



IMMUNOLÓGIAI ÉS
BIOTECHNOLÓGIAI
INTÉZET



Vaccines

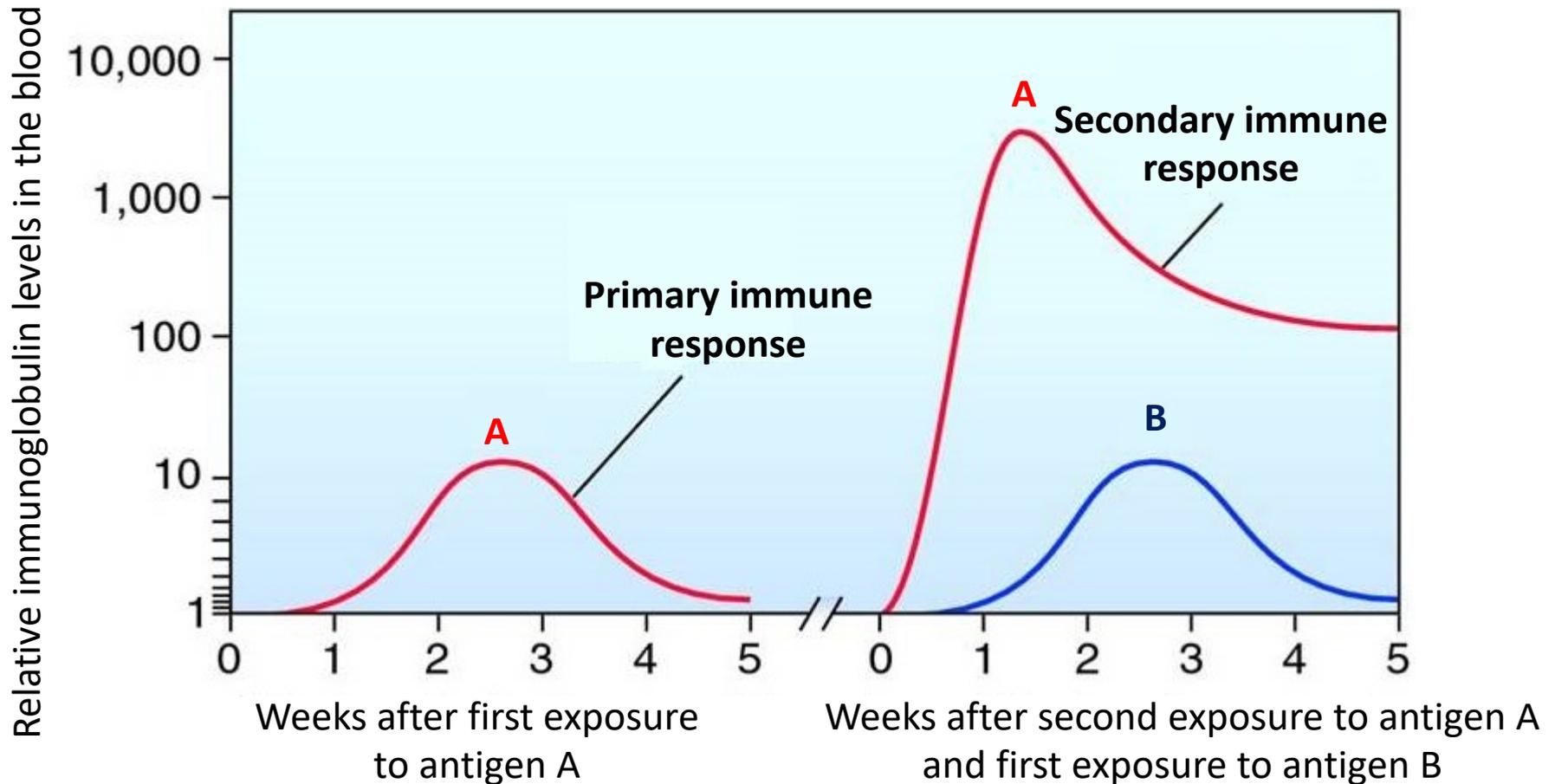
Basic Immunology

University of Pécs, Clinical Center

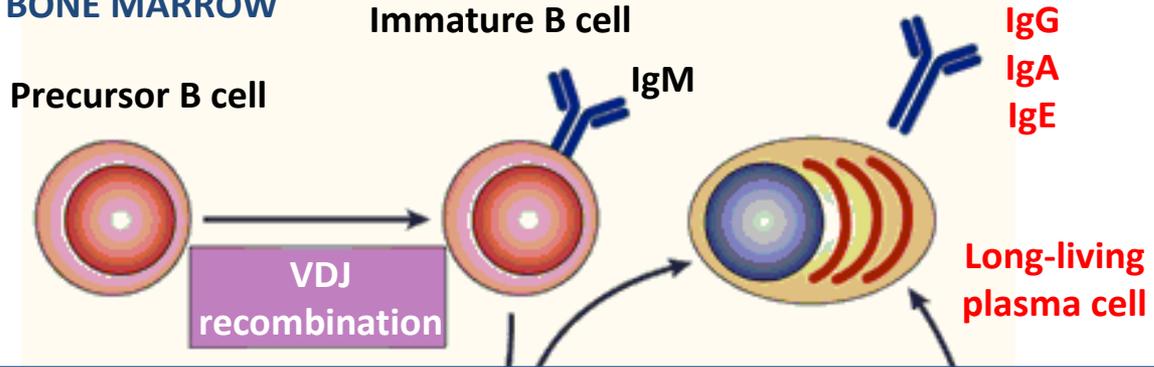
Department of Immunology and Biotechnology

Pécs, 2023.

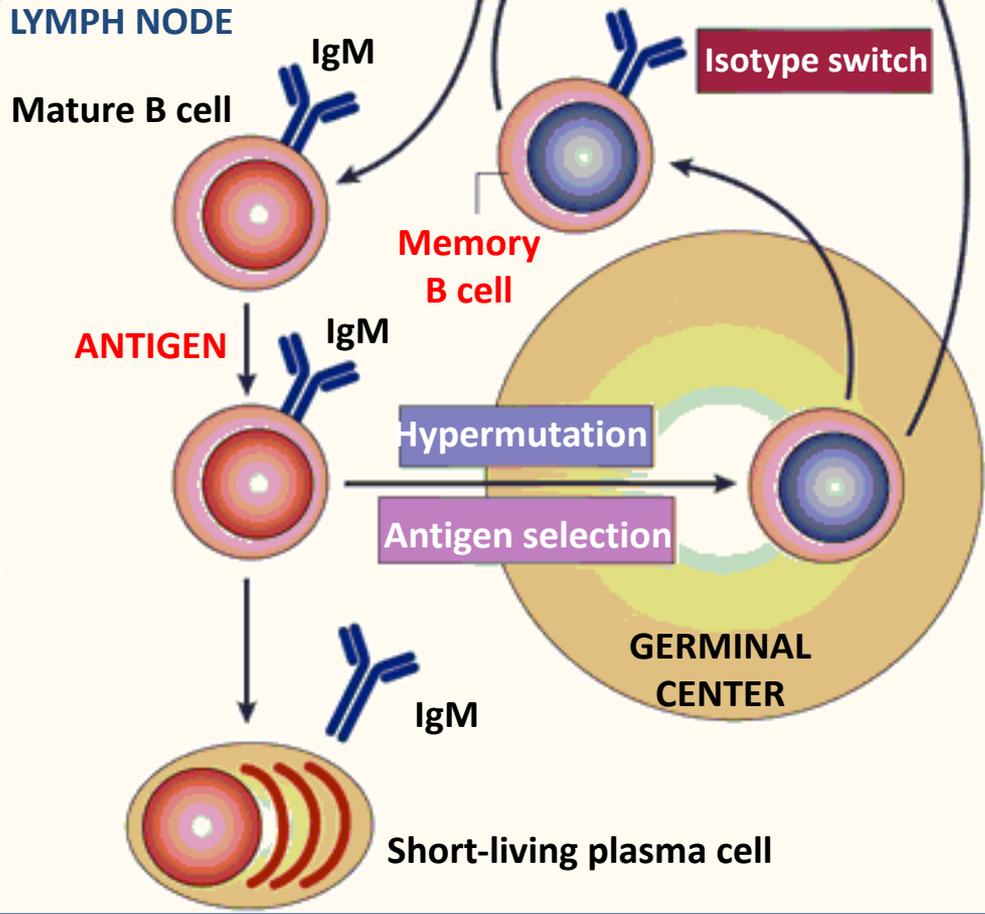
Primary and secondary immune response



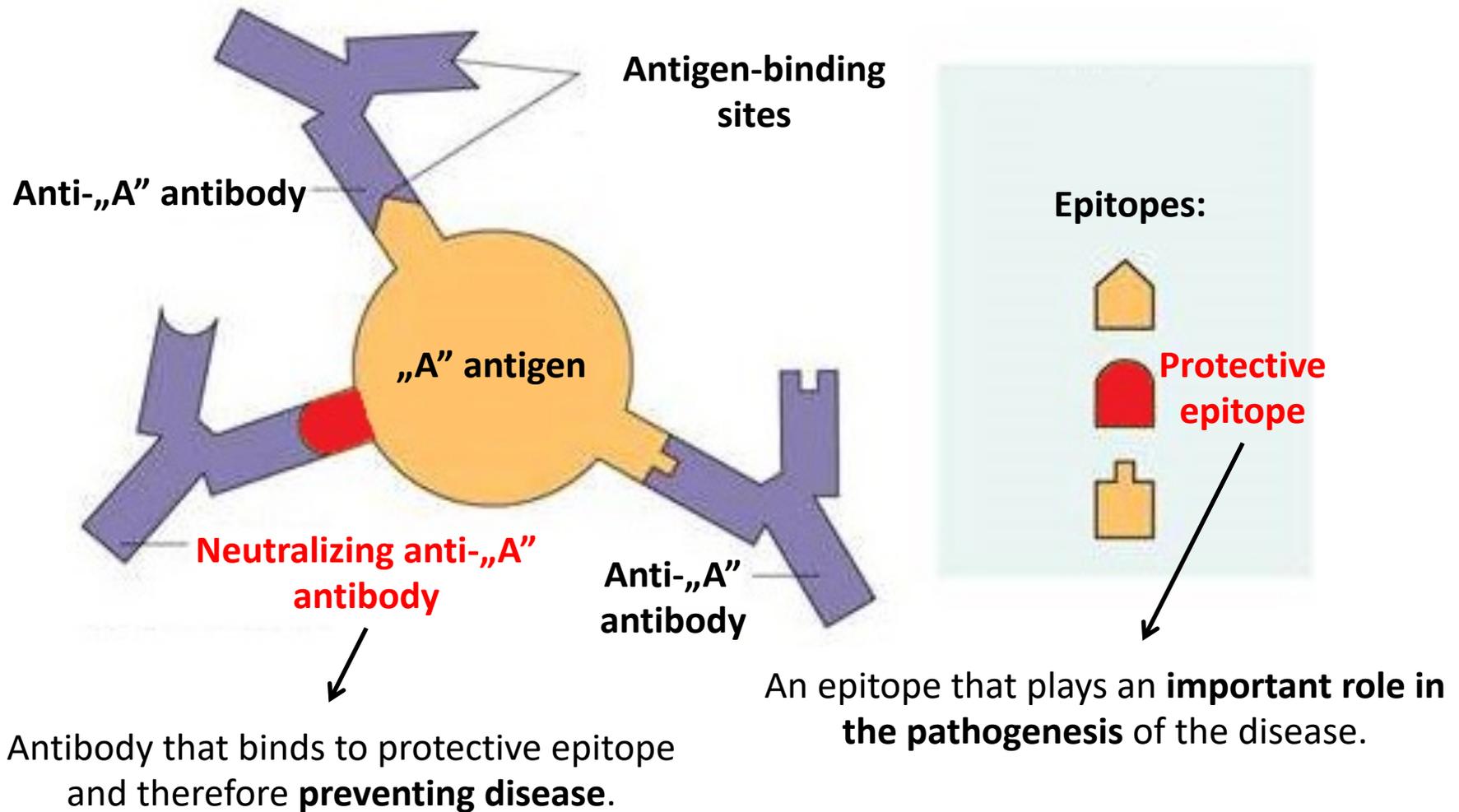
BONE MARROW



LYMPH NODE



Neutralizing antibodies



Passive and active immunity

Natural active



Acquiring an
infection



Immunological memory

Natural passive



Breastfeeding:
maternal
antibodies
temporarily
protect the baby

Artificial active



Vaccine (active immunization
with an antigen)



Immunological memory

Artificial passive

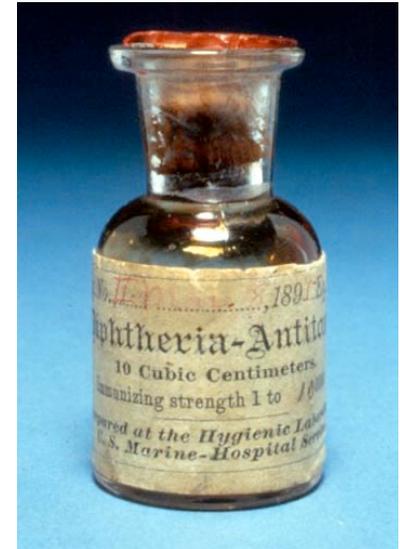
Antiserums (passive
immunization with antibodies)



**Quick but only
temporary protection**

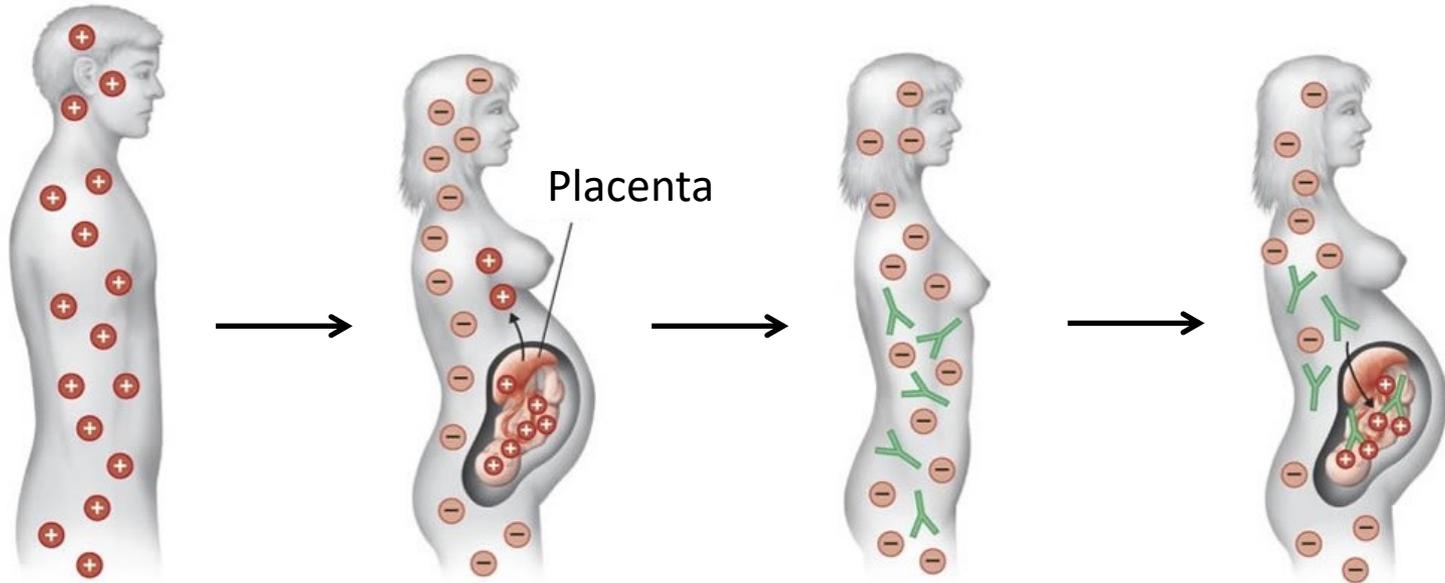
Passive immunization

- **Antibodies** against a specific antigen are administered. → Quick neutralization of the pathogen/toxin that already entered the body → Rapid, but **only temporary protection**. E.g.:
 - **Anti-Rh(D) immunoglobulin**: (RhIG) Prevention of Rh alloimmunization in pregnancy^[1,2.]
 - **Tetanus antitoxin** (neutralizing tetanus toxin^[3.])
 - **Anti-HBsAg immunoglobulin** (HBIG, against a certain antigen of HBV^[4.])
 - Immunoglobulins against **venoms** (e.g. the venoms of snakes, scorpions, spiders, so-called „antivenoms“^[5,6.])
 - Immunoglobulins against **Lyssavirus** (pl. HRIG = Human Rabies Immunoglobulin^[7.])
- Many of the above mentioned antibodies (especially the antivenoms) **originate from animals**. (humans are not immunized with snake venoms...) These are foreign proteins for the human immune system and can have serious side-effects but in many cases they still **make the difference between life and death**.^[8.]



Animal-derived diphtheria antitoxin from 1895.

Rh alloimmunization



Rh+ father

First Rh+ pregnancy
of Rh- mother

Immunization of mother

Second Rh-
pregnancy

The blood of the mother and the fetus **do not mix** during pregnancy!

During delivery some of newborn's blood will inevitably **enter the mother**.

Anti-Rh antibody

Anti-Rh IgG crosses the placenta and causes hemolysis!

Prevention of Rh alloimmunization

The Rh- mother is treated with **anti-Rh(D) antibodies** (RhIG) after delivery.



The antibody is thought to **eliminate all the Rh+ erythrocytes** that have entered the mother.



It prevents the recognition of Rh+ erythrocytes by the mother's immune system.



If the Rh- mother has another Rh+ fetus, there won't be any anti-Rh antibodies that cross the placenta and do harm to the baby.



Human anti-Rh(D)
immunoglobulin

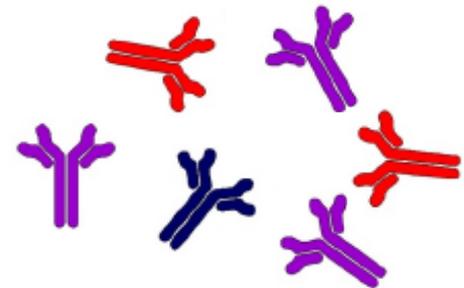
Antivenoms



Milking the snake, gathering toxin A



Administering toxin A to a rabbit (**active immunization of the rabbit**)



Polyclonal rabbit anti-A antibodies



Administering anti-A antibodies after snakebite (**passive immunization of the human**)

Neutralization of toxin A



Active immunization

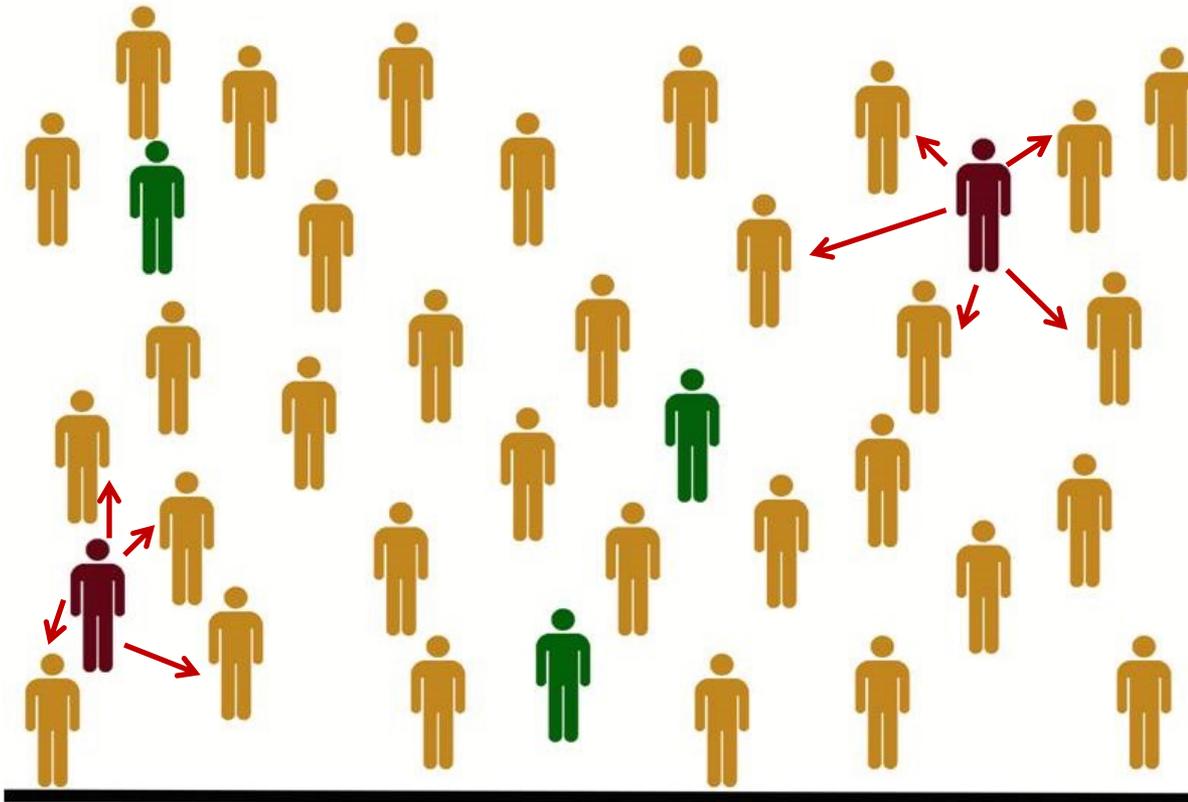
- **Administration of an antigen** in order to **provoke an immune response** against the antigen.
- In case of research animals:
 - **Production of antibodies** (e.g. hybridoma technique, antivenoms)
 - **Triggering autoimmunity** (e.g. human cartilage proteoglycan-induced arthritis in mice) for the **modelling** of human autoimmune disorders
- In case of people:
 - To develop a **long-lasting immunological memory** against a pathogen or a toxin
- **Adjuvants** → Immune response ↑^[9.]
- **Herd immunity:** Non-immunized are also protected.^[10.]
- First vaccine: **Edward Jenner** vaccinated people with cowpox to prevent smallpox. vacca = cow in Latin

↓
Vaccination



Edward Jenner
(1749-1823)

Herd immunity I.



A large percentage of the population is vaccinated.



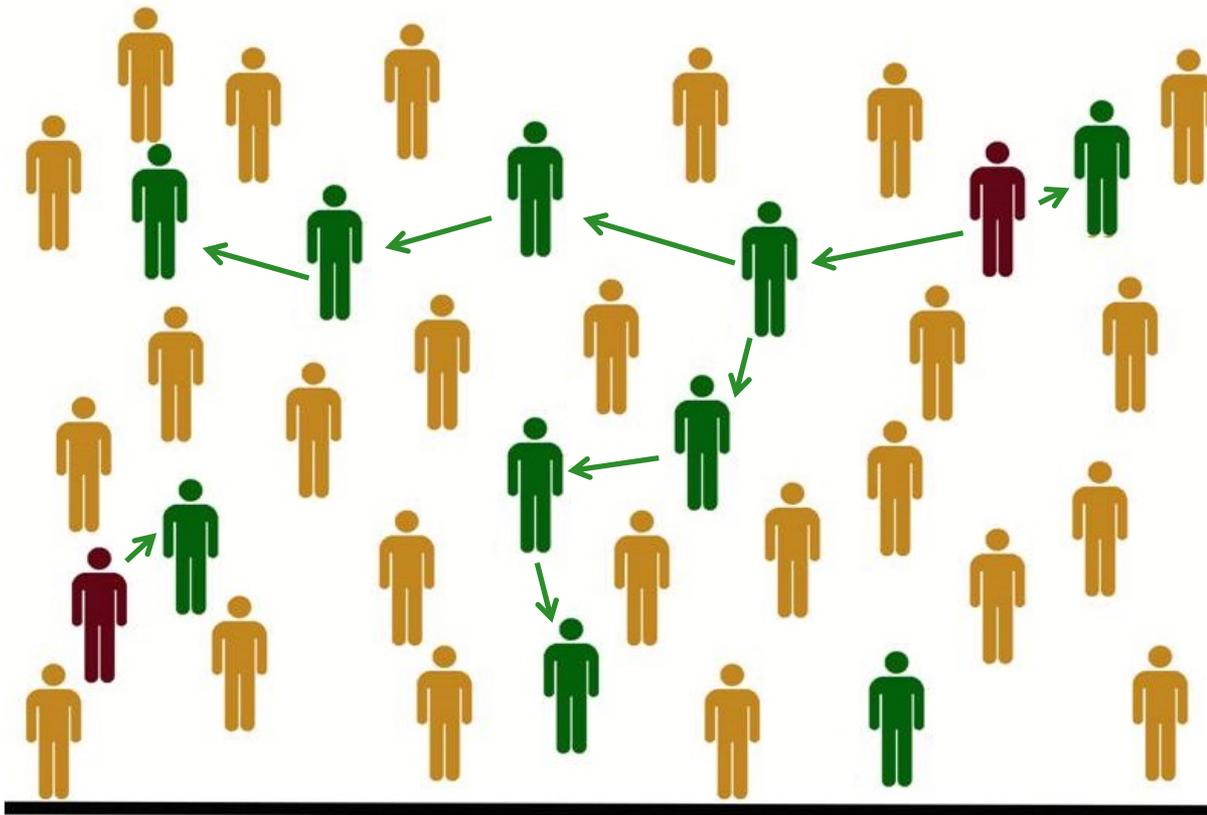
The **infection cannot spread** in the population and even the unvaccinated people are protected.

● Healthy,
vaccinated

● Healthy,
unvaccinated

● Infected

Herd immunity II.



A relatively large percentage of the population is unvaccinated.



The infection can spread in the population.

● Healthy, vaccinated

● Healthy, unvaccinated

● Infected

Side effects of vaccines I.

Vaccines can have **side effects**. The safety of vaccines is of uttermost importance because **vaccines are administered to healthy individuals**.

- **Vaccine reaction** → Frequent, usually mild, **NOT PATHOLOGICAL!** E.g.:
 - Erythema or swelling, mild pain at the site of injection
 - Low fever, malaise
- **Complication** → **Unpredictable side effect and reactions, PATHOLOGICAL!** E.g.:
 - **Anaphylaxis**^[11.] (hypersensitivity to certain components of the vaccine)
 - Ulcer or abscess at the site of injection^[12.] (e.g. contaminated vaccine or improper administration)
 - Triggering autoimmunity (e.g. Guillain-Barré syndrome after flu vaccines^[13.])

Side effects II.



Skin rash (urticaria) throughout the entire body after MMR vaccination (hypersensitivity^[14.])



Nonsuppurative inflammation of the axillary lymph nodes after BCG vaccination^[15.]

Both of these are **complications!**

Types of vaccines

1. **Live, attenuated** vaccine: contains **live** and attenuated (= weakened) pathogens
2. **Inactivated** vaccine: contains **dead** pathogens
3. **Subunit** vaccine: contains only certain antigens of the pathogen
4. **Toxoid** vaccine: contains **inactivated toxin**
5. **Conjugated** vaccine: contains a T-independent antigen (**polysaccharide**) conjugated to a carrier **toxoid**
6. **DNA/RNA** vaccine: contains the DNA/RNA that encodes the antigen of the pathogen
7. **Recombinant vector** vaccine: attenuated **viral vectors** are used to deliver the genes encoding the pathogen's antigen
8. **Tumor vaccines** (vaccines used to treat cancer, most of them are experimental)

Live, attenuated vaccines

- Contain **living pathogens** with a **limited potential to replicate** in the host.^[16.]
- Viruses are attenuated by growing them in cells in which they do not replicate well. (**Serial passage**). They will slowly adapt to the new environment gradually losing their virulence to their original host in the meantime.
- **Advantages:**
 - The usage of live organisms **mimics the course of natural infections** the best, it triggers both the **humoral** and **cellular immune response** and leads to **long-lasting protection**. (Fewer booster shots are necessary.)
- **Disadvantages:**
 - The pathogen **might regain its virulence** after vaccination. → The vaccine itself can cause the very same disease it should prevent.
 - **Cannot be given to immunocompromised patients.**
 - Needs to be refrigerated → Logistical difficulties.
 - **Bacteria are hard to attenuate** as they are more complex organisms than viruses.

Examples for live, attenuated vaccines

- Viral:
 - **MMR** (Measles Mumps Rubella combined vaccine) → Protects against all three
 - LAIV^[17.] (live attenuated influenza vaccine) → One form of seasonal flu vaccine used as a nasal spray
 - Varicella vaccine → Against Varicella
 - **OPV** (oral polio vaccine, Sabin vaccine) → Oral vaccine against Poliomyelitis
 - Rotavirus vaccine^[18.] → Oral vaccine against rotavirus (causes diarrhea in infants)
 - Rabies vaccine^[19.] (for the preventive vaccination of animals) → Against rabies
 - Smallpox vaccines^[20.] (no longer used, see later)
- Bacterial:
 - **BCG** (Bacillus Calmette–Guérin vaccine) → Against tuberculosis
 - Ty21a^[21.] → Against Typhoid fever (Contains attenuated *Salmonella typhi* Ty2 strain, given orally)

MMR



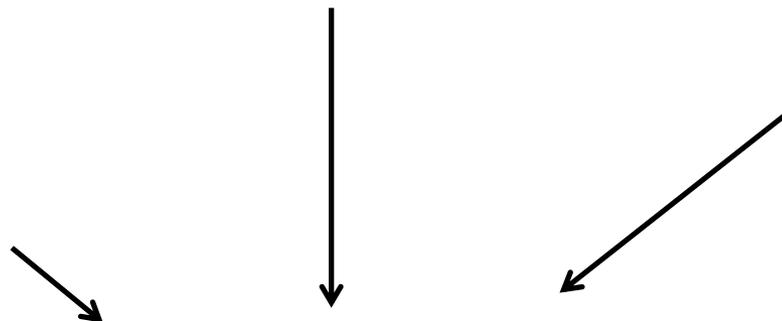
Measles



Mumps (Epidemic parotitis)



Rubella



Common features:

- **No specific therapy against any of them!**
- All three can have **serious complications.**



The MMR scandal

- February of 1998: Andrew Wakefield and his colleagues publish an article in the Lancet (one of the leading journals in medicine) about the possibility of **MMR to cause autism**.^[22.]
- MMR vaccination at that time was **compulsory in many countries** (including Hungary).



SCANDAL

- Between 2002 and 2003 more and more studies denied Wakefield's claim as they did not find a correlation between autism and the MMR vaccine^[23.], many regulators and organizations (including the American CDC) declared that **there was no correlation**.
- 2004: A reporter at the Sunday Times identified undisclosed **financial conflict of interest** on Wakefield's part and it was found out that Wakefield also **falsified data** in his research.^[24,25,26.]
- Ten of the twelve co-authors retracted the article in 2004, and the **article was fully retracted** by Lancet in 2010.^[27.]
- Wakefield was **struck off the UK medical register** by the GMC in 2010.^[28.]



Dr. Andrew Wakefield in front of the GMC headquarters shortly after losing his medical registration in 2010.

„Possibly the most damaging medical hoax of the last 100 years^[29.]”



EFFECT: A GENERAL DISTRUST IN WESTERN MEDICINE, RISE OF ANTI-VACCINATION MOVEMENTS

OPV

- Administered orally, **contains live, attenuated poliovirus**.
- Only used in countries where poliovirus is still endemic, most countries **use IPV instead**. (see later)
- Advantage: **Triggers a strong response, especially effective in mucosal defense**. (poliomyelitis is characterized by fecal-oral transmission)



A girl receives OPV.

Main risk: **Virulent reversion**



Vaccine-induced poliomyelitis

VDPV (Vaccine-derived polio virus): Poliovirus that regained its virulence.^[30.]

WHO: Almost **3 billion children** have been vaccinated with OPV since **2000** worldwide which **prevented 13 million cases**. During this period **760 vaccine-induced poliomyelitis** cases were registered.^[31.]

Poliomyelitis



BCG



Scar at the site of BCG vaccination.

- Contains attenuated *Mycobacterium bovis* bacteria.
 - Used for the **prevention of severe tuberculosis** and the **complications of TB**.
 - Also used to treat **bladder cancer** (injected into the lumen of the bladder).^[32.]
- Administered intradermally, **leaves a scar**.
- **Efficacy is variable** and somewhat controversial.^[33,34,35.]
- Not compulsory in many countries. (had been in the UK till 2005, but the USA never introduced it) In Hungary it is compulsory.
- **WHO recommendation:** Every infant should be vaccinated **in places where TB is endemic** to prevent **miliary tuberculosis** and **TB meningitis**.^[36.]
- Provides some protection against **Leprosy** as well.^[37.]

Inactivated vaccines

- **Contain dead pathogens.** (viruses are inactivated by heat or with the use of formaldehyde)
- **Advantages:**
 - **More safe than attenuated vaccines**
 - Can be stored and transported more easily
- **Disadvantages:**
 - Trigger a weaker immune response than attenuated vaccines
 - **Repeated booster shots are usually necessary**
- **Examples:**
 - **IPV** (inactivated polio vaccine) → Against poliomyelitis
 - **Seasonal flu vaccines** → Contain 3 or 4 inactivated influenza strains

IPV

- Contains **poliovirus inactivated** with formaldehyde.^[38.]
- Provides a weaker immunity compared with OPV, especially for mucosal immunity.
- **No risk of vaccine-induced poliomyelitis.**
- Administered as an intramuscular injection, booster shots are necessary.
- **More expensive than the OPV.**
- Insufficient protection in countries where poliovirus is endemic but it the preferred polio vaccine in most countries. In Hungary it is compulsory.
- **Can be combined with other vaccines** such as:
 - **DTaP** = Diphtheria-Tetanus-acellular Pertussis vaccine
 - **Hib**= Haemophilus influenzae B vaccine

Pentacel[®], the combined vaccine of the French Sanofi Pasteur[®]:

DTaP + IPV + Hib **combined vaccine**^[39.]



Seasonal flu

- **Influenza ≠ Common cold!** (see in the clinical phase of your studies)
- Seasonal flu epidemics occur annually during the cold half of the year.
- **250-500 thousand deaths each year.**
- Groups at risk^[40.] (Should receive vaccination according to the WHO):
 - Pregnant women
 - 0,5-5 year old infants
 - ≥65 years old, elderly
 - People with chronic diseases
 - **HEALTHCARE WORKERS**



Ad of the American CDC.



Seasonal flu vaccines

- Influenza viruses **constantly change their antigens**. (due to mutations and antigenic shift → see the 10th practice)
- Tri- or quadrivalent vaccine (contain 3 or 4 strains of influenza viruses)
 - H1N1 subtype
 - H3N2 subtype
 - 1 or 2 strains of type B influenza

} Type A influenza
- The specific strains of influenza viruses are selected each year by the **estimation of the WHO**.



It is possible that other strains will circulate in the population.



LIMITED PROTECTION



The quadrivalent Fluzone® 2015/16 flu vaccine of Sanofi Pasteur®.

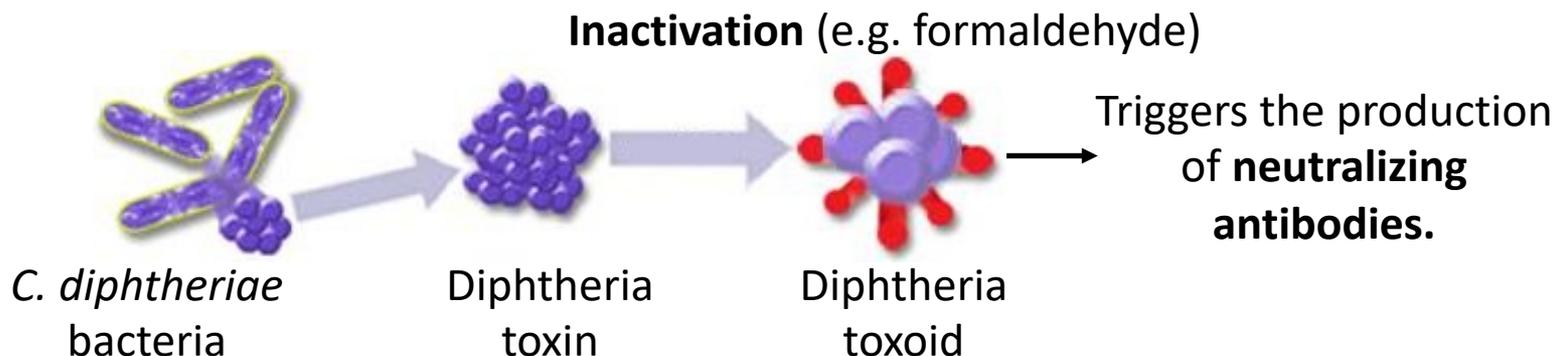
Subunit and toxoid vaccines

SUBUNIT VACCINES

- Only **contain specific antigens** of the pathogen and not the entire organism.
- More safe, even compared to inactivated vaccines.
- Possible ways of production:
 - Culturing of the microbe and isolating the antigens
 - **Recombinant subunit vaccine:** produced in genetically altered yeast

TOXOID VACCINES:

- **Contain inactivated toxins.** (so called toxoid)
- Toxoid are **immunogenic** but are **no longer toxic.**
- Effective against diseases caused by secreted toxins.

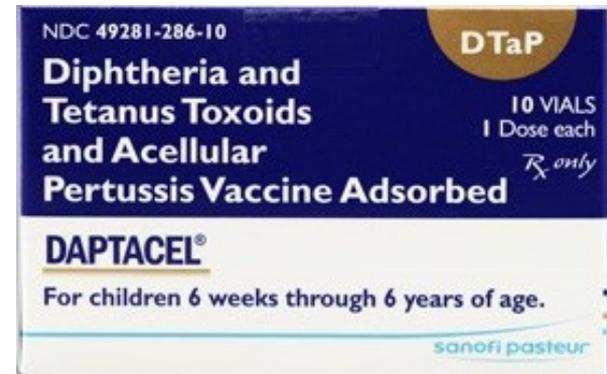


DTaP

- **Combined vaccine**, DTaP = **D**iphtheria, **T**etanus, **a**cellular **P**ertussis
- Contains diphtheria and tetanus toxoids and some selected antigens of *Bordetella pertussis* (subunit vaccine).
- **Can be combined with other vaccines**, usually with **IPV** and **Hib** (*Haemophilus influenzae* B). The **DTaP+IPV+Hib** vaccine is compulsory in Hungary.



Infanrix®, the combined vaccine of GlaxoSmithKline®:
DTaP+IPV+Hib combined vaccine



Daptacel® of Sanofi Pasteur®:
DTaP



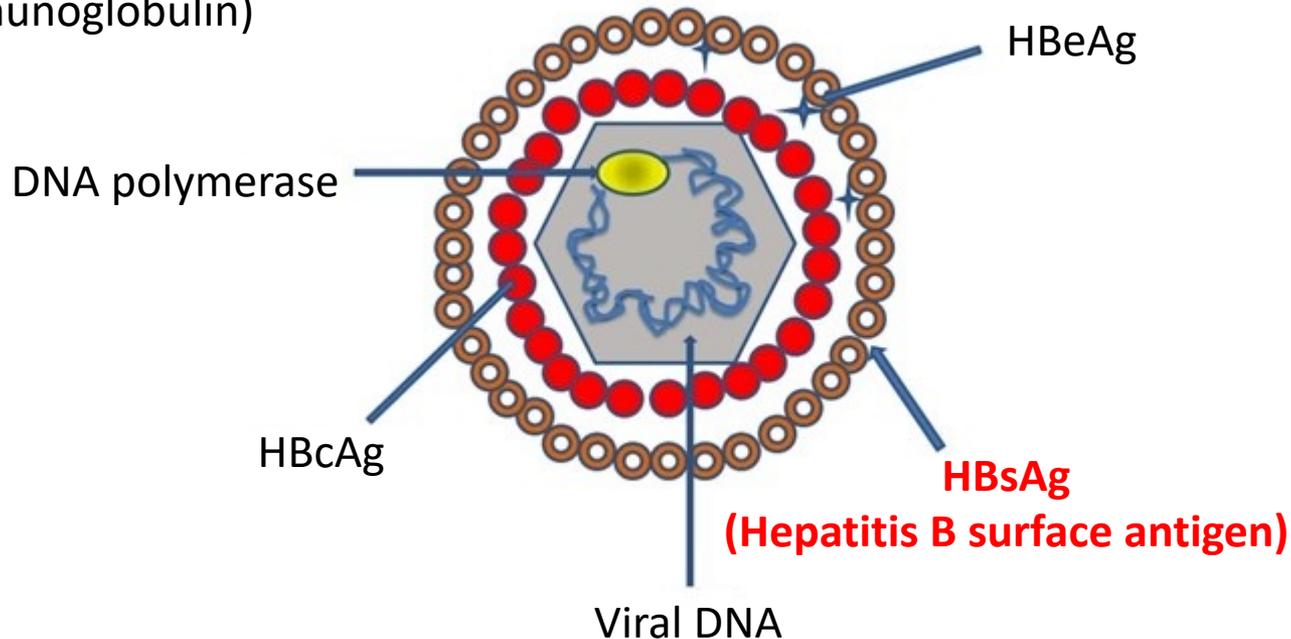
Diphtheria



Tetanus

HBV vaccine

- Contains the **surface antigen** (HBsAg) of hepatitis B virus (HBV).
- **Recombinant subunit vaccine**, the viral antigen is produced in yeast.^[39.]
- Needs to be administered multiple times, the produced **anti-HBsAg antibodies** provide protection against the infection. → Long-term protection is variable but the **antibody levels can be measured**.
- It is compulsory in Hungary.
- **Can be combined with other vaccines**^[42,43.], e.g. DTaP+IPV+Hib+Hep B.
- Passive immunization can be used after HBV exposure. (HBIG= hepatitis B immunoglobulin)



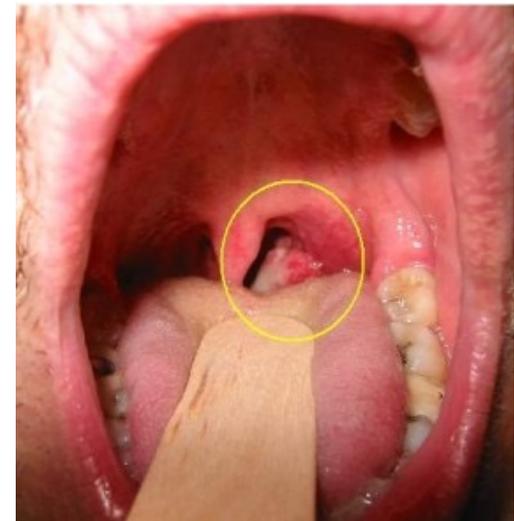
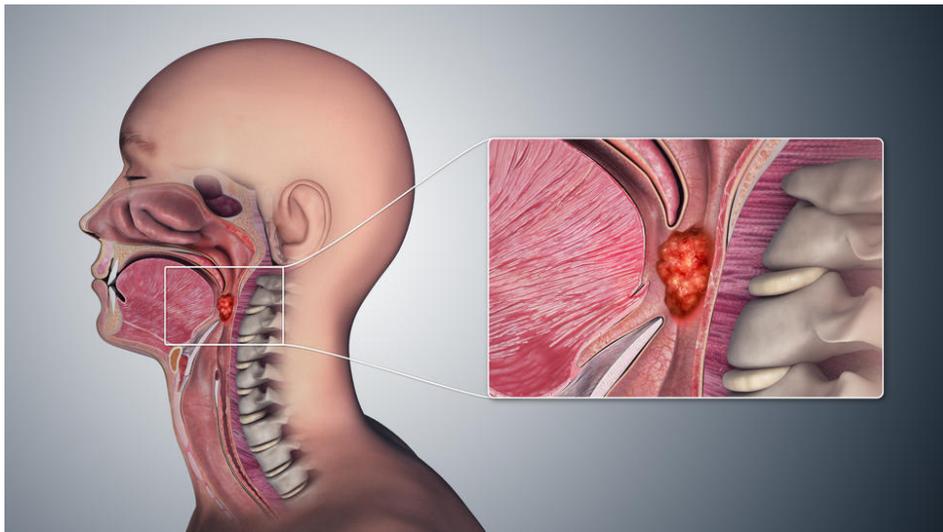
HPV vaccine

- **Recombinant subunit vaccine**, contains the antigens of some selected strains of HPV. Not compulsory in Hungary.^[44.]
- Three vaccines have been approved^[45.]:
 - Cervarix[®]: against **HPV-16** and **18** (bivalent)
 - Gardasil[®]: against **HPV-16, 18** and **6, 11** (quadrivalent)
 - Gardasil 9[®]: against 9 different strains of HPV (for both men and women)
- HPV-16 and 18: Cause **70% of cervical cancer**, 80% of anal cancer and 60% of vaginal cancer.^[46.]
- HPV-6 and 11: Cause 90% of **genital warts**.
- WHO: Young, 9-13 year old girls should be vaccinated **before sexual activity**.^[45.]



HPV-related oropharyngeal cancer

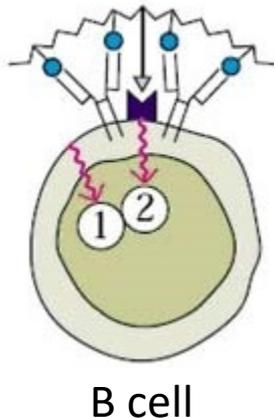
- OPCs include those found in the **soft palate, base of tongue, lingual and palatine tonsils, and surrounding tissues**
- **Increase in a subset of OPC linked to human papillomavirus (HPV)**
- Cryptic epithelium overlying the tonsils and tongue base acts as a **reservoir for the virus, providing access to its basal layer for viral replication.**
- Overwhelming majority of **HPV-related OPC cases are caused by HPV16**
- **American Academy of Pediatrics:** 15.5% of the pediatricians polled were not aware of the link between OPC and HPV, and less than half knew that HPV-related OPC incidence was increasing



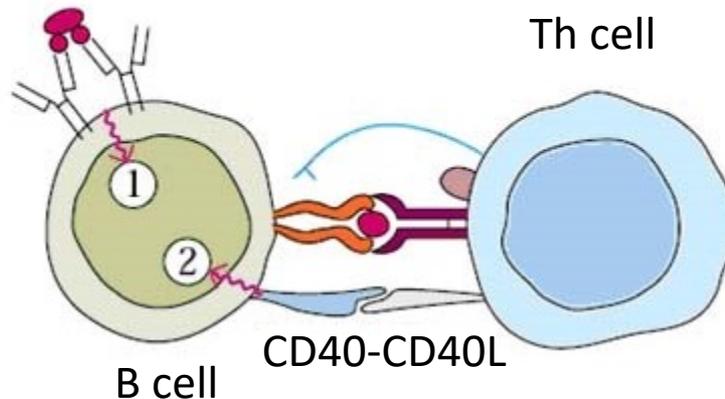
Conjugated vaccines

- Many encapsulated bacteria have polysaccharides in their capsules.
 - *Haemophilus influenzae*
 - *Neisseria meningitidis*
 - *Streptococcus pneumoniae*
- Cause suppurative inflammations (mainly in children and people who underwent splenectomy)
- Polysaccharide = **T-independent antigen**: T cells are not activated by them:
 - Produced antibodies are of **low affinity** and usually **IgM** isotype.
 - **Children are at higher risk.**
 - Solution: conjugation of polysaccharides to **protein carriers**.^[48.]

T-independent:



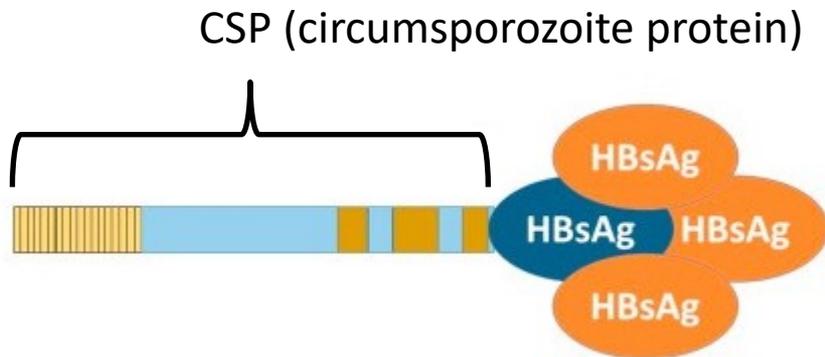
T-dependent:



Novel vaccines I.

RTS,S (Mosquirix®)

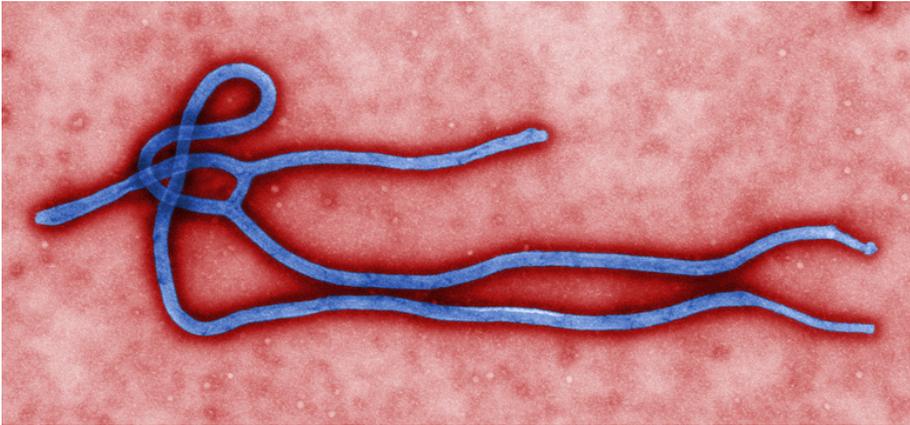
- The **first anti-parasite vaccine** against **malaria** that was approved in the EU in 2015.
- Efficacy is **25-50 %** in children.^[49.]
- It is a recombinant subunit vaccine:
 - Liposome-based adjuvant
 - **Recombinant fusion protein**: Some epitopes of *P. falciparum*'s **CSP + HBsAg**



News report about the European approval of Mosquirix® on CNN.

Novel vaccines II.

Vaccines against Ebola:



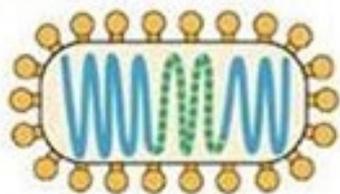
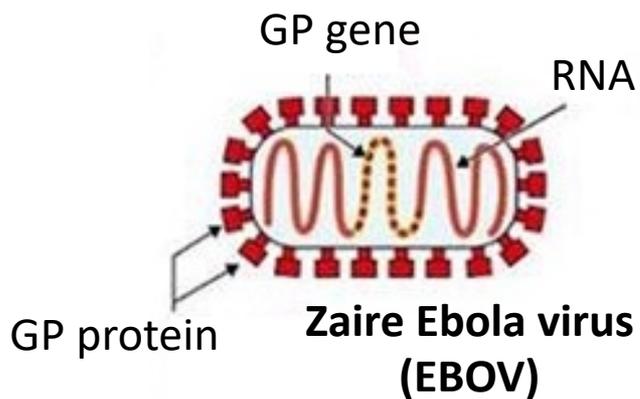
Ebola virus (Transmission electron microscopy)

- **West African Ebola epidemic in 2014** → general panic, Ebola related research accelerated
- Several Ebola vaccines were developed, one was tested in a phase III. clinical trial with **almost a 100% efficacy**^[50.]:

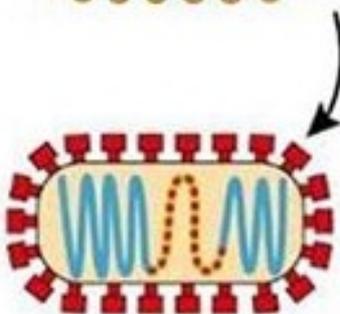
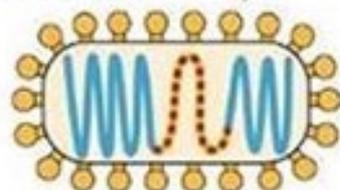
↓

VSV-EBOV

VSV-EBOV vaccine

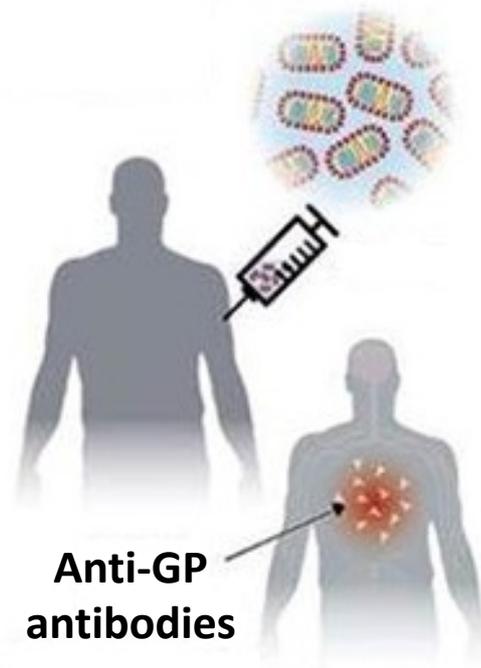


Insertion of the GP gene into VSV



Recombinant VSV with the GP protein of EBOV

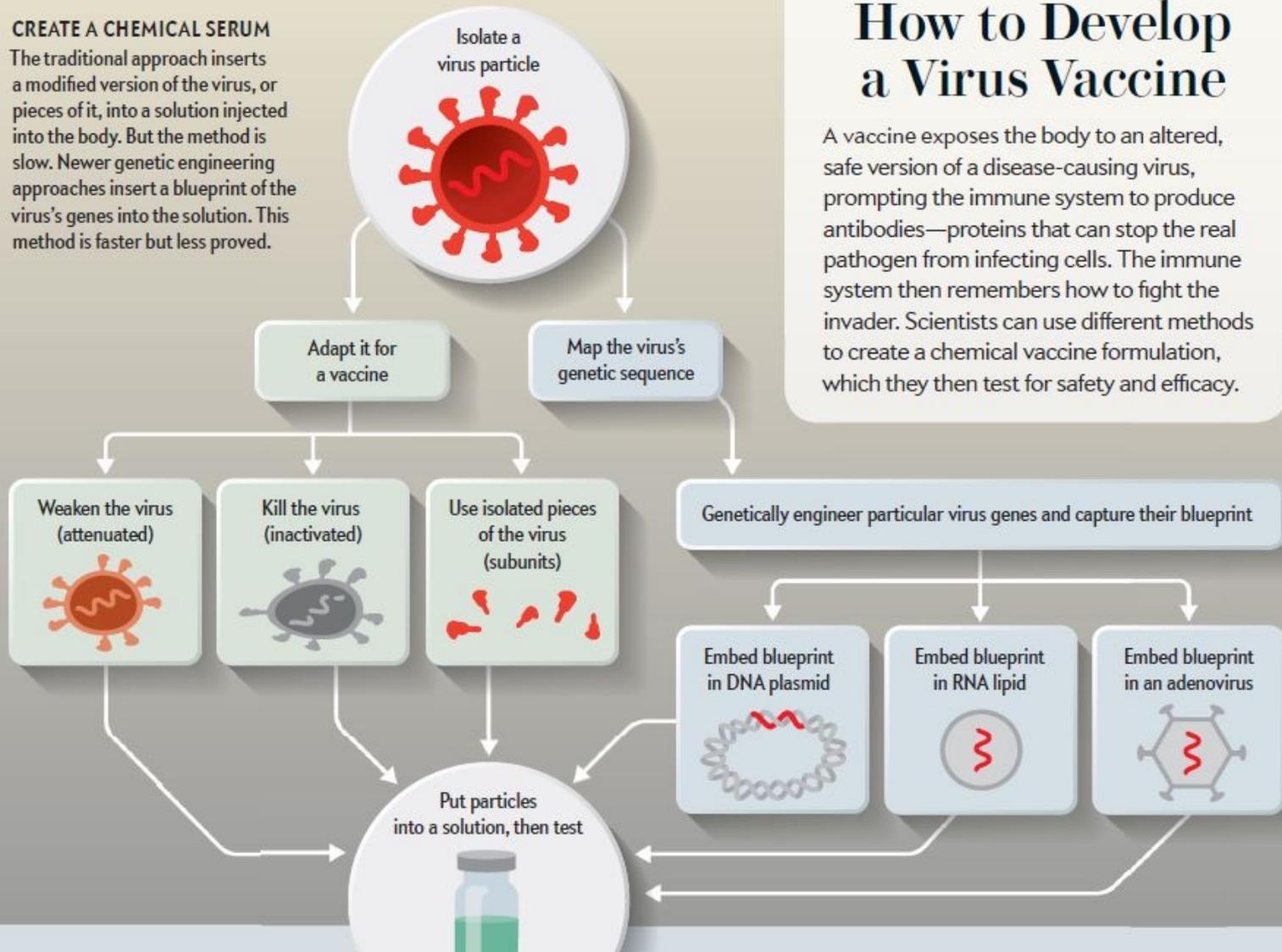
Administering recombinant VSV



Vaccine development steps 1.

CREATE A CHEMICAL SERUM

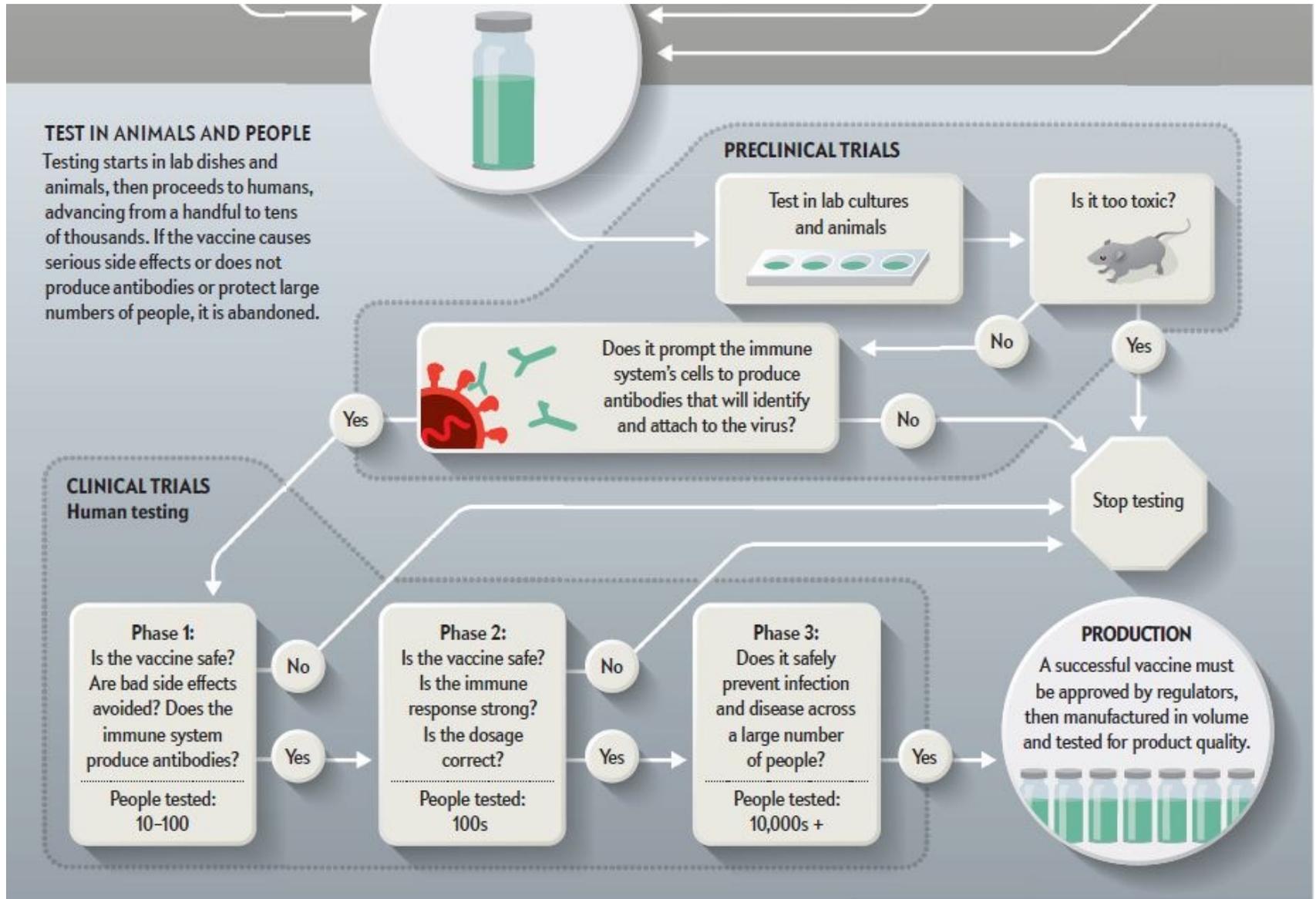
The traditional approach inserts a modified version of the virus, or pieces of it, into a solution injected into the body. But the method is slow. Newer genetic engineering approaches insert a blueprint of the virus's genes into the solution. This method is faster but less proved.



How to Develop a Virus Vaccine

A vaccine exposes the body to an altered, safe version of a disease-causing virus, prompting the immune system to produce antibodies—proteins that can stop the real pathogen from infecting cells. The immune system then remembers how to fight the invader. Scientists can use different methods to create a chemical vaccine formulation, which they then test for safety and efficacy.

Vaccine development steps 2.



Significance of vaccines

Life expectancy at birth in the world^[51,52.]:

1900 → 31 years (under 50 even in developed countries)

1950 → 48 years

2013 → 71 years (reached 80 in some countries)

Causes:

- Overall improvement of **life conditions** (e.g. hygiene)
- **Decreased numbers of wars**
- Medicine contributed in 2 major ways:
 - Introduction of **antibiotics**
 - Effective **vaccination programs**



Smallpox, which still caused 15 million infections and 2 million deaths worldwide in 1967 was **officially declared eradicated** by the WHO in 1979.^[53.]



Smallpox (variola vera)

Some notable cases in the past



December of 2014.: Measles outbreak in the American Disneyland with 189 patient, most of them did not receive vaccination against Measles.^[54.]

First Case of Diphtheria in Spain Since 1986 After Parents Shun Vaccination

TIME

June of 2015.: A 6 year old boy died of Diphtheria in Spain where this disease haven't been encountered since 1986. The parents did not allow the child to receive vaccination as an infant.^[55.]

Children paralysed in Ukraine polio outbreak

BBC

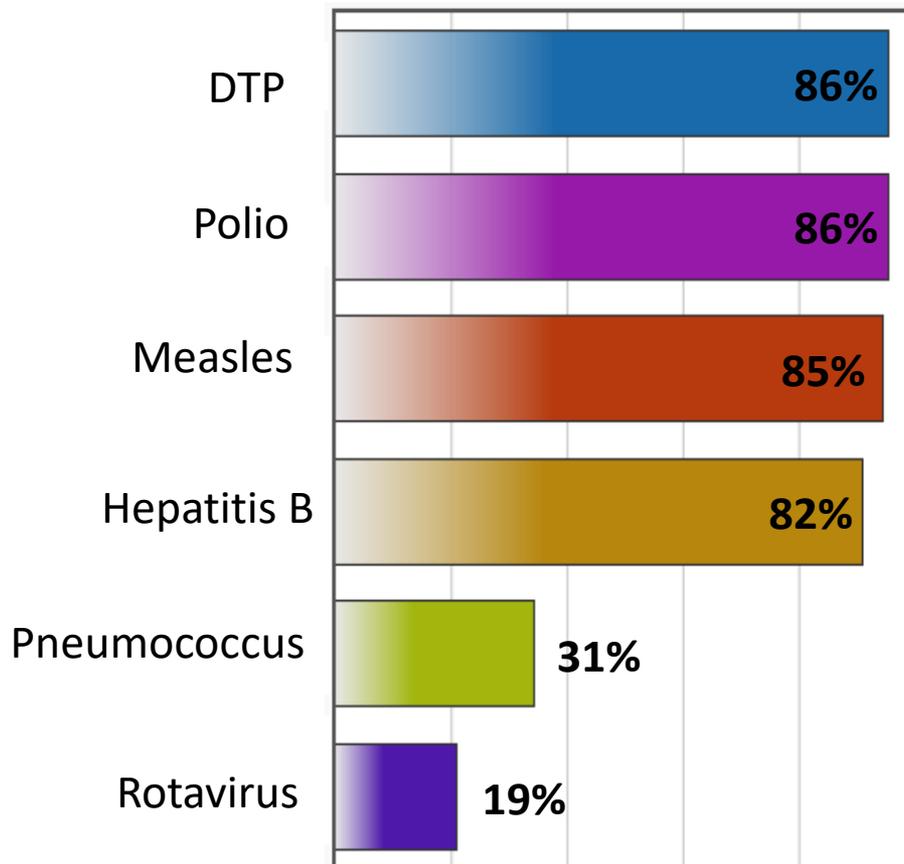
By James Gallagher
Health editor, BBC News website

🕒 2 September 2015 | **Health**

Poliovirus showed up in Europe again after 5 years.^[56.]

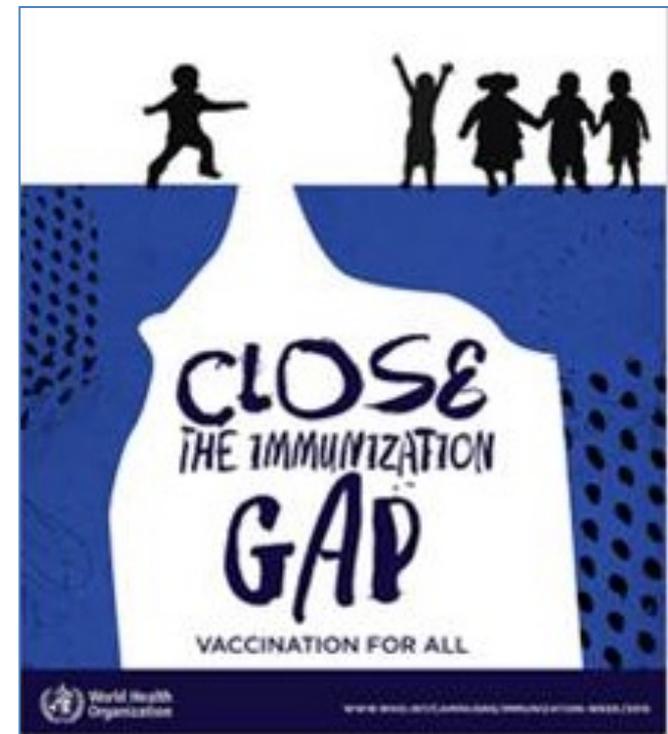
Achievements of the WHO

Global immunization coverage in
2014^[57.]:



Goals of the Global Vaccine Action Plan:

- >90% coverage
- **ERADICATION OF POLIO**



Thank you for your attention!



Emil Adolf von Behring

Was awarded the 1901 Nobel Prize in Physiology and Medicine: For his work on serum therapy, especially its application against diphtheria.^[58.]



Max Theiler

Was awarded the 1951 Nobel Prize in Physiology and Medicine: For his discoveries concerning yellow fever and how to combat it.^[59.]

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