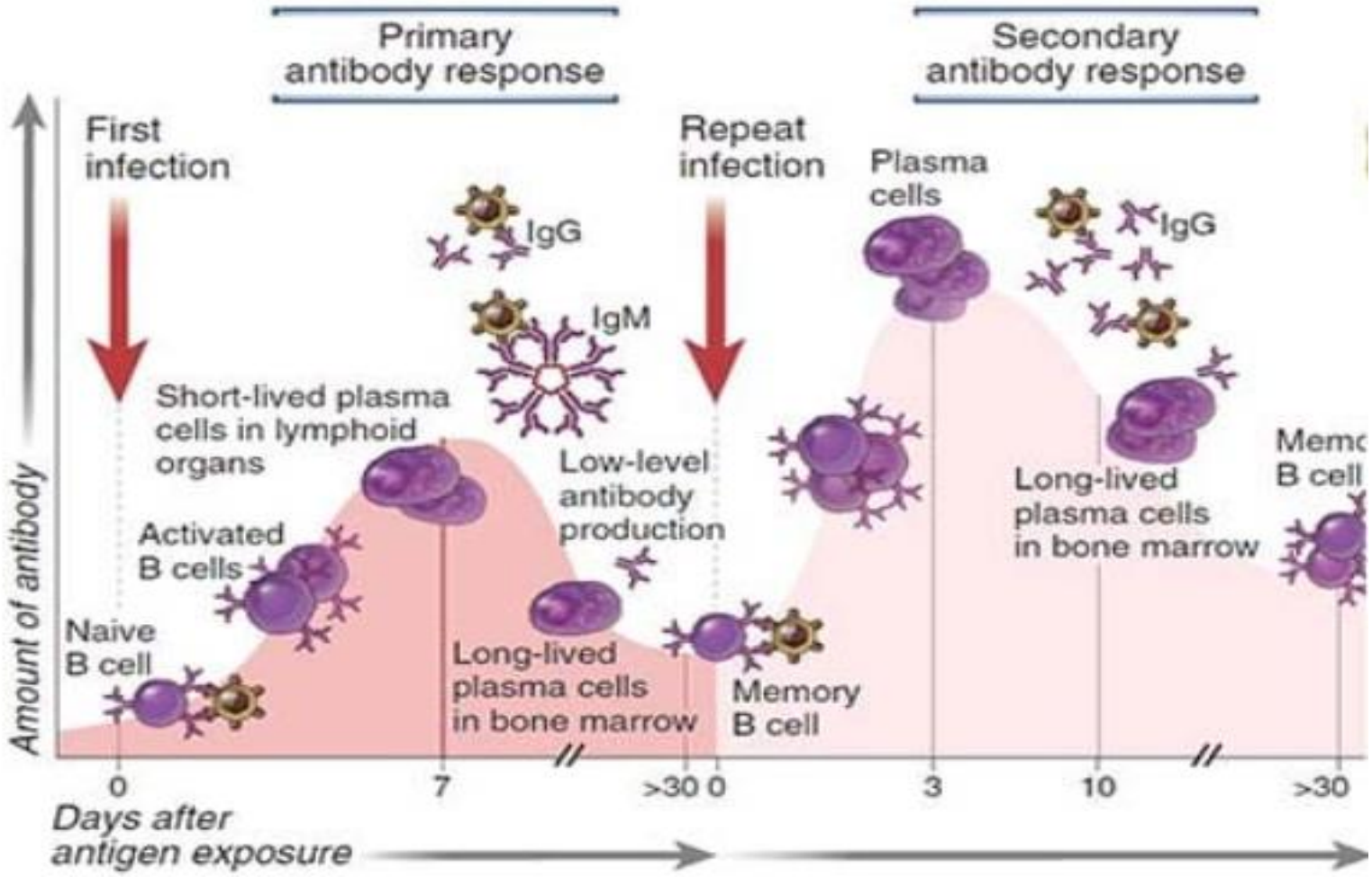
A molecule that, as a result of its ability to bind to certain TCR variable regions, can cause certain T cells to divide.



Homework: answer the question

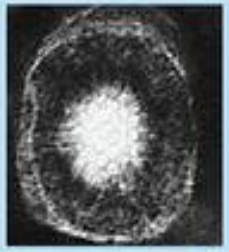
What is the difference between antigen and epitope?

Immunological foundations of vaccinology

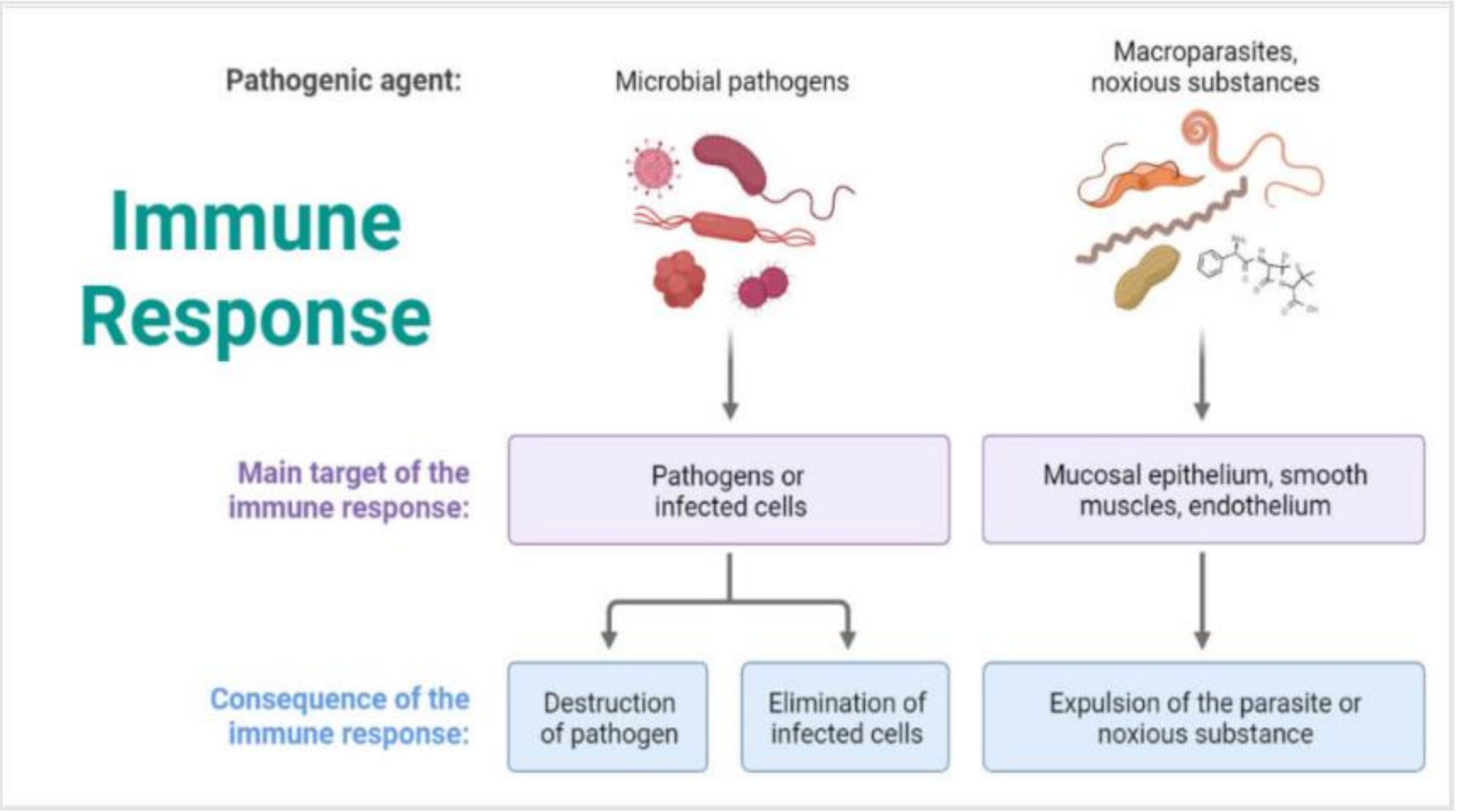


2022

Types of Pathogens

Type of pathogen	Description	Human diseases caused by pathogens of that type
Bacteria *Escherichia coli* 	Single-celled organisms without a nucleus	Strep throat, staph infections, tuberculosis, food poisoning, tetanus, pneumonia, syphilis
Viruses *Herpes simplex* 	Thread-like particles that reproduce by taking over living cells	Common cold, flu, genital herpes, cold sores, measles, AIDS, genital warts, chiken pox, small pox
Fungi *Death cap mushroom* 	Simple organisms, including mushrooms and yeasts, that grow as single cells or thread like filaments	Ringworm, athlete's foot, tinea, candidiasis, histoplasmosis, mushroom poisoning
Protozoa *Giardia lamblia* 	Single-celled organism with a nucleus	Malaria, "traveler's diarrhea" giardiasis, trypanosomiasis ("sleeping sickness")

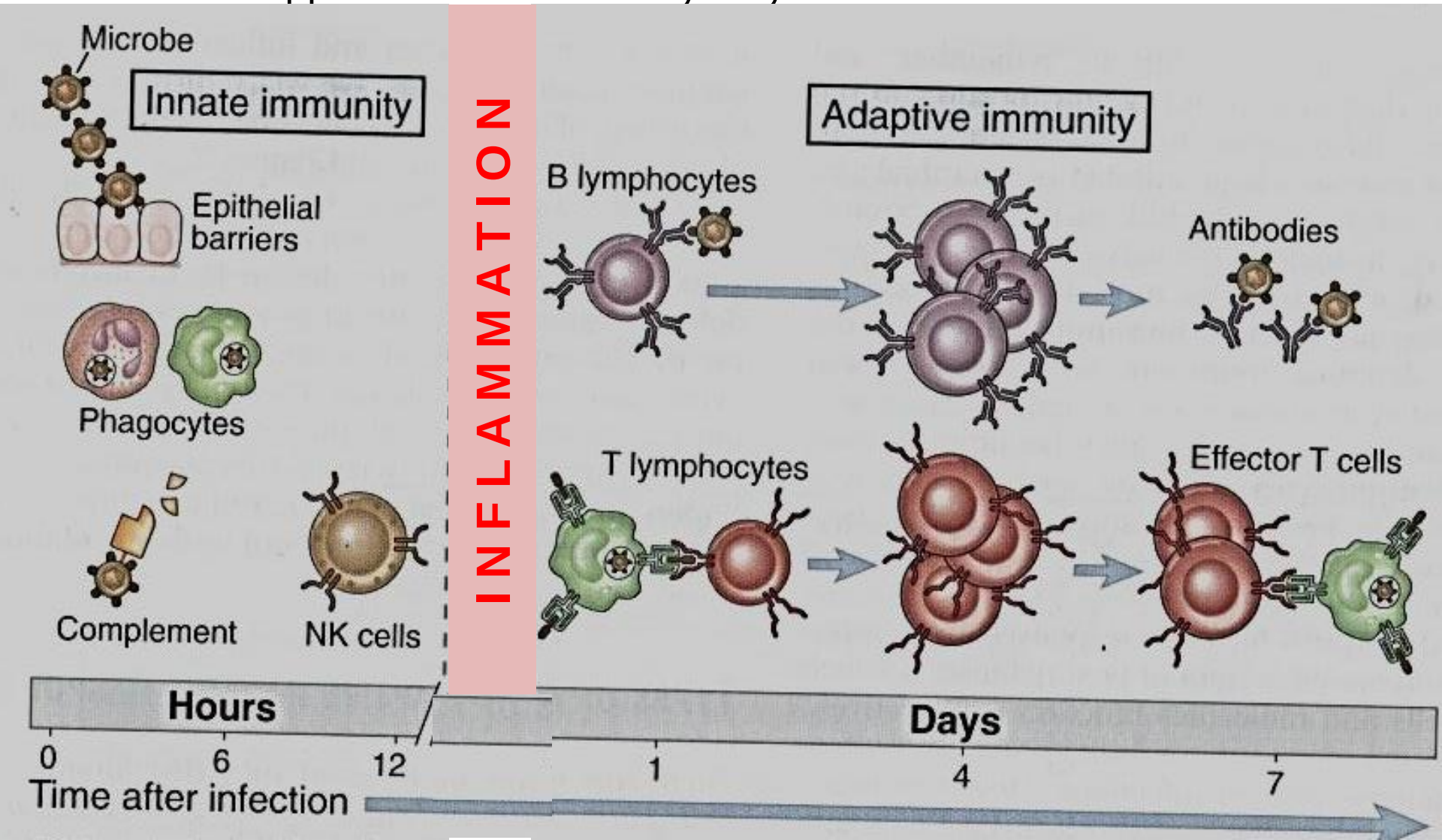
Immune Response is a mechanism of how the immune system of the host's body responds to a harmful foreign particle or pathogen (antigen) in the body.



https://microbenotes.com/immune-response/

Innate and adaptive immunity

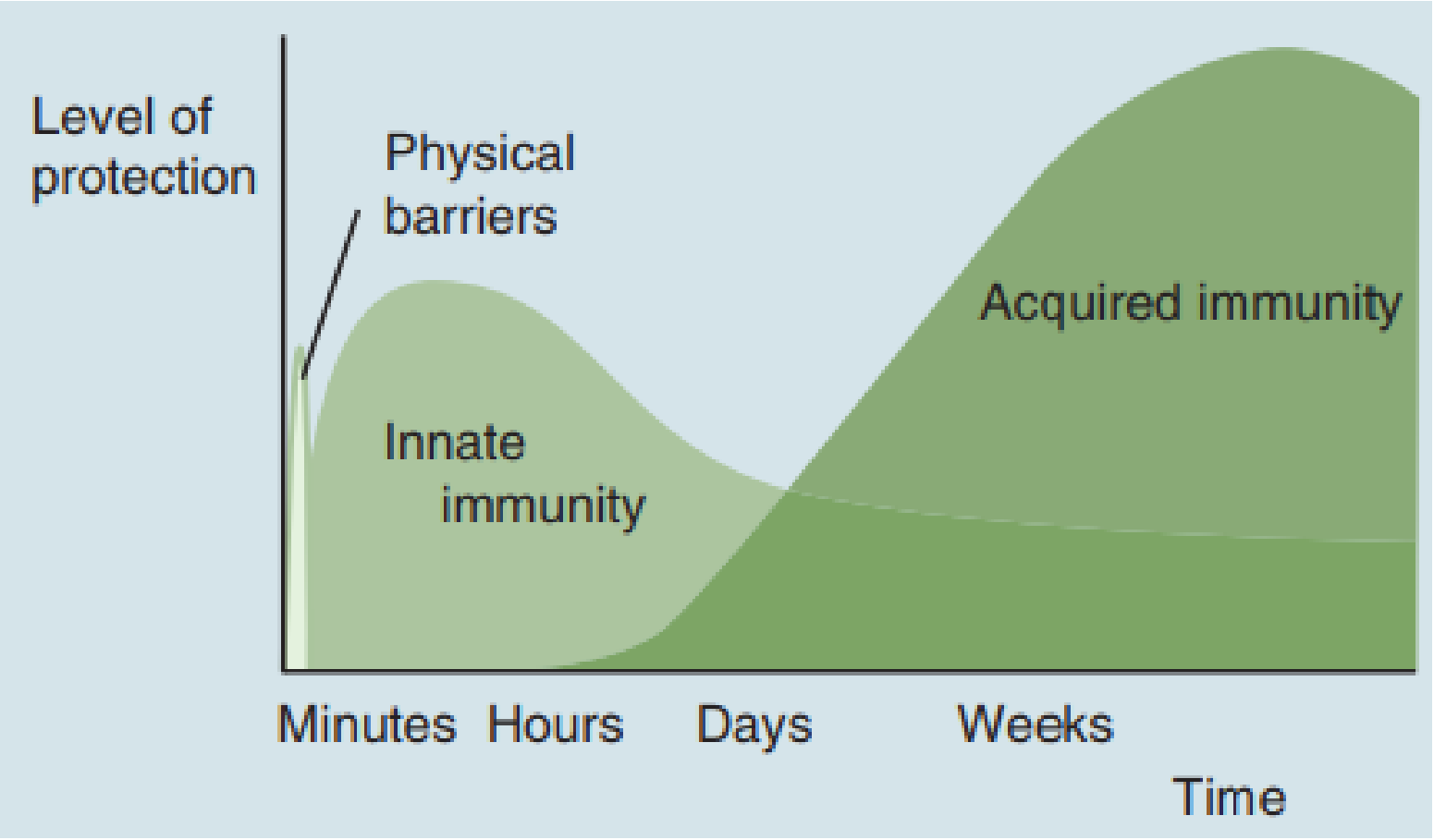
The mechanisms of innate immunity provide the initial defense against infections. Adaptive immune responses develop later and consist of activation of lymphocytes. The kinetics of the innate and adaptive immune responses are approximations and may vary in different infections.



The time course of innate and adaptive immunity.

Physical barriers provide immediate protection.

Innate mechanisms provide rapid protection that keeps microbial invaders at bay until adaptive immunity can develop. It may take several days or even weeks for adaptive immunity to become effective.



Phagocytes

- **Phagocytes –** cells whose prime function is to eat foreign particles, especially bacteria. They include macrophages and related cells, neutrophils, and eosinophils.
- **Phagocytosis** – the ability of some cells to ingest foreign particles. Literally, “eating by cells.”

Types of phagocytes:

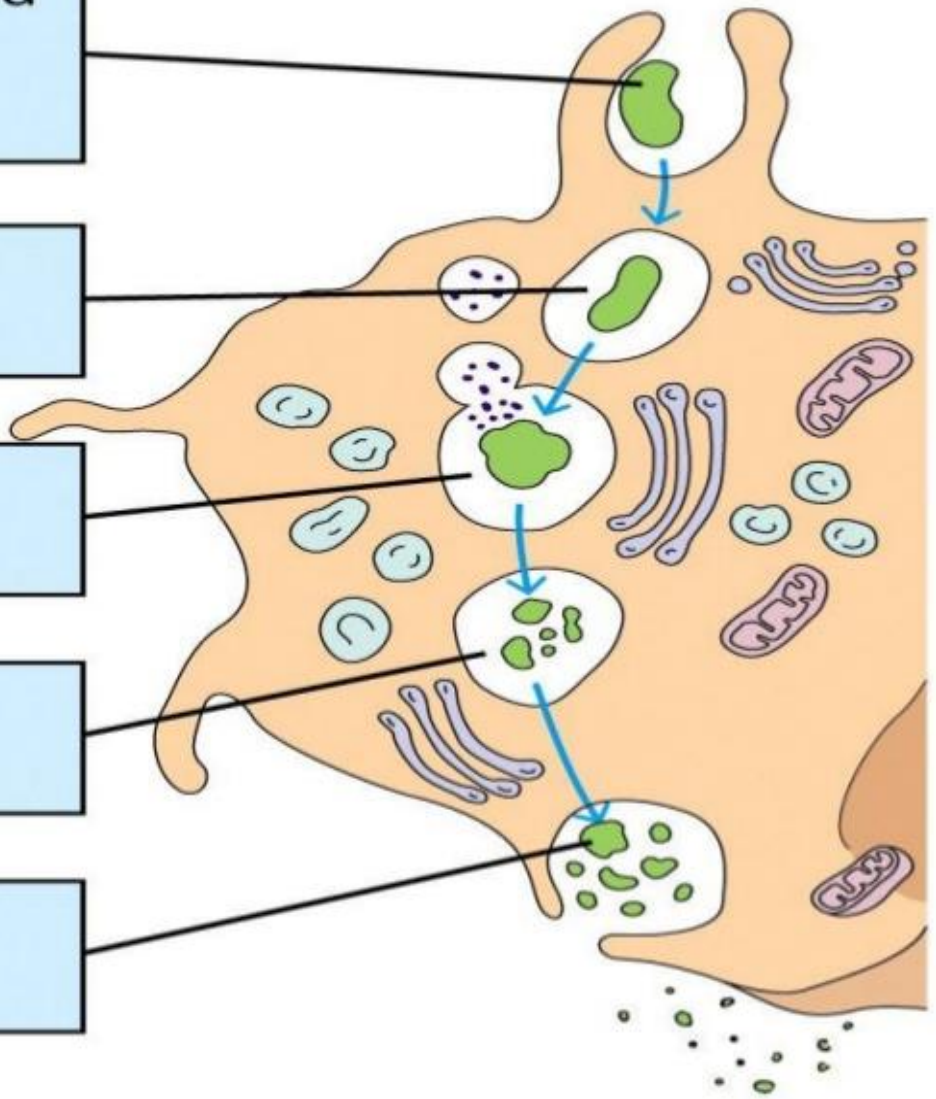
a) Neutrophils,

b) Sentinel cells or macrophages (monocytes, dendritic cells, mast cells),

c) B lymphocytes.

Dynamics of Phagocytosis

1. Bacterium becomes attached to membrane evaginations called pseudopodia
2. Bacterium is ingested, forming phagosome
3. Phagosome fuses with lysosome
4. Lysosomal enzymes digest captured material
5. Digestion products are released from cell



How Invaders Are Recognized

- The body uses receptors that can bind and respond to abundant, essential molecules that are common to many different microorganisms but are absent from normal animal tissues. They are, in effect, widely distributed molecular patterns.
- For example, the walls of Gram-positive bacteria are largely composed of peptidoglycans and contain lipoteichoic acids.
- The cell walls of Gram-negative bacteria consist of peptidoglycans covered by a layer of lipopolysaccharide (LPS).
- Acid-fast bacteria are covered in glycolipids.
- Yeasts have a mannan- or β-glucan–rich cell wall.
- Viruses, in contrast, grow within infected host cells, so the main targets of antiviral molecular patterns are unique viral nucleic acids.

Stages of adaptive immune response

(1) The macrophage or other antigen-presenting cell (APC) encounter, processing and present the antigen;

(2) The APC interact the T-helper cell and synthesizes mediators (interleukins) that activate T-helper and other cells;

(2) After proliferation and differentiation the T-helper cells activate the T-killer cells or the B cells for immune response (with mediator - interleukins);

(3)The T-killer cells cause cytolysis and cell death of target cells (virus-infected cells and tumor cells).

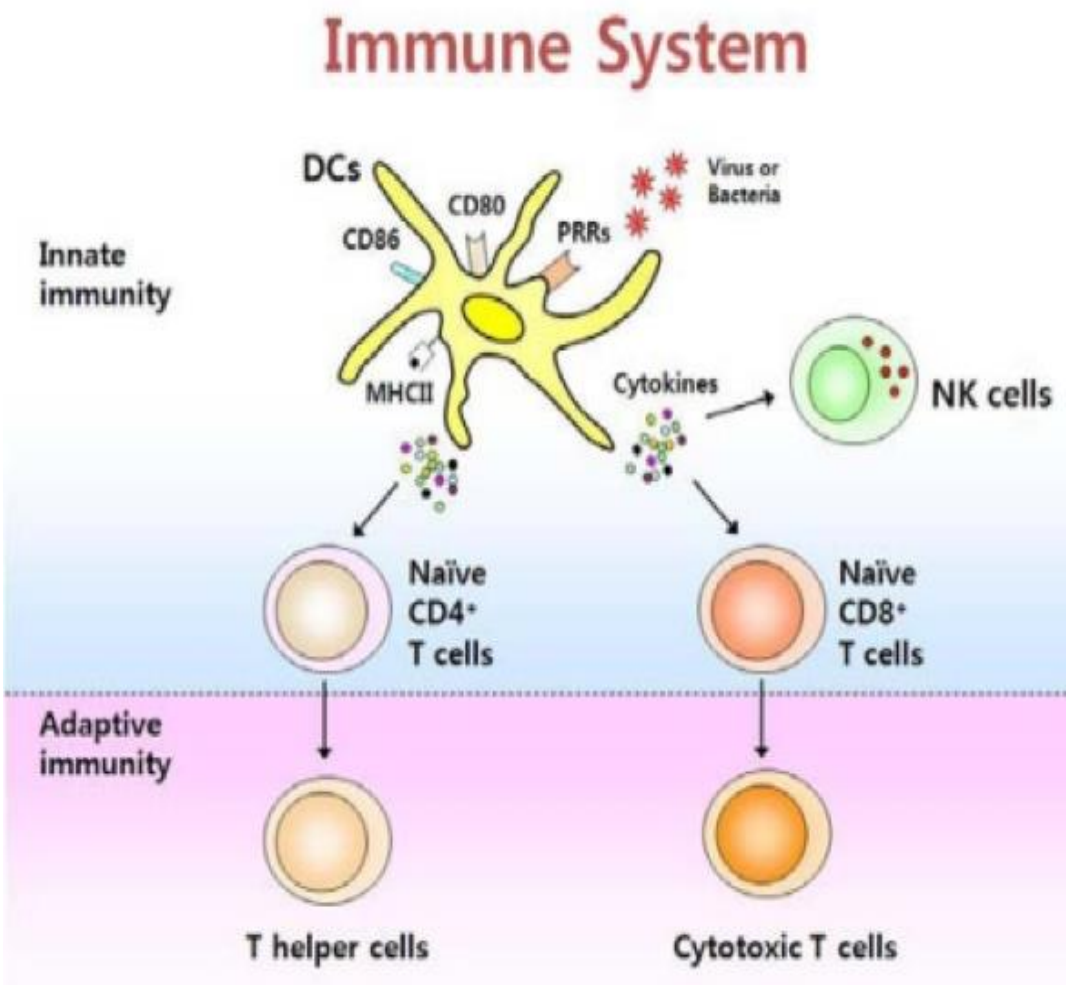
(3)The B cells proliferate and differentiate into plasma cells, that respond to antigens by making specific antibodies

(4) A part of the cells transform into memory T-cells and memory B-cells

(5) When antigen inactivated the T-supressor cells suppress activity of the T-killer cells and the B cells

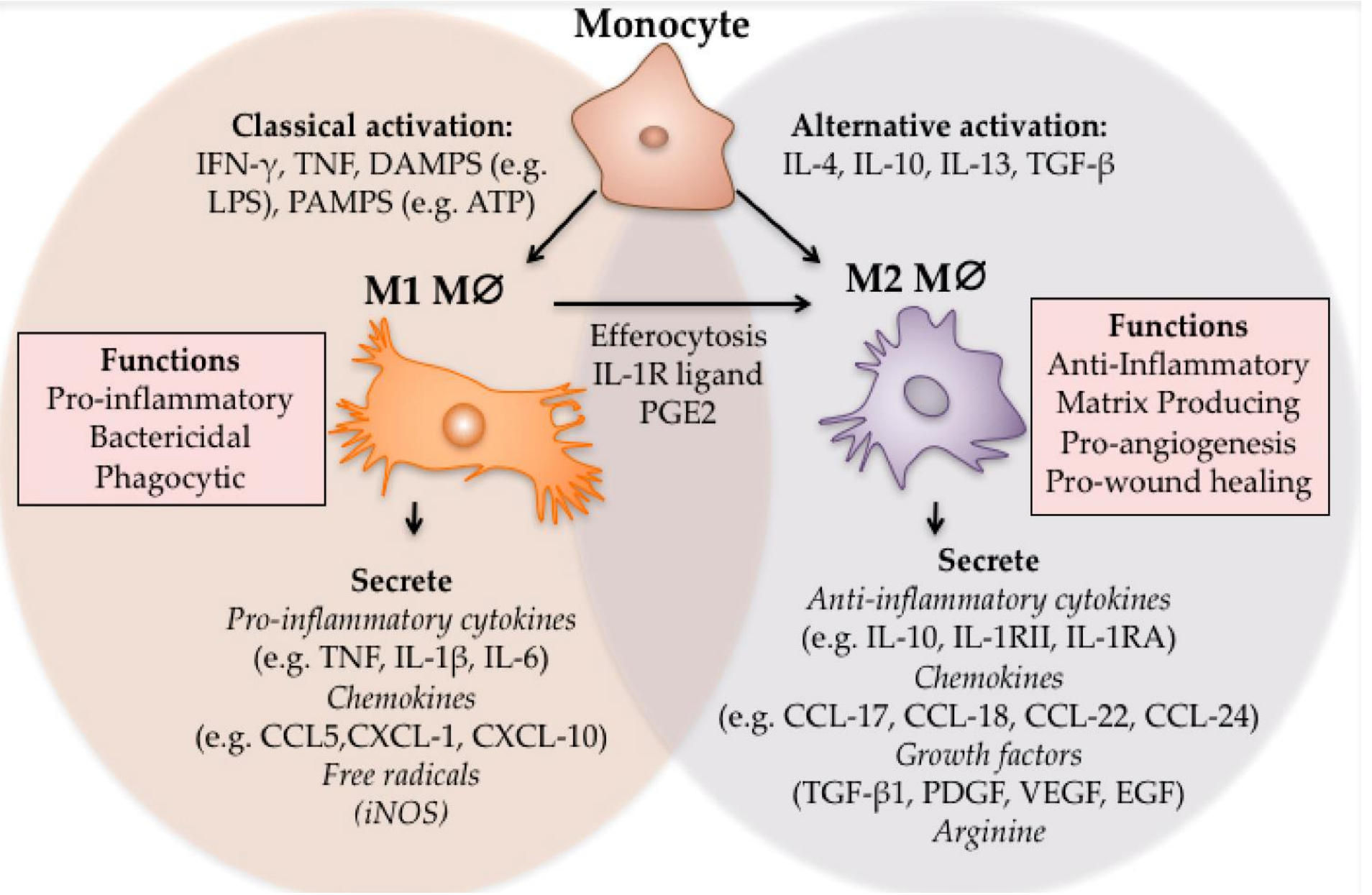
The role of DC

Dendritic cells (DCs) bridge both innate and adaptive arms of the immune system. In an innate immune role, upon stimulation with PAMPs, DCs secrete cytokines that activate natural killer (NK) cells and also help to differentiate CD4+ and CD8+ T cells.



In an adaptive immune role, upon encounter and internalization of antigen, DC load antigen-derived peptides onto Major Histocompatibility Complex (MHC) molecules. Peptides loaded onto MHC II (HLA-DR) molecules are recognized by CD4 T cells. Peptides loaded onto MHC I (HLA-ABC) molecules (a process called cross-presentation) are recognized by antigen-specific CD8 cells, driving their proliferation, activation, and cytotoxicity.

Types of monocytes



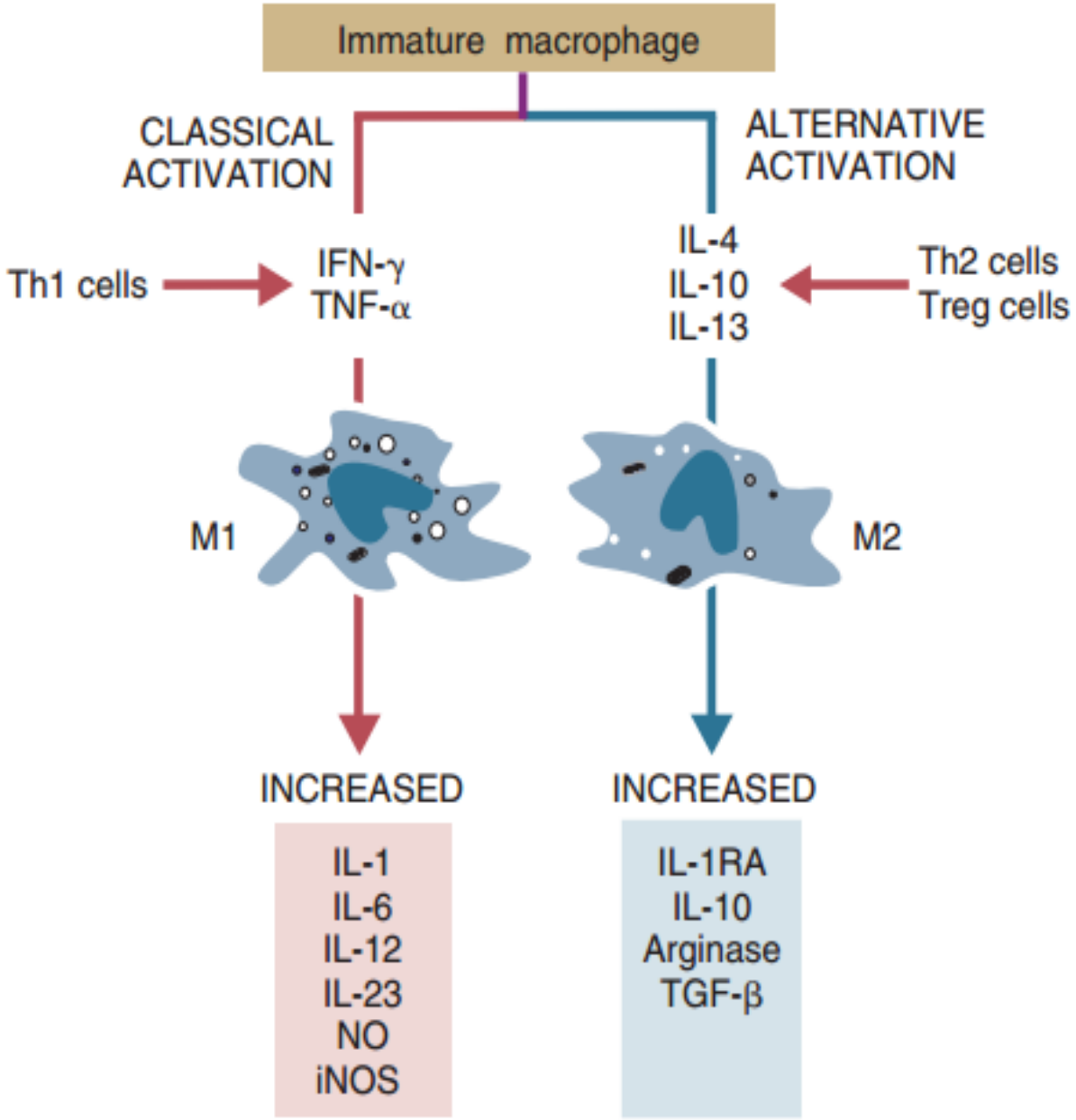
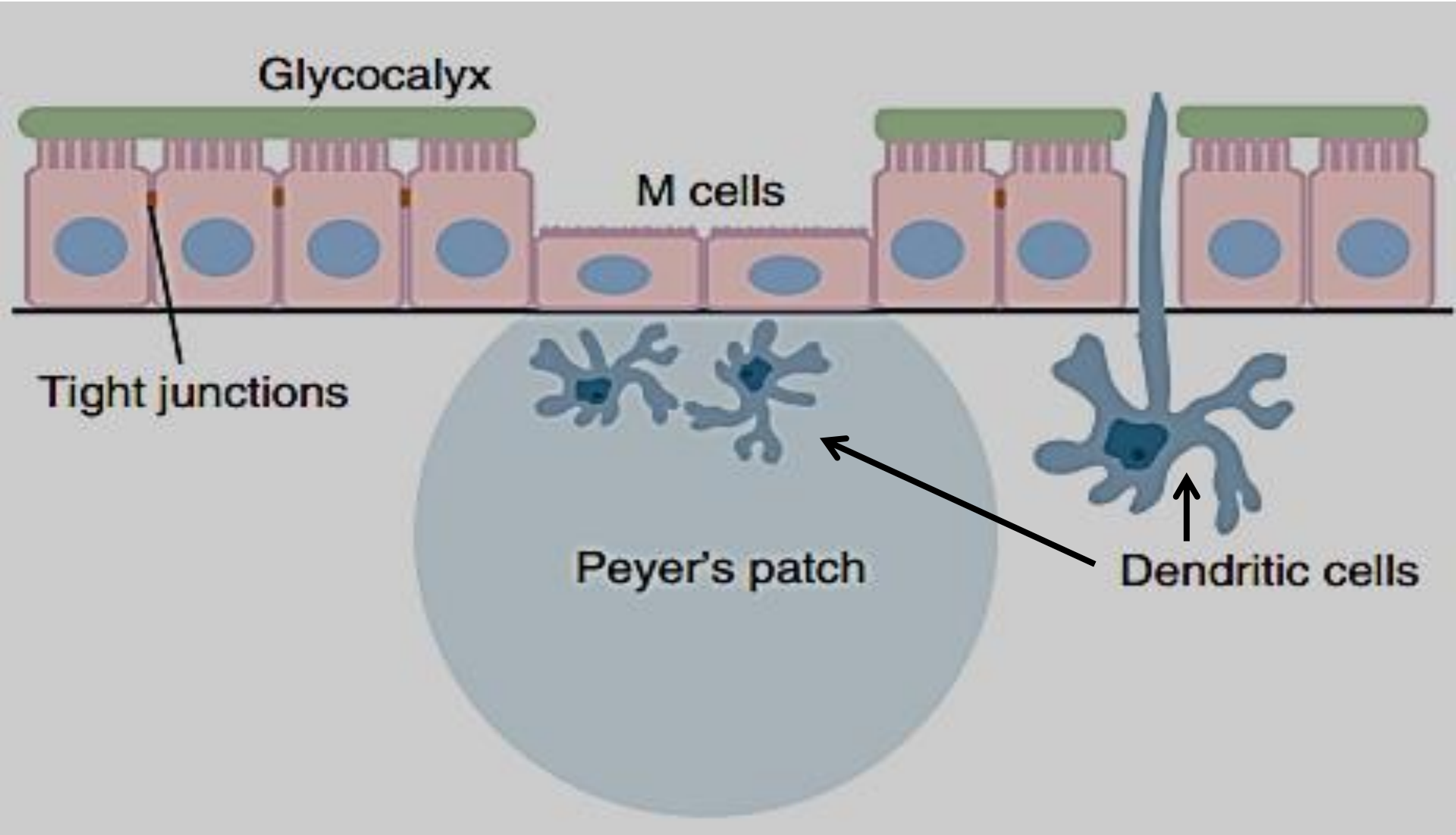


FIGURE 18-17 Depending on their cytokine exposure, macrophages may be classically activated (M1 cells) or become alternatively acti-

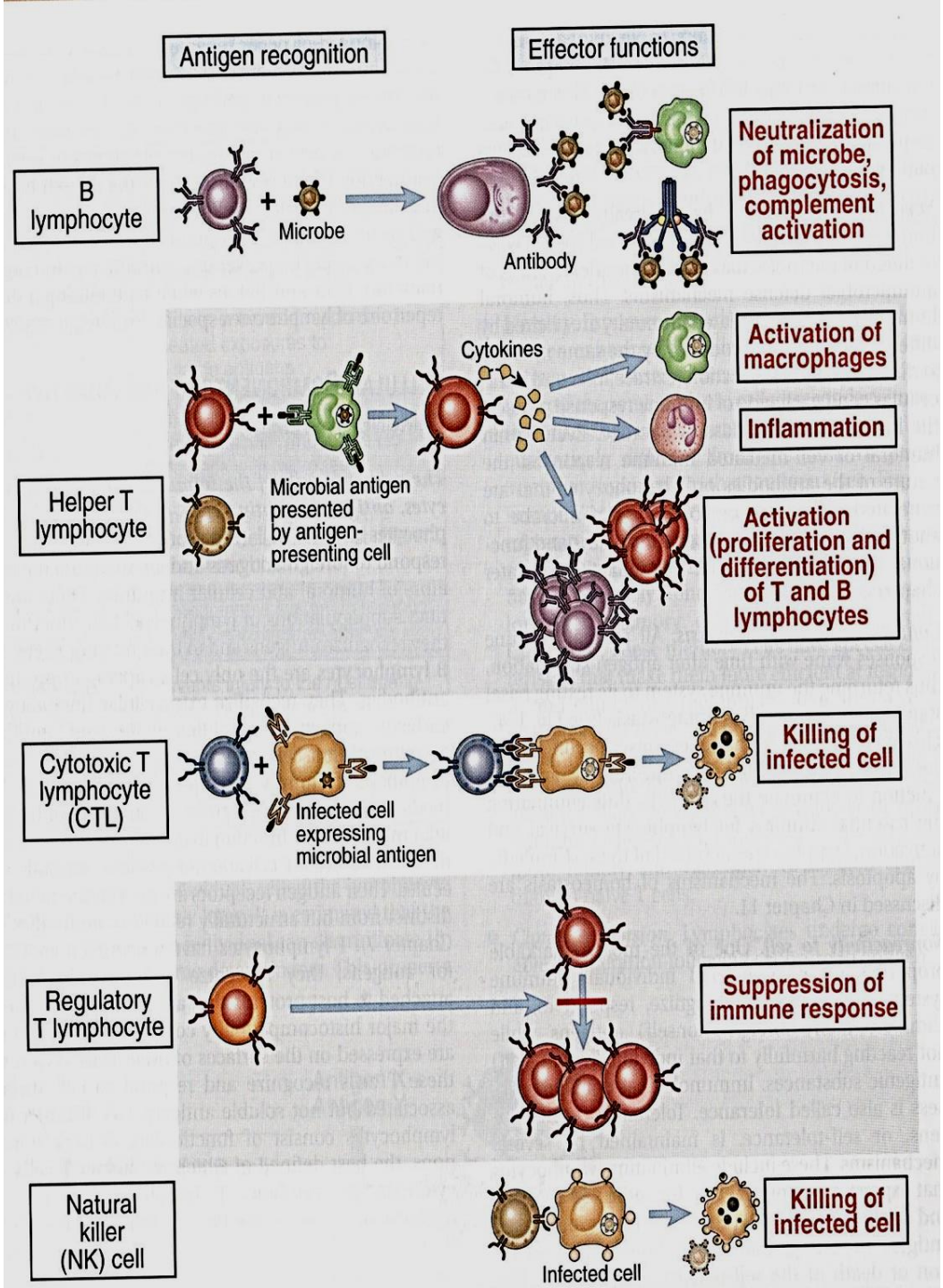
Depending on their cytokine exposure, macrophages may be classically activated (M1 cells) or become alternatively activated (M2 cells). M2 cells have a major regulatory role and are critical to granuloma formation and wound healing. They produce very different cytokine mixtures.

The epithelial defenses of the gut and the ways by which microbial antigens can enter the body



Lymphocytes are central to the adaptive immune system and the defense of the body.

- Lymphocytes are the cells that can recognize and respond to foreign antigens.
- Lymphocytes all look the same but can be differentiated by their characteristic cell surface molecules – CD (cluster of differentiation) system.
- Lymphocytes possess antigen receptors plus the signal transducing molecules required to activate the cell.
- They also possess receptors for cytokines, immunoglobulins, and complement.
- In domestic animal species, some cell surface molecules are unique to each species. These are classified by the WC (workshop cluster) system.
- The collection of cell surface molecules on a lymphocyte is called its **immunophenotype**.



Classes of lymphocytes.

B lymphocytes recognize antigen on the surfaces of APCs and secrete cytokines, which stimulate different mechanisms of immunity and inflammation.

CTLs (T killer) recognize antigen on infected cells and kill these cells.

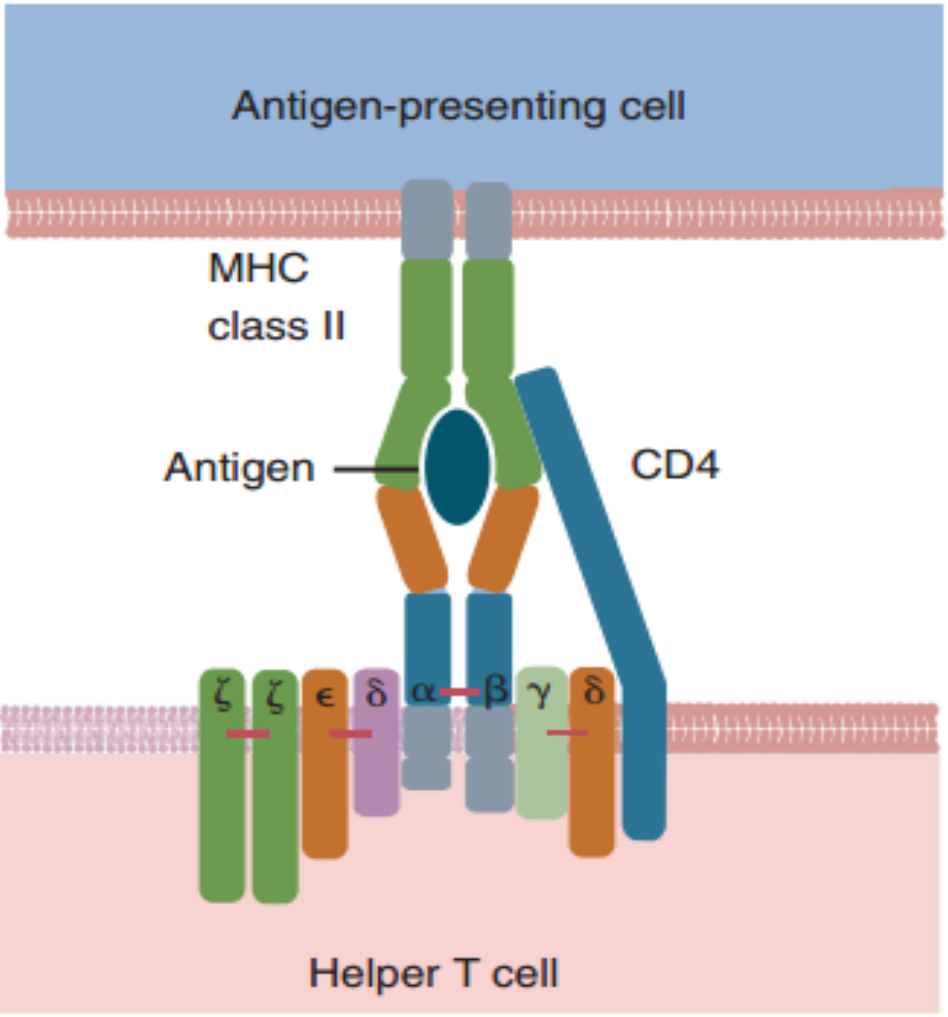
Regulatory T cells suppress and prevent immune response, e.g.to self antigens.

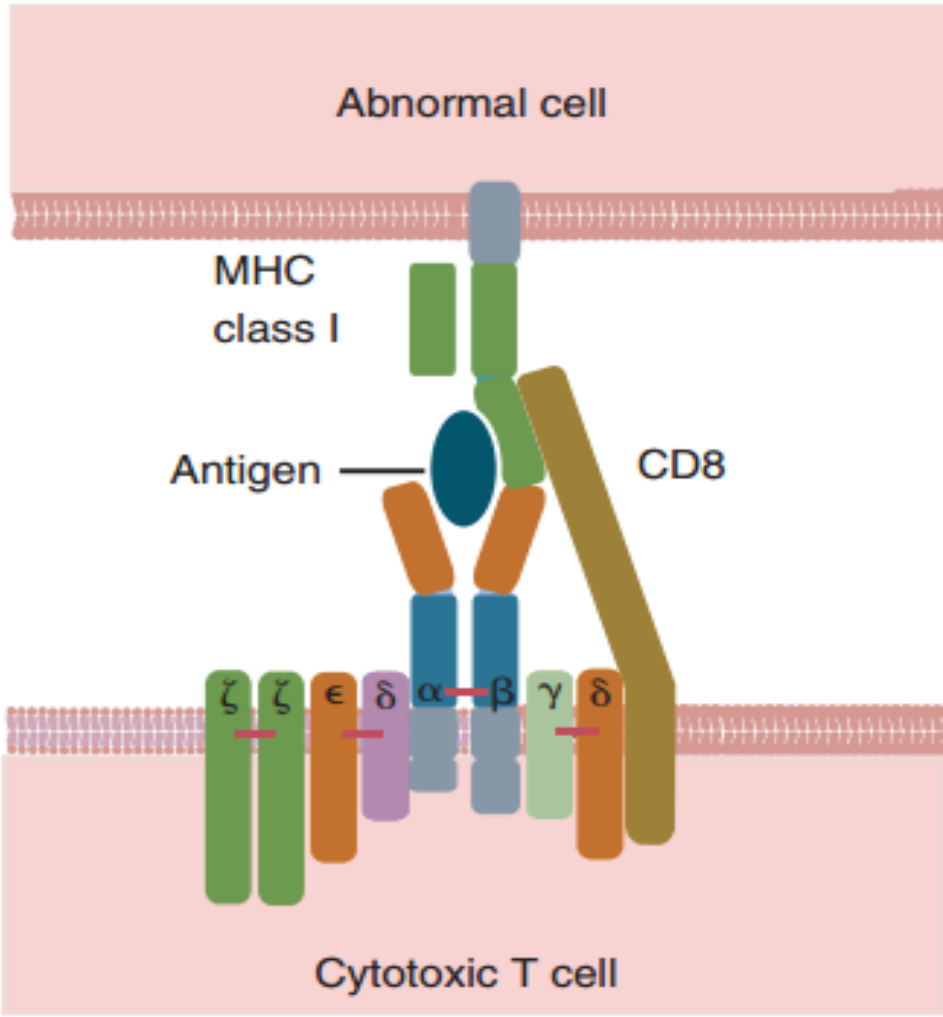
NK cells use receptors with more limited diversity than T or B cell antigen receptors to recognize and kill their target, such as infected cells.

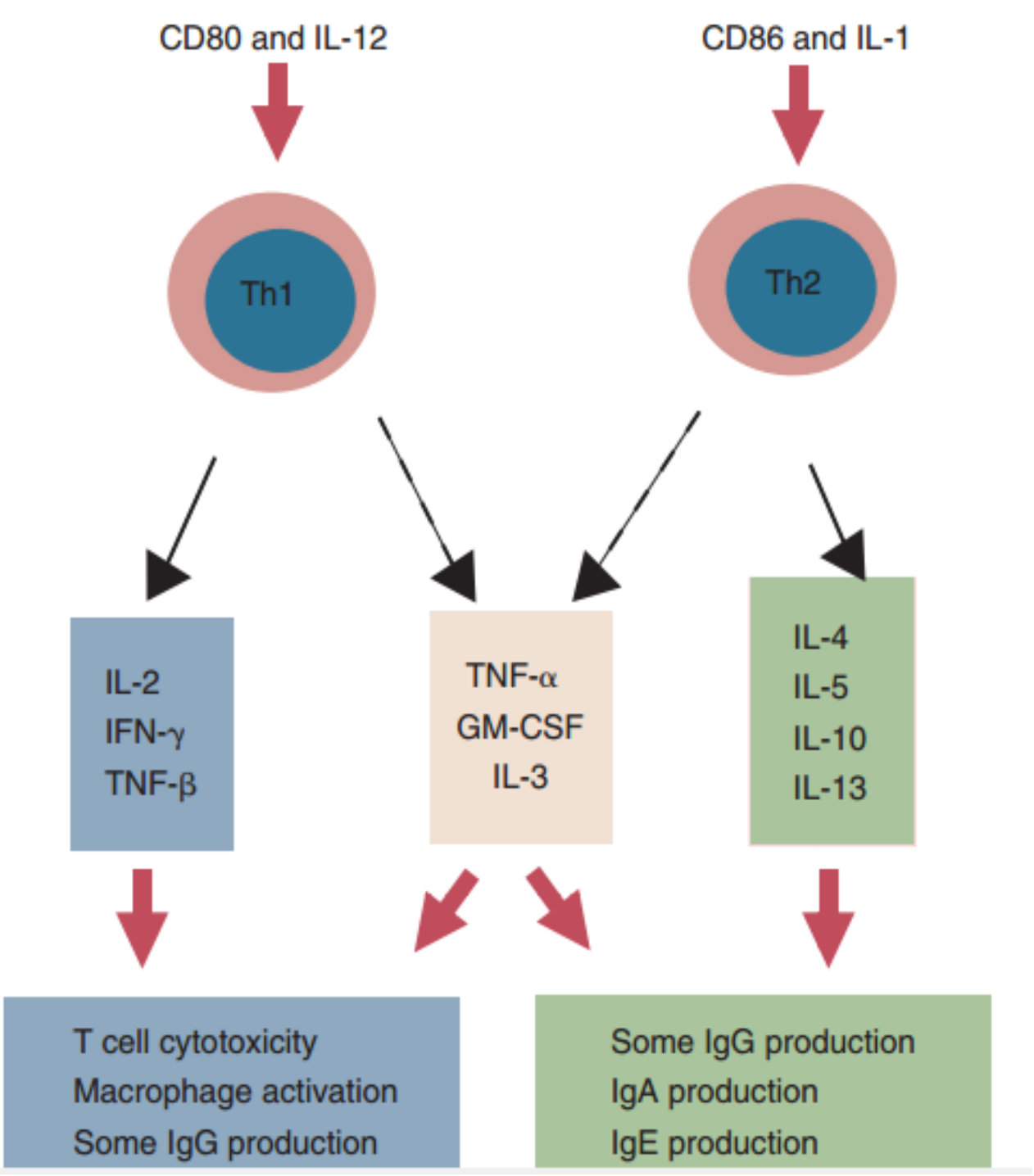
T Cells and Their Response to Antigen

- T cells express antigen receptors (TCRs) consisting of paired peptide chains, that form antigen-binding receptors whose ligands are peptides linked to major histocompatibility complex (MHC) molecules on antigen-presenting cells.
- The antigen-binding chains of the TCR connect to a complex signal transducing component called CD3.
- Each TCR is also associated with either CD4 or CD8. CD4 binds to MHC class II molecules on antigen-presenting cells. CD8 binds to MHC class I molecules expressed on all nucleated cells.
- To respond to antigens, T cells must bind to antigenic peptides linked to MHC molecules. They must also receive co-stimulation from cytokines and other molecules.
- The multiple signals sent by an antigen-presenting cell are communicated to a T cell through an immunological synapse.

Role of CD4 and CD8 in promoting T cell responses. These molecules link the T cell to the antigen-presenting cell, binding the two cells together and ensuring that an effective signal is transmitted between them. CD4 binds to MHC class I molecules.



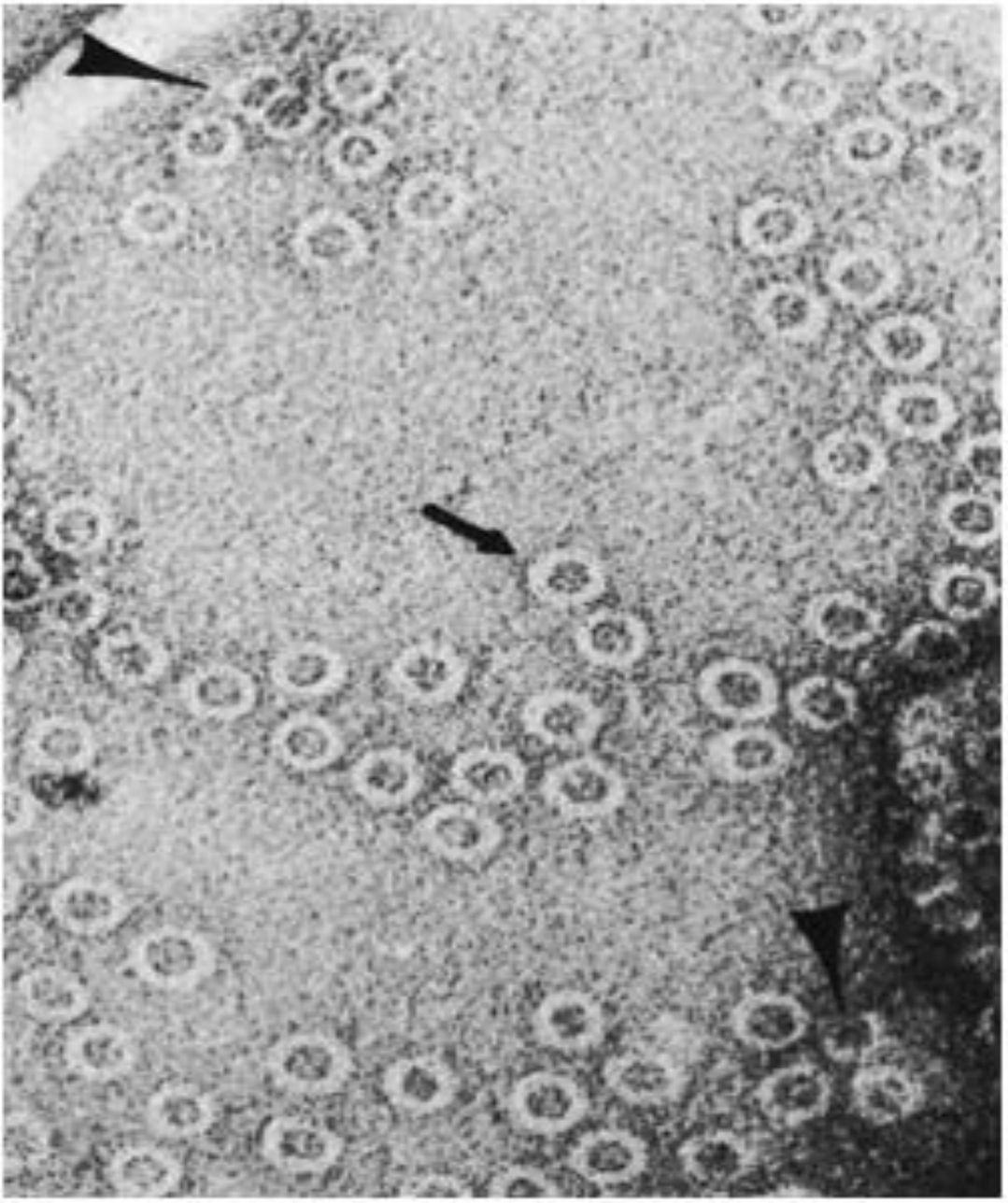




Major differences between Th1 and Th2 populations. Note that the co-stimuli that trigger them are different as are the set of cytokines they secrete.

CD8+ T Cell Function and the Destruction of Cell-Associated Invaders

- Cytotoxic T cells use two mechanisms to kill targets. They may trigger the extrinsic pathway using perforins and granzymes. Alternatively, they may trigger the intrinsic pathway using the death receptor Fas and its ligand.
- Some bacteria and parasites may evade destruction by living within the endosomes of phagocytic cells, especially macrophages.
- The elimination of these intracellular organisms is mediated by activation of macrophages by interferon-γ (IFN-γ) produced by Th1 cells.



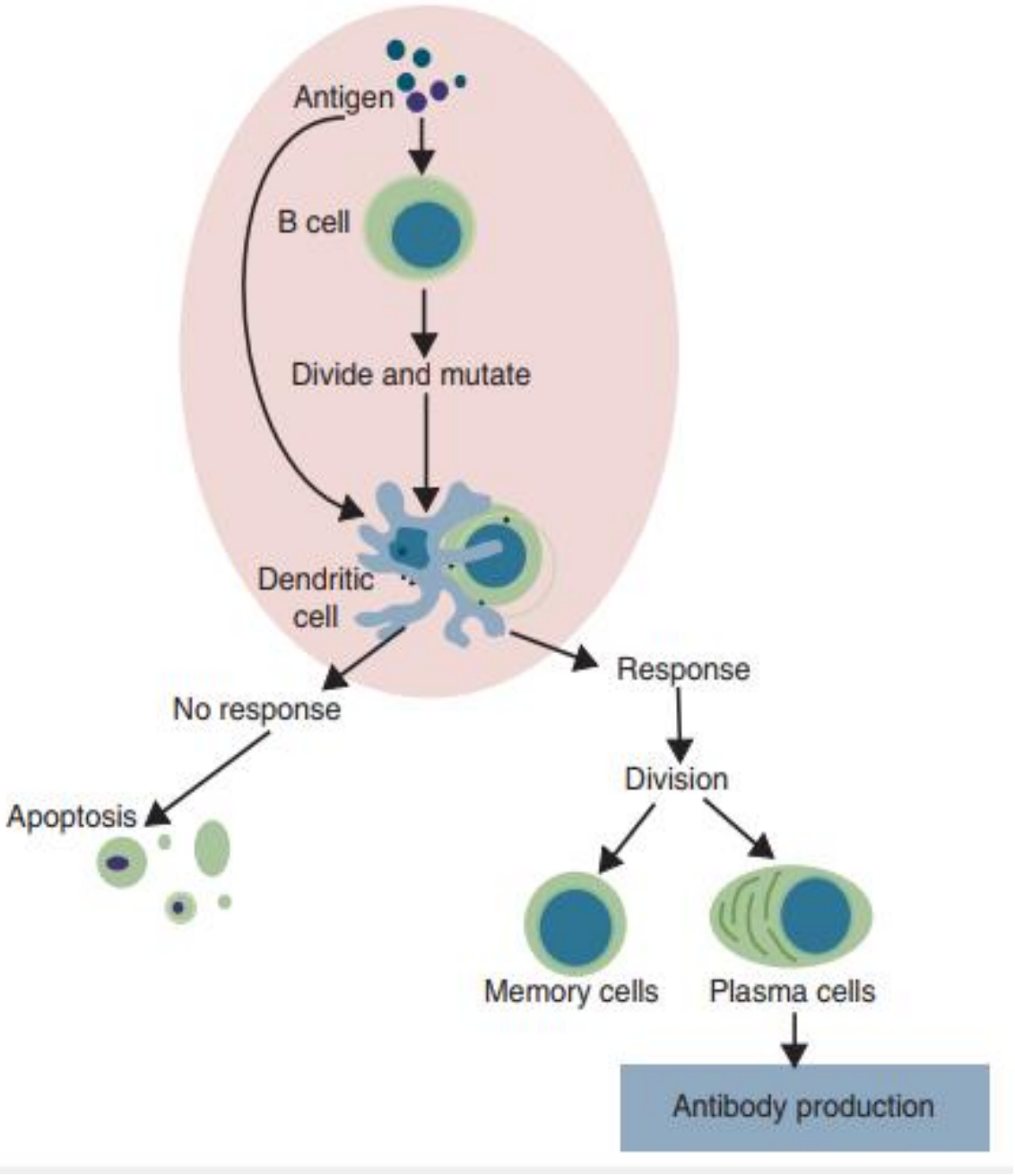
Perforins from human natural killer cells on the surface of a rabbit erythrocyte target. The arrowheads point to incomplete rings and double rings. (From Podack ER, Dennert G, Assembly of two types of tubules with putative cytolytic function by cloned natural killer cells, Nature 302(5907):442–445, 1983.)

Effector T Cell Memory

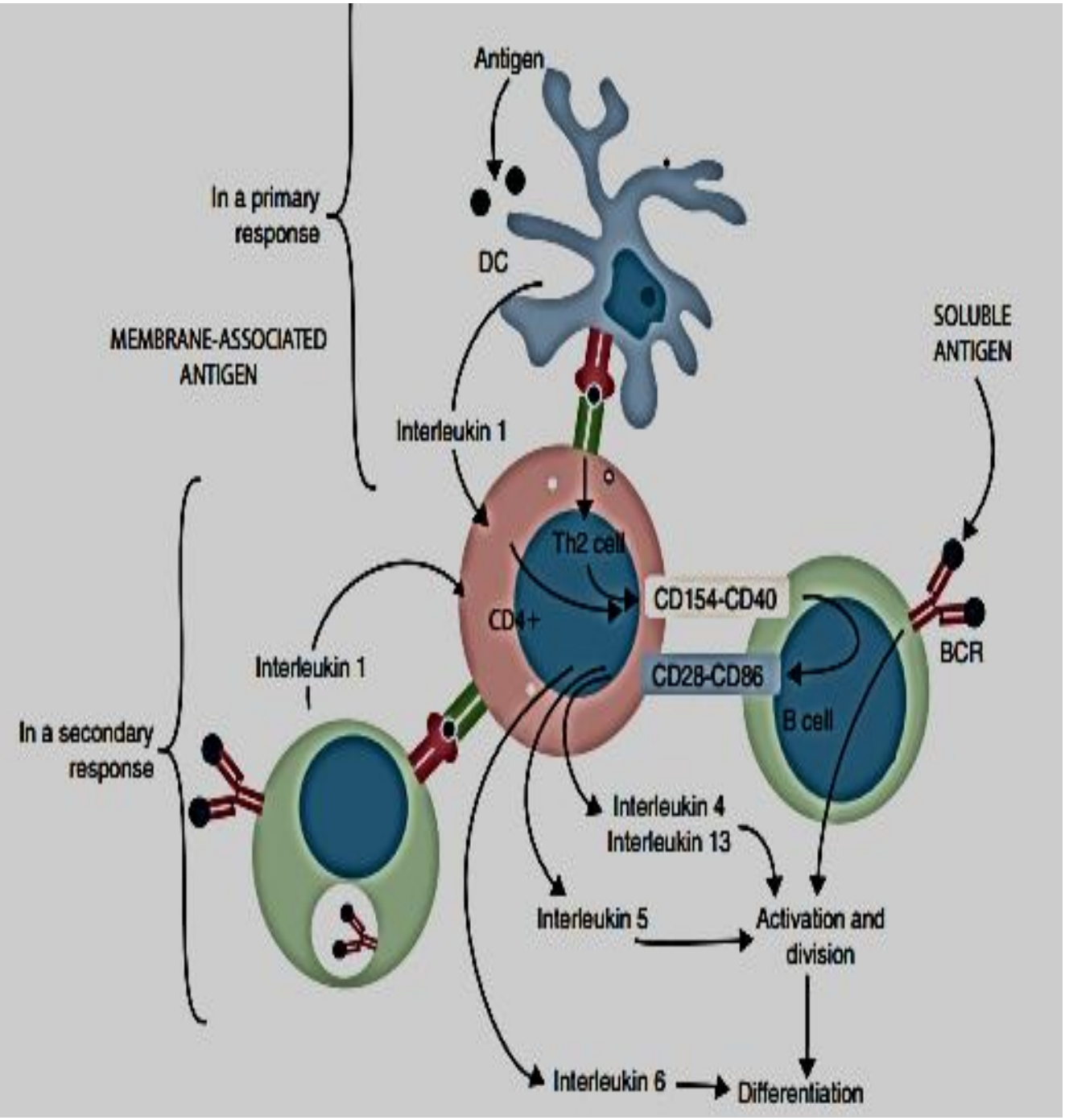
- In contrast to the prolonged antibody response, the effector phase of T cell responses is relatively brief. Indeed, cytotoxicity is seen only in the presence of antigen.
- Naïve CD8+T cells are long-lived resting cells that continuously recirculate between the bloodstream and lymphoid organs.
- Once they encounter antigen, they multiply rapidly in an effort to keep pace with the growth of invading pathogens.
- The number of responding cells may increase more than 1000-fold within a few days. They reach a peak 5 to 7 days after infection when pathogen-specific, cytotoxic T cells can make up 50% to 70% of the total CD8+ T cells.
- Once the infection has cleared, most of these cells are superfluous.

B Cells and Their Response to Antigen

- B cells express multiple identical antigen binding receptors (BCRs) on their surface. When BCRs are shed into body fluids, they are called immunoglobulins or antibodies.
- Each B cells can only bind and respond to a single antigen.
- Each B cell thus makes antibodies of the same binding specificity as its receptors.
- B cells can recognize most antigens without prior processing and secrete **only Ig M**.
- Helper T cells stimulate B cells through an immunologic synapse. Responding B cells may become either memory cells or antibodysecreting plasma cells (in the germinal centers of the secondary lymphoid organs). Plasma cells are the progeny of B cells that have differentiated to secrete very large amounts of **antibodies (Ig M, IgG, IgA, IgE**).
- Plasma cells can make and secrete up to 10,000 molecules of immunoglobulin per second.



B cells in the germinal center undergo somatic mutation as they respond to antigen presented by dendritic cells. If the mutation enables them to bind antigen more strongly, they will be stimulated to grow still further. If, on the other hand, the mutation reduces their antigen-binding ability, they will undergo apoptosis.



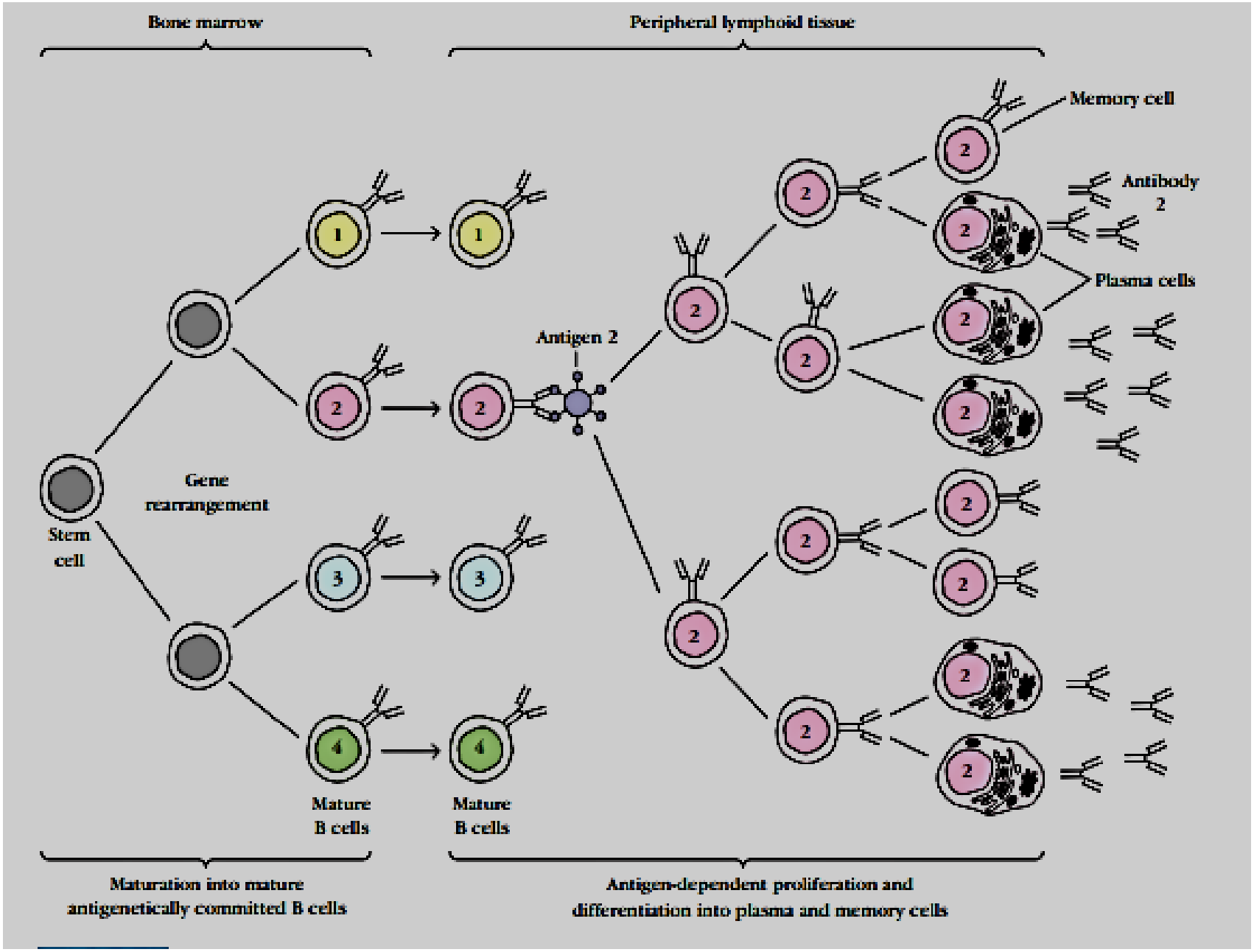
The sequence of events that must occur for a B cell to respond to antigen.

Not only must the B cell be stimulated by antigen, but it must also receive costimulation from helper T cells and their cytokines

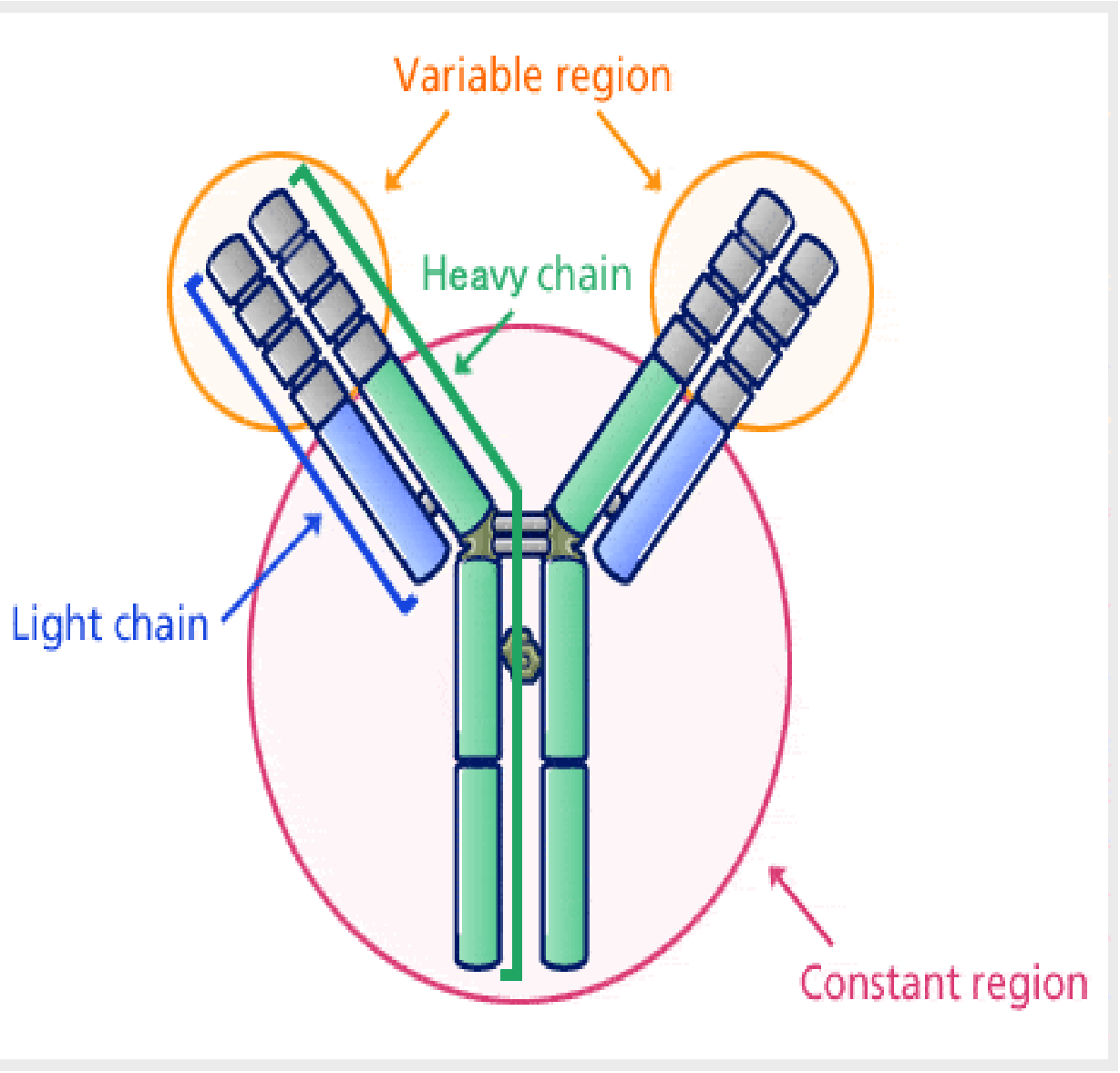
Maturation and clonal selection of B lymphocytes.

- Maturation, which occurs in the absence of antigen, produces antigenically committed B cells, each of which expresses antibody with a single antigenic specificity.
- Clonal selection occurs when an antigen binds to a B cell whose membranebound antibody molecules are specific for epitopes on that antigen.
- Clonal expansion of an antigen-activated B cell leads to a clone of memory B cells and effector B cells, called plasma cells; all cells in the expanded clone are specific for the original antigen.
- The plasma cells secrete antibody reactive with the activating antigen.

Maturation and clonal selection of B lymphocytes.

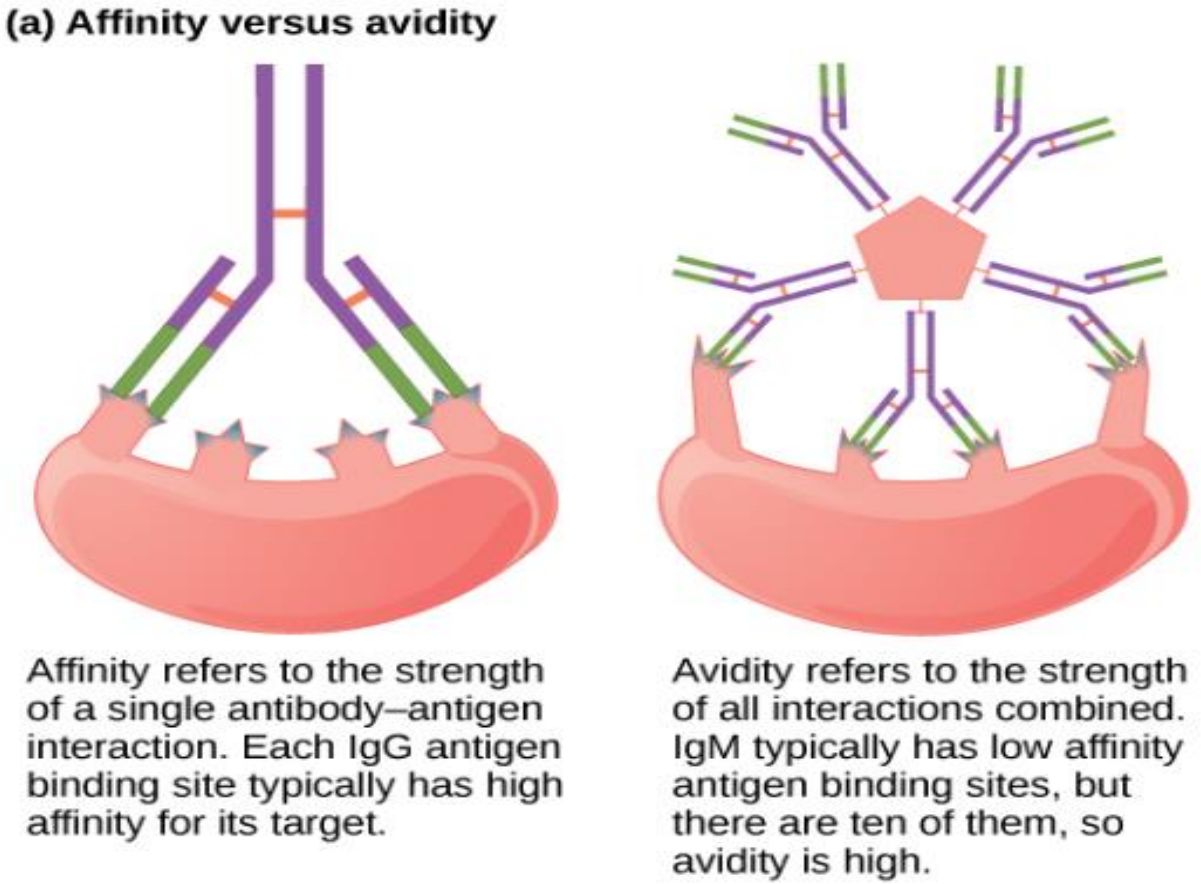


Antibody (Ab, immunoglobulin, Ig) is the large Y shaped protein. The basic structure of all antibodies are same.



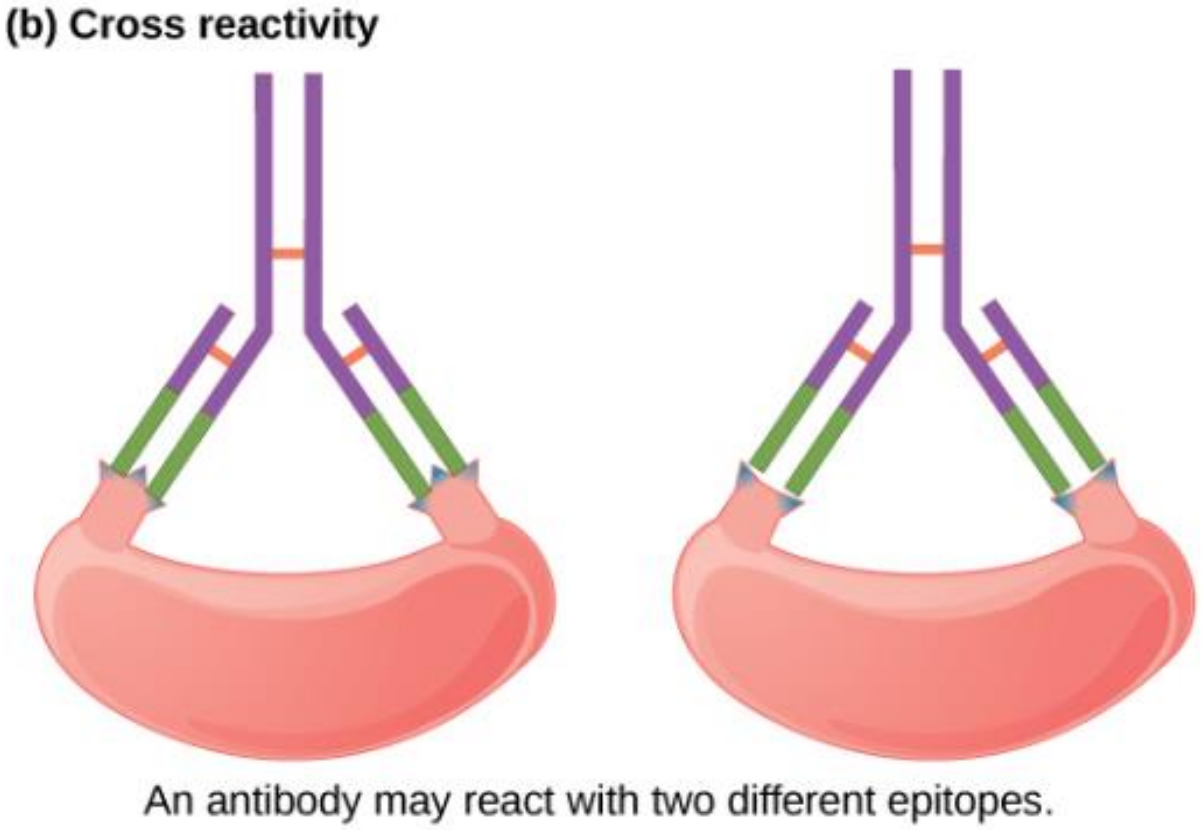
Affinity, Avidity, and Cross Reactivity

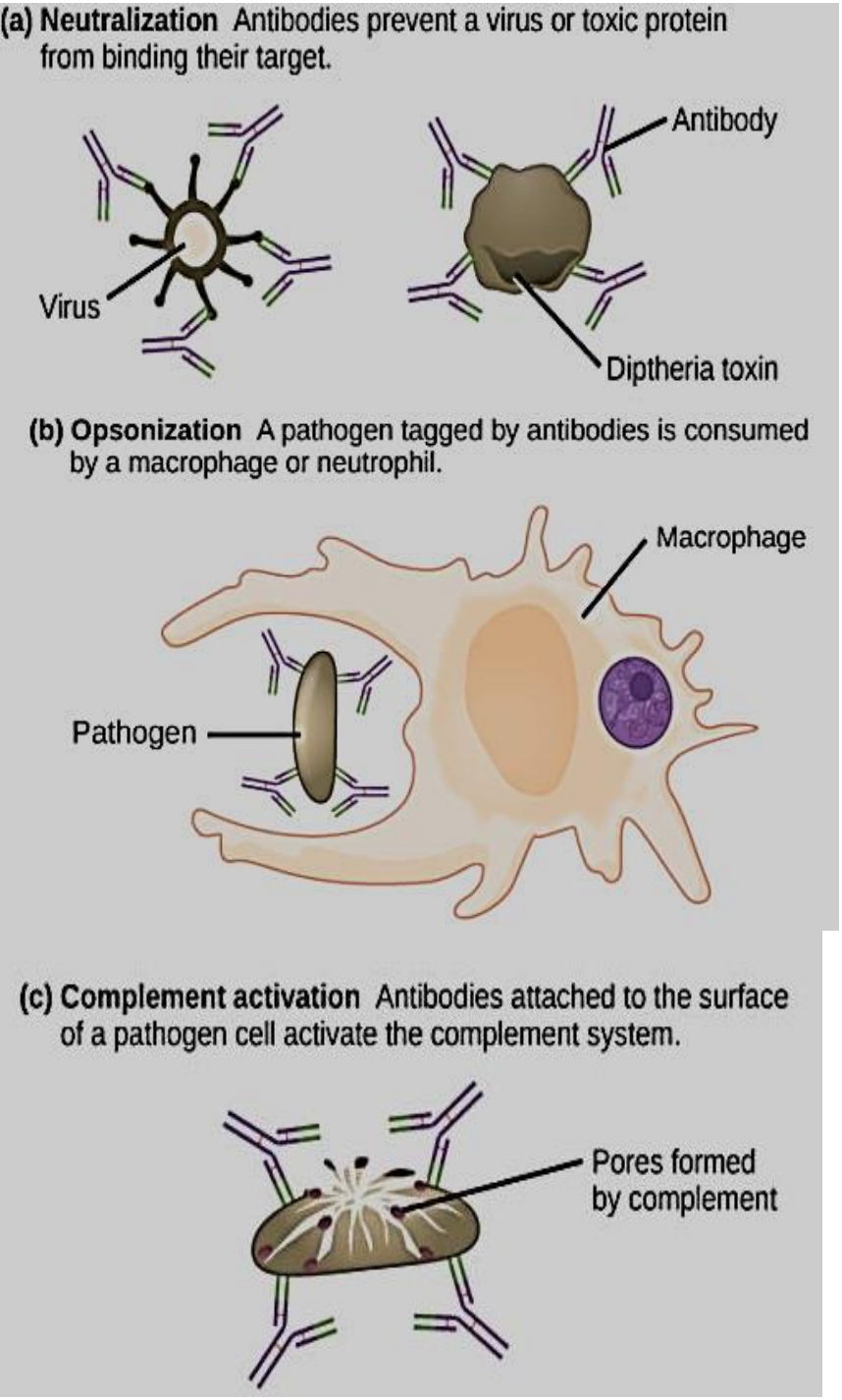
Not all antibodies bind with the same strength, specificity, and stability. In fact, antibodies exhibit different **affinities** (attraction) depending on the molecular complementarity between antigen and antibody molecules. An antibody with a higher affinity for a particular antigen would bind more strongly and stably.



Affinity, Avidity, and Cross Reactivity

Affinity refers to the strength of single interaction between antigen and antibody, while avidity refers to the strength of all interactions combined. (b) An antibody may cross react with different epitopes.

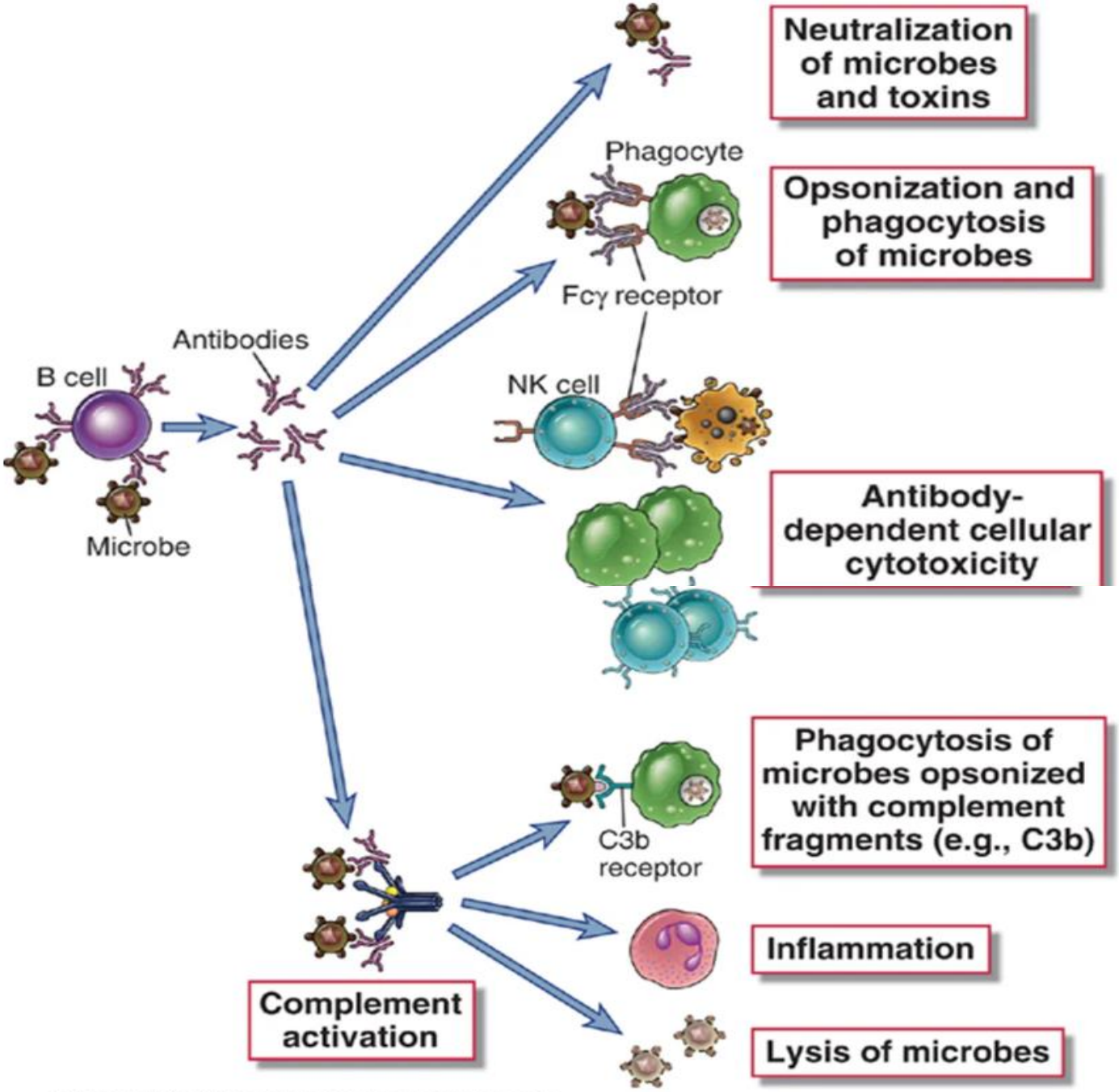




Function of the antibodies

- Neutralization of infectivity,
- Phagocytosis,
- Antibody-dependent cellular cytotoxicity (ADCC),
- Complement-mediated lysis of pathogens or of infected cells: Antibodies activate the complement system to destroy bacterial cells by lysis
- Transcytosis, mucosal immunity & neonatal immunity

Major functions of the antibodies

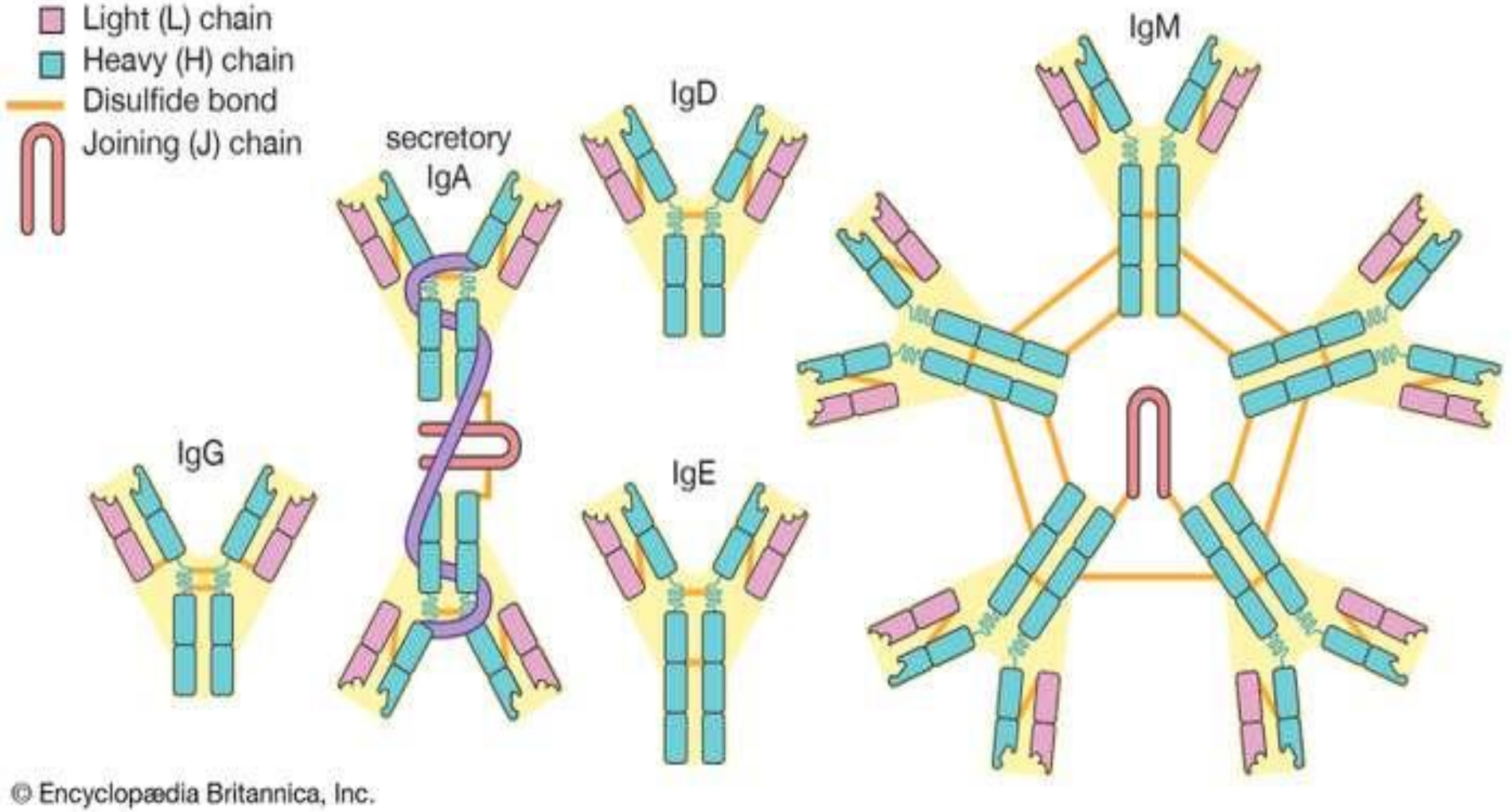


Classes of antibodies

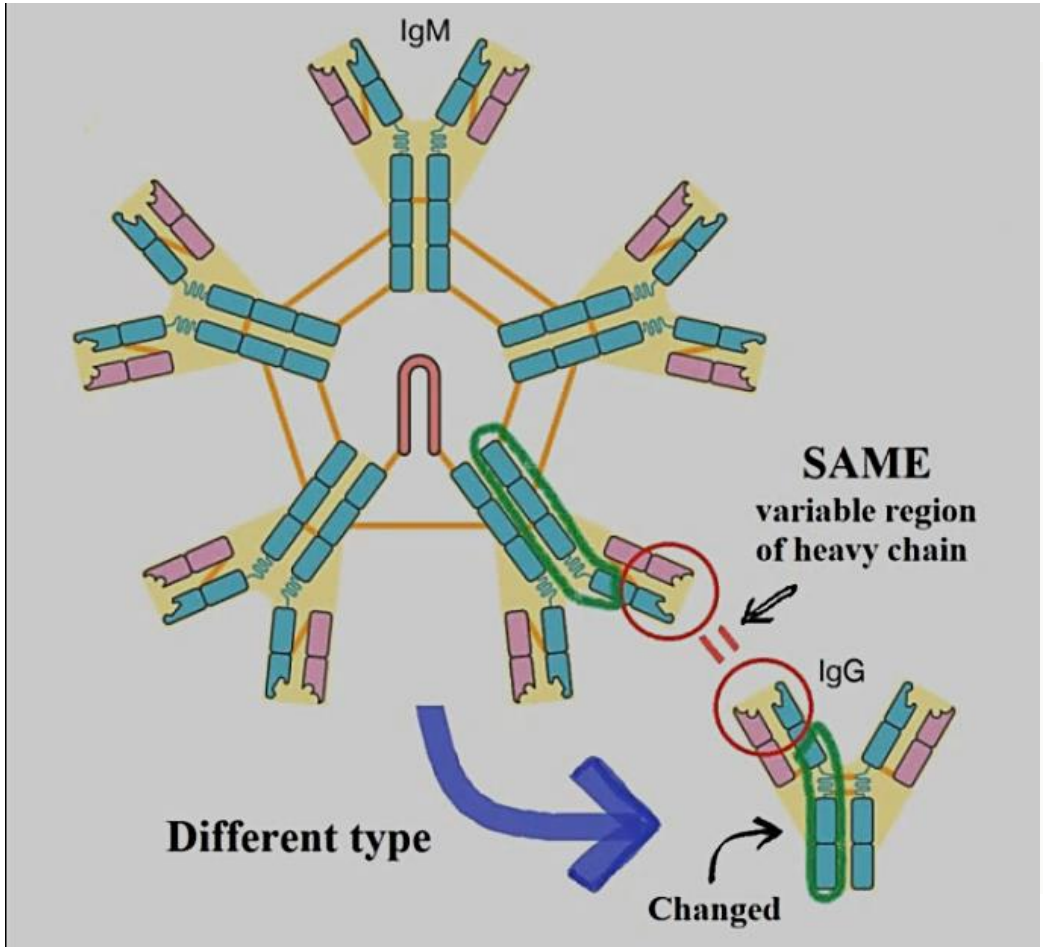
• Mammals make five classes of immunoglobulins: immunoglobulin G (IgG), IgM, IgA, IgE, and IgD. All originate as B cell antigen receptors (BCRs) shed into body fluids.
• IgG is the predominant immunoglobulin in serum and is mainly responsible for systemic defense.
• IgM is a very large immunoglobulin mainly produced during a primary immune response.
• IgA is the immunoglobulin produced on body surfaces. It is responsible for the defense of the intestinal and respiratory tracts.
• IgE is found in very small quantities in serum and is responsible for immunity to parasitic worms and for allergies.
• IgD is found on the surface of immature lymphocytes. Its function is unknown.

Classes of antibodies

The five main classes of antibodies (immunoglobulins): IgG, IgA, IgD, IgE, and IgM.



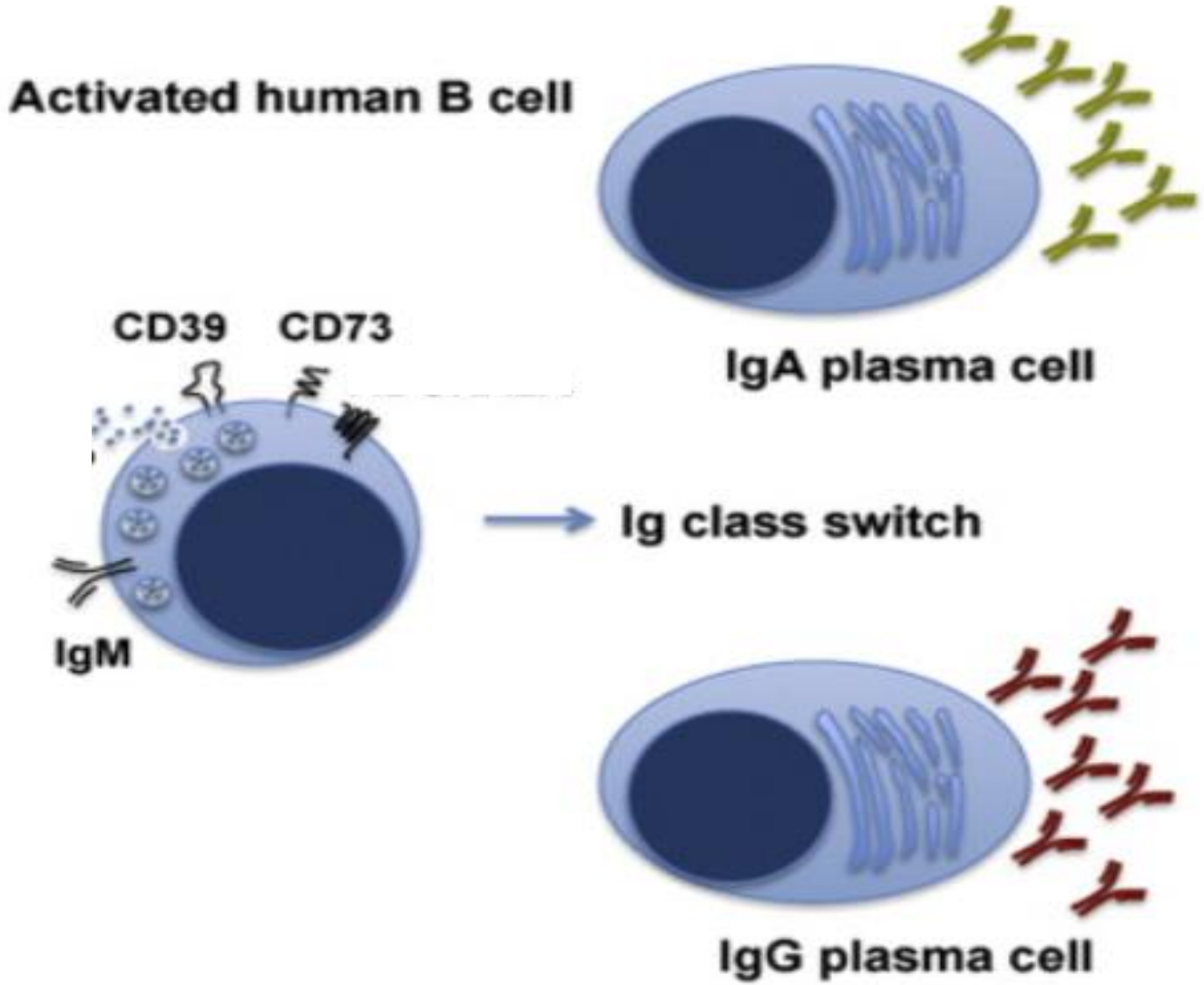
Immunoglobulin class switching (isotype switching, class-switch recombination, CSR)



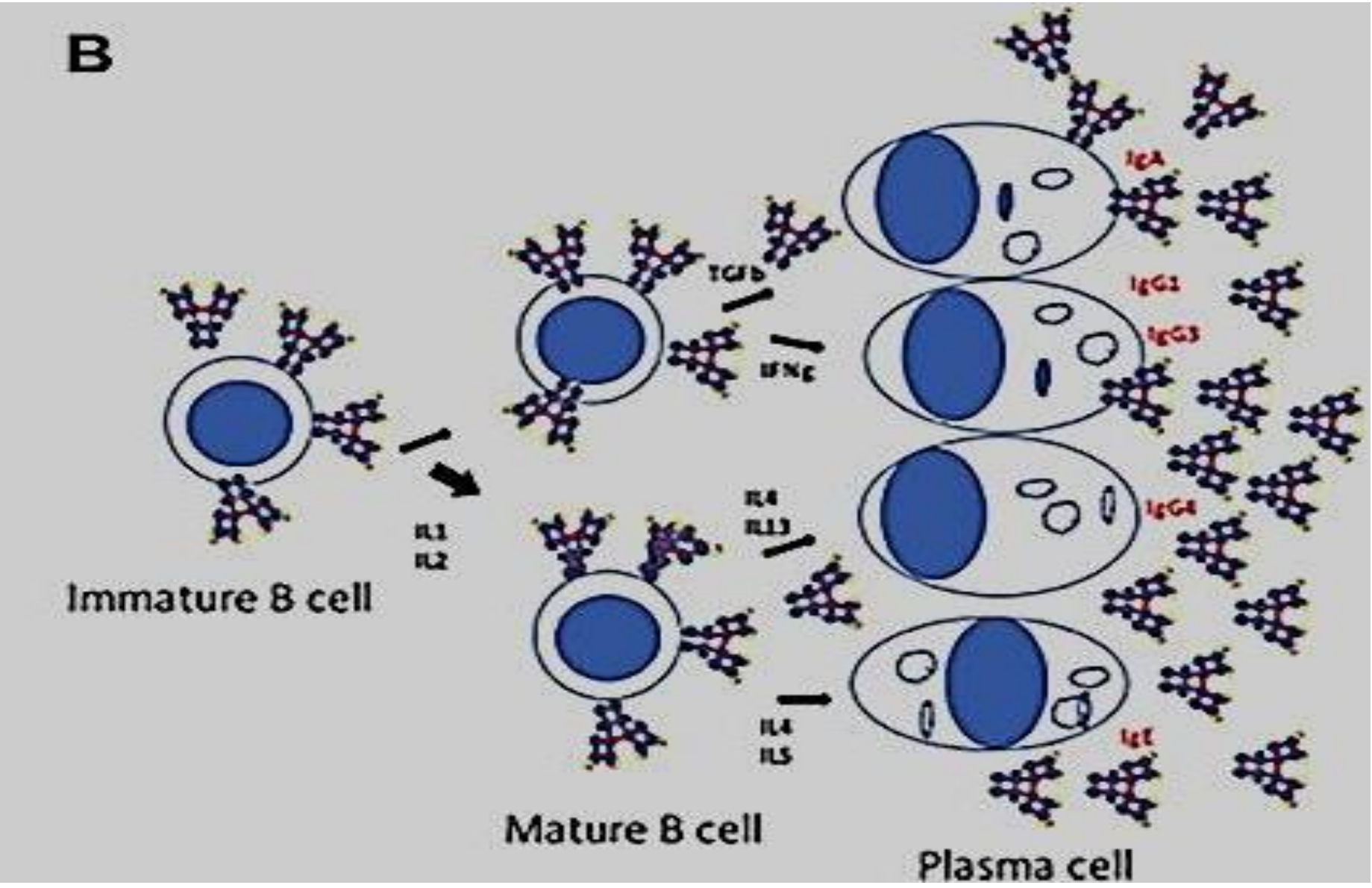
A biological mechanism that changes a B cell's production of immunoglobulin from one type to another, such as from the isotype IgM to the isotype IgG. During this process, the constant-region portion of the antibody heavy chain (e.g. Fc portion) is changed, but the variable region of the heavy chain stays the same. Since the variable region does not change, class switching does not affect antigen specificity. Instead, the antibody retains affinity for the same antigens, but can interact with different effector molecules.

https://www.youtube.com/watch?v=8jxI0DH0pAU

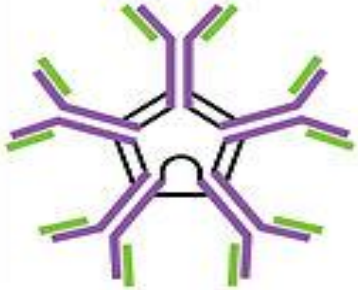
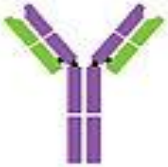
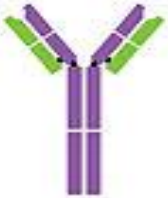
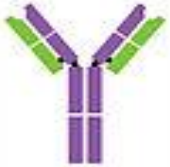
Immunoglobulin (Ig) isotype diversification by class switch recombination is an essential process for mounting a protective humoral immune response.



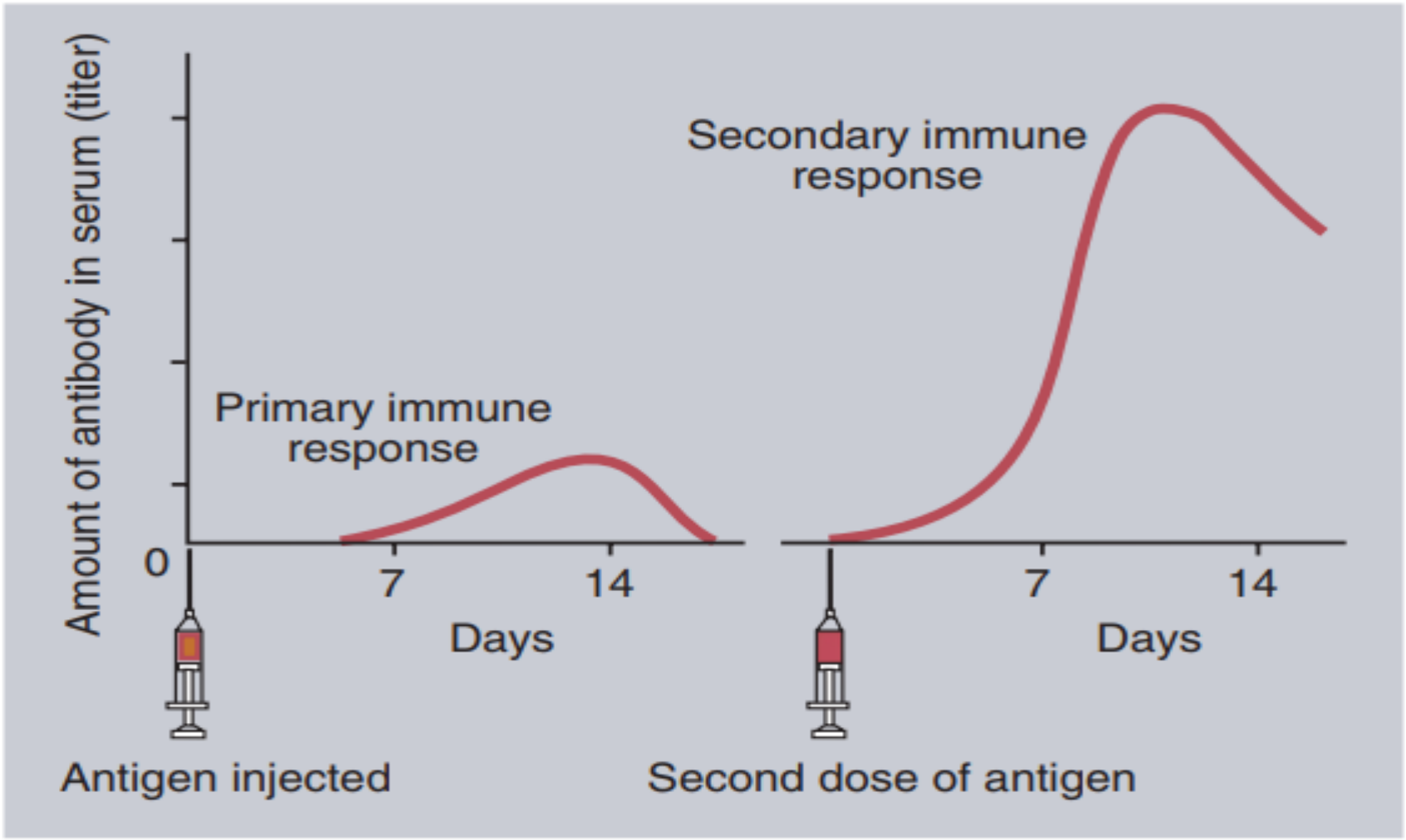
B Cell Maturation and Antibody Class Switching



https://www.researchgate.net/figure/B-Cell-Maturation-and-Antibody-Class-Switching-A-The-heavy-gene-on-chromosome-22_fig1_321214290

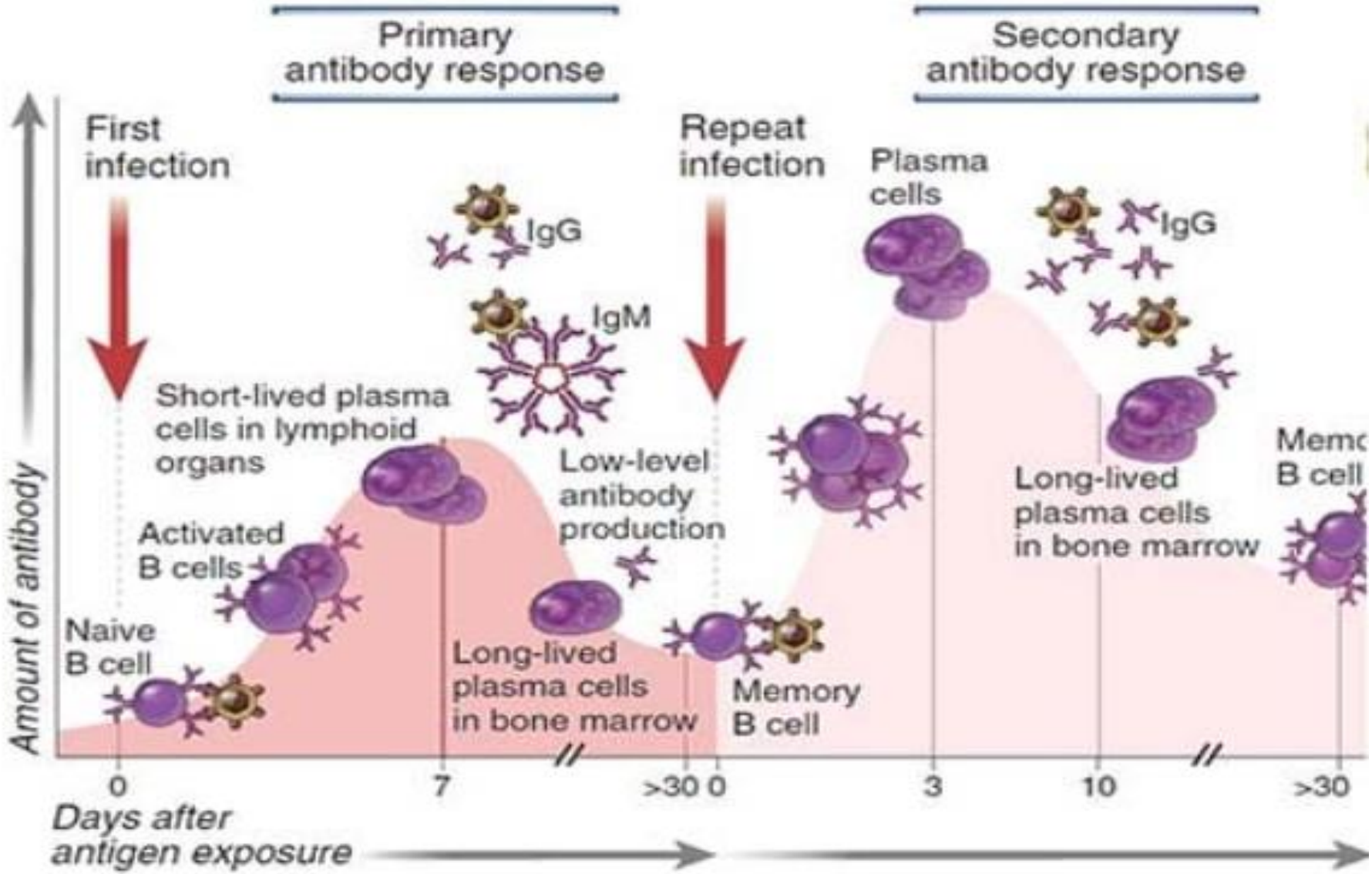
The Five Immunoglobulin (Ig) Classes					
	IgM pentamer	IgG monomer	Secretory IgA dimer	IgE monomer	IgD monomer
					
Heavy chains	μ	γ	α	ε	δ
Number of antigen binding sites	10	2	4	2	2
Molecular weight (Daltons)	900,000	150,000	385,000	200,000	180,000
Percentage of total antibody in serum	6%	80%	13%	0.002%	1%
Crosses placenta	no	yes	no	no	no
Fixes complement	yes	yes	no	no	no
Fc binds to		phagocytes		mast cells and basophils	
Function	Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor	Main blood antibody of secondary responses, neutralizes toxins, opsonization	Secreted into mucus, tears, saliva, colostrum	Antibody of allergy and antiparasitic activity	B cell receptor

The characteristic time course of the adaptive immune response to an antigen as measured by serum antibody levels. Note the differences between a primary and a secondary immune response. These differences account for the success of the adaptive immune responses.



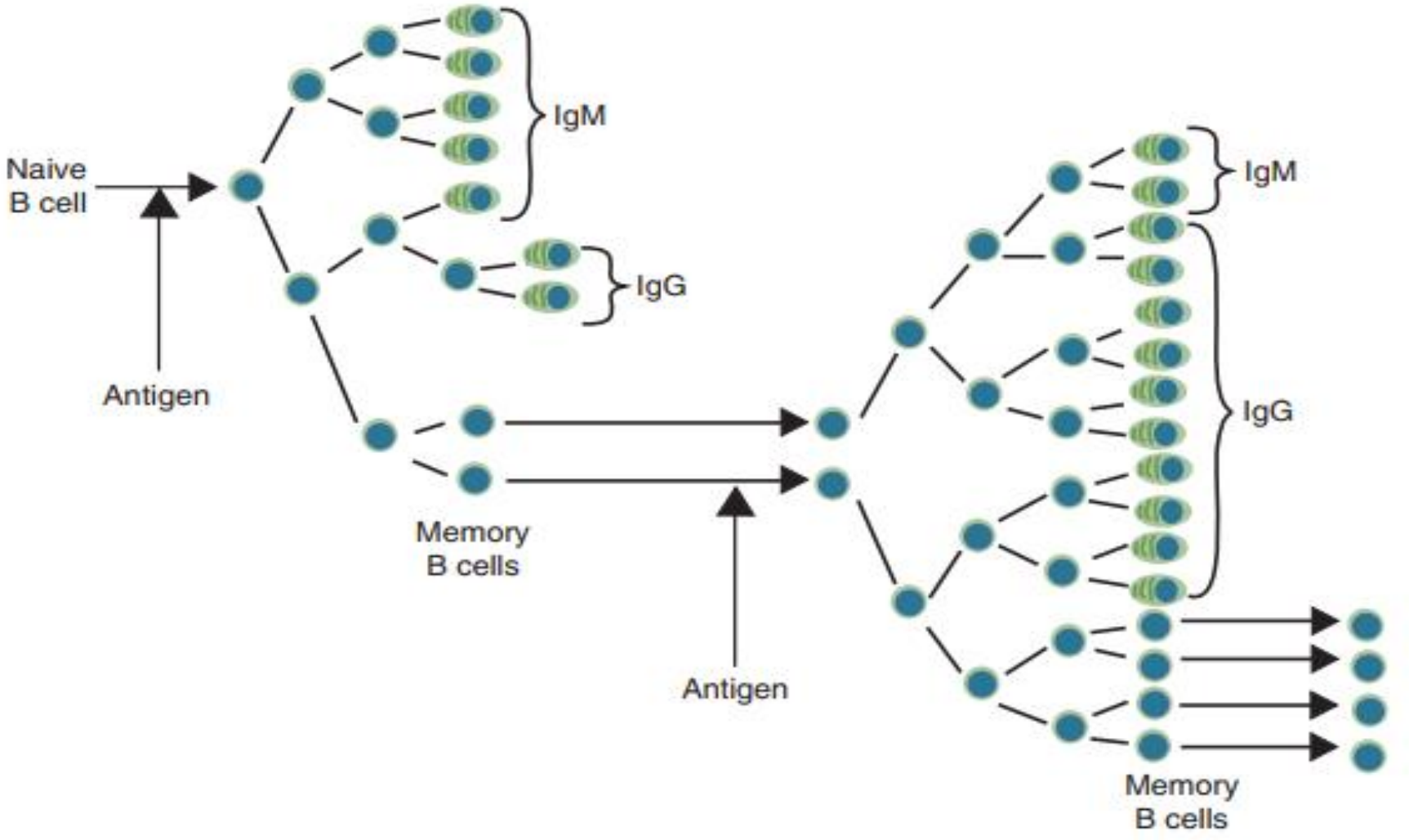
Primary and secondary humoral immune responses

(Source: Cellular and Molecular Immunology, Abbas, 9th Edition)



Primary vs Secondary Immune Response

Note how some IgG is made in the primary immune response, whereas a small amount of IgM is made in a secondary immune response.



Primary vs Secondary Immune Response

Characteristics	Primary Immune Response	Secondary Immune Response
Definition	The primary Immune Response is the reaction of the immune system when it contacts an antigen for the first time.	Secondary Immune Response is the reaction of the immune system when it contacts an antigen for the second and subsequent times.
Appearance	Appears mainly in the lymph nodes and spleen.	Appears mainly in the bone marrow and then, in the spleen and lymph nodes.
Occurrence	This occurs in response to the primary contact of the antigen.	This occurs in response to the second and subsequent exposure to the same antigen.
Antibody Peak	The antibody level reaches its peak in 7-10 days.	The antibody level reaches its peak in 3-5 days.
Affinity of Antibody	Low affinity to their antigens.	High affinity to their antigens.
Responding Cells	Naive B cells and T cells	Memory B cells

Primary vs Secondary Immune Response

Characteristics	Primary Immune Response	Secondary Immune Response
Antibodies	Both thymus-dependent and thymus-independent antibodies are involved in the primary immune response.	Only thymus-dependent antibodies are involved in the secondary immune response.
Lag Phase	Long (4-7 days)	Short (1-4 days)
Types of Antibodies	A large amount of IgM and a small amount of IgG are produced during the primary immune response.	A large amount of IgG, a small amount of IgM, IgA, and IgE are produced during the secondary immune response.
Amount of Antibody	Few antibodies are produced in the primary immune response.	100-1000 times more antibodies are produced in the secondary immune response.
Strength of the Response	The primary immune response is usually weaker than the secondary immune response.	The secondary immune response is stronger.
Antibody level	Antibody level declines to the point where it may be undetectable.	The antibody level tends to remain high for longer.

Regulation of Adaptive Immunity

A key feature of the adaptive immune system is that, while poised to launch a potent array of destructive mechanisms against invaders, the body maintains control of the process. It is critically important to limit and eventually terminate a response by inactivating or eliminating pathways that are no longer required.

The mechanisms Regulation of Adaptive Immunity

- Antigen
- Antibody
- Tolerance
- Regulatory T Cells
- Inhibitory Receptors
- An immunoregulatory cytokines: IL-10, TGF-β
- Regulation of Apoptosis
- Neural Regulation of Immunity and stress

Antigen Regulation of Immune Responses

- Adaptive immune responses are antigen driven. Antigens stimulate immune responses, although very low or very high doses of antigen may cause tolerance.
- They commence only on exposure to an antigen, and once its concentration drops below a critical threshold, they stop. If an antigen persists, the stimulus persists and the immune response is prolonged.
- The self-antigens restricted to sites such as the brain, that never enter lymphoid organs, are usually ignored by the immune system.

Antibody Regulation of Immune Responses

- Antibody responses are also regulated by antigen. Rigid polymeric antigens such as those on a bacterial surface or antigens linked to TCR activators such as LPS can induce B-cell responses in the absence of T cell help (T-independent immune response).
- On the other hand, nonpolymeric, flexible antigens such as soluble proteins induce B cell responses only in the presence of CD4+ T cells (T-dependent immune response).
- Antibodies tend to regulate antibody production through negative feedback mechanisms. Antibodies generally suppress B cell responses. IgG antibodies tend to suppress the production of both IgM and IgG, whereas IgM antibodies tend to suppress only the synthesis of IgM.
- This can prevent the successful vaccination of newborn animals as a result of maternal immunity.

Neural Regulation of Immunity

- The immune system and the central nervous system are closely interconnected and influence each other.
- The central nervous system communicates with the immune system through parasympathetic and sympathetic nerves and by soluble neurotransmitters.
- Neuroendocrine hormones such as corticotrophin-releasing factor and α-melanocytestimulating hormones, as well as some neurotransmitters, act on cells of the immune system to regulate cytokine balances.
- Conversely, cytokines and chemokines modulate central nervous system activities such as appetite, body temperature, and behaviors.

Stress

- Mental attitudes, especially stress, influence resistance to infectious diseases. Small bouts of stress are believed to enhance immune responses, but prolonged stress is detrimental.
- Stress can depress T cell responses, NK cell activity, IL-2 production, and expression of IL-2R on lymphocytes.
- Stress in pregnant animals results in immunosuppression of their offspring.
- A dominance hierarchy regulates many mammalian populations. If new individuals are introduced into a group, or a dominant animal loses its position, stresses occur as a result of the reorganization.

Factors that Influence the Type of Immune responses

- **Type of antigen-** Primary immune responses are activated by interaction with any type of antigen unlike the secondary immune response that is produced due to an interaction with a protein antigen
- **Route of antigen entry-** The initial response to an antigen is influenced by the route of entry and entry of an antigen that occurs in either of the three routes. i.e entry through the bloodstream which generates an immune response in the spleen, or entry through the skin and the subcutaneous tissue, which elicits an immune response in the regional nodes of the lymphoid system. Thirdly, antigens may gain entry into the body via the mucosal surfaces such as the gastrointestinal, lung, or reproductive tract which invokes an immune response in the submucosal lymphoid tissues.
- **Antigen-presenting cells-** The processing of antigens is done by antigen-presenting cells which include dendritic cells, macrophages, and B-lymphocytes with the dendritic cells being the most effective. These cells play a major role in interacting with the antigen, Dendritic cells are predominant in presenting processed antigens to T-cells in primary immune responses. The B-cells function effectively as antigen-presenting cells in secondary immune responses. Antigen-processing and presentation are facilitated phagocytic mechanisms presenting an antigen that has been broken down into peptides in association with the Major Histocompatibility Complex (MHC).

Factors that Influence the Type of Immune responses

- **Antigen Receptors-** Antigen interactions with immune cells including the B and T-cells are by the ability of these cells to recognize them (antigens). B-cells possess the B-cell Receptors (BCR) also known as immunoglobulins, to which the antigen bind while the T-cells must recognize antigens that have been processed and bound to the MHC complex molecules to bind to the T-cell Receptors (TCR).
- **Antigen Complexity-** Antigens have various shapes and sizes and the antigen determinants are also known as epitopes. These epitopes must be recognized by T and B-cells and they must be able to induce an immune response for them to activate B-cells which in turn pass through the Thymus and activate the T-cells. However, some antigens are not immunogenic and therefore they need a carrier protein such as an immunoglobulin for them to be immunogenic thus inducing an immune response against them.
- Other factors that influence the type of immune response include clonal expansion, affinity maturation, class switching, and memory cells.

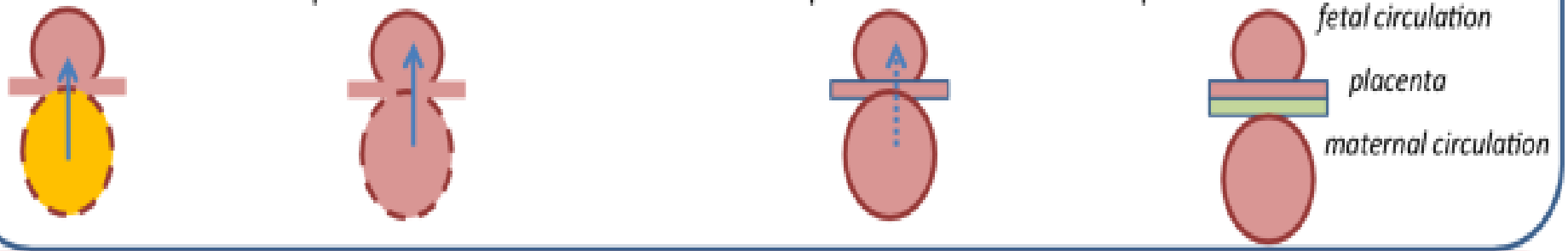
Passive Immunity

- A critical aspect of adaptive immunity in veterinary species involves maternal immunity that is "passively" transferred to neonatal animals. For most mammalian species, neonates are born with a naı̈ve immune system. The final stages of immunological development occur after birth, following separation from the maternal blood and population by the microbiome.
- During pregnancy, placental structure influences immunoglobulin transfer and only in a few species, notably humans and to a lesser extent carnivores, does antibody, usually of the IgG isotype, cross the placenta to circulate in the fetus.
- In most mammals, including all farm animal species, passive transfer of antibodies occurs through the neonate's ingestion of colostrum immediately after birth. Colostrum contains immunoglobulin at 10-100-fold its concentration in milk.

Transfer of maternal immunoglobulin to offspring is controlled by the interface between the maternal circulation and the placenta (or yolk sac in fish and birds).

Fetal stage – mother to embryo immunoglobulin transport

FISH & BIRDS	PRIMATES & RODENTS	DOG, CAT, MINK	RUMINANTS, PIGS, HORSES
Active transport /yolk sac	Active transport Hemochorial placenta	Limited transport Endotheliochorial placenta	No transport Epitheliochorial placenta

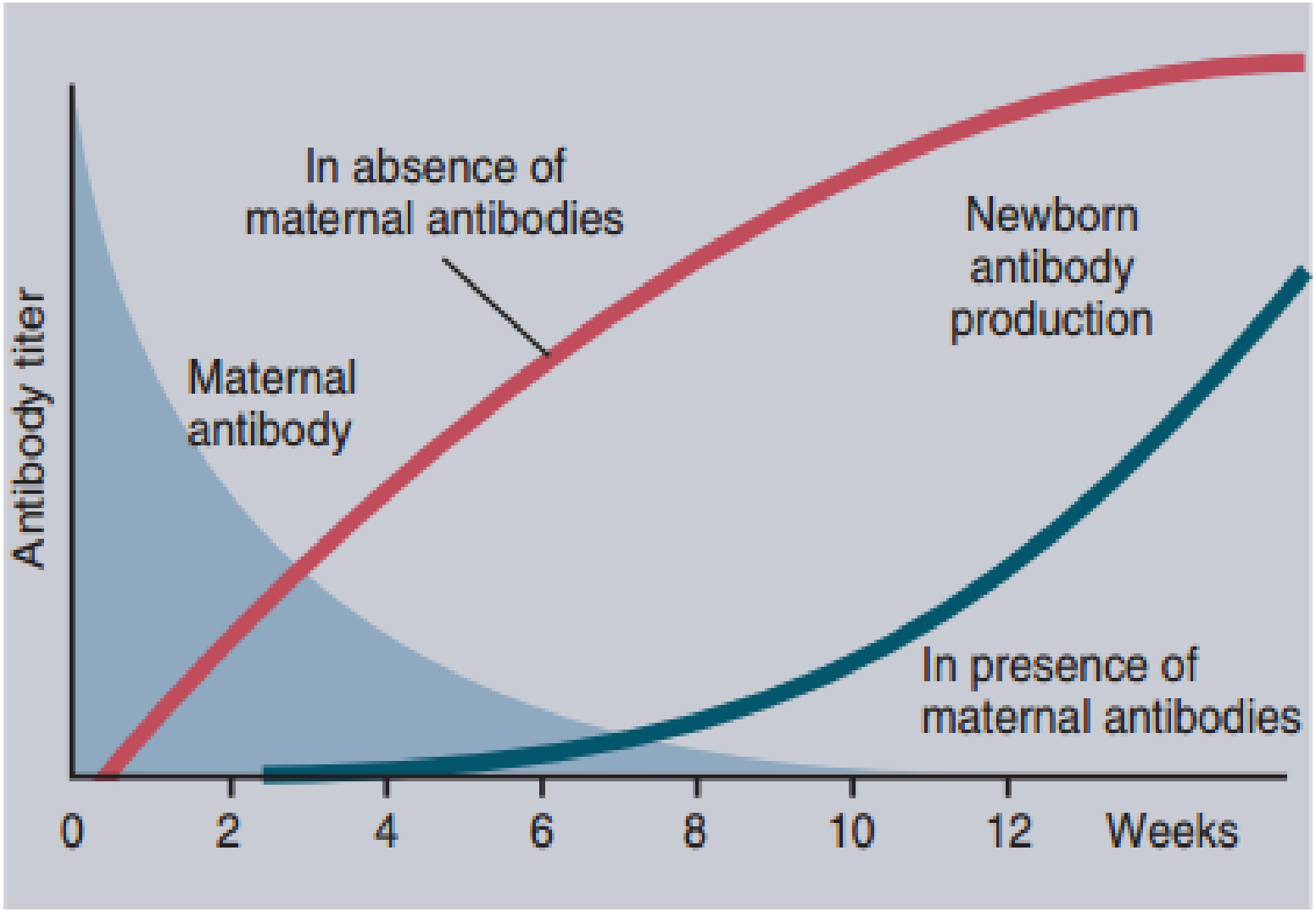


Neonatal stage – circulating immunoglobulins

IgM (fish) **IgY** (birds)	**IgG**	**IgG** (low levels)	No circulating Ig's
Gut uptake: (open gut)			
No	**No**	**Yes** (< 36 h after birth)	**Yes** (< 24 h after birth)

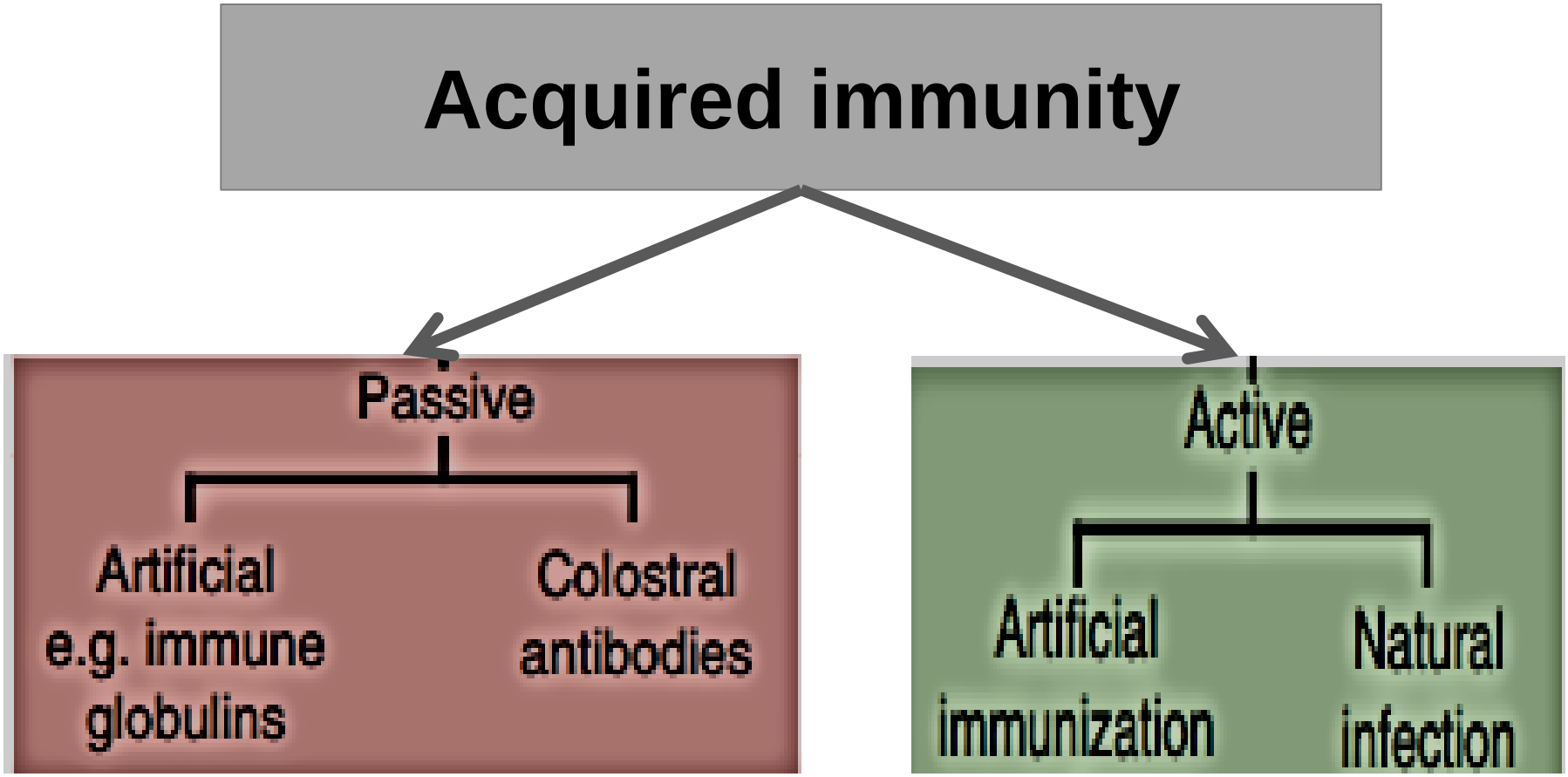
https://veterinaryresearch.biomedcentral.com/articles/10.1186/s13567-018-0558-2

The presence of maternal antibody in a newborn animal effectively delays the onset of immunoglobulin synthesis through a negative feedback process.



Types of vaccines

2022


Acquired immunity
Passive
Artificial
e.g. immune
globulins
Colostral
antibodies
Active
Artificial
immunization
Natural
infection

Herd immunity is an important feature of vaccine-induced protection.

- The concept of herd immunity for a highly contagious disease such as measles.
- Susceptible individuals include those who have not yet been immunized (for example, being too young), those who cannot be immunized (for example, as a result of immunodeficiency), those for whom the vaccine did not induce immunity, those for whom initial vaccine-induced immunity has waned and those who refused immunization.

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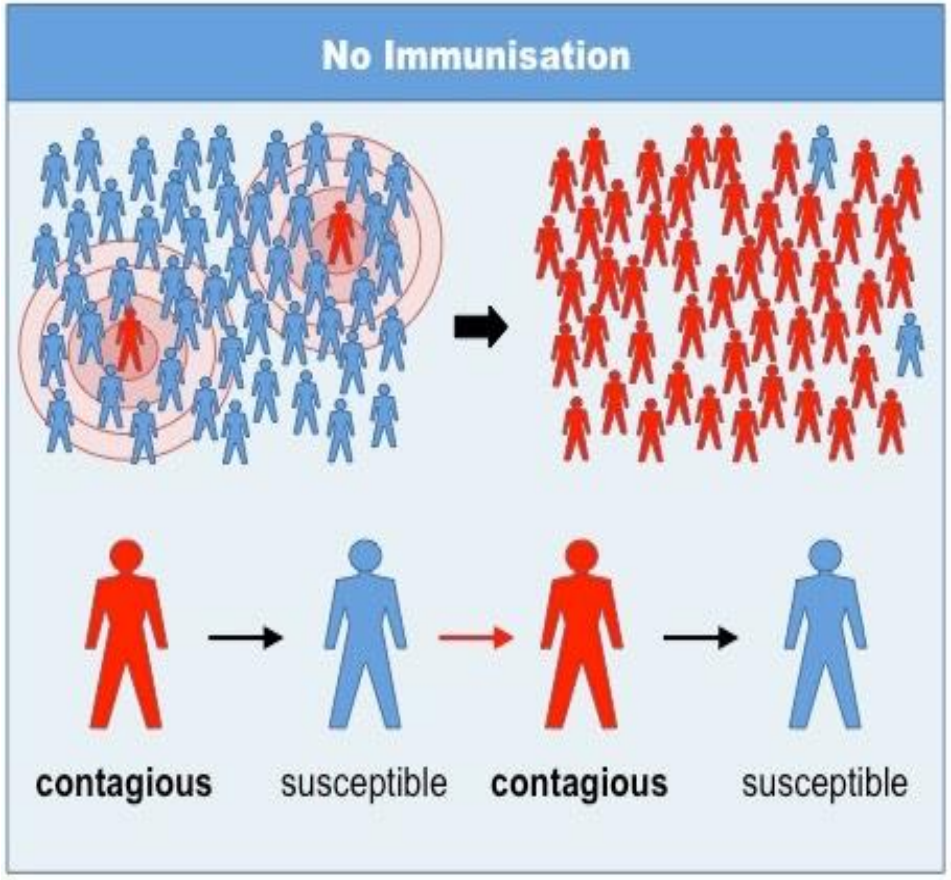
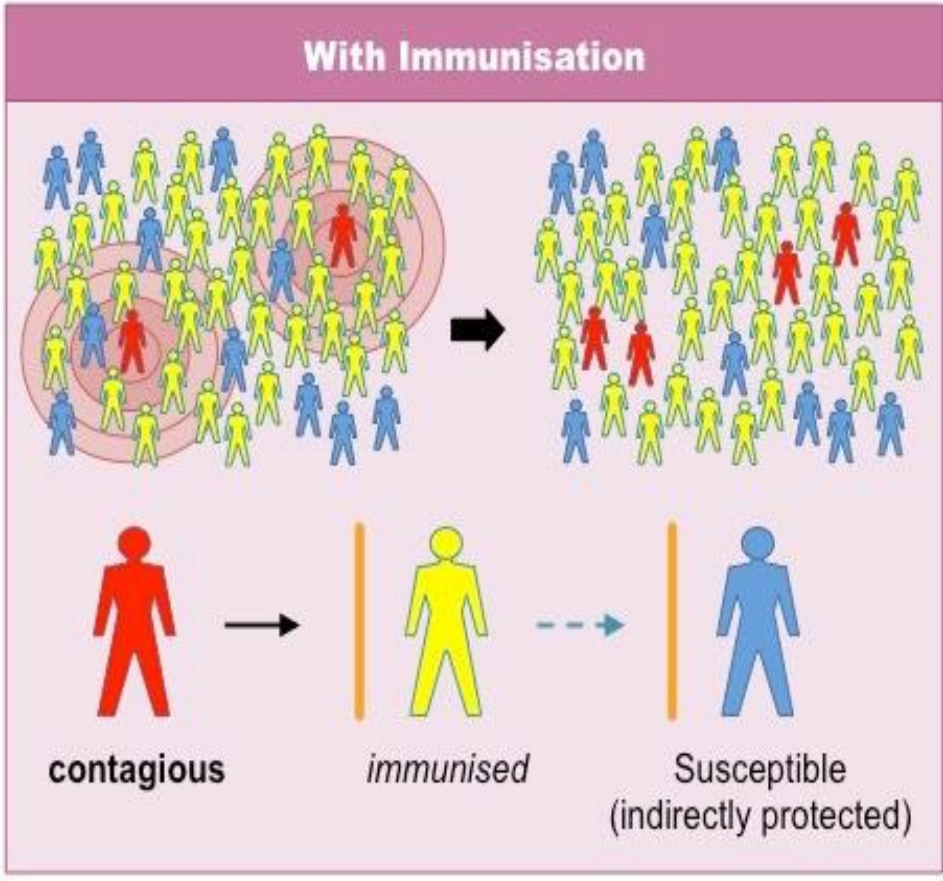
Normally, the number of vaccinated individuals is high enough that it confers what is termed **‘herd immunity’** to a population, where the incidence of contracting the disease is so low that even unvaccinated individuals will be protected. However, if the number of unvaccinated individuals increases, herd immunity is no longer effective and the population becomes at risk of a disease epidemic

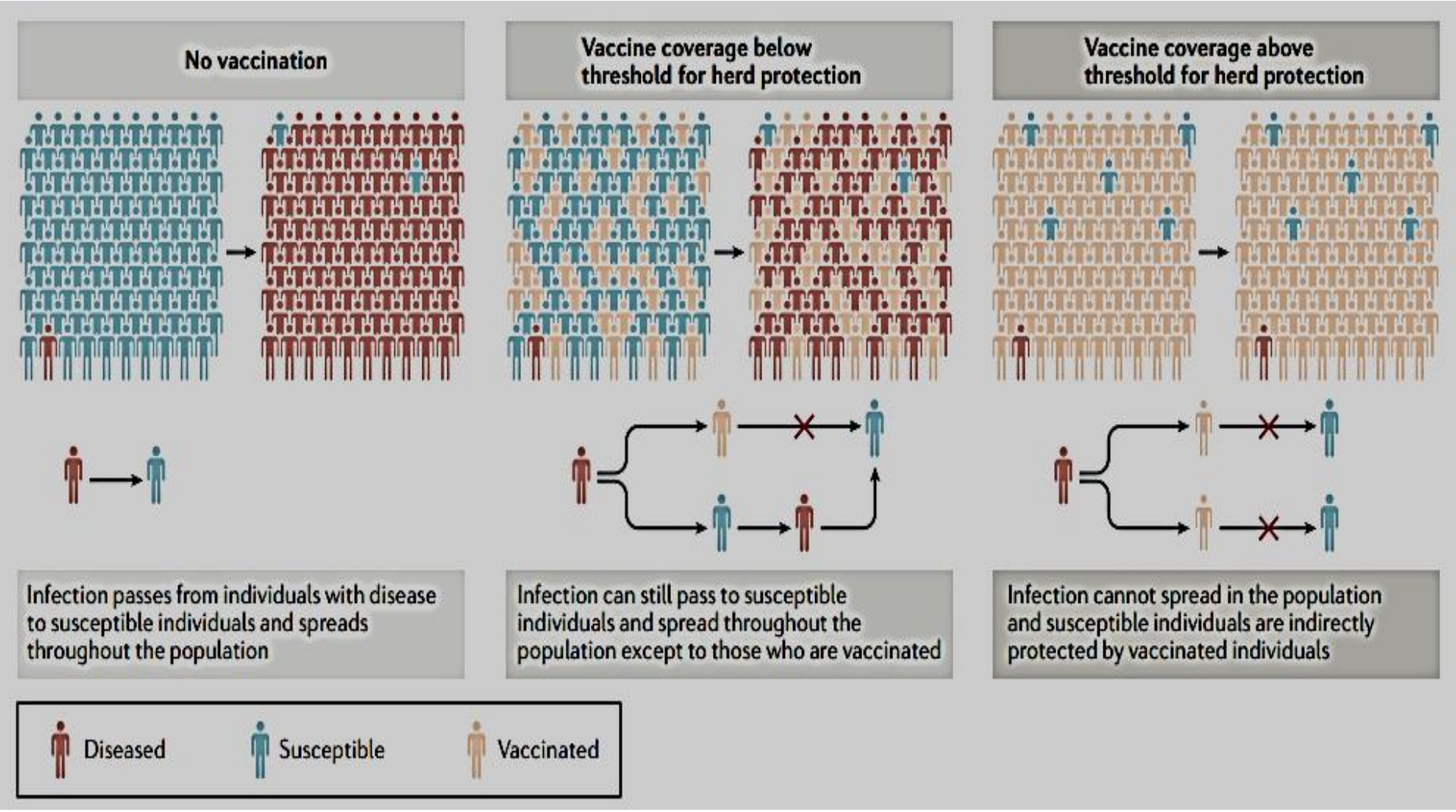


Infectious agent passes freely from contagious to susceptible



Contagion **cannot** freely pass via immunised to susceptible

Herd immunity is an important feature of vaccine-induced protection.



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Vaccines and Immunizations

A **VACCINE** [Latin *vacca,* cow] – is an immuno-biological substance designed to produce specific protection against a given disease.

A vaccine is “antigenic” but not “pathogenic”.

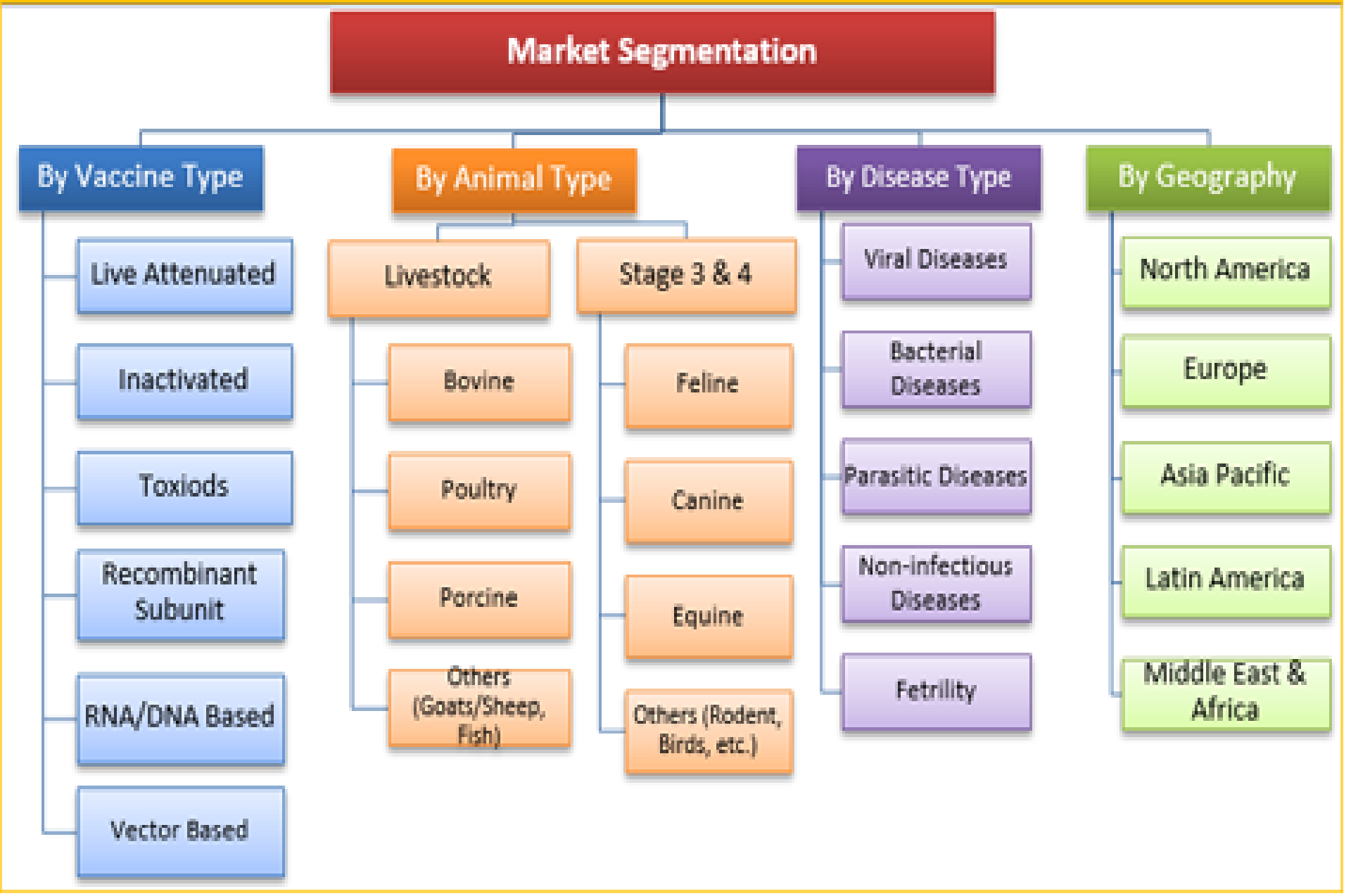
Active immunization is the protection of susceptible humans and domestic animals from communicable diseases by the administration of **vaccines (vaccination).**

Other immunizing agent

Specific immunoglobulin (Antisera):

Tetanus; Gas gangrene; Botulism; Rabies

Global Veterinary Vaccines Market Segmentation



History of Vaccination

- 1796 -Jenner – cowpox
- 1885 - Pasteur – cholera, diphtheria, chickenpox, rabies
- 1911 - first typhoid vaccine
- 1927 - first tetanus vaccine
- 1931 - Calmette & Guerin – first crude BCG
- 1936 - influenza

Modern era of vaccination

- 1940 - diphtheria national programme in UK
- 1950's - polio, pertussis, modern BCG
- 1960's - measles, mumps & rubella, modern tetanus
- 1980's - *H. Influenzae B* (Hib)
- 2000's - Meningitis C, Human papilloma virus (HPV)

ERADICATION OF VIRAL DISEASES

- Disease control, whether by vaccination alone or by vaccination in combination with the various methods, is a continuing process that must be maintained as long as the disease is of economic and/or social importance. Successful eradication of a disease that is endemic often requires a sustained and substantial financial commitment.
- Foot-and-mouth disease has now been eradicated from a number of countries in which it was once important, but outbreaks of the disease in previously free countries continue to occur regularly, often with devastating economic consequences.

ERADICATION OF VIRAL DISEASES

- So far, global eradication has been achieved for only one human disease: smallpox. The last endemic case of smallpox occurred in Somalia in October 1977. Global eradication was achieved by an intensified effort led by the World Health Organization, which involved a high level of international cooperation and made use of a potent, inexpensive, and very stable vaccine.
- A similar global effort to eradicate polio has not met with similar success to date as the disease is still endemic in Afghanistan, Nigeria, and Pakistan.

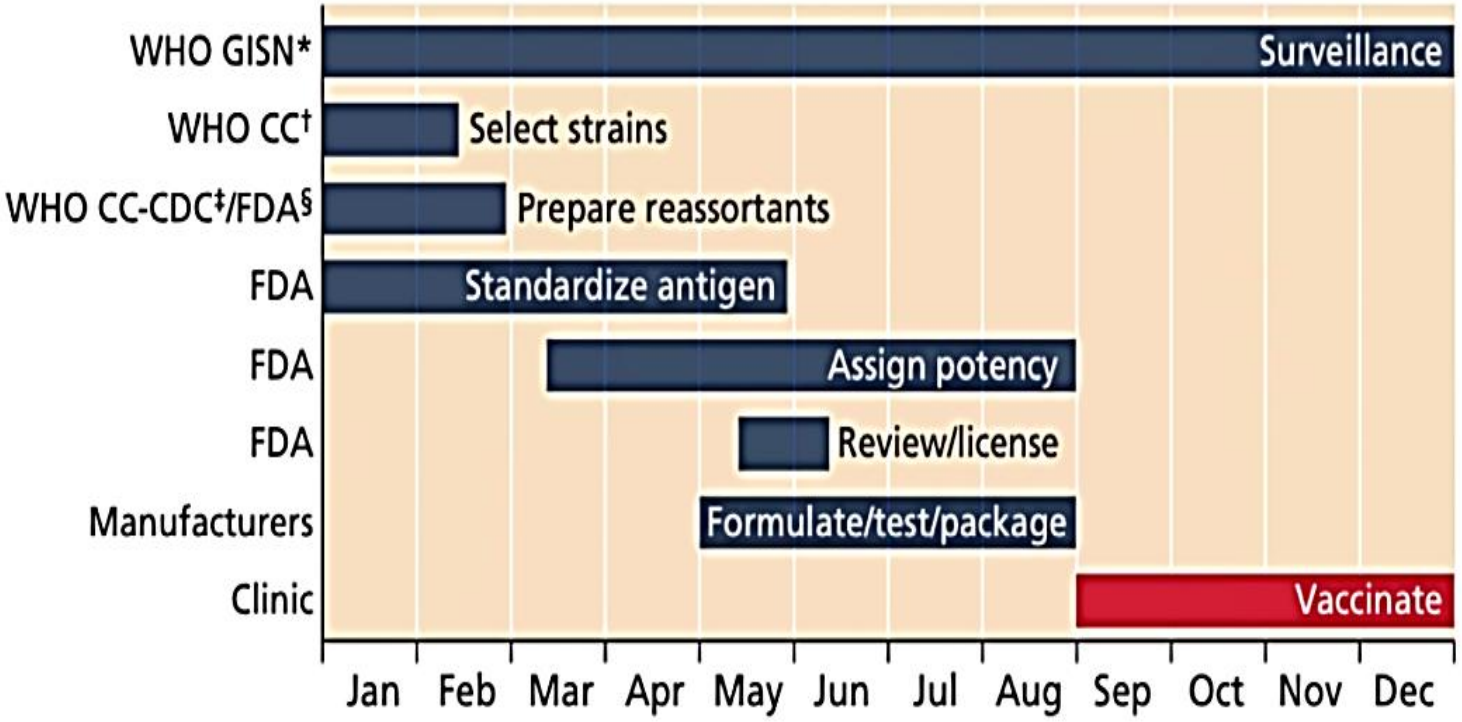
ERADICATION OF VIRAL DISEASES

- Rinderpest is the first animal disease to have been globally eradicated. Rinderpest was a devastating disease of cattle in Europe before it was finally eliminated from the continent in 1949, and was a scourge in sub-Saharan Africa it was very nearly eliminated from Africa in the 1980s by massive cattle vaccination programs, but regional wars and violence interceded, programs were stopped, and the disease made a rapid comeback in many areas before its eventual eradication.
- The lessons learned from these vaccination programs, additional lessons from the success in eradicating smallpox and in the control of polio, and the availability of an effective vaccine, contributed to successful global eradication of rinderpest in 2011.

ERADICATION OF VIRAL DISEASES

- An outbreak of foot-and-mouth disease occurred in the United Kingdom in 2001, some 34 years after the last such outbreak. The 2001 outbreak precipitated a crisis that led to the slaughter of more than 10 million cattle and sheep, and which had a devastating impact on British agriculture, tourism, and the economy: this event is estimated to have cost the British economy up to US$16 billion.
- Similarly, devastating foot-and-mouth disease epidemics occurred in Japan and North and South Korea in 2010-2011, and again in Korea in 2014-2015.

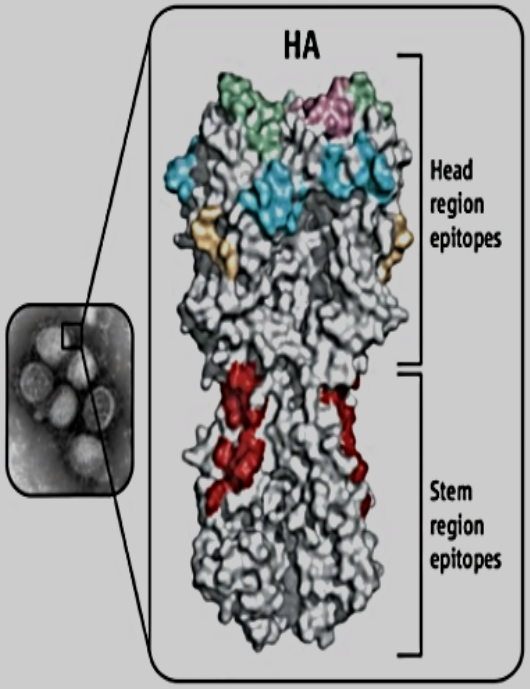
Selecting an influenza virus vaccine

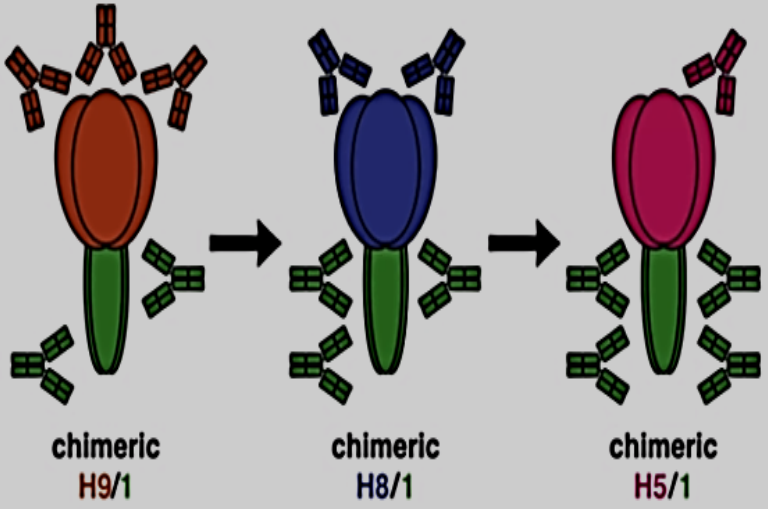


*World Health Organization Global Influenza Surveillance Network
†WHO Collaborating Centres
‡US Centers for Disease Control and Prevention
§US Food and Drug Administration

http://www.microbe.tv/twiv/twiv-413/ on how strains are selected

Universal influenza vaccine

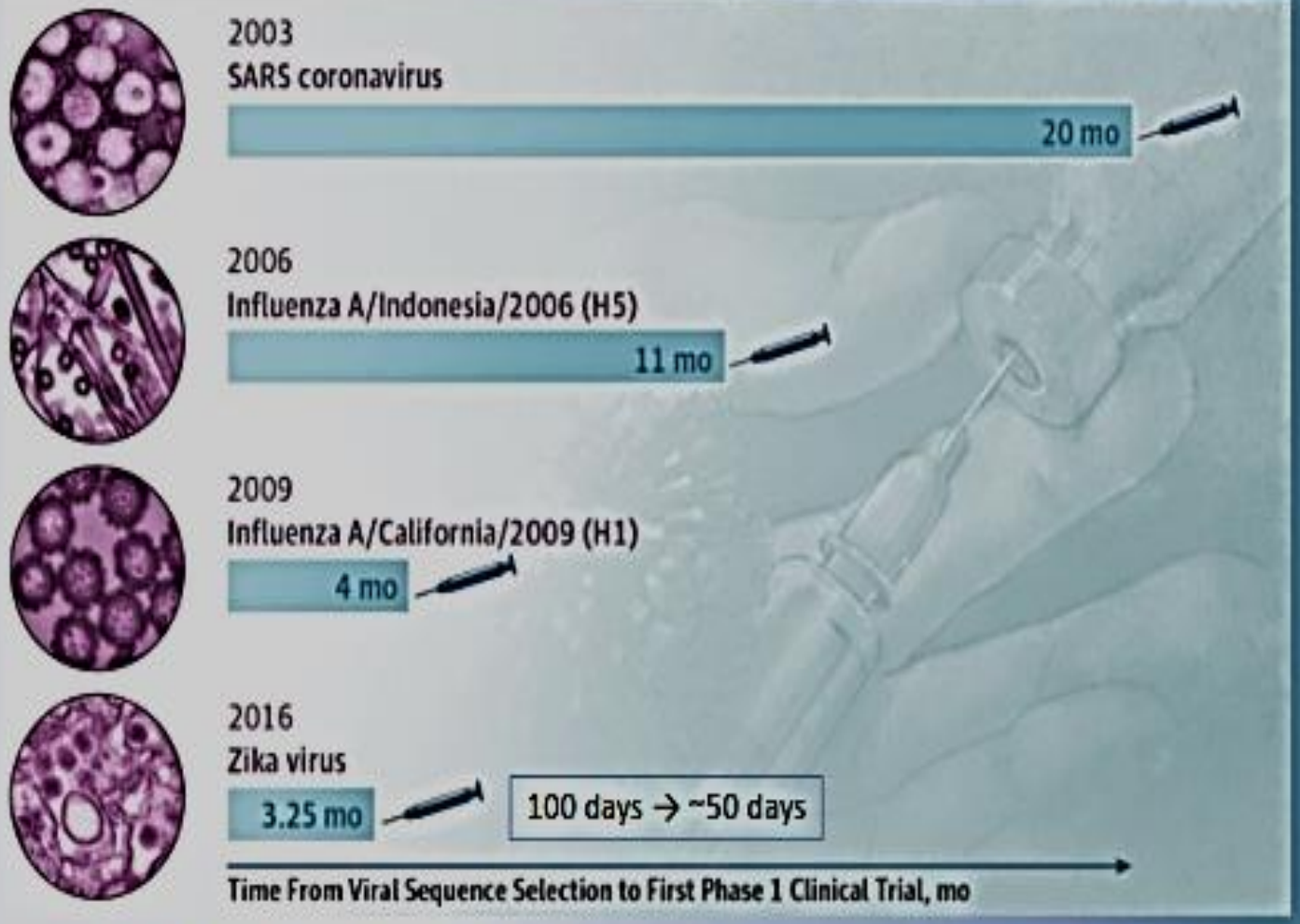




By exchanging the HA head domains, but retaining the same HA stalk domain, the antibody response can be redirected towards the otherwise immuno-subdominant stalk region.

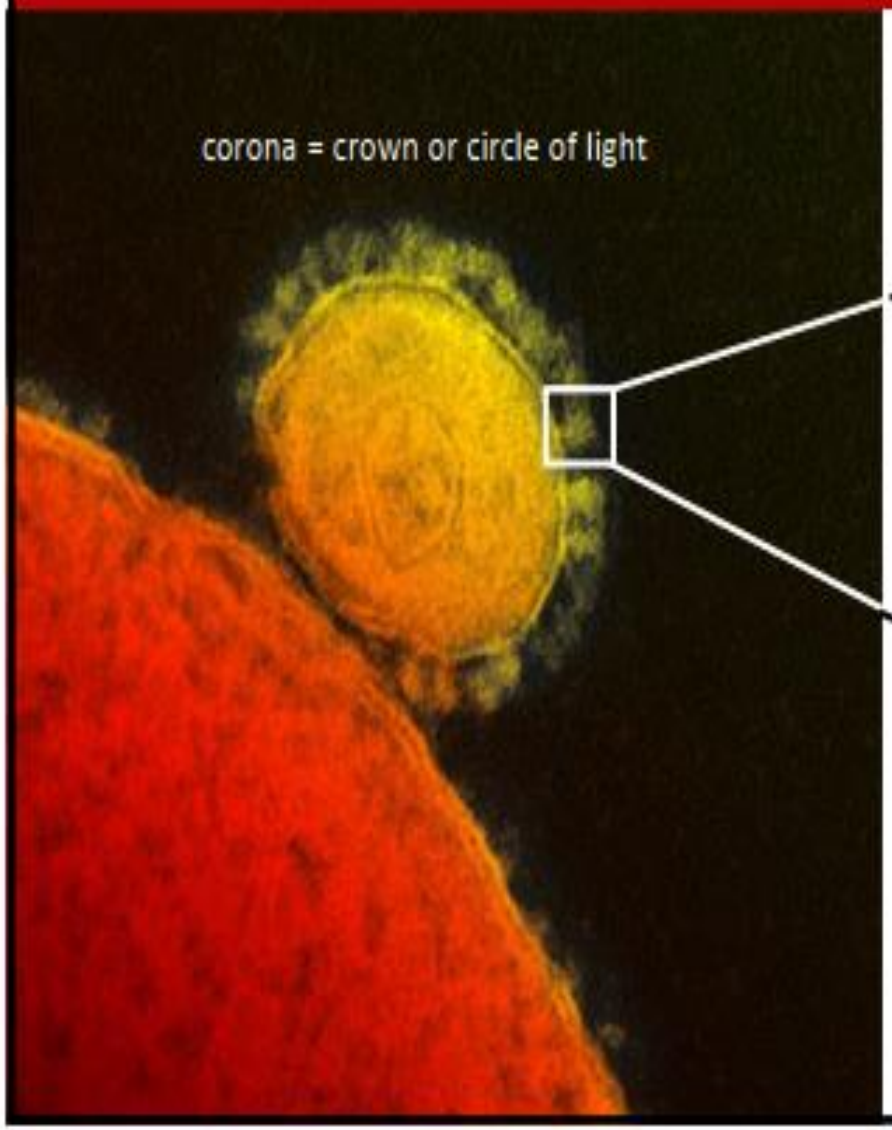
NPJ Vaccines. 2017; 2: 26.

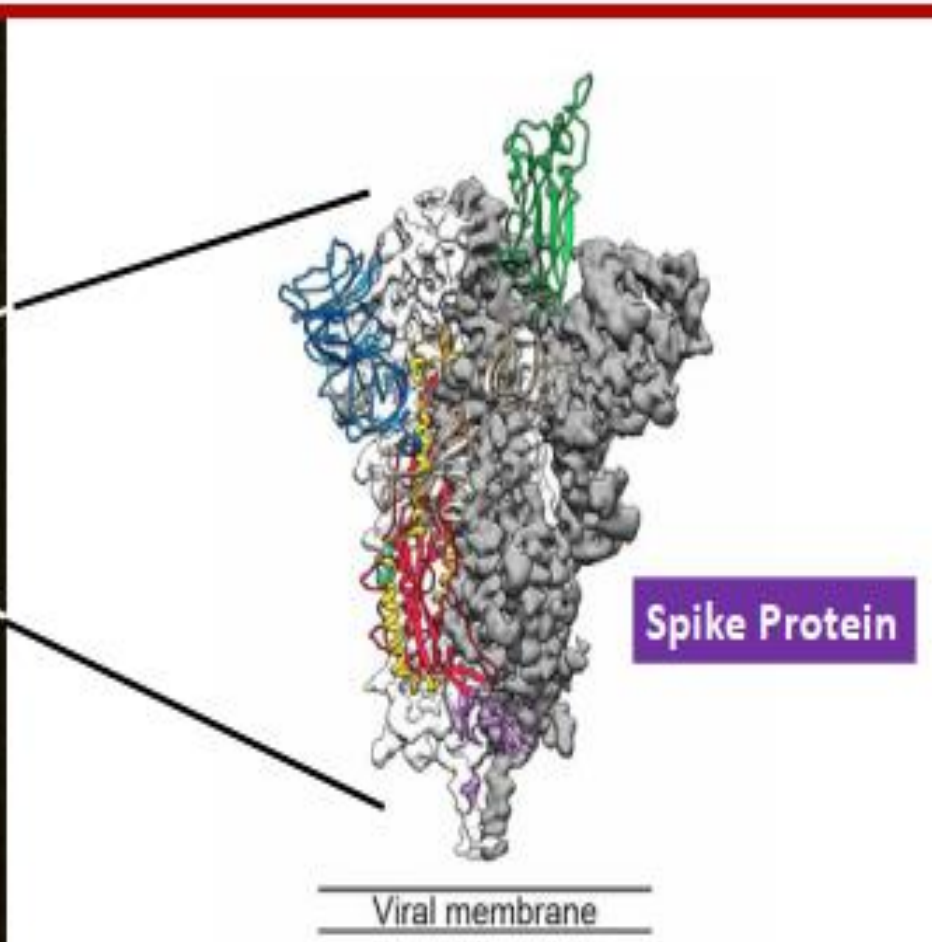
Platform Technologies Shorten Manufacturing Timelines



Graham, Mascola, Fauci. Novel Vaccine Technologies: Essential Components of an Adequate Response to Emerging Viral Diseases JAMA 2018

Coronavirus Biology and Nomenclature

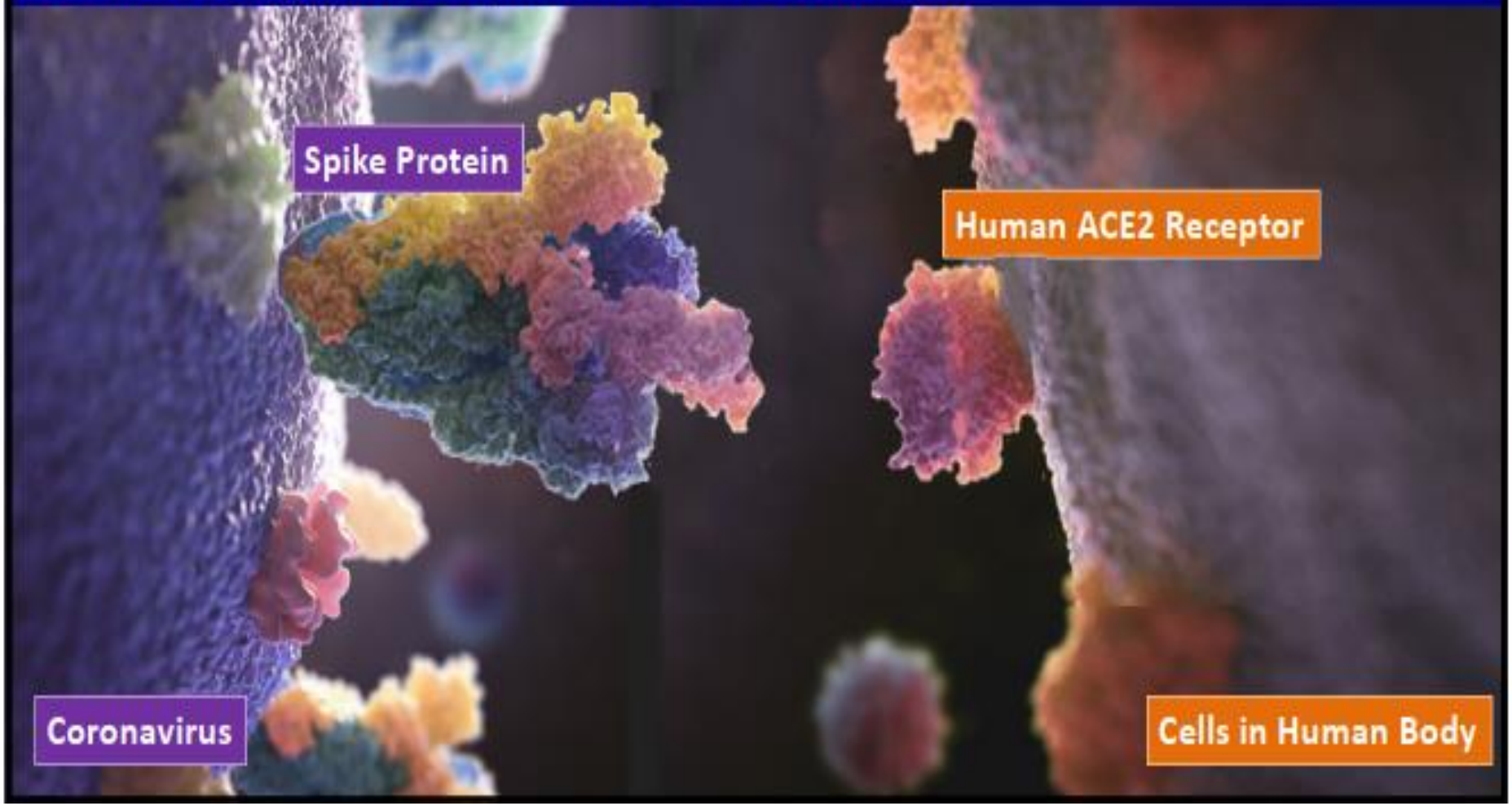




Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020 Feb 19:eabb2507. doi: 10.1126/science.abb2507.

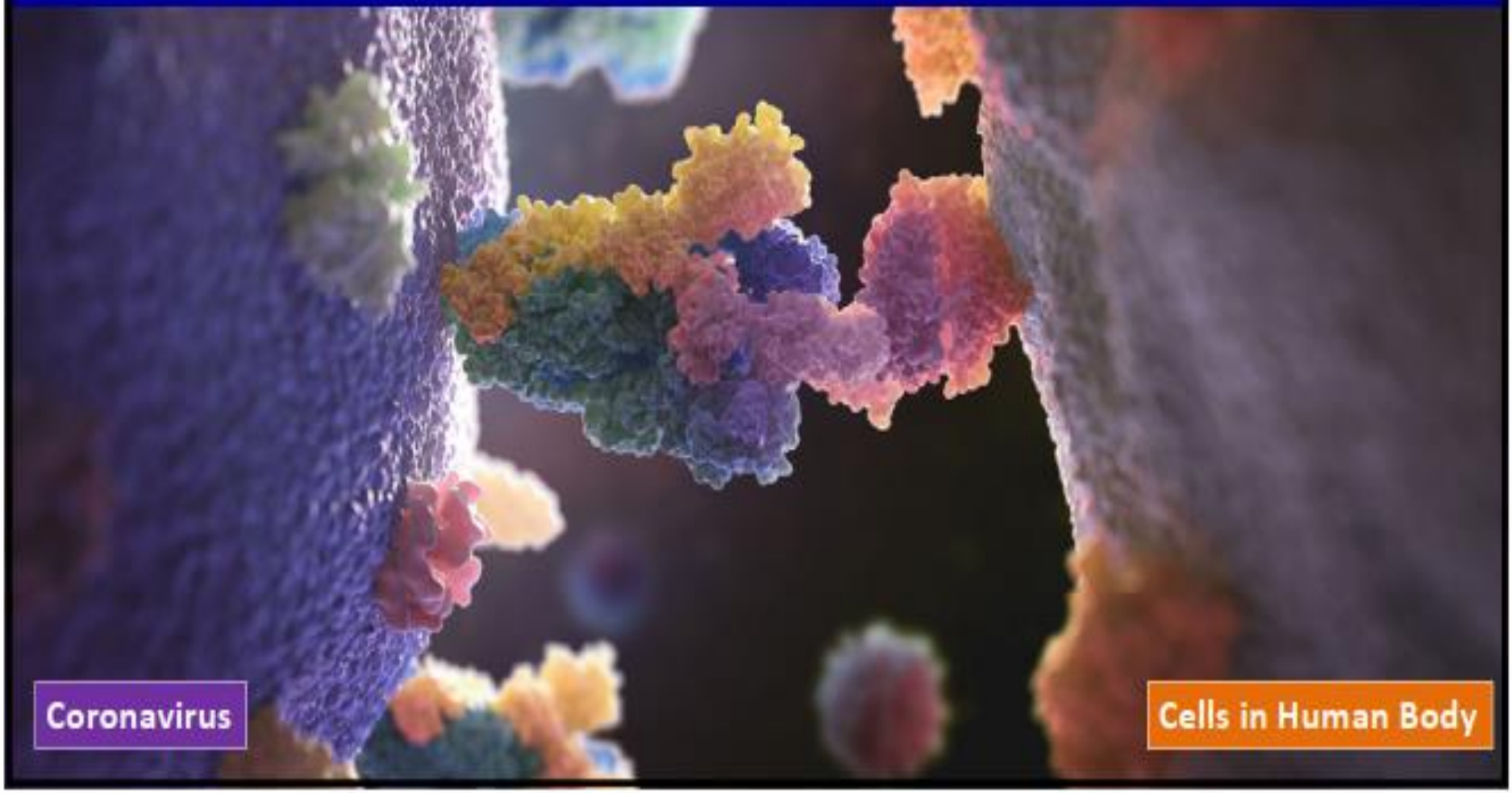
Vaccine Target: Coronavirus Spike Protein

- Coronavirus spike protein is on the viral surface and mediates attachment to cells to start the infection process
- Ideal vaccines target coronavirus spikes in order to block viral infection



Vaccine Target: Coronavirus Spike Protein

- Coronavirus spike protein attaches to ACE2 protein to start infection



Vaccine Target: Coronavirus Spike Protein

- Vaccine-induced antibodies will block the interaction and function of CoV spike protein

Covid-19 VACCINE DEVELOPMENT PLATFORMS

Current CEPI COVID-19 portfolio

	Technology platform	Antigen	Partner type	Geo allocation	Manufacturing scalability (High/medium/low)
Inovio	DNA	Spike	Biotech	US	Medium/Low
Moderna	mRNA	Spike	Biotech	US	High
CureVac	RNA	Spike	Biotech	EU	Proprietary
Queensland	Subunit	Spike	Academic	Australia	High
Novavax	VLP	Spike	Biotech	USA	High
University of Oxford	ChadOX	Spike	Academic	UK	Low
University of HongKong	Viral vector	Spike RBD	Academic	Hong Kong	High
IP Themis	Viral vector	Spike	Academic/Industry	France/Germany/India	High

CEPI

Moderna already in first in human clinical trial – in just 63 days

Vaccine Production

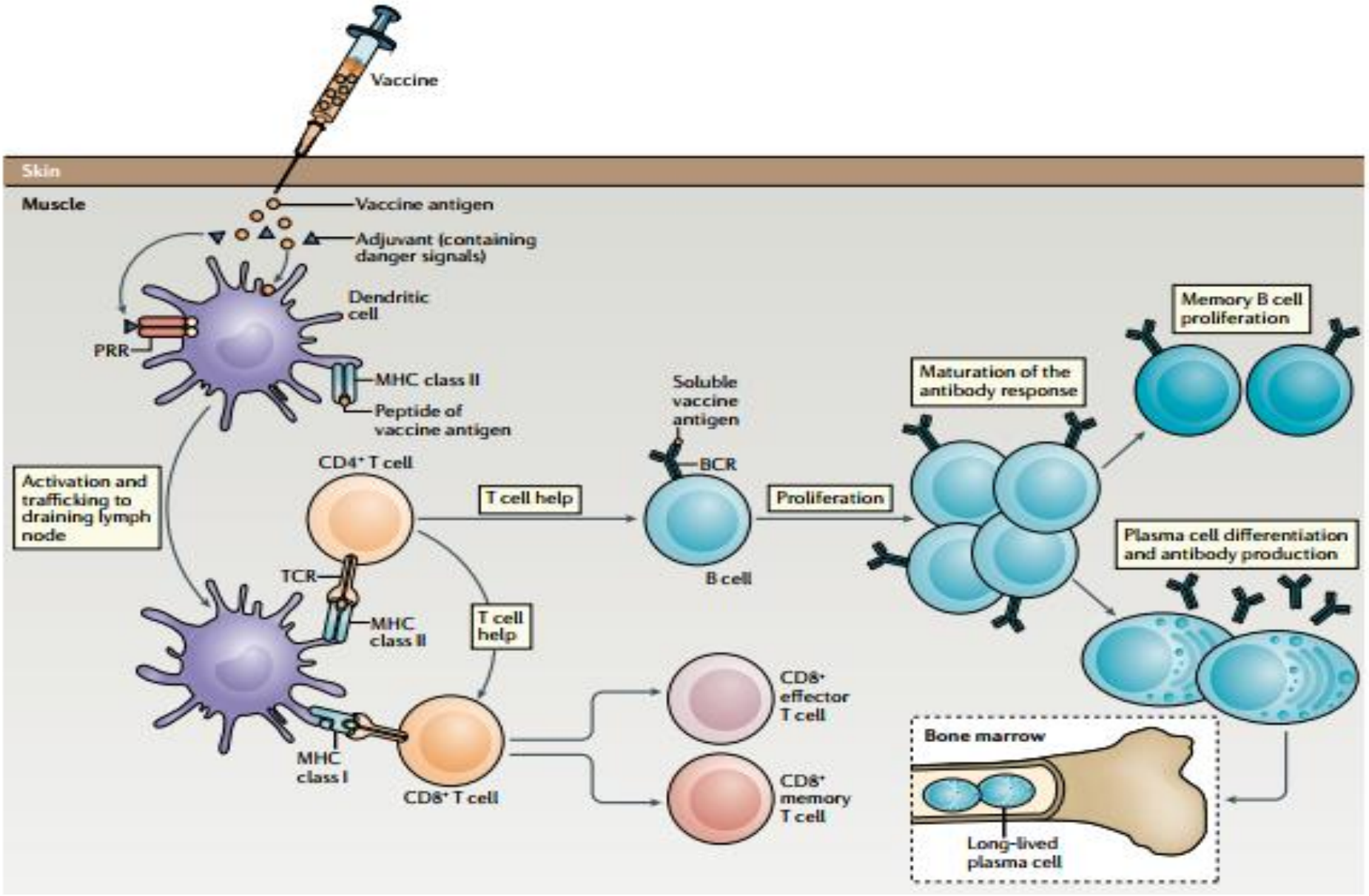
Two main stages:

- Biological – antigen preparation,
- Pharmaceutical – ready to use product

General issues to consider in vaccine development:

- Efficacy – how well the vaccine protects the immunized population as a whole (most vaccines more than 85-95% protective)
- Safety – potential revirulence and or increased pathology
- Stability of antigen and adjuvants
- Drug resistance – new drug resistance by many bacteria has increased urgency for bacterial vaccines
- Cost – number of animals vaccinated versus cost to manufacture

The generation of an immune response to a vaccine



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Immune responses to polysaccharide and protein–polysaccharide conjugate vaccines.

- Polysaccharide vaccines induce antibody-producing plasma cells by cross-linking the B cell receptor (BCR). However, affinity maturation of the antibody response (only IgM) and the induction of memory B cells do not occur.

- Protein–polysaccharide conjugate vaccines can engage T cells that recognize the carrier protein, as well as B cells that recognize the polysaccharide. T cells provide help to B cells, leading to affinity maturation and the production of both plasma cells(two classes of antibodies are synthesized – IgG and IgM) and memory B cells.

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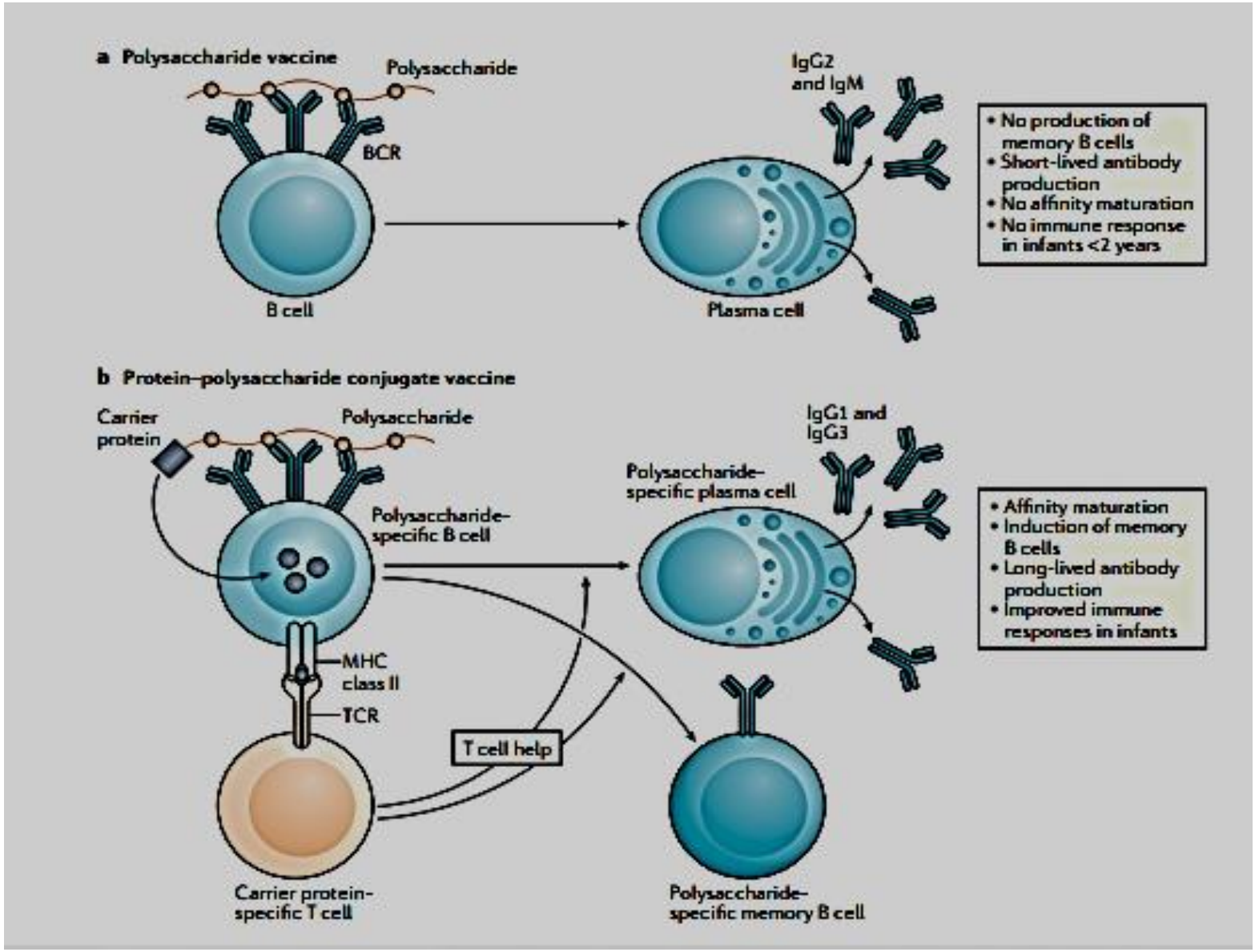
Immune responses to polysaccharide and protein–polysaccharide conjugate vaccines.



Adapted from reF.35, Springer Nature Limited

COMMON COMPONENTS OF VACCINES

As well as the active components, vaccines contain a number of other substances. This graphic examines these and the reasons for their inclusion.

ACTIVE COMPONENTS

A form of the virus, bacteria or toxin that causes the disease is used as the antigen. This antigen is modified from the original form so it no longer causes disease, but still elicits an immune response from the body. To modify the disease-causing agent, it can be treated with specific chemicals, so it cannot replicate. It can also be treated so it does not cause serious disease, or only parts of the disease-causing agent that do not cause serious symptoms can be used.

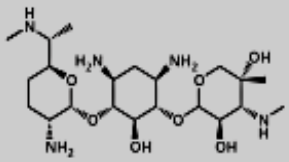
ADJUVANTS

$Al(OH)_3$
ALUMINIUM HYDROXIDE

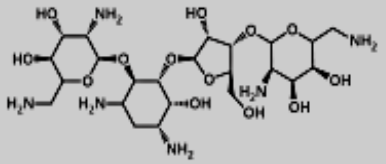
$AlPO_4$
ALUMINIUM PHOSPHATE

Added to enhance the body's immune response to the vaccine. How they work isn't entirely understood, but it's thought they help keep antigens near the site of injection. This means they can be easily accessed by the immune system cells. There is no evidence of any serious adverse effects from adjuvants, though they can cause some minor reaction near the injection site.

ANTIBIOTICS

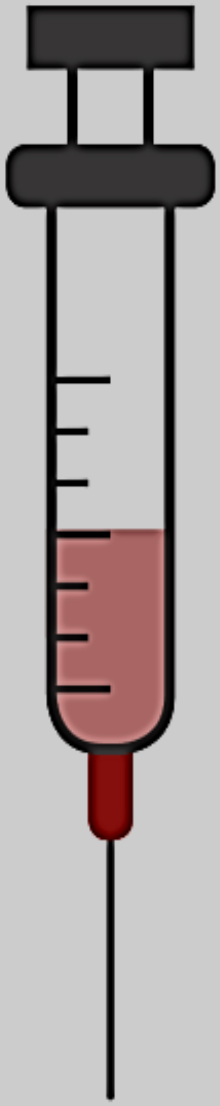


GENTAMICIN

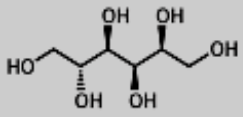


NEOMYCIN

Antibiotics are used in the manufacturing process of the vaccine to prevent bacterial contamination. They are later removed, and only residual quantities remain in the vaccine after the production process.



STABILISERS

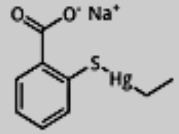


SORBITOL

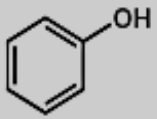
$MgSO_4$
MAGNESIUM SULFATE

Vaccines need to be storable, so stabilisers are added to ensure the various components remain stable and effective. A variety of different stabilisers are used; either inorganic magnesium salts such as magnesium sulfate or magnesium chloride, or mixtures of lactose, sorbitol and gelatin. Monosodium glutamate and glycine are also used in some cases.

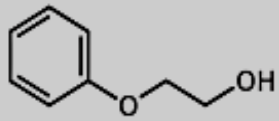
PRESERVATIVES



THIOMERSAL



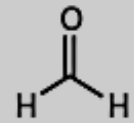
PHENOL



PHENOXYETHANOL

Preservatives help prevent contamination of vaccines. They are used particularly in multi-dose vaccines. Thiomersal is a common preservative, though its use declined in the late 1990s when vaccines were falsely linked to child autism. This link was later shown to be an elaborate medical hoax, and there is no link between thiomersal and autism.

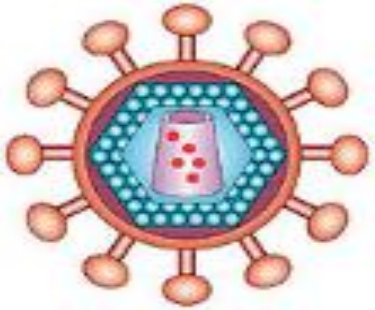
TRACE COMPONENTS



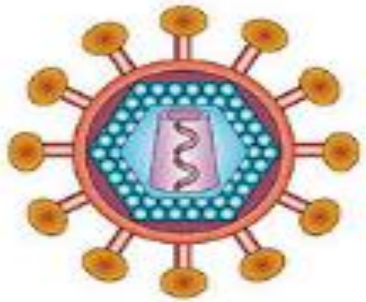
FORMALDEHYDE

These are left-over from the vaccine production process. Though they are purposefully removed, residual amounts remain. Formaldehyde is one such agent, used to deactivate viruses and detoxify bacteria, but amount remaining is several hundred times lower than the smallest amount known to cause harm in humans.

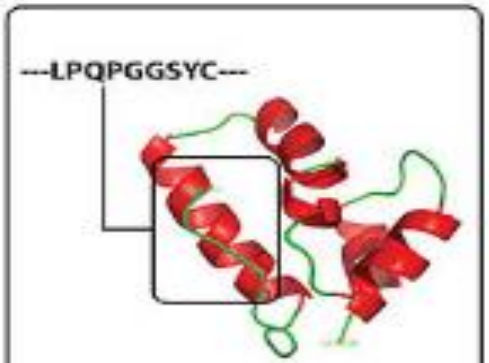
Types of vaccines



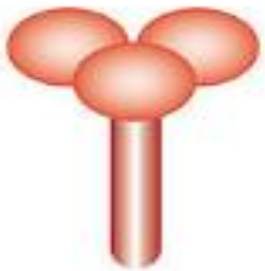
Whole inactivated



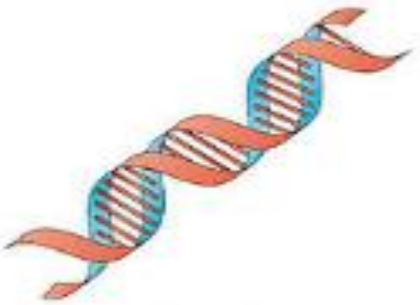
Live attenuated



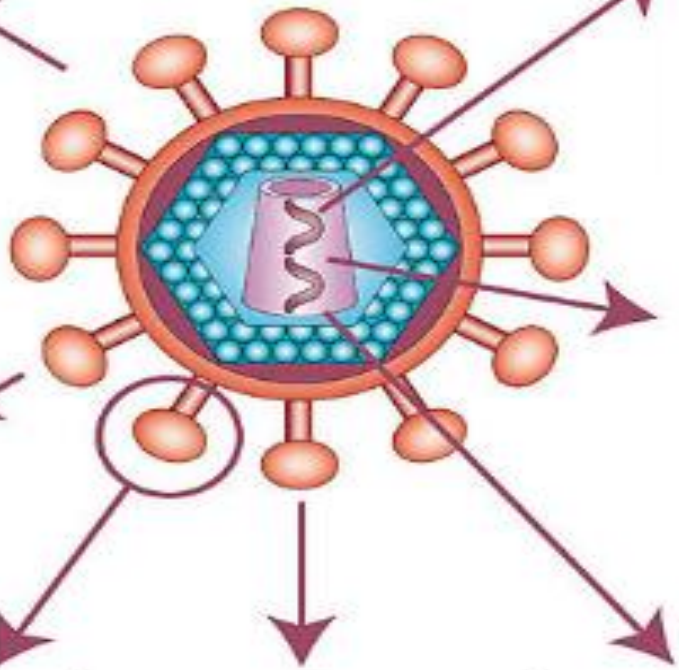
Synthetic peptides



Recombinant subunit



DNA



Recombinant viral vectors

Recombinant bacterial vectors

Types of vaccine

Type of vaccine		Licensed vaccines using this technology	First introduced
Live attenuated (weakened or inactivated)		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster	1798 (smallpox)
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	1896 (typhoid)
Toxoid		Diphtheria, tetanus	1923 (diphtheria)
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A	1970 (anthrax)

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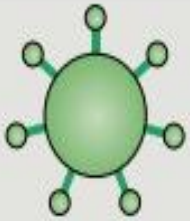
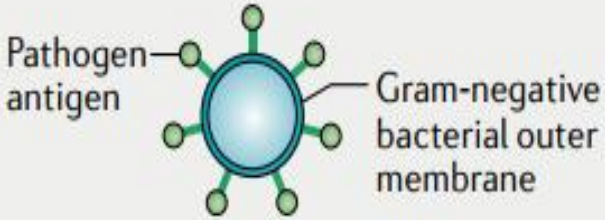
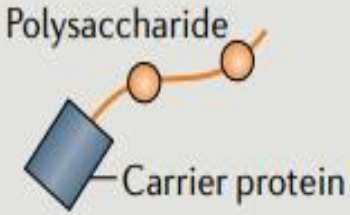
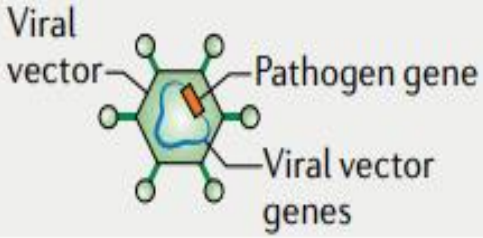
Types of vaccine

Type of vaccine		Licensed vaccines using this technology	First introduced
Virus-like particle		Human papillomavirus	1986 (hepatitis B)
Outer membrane vesicle		Group B meningococcal	1987 (group B meningococcal)
Protein–polysaccharide conjugate		*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid	1987 (*H. influenzae* type b)
Viral vectored		Ebola	2019 (Ebola)

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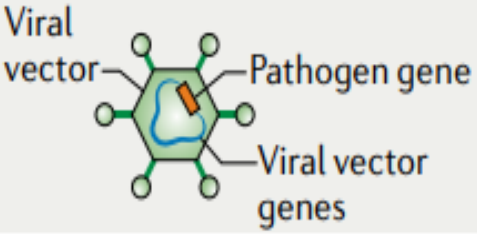
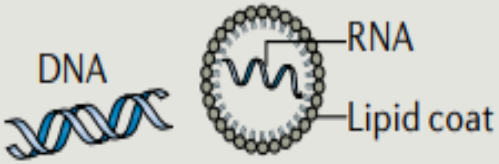
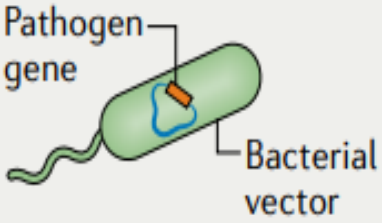
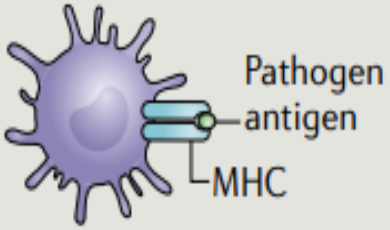
Types of vaccine

Type of vaccine		Licensed vaccines using this technology	First introduced
Viral vectored		Ebola	2019 (Ebola)
Nucleic acid vaccine		SARS-CoV-2	2020 (SARS-CoV-2)
Bacterial vectored		Experimental	–
Antigen-presenting cell		Experimental	–

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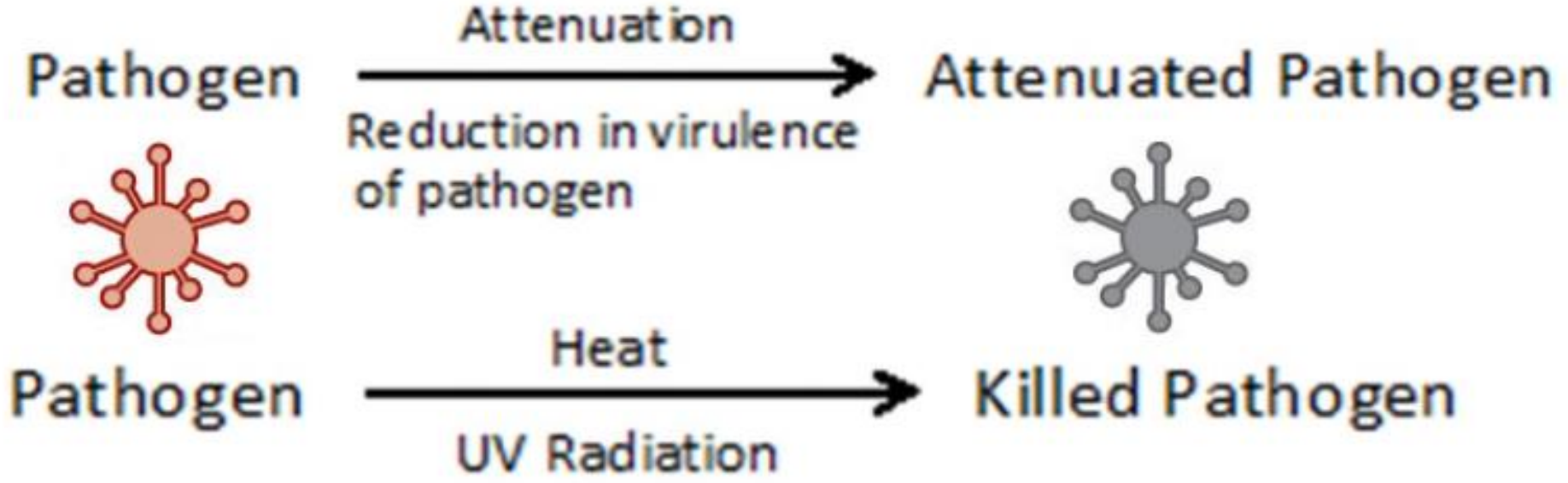
Whole-Organism Vaccines

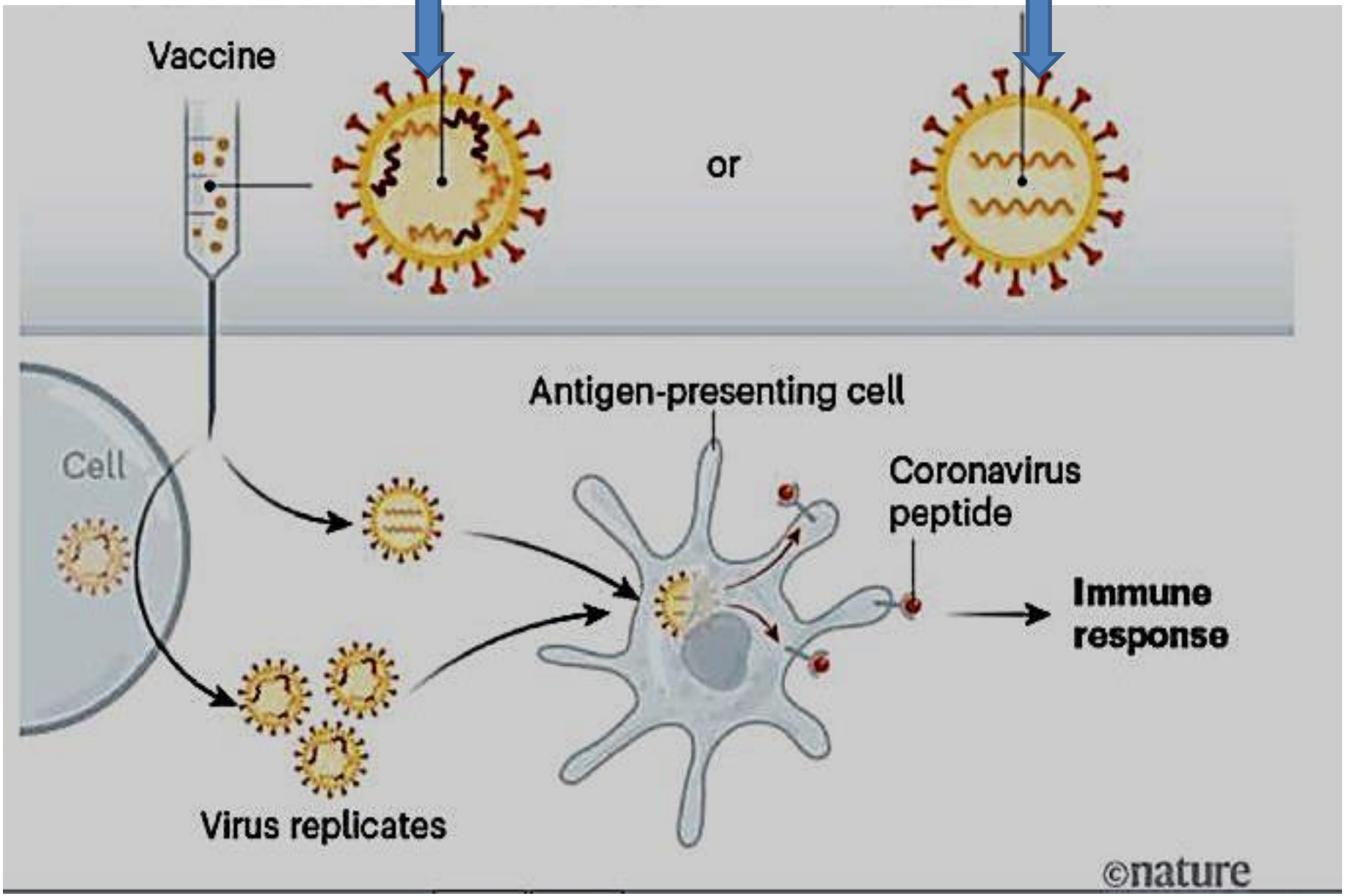
Many of the current vaccines in use for animals that are effective against viral and bacterial diseases consist of whole microorganisms that are either **inactivated** (killed) or **attenuated** (live but avirulent).

These are termed **whole-organism vaccines.** The major characteristics of these vaccines are compared and contrasted in next slides.



Live vaccine

Inactivated vaccine



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Whole-Organism Vaccines

Attenuated viruses can at times mutate in ways that restore virulence, as has happened in some monkeys given an attenuated simian form of the AIDS virus. In the case of very lethal diseases, the risk of reversion to virulence is intolerable.

Whole-organism vaccines, whether live or dead, have another big drawback. Since they are composed of complete pathogens, they retain molecules that are not involved in evoking immunity. These molecules, as well as contaminants that are unavoidable byproducts of the manufacturing process, can trigger allergic or other disruptive reactions.

Live vaccines

1. Live-attenuated (weakened) vaccines

These vaccines contain modifed strains of a pathogen (bacteria or viruses) that have been weakened but are able to multiply within the body and remain antigenic enough to induce a strong immune response. The varicella-zoster vaccine, oral poliovirus (OPV) vaccine, or yellow fever virus vaccine are some examples of this type of vaccine.

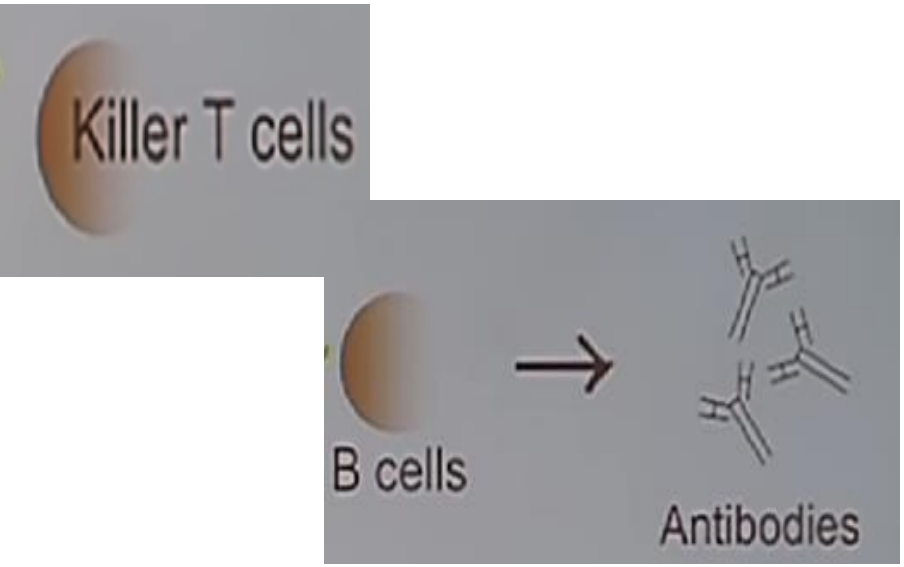
2.Heterologous vaccines

- Heterologous vaccines are a sub-group of live attenuated vaccines produced from strains that are pathogenic in animals but not in humans. It is a vaccine that confers protective immunity against a pathogen that shares cross-reacting antigens with the microorganisms in the vaccine. example cowpox virus that protects against smallpox in humans.

Live (self-replicating, attenuated) vaccines

Advantages

- Self-replicating
- Authentic antigen presentation
- Low cost
- Single dose (booster)
- More effective: generates cell mediated immunity and humoral immunity – IgG + IgA)



Disadvantages

- Need selection for avirulent organisms
- Reversal of virulence. Attenuated vaccines that do work can also cause full-blown illness in individuals whose immune system is compromised (cancer patients, the elderly). These same animals may also contract the disease from healthy animal who have been vaccinated recently.
- One lab-adapted strain does not deal with strain variability
- Need the "Cold chain"
- Less stable

The “Cold Chain”

- The “cold chain” is a system of storage and transport of vaccines at low temperature from the manufacturer to the vaccination site
- The “cold chain” system is necessary because vaccine failure may occur due to failure to store and transport under strict temperature controls

Killed- inactivated vaccines

- Inactivated vaccines are effective, but they often require
- Several boosters and normally do not adequately stimulate cell-mediated immunity or secretory IgA production.
- In contrast, attenuated vaccines usually are given in a single dose and stimulate both humoral and cell-mediated immunity.
- Even though whole-organism vaccines are considered the “gold standard” of existing vaccines, they can be problematic in their own way. For example, whole-organism vaccines fail to shield against some diseases.

Adjuvants

- Added to non-replication vaccines in order to enhance immunogenicity: provide inflammatory response, activate antigen-presenting cells and T-cells
- Inorganic salts are routinely used in animals:
  - aluminum hydroxide
  - aluminum phosphate
  - calcium phosphate
- New lipid adjuvants:
  - liposomes
  - immune stimulating complexes

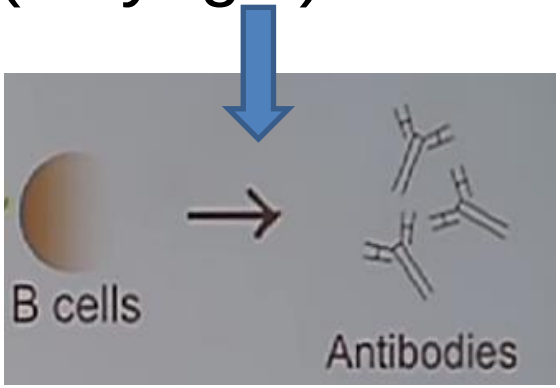
Inactivated vaccines

Advantages

- No virulence
- All antigens present
- No reversion: Cannot revert to virulent form
- More stable

Disadvantages

- No replication of pathogen
- Poor antigen presentation
- Need adjuvants
- Short lived immunity
- Requires multiple boosters
- Produces mainly humoral immunity (only IgG)

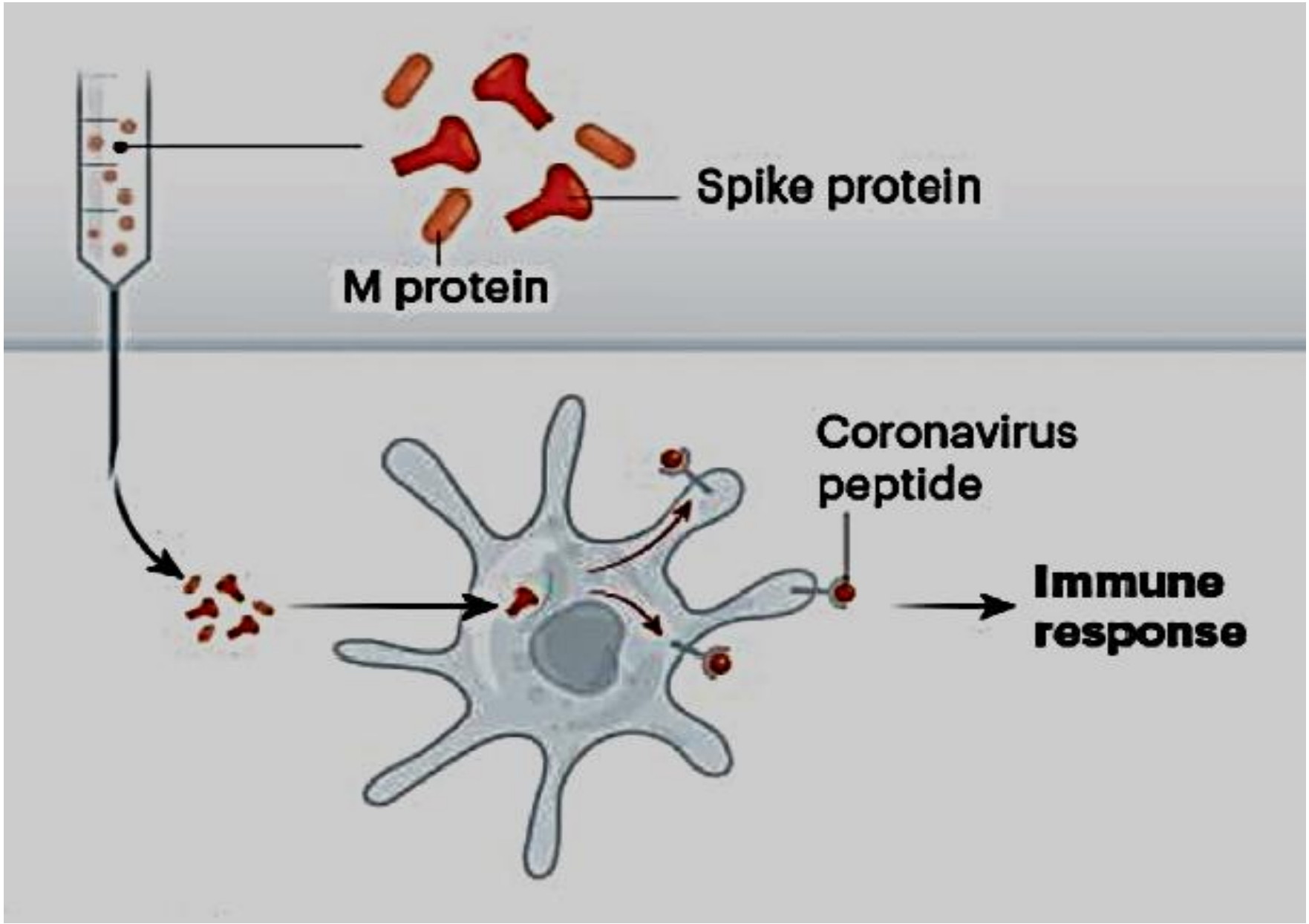


Chemical vaccine

Chemical vaccine – is prepared of chemical substances of bacterial structures (polysaccharides, proteins and other). These chemical substances must be antigenic and immunogenic. Chemical vaccine may be bacterial (vaccines against S.pneumoniae, N.meningitidis, Haemophilus influenzae) and virus (hepatitis B vaccine, influenza vaccine).

Chemical vaccine –
is produced with chemical and physical methods.
Chemical vaccine
may be **split vaccines**
and **subunit vaccines.**

Split-vaccine



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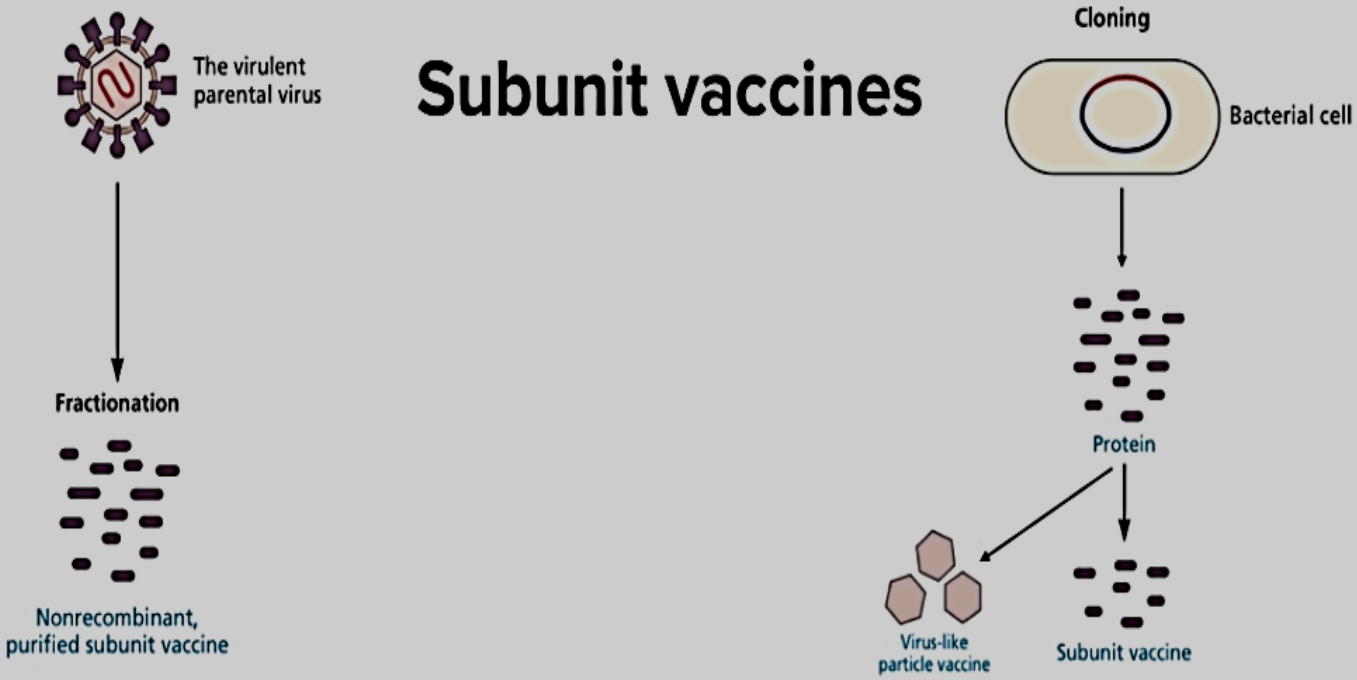
Subunit vaccines

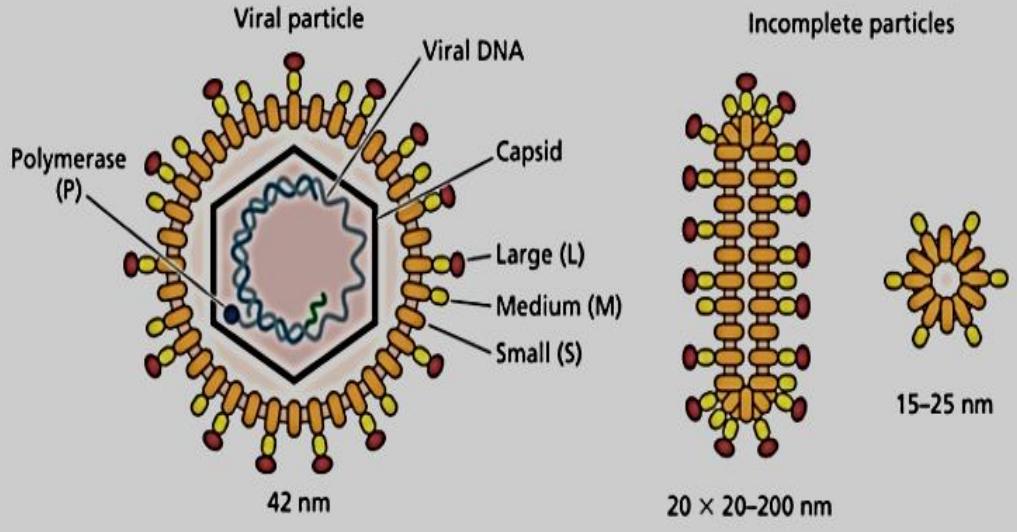


- Break virus into components, immunize with purified components
- Clone viral gene, express in bacteria, yeast, insect cells, cell culture, purify protein
- Antigen usually a capsid or membrane protein

Some successful subunit vaccines

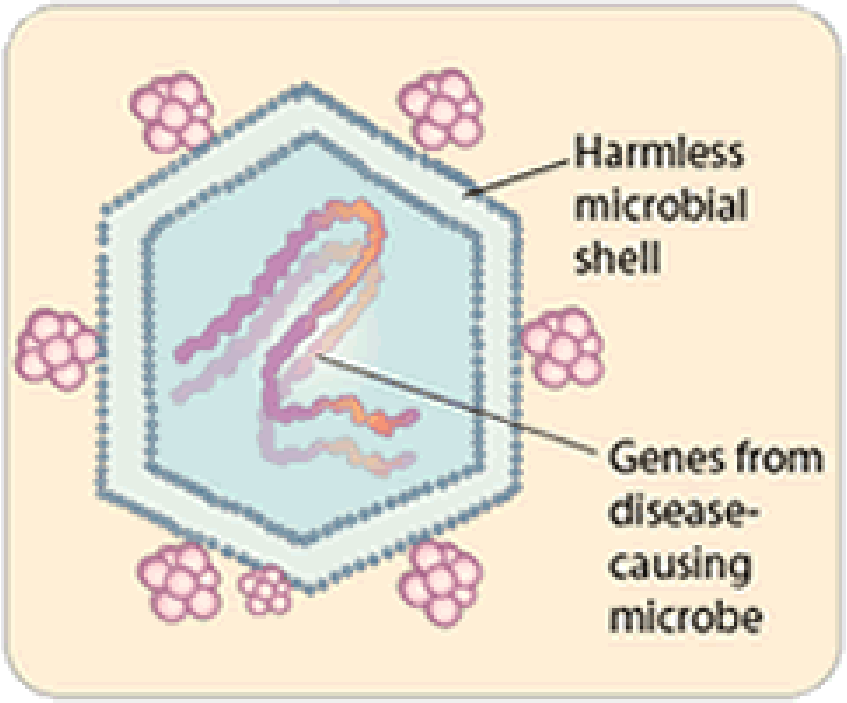
Cancer vaccine

- Hepatitis B virus (HBV) - HBsAg protein produced in yeast
- Assembles into empty particles

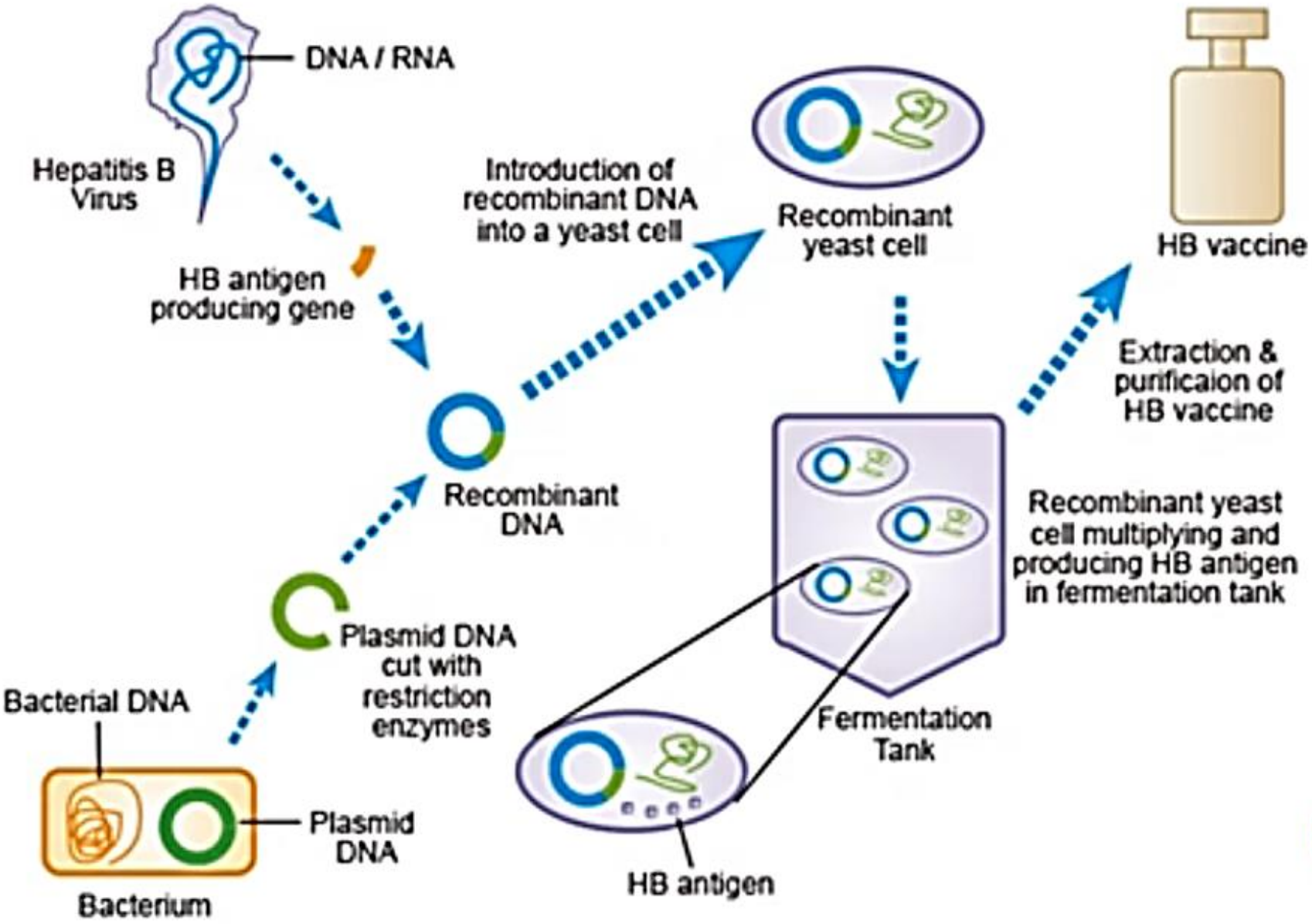


Recombinant-Vector Vaccines

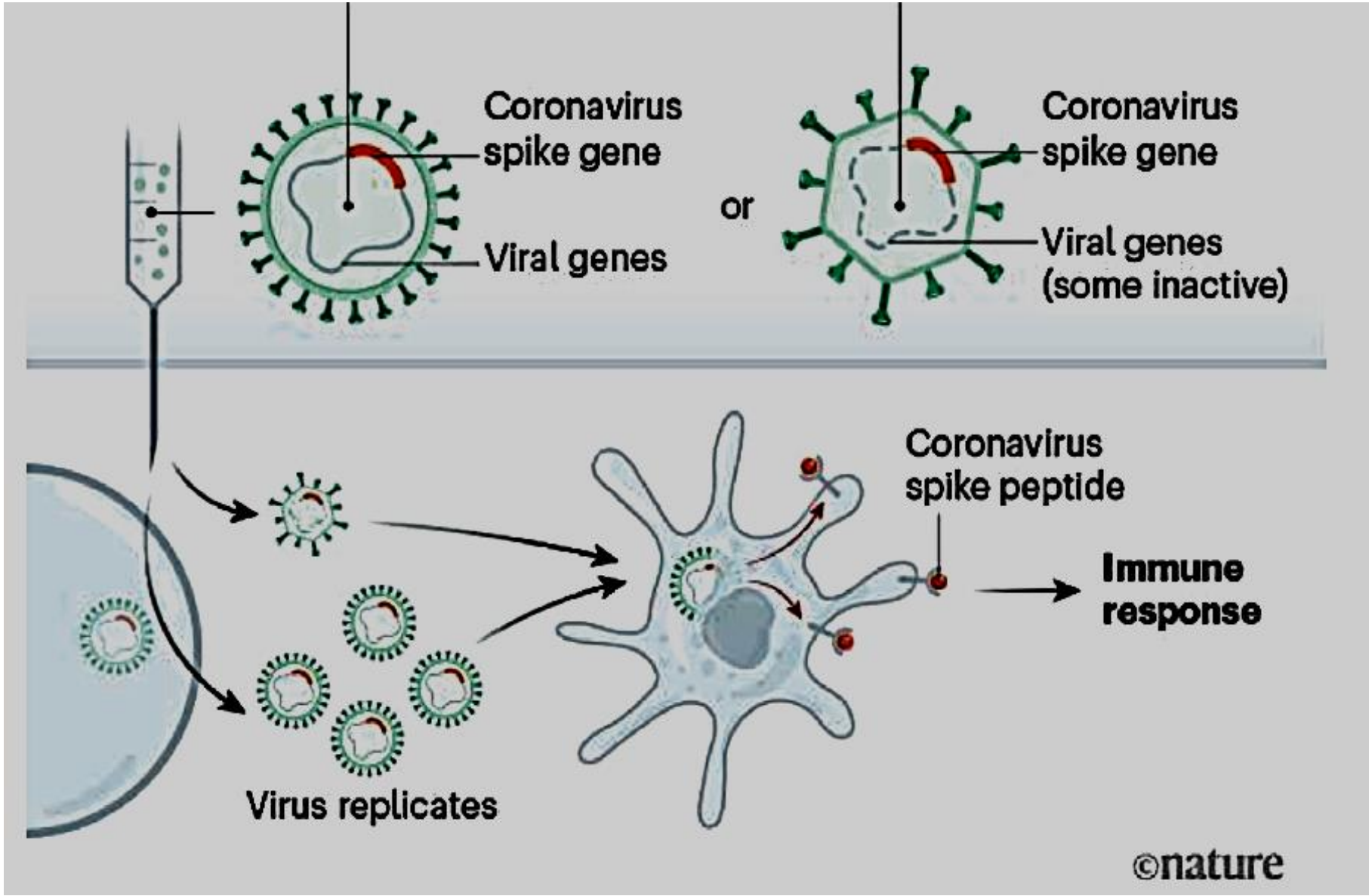
- Genetic vaccines are quite different in structure from whole organism vaccines.
- It is now possible to isolate genes that encode major antigens from a pathogen and insert them into nonvirulent viruses or bacteria.
  - The vaccines are usually delivered by needle injection or by a device called a gene gun.



Second Generation Vaccine



Recombinant vector vaccines



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Subunits vaccines in live vectors

Advantages

- Self-replicating vectors
- Vector acts as adjuvant
- Good for cell mediated immunity

Disadvantages

- Infecting with other virus or bacterium
- May be less efficient for antibodies

Recombinant proteins (or sysnthetic peptides)

Advantages

- Potentially less expensive production
- No reversion

Disadvantages

- No replication of pathogen
- Need adjuvant
- Poor for cell mediated immunity
- Short lived immunity

DNA Vaccines

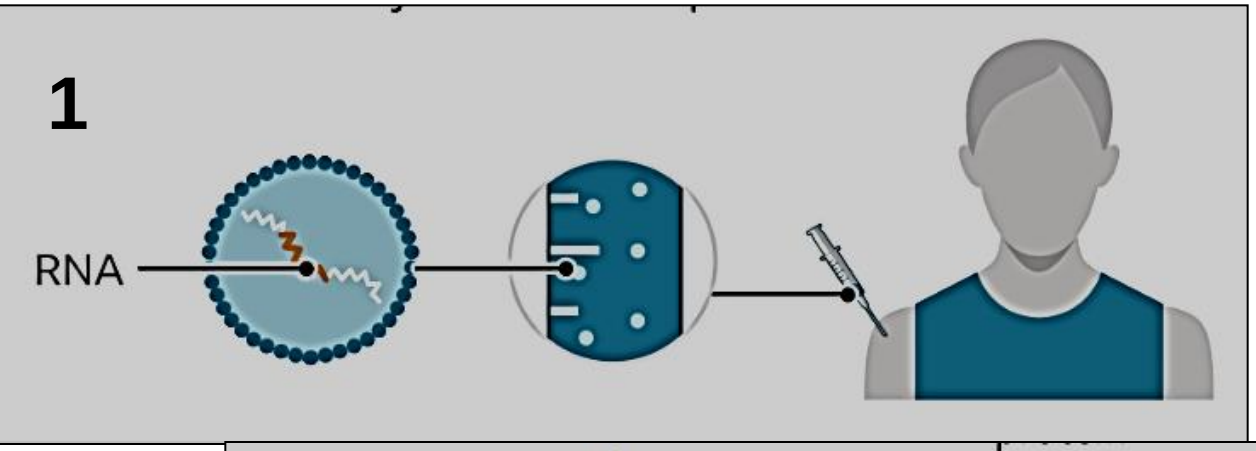
A more complicated genetic vaccine to emerge in recent years is the DNA vaccine. A DNA vaccine elicits protective immunity against a microbial pathogen by activating both branches of the immune system: humoral and cellular.

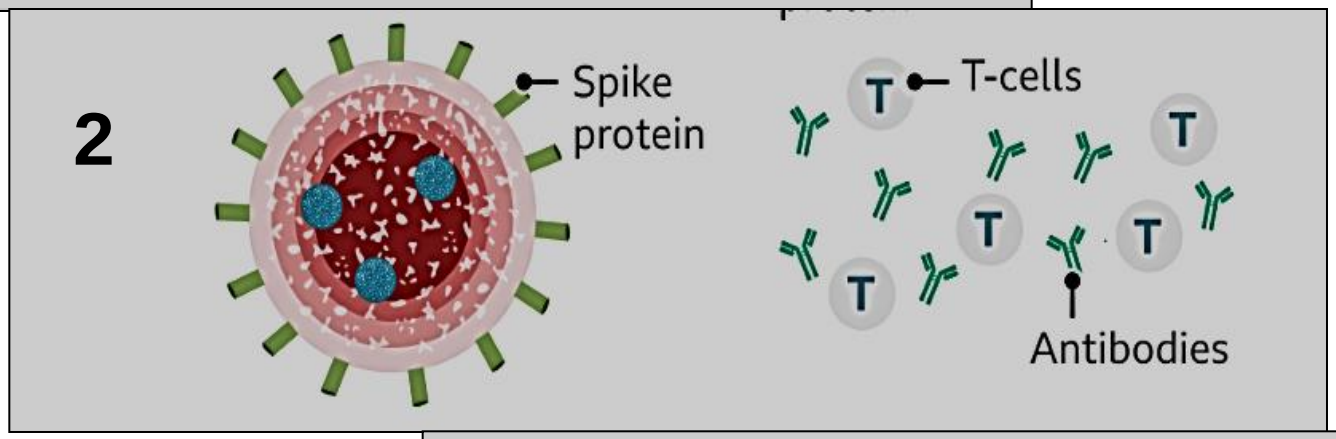
Long-lasting memory cells also are generated.

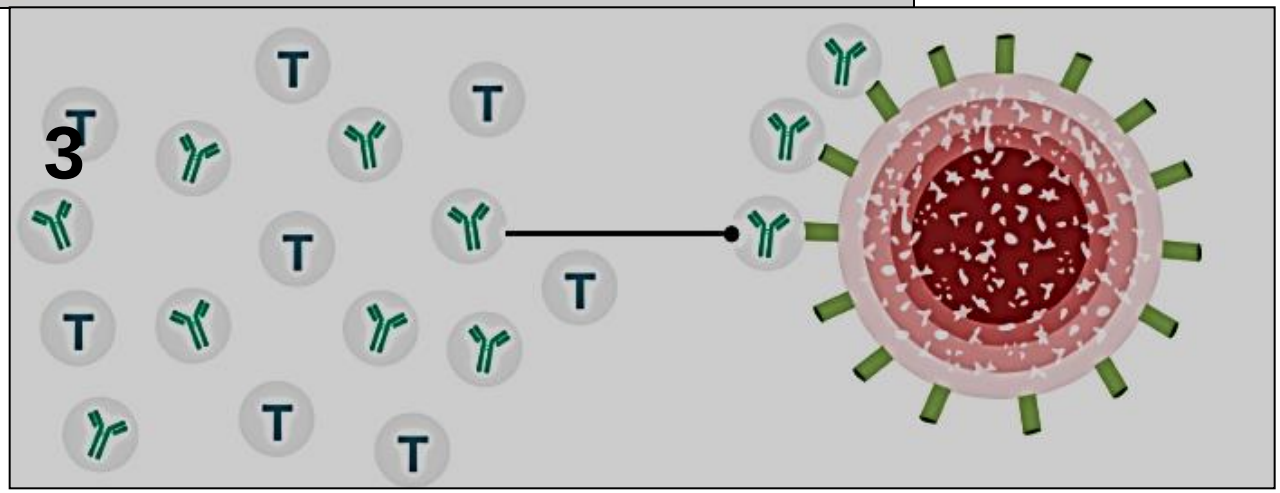
The immunization procedure begins with the injection into muscle of a plasmid preparation that contains genes for pathogen antigens. The plasmids are taken up by muscle cells, enter the cell nuclei, and express their antigen genes.

The muscle cells commence protein synthesis and produce the pathogen's antigenic proteins.

DNA- vaccine







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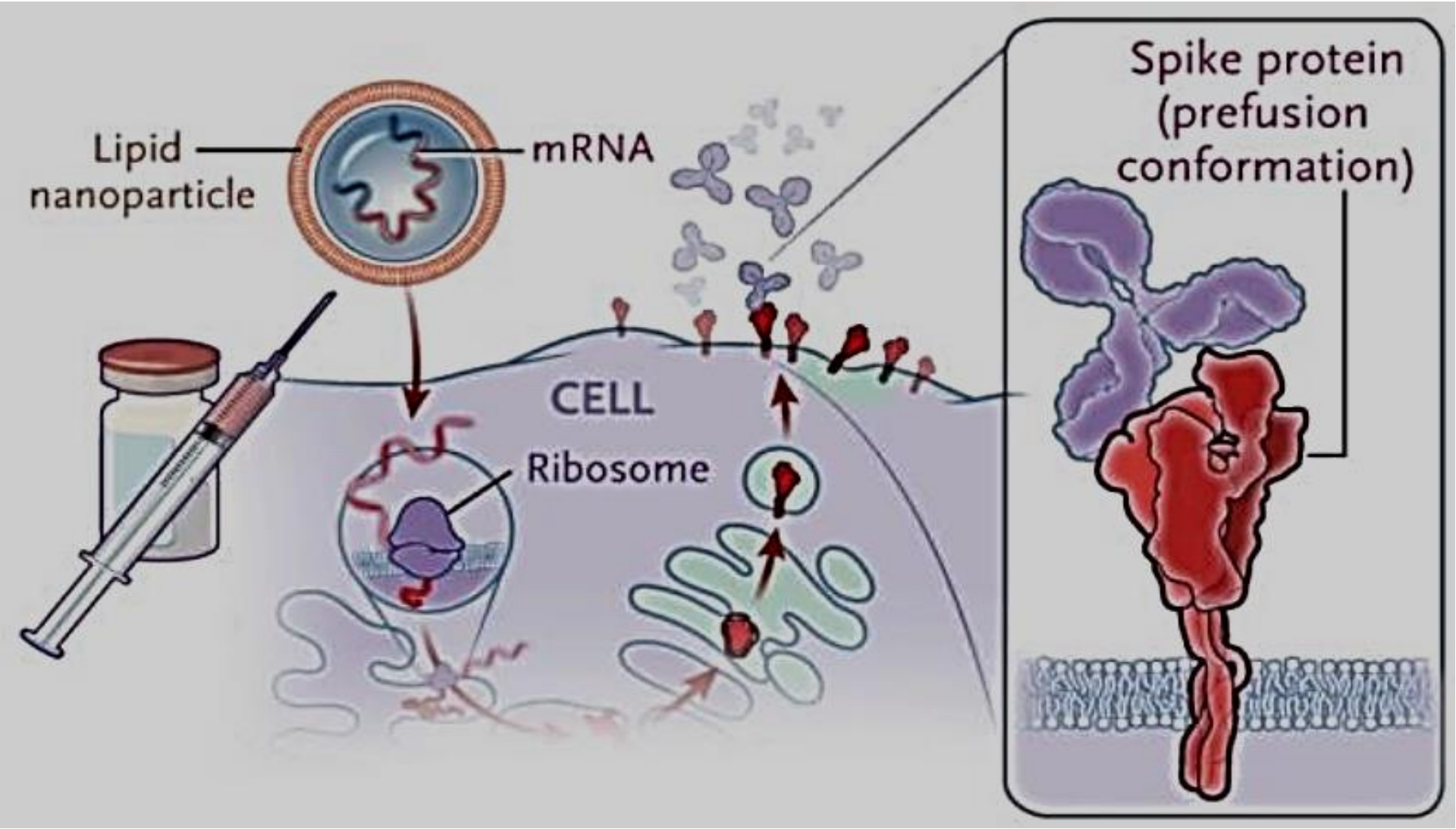
RNA-vaccine

https://www.youtube.com/watch?v=pVWOdnr90JQ - Next Generation of mRNA Vaccinology



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Multiple-Antigen Vaccines

- When different antigens in a mixture are inoculated simultaneously, competition occurs between antigens. Manufacturers of multipleantigen vaccines take this into account and modify their mixtures accordingly.
- Vaccines should never be mixed indiscriminately since one component may dominate the mixture or interfere with the response to the other components.
- For respiratory diseases of cattle, for example, vaccines are available that contain infectious bovine rhinotracheitis (BHV-1), bovine virus diarrhea (BVDV), parainfluenza 3 (P13).
- Dogs may be given vaccines containing all of the following organisms: canine distemper virus, canine adenovirus 1, canine adenovirus 2, canine parvovirus 2, canine parainfluenza virus, leptospira bacterin, and rabies vaccine.

VACCINE	ESTIMATED MINIMUM DOI	ESTIMATED RELATIVE EFFICACY (%)
Essential		
Canine distemper (modified live virus [MLV])	>7 yr	>90
Canine distemper (recombinant [R])	>1 yr	>90
Canine parvovirus-2 (MLV)	>7 yr	>90
Canine adenovirus-2 (MLV)	>7 yr	>90
Rabies virus (killed [K])	>3 yr	>85
Optional		
Canine coronavirus (K or MLV)	N/A	N/A
Canine parainfluenza (MLV)	>3 yr	>80
Bordetella bronchiseptica (ML)	<1 yr	<70
Leptospira canicola (K)	<1 yr	<50
Leptospira grippotyphosa (K)	<1 yr	N/A
Leptospira icterohaemorrhagiae (K)	<1 yr	<75
Leptospira pomona (K)	<1 yr	N/A
Borrelia burgdorferi (K)	1 yr	<75
Borrelia burgdorferi OspA (R)	1 yr	<75
Giardia lamblia (K)	<1 yr	N/A

From Paul MA, Appel M, Barrett R, et al: Report of the American Animal Hos-

Estimated Minimum Duration of Immunity (DOI) of Select Commercially Available Canine Vaccine Antigens