Acute neurological syndromes

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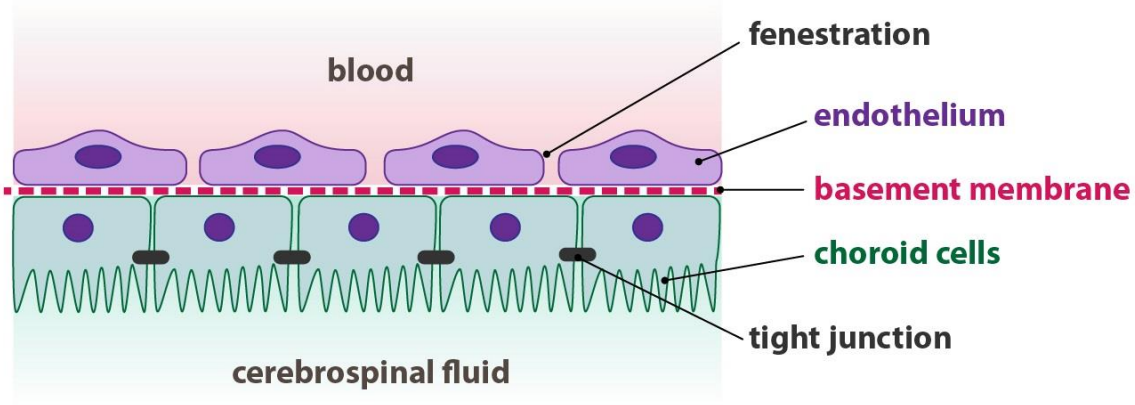
Medical Virology,
11 Dec 2015.

Contents of Teaching in Medical Virology Lecture:

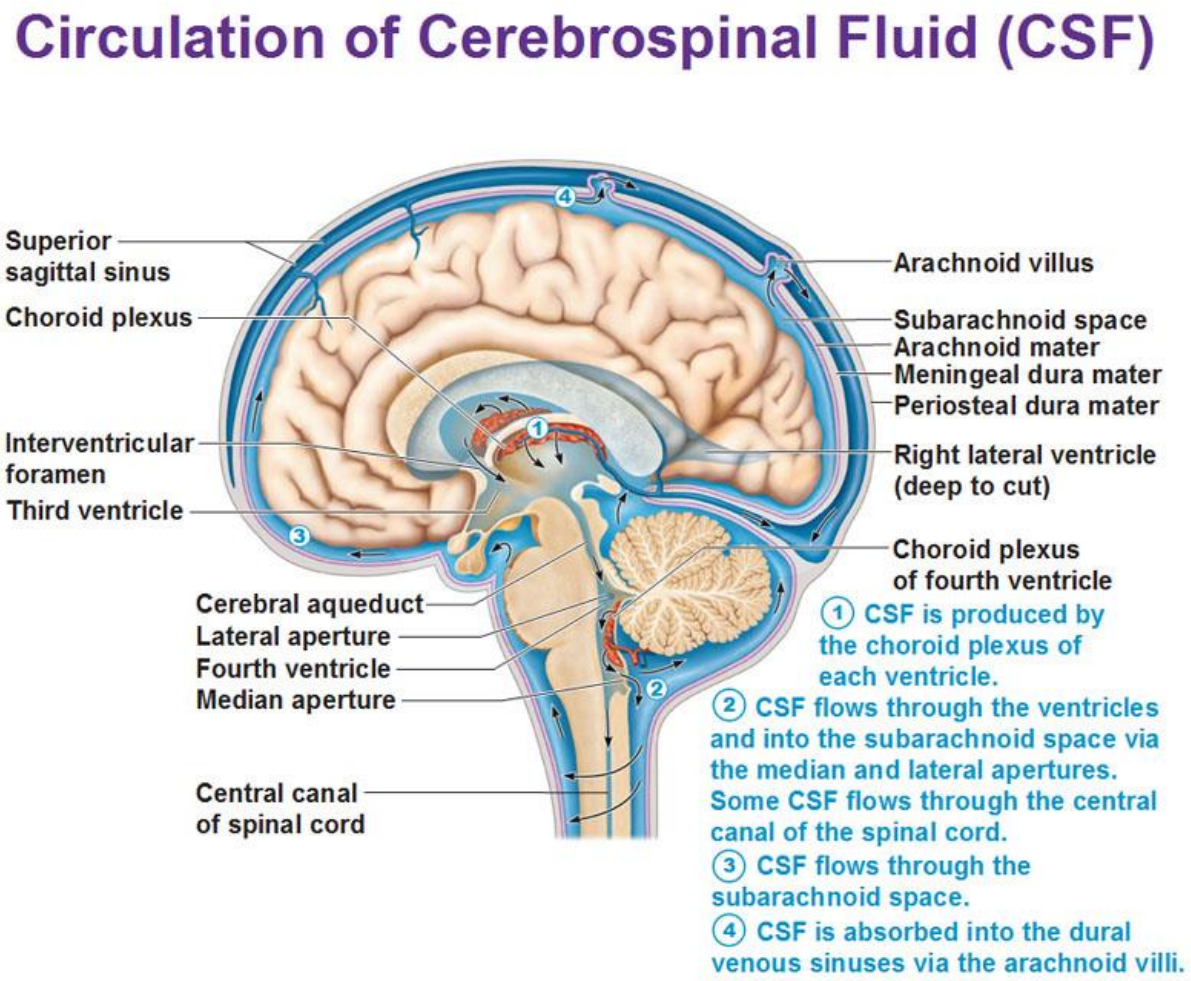
1. Cerebrospinal Fluid
2. Blood-Brain Barrier
3. Blood-CSF Barrier

- **Liquor** (**cerebrospinal fluid – CSF**) is a clear, colourless fluid found in CNS either **intracerebrally** in the ventricular system of the brain (making up 20 % of the total CSF volume) or **extracerebrally** in the subarachnoid space (the remaining 80 % of the total volume).
- The total **volume** of cerebrospinal fluid is approximately **150 ml** and it is produced at a **rate of 450 ml per day**.



Cerebrospinal Fluid

- CSF is formed in the **choroid plexuses** in all the four brain ventricles and they are scattered around.
- The choroid plexuses are composed of **ependymal cells** and capillaries that are attached to pia mater and create the CSF.
- The cilia from them stick out into the space in the ventricles. Underneath the ependymal cells are capillaries.
- Blood plasma diffuses out the capillaries and moves into the ependymal cells. Once the blood plasma goes out, it is called CSF.
- Inside it is water, sodium, glucose, oxygen, vitamins, etc. When things go in the other direction, ependymal cells absorb waste.



Acute neurological syndromes caused by viruses

- Clinically, neurological diseases caused by viruses can be divided into acute and chronic syndromes.
- The pathology may be due either to multiplication of virus in the cells of the brain or, due to the (misdirected) immune response of the host - post-infectious encephalo-myelitis
- Viruses which infect the brain may reach the central nervous system either by the blood stream or by spread along peripheral nerves.
- Asymptomatic infection of the brain is common. Where a virus infects the brain directly, it can usually be isolated either from brain tissue or from the cerebrospinal fluid.

Acute neurological syndromes

There are four main syndromes

1. Aseptic meningitis
2. Acute flaccid paralysis
3. Encephalitis
4. Post infectious encephalo-myelitis

1. Aseptic meningitis

- This is the commonest viral syndrome.
- The condition is self-limiting and has a good prognosis.
- Infection is confined to the meninges. The clinical features include fever, headache, neck stiffness, photophobia and vomiting.
- CSF findings include a pleocytosis consisting of both polymorphs and lymphocytes, but usually with a lymphocyte predominance, normal glucose and no bacterial growth (hence the term aseptic).
- Common viral agents include: **enteroviruses** and **mumps virus** (and less commonly **HSV-2** and **varicella-zoster virus**).

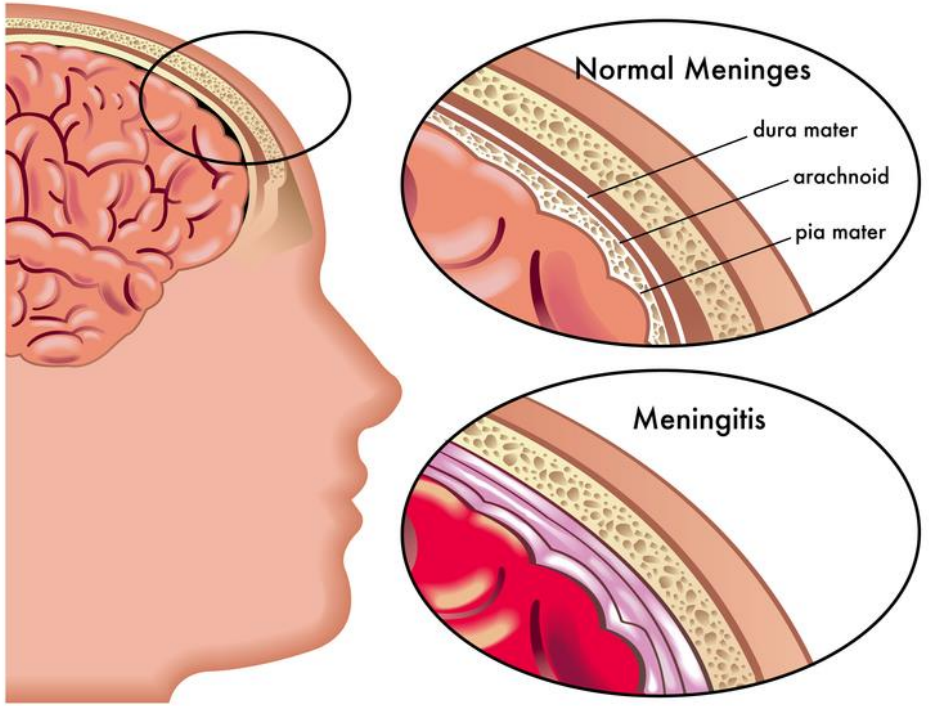


Table 4. Normal CSF characteristics and main pathological alterations

		Meningitis		
Characteristics	**Normal**	**Acute bacterial**	**Viral**	**Chronic**
Pressure (mm/H_2O)	100-200	N or ↑	N or ↑	N or ↑
Aspect	Clear	Turbid/purulent	clear/cloudy	Clear/cloudy
Color	Clear	white	Clear	Clear/white
Cytology (mm^3)	Until 4	> 1,000	500-1,000	< 500
Cell type	Lymphocytes	Neutrophils	Lymphocytes	Lymphocytes
Protein (mg/dL)	V 5-10 SO 10-25 L 15-45	↑↑	Normal or ↑	Normal or ↑
Glucose (mg/dL)	2/3 from serum	↓	Normal	Normal or ↓
Lactic acid (mmol/L)	< 3.5	> 3.5	< 3.5	< 3.5

Almeida SM *et* al., Braz J Infect Dis 2007; 11(5): doi.org/10.1590/S1413-86702007000500010

Table 2. Etiological diagnostic methods for acute bacterial meningitis

Traditional bacteriologic methods
Direct bacterioscopy (Gram stain)
Cultures
Immunologic methods
Latex particles agglutination
Co agglutination
Counter immunoelectrophoresis (CIE)
ELISA
Polymerase chain reaction (PCR)

Almeida SM *et* al., Braz J Infect Dis 2007; 11(5): doi.org/10.1590/S1413-86702007000500010

Table 7. Virus responsible for lymphocytic meningitis

Common	Less frequent	Rare
Enterovirus	HSV-1	Adenovirus
Coxsackie virus A e B	LCV	CMV
Echovirus	Mumps	EBV
Arbovirus*		Influenza A, B
HIV		Measles
HSV-2		Parainfluenza
		Rubella
		VZV
		HHV-6

*The types of arbovirus are different depending on the area, it is important to investigate areas or countries visited by the patients. LCV=Lymphocytic choriomeningitis virus.

Almeida SM *et* al., Braz J Infect Dis 2007; 11(5): doi.org/10.1590/S1413-86702007000500010

Table 8. Laboratorial investigation of lymphocytic meningitis

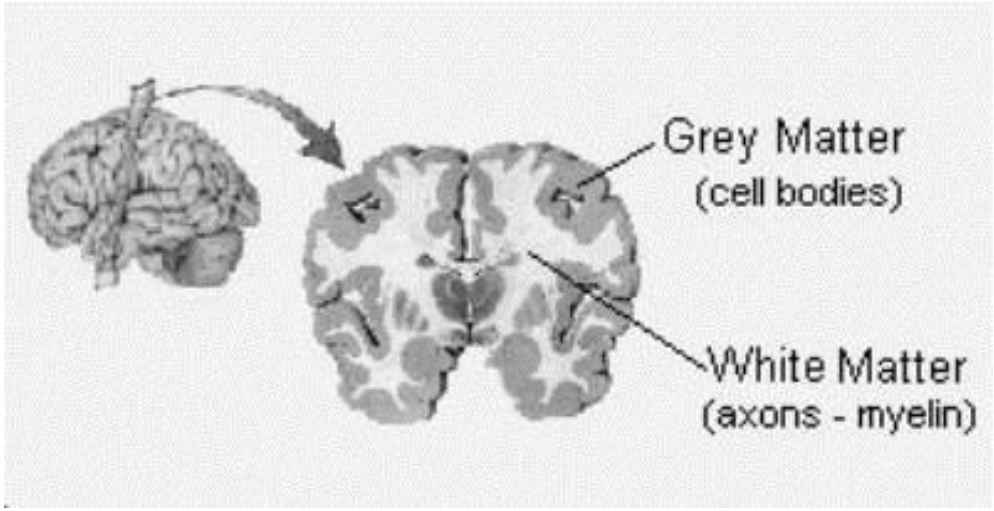
LCR	Serum
RT-PCR to Enterovirus	Anti HIV
PCR to HSV2 DNA	VDRL/ FTA-ABS
PCR to EBV DNA	
PCR to CMV	
PCR to HIV-1 RNA	
VDRL	
ELISA to neurocysticercosis	
Direct research of BAAR*	
M. tuberculosis culture	
PCR to *M. tuberculosis*	
Capsular antigen to *C. neoformans*, latex**	
Histoplasmosis research	
Neoplasic cells	

Bacterial infections always must be ruled out. *10 mL to direct search. ** *C. neoformans* capsular antigen could be associated by latex agglutinations in the urine or serum.

Almeida SM *et* al., Braz J Infect Dis 2007; 11(5): doi.org/10.1590/S1413-86702007000500010

2. Encephalitis (grey matter disease)

- Viral replication occurs in the brain tissue itself, causing destructive lesions in the grey matter.
- The main symptoms include: fever, drowsiness, confusion, depressed level of consciousness, convulsions and focal neurological signs.
- Morbidity and mortality is very high.
- Viruses that cause this condition include **herpes simplex, rabies** and some of the **arboviruses**.



Common Viral Causes of Encephalitis

Epidemic	Arboviruses	WEE
		EEE
		SLE
		California
	Picornaviruses	Polio
		Coxsackie
		Echo
Sporadic	Herpes	Herpes Simplex
		VZV
		CMV
		EBV
	Adenoviruses	
	Postvaccinal	

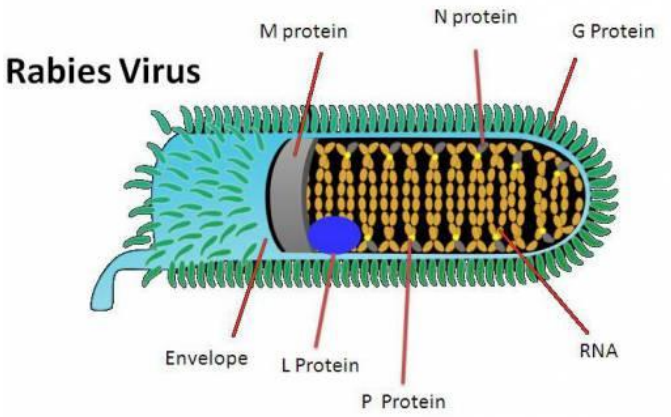
- Arboviruses = arthropod-borne viruses
- Arboviruses are maintained in nature through biological transmission between susceptible vertebrate hosts by blood-feeding arthropods
- Vertebrate infection occurs when the infected arthropod takes a blood meal

Major Arboviruses That Cause Encephalitis

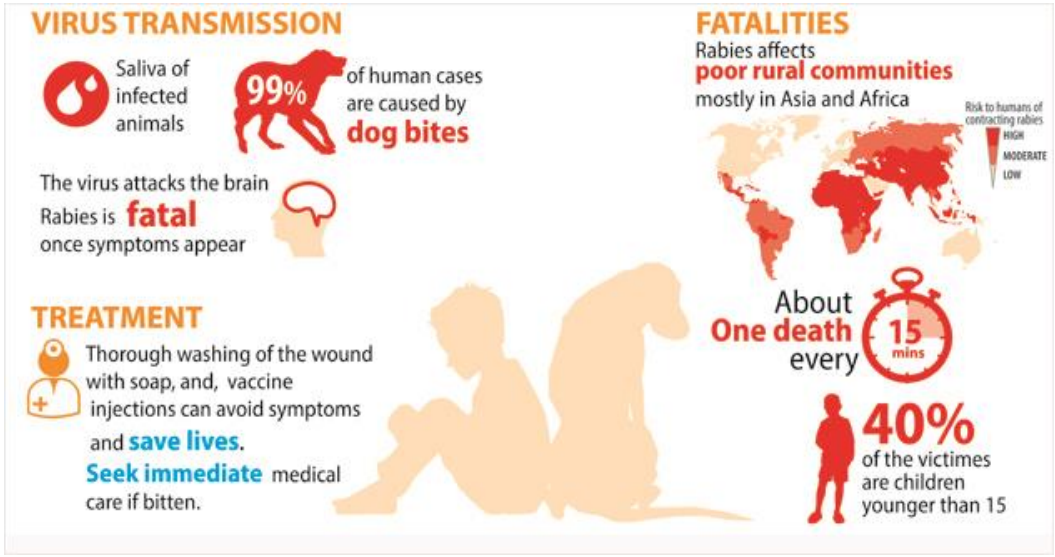
- Flaviviridae
  - Japanese encephalitis
  - St. Louis encephalitis
  - West Nile
- Togaviridae
  - Eastern equine encephalitis
  - Western equine encephalitis
- Bunyaviridae
  - La Crosse encephalitis

Rabies:

- Rabies virus is an enveloped (bullet shaped) ssRNA virus.
- It primarily infects warm blooded vertebrates. It is enzootic in most parts of the world.
- Virus is shed in the saliva of infected animals and humans are occasionally infected if bitten by an infected animal.
- The behaviour of the infected animal is altered and it is more likely to bite humans or other animals that it comes into contact with (thus ensuring the viruses survival).
- The most common sources of human infection are dogs and bats.



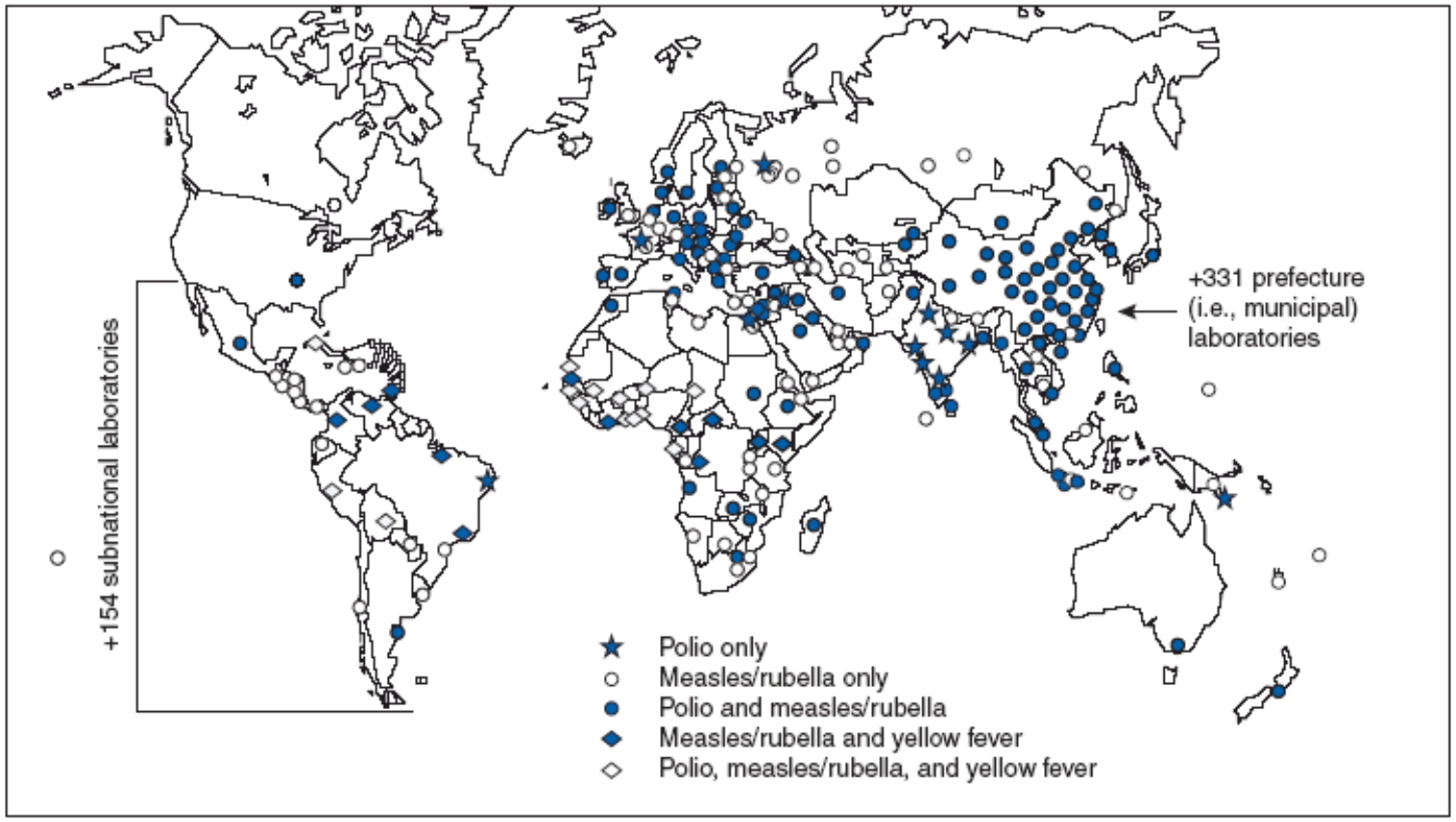
- Pathogenesis: Virus is introduced into the tissues through a bite. It enters peripheral nerves and travels up the axon to the brain where it replicates. It causes a fatal encephalitis.
- Incubation period: It varies from 9-90 days, depending on the severity and site of the bite. Incubation period is determined by how long the virus takes to reach the brain. (Bites on the foot take longer than bites on the face.)
- The disease can be prevented in an exposed person by administration of post exposure prophylaxis in the form of rabies vaccine and rabies immunoglobulin



3. Acute flaccid Paralysis

- This syndrome is due to direct infection of motor neurones (grey matter) in the spinal cord by a virus.
- Patients present with fever and flaccid paralysis of a group of muscles.
- Signs of meningitis such as headache and neck stiffness are frequent accompanying features.
- The most common aetiological agents include the **Polioviruses 1, 2 and 3,** but with the reduction in prevalence of wild type polio due to successful global vaccination, other (non polio) **enteroviruses** are responsible for most cases.

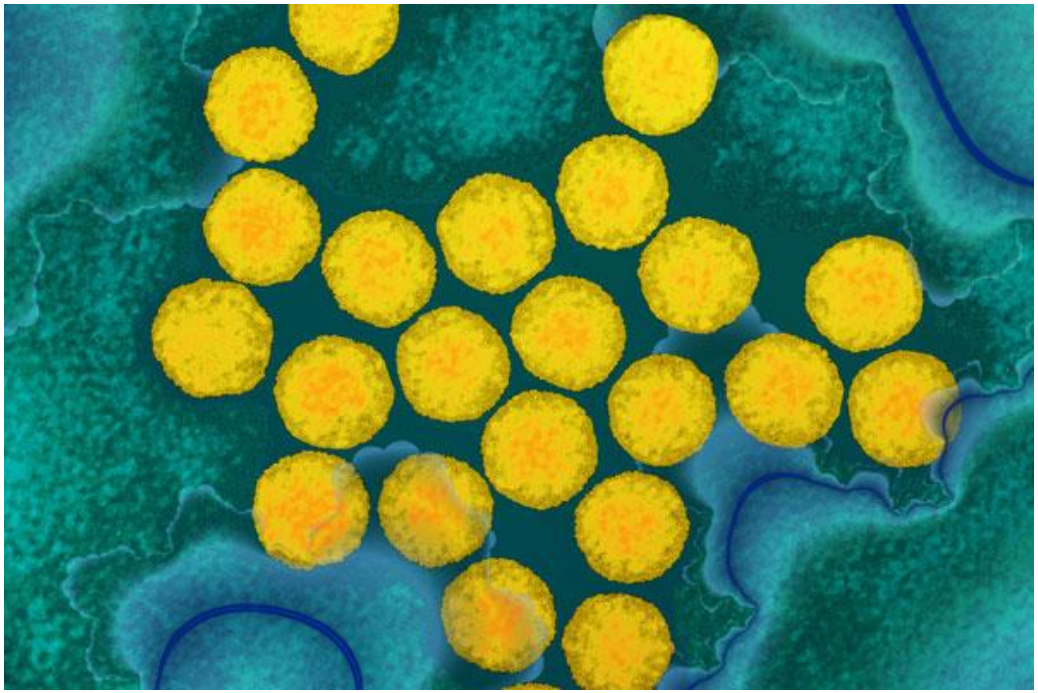
FIGURE. Global vaccine-preventable disease laboratory network — September 2004*



* The designation employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the secretariat of the World Health Organization concerning the legal status of any country, territory, city, or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

Poliovirus

- Three related enteroviruses, **poliovirus 1, 2 and 3** are responsible for the clinical disease **poliomyelitis.** This was a dreaded disease before effective vaccines were developed to combat the infection. Global use of vaccine has brought the disease to the point of eradication. Circulation of poliovirus is now limited to certain parts of Africa and the Indian sub-continent. The infection has been targeted for eradication by the world health organization (WHO).
- Pathogenesis Virus gains access to the body via ingestion. It replicates in gut associated lymphoid tissues. In some individuals this may be followed by a viraemia and haematogenous spread to the CNS. Lytic infection of motor neurons in the anterior horns of the spinal cord leads to a lower motor neuron weakness of muscles supplied by affected motor neurons (Flaccid paralysis).
- Incubation period 7-14 days



Poliovirus, pictured in this colored transmission electron micrograph, is transmitted via direct person-to-person contact with infected mucus, phlegm or feces. Symptoms can include fever; fatigue; muscle pain or weakness; stiff neck and back; and difficulty swallowing or breathing. It is important to remember that many people with polio are asymptomatic, but can still spread the virus to others.

Control through an effective vaccine

- Two effective poliovirus vaccines are in wide spread use around the world: the **live attenuated (Sabin)** and the **formalin inactivated (Salk)** vaccine.
- Both contain the 3 strains of virus responsible for paralytic polio, namely polioviruses 1, 2 and 3.
- Both vaccines were developed in the 1950s: the live attenuated vaccine was created by serial passage of the virulent virus in cell culture to produce strains of poliovirus which retained the antigenicity, but were unable to cause disease.
- The inactivated (killed) vaccine contains formalin-inactivated polioviruses. Both vaccines are highly effective at protecting against infection

Sabin vaccine

Salk vaccine

Attributes of polio vaccines

	Formalin inactivated vaccine (Salk)	**Live attenuated vaccine (Sabin)**
Route of administration	Injection	Oral drops
Immune response	Good, IgG in blood	Good, IgA in gut
Duration of immunity	Medium	long
Cost	expensive	cheap
Stability of vaccine	stable	Not stable, cold chain important
Transmission to vaccine contacts	No	yes
Dangers	None	Reversion to virulence (very rare) Prolonged shedding in immuno-compromised patients

4. Post infectious encephalitis (white matter disease)

- This uncommon complication may develop in the convalescent phase, following a number of common viral infections, including: **measles, mumps, rubella** and **primary varicella-zoster virus infection.**
- In addition it may develop following exposure to certain vaccines, such as: **vaccinia virus** and the older **neurotissue rabies vaccines**.
- Widespread demyelinating lesions develop involving the white matter in the brain and spinal cord.
- Characteristic histological features include: lymphocytic infiltration and perivascular cuffing of adjacent blood vessels.
- The causative agent cannot be isolated from brain tissue or CSF.
- The aetiology is somewhat obscure, but it is thought to be a T cell-mediated auto-immune phenomenon, triggered by exposure to foreign antigens which are closely related to host proteins normally present in brain tissue (molecular mimicry).