# "RNA non-Enveloped Viruses"

## Picornaviruses

A picornavirus is a virus belonging to the family picornaviridae. The name is derived from ***pico*** meaning "small" typically 18-30 nm and ***RNA*** referring to the ribonucleic acid genome, thus "pico-rna-virus" literally means "small RNA virus". There are currently 50 species in this family divided among 29 genera.

**Classification of human picornaviruses:**

1- **Enteroviruses:** ⟶ **Polioviruses serotypes (1-3)**
**Coxcakieviruses A serotypes (1-24)**
**Coxcakieviruses B serotypes (1-6)**
**Echoviruses serotypes (1-33)**
**Enteroviruses serotypes (68-71)**

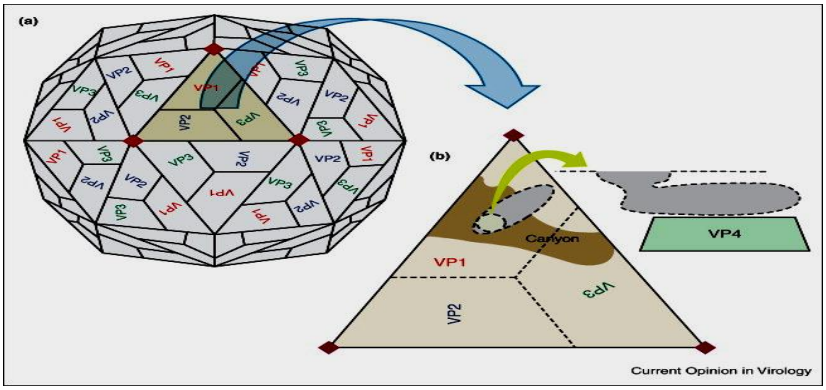
2- **Rhinoviruses: more than 100 serotypes**
3- **Hepatovirus: Hepatitis A virus.**

Two genera of picornaviridae are important… enteroviruses and rhinoviruses, have an identical morphology but can be distinguished based on clinical, biophysiology and epidemiological studies. Enteroviruses are stable at acid pH (3.0-5.0), whereas rhinoviruses are acid liable. Enteroviruses can grow at 37$^{o}$C while rhinoviruses are growing at 33$^{o}$C. Enteroviruses and some rhinoviruses are stabilized by magnesium chloride against thermal inactivation.

### Viral Structure:

**The virion** of enteroviruses and rhinoviruses is icosahedral consist of a capsid shell of 60 subunits each of four proteins (VP1- VP2- VP3- VP4), VP1- VP2 and VP3 are protein in structure act as antibodies- binding sites, VP4 play important role in viral replication. There is a prominent cleft or canyon in the VP1 structure it is too narrow to permit deep penetration of antibody molecules.

**Genome** is single stranded RNA, linear, positive – sense. It is polyadenylated at the 3` end and has a small viral coded protein (Vpg) covalently bound to the 5` end. The positive-sense genomic RNA is infectious. Non- Enveloped family and all replication events occur in the cytoplasm.

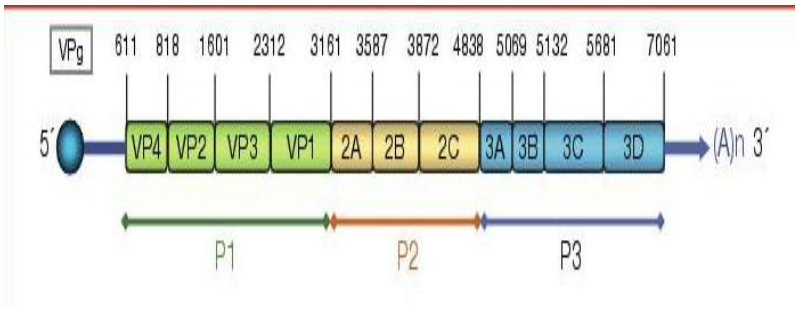



**(A) A schematic view of rhinovirus icosahedral capsid**
**(*B*) Capsid surface.**

## Replication Cycle:

## Genome Structure:

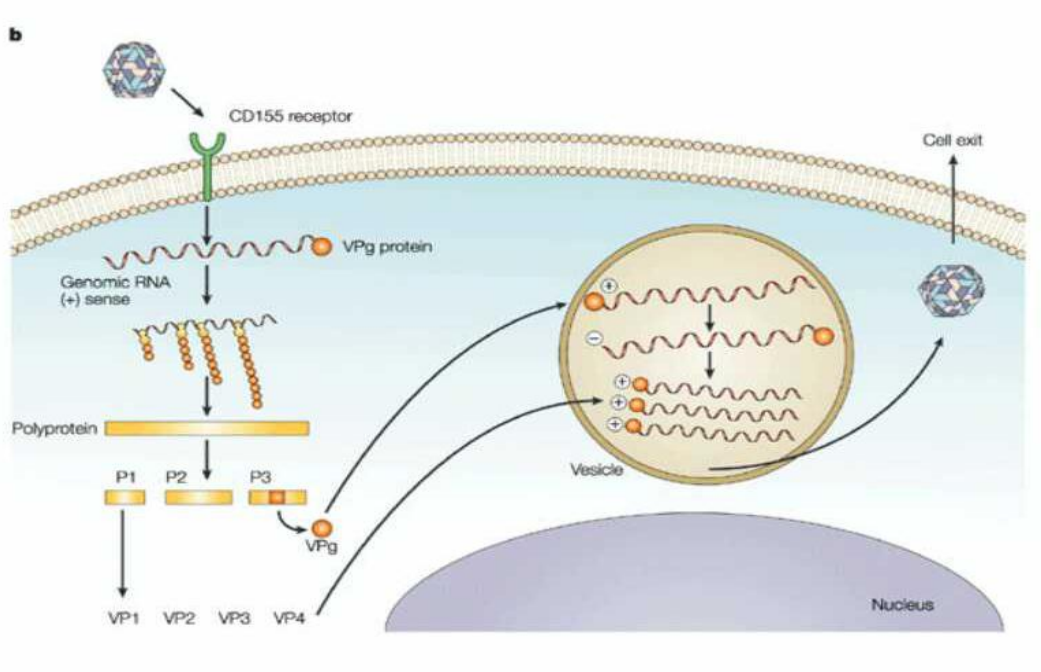
Picornaviruses are classes as group IV viruses; they contain a single stranded positive sense RNA genome**.** Like most positive sense RNA genomes, the genetic materials alone is infectious and unlike positive sense RNA genome because it has a protein on the 5` end that is used as a primer for transcription by RNA polymerase and have a poly (A) tail at the 3` end. Both ends of the genome is an un-translated. The rest of the genome encodes structural proteins at the 5` end and non- structural proteins at the 3` end.




**Schematic Representation of Genome Organization of Rhinovirus.**

## Replication:

The viral particle binds to cell surface receptors (Rhinovirus bind to ICAM-I and Poliovirus bind to CD155). This cause conformational changes in the viral capsid proteins and myristic acid are released, these acids form a pore in the cell membrane through which RNA injected. One inside the cell + strand RND genome is replicate using viral RNA-Dependent RNA polymerase. Translation by host cell ribosomes is not initiated by a 5` cap as usual but rather is initiated by IRES (Internal Ribosome Entry Site). The viral life cycle being completed on average within 8 hours, however as 30 minutes after initial infection. After 4-6 hr. of replication of the virus particles assemble and the cell plasma membrane become permeable at around 8 hours the cell is effective dead and lyses to release.




**"Replication Cycle of Picornaviruses"**

## Epidemiology:

Most enteroviruses survive well in moist or wet environment and are readily transmitted via the fecal- oral route. Enterovirus infections occur in warmer and in temperate climate (including summer and fall months). Infection has no age predilection.

Rhinoviruses have a well- established seasonal pattern, in temperate climates rhinoviral infection have fall and spring beak especially during autumn and spring also colder weather. Infection range in 2y to age school.

# Polioviruses

Poliovirus, the causative agent of poliomyelitis, it is a human enterovirus and member of the family of picornaviridae. Poliovirus was first isolated in 1909 by Karl and Erwin.

**Pathogenesis:**

The mouth is the portal of entry of the virus, primary replication take place in the oropharynx and intestine. The virus is regularly present in the throat, the stool and may be found in the blood at patients with non- paralytic poliomyelitis. It is believed that the virus first multiplies in the tonsils, the lymph nodes of the neck, pyere's patches and the small intestine. The nervous system may then be invaded by way of the circulating blood. Poliovirus can spread along axons of peripheral nerves to the central nervous system, where it continuous to progress along the fibers of the lower motor nervous involve the spinal cord or the brain and in the process of its intracellular multiplication it may damage or completely destroy these cells.

**Clinical Findings:**

The incubation period is usually 7-14 days; the infection may be ranges from inapperent infection without symptoms to a mild febrile illness to sever and permanent paralysis.

**A- Mild Disease:** this is most common form of disease characterized by fever, malaise, headache, nausea, vomiting, sore throat and constipation. Recovery occurs in a few days.

**B- Non- Paralytic Poliomyelitis (Aseptic meningitis):** in addition to the symptoms listed above, patient with the non-paralytic form has stiffness and pain in the back and neck. The disease lasts 2-10 days and recovery is rapid and complete.

**C- Paralytic Poliomyelitis:** the predominating complaint is flaccid paralysis resulting from lower motor neuron damage, maximal recovery usually occurs with 6 months, with residual paralysis lasting much longer.

**D- Progressive post poliomyelitis muscle atrophy:** it's observed in individuals' decades after their experience with paralytic poliomyelitis, it is a specific syndrome. Although progressive post poliomyelitis muscle atrophy is rare, it is a result of physiologic and aging changes in paralytic patients burdened by loss of neuromuscular function.

**Laboratory Diagnosis:**

Specimen: stool (up to 4 weeks of infection) - throat swab (15 day after infection) - CSF (during manifestation 2-3 weeks).

Cell Culture: monkey kidney cell and human embryonic fibroblast.

Serology: Neutralization test against the 3 serotypes.

**Prevention and control:**

Live-virus, Killed- virus vaccines and Gamma- globulin are available. Live attenuated vaccine also named live polio vaccine (LPV), oral polio vaccine (OPV) or Sabin vaccine. Oral vaccines contain live attenuated virus grow in primary monkey kidney or human diploid cell culture with stabilizer agent like Mgcl2. Program of vaccination involve the following doses: (2-4 months…6-18 months… 4-6 years "before school entry). Killed vaccine or inactivated virus vaccine (KPV), (IPV) or Salk vaccine is (Monkey Kidney culture). Program of vaccination involve the following doses: (2-4 months…12-18 months… 4-6 years "before school entry).

**"Important features of Polio vaccines"**

| Attribute | Killed (Salk) | Live (Sabin) |
|---|---|---|
| 1.Route of administration | injection | oral |
| 2.Prevent disease | yes | yes |
| 3.Interupts transmission | No | yes |
| 4.Induce humoral IgG | yes | yes |
| 5.Induce intestinal IgA | No | yes |
| 6.Interfer with replication of virulent virus in gut | No | yes |
| 7.Can cause disease ICP in pregnancy | No | yes |
| 8.Revert of virulence | No | yes |
| 9.Duration of immunity | shorter | longer |
| 10.Cost | high | Low |

# Coxsackieviruses

Coxsackieviruses are a large subgroup of the enteroviruses divided into two groups A (3 types) and B (6 types). they produce a variety of illness in humans. The Coxsackieviruses tend to be more pathogenic than echoviruses.

**Pathogenesis:**

The incubation period of Coxsackieviruses infection ranges from 2-9 days. The virus has been recovered from the blood, throat and the stool. The disease range from mile febrile illness to central nervous system and respiratory diseases.

A. **Aseptic meningitis:** it is caused by all types of group B and by many group A Coxsackieviruses, most commonly A7 and A9. The disease suggestive of paralytic poliomyelitis.
B. **Herpangina:** is a severe febrile pharyngitis with discrete vesicles on the posterior of the palate that is caused by certain group A viruses. It is infect small children.
C. **Hand-foot and mouth disease:** characterized by oral and pharyngeal ulcerations and vesicular rash of the palms and soles that may spread to the arms and legs. Vesicles heal without crusting which clinically differentiates from the vesicles of Herpesviruses and poxviruses. The disease has been associated particularly with coxsackievirus A16 in young children.
D. **Epidemic Pleurodyuria** (epidemic myalgia) or Bomholm disease: characterized by fever and chest pain last 2 days – 2 weeks.
E. **Myocarditis** also caused by coxsackievirus B virus in adult and children involve acute myocarditis and pericarditis.

**Laboratory Diagnosis:**

A- Recovery of virus: virus can be isolated from throat washing during the first few days of illness and from stools during the first few weeks. Specimens are inoculated into tissue cultures like human amnion, human embryonic lung fibroblast and monkey kidney cell and cytopathogenic effect appears within 5-14 days.
B- Nucleic acid detection: Reverse- transcriptase-PCR tests provided rapid and sensitive assays useful for direct detection.
C- Immunology: using neutralization test and immunoflourescent test.

# Echoviruses:

An ECHO (Enteric Cytopathic Human Orphan Virus) is a type of RNA viruses that belongs to the enteroviruses, more than 30 serotypes are known. Echoviruses are found in the gastrointestinal tract, it is highly infectious and its primary target male and children, it is the most cause of a septic meningitis (summer out break). Infection of infant following birth may cause severe systemic disease. Main causes of infection are from overcrowded conditions such as the poor districts of a city and poor hygiene; many serotypes can cause cardiac disease and rash in young children.

**Laboratory Diagnosis:**

**A-isolation of virus:** suitable specimens are throat swabs, rectal swab, CSF and stool. Culture in monkey kidney cell, human amnion cells and HeLa cell.

**B- Serology:** involve neutralization test, Haemagglutination inhibition test and complement fixation test.

**Treatment:**

The antiviral drug pleconaril interferes with the binding of echovirus particle to the cell membrane and the drug also hinders the uncoating of virion by attaching itself to the viral protein capsid.

# Enteroviruses

Four enteroviruses types (68-69-70-71) cause human disease:

Enterovirus 68: isolate from the respiratory tract of children with bronchiolitis or pneumonia.

Enterovirus 70: is the chief cause of acute hemorrhagic conjunctivitis.

Enterovirus 71: cause meningitis, encephalitis and paralysis resemble poliomyelitis.

# Rhinoviruses

Rhinoviruses are the common cold virus; they are the most commonly recovered agents from people with mild upper respiratory illnesses. They are usually isolated from nasal secretions but may also be found in throat and oral secretion. These viruses as well as coronaviruses, adenoviruses, enteroviruses, parainfluenza viruses and influenza cause upper respiratory tract infections including the common cold syndrome. Rhinoviruses are also responsible for about one-half of asthma exacerbations. More than 100 serotypes are known.

Human rhinoviruses can be divided into major and minor receptor groups. Viruses of the major group use ICAM-1 as receptor and those of the minor group bind members of LDL receptor.

**Pathogenesis:**

The common cold refers to the upper respiratory tract infection also known as (nasopharyngitis, rhinopharyngitis, acute coryza, head cold or simply a cold) is a viral infectious disease involve air passage above the lungs including the bronchi, trachea, throat, nose and sinuses. Symptoms include coughing, sore throat, runny nose, sneezing, headache and fever which usually resolve in seven to ten days with some symptoms lasting up to three weeks. The nose is the main portal for rhinovirus entry, although the eye and oral inhalation serve as entry routes, a series of upper airway biopsies suggested that rhinovirus infection may initiate in the nasopharynx and area of adenoid. Infection can be occur with an inoculums of less than $10^4$ tissue culture infectious dose ($TCID_{50}$) when deposited in the nose**.**

Rhinovirus infection does not produce extensive cytopathology of the nasal mucous membrane, however this depend on the serotype and the titer of virus, while in an early compromised epithelium such as in the case of asthma rhinovirus induce considerable epithelial cytotoxicity, mucosal edema with spars infiltration of inflammatory cells mainly neutrophils are the predominant histological changes. Viraemia has not been detecting in normal individuals.

**Complications of Rhinovirus Infection:**

1. **Ear Infection:** frequent viral upper respiratory tract infections are considered to be risk factors for otitis media with effusion (OME) and acute otitis media (AOM) is the most common complication of viral upper respiratory infection especially in children. Sinusitis demonstrated in many individuals with typical common cold infection, about 3% of people with colds develop sinusitis
2. **Lower Respiratory Tract Infection:** the common nature of mixed of viral/bacterial aetiology in patient with community acquired pneumonia (CAP) and the association between mixed rhinovirus/pneumococcal infection and severe disease have been described**,** adherence of *Streptococcus pneumoniae* to human tracheal epithelial cells is increased in the presence of rhinovirus.
3. **Aggravation of Asthma:** rhinovirus infection induces the release of chemokines from airway epithelial cells, attracting inflammatory cells to the airways. In patients with preexisting airway inflammation the influx of additional inflammatory cells caused by rhinovirus infection will lead to additive or synergistic effects and an exacerbation of airways disease. Particularly, human rhinovirus is strongly suggested as a major candidate for the associations of the virus- induced asthma.

**Laboratory Diagnosis:**

1. **Virus isolation:** The optimal specimen for virus isolation is a nasal washing or a nasal aspirate. Throat or nasal swabs are used as an alternative in the field, or from children where nasal washings are difficult to obtain. Rhinoviruses replicate best in human fetal lung fibroblasts (WI38, MRC5) and strains of HeLa cells at 33$^{o}$C. Cytopathogenic effect (CPE) is easiest to observe in fibroblast lines include foci of small and large rounded, refractive cells with pyknotic nuclei and cellular debris after 24 hr. of inoculation.
2. **Serological tests:** Enzyme linked immune sorbent assay is faster and much easier to perform offers better sensitivity and can be readily adapted to measure different antibody isotypes in both serum and nasal secretions.
3. **Nucleic acid detection:** A rapid and sensitive microwell reverse transcription RT-PCR hybridization assay was developed to detect human rhinoviruses in clinical specimens and cell culture suspensions.

**Treatment and control:**

- Interferon (IFN- α) effective if given intranasally before or shortly after exposure to the virus.
- Pleconaril is an antiviral with good activity against the rhinoviruses had modest effects on the symptoms of the common cold in healthy adults.
- There are specific therapies include the use of ascorbic acid, zinc gluconate, echinacea and the inhalation of humidified hot air.
- Identification of the specific viral serotypes responsible for the manifestation of a disease and development and set up of a viral vaccine. Rhinoviruses have been a very difficult target for vaccine design, since more than 100 rhinovirus serotypes exist.