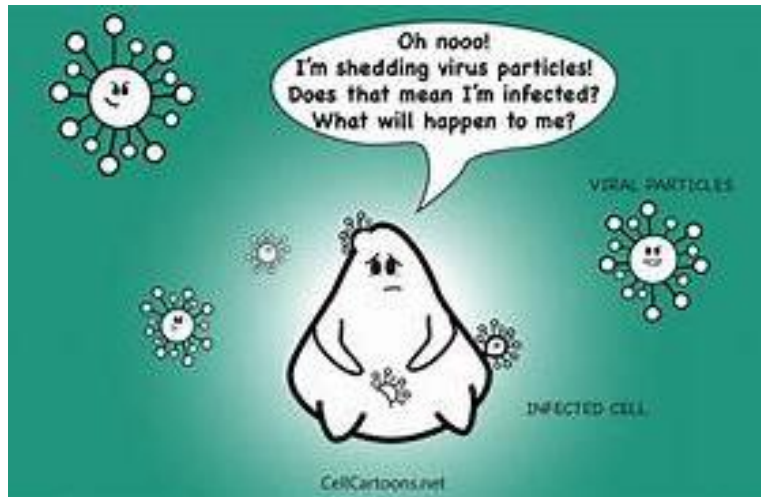


M1 D²HP Development of Drugs and Health Products



Host - Virus interactions

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February 7th 2025

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I- Generalities

II- Host - virus interactions in the Human organism

1- Notion of reservoir

2- Modes of transmission

3- Portals of entry for infection

4- Portals of exit

5- Different types of viral infections

6- Immune response

III- Host - virus interactions in the Cell

1- Disruption of cell function

2- Antiviral defense of the cell

I- Generalities

Generalities and definitions (1)

☞ **Infectious diseases**

= they include all diseases caused by the transmission of a micro-organism or an infectious agent with clinically manifested tissue damage

↳ viruses, bacteria, parasites, fungi, and protozoa

☞ **Infection**

= pathological consequence at the level of a tissue or an organism of the abnormal presence and/or multiplication of a bacterial, viral or fungal micro-organism

☞ **Host**

= a person (or animal) who permits the multiplication of an infectious disease agent under natural conditions

↳ once an agent infects the host, the degree and severity of the infection will depend on the host's ability to fight off the infectious agent

☞ **Pathogen**

= a micro-organism capable of causing disease in a susceptible host

Generalities and definitions (2)

☞ **Virus-host interactions**

☞ they are the viral and host processes that occur during viral infection, which enable both partners to respond to each other

☞ **Contamination**

= entry of the infectious agent into a host organism

☞ **Contagiousness and mode of transmission**

☞ they differ depending on the nature of the infectious agent

☞ The **severity** of infections varies greatly

☞ **benign** and **self-limiting** (cold) to **severe** and **complicated life-threatening forms** (encephalitis)

☞ **Virulence**

☞ term to indicate the degree of pathogenicity of a micro-organism and the severity of the caused disease

☞ **Opportunistic pathogen**

= micro-organism that can become pathogenic in certain situations, particularly when the host's defenses are disturbed

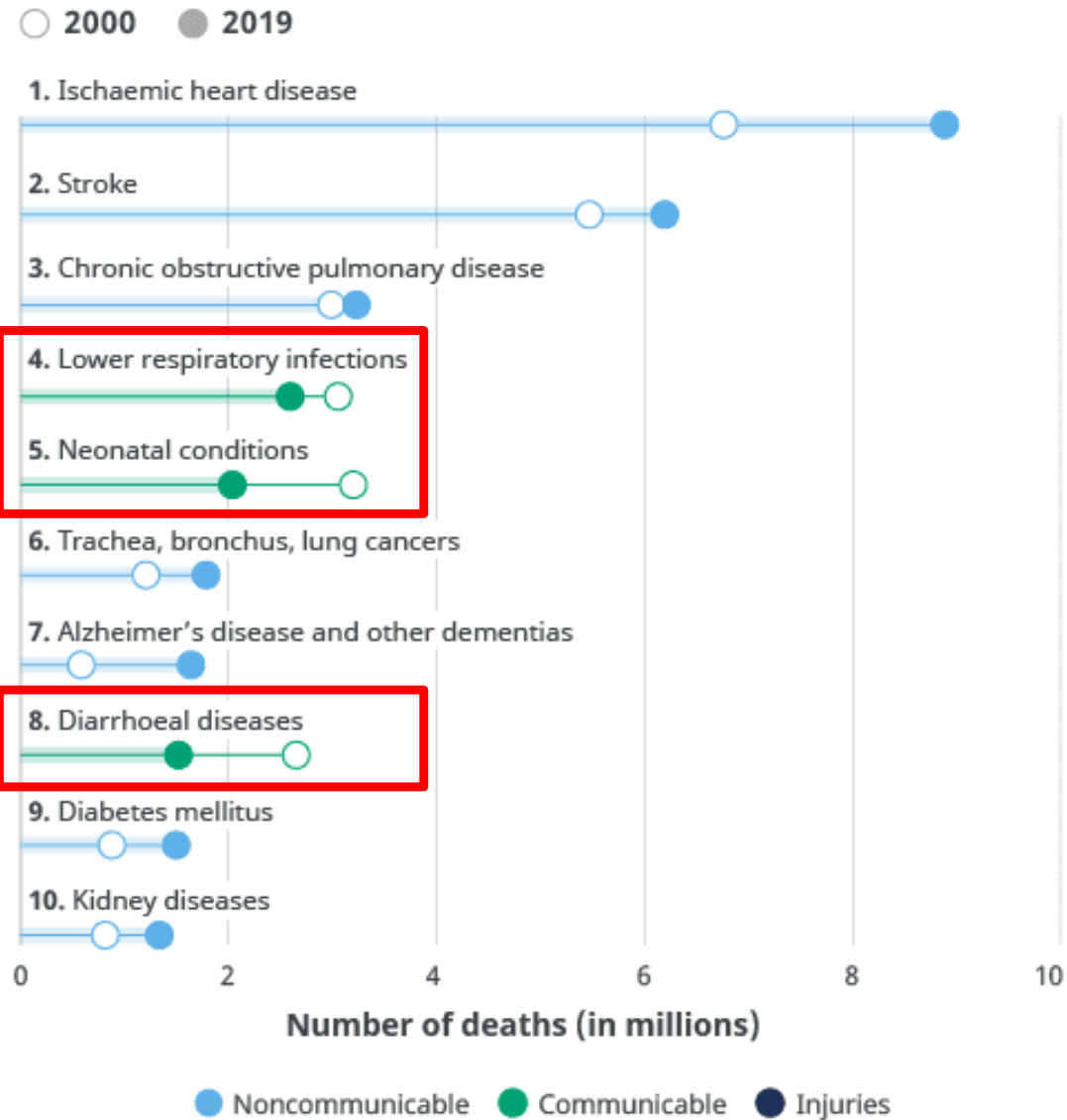
Generalities and definitions (3)

- ☞ One of the leading causes of death worldwide
 - = **17 million deaths per year**
- ☞ Three great plagues
 - = HIV, tuberculosis, malaria, etc.
- ☞ Despite advances in treatment and prevention, there are very few **eradicated** infectious diseases
 - ☞ **smallpox**
- ☞ The situation would even tend to reverse
 - re-emergence of old pathologies related to changes in human behaviour
 - emergence of new pathogens
 - emergence of multi-resistant bacteria with the spectrum of a post-antibiotic era

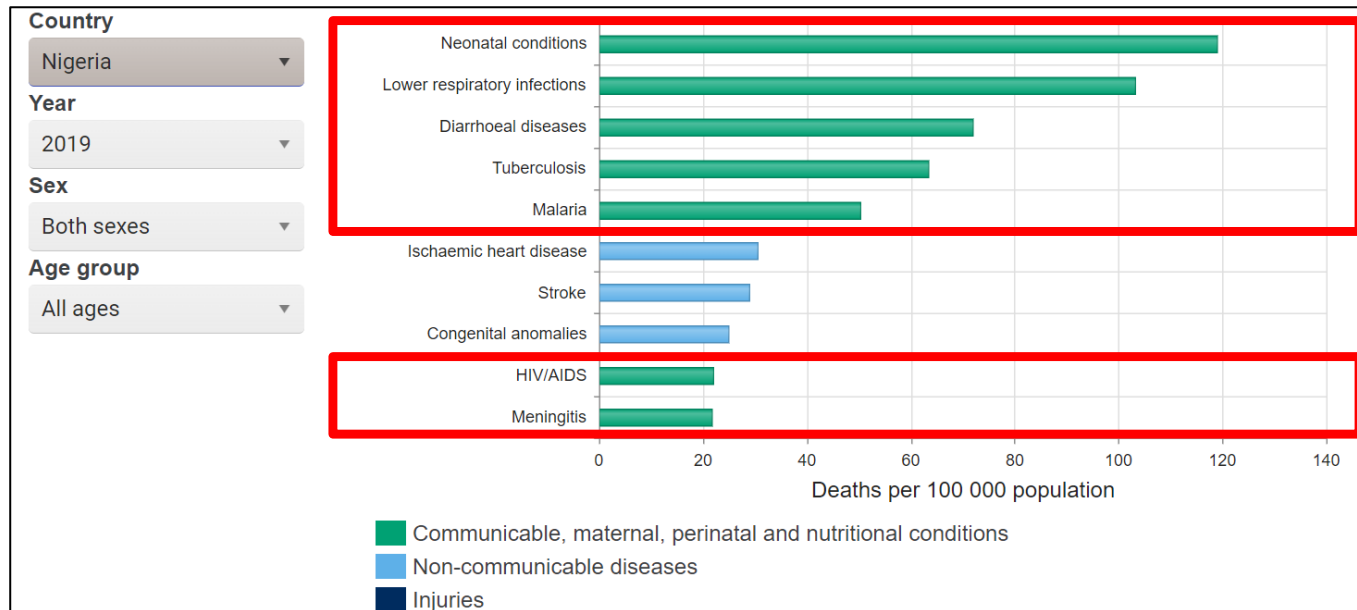
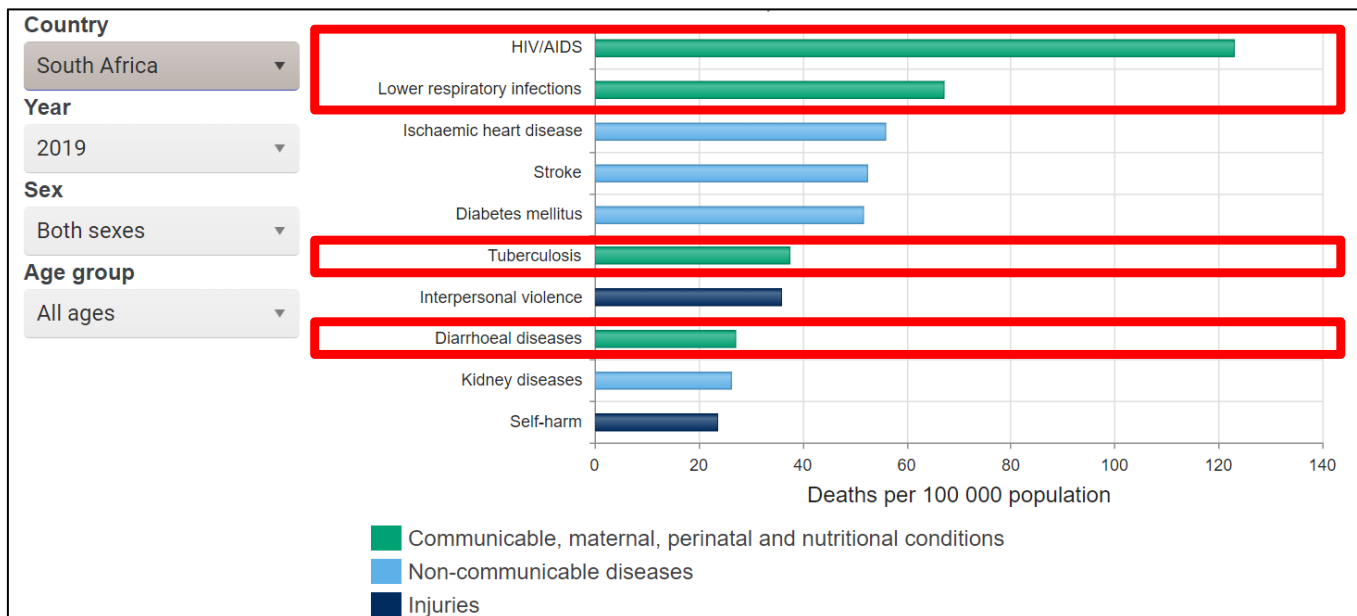
Leading causes of death worldwide



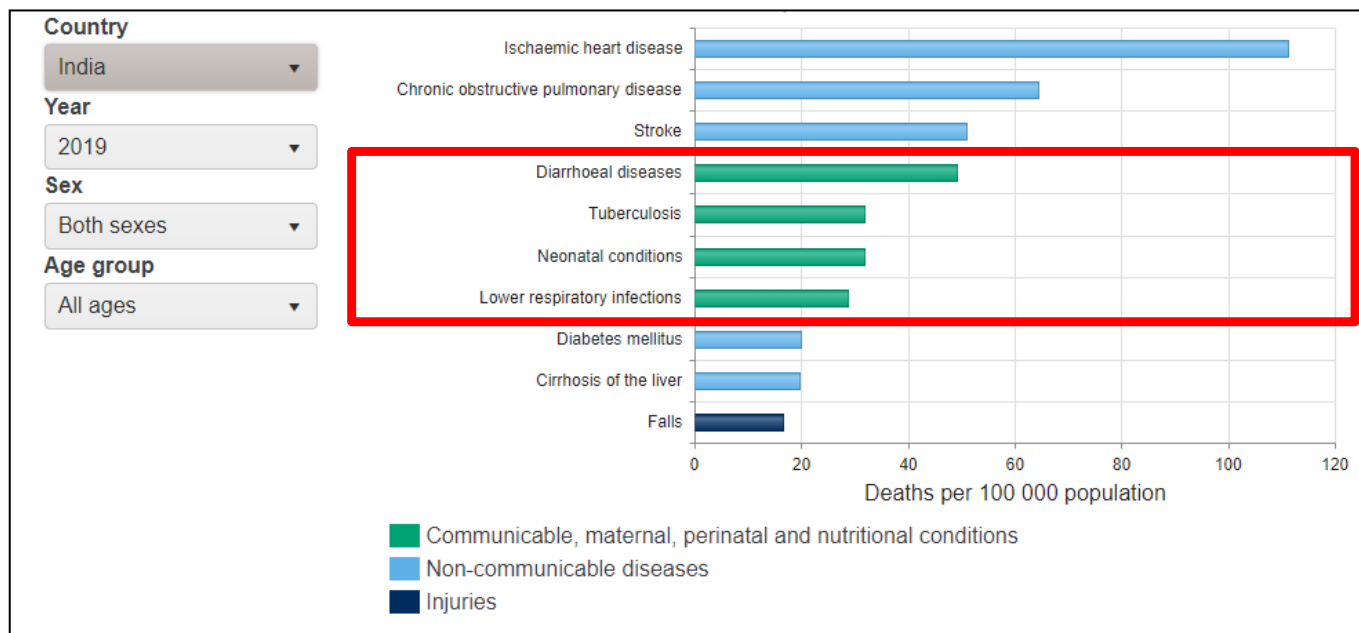
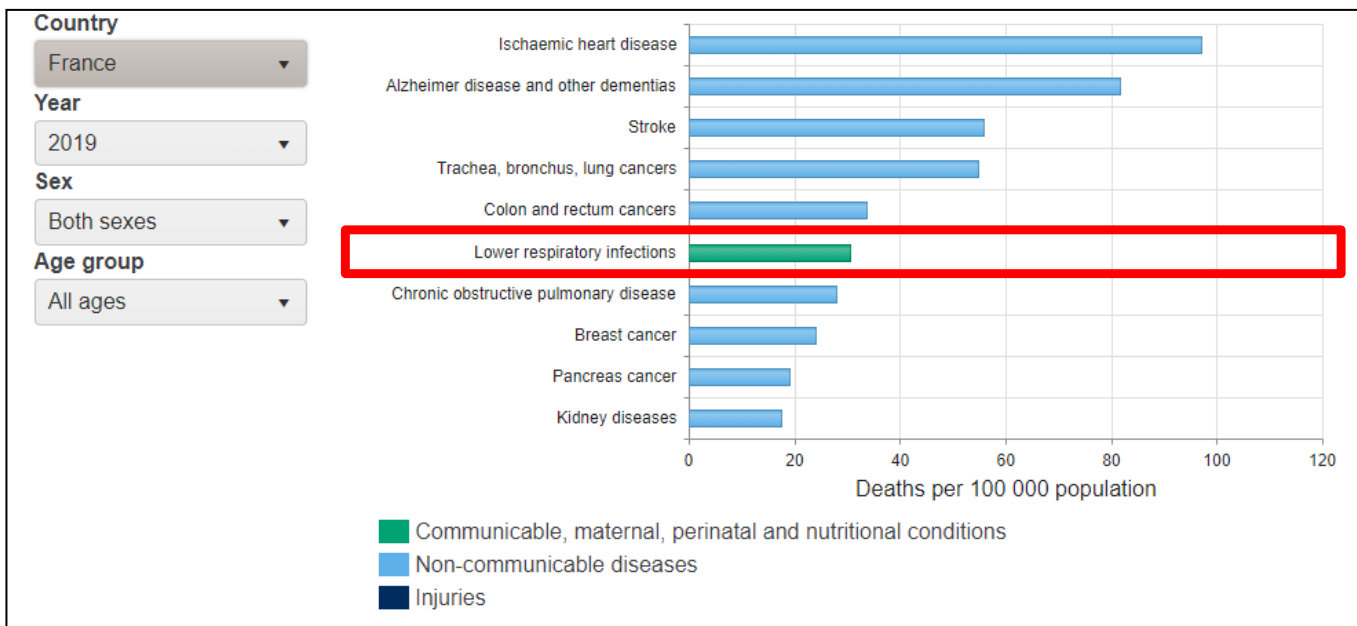
55.4 million deaths worldwide in 2019



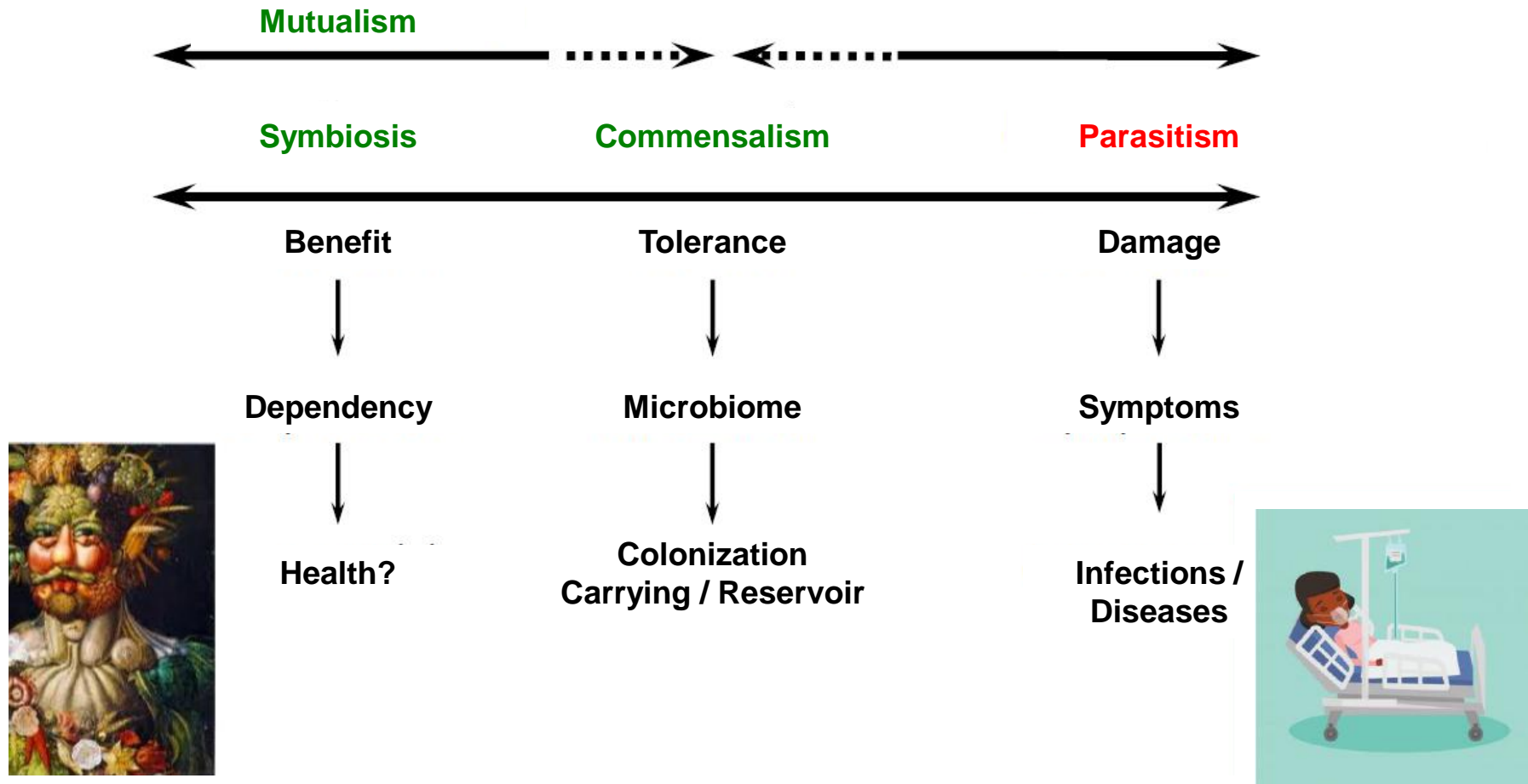
Examples of leading causes of death by country (1)



Examples of leading causes of death by country (2)



Daily life with micro-organisms



II- Host - virus interactions in the Human organism

1- Notion of reservoir

Reservoir

☞ Human

= **main reservoir of viruses for the animal species**

direct contact transmission

indirect contact transmission through the external medium

☞ Intermediate host

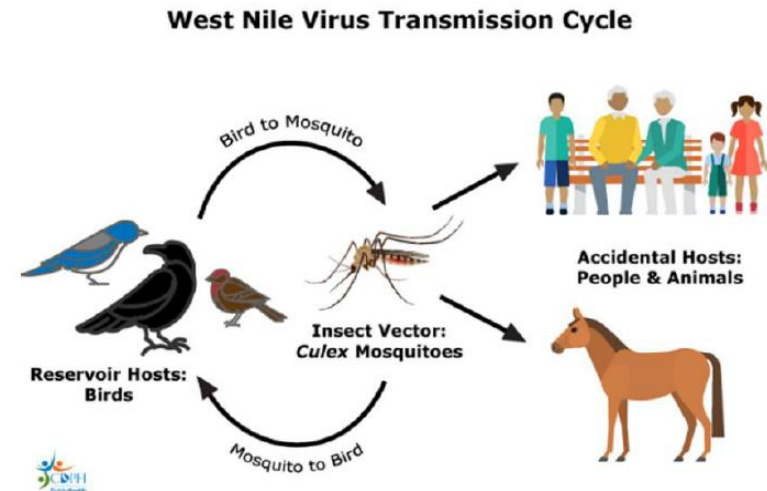
☞ arthropods, mosquitoes, ticks

☞ Animal

☞ Human = accidental host

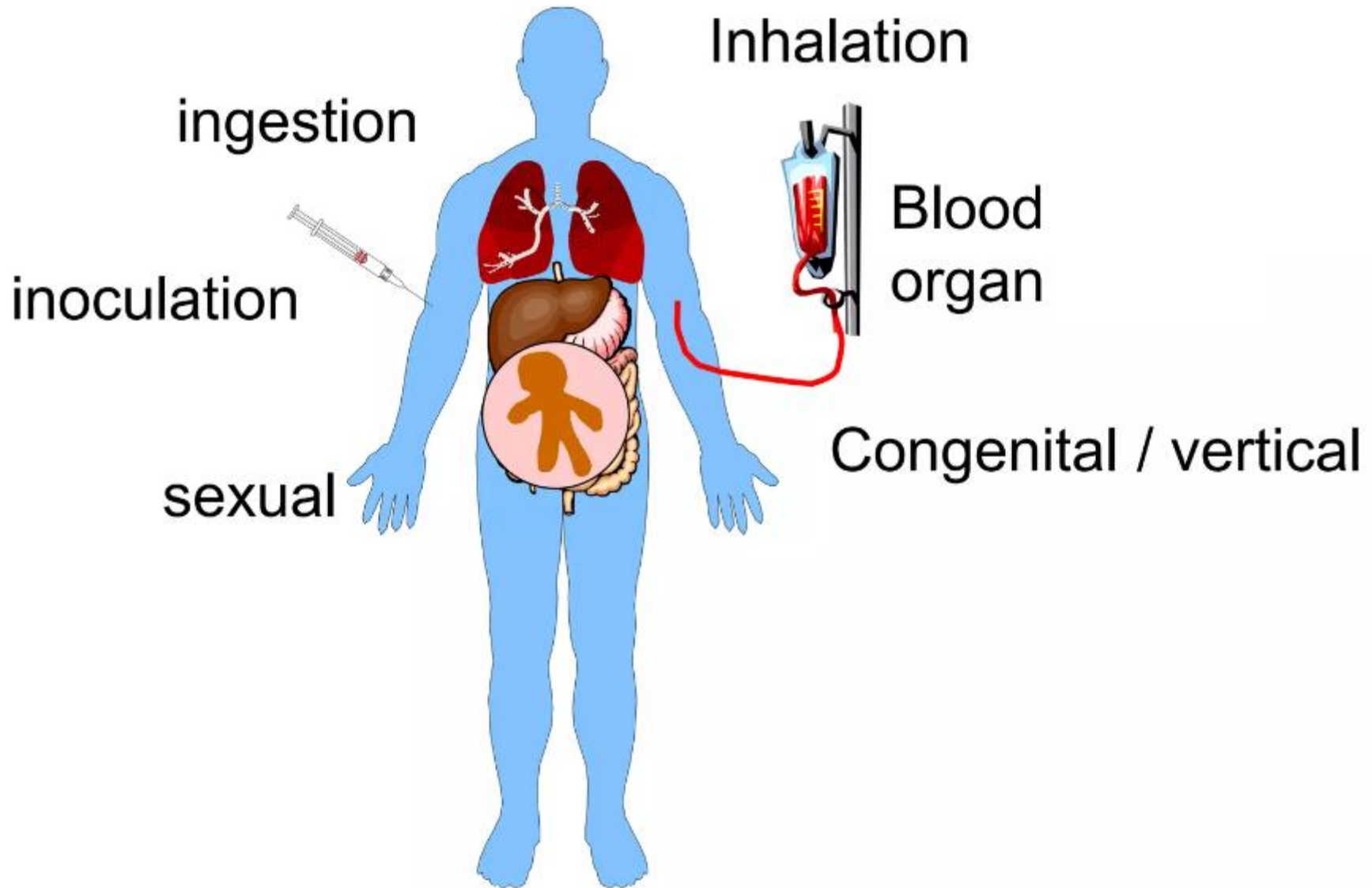
☞ Dead-end hosts

☞ rabies, hantavirus, West-Nile virus



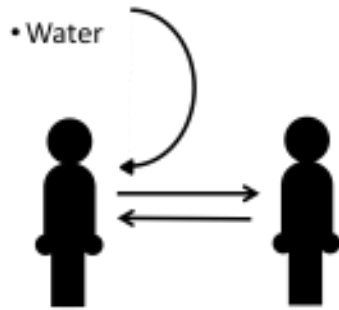
2- Modes of transmission

Modes of transmission (1)



Modes of transmission (2)

Abiotic environmental factors



Animal vectors

Rabies virus, dengue virus, hantavirus



HIV, HBV, HCV

Direct Contact



HIV, Ebola virus, HPV, HSV-1



Indirect Contact



Flu virus, norovirus

Droplets



Ebola virus, flu virus



Airborne



Flu virus, SARS-CoV-2

Fecal - Oral



HAV, HEV, rotavirus



Pregnancy, delivery and breastfeeding



HIV, HBV, CMV, HSV-1, rubella virus

Modes of transmission (3)

☞ Iatrogenic transmission

= during medical procedures

↳ syringes, blood-derived drugs, invasive explorations, transplants, etc.

= HIV, HBV, HCV, CMV



☞ Transmission by an arthropod vector

= by mosquitoes, ticks, etc.

= Zika, Dengue, Yellow fever



Modes of transmission (4)

LONDON
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& TROPICAL
MEDICINE



How zoonotic diseases are transmitted

Vector-borne disease

Vectors
transmitting infected agents
from animals

Direct contact with animals

Bites from an infected animal

Airborne
Transfer of viruses

Close proximity to animals

Faecal oral transfer/
animal body fluid
in cuts

Food-borne

Consuming infected
meat or milk



Source: WHO
Credit: Rebecca Robinson/LSHTM

3- Portals of entry for infection

Portals of entry for infection (1)

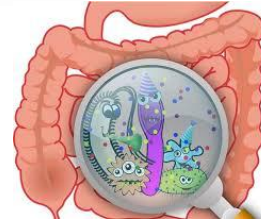
☞ Respiratory airway

☞ flu virus, enterovirus



☞ Alimentary tract

☞ norovirus, rotavirus, HAV



☞ Conjunctiva

☞ adenovirus



☞ By inoculation

- insect bites

☞ dengue virus, Zika virus



- bites

☞ rabies virus

- intravenous injection (IV drug addiction)

☞ HIV, HBV, HCV



☞ Cutaneous route

- contact without injury

☞ HPV, HSV-1

- contact with a lesion

☞ HIV, HBV

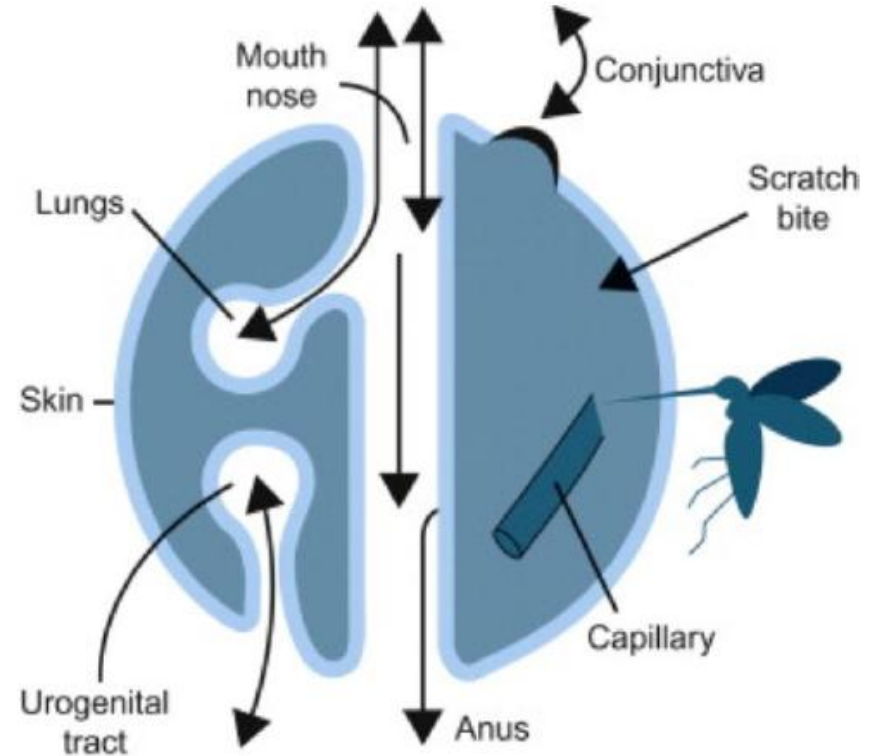
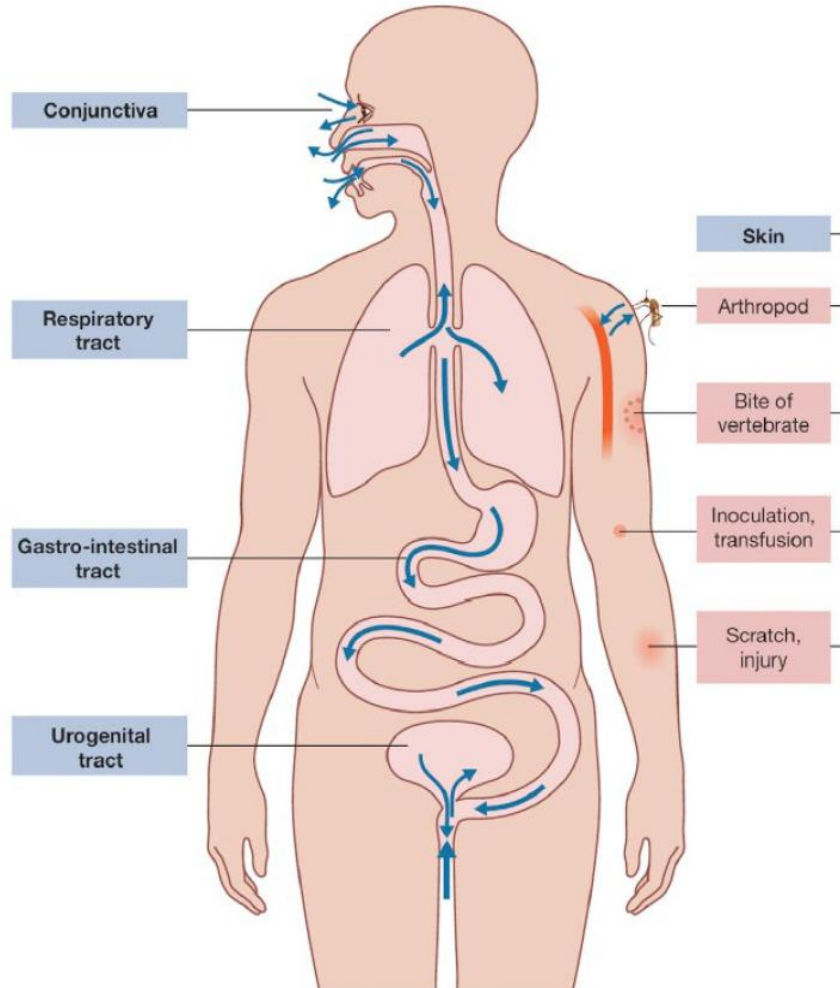


☞ Urogenital tract

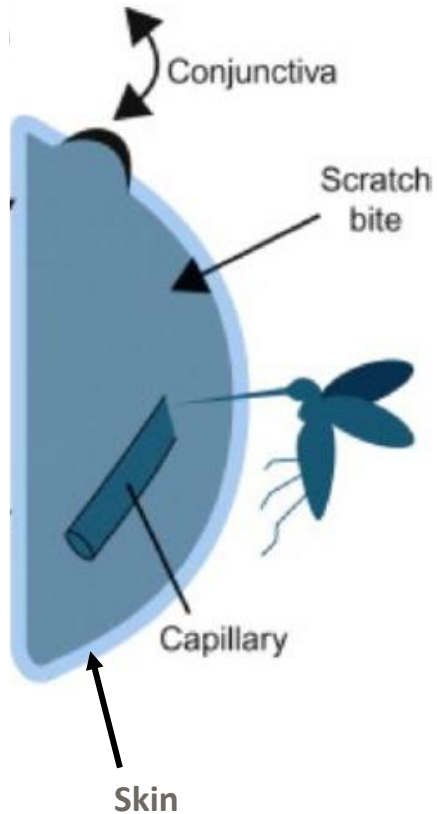
☞ HPV, HSV-2, HIV

Portals of entry for infection (2)

☞ Surfaces of the body in relation to the entry and shedding of viruses



Skin and conjunctiva



☞ Skin

- Arthropod bites

↳ **arbovirus**: dengue virus, yellow fever virus

- Minor lesions

⇒ multiplication in the cells of the dermis and epidermis

↳ HPV, poxvirus, herpesvirus

- Major lesions

- Animal bites

↳ rabies virus

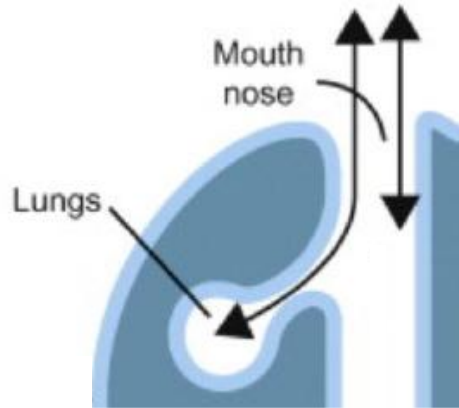
- lesions in contact with soiled materials

↳ HBV, HCV, HIV

☞ Conjunctiva

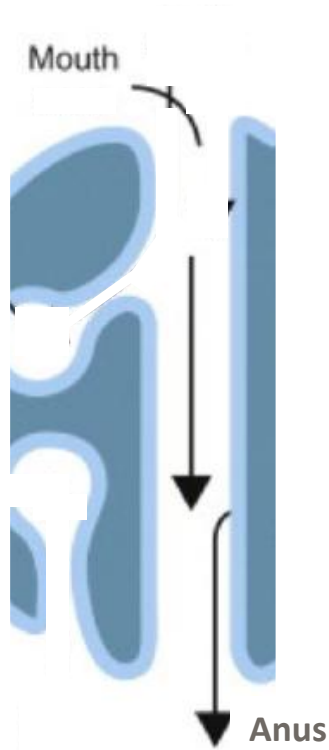
↳ Adenovirus, HSV-1

Respiratory tract



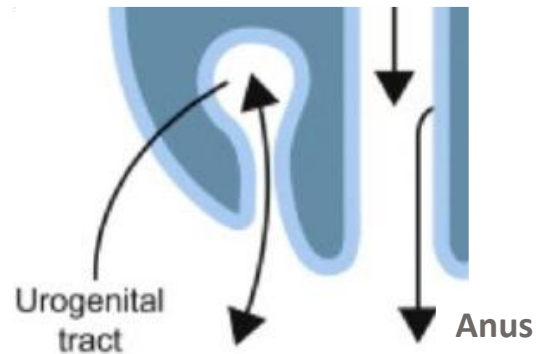
- ☞ **Aerosol production by coughing and sneezing**
- ☞ **Local respiratory tract infections**
 - ☞ orthomyxovirus, paramyxovirus, rhinovirus
- ☞ **Generalized infections with respiratory starting point**
 - ☞ measles, rubella, mumps

Alimentary tract



- ☞ **Fecal-oral transmission through water and food contaminated with viruses released into the stool**
- ☞ **Resistance of these viruses to acidic pH, proteases and bile salts**
- ☞ **Localized infections**
 - ↳ rotavirus, enterovirus
- ☞ **Generalized infections**
 - ↳ poliovirus

Urogenital tract



- ☞ **Sexually transmitted infections (STI)**
- ☞ **Localized infections**
 - ☞ Papillomavirus ⇒ condylomas (genital warts)
 - ☞ HSV-2 ⇒ genital herpes
 - ☞ Adenovirus ⇒ cystitis
- ☞ **Generalized infections**
 - ☞ HIV, HBV, CMV

4- Portals of exit

Release of the virus from the body

☞ Saliva

↳ EBV, CMV, HSV-1

☞ Respiratory secretions

↳ Flu viruses, measles, VZV

☞ Stool

↳ rotavirus, enterovirus, adenovirus, poliovirus

☞ Urine

↳ mumps, CMV, measles

☞ Skin rash

↳ HSV-1, VZV

☞ Blood

↳ HIV, HBV, HCV, CMV

☞ Maternal milk

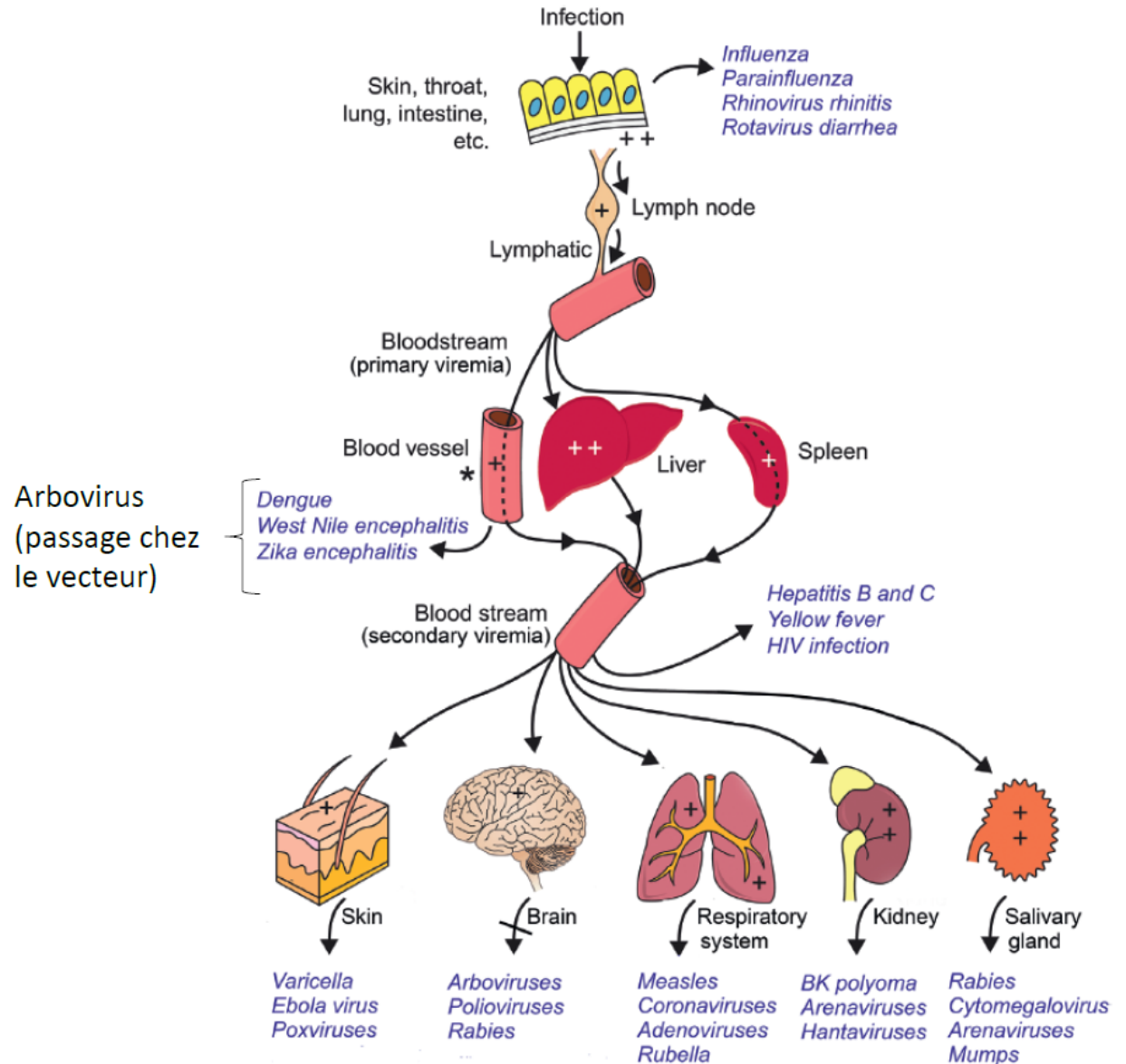
↳ HIV, CMV

☞ Genital secretions

↳ HIV, HBV, HSV-2

5- Different types of viral infections

Pathophysiology of viral infections (1)



+ and ++ sites of replication
Blue route of shedding

Pathophysiology of viral infections (2)

- ☞ The viral infection starts at a specific entry door to the body
- ☞ Primary replication of the virus at a site near the entry site
 - = **localized / local infection**
- ☞ Passage through the lymphatic system, local lymph nodes and blood dissemination
 - = **viremia**
- ☞ Reaching the target organ where multiplication leads to disease
 - = **generalized / systemic infection**
- ☞ Viral infection is the consequence of interaction between viral factors and host response
- ☞ The balance between these elements defines the duration of infection
 - ↳ **acute or persistent infections**

Pathophysiology of viral infections (3)

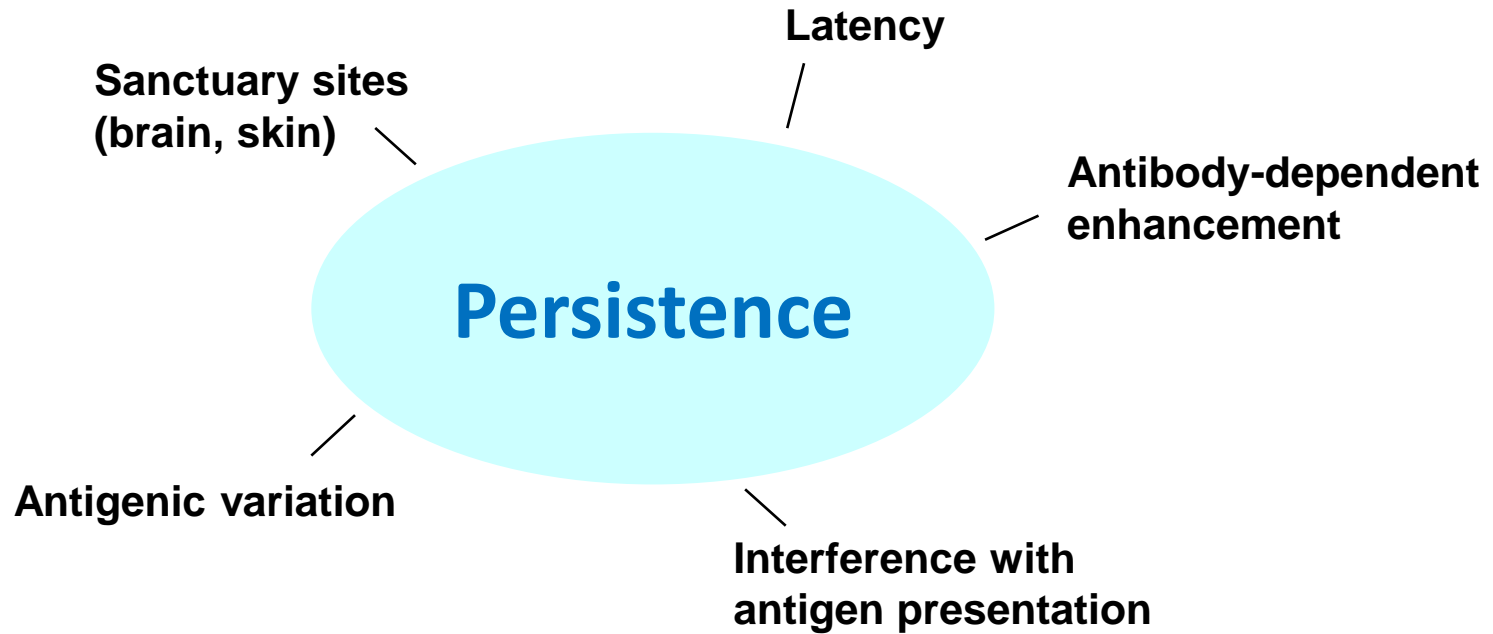
**Acute
transient**



persistent

1- Inadequate immune response

2- Strategies



Viral factors

- ☞ **Mode of release into the organism**
- ☞ **Cell tropism**
- ☞ **Number of infected cells**
- ☞ **Direct or indirect cytopathic effect**
- ☞ **Virulence proteins**
 - ☞ factors involved in viral replication
- ☞ **Escape to the host's defenses**
 - ☞ inaccessible replication sites

Factors related to the host = risk factors



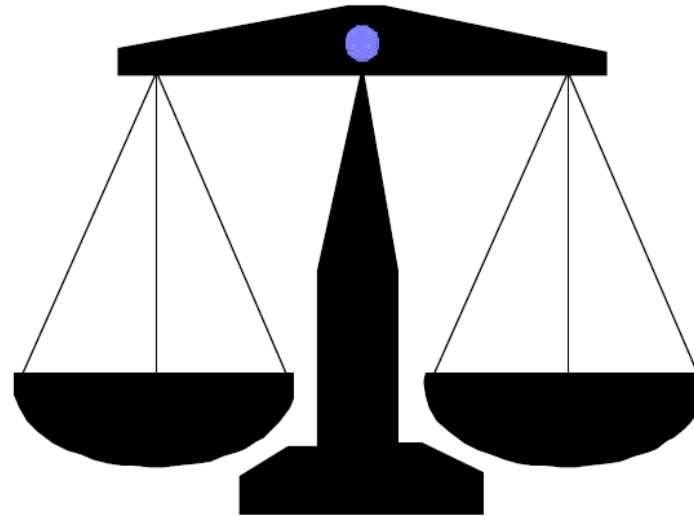
- ☞ **Extreme ages of life**
 - ↳ newborns, infants and the elderly
- ☞ **Pregnancy**
 - ↳ possible viral reactivations in pregnant women
- ☞ **Hormonal status**
 - ↳ neurological complications of mumps more common in boys
- ☞ **Innate or acquired immune deficiency**
 - ↳ immune system diseases, immunosuppressive therapies, chemotherapy
- ☞ **Undernutrition and/or malnutrition**
 - ↳ impact on immunity
- ☞ **Chronic pathologies**
 - ↳ diabetes, liver cirrhosis, mucoviscidosis, etc.
- ☞ **Genetic factors**
 - ↳ example of CCR5 co-receptor mutation for HIV entry
- ☞ **Travel to endemic areas**
- ☞ **Contact with animals**

Host - virus interactions

Host factors

Fragility, comorbidities,
impaired defense
mechanisms, nutrition,
stress, medication

Risk factors



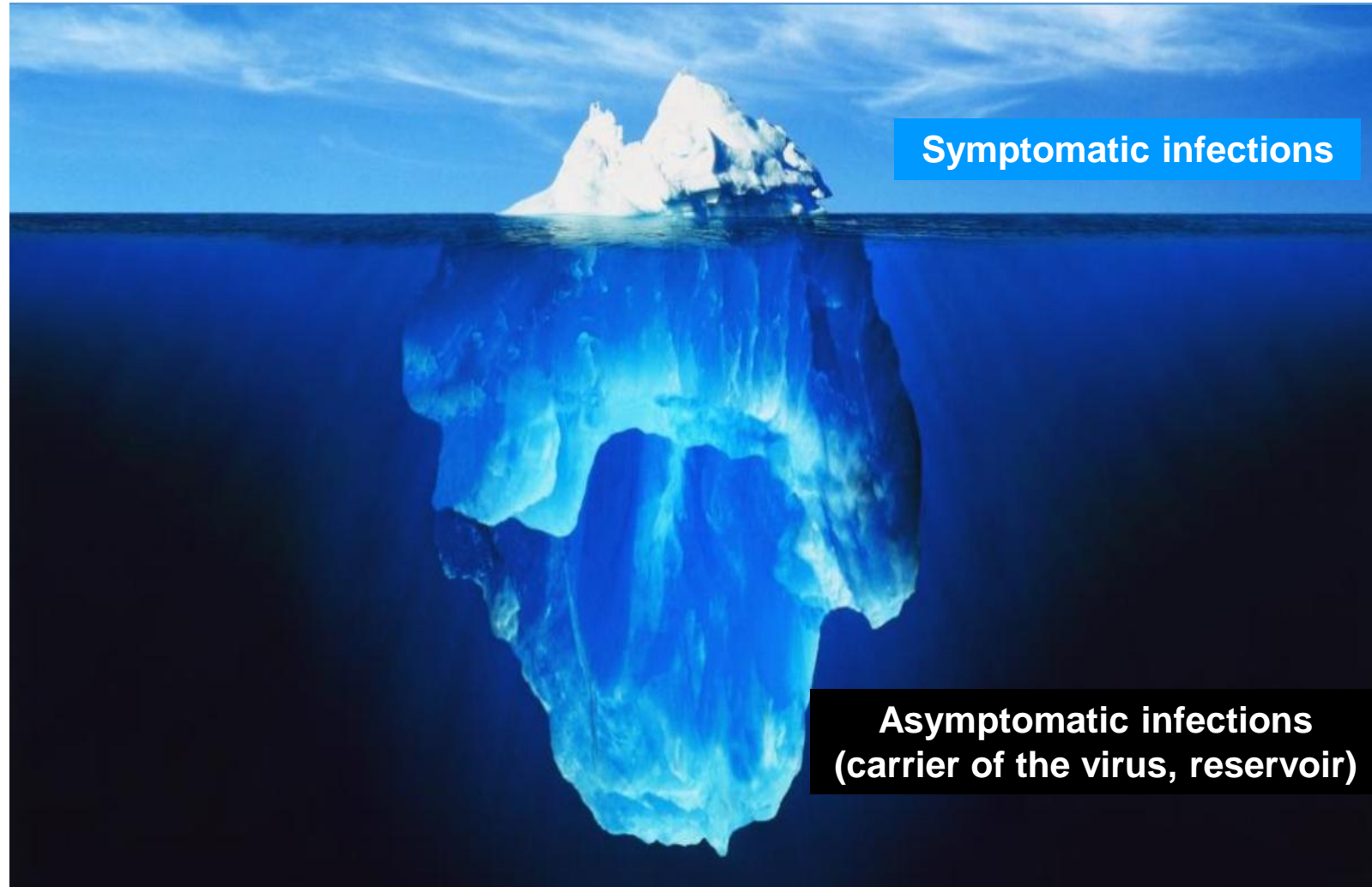
Virus factors

Ability to multiply and
spread, escape to the
host's defenses

**Virulence factors and
pathogenicity**

**If imbalance in favour of
the virus ⇒ disease**

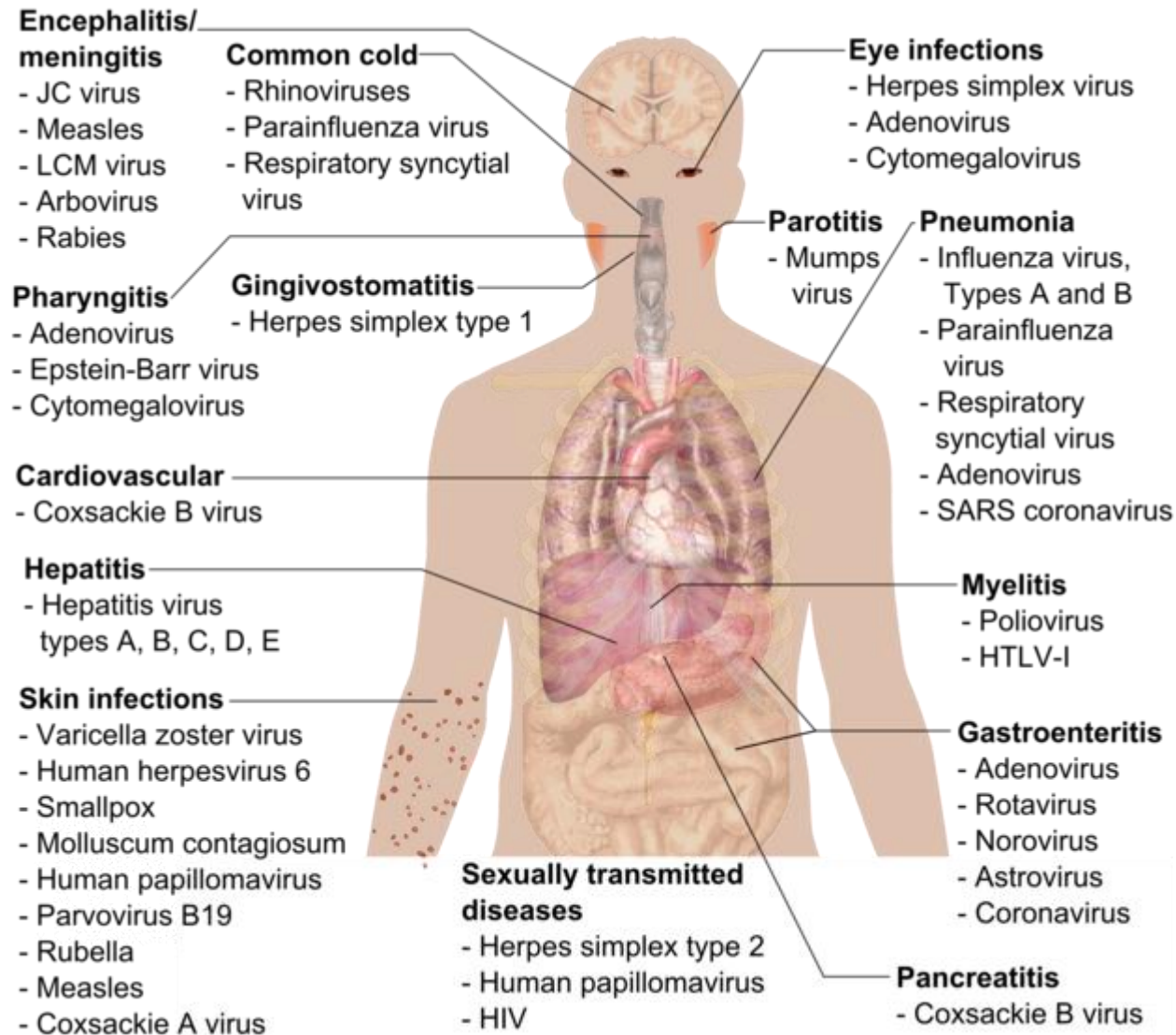
Overview of the viral infections (1)



Symptomatic infections

**Asymptomatic infections
(carrier of the virus, reservoir)**

Overview of the viral infections (2)



Localized / local infections

☞ Infection that remains localized to epithelial cells at the primary site of infection

↳ respiratory infections: flu virus, rhinovirus, RSV (respiratory syncytial virus)

↳ gastroenteritis: rotavirus, norovirus, calicivirus

☞ Some factors are involved in localization

1- Temperature sensitivity of the virus

In the lung, 33°C after nasal passage, 37°C in the pulmonary alveoli

Rhinovirus at 33°C ⇒ upper respiratory tract infection

Flu virus at 37°C ⇒ lower respiratory tract infection

2- Lack of permissiveness of cells

Only permissiveness of epithelial cells

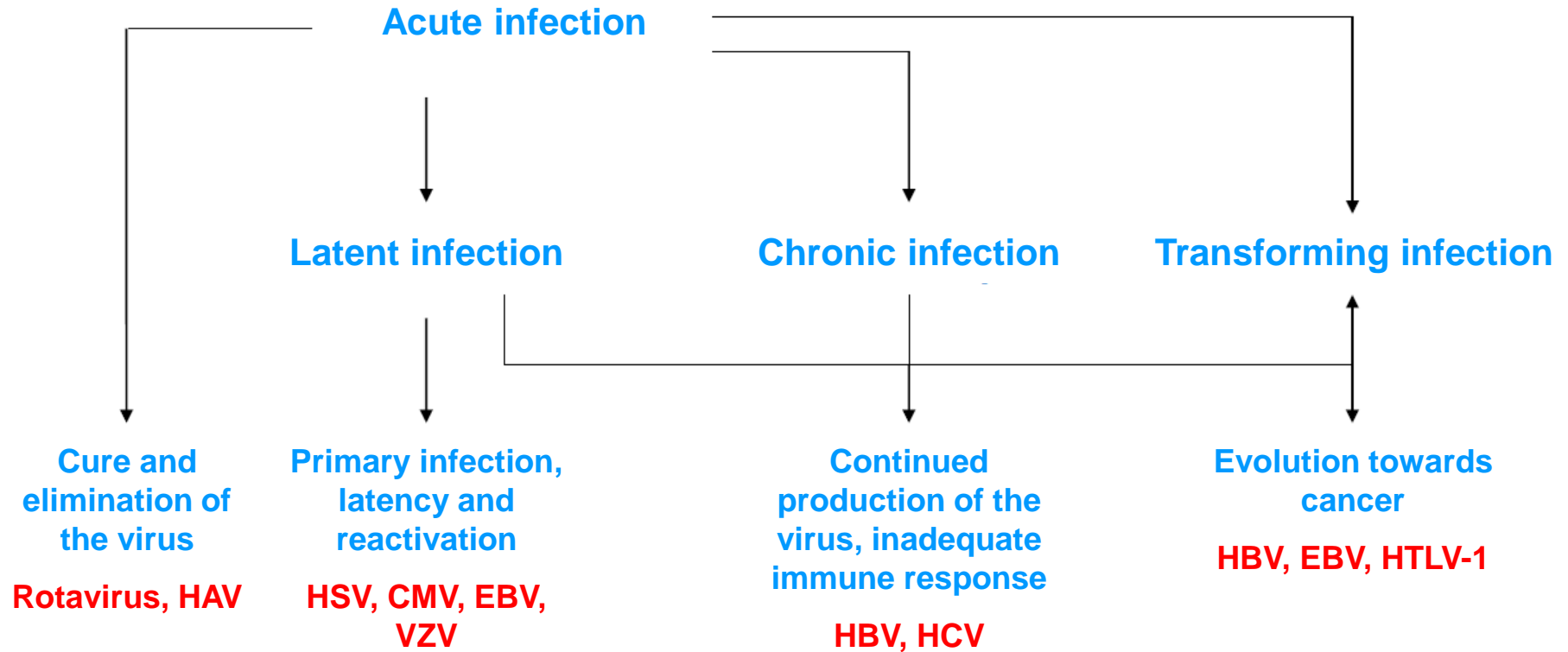
3- Polarization of epithelial cells

Mode of release by the apical pole or the basal pole

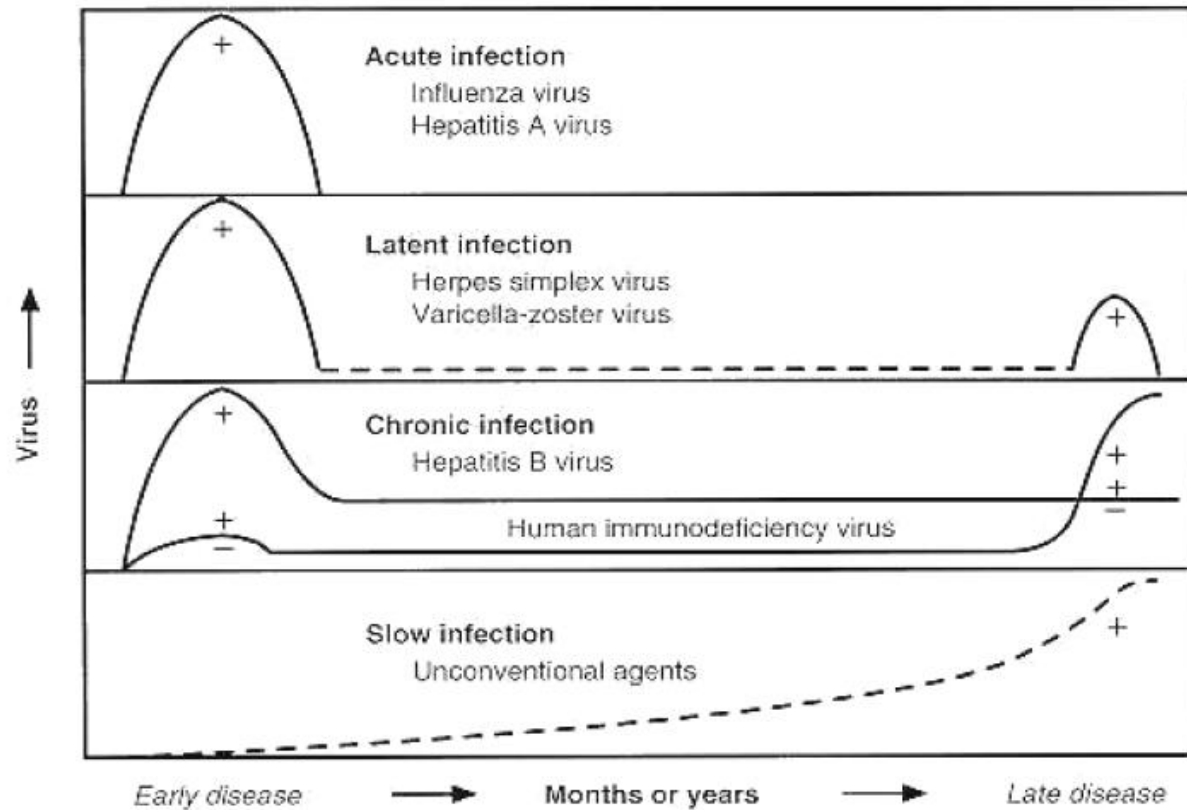
Generalized / systemic infections

- ☞ After primary infection, passage into the lymphatic system, the local lymph nodes, and into the bloodstream
- ☞ Blood distribution in the body ⇒ **viremia**
 - ↳ the fastest and most efficient route
- ☞ Reaching the target organ in which viral multiplication causes the disease

Different types of viral infections (1)



Different types of viral infections (2)



Acute infection

- ☞ **Virus replication**
- ☞ **Elimination of the virus by the immune response**
- ☞ **Symptomatic or asymptomatic**

Persistent infection

- ☞ **Maintenance of the viral genome in the cell**
- ☞ **Sufficient number of surviving cells**
 - ☞ low cytopathic effect
 - ☞ no disruption of transcription or translation of genes necessary for the survival of infected cells
- ☞ **No clearance of the virus by the immune system**
 - invisible to the immune system
 - ☞ sites, no viral antigens, replication in immune cells
 - escape to immune response
 - ☞ interference with antigen presentation, expression of MHC molecules
- ☞ **Two main categories**
 - **Latent** infection
 - **Chronic** infection

Latent infection

- ☞ **Essentially for DNA viruses**

 - ↳ greater chemical stability than RNA in the cell

- ☞ **Examples**

 - *Orthoherpesviridae*: HSV-1, HSV-2, VZV, EBV, CMV

- ☞ **No viral production during latency**

- ☞ **Possible transmission of the virus during reactivations**

- ☞ **Latency in sites that are characteristic of the virus**

 - quiescent cells: neurons for HSV and VZV

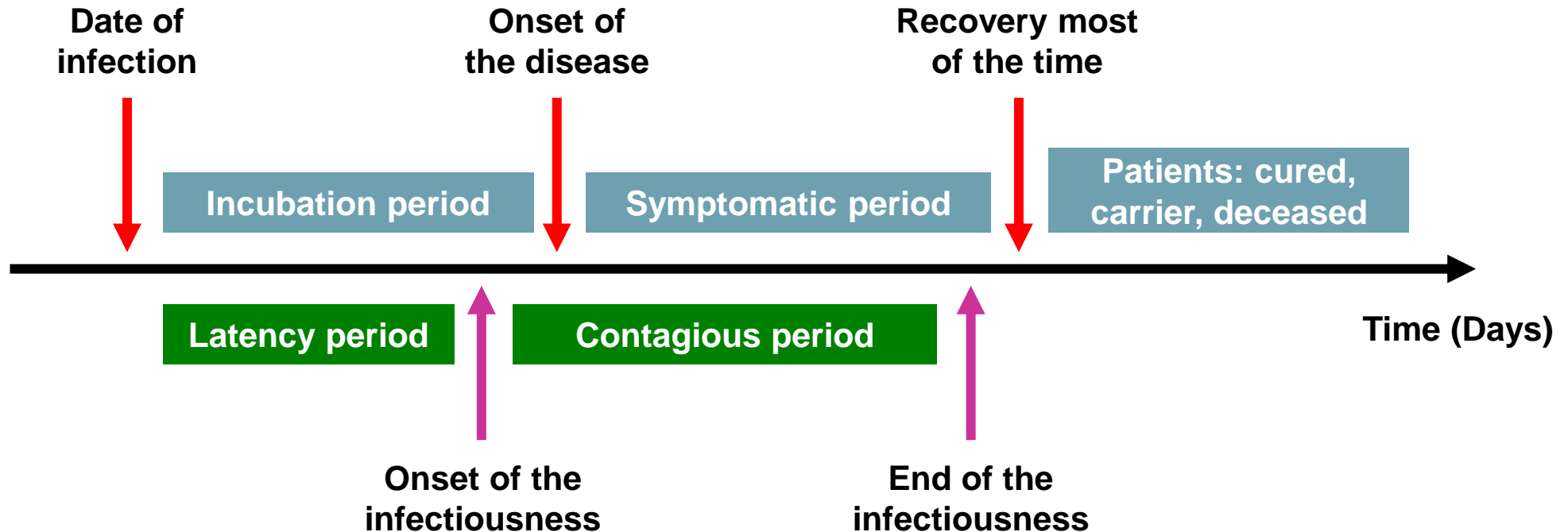
 - cells in division: B lymphocytes for EBV

Chronic infection

- ☞ **Continuous production of viral particles**
- ☞ **Viral transmission for very long periods**
- ☞ **Viral genome maintained in the host**
- ☞ **Persistence sites**
 - organs: liver (chronic hepatitis)
 - heterogeneous: lymph nodes, blood (HIV)
- ☞ **Inadequate and/or inappropriate immune response ⇒ persistence**

Host disease and infectiousness dynamics

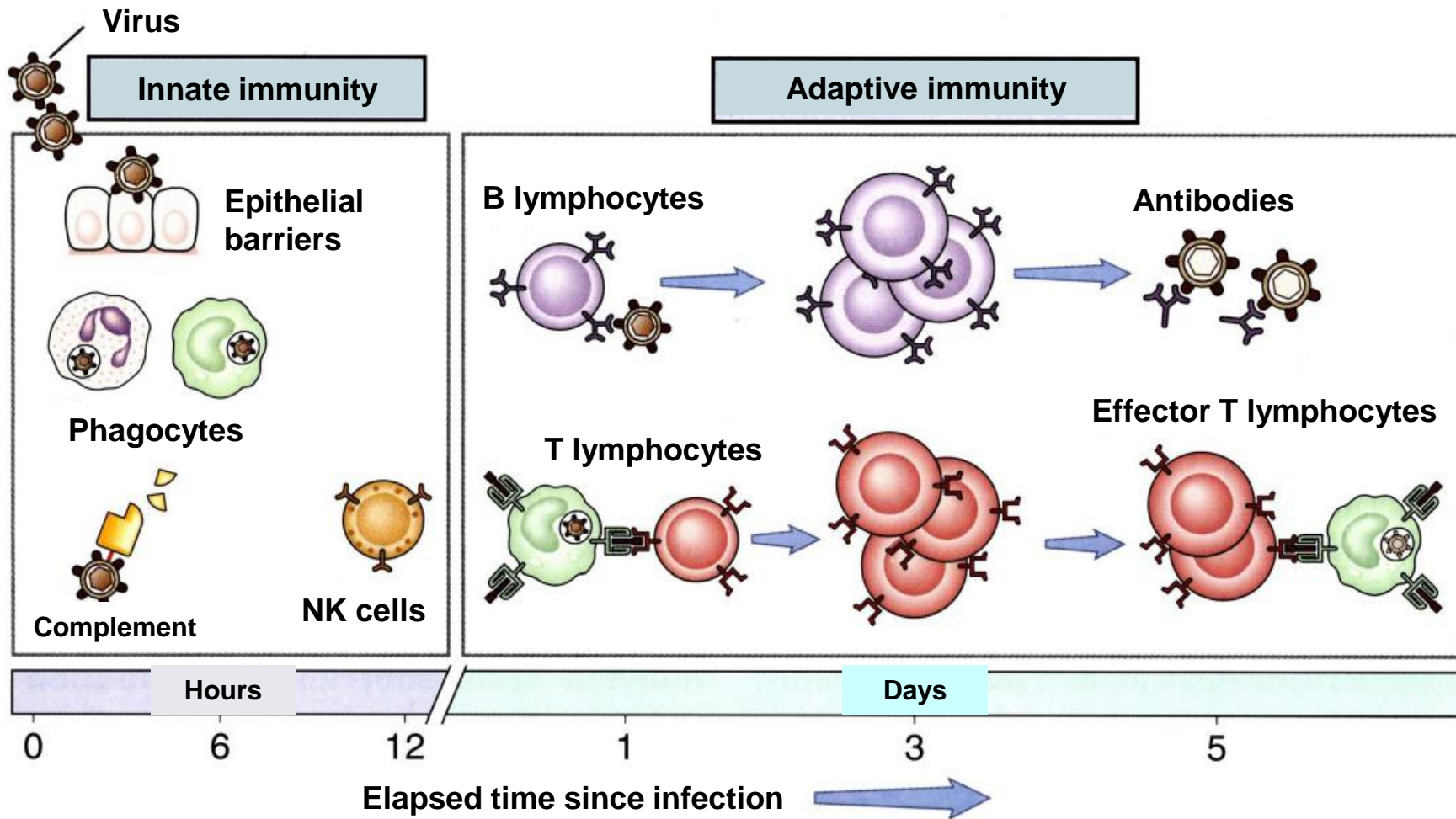
Disease dynamics



Infectiousness dynamics

6- Immune response

Several lines of defense (1)



Several lines of defense (2)



Immediate action

Orientation of the immune response

Innate immunity

Activation of the adaptive response

Limitation of the damage



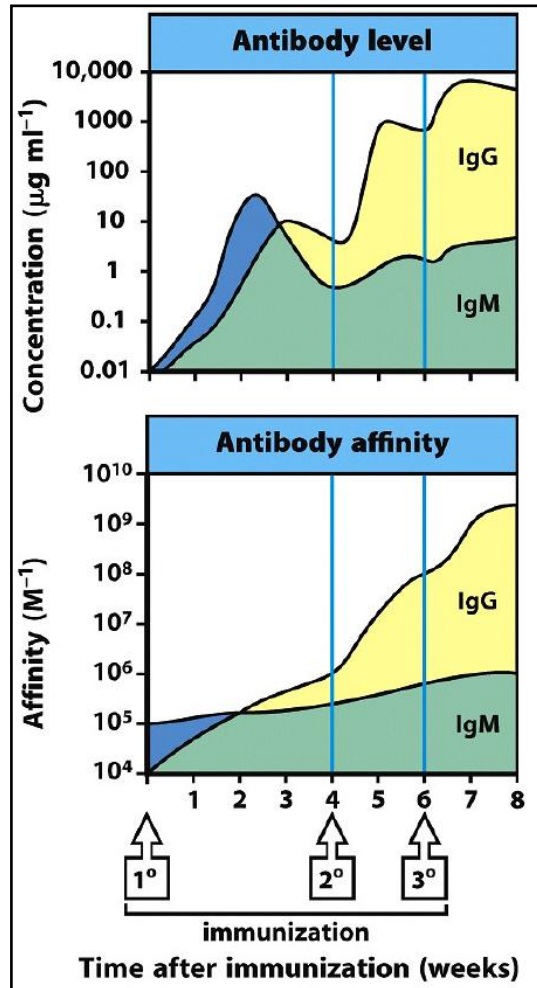
Ability to adapt

Adaptive immunity

Setting up a memory

Dynamics of the antibody response

☞ Several contacts with the virus / Successive immunisations



⇒ **Primary response**

IgM > IgG

Weak affinity

Low level of somatic hypermutation

⇒ **Secondary response**

Isotypes IgG and IgA

Strong affinity

High level of somatic hypermutation

Memory

III- Host - virus interactions in the Cell

Cell - virus interactions

👉 **Virus** = mandatory parasites

- they depend on the cell for the replication of their genome and the production of their components (proteins, envelopes, etc.)
- they divert the functioning of the cell to their benefit
- they promote the survival of the host cell

👉 **Cell** and its antiviral defenses

- innate intracellular mechanisms
 - ↳ RNA interference, apoptosis, autophagy
- soluble immune system factors: interferons
 - ↳ stop translation
- adaptative mechanisms

1- Disruption of cell function

Use of cellular machinery

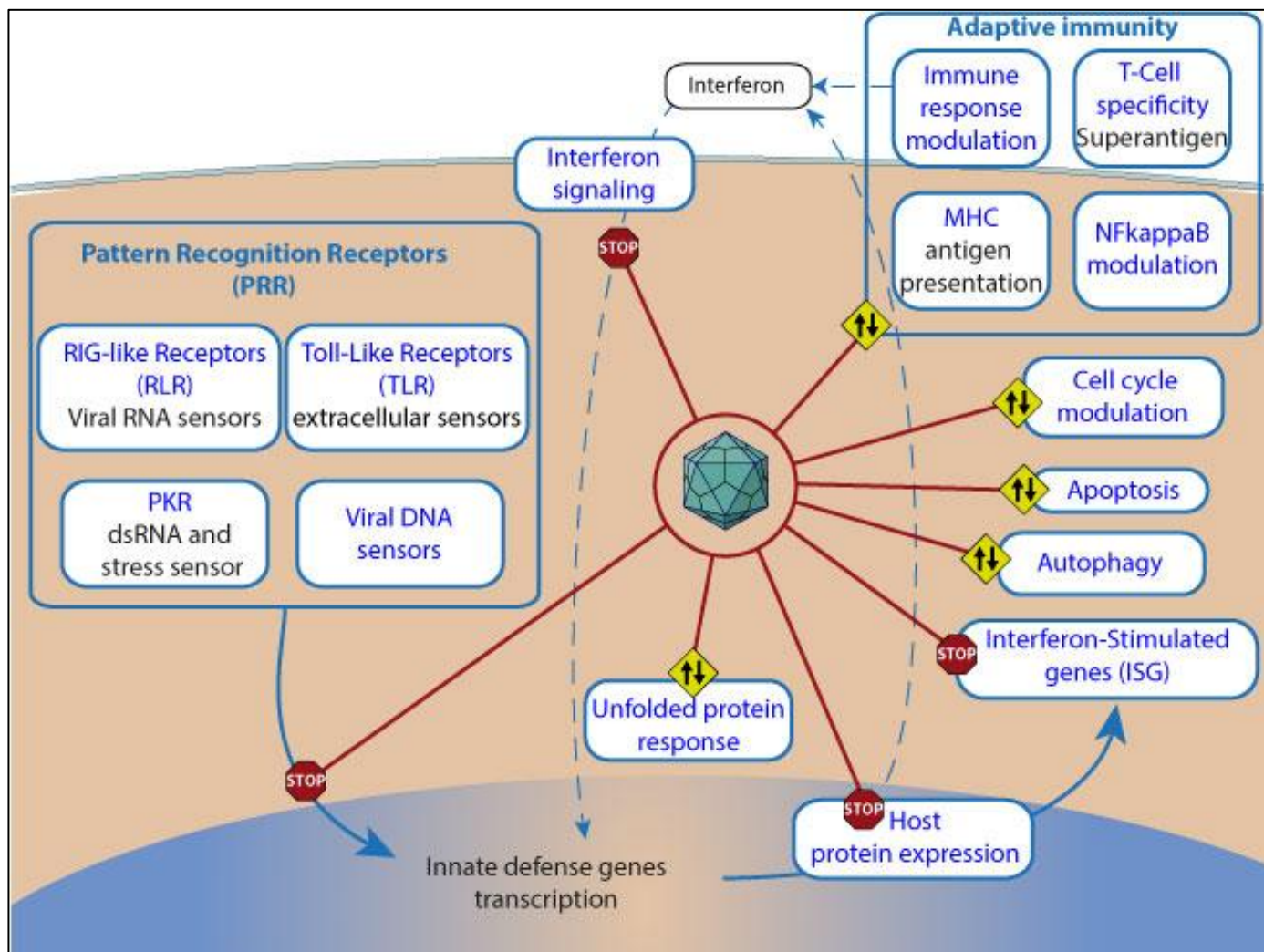
- ☞ **Lack of enzymes and associated systems to conduct most metabolic and biosynthetic reactions**
 - ⇒ so viruses depend on the cell for the majority of their functions (energy, metabolites, machinery...)
 - ☞ although most viruses have polymerases and enzymes that modify nucleic acids as well as various enzymes
- ☞ **Viruses have mechanisms for recruiting, adapting, modifying or usurping cellular machinery**
- ☞ **A large part of the viral genome encodes regulatory molecules**
- ☞ **Examples**
 - direct use of cell function and components
 - ☞ replication and transcription of HPV DNA identical to cellular DNA
 - turning the cellular machinery against itself
 - ☞ induction of apoptosis by rotavirus

Survival of the virus in the host cell

- ☞ **Role of viral non-structural proteins**
- ☞ **Virus replication**
 - ↳ RNA-dependent RNA polymerase
- ☞ **Cell cycle blocking**
 - ↳ Vpr (HIV), T antigen (SV40)
- ☞ **Immortalization of cells**
 - ↳ E6 and E7 proteins (HPV)
- ☞ **Modulation of cell gene expression**
 - ↳ HBx protein (HBV) which is a transactivator protein
- ☞ **Blockage of the splicing of the cell mRNA**
 - ↳ ICP27 protein (HSV-1)

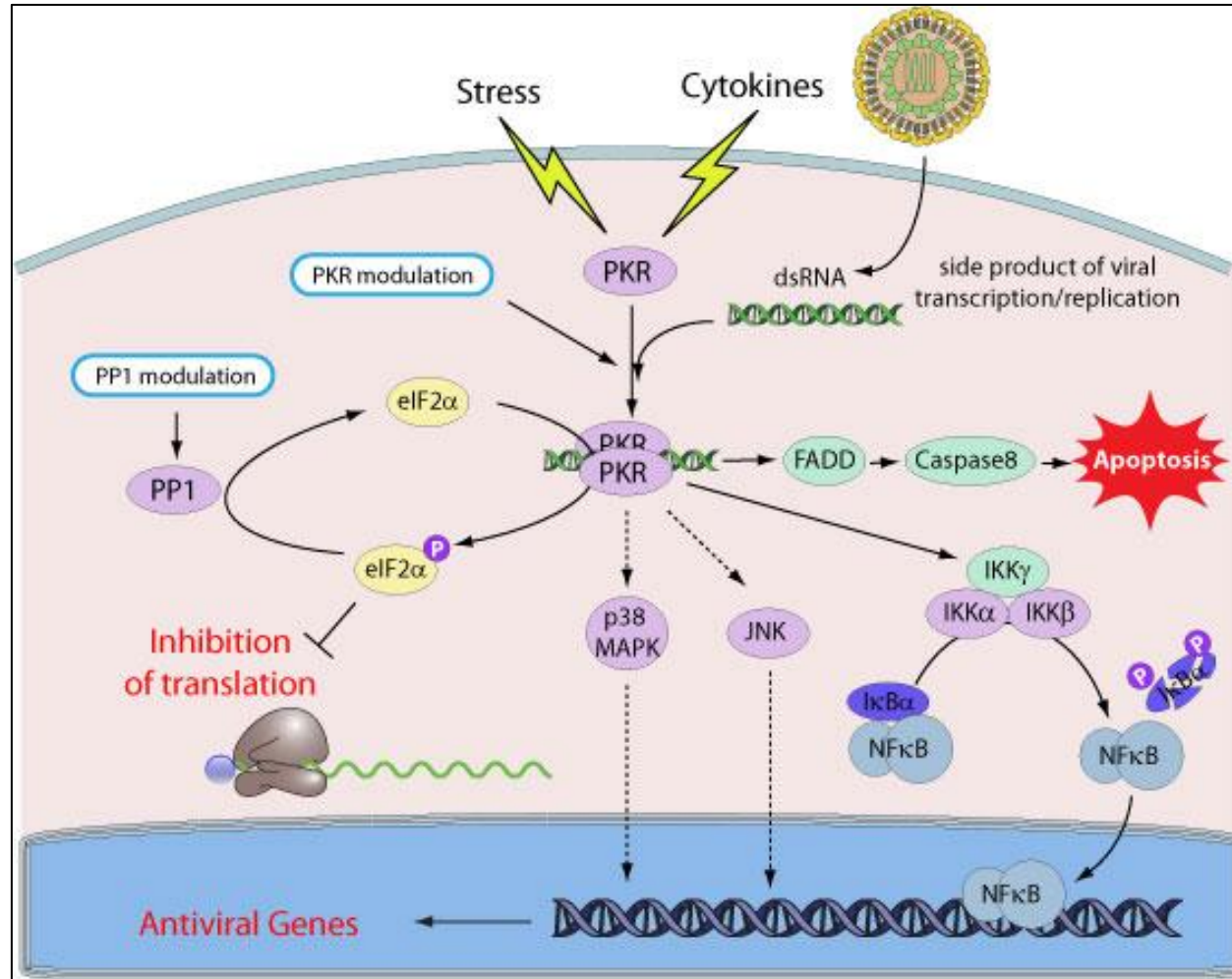
2- Antiviral defense of the cell

Viral modulation of the antiviral defense



Example of the PKR protein (1)

☞ PKR = dsRNA and stress sensor



Example of the PKR protein (2)

👉 Inhibition of PKR by many virus

