JAPANESE ENCEPHALITIS

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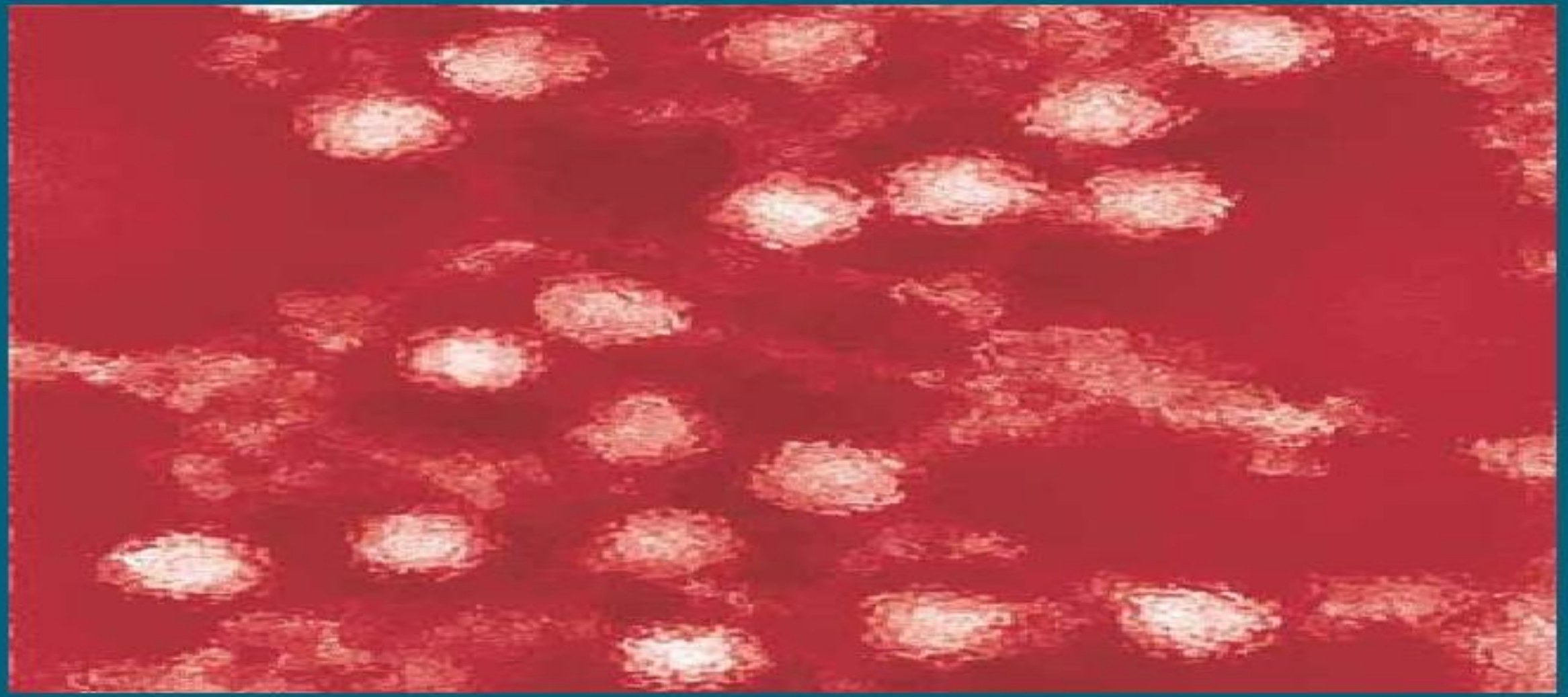


JAPANESE ENCEPHALITIS

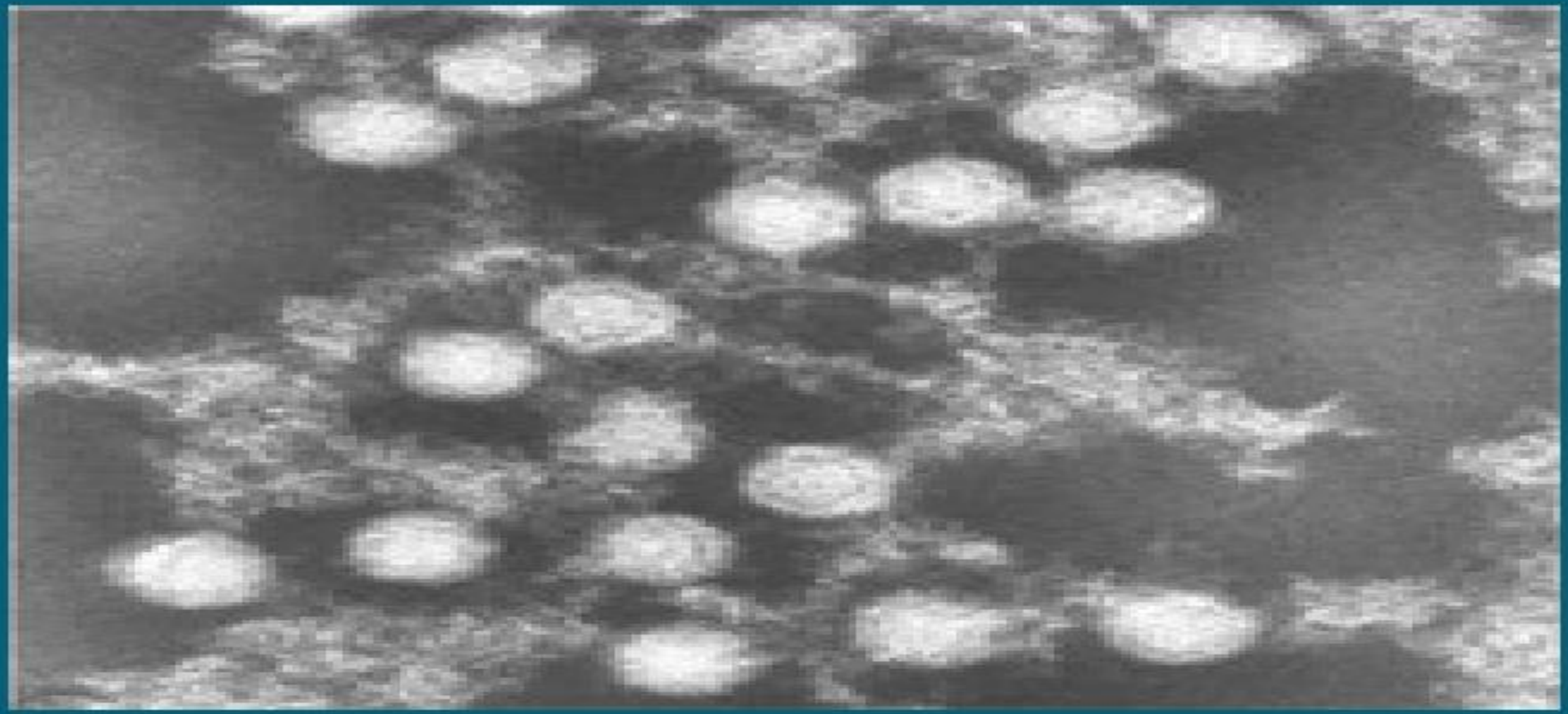
"INTRODUCTION"

- *SYNONYMS:* Japanese B Encephalitis, Arbovirus B Encephalitis, Mosquito-Borne Encephalitis, Russian Autumnal Encephalitis, Brain Fever, Summer Encephalitis.

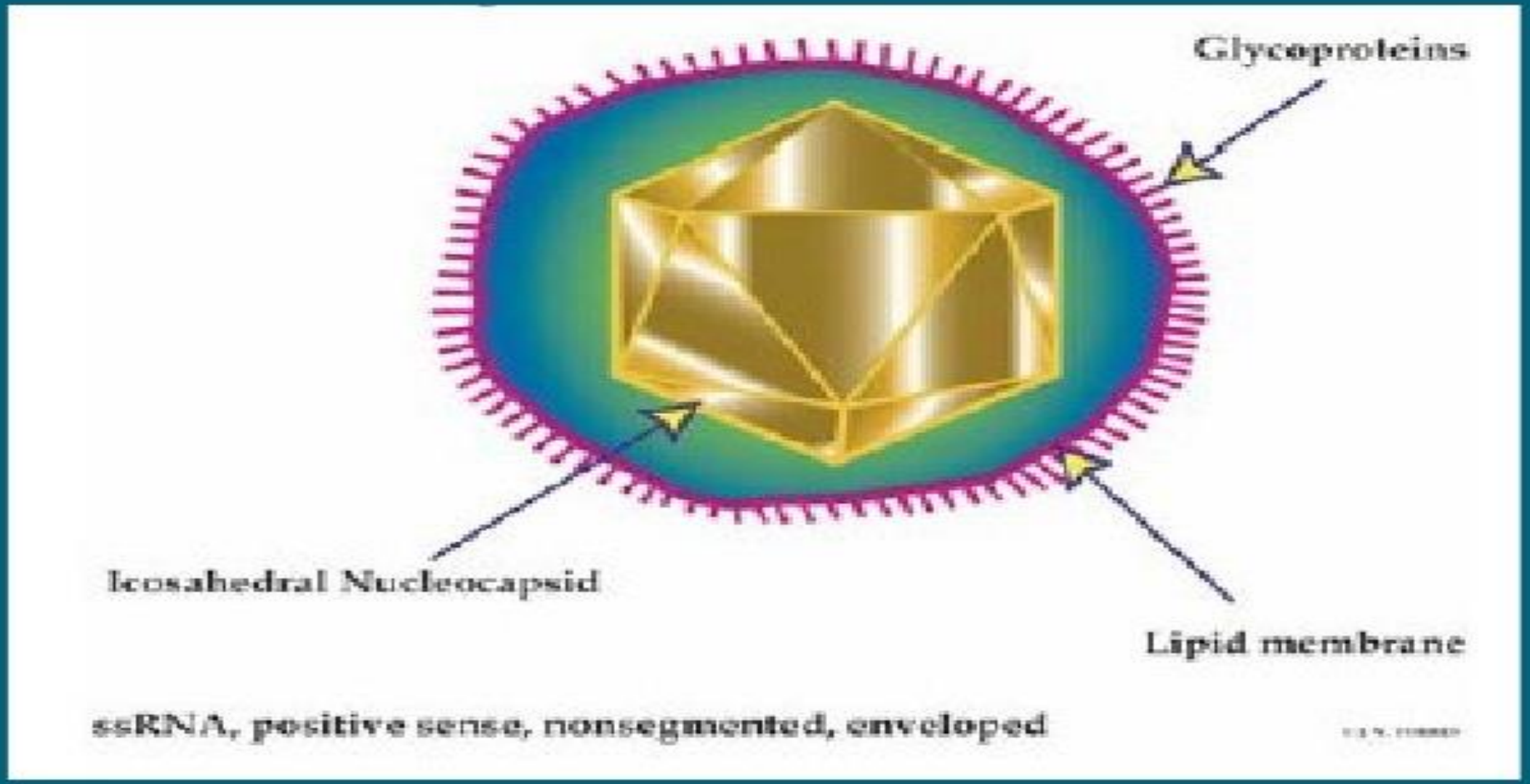
- *Definition:* JE is an inapparent to acute arboviral infection of horses, pigs and humans. It's a zoonotic disease i.e. infecting mainly animals and incidentally man.

AETIOLOGY:

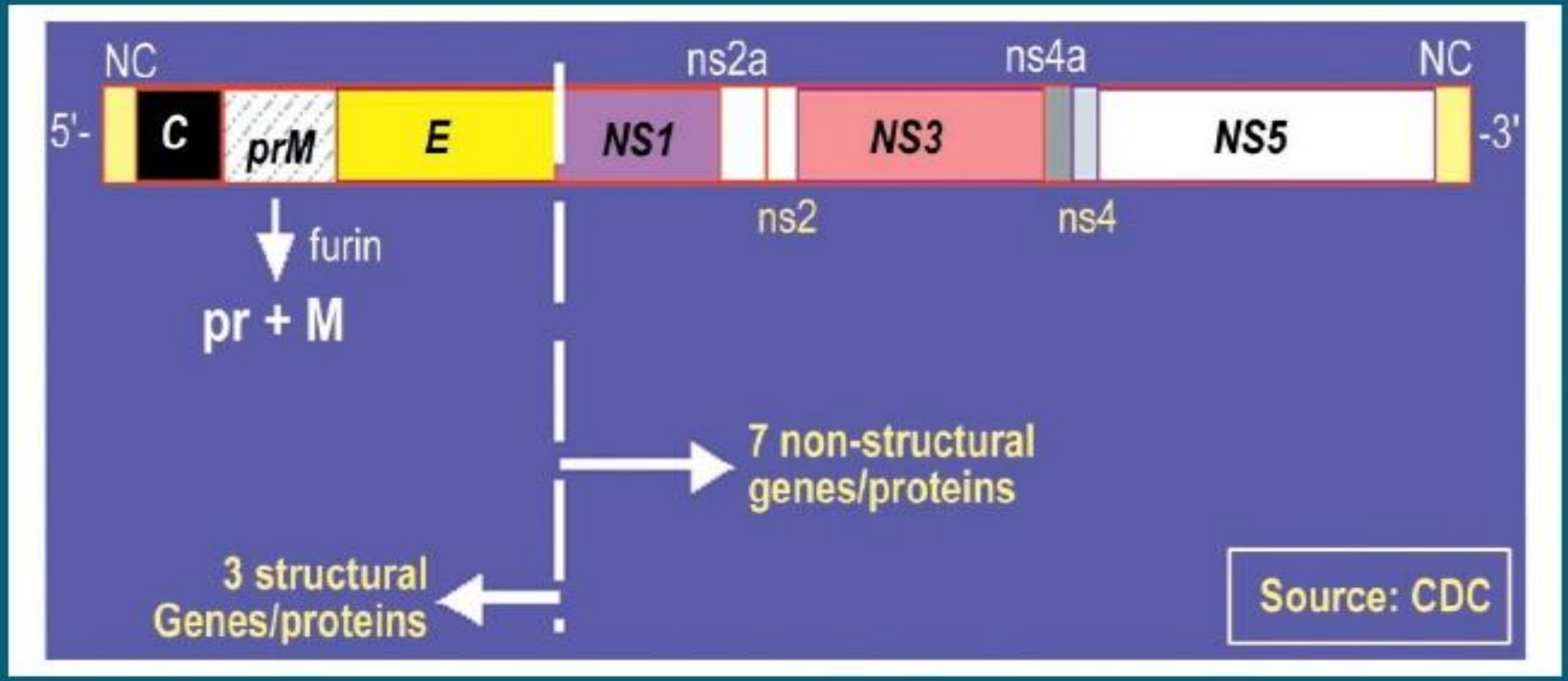
- Family: Flaviviridae
- Genus: Flavivirus
- Virions: Spherical, lipoprotein-enveloped particles being 40-50nm in diameter, 3 structural and 7 non-structural proteins
- Genome: Single stranded positive sense RNA of molecular weight 3×10^6 daltons
- Antigenic Structure:
  Hemagglutinins, Complement Fixing and Neutralising Antigens



FLAVIVIRUS


Glycoproteins
Icosahedral Nucleocapsid
Lipid membrane
ssRNA, positive sense, nonsegmented, enveloped

FLAVIVIRUS



Flavivirus Genome

Resistance To Physical And Chemical Action

- Temperature: Destroyed by heating for 30mins above 56°C; Thermal Inactivation Point is 40°C
- pH: Inactivated in acid environment of 1-3 (Stable in alkaline environment of pH 7-9)
- Chemicals/Disinfectants: Inactivated by organic & lipid solvents, common detergents, phenol iodophors, 70% ethanol, 3-8% formal dehyde, 2% gluteraldehyde, 1% sodium hypochlorite
- Survival: Sensitive to UV light & gamma irradiation

ARBOVIRUSES (ABV):

- *Viruses of vertebrates biologically transmitted by hematophagus insect vectors*
- *Special characteristic: Ability to multiply in arthropods*
- *Worldwide in distribution but far more numerous in tropical than in temperate zones*
- *India: Over 40 ABV detected, >10 are known to produce human disease*

Taxonomy Of Some Important Arboviruses

FAMILY	GENUS	IMPORTANT SPECIES
Togaviridae	Alphavirus	Chikungunya, Mayaro, O'nyong-nyong, EEE,WEE,VEE virus etc
Flaviviridae	Flavivirus	Japanese Encephalitis, West Nile, Dengue types 1, 2, 3,4, KFD, MVE, Yellow fever virus
Bunyaviridae	Bunyavirus Phlebovirus Nairovirus Hantavirus	California encephalitis, Oropouche, Turlock Rift valley fever, Sandfly fever virus Ganjam virus, Nairobi sheep disease virus Prospect hill, Hantan, Seoul, Puumala
Reoviridae	Orbivirus	African horse sickness, Blue tongue viruses
Rhabdoviridae	Vesiculovirus	Vesicular stomatitis virus, Chandipura virus

HISTORY

- *1870's: Japan*
  - *"Summer encephalitis" epidemics*
- *1924: Great epidemic in Japan*
  - *6,125 human cases; 3,797 deaths*
- *1935: First isolated*
  - *From a fatal human encephalitis case*
- *1938: Isolated from Culex tritaeniorhynchus*

HISTORY (contd.)

- 1940-1978
  - Disease spread with epidemics in China, Korea and India
- 1983: Immunization in South Korea
  - Started as early as age 3
  - Endemic areas started earlier
- 1983-1987: Vaccine available in U.S. on investigational basis

EPIDEMIOLOGY

- *Geographical Distribution*
- *Hosts*
- *Transmission*
- *Morbidity and Mortality*

Geographic Distribution

- Endemic in temperate and tropical regions of Asia
- Reduced prevalence in Japan
- Has not occurred in U.S
- India - Epidemics

HOSTS

- **Horses** are the primary affected domestic animals of JE though essentially a dead-end host; other equids **(donkeys)** are also susceptible

- **Pigs** act as **"amplifiers"** of the virus producing high viraemias which infect mosquito vectors

- The natural maintenance **reservoir** for JE virus are **birds** of the family Ardeidae **(herons and egrets)**

Contd..

PIG - AMPLIFYING HOST

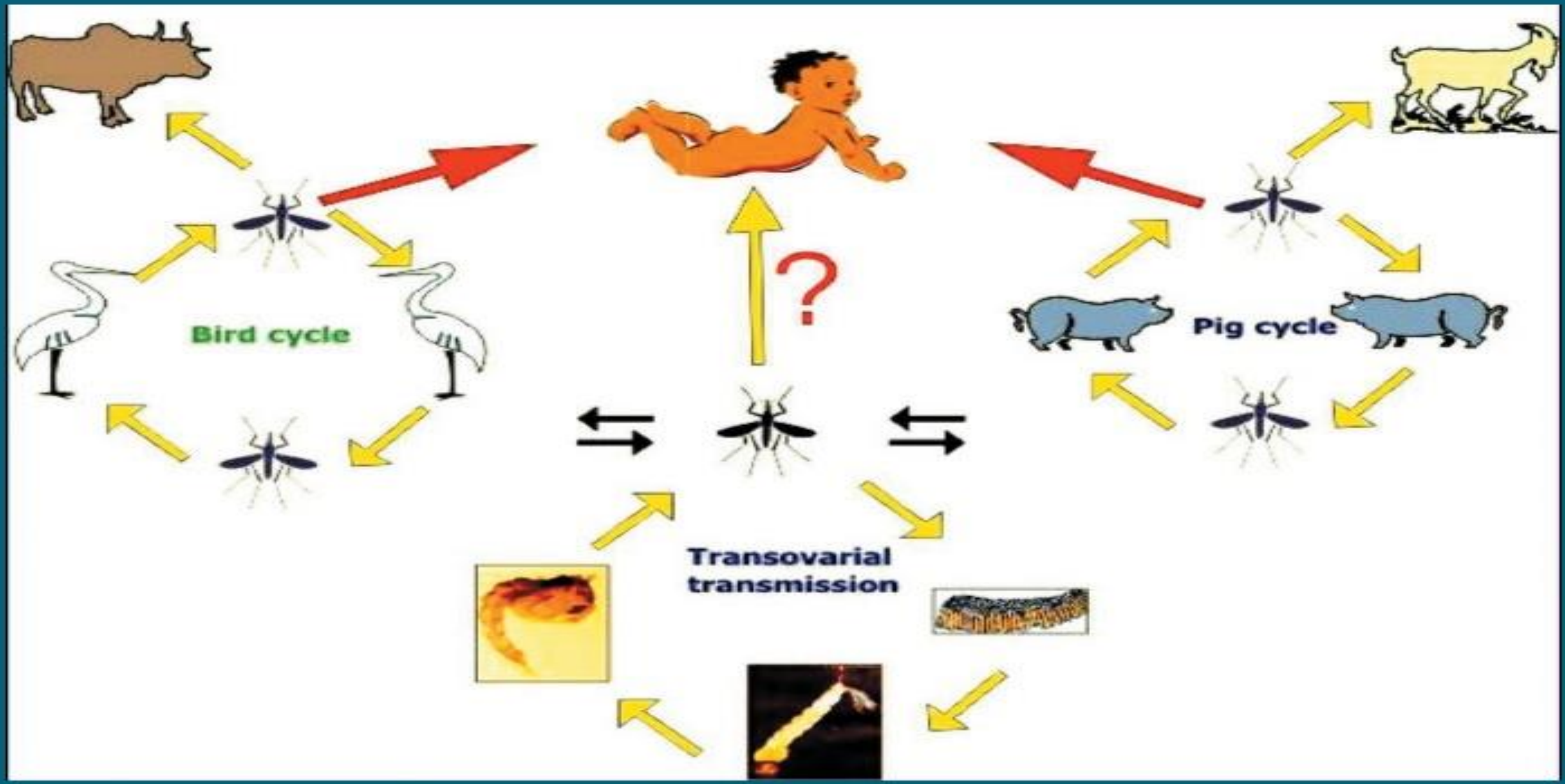
EGRET {RESERVOIR HOST}

POND HERON

...Although they (birds) do not demonstrate clinical disease they do generate high viraemias upon infection

- ***Humans*** *are vulnerable to this disease and this disease is a primary public health concern in Asia; humans are considered a* ***dead-end host***

- *Other subclinically infected animals which likely do not contribute to spread include: cattle, sheep, goats, dogs, cats, chickens, ducks, wild mammals, reptiles and amphibians*



LIFE CYCLE OF JAPANESE ENCEPHALITIS

TRANSMISSION

➢ *JE presents two recognised epidemiologic patterns in Asia:*

- ***Late summer/early autumn-associated epidemic disease of northern temperate areas***
  - *Large numbers of mosquitoes feed on Ardeid birds (spring season)*
  - *Ardeid birds migrate between rural and urban ecosystems introducing JE virus(spring season); these birds also amplify virus*
  - *Increased vector activity leads to spill-over and infection of swine by mosquito vectors shared by birds and pigs*

- *Infection of pigs produces additional amplification of virus; also large populations of vector-accessible swine with rapid generational overturn facilitate JE virus infection (summer)*
- *with profusion of JE virus circulating, mosquitoes of horses and humans also transmit agent to these hosts; usually sporadic & localised epizootics or epidemics (late summer or early autumn)*

- ***Year-round endemic disease of southern tropical areas***
  - *continual cycle between birds, swine & mosquitoes*
  - *principal vectors: Culex tritaeniorhynchus and Culex gelidus*

-minor sporadic outbreaks in horses and humans during monsoon season

- **Actual transmission of JE virus occurs by means of Mosquitoes**
  - Principally Culex species mosquitoes; **Culex tritaeniorhynchus** is important as it has a wide host range that includes birds, horses, swine and humans
    - **C. tritaeniorhynchus** oviposits in flooded fields (fish ponds, rice paddies and ditches) & is most active at twilight hours

Culex tritaeniorhynchus

(*Cx vishnui* group)

CULEX MOSQUITO BITING HUMAN

A TYPICAL BREEDING HABITAT FOR MOSQUITOES

- *Aedes spp. of mosquitoes have also been implicated*
- *JE virus has been isolated from other species of mosquitoes (i.e. Anopheles and Mansonia) but their role is unclear*
- *vertical transmission in mosquitoes has been documented*

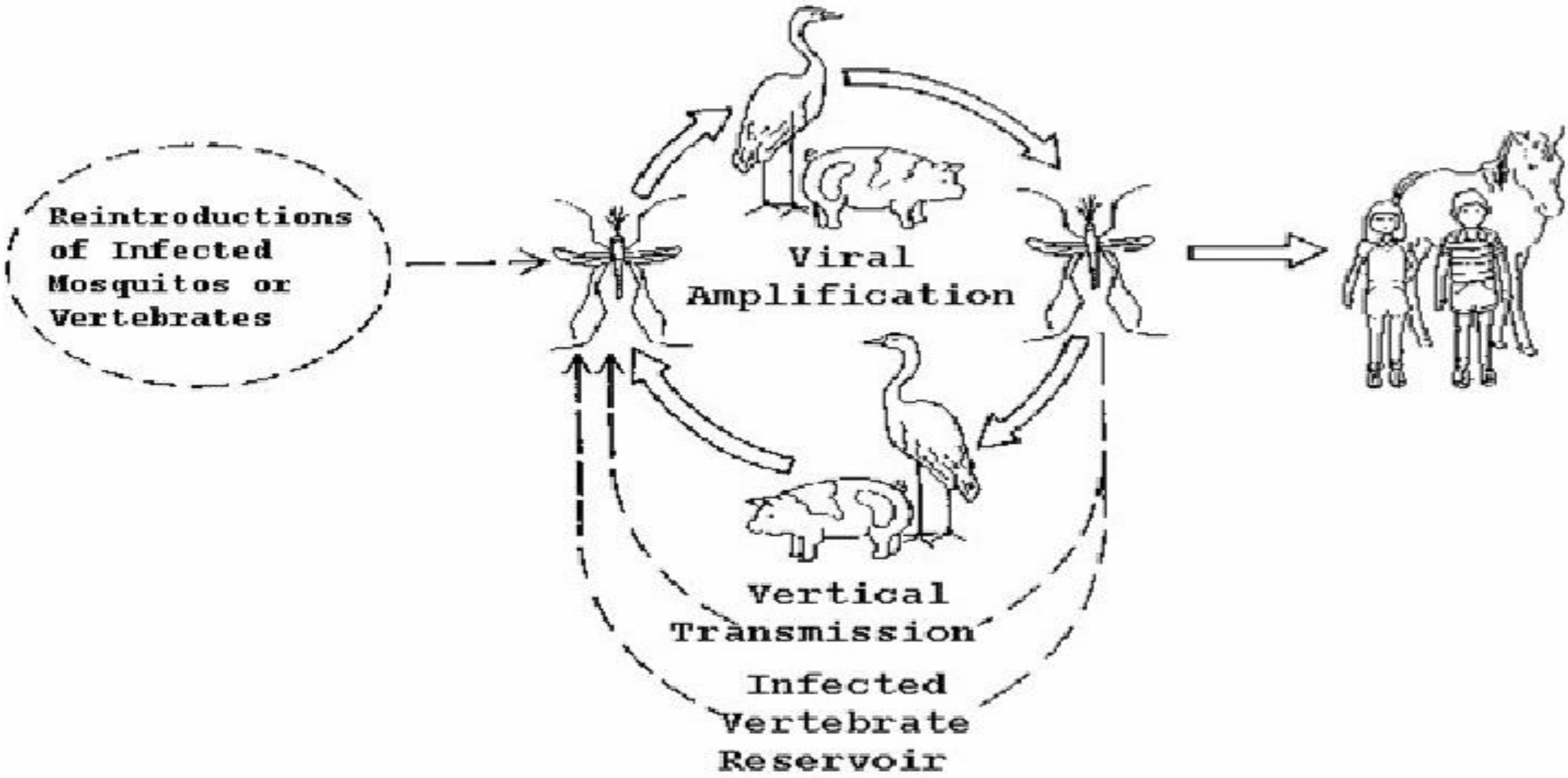
- *JE virus cycles in Ardeid birds by means of mosquitoes*
- *Although horses may produce viraemias sufficient to infect mosquito vectors, their populations are usually inadequate to maintain the virus or have any important epidemiological impact*

➢ Sources of virus :

- ✓ Water birds of the family Ardeidae; herons and egrets
- ✓ Mosquito vectors as described above
- ✓ Once infected, swine amplify JE virus and high titres in blood, provide more infectious agent to vectors
  - JE virus could be transmitted in boar semen

- ✓ Overwintering of epizootic/epidemic JE virus has not been elucidated
  - introduction of JE virus strains from endemic areas
  - hibernating mosquitoes may maintain virus; also through transovarial passage
  - maintenance in reptiles, amphibians or bats

Figure 2. Transmission Cycle of Japanese Encephalitis Virus



Morbidity/Mortality

- **Swine**
  - High mortality in piglets
  - Death rare in adult pigs
- **Equine**
  - Morbidity: 2%, during an outbreak
  - Mortality: 5%
- **Humans**
  - Mortality: 5-35%
  - Serious neurologic sequelae: 33-50%

DYNAMICS OF JE TRANSMISSION

Environment

Vector Mosquito

Victim-Accidental

Full Recovery

Recovery with residual complications

Death

Host - Amplifying

Host - Carrier

PATHOGENESIS

Virus enters the body through the bite of the insect vector - mosquitoes

↓

After multiplication in R.E. system, viremia of varying duration ensues

↓

Virus is transported to target organ (brain) via blood

↓

Virus proliferate & damage the neuronal tissue, thereby elicits nervous manifestations

JE IN ANIMALS

(Most commonly seen in late summer to early fall)

A} HORSE:

- **Incubation period:**
  - 4 to 14 days (experimentally determined)
  - 8 to 10 days (average range)

- Subclinical disease is most common, clinical signs if present vary, disease usually presents itself in sporadic or localised clusters

THREE SYNDROMIC MANIFESTATIONS IN HORSE

Three Syndromic manifestations:

- ***Transitory Type Syndrome:***

  -Moderate fever lasting 2-4 days

  -Inappetance, Impaired Locomotion, Congested or Jaundiced Mucosa; most commonly with swift recovery of 2-3 days

- ***Lethargic Type Syndrome:***

  -Variable febrile periods (as high as 41°C)

  - Pronounced Stupor, Bruxism, Chewing Motions Difficulty in Swallowing, Petechiation of Mucosa, Paralysis; Recovery usually occurs within about a week

B} JE IN SWINE:

- **Incubation Period:**

  -Not been clearly established

- Signs of disease manifested as early as 3 days but viraemia & accompanying fever may appear within 24hrs post inoculation

- In Swine most commonly JE manifests as a **Reproductive disease;**

  Reproductive Losses - 50 to 70%

a) Abortion in Sows: Still births or mummified fetuses; usually at term

b) Reduced No. & Motility of Sperm In Boars

STILLBORN FETUSES

- *Live born piglets most often demonstrate neurologic signs of tremors & convulsions & may die soon after birth*
- *Mortality in non-immune, infected piglets can approach 100%*
- *Mild febrile disease or subclinical disease in non-pregnant females*
- *Natural infection results in long lasting immunity*
- *Mortality is near Zero in adult swine*

LESIONS

A} IN HORSES:

- P.M. gross lesions of CNS associated with JE are, in general, non-specific
- Histopathologic examination reveals a non-suppurative encephalomyelitis with apparent perivascular cuffing; phagocytic destruction of nerve cells & focal gliosis
- Blood vessels appear dilated with numerous mononuclear cells.

B} IN SWINE:

- *Litters of infected sows contain mummified or stillborn fetuses; some fetuses dark in appearance*

- *Evidence of congenital neurologic damage; hydrocephalus, cerebellar hypoplasia & spinal hypomelinogenesis observed in some litters*

- *Also subcutaneous oedema*

DIFFERENTIAL DIAGNOSIS

- **EQUINE:**
  - WEE, EEE, other viral encephalatides, Hendra virus, Rabies, Neurotoxins, Toxic encephalitis

- **SWINE:**
  - Myxovirus-parainfluenza 1, Corona virus, Menangle virus, Porcine Parvovirus, Porcine Reproductive and Respiratory Syndrome

SAMPLING

- *Before collecting or sending any samples from animals with a suspected foreign animal disease; the proper authorities should be contacted*

- *Samples should be sent under secure conditions & to authorized laboratories to prevent the spread of the disease*

Diagnosis in Animals:

- Clinical
  - Horses: Fever and CNS disease signs
  - Swine: High number of stillborn piglets
- Laboratory Tests
  - Definitive: Viral isolation
    - Blood, spinal cord, brain, CSF
  - Rise in antibody titre
    - Neutralization, HI, IF, CF, ELISA
    - Cross reactivity of Flaviviruses

TREATMENT IN ANIMALS:

- *No effective treatment*

- *Supportive Care:*
  - *Antipyretics*
  - *Anticonvulsants*
  - *Maintenance of Nutrition*
  - *Treatment of Secondary Bacterial Infection*

JE IN MAN : CLINICAL FEATURES

- Incubation Period - 5 to 15 days
- Only 1 in 300 to 1 in 1000 infections develop into encephalitis, rest asymptomatic

- Course of disease- 3 stages:
  a} **Prodromal stage:** Fever, headache and malaise. Duration- 1 to 6 days.
  b} **Acute encephalitic stage:** Fever, 38 to 40.7°C, nuchal rigidity, focal CNS signs, convulsion & altered sensorium progressing in many cases to coma.
  c} **Late stage and sequelae:** Temperature & ESR touch normal level, neurological signs become stationary

- **Case Fatality Rate (CFR) :**
  -Varies between 20-40% but it may reach 58% & over , higher in children

- 30-50% of the people that survive the infection develop paralysis, brain damage, or other serious permanent sequelae

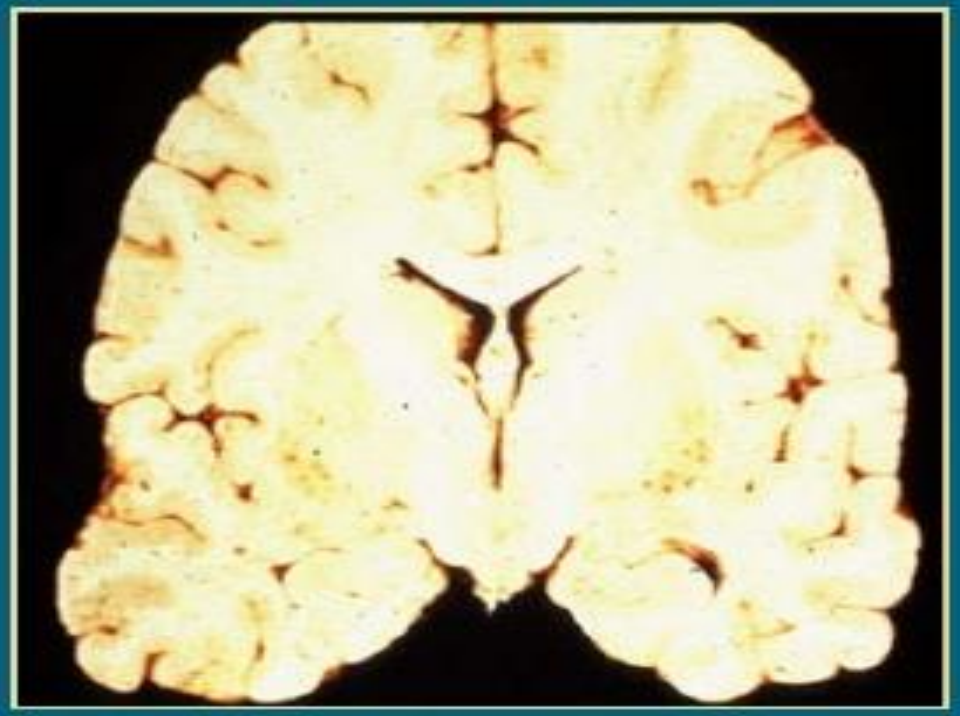
- Average period between the onset of illness & death is about 9 days

- In utero infection possible:
  - Abortion of fetus

Figure 41.7: A 5-year-old boy with Japanese encephalitis.

Post Mortem Lesions

- Pan-encephalitis
- Oedema and congestion of brain & meninges
- Infected neurons scattered throughout CNS
- Occasional microscopic necrotic foci
- Thalamus generally severely affected



Differential Diagnosis

- Meningitis
- Febrile Convulsions
- Rey's Syndrome
- Rabies
- Cerebral Malaria
- Toxic Encephalopathy

Diagnosis and Treatment In Man:

- Clinical
- Laboratory Tests
  - — Tentative diagnosis
    - Antibody titer : HI, IFA, CF, ELISA
    - JE-specific IgM in serum or CSF
  - — Definitive diagnosis
    - Virus isolation : CSF sample, brain
    - Treatment:
      - No Specific treatment
      - Supportive care

PREVENTION AND CONTROL

A} SANITARY PROPHYLAXIS:

- Housing of animals in-doors in screened stabling can provide protection from mosquitoes

  - Especially during active JE outbreaks & during peak vector activity (usually dusk to dawn)

  -Insecticides, repellants & fans also provide protection

- Vector control reduces transmission

IN AFFECTED VILLAGES:

-Aerial or ground fogging with ultra low volume insecticides

-Spraying should cover vegetation around houses, breeding sites & animal shelters

IN UNINFECTED VILLAGES:

- Those falling within 2-3 km radius of infected villages should also receive spraying as a preventive measure

- Use of mosquito nets should be advocated

B} MEDICAL PROPHYLAXIS

- ***VACCINATION OF SWINE & HORSES:***
  - *Modified Live or Inactivated Vaccines*

- *Vaccination of swine prevents reproductive disorders & directly impacts JE viral amplification; especially in enzootic areas*
  - *vaccinated breeding sows & boars; protects animals, reduces amplification, ensures healthy litters & decreases likelihood of aspermia*

- *Vaccines also protect horses from clinical disease & possible sequelae*

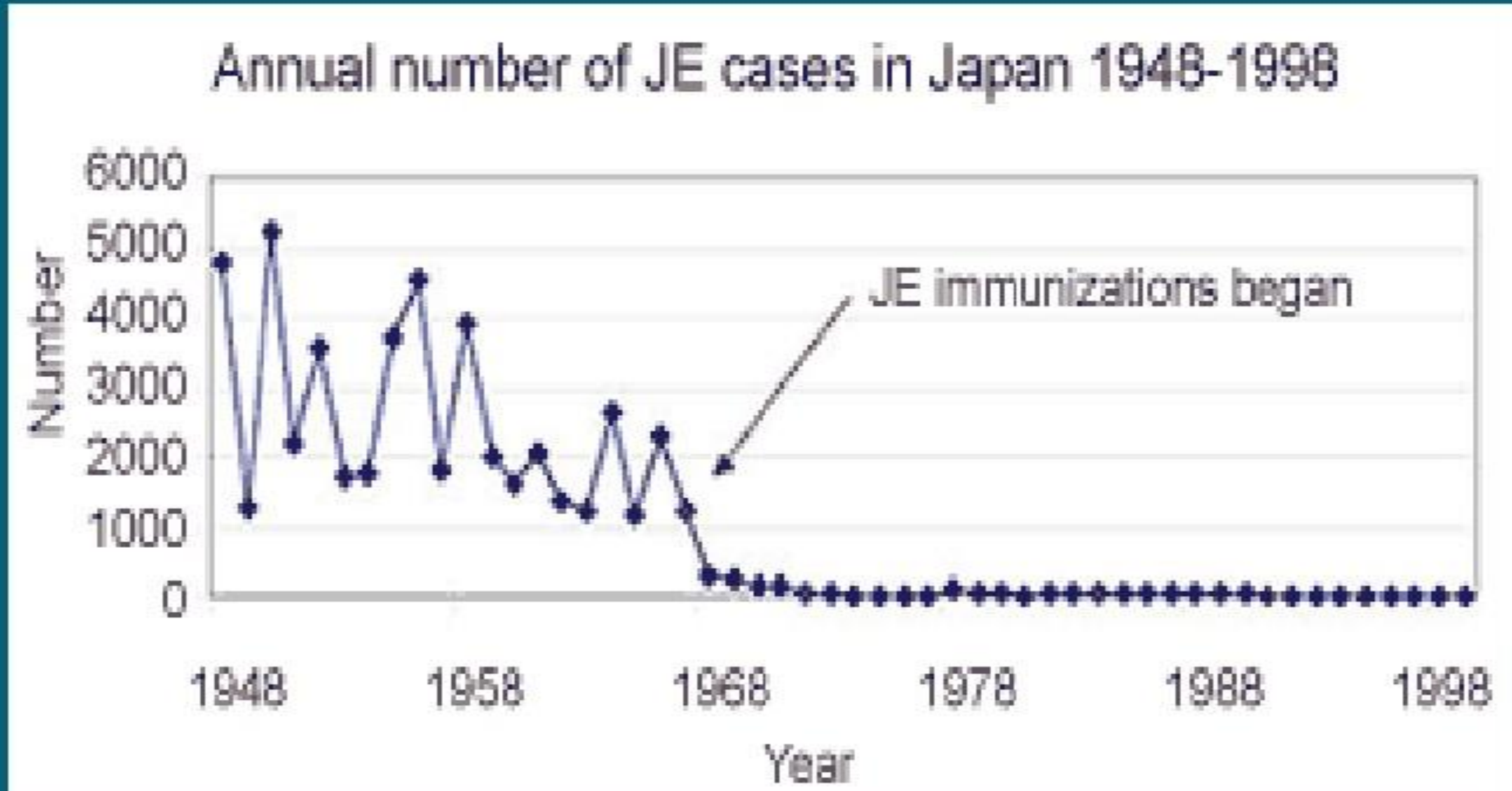
➢ VACCINATION OF HUMAN BEINGS:

- Currently 3 types of JE vaccines in large scale use are:

1. Mouse Brain-derived Purified & Inactivated Vaccine (Nakayama or Beijing strain of JE virus)

2. Cell Culture Derived Inactivated JE Vaccine (Beijing P-3 strain)

3. Cell Culture Derived, Live Attenuated Vaccine (SA 14 – 14 – 2 strain of JE virus)


Annual number of JE cases in Japan 1948-1998
Number
6000
5000
4000
3000
2000
1000
0
JE immunizations began
1948
1958
1968
1978
1988
1998
Year

C} AGRICULTURAL PRACTICES :

- water management practice of Paddy cultivation-

- At least one dry day every week will conserve water, reduce larval population increase rice grain yield, and reduce the emission of methane into the environment thereby reducing the Global warming effect. Using neem products as fertilizers will also reduce the mosquito population

D} Animal Reservoir:

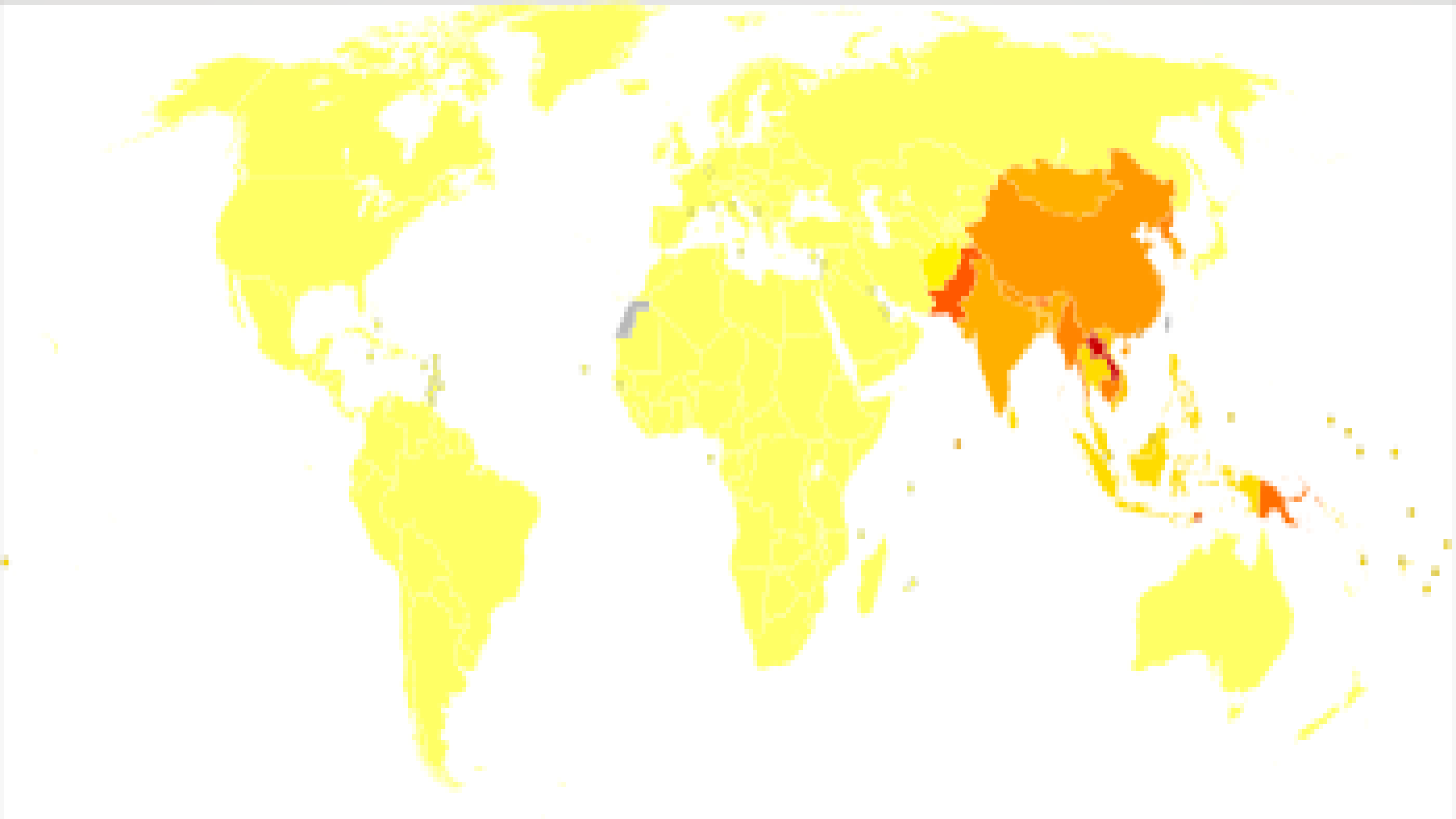
- JE was controlled in Japan by vaccinating the pig population. But this is unlikely to be possible in India since there is no centralized pig rearing. So all pig rearing practices should be undertaken at least 5 Kms away from human habitations and all measures to promote pig husbandry (Bank Loans) should be subject to this condition

JE – GLOBAL SCENARIO

- Major public health disease in Asia
- Virus first isolated in Japan in 1935
- As per WHO estimates 50 thousand serious cases and 10 thousand deaths each year
- Disease is prevalent in Indian Sub-continent, Nepal, India, Sri Lanka and some areas in Bangladesh

Global scenario contd..,

- Other SE Asian countries reporting cases include:
- Myanmar, Thailand, Cambodia, China
- Indonesia, Laos, Vietnam, Malaysia, Philippines, Taiwan,
- Hong Kong and
- Korea



Evolution

The virus appears to have originated from its ancestral virus in the mid-1500s in the Indonesia-Malaysia region and evolved there into five different genotypes and spread across Asia.The mean evolutionary rate has been estimated to be 4.35×10^{-4} (range: 3.4906×10^{-4} to 5.303×10^{-4}) nucleotide substitutions per site per year.

JE Vaccines : Today

Vaccine Type	Strain & Substrate	Producer	Licensure & distribution
Inactivated	Nakayama Mouse Brain	Biken (Japan); Green Cross (South Korea); CRI (India); Vabiotech (Vietnam); GPO (Thailand)	International Local& Region Local Local & India Local & Region
	Beijing 1 Mouse Brain	Kaketsuken; Biken; Kitasota (Japan)	Production stopped; Bulk storage
	P3 PHK or Vero	Multiple (China)	Domestic
Live, Attenuated	SA14-14-2 on PHK	Chengdu; Wuhan; Lanzhou (China)	China; India, Nepal, South Korea, Sri Lanka

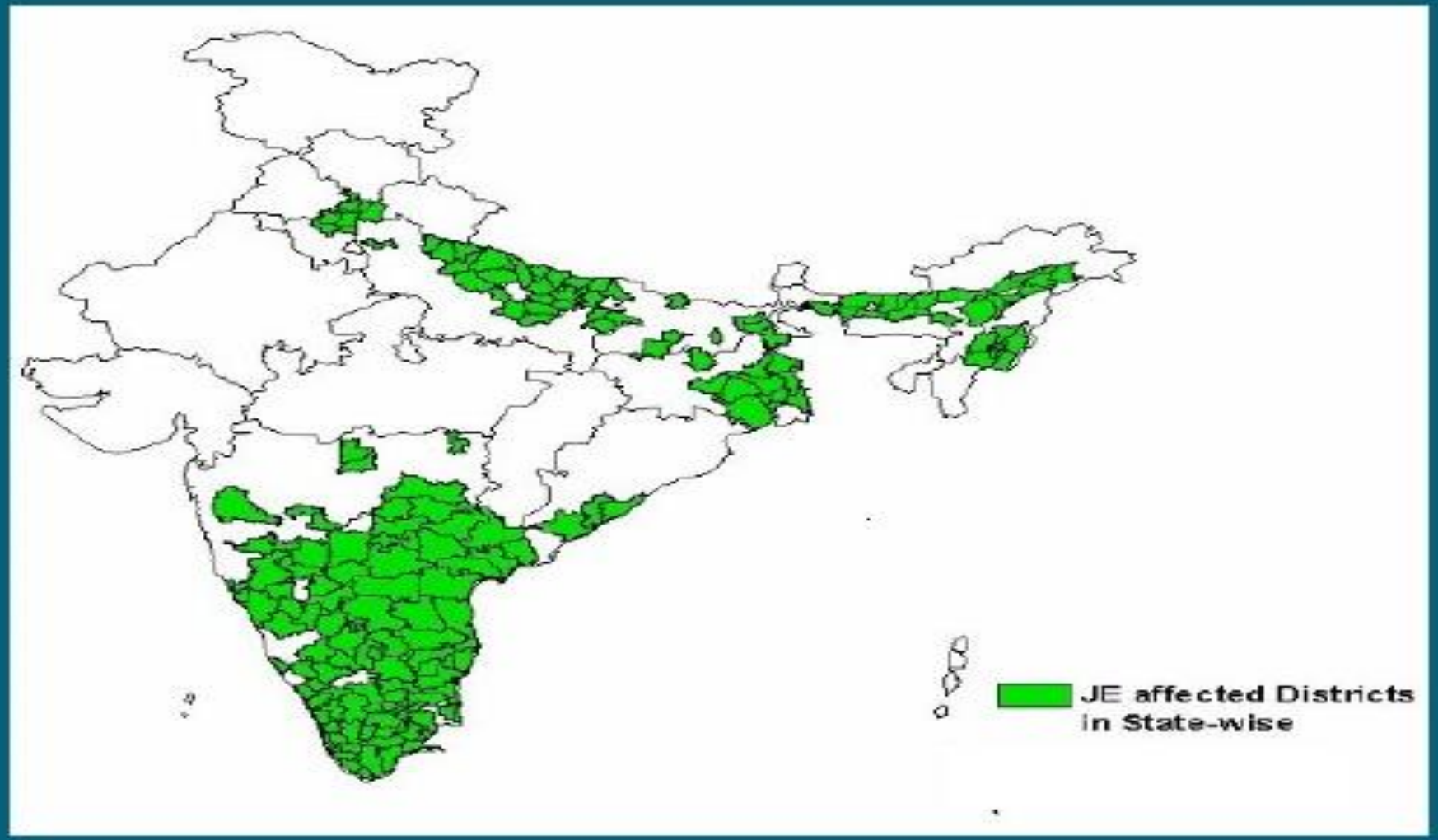
In Pipeline

Vaccine type and strain	Producer	Status	Commercial Strategy
Inactivated, Vero cell derived Beijing 1	Biken; Kaketsuken	Phase 3	Japan –pediatric ?International [Licensure: 2008]
Inactivated Vero Cell derived SA14-14-2 [IC51]	Intercell; Biological E	Pediatric (1-3 years in India) Phase 2	Traveler & Military Pediatric [2009]
Live , recombinant, Vero Cell derived SA14-14-2 pr M&E in 17 D YF backbone	Acambis; BBIL	Clinical (Ph2 in Adult; ph 2 pediatric initiated in India)	Traveler & Military Pediatric [2009]

JAPANESE ENCEPHALITIS IN INDIA

- 1952 - First evidence of JE viral activity by VRC (NIV) during sero-surveys for arbo-viruses.
- 1955 - First human case of JE.
- 1958 - First viral isolation from JE case.
- 1973 - First outbreak- Bankura and Burdwan in West Bengal.
- 1976 - Repeat outbreak in Burdwan.
- 1978 -Widespread occurrence of suspected JE cases.
  -National level monitoring initiated by NMEP in 1978.
  -Initiation of immunization using inactivated mouse brain vaccine

JE ENDEMIC AREAS IN INDIA

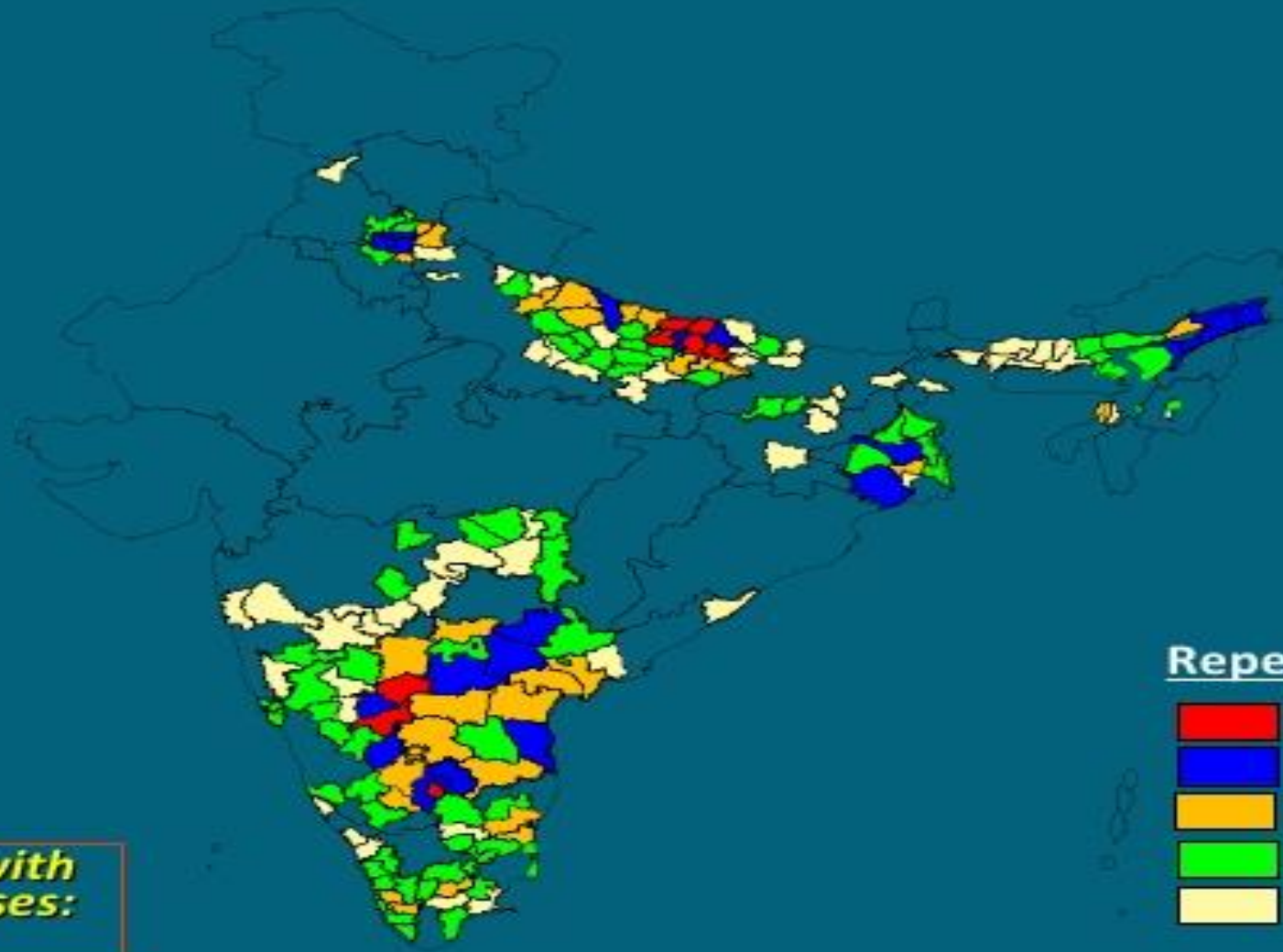


JE affected areas

- Andhra Pradesh
- Assam
- Bihar
- Haryana
- Kerala
- Karnataka
- Maharashtra
- Manipur
- Nagaland
- Tamil Nadu
- Uttar Pradesh
- West Bengal

Number of endemic districts: 135;
Population: 330 million

Frequency of Japanese Encephalitis episodes in India (1996-2007)



Repeat Occurrences

- 10 Times
- 8-9 Times
- 5-7 Times
- 2-4 Times
- 1 Time

No. of States with reported JE cases: 15

YEAR	TOTAL CASES (INDIA)	TOTAL DEATHS (INDIA)
2005	6,527	1,682
2006	2,832	658
2007(JULY)	391	92
	4,017 (WHO)	
2008	294 (WHO)	
2009	2,868 (U.P)	505

- ***FOR CLINICAL MANAGEMENT OF JAPANESE ENCEPHALITIS FOLLOWING DEFINITIONS ARE FOLLOWED BY:***

GOVT. OF INDIA,

DIRECTORATE OF NATIONAL VECTOR BORNE DISEASES CONTROL PROGRAMME, DELHI

Case Definition : Suspected case

. Acute onset of fever (≤ 7 days)

. change in mental status
With/ without

. New onset of seizures (excluding febrile seizures)

. (Other early clinical findings - may include irritability, somnolence or abnormal behaviour greater than that seen with usual febrile illness)

Probable Cases

Suspected case in close geographic and temporal relationship to a laboratory-confirmed case of JE in an outbreak

Acute Encephalitis Syndrome due to other agent

- *A suspected case in which diagnostic testing is performed and an etiological agent other than JE is identified*

Acute Encephalitis Syndrome due to unknown agent

- *A suspected case in which no diagnostic testing is performed / no etiological agent was identified / test results were indeterminate*

JE CASE CLASSIFICATION, NICD, NEW DELHI

- **SUSPECT:**
  A CASE THAT IS COMPATIBLE WITH THE CLINICAL DESCRIPTION

- **PROBABLE:**
  A SUSPECT CASE WITH PRESUMPTIVE LABORATORY RESULTS

- **CONFIRMED:**
  A SUSPECTED CASE THAT IS LABORATORY CONFIRMED

Economic Impact

1} Animals:

- Porcine
  - High mortality in piglets
- Equine
  - Up to 5% mortality rate

2} Humans:

- Medical cost for immunization and medical treatment

Public Health Significance :

- Vectors in U.S.
- Disease has spread in last 100 years
- Reservoirs: swine and birds
- Human mortality
- Animals deaths
  - —Lost income