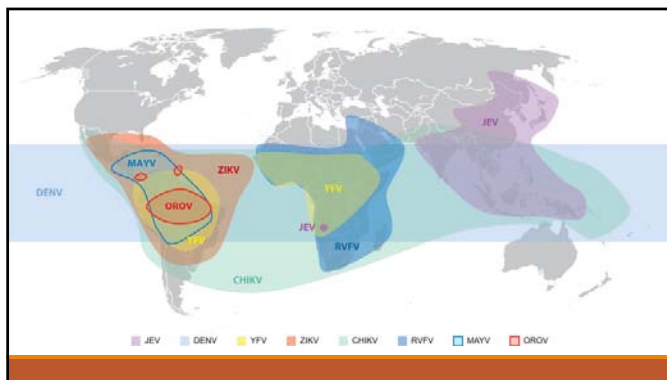
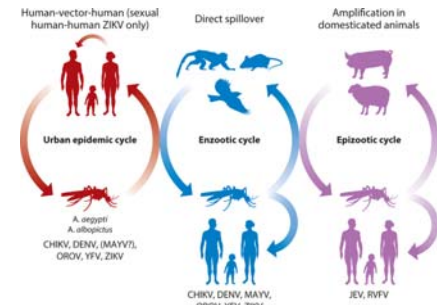


# Dengue and Other Arboviruses

พญ.พิมพ์พรรณ พิสุทธิศาล  
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โรงพยาบาลเวชศาสตร์เขตร้อน

**Flavivirus**  
-Yellow fever Virus  
-Dengue virus  
-Japanese encephalitis  
-West Nile virus  
-Zika virus  
**Togavirus**  
-Chikungunya  
**Bunyaviruses**  
**Nairovirus**  
**Phleboviruses**  
**Orbiviruses**  
**Vesicoviruses**  
**Thogotoviruses**  
**Asfavirus**

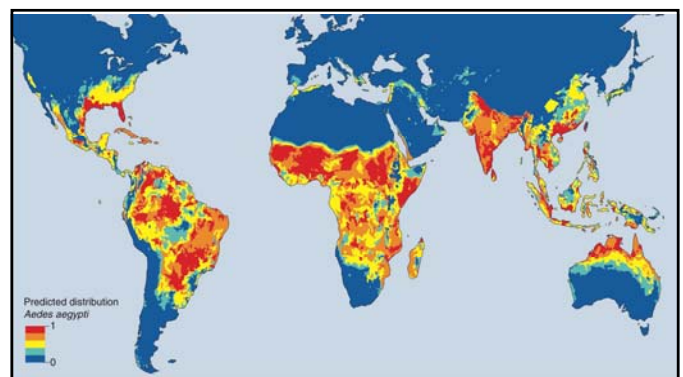


## Overview

- Dengue virus (DENV), Chikungunya virus (CHIKV), Zika virus (ZIKV), Yellow fever (YFV), Japanese Encephalitis (JEV)
- Mosquito-borne viruses
- Aedes aegypti* and *A. albopictus*
- Increased transmission
  - population growth, urbanization, globalization, travel, and climate change
- Extend into temperate areas => outbreaks in nonendemic regions

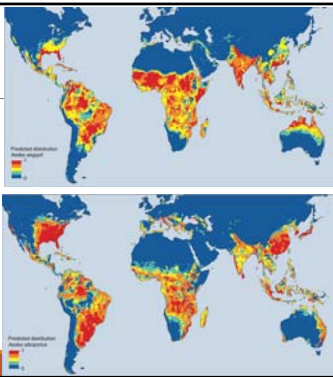
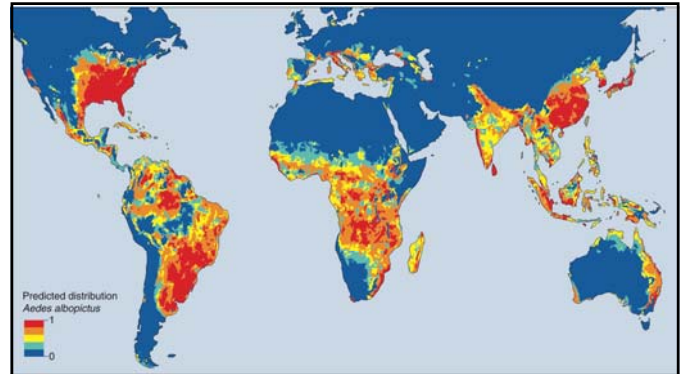
## *A. aegypti*

- Tropical, subtropical, and some temperate climates
- Daytime biters
- Preference for the morning and late afternoon hours
- Adapted to cohabit with humans both urban and rural environments
- Lay eggs in manmade or artificial containers
- In or around the home
- Can bite indoor



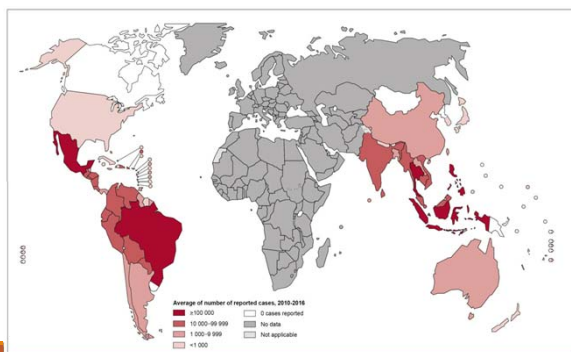
## *A. albopictus*

- Asian tiger mosquito
- Broader temp. range and cooler temp. than *A. aegypti*
- Wider geographic distribution
- Extending into temperate region
- Prefer natural habitat
- Usually bite outdoor
- Less efficient vector of human disease than *A. aegypti*



## Flavivirus

- Belong to Flaviviridae family
- Positive, single stranded, enveloped RNA virus
- Found in arthropods (ticks and mosquitoes), occasionally infect humans
  - Yellow fever, Dengue fever, Japanese encephalitis, West Nile Virus, Zika virus
- Mosquitoes-transmitted virus
- Tick-borne virus
  - Tick-borne Encephalitis (TBE), Kyasanur Forest Disease (KFD), Alkhurma disease, Omsk hemorrhagic fever



## Dengue virus

## Dengue virus

- Flavivirus
- Most common and most important arbovirus globally
- 400 million infections occur worldwide annually
- 70% of cases in Asia
- 4 serotypes (DENV 1-4)
- Immunity
  - lifelong serotype-specific protection
  - Short-lived cross-protection to other serotypes (6-12 months)

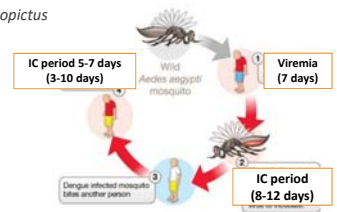
## Dengue Transmission

- Mosquitoes; *Aedes aegypti*, *Aedes albopictus*

- Bloodborne: Blood transfusion, Organ transplants

- Perinatal transmission

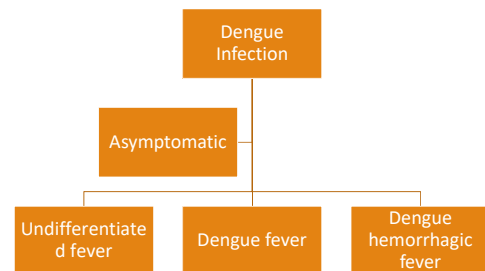
- Breast milk



## Clinical presentation

- Wide spectrum of clinical presentation (asymptomatic to severe and fatal disease)
- 75% asymptomatic
- Symptomatic: mild to moderate, nonspecific, acute febrile illness
- Severe dengue ~ 1-3%, case fatality rate <1%-5%

## Clinical manifestation



## Clinical presentation

- Fever, headache, retroorbital pain, muscle/joint/bone pain,
- Macular or MP rash
- Minor hemorrhagic manifestation (petechiae, ecchymosis, purpura, epistaxis, bleeding per gum, hematuria, tourniquet test positive)
- Plasma leakage ± bleeding, severe organ impairment => severe dengue

## Clinical presentation

### Febrile phase

- 2-7 days, biphasic
- Erythema, MP rash
- Tourniquet positive



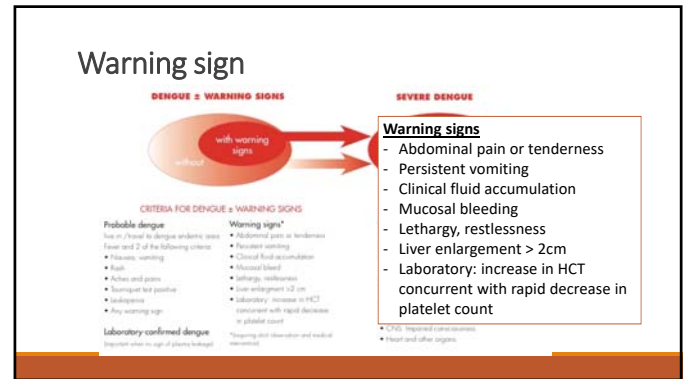
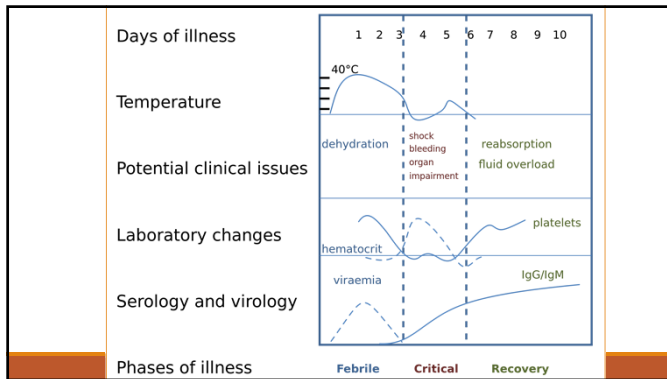
### Critical phase

- Plasma leakage 24-48 hr → hypovolemic shock

### Convalescent

- Confluent petechial rash





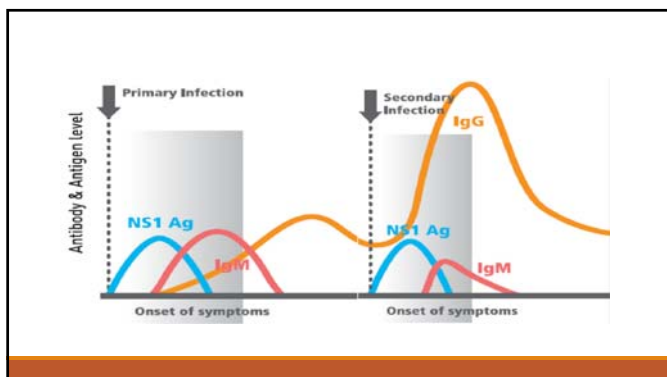
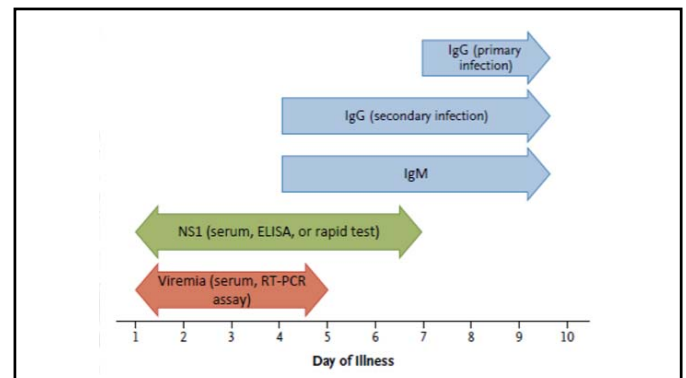
### เกณฑ์การวินิจฉัย

อาการทางคลินิก

- ใช้เชิบบพื้นและสูงลอย 2-7 วัน
- ภาวะเลือดออก โดยตรวจพบ tourniquet test ให้ผลบวก ร่วมกับอาการเลือดออกอื่น ๆ
- ตันโต มีกดเจ็บ
- มีการเปลี่ยนแปลงในระบบไหลเวียนโลหิต หรือมีภาวะช็อก

การตรวจทางห้องปฏิบัติการ

- จำนวนเกล็ดเลือดน้อยกว่า/เท่ากับ 100,000 ตั/ลบ.มม.
- เลือดข้นเกิน มากกว่า 20% (hemoconcentration) หรือมีหลักฐานการรั่วของพลาสมา เช่น มี pleural effusion หรือ ascites หรือมีโปรตีน/อัลบูมินเลือดต่ำ
- ตรวจพบมีเม็ดเลือดขาวต่ำ จำนวนนิวโทรฟิลต่ำ และตรวจพบ atypical lymphocyte



### Management of DENV infection

Does the patient have dengue or other illnesses?

Which phase of dengue (febrile/critical/recovery)?

- Date/onset of illness, time to defervescence, trending of Hct, WBC, Platelet count

What is the hydration state?

- Oral fluid intake/ diarrhea/vomiting/ urine output

Are dengue warning signs present?

- Yes → hospitalization for close monitoring

What is the hemodynamic state?

- Stable/compensated shock/hypotensive shock

What is the best medical plan for the patient?

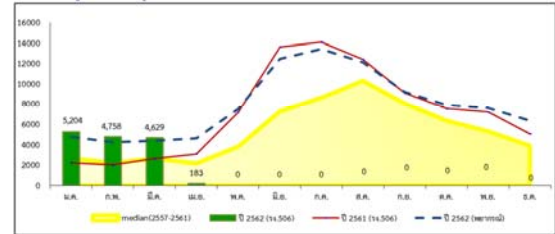
## สถานการณ์โรคไข้เลือดออกในประเทศไทย

	2562	2561	2560	2559	2558	2557
ป่วย (ราย)	14,774	6,565	7,881	14,825	8,295	5,449
ตาย (ราย)	19	9	11	12	5	3
อัตราป่วยต่อแสน	22.36	9.97	12.05	22.66	12.74	8.39
อัตราป่วยตาย(%)	0.13	0.14	0.14	0.08	0.06	0.06

สัปดาห์ที่ 13 มีรายงานผู้ป่วยเพิ่มขึ้นจากสัปดาห์ที่ผ่านมา 1,097 ราย  
ณ ช่วงเวลาเดียวกัน ปี 2562 มีรายงานผู้ป่วยมากกว่าปี 2561 : 2.3 เท่า

สำนักงานป้องกันโรคเขตร้อน กรมควบคุมโรค ข้อมูล ณ วันที่ 10 เมษายน 2562

แผนภูมิที่ 1 จำนวนผู้ป่วยโรคไข้เลือดออกสะสมจำแนกรายเดือน ปี 2562



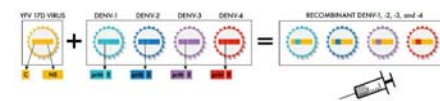
สำนักงานป้องกันโรคเขตร้อน กรมควบคุมโรค ข้อมูล ณ วันที่ 10 เมษายน 2562

ตารางที่ 4 อัตราป่วยสะสมในช่วง 4 สัปดาห์ที่ผ่านมา ตั้งแต่ 3 - 30 มีนาคม 2562 (สัปดาห์ที่ 9 - 12) พบจังหวัดที่มีอัตราป่วยสูงสุด 10 อันดับแรก ดังนี้

อันดับ	จังหวัด	จำนวนป่วย (ราย)	อัตราป่วย (ต่อประชากรแสนคน)
1	สตูล	125	16.51
2	เพชรบุรี	73	15.16
3	สมุทรสาคร	78	13.86
4	อุบลราชธานี	225	12.06
5	ราชบุรี	104	11.94
6	นครปฐม	104	11.45
7	ศรีสะเกษ	165	11.22
8	นครราชสีมา	287	10.89
9	บุรีรัมย์	85	10.72
10	ระยอง	75	10.63

สำนักงานป้องกันโรคเขตร้อน กรมควบคุมโรค ข้อมูล ณ วันที่ 10 เมษายน 2562

## Dengue vaccine: Chimeric Yellow fever 17D-Tetravalent Dengue Vaccine (CYD-TDV)



- 4 live-attenuated recombinant viruses serotypes 1-4
- 3 injections of 0.5 mL administered at 0, 6, 12 months
- The indication in individuals 9-45 years or 9-60 years of age, living in dengue endemic areas

## Dengue vaccine: Vaccine Efficacy and Safety



## For each Serotype

DENV-1: 58.4% (95% CI: 47.7 - 66.9)  
DENV-2: 47.1% (95% CI: 31.3 - 59.2)  
DENV-3: 73.6% (95% CI: 64.4 - 80.4)  
DENV-4: 83.2% (95% CI: 76.2 - 88.2)

By dengue serostatus (by PRNT<sub>50</sub>)

Seropositive: 81.9% (95% CI: 67.2 - 90.0)  
Seronegative: 52.5% (95% CI: 5.9-76.1)

## Dengue vaccine

Sanofi updates information on dengue vaccine

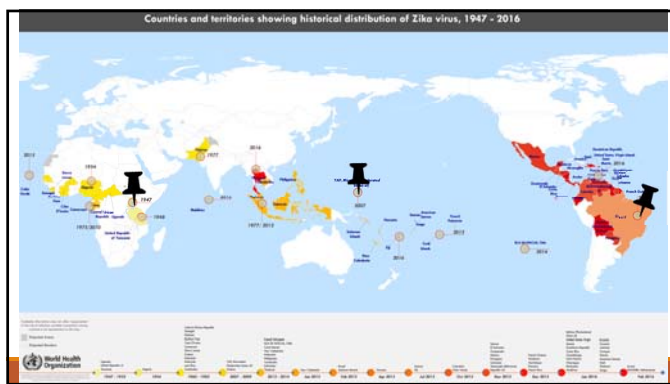
Based on up to six years of clinical data, the new analysis evaluated long-term safety and efficacy of Dengvaxia in people who had been infected with dengue prior to vaccination and those who had not. The analysis confirmed that Dengvaxia provides persistent protective benefit against dengue fever in those who had prior infection. For those not previously infected by dengue virus, however, the analysis found that in the longer term, more cases of severe disease could occur following vaccination upon a subsequent dengue infection.

The analysis also found that Dengvaxia was safe and effective in people who had been infected with dengue prior to vaccination and those who had not. The analysis confirmed that Dengvaxia provides persistent protective benefit against dengue fever in those who had prior infection. For those not previously infected by dengue virus, however, the analysis found that in the longer term, more cases of severe disease could occur following vaccination upon a subsequent dengue infection.

Preferred vaccine to only previously dengue infected individuals



## Zika virus

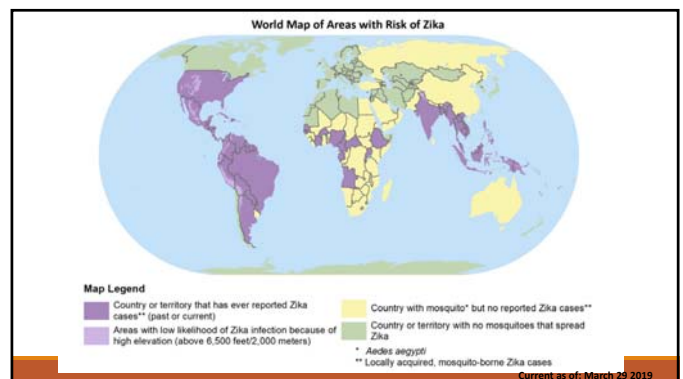


## Zika virus

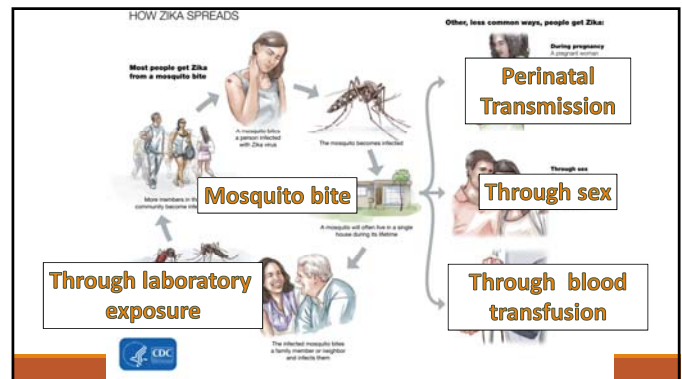
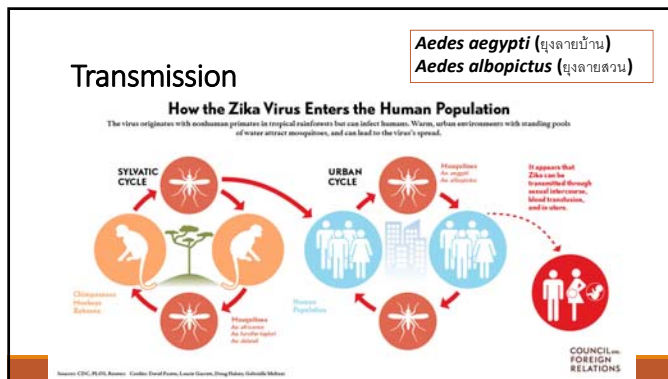
- Flavivirus, 1<sup>st</sup> isolated in 1947
- Rhesus monkey in the Zika Forest of Uganda
- First human cases detected in Uganda and Tanzania in 1952
- Only 14 cases reported until 2007
- Explosive outbreak infected ~3/4 of the population of Yap, Federated States of Micronesia

## Zika virus

- A single-stranded **RNA virus** in family **Flaviviridae**
- Classified into distinct **African and Asian lineages**
  - Both : From East Africa during the late 1800s or early 1900s
  - The Asian lineage : during the virus's migration from Africa to SEA





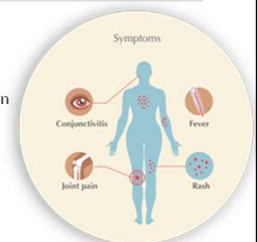


## Clinical Manifestations

- Incubation period : typically 2-14 days
- 80% of cases = asymptomatic**
- Symptoms = typically mild, self-limiting, non specific
- Symptoms resolve within 2 weeks

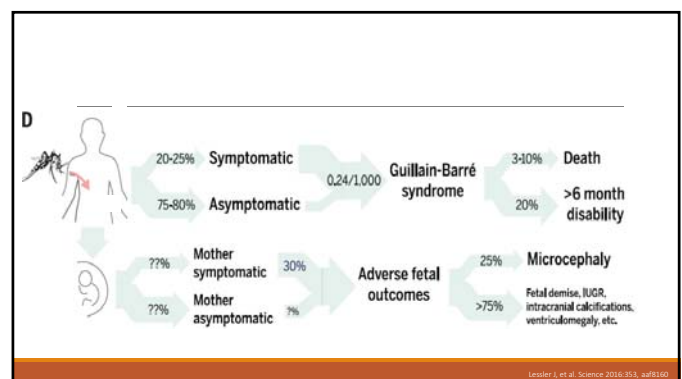
## Clinical Manifestations

- Fever** : low grade (37.4 -38 C)
- Rash** : MP and pruritic, begins proximally and spreads to extremities with spontaneous resolution within 1-4 days of onset
- Joint pain**
- Conjunctivitis**



## Clinical Manifestations

- Neurological complications
  - Guillain-Barré syndrome (GBS), Meningoencephalitis, Myelitis
- Adverse fetal outcome
  - Microcephaly, Congenital Zika syndrome



## Microcephaly

- In 2015, the number of infants born with microcephaly increased in Brazil, after a suspected Zika virus outbreak
- Transplacental transmission and cause congenital malformations.



## Zika virus infection in pregnancy

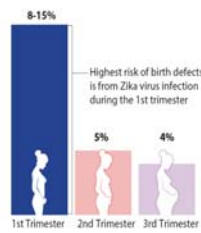
### Zika and Microcephaly

- Baby's head is smaller than expected, often with smaller brain

### Congenital Zika syndrome

- Severe microcephaly in which the skull has partially collapsed
- Decrease brain tissue with a specific pattern of brain damage (Subcortical calcifications)
- Damage to the back of the eye (macular scarring and focal pigmentary retinal mottling)
- Joints with limited range of motion, such as clubfoot
- Hypertonia restricting body movement soon after birth

### Zika in Early Pregnancy Increases Risk of Birth Defects



### Symptoms *Not* Associated With Increased Risk of Birth Defects



## Diagnosis of Zika virus infection

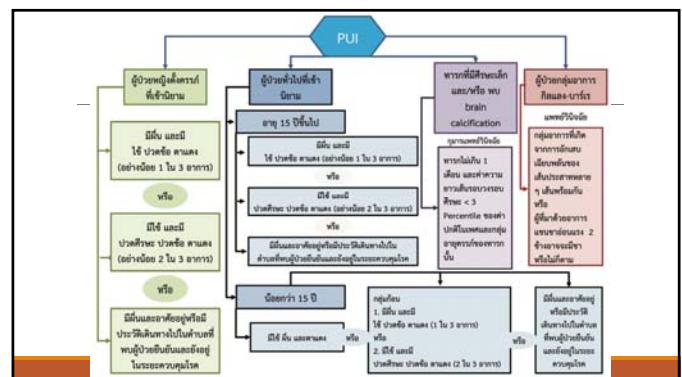
### Detection of viral nucleic acid by RT-PCR

- Can be detected in serum at mean time of 3-5 days after illness
- Can be detected in serum ~ 10 weeks after infection in a pregnant woman whose fetus had congenital infection

### Detection of IgM antibodies by IgM-capture enzyme-linked immunosorbent assay (MAC-ELISA)

- Serum should be collected after 7 days
- Plaque-reduction neutralization (PRNT) is the gold standard for anti-flavivirus antibody differentiation
- Problem of cross reactivity with other flaviviruses

- ผู้ป่วยทั่วไป
- หญิงตั้งครรภ์
- พสกนิกรที่มีความผิดปกติที่ศีรษะเล็ก
- กลุ่มอาการ Guillain-Barre Syndrome และ ผู้ป่วยระบบประสาทอักเสบอื่น ๆ



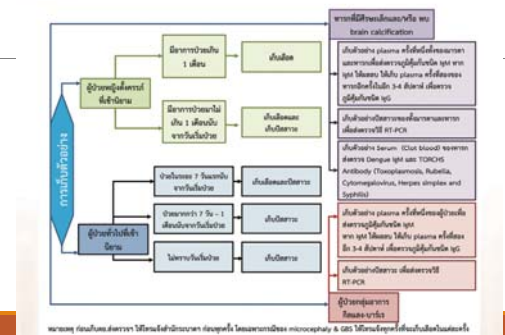


## Diagnosis

### การวินิจฉัยโรคไข้ซิกา

- วินิจฉัยจากประวัติ และอาการของผู้ป่วย
- วินิจฉัยทางห้องปฏิบัติการ: เก็บตัวอย่างเลือด ปัสสาวะและสารคัดหลั่ง เช่น น้ำลาย
- การเก็บตัวอย่างในผู้ป่วยสงสัย
  - ภายใน 5 วัน นับจากวันเริ่มป่วย เก็บ serum, ปัสสาวะ ส่งตรวจโดยวิธี Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)
  - ช่วงระยะ 5-14 วัน นับจากวันเริ่มป่วย ให้เก็บปัสสาวะเพื่อส่งตรวจหาเชื้อซิกาโดยวิธี RT-PCR
- การเก็บตัวอย่างในทารกแรกเกิด
  - ทารกที่มีความผิดปกติศีรษะเล็ก เก็บ serum ทั้งก่อนมารดาและทารกเพื่อตรวจหาภูมิคุ้มกัน (IgM)

แผนภูมิที่ 2.2 แนวทางการเก็บตัวอย่างส่งตรวจทางห้องปฏิบัติการส่วนกลาง สำหรับการวินิจฉัยโรคติดเชื้อไวรัสซิกา



## Persistent of Zika virus

Semen

Sexual transmission

Serum of non-pregnant person

Serum of pregnant woman

Whole blood of a non-pregnant person

## Additional Consideration

**Men** (whether symptomatic or not) should wait at **least 3 months** after symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic) before unprotected sex

**Women** (whether symptomatic or not) should wait at **least 2 months** after symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic) before unprotected sex

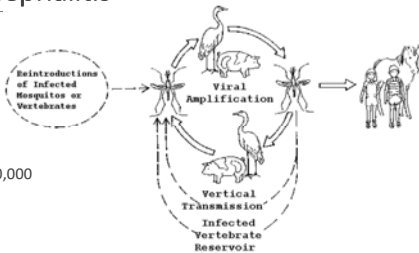
## Treatment

- Symptomatic treatment
- Counselling

## Japanese encephalitis

## Japanese Encephalitis

- Single-stranded RNA virus
- Genus **Flavivirus**
- Reservoir: Pig, horse, cow, buffalo, bird
- Transmission: *Culex* spp.
- Burden: 5-50 cases per 100,000 children per year



## High burden of Japanese Encephalitis

### Disease is present only in Asia

- More than 60,000 cases/ year in 24 endemic countries
- Overall incidence of 1.8 per 100,000

### 25%-30% cases are fatal

- Up to 15,000 deaths reported annually
- 75% of cases in Children aged 0-14 years

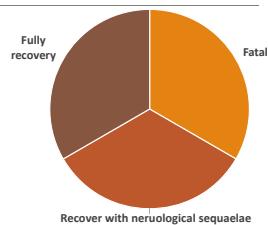
### Leading cause of childhood encephalitis in Asia

- Sequelae are present in more than 30% of cases.



## Clinical Manifestation

- Incubation period: 5-15 days
- Asymptomatic (most human) → <1% developed clinical disease
- Mild symptoms – fever, diarrhea, headache, Nausea, vomit, fatigue
- Encephalitis (1 in 300-500)
- 1/3 – Fatal
- 1/3 – Neurological sequelae
- 1/3 - Recovery



## How important of single case of JE encephalitis ?

1 case of JE encephalitis

=

500-1000 cases of JE infection

1 case of JE encephalitis

=

outbreak of JE infection

Chokephaibulkit K. Pediatr Infect Dis J 2001;20:216-8



- Endemic countrywide
- Seasonal epidemics in the northern provinces
- Year-round with peak season **May-October**
- 80% seroprevalence in Thai adult aged 31-60 years

## Study of Encephalitis in Children: Siriraj 1996-8

Etiologies (Dx method)	No. (N=44)
• Dengue (clinical, PCR, sero)	8 (18%)
• HSV (clinical, CSF-PCR)	8 (18%)
• JE (sero)	6 (14%)
• HHV-6 (CSF-PCR)	3 (7%)
• Mumps (parotitis+sero)	2 (5%)
• Enterovirus (CSF-PCR), Rabies (autopsy), VZV (rash)	1 each
• Unknown	14 (32%)

Chokephaibulkit K. Pediatr Infect Dis J 2001;20:216-8



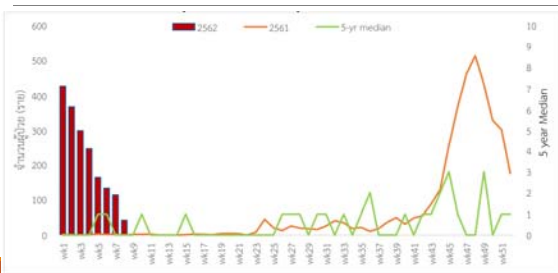
## Chikungunya

- Mosquito-borne **alphavirus**, 1st isolated in Tanzania
- Chikungunya = **Bent posture** → seen with severe arthralgia
- In Africa, CHIKV exists in an enzootic sylvatic transmission cycle
  - Between nonhuman primates, small mammals, and *Aedes* mosquitoes
- Introduction of CHIKV into Asia in 1950s
- Outbreak in India and Southeast Asia

Countries and territories where chikungunya cases have been reported\*  
(as of May 29, 2018)



## สถานการณ์โรคไข้วัดชื่อยุกลาย (5 มีนาคม 2562)



## Clinical presentation

- Incubation period 2-7 days (range 3-12 days)
- Most chikungunya infection are **symptomatic**, > 85%
- **Rapid onset of severe arthralgia**
- Associated with myalgia, high fever, generalized lymphadenopathy and conjunctivitis
- Generalized maculopapular rash about half of patients
- Fully recover in few weeks
- 5-10% experience chronic joint symptoms including pain, stiffness and swelling

## Diagnosis

- Clinical diagnosis
- CBC – leukocytosis, normal platelets level
- Virus can be detect in serum in the first 3-4 days
  - PCR method
  - Culture
- Serology test

## Chikungunya VS Zika VS Dengue

Parameters	Chikungunya	Zika	Dengue
Genus	Alphavirus	Flavivirus	Flavivirus
Ratio of symp/asym	8.5/10	1/5-1/6	1/4-1/9
Headache	+	+	+++
Arthralgia	+++	+	+/-
Myalgia	++	+	+++
Conjunctivitis	++	+++	-
Fever	++	+	+++
Maculopapular rash	++	+++	+
Neutropenia	+	-	++
Lymphopenia	+++	-	++
Thrombocytopenia	+/-	+/-	+++
Shock syndrome	-	-	+++
Edema of extremities	-	++	-

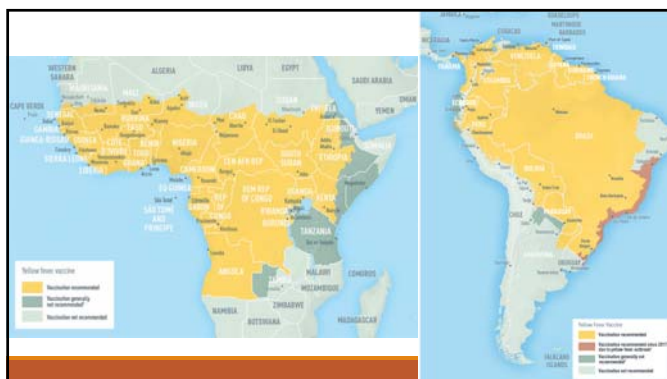
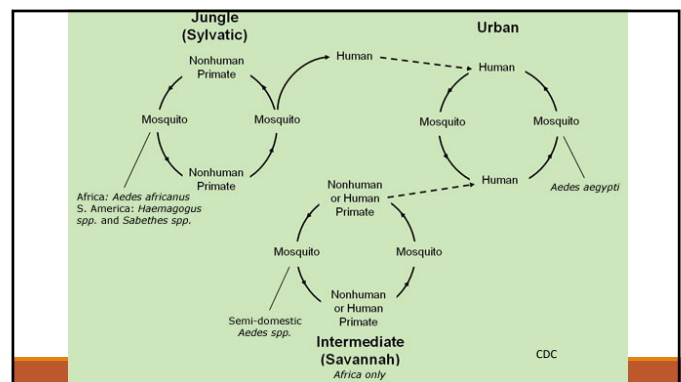
# Yellow fever

## Yellow fever (YF)

- Acute viral hemorrhagic disease
- First account of sickness diagnosed as YF occurred in 1648
- In 1881, Carlos Juan Finlay, a physician in Havana, first proposed that yellow fever was a mosquito-borne illness
- Walter Reed, U.S. Army doctor Discovered the cause of Yellow Fever August 27, 1900

## Yellow fever

- Acute viral hemorrhagic disease
- A single-stranded RNA virus in the genus *Flavivirus*
- **Vector:** *Aedes* spp., *Haemagogus* spp.
- Reservoirs: Human and nonhuman primates
- **Blood borne transmission:** Blood transfusion, needle sticks injury, perinatal transmission



## Epidemiology

- **Risk group**
  - Africa: infants and children
  - South America: unimmunized young men
- **Risk in travelers:** For a 2-week stay, risk for illness and death for an unvaccinated travellers visiting an endemic area in
  - West Africa: 50 per 100,000 and 10 per 100,000
  - South America: 5 per 100,000 and 1 per 100,000
- **Incubation period:**
  - Intrinsic IP: 3 to 6 Days
  - Extrinsic IP: 1 to 2 weeks
- **Period of communicability:** First 3-5 days of illness (due to high level of viremia)

## Clinical presentation

Mostly asymptomatic

### Period of infection

- Nonspecific influenza-like syndrome with sudden onset of fever, chills, headache, backache, myalgia, nausea and vomiting

### Period of remission

- Improve after initial presentation with brief remission of hours to a day

### Period of intoxication

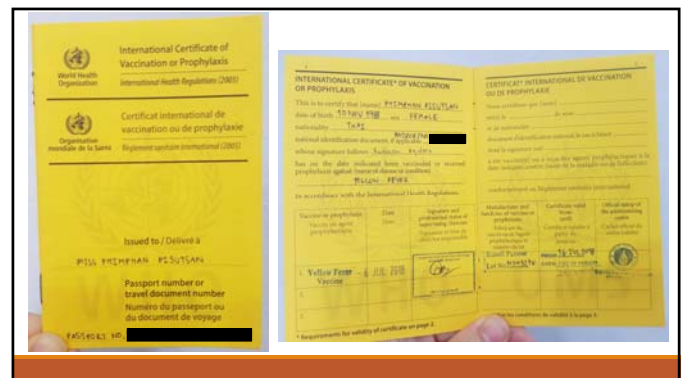
- 15% of patients progress to a more serious or toxic form of the disease (jaundice, haemorrhage, shock, multiorgan failure)
- 20-50% dead within 7-10 days

## Treatment

- No specific medication
- Symptomatic relief or life-saving intervention
- Should be protected from further mosquito exposure during the first few days of illness

## Prevention

- Personal protection measures: Avoid mosquito bites
- Vaccine
  - Safe and effective vaccine
  - 1 single dose, life-long protection
  - Live-attenuated vaccine



### Thai Travel Clinic

Hospital for Tropical Diseases  
Faculty of Tropical Medicine, Mahidol University



[www.thaitravelclinic.com](http://www.thaitravelclinic.com)

Thank you