Viral Encephalitis

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VIRAL INFECTIONS IN THE CNS

Aseptic meningitis

– inflammation of meninges with sterile CSF

Encephalitis

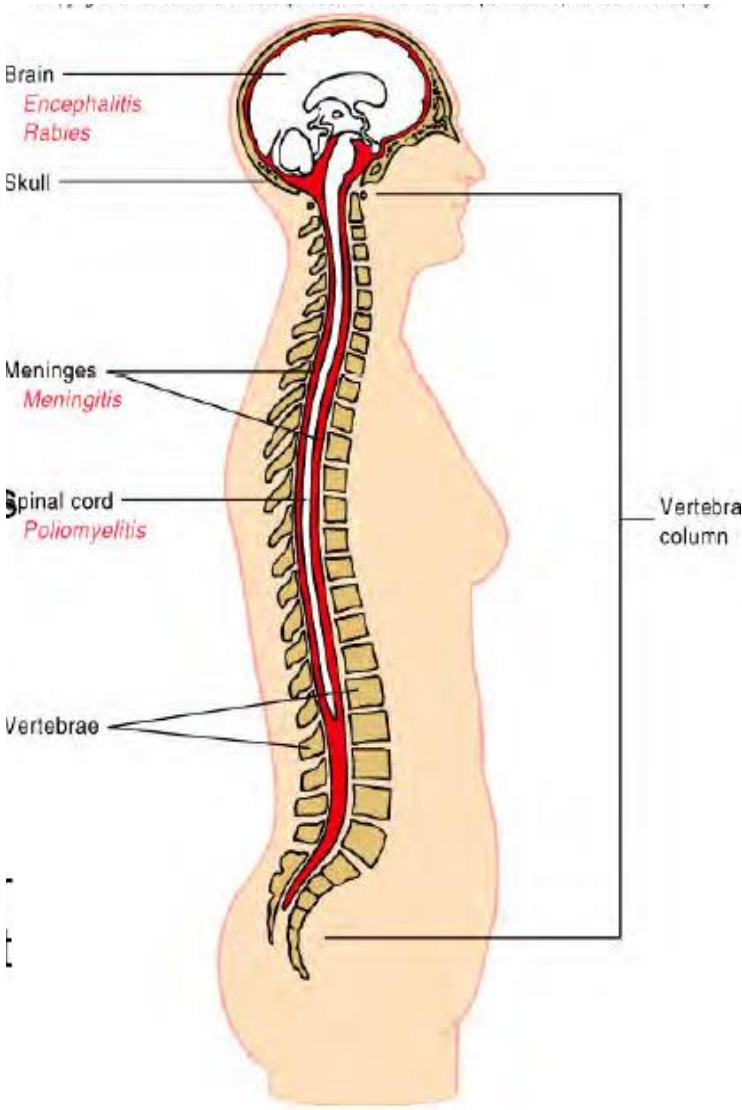
– infection of the brain parenchyma

Meningoencephalitis

– inflammation of brain + meninges

Myelitis

– inflammation of the spinal cord



What is encephalitis?

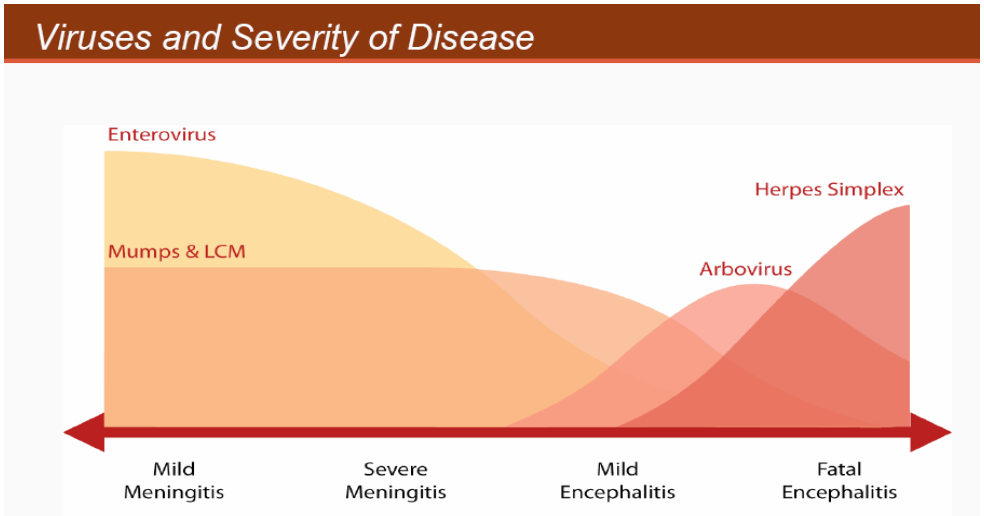
- Encephalitis is an inflammation of the brain tissue due to infection.
- Most often caused by viruses that pass the blood stream into the CSF leading to destruction of neural cells and inflammation of brain parenchyma.
  - Primary or acute encephalitis
- May also result from a viral-mediated inflammatory response in the brain following an acute, systemic infection.
  - Secondary or post-infectious encephalitis

Secondary or post infectious encephalitis

- Subacute sclerosing panencephalitis
  - CNS involvement (encephalitis) due to cytotoxic (CD8) T-cells which react with virus infected cells.
  - SSPE (1 in 100,000) chronic measles virus infection to CNS. SSPE: personality change, intellectual deterioration, myoclonus, spasticity, tremor and ocular abnormalities
  - Occur 2-10 yrs after infection. No treatment
- Progressive postrubella encephalitis
  - Mimics SSPE
  - Associated with either persistent rubella virus infection of the CNS or late sequela of congenital rubella infection which manifests in adults.
- Progressive multifocal encephalopathy (polyomavirus JC)
  - Subacute degenerative disease of the brain found in:
    - Immunosuppressive disease: AIDS and hematologic malignancies
    - Disease requiring immunosuppressive therapy
  - No specific treatment
- Persistent Enterovirus infection
  - Seen in patients with congenital or acquired immunodeficiency where they develop chronic CNS infection
  - Headache, confusion, lethargy, seizure and CSF pleocytosis.
  - Temporary improvement with type specific immunoglobulins, relapse on withdrawal

How to distinguish encephalitis from viral meningitis?

- Unfortunately, the clinical syndromes and results of routine laboratory tests are typically nonspecific and often do not help distinguish encephalitis and viral meningitis.
- Patients may have symptoms of both parenchymal and meningeal processes.
  - i.e., A patient with stiff neck and photophobia, though classic signs of meningitis, could in fact also have encephalitis! (called Meningoencephalitis)



Encephalitis vs. meningitis

Constitutional symptoms	**Encephalitis**	**Viral Meningitis**
Fever	**Yes**	**Yes**
Headache, nausea, vomiting, lethargy	**Yes**	**Yes**
Photophobia, neck stiffness	**No**	**Yes**
Neurologic dysfunction		
Seizures	**Yes**	**Minimal**
Cranial nerve palsies, paralysis	**Yes**	**No**
Altered mental status (i.e. confusion, coma)	**Yes**	**Minimal**

VIRAL MENINGITIS / ENCEPHALITIS

HERPESVIRIDAE

- Herpes simplex
- Varicella-zoster
- Epstein Barr
- Cytomegalovirus

PARAMYXOVIRIDAE

- parainfluenzae
- Mumps
- Measles

MISCELLANEOUS

- Adenoviridae
- Rhabdoviridae
- Retroviridae (HIV)

ENTEROVIRUS

- **Polioviruses**
- **Coxsackie viruses**
- **Echoviruses**

TOGAVIRIDAE

- **Eastern equine**
- **Western equine**
- **Venezuelan equine**

FLAVIVRIDAE

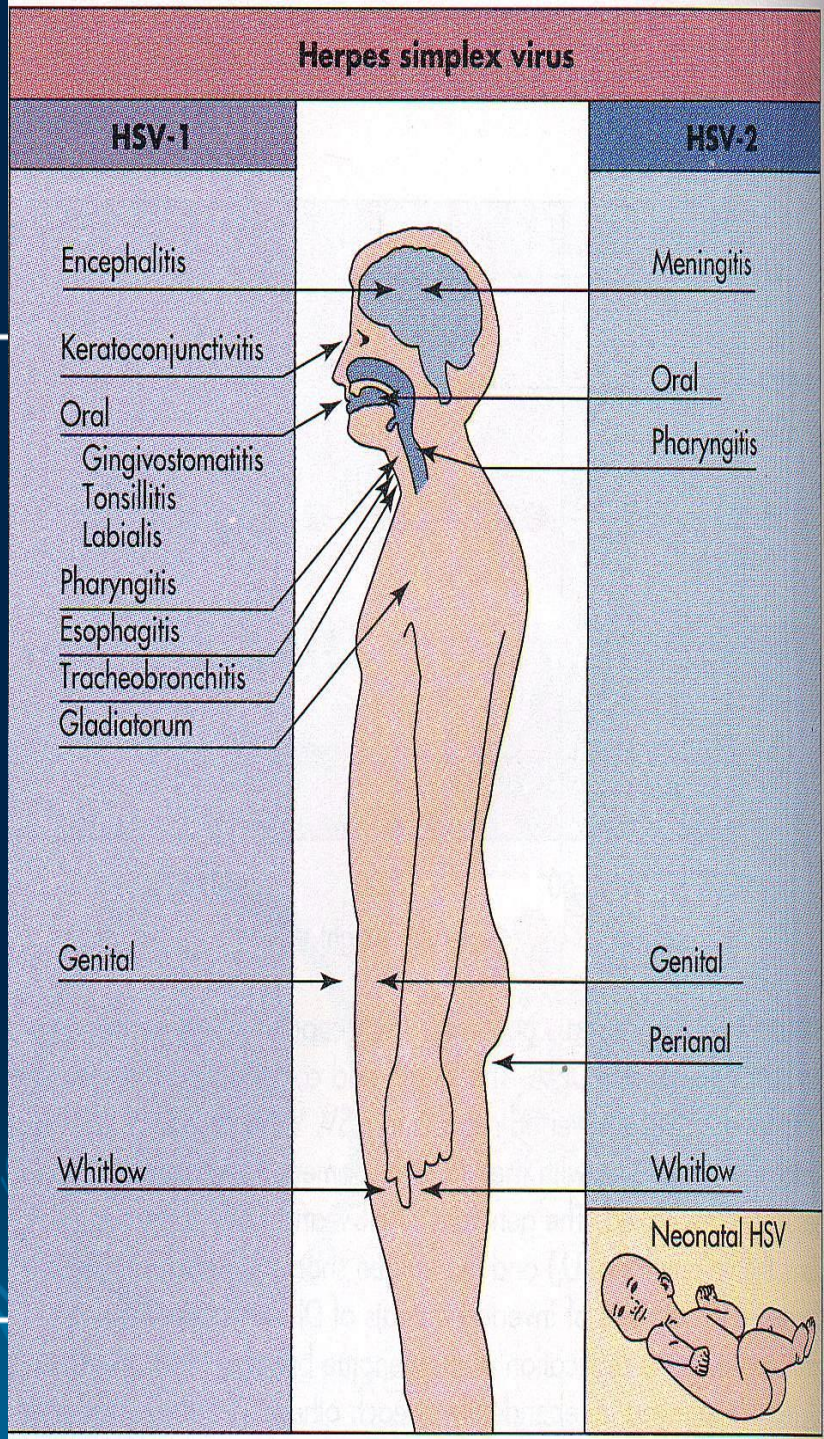
- **St. Louis**
- **West Nile**
- **Murray valley**
- **Powassan**
- **Japanese B**

BUNYAVIRIDAE

- **California**

Herpesviridae

1-Herpes simplex virus type -1	HSV-1
2-Herpes simplex virus type -2	HSV-2
3-Varicella –Zoster virus	VZV
4-Epstein- Barr virus	EBV
5-Cytomegalovirus	CMV
6-Human herpes virus type-6	HHV-6
7-Human herpes virus type-7	HHV-7
8-Human herpes virus type-8	HHV-8



Herpes Simplex Encephalitis

- Herpes Simplex encephalitis is one of the most serious complications of herpes simplex disease. There are two forms:
- Neonatal – there is global involvement and the brain is almost liquefied. The mortality rate approaches 100%.
- Focal disease – the temporal lobe is most commonly affected. This form of the disease appears in children and adults. It is possible that many of these cases arise from reactivation of virus. The mortality rate is high (70%) without treatment.
- It is of utmost importance to make a diagnosis of HSE early. It is general practice that IV acyclovir is given in all cases of suspected HSE before laboratory results are available.

Family *Paramyxoviridae*

Subfamily *Paramyxovirinae*

- Genus *Respirovirus*
  e.g., Human parainfluenza virus 1 and 3
- Genus *Rubulavirus*
  e.g., Human parainfluenza virus 2 and 4, Mumps virus
- Genus *Morbillivirus*
  e.g., Measles virus
- Genus *Henipavirus*
  e.g., Hendra virus, Nipah virus

Subfamily *Pneumovirinae*

- Genus *Pneumovirus*
  e.g., Human respiratory syncytial virus
- Genus *Metapneumovirus*
  e.g., Human metapneumovirus

PARAMYXOVIRIDAE

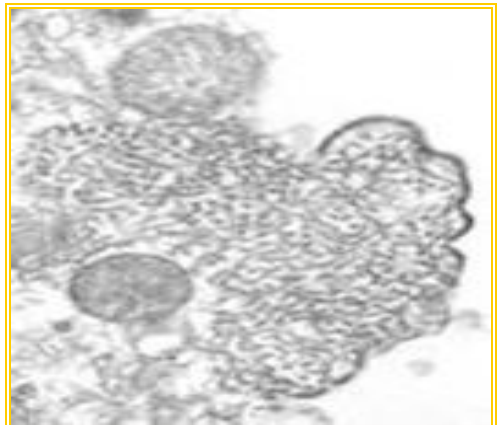
- Genus Henipavirus
  - Newly discovered virus
  - Hendra virus,Nipha virus (HENIPA VIRUS)
- Severe, rapidly progressive encephalitis in humans
  - High mortality rate
  - Close contact with infected pigs
- Severe, respiratory disease in pigs

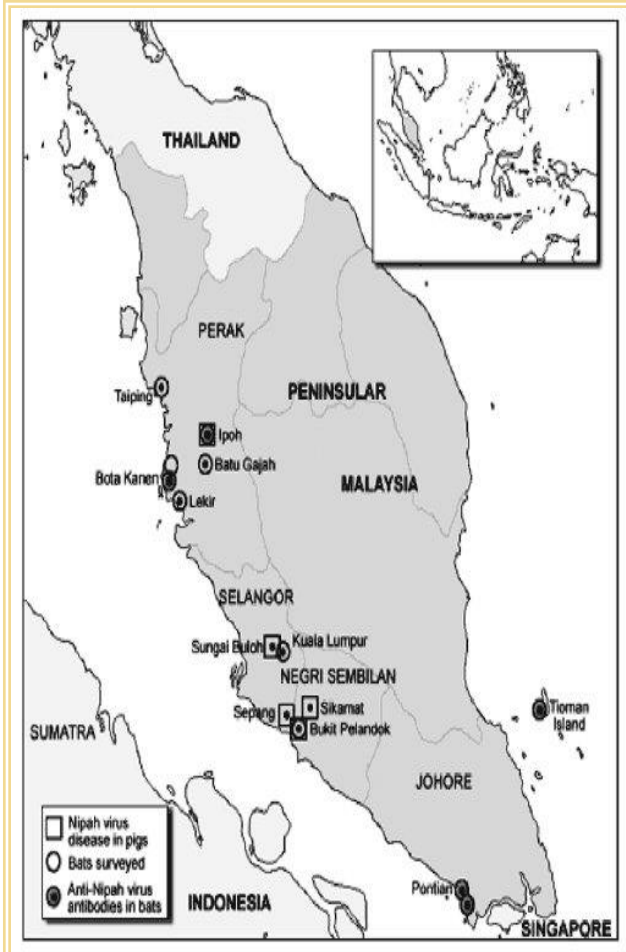
EMERGING VIRUSES- Nipha virus

- 1998-1999: Peninsular Malaysia
  - Human febrile encephalitis with high mortality
  - Cases similar to Japanese encephalitis

1999: Singapore
- Outbreak in abattoir workers
- Pigs imported from Malaysia

2004:Bangladesh





Reservoir

- Flying foxes (fruit bats)
  - Carry the virus
  - not infected
  - Virus found in urine , Partially eaten fruit

- Transmission

  Pig-Direct contact
  Contact with body fluids
  Aerosolization of respiratory or urinary secretions
  No person-to-person transmission
  No bat-to-human transmission

Human Illness

- Incubation period: 3-14 days
  - Fever and headache
  - Encephalitis
    - Dizziness, drowsiness, vomiting Seizures
    - Progresses to coma in 24-48 hours
  - Respiratory difficulty

Complications

  - Septicemia (24%)
  - GI bleeding (5%)
  - Renal impairment (4%)
- Asymptomatic
  - Relapse or late-onset encephalitis
  - Residual neurological deficits
- Treatment: Supportive, ribavirin

The term ARBO is an abbreviation of "**AR**thropod **BO**rne".

"Arbovirus" is the name given to Arthropod-borne viruses, that is, viruses that are transmitted to vertebrates, such as people and mammals, by blood-feeding insects called arthropods. Vertebrate infection occurs when the infected insect bites an animal or person and takes a blood meal.

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They can multiply in the tissues of the arthropod without evidence of disease or damage. The vector acquires a lifelong infection through the ingestion of blood from a viremic vertebrate.

All arboviruses have an RNA genome, and most have a lipid-containing envelope and consequently are inactivated by ether or sodium deoxycholate.

Current taxonomic status of some arboviruses

- **Togaviridae** Genus ***Alphavirus***
- **Flaviviridae** Genus ***Flavivirus***
- **Bunyaviridae** Genus ***Bunyavirus***

Approximately 80 arboviruses known to cause human disease

Transmission Cycles

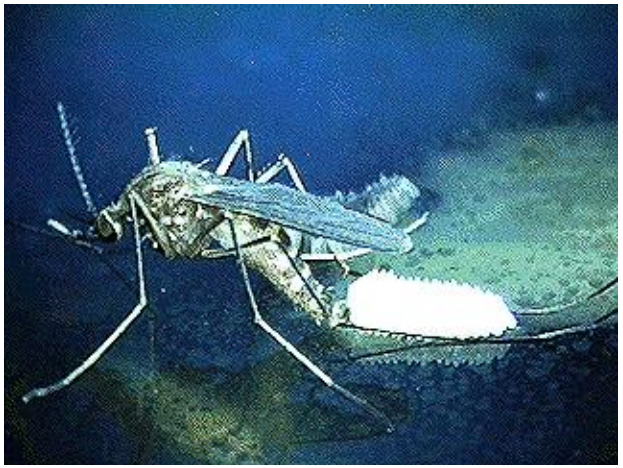
- Man - arthropod - man
  - e.g. dengue, urban yellow fever.
  - Reservoir may be in either man or arthropod vector.
  - In the latter transovarial transmission may take place.
- Animal - arthropod vector - man
  - e.g. Japanese encephalitis, EEE, WEE, jungle yellow fever.
  - The reservoir is in an animal.
  - The virus is maintained in nature in a transmission cycle involving the arthropod vector and animal. Man becomes infected incidentally.
- Both cycles may be seen with some arboviruses such as yellow fever.

Animal Reservoirs

In many cases, the actual reservoir is not known. The following animals are implicated as reservoirs

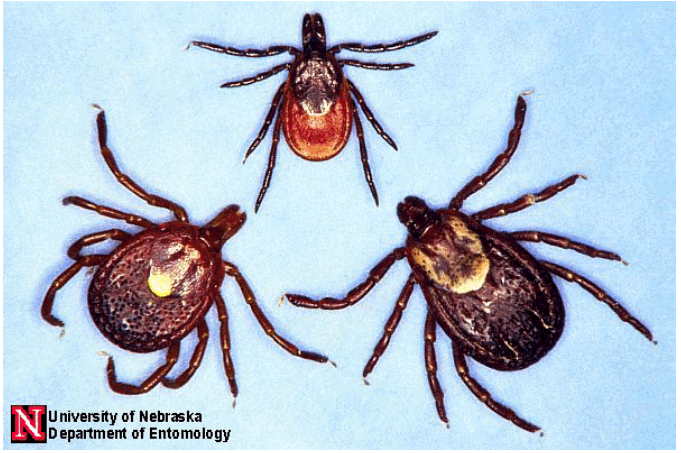
Birds	Japanese encephalitis, St Louis encephalitis, EEE, WEE
Pigs	Japanese encephalitis
Monkeys	Yellow Fever
Rodents	VEE, Russian Spring-Summer encephalitis

Examples of Arthropod Vectors



Aedes Aegypti

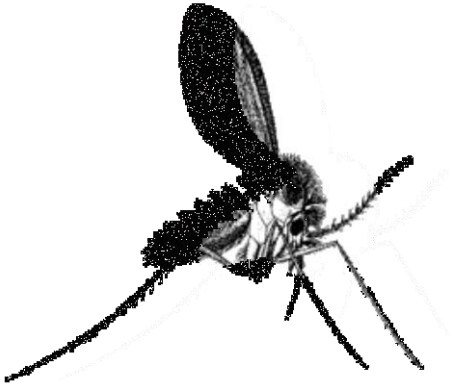
dengue fever, chikungunya and yellow fever



Assorted Ticks

Culex Mosquito

Japanese encephalitis, St. Louis encephalitis

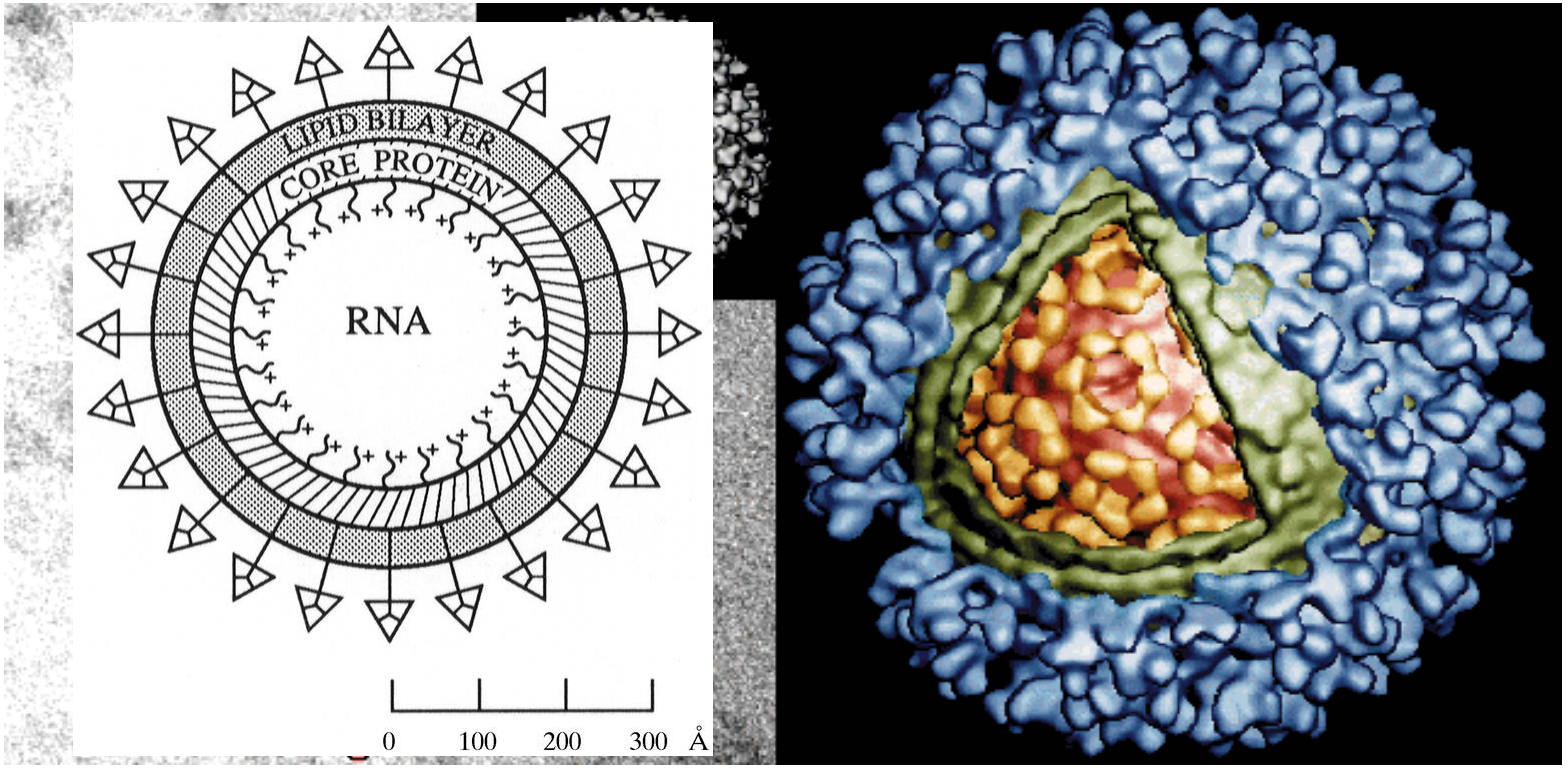


Phlebotmine Sandfly

Diseases Caused

- Fever and rash - this is usually a non-specific illness resembling a number of other viral illnesses such as influenza, rubella, and enterovirus infections. The patients may go on to develop encephalitis or haemorrhagic fever.
- Encephalitis - e.g. EEE, WEE, St Louis encephalitis, Japanese encephalitis.
- Haemorrhagic fever - e.g. yellow fever, dengue, Crimean-Congo haemorrhagic fever.

Structures of Alphaviruses



- Single stranded, +ve sense, enveloped RNA virus with Icosahedral capsid
- Glycoproteins E1 and E2
- Hemagglutinate via fusion of E1 with lipids on erythrocyte membrane.

Principal medically important Alphaviruses

Virus	Antigenic Clinical Syndrome	Vector	Host	Distribution
Eastern equine encephalitis	Encephalitis (EEE)	Mosquito	Birds	Americas
Western equine encephalitis	Encephalitis (WEE)	Mosquito	Birds	North America
Venezuelan equine encephalitis	Febrile illness, encephalitis (VEE)	Mosquito	Rodents, horses	Americas

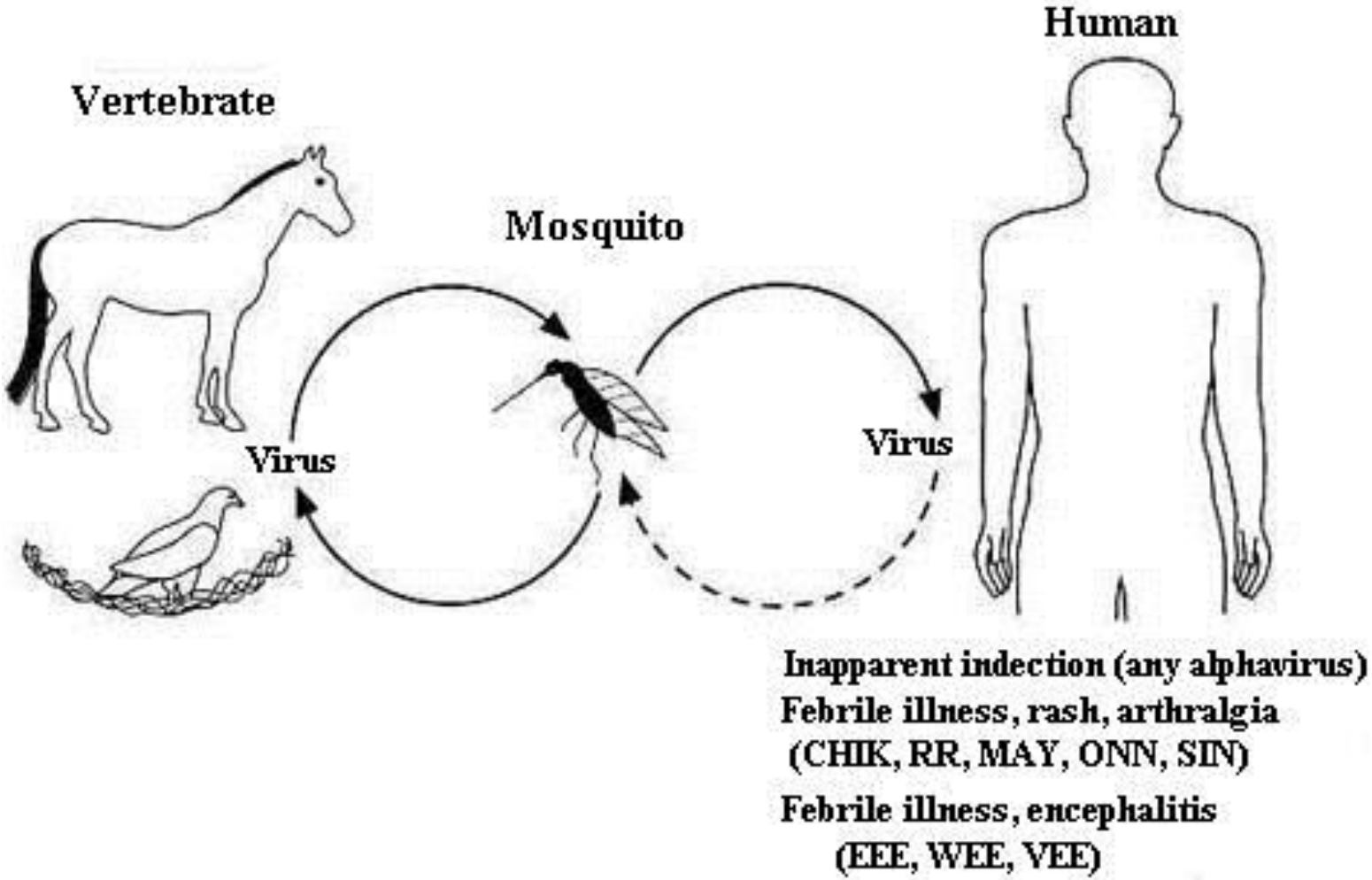
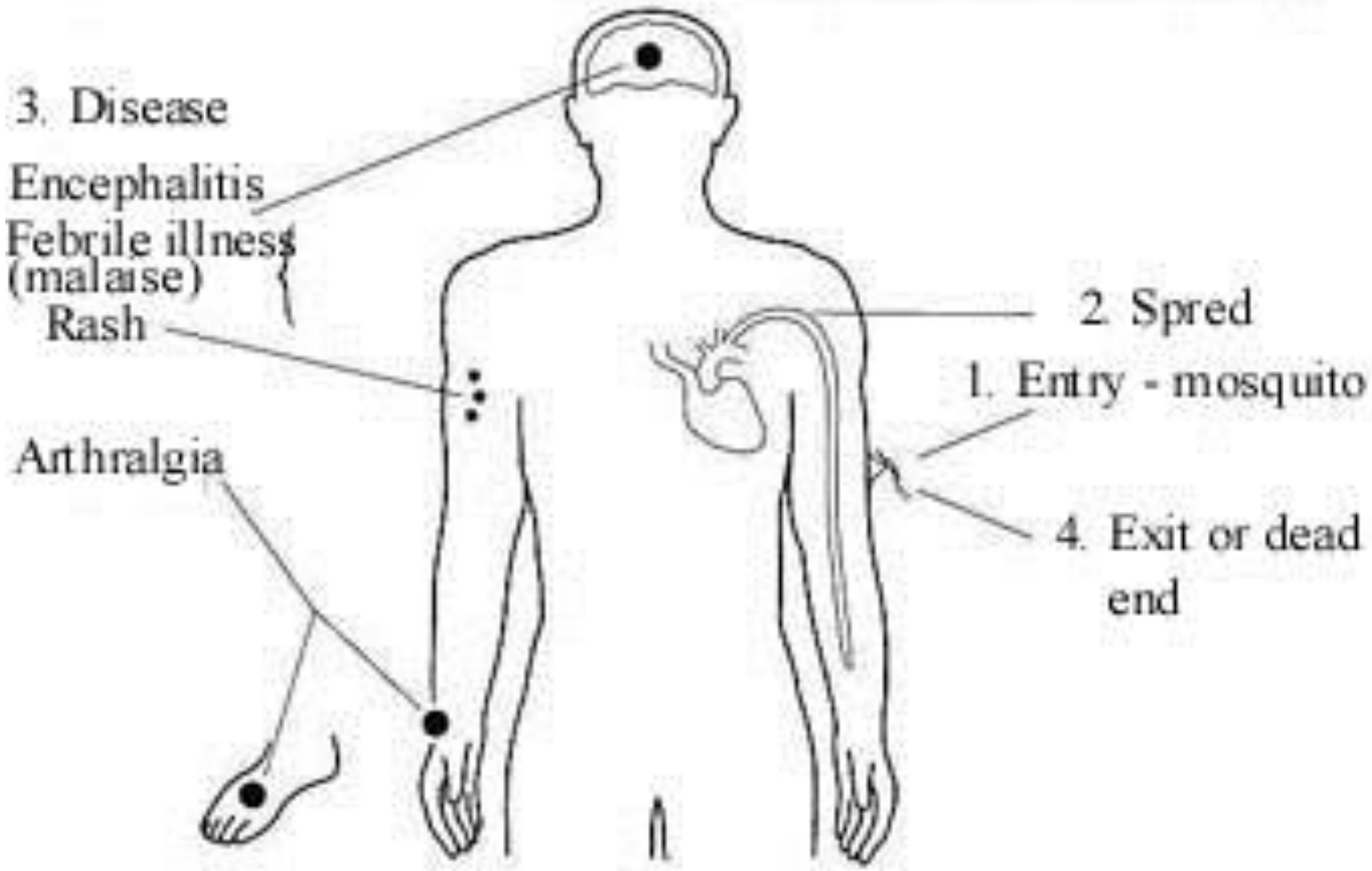


FIGURE Alphavirus transmission. Virus abbreviations: Chik, chickungunya; RR, Ross River; May, Mayaro; ONN, O'nyong-nyong; SIN, Sindbis; EEE, eastern equine encephalitis; VEE, Venezuelan equine encephalitis.

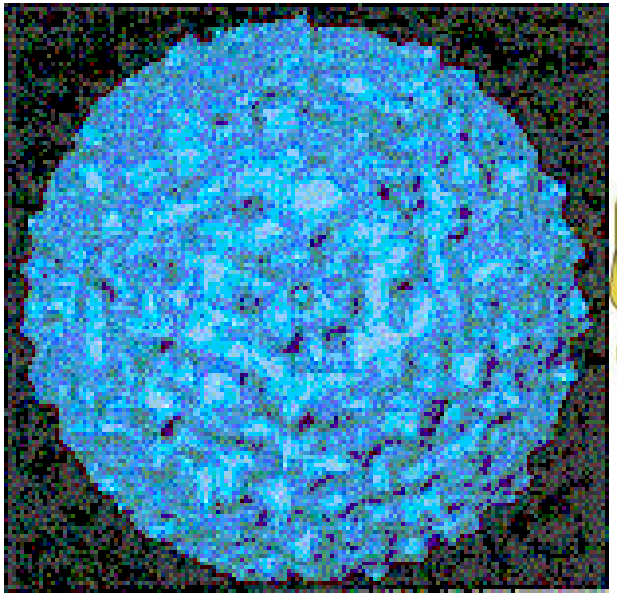
Pathogenesis of Alphaviruses

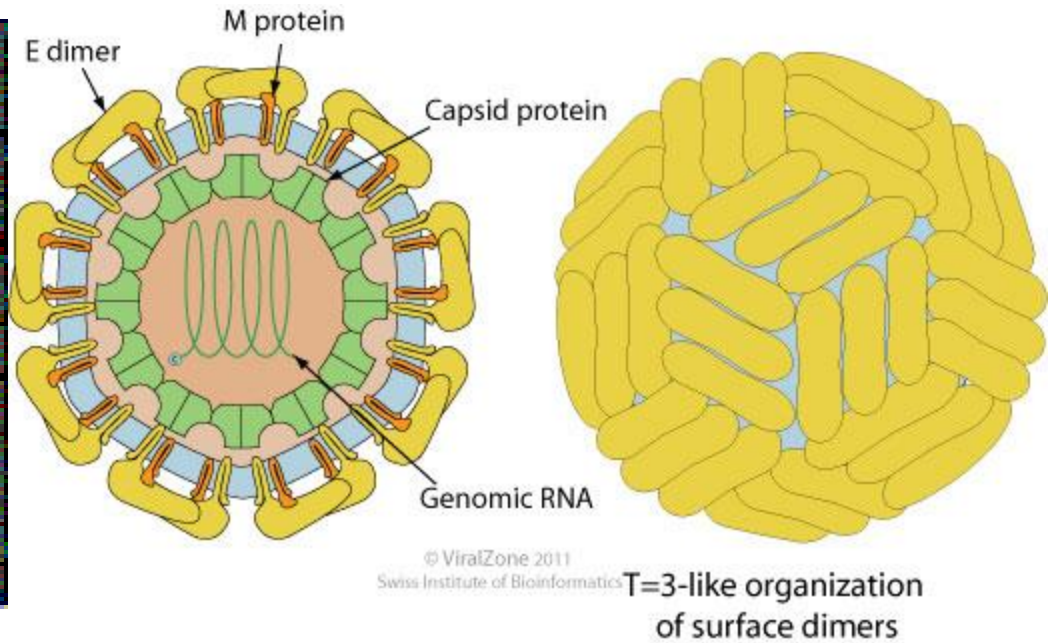


Symptoms : EEE

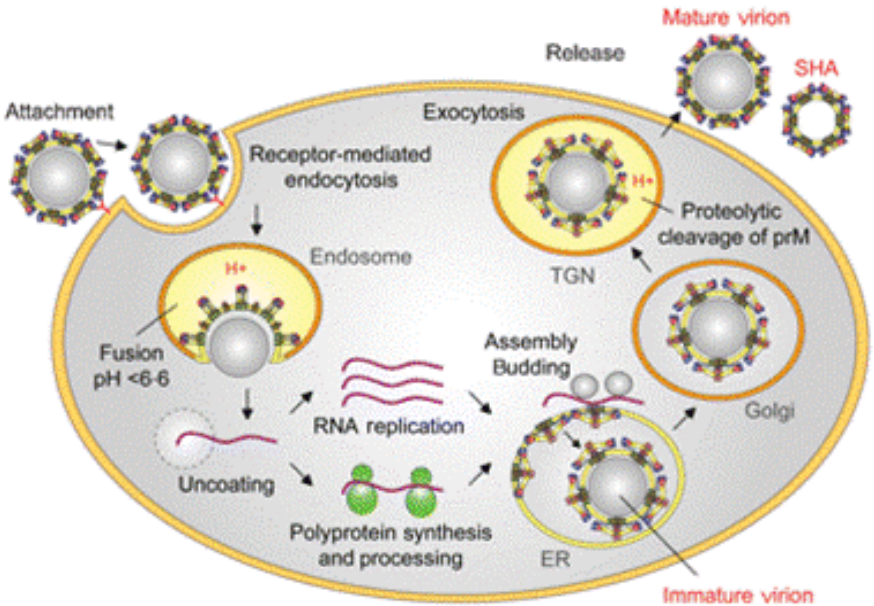
- Most people have no symptoms
- Central Nervous system symptoms develop 4-10 days after being bitten
- Sudden onset of fever, muscle aches, headache
- May progress to more severe symptoms such as seizure and coma (encephalitis)
- 30 to 50% of patients with encephalitis die of the disease

Structure of Flaviviruses





Positive sense, single stranded, enveloped RNA viruses with icosahedral capsid.



Principal medically important Flaviviruses

Virus	Antigenic Clinical Syndrome	Vector	Host	Distribution
Murray valley	Encephalitis	Mosquito	wild water birds	Australia
Powassan	Encephalitis	Tick	Squirrels snowshoe hare Rabbit	Canada
St. Louis encephalitis (SLE)	Encephalitis	Mosquito	Birds	Americas

Principal medically important Flaviviruses

Virus	Antigenic Clinical Syndrome	Vector	Host	Distribution
Japanese encephalitis (JE)	Encephalitis	Mosquito	Pigs, birds	India, China, Japan, South-East Asia
West Nile	Febrile illness or encephalitis	Mosquito	Birds	Africa, Middle East, Europe
Tick-borne encephalitis (TBE)	Encephalitis	Tick	Rodent	Europa, Asia

Human infection with both mosquito-borne and tick-borne flaviviruses is initiated by deposition of virus through the skin via the saliva of an infected arthropod (Fig).

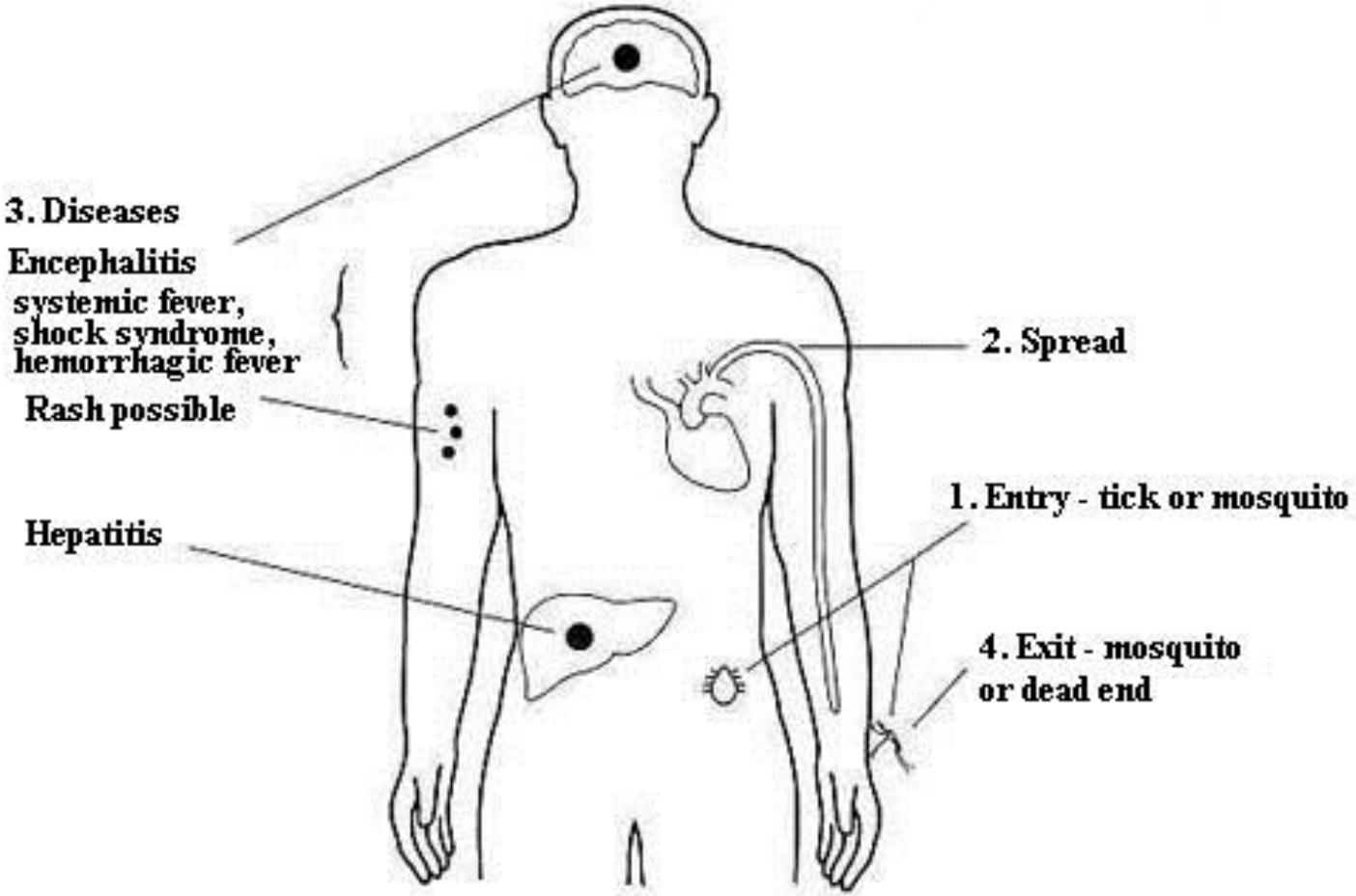
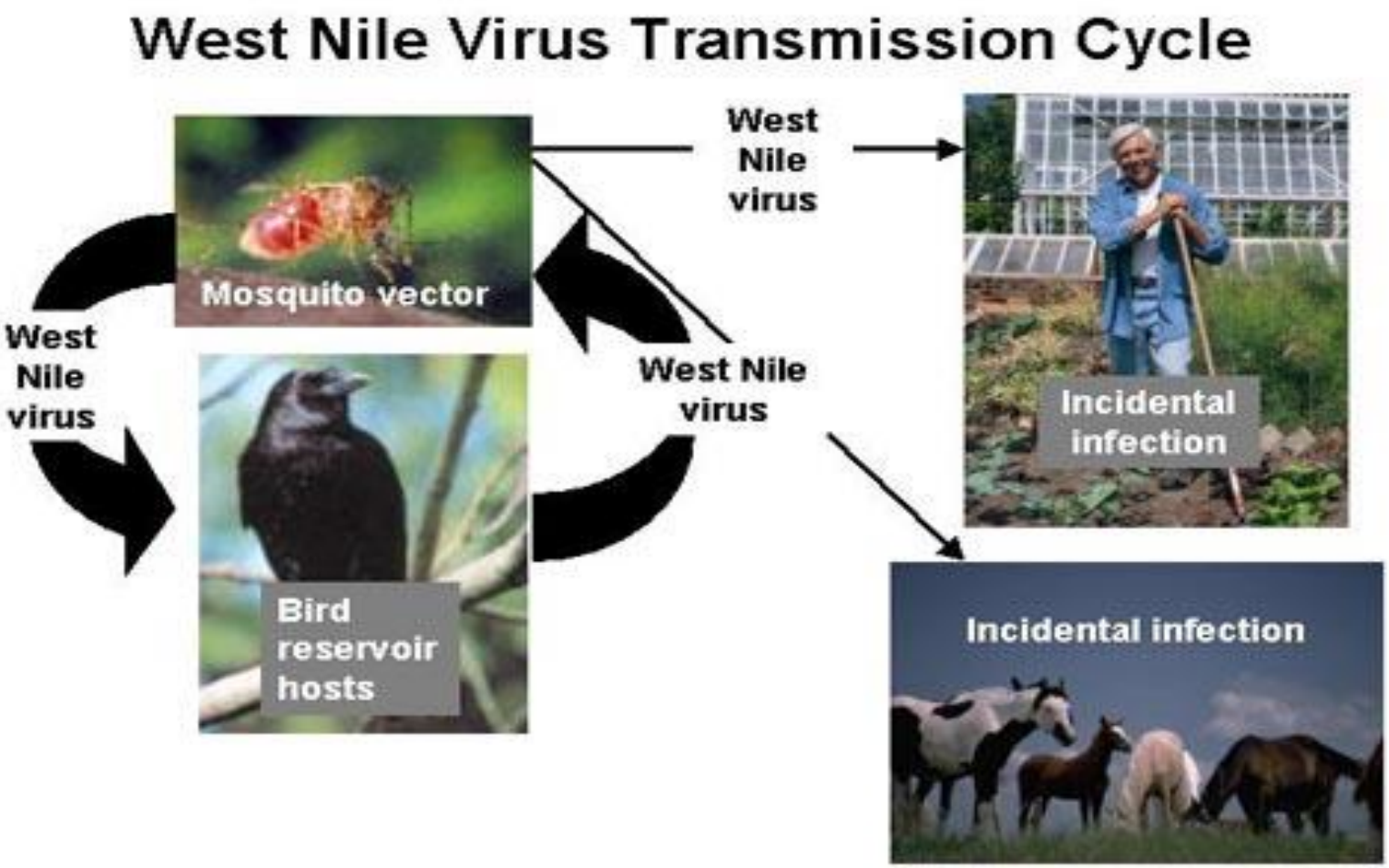


Figure. Pathogenesis of flaviviruses.

Japanese Encephalitis

- First discovered and originally restricted to Japan. Now large scale epidemics occur in China, India and other parts of Asia.
- Most human infections are subclinical: the inapparent to clinical cases is 300:1
- In clinical cases, a life-threatening encephalitis occurs.
- The disease is usually diagnosed by serology.
- No specific therapy is available.
- Since Culex has a flight range of 20 km, all local control measures will fail. An effective vaccine is available.

Transmitting WNV infection

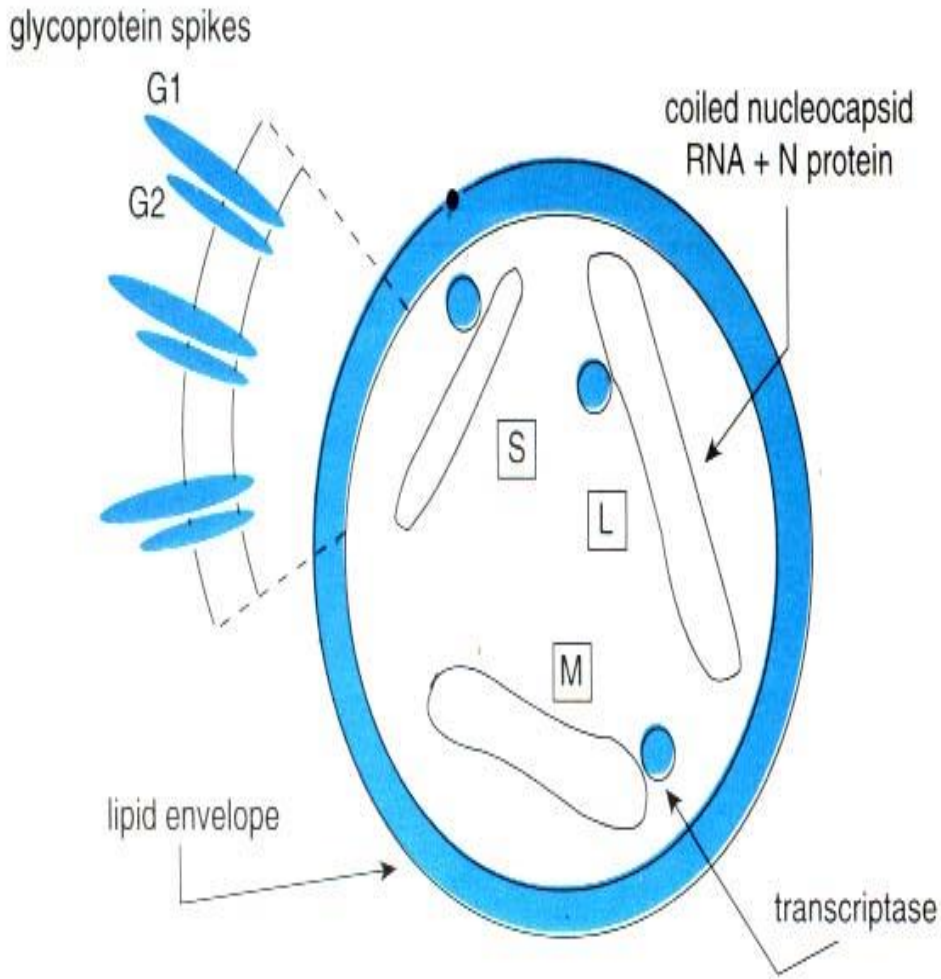


Symptoms : West Nile virus

- Most people do not develop symptoms
- An estimated 20% become ill 3-15 days after being bitten
  - Mild illness: fever, headache, body aches, and sometimes skin rash and swollen glands
- An estimated 1 in 150 persons infected develop a more severe form of the disease
  - West Nile encephalitis: inflammation of the brain, high fever, stiff neck, stupor, disorientation, coma, tremors, convulsions, muscle weakness, and paralysis; few cases have been fatal

Bunyaviridae

- It is a family of arthropod-borne or rodent-borne viruses.
- spherical, enveloped, single stranded, negative sense RNA viruses.
- Envelope contain 2 glycoproteins G1 and G2.
- Contain 3 nucleocapsids L,M and S associated with RNA-dependent RNA polymerase (L) and nonstructural protein (N).
- Lack matrix protein
- M strand encodes G1 and G2 and nonstructural proteins.
- L strand encodes L protein
- S strand encodes nonstructural proteins
- Bunyaviruses are responsible for a number of febrile diseases in humans and other vertebrates. They have either a rodent host or an arthropod vector and a vertebrate host.



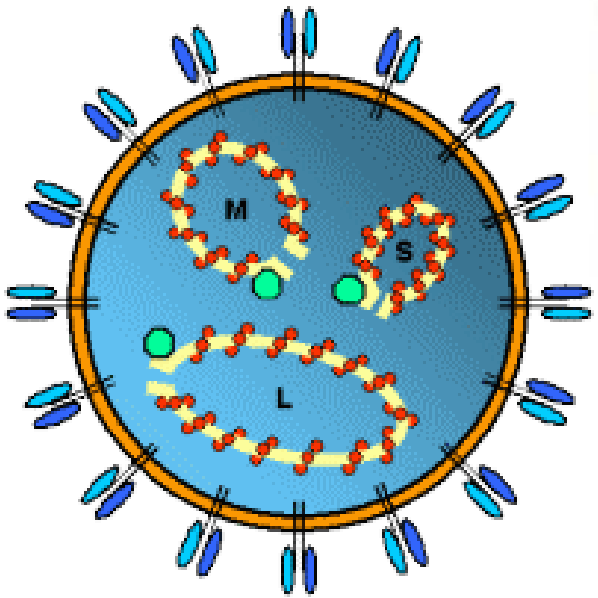


FIGURE 47-4 Diagram of a bunyavirus particle. Glycoprotein spikes present in the virus envelope are denoted by the filled ellipses. The hatched circles represent virion-encoded transcriptase present in virus particles. S, M, and L denote the three RNA segments that make up the bunyavirus genome. See text for additional details.

Human diseases Caused by Viruses

of the Family Bunyaviridae

Genus and Group	Virus	Disease	Vector	Distribution
Bunyavirus				
California	California encephalitis	Encephalitis	Mosquito	North America

- Rift valley fever Encephalitis Mosquito
- La crosse Encephalitis Mosquito

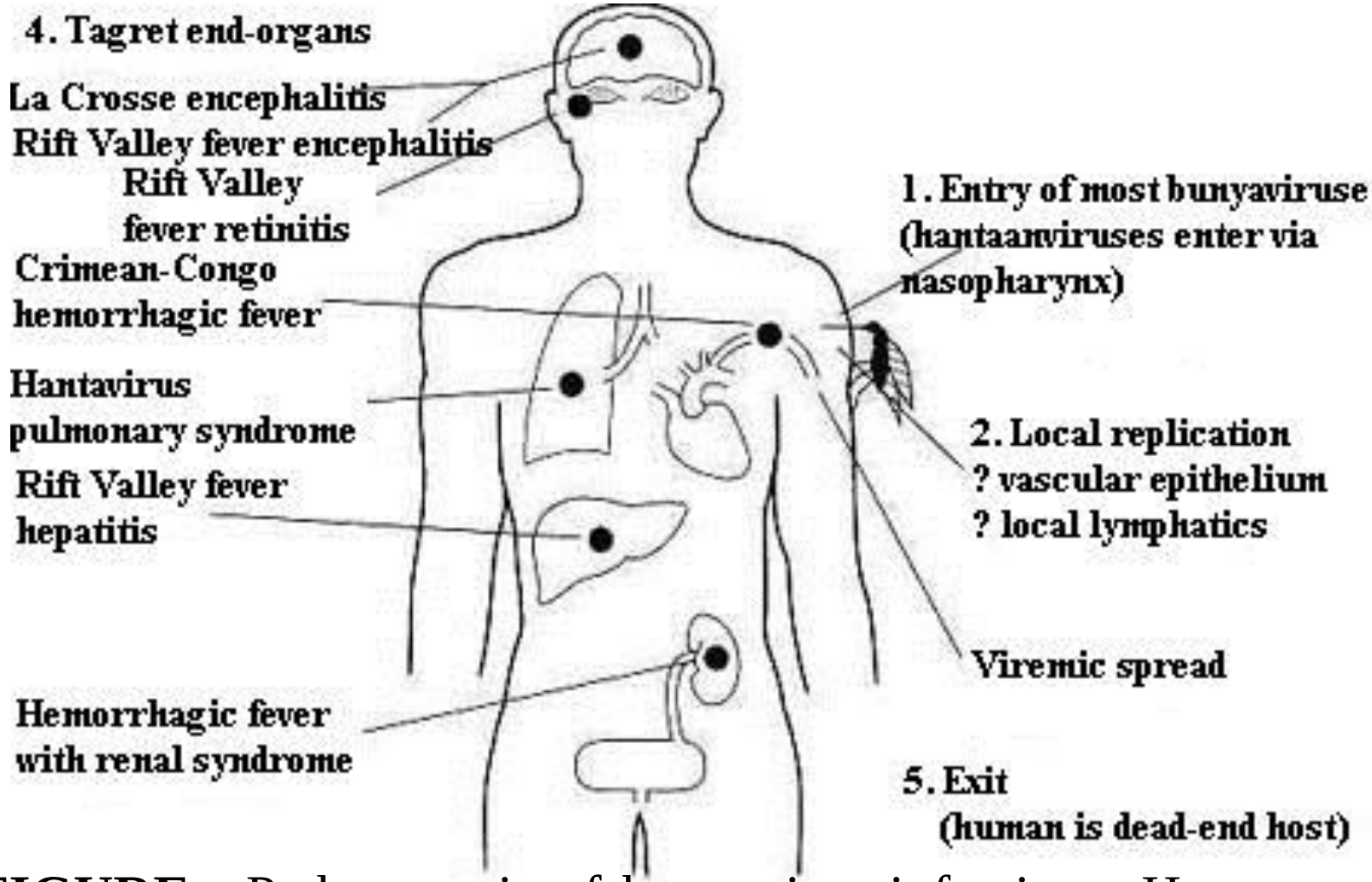


FIGURE. Pathogenesis of bunyavirus infections. Humans are dead-end hosts of most bunyaviruses; however, the blood of Crimean-Congo hemorrhagic fever patients may be highly infectious.

Diagnosis

- Serology - usually used to make a diagnosis of arbovirus infections.
- Culture - a number of cell lines may be used, including mosquito cell lines. However, it is rarely carried out since many of the pathogens are group 3 or 4 pathogens.
- Direct detection tests - e.g detection of antigen and nucleic acids are available but again there are safety issues.

Prevention

- Surveillance - of disease and vector populations
- Control of vector - pesticides, elimination of breeding grounds
- Personal protection - screening of houses, bed nets, insect repellants. When possible, wear protective clothing while outdoors.
- Vaccination - available for a number of arboviral infections e.g. Yellow fever, Japanese encephalitis, Russian tick-borne encephalitis

Treatment

- No specific therapy
- Arboviral encephalitis treated by hospitalization, intravenous fluids, respiratory support, prevention of secondary infections, and good nursing care