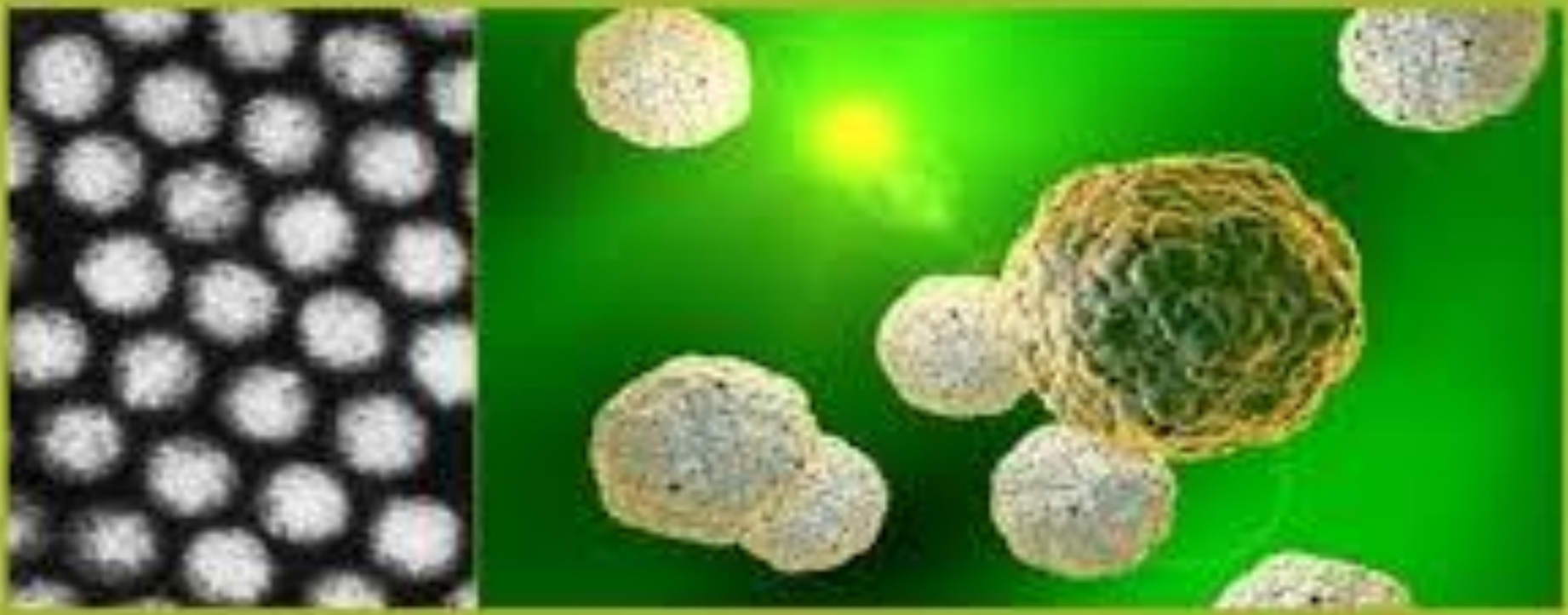
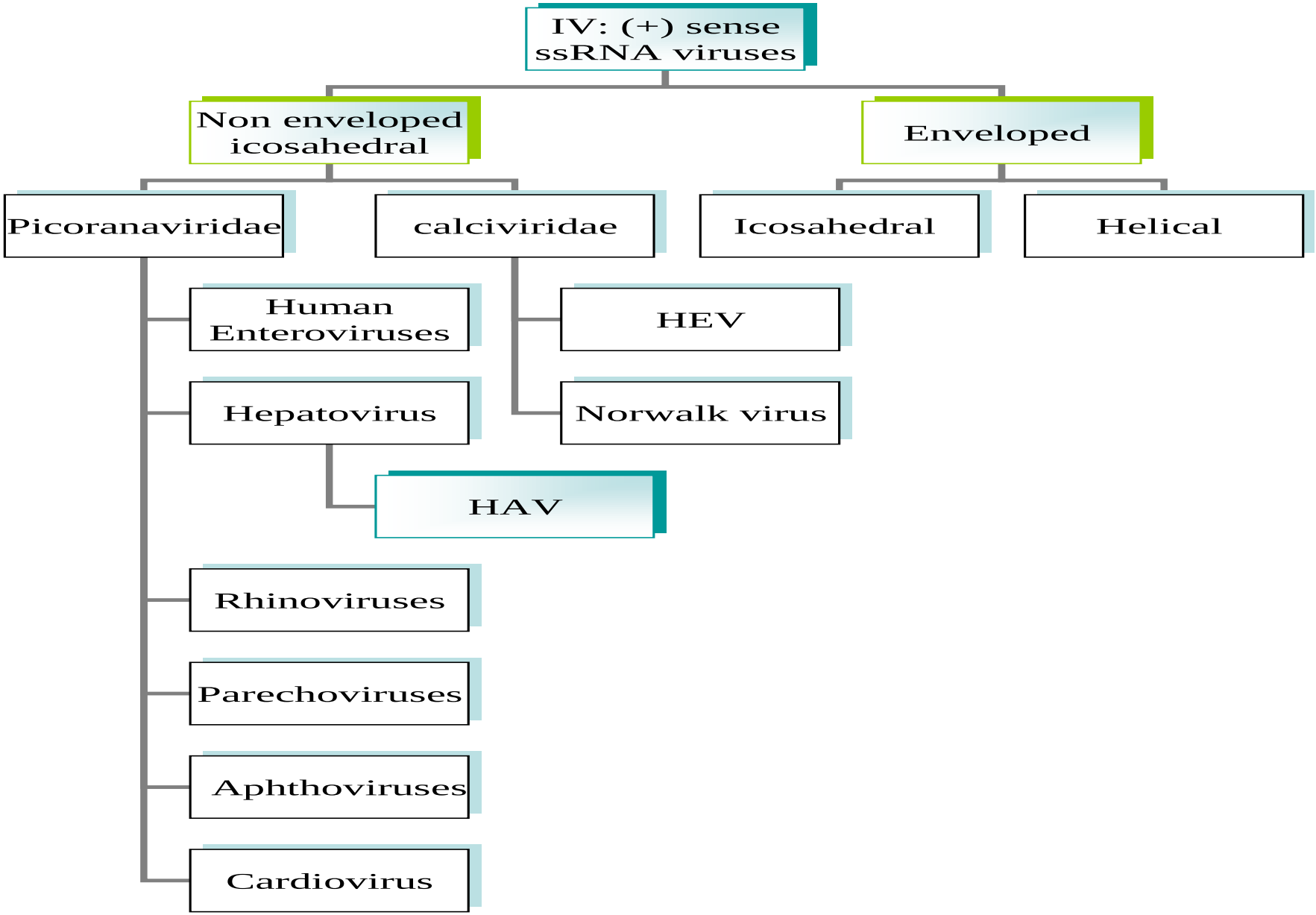


Picornavirus (Picornaviridae)

By Dr. Ekram Abd El Rahman

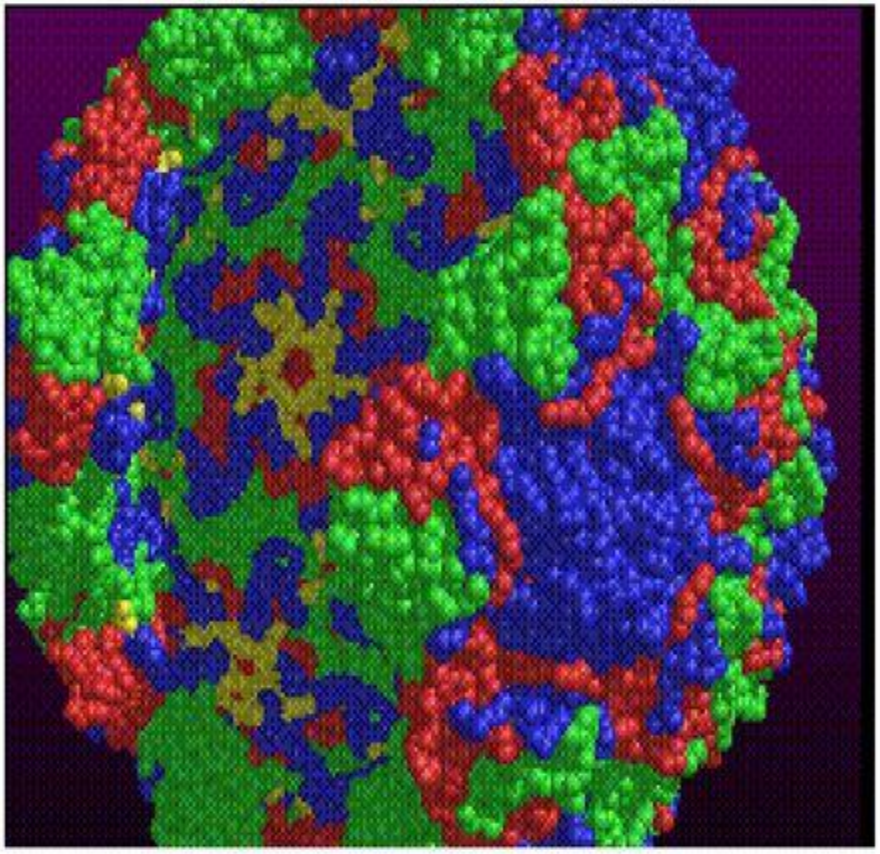

IV: (+) sense ssRNA viruses
Non enveloped icosahedral
Enveloped
Picoranaviridae
calciviridae
Icosahedral
Helical
Human Enteroviruses
HEV
Hepatovirus
Norwalk virus
HAV
Rhinoviruses
Parechoviruses
Aphthoviruses
Cardiovirus

PicoRNAviruses

ss, positive sense RNA, icosahedral capsid, 25-30nm, and no envelope

Pico= small [Greek]

Positive sense
ICOsahedral
RNA genome



Properties:

- **1. Structure:**
- Very small viruses, 25-30 nm in diameter.
- Icosahedral, +ssRNA (i.e. genome is mRNA), non-enveloped.
- Naked genome is sufficient for infection.

2. Replication:

- Genome replication and maturation occurs in the cytoplasm.
- Virus RNA is translated into polyprotein which is then processed into enzymatic & structural proteins.
- Most viruses are cytolytic; released by cell lysis (except Hepatitis A virus released by exocytosis).
- On tissue culture they cause granulation and rounding of infected cells.

3. Reaction to physical and chemical agents:

- Ether and chloroform resistant.
- Enteroviruses are resistant to pH 3-9, detergents and heat and optimum growth temperature is 37º C.
- Rhinoviruses are labile at acidic pH and optimum growth temperature is 33º C.
- Infection is often asymptomatic or cause mild flu-like or URT disease.

- **Classification:**
- **1- Human Enteroviruses (HEV):**
- Their capsids are very resistant to harsh environmental conditions, heat and detergents. Also, they are stable at pH 3, i.e. can resist the acidity of the stomach thus they can infect with the oral route.
- **They include 5 species & several serotypes:**
- A) Polioviruses types 1-3.
- B) HEV-A includes 12 types of coxscackieviruses A and enterovirus type 71.
- C) HEV-B includes 7 types of coxscackieviruses B and 33 types of echo viruses.
- D) HEV-C includes 12 types of coxscackieviruses A.
- E) HEV-D includes enterovirus types 68 and 70

- **2-Hepatovirus:**
- It is hepatitis A virus which was classified as enterovirus type 72. It is now placed in a separate genus (Heparnavirus).
- **3-Rhinoviruses**:
- They include more than 150 antigenic serotypes. These infect by respiratory route and are acid labile at pH 3. They replicate poorly at temperature above 33º C.

- **4-Parechoviruses**:
- 14 serotypes. They cause common cold, gastroenteritis, neonatal sepsis, aseptic meningitis, encephalitis and myocarditis.
- **5-Aphthoviruses**:
- They cause foot & mouth disease in cattle, sheep and goats, which may be transmitted to man by contact or ingestion of infected meat.
- **6-Cardiovirus** cause encephalitis and myocarditititis in mice.

Human Enteroviruses (HEV)

- **Pathogenesis of Enteroviruses:**
- Contrary to their name, enteroviruses don't usually cause enteric disease, but they replicate within GIT and are transmitted by fecal-oral route.
- Viral replication is initiated in the mucosa of the pharynx & lymphoid tissue of tonsils and the virus then infects the lymphoid cells of Payer's patches.
- 1ry viremia spreads the virus to receptor-bearing target tissues to initiate a second phase of replication resulting in symptoms and 2ry viremia may occur.

- Diseases produced by enteroviruses are determined mainly by tissue tropism and cytolytic capacity of the virus.
- Most enteroviruses are cytolytic (viral rather than immune pathogenic effects are usually responsible for causing disease symptoms), replicating rapidly and causing direct damage to the target cell.

Immunity to Enteroviruses:

- **1. Humoral immunity:**
- It is the major protective immune response to enteroviruses. Secretory IgA antibodies can prevent the initial establishment of infection in the oropharynx and GIT, and serum antibodies can prevent viremic spread to target tissues and therefore the disease.

- **CMI:**
- It is not usually involved in protection but may play a role in pathogenesis.

1- Polioviruses

- They cause poliomyelitis which in its full picture affects the CNS and cause flaccid paralysis. Man is the only natural host. Fortunately, most poliovirus infections are subclinical.

Properties of the virus:

- The virus is 25-30 nm in diameter, icosahedral, +ssRNA, non-enveloped.
- There are 3 antigenic types.
- The virus infects only primates, e.g. man & monkeys as they possess specific receptors for viral attachment.
- They are grown in primary or continuous cell lines derived from man or monkey tissues causing characteristic cyptopathogenic effects (CPE).

- **Replication:**
- It begins by attachment to specific receptors on the cell membrane (pvr/CD155) & entry into the cell, this is followed by un-coating.
- The genome RNA functions as mRNA and is translated into one large polypeptide, which is cleaved by virus encoded protease into structural proteins & enzymes.
- Replication of genome occurs followed by assembly of virus components, the virus accumulates in the cytoplasm & released by cell lysis.

- **Pathogenesis:**
- Mode of Infection:
- By ingestion of food or drink contaminated by stools of cases or carriers (convalescent carriers). The oropharynx and the intestinal tract are the portals of entery.
- Incubation Period:
- 7-14 days.

- **Outcome of infection:**
- **Inapparent infection (> 90%):** The organism multiplies in the oropharynx (Tonsils) and the Payer's patches in the intestine and it is excreted in the stool and infection stops at this stage.

- **Abortive infection (5%)**: infection continues and the virus passes to deep cervical and mesenteric lymph nods, then invade the blood (viremia). Viremia is associated with mild symptoms of fever, malaise, headache, nausea and vomiting. The disease stops at this stage.
- **Non paralytic poliomyelitis (Aseptic meningitis):** when occurs; it is manifested by stiffness and pain in the back and neck. Usually recovers but may progress to paralysis.

- **Paralytic poliomyelitis:**
- **A- Flaccid paralysis (with no sensory loss):**
- It occurs in 0.1-1% of cases and it may be one of the following forms:
- Spinal paralysis due to virus effect on the anterior (motor) horn cells of spinal cord. It manifests as flaccid paralysis

- Bulbar poliomyelitis (cranial paralysis) may involve a combination of cranial nerves & even the medullary respiratory center and manifested by:
  - Accumulation of secretions in throat (difficulty in breathing).
  - Nasal regurgitation of fluids and saliva.
  - Palatal deviation
  - Involvement of the respiratory center (irregular rhythm and depth of respiration)
  - Nystagmus.
  - Deviation of mouth.
- Bulbo-spinal poliomyelitis (mixed)

- **Flaccid paralysis (with sensory loss):**
- In severe cases, the disease may affect the posterior horn cells (sensory cells), the vestibular nuclei and motor cortex. Death occurs due to respiratory muscle paralysis. Adults are more liable to develop severe paralysis & the risk increases with pregnancy, operations (tonsillectomy), fatigue, trauma, I.M injections.

- **No permanent carrier state** occurs, but virus excretion in stool can occur for several months (convalescent carriers). Immunity is permanent to the type of poliovirus causing infection.

MUSCLES COMMONLY AFFECTED IN POLIOMYELITIS

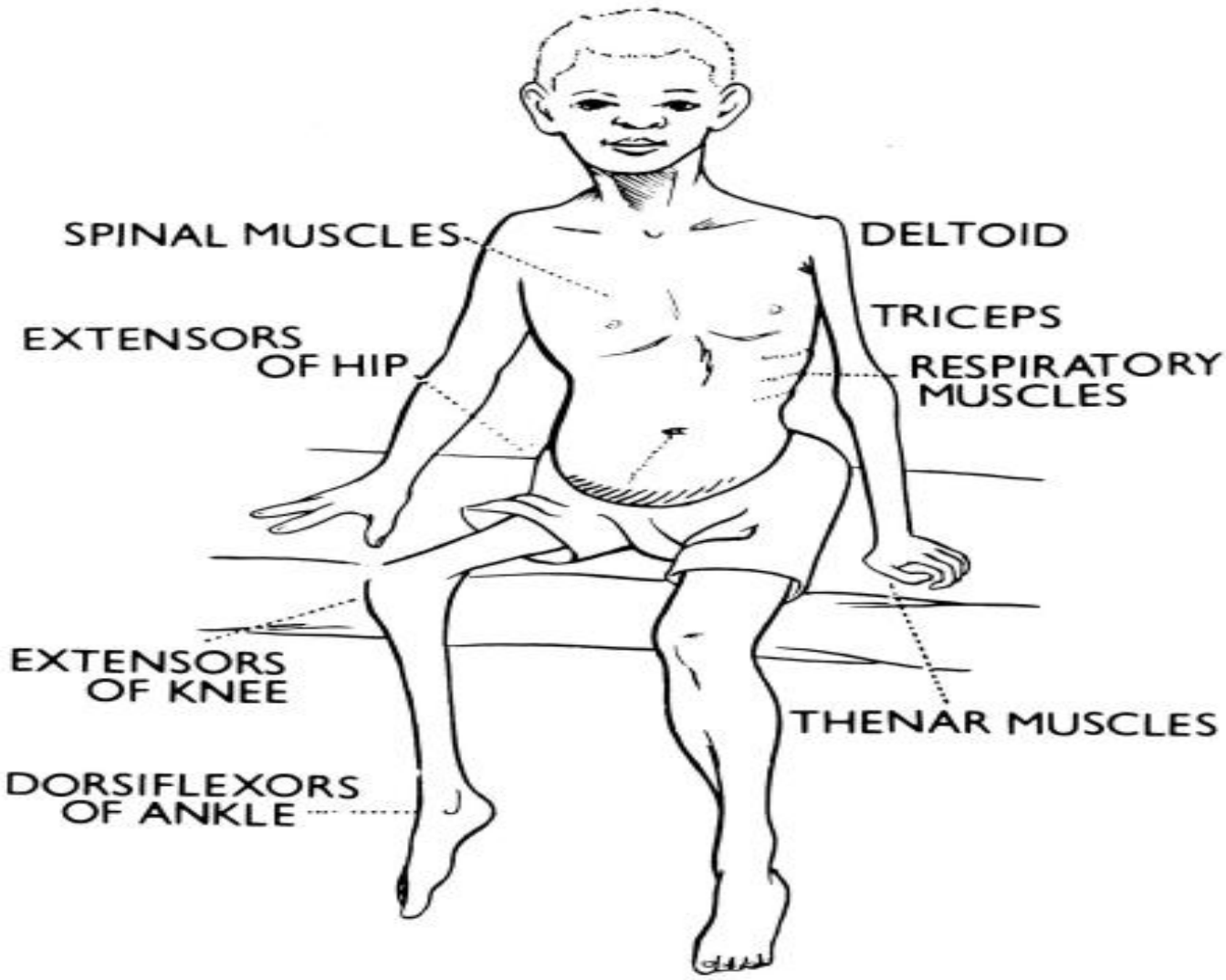


Fig. 6(b)

ANALYSIS of PATIENTS PARALYSED in POLIOMYELITIS

THE MAJORITY OF THOSE WHO ARE ILL WITH POLIOMYELITIS

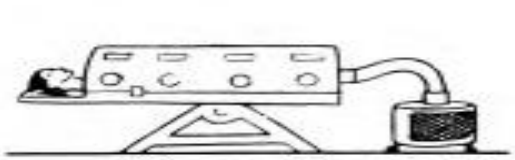
ARE NEVER PARALYSED

OF THOSE PARALYSED

30%
ARE PARALYSED BUT RECOVER COMPLETELY

30%
HAVE MILD PARALYSIS

30%
HAVE MODERATE OR SEVERE PARALYSIS



10%

HAVE SEVERE RESPIRATORY INVOLVEMENT OR HAVE BULBAR POLIOMYELITIS OR DIE

Fig. 12(a)

- **Diagnosis:**
- CSF chemistry: increased lymphocytic count, glucose level is normal or slightly decreased. CSF is rarely +ve for the virus.
- Isolation of the virus from stool or throat washing is done on tissue culture. CPE (roundness and granulation) appear in +ve cases. Neutralization of CPE by specific antibodies is used for identification & serotyping.
- PCR for rapid detection of viral RNA in blood.
- Paired serum samples are recommended for detection of rising titer (4 fold increase) using neutralization, CFT, IF, ELISA.

Prophylaxis:
A- Active immunization

Salk vaccine (IPV = inactivated polio vaccine)	Sabin vaccine (OPV = oral polio vaccine)
Type: Formalin inactivated vaccine.	**Type:** Living attenuated vaccine.
Preparation: Prepared by the 3 types of virus grown in monkey kidney cell cultures and inactivated by formalin	**Preparation:** prepared from non-paralytogenic mutants of the 3 types of virus grown on human diploid cell cultures and stabilized by MgCl2.
Administration: 4 S.C doses at 2, 4 and 6 months and a booster injection dose given at 4-6 years. Used in USA.	**Administration:** Orally as 4 doses at the age 2, 4 and 6 months and booster dose at 4-6 years. Used in Egypt.

Mechanism of action: *** The vaccine produces neutralizing antibodies (Ig G & Ig M) and prevents infection of the CNS.** *** It does not prevent replication of virus in the intestine i.e. no local mucosal immunity.**	**Mechanism of action:** *** It is a live vaccine so the virus multiplies in the intestine leading to production of local immunity in the intestine by IgA and Interferon.** *** It leads also to production of serum neutralizing antibodies (IgG&IgM).**
Advantages: 1. Heat stable. Not affected by temperature of storage or transport. Also it is not affected by co-infection with other enterovirus.	**Disadvantages:** 1. Failure of vaccination which may be due to: * Loss of potency of vaccine due to improper refrigeration during storage or transportation. * Interference with replication of the virus in the intestine if the child is already infected with another enterovirus.

2. Given safely to immunosuppressed children & during pregnancy.	The vaccine may cause paralytic disease in immunodeficient children, therefore Salk vaccine is recommended in these children.
3. never revert to virulent type i.e. no vaccine associated paralytic poliomyelitis (VAPP).	3. Rarely (1/million; small but significant number), VAPP may occur due to reversion of attenuated virus to virulent type during its replication in the vaccinated children (particularly type 2 & 3).

Disadvantages:	Advantages:
1. Administrated by SC injection. 2. It does not prevent intestinal infection with the virus, thus it does not prevent non- paralytic poliomyelitis. 3. No herd immunity	1. Easily administered (orally). 2. It prevents intestinal infection with the virus, thus preventing paralytic and non- paralytic infection. 3. The vaccine strain passes with the stools and is disseminated in the environment and can be transmitted to non-immunized children by faeco-oral route. This leads to spread of immunity in the community called "herd immunity" which may eventually lead to eradication of the wild poliovirus.
4. it does not interrupt transmission of wild polio virus.	4. Interrupts transmission of wild polio virus.

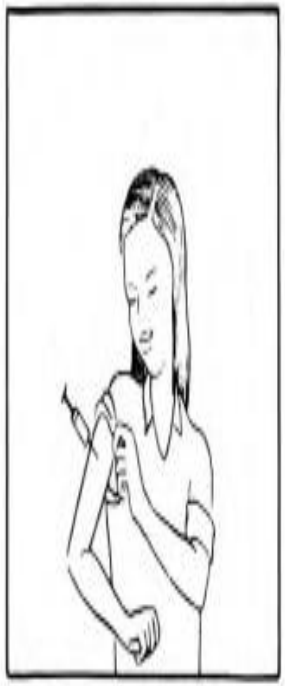
PROPHYLACTIC IMMUNIZATION

SABIN

vaccine
by mouth

SALK

vaccine
by injection



- **N.B.:**
- 1- In USA they use Salk and not Sabin for the vaccination of children to avoid occurrence of (VAPP). The current version of inactivated vaccine used in USA in 2007 is the enhanced polio-inactive vaccine (eIPV) which proved to be as immunogenic as OPV and is not associated with paralysis.
- 2- The WHO recommends a major campaign in which OPV mass vaccination is done to eradicate poliovirus from the world as was done with smallpox.

- **B- Passive Immunization:**
- Gamma globulins given early to susceptible unimmunized contacts may be effective in preventing paralytic poliomyelitis.

- **Treatment:**
- Pleconaril can be used as it inhibits viral penetration.

2- Coxsackie viruses

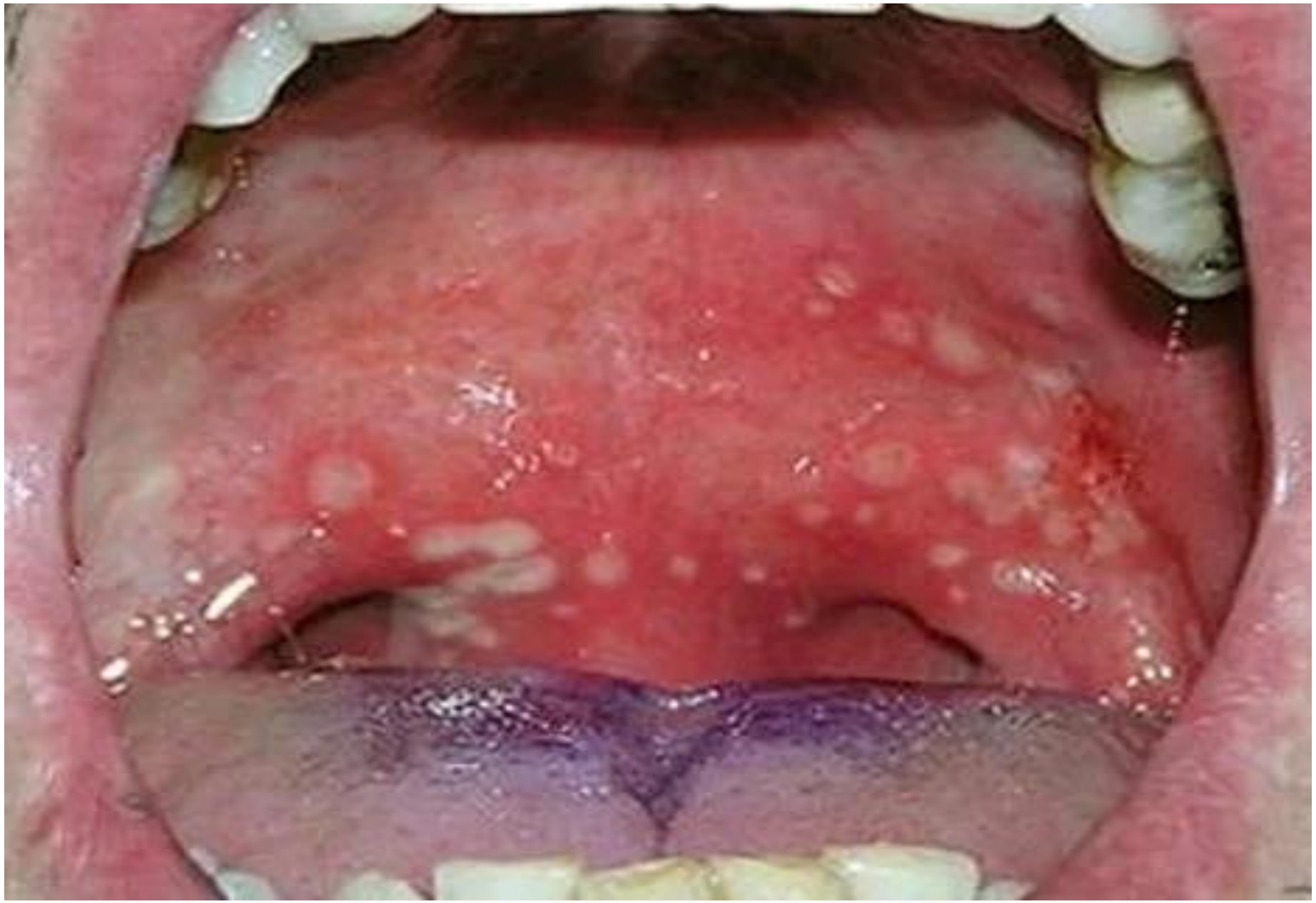
- (Named after Cox town, New York)
- **Classification:**
- Coxsackie viruses are classified into A and B based on their pathogenicity in new born suckling mice:
- **Coxsackie viruses A:**
- They include 12 types in HEV-A species & 12 types in HEV-C species.
- **Coxsackie viruses B**:
- They include 7 types in HEV-B species.

- **Diseases caused by Coxsackie viruses:**
- They are transmitted by the faeco-oral or respiratory route. They multiply in the GIT or oropharynx & disseminate via the blood stream.
- a. Infection is usually asymptomatic or manifested as mild upper respiratory tract (flu-like) disease.

- b. They also can cause several disease syndromes in man:
- Coxsackie viruses A can produce flaccid paralysis (polio-like) and widespread myositis, which is rapidly fatal without other observable lesions.
- Coxsackie viruses B produce focal myositis and other generalized mild lesions of CNS, heart & pancreas.
- The syndromes produced by coxsackie viruses include:

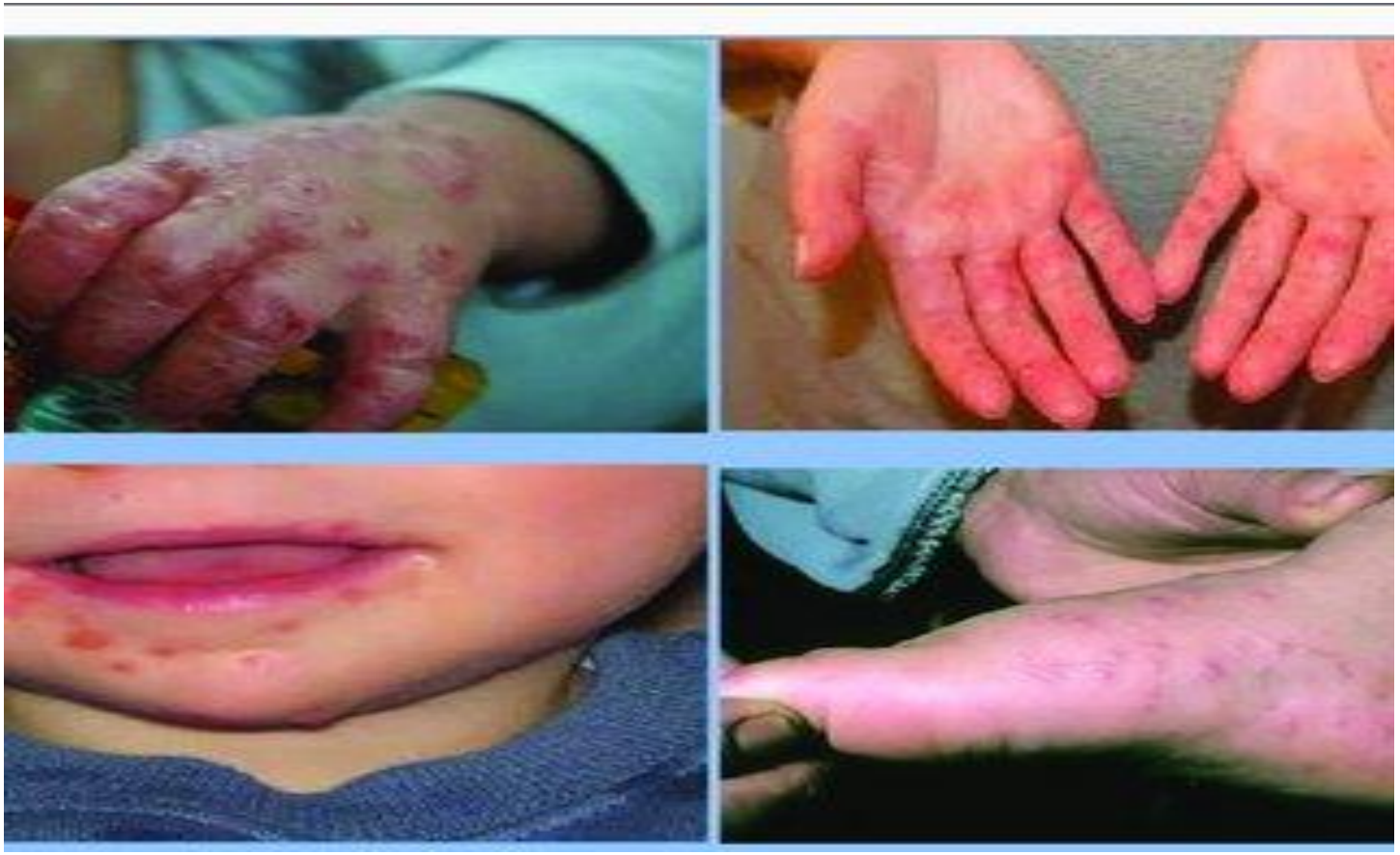
Disease	Caused by	Clinical manifestations
Herpangina	group A	A self limited disease mainly of children. Fever, sore throat, anorexia, dysphagia, vomiting and abdominal pain. Vesicles appear on the throat and tongue. The virus can be recovered from the lesions or from faeces.

herpangina



Hand, foot and mouth diseases	group A16	Vesicular rash on the hand and feet and ulceration in the mouth mainly in children.
Pleurodynia	group B	Fever and severe pleuritic chest pain. Abdominal pain, with sudden unexplained onset of heart failure.
myocarditis and pericarditis	group B	infection may be fatal to neonates or may cause permanent heart damage and cardiomyopathy

Hand foot & mouth diseases

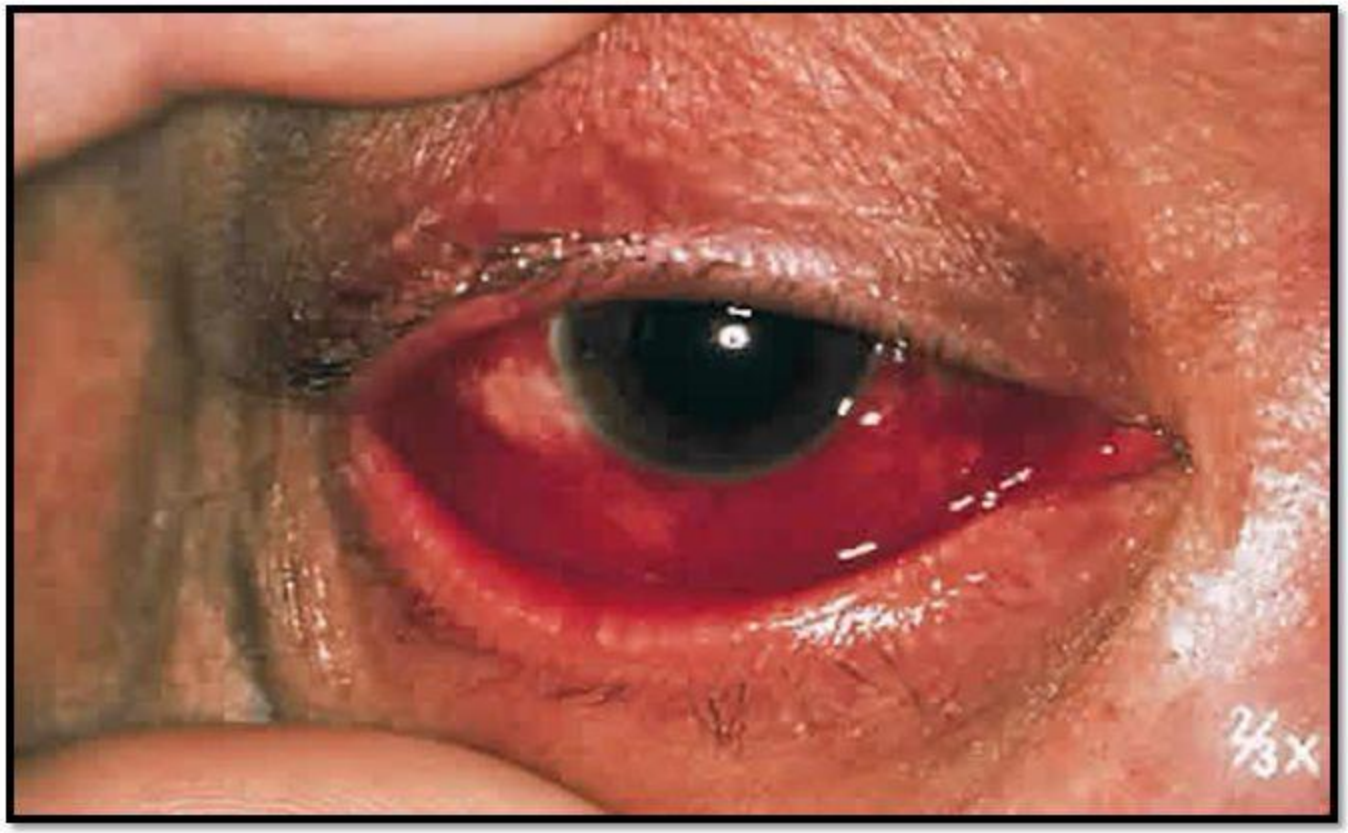


(type 1) Diabetes mellitus	Group B 3,4	due to destruction of islands of Langerhans
Aseptic meningitis	A &B types	Fever, malaise, headache, nausea and vomiting, stiff neck or back.
Summer minor illness	A or B types.	An acute febrile illness of short duration during the summer with or without rash.

Acute haemorrhagic conjunctivitis	Group A24	
Diarrhea and hepatitis	Group A and B	

- **Acute hemorrhagic conjunctivitis**

a highly contagious disease caused by:
Enterovirus 70 and **Coxsackievirus A_{24}**.



- **Diagnosis:**
- By isolation of the virus from throat, stool, CSF (in meningitis) in 1ry monkey kidney cell culture for Coxsackie viruses B or in suckling mice for Coxsackie viruses A (not grow on tissue cultures).
- Or by detection of rising antibody titers.
- Neither vaccine nor treatment is available for coxsackie viruses' infections.

3- Echo Viruses

- **(Enteric, Cytopathic Human Orphan)**
- They include 33 serotypes in HEV-B species. They are transmitted by faeco-oral route.
- **Diseases caused by echoviruses:**
- Aseptic meningitis.
- Myocarditis.
- Pericarditis.
- Febrile illness with or without rash.
- Common cold (ECHO 11, 20).
- Gastroenteritis (infantile diarrhea less than 1 year).

4- Human Enteroviruses (types 68, 70 & 71)

- **Enterovirus 68 & 70**:
- They are included in HEV-D species.
- Enterovirus 68 causes pneumonia in children.
- Enterovirus 70 causes acute haemorrhagic conjunctivitis & encephalitis
- **Enterovirus 71:**
- It is included in HEV-A species. It causes meningitis, encephalitis and paralysis resembling poliomyelitis.

Rhinoviruses

- More than 150 antigenic types are known. They cause upper respiratory tract infections especially common cold. They grow better at a temperature of 33°C which is the temperature of the nasopharynx
- **Pathogenesis and clinical manifestations:**
- The virus is transmitted via respiratory droplets.
- It enters the respiratory tract where it binds to its receptor on cell surface .
- The virus multiplies locally in the mucous membranes causing the manifestations of the disease. There is no blood invasion and the disease is self limited.

- Incubation period is short 2-4 days followed by headache, nasal discharge, mild cough and malaise.

- **Several attacks may be acquired during one season due to:**
  - Immunity is due to local IgA and interferon which is short lived. No serum antibodies.
  - Multiplicity of antigenic types.

- Secondary bacterial infections may cause otitis media, sinusitis, bronchitis or pneumonitis, especially in children.


Thank
You