Virusology

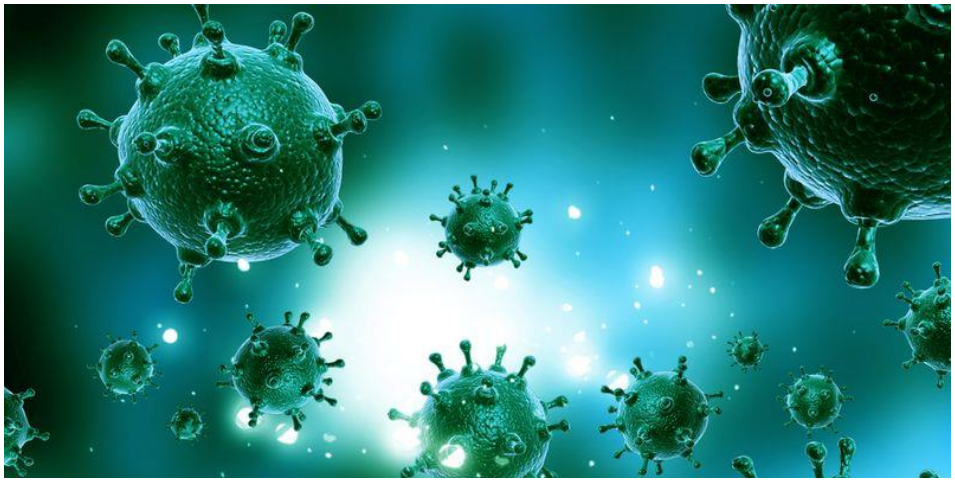
Virusology

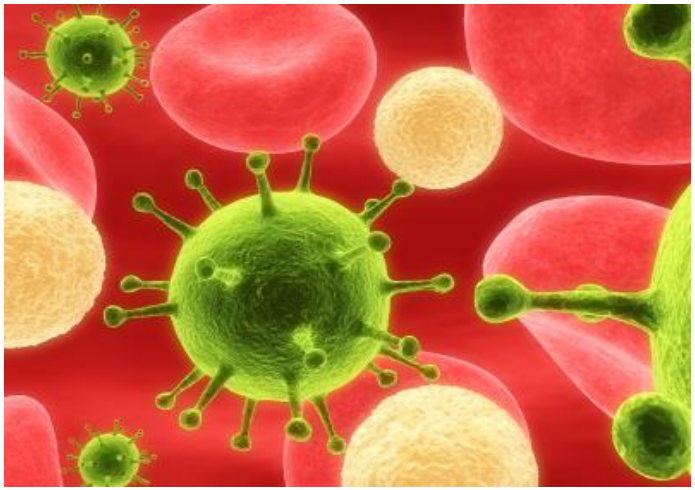
- Virus biology
- Antiviral drugs
- Picornaviruses and coronaviruses
- Viruses that cause gastroenteritis: Rotavirus, Norovirus
- Adenoviruses
- Paramyxoviruses: Measles virus, Respiratory syncytial virus RSV, Mumps virus, Variola virus, Rubivirus
- Influenza virus


Virus biology

Method of reproduction

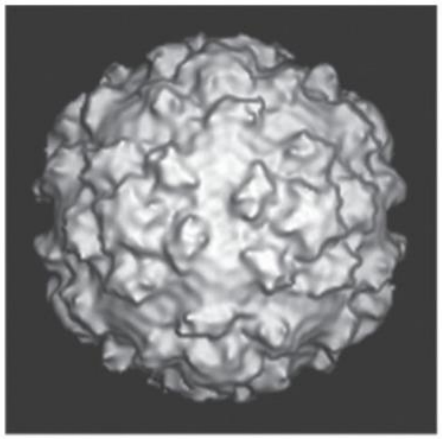
- Viruses do not multiply by simple division.
- Replication is performed by the "machinery" of the host cell, which synthesizes copies of the viral genome and viral proteins.
- Viral components spontaneously combine and assemble into viral particles.
- Obligatory intracellular parasites.





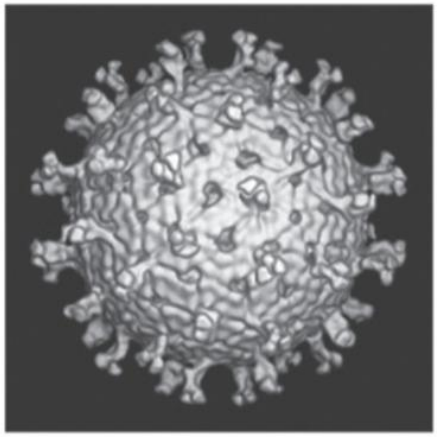
Virus morphology

Poliovirus



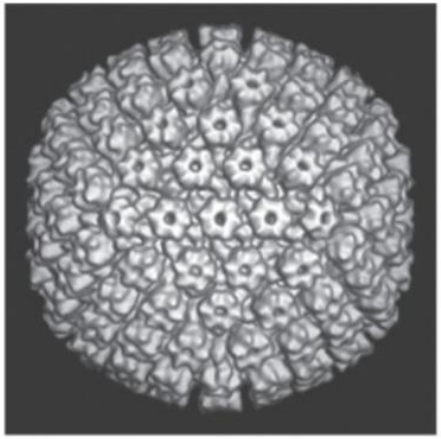
32 nm

Rotavirus



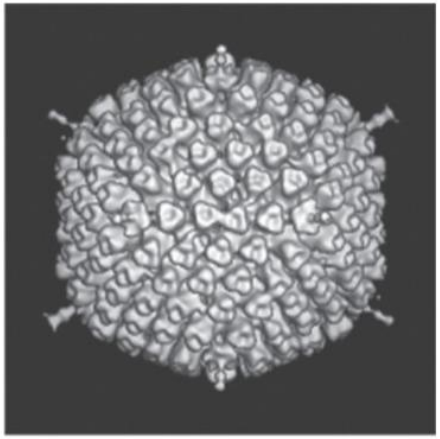
100 nm

Human papillomavirus



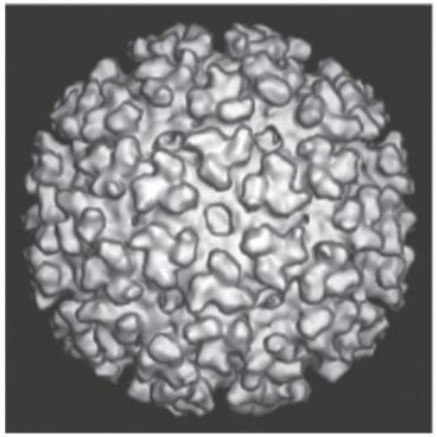
60 nm

Adenovirus



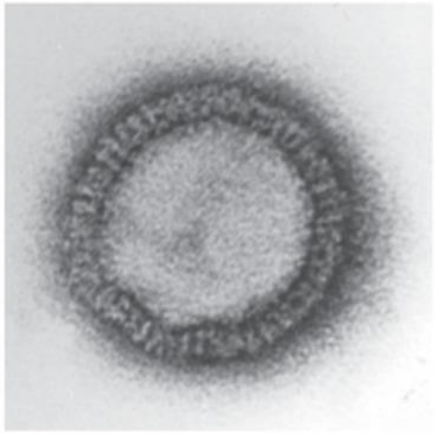
110 nm

Semliki Forest virus



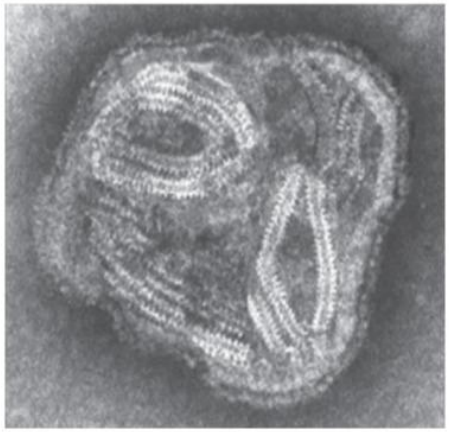
70 nm

Influenza virus



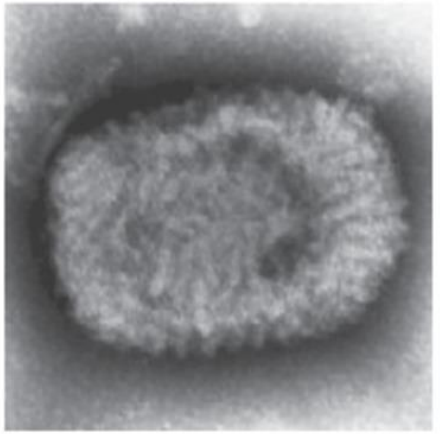
80-120 nm

Paramyxovirus



150-350 nm

Smallpox virus

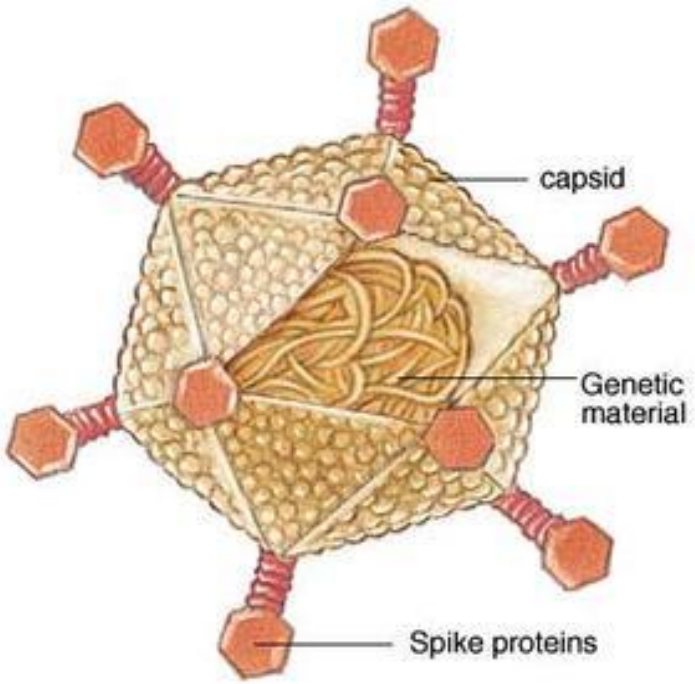


200 x 300 nm

Virus structure

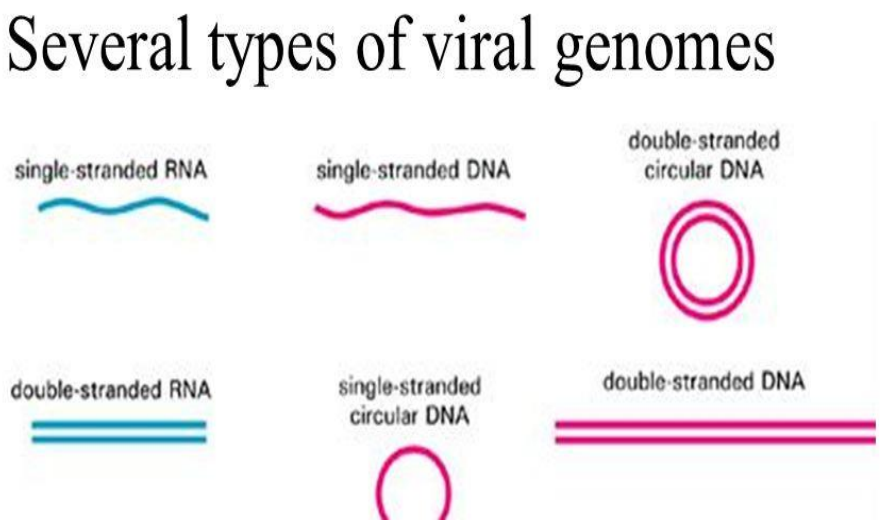
- Viral particle- virion.

- The capsid (delivery system) surrounds the internal contents of the virus:
  -structural components that allow the virus to survive in the external environment and bind to the target cell.
- Internal virus content:
  -viral genome
  -enzymes required for replication



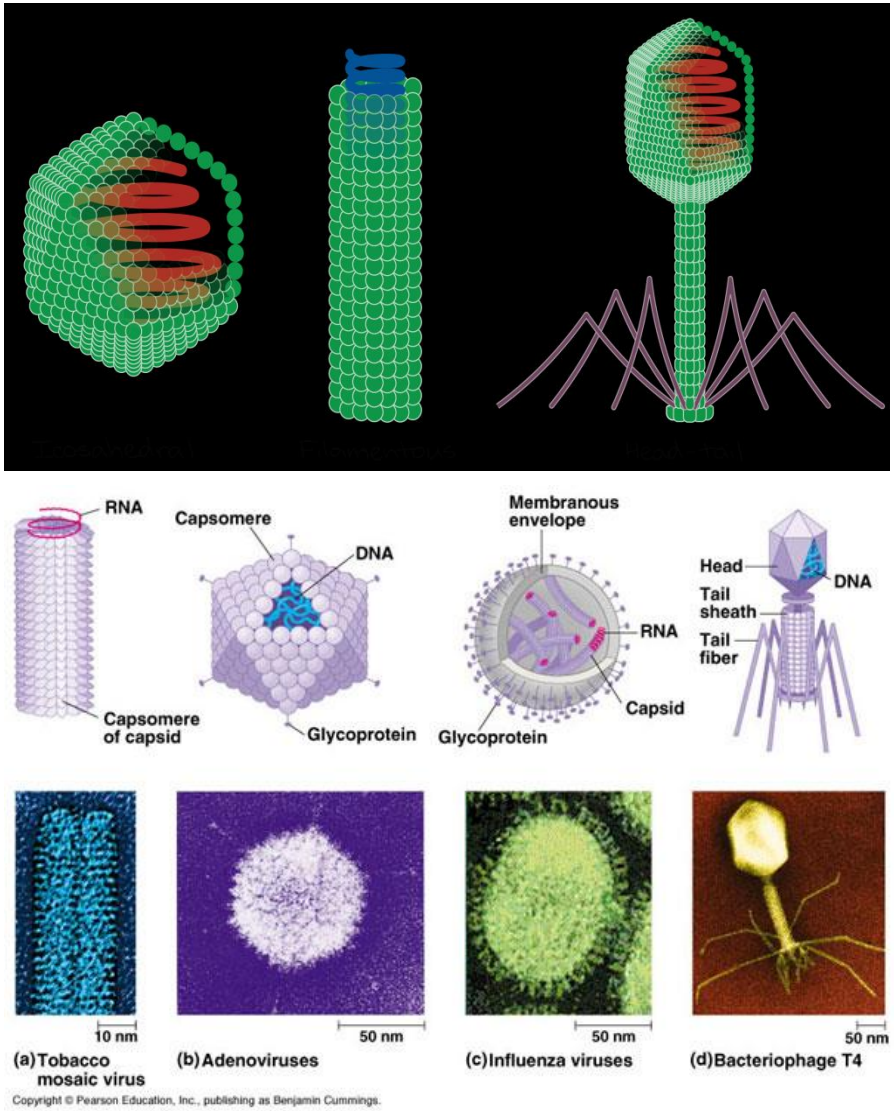
Viral genome

- RNA or DNA, single-stranded or double-stranded
- The smallest viral genome encodes 3-4 proteins
- The largest encodes more than 100 structural proteins and enzymes
- The same nucleic acid sequence may contain multiple different transcription frames or multiple overlapping regions, for different RNA information.

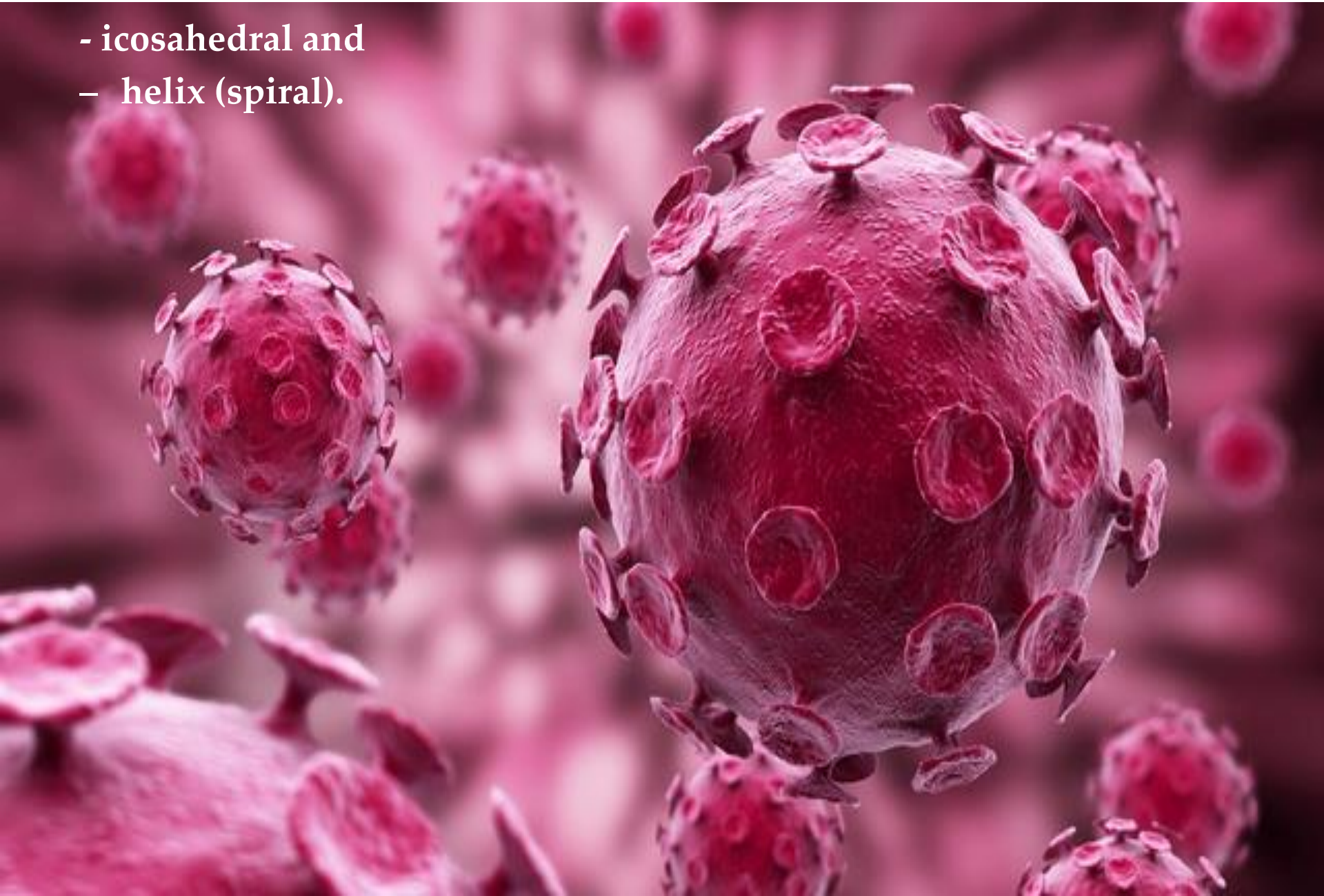


Virus structure - capsid

- Viral nucleic acid is surrounded by a capsid, a **single-layer or double-layer protein coat**
- Viral nucleic acid and capsid → **nucleocapsid**
- The capsid is made up of subunits (capsomers)
- Each capsomere spontaneously binds the other → viral capsid



- Proteins in the viral capsid are organized in one of two basic ways:

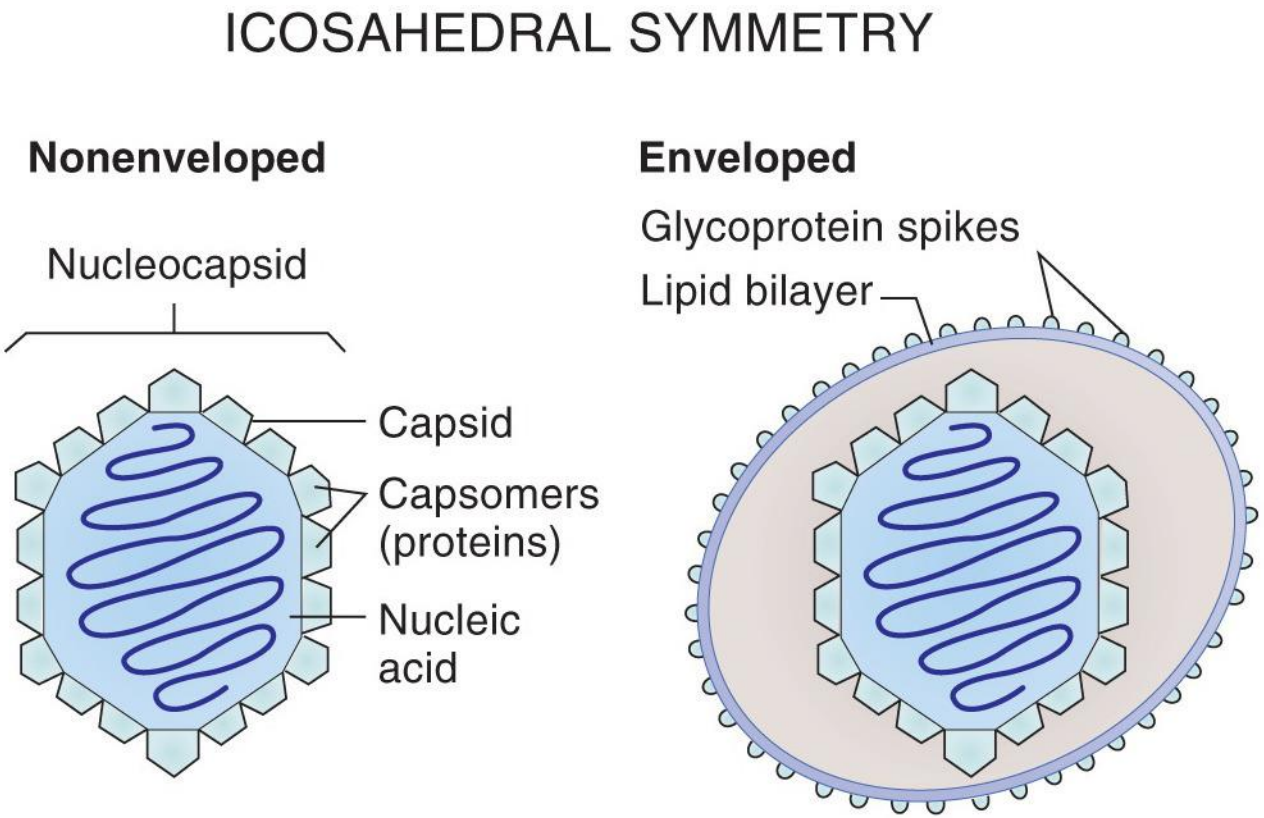


- icosahedral and

– helix (spiral).

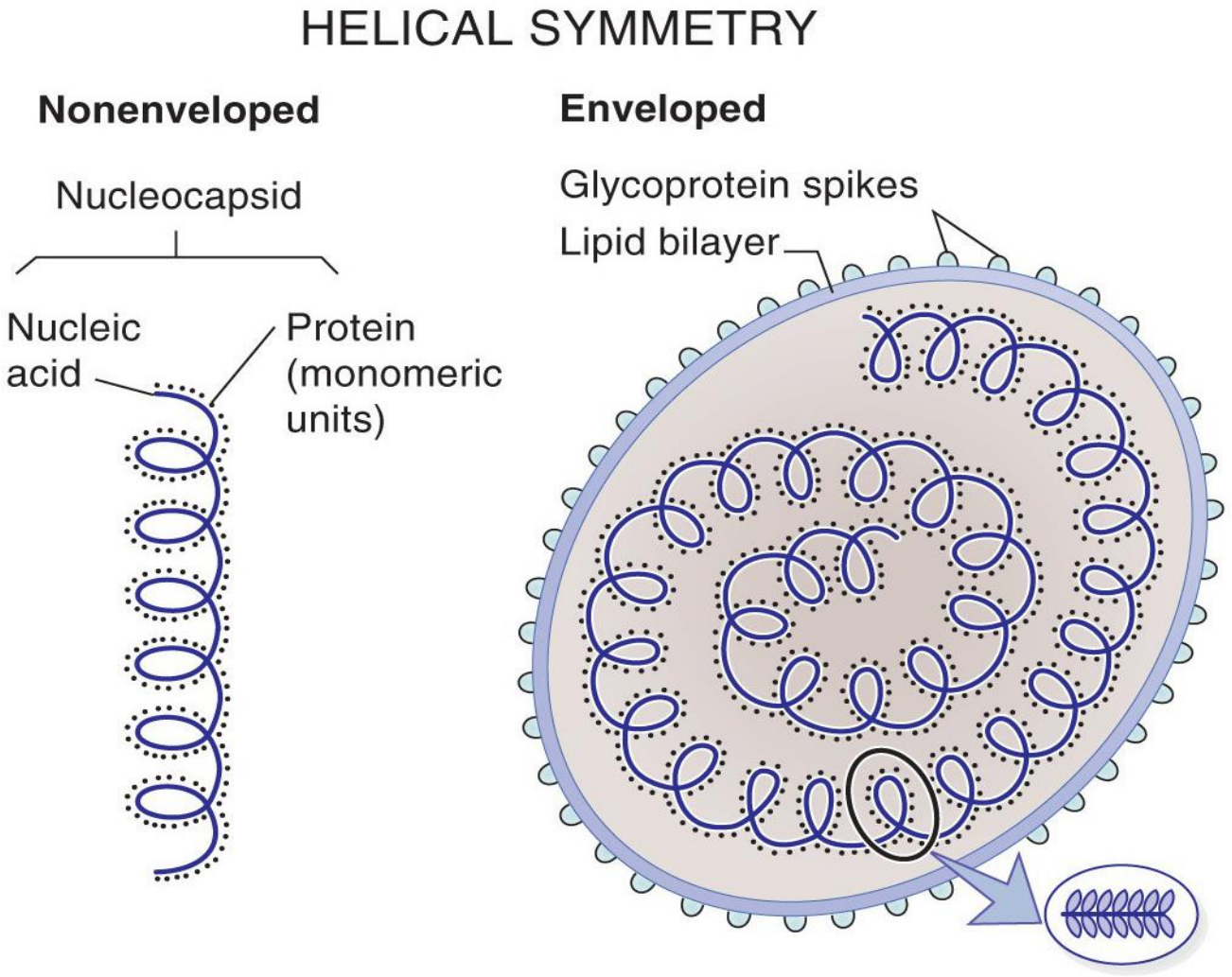
Icosahedral symmetry

- Defined number of structural subunits (basic structure is 20 equilateral triangles that merge into 12 prongs)
- Usually the shape of a sphere, like a soccer ball
- The nucleic acid is packaged inside the nucleus of the sword and is often tightly bound to specific capsule proteins.



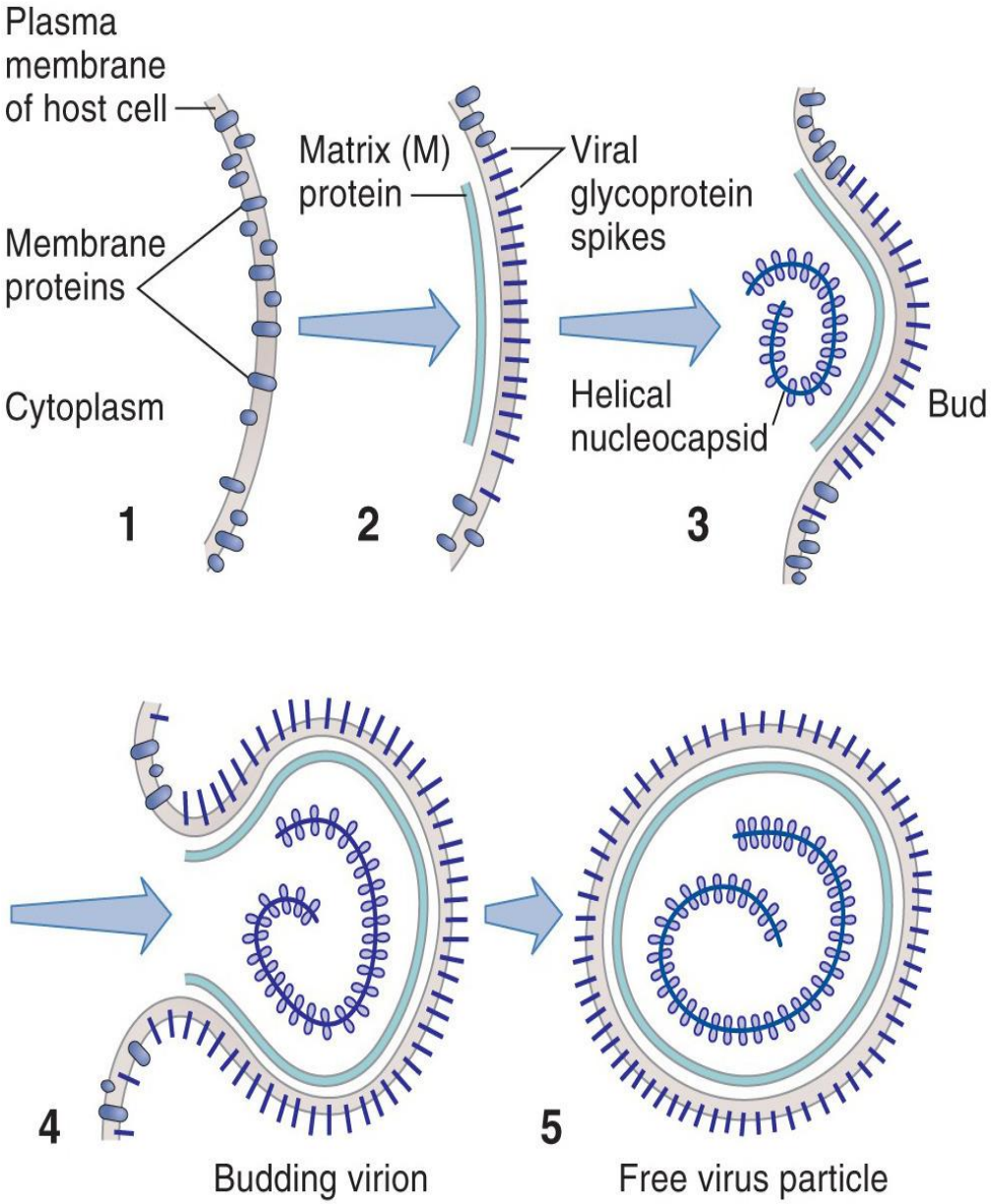
Spiral symmetry

- The number of subunits varies
- The protein subunits of the capsid are linked around the nucleic acid.



Viral envelope

- Many viruses have envelope
- Virus-specific proteins and lipids and carbohydrates, of host cell origin (eg nuclear membrane, endoplasmic reticulum, Golgi apparatus or cell membrane).

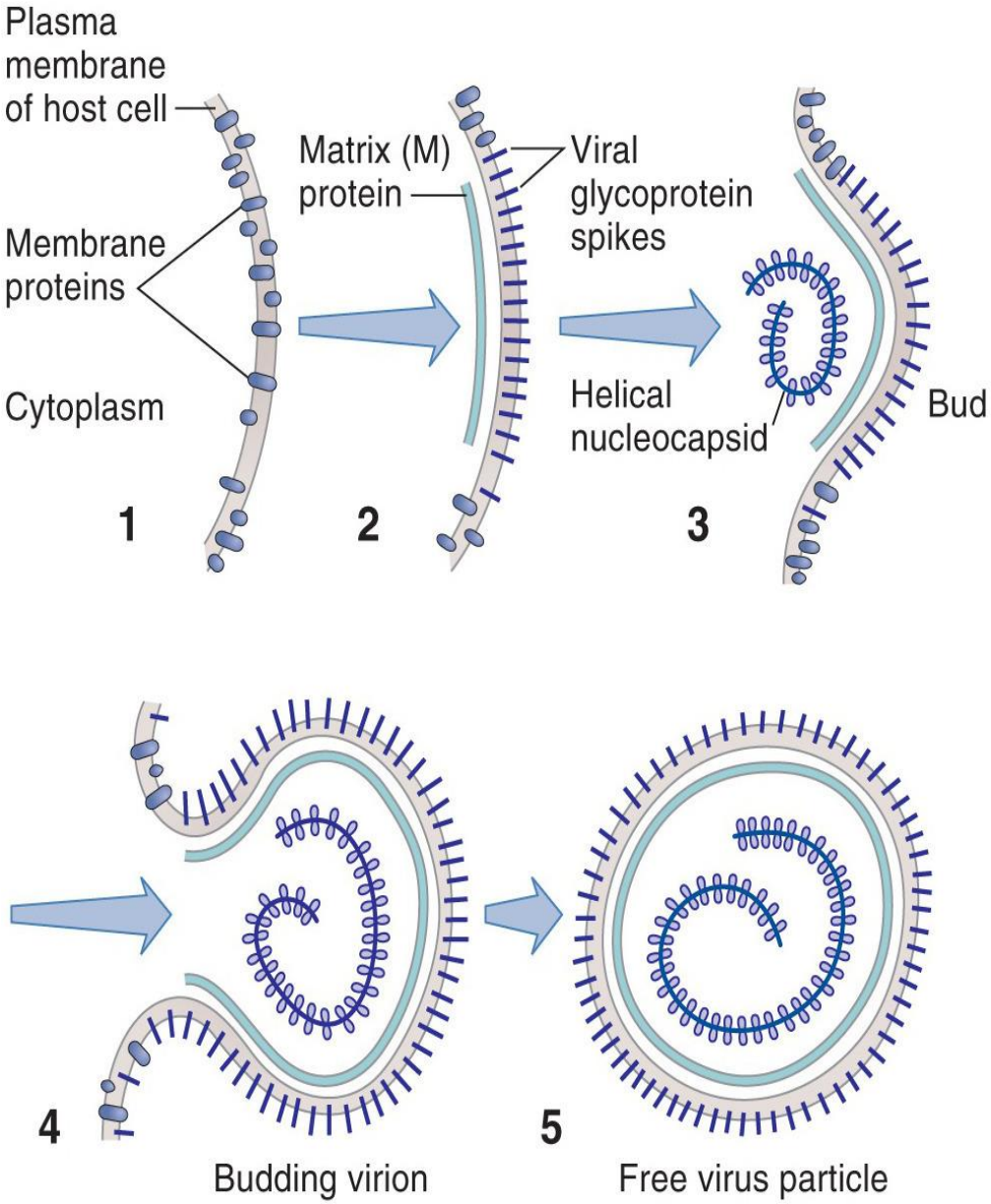


Virus-specific coat proteins

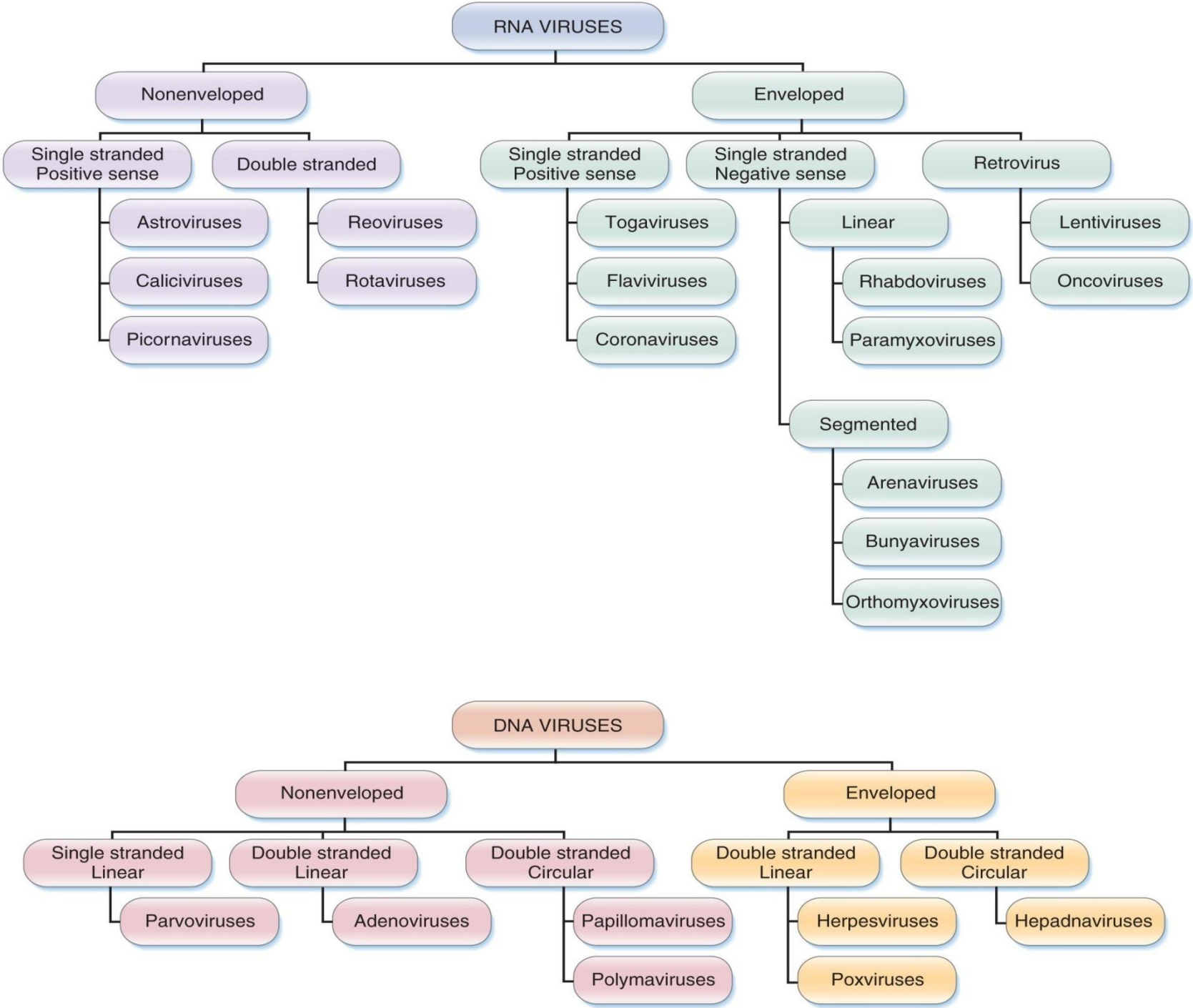
- Matrix (M) protein

- It is on the inner surface of the shell and in contact with the nucleocapsid.
- It stabilizes the complex of viral glycoproteins and lipid envelope and directs the viral genome intra-cellularly, during infection.

- Virus-specific envelope glycoproteins protrude through the outer surface of the lipid envelope.



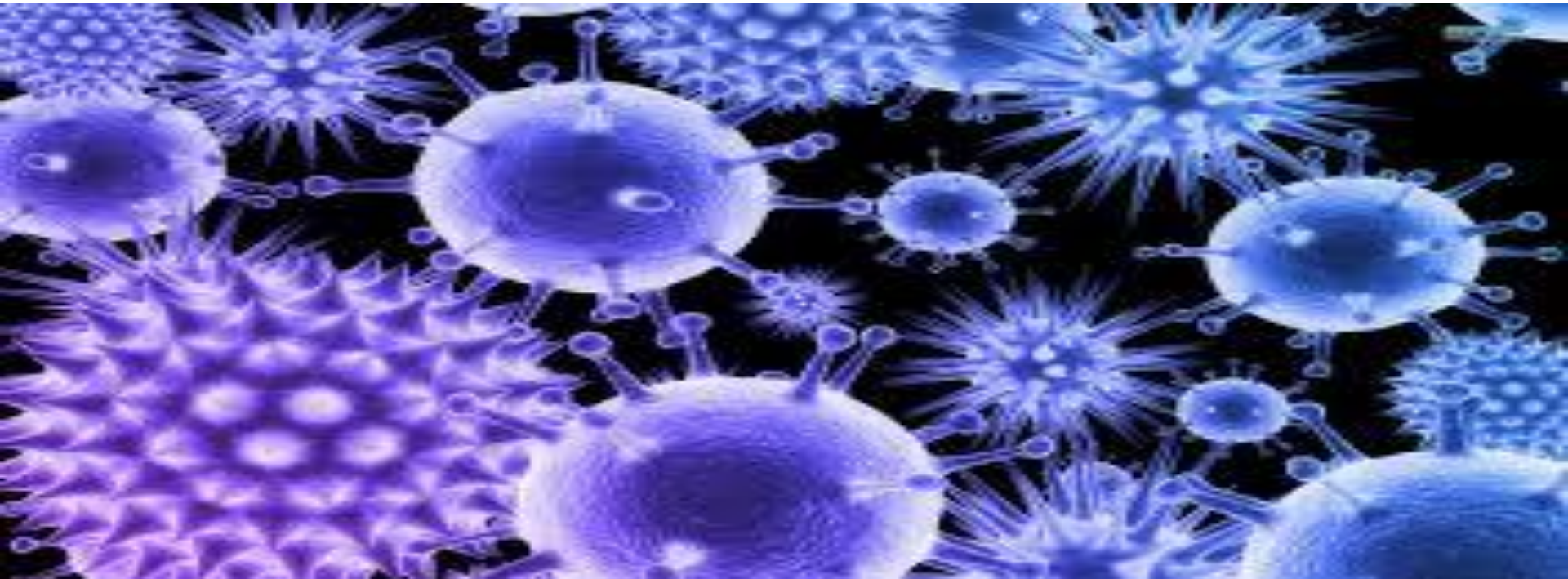
Family	Example	Nucleic Acid Polarity or Structure	Genome Size (kb or kbP)	Envelope
RNA Viruses				
Single Stranded				
Picornaviridae	Poliovirus	(+) RNA	7–9	No
Caliciviridae	Norwalk virus	(+) RNA	7–8	No
Togaviridae	Rubella virus	(+) RNA	10–12	Yes
Flaviviridae	Yellow fever virus	(+) RNA	10–12	Yes
Coronaviridae	SARS-CoV	(+) RNA	28–31	Yes
Rhabdoviridae	Rabies virus	(−) RNA	11–15	Yes
Paramyxoviridae	Measles virus	(−) RNA	13–18	Yes
Arenaviridae	Lassa fever virus	Two ambisense RNA segments	11	Yes
Bunyaviridae	Hantavirus	Three (−) RNA segments	11–19	Yes
Orthomyxoviridae	Influenza virus	Eight (−) RNA segments[a]	10–15	Yes
Double Stranded				
Reoviridae	Rotavirus	10–12 dsRNA segments[b]	19–32	No
RNA and DNA Reverse-Transcribing Viruses				
Retroviridae	HIV	Two identical molecules (+) RNA	7–13	Yes
Hepadnaviridae	Hepatitis B virus	Circular dsDNA with ss portions	3–4	Yes
DNA Viruses				
Single Stranded				
Parvoviridae	Human parvovirus B-19	(+) or (−)	4–6	No
Double Stranded				
Polyomaviridae	JC virus	Circular	5	No
Papillomaviridae	Human papillomavirus	Circular	7–8	No
Adenoviridae	Human adenoviruses	Linear	26–45	No
Herpesviridae	Herpes simplex virus	Linear	125–240	Yes
Poxviridae	Vaccinia virus	Linear with covalently closed ends	130–375	Yes

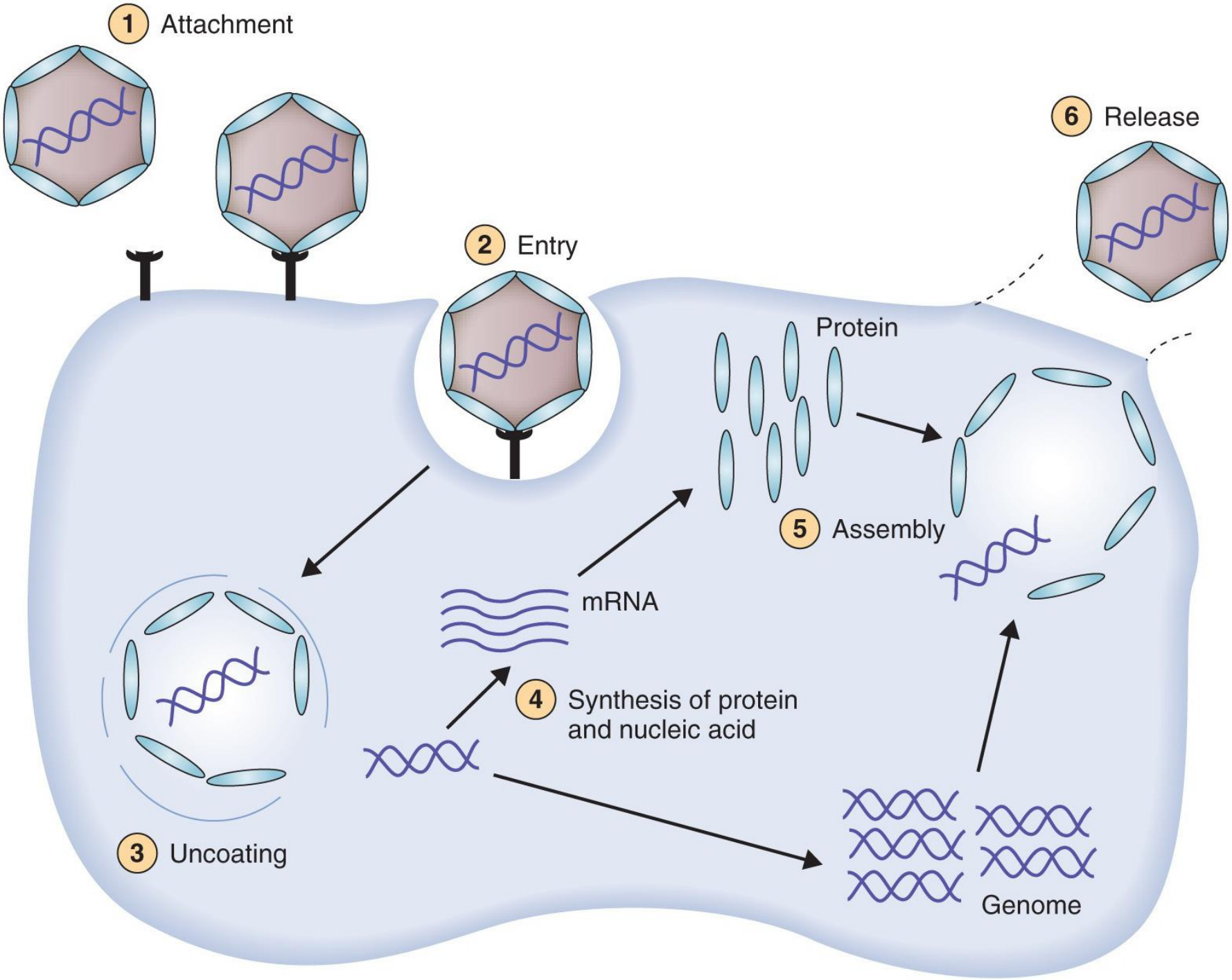


Virus replication

- Sensitive cell infection
- Viral nucleic acid and protein amplification
- Virus assembly and release

- The structural and genetic diversity of viruses is reflected through different ways of reproduction.





Adsorption and penetration

- The first step in viral infection → binding of the virus to the cell surface - adsorption
- It is reversible

- Enveloped viruses - a protein that protrudes through the envelope itself (influenza virus haemagglutinin)
- Sheathless viruses - surface parts of capsid proteins

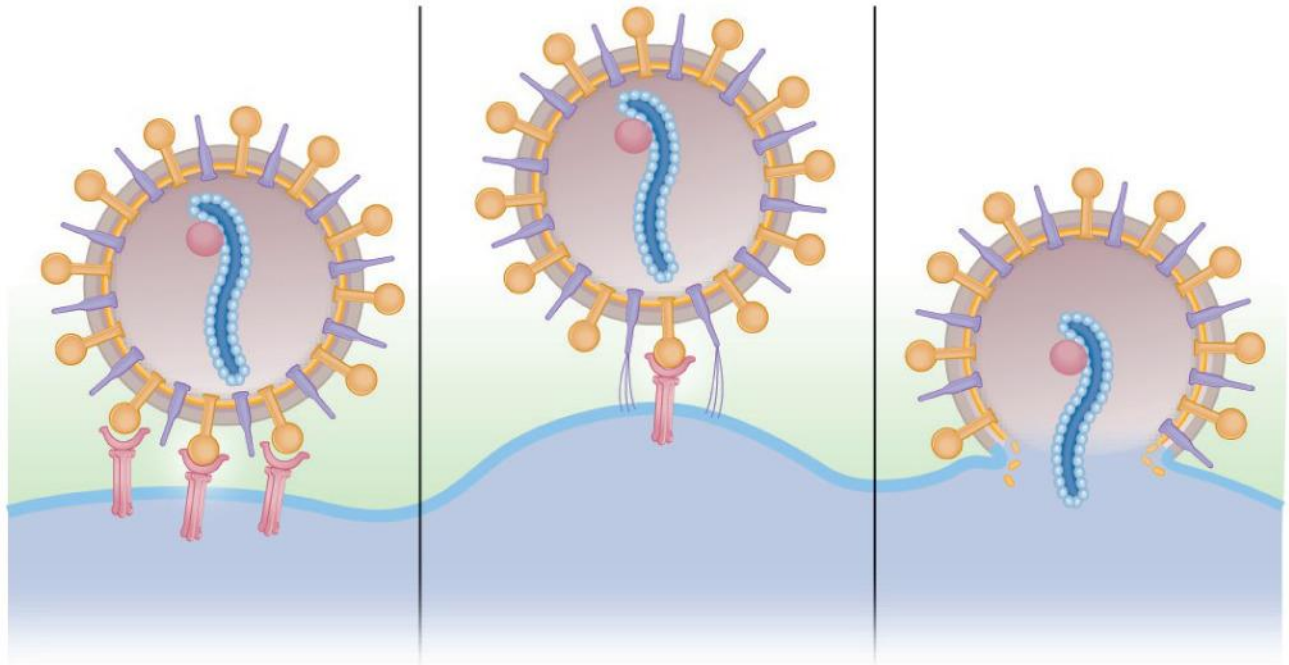
- Viruses ↔ different receptors:
- with narrowly limited tissue distribution (CD4)
- ubiquitous components of the cell membrane (adhesion molecules)
- multiple different receptors

- Many viruses use different molecules to bind to and enter the target cell.

Adsorption and penetration

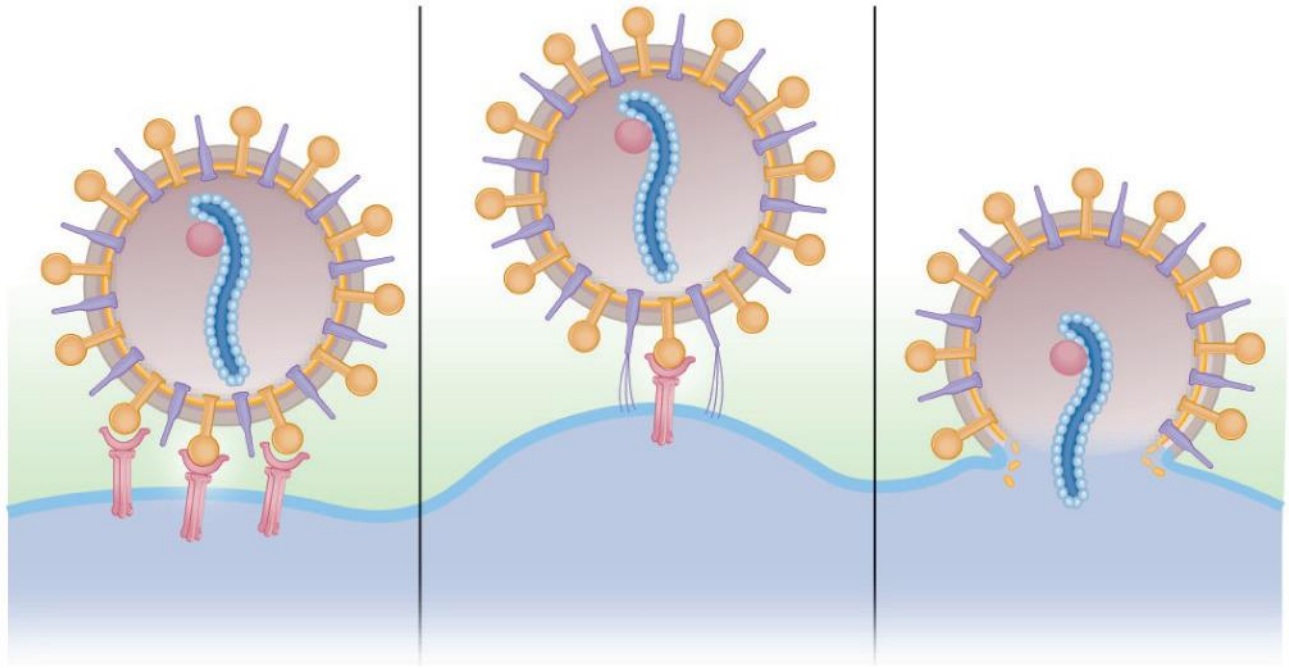
- Adsorption → penetration through the membrane
- All or part of the internal content of the virus containing the viral genome and virus-associated polymerases

- Envelope virus: fusion of envelope with cell membrane → release of nucleocapsids into cell



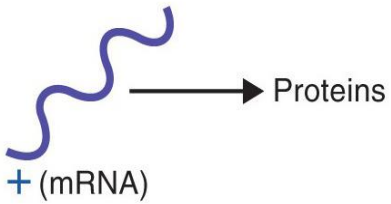
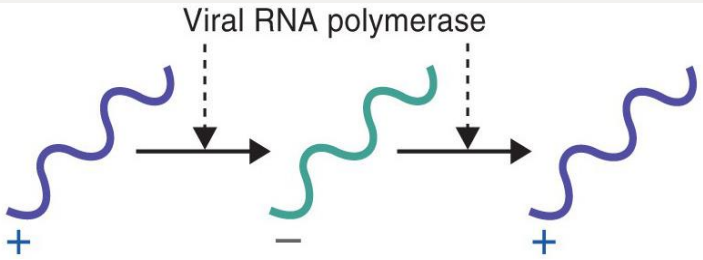
Adsorption and penetration

- Fusion begins on the cell membrane itself
- The virus enters the cell by endocytosis → fusion of the envelope with the endosomal membrane, inside the cell
- Uncoated viruses enter the cell by endocytosis → enter the cytoplasm by penetrating the endosomal membrane



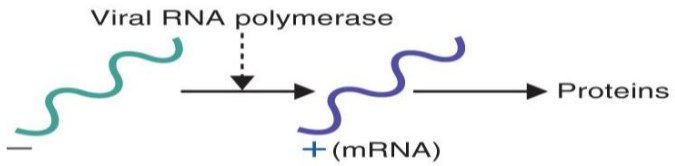
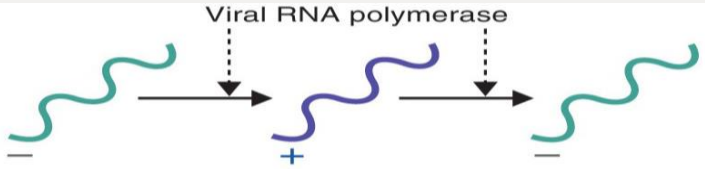
release of the viral genome

Viruses with single positive RNA

Virus Type	Viral Protein Synthesis (using host cell translation machinery)	Viral Genome Replication
Single-stranded +RNA viruses (e.g., poliovirus, West Nile virus)		

- Poliovirus: mRNA translation gives one large polyprotein that is subsequently cleaved by viral proteases into individual viral proteins. All proteins are equally expressed.

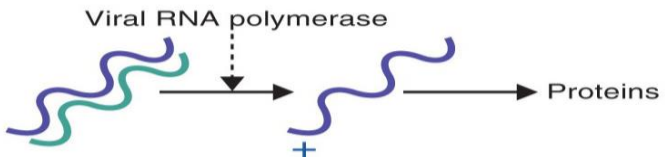
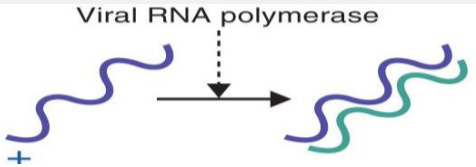
Viruses with single negative RNA

Virus Type	Viral Protein Synthesis (using host cell translation machinery)	Viral Genome Replication
Single-stranded –RNA viruses (e.g., influenza virus, measles virus)		

- Genomic negative RNA is used as a template for mRNA transcript synthesis for each viral gene separately.

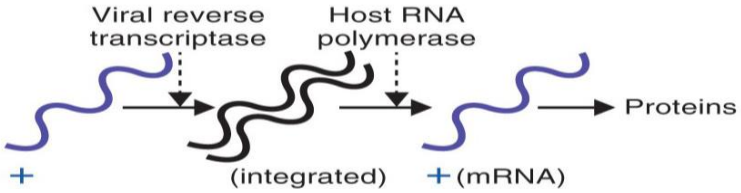
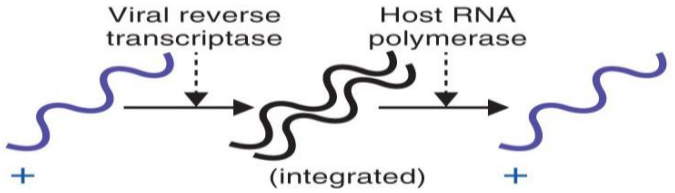
- Such viruses contain RNA-dependent RNA polymerase in the virion, which enters the host cell during infection.

Double RNA viruses

Virus Type	Viral Protein Synthesis (using host cell translation machinery)	Viral Genome Replication
Double-stranded RNA viruses (e.g., rotavirus)		

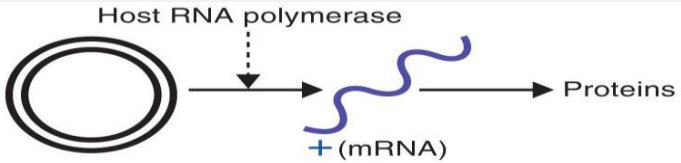
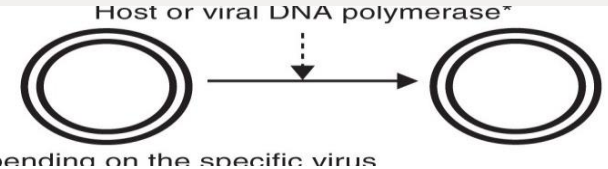
- Double RNA → positive RNA, mRNA
- Viral RNA-dependent RNA polymerase transcribes single positive RNA using the negative strand of double RNA as a template.

RNA viruses that replicate through DNA mediators

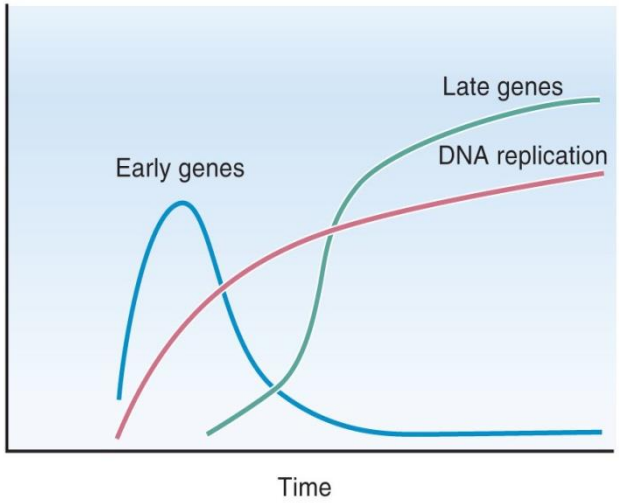
Virus Type	Viral Protein Synthesis (using host cell translation machinery)	Viral Genome Replication
Retroviruses (e.g., HIV)		

- Single positive RNA-template viral RNA-dependent DNA polymerase (reverse transcriptase).
- The DNA is then incorporated into the chromosomal DNA of the host
- Transcription of integrated viral DNA, as transcription of the host gene, is mediated by cellular DNA-dependent RNA polymerase.

DNA viruses

Virus Type	Viral Protein Synthesis (using host cell translation machinery)	Viral Genome Replication
Double-stranded DNA viruses (e.g., papillomaviruses, [circular genome] and herpesviruses [linear genome])		

- Transcription of viral DNA into nuclear mRNA
- Early transcripts
- Late transcripts
- Adenoviruses and human papilloma viruses
- stimulate the cell cycle:
- E7 → pRB → releases E2F; E6 degrades p53

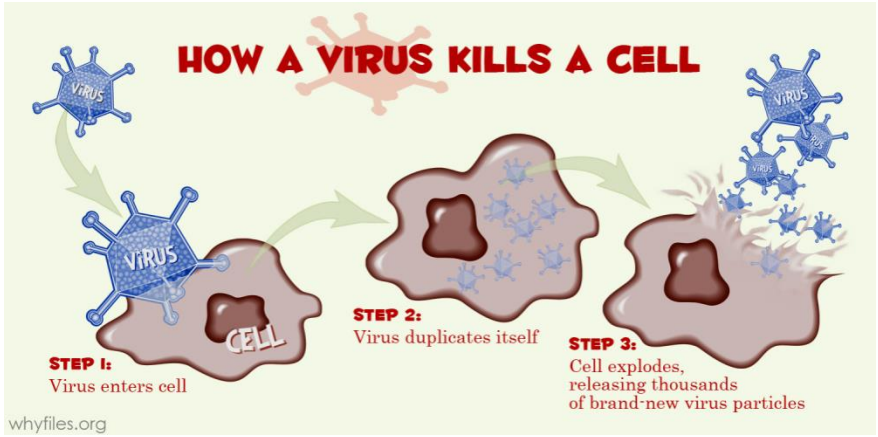


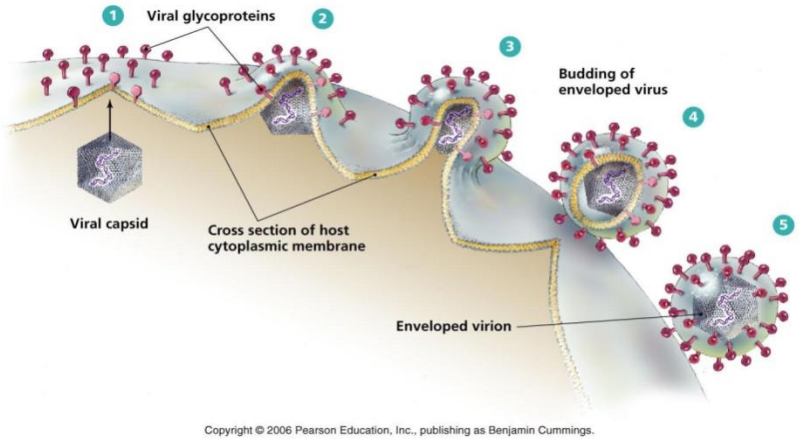
- Pox viruses: transcription and translation in the cytoplasm
- They do not use host RNA polymerase, which is found in the nucleus
- They have their own DNA-dependent RNA polymerase

Assembly of virions and release from the cell

- Assembly of viruses with / without envelopes usually occurs **spontaneously, by crystallization of viral capsids**
- When capsids are formed, they are filled with viral nucleic acid - viable virion
- **Viruses without envelope are usually released during cell lysis**

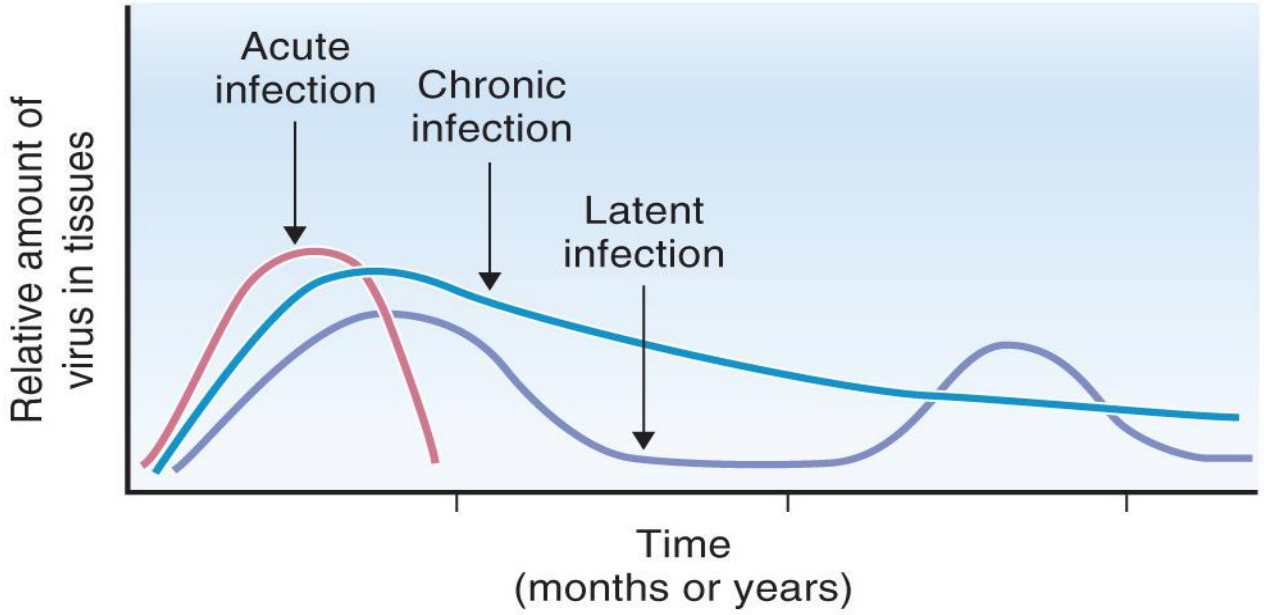
- **Enveloped viruses are usually released by membrane swelling.** Viral capsids bind to viral M (matrix) proteins inserted into the cell membrane. Many viruses induce host cell apoptosis in this way





The relationship between viruses and cells, types of viral infections

- **Acute** infection: intensive replication → host cell death (polio or influenza)
- **Latent** infection: DNA viruses or retroviruses, viral DNA as extrachromosomal (herpesviruses) or integrated into the host genome (retroviruses). Malignant cell transformation.
- **Chronic** infection: release of the virus, sometimes without dying or damaging the host cell. RNA viruses. Small amount of synthesized viruses, defective immune response (hepatitis C)



Routes of entry of the virus into the host organism and spread through the organism

- Source of infection: acutely ill or carriers

- Transmission:
  - Direct contact, sexual contact (HIV infection)

  - Indirectly:
    - ❑ feco-oral (diarrhea caused by rotaviruses)

    - ❑ aerosol (smallpox)

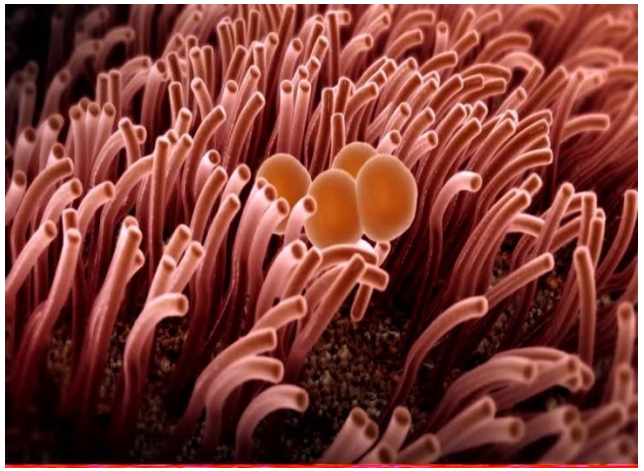
    - ❑ by inoculation from infectious needles or blood products (hepatitis B and C)

    - ❑ transmission of the disease from animals to humans usually occurs through the bite of an infected animal (rabies) or the bite of an infected vector (many viral encephalitis).

Entry through the respiratory tract

- Respiratory infections are transmitted by aerosol (coughing and sneezing), nasal secretions or saliva

- Ebstein-Barr virus (EBV) → saliva, and some respiratory viruses (in children's institutions) → contaminated toys
- Rhinoviruses → contaminated hands on eyes, nose or mouth



- Overcoming defense mechanisms: glycocalyx, tracheobronchial mucus (captures viral particles), ciliary epithelium, IgA, NK, Mf

Entering through the gastrointestinal tract (GIT)

- Fecal viruses contaminate food or water
- Feces of infected hands
- Acidity of gastric juice, bile salts (surviving viruses without envelope), proteolytic enzymes, IgA
- Some enteroviruses cross the mucosal barrier through M cells

- Entry through the skin
- Stratum corneum- physical and biological barrier
- Direct inoculation by bite or mechanical (needles)
- Viremia allows vector infection
- "Dead-end" host

- Entry through the urogenital tract (UGT)
- Sexual transmission through the mucosa of the UGT or rectum is an important way of spreading infection with HIV (hepatitis B), HSV (herpes simplex), HIV…

Spread through the body

- Host entry, primary replication and tissue tropism in one anatomical part of the organism:

  respiratory tract infections caused by orthomyxoviruses, paramyxoviruses or rhinoviruses

  rotavirus-induced enteritis

- Entering the body in one place and then going to different parts of the body.
- Primary viral replication
- Secondary replication in target organs
- Enteroviruses enter through the GIT and go into the CNS where they cause meningitis, encephalitis or polymyelitis.

Spread through the organism

- Nervous system spread (HSV, rabies, VZV)
- HSV reaches nerves through receptors located near the ends of sympathetic nerve fibers
- The rabies virus accumulates in the motor plate of the neuromuscular synapse.

- Hematogenous spread
- Primary replication - initial viremia, asymptomatic or accompanied by prodromal symptoms

- Enteroviruses: primary replication (Peyer's patches, peritonsillar lymph tissue) → primary viremia → dissemination to spleen and liver → replication → secondary viremia

Antiviral drugs

- Penetration, decapsidation, nucleic acid synthesis, assembly of viral particles and release of virus from infected cells

- **Interferons**
- Interferons released from an infected cell induce resistance to infections by many different viruses, **they are not virus-specific**
- They are present in very small quantities
- Isolated and purified - effective therapeutic agents
- (headache, shivering, myalgia, bone marrow suppression)
- They are used in the treatment of a small number of viral infections (HCV)
- Primarily on RNA virus infections.

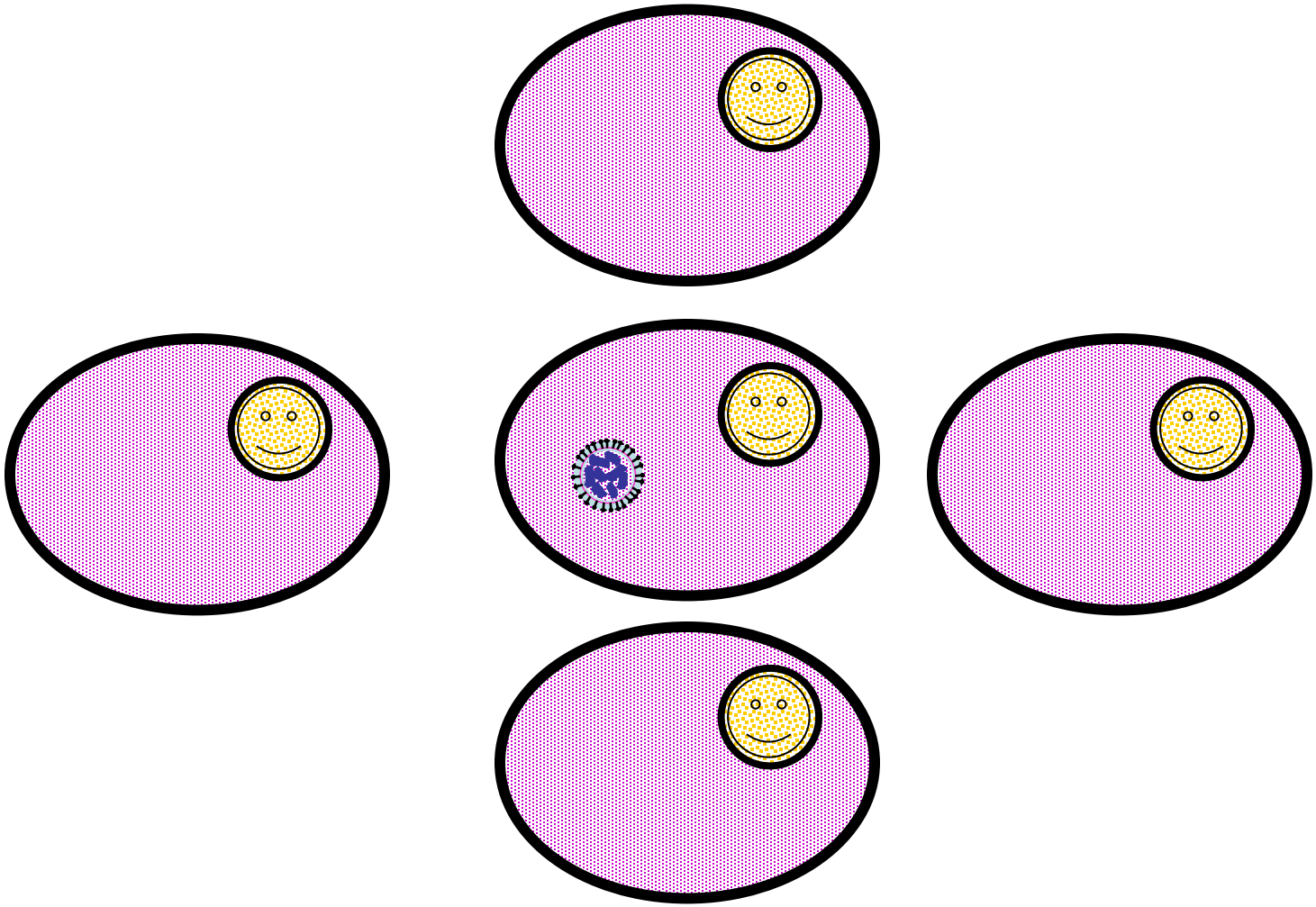
interferon-alpha and interferon-beta

- The main sources of **IFN-α** are plasmacytoid dendritic cells and mononuclear phagocytes.
- **IFN-β** is produced by many cells, most commonly fibroblasts.
- The most potent stimuli for type I interferon synthesis are **viral nucleic acids** that bind to various intracellular receptors.

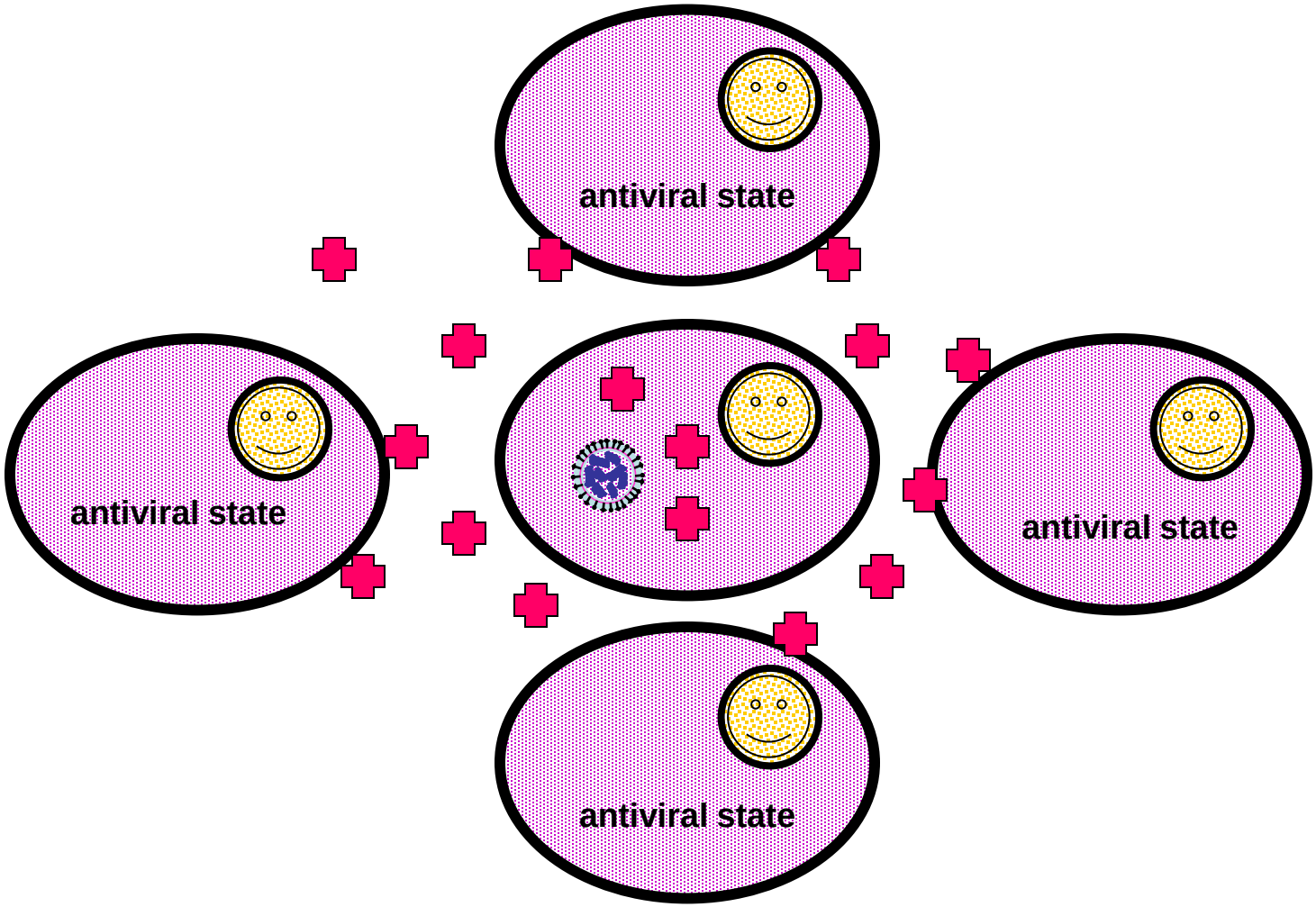
- Type I IFNs inhibit virus replication in the cell. **Under the action of this cytokine, the cell synthesizes numerous enzymes that prevent the transcription and replication of viral nucleic acids or cause their degradation.**
- A cell infected with the virus secretes IFN type I, which pacracrine protects neighboring cells that are not yet infected. Cells that become resistant to virus infection under the influence of IFN type I are said to be in an "antiviral state". The type I IFN secreted by an infected cell may also have an autocrine effect on that cell.

- Increase the expression of MHC I (cytotoxic T lymphocytes)
- Activate NK cells (killing virus-infected cells)

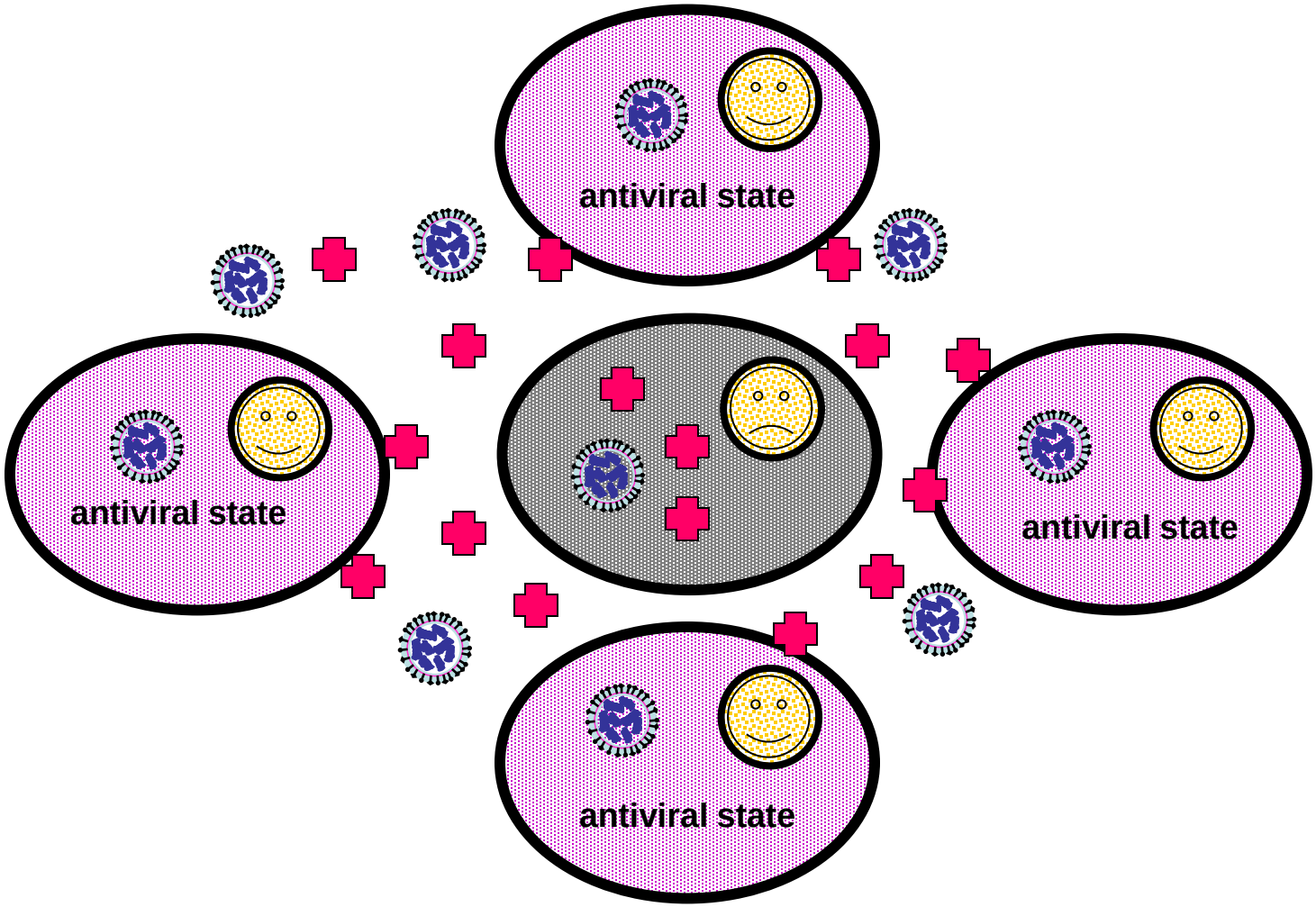
Interferon type 1



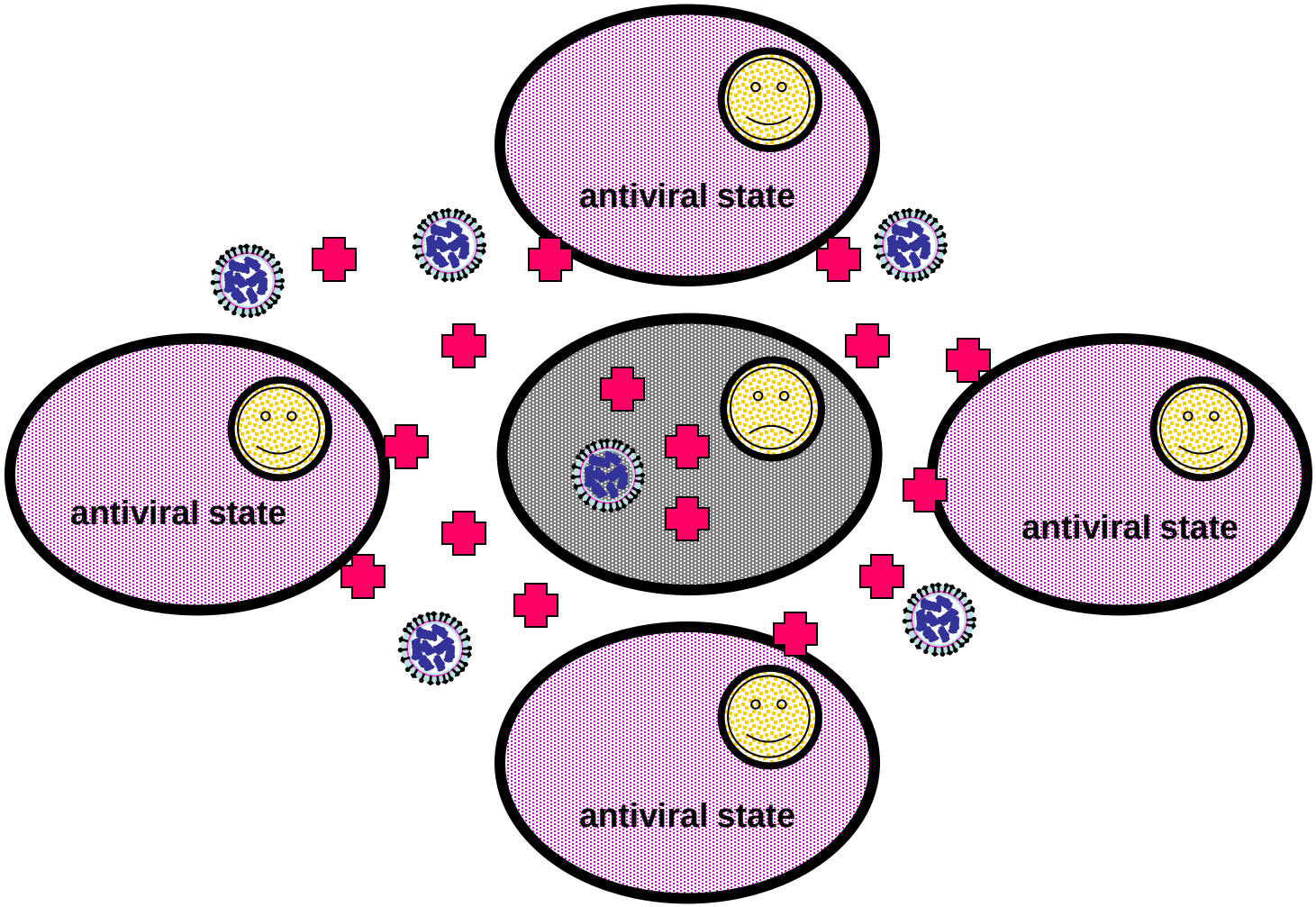
Interferon type 1



Interferon type 1



Interferon type 1



Antiviral drugs

Ribavirin

- Inhibits some DNA and many RNA viral infections (Influenza A and B viruses, parainfluenza virus, respiratory syncytial virus and some arenaviruses)
- Purine nucleotide analog, inhibits virus replication
- Inhibits virus-encoded DNA-dependent DNA polymerase and possibly RNA-dependent RNA polymerase

- Inhibits inosine monophosphate dehydrogenase, reducing GTP which limits the synthesis of nucleic acids (both host and viral)

- Treatment of hemorrhagic fevers caused by Lasa virus, severe infections caused by RSV

Antiviral drugs

Acyclovir

- The first antiviral drug approved for clinical use
- Inhibits DNA polymerase by several hepres viruses
- HSV encodes **thymidine kinase** → phosphorylates acyclovir → acyclovir monophosphate → acyclovir trophosphate → inhibits herpes viral DNA polymerase.

Antiviral drugs

Amantadine and Rimantadine

- Influenza drugs
- They inhibit the late stages of Influenza A entering cells
- They are not effective against Influenza B virus

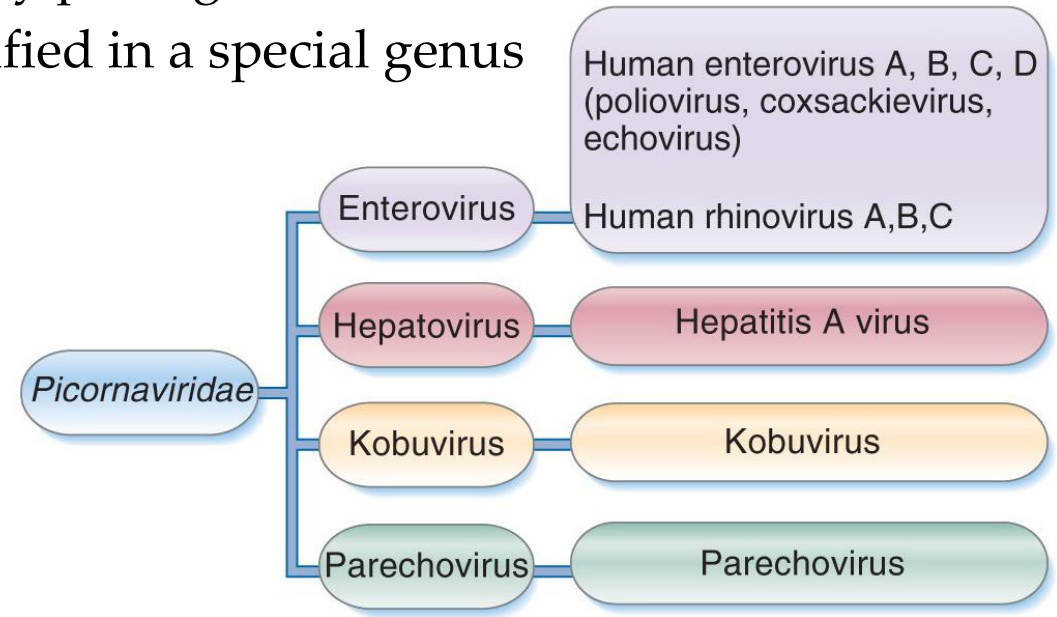
- They inhibit the ion channels of the Influenza A virus by physically blocking the flow of hydrogen ions
- Accelerates virion degradation upon entry into endosomes

- Before exposure to the virus, amantadine and rimantadine prevent the occurrence of clinically manifest disease in more than 75% of cases
- Prophylaxis
- People at increased risk of severe infections during the Influenza A virus epidemic: the elderly and patients with chronic heart and lung disease

Picorna and coronaviruses

Enteroviruses

- They replicate in the GIT
- Poliovirus, the cause of poliomyelitis
- Three antigenic types / serotypes, polioviruses
- Most epidemics are caused by type 1
- Coxsackievirus
- Echoviruses (isolated from feces of asymptomatic persons)
- Rhinoviruses, respiratory pathogens
- Hepatitis A virus, classified in a special genus



Mode of transmission

- Like most enteroviruses, polioviruses are excreted in the feces
- Feco-oral route
- The source may be an individual who excretes large amounts of virus from the GIT
- In temperate climates, during summer and early autumn
- In the tropics, all year round

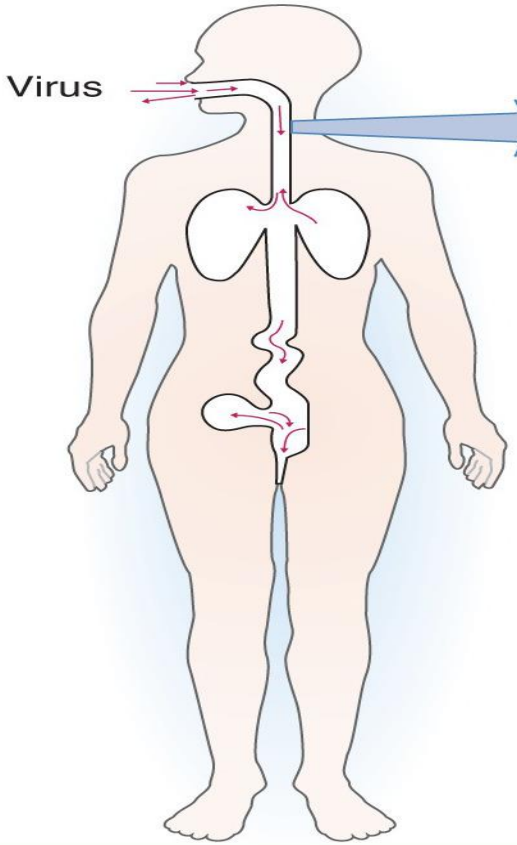
Propagation and multiplication

- Ingestion → replication in the oropharyngeal and intestinal mucosa → passage through the basement membrane → entry into the bloodstream - viremia → dissemination to all parts of the body

- In most cases, viral replication does not progress beyond mucosa or initial viremia → asymptomatic or mild disease

- In about 1% of infections, it invades the brain and spinal cord, directly from the bloodstream or retrogradely through axons, paralysis usually occurs 11 to 13 days after infection

- The polio virus receptor **CD155** is necessary for the virus to enter cells and multiply
- Some cells are protected by interferon production



Enteroviruses A,B,C and D

Viral replication in oropharynx and intestine

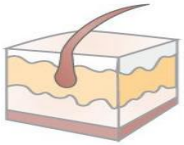
Rhinoviruses A,B, and C

Viral replication in upper respiratory tract

Viral replication in lymphoid tissues

Viremia

Skin

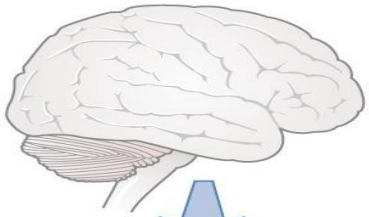


Coxsackievirus A
Hand-foot-and-mouth disease
Rash, herpangina

Muscle

Echovirus
Coxsackievirus A and B
Myocarditis
Pericarditis
Pleurodynia

Brain/spinal cord



Poliovirus
Coxsackievirus A and B
Paralytic disease
Encephalitis

Meninges

Poliovirus
Coxsackievirus A and B
Echovirus
Meningitis

Propagation and multiplication

- Positive RNA, functions as information RNA

- Virus binding to poliovirus receptor (PVR) or CD155
- The virion enters by endocytosis and the viral genome is released into the cytoplasm
- The 5` end of RNA is covalently bound to a viral protein called **VPg**, a primer for the synthesis of viral RNA (RNA-dependent-RNA polymerase)
- Genomic RNA is translated on ribosomes
- Translation results in a polypeptide called a polyprotein, 4 structural and 10 non-structural proteins
- Viral RNA enters mature virions
- Viral particles leave the cell by lysis

- The complete cycle lasts 6-8 hours

Tissue damage

- Lytic virus
- It multiplies in the gray matter neurons of the brain and spinal cord
- Flaccid paralysis of the muscles of the extremities → infection destroys the cells of the anterior horns of the spinal cord- bulbar polymielitis
- paralysis of the respiratory musculature → involvement of the medulla oblongata by infection
- Mortality around 50%
- Development of "iron lungs"

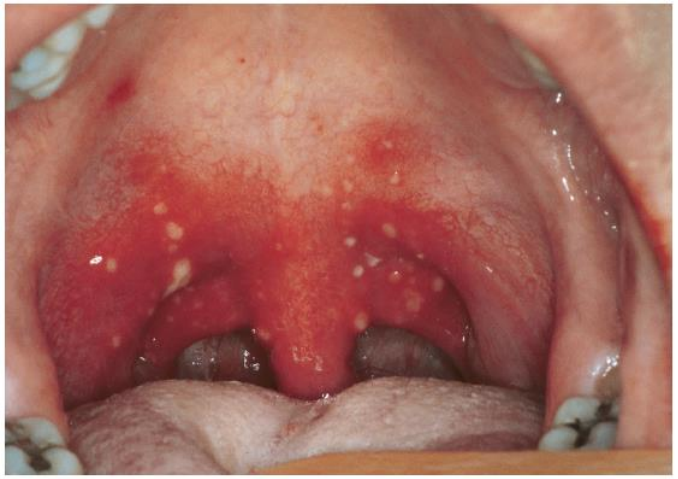
Tissue damage

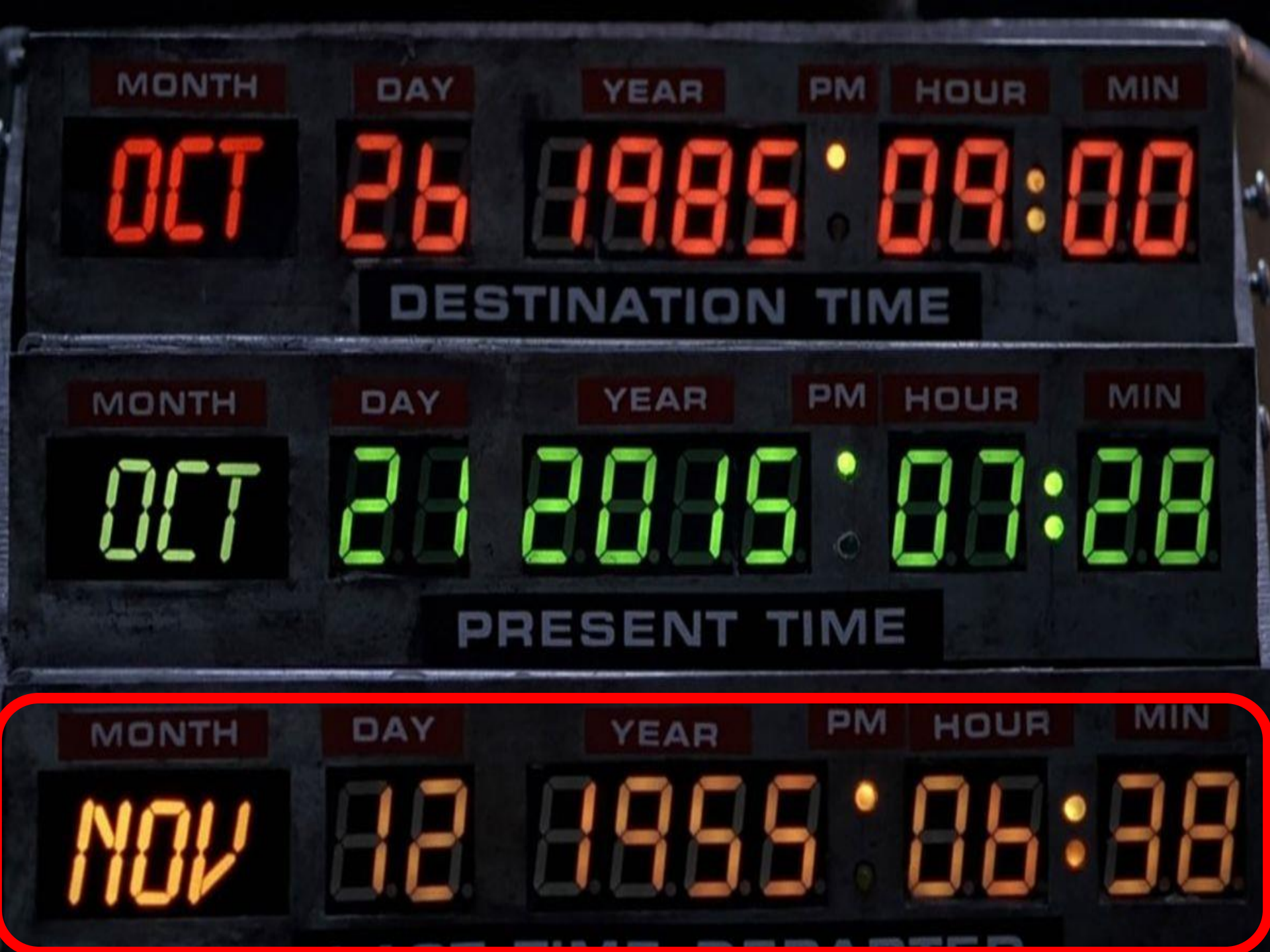
- Inoculum size
- Blood virus concentration
- Virulence of the virus
- Amount of specific circulating antibodies

- Physical exertion
- Intramuscular injection
- Skeletal muscle injury

Coxsackie viruses A and B

- Both groups **cause aseptic (nonbacterial) meningitis**
- Group A causes **herpangina**, a fever that starts abruptly with vesicles or ulcerations on the tonsils and palate**; hand, foot and mouth disease**
- **Group B virus** infects various organs, especially he **heart**
- Most enterovirus infections are accompanied by viremia
- All enteroviruses multiply in the CNS, and some in the heart (**myocarditis**), respiratory tract (**pleurodynia**) or in the mucous membranes of the eye (**hemorrhagic conjunctivitis**)

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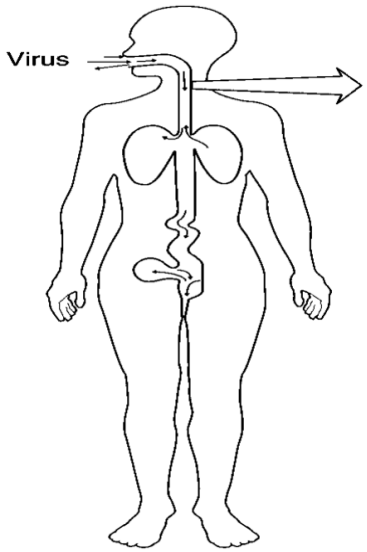
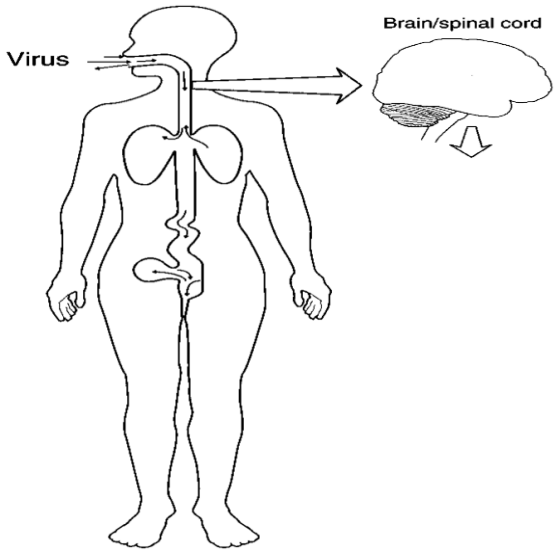
Polio virus

Year: 1955



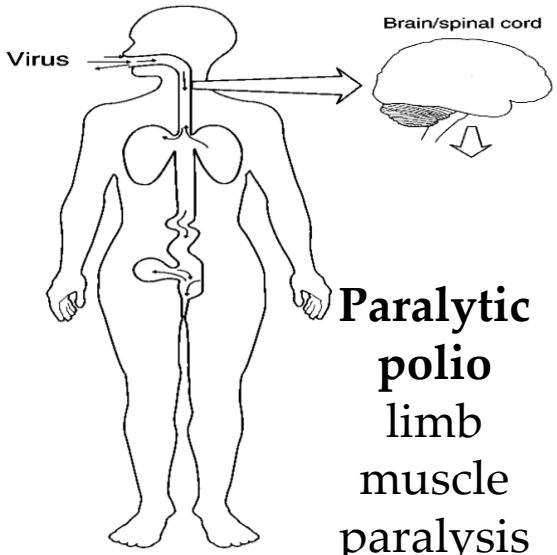
Polio virus

Year: 1955



Polio virus

Year: 1955

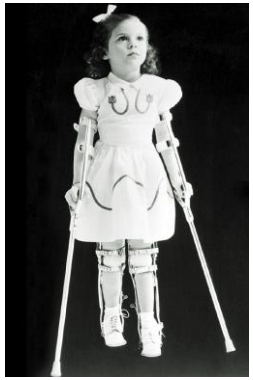


Paralytic polio

limb

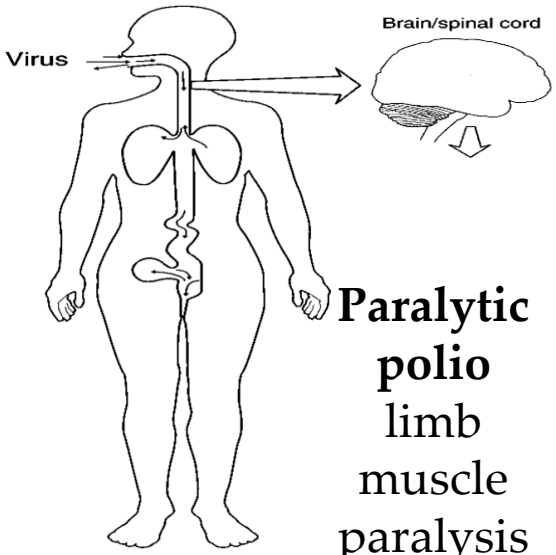
muscle

paralysis



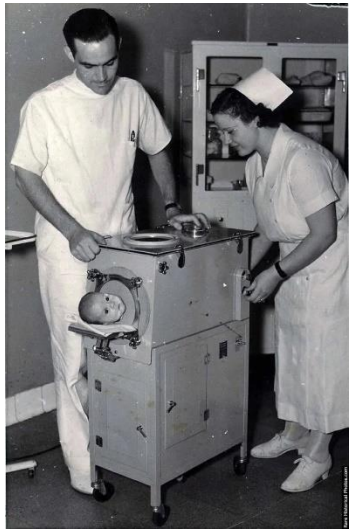
Polio virus

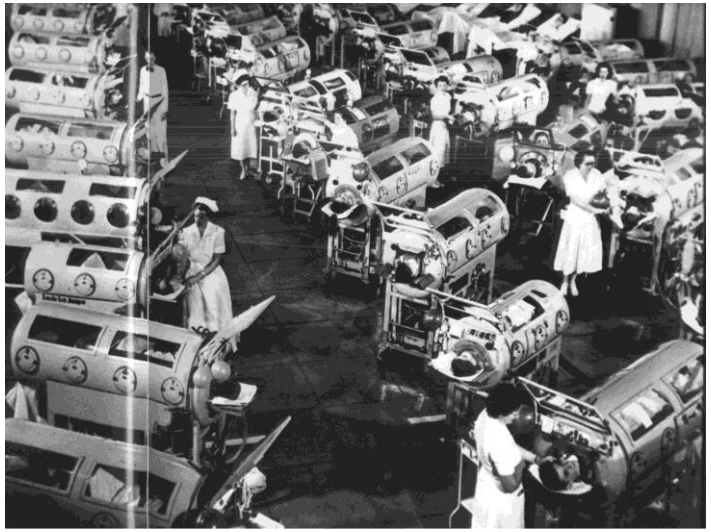
Year: 1955

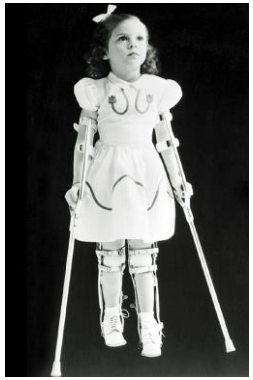


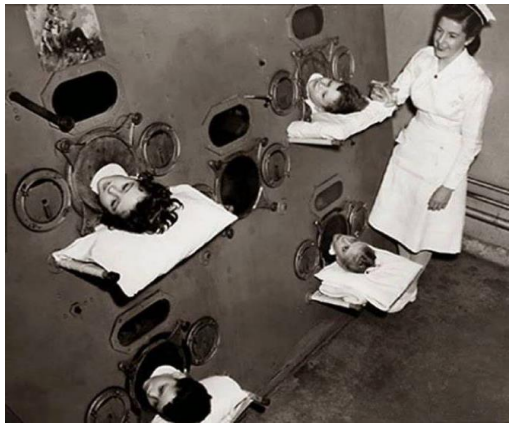
Paralytic polio limb muscle paralysis

Bulbar polio paralysis of the respiratory muscles









Polio vaccines

Polio vaccines

Salk`s vaccine
1955


All Local Teams Are

Journal American

SALK'S VACCINE WORKS!

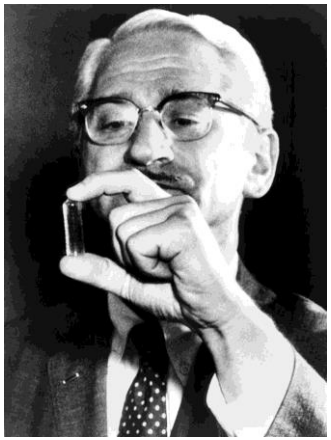
Official Count

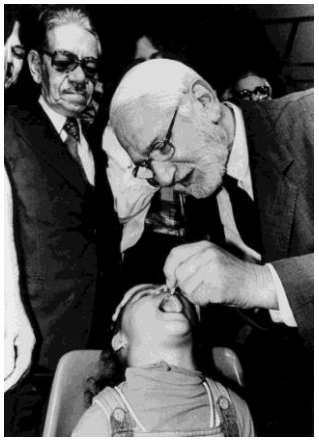
All Local Teams Are Rained Out

Polio vaccines

Salk`s vaccine
1955

Sabin`s vaccine
1960





Polio vaccines

- Poor response to vaccination (obvious similarity to the response to vaccination today)

- Why?

Polio vaccines

- Fear of unknown
- Distrust of citizens

Polio vaccines

- Fear of unknown
- Distrust of citizens

Backstage at CBS Studio 50, before airing of
The Ed Sullivan Show, 1956

Polio vaccines

- Fear of unknown
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Backstage at CBS Studio 50, before airing of The Ed Sullivan Show, 1956

The Herald journal

Parents and children lined up for Sabin oral polio vaccine at Stratford Manor Clinic in Madisonvile. 1960.

Polio vaccines

Immunization level in the USA rises from 0.6% to 80% in just 6 months

Backstage at CBS Studio 50, before airing of The Ed Sullivan Show, 1956

The Herald journal

Parents and children lined up for Sabin oral polio vaccine at Stratford Manor Clinic in Madisonvile. 1960.


BACK
TO
THE
FUTURE

Diagnosis and therapy

- During the endemic months, people with or without symptoms of the disease can often be isolated from the throat or feces
- Identification by inoculation of a clinical specimen into cell culture
- Enteroviruses are most often isolated from stool, rectal swabs, throat and cerebrospinal fluid
- Viral genomic RNA can be detected by RT PCR

- There is no conventional therapy
- Intravenous immunoglobulin administration is effective in preventing CNS damage in immunocompromised patients with severe coxsackie or echovirus infections

Rhinoviruses

Most commonly isolated viruses from people with mild upper respiratory tract infections (colds)

Members of the family Picornaviridae

Antigenic diversity, over 100 serotypes: human rhinoviruses A (75 serotypes), human rhinoviruses B (60 serotypes) and human rhinoviruses S (48 virus types to date)

Rino Vs. Entero

Enteroviruses are resistant to gastric juice and bile, GIT infections

Rhinoviruses are susceptible

They multiply the fastest at 33 ° C, the temperature of the upper parts of the respiratory tract

Rhinovirus
- method of transmission-

- One person has an average of one infection during the year, and children more often
- Infections are more common in autumn and spring
- **Many serotypes circulate in the population**
- Dominant serotypes change over the years
- The only known reservoirs of the virus are infected
- When people touch their nose or eyes with previously contaminated hands
- Aerosol- sneezing

Colonization and spread of infection

Virus → respiratory tract → specific receptors on epithelial cells:

Large group receptor - ICAM-1
"Small group" receptor - VLDL

Reproduction of rhinovirus in infected cells

Primary infection - epithelial surface of the nasal mucosa

The incubation period from the beginning of the infection to the spread of the virus is 1 to 4 days

Tissue damage

The nose of a person with a cold becomes swollen and red (hyperemic) as a result of dilatation of blood vessels
Serous (clear, sparse) nasal secretions contain a lot of serum proteins
As the disease progresses, nasal secretions become **mucopurulent** and contain many cells, especially neutrophils

Disease severity- amount of viruses in respiratory tract
Clinical symptoms- sequel of anti-viral immune response

Most colds are **mild**
Secondary complications: sinusitis or otitis media, caused by bacteria
Rhinoviruses can cause **lower respiratory tract disease** and worsening asthma

Therapy and prevention

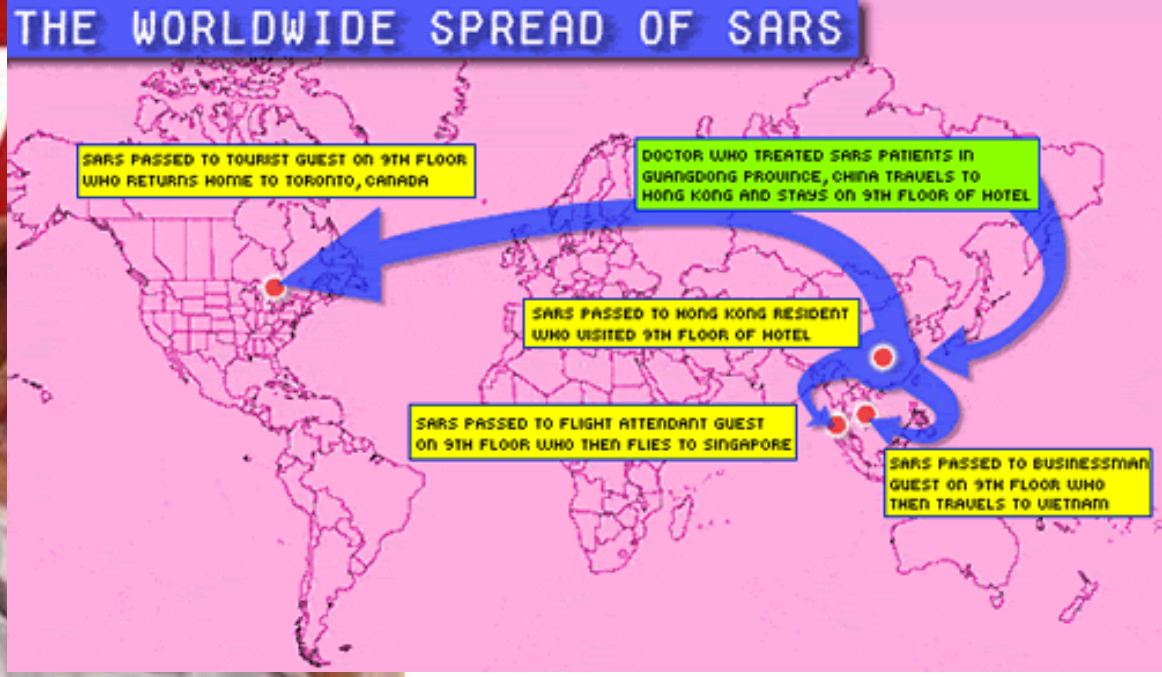
- During infection, neutralizing antibodies are formed in serum and nasal secretions
- Reinfection with another serotype is common
- Use of recombinant interferon α applied by nasal spray
- When administered 5 days before viral infection, interferon was effective in 80% of cases in preventing the disease
- When given for more than 5 days, it induces cold-like nasal symptoms
- Interferon α is no longer used because it cannot effectively remove the virus.

- Designing a rhinovirus vaccine is not feasible as it should include over 100 serotypes

Coronaviruses, SARS.

- With envelope and positive RNA
- They can "go through" rapid genetic changes with changes in the clinical picture
- Spring / Summer 2003, Coronavirus Causes Severe Acute Respiratory Syndrome (SARS)
- Southeast China, worldwide, potential for high mortality
- SARS is thought to be an animal virus from bats
- RNA-dependent RNA polymerase has a high degree of error during operation with a high potential to make numerous changes in the nucleotide sequence, during replication

Newsw

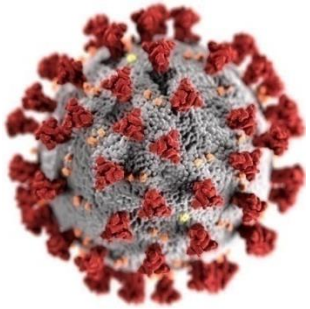


SARS

What You Need to Know

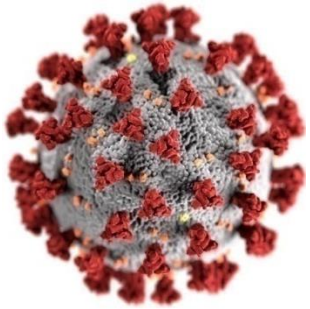
The New Age of Epidemics

Coronaviruses, SARS COV-19



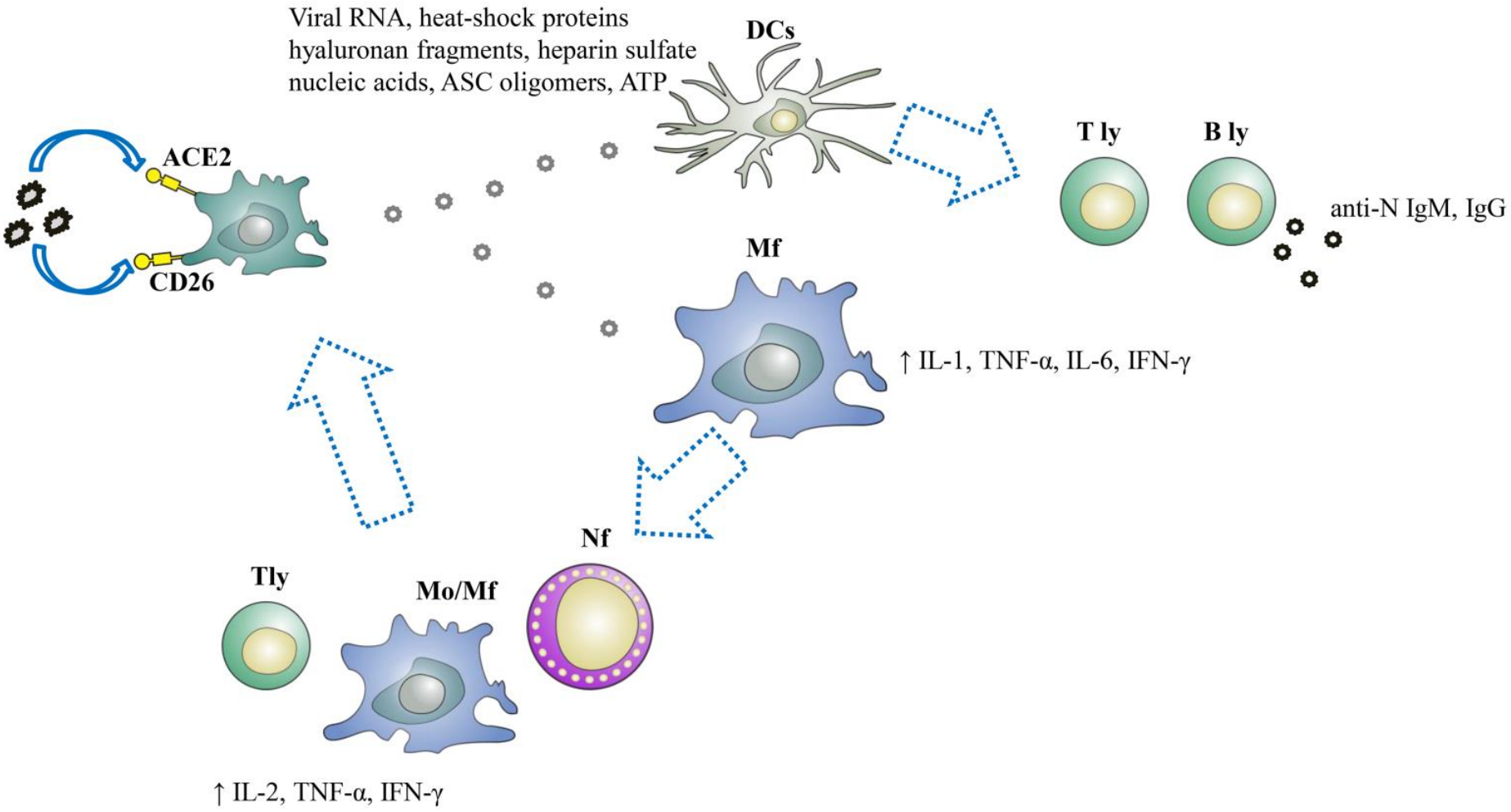
- Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) - a new corona virus discovered in 2019.
- COVID-19 is the name of a disease caused by a virus.
- Bats are the natural hosts of the corona virus.
- Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was transmitted to humans from a camel.
- In the first eleven months of the COVID-19 pandemic (December 31, 2019 to December 14, 2020), there were over 71 million cases worldwide and more than 600,000 deaths.
- SARS-CoV-2 is mainly transmitted through respiratory droplets and aerosols.
- The virus has also been isolated from faeces, indicating that faecal transmission is a possible route of infection.

SARS COV-19

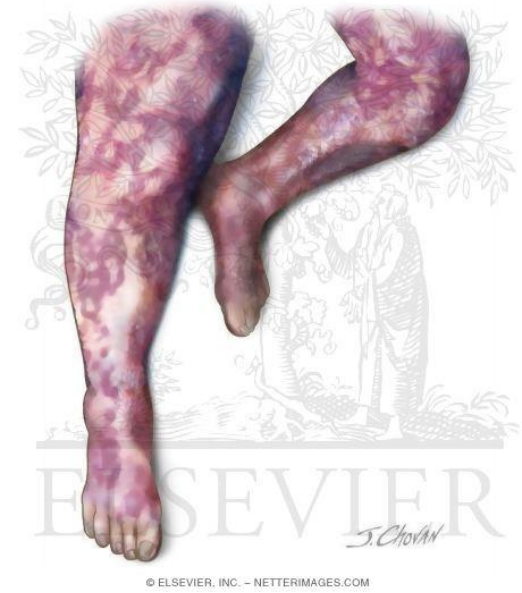


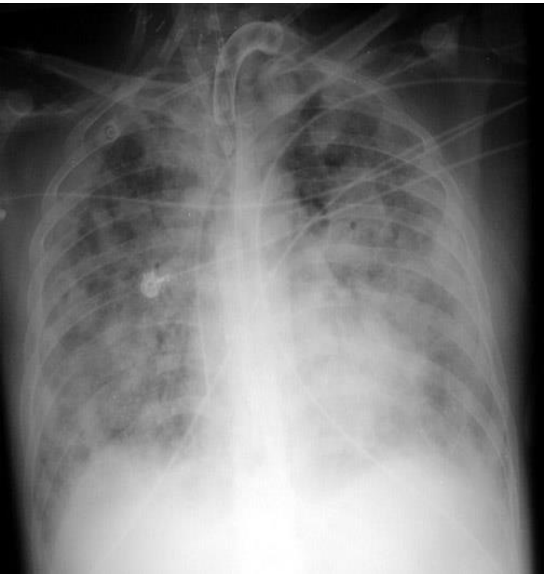
- The incubation period for COVID-19 is estimated at one to 14 days.
- The infectious period begins about two days before symptoms appear, but people are most contagious during the symptomatic period, even if the symptoms are mild and nonspecific.
- About 10% of diagnosed cases of COVID-19 are hospitalized, depending on age, and up to 20% of those hospitalized need ventilation support

SARS COV-19 immunopathogenesis



SARS COV-19 clinical picture





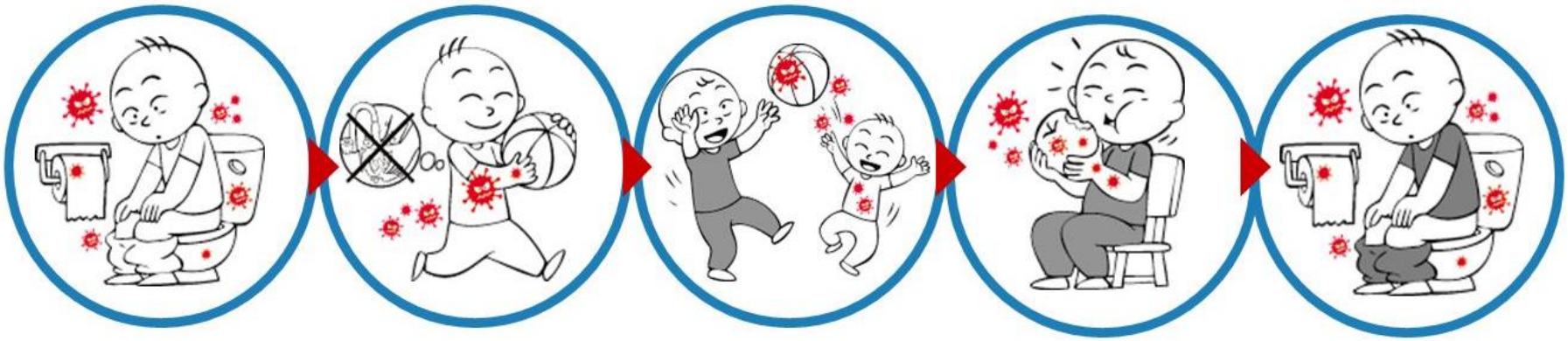
- Fever, malaise, cough, headache, loss of taste and smell, itching and burning of the skin, sneezing, feeling of dry throat
- Hypoxia, haemoptysis, lymphopenia, diarrhea
- Venous thromboembolism
- Systemic inflammatory response syndrome (SIRS) (cytokine storm)
- Acute respiratory distress syndrome- ARDS

Viruses that cause gastroenteritis : *Rotavirus, Norovirus*

- Primary rotavirus infection between 6 months and 2 years
- Most people have been in contact with the virus and are immune to more severe infections by the age of four
- Complication - dehydration that "accompanies" viral gastroenteritis, malnourished children and adults, in developing countries and the elderly
- Seasonal character, in the winter months.
- In the tropics, endemic infections throughout the year
- The disease can occur after contact with asymptomatic carriers
- Rotavirus excretion is possible weeks before diarrhea and days after withdrawal

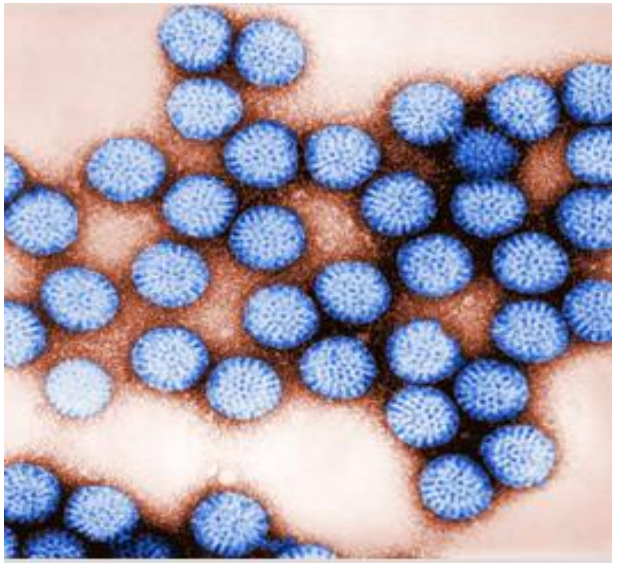
Rotavirus
- colonization and spread of infection-

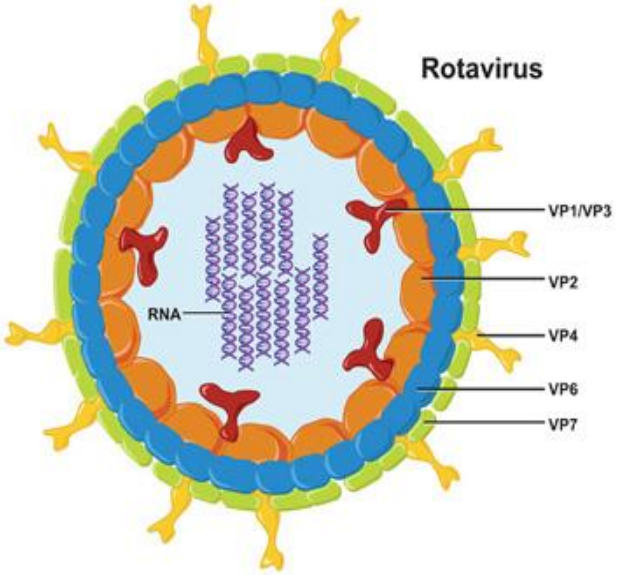
- In endemic areas, infections are primarily transmitted by contact, **feco-oral route**
- Rotaviruses are excreted in the faeces
- Infection is rarely transmitted by contaminated food and water
- Respiratory, aerosol?



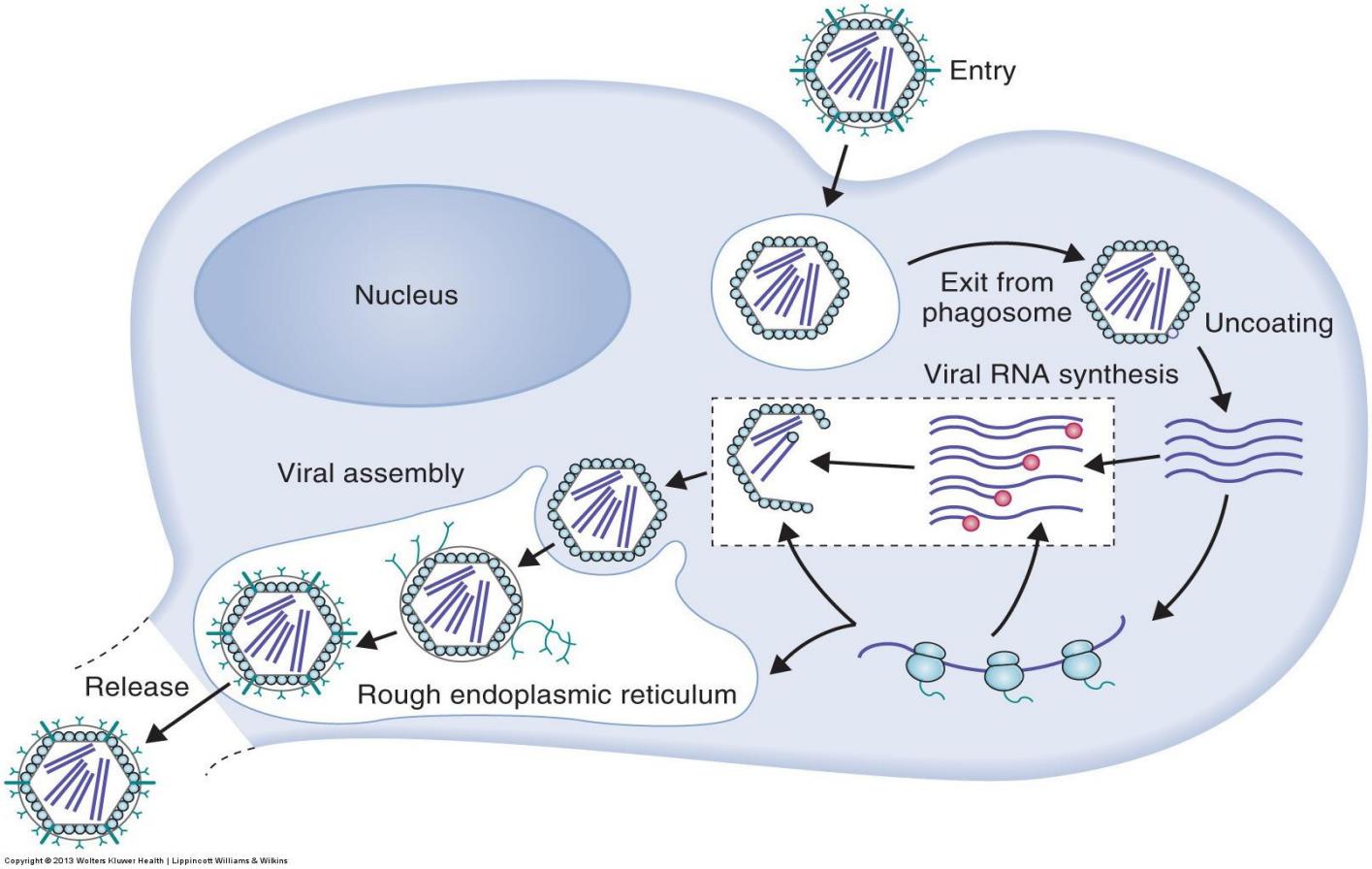
Rotavirus - virion structure

- **Double RNA**, whose structure resembles double DNA
- **Segmented genome** (as well as orthomyxoviruses)
- Icosahedral structure with inner and outer capsid
- Two outer capsid proteins, **hemagglutinin** (VP4) and **glycoprotein** (VP7) induce the formation of neutralizing antibodies
- The capsid contains 11 double RNA segments as well as viral **RNA-dependent RNA polymerase** (transcriptase) for the transcription of individual RNA segments into information RNA
- Based on antigenic characteristics, we distinguish 6 groups of viruses (A to F)





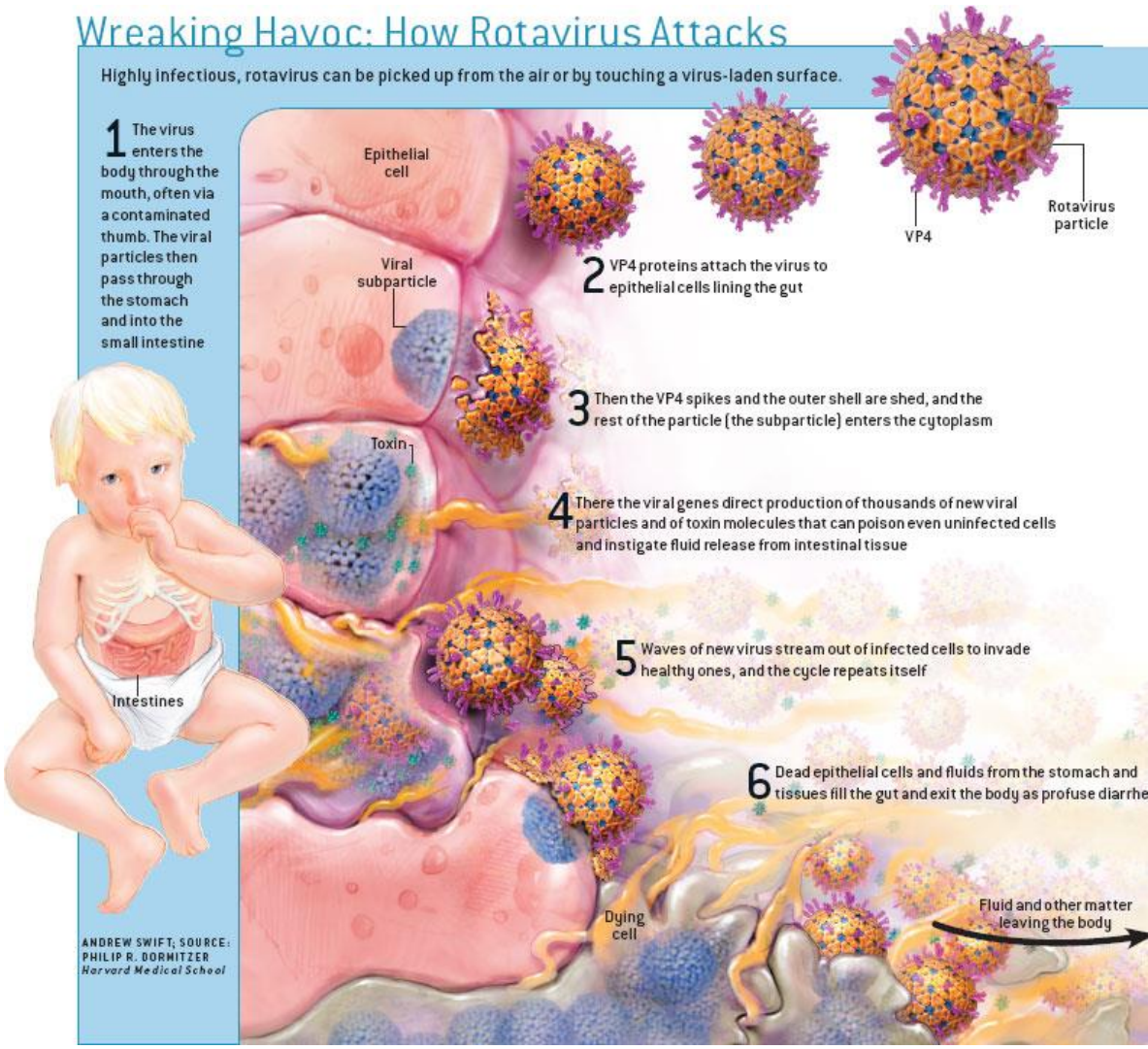
Rotavirus -replication



The virus multiplies in the cytoplasm, forming both positive and negative RNA. Positive RNA serves as a template for translation (as information RNA) and for replication of negative RNA. Viral particles assemble in the cytoplasm and mature in the endoplasmic reticulum. Mature viral particles emerge from the cell by lysis of the infected cell.

Tissue damage

- From asymptomatic infections to **severe diarrhea** with potentially fatal **dehydration** (in children 6 to 24 months)
- Two-day incubation period
- **Vomiting** precedes diarrhea, 2-3 days
- **Watery stools** can last 3-8 days in children
- Fever and stomach cramps are common symptoms



Tissue damage

- Upper parts of the small intestine: shortening and atrophy of the fork, mononuclear infiltrate in Lamina propria
- Virus invasion → destruction of cells that replace new, immature cells without virus → diarrhea
- reduced water and mineral absorption capacity
- reduced disaccharide production capacity → carbohydrate malabsorption
- production of proteins that function as endotoxins and stimulate the secretion of minerals and water into the lumen of the GIT
- activation of the enteric nervous system

- Chronic diarrhea and prolonged germination are characteristic of children with T-cell immunodeficiencies or people on immunosuppressive therapy.

Diagnosis, therapy and prevention

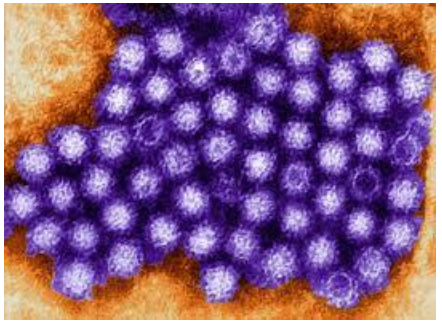
- Essays that detect viral antigens in stool are most often used in diagnostics.

- There is no specific therapy for viral gastroenteritis
- Patient care is focused on symptomatic therapy, intravenous and oral rehydration.
- Oral immunization with live attenuated rotavirus vaccine is effective in preventing severe forms of the disease.
- Two live attenuated vaccines (human and cow's) have been registered for use and vaccination is recommended from 6 to 14 weeks of age.
- This vaccine should not be given to immunocompromised children
- The use of vaccines today makes rotavirus-induced gastroenteritis a disease that we can easily prevent.

Norovirus, Norwalk virus

- Noroviruses are members of the family Caliciviridae, genus Norovirus
- They are named after the geographical areas where the epidemics occurred (Hawaii, Snow Mountains and Montenegro agent) and are very diverse.

- These viruses cause epidemics with an incubation period of 1-2 days after exposure to the source of infection
- During the **winter months**



- Contaminated food or water as well as direct contact
- Feco-oral route, aerosols, after vomiting

- People of all ages, most often adults and school children
- After rotavirus, they are the **second leading cause of diarrhea in children**
- Asymptomatic infections are common

Norovirus, Norwalk virus -replication and tissue damage-

- They cannot be cultivated in the laboratory

- **Gastroenteritis** is mostly mild and self-limiting
- The disease can last from **24 to 48 hours**

- Vomiting and diarrhea, just vomiting, just diarrhea

- Nausea, abdominal cramps, diarrhea, vomiting and general weakness

- Prolonged gastroenteritis (months or years) may occur in immunocompromised patients

- Peristalsis was slowed and malabsorption of fat, xylose and lactose was detected.

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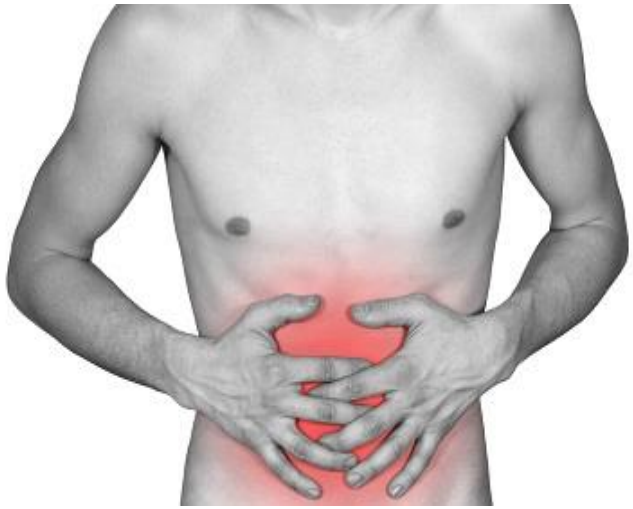


Therapy and prevention

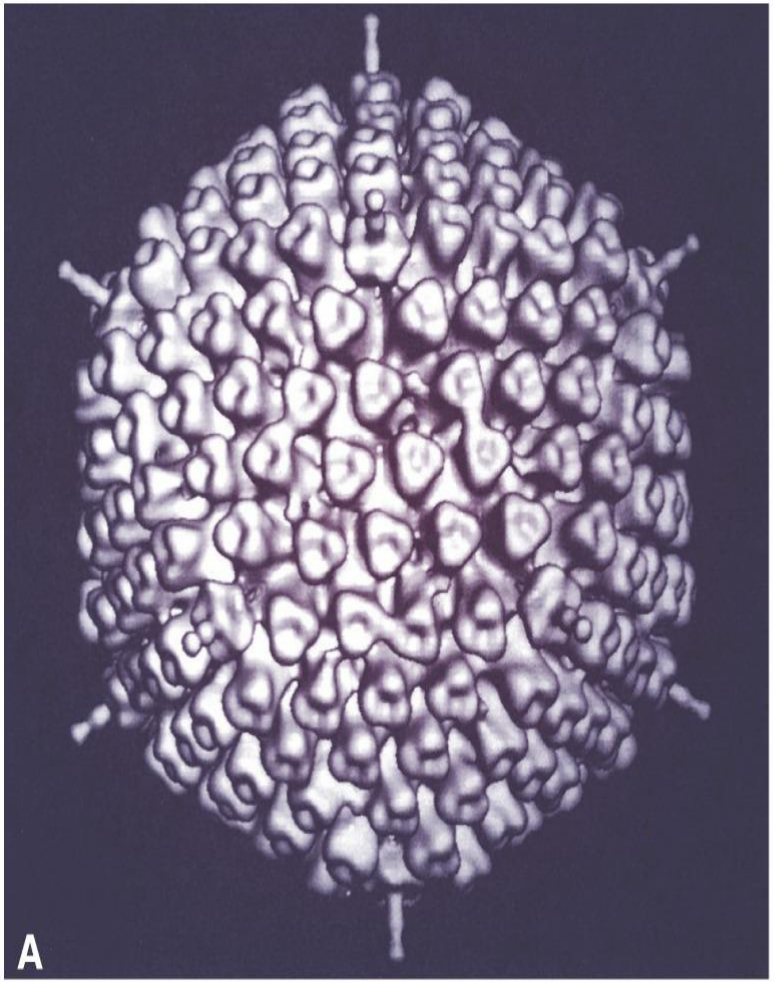
- There is no specific therapy
- The symptoms of the disease usually pass without complications and oral fluid and electrolyte replacement is usually sufficient
- In severe cases of vomiting and diarrhea, parenteral fluid replacement is required

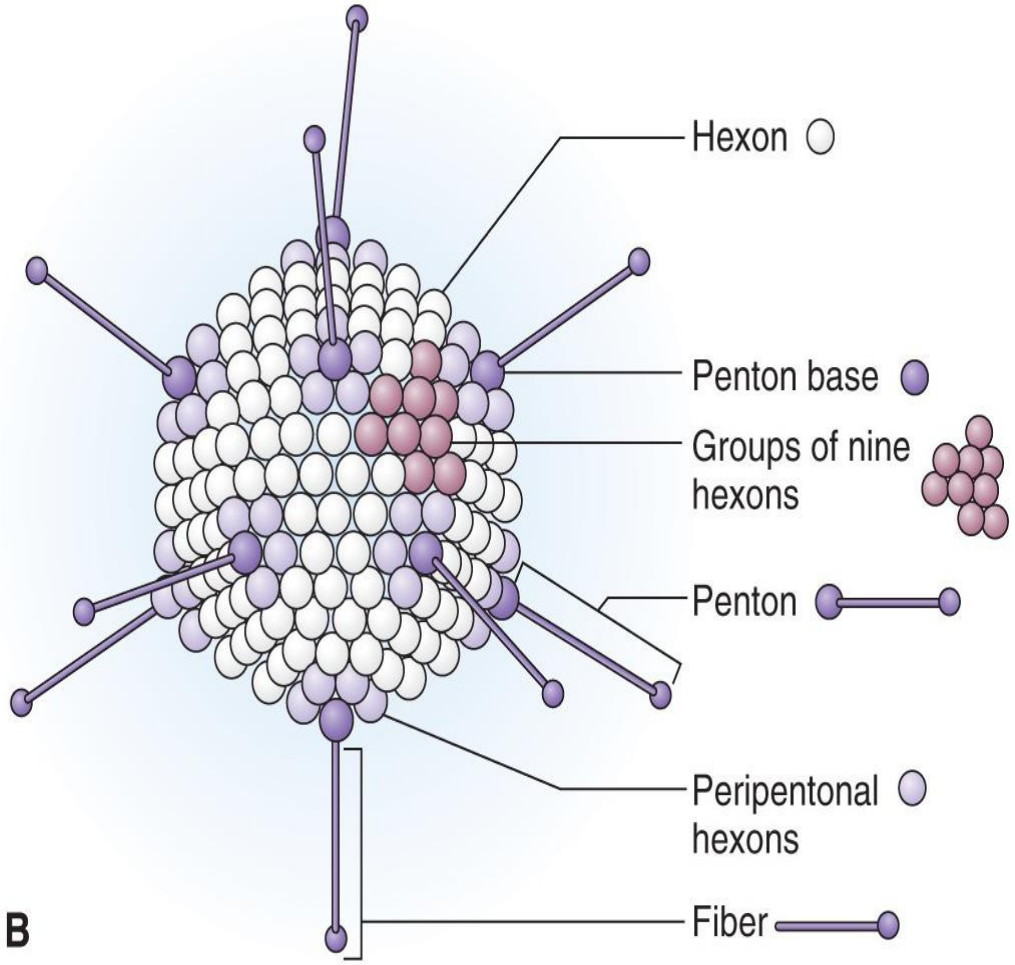
- Norovirus vaccines are being tested.

Family *Adenoviridae*

- Sheathless virions with icosahedral structure
- Single capsomeres (hexones and pentones)
- Pentons have fibers that give the virion its characteristic appearance
- Viral DNA is linked to the "**nucleus**" (neutralization of negative charge)

- Adenovirus genes with associated functions are usually grouped in the genome and expressed by a common promoter
- **Gene grouping**:
- those whose products interact with the host immune system (early region genes 3; E3)
- participate in post-transcription events (E1V and E4)
- participate in viral DNA replication (E2)
- form a virion or are involved in its assembly (L1-L5)





Adenoviridae
-mode of transmission-

- Widespread infections
- Most in childhood: 75% before 14 years of age, and almost half of all infections before 5 years

- **Respiratory** or **gastrointestinal** tract, almost equally

- Deaths have also been reported in previously healthy people with some manifestations of the disease (pneumonia) or in immunocompromised

- Antibodies produced during adenovirus infection do not provide protection against infection with another strain of the virus
- Many adenovirus serotypes allow for recurrent infections throughout life

Adenoviridae
- colonization and spread-

- Aerosols or infected body fluids such as saliva (for respiratory infections)
- Food and water or faecal contaminated surfaces (for enteric infections)
- Direct inoculation of the virus into the eye

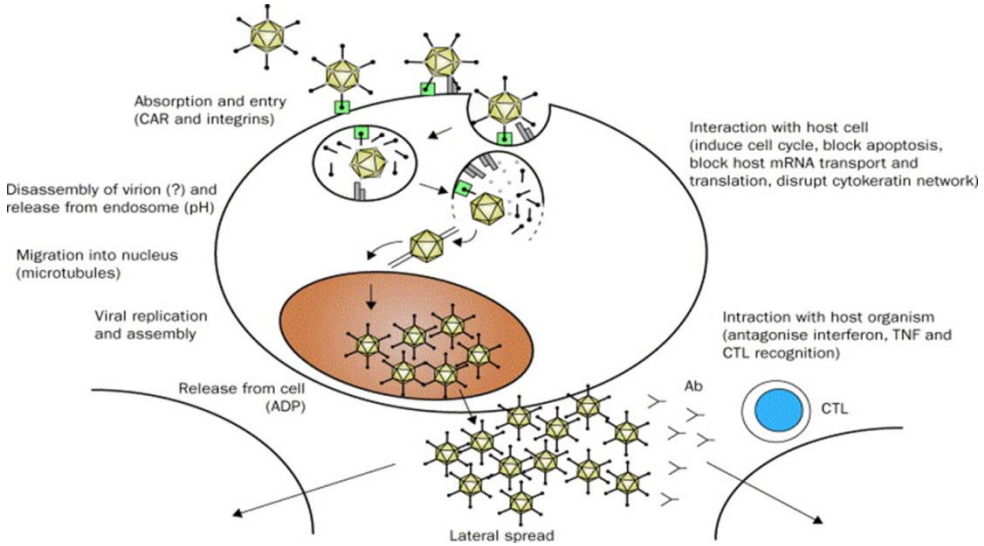
- The place of initial replication of the virus is most often the oropharynx
- Local infection → viremia → spread through the bloodstream

- Destruction of infected cells and the immune response to infection are the main mechanisms of tissue damage

- The virus is released from the lungs, oropharynx and stool and is thus transmitted to new individuals.

Adenoviridae -replication

- Adenoviruses → receptors on host cells via fibrous protein - CAR (Coxsackievirus and Adenovirus Receptor)
- The virus-receptor complex migrates into clathrin-coated wells, which form endosomes that carry viral particles into the cell.
- After entering the cell, the pH in the endosomes decreases and the pentones are removed from the virus particle.
- Rupture of the endosome membrane → transition of the virus into the cytoplasm → migration into the nucleus, the nucleus of the virus enters the nucleus, leaving out the rest of the capsid



Replication. Gene expression

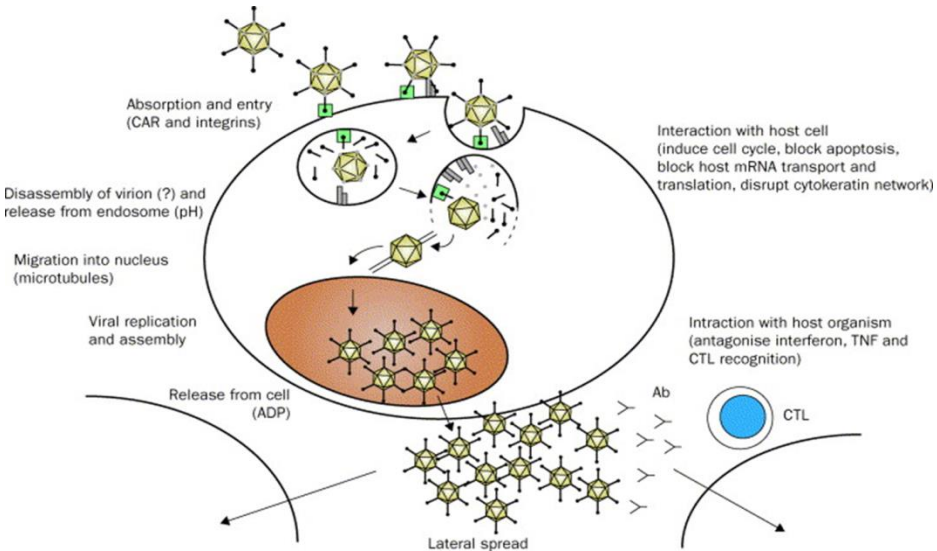
- Temporary gene expression, synthesis of a specific set of proteins
- The synthesis of proteins required for viral DNA replication precedes the synthesis of proteins that form the viral particle

- Accumulation of copies of viral DNA before their packaging in capsids

- Gene expression goes through three stages:
- Immediate phase
- Early phase
- late phase

Adenoviridae -replication

- When enough capsid protein accumulates, virion assembly begins
- It starts with the formation of hexones and pentones (capsomeres)
- Pentons assemble spontaneously, while hexon assembly requires the engagement of proteins that are not part of the viral particle - protein scaffolding
- Empty viral particles - hexons
- Pentones and fibrous proteins then bind to the capsid
- Adenoviruses come out of the cell, by lysis



Adenoviridae
- tissue damage-

- **Respiratory infection** resembling a cold
- Systemic symptoms: chills, headache, malaise and fever are common
- Conjunctivitis
- Pneumonia

- **Acute GIT diseases** in children
- Adenovirus type 12 is associated with the pathogenesis of celiac disease (gluten enteropathy), due to the homology of Ad12 early protein and gliadin-α

- Mild "**pool conjunctivitis**" is most likely caused by an adenovirus infection

Adenoviridae
-immune response

- The antiviral response is mediated by cellular mechanisms: destruction of infected cells by **cytotoxic T lymphocytes**
- Adenoviruses induce resistance to apoptotic signals from cells of the immune system

- Antiviral state of the cell induced by interferon α and β
- Adenoviruses block the effect of interferon through small RNA molecules (VA RNAs), VA RNAs bind to PKR proteins and inhibit their activity, thus keeping the translational machinery functional

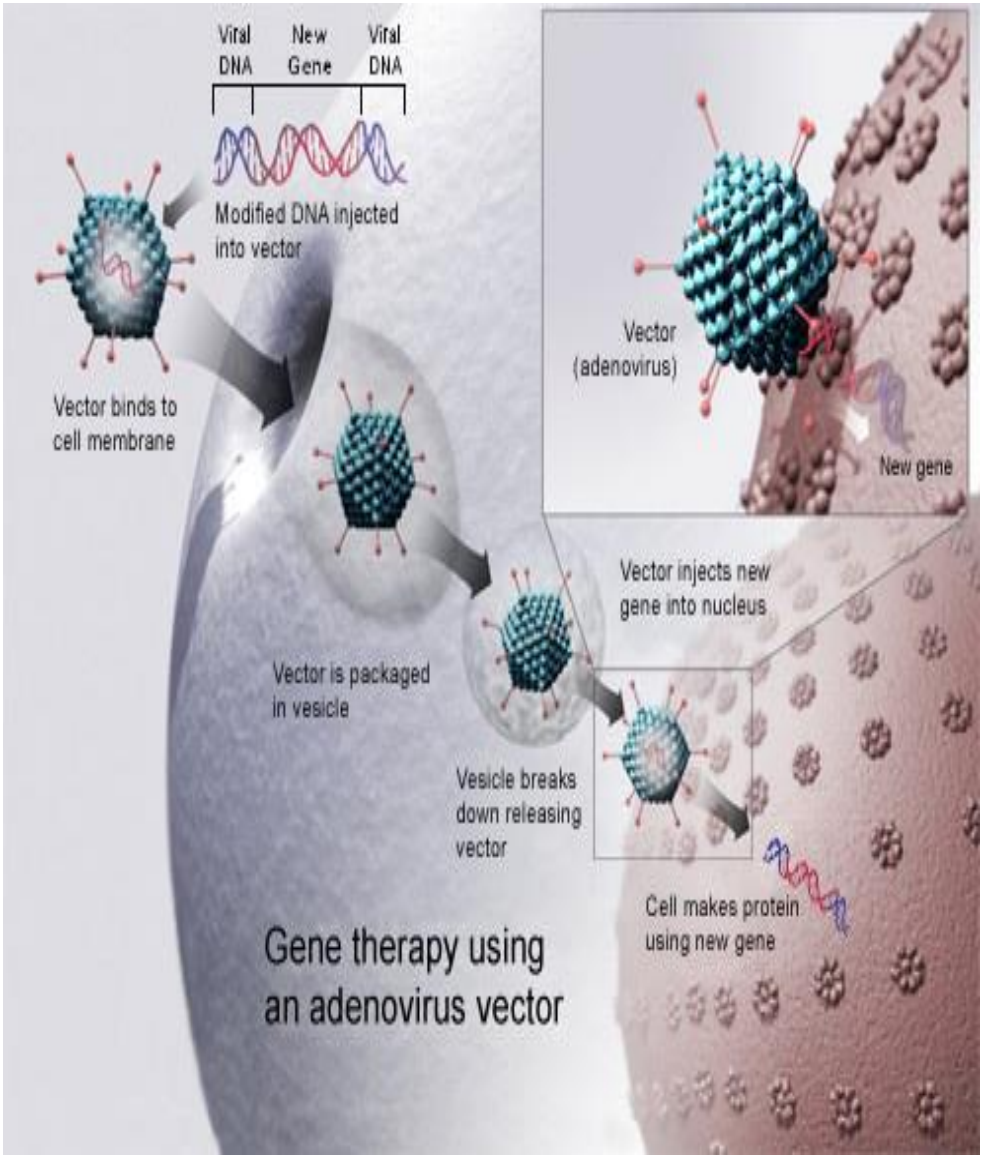
- Adenoviruses inactivate DNA repair systems in the cell by proteolytic degradation

Adenoviruses as gene transfer vectors

- During the development of a safe and effective vaccine to prevent acute respiratory disease, the idea of using recombinant adenoviruses to immunize against other pathogens was developed.

- **Gene therapy**. The introduction of a functional factor VIII gene into the corresponding cells can restore the function of this factor and the coagulation process itself.

- **Tumor therapy**



Therapy and prevention

- Mainly due to the risk of severe infections in patients after transplantation, great effort has been made in finding anti-adenoviral drugs
- Several developed drugs have been shown to be effective against adenovirus in cell cultures, but have not yet shown the desired results in animals to justify use in humans.

- Adenoviruses are not a major social health problem that would justify vaccine design.
- However, **acute respiratory disease** is a severe manifestation of the disease, common in recruits during basic training. 25-50% of cases require hospitalization.
- The live oral adenovirus vaccine was developed in the 1960s.

Family *Paramyxoviridae*

Morbilli virus, *Mumps* virus, Respiratory syncytial virus(RSV)

- Single negative RNA
- Viral RNA - dependent RNA polymerase
- The virion leaves the cell by budding
- Lipid envelope, originating from the cell membrane
- Membrane glycoproteins (virulence and tropism), antigens for protective neutralizing antibodies

- Respiratory transmission → **respiratory infections** (CNS)

Paramyxoviruses are rarely recombined

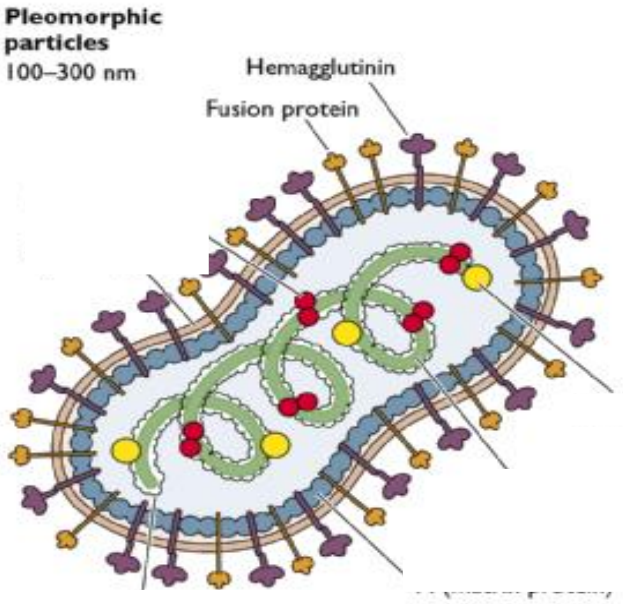
Genetic diversity is possible only through point mutations, during replication

Measles- Morbilli virus

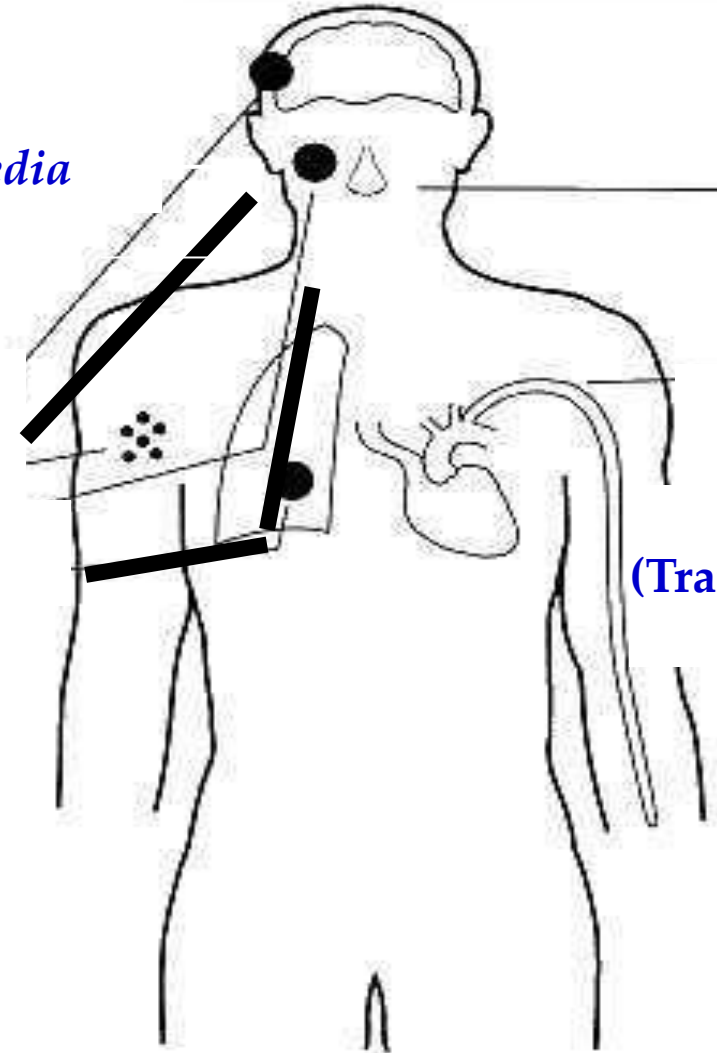
- RNA gene that encodes 8 proteins

- Hemaglutinin (H) serves as a binding protein and binds for receptors on host cells
- The F protein mediates in the connection of a cell membrane viral sheath and makes it easier to enter the cell in the cell
- F protein- formation of gigantic cells or syncitions

- One serotype circulates by population



Morbilli virus
-pathogenesis-



encephalitis

otitis media

replication in the upper part of resp. tract

primary viremia

rash, highт°

pneumonia

Lymph tissue (Transient immunosuppression)

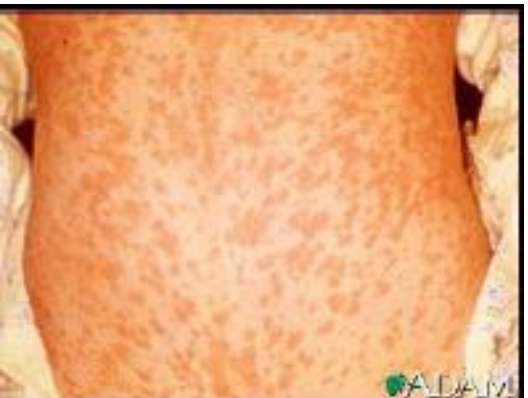
secondary viremia

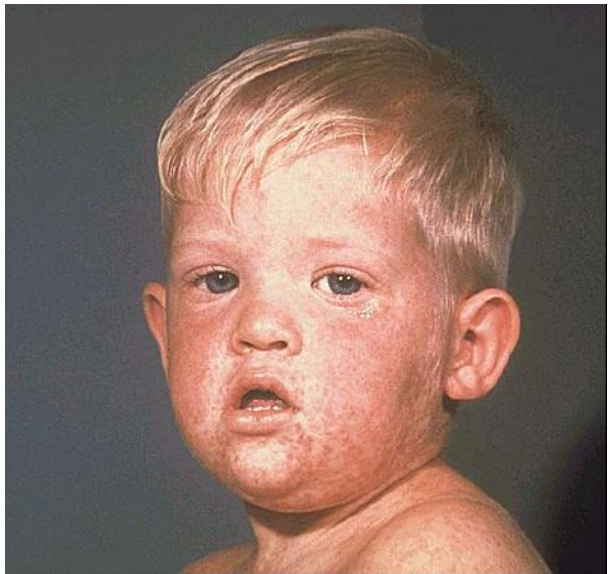
dissemination (skin, lungs, brain)

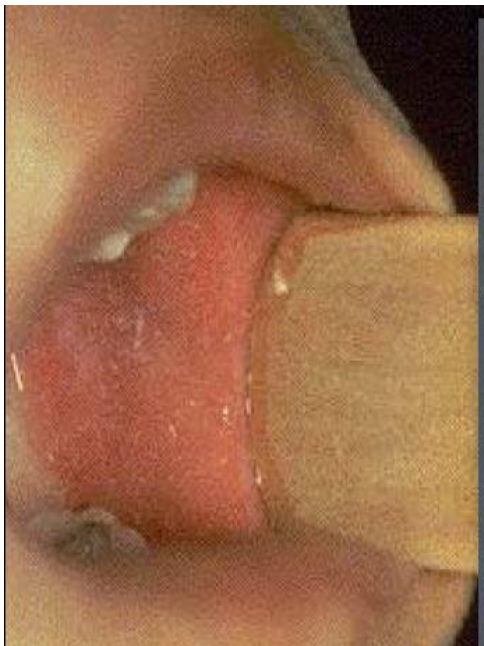
virus induces the appearance of giant multi-nucleus cells

Morbilli virus
-tissue damage-

- **Damage to the epithelium and endothelium** by cytotoxicity of the virus
- Epithelial cell infection → Gigantic cells
- Endotel cell infection → dilatation and increased permeability of blood vessels
- **Immune host response** contributes to tissue damage
- **Koplik's spots**
- Organ-specific complications as pneumonia, diarrhea and encephalitis can also occur

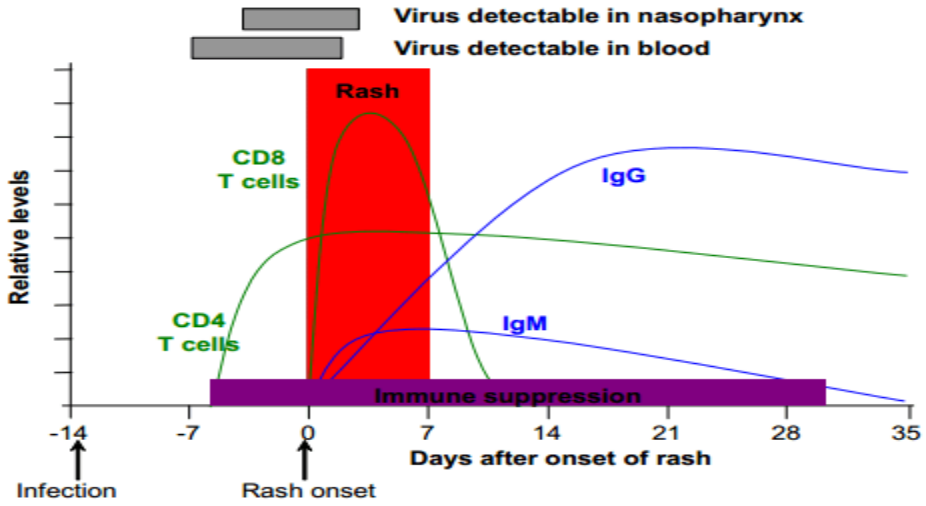






Morbilli virus
- Immune response-

- The appearance of the rash coincides with the appearance of virus-specific antibodies
- IgM, IgG antibodies persist for life
- Cellular immune response
- Postinfectious immunosuppression, secondary infections
- Vitamin deficiency
- Morbilli virus nucleocapsid protein binds to the inhibitory receptor on V lymphocytes (FcγRII) and stops the production of antibodies



Morbilli virus -complications

- **Respiratory superinfections**: pneumonia, otitis media and laryngotracheobronchitis commonly caused by S. pneumonie, S. aureus and Haemopilus influenzae
- **Eye diseases** can occur, especially in children with vitamin A deficiency and are an important cause of blindness in endemic areas of Africa and India.
- **Acute disseminated encephalomyelitis**, neurological consequences of deafness or intellectual impairment
- **Subacute sclerosing panencephalitis** (SSPE), with mental and personality disorders

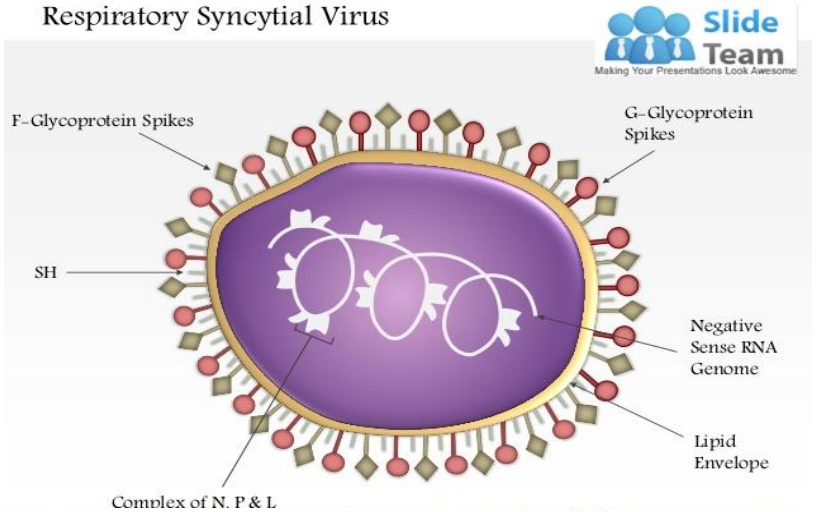
Diagnosis, therapy and prevention

- A prodromal period of 2-3 days with fever, cough and conjunctivitis, followed by the appearance of a rash indicates smallpox. Koplik's spots are pathognomonic for smallpox. The rash that follows spreads from the head to the trunk and begins as discrete macules and papules that merge over time.
- Morbilli virus- specific IgG antibodies. Methods that detect the viral genome (PCR) are very sensitive but not available everywhere.

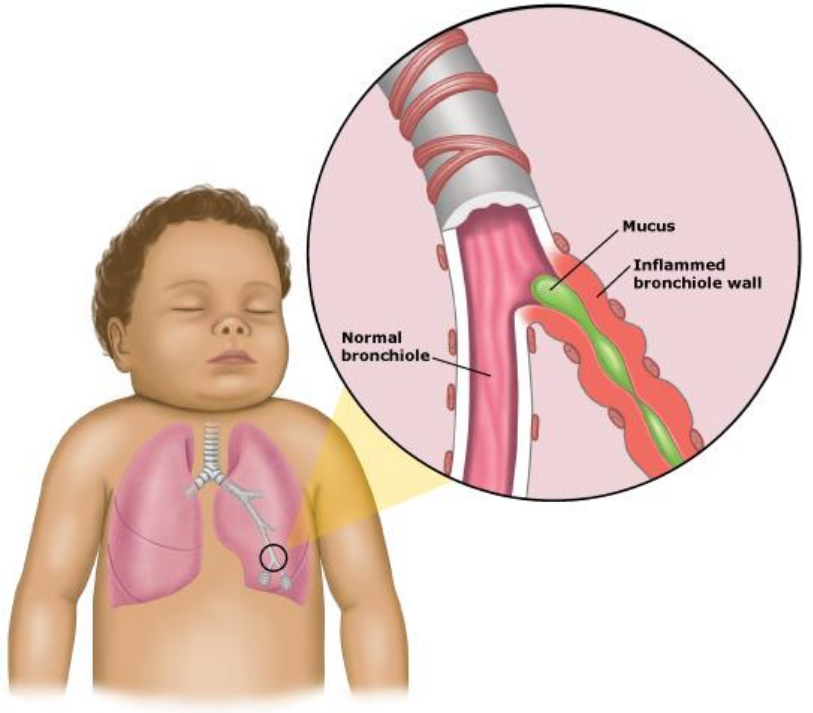
- Giving vitamin A to children with smallpox in high-risk regions.
- A combination of Morbilli-Mumps-Rubella (MMR) vaccines containing attenuated all three virus types. The first dose of the vaccine is given at 12-15 months of age. The second dose is taken in 4-6 years. The presence of maternal antibodies in the circulation prevents the response to the vaccine, which is a problem in endemic areas.

Respiratory syncytial virus(RSV)

- Ubiquitous causative agent of respiratory tract infection in children
- The major surface glycoproteins are highly glycosylated (G) protein and fusion (F) protein

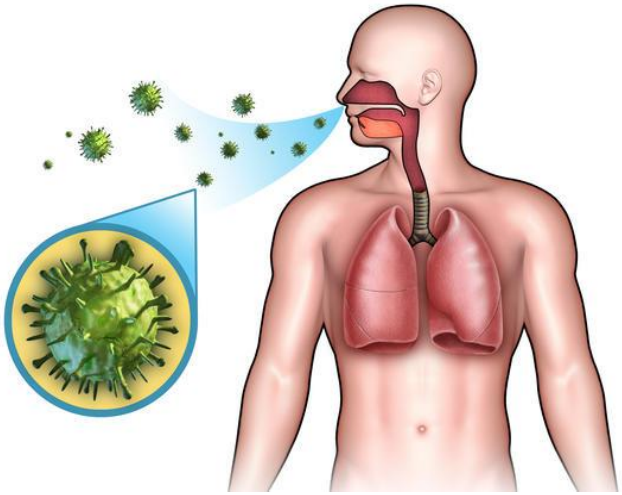


- **Bronchiolitis** with cough, dyspnea and accompanying respiratory sound phenomena
- Laryngo-tracheo-bronchitis or **croup** and focal alveolar disease
- RSV is associated with **asthma**



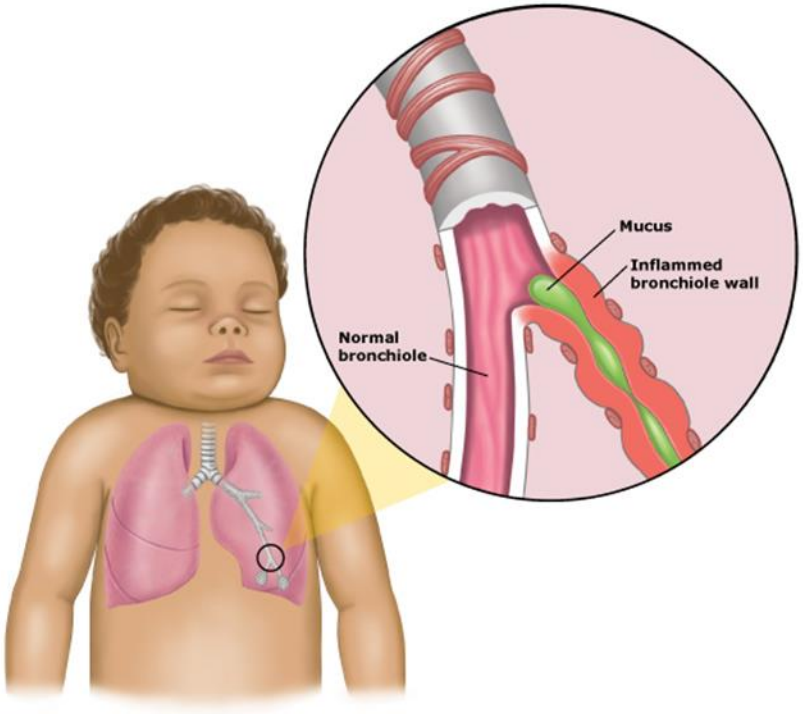
RSV
- mode of transmission and colonization-

- People are the only known hosts
- **Flige's drops**
- Immunity does not protect against diseases of the upper parts
- Antigenic variations of the virus
- In temperate climates, during the winter months
- In the tropics, all year round
- Almost all children have symptomatic primary infection, and 40% have signs of involvement of the lower parts of the respiratory tract



RSV
- spreading and tissue damage-

- RSV infection does not spread to other parts of the body
- Children are infectious a few days before they get sick
- RSV is **cytotoxic to the epithelial cells of the respiratory tract**, impairing cilia function
- The host's immune response plays an important role in the pathogenesis of the disease
- **Intense leukocyte infiltration peribronchially with edema contributing to airway obstruction**



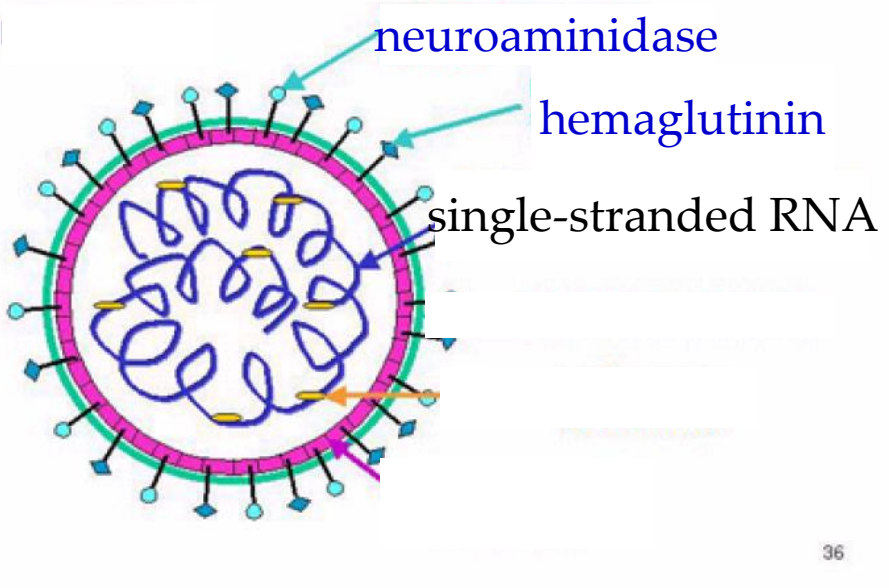
Therapy and prevention

- There is no effective antiviral therapy against RSV
- Oxygen and fluid replacement are extremely important
- Bronchodilators are of little importance

- There is no licensed vaccine for RSV today
- The need for vaccination very early in childhood
- The perfect balance of attenuation and immunogenicity of vaccines
- Passive immunoprifylaxis. Palivizumab is a humanized monoclonal antibody specific to the F protein. Antibody is given once a month intramuscularly during the RSV infection season during the first year of life. Palivizumab is one of the most successful and most usable monoclonal antibodies today.

Mumps virus

- family*Paramyxoviride*
- The virus genome is a single-stranded negative RNA



Mumps virus -pathogenesis

Entrance:
Nose mucosa and the lips of the cavity

↓

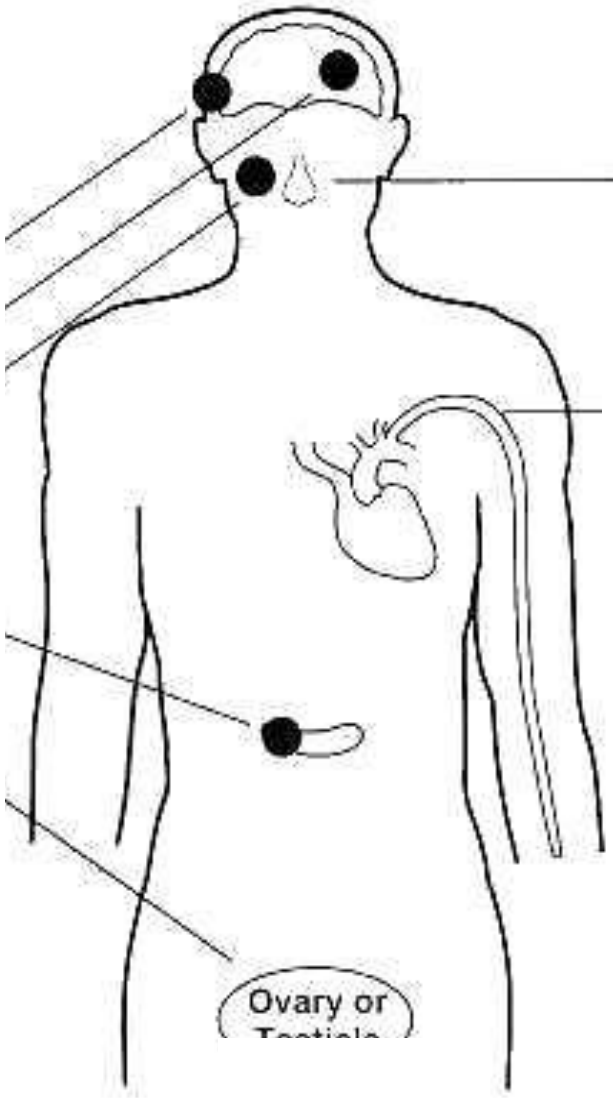
Regional lymph nodes

↓

transient viremia

↓

dissemination



CNS

parotide gland

miocard

pancreas

testicle and ovaries

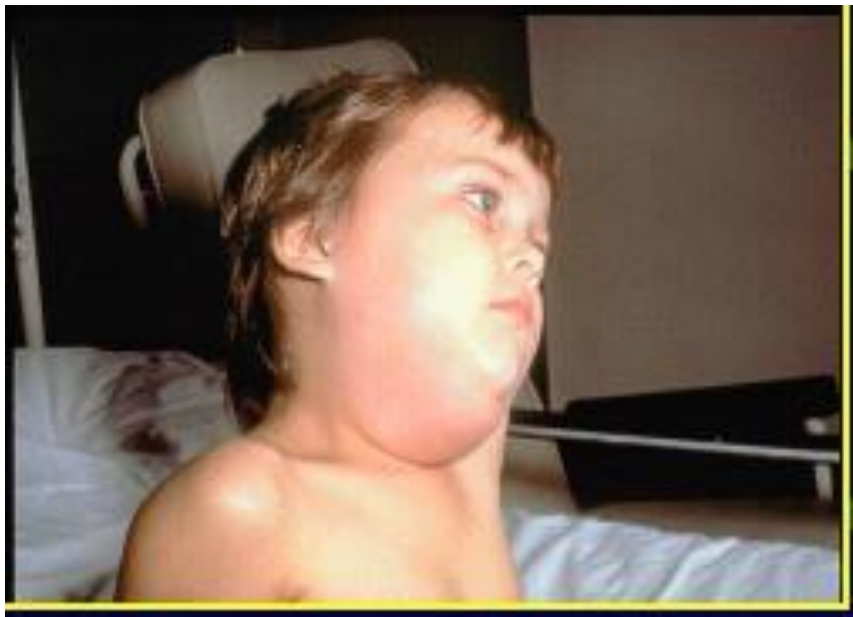
The cytocidal effect of the virus induces the inflammatory reaction

Mumps virus
-Clinical manifestations-

- salivary glands: parotitis (mumps)
- CNS: meningitis, encephalitis
- Pankreas: Pancreatitis
- Testis: Epididyme-Orhitis
- ovaries: oophoritis
- Less often complications: myocarditis

salivary glands edema,

The virus is in saliva 7 days before and 9 days after the symptoms



Diagnosis and prevention

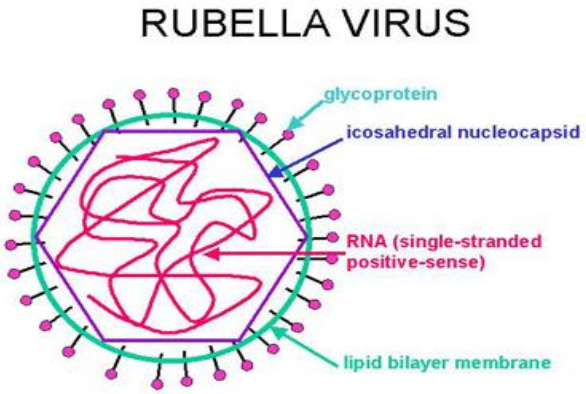
- Virus insulation (saliva, urine, lickvor)
- Detection of virus (IF)

- MMR vaccine (Mumps-Morbilli-Rubella)

Family *Togaviridae*, genus *Rubivirus*
Rubella virus

Causative agent of a **mild rash disease** of children and adults (originally considered a form of small pox) and **severe congenital infections**

- Unsegmented positive RNA
- Sheath
- Icosahedral symmetry
- One antigenic type



Rubella virus -etiology and pathogenesis

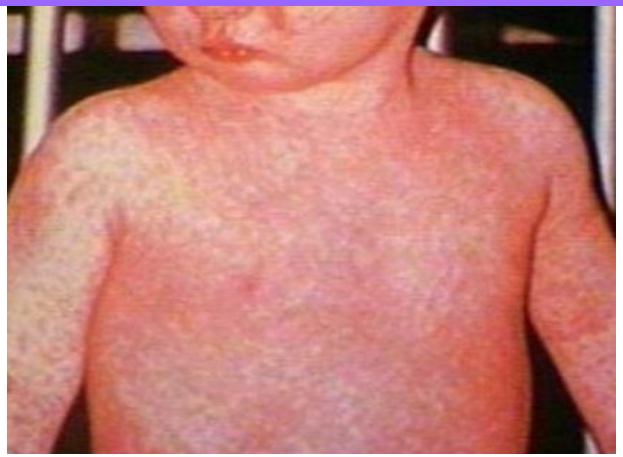
- The man is the only host
- Periodic epidemics in unvaccinated populations
- Pre-existing infection leaves lifelong immunity
- It is transmitted by aerosol

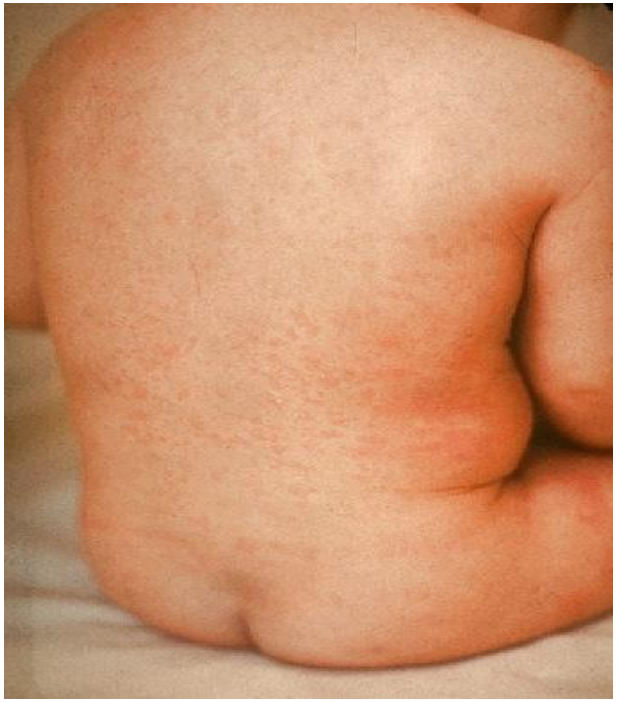
- The entry point is mucosa in upper part of respiratory tract
- Primary replication in upper respiratory tract epithelium and regional lymph nodes
- Viremia (until rash) and dissemination
- The disease has a benign course

Rubella virus
- clinical manifestations-

- Low fever, sore throat, lymphadenopathy (retroauricular)

- **The rash** occurs after an incubation of 2 weeks (occurs at the time of disappearance of the virus from the blood and the appearance of specific antibodies, **immune complexes**)
- The rash starts on the face and lasts for up to 5 days
- Adults may have arthralgias



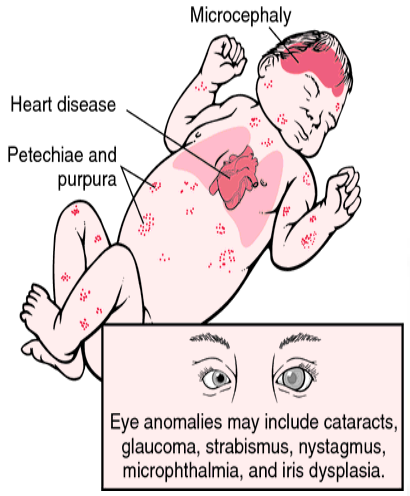


Rubella virus -complications-

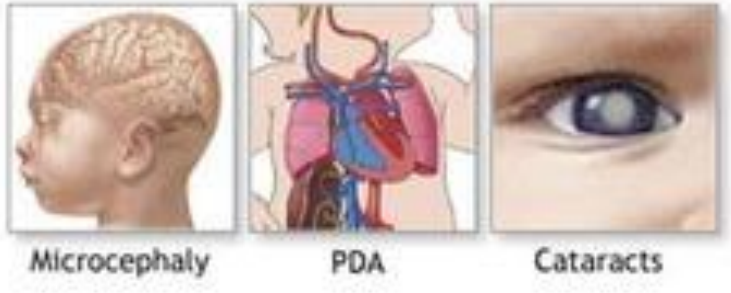
- Complications are rare.
- Encephalopathy - 6 days after the appearance of the rash.
- (headache, vomiting, stiff neck, convulsions)
- Complete recovery
- **Other** complications are extremely rare orchitis, neuritis, panencephalitis
- **Progressive rubella panencephalitis**
- A rare disease ultimately ends in death
- Usually associated with congenital rubella

Congenital rubella

- Hearing loss
- Heart defects (ductus arteriosus)
- Eye problems (**cataract**, glaucoma, microphthalmia)
- Neurological problems (retardation, **microcephaly**)
- Thrombocytopenic purpura
- Hepatomegaly
- Splenomegaly

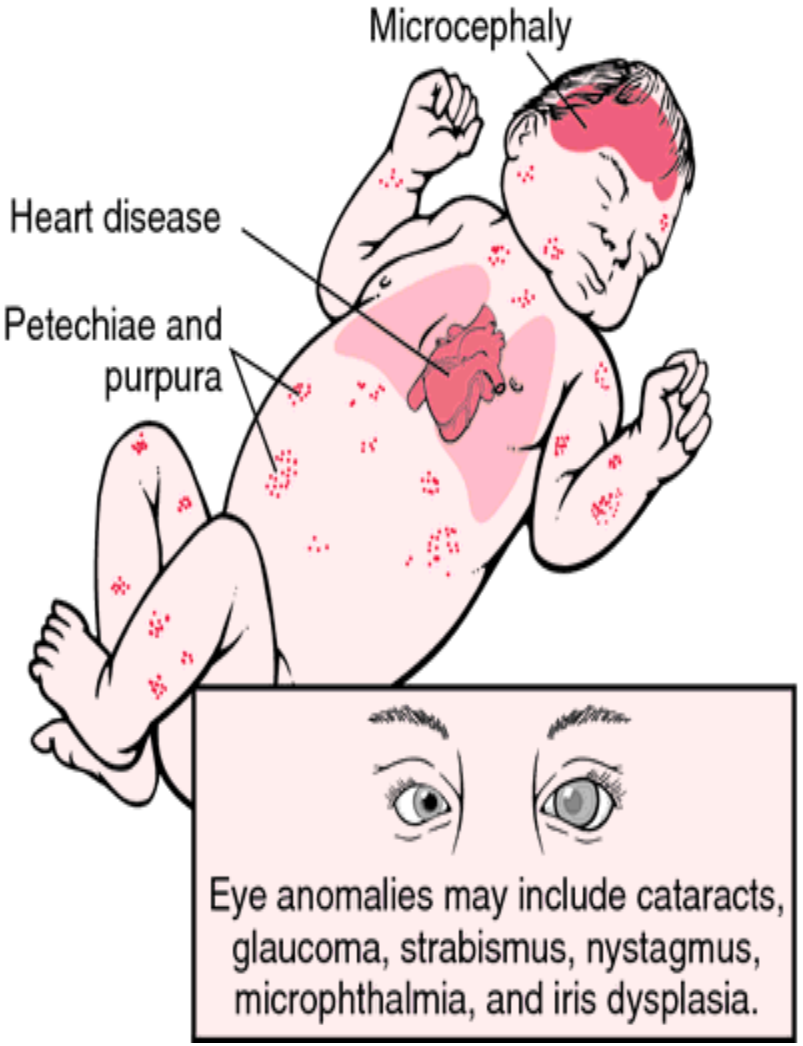


Rubella syndrome



Congenital rubella

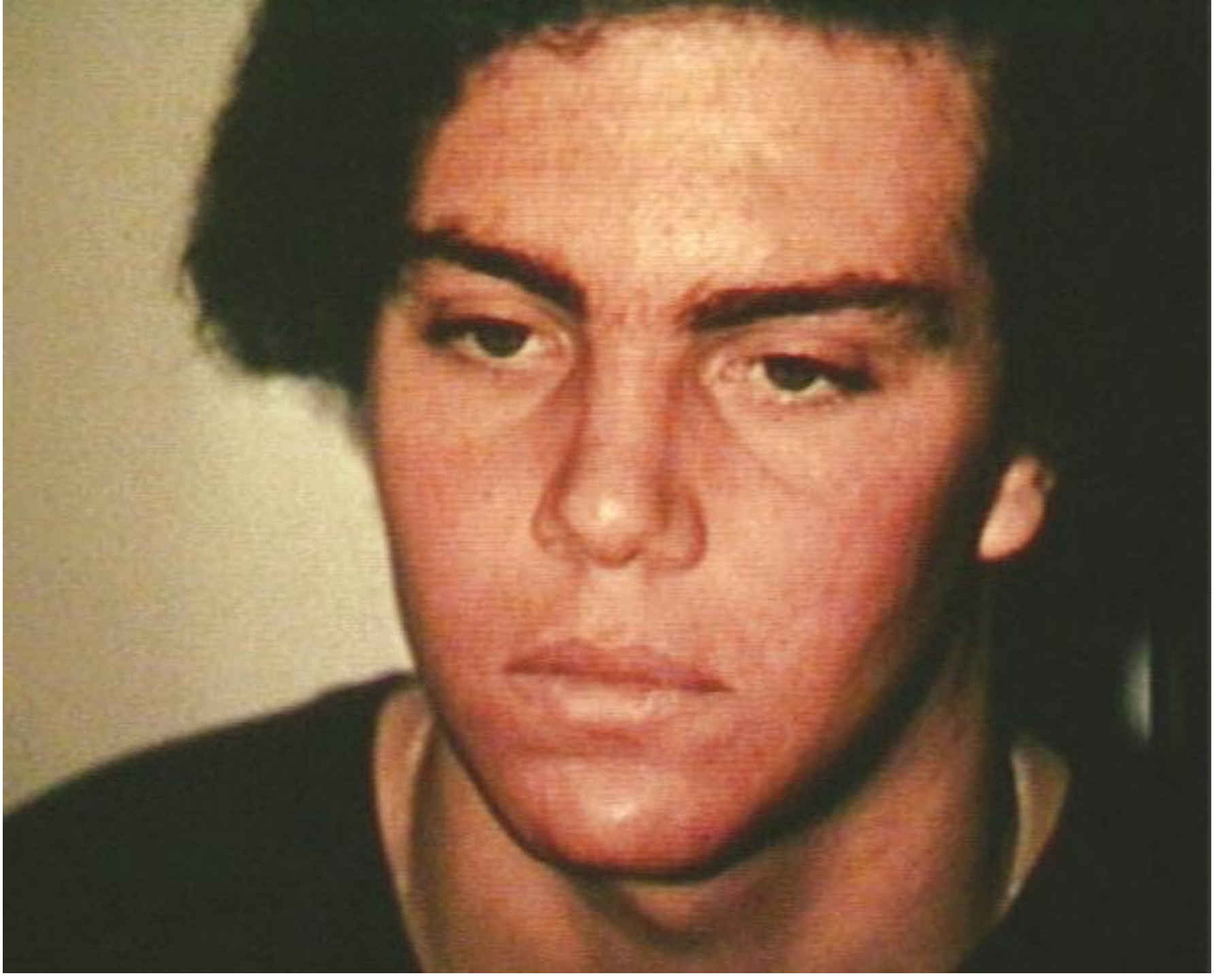
- **The risk is greatest in the first weeks of pregnancy**
- In non-immunized mothers, infections in the first trimester give sequelae in 80% of cases
- The virus infects the placenta and then the fetus
- The virus persists in the body for one year after birth - nasopharyngeal secretions, urine, feces
- In 20% of cases, there are additional complications such as diabetes, lack of growth hormone, eye lesions



Diagnosis and prevention

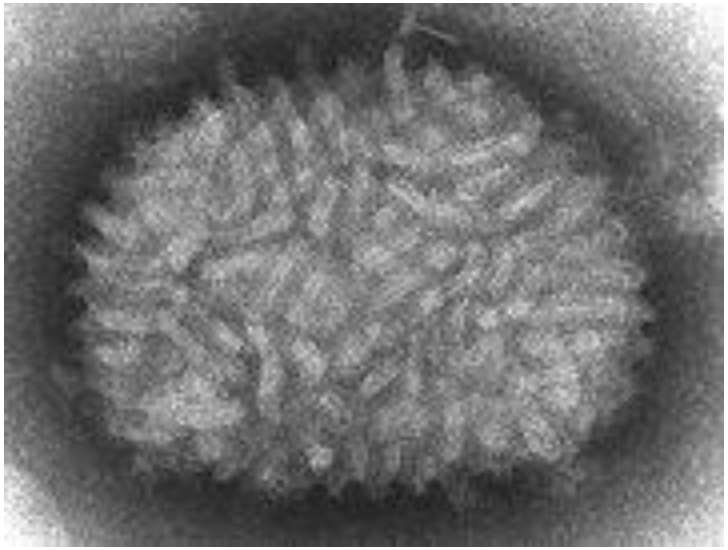
- 50% of infections are asymptomatic
- The developed disease often goes undiagnosed
- Other viruses give similar clinical manifestations
- parvovirus, arbovirus, enterovirus-picornavirus, adenoviruses, EBV
- Virus isolation
- Serology (IgM)

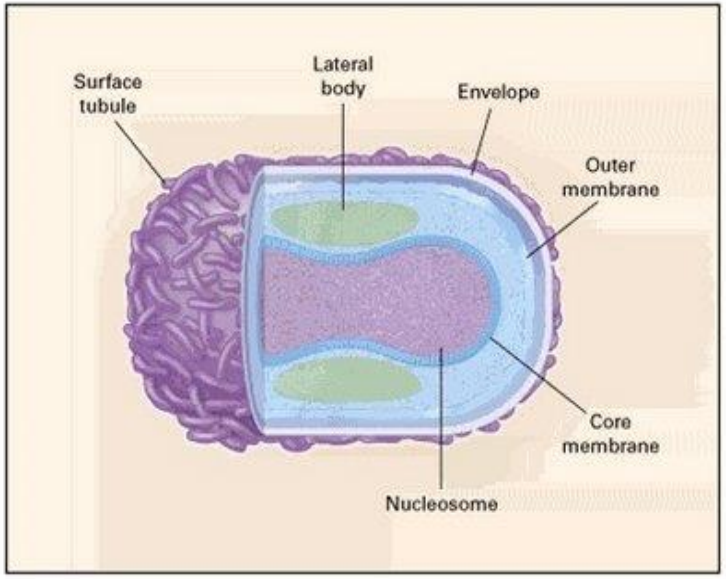
- Live-attenuated vaccine
- Lifetime immunity - one serotype A
- It is important for women to be vaccinated before their first pregnancy
- The vaccine is contraindicated in pregnant women
- If the pregnant woman is IgM positive - termination of pregnancy



Family *Poxviridae*
Variola virus

- The largest and most complex viruses
- They can be seen with a light microscope
- Complex symmetry, oval shape
- Core and lateral bodies
- Spikes on the outer surface

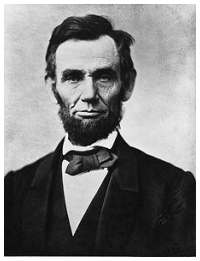


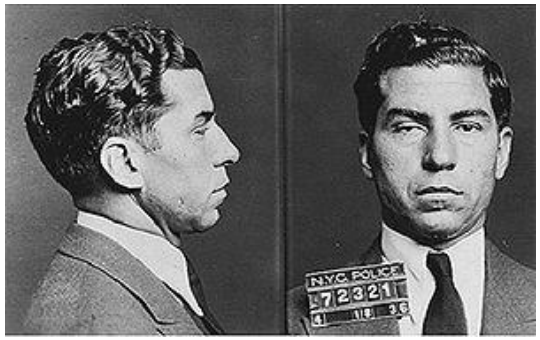


Variola virus

- Causative agent of smallpox(Variola vera, smallpox)
- Egyptian mummies 3000 BC
- The first written sources– China1122 BC, India1500 BC
- Europe– VII century
- South America – XVI century
- North America – XVII century
- XVIII century– endemic disease worldwide

- Ramses V
- Peter II
- Henry VIII
- Elizabeth I
- Mary of Scotland
- Louis XV
- Mozart
- Beethoven
- George Washington
- Sitting bull
- Abraham Lincoln
- Lucky Luciano





Variola virus

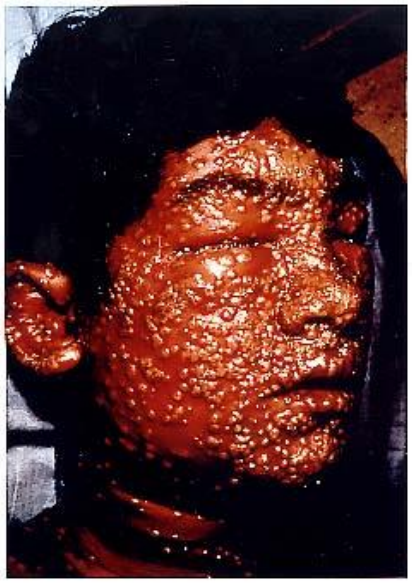
- Man is the only reservoir of the virus
- Smallpox is a very contagious disease
- The virus is stable in the external environment, can survive for a long time on clothes or other objects and cause infection
- It is most commonly transmitted by the respiratory tract
- Recovering leaves permanent immunity

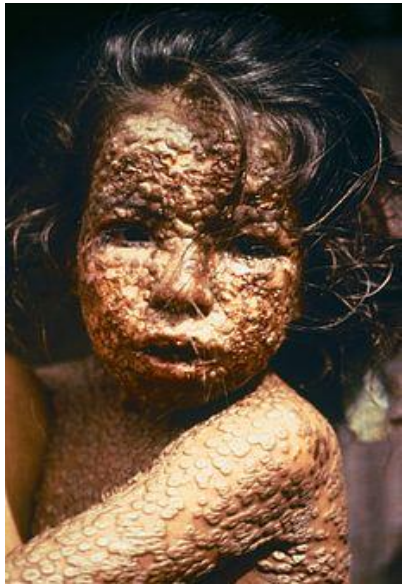
Variola virus -pathogenesis

- The entrance door is the mucous membrane of the upper respiratory tract
- Primary multiplication in regional lymph tissue
- Transient viremia and Mo / Mf cell infection throughout the body
- Secondary multiplication in Mo / Mf cells
- Secondary, more intense viremia
- Clinically manifest disease

Variola virus
-clinical picture-

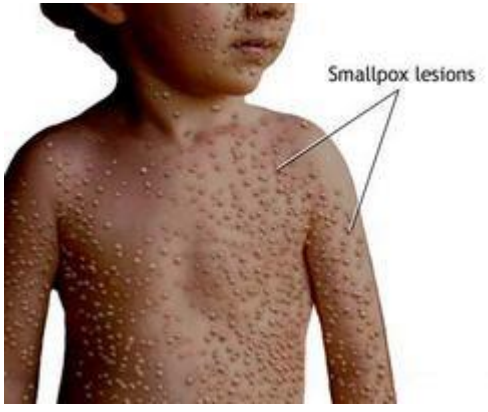
- Incubation lasts about 12 days
- The onset of the disease is usually abrupt
- Fever, fever, malaise, muscle aches, headache
- Maculopapular rash first appears on the buccal and nasopharyngeal mucosa, and then on the face and body





Variola virus
-clinical picture-

- **Characteristic distribution of lesions -** they are most pronounced on the face, and less often on the body
- The changes on the skin begin in the form of **macules**, which turn into **papules**, and then into **vesicles**
- In the second week of the disease, the changes turn into **pustules**, sometimes hemorrhagic
- The dried pustules turn into **crusts** that pass, leaving scars
- Similar changes occur on the mucous membrane of the oral cavity and the upper part of the respiratory tract



Variola virus
-clinical picture-

- The clinical picture of smallpox, its course and outcome depend on the virulence of the virus and the immune status of the patient
- The disease can manifest itself as:
- Variola major - severe form of the disease, mortality 30-50%
- Variola minor - a milder form of the disease, mortality <1%
- Purpura variolosa - hemorrhagic type, high mortality
- Malignant type - lesions in the plane of the skin that develop more slowly, high mortality

Diagnosis and prevention

- Sample from skin lesions
- Identification of antigens from lesions
- Detection of antibodies in the blood

- Metisazone is the only important chemotherapeutic agent against Poxvirus, but it is effective in prophylaxis, but not in the treatment of pre-existing diseases.

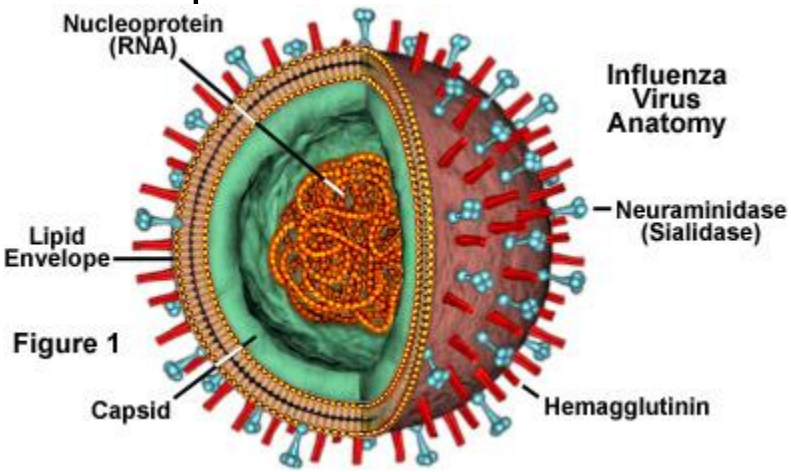
- Vaccine
- The virus is thought to have been eradicated in 1977
- People are no longer vaccinated against this virus, so it is believed that it could be used as a biological weapon

Family *Orthomyxoviridae*
Influenza virus

- The RNA genome of Influenza A virus consists of 8 segments encoding 12 proteins
- Influenza viruses type B or C are quite different from Influenza type A viruses (as well as each other)
- The envelope of the virus is a lipid bilayer membrane that originates from a virus-producing cell into which viral hemagglutinin-HA and neuraminidase-NA are inserted.
- Only Influenza A viruses have subtypes, based on variations in HA and NA molecules. Currently, 16 HA and 9 NA subtypes have been registered.

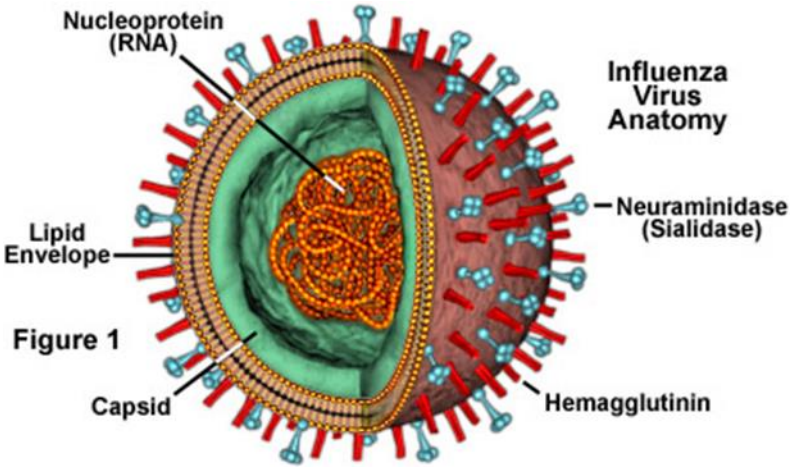
Hemagglutinin

- Hemagglutinin is a glycoprotein
- It passes through the lipid membrane so that the larger part (head), which contains at least 5 antigenic domains, is presented on the outer surface
- Hemagglutinin is involved in the **binding of the virus to receptors on the host cell** and is the **major antigen for neutralizing antibodies**
- **HA is a ligand that binds to sialic acid** (N-acetyl neuraminic acid) and induces penetration of the inner part of the viral particle by merging with the membrane
- Its variability is responsible for the continuous evolution of the virus and the emergence of epidemics and pandemics of influenza



Neuraminidase

- Neuraminidase (NA or N) is also a glycoprotein, which is found on the surface of the virus
- The NA molecule presents its main part on the outer surface of the virus, passes through the entire lipid bilayer and has a small tail in the cytoplasm
- NA is **responsible for releasing virion-offspring from the cell surface** and **penetrating the virus through the mucin layer** of the respiratory epithelium. It is also a significant antigen of the influenza virus



Influenza

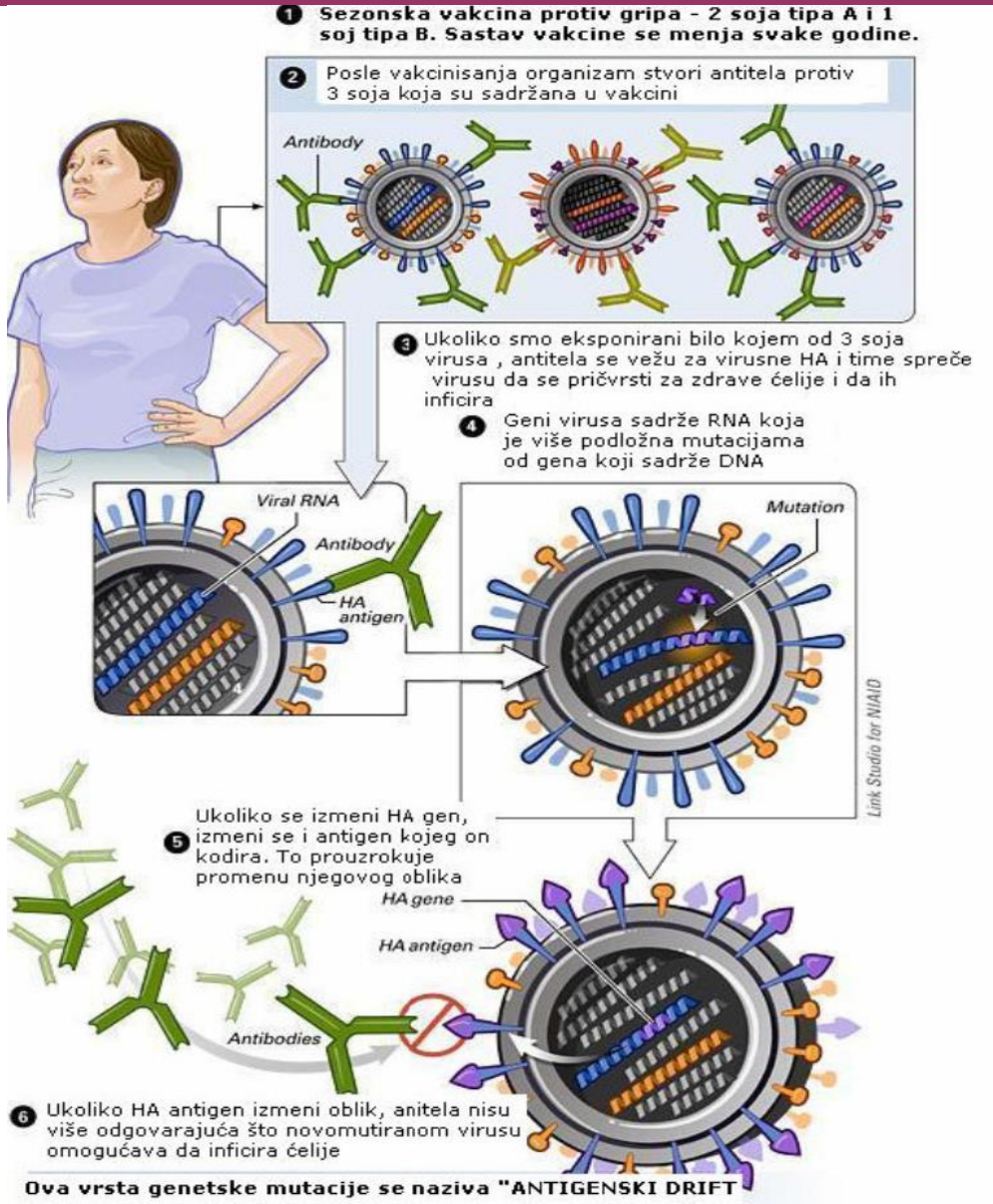
Antigenic drift

- New epidemic strains of influenza A occur every 1-2 years, by creating selected point mutations on two surface glycoproteins: hemagglutinin (HA) and neuraminidase (NA).
- The immune response to HA / NA antigens involves the production of neutralizing antibodies, which is the basis for the resolution of infection and the creation of immunity in the population.
- Antigen variations caused by these mutations prevent the binding of neutralizing antibodies, and such altered strains can evade host defense mechanisms, allowing a new strain of the virus to spread in the non-immune population.
- These mutations represent a molecular explanation for seasonal influenza **epidemics** during the winter in temperate climates.
- This phenomenon is called **antigenic drift** or **antigenic deviation**.

Antigenic drift

- **Antigenic drift is a consequence of mutations in HA and NA proteins**

- **Antigenic drift is responsible for the outbreak**



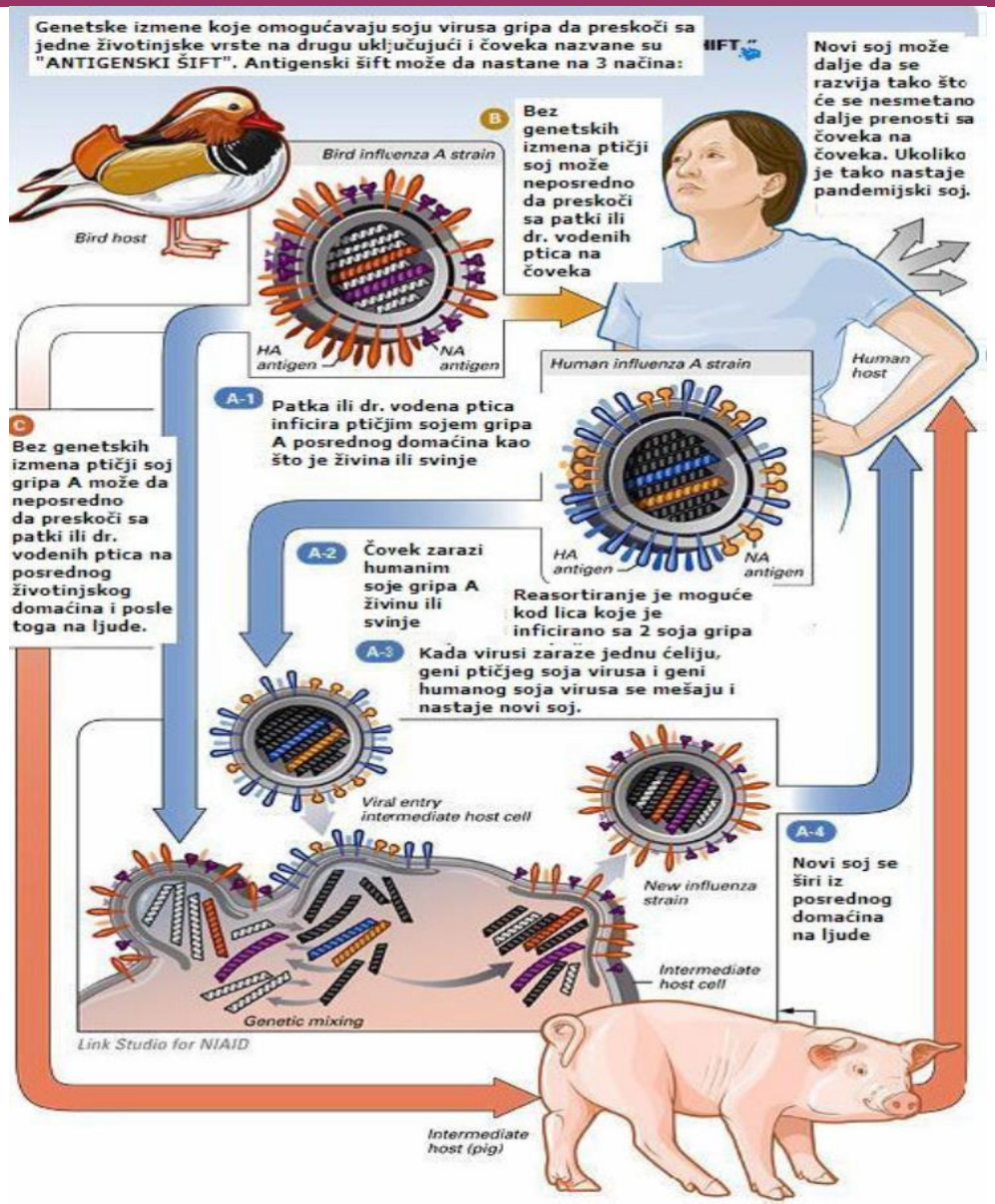
Antigenic shift

- Antigenic **shift** is a consequence of the selection of new HA / NA proteins from the natural population and is responsible for the emergence of **pandemics**
- This change results in the appearance of new HA / NA proteins and can occur due to:
- rearrangement of the segmented genome of two parent viruses
- gradual mutations of one animal virus.
- In order to rearrange, the virus is a candidate for a new pandemic, usually of bird origin, and already circulating human virus, ie. H3N2 or H1N1 must infect the same host cell (pig).
- Within the cell, the genes of both viruses are exchanged, for example when H1 is replaced by H5, resulting in the emergence of a new virus.

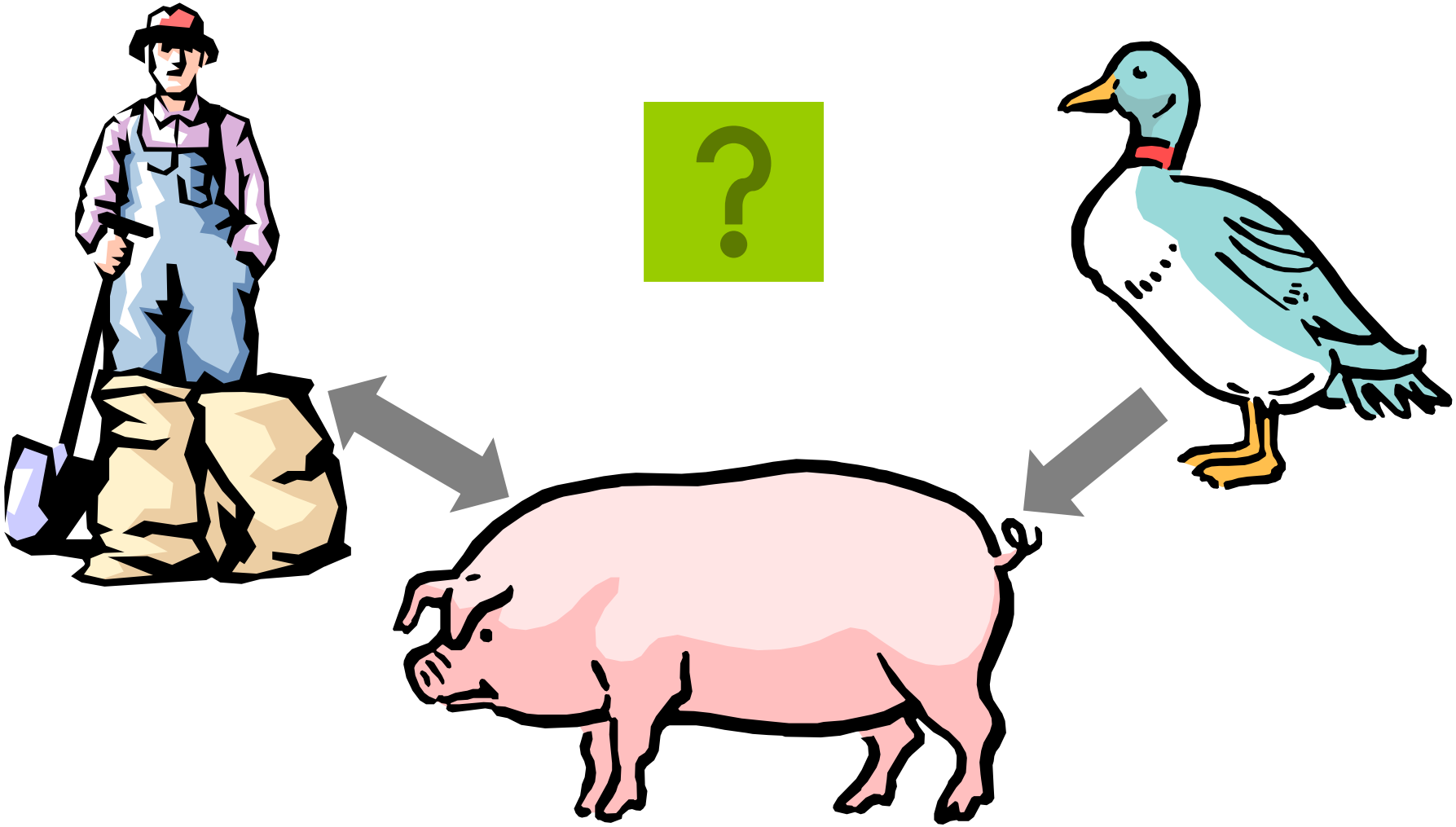
Antigenic shift

- **Antigen shift is a consequence of the selection of new HA / NA proteins from the natural population**

- **Antigenic shift is responsible for epidemics and pandemics**



Where do the "new" HA and NA originate?



Antigenic shift

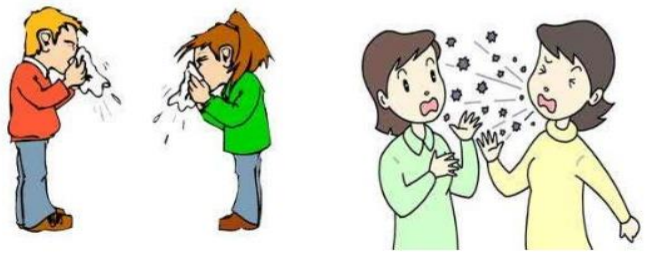
- At the end of the First World War, about 50 million people died from the Spanish flu, and millions had a severe disease. During the 1918 pandemic, the Influenza A virus, the **H1N1** subtype became and remained dominant until 1957.
- For the next 11 years, from 1957 to 1968, the **H2N2** virus (Asian flu) circulated.
- Since 1968, the Hong Kong subtype (H3N2) has become dominant. The H1N1 virus reappeared in 1977 and circulates along with the **H3N2** virus to this day

- In 1968, the new HA (H3) replaced H2 HA, and the RV1 gene was also altered. Probably these two genes were taken from bird flu, while the remaining 6 genes are from H2N2.
- In April 2009, a new H1N1 virus emerged, which the World Health Organization declared pandemic. This pandemic H1N1 virus was also created by rearranging (rearranging) five swine virus genes (including HA and NA), two avian genes and one human Influenza virus gene.

Mode of transmission and dissemination

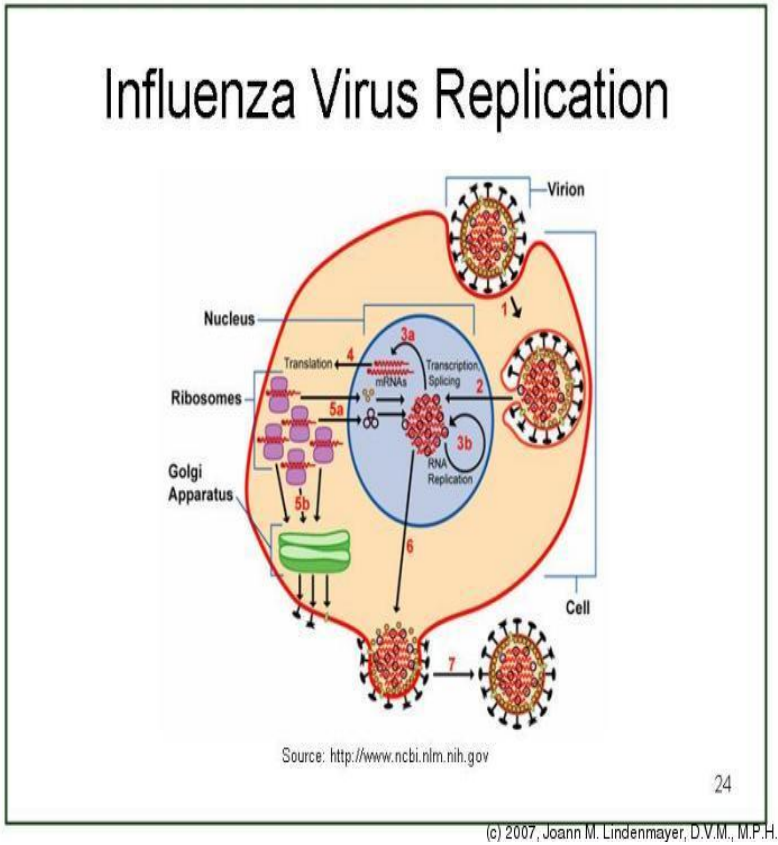
- Flige drops and direct contact
- The virus infects the mucous membranes of the upper and lower respiratory tract
- Viremia and invasion of tissues outside the respiratory tract are rare.

- It first infects cells without cilia
- The specific receptor is galactose-bound terminal sialic acid



Influenza virus
-spreading and multiplying-

- Binding of HA to a specific receptor → entry of virus into the endocytic vesicle → fusion of viral envelope and vesicle
- M2 → entry of H+ ions from the vesicle into the interior of the virus → removal of the envelope from the virus and release of viral gene segments
- These processes are inhibited by amantadine and rimantadine
- Nuclear entry → transcription and replication of RNA Influenza virus
- Assembly and budding of viral particles across the cytoplasmic membrane



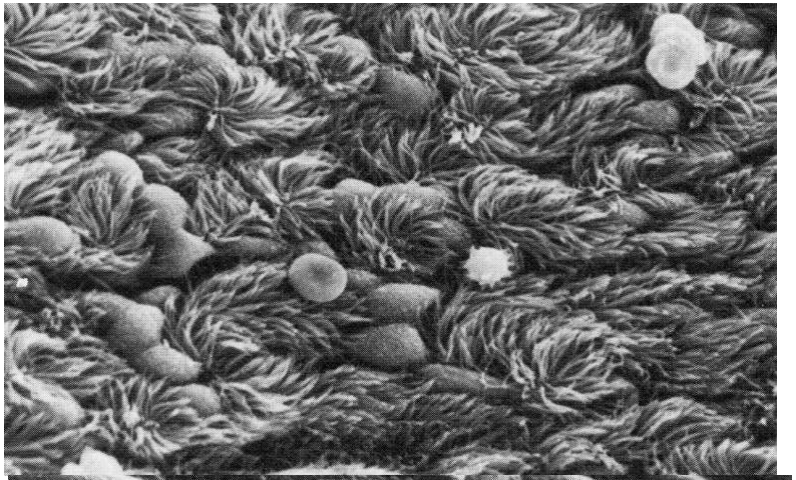
Influenza virus -tissue damage-

- The function of the respiratory epithelium is impaired by the infection itself
- **Edema** as a consequence of inflammation
- **Mononuclear infiltration** in Lamina propria
- Hemorrhage and airless lungs and necrotizing tracheobronchitis and bronchiolitis
- **Direct cytopathogenic effect**

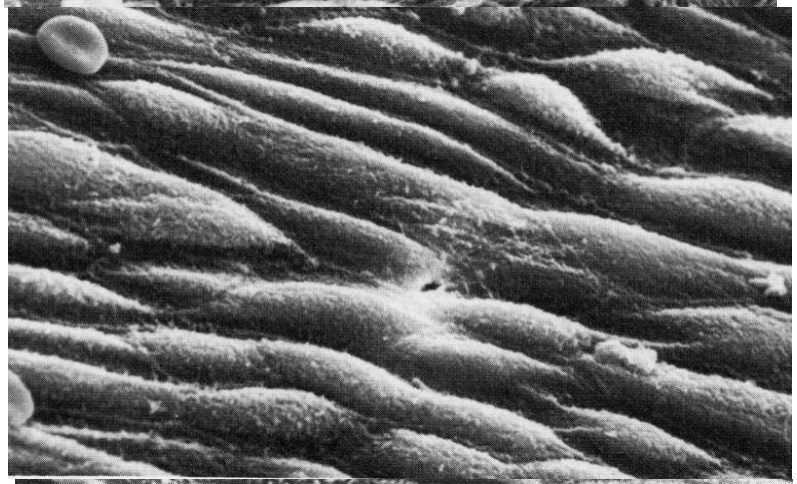
- Complications
- primary viral pneumonia
- secondary bacterial pneumonia and otitis media
- Ray syndrome - brain edema and fatty liver degeneration

Complications- epithelial damage

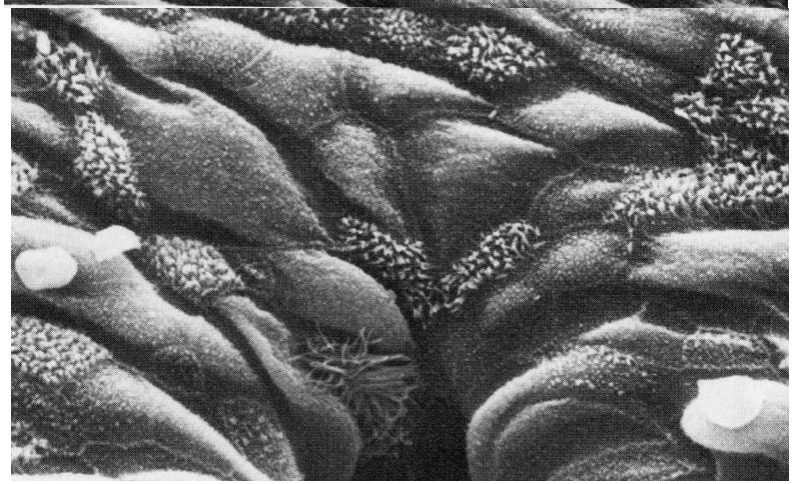
normal tracheal mucosa



3 days after infection



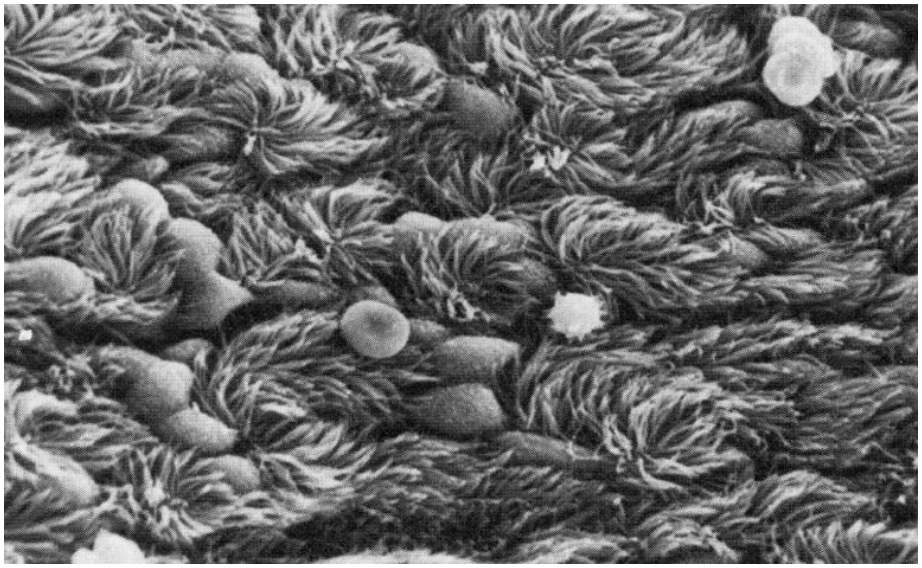
7 days after infection

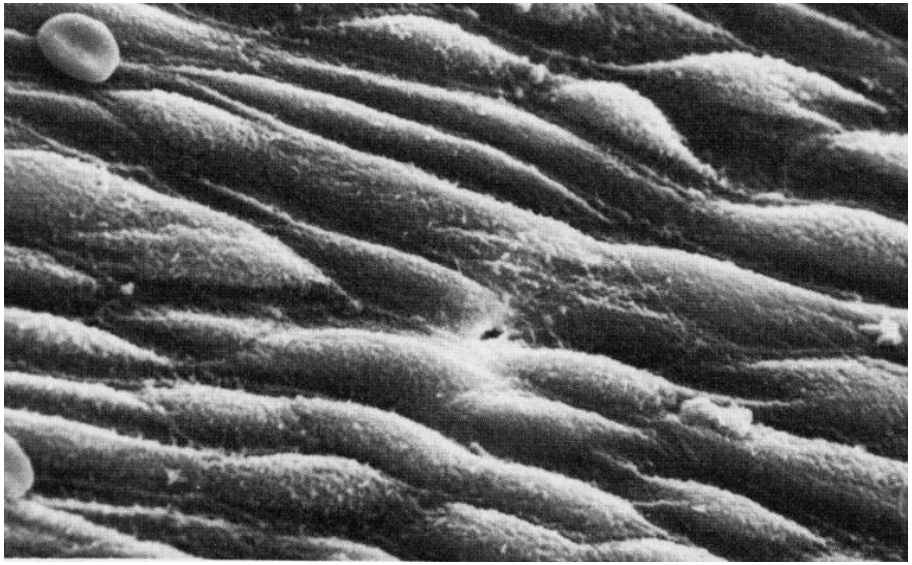


Lycke and Norrby Textbook of Medical Virology 1983

damaged epithelium

- Decreased ability to remove microorganisms
- Increased risk of bacterial infections
- Very rarely viremia





Diagnosis, therapy and prevention

- Isolation of the virus from clinical specimens, including sputum and nasal and pharyngeal swabs
- Antigen detection, RT-PCR for viral RNA detection

- Influenza is often treated only symptomatically
- Amantadine and rimantadine are effective only against Influenza A virus
- NA inhibitors such as oseltamivir and zanamivir are effective in the treatment of both Influenza A and B viral infections and may be used prophylactically.
- Virus was inactivated and treated with formaldehyde. Vaccines are injected intra-muscularly and the level of efficiency is 60-90% in healthy children and adults. Injection may cause a local reaction, while inactivated vaccine may not cause flu-like symptoms
- The live, attenuated vaccine induces a local response on the mucosa, because it is applied with a nasal spray.