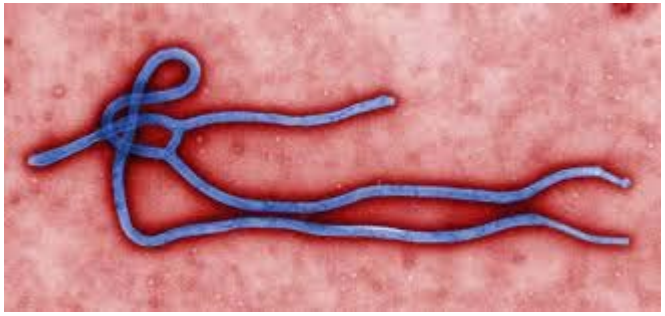
Ebola and arboviral infections



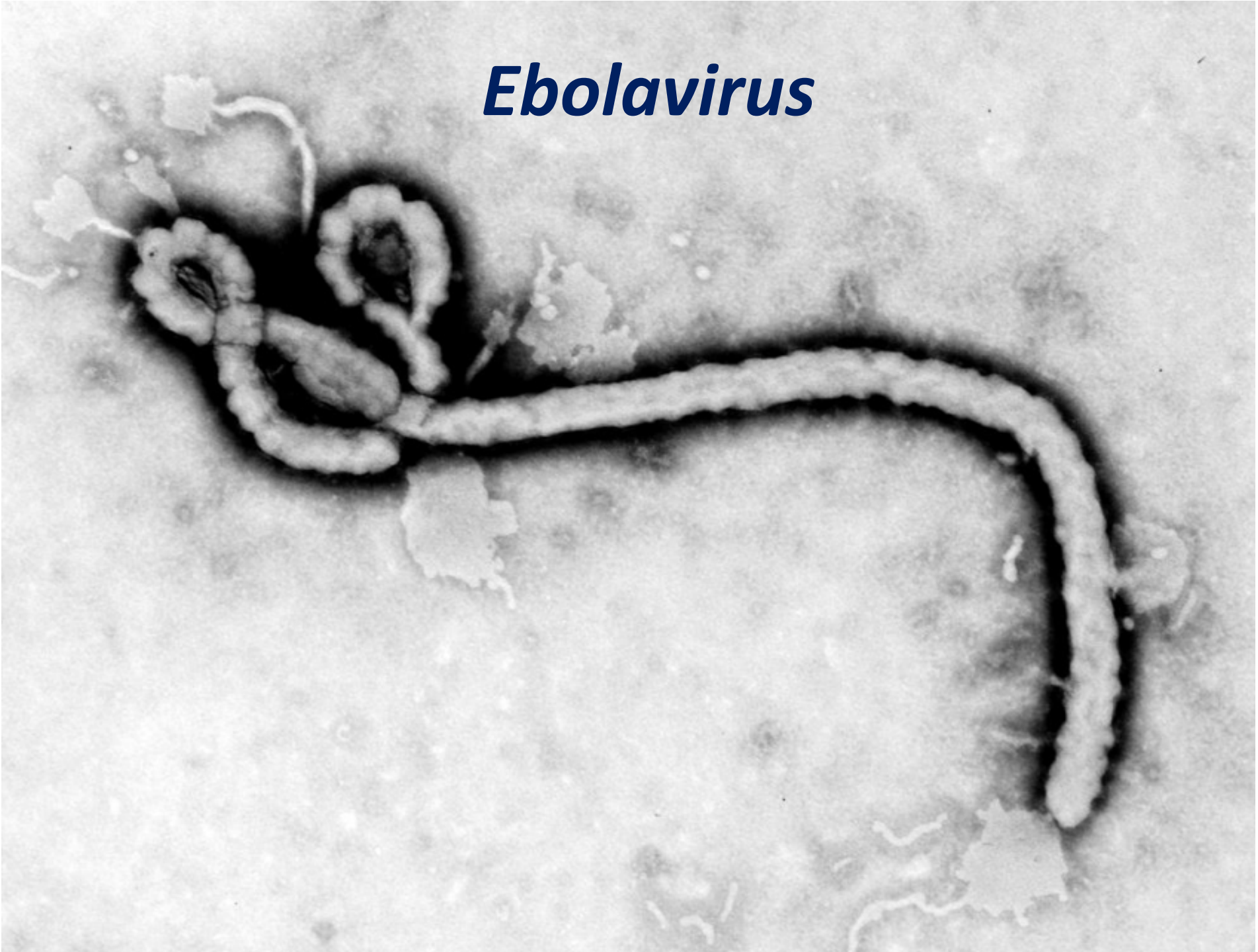
Introduction and talk outline

Ebola (not an arbovirus!)

Dengue
Chikungunya
Yellow Fever
Japanese Encephalitis
West Nile

Others…

Ebolavirus



West Africa Ebola outbreak

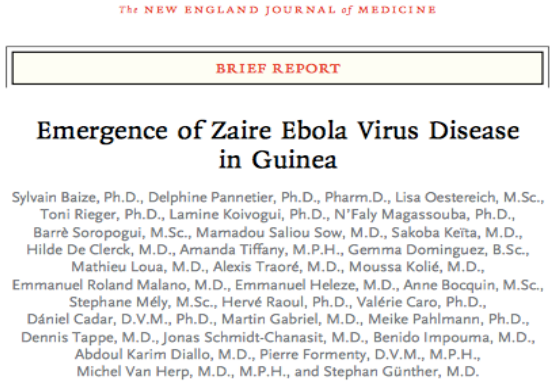
Index case occurred in a family in Guéckédou, Guinea

- 18 month old child, died after 2 days of illness
- December 2013 / January 2014

Spread to a number of health care workers and then among their family members

- January to March 2014

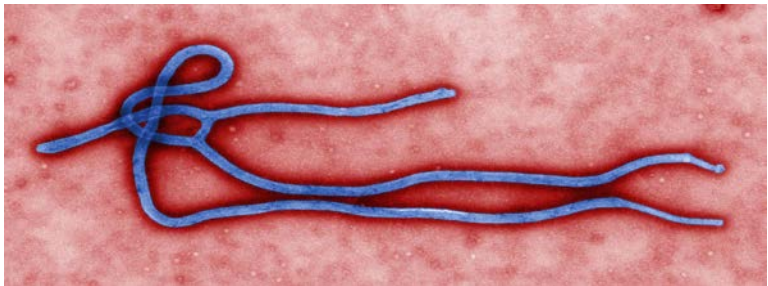
Spread to peri-urban areas by March 2014



Ebolavirus species

Filovirus (family also includes *Marburgvirus* and *Cuevavirus*)
Cause of Ebola virus disease (EVD)
Filamentous single-stranded negative sense RNA virus

Zaire ebolavirus: 1976, Democratic Republic of Congo.
Sudan ebolavirus: 1976, Sudan.
Bundibugyo ebolavirus: 2007, Uganda.
Taï Forest ebolavirus 1994, Ivory Coast.
    Single case, veterinary worker handling primate.
Reston ebolavirus: 1989, Philippines.
    Macaques, swine.
    Human laboratory workers seropositive but no clinical disease



Ebolavirus Ecology

Enzootic Cycle

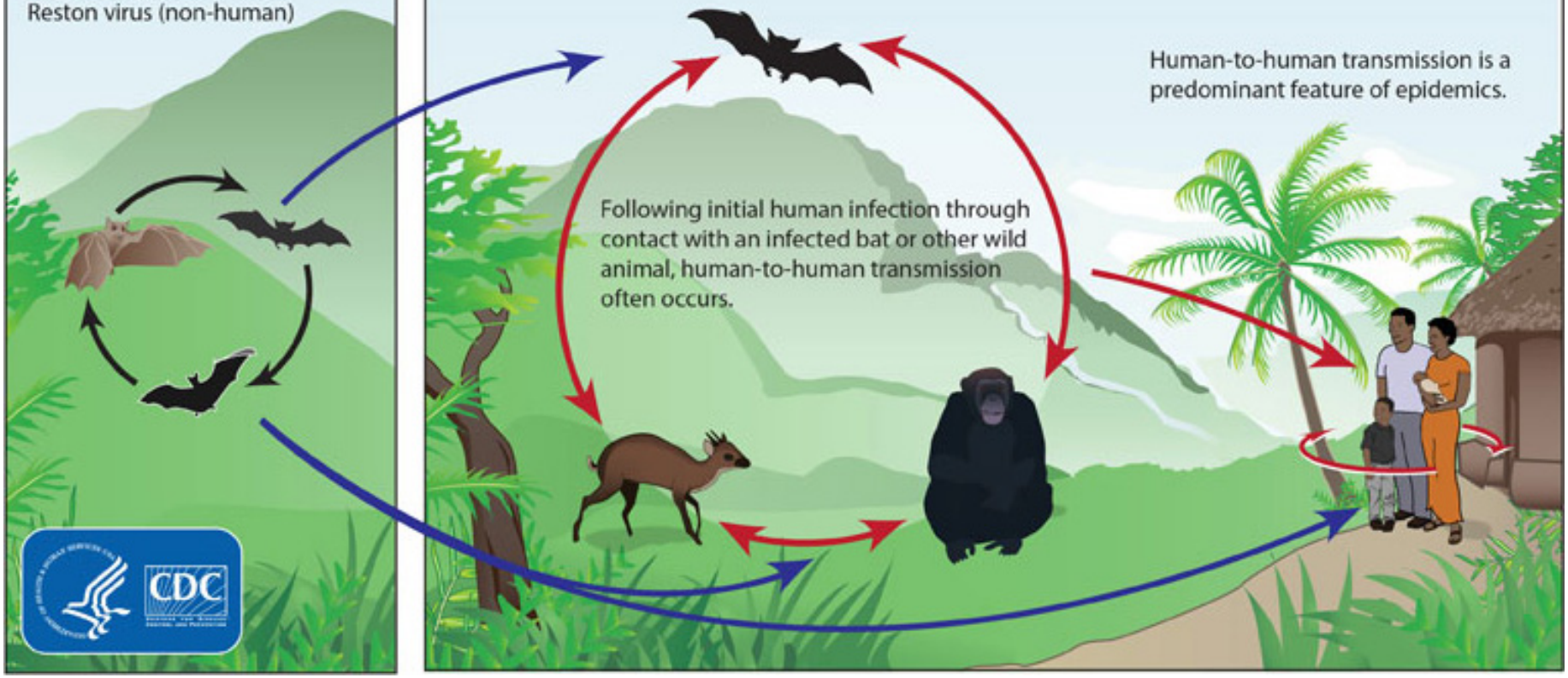
New evidence strongly implicates bats as the reservoir hosts for ebolaviruses, though the means of local enzootic maintainance and transmission of the virus within bat populations remain unknown.

Ebolaviruses:

Ebola virus (formerly Zaire virus)
Sudan virus
Taï Forest virus
Bundibugyo virus
Reston virus (non-human)

Epizootic Cycle

Epizootics caused by ebolaviruses appear sporadically, producing high mortality among non-human primates and duikers and may precede human outbreaks. Epidemics caused by ebolaviruses produce acute disease among humans, with the exception of Reston virus which does not produce detectable disease in humans. Little is known about how the virus first passes to humans, triggering waves of human-to-human transmission, and an epidemic.



Clinical features

Incubation: 2 to 21 days (most common 4-10 days)

→ Patient is not contagious during this period

Initial phase: vague flu-like symptoms – fever, headache, sore throat, myalgia, arthralgia

Next: asthenia, nausea, vomiting, diarrhoea (often severe), abdominal pain

Late (5-7 days from onset): shock, haemorrhage, multi-organ failure

Death usually 7-10 days from onset

Poor prognosis :

Pregnant women

Young children

Convalescence:

Arthralgia

Myalgia

Abdominal pain

Asthenia

Anorexia

Eye manifestations

Routes of transmission

Contact with the sick, dead, infectious body fluids (vomit, blood, faeces, saliva, sweat, milk, semen), soiled linen/clothes

Hands to mucus membranes: eyes, nose, mouth

Broken skin

Puncture with contaminated instrument

Large droplet projection to mucus membranes (in patients with late-stage disease)

Sexual intercourse: virus in the semen up to 3 months

Breast milk: virus in the milk up to 3 months

Dead bodies particularly dangerous

Ebola symptoms – 3 phases

Phase 1

Flu like illness (fever, chills, malaise, headache, anorexia, arthralgia, myalgia)

Conjunctival injection

Rash

Phase 2

Diarrhoea,

Vomiting

Abdominal pain (RUQ / epigastric)

Phase 3

Haemorrhage – bleeding ranges from mild (bruising, mucosal bleeding, oozing from venepuncture sites) to severe (haematemesis / malaena)

Confusion / seizures

Hiccups

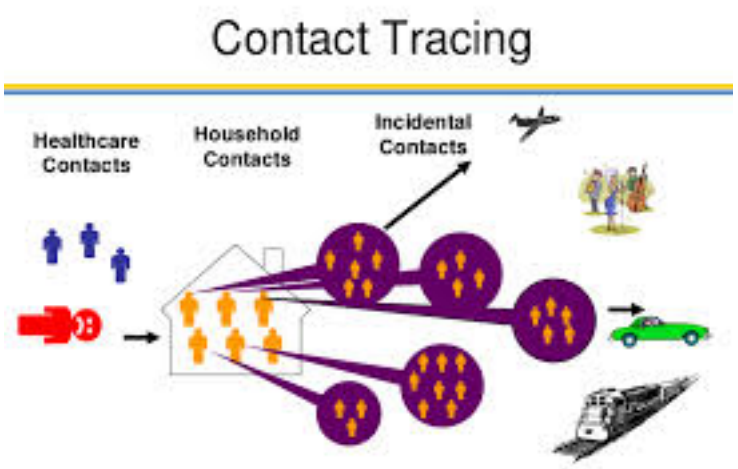
The most common feature of EVD during this outbreak has been progressive gastrointestinal symptoms:

- anorexia, nausea, abdominal discomfort
- vomiting and severe diarrhoea
- Progressive volume depletion

The most important, life-saving treatment currently available is fluid resuscitation

Infection control

Fundamental to outbreak control
Households of infected contacts quarantined
21 days of temperature monitoring
Good community engagement vital



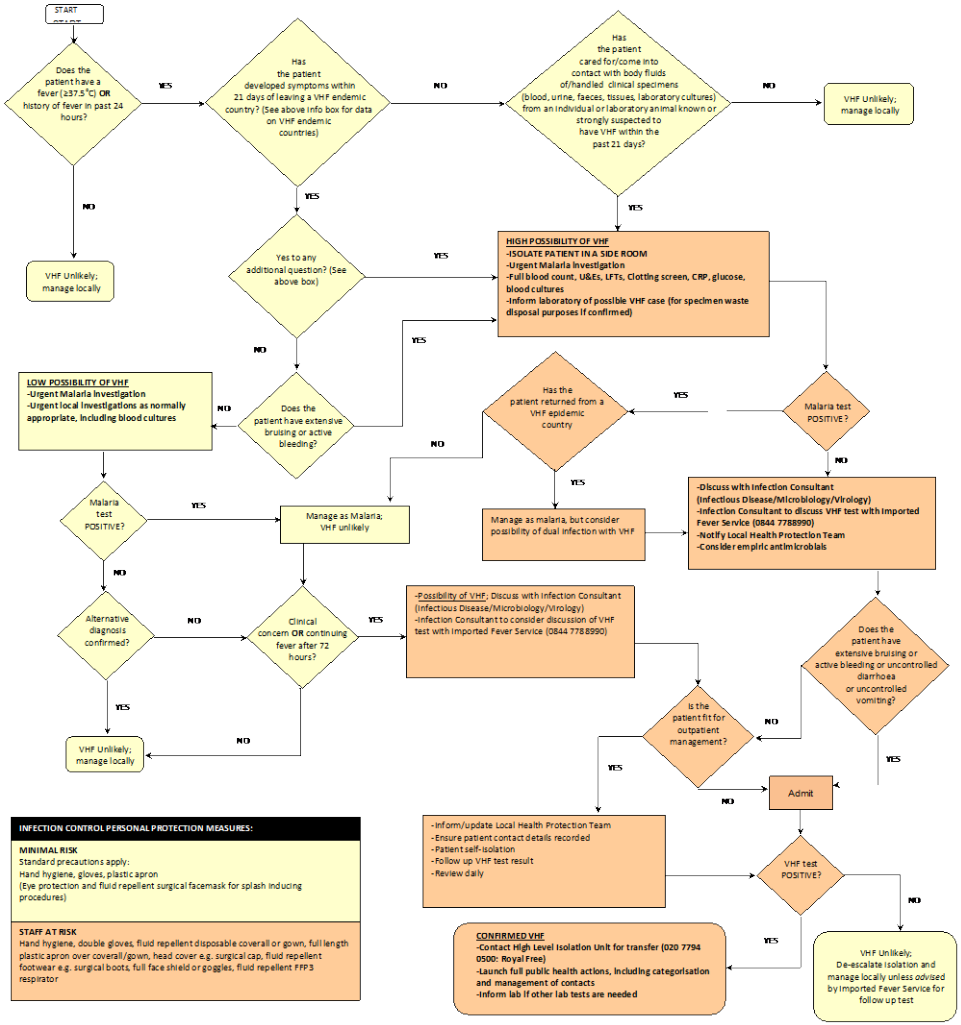
VIRAL HAEMORRHAGIC FEVERS RISK ASSESSMENT (Version 6: 15.11.2015)

VHF ENDEMIC COUNTRIES:

Information on VHF endemic countries can be found at https://www.gov.uk/viral-haemorrhagic-fevers-origins-reservoirs-transmission-and-guidelines or see VHF in Africa map at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/358895/VHF_Africa_960_640.png

ADDITIONAL QUESTIONS:

-Has the patient travelled to any area where there is a current VHF outbreak? (http://www.promedmail.org/) **OR**
-Has the patient lived or worked in basic rural conditions in an area where Lassa Fever is endemic? (https://www.gov.uk/lassa-fever-origins-reservoirs-transmission-and-guidelines) **OR**
-Has the patient visited caves / mines, or had contact with or eaten primates, antelopes or bats in a Marburg / Ebola endemic area? (https://www.gov.uk/ebola-and-marburg-haemorrhagic-fevers-outbreaks-and-case-locations) **OR**
-Has the patient travelled in an area where Crimean-Congo Haemorrhagic Fever is endemic (http://www.who.int/csr/disease/crimean_congoHF/Global_CCHFRisk_20080918.png?ua=1) AND sustained a tick bite* or crushed a tick with their bare hands OR had close involvement with animal slaughter? (*If an obvious alternative diagnosis has been made e.g. tick typhus, then manage locally)



INFECTION CONTROL PERSONAL PROTECTION MEASURES:

MINIMAL RISK
Standard precautions apply:
Hand hygiene, gloves, plastic apron
(Eye protection and fluid repellent surgical facemask for splash inducing procedures)

STAFF AT RISK
Hand hygiene, double gloves, fluid repellent disposable coverall or gown, full length plastic apron over coverall/gown, head cover e.g. surgical cap, fluid repellent footwear e.g. surgical boots, full face shield or goggles, fluid repellent FFP3 respirator

What are arboviruses?

- Arboviruses = **Ar**thropod-**Bo**urne **viruses**

DENGUE

Dengue: an emerging infectious disease

- Dengue is an emerging infectious disease of tropical and sub-tropical regions
- Caused by dengue virus (DENV)
  - 4 serotypes (DENV-1-4); Flavivirus
- Transmitted by *Aedes* mosquitoes
- Clinically apparent infections present as a spectrum:
  - Dengue
  - Severe dengue
- Estimated annual global burden:
  - 70 – 500 million infections
  - 2.1 million severe dengue cases
  - 21,000 deaths
- Can be epidemic and/or endemic

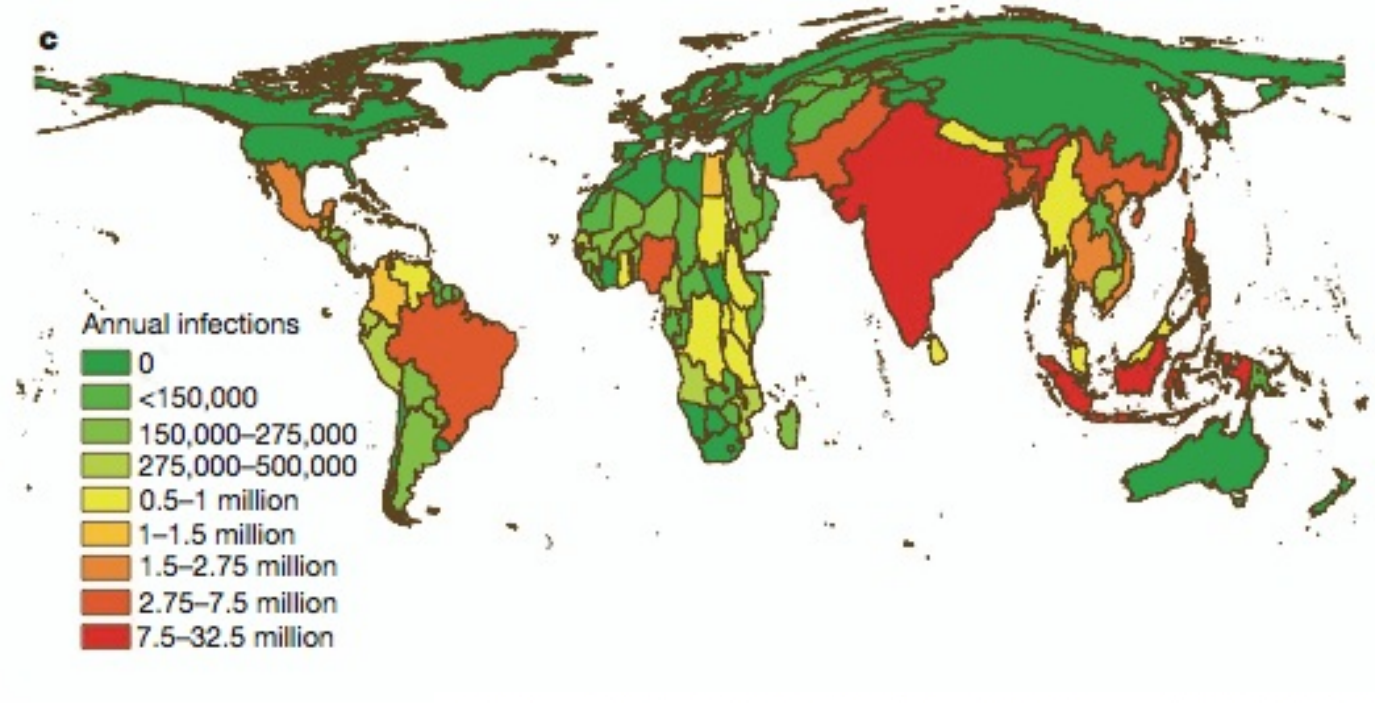
Sources: Wellcome Trust Topics in International Health: Dengue 2001; M. Beatty, PDVI (http://www.pdvi.org/about_dengue/GBD.asp)

LETTER

doi:10.1038/nature12060

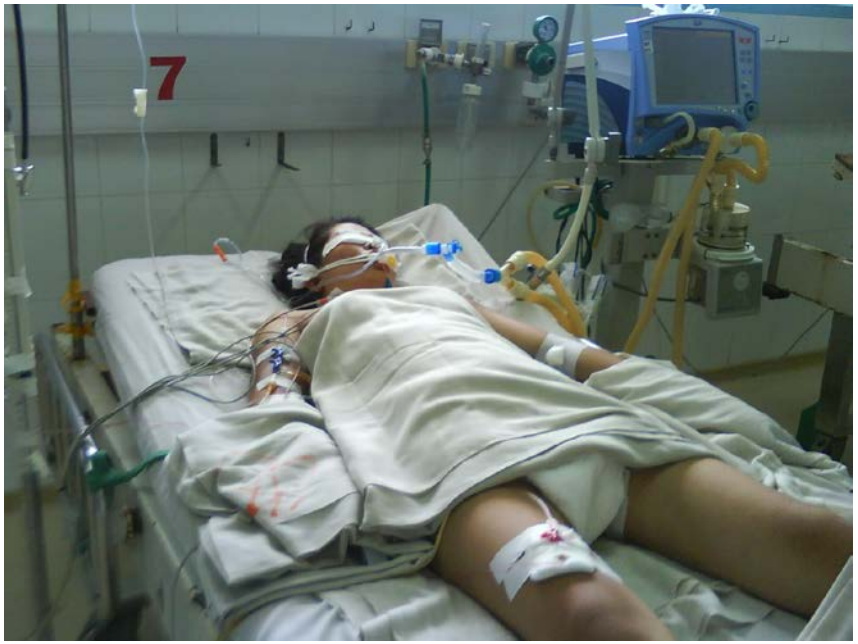
The global distribution and burden of dengue

Samir Bhatt[1], Peter W. Gething[1], Oliver J. Brady[1,2], Jane P. Messina[1], Andrew W. Farlow[1], Catherine L. Moyes[1], John M. Drake[1,3], John S. Brownstein[4], Anne G. Hoen[5], Osman Sankoh[6,7,8], Monica F. Myers[1], Dylan B. George[9], Thomas Jaenisch[10], G. R. William Wint[1,11], Cameron P. Simmons[12,13], Thomas W. Scott[9,14], Jeremy J. Farrar[12,13,15] & Simon I. Hay[1,9]



Nature **496**, 504–507 (25 April 2013) doi:10.1038/nature12060

A significant impact on both health systems and individuals…



Clinical features of acute dengue

- Fever
- Anorexia and nausea
- Rash (acute macular erythematous)
- Aches and pains (retro-orbital pain in adults)
- (Thrombocytopenia and leucopenia)

Clinical features of severe dengue

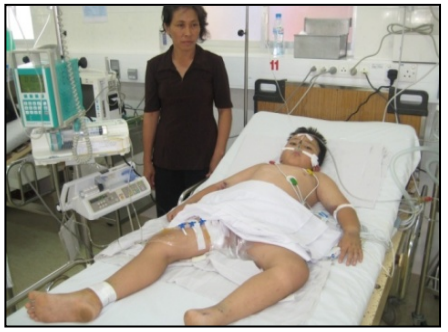
Intravascular volume depletion secondary to increased systemic vascular permeability

A variety of haemorrhagic manifestations due to the combined effects of:-

- Thrombocytopenia
- Deranged haemostasis

Severe organ impairment:-

- Usually secondary
- May be idiosyncratic



Risk factors for severe disease

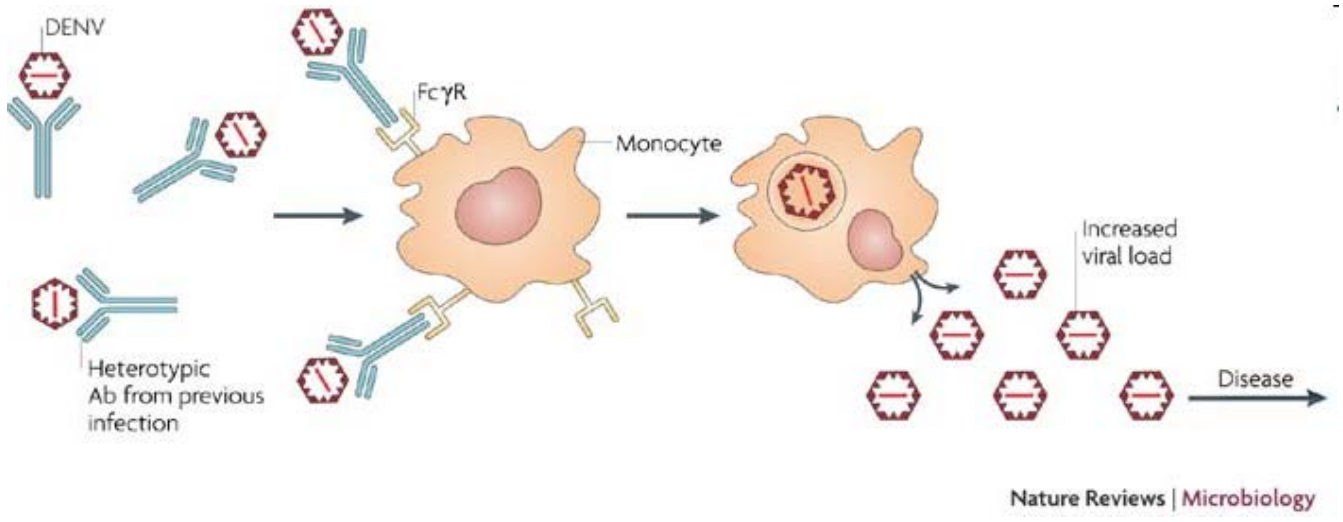
Why do some patients develop severe dengue and others not?

1. **Secondary infection with a heterologous serotype:**

- Studies in Thailand, Cuba and elsewhere have shown that individuals with pre-existing antibody to a different DENV serotype are at higher risk of developing severe dengue than those experiencing a first infection
- The proposed mechanism explaining this observation is *antibody-dependent enhancement:*

Antibody dependent enhancement (ADE)

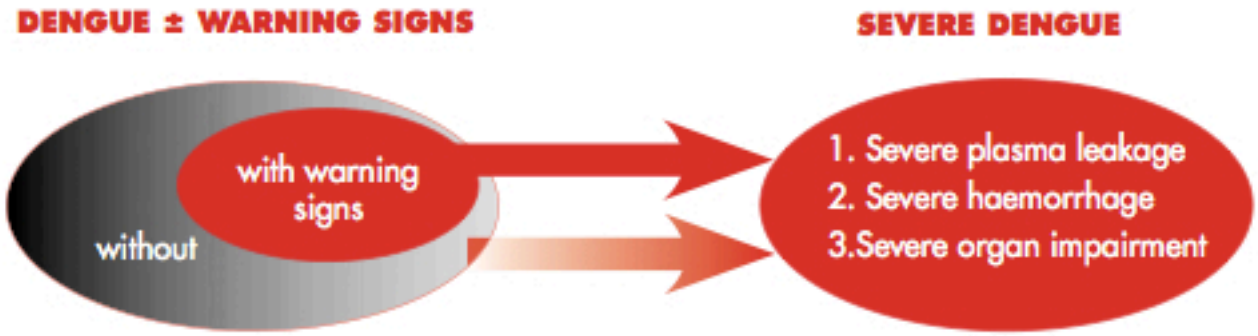
- pre-existing antibodies bind to heterologous serotype but fail to neutralise it. Can occur in;
  - Secondary infection
  - Primary infection in infants born to immune mothers
- Results in altered cellular tropism and higher virus burden



Host determinants of outcome

- Age
- Gender
- Flavivirus-infection history
- Genotype
- Co-morbidities

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

- Often made clinically – not ideal!
- Confirmed:
  - (PCR)
  - (Virus culture)
  - IgM seroconversion in paired samples or IgG rise in paired samples
- Suspected:
  - IgM + in single sample
  - IgG + at HI titre >1280 in single sample
- Rapid diagnostic tests:
  - NS1 rapid tests – useful in 1st 5 days fever; “field friendly”; sensitivity varies across serotypes

Treatment

- Only supportive care
- IV fluids + careful resuscitation
- Anti-pyretics…
- Prevention: vector control…

Management

- Most cases can be managed as outpatients
- Consider admission if warning signs present
- Pulse pressure <20mmHg or poor perfusion = shock…
- IV fluids:
  - Warning signs: start with 5-7ml/kg/hr
  - Shock: start with 10ml/kg/hr for 1 hour
  - Reassess frequently – SERIOUS risk of overload
  - Reserve colloids for refractory shock
  - Blood products in haemorrhage

Warning signs (not validated…)

- Abdominal pain
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleeding
- Lethargy or restlessness
- Liver enlargement >2cm
- Rise in haematocrit with concurrent fall in platelets

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 8, 2015 VOL. 372 NO. 2

Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America

Luis Villar, M.D., Gustavo Horacio Dayan, M.D., José Luis Arredondo-García, M.D., Doris Maribel Rivera, M.D., Rivaldo Cunha, M.D., Carmen Deseda, M.D., Humberto Reynales, M.D., Maria Selma Costa, M.D., Javier Osvaldo Morales-Ramírez, M.D., Gabriel Carrasquilla, M.D., Luis Carlos Rey, M.D., Reynaldo Dietze, M.D., Kleber Luz, M.D., Enrique Rivas, M.D., Maria Consuelo Miranda Montoya, M.D., Margarita Cortés Supelano, M.D., Betzana Zambrano, M.D., Edith Langevin, M.Sc., Mark Boaz, Ph.D., Nadia Tornieporth, M.D., Melanie Saville, M.B., B.S., and Fernando Noriega, M.D., for the CYD15 Study Group*

ABSTRACT

BACKGROUND

In light of the increasing rate of dengue infections throughout the world despite vector-control measures, several dengue vaccine candidates are in development.

METHODS

In a phase 3 efficacy trial of a tetravalent dengue vaccine in five Latin American countries where dengue is endemic, we randomly assigned healthy children between the ages of 9 and 16 years in a 2:1 ratio to receive three injections of recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV) or placebo at months 0, 6, and 12 under blinded conditions. The children were then followed for 25 months. The primary outcome was vaccine efficacy against symptomatic, virologically confirmed dengue (VCD), regardless of disease severity or serotype, occurring more than 28 days after the third injection.

RESULTS

A total of 20,869 healthy children received either vaccine or placebo. At baseline, 79.4% of an immunogenicity subgroup of 1944 children had seropositive status for one or more dengue serotypes. In the per-protocol population, there were 176 VCD cases (with 11,793 person-years at risk) in the vaccine group and 221 VCD cases (with 5809 person-years at risk) in the control group, for a vaccine efficacy of 60.8% (95% confidence interval [CI], 52.0 to 68.0). In the intention-to-treat population (those who received at least one injection), vaccine efficacy was 64.7% (95% CI, 58.7 to 69.8). Serotype-specific vaccine efficacy was 50.3% for serotype 1, 42.3% for serotype 2, 74.0% for serotype 3, and 77.7% for serotype 4. Among the severe VCD cases, 1 of 12 was in the vaccine group, for an intention-to-treat vaccine efficacy of 95.5%. Vaccine efficacy against hospitalization for dengue was 80.3%. The safety profile for the CYD-TDV vaccine was similar to that for placebo, with no marked difference in rates of adverse events.

CONCLUSIONS

The CYD-TDV dengue vaccine was efficacious against VCD and severe VCD and led to fewer hospitalizations for VCD in five Latin American countries where dengue is endemic. (Funded by Sanofi Pasteur; ClinicalTrials.gov number, NCT01374516.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Dayan at Sanofi Pasteur, Discovery Dr., Swiftwater, PA, 18370, or at gustavo.dayan@sanofipasteur.com.

*A complete list of investigators in the CYD15 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 3, 2014, at NEJM.org.

N Engl J Med 2015;372:113-23.
DOI: 10.1056/NEJMoa1411037

CHIKUNGUNYA

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

SEPTEMBER 4, 2014

Chikungunya at the Door — Déjà Vu All Over Again?

David M. Morens, M.D., and Anthony S. Fauci, M.D.

Chikungunya

- Chikungunya
  - *Aedes* mosquitoes
  - *Alphavirus (*Togaviridae)
  - Big outbreak in Indian Ocean region
  - Now threatening USA
  - 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) (1st 5 days), serology (IgM appears after ~5 days), in many settings diagnosis is clinical (wide differential)

- No vaccine and no specific therapeutic: role of chloroquine not supported; only therapeutic options are supportive

YELLOW FEVER

47 year old woman

- Holiday in the Gambia
- No YF vaccine
- On last day developed fever, headache, myalgia
- Returned to Europe – diarrhoea and dizziness on flight
- Admitted to hospital as symptoms progressed
- Noted to be jaundiced…

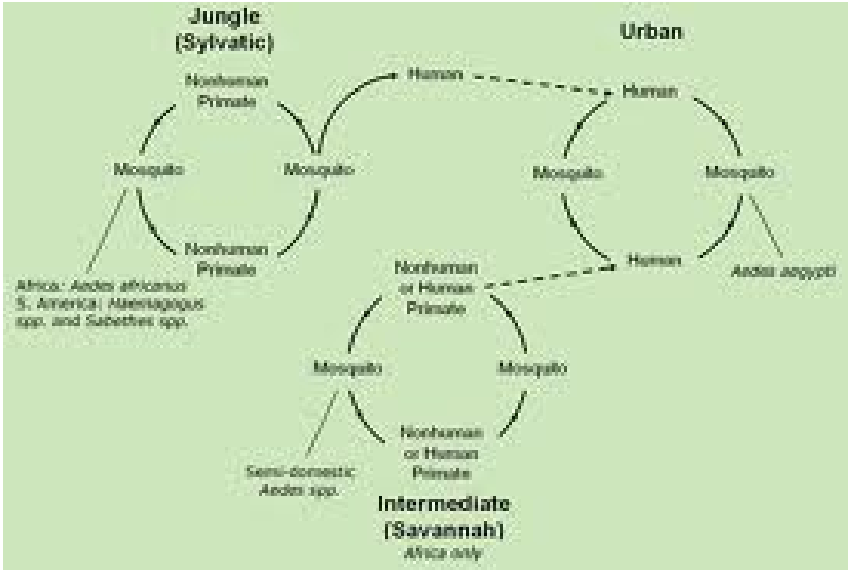
Continued….

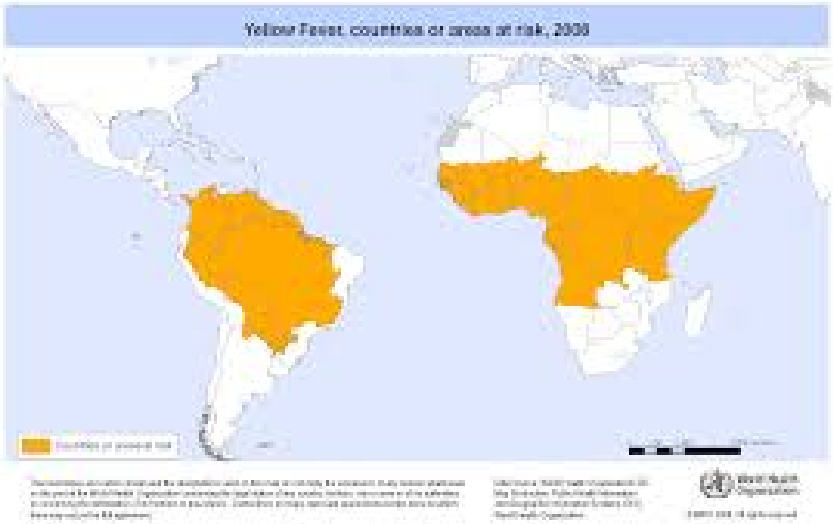
- Lab results:
  - Hb 12.9 g/dL
  - WCC 4100 cell/mm^3
  - PLT 95000 plt/mm^3
  - AST 49000 U/L
  - ALT 23000 U/L
  - INR 3.3
  - Yellow fever RT-PCR positive
- Progress:
  - Increasing somnolescence
  - Increased coagulopathy
  - Increasing acidosis
  - Massive GI bleeding
  - Died 6 days after illness onset

Introduction

- Namesake of Flavivirus family
- Transmitted by *Aedes* mosquitoes
- ~600 million live in at risk areas
- Significant impact on history
- **Vaccine preventable**

Transmission and distribution





Clinical features

- Many (?most) infections inapparent
- 3-6 day incubation
- Headache, myalgia and fever & in most cases resolution
  - Subconjunctival haemorrhage, Faget's sign and leucopenia
- In a few cases fever returns + nausea, vomiting, back pain, somnolescence

  Progresses to prostration, icteric hepatitis, GI haemorrhage, renal failure

Laboratory tests

- Simple lab tests: albuminuria, AST may be higher than ALT (cardiac damage) – note similar pattern seen in dengue…

- Diagnostic tests: virus isolation (RT-PCR), serology, post-mortem diagnosis using immunohistochemistry

Treatment & prevention

- Supportive – needs ICU ideally
- Isolate from mosquitoes
- Live attenuated 17D vaccine – good protection
- Vaccine associated with viscerotropic disease – systemic infection (like YF) or CNS disease
- New XRX-001 vaccine may be safer...
- WHO requirement for 10 year booster is changing – immunity from single dose thought to be lifelong

JAPANESE ENCEPHALITIS

20 year old Spanish martial artist

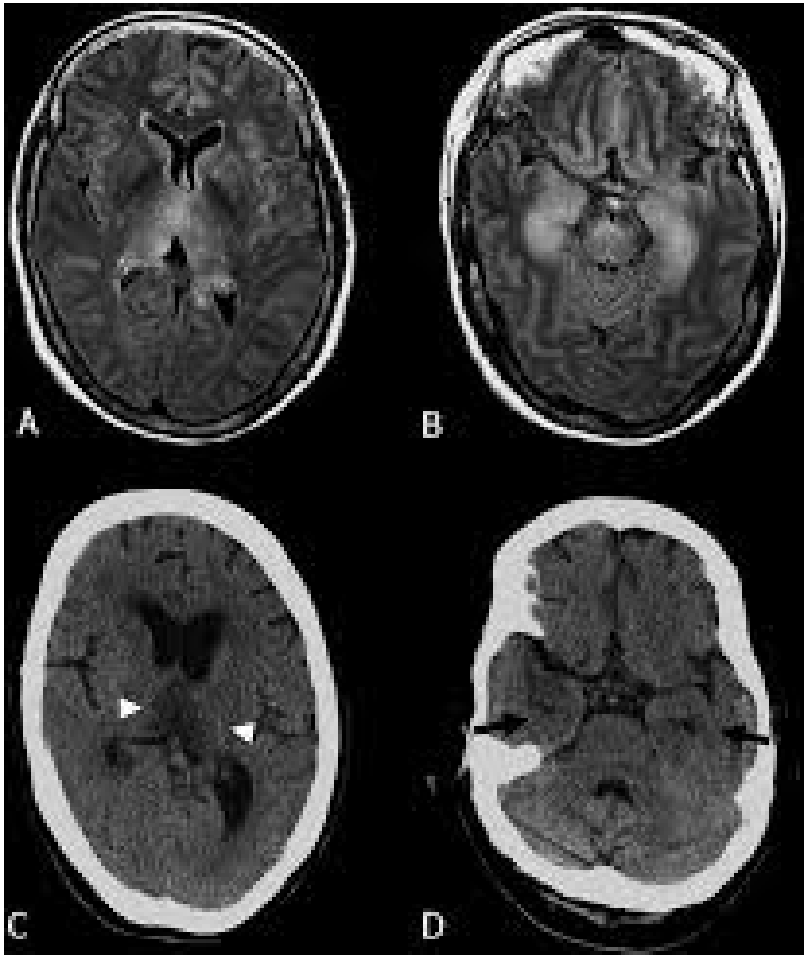
- Travelled to Thailand to take part in a Thai boxing competition
- Travelled in rural areas + stayed in basic accommodation
- Admitted to local hospital with fever, myalgia, malaise and headache

Continued…

- Condition worsened – photophobia, vomiting and reduced GCS (11)
- Next day: developed seizures, V and VII cranial nerve palsies, left hemiparesis + further fall in GCS (9)
- Intubated and ventilated
- Treated with ceftriaxone, doxycycline, aciclovir, dexamethasone + phenytoin

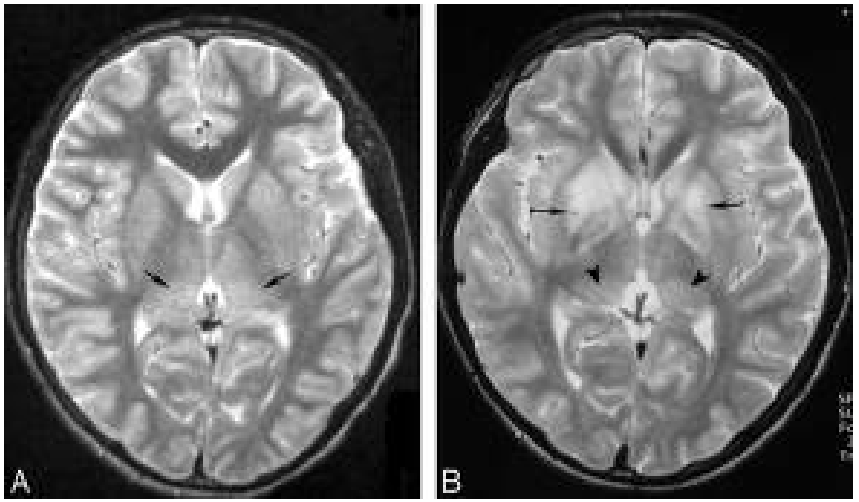
Continued…

- CSF: 960 wcc/mm^3 (90% lymphocytes)
- CSF biochemistry NAD
- Other bloods NAD
- Japanese encephalitis IgM positive in blood and CSF



Progress

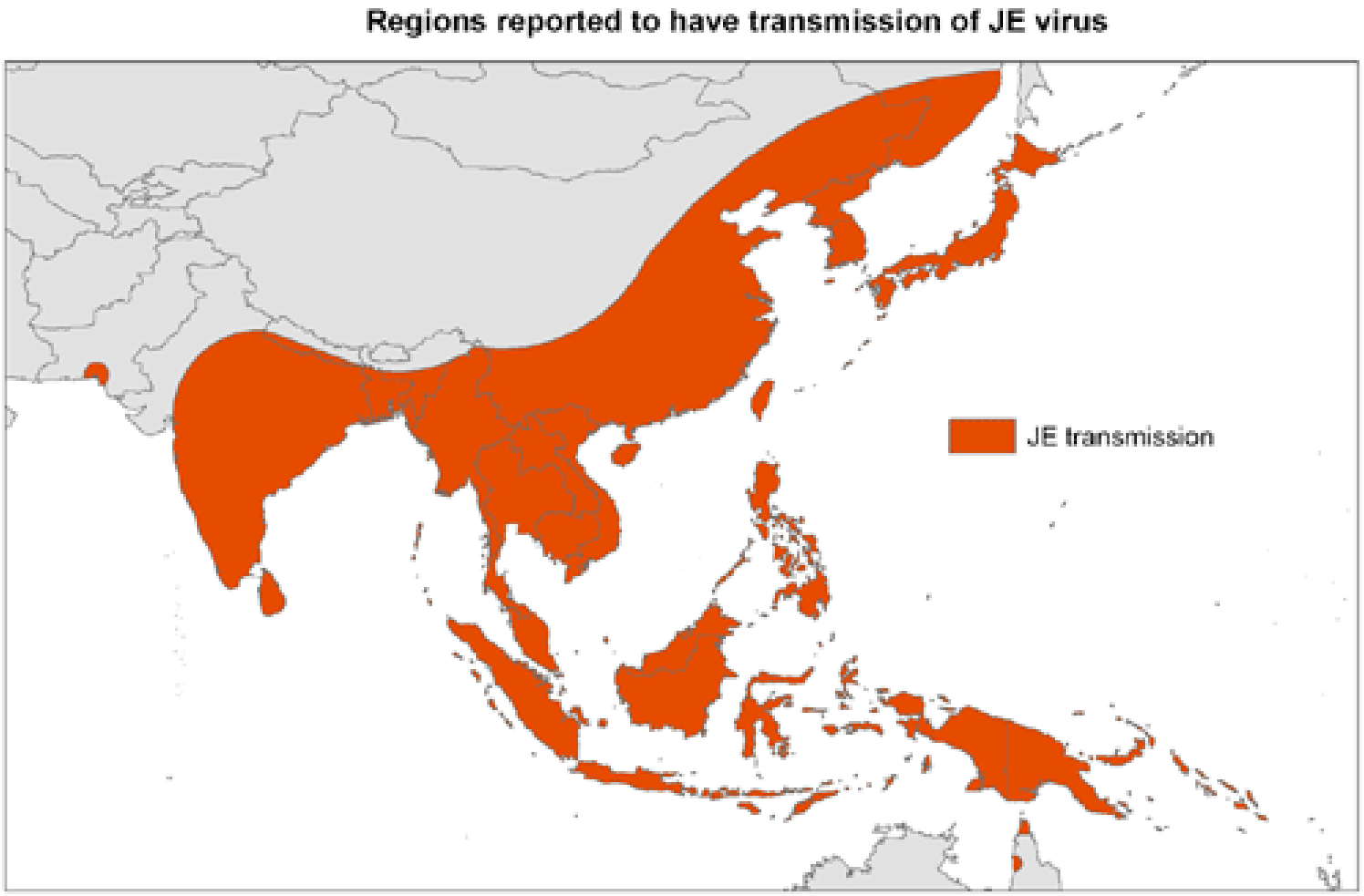
- Transferred back to Spain
- Made slow improvement over 2 months
- Residual ataxia, memory impairment and emotional lability



Japanese Encephalitis

- Flavivirus spread by mosquitoes (*Culex spp.*)
- The leading cause of viral neurological disease in Asia… (poliomyelitis gone, but HFM…)
- 3 billion people live in areas where JE is transmitted
- Up to 50,000 cases of JE are reported to WHO each year
- Up to 10,000 to 15,000 deaths are reported each year

Geographical Distribution



Transmission of JE

- JE is spread by mosquitoes
- *Culex tritaeniorhynchus* is the main vector: species that breed in rice paddies, ditches, and ground pools are also important

Culex mosquito laying eggs on water

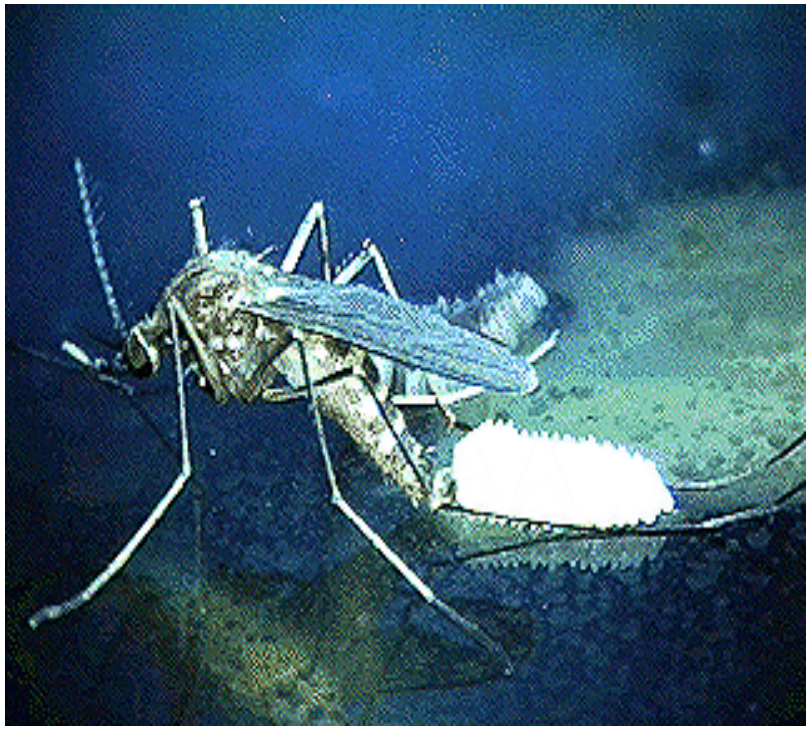


Photo credit: Richard G. Weber

Clinical Features

- Incubation period 5-15 days
- Characteristically children
- Fever and confusion
- 30% death rate
- Survivors
  - Marked extra-pyramidal features during recovery phase
  - Approx 50% of survivors left with neurological disability – subtle neurocognitive – marked ataxia

JEV - Diagnosis

- Diagnosis based upon clinical syndrome and serology
- Demonstration of rising titres of IgM in CSF
- Virus not detectable in CSF or blood when symptomatic

JEV - investigations

- FBC – leucopenia, sometimes mild anaemia, mild thrombocytopenia
- Hyponatraemia
- Virus isolation from brain tissue...
- IgM – blood or CSF (takes 7 days to rise)
- MRI – frequently thalamic lesions +/- haemorrhage. Basal ganglia, brain stem and cerebellum also affected

JEV- Treatment

- Supportive
- Manage raised intracranial pressure
- Treat nosocomial infections
- Interferon 2a – trialled – no effect
- Steroids – not demonstrated to be beneficial
- An effective vaccine is available (countries have differeing guidelines on who should receive JE vaccine)

WEST NILE

History and epidemiology

- Originally isolated in West Nile region in 1937
- Sporadic outbreaks of febrile disease in Africa and Middle East since then
- Increasing severity observed since 1990s & emergence in Western hemisphere in 1999
- Naturally circulates between mosquitoes and birds

Its raining crows….

Mandell, Douglas, and Bennett's
PRINCIPLES AND PRACTICE OF seventh edition
INFECTIOUS DISEASES
GERALD L. MANDELL • JOHN E. BENNETT • RAPHAEL DOLIN

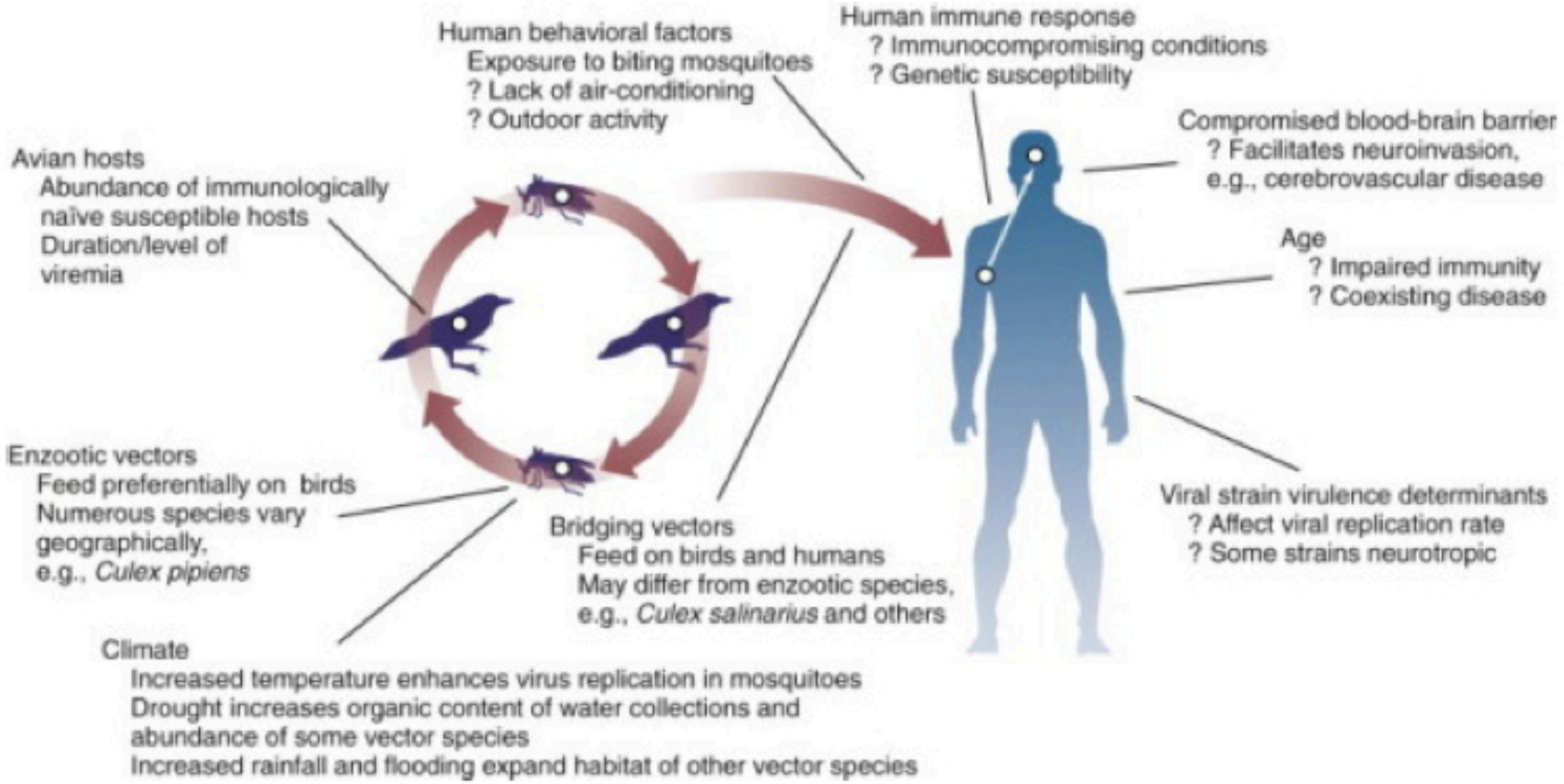


Figure 153-3 West Nile virus transmission cycle and examples of modifying climatologic, vertebrate, mosquito, and human factors on infection and illness.

Clinical features

- Asymptomatic in majority
- Incubation: 2-6 days
- Symptomatic in ~20%:
  - Non-specific febrile illness; varied symptoms
- Neurological disease in ~1%:
  - Febrile prodrome
  - Encephalitis, flaccid paralysis, cranial neuropathies, optic neuritis…
  - Sequelae common

Diagnosis and treatment

- Mainstay = serology (IgM positive on MAC-ELISA suggestive of diagnosis) but PCR is also useful (for CSF, not plasma)
- No specific therapy
- No vaccine

Table 1 | **Medically important mosquito-borne alphaviruses and flaviviruses**

Virus	Human disease syndrome	Reservoir hosts	Main enzootic/endemic vectors	Secondary amplification hosts	Epidemic vectors
Alphavirus					
Eastern equine encephalitis	Febrile illness, encephalitis	Passerine, birds	*Culiseta melanura*, *Culex (Melanoconion)* spp. (Latin America)	None	*Aedes*, *Ochlerotatus* and *Coquilletidia* spp.
Venezuelan equine encephalitis	Febrile illness, encephalitis	Rodents	*Culex* (*Melanoconion*) spp.	Equines	*Ochlerotatus* and *Psorophora* spp.
Western equine encephalitis	Febrile illness, encephalitis	Birds	*Culex tarsalis*, *Culex quinquefasciatus* (North America)		
Chikungunya	Arthralgia/rash	Primates	*Aedes* spp.	Humans	*Aedes aegypti*
O'nyong-nyong	Arthralgia/rash	Unknown	Unknown	Humans	*Anopheles funestus*, *Anopheles gambiae*
Ross River	Arthralgia/rash	Marsupials	*Culex annulirostris*, *Oculerotatis vigilax*	Humans?	
Flavivirus					
Dengue 1,2,4 (sylvatic genotypes)	Febrile illness, haemorrhagic syndrome	Primates	Arboreal *Aedes* spp.		
Dengue 1–4 (endemic genotypes)	Febrile illness, haemorrhagic syndrome	Humans	*Aedes aegypti*, *Aedes albopictus*		
Japanese encephalitis	Febrile illness, encephalitis	Birds	*Culex tritaeniorhynchus*, *Culex* spp.	Pigs	*Culex tritaeniorhynchus*, *Culex* spp.
St Louis encephalitis	Encephalitis	Birds	*Culex quinquefasciatus*		
West Nile	Febrile illness, encephalitis	Birds	*Culex* spp.		
Yellow fever	Hepatitis, haemorrhagic disease	Primates	*Aedes*, *Sabethes* and *Haemagogus* spp.	Humans	*Aedes aegypti*

Zika virus

- Zika
  - *Aedes* mosquitoes
  - *Flavivirus*
  - Africa, Southeast Asia & Pacific; emergence in South America
  - Illness usually mild: fever, rash, joint pain and conjuctivtitis
  - Linked to microcephaly in newborn (presumably by placental infection)
  - Case report of sexual transmission of Zika…
  - No specific therapeutic available

Thank you