



**MEDICAL UNIVERSITY – PLEVEN**  
**FACULTY OF MEDICINE**  
**DEPARTMENT OF INFECTIOUS DISEASES, EPIDEMIOLOGY,  
PARASITOLOGY AND TROPICAL MEDICINE**

**Lecture № 14**

**ARBOVIRAL INFECTIONS**  
**DENGUE AND DENDGUE FEVER**

*Assoc. Prof. Galya Gancheva, MD, PhD*

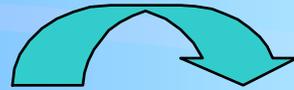
# Arthropod-borne Viruses

- Arthropod-borne viruses (arboviruses) are viruses that can be transmitted to man by arthropod vectors. The WHO definition is as follows  
“Viruses maintained in nature principally, or to an important extent, through biological transmission between susceptible vertebrate hosts by haematophagous arthropods or through transovarian and possibly venereal transmission in arthropods.”
- Arboviruses belong to three families:
  - Togaviruses – EEE, WEE, and VEE;
  - Bunyaviruses – Sandfly Fever, Rift Valley Fever, Crimean-Congo Haemorrhagic Fever;
  - Flaviviruses – Yellow Fever, dengue, Japanese Encephalitis.

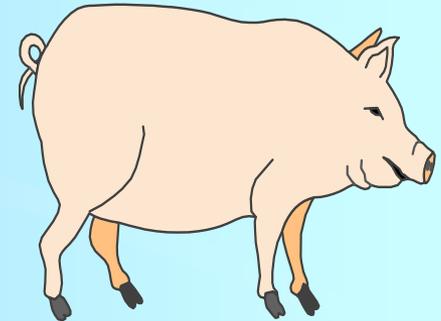
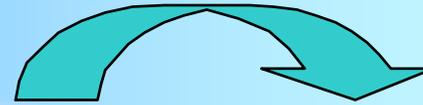
# Transmission cycles

- 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.

# *Man-Arthropod-Man Cycle*



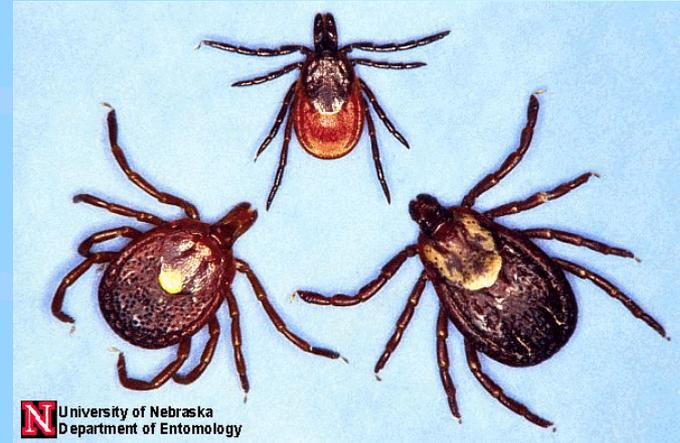
# *Animal-Arthropod-Man Cycle*



# *Examples of Arthropod Vectors*



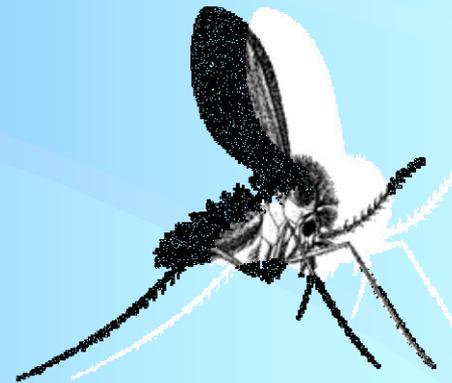
*Aedes Aegypti*



Assorted Ticks



*Culex Mosquito*



*Phlebotmine Sandfly*

# Dengue

- Agent – the dengue viruses are mosquito-borne viruses belonging to the family Flaviviridae, which gets its name from the prototype yellow fever virus. Four distinct serotypes of dengue virus have been defined; these are named dengue types 1 to 4.
- Worldwide distribution, 300 millions cases annually.
- Increased incidence due to increasing travel to tropical countries.

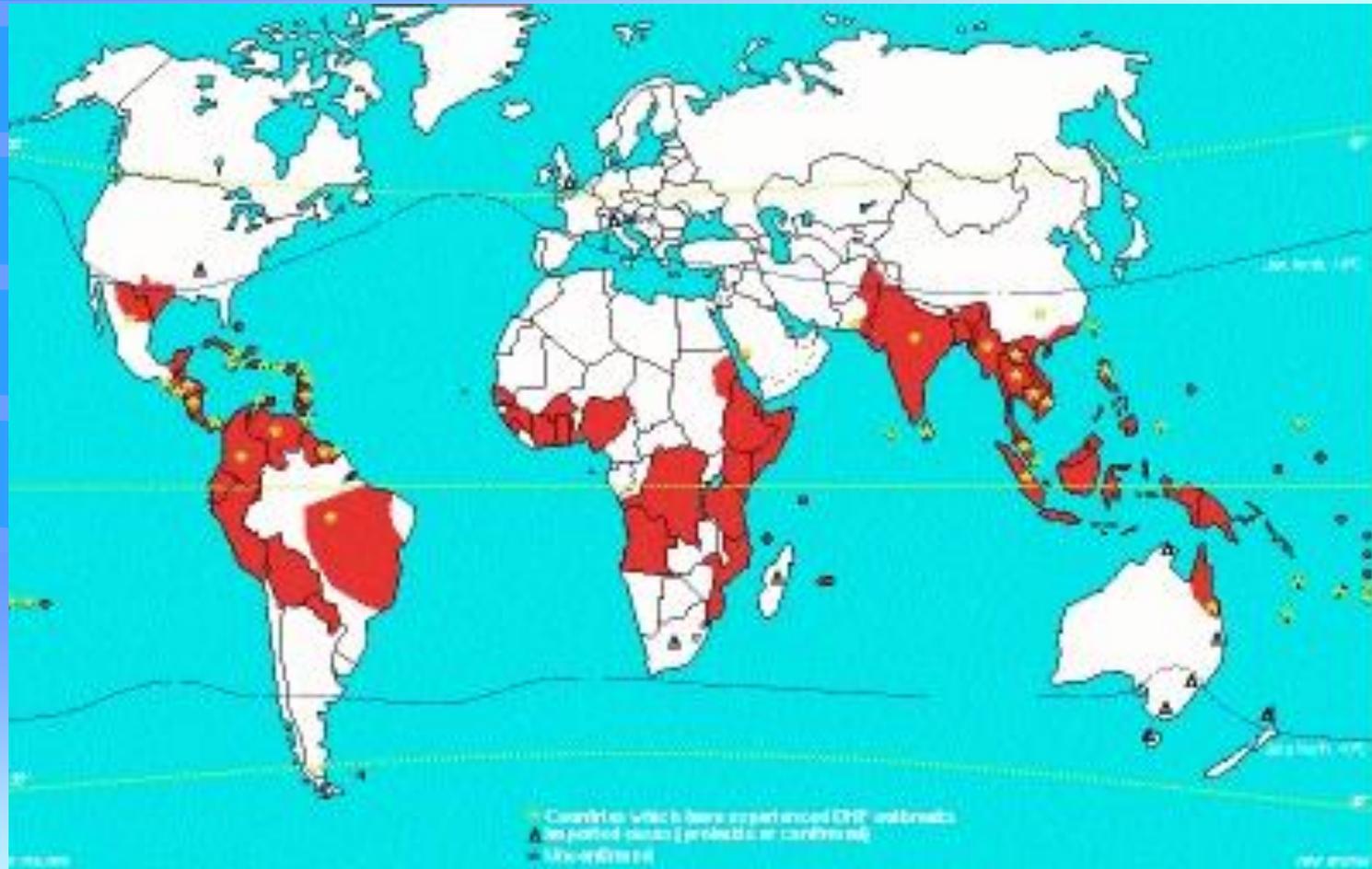
# Dengue – the vector

- Aedes aegypti is the main mosquito vector responsible for transmission of dengue virus infection.
- Human natural reservoir; mosquito-man-mosquito cycle.
- Aedes aegypti breeds near human habitation: pools of water, open sewers, etc. It has a domestic habitat and the female mosquito bites during the day.
- After the female Aedes aegypti has had a blood meal from a viraemic person, the virus multiplies in its salivary gland and can be transmitted after an incubation period of 8 to 10 days. It is also possible for the mosquito to transmit the virus immediately if its blood meal is interrupted and it bites someone else.
- Other known vectors are Ae. albopictus, Ae. Polynesiensis.

# Dengue – epidemiology

- Dengue virus infections have been recognized for more than a century in many parts of the world, and dengue haemorrhagic fever has been of great importance in some countries of South-East Asia, it is now emerging as a principal endemoepidemic disease entity in the tropical and subtropical world.
- Outbreaks are most frequent in areas where dengue infection occurs in early childhood and so classical dengue fever is rarely recognizable among the indigenous people. Annual outbreaks are observed in Burma, Indonesia, Thailand, and Vietnam. The vast majority of cases and deaths have been in children.

# *Distribution of Dengue*



# Dengue infection

- First episode of dengue infection is self-limited biphasic febrile illness.
- Incubation period – 4-7 days.
- Initial phase – 3-7 days:
  - fever, chills, “break bone” ache;
  - prostration, malaise;
  - conjunctival hyperemia, flushing of the skin.
- Second phase – 1-2 days:
  - fever decreases and rises again (“saddle” back fever);
  - maculopapulous rash – in 50%;
  - petechia, epistaxis;
  - thrombocytopenia, leucopenia, increased ALAT.

# Dengue haemorrhagic fever - definition

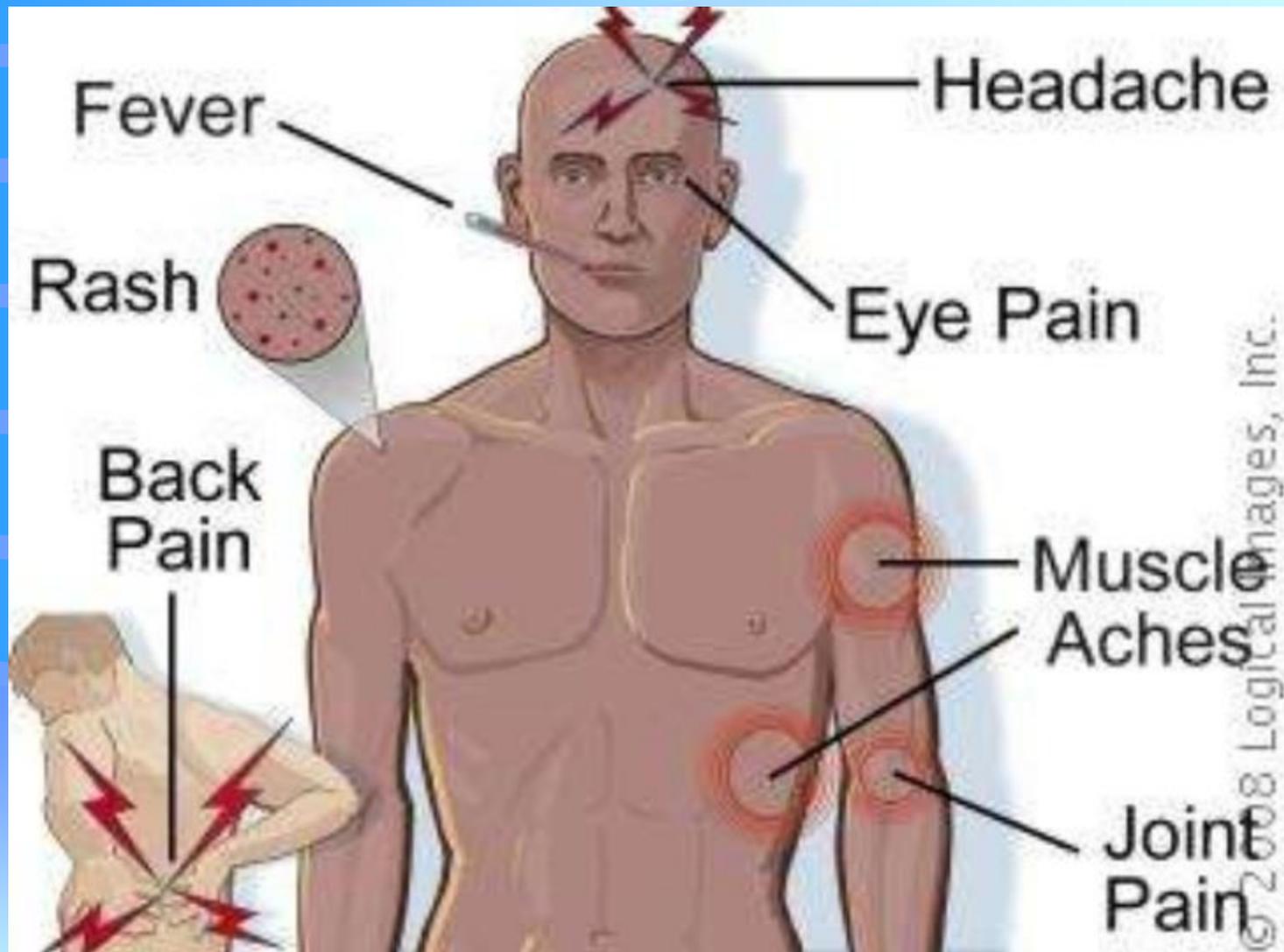
- Dengue haemorrhagic fever is a severe form of dengue infection in which there is haemorrhage and a tendency to develop fatal shock (dengue shock syndrome). Secondary infection with different serotype (type 2) → Dengue haemorrhagic fever (**DHF** – hypersensitivity reaction).

# Dengue haemorrhagic fever – the host immune response and pathogenesis

- A person may be infected by dengue virus more than once. It is generally accepted that infection by one dengue virus serotype leads to an immune response that confers protection against reinfection by the same serotype.
- Some attention has also been given to the study of cell-mediated immune responses and the role of cytokines in the pathogenesis of dengue haemorrhagic fever.

# Dengue haemorrhagic fever – clinical features

- Typically the disease begins suddenly with high fever, facial flushing, and headache. Anorexia, vomiting, and abdominal pain are common.
- During the first few days, the illness resembles classical dengue fever in many respects but the maculopapular rash is infrequent.
- A **haemorrhagic diathesis** is frequently observed in the skin as scattered fine petechiae on extremities, axillae, trunk, and face. A positive tourniquet test and a tendency to bruise at venepuncture sites are invariably present. Bleeding from the nose, gums, and gastrointestinal tract is less common. Gross haematuria is extremely rare.
- The liver is often enlarged, soft, and tender.



# *Denga – haemorrhagic rash*



# Dengue with Rashes



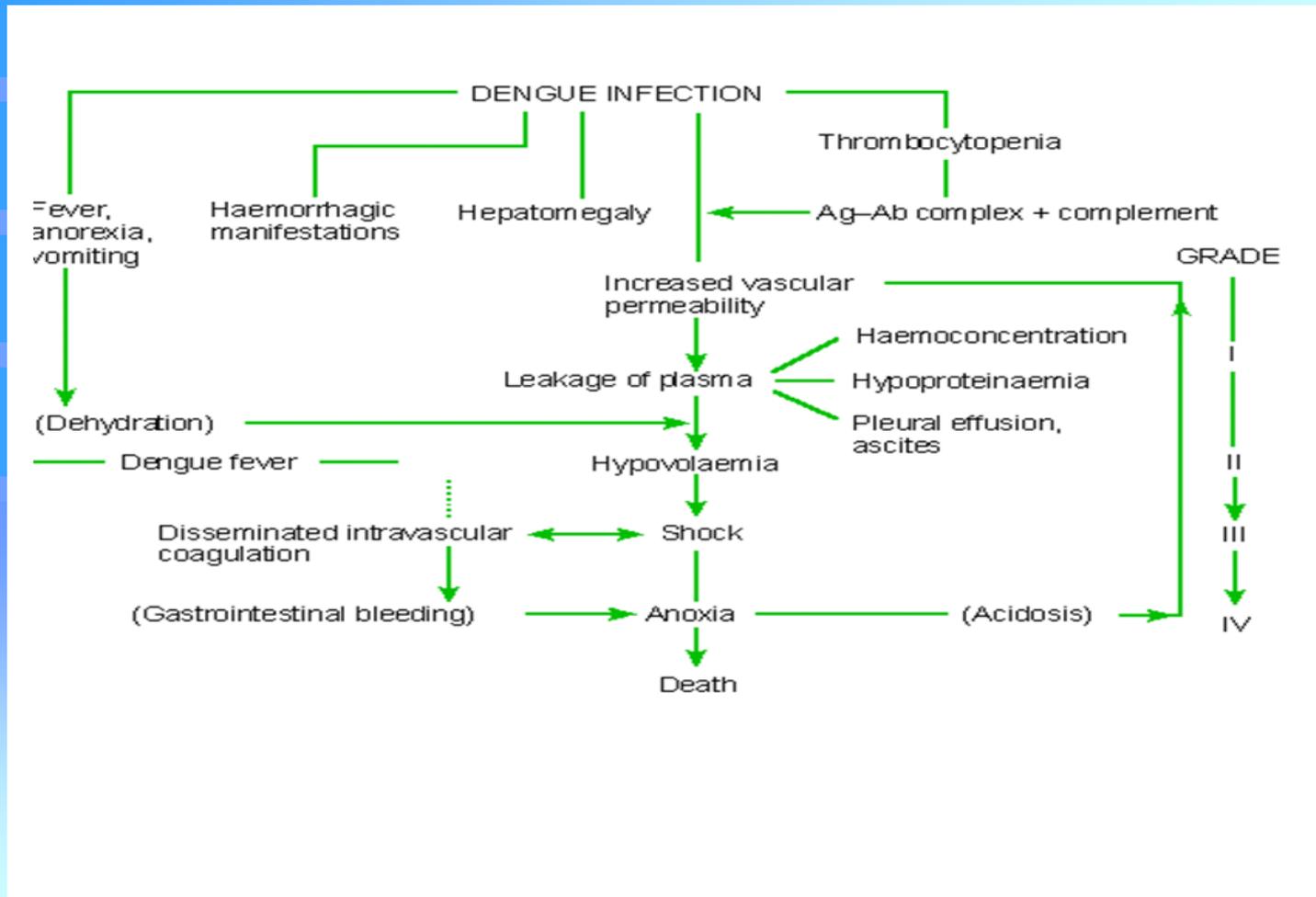
# Dengue haemorrhagic fever – clinical features

- The critical stage is reached after 2 to 7 days when the fever subsides. During or shortly after a rapid fall in the temperature there are circulatory disturbances of varying severity.
- The child may be sweating and restless, with cool extremities.
- In less severe cases, the changes in vital signs are minimal and transient, and the patient recovers spontaneously or after a brief period of fluid therapy.

# Dengue haemorrhagic fever – clinical features

- In more severe cases, shock ensues. The skin is cold, and sometimes cyanosed and the blood pressure is often narrow (<20 mm Hg). The course of shock is short and stormy, and the patient may die within 24 to 48 h.
- Prolonged shock is often complicated by metabolic acidosis and severe bleeding, which indicate a poor prognosis. However, if the patient is properly treated before irreversible shock has developed, rapid, often dramatic, recovery is the rule.
- Infrequently, encephalitic signs associated with metabolic and electrolyte disturbances, intracranial haemorrhage, and hepatic failure (Reye's syndrome) occur and give rise to a more complicated course with a grave prognosis.
- Convalescence is generally short and uneventful. Sinus bradycardia is common and occasionally a confluent petechial rash is observed, mostly on the lower extremities. The illness lasts from 7 to 10 days in most cases.

# Dengue haemorrhagic fever – pathophysiology



# Dengue haemorrhagic fever – laboratory changes

- A normal white blood-cell count or leucopenia are common initially and neutrophils may predominate.
- A relative lymphocytosis with more than 15 per cent of atypical lymphocytes is usually observed towards the end of the febrile period.
- **Thrombocytopenia and haemoconcentration are constant findings.**  
The platelet count drops shortly before, or at the same time as, the haematocrit rises; both changes occur before fever has subsided and before onset of shock.
- Clotting abnormalities are found, especially in patients with shock.
- Other changes include hypoalbuminaemia, hyponatraemia, and mild elevation of serum alanine aminotransferase.

# Dengue haemorrhagic fever – laboratory changes

- The **hallmarks of the disease** are leakage of plasma and abnormal haemostasis. **Shock is caused by a critical loss of plasma volume, presumably resulting from increased vascular permeability.** Evidence of plasma leakage includes the rapid rise in haematocrit, the development of pleural effusion, ascites and hypoproteinaemia, and the reduction in plasma volume. The acute onset of shock and the rapid and often dramatic clinical recovery when the patient is treated properly, together with the absence of inflammatory vascular lesions, suggest a transient change in vascular permeability.

# Dengue haemorrhagic fever – diagnosis

- Detection of virus:

Virus is normally detected by using monoclonal antibodies and the immunofluorescence technique.

- Detection of antibody:

- Haemagglutination inhibition test.

- The IgM capture assay.

The detection of anti-dengue IgM in serum has been successfully applied to confirm dengue infection.

- Dot enzyme immunoassay.

# Dengue haemorrhagic fever – management and treatment

- The management of dengue haemorrhagic fever is entirely symptomatic and is aimed at correcting hypoalbuminaemia during the period of leakage, that is for 24 to 48 h.
- Prognosis depends on early clinical recognition and frequent monitoring of patients for a drop in platelet count and rise in haematocrit. When the haematocrit rises sharply as plasma leaks out, early volume replacement can prevent shock.

# Dengue haemorrhagic fever – management and treatment

- When shock has developed, satisfactory results have been obtained with the following regimen: replace plasma volume losses immediately and rapidly with isotonic saline and plasma or plasma expander in cases of profound shock, then continue to replace further plasma losses to maintain effective circulation for a period of 24 to 48 h.
- Correct metabolic and electrolyte disturbances (acidosis and hyponatraemia).
- Give fresh blood transfusions and occasionally platelet-rich plasma in cases of significant bleeding.
- It is important to stop replacement when the haematocrit returns to normal, the vital signs become stable, and diuresis ensues. Excessive fluid replacement at this stage can cause heart failure and pulmonary oedema when extravasated plasma is reabsorbed.

# Japanese encephalitis (B-encephalitis)

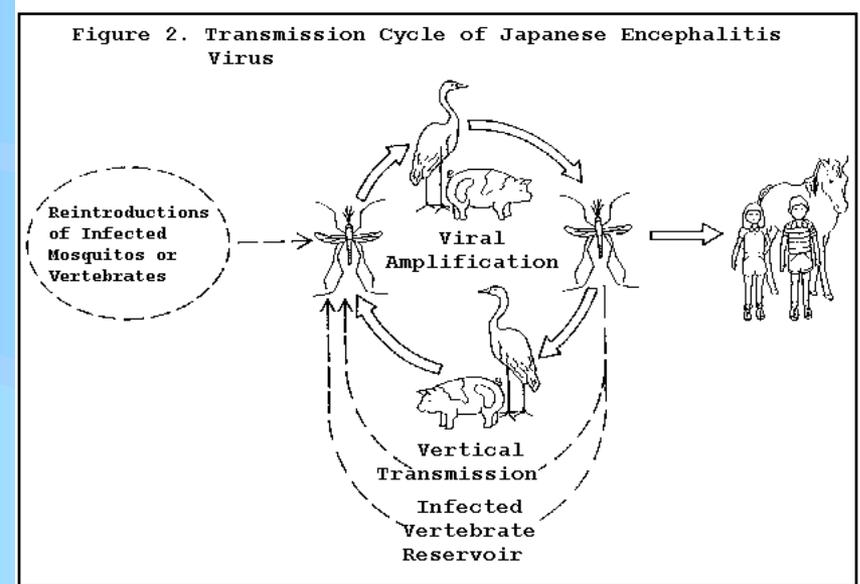
- This encephalitic disease was described clinically in 1871.
- The virus was isolated from brain tissue in 1935, and mosquito transmission was proven in 1938.
- The virus exists as a single serotype, but strains circulating in distinct geographical regions are distinguishable by RNA sequencing.
- Among the flaviviruses, Japanese encephalitis is closely linked antigenically to St Louis encephalitis, Murray Valley encephalitis, and West Nile viruses.

# Japanese encephalitis - epidemiology

- Japanese encephalitis virus causes disease in man, horses, and pigs. The virus is widely distributed in Asia, from Japan and eastern Siberia to Indonesia and westward to India.
- The vector breeds in irrigated rice fields, and the distribution of human cases is linked to exposure in this ecological setting. **Culex vectors** bite preferentially at sunset and sunrise. **Rice field breeding mosquito** primarily *Culex tritaeniorhynchus*
- No human to human transmission.
- Children suffer the highest attack rates in endemic areas, presumably because of cumulative immunity with age in the population. Elderly non-immune people are at higher risk of severe disease than young adults.

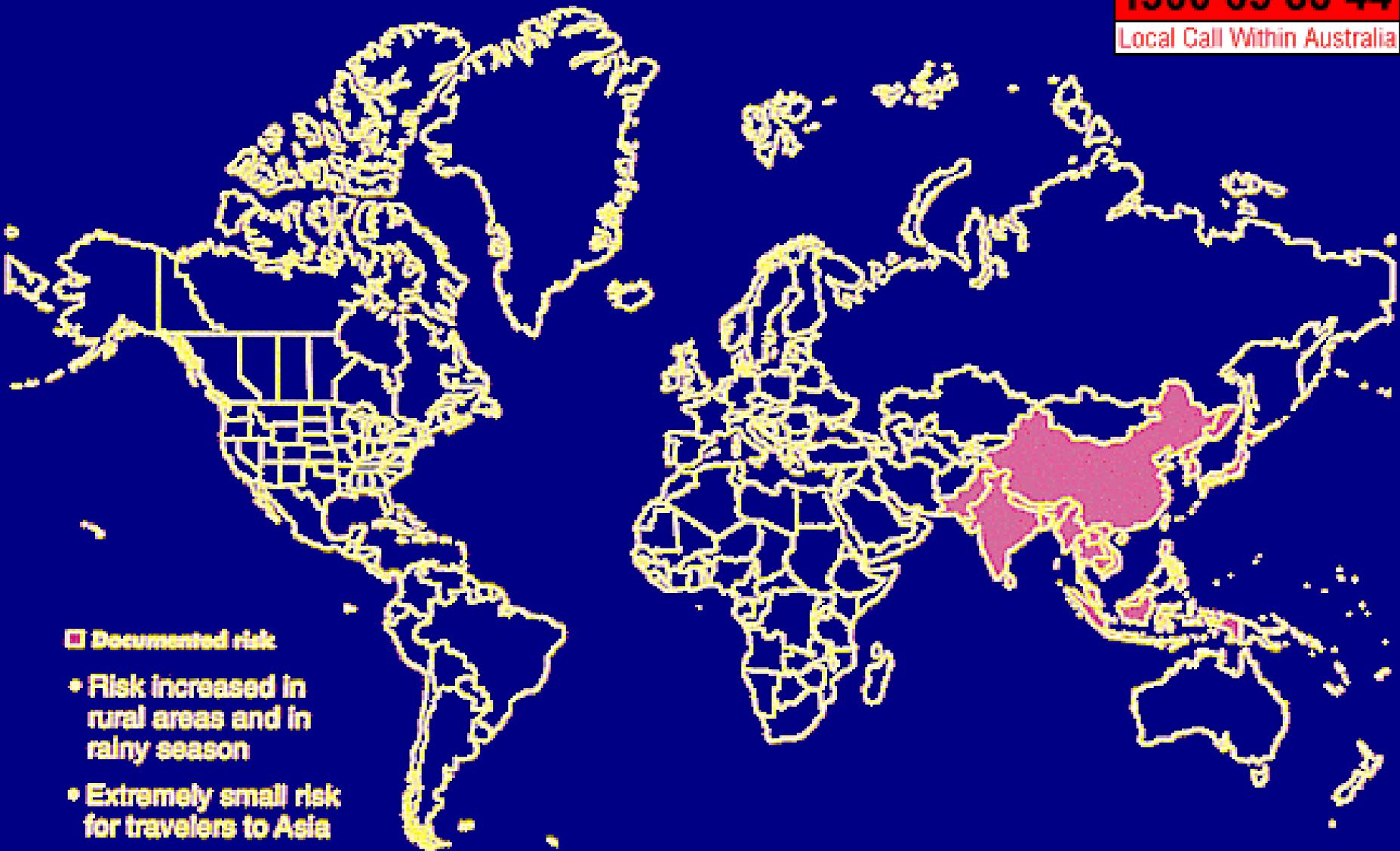
# Basic Transmission Cycle

- Mosquitos become infected by feeding on pigs and wild birds infected with JEV.
- The JE virus is amplified in the blood of pigs and wild birds.
- The infected mosquitos transfer the amplified virus to humans and animals.



# RISK OF JAPANESE ENCEPHALITIS WORLDWIDE, 1996

**TM+VC**  
**1300 65 88 44**  
Local Call Within Australia

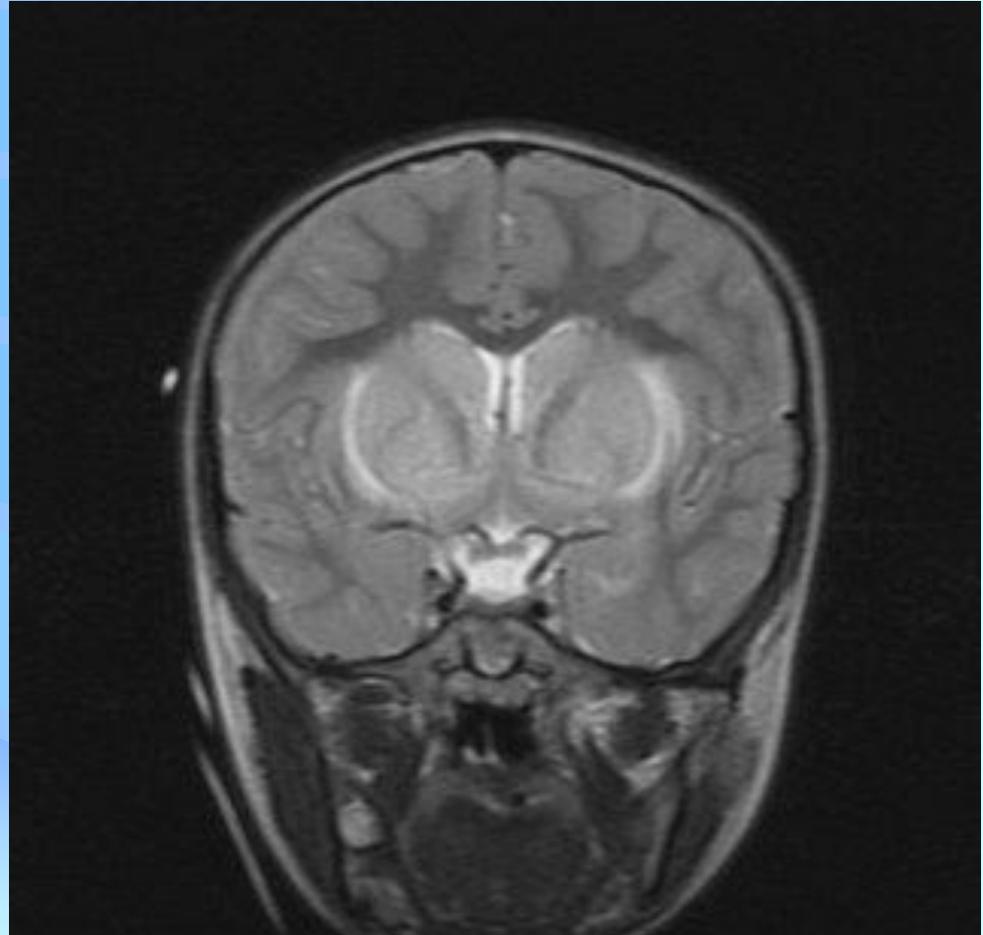


- Documented risk**
- Risk increased in rural areas and in rainy season**
- Extremely small risk for travelers to Asia**

Information based on CDC data for international travel, 1996

# Pathophysiology

- The virus initially propagates at the site of the bite and the regional lymph nodes.
- Viremia develops causing inflammatory changes in heart, liver, lungs and reticuloendothelial system.
- Neurologic invasion can develop, possibly by growth of the virus across vascular endothelial cells.
- Large areas of brain can be involved including basal ganglia, thalamus, brains stem, hippocampus and cerebral cortex



# Japanese encephalitis – clinical features

- Most human infections are asymptomatic or so mild as to escape medical attention.
- Although estimates vary, only approximately 1 in 300 infections results in typical encephalitis.
- In such cases, after an incubation period of 6 to 16 days, illness begins with a non-specific prodrome lasting 2 to 3 days, followed by **abrupt onset of high fever, chills, severe headache, meningism, photophobia, nausea, vomiting, abdominal pains, dizziness, restlessness, hyperexcitability, or drowsiness and obtundation.**

# Japanese encephalitis – clinical features

- Generalized seizures occur in a high proportion of childhood cases.
- As the disease progresses, objective neurological signs appear, including cranial-nerve palsies, tremors, ataxia, rigidity and parkinsonian manifestations, abnormal reflexes, and upper motor-neurone paralysis, most commonly of the upper extremities.
- Neurological signs fluctuate and are highly variable, particularly alterations of consciousness, which include delirium, confusion, and ultimately coma.
- **Lumbar puncture** reveals elevated cell counts, generally under 1000/mm<sup>3</sup> (polymorphonuclear initially, followed by lymphocytic), and mildly elevated protein and normal glucose levels.
- Respiratory dysregulation, coma, abnormal plantar reflexes, prolonged convulsions, and advanced age are associated with poor prognosis.

# Japanese encephalitis – clinical features

- Computerized tomography has revealed areas of low density and magnetic resonance scans have shown abnormal signals in deep areas of the brain (thalamus and basal ganglia).
- Japanese encephalitis is with a lethality in excess of 25 per cent.
- Neuropsychiatric sequelae including parkinsonism, paralysis, and retardation occur in 30 to 70 per cent of survivors.
- In pregnant women infected during the first or second trimester, spontaneous abortion, and fetal death have been documented and the virus isolated from the conceptus.
- Data are insufficient to determine the quantitative risk of congenital infection or the risk of infection in the third trimester. There are several reports of recurrent encephalitic disease in children, with intervals of up 6 to 12 months between these occurrences.

# Japanese encephalitis – diagnosis

- Specific diagnosis is by serological tests, particularly IgM enzyme immunoassay, which should be done on acute and convalescent sera and cerebrospinal fluid.
- From fatal cases, virus may be isolated from brain tissue or demonstrated by immunofluorescence.
- Virus is very rarely recoverable from blood during the acute phase.

# Japanese encephalitis – differential diagnosis

- The differential diagnosis includes other viral encephalitis (especially herpes encephalitis), as well as cerebral malaria and treatable bacterial, mycobacterial, and fungal infections of the central nervous system.
- Epidemiological features (place of travel or residence, season of the year, and occurrence of other cases in the community) provide important clues to the diagnosis.

# Japanese encephalitis – treatment

- No specific treatment is available.
- Uncontrolled trials of intrathecal interferon- $\alpha$  are inconclusive.
- Treatment is supportive, and includes attention to fluid management, respiratory support if required, avoidance of infection and bed sores, and use of anticonvulsants.
- Cerebral oedema may represent an important complication and requires prompt diagnostic evaluation and intervention.

# Japanese encephalitis – prevention

- A formalin-inactivated purified vaccine derived from mouse brain has been in routine use for childhood immunization in Japan and some other Asian countries since the 1960s.

# Tick-borne encephalitis – etiology

- The disease was described in 1932 in the Far East of the former Soviet Union, and a virus (now called **Russian spring-summer encephalitis' virus, RSSE virus**) isolated from blood of patients and from Ixodes ticks in 1934.
- RSSE virus belongs to a medically important antigenic complex of the Flaviviridae, that includes the closely related **Central European encephalitis** (CEE) virus, as well as looping ill, Powassan, Kyasanur forest disease, and Omsk haemorrhagic fever viruses.

# Tick-borne encephalitis – epidemiology

- In addition to being transmitted by ticks, viruses in this complex have certain other biological peculiarities: many are transmissible via the milk of infected domestic livestock, and they are notorious for producing laboratory infections via the aerosol route.

# Tick-borne encephalitis – epidemiology

- The distribution of RSSE and CEE viruses is determined by that of their vectors, Ixodes persulcatus and Ixodes ricinus, respectively.
- RSSE causes human disease principally in the Far East, the Ural region, and western Siberia, whereas CEE occurs at highest incidence in Eastern and Central Europe, Moldavia, the Ukraine, and Belarus, with smaller numbers of cases from Western Europe, the Balkan region, and Scandanavia.
- These infections are highly seasonal, occurring only during the period of tick activity, and incidence varies from year to year.

# Tick-borne encephalitis – clinical features

- The incubation period is 7 to 14 days.
- The disease caused by RSSE virus is more severe than CEE.
- Onset is generally acute, with fever, headache, photophobia, chilliness, nausea and vomiting, followed by meningismus, and evolution of the encephalitic syndrome over several days.
- Asymmetrical lower motor-neurone paralyses, especially of the upper extremities, shoulders, face and neck, are typical.
- There are convulsions, tremor, ataxia, hyperesthesia and sensory loss, and variable changes in sensory.
- The case-fatality rate is approximately 20 per cent, and up to 60 per cent of survivors are left with neurological sequelae, including flaccid paralysis.

# Tick-borne encephalitis – clinical features

- CEE is a milder disease, which typically has a biphasic course. The first phase is a non-specific influenza-like illness with fever, headache, nausea, and vomiting lasting about a week.
- After a period of remission lasting a few days, fever returns, with aseptic meningitis or encephalomyelitis.
- The case-fatality rate is 1 to 5 per cent; about 20 per cent of survivors have neurological effects. Residual motor deficits are rare.

# Tick-borne encephalitis – diagnosis and differential diagnosis

- The differential diagnosis of is similar to that described previously (see under Japanese encephalitis above); the pattern of flaccid paralysis may be confused with poliomyelitis.
- Epidemiological features of the case and history of tick exposure provide important clues; as in Lyme disease, however, a history of bite by small Ixodes ticks is elicited in fewer than half the cases.
- Specific diagnosis is made by virus isolation from blood or cerebrospinal fluid during the first week of illness, or by serological tests, including IgM enzyme immunoassay, done on serum and cerebrospinal fluid.

# Tick-borne encephalitis – treatment and prevention

- Treatment is supportive.
- Prevention – effective inactivated vaccines prepared in tissue culture are produced in Russia, Austria, and Germany.

# Other arboviral infections

- With increasing of the number of travelers many of these diseases increase in North America and parts of Europe where they have not been seen earlier.
- **West Nile fever (WNE) – emerging viral disease.** It was reported for first time in 1999 in USA. It is epizootic disease with avian reservoirs. There are severe muscle weakness or flaccid paralysis, suggestive Guillain-Barre syndrome.
- Eastern equine encephalitis – the most serious.
- Western equine encephalitis.
- St Louis encephalitis.
- California encephalitis.
- Venezuelan encephalitis.

**THANKS  
FOR YOUR ATTENTION!**