Many different viruses can invade the central nervous system and cause neurological disease in humans. These infections may occur as the result of either acute or slow and chronic infections where the CNS is the ultimate target site for virus replication. In rare cases, CNS infections may arise as a post-infection complication or the consequence of vaccination. The viruses that are important in the United States are listed below:

<table>
<thead>
<tr>
<th>Virus Families</th>
<th>Genus</th>
<th>Specific Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RNA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Picornaviruses</td>
<td>Enteroviruses</td>
<td>Polio, Echo, Coxsackie</td>
</tr>
<tr>
<td>Togaviruses</td>
<td>Alphaviruses</td>
<td>WEE, EEE, VEE</td>
</tr>
<tr>
<td>Flaviviruses</td>
<td>Coltivirus</td>
<td>St. Louis Encephalitis</td>
</tr>
<tr>
<td>Reoviruses</td>
<td>Paramyxovirus</td>
<td>Colorado Tick Fever</td>
</tr>
<tr>
<td>Paramyxoviruses</td>
<td>Morbillivirus</td>
<td>Measles - SSPE</td>
</tr>
<tr>
<td>Rhabdoviruses</td>
<td></td>
<td>Rabies</td>
</tr>
<tr>
<td>Bunyaviruses</td>
<td></td>
<td>California Encephalitis</td>
</tr>
<tr>
<td>Retroviruses</td>
<td></td>
<td>HIV, HTLV-1</td>
</tr>
<tr>
<td><strong>DNA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpesviruses</td>
<td>alpha-herpes</td>
<td>HSV 1, HSV 2, Varicella-Zoster</td>
</tr>
<tr>
<td>Papovaviruses</td>
<td>polyoma</td>
<td>JC</td>
</tr>
</tbody>
</table>

**UNCONVENTIONAL**

Prions: Creutzfeldt-Jacob agent
**Picornaviruses**

The Picornaviridae family is the largest and most important family of viral pathogens that infect plants as well as animals. It is divided into 6 genera; 4 of which are important in humans:

A. Classification:

1. **Enteroviruses**
   - **Serotypes**
     - a. polioviruses: 3
     - b. coxsackie viruses
       - 1) group A: 23
       - 2) group B: 6
     - c. echoviruses: 31
     - d. new enteroviruses: 4

2. **Hepatitis A** virus: 1

3. **Rhinoviruses**: 115

B. Diseases caused by Picornaviruses

1. Enteroviruses:
   - spread by fecal-oral route
   - grow in GI mucosa
   - a. Paralytic Poliomyelitis
   - b. Encephalitis
   - c. **Meningitis**
   - d. Epidemic myalgia
   - e. Herpangina = vesicular rash
   - f. Hand-foot-and-mouth disease
   - g. Infantile diabetes and pancreatitis
   - h. Pericarditis and Myocarditis
   - i. Dilated Myocardiopathy
   - j. Exanthems

2. Hepatitis viruses A - acute hepatitis

3. Rhinoviruses - common cold
4. new enteroviruses - hemorrhagic conjunctivitis

C. Properties of Picornaviruses.

These viruses are small (24-30 nm) icosahedrons and do not contain an envelope. They consist of protein (70%) and RNA (30%). The capsids are made up of 4 different polypeptides (60 molecules each). There are 3 polypeptides on the surface of the capsids, which are designated as VP1, VP2 and VP3. These polypeptides are antigenic. The internal polypeptide, VP4, is associated with viral RNA. The RNA is single-stranded, in one piece and of positive (message) sense. The viruses replicate rapidly in the cytoplasm and do **not** require DNA for their reproduction.
2. Function of viral components

a. Nucleic acid = genome = mRNA = the only known mRNA without a cap
   1) is infectious by itself
   2) serves as template for its replication
   3) codes for unique polymerase needed for its replication = RNA dependent

b. Proteins derived from one precursor and processed by post-translational proteolysis
   1) structural
      a) host tropisms
      b) protection of genome
      c) immunogens
      d) internal ribosome entry = VPg
   2) non-structural
      a) post-translational processing
      b) viral RNA synthesis
      c) turn-off of host cell syntheses

D. Virus Replication.

The viruses replicate rapidly in the cytoplasm and do not require DNA for their reproduction. The viruses are usually released with destruction of the cells (lysis).
The viral genome is translated immediately after it is uncoated into a large precursor polyprotein. The protein undergoes post-translational processing into non-structural proteins (e.g. proteases and polymerase) and structural proteins (i.e., capsid proteins -VP1-4 and a protein that becomes covalently linked to the 5' end of the viral genome-VPg). The RNA genome serves as a template for its replication through a complementary (-) strand. Since the RNA genome is positive stranded, it is infectious. That is, it can be transfected into cells and be translated and transcribed directly with the production of complete virus particles.

E. Pathogenesis:

1. **Enteroviruses**: The enteroviruses are named for their site of entry and initial site of replication. They are ingested and infect cells of the gastrointestinal tract. If the infection remains in the GI tract, it is asymptomatic. Yet, life-long immunity is acquired. **Pathogenesis depends on the stability of the virus over a wide pH range (pH 3-9) and the systemic spread of the virus through lymph and blood.** When the infections spread systemically, these viruses can cause a variety of diseases. **All of the enteroviruses have the capability of invading the central nervous system and replicating in neurons resulting in meningitis or encephalitis.** Other diseases result from infections of cells in the skin, intestinal and respiratory mucosa, heart muscles and conjunctiva.

![Diagram of enterovirus pathogenesis](image-url)
2. **Hepatitis A** virus - refer to lecture on viral hepatitis.

3. The **rhinoviruses** cause a localized infection of the nose and are responsible for most cases of the common cold. They are more heat and pH labile than the enteroviruses. Symptoms occur 2 to 4 days after exposure and last about one week.

F. Immune Responses of Picornaviruses

Protective immune responses occur in 2 - 3 weeks after infection. Humoral immunity is important in protection from infections. Intestinal immunity is especially important for enteroviral infections and is the basis for the effectiveness of the poliovirus vaccines. Inactivated (Salk) and attenuated (Sabin) poliovirus vaccines have been highly successful in elimination of poliomyelitis from developed countries. Since these viruses can undergo a high rate of mutation through recombination, concern over use of attenuated viruses in vaccines has led to research and development of recombinant and/or component vaccines with deletion of the virulence genes. Vaccines are not available for the other enteroviruses.

Secretory mucosal IgA is important in protection from rhinovirus infections. However, the large number of rhinovirus serotypes has prevented the development of an effective vaccine for the common cold.

G Laboratory Diagnosis

The neutralization test is the most sensitive test for the identification of viruses isolated from patients and for determination of their immune state. You will perform this test in the laboratory.

Required Reading: Mechanisms of Microbial Disease, edition 3., Schaechter et al.pg.305-312
Study Questions

Picornaviruses

1. Describe properties that distinguish between enteroviruses and rhinoviruses

2. How may knowledge of differences between viruses contribute to diagnosis of infections by different viruses?

3. What immune mechanisms are involved in protection from reinfection by picornaviruses?

4. Would you use attenuated or inactivated poliovirus as a vaccine? What are the reasons for your choice?

5. How would you select an ideal anti-viral drug for treatment of picornavirus infections (i.e. at which stage of virus replication would it be effective?)

Answers:

1. The thermostability, pH range and density of the two groups of viruses differ. Most important property is that enteroviruses survive at higher temperature and wider pH range than rhinoviruses.

2. Differences between viruses such as antigenicity (serotypes) and laboratory hosts (animal and cell cultures) aid in diagnosis. Also, the ability to agglutinate RBC can be used for HI determinations.

3. Intestinal immunity is the first line of defense (Anti-viral IgA). If viruses escape immunosurveillance by IgA, Anti-viral IgG in the serum is the next line of defense leading to neutralization of the virus.
4. **Inactivated**

   **Advantages:**
   - non-infectious
   - can reproduce and stimulate a greater immune response -esp. IgA and intestinal immunity
   - doesn't need boosters

   **Disadvantages:**
   - need booster
   - require injection
   - no IgA induction
   - no intestinal immunity

5. You would select a drug that inhibits virus reproduction without damaging cells. Therefore, need a drug that recognizes unique viral components such as VPg and capsid proteins, or that inhibits synthesis or action of the viral replicase (RNA dependent RNA polymerase) or inhibit the entry or uncoating of the viral genome.