IMMUNOLÓGIAI ÉS BIOTECHNOLÓGIAI INTÉZET

10th practice: Vaccines

Basic Immunology

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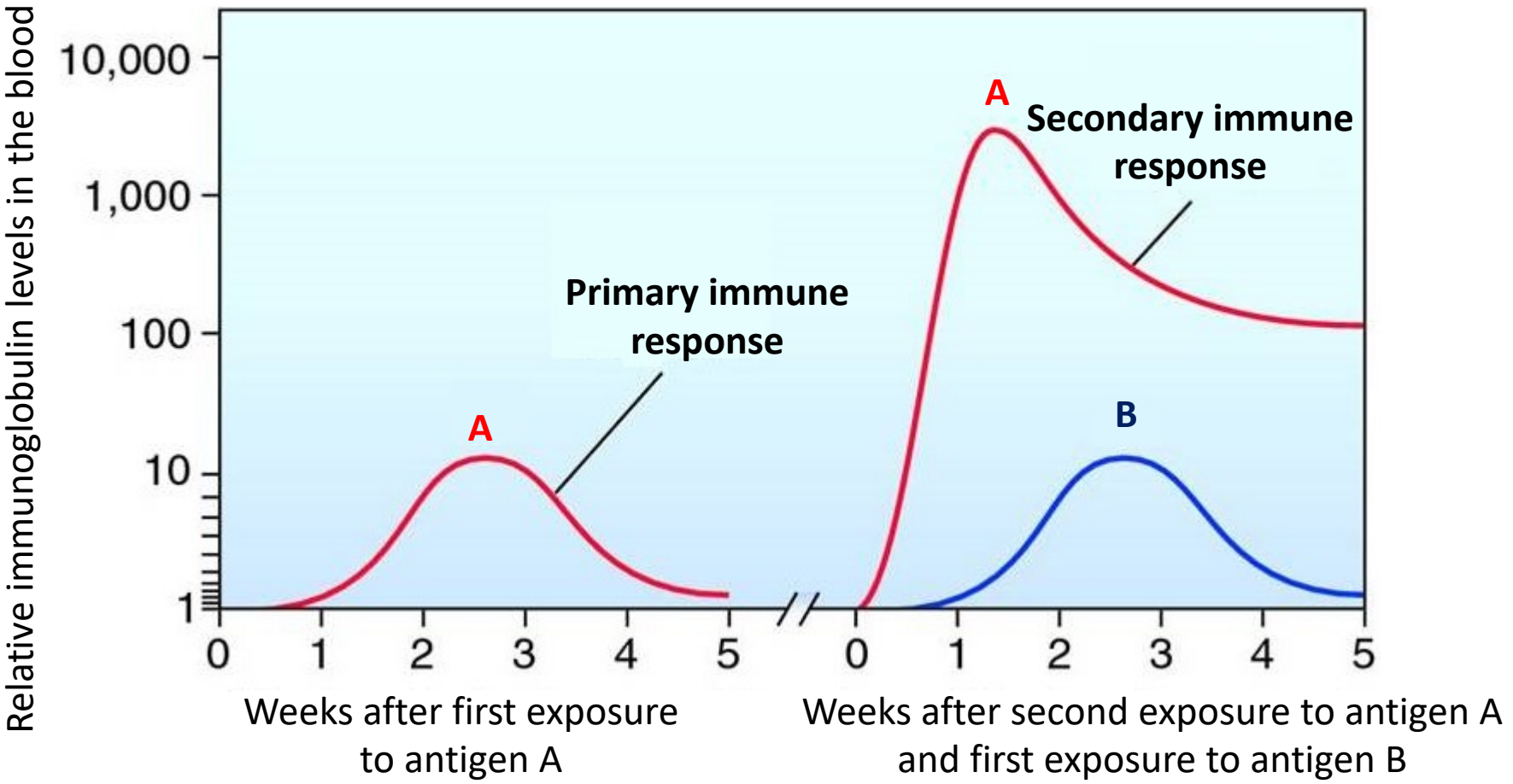
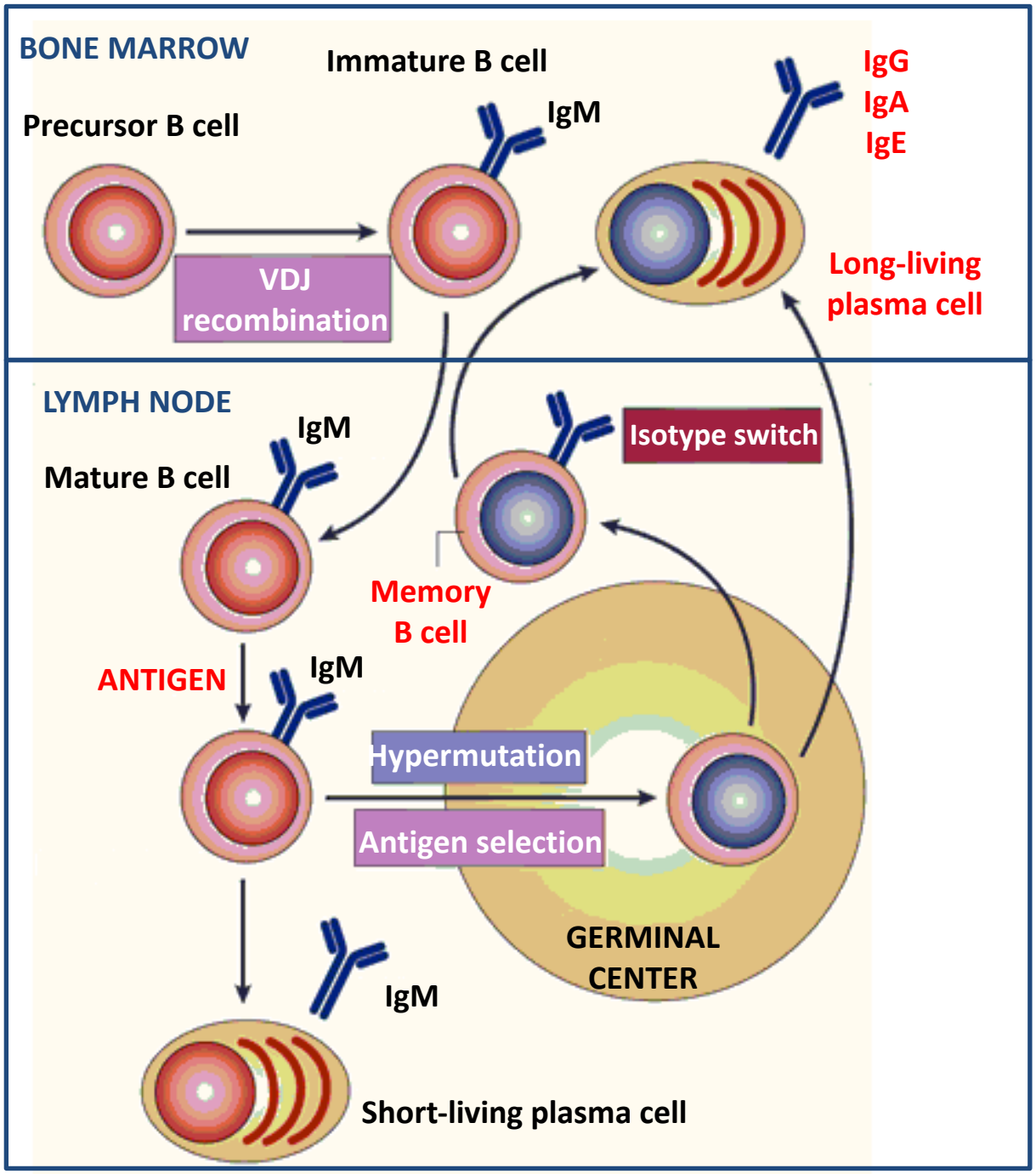
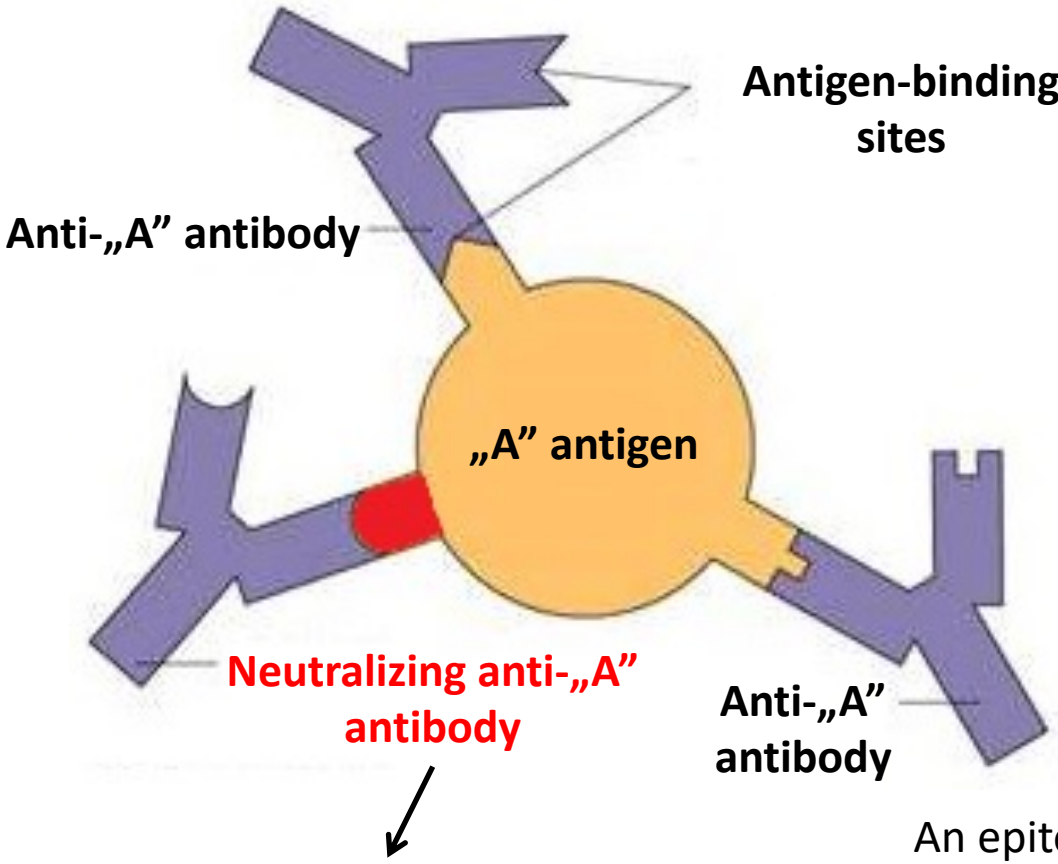
Pécs

Primary and secondary immune response

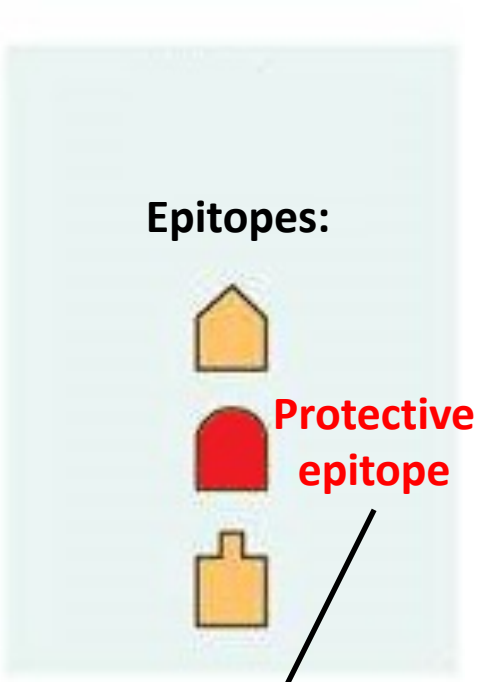



BONE MARROW
Immature B cell
Precursor B cell
IgM
IgG
IgA
IgE
VDJ recombination
Long-living plasma cell
LYMPH NODE
IgM
Mature B cell
Isotype switch
Memory B cell
ANTIGEN
IgM
Hypermutation
Antigen selection
GERMINAL CENTER
IgM
Short-living plasma cell

Neutralizing antibodies



Antibody that binds to protective epitope and therefore **preventing disease**.



An epitope that plays an **important role in the pathogenesis** of the disease.

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

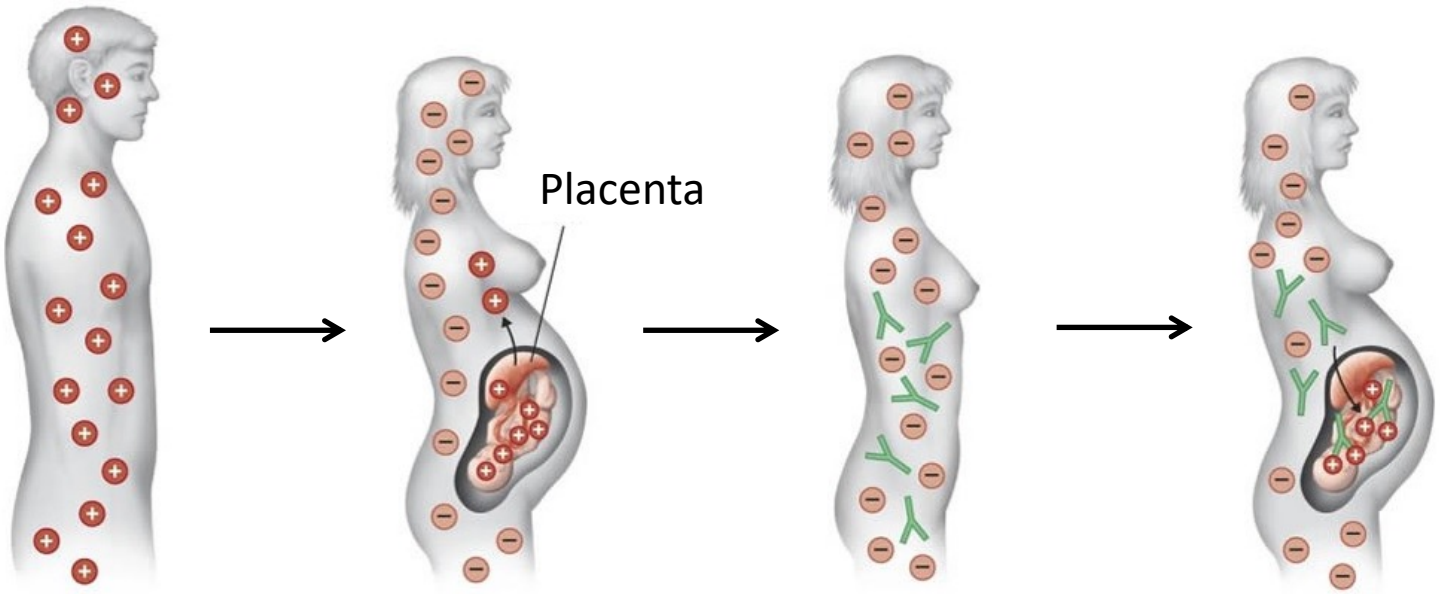
Passive immunization

- **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.])

Animal-derived diphtheria antitoxin from 1895.

- 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.]

Rh alloimmunization



Rh+ father

First Rh+ pregnancy of Rh- mother

Immunization of mother

↓

Anti-Rh antibody

Second Rh- pregnancy

↓

Anti-Rh IgG crosses the placenta and causes hemolysis!

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**.

Prevention of Rh alloimmunization

Human anti-Rh(D) immunoglobulin

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.

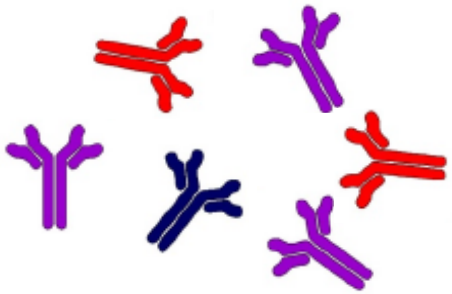
↓

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.

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

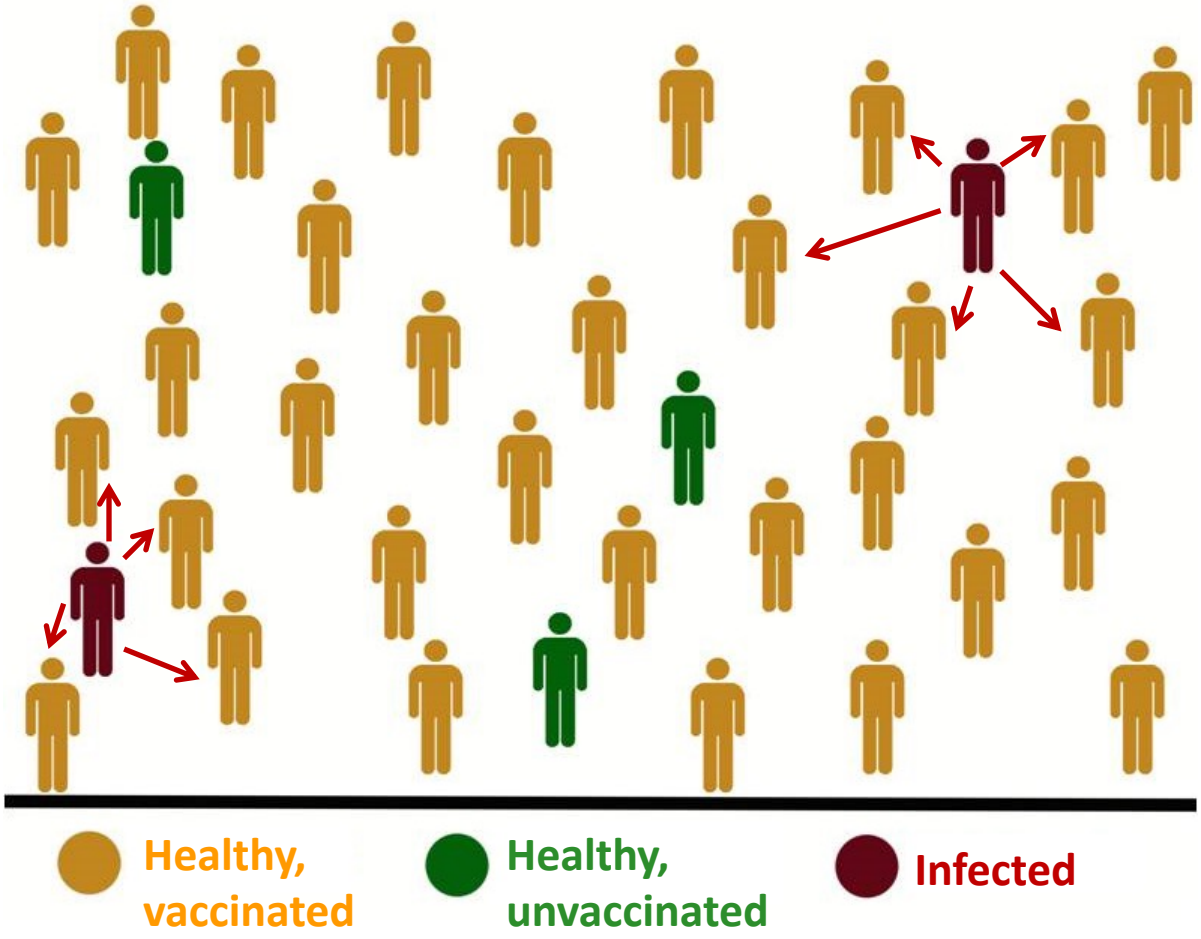
- **Administration of an antigen** in order **to provoke an immune response** against the antigen.
- In case of research animals:
  - **Production of antibodies** (e.g. hybridoma technique, antivenoms)
  - **Triggering autoimmunity** (e.g. human cartilage proteoglycan-induced arthritis in mice) for the **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.] (see 3rd practice)
- **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)

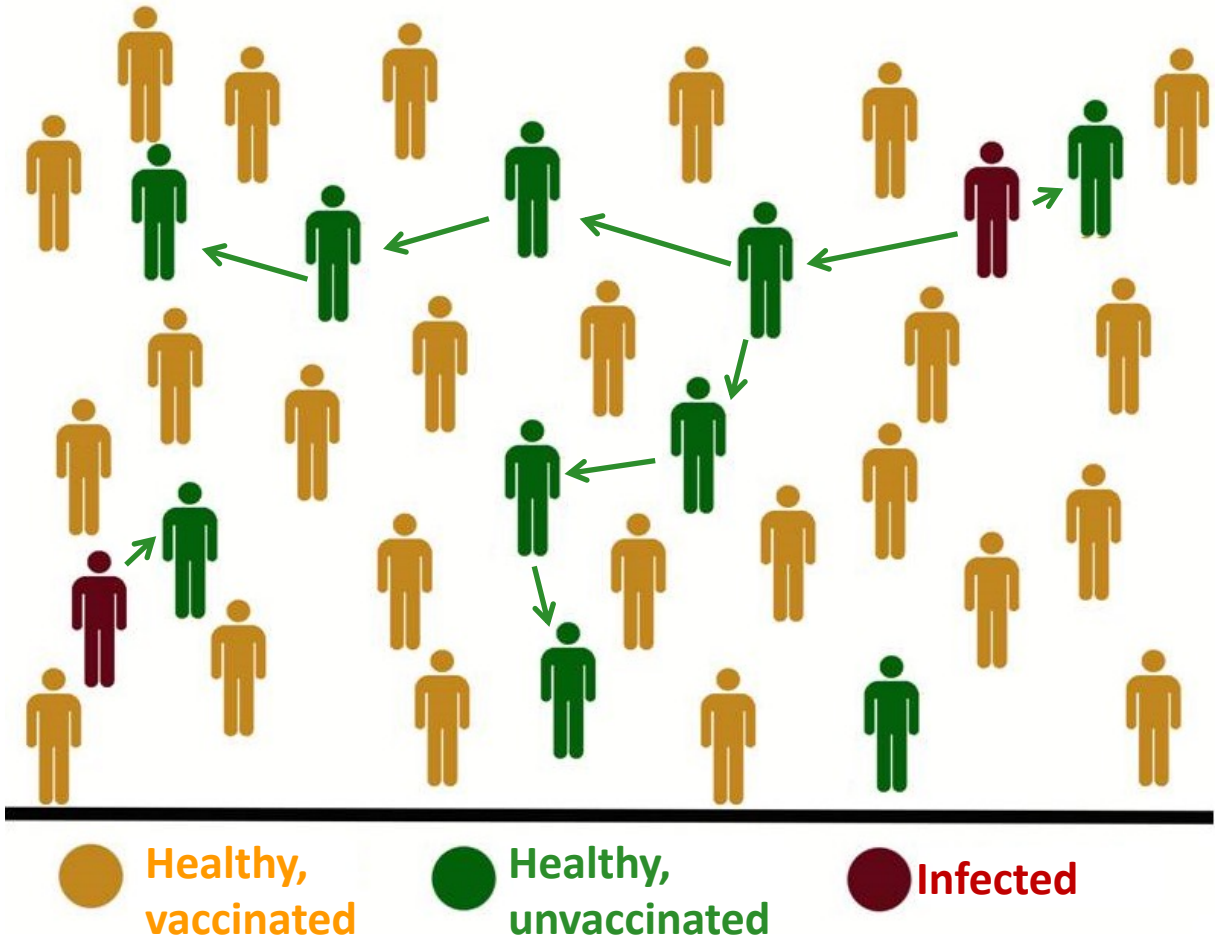
Herd immunity I.



A large percentage of the population is vaccinated.

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

Herd immunity II.



A relaitvely large percentage of the population is unvaccinated.

↓

The infection can spread in the population.

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. **RNA, DNA** vaccine: contains the RNA or DNA 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, see the 12th practice)

Live, attenuated vaccines

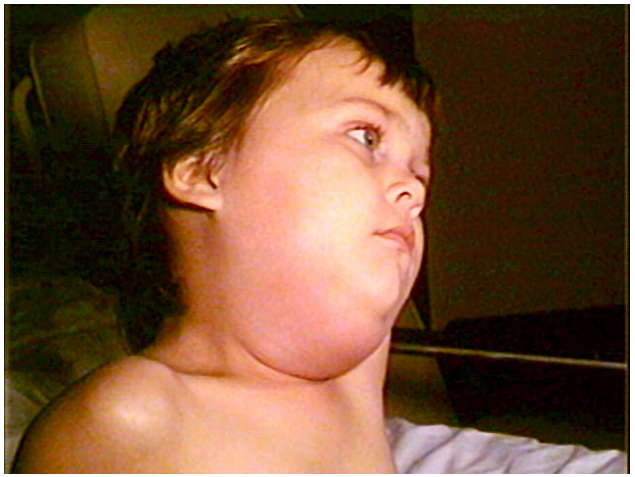
- Contain **living pathogens** with a **limited potential to replicate** in the host.[16.]
- Viruses are attenuated by growing them in cells in which they do not replicate well. (**Serial passage**). They will slowly adapt to the new environment gradualy losing their virulence to their original host 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 thy 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.]

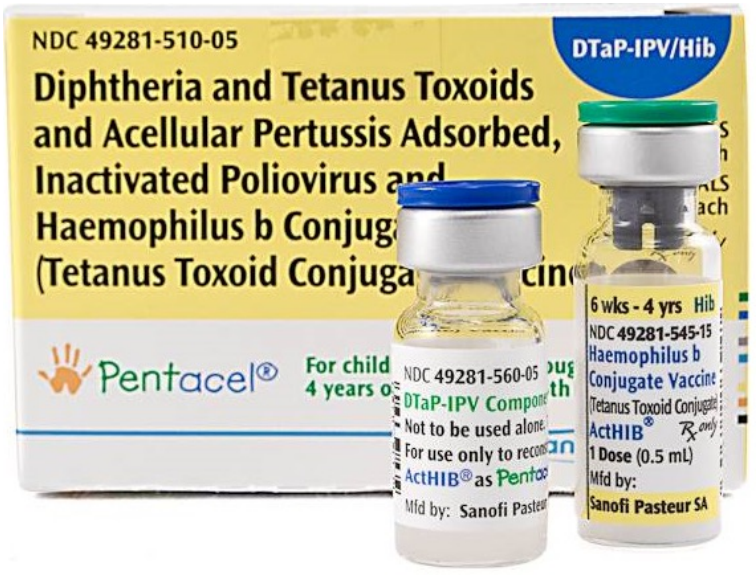
Inactivated vaccines

- **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** =**D**iphtheria-**T**etanus-**a**cellular **P**ertussis vaccine
  - **Hib**= ***H****aemophilus* ***i****nfluenzae* **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

  } Type A influenza
  - 1 or 2 strains of type B 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®.

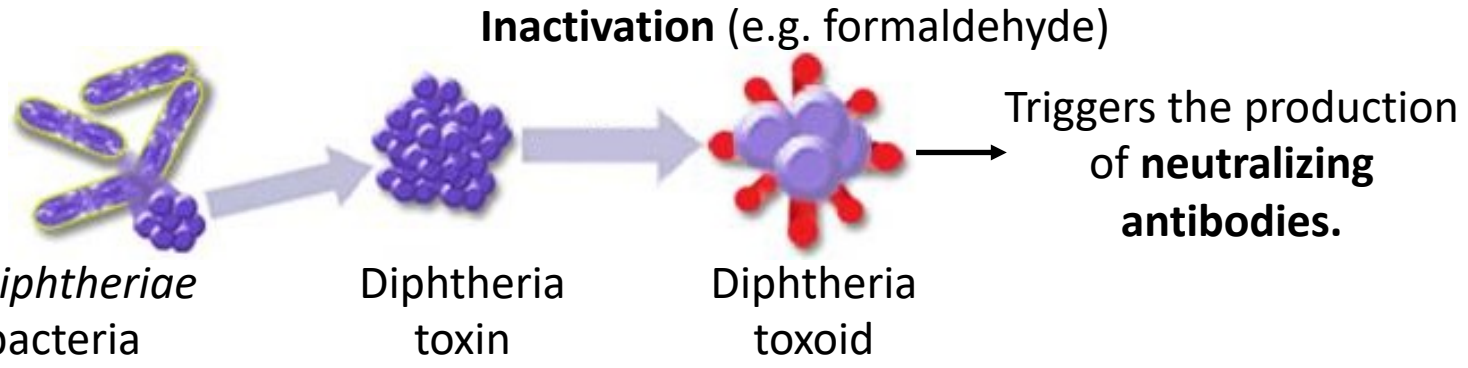
Subunit and toxoid vaccines

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

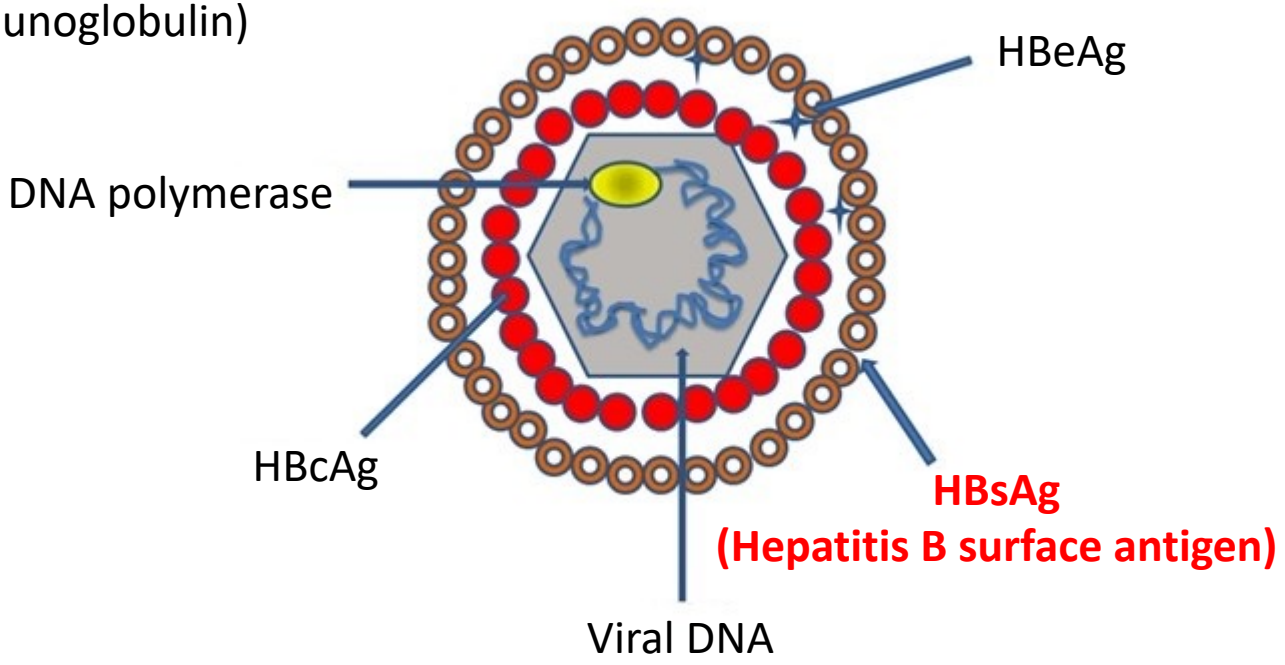
Daptacel® of Sanofi Pasteur®:
DTaP

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

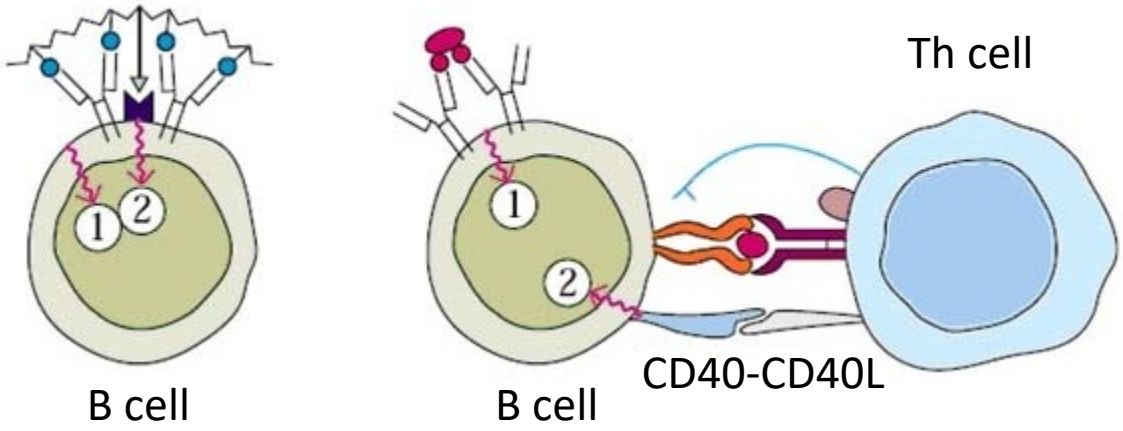
- **Recombinant subunit vaccine**, contains the antigens of some selected strains of HPV. Not compulsory in Hungary.[44.]
- Three vaccines have been approved[45.]:
  - Cervarix®: against **HPV-16** and **18** (bivalent)
  - Gardasil®: against **HPV-16**, **18** and **6, 11** (quadrivalent)
  - Gardasil 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.]

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.]

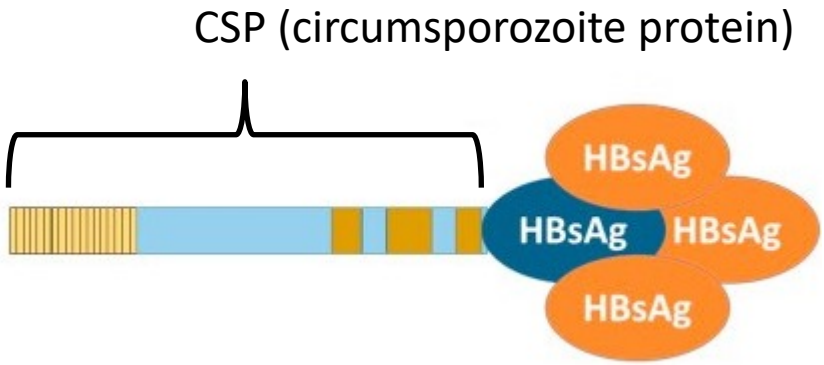
T-independent: **T-dependent:**



Novel vaccines I.

RTS,S (Mosquirix®)

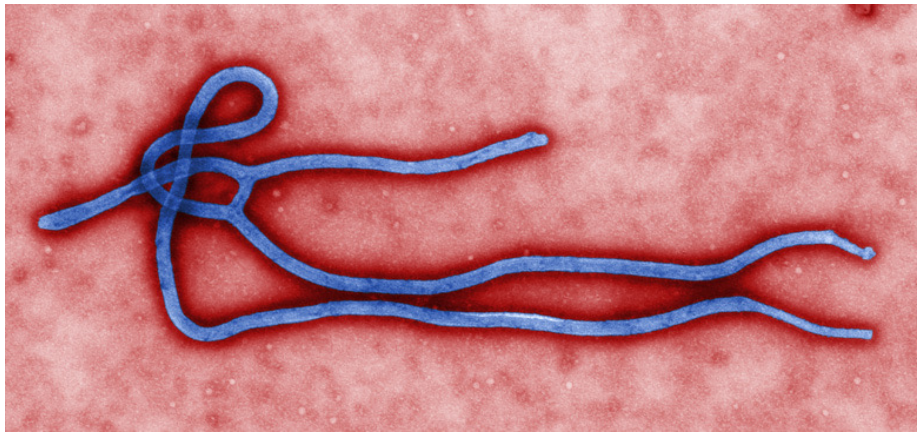
- The **first anti-parasite vaccine** against **malaria** that was approved in the EU in 2015.
- Efficacy is **25-50 %** in children.[49.]
- It is a recombinant subunit vaccine:
  - Liposome-based adjuvant
  - **Recombinant fusion protein**: Some epitopes of *P. falciparum*'s **CSP + HBsAg**



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

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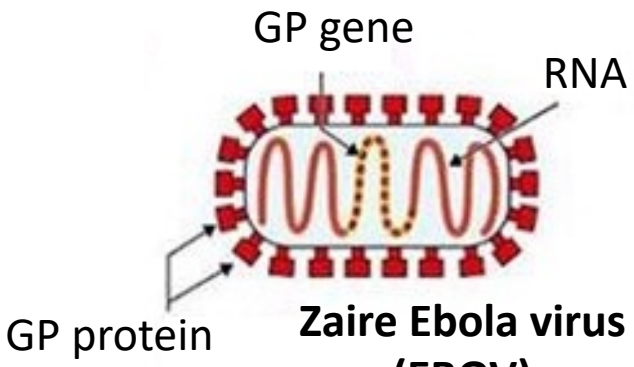
- Several Ebola vaccines were developed, one was tested in a phase III. clinical trial with **almost a 100% efficacy**[50.]:

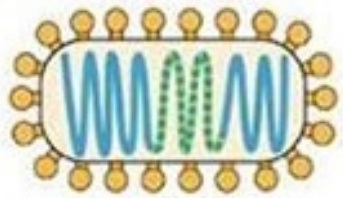
↓

VSV-EBOV

VSV-EBOV vaccine

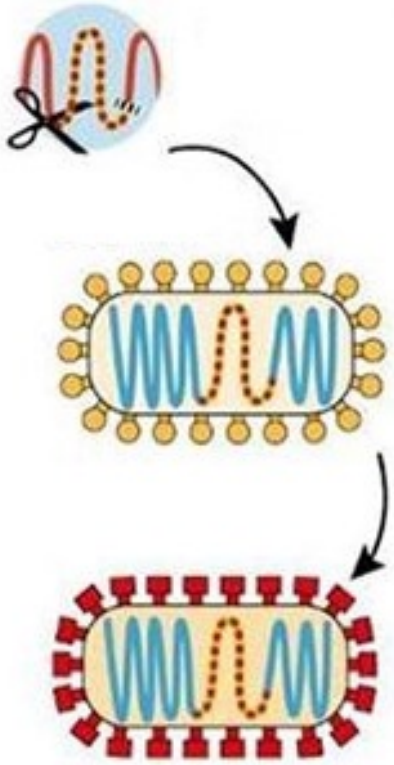


Zaire Ebola virus (EBOV)



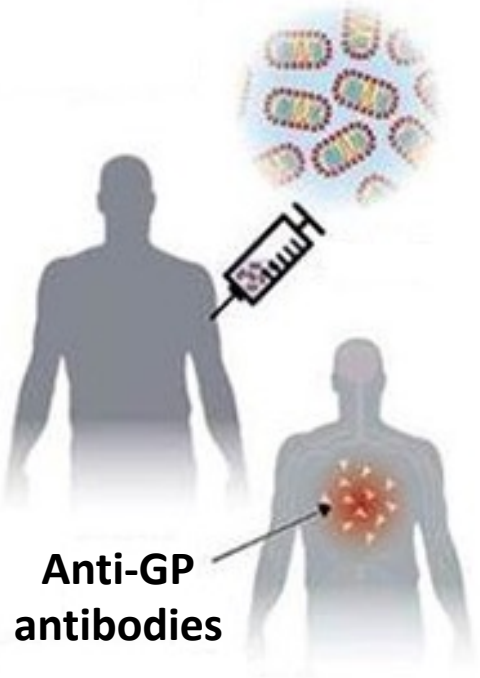
Vesicular stomatitis virus (VSV, not a human pathogen)

Insertion of the GP gene into VSV

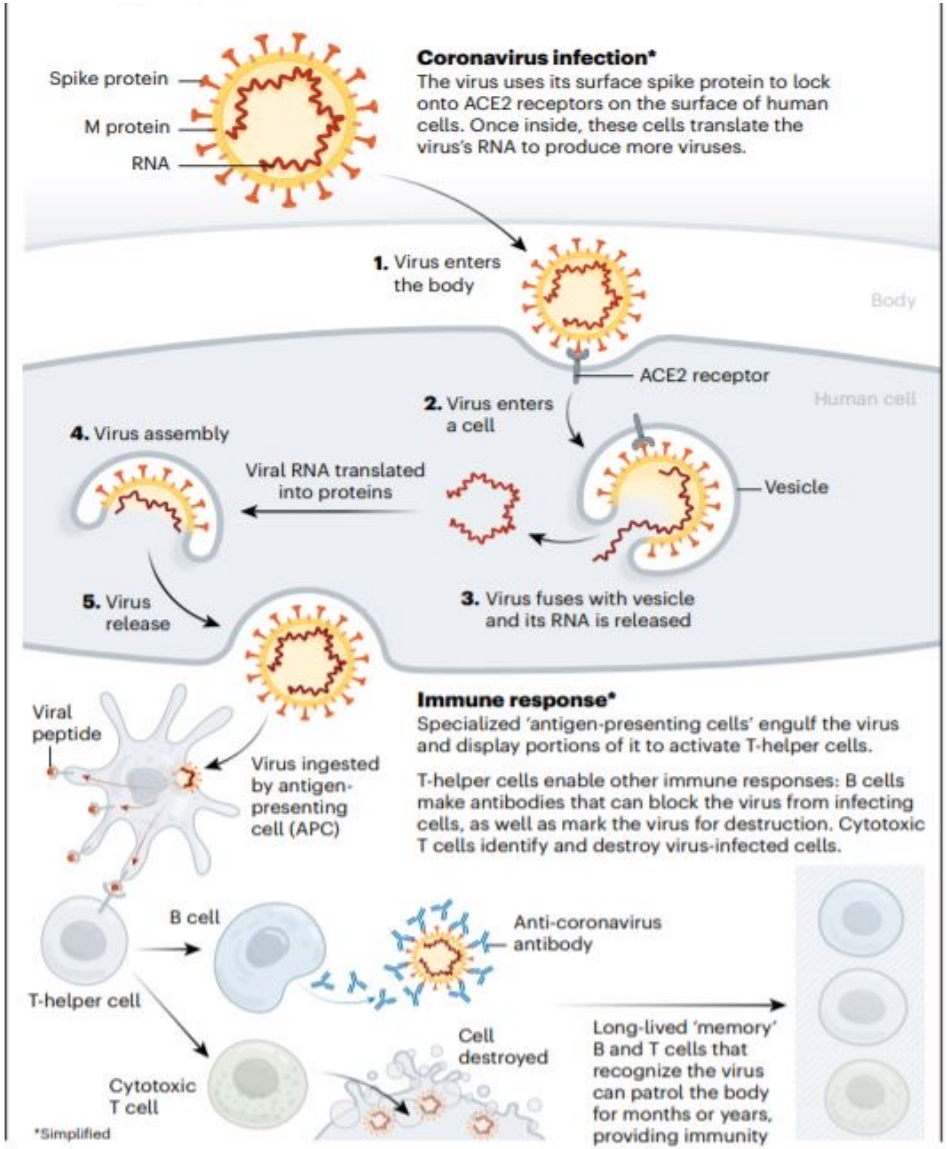


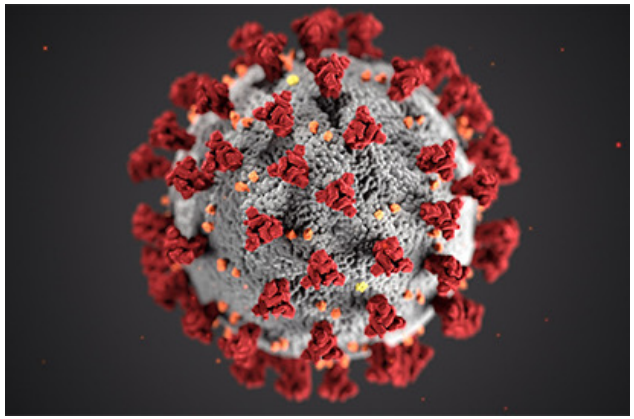
Recombinant VSV with the GP protein of EBOV

Administering recombinant VSV



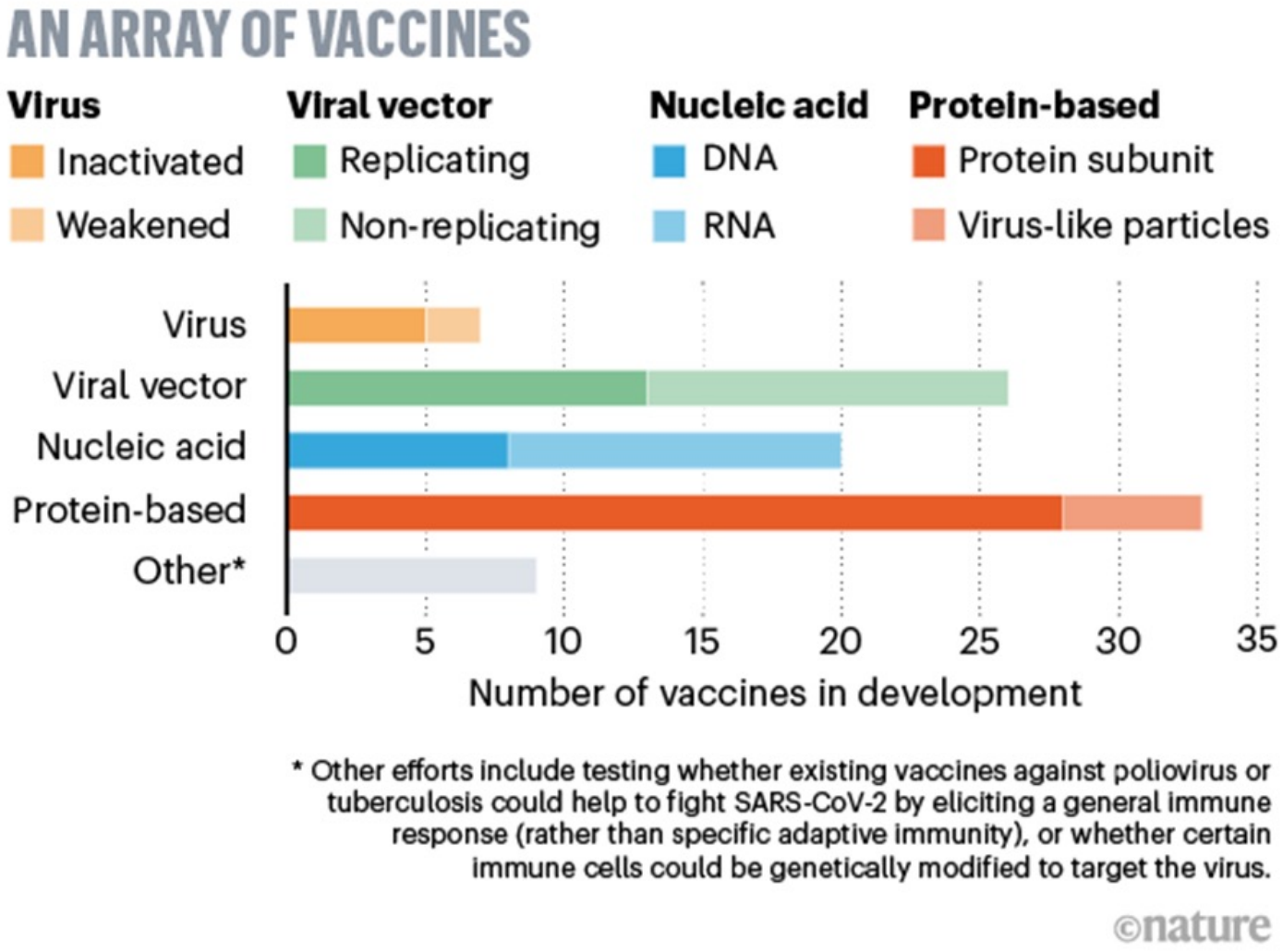
Steps of the immune response during viral infection



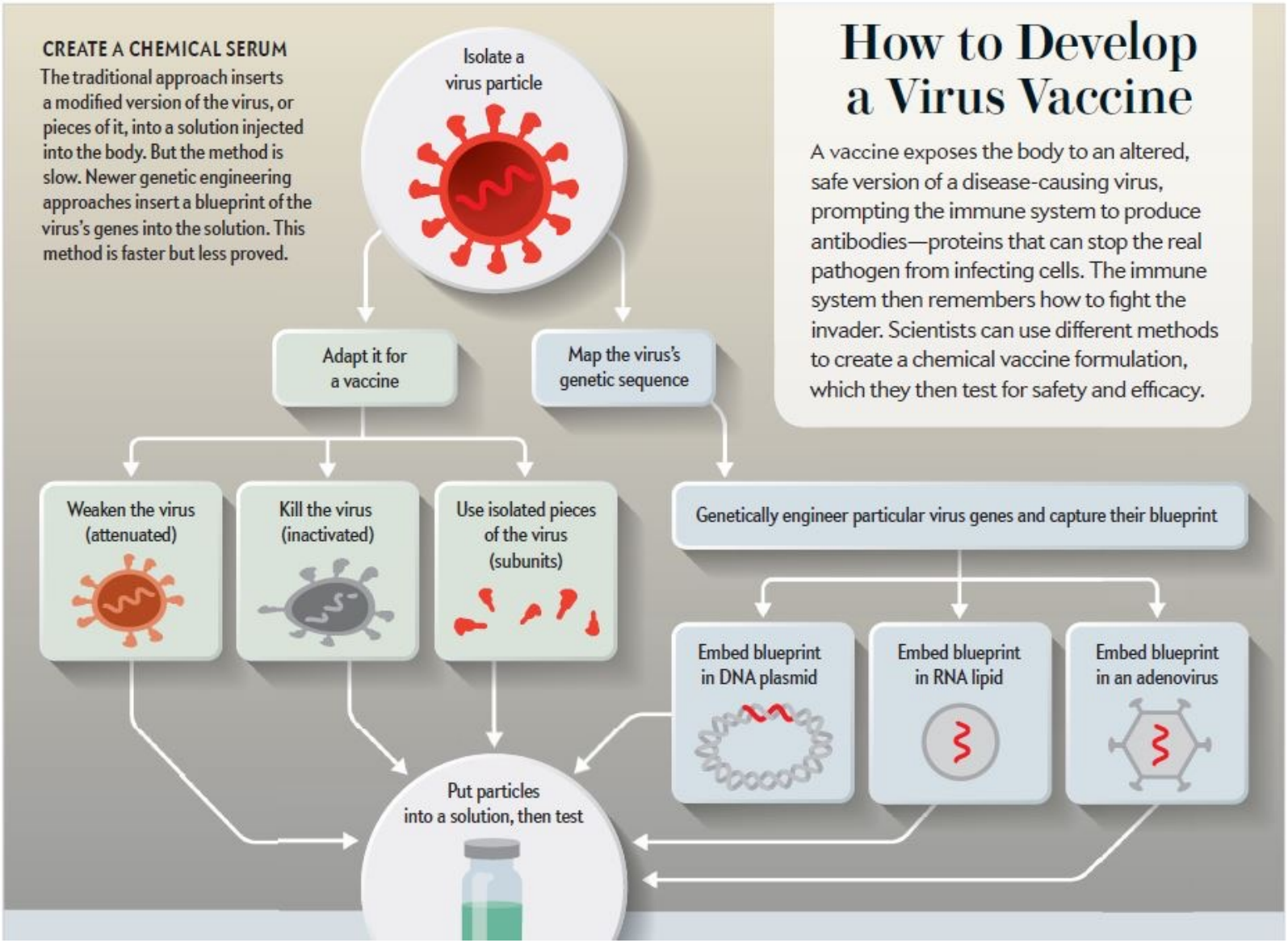


SARS-Cov2 virus got its name from the spike proteins on its surface, which gives a corona-like appearance. This so-called **Spike-1 (S1) protein** is responsible for the binding of the virus to human cells.

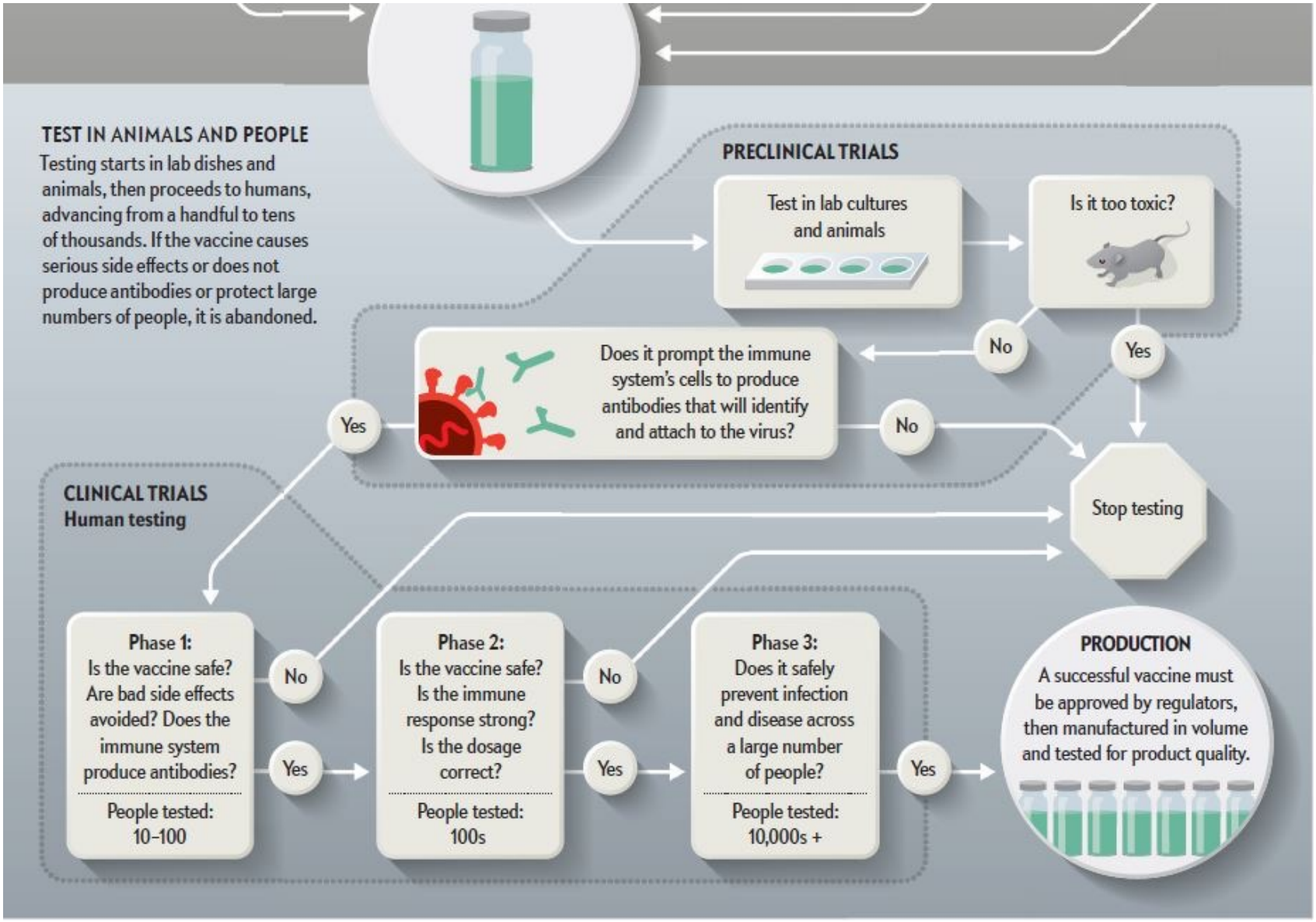
Ongoing vaccine development strategies



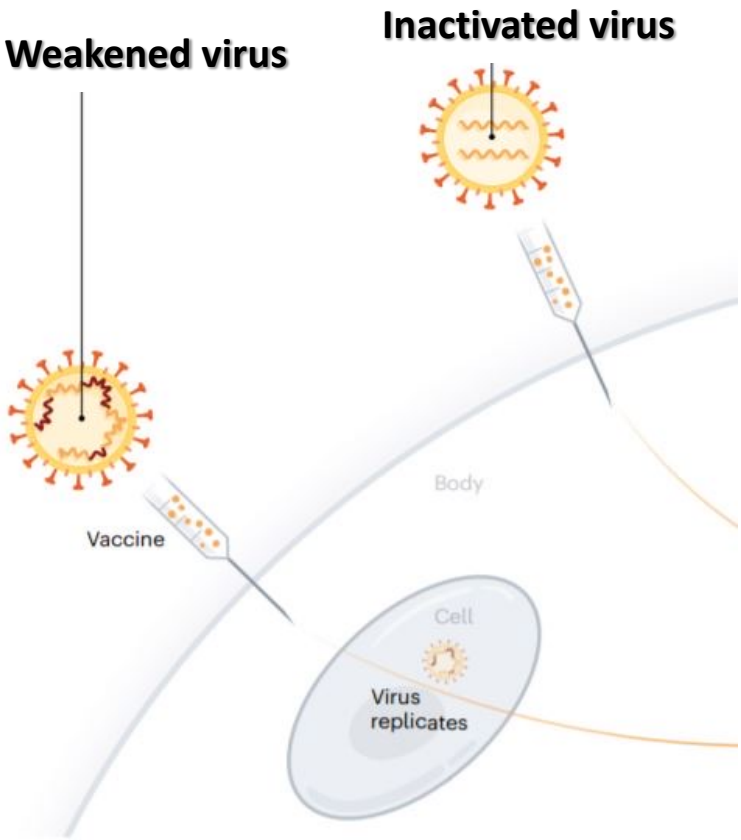
Vaccine development steps 1.



Vaccine development steps 2.



Coronavirus vaccines



- A virus is conventionally weakened for a vaccine by being passed through animal or human cells until it picks up mutations that make it less able to cause disease. **Codagenix in Farmingdale**, New York, is working **with the Serum Institute of India**, a vaccine manufacturer in Pune, to weaken SARS-CoV-2 by altering its genetic code so that viral proteins are produced less efficiently.
- In 2020, the **Beijing Institute of Biological Products** developed an inactivated coronavirus vaccine called **BBIBP-CorV**. According to clinical trials conducted by the state-owned company **Sinopharm**, the vaccine was **79% effective**.

Replicating viral vector

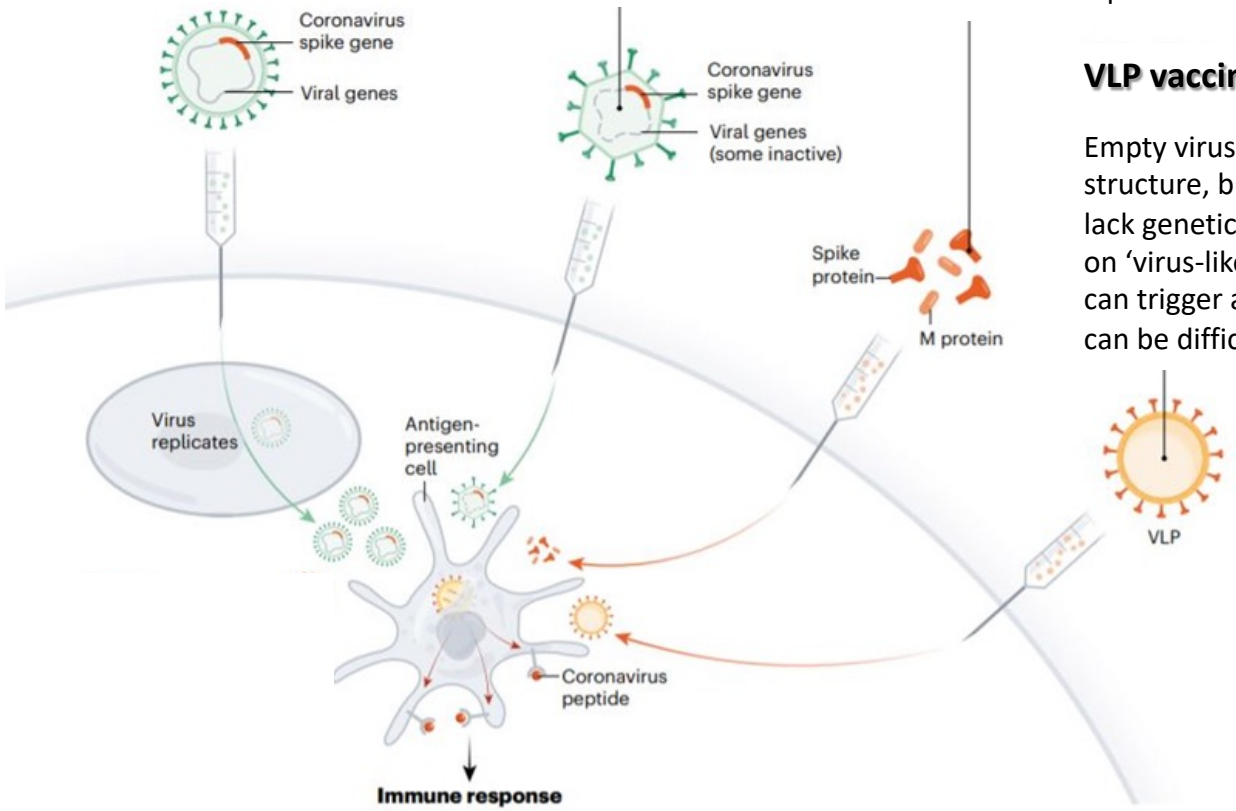
The Ebola vaccine is a good example of a viral vector vaccine that replicates within cells. Such vaccines tend to be safe and provoke a strong immune response. However, existing immunity to the vector could blunt the efficacy of the vaccine.

Non - replicating viral vector

- **Johnson & Johnson**: Ad26, **66%** efficiency
- **Sputnyik V**: Ad26 / Ad5, **91.6%** efficiency
- **AstraZeneca-Vaxzevria**: chimpanzee adenovirus, **70%** efficacy
- **Covishield**: astrazeneca collaboration with Serum Institute of India
- **Convidencia**: Ad5, **91%** efficiency

Protein subunits

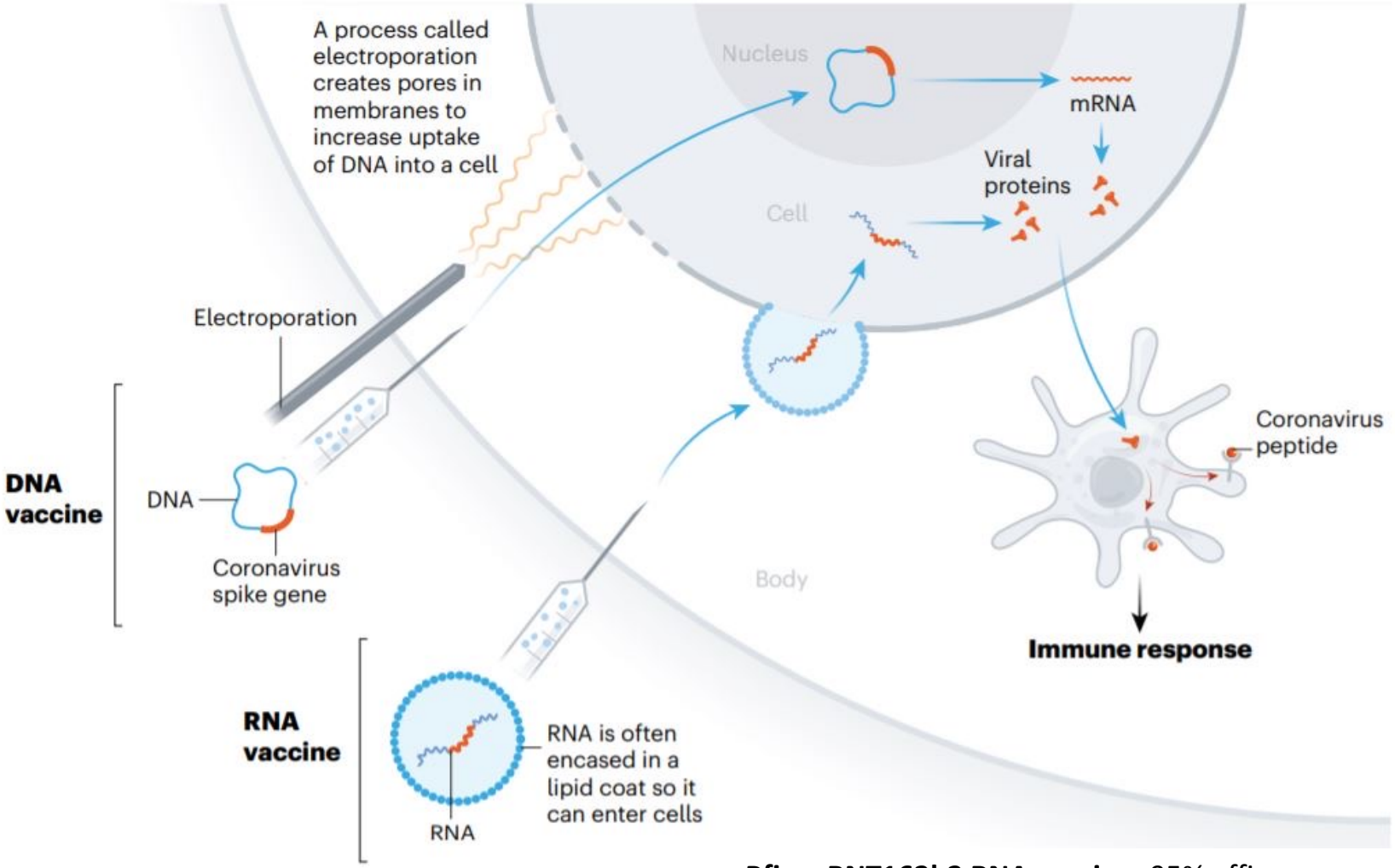
Protein subunits Twenty-eight teams are working on vaccines with viral protein subunits — most of them are focusing on the virus's spike protein or a key part of it called the receptor binding domain. Similar vaccines against the SARS virus protected monkeys against infection but haven't been tested in people. To work, these vaccines might require adjuvants — immune-stimulating molecules delivered alongside the vaccine — as well as multiple doses.



VLP vaccines (virus-like particles)

Empty virus shells mimic the coronavirus structure, but aren't infectious because they lack genetic material. Five teams are working on 'virus-like particle' (VLP) vaccines, which can trigger a strong immune response, but can be difficult to manufacture.

Nucleic acid vaccines



Pfizer BNT162b2 RNA vaccine: 95% efficacy
Moderna: 94% efficacy

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 (variola vera)

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

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

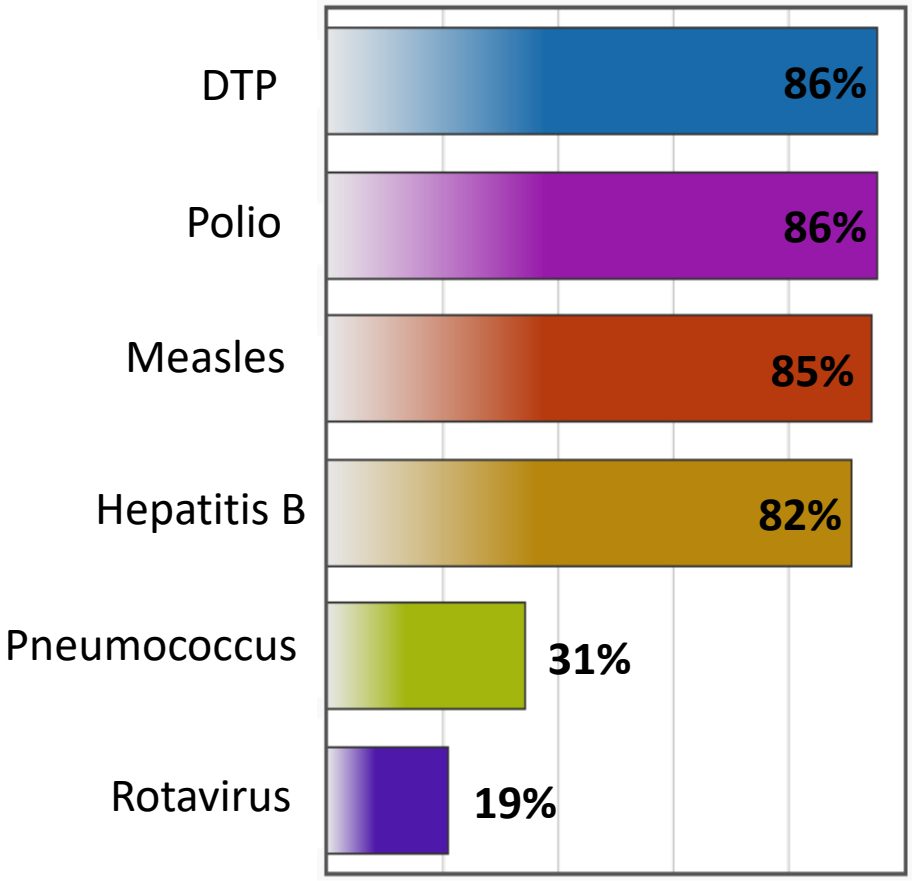
By James Gallagher
Health editor, BBC News website

2 September 2015 | Health

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

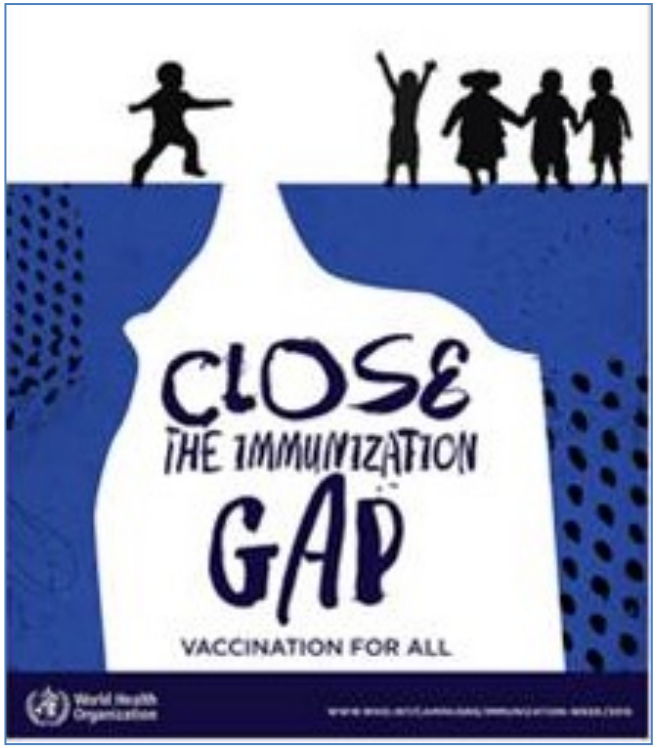
Achievements of the WHO

Global immunization coverage in 2014[57.]:



Goals of the Global Vaccine Action Plan:

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



Thank you for your attention!

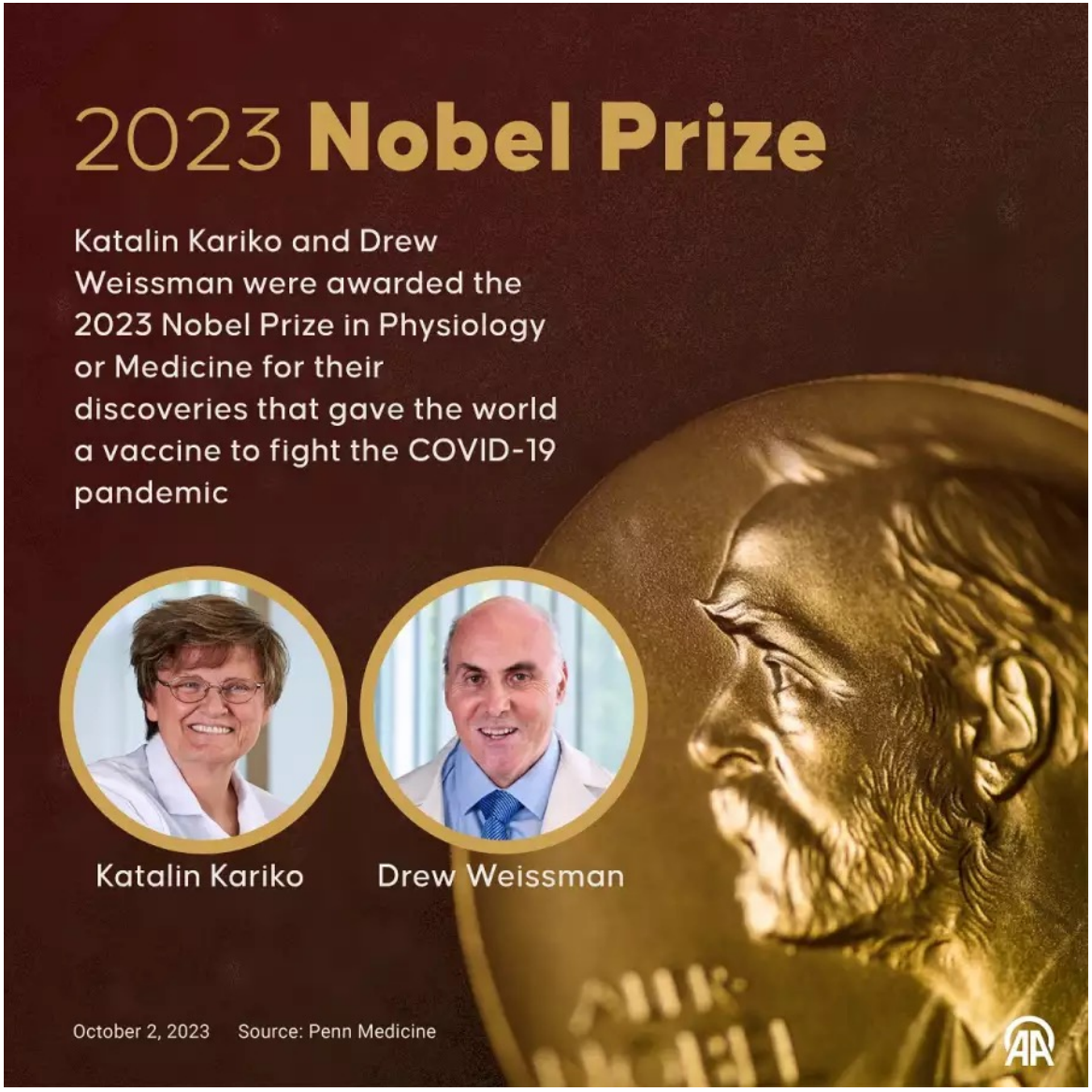
Emil Adolf von Behring

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.]

Thank you for your attention!



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    (PDF-ben, http://www.who.int/immunization/wer7904BCG_Jan04_position_paper.pdf)

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