Fever in Travelers Returning from Brazil

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Rio2016
RIO 2016

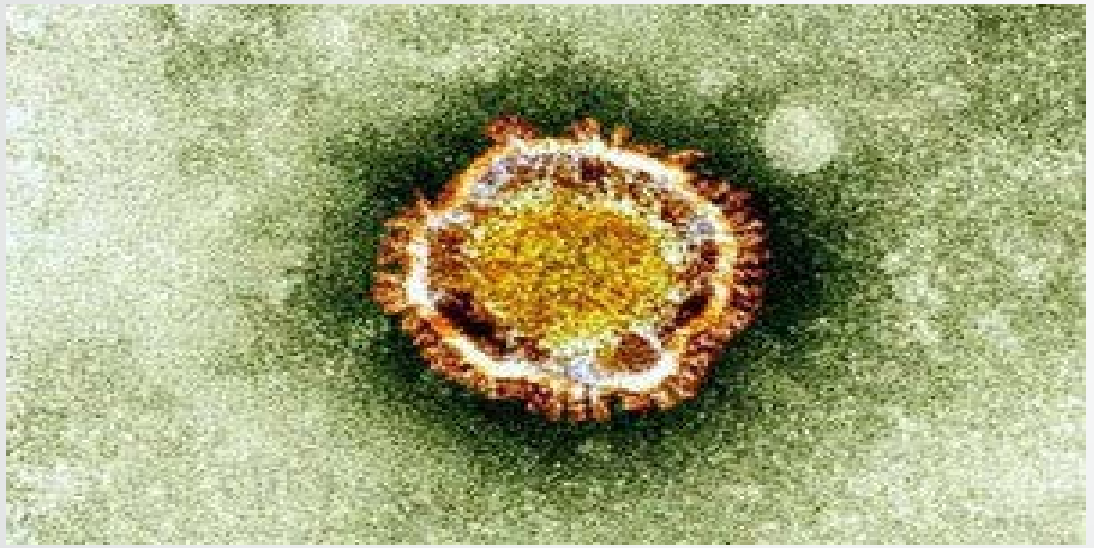

秘鲁
利马
Lima
巴西
玻利维亚
巴拉圭
智利
亚松森
Asuncion
里约热内卢
Rio de Janeiro
萨尔瓦多
Salvador
Fortale
阿克雷州
朗多尼亚州
马托格罗索
托坎廷斯
戈亚斯州
巴伊亚州
米纳斯吉拉斯
南马托格罗索州
圣保罗州
柏拉拿州
圣卡塔琳娜州
南里奥格兰德州
科尔多瓦

Case

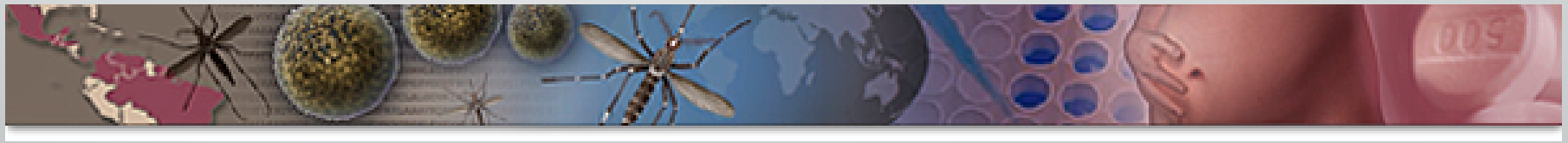
- F/25 GPH
- Olympic athlete, back to HK for 1 week
- Fever, headache, myalgia for 1 day
- Mosquito sting+ near the Olympic Village
- No GI symptoms
- DDx??

Arboviruses

- Arboviruses = **A**rthopod-**B**ourne Viruses
- Zika
- Dengue
- Yellow fever
- Chikungunya



Zika virus

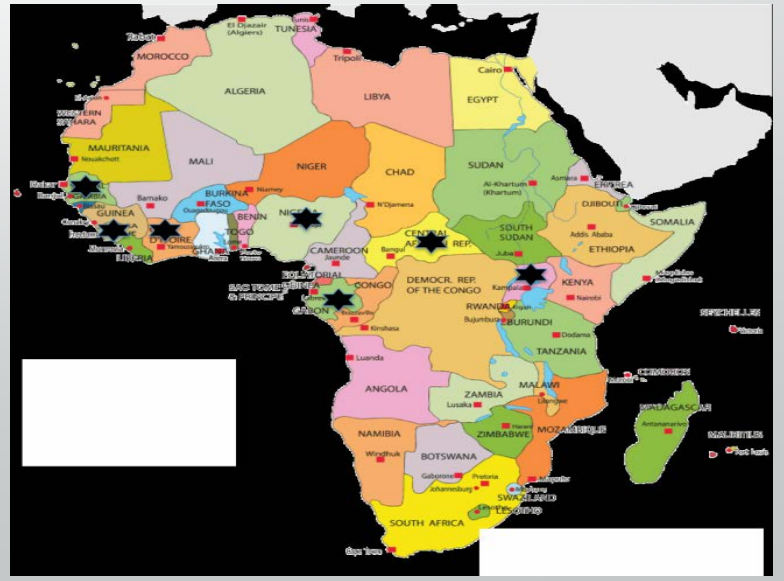


Zika Virus (ZIKV)

- Zika virus is an RNA virus of the Flaviviridae family
- Genetically close to Yellow fever, dengue, West Nile, and Japanese encephalitis viruses
- Mosquito-borne disease transmitted by the Aedes mosquitoes, particularly Aedes Aegypti

History of Zika virus: Africa

- 1939: West Nile discovered in Uganda
- **1947**: First ZIKV isolation from Rhesus monkey in **Zika forest** near Lake Victoria in Uganda
- 1948: isolated in same forest from mosquitos
- 1969-1970: Uganda
- 1971-1975: Nigeria
- 1972: Sierra Leone
- 1975: Gabon
- 1979: Central African Republic
- 1988-1991; 2011-2012: Senegal
- 1999: Cote d'Ivoire



History of the Zika virus: Asia

- 1977-78: Pakistan, Malaysia, Indonesia
- 2007: First large outbreak at Yap Island, Micronesia
  - 49 confirmed cases
  - 73% of residents >3 yrs had antibodies to ZIKV
  - Aedes hensilli as the predominant mosquito
- 2010: Cambodia
- 2013-14: French Polynesia, population: 270,000
  - 5895 suspected cases

To date

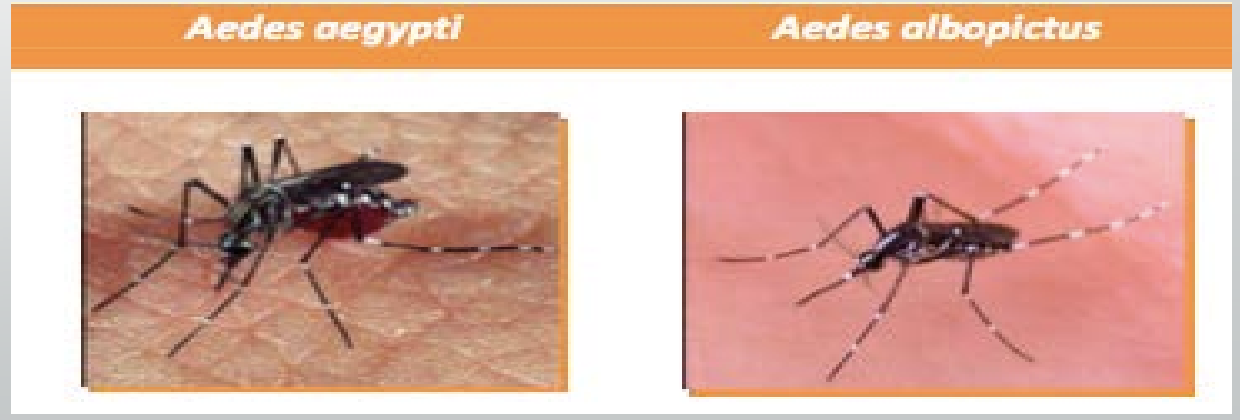
- 67 countries/ areas have documented mosquito-borne Zika virus transmission since 2007
- 11 countries reported evidence of person-to-person transmission probably by sexual contact

- Outbreak in Brazil is ongoing
- As of July 28, 2016, a total of 165932 suspected and 66180 confirmed cases of Zika virus infection
- Rio de Janeriro ranked third in Brazil in the incidence rate of Zira infection
- 4 deaths (at least one from Rio de Janeiiro) since May 2015

Vectors

- Aedes mosquitoes
  - A. aegypti, A. albopictus
- 2-10mm long
- Flies and feed in daytime , peaking during early morning and late afternoon/evening
- Both active in indoor and outdoor
- Short flying range <200m

- Larval development can occur in <30ml of water
- Attracted by CO_2 and organic substance produced by host
- Sensitive, requiring multiple bites for a full blood meal



Clinical presentations of ZIKV

- Incubation period is not clear, but likely to be a few days
- Transmitted by mosquito bite and possible sexual transmission
- Self-limited febrile illness
- Maculopapular rash
- Arthralgia
- Non purulent conjunctivitis or conjunctival hyperemia
- Myalgia, headache, malaise
- Less commonly: retro-orbital pain, anorexia, vomiting, diarrhea and abdominal pain

Neurological Complications

- Guillain-Barre syndrome (GBS)
  - Case-control study provided evidence of Zika Virus infection causing GBS in French Polynesia
  - Acute motor axonal neuropathy *(Lancet 2016;387:1531-39)*
- Meningitis, meningoencephalitiis, myelitis

- **Microcephaly**
  - Studies investigating Zika outbreak in French Polynesia 2013-2014,
    - estimated that the risk of microcephaly due to ZIKV infection in the first trimester of pregnancy was 0.95%
  - In Northeast Brazil, reported an unusual increase in the number of cases since October 2015
    - Presence of Zika virus genome in the amniotic fluid of pregnant women
    - Presence of virus in tissue specimens and blood samples of a dead newborn with microcephaly
    - Strong association between the risk of microcephaly and infection risk in the first trimester

Management and prevention

- Statutory notifiable disease since 5 February 2016
- Supportive treatment
- Wear loose, light colored, long sleeved tops and trousers
- DEET-containing insect repellent on exposed parts of body and clothing
- Pregnant women should consider deferring their trip to areas with past or current evidence of ongoing zika virus transmission

Special note

- Travellers returned from affected areas should apply insect repellent for 14 days after arrival to Hong Kong
- If a female partner is at risk of getting pregnant, or is already pregnant, condom use is for a male traveller
  - For 28 days after his return from an active Zika transmission area if he had no symptoms of unexplained fever and rash
  - For 6 months following recovery if a clinical illness compatible with Zika virus infection or laboratory confirmed infection

Blood donation after returning from Brazil

- Hong Kong Red Cross Blood Transfusion Service has particular screening policy
- Blood donors are deferred from donation for 28 days upon departure from affected areas

Dengue Fever

Dengue fever

- Positive-strand RNA dengue viruses (DENV)
  - 4 Serotypes (DENV-1-4); Flavivirus
- Transmitted by Aedes mosquitoes
- Endemic throughout the tropic and subtropics
- Estimated annual 70- 500 million infections

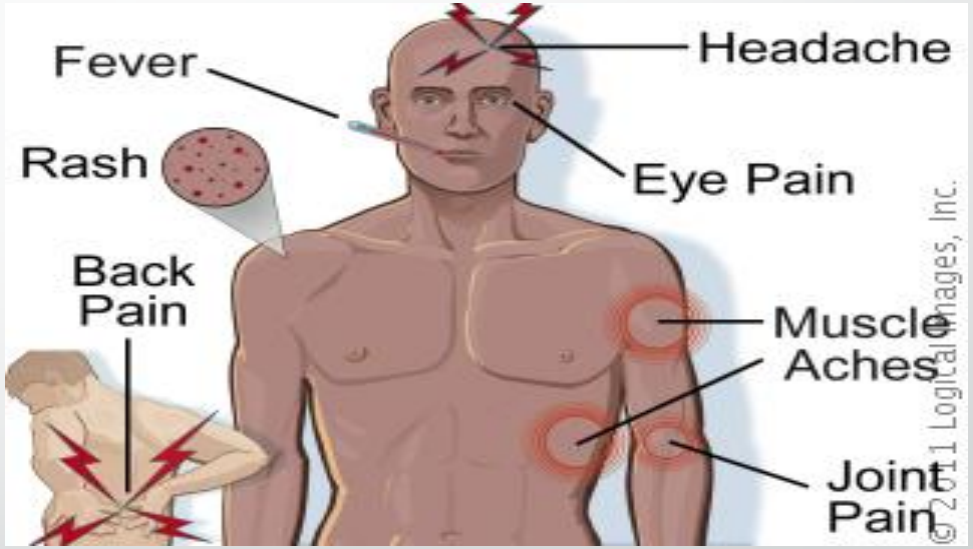
Dengue fever in Brazil

- Up to 15 July 2016, a total of 1,244,583 probable cases of DENV was made in Brazil
- 214,032 laboratory confirmed cases
- Involving all DEN1,2,3,4
- 455 classified as severe dengue, with 288 deaths

Data from WHO

Clinical features of acute dengue

- Incubation period 4-7 days (range 3-14 days)
- Fever
- Anorexia and nausea
- Rash (acute macular erythematous
- Aches and pains (retro-orbital pain in adults)
- Thrombocytopenia and leucopenia

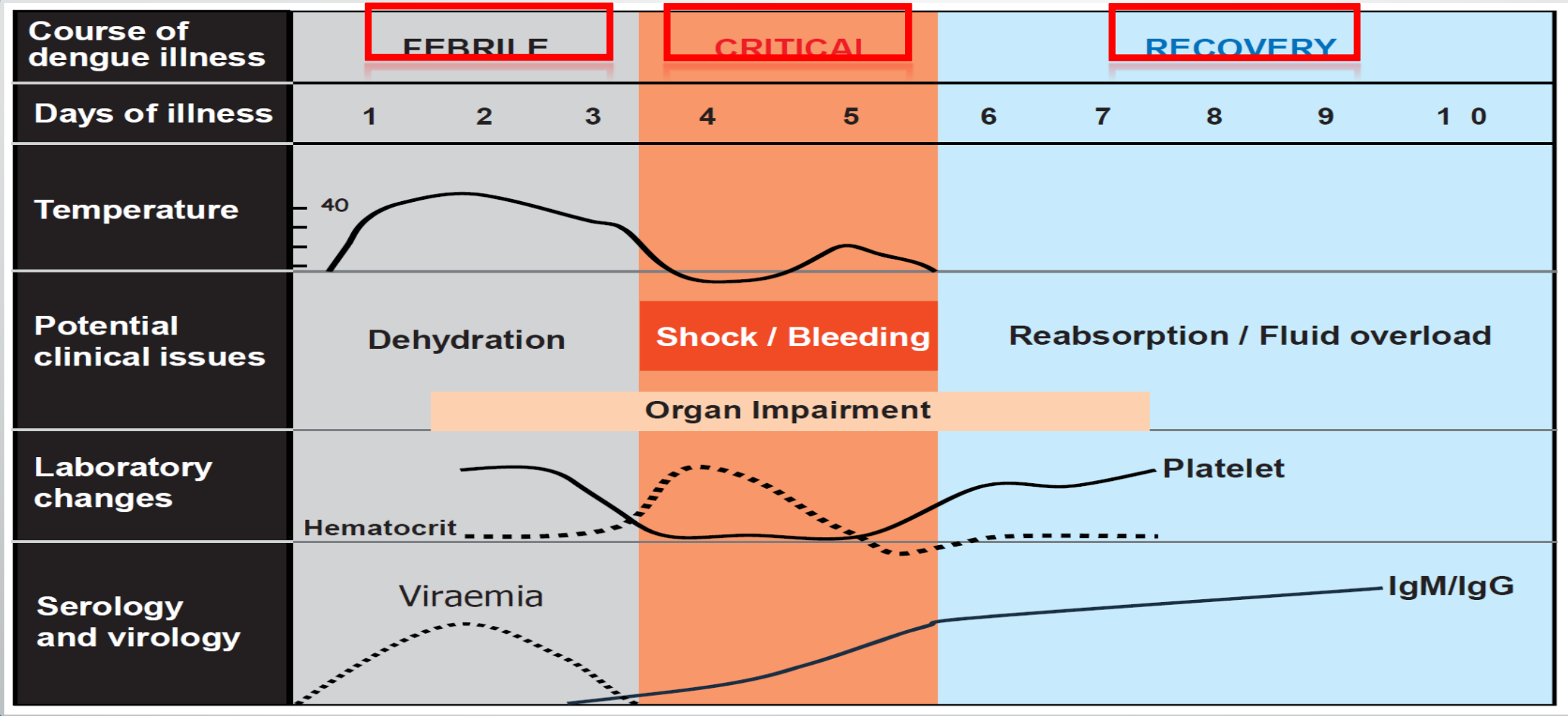


Clinical features of severe dengue

- **Intravascular volume depletion secondary to increased systemic vascular permeability**
  - **Low albumin, rise in hemotocrit >20%**
  - **Pleural effusion, ascites**
  - **Shock**
- **A variety of haemorrhagic manifestations due to the combined effects of**
  - **Thrombocytopenia**
  - **Deranged haemostasis**
- **Severe organ impairment**
  - **Secondary or idiosyncratic**

Clinical photos from Dengue fever patients

Clinical course

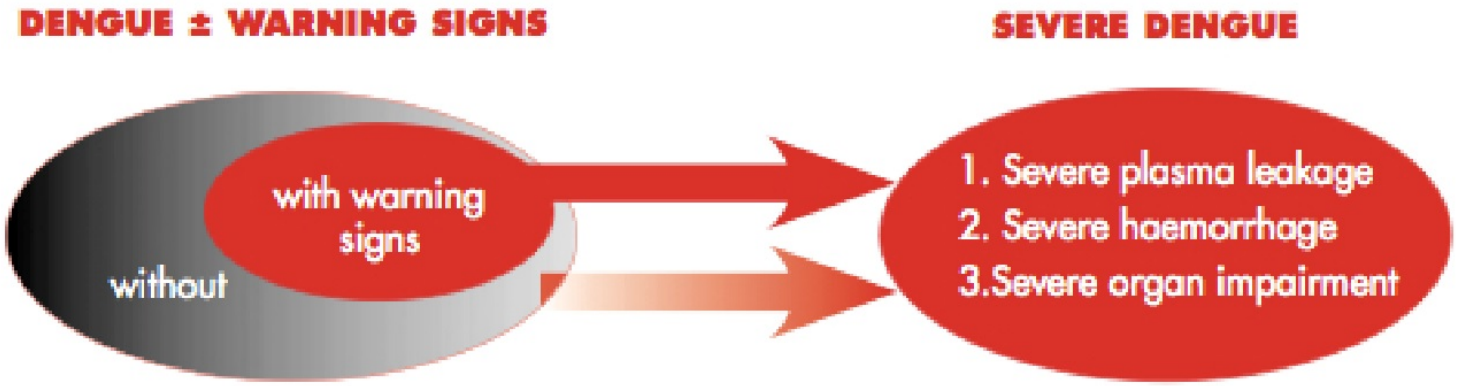


WHO 2012 Handbook for clinical management of dengue

Clinical Pearls

- **Leucopenia** followed by progressive **thrombocytopenia** is suggestive of dengue infection in endemic areas
- **Atypical lymphocyte** is common in dengue infection
- A rising **HCT** accompanying **progressive thrombocytopenia** is critical phase
- Evidence of **increased vascular permeability**: pleural effusions, ascites

Figure 1.4 Suggested dengue case classification and levels of severity



CRITERIA FOR DENGUE ± WARNING SIGNS

Probable dengue

live in /travel to dengue endemic area.

Fever and 2 of the following criteria:

- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leukopenia
- Any warning sign

Laboratory-confirmed dengue

(important when no sign of plasma leakage)

Warning signs*

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargment >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)

CRITERIA FOR SEVERE DENGUE

Severe plasma leakage

leading to:

- Shock (DSS)
- Fluid accumulation with respiratory distress

Severe bleeding

as evaluated by clinician

Severe organ involvement

- Liver: AST or ALT >=1000
- CNS: Impaired consciousness
- Heart and other organs

Diagnosis and treatment

- Acute phase serum specimen for Dengue PCR (within 5 days after fever onset)
- Dengue IgM by ELISA (>=4 days after fever onset)
- Treatment
  - No specific antiviral agents
  - Avoid anticoagulant agents
  - Symptomatic Rx
  - Supportive Rx for severe dengue infection

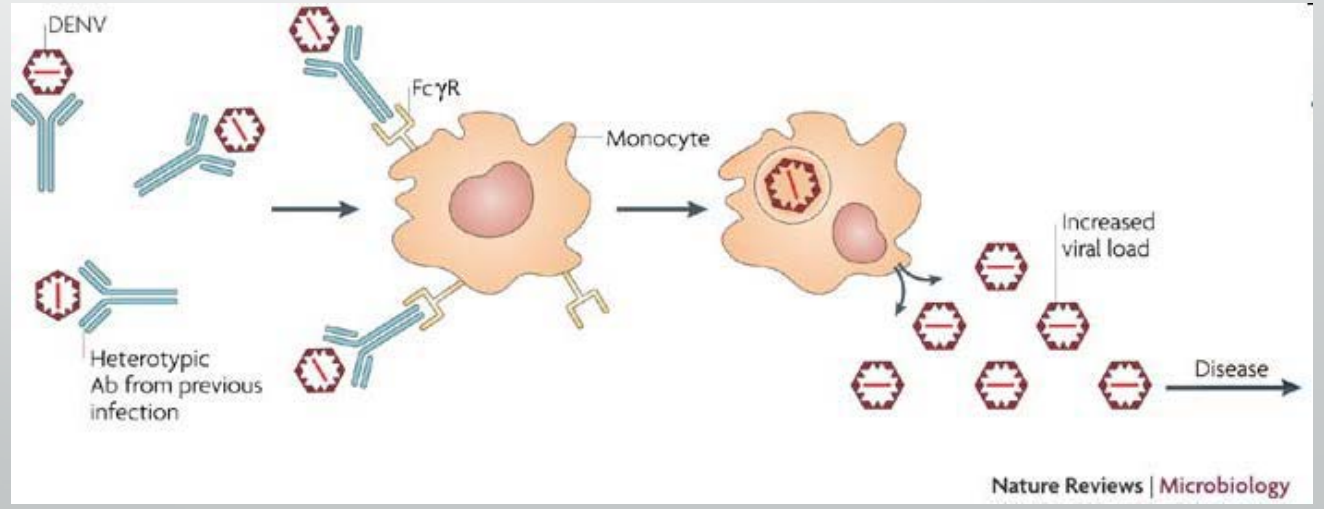
Why do some patients develop severe dengue and others do not?

Secondary infection with a heterologous serotype

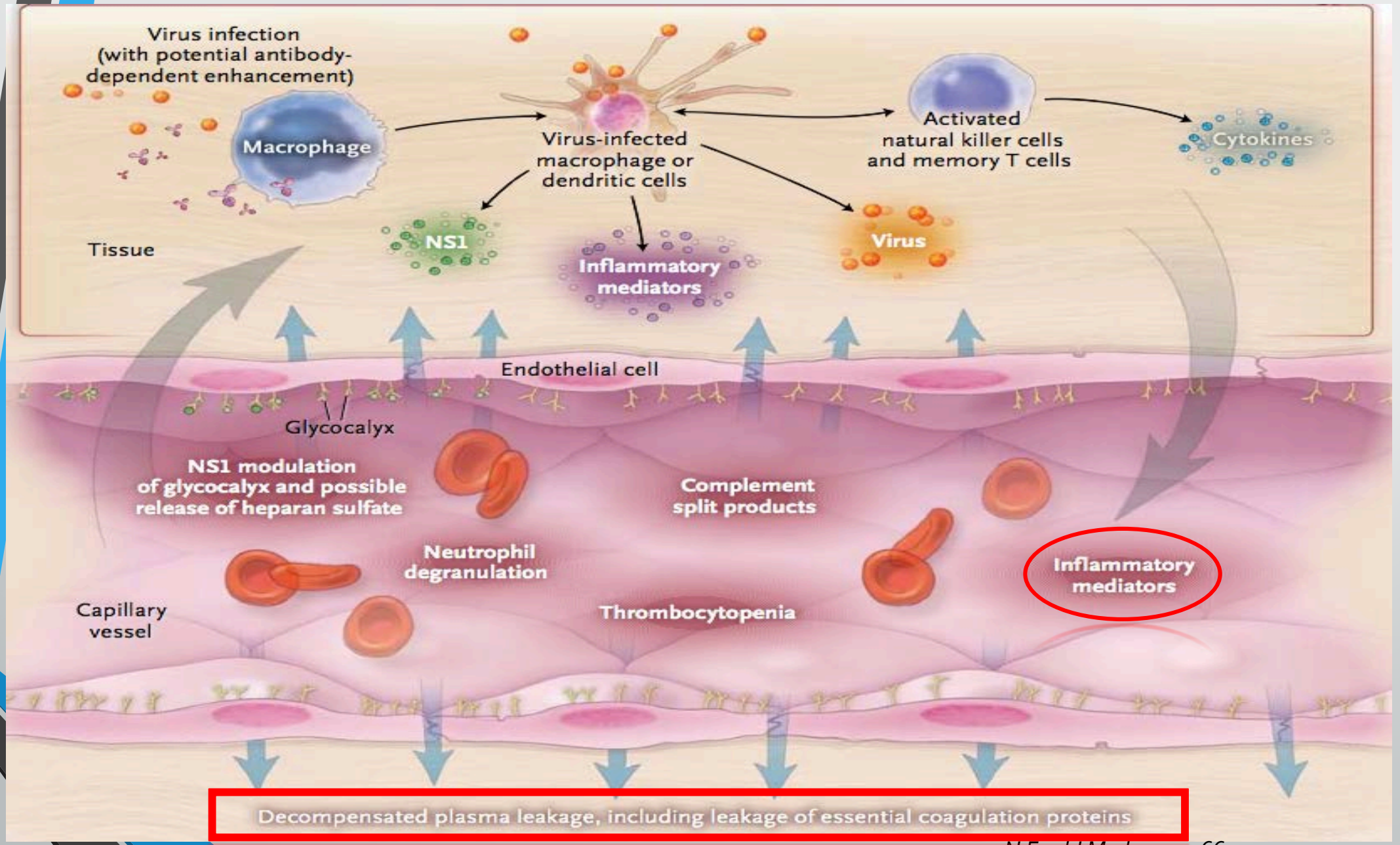
- Studies in Thailand, Cuba have shown that individuals with pre-existing antibody to a different DENV serotype are at higher risk of developing severe dengue than those with first infection
- Proposed mechanism: *ANTIBODY-DEPENDENT ENHANCEMENT*

Antibody dependent enhancement (ADE)

- Pre-existing antibodies bind to heterologous serotype but fail to neutralise it. Can occur in:
  - Secondary infection
  - Primary infection in infants born to immune mothers
- Results in altered cellular tropism and higher virus burden



DHF pathogenesis



N Engl J Med 2012;366:1423-32.

Vaccines for Dengue virus

Dengue	
Acambis and Sanofi Pasteur	Live, attenuated chimeric dengue–yellow fever
WRAIR and GlaxoSmithKline	Live, attenuated
NIH, Biologicals E (India), Panacea (India)	Live, attenuated chimeric dengue–dengue
Mahidol University (Bangkok)	Live, attenuated
CDC, Inviragen, Shantha (India)	Live, attenuated chimeric dengue–dengue
Hawaii Biotech	Recombinant, subunit
U.S. Navy	DNA

N Engl J Med 2007;357:2222

Efficacy of Recombinant live-attenuated tetravalent Dengue vaccines

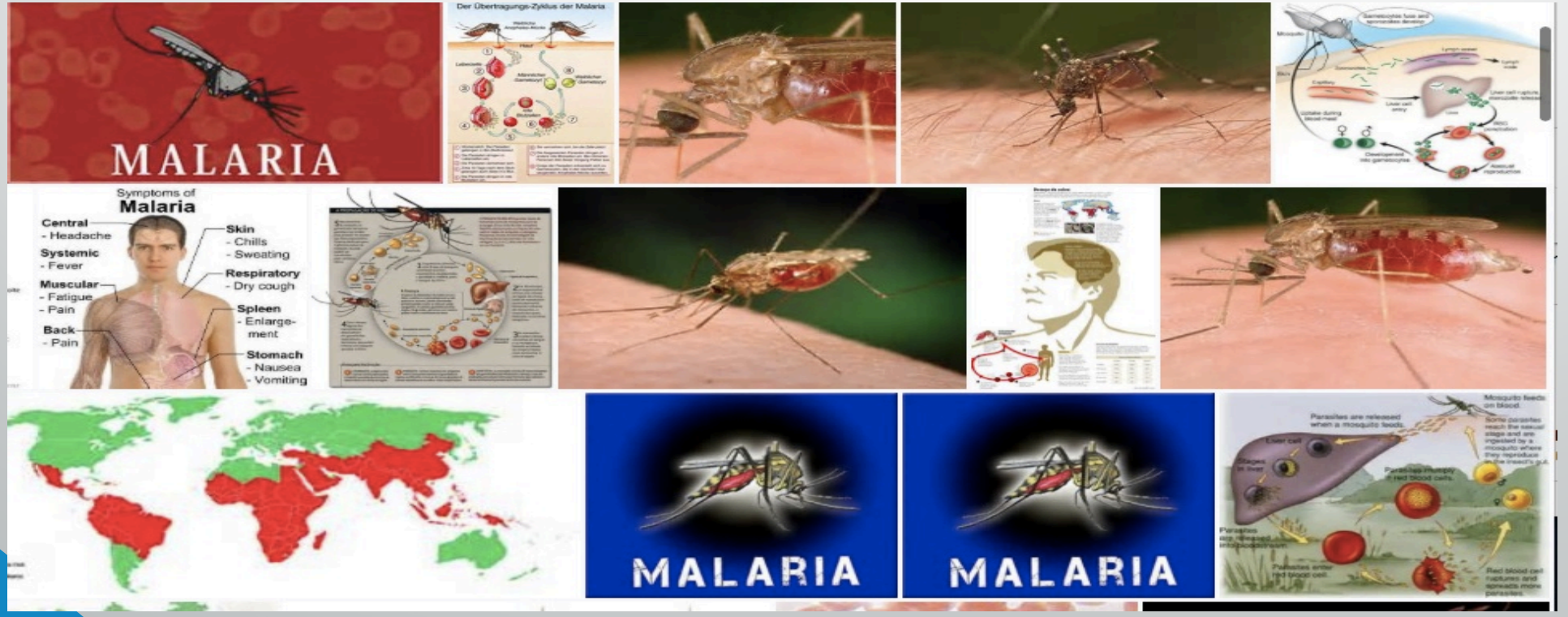
Year	Phase	Setting	Cases	Dose	FU	Efficacy
2012	2b	Thailand	4002 cases, 4-11 yo	Injection at 0, 6 & 12 m	25m	**Overall: 30.2%** DEN-1: 55.6% DEN-2: 9.2% DEN-3: 75.3% DEN-4: 100%
2014	3 (CYD14)	5 Asian countries (Indonesia, Malaysia, Philippines, Thailand and Vietnam)	10275 cases, 2-14 yo	Injection at 0, 6 & 12 m	25m	**Overall: 56.5%** DEN-1: 50.2% DEN-2: 34.7% DEN-3: 65.2% DEN-4: 72.4% **Vs DHF: 80%** **Vs severe disease: 70%**
2014	3 (CYD15)	5 Latin American countries (Brazil, Colombia, Honduras, Mexico, Puerto Rico)	20869 cases, 9-16 yo	Injection at 0, 6 & 12 m	25m	**Overall: 60.8%** DEN-1: 50.3% DEN-2: 42.3% DEN-3: 74% DEN-4: 77.7% **Vs severe disease: 95.5%** **Vs admission: 80.3%**

Licensure and Introduction of CYD-TDV vaccine, *Dengvaxia*™

(as of 4 April 2016)

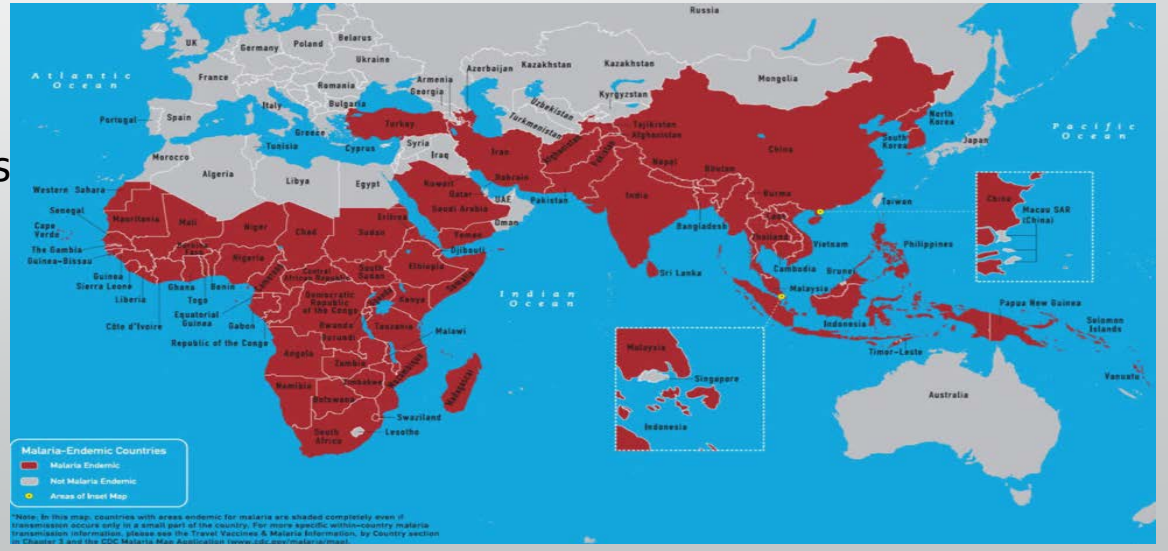
- **Licensed** by 5 countries
  - 4 in Latin America (Mexico, Brazil, El Salvador, Paraguay)
  - 1 in Asia (Philippines)
- **Schedule** 3-doses – 0/6/12 month intervals
- **Indication** varies
  - 9-45 years in 4 countries
  - 9-60 years in 1 country (Paraguay)
- **Vaccine introduction** in one country (Philippines)
  - Routine, school-based program targeting 4th grade children (9-10 year olds) in highly endemic regions (~1,000,000 children)

Malaria infection

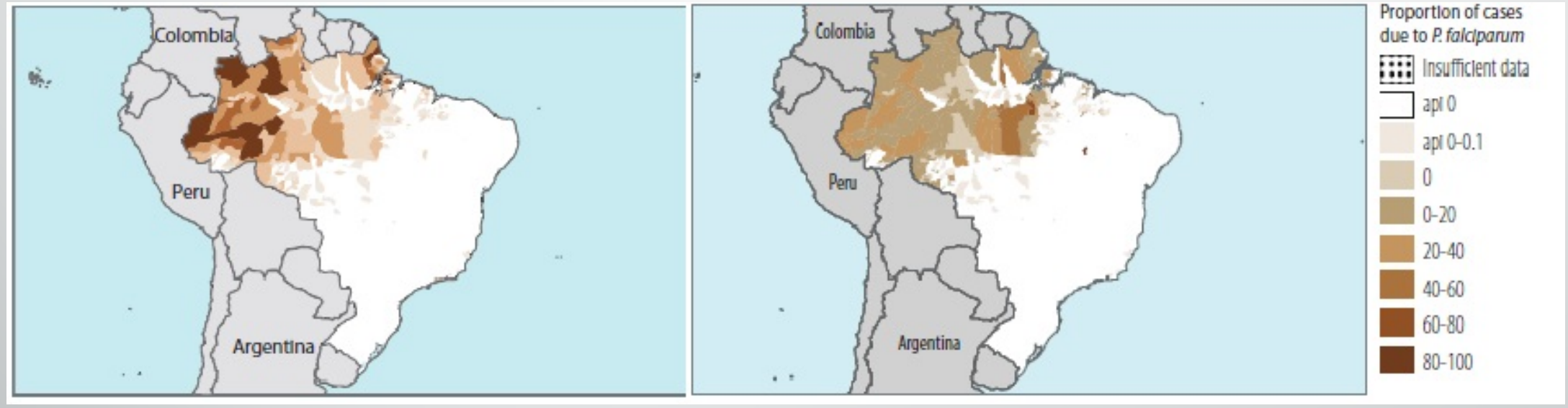


Malaria

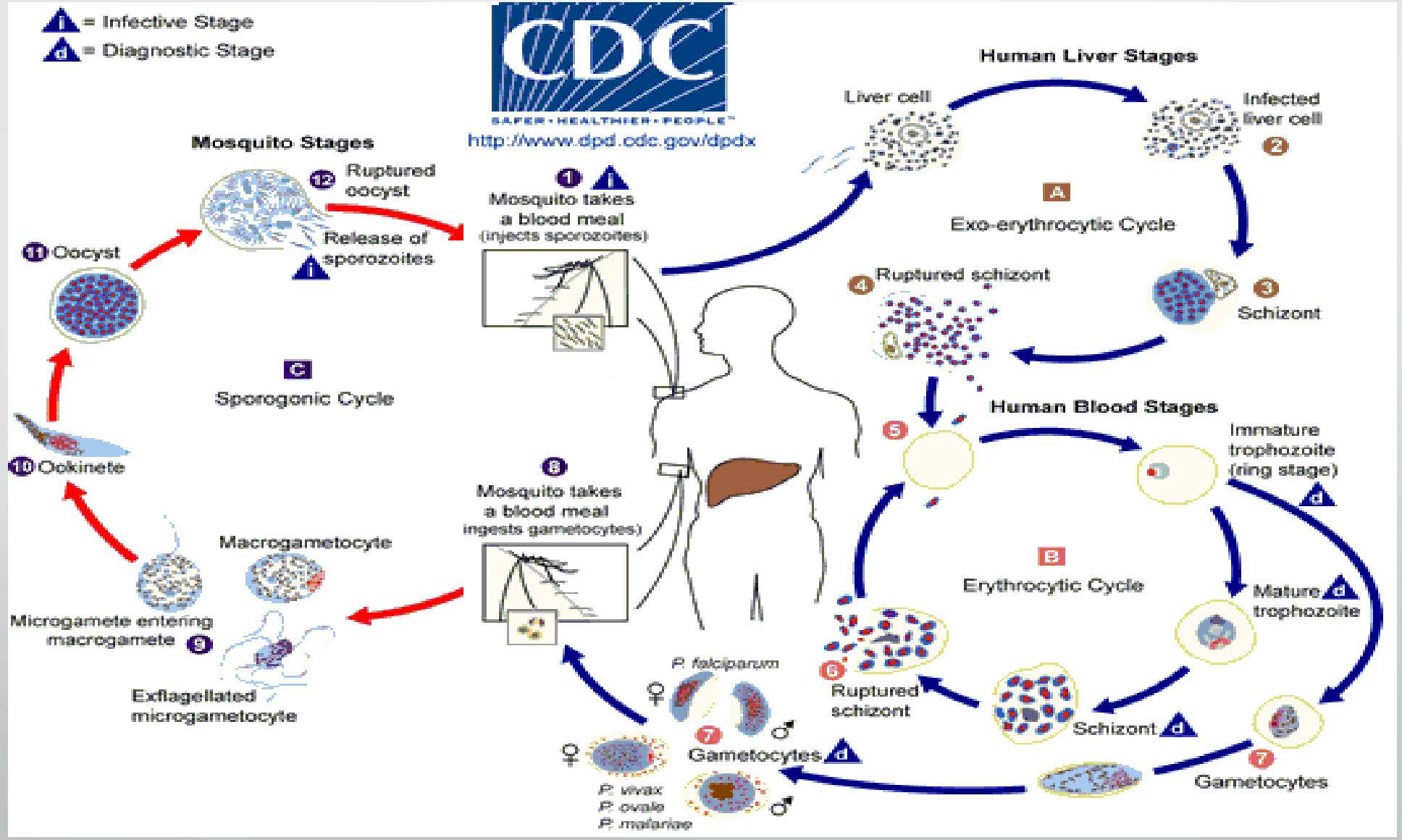
- Estimated 215 million infections worldwide and 655000 deaths annually
- Large areas of Africa, Central and South America, parts of Caribbean, Asia, South Pacific
- Transmitted by bite of Anopheles mosquitoes usually between dusk and dawn



Malaria in Brazil



Life cycle


= Infective Stage
= Diagnostic Stage
CDC
SAFER·HEALTHIER·PEOPLE™
http://www.dpd.cdc.gov/dpdx
Human Liver Stages
Liver cell
Infected liver cell
A
Exo-erythrocytic Cycle
Ruptured schizont
Schizont
Human Blood Stages
Immature trophozoite (ring stage)
B
Erythrocytic Cycle
Mature trophozoite
Ruptured schizont
Schizont
Gametocytes
P. falciparum
Gametocytes
P. vivax
P. ovale
P. malariae
Mosquito Stages
Ruptured oocyst
Release of sporozoites
Oocyst
C
Sporogonic Cycle
Ookinete
Macrogametocyte
Microgamete entering macrogamete
Exflagellated microgametocyte
Mosquito takes a blood meal (injects sporozoites)
Mosquito takes a blood meal ingests gametocytes)

Clinical Presentations
fever

- Classic malaria paroxysms:

  Chills and rigors -> Fever spike (40C)

  -> Profuse sweating -> extreme fatigue

  -> sleep

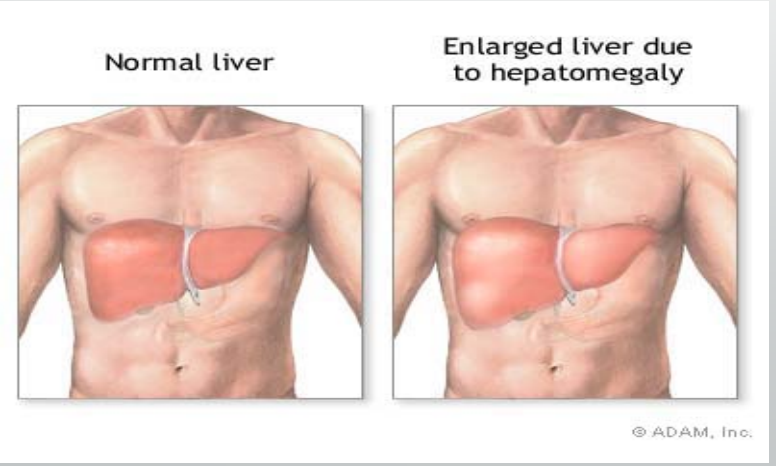
- Lasts several hours
- Can occur with a regular periodicity coinciding with the synchonous rupture of blood schizonts
- Can be in tertian (48-hr) or quartan (72-hr) cycles

Diagnosis

- Clinical
- Parasitological
  - Plasmodium falciparum
  - Plasmodium vivax
  - Plasmodium ovale
  - Plasmodium malariae
  - *Plasmodium knowlesi**

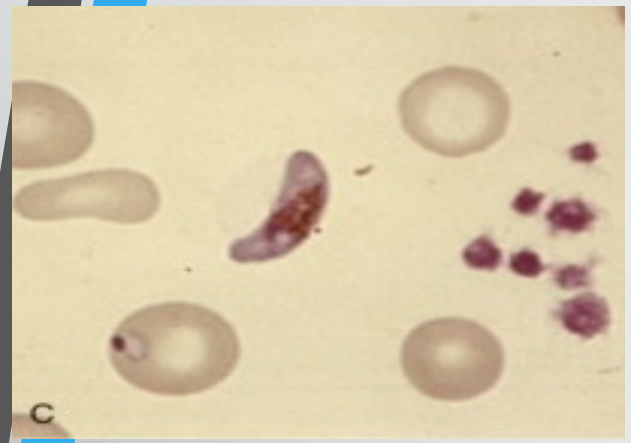
Presentations

- 

- 

- Headache
- Malaise
- Joint pain
- Diarrhea
- Abdominal pain

Severe malaria



P falciparum !!

Cerebral malaria
www.WHO.int

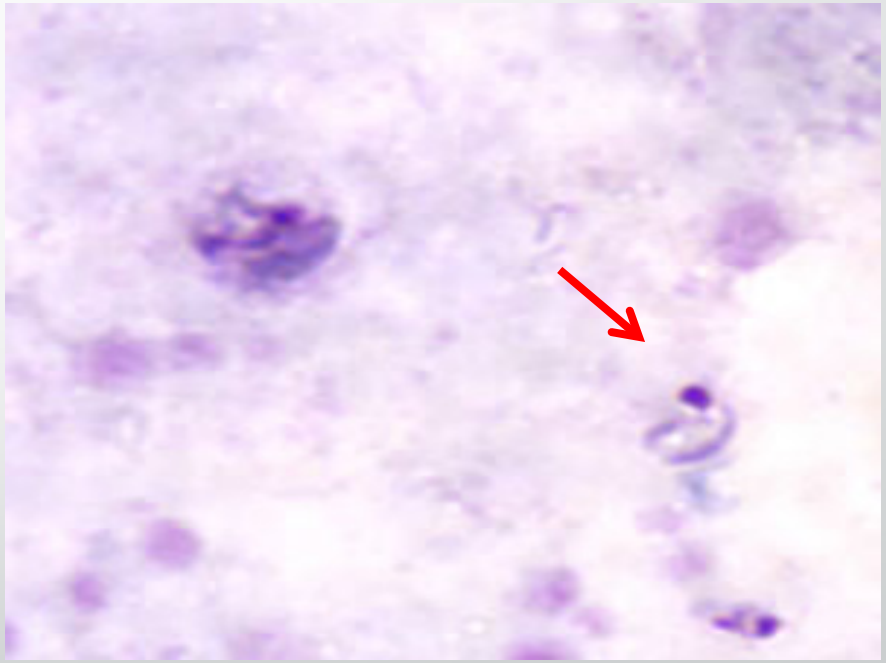
Pulmonary edema

Laboratory Diagnosis

Blood smears

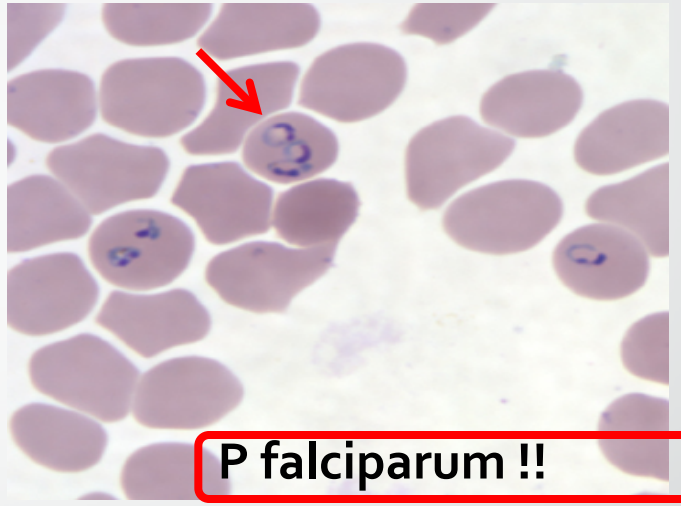
- Giemsa stain
- Erythrocyte – stained pink

- **Thick smear** – concentrate red cell layers 40-fold, as screening relatively large amount of blood

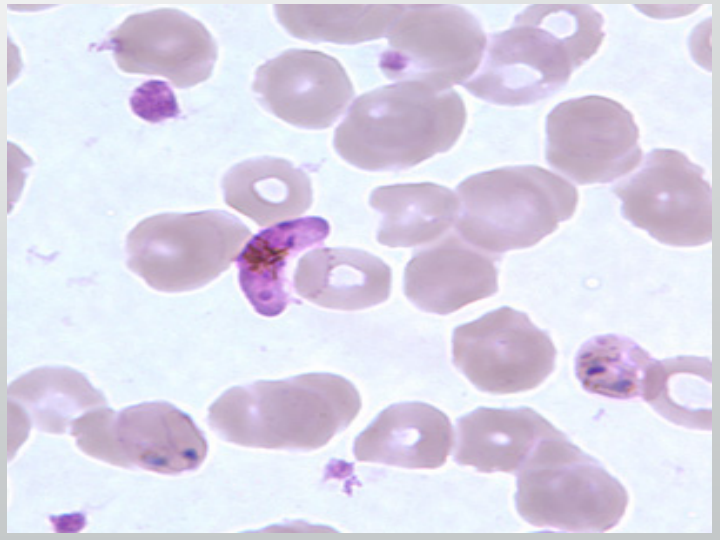


Blood smears

- **Thin smear**
  - Smaller amount of blood
  - Determine the plasmodium species



P falciparum !!



Gametocyte

Rapid diagnostic test kit

- FDA approved
- Use in endemic areas
- Antigens HRP-2 and aldolase
- P falciparum
  - Sensitivity 95%
  - Specificity 94%
- P vivax
  - Sensitivity 69%
  - Specificity 100%

Malaria chemoprophylaxis

- To know different plasmodium species in different areas
- Drug resistance in certain areas
  - All falciparum cases are chloroquine resistant, except the Caribbean, Central America of the Panama Canal, and some countries in Middle East
  - Mefloquine resistance in borders of Thailand/ Myanmar/ Cambodia
  - Chloroquine resistant vivax in Papua New Guinea and Indonesia
- Potential side effects

Malarone (Atovaquone-proguanil) Pros and cons

- Once per day
- Start 1-2 days before travel, continue during travel, 7 days after travel
- Well tolerated, side effects uncommon
- Pediatric tablets available

Mefloquine

- Once per week dose
- 250 mg 1 tab once per week
- Pregnant friendly

- Beware of drug resistant areas (Thailand/ Myamar/ Cambodia border)
- Pre-existing psychiatric conditions, epilepsy
- Prolong QT interval
- Start 2-3 weeks before, during and 4 weeks after travel

Doxycycline

- Daily dose, 100mg daily
- Start 1-2 days before travel
- Least expensive drug
- Additional preventions
  - Rickettial infection
  - Leptospirosis

- C/I in pregnant and children <8 yo
- Continue 4 weeks after travel
- Increased risk of photosensitivity
- GI upset, erosive esophagitis (esp take at bedtime)

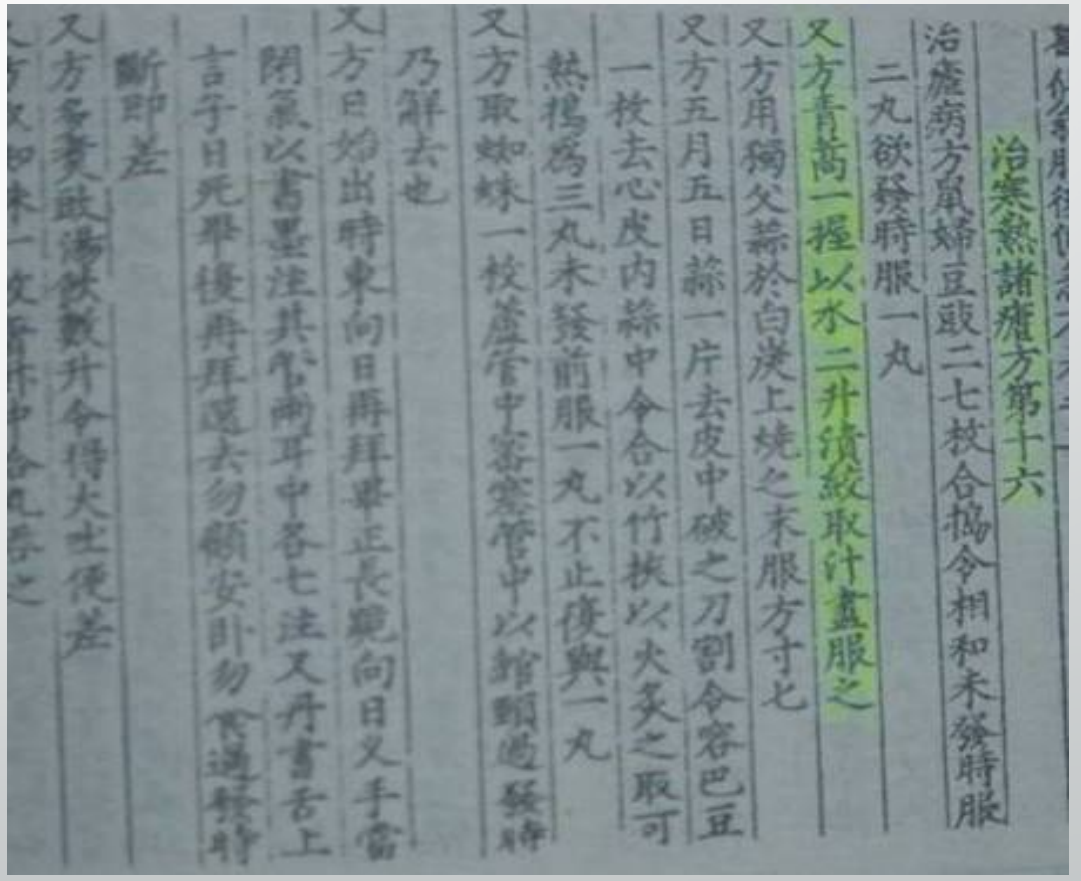
Management of malaria infection

Management

- Monitor vital signs
  - GCS, blood pressure, pulse, oxygenation, Hstix
- Report the case to CHP
- Prompt use of anti-malarial drugs

青蒿素

Great discovery of Chinese ‘Artemisinin’ Derived from Artemisia annua (Qinghao)



Timeline

340 AD: Qinghao

1630: Cinchona bark

1820: **Quinine** isolated from Cinchona bark

1844: Sporadic resistance to Quinine reported

1934: **Chloroquine**

1944: Proguanil

1945: Amodiaquin, **Primaquine**

1952: Pyrimethamine

1974 - 75: **Mefloquine**

1971: **Artemisinin** isolated in China

1998: **Malarone** (Atovaquone + Proguanil)

1992: Atovaquone

Combination therapy

- **Definition**:
  - ≥ 2 schizontocidal drugs with independent modes of action
- **Rationale**:
  - Often more effective
  - Mutant parasites arise de novo can be killed by the other drug
- **Choices**:
  - Artemisinin-based (recommended)
  - Non-artemisinin-based

Yellow fever

Yellow fever

- Flavivirus, a single-stranded RNA virus
- Transmitted by bite of mosquito, primarily Aedes spp, esp Aedes aegypti
- Risk for infection in South America is highest during the rainy season (Jan-May)
- Risk of infection in rural West Africa is seasonal, during the end of rainy season and the beginning of dry season (July-Oct)

Clinical presentation

- Asymptomatic or clinically inapparent infection in most people
- Incubation period 3-6 days
- Non specific flu-like symptoms, fever, chills, headache, myalgia, nausea, vomiting
- Small percentage of patients progress to a more severe or toxic form, characterized by jaundice, hemorrhagic symptoms, shock and multi-organ failure
- Mortality for severe cases with hepatorenal dysfunction is 20-50%

Diagnosis and treatment

- Diagnosis:
  - by serological assay to detect Yellow fever virus IgM/ IgG
  - RT-PCR
- Treatment:
  - NO specific antivirals
  - Symptomatic relief
  - Supportive treatment

Prevention

Yellow fever vaccine

The certificate only valid 10 days after vaccination

- Live attenuated viral vaccine
- Single injection given subcutaneously

Yellow fever map in South America

cdc.gov

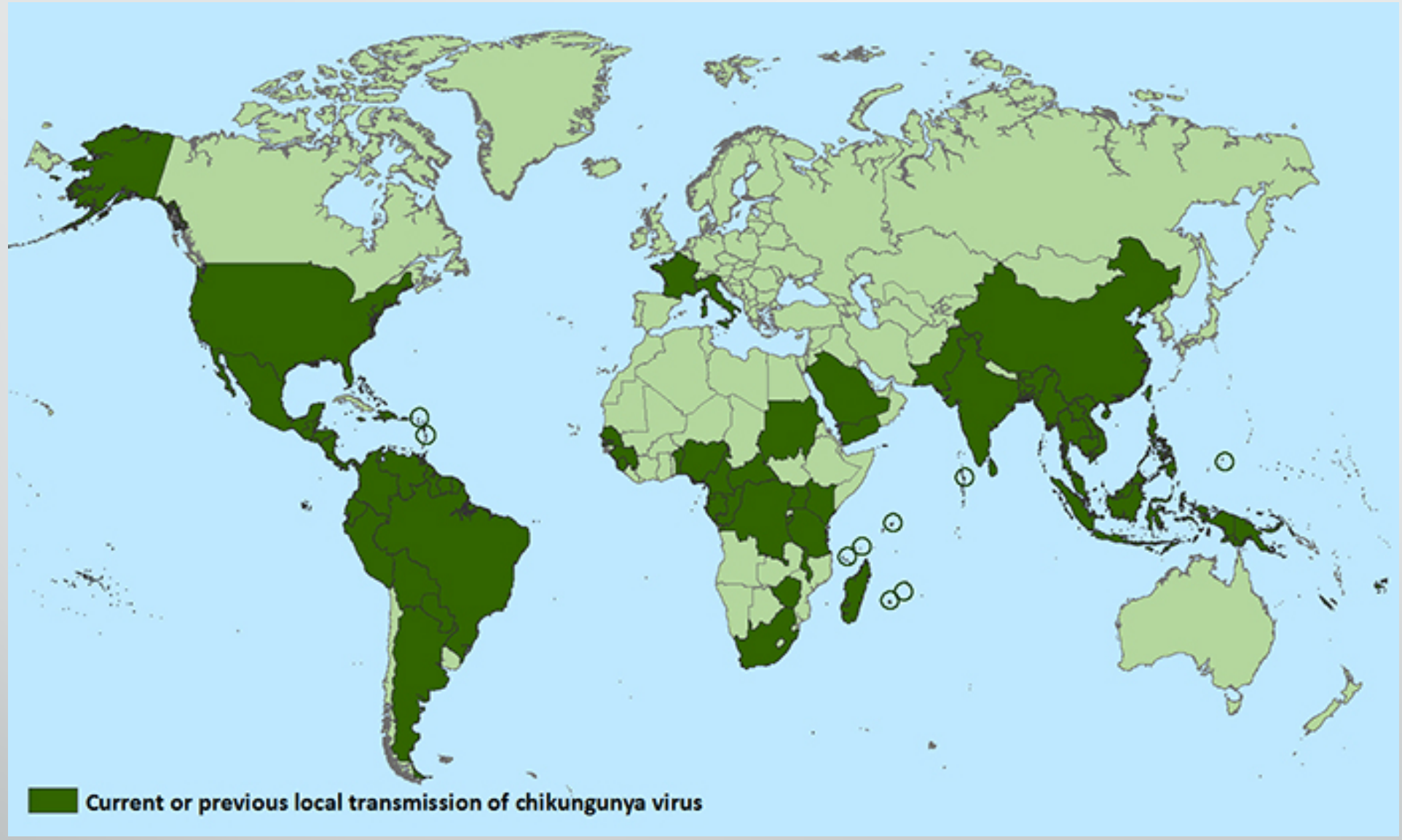
International Certificate of Vaccination or Prophylaxis (ICVP)

Table 3-25. Countries that require proof of yellow fever vaccination from all arriving travelers[1]

Angola	Ghana
Benin	Guinea-Bissau
Burkina Faso	Liberia
Burundi	Mali
Cameroon	Niger
Central African Republic	Rwanda
Congo, Republic of the	São Tomé and Príncipe
Côte d'Ivoire	Sierra Leone
Democratic Republic of the Congo	Togo
French Guiana	
Gabon	

[1] Country requirements for yellow fever vaccination are subject to change at any time; therefore, CDC encourages travelers to check with the destination country's embassy or consulate before departure.

Chikungunya


Current or previous local transmission of chikungunya virus

Cdc.gov

Chikungunya

- Aedes mosquitoes
- Alphavirus
- Incubation 2-4 days (range 1-14)
- Fever, polyarthalgia (2-5 days after fever onset, hands, wrist, ankles)
- Headache, myalgia, rash (macular/ maculopapular)

- Clinically similar to DENV but no shock and only minor bleeding
- Chronic joint symptoms ? Mediated by TNF-alpha
- Severe disease – myocarditis, encephalitis

Diagnosis and treatment

- Diagnostic tests: virus isolation (RT-PCR) during the first 5 days
- Serology IgM (after 5 days)
- No vaccination or specific treatment
- Supportive care

Case

- M/32 Triathlon athelete, returned to HK 2 weeks
- Fever, malaise, headache, jaundice
- Recalled history of skin abrasion over lower limbs during competition event

Investigations

- Hb 13.4 WCC 9.5 Neu 8.4 Plt 232 ESR 39 CRP 137
- Na 134 K 4.3 Urea 8.0 Cr 101 Bil 55 ALT 201
- Ddx?

Leptospirosis

Outbreak of leptospirosis at Ecochallenge Expedition

Leptospirosis in "Eco-Challenge" Athletes, Malaysian Borneo, 2000

James Sejvar*✉, Elizabeth Bancroft*†, Kevin Winthrop*†, Julie Bettinger*, Mary Bajani*, Sandra Bragg*, Kathleen Shutt*, Robyn Kaiser*, Nina Marano*, Tanja Popovic*, Jordan Tappero*, David Ashford*, Laurene Mascola‡, Duc Vugia†, Bradley Perkins*, Nancy Rosenstein*, and the Eco-Challenge Investigation Team

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Suggested citation for this article

Article Contents

- Methods
- Results
- Discussion
- Acknowledgment
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- Table 1
- Table 2
- Suggested Citation

- Sabah, Borneo
- 20th August- 3rd September, 2000
- 312 athletes from 26 countries
- Each team race 300 miles non-stop, using Kayaks, mountain bikes, white water rafts, horses, swum through rivers and climbing ropes..

Leptospirosis

- Obligate aerobic spirochete bacteria, *leptospira interrogans*
- Survives for weeks in water
- Transmitted through abrasions in the skin or through conjunctiva and mucous membranes
- Direct contact with urine or reproductive fluids from infected animals, or with water or soil contaminated with those fluids
- Travellers participating in recreational water activities are at increased risk, particularly after heavy rainfall or flooding

Leptospirosis

- Leptospira interrogans
  - Over 200 serovars
  - Over 160 mammalian species, birds and reptiles
- L. icterohaemorrhagiae (rats)
- L. hardjo (cattle)
- L. canicola (dogs)

Clinical manifestations

Acute phase

- Incubation 2- 21 days
- Mild infection (>90%)
  - Fever, headache, myalgia, self-limiting
- Moderate (~9%)
  - Sudden prostration, muscle tenderness, pretibial macular rash, jaundice, pneumonitis

Icteric or severe form (<1%)

- Weil's disease
- Almost always L. icterohaemorrhagiae
- Acute hepatic and renal failure
- Extensive haemorrhage
- Myocarditis
- 10% mortality

Diagnosis and management

- Diagnosis:
  - Albuminuria, deranged LFT, thrombocytopenia
  - Serology: serum IgM, microscopic agglutination test, ELISA
  - PCR
- Treatment
  - Mild: doxycycline 100mg BD x 5-7 days
  - Severe disease: Pen G 1.5 mu iv q6H, rocephin 1g daily iv
  - Jarisch-Herxheimer reaction may occur after penicillin therapy

Prevention

- No vaccine available
- Wear protective clothing, especially foot wear
- Covering cuts and abrasions with occlusive dressings
- Chemoprophylaxis: doxycycline 200mg weekly, 1-2 days before and continue through the period for high risk people

General assessment and management in travelers returning from brazil

- Detailed history of the route of travel, particular events, exposure, sexual behavior, chemoprophylaxis and vaccination
- Look for hydration state, rash, bleeding tendency, warning signs
- Routine blood counts including blood smears, liver and renal functions
- +/- Specific diagnostic tests (PCR/ serology/malaria blood smear)
- Contraception and pregnancy issue in view of recent Zika virus threat

Thank you