Chapter 39

RNA viruses (2)

Paramyxoviruses (contd)

Respiratory syncytial virus

-- **Respiratory syncytial virus (RSV)** is the **most common cause of pneumonia and bronchiolitis in infants**.

-- It also causes **otitis media in children** and **pneumonia in elderly** and in patients with **cardiopulmonary diseases.**

-- **Structure is similar to typical myxoviruses.**

-- Its spikes are **fusion proteins** causing cells to fuse to form **multinucleated giant cells (syncitia).**

-- Antibody against the fusion protein **neutralizes infectivity**.

-- **Replicative cycle is similar to measles virus.**

Pathogenesis and immunity

-- **RSV** infection in **infants is more severe** and **more often involve lower respiratory tract** than in older children and adults.

-- **Viremia does not occur.**

-- Immunity is **incomplete** and **multiple infections** are usual.

-- **IgA respiratory antibody** reduces the frequency of **RSV** infection as a person ages.

Clinical findings

-- **RSV** is an important cause of **bronchiolitis**, **pneumonia** and **otitis media** in young children.

-- In older children and adults it causes **common cold** and **bronchitis**.

-- In persons **above 65 years** age and **those with cardiopulmonary disease**, severe lower respiratory disease such as **pneumonia** may occur.

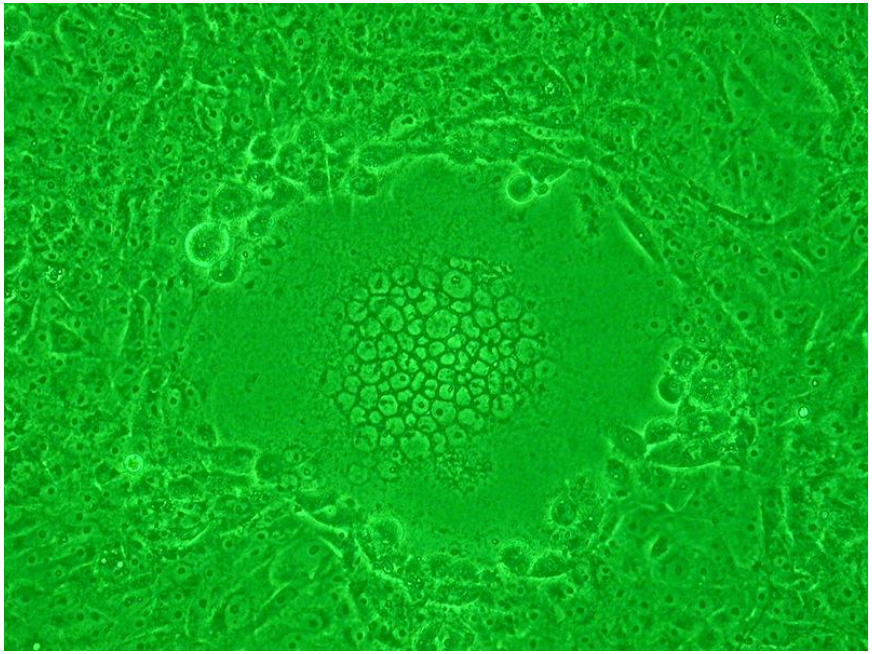
Laboratory diagnosis

-- An enzyme immunoassay (**rapid antigen test**) that **detects RSV antigens** in respiratory secretions is commonly used.

-- **CPE** is characterized by formation of **syncitia**.

-- A **four-fold rise in antibody** is also **diagnostic**.

-- **RT PCR** is also available.



Treatment

-- Aerosolized ribavirin (**Virazole**) is recommended for severely ill hospitalized infants but its effectiveness is not proved.

-- A combination of ribavirin and hyperimmune globulins against **RSV** may be more effective.

Prevention

-- There is **no vaccine**.

-- **Hyperimmune Ig** may also be used in these infants and children with **chronic lung disease**.

-- **Nosocomial outbreaks** may be limited by hand washing and use of gloves.

Parainfluenza viruses

These viruses cause **croup** (acute laryngotracheobronchitis), **laryngitis**, **bronchiolitis**, and **pneumonia** in **children** and a disease resembling the **common cold in adults**.

Important properties

-- **Structure is similar to typical myxoviruses.**

-- **Surface spikes** consists of **haemaglutinin (H), neuraminidase (N)** and **fusion (F) proteins**.

-- **F protein** is on a separate spike and **mediates formation of syncitia**.

-- There are **4 types** distinguished by **antigenicity, CPE,** and **pathogenicity**.

-- **Replication cycle is similar to measles virus.**

Transmission and Epidemiology

-- These viruses are transmitted via **respiratory droplets.**

-- They cause disease **worldwide** mainly in winter.

Pathogenesis and Immunity

-- These viruses cause **upper and lower respiratory tract infections without viremia**.

-- Many infections are **subclinical**.

-- **Parainfluenza virus 1** and **2** are major causes of **croup**.

-- **Type 3** commonly causes **lower respiratory tract infections**.

-- **Type 4** may rarely cause **common cold**.

Clinical findings

-- They are the **main cause of croup in children younger than 5 years of age.**

-- Croup is characterized by **harsh cough** and **hoarseness**.

-- They may also cause **common cold, pharyngitis, laryngitis, otitis media, bronchitis**, and **pneumonia.**

Laboratory Diagnosis

-- Most infections are **diagnosed clinically**.

-- In the laboratory, diagnosis may be made either by isolating the virus in cell culture or by observing **four fold or greater rise in antibody titer.**

-- **PCR** can also be used.

Treatment and Prevention

-- There is **neither an antiviral therapy nor a vaccine** available.

Rhabdoviruses

Rabies virus

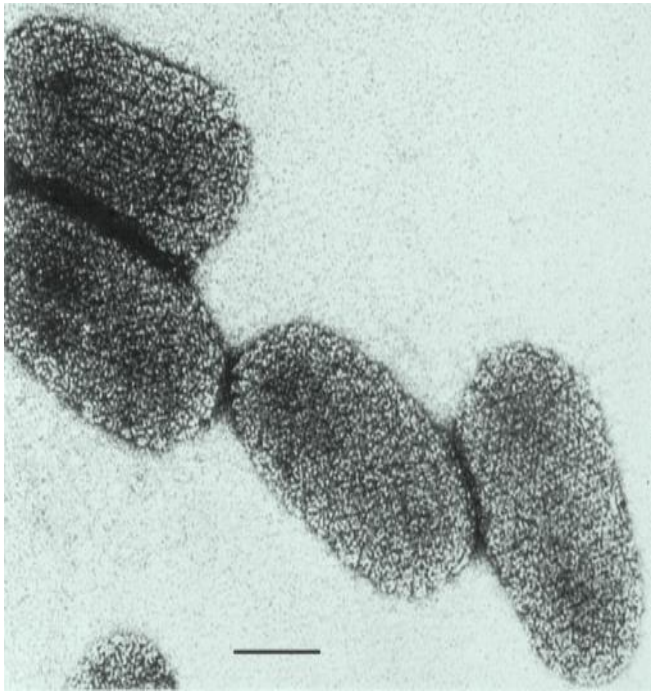
It causes **rabies**.

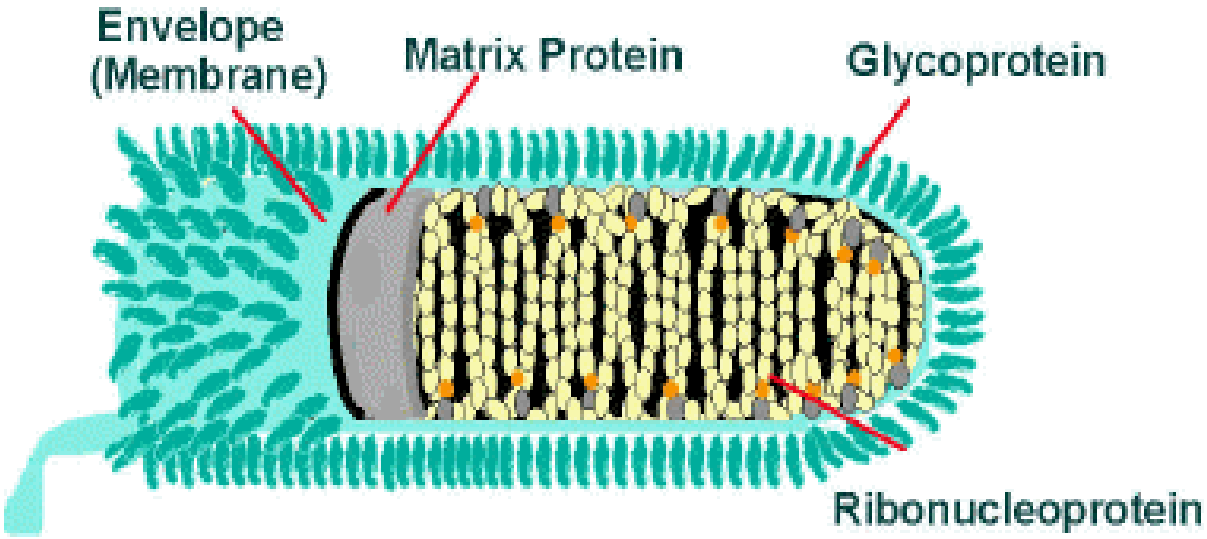
Important properties

-- **Rabies virus** is a **rod- or bullet-shaped**, **single-stranded, negative-sense, unsegmented, enveloped RNA virus.**

-- The virus genome encodes **five proteins**.

-- Genome is contained within a **bullet shaped capsid** surrounded by a **lipoprotein envelope**.




Envelope
(Membrane)
Matrix Protein
Glycoprotein
Ribonucleoprotein

-- Because the genome has **negative polarity**, the virion contains an **RNA-dependent RNA polymerase**.

-- There is **single antigenic type** based on **surface glycoprotein**.

-- It has a **broad host range**.

-- It can **infect all mammals** but only a few can cause infection in humans.

-- **Rabies virus** attaches to **acetylcholine receptor** on the cell surface.

-- After **entry into the cell**, the **virion RNA polymerase** synthesizes **five mRNAs** that code for **viral proteins.**

-- After **replication** of viral genome RNA by a viral encoded RNA polymerase, progeny RNA is assembled with virion proteins to form **nucleocapsid**.

-- **Envelope** is acquired as the **virion buds** through the cell membrane.

Transmission and Epidemiology

-- The virus is transmitted by the **bite of a rabid animal** that manifests aggressive, biting behavior induced by **viral encaphilitis**.

-- **Dogs** and **cats** are especially relevant.

-- The country of origin and the reservoir host of a rabies strain can be identified by **molecular methods**.

Pathogenesis and immunity

-- The virus may enter the peripheral nervous system **directly** and move by **axonal transport to CNS**.

-- The virus then begins to pass **centrifugally** to many tissues and organs, such as the **salivary glands**.

-- From salivary glands, it **enters saliva to be transmitted by the bite**.

-- There is **no viremic** stage.

-- Within the CNS, **encephalitis** develops with the **death of neurons and demyelination**.

-- Infected neurons contain an eosinophilic cytoplasmic inclusion called **Negri body**.

-- **Few individuals survive rabies so immunity is poorly understood.**

Clinical findings

-- The **incubation period varies according to the location of bite**, from 2-16 weeks or longer depending on the **distance of bite site from CNS**.

-- There are **non specific symptoms** such as fever, anorexia and changes in sensation at bite site.

-- Within a few days signs such as **confusion, lethargy** and **increased salivation** develop.

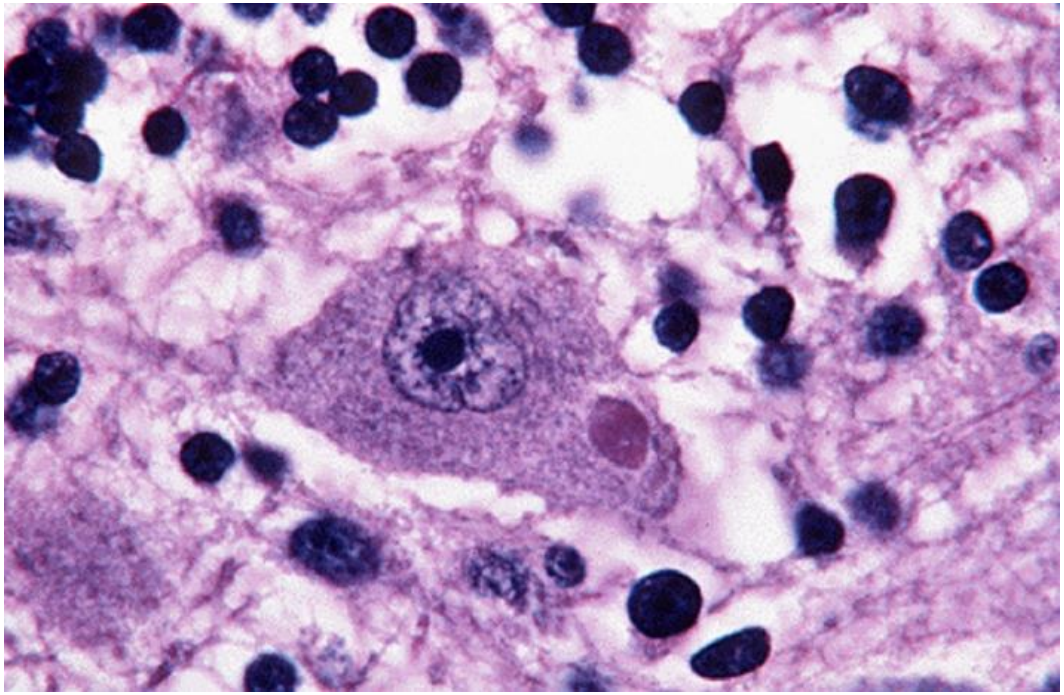
-- **Most notable is painful spasm of throat muscles while swallowing**. This results in **hydrophobia**.

-- Within several days, the disease progresses to **seizures, paralysis, coma,** and ultimately **death.**

Laboratory Diagnosis

Rapid diagnosis in **animals** can be made by examination of brain tissue by **PCR assay**, **fluorescent antibody to rabies virus** or by observation of **Negri bodies** in the cytoplasm of **hippocampal neurons**.

Virus can be isolated by **cell culture** but it takes too long for decision for vaccination.



-- In **humans** diagnosis can be made by **PCR,** or **fluorescent antibody staining of a biopsy specimen** usually taken from **skin of the neck at hairline**.

-- Or by **isolation of virus from saliva**, **CSF** and **brain tissue**.

-- Or by a **rise in titer of antibody to virus**.

-- **Negri bodies** can be demonstrated in **corneal scrapings** and in **autopsy specimens of the brain**.

Treatment

-- There is **no antiviral therapy**.

-- Only **supportive treatment** is available.

Prevention

-- **Animal rabies** is prevented by **vaccinating susceptible species**, particularly **dogs** and **cats**.

-- **Human rabies** is best prevented by **avoiding exposures** to the diseased animals.

-- If treatment (post exposure prophylaxis) is necessary, it should be **initiated promptly**.

-- **Post exposure prophylaxis** consists of the **combination** of **local wound cleansing**, **human rabies immune globulin (HRIG)** and **rabies vaccine**.

-- Two cell culture products currently licensed include the **human diploid cell vaccine (HDCV)** and **rabies vaccine adsorbed (RVA).**

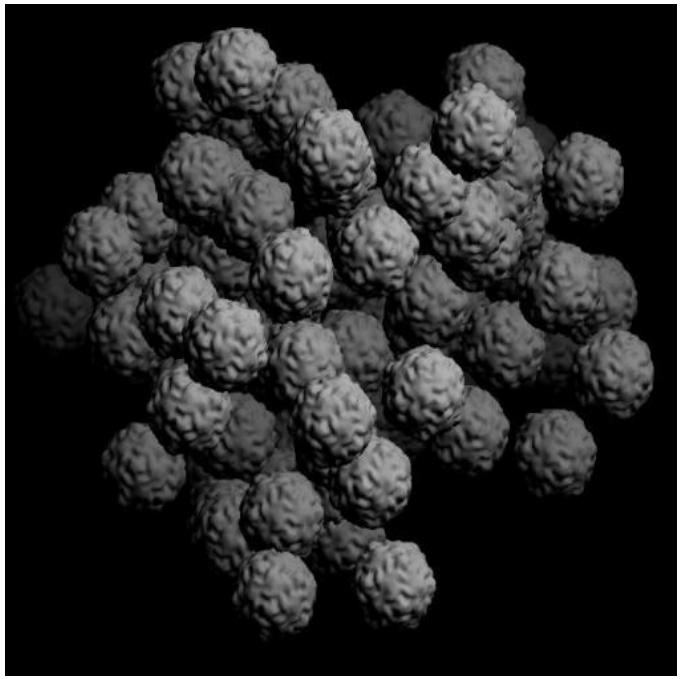
-- **Post exposure treatment will abort the infection, but there is no cure for clinical disease.**

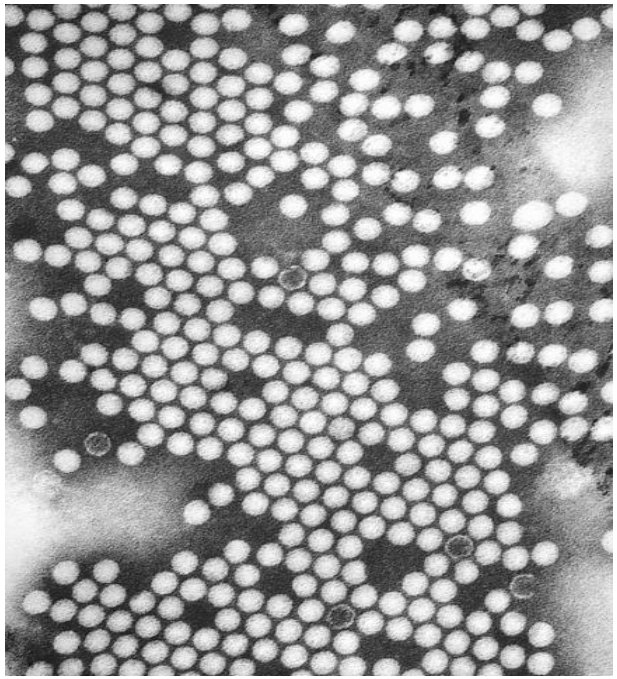
-- **Pre exposure immunization** may be offered to **persons at high risk** such as veterinarians, animal handlers, and certain laboratory workers.

Picornaviruses

Picronaviruses are small (20-30 nm) **nonenveloped viruses** composed of an **icosahedral nucleocapsid** and a **single stranded RNA genome**.

It has **positive polarity** so it serves as **mRNA**.





-- These viruses replicate in **cytoplasm**.

-- There are two medically important groups, **enteroviruses** (enteric tract) and **rhinoviruses** (nose and throat).

-- **Enteroviruses** are **stable at pH 3-5** which help in their survival against gastric acid.

-- **Poliovirus** is the most important member of **enteroviruses**.

Poliovirus

It causes **poliomyelitis**.

Important properties

-- Host range is **limited to primates** because receptor for virus is found only on primate cell membranes.

-- There are **three** serological types.

-- **Immunity against one does not protect against others.**

Replicative cycle

-- After entering the cell, capsid proteins are removed.

-- Genome RNA works as mRNA and a very **large polypeptide called noncapsid viral protein 00** is formed.

-- It is **cleaved** by a **virus encoded protease in multiple steps** to form both the **capsid proteins** of **progeny virions** and several noncapsid proteins including the **RNA polymerase that synthesizes the progeny RNA genomes.**

-- **Replication** of genome occurs by **synthesis of a complementary negative strand** which then **serves as a template for positive strands.**

-- Some of these **positive strand mRNAs function as mRNA** to make more viral proteins and the remainder become **progeny virion genome RNA** which are then coated with capsid proteins.

-- Virions accumulate in **cytoplasm** and are released upon **cell death**.

-- They **do not bud** from cell membrane.

Transmission and epidemiology

-- Transmission is by **fecal oral route**.

-- It replicates in **oropharynx** and **intestinal tract**.

-- **Humans are the only natural hosts.**

-- Due to successful vaccination, the disease is now restricted only to four countries **Afghanistan, Pakistan, India** and **Nigeria.**

Pathogenesis and immunity

-- After replicating in the oropharynx and small intestine, esp. in **lymphoid tissue**, the virus **spreads through the blood stream to the CNS**.

-- It can also spread **retrograde along nerve axons**.

-- In the **CNS**, poliovirus **preferentially replicates in the motor neurons** located in the **anterior horn of the spinal cord.**

-- **Death of these cells results in paralysis of muscles innervated by those neurons.**

-- Paralysis is **not due to** viral infection of muscle cells.

-- The virus also affects **the brain stem** leading to **“bulbar” poliomyelitis** with **respiratory paralysis** but rarely damages the cerebral cortex.

-- Immune response is **life long** and based on both **intestinal IgA** and **humoral IgG** to specific serotype.

Clinical findings

Responses to infection may be:

1. **Inapparent** asymptomatic infection.
2. **Abortive** poliomyelitis
3. **Non paralytic** poliomyelitis
4. **Paralytic** poliomyelitis

Roughly 1% infections are clinically apparent.

The incubation period is **10-14** days.

Abortive poliomyelitis

Most common clinical form is **abortive poliomyelitis** which is a **mild, febrile illness** characterized by headache, sore throat, nausea and vomiting.

Most patients **recover spontaneously**.

Non paralytic poliomyelitis

It manifests as **aseptic meningitis** with fever, headache and a stiff neck.

It also usually **resolves spontaneously**.

Paralytic poliomyelitis

Flaccid paralysis is the **predominant finding** but **brainstem involvement** can lead to **life threatening respiratory paralysis**.

Painful muscle spasms also occur.

The **motor nerve damage is permanent**, but some recovery of muscle functions occurs as other nerve cells take over.

Both the **meninges** and **brain parenchyma** (**meningoencephalitis**) are often involved.

If the **spinal cord is also involved**, term **meningomyeloencephalitis** is often used.

There is **no permanent carrier state** but **virus excretion in feces can occur for several months**.

Laboratory diagnosis

-- The diagnosis is made either by **isolation of the virus** or by a **rise in antibody titer**.

-- Virus can be recovered from the **throat, stool or CSF** by inoculation of cell cultures.

-- It causes a CPE and can be identified by **neutralization of the CPE** with specific antisera.

Treatment

-- There is **no antiviral therapy**.

-- Treatment is limited to **symptomatic relief** and **respiratory support** if needed.

-- **Physiotherapy for affected muscles is important.**

Prevention

-- **The disease can be prevented by vaccines.**

-- There are two vaccines **Salk vaccine (IPV)** which has killed viruses and **Sabin vaccine (OPV)** which has live, attenuated viruses.

-- **Both induce antibodies that kill the virus** and hence prevent CNS infection.

-- **Sabin vaccine** is preferred.

-- Latest version of killed vaccine is called **enhanced polio vaccine** or **eIPV**.

-- It induces **higher titers of antibody** than OPV, but amount of induced IgA is significantly less than OPV.

-- In endemic countries a **monovalent OPV** is given because it has higher seroconversion rates than trivalent vaccine.

-- Each vaccine needs a **booster dose**.

-- **OPV** has advantages of **oral administration** and **induction of secretory IgG in GIT**, but there are rare chances of **reversion**.

-- It can also cause disease in **immunodeficient persons** and can be affected if there is infection by other **enteroviruses**.

-- In addition, it should **always be refrigerated**.

-- A **complication** is polio caused by **vaccine derived polioviruses (VDPV)** which become **virulent** by **acquiring genes from enteroviruses by recombination**.

-- It can be contained by use of OPV in affected areas.

RNA non enveloped viruses

Reoviruses

REO is for **respiratory enteric orphan** because when initially isolated, their disease association was not known.

Rotaviruses are the main human pathogens.

Rotaviruses

-- It is the **most common cause of viral gastroenteritis in children**.

-- The virus is transmitted through **oral-fecal route**.

-- Infections occur **worldwide**.

-- They have a **segmented, double stranded RNA genome** surrounded by a **double-layered icosahedral capsid without an envelope.**

-- Genome has **11 segments**.

-- **Animal rotaviruses do not infect humans.**

-- Human rotavirus has **six serotypes**.

-- **Outer surface protein** (viral hemagglutinin) is the **type specific antigen** and elicit protective antibody.

Replication cycle

-- It attaches to **β-adrenergic receptor**.

-- After entry in cell, **replicase synthesizes mRNAs from each segment** in the cytoplasm which are translated into corresponding proteins.

-- Viral release is after **cell lysis**.

Pathogenesis and immunity

-- The virus **replicates in the mucosal cells of small intestine** resulting in **excess secretion of fluids and electrolytes** into the bowel lumen.

-- The consequent **loss of salt, glucose and water** leads to **non-bloody diarrhea**.

-- **Probably** the diarrhea is caused primarily by **stimulation of the enteric nervous system**.

-- It is probable the there is **IgA production** that protects against the causative serotype.

Laboratory diagnosis

-- **Rotavirus** can be detected in stool by **radioimmunoassay** or **ELISA**.

-- **Antibody titer rise may also be useful**.

Treatment and prevention

-- Two **oral, live attenuated vaccines** are available.

-- **Rotarix** is based on serotype G1.

-- **Rotateq** is based on 5 serotypes.

-- The constituent viruses of **Rotateq** are of **bovine origin** in which gene for **human rotavirus outer surface protein** has been inserted.


Thank You!