Arbovirus infections

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What is an arbovirus?

What is an arbovirus?

- Arthropod borne virus
- Arthropod: invertebrate with exoskeleton, segmented body and paired joint appendages:
  - Insects (mosquitoes etc)
  - Arachnids (mites, ticks)
  - Myriapods
  - Crustaceans

https://en.wikipedia.org/wiki/Arthropod

Case Female Age 36 From Sri Lanka

History:

3 days: abrupt onset

Headache, Muscle (back) pain, Rigors

1 day

Nosebleeds

Examination:

T 38.4˚ BP 95/60 Resp 20

Alert but weak and lethargic

Bleeding from nose and gingiva

No rash, lymph nodes, splenomegaly

Case continued

Results:

Haemoglobin	95 g/L
White cells	1.8 x 10^9/L
Platelets	21 x 10^9/L
ALT	60 u/L (normal <35)

Diagnosis?

Case continued

Results:

Haemoglobin 95 g/L

White cells 1.8×10^9/L

Platelets 21×10^9/L

ALT 60 u/L (normal <35)

Diagnosis?

Dengue

Severe scrub typhus

Other

But if you were in

Gujarat

Crimean Congo haemorrhagic fever

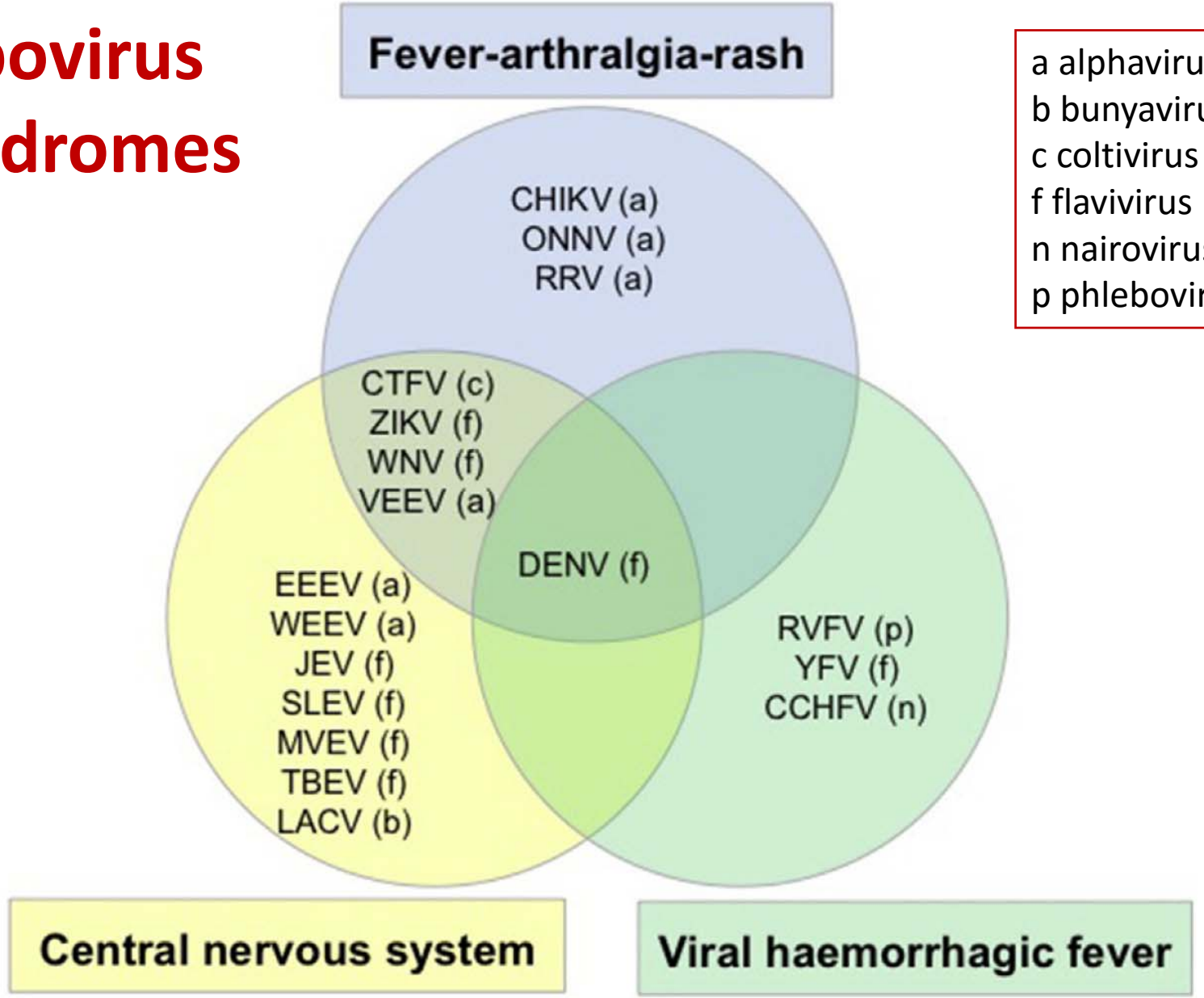
Liberia

Ebola virus infection

Brazil (Amazonia)

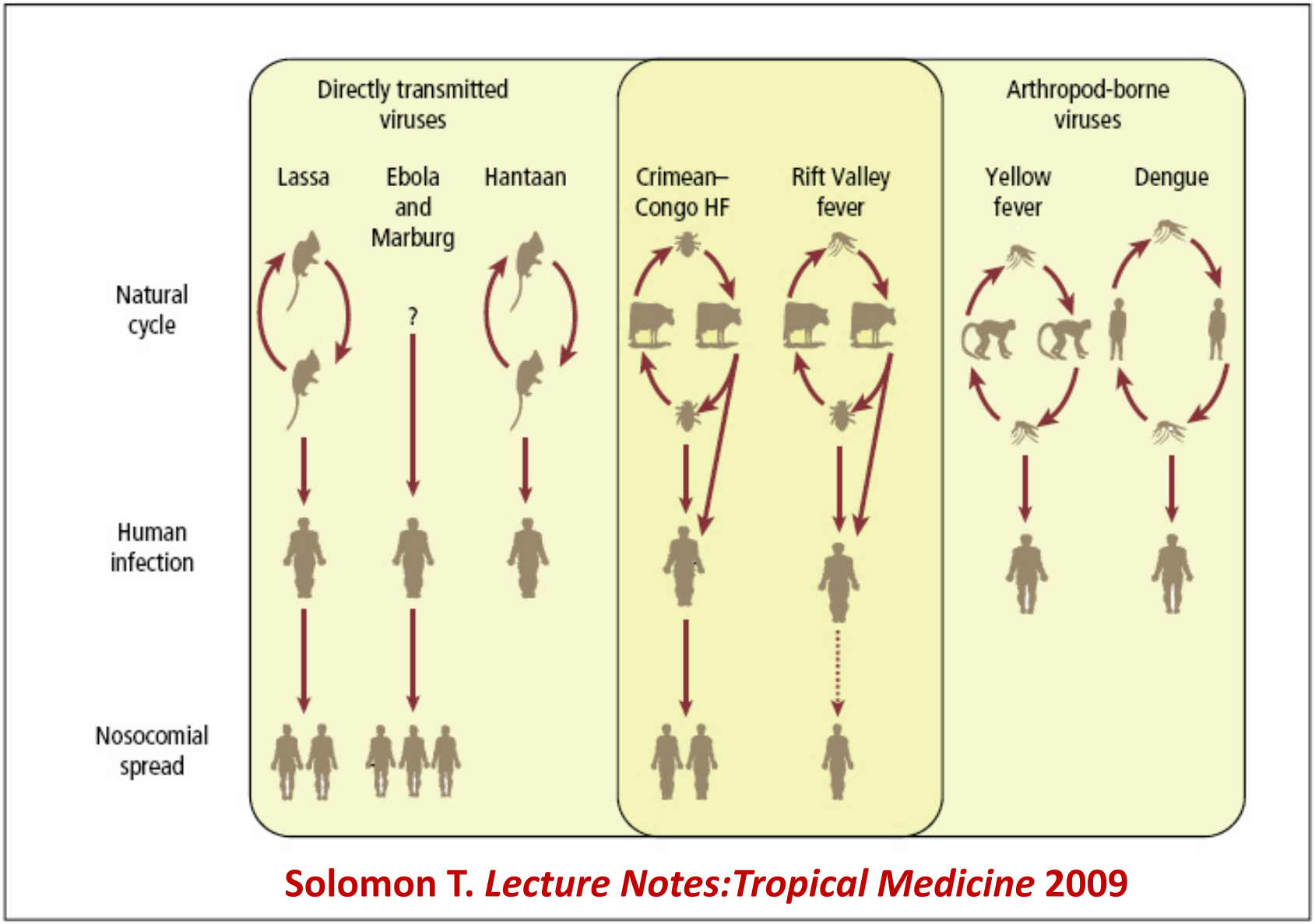
Oropouche virus infection

Arbovirus syndromes



a alphavirus
b bunyavirus
c coltivirus
f flavivirus
n nairovirus
p phlebovirus

Eckerle I *et al. Clin Microbiol Infect* 2018; 24: 240-5



Solomon T. *Lecture Notes:Tropical Medicine* 2009

Figure 41.1 Ecological overview of viral haemorrhagic fevers showing natural cycle, transmission to humans and potential for nosocomial spread. Note the distinction between directly transmissible viruses (Lassa, Ebola, Marburg and Hantaan), arboviruses (yellow fever and dengue), and those transmitted by both routes (Crimean–Congo haemorrhagic fever and Rift Valley fever). (Modified from Solomon [2002], with permission from Elsevier Science.)

Factors in imported disease

- Changes in travel
- Changes in ecology
- Changes in vectors
- Changes in local populations - conflict
- Changes in behaviour
- Changes in host
- Risk avoidance
  - Bite avoidance etc
  - Vaccines

50 year old woman with fever, rash and chest pain from Mauritius in March 2006

2 week holiday in Mauritius

Returned 4 days ago

Injured leg and admitted to hospital on day 9 for antibiotics

Many patients on ward with fever

No mosquito bites remembered

4 days later fever and headache for 3 days

Improved as flew back to UK

Full immunisations, no malaria chemoprophylaxis

Now has 2 days

Fever to 39^{o} C

Migratory joint pains

Headache

Photophobia

Rash

Pleuritic chest pain

Temp 38.9^{o} C P100

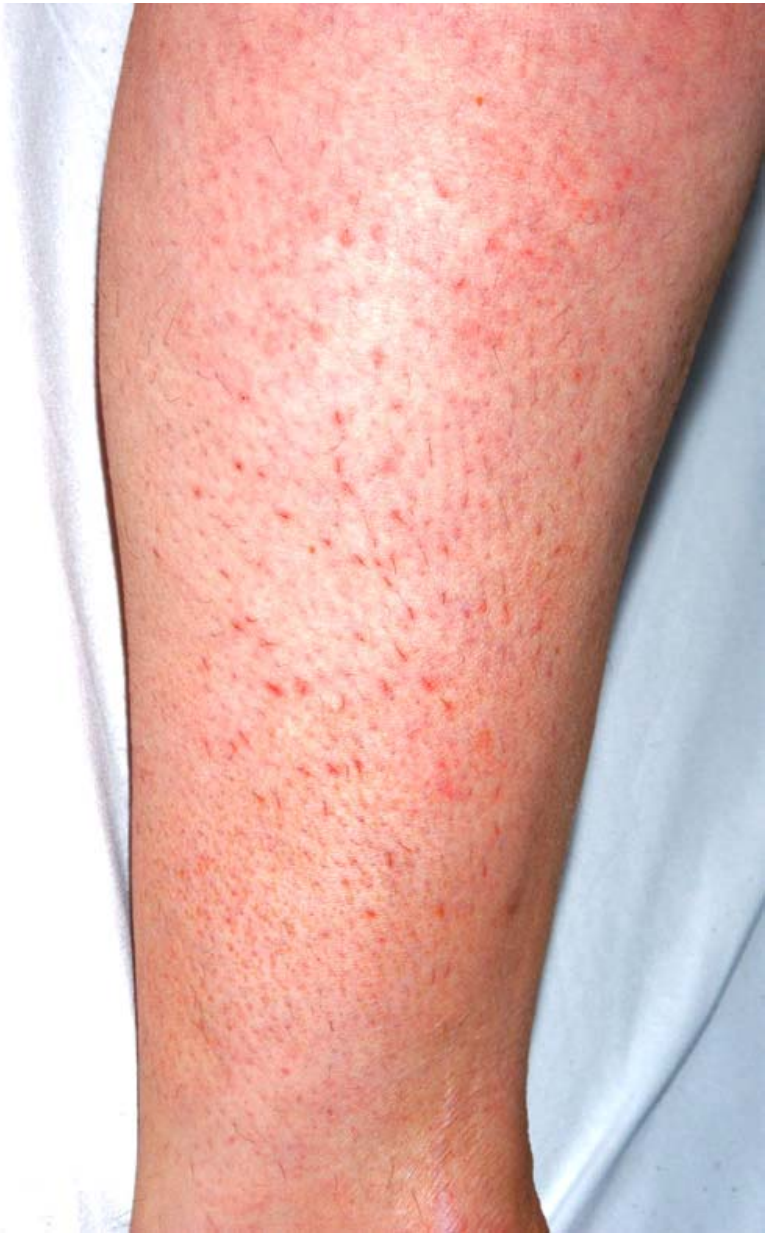
BP 120/85 RR 12

Discrete rash on legs

Chest clear

No neck stiffness

Joints normal



Investigations

Hb 11.0 g/dL (>11.5)

WBC 6.1 x 10^9/L

- Lymph 0.6 (1.5-4)
- Mono 0.2 (0.2-0.8)
- Neut 5.2 (2-7.5)

Plt 270 x 10^9/L (>150)

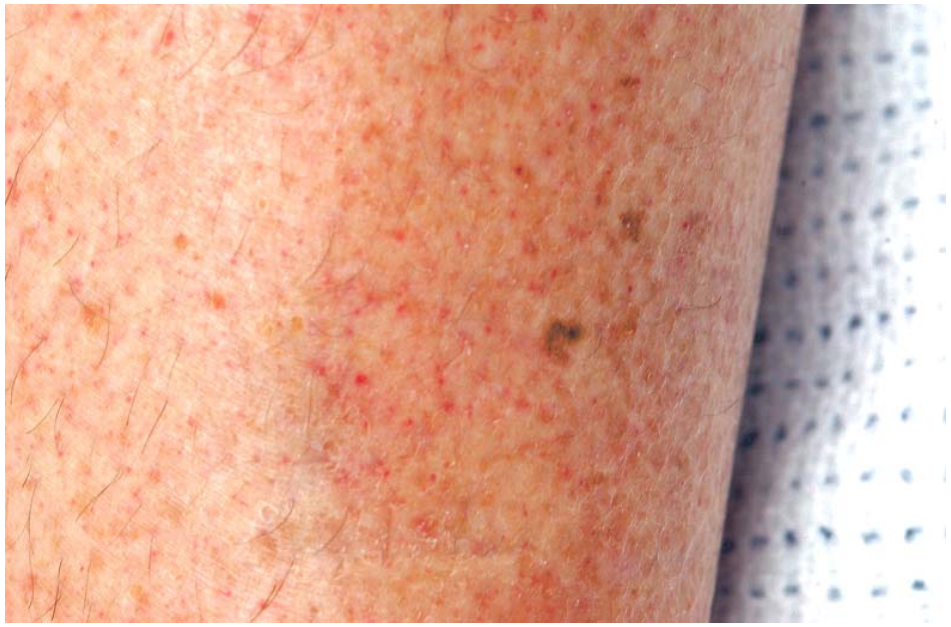
ESR 12 mm/hr

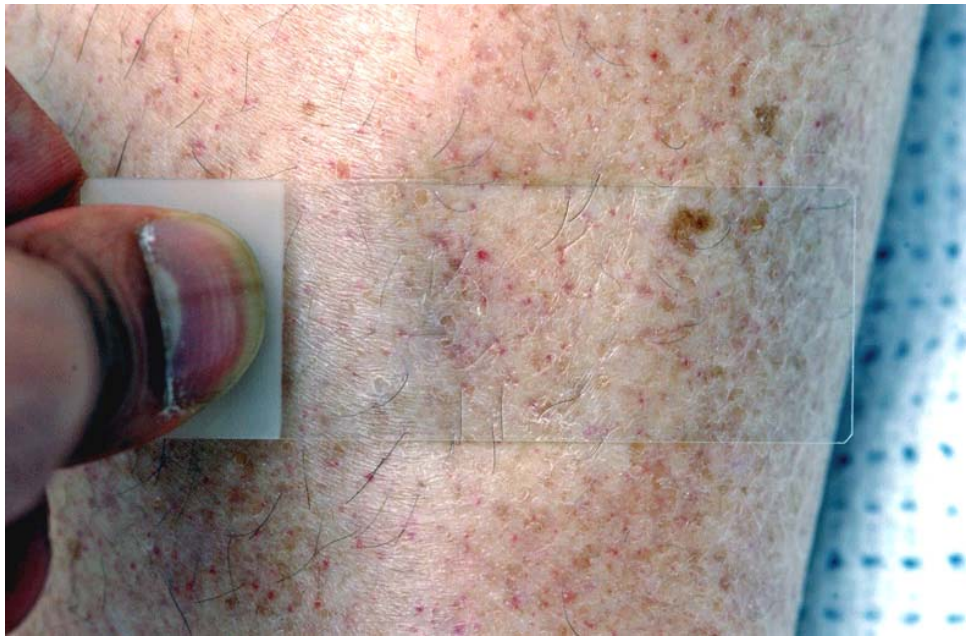
Malaria smears neg

Liver function

normal

Chest X ray normal





What is your diagnosis? (choose one)

1. Dengue
2. Malaria
3. Meningococcal meningitis
4. O'nyong-nyong
5. Something else

Initial diagnosis & progress

- Concern about meningococcal disease
  - CT of head normal
  - Given ceftriaxone
  - No lumbar puncture
  - Transferred to Liverpool

Initial diagnosis & progress

- Concern about meningococcal disease
  - CT of head normal
  - Given ceftriaxone
  - No lumbar puncture
  - Transferred to Liverpool

- Diagnosis presumed chikungunya
  - Pulmonary embolus excluded

Pialoux G *et al. Lancet Inf Dis* May 2007; 7: 319-27

Chikungunya

- Alphavirus
- Mosquitoes
- “that which bends you up” in Makonde

- Similar to dengue but joint pain predominates and may persist for months
- Can cause variety of skin rashes

Clinical features chikungunya

	Malaysia 1998 (%)	Réunion 2005–Feb 2006 (%)
Skin rash	50	39
Myalgia	50	60
Headache, spinal pain	50, 50	70, NR
Arthralgia (all types)	78	100
Large joints	18	NR
Fever	100	100
Number of reported cases	51	504

NR=not reported. Data for Malaysia from Lam and colleagues (2001)[19] and data for Réunion from http://www.invs.sante.fr.

Table: **Frequency of clinical manifestations during the 1998 Malaysian epidemic and the 2005 Réunion epidemic**

Vectors

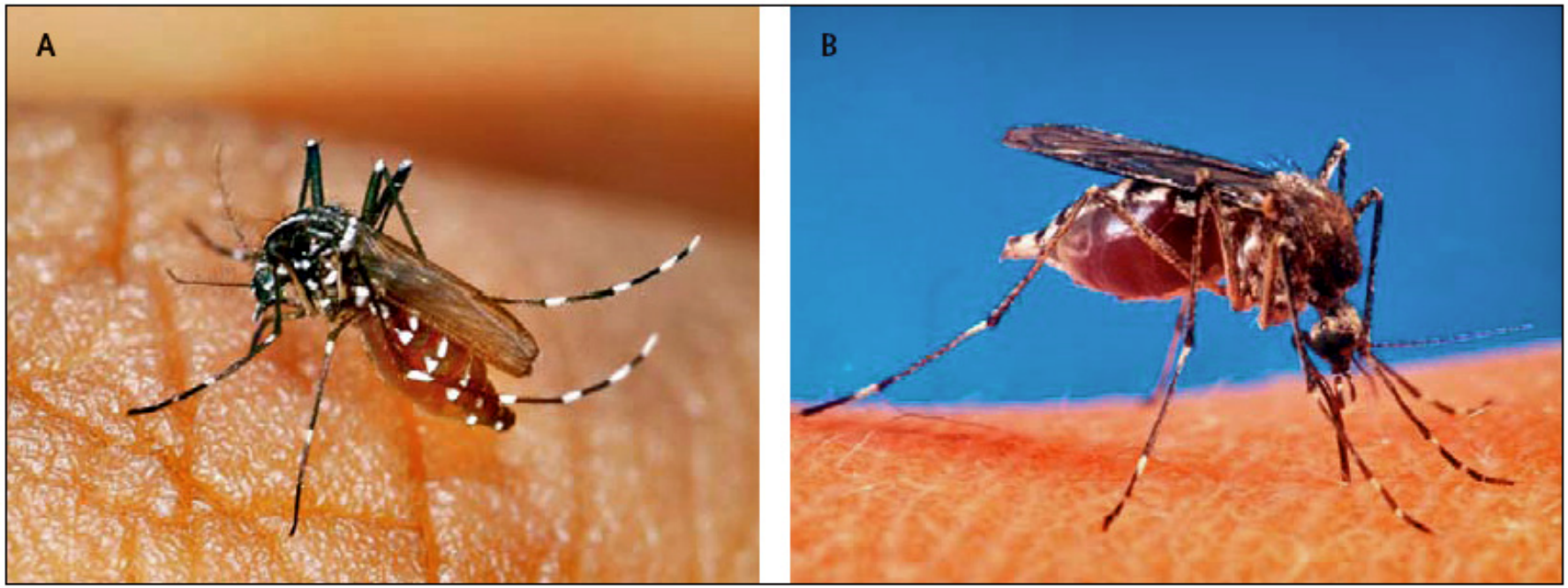
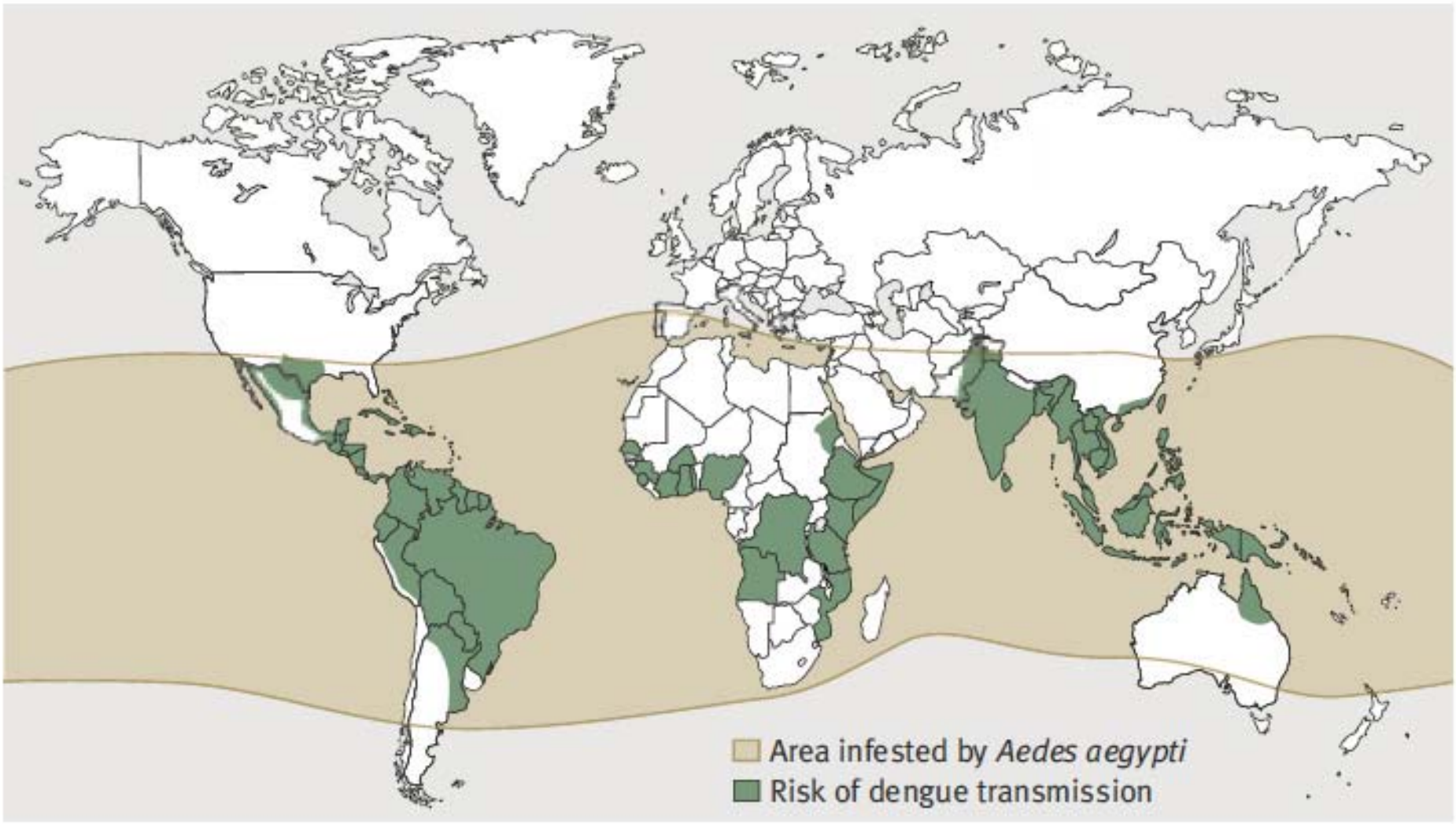


***Figure 1*: Mosquito vectors of chikungunya virus**
(A) Blood-gorged *A albopictus* female feeding on a human host. *A albopictus* is the primary chikungunya virus vector in the current Indian Ocean outbreak. (B) *A aegypti* mosquito. *A aegypti* is the primary chikungunya virus vector in Asian chikungunya outbreaks. Images from United States Department of Agriculture.

Pialoux G *et al. Lancet Inf Dis* May 2007; 7: 319-27



Presence of dengue worldwide and areas infested by the main vector, *Aedes aegypti*

Teixera M. *BMJ* 2009;339:b4338 doi: 10.1136/bmj.b4338

Clinical Microbiology and Infection 24 (2018) 240–245

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journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Emerging souvenirs—clinical presentation of the returning traveller with imported arbovirus infections in Europe

I. Eckerle [1, *], V.T. Briciu [2], Ö. Ergönül [3], M. Lupşe [2], A. Papa [4], A. Radulescu [2], S. Tsiodras [5], C. Tsitou [6], C. Drosten [7], V.R. Nussenblatt [8], C.B. Reusken [9], L.A. Sigfrid [10], N.J. Beeching [11]

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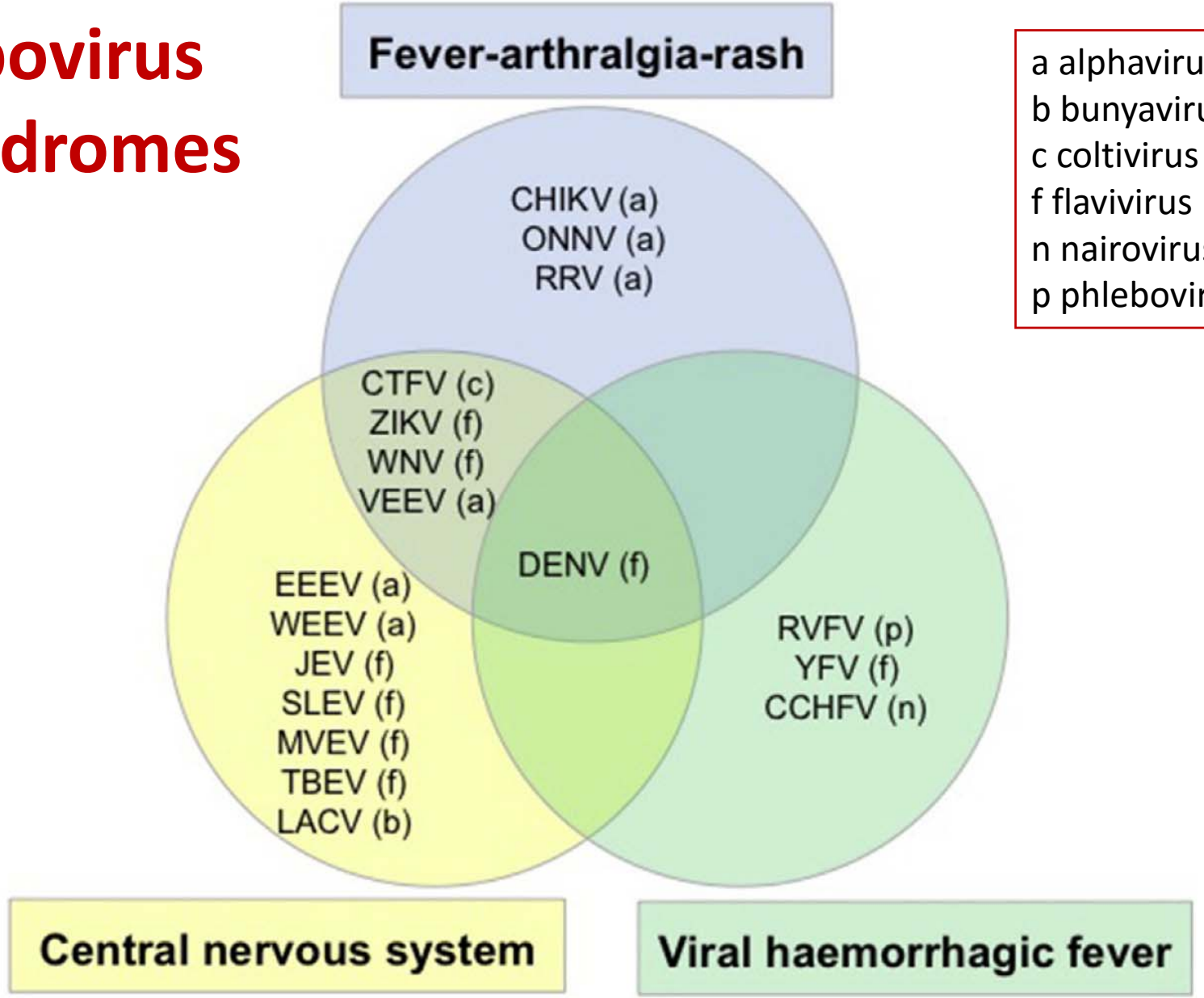
[9] *Viroscience, Erasmus Medical Centre Rotterdam, Rotterdam, The Netherlands*
[10] *Centre for Tropical Medicine, University of Oxford, Oxford, UK*
[11] *Department of Clinical Sciences, Liverpool School of Tropical Medicine, Tropical and Infectious Disease Unit, Royal Liverpool University Hospital, Liverpool, UK*

Eckerle I *et al. Clin Microbiol Infect* 2018; 24: 240-5

Arbovirus syndromes



a alphavirus
b bunyavirus
c coltivirus
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n nairovirus
p phlebovirus

Eckerle I *et al. Clin Microbiol Infect* 2018; 24: 240-5

Dengue

- Common arbovirus infection
- 4 strains of flavivirus
- Aedes mosquitoes

- Febrile illness
- Often fatigue afterwards
- Can cause severe haemorrhage
- Especially after reinfection with different strain

Dengue

Main differential diagnosis

Dengue from Vietnam

Jan 2008

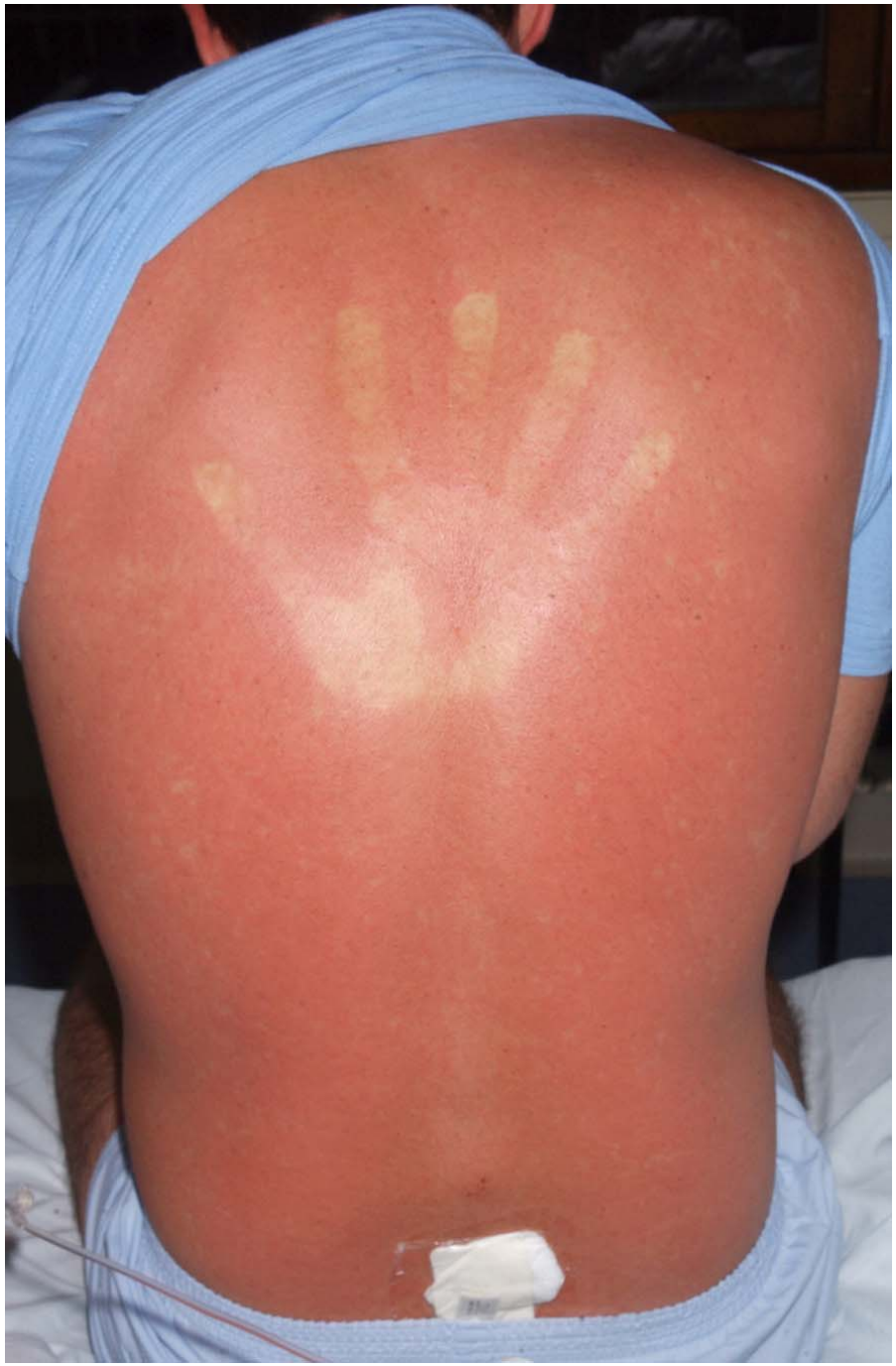

Table 1
Comparison of selected clinical findings in chikungunya, dengue and Zika infections

Clinical presentation	Chikungunya	Dengue	Zika
Fever	+++	+++	+
Rash	++	++	+++
Myalgia	+	+++	+
Arthralgia	+++	+	++
Oedema	−	−	++
Retro-orbital pain	+	++	+
Conjunctivitis	+++	−	+++
Lymphadenopathy	++	++	+
Hepatomegaly	+++	−	−
Haemorrhage	−	+	−

Adapted and modified with permission from [33,34].
+++, very common; ++, frequently observed; +, sometimes observed; −, not typical.

Eckerle I *et al. Clin Microbiol Infect* 2018; 24: 240-5

Table 2
Comparison of baseline laboratory findings in chikungunya, dengue and Zika infections

Laboratory finding	Chikungunya	Dengue	Zika
Anaemia	+	−	−
Leucopenia	++	+++	−/+
Neutropenia	+	+++	−
Lymphocytopenia	+++	++	−/+
Thrombocytopenia	+	+++	−/+[a]
Increased CRP	++	+++	−
Increased ALT	++	+++	−

Adapted and modified with permission from [33]; additional data from [35,36].
ALT, alanine aminotransferase; CRP, C-reactive protein; +++, very common; ++, frequently observed; +, sometimes observed; −, not typical.
[a] If observed, thrombocytopenia is usually mild.

Eckerle I *et al. Clin Microbiol Infect* 2018; 24: 240-5

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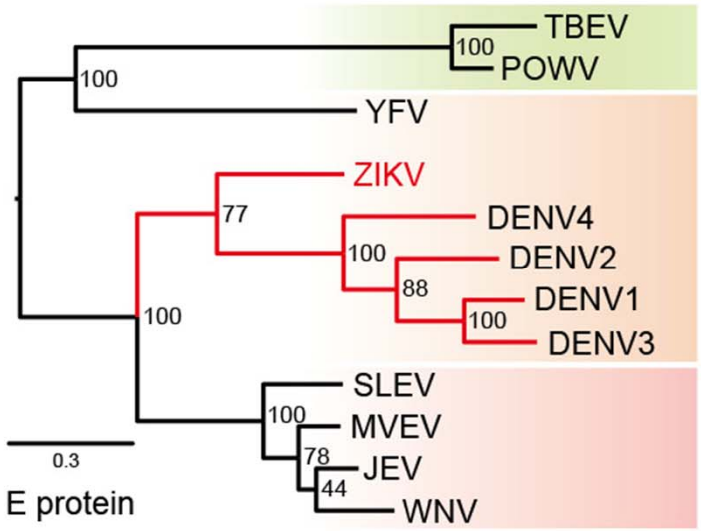
Eckerle I *et al. Clin Microbiol Infect* 2018; 24: 240-5

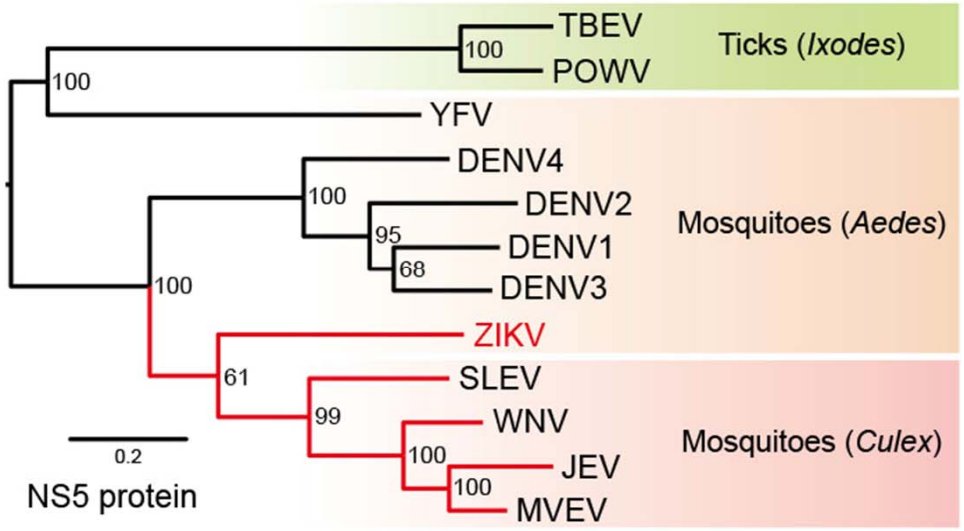
Points

- Differential diagnosis of fever and rash from tropics is wide
- Case of probable nosocomial chikungunya infection
- As part of (then) current large epidemic
- More severe and prolonged sequelae than dengue, especially joint disease
- *Aedes* vectors spreading and climate change may exacerbate

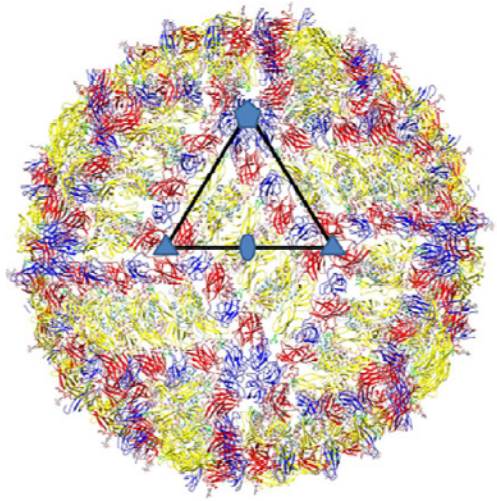
Pialoux G *et al. Lancet Inf Dis* 2007; 7: 319-27
Suhrbier A *et al. Nat Rev Rheumatol* 2012; 8: 420-9

Zika virus = family *Flaviviridae*, genus *Flavivirus*





Barba-Spaeth *et al.* Nature. 2016 Jun 23.



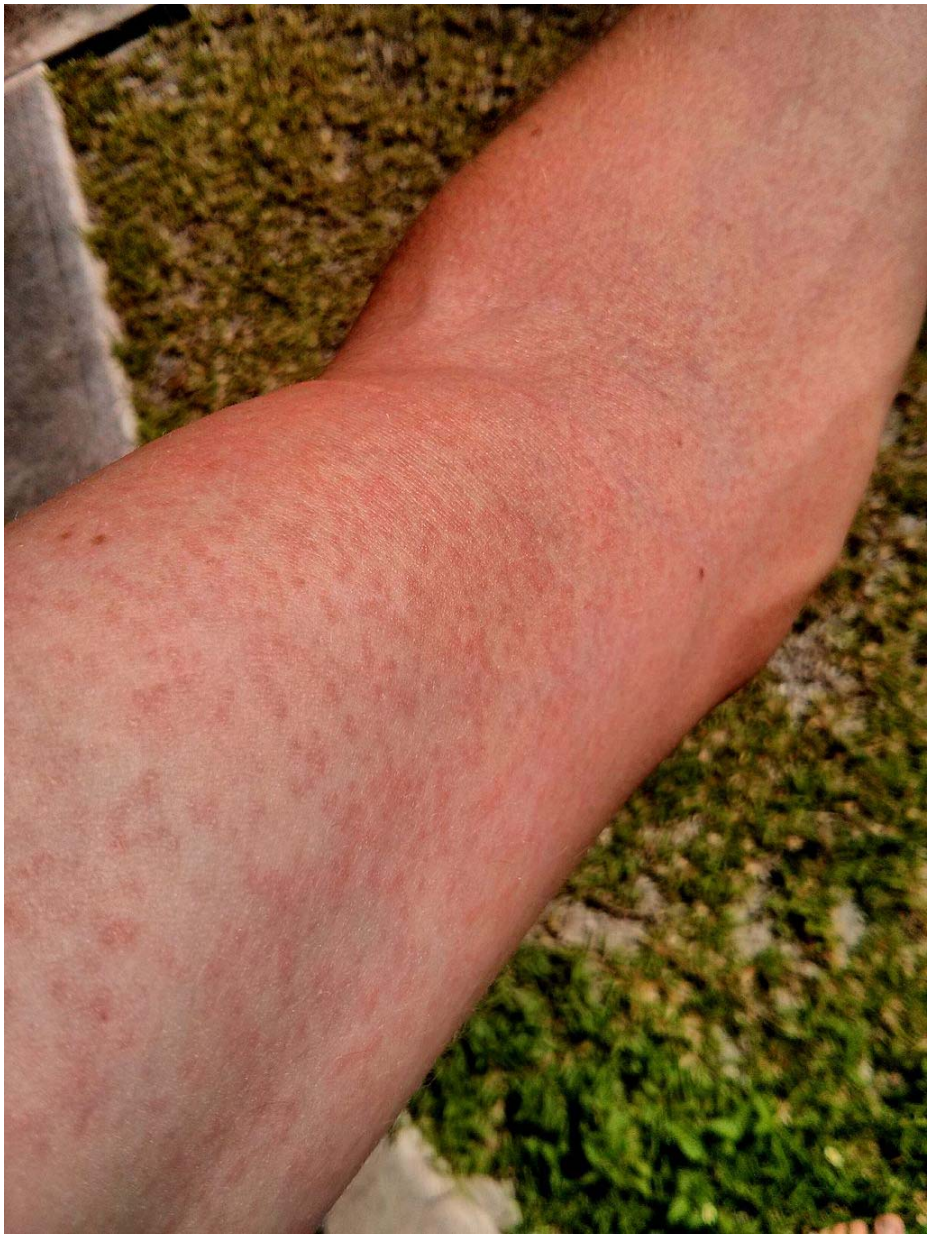
Sirohi *et al.*
Science 2016

Zika

Fever arthralgia rash syndrome
80 % asymptomatic

Maculopapular rash
Conjunctivitis
Lymphadenopathy

Less lymphopenia
Less thrombocytopenia
(compared to DEN, CHIK)



Arm rash c/o
Wikimedia commons

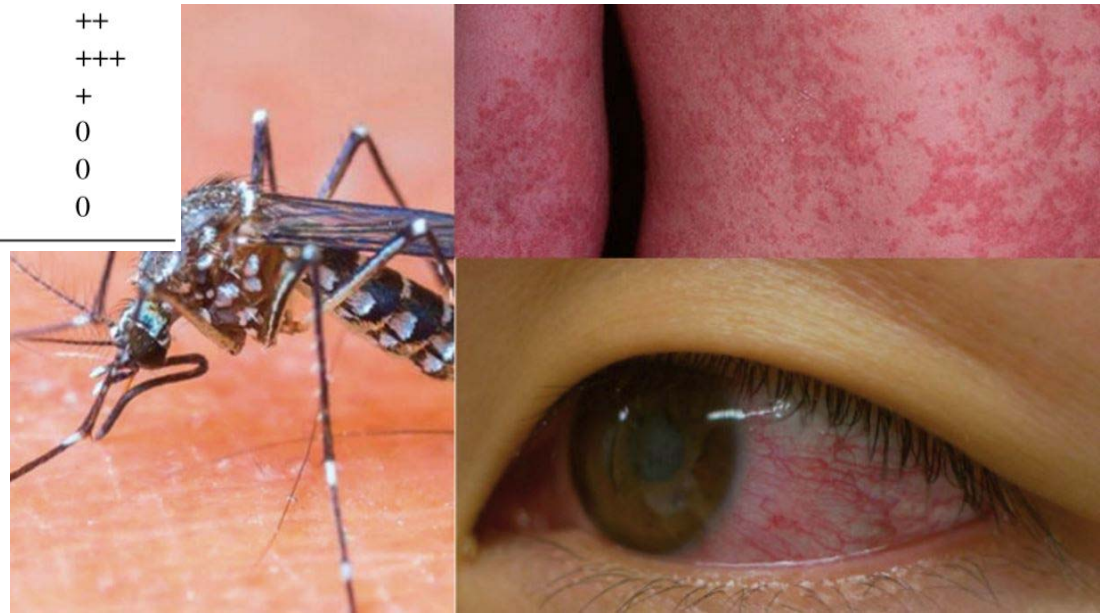
What are the symptoms of a Zika virus infection?

Comparison of symptoms for dengue fever, chikungunya, and Zika.
Clinique comparée de la dengue, du chikungunya et du Zika.

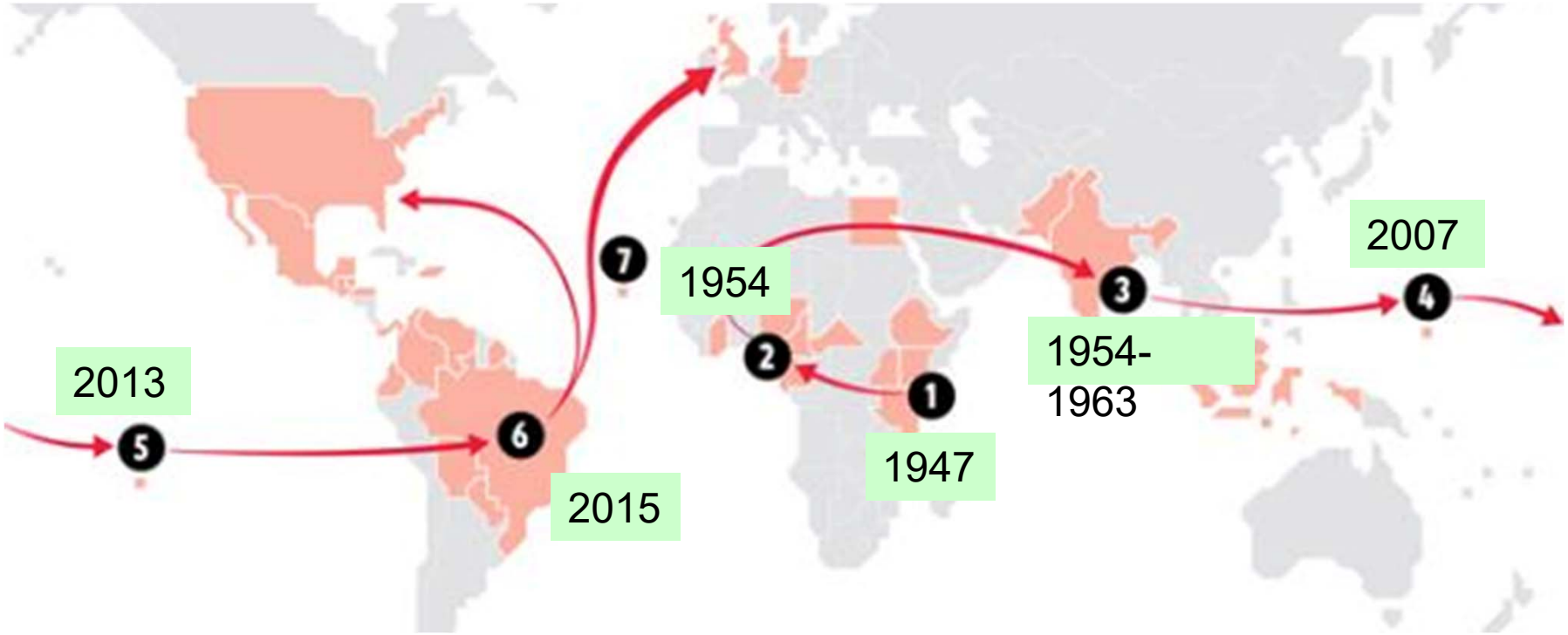
Symptoms	Dengue	Chikungunya	Zika
Fever	++++	+++	+++
Myalgia/arthralgia	+++	++++	++
Edema of extremities	0	0	++
Maculopapular rash	++	++	+++
Retro-orbital pain	++	+	++
Conjunctivitis	0	+	+++
Lymphadenopathies	++	++	+
Hepatomegaly	0	+++	0
Leukopenia/thrombopenia	+++	+++	0
Hemorrhage	+	0	0

The US Centers for Disease Control and Prevention (CDC) put it pretty clearly:
"The illness is usually mild… Severe disease requiring hospitalization is uncommon. Deaths are rare."

75-80% OF ALL CASES ARE ASYMPTOMATIC



Spread of Zika 1950-2015



Nigeria, 1953 (2): first recognition of human illness caused by Zika virus
Only 13 more cases reported in next 57 years!
Then:
Yap (Micronesia), 2007 (4): 5000 infections out of 6700 population (75% incidence)
French Polynesia, 2013-14 (5): 32,000 infections
Brazil, 2015-16 (6): 16000ish infections suspected **in pregnant women!**

PNAS 2017; 119–124, doi: 10.1073/pnas.1614303114

Global risk model for vector-borne transmission of Zika virus reveals the role of El Niño 2015

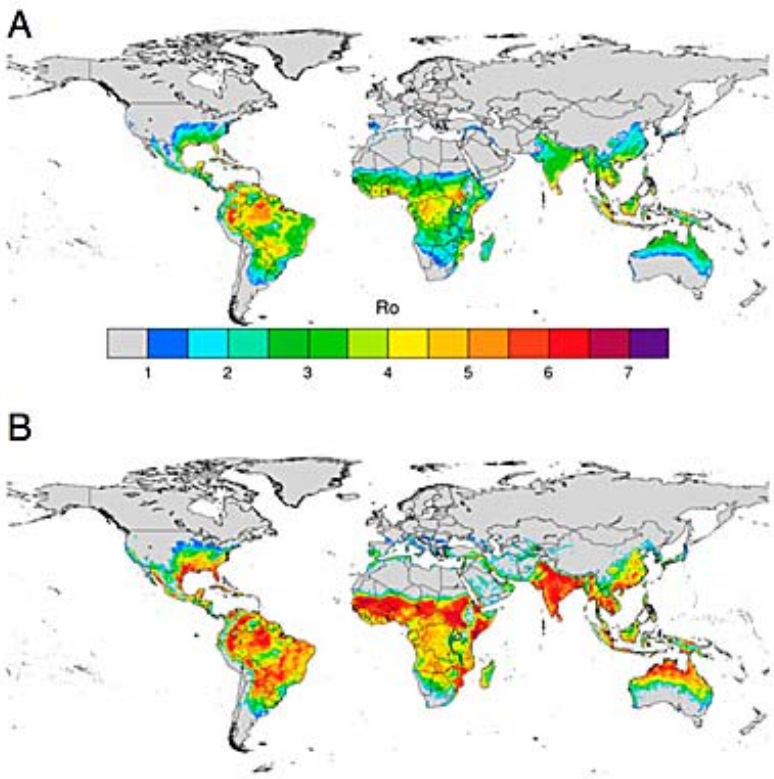
Cyril Caminade[a,b,1], Joanne Turner[a], Soeren Metelmann[b,c], Jenny C. Hesson[a,d], Marcus S. C. Blagrove[a,b], Tom Solomon[b,e], Andrew P. Morse[b,c], and Matthew Baylis[a,b]

[a]Department of Epidemiology and Population Health, Institute of Infection and Global Health, University of Liverpool, Liverpool CH64 7TE, United Kingdom; [b]Health Protection Research Unit in Emerging and Zoonotic Infections, University of Liverpool, Liverpool L69 3GL, United Kingdom; [c]Department of Geography and Planning, School of Environmental Sciences, University of Liverpool, Liverpool L69 7ZT, United Kingdom; [d]Department of Medical Biochemistry and Microbiology, Zoonosis Science Center, Uppsala University, Uppsala 751 23, Sweden; and [e]Department of Clinical Infection, Microbiology and Immunology, Institute of Infection and Global Health, University of Liverpool, Liverpool L69 7BE, United Kingdom

Edited by Anthony A. James, University of California, Irvine, CA, and approved November 14, 2016 (received for review September 2, 2016)

Zika, a mosquito-borne viral disease that emerged in South America in 2015, was declared a Public Health Emergency of International Concern by the WHO in February of 2016. We developed a climate-driven R_0 mathematical model for the transmission risk of Zika virus (ZIKV) that explicitly includes two key mosquito vector species: *Aedes aegypti* and *Aedes albopictus*. The model was parameterized and calibrated using the most up to date information from the available literature. It was then driven by observed gridded temperature and rainfall datasets for the period 1950–2015. We find that the transmission risk in South America in 2015 was the highest since 1950. This maximum is related to favoring temperature conditions that caused the simulated biting rates to be largest and mosquito mortality rates and extrinsic incubation periods to be smallest in 2015. This event followed the suspected introduction of ZIKV in Brazil in 2013. The ZIKV outbreak in Latin America has very likely been fueled by the 2015–2016 El Niño climate phenomenon affecting the region. The highest transmission risk globally is in South America and tropical countries where *Ae. aegypti* is abundant. Transmission risk is strongly seasonal in temperate regions where *Ae. albopictus* is present, with significant risk of ZIKV transmission in the southeastern states of the United States, in southern China, and to a lesser extent, over southern Europe during the boreal summer season.

Zika virus | R_0 model | El Niño | *Ae. aegypti* | *Ae. albopictus*



Factors in Brazil

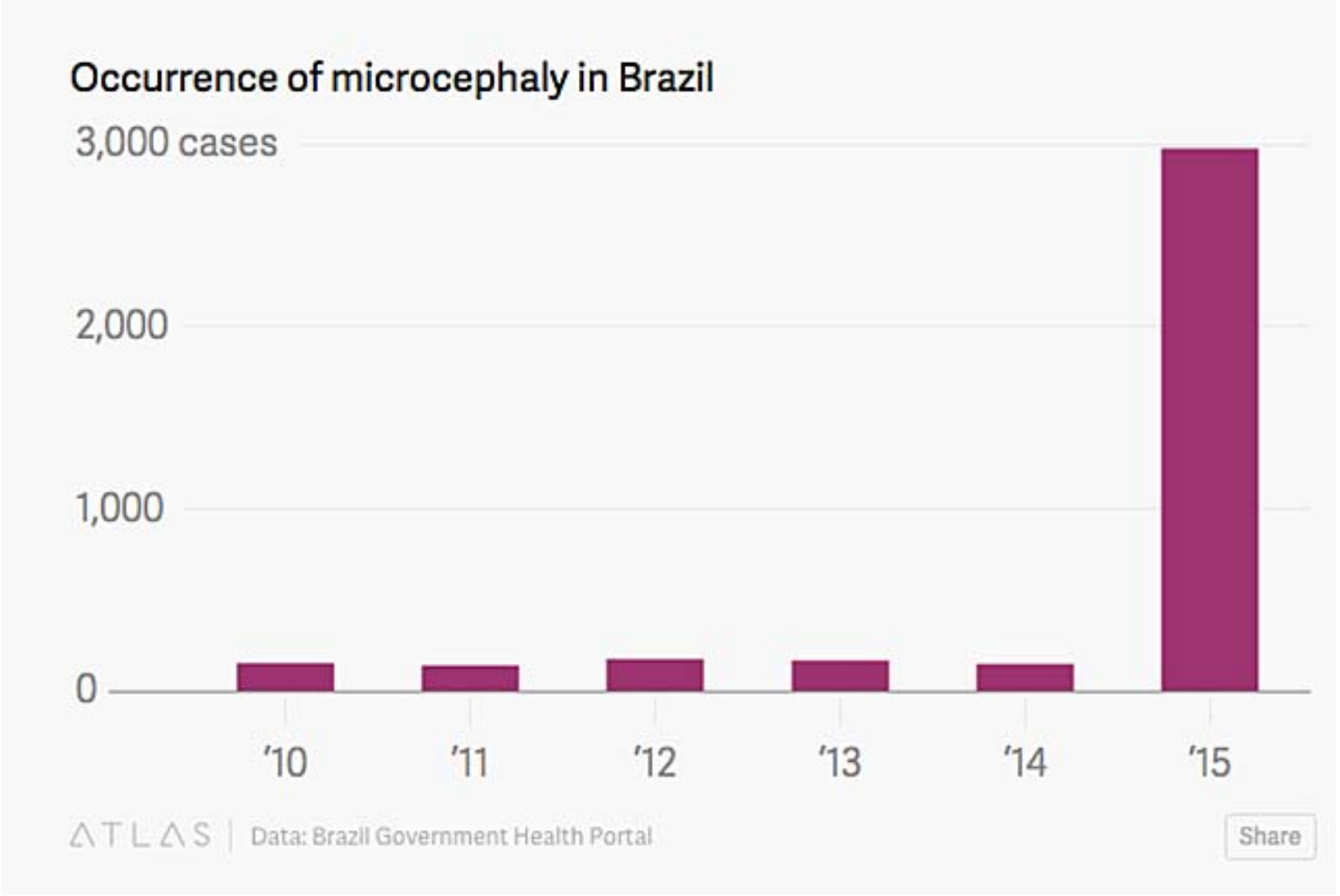
- Non immune population
- Urban crowding
- Poor control of vectors

- Perfect climatic conditions following 2015 El Niño
- Introduction of virus

ZIKA & MICROCEPHALY

Image:
CDC

Zika virus (ZIKV) and microcephaly



Zika virus (ZIKV) and microcephaly

ZIKV RNA found in amniotic fluid in cases of microcephaly

ZIKV RNA and antigen found in tissues from children with microcephaly who died shortly after birth

ZIKV RNA in placenta of a fetus with microcephaly that miscarried

ZIKV IgM in CSF of infants with microcephaly

ZIKA & GUILLAIN BARRÉ SYNDROME

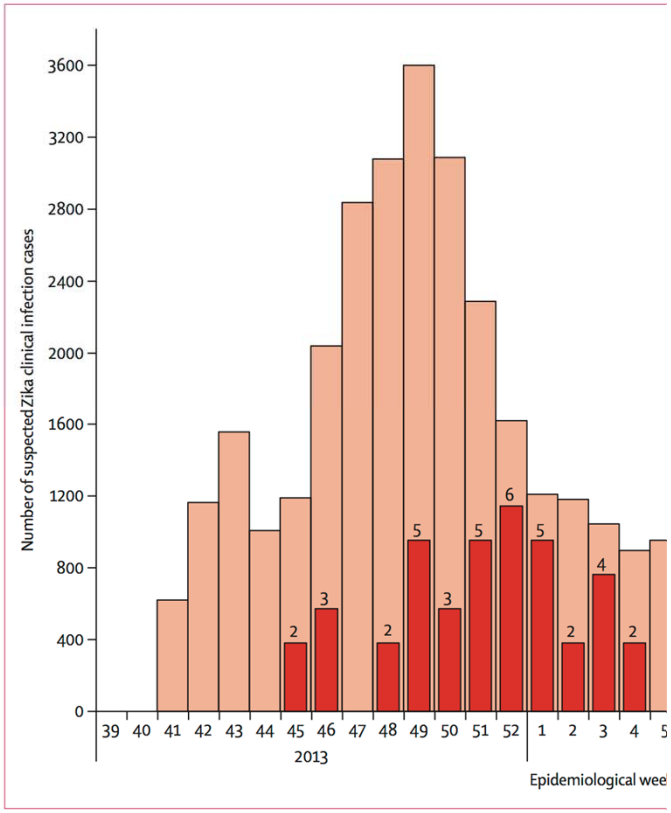
Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study

Van-Mai Cao-Lormeau, Alexandre Blake*, Sandrine Mons, Stéphane Lastère, Claudine Roche, Jessica Vanhomwegen, Timothée Dub, Laure Baudouin, Anita Teissier, Philippe Larre, Anne-Laure Vial, Christophe Decam, Valérie Choumet, Susan K Halstead, Hugh J Willison, Lucile Musset, Jean-Claude Manuguerra, Philippe Despres, Emmanuel Fournier, Henri-Pierre Mallet, Didier Musso, Arnaud Fontanet*, Jean Neil*, Frédéric Ghawché**

Lancet 2016; 387: 1531-39

Summary

Background Between October, 2013, and April, 2014, French Po
ever described at that time. During the same period, an increase i
a possible association between Zika virus and Guillain-Barré syn
dengue virus infection in developing Guillain-Barré syndrome.



Case Report

Zika virus found by PCR in CSF

Lancet 2016; 387: 1482

Guillain-Barré syndrome associated with Zika virus infection

Patrícia Brasil, Patricia Carvalho Sequeira*, Andrea D'Avila Freitas, Heruza Einsfeld Zogbi, Guilherme Amaral Calvet, Rogerio Valls de Souza, André Machado Siqueira, Marcos Cesar Lima de Mendonca, Rita Maria Ribeiro Nogueira, Ana Maria Bispo de Filippis, Tom Solomon*

Lancet 2016; 387: 1482

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Correspondence to:
Dr Patrícia Brasil, Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil
patricia.brasil@ini.fiocruz.br

See Online for appendix

A 24-year-old housekeeper presented to hospital in Rio de Janeiro in June, 2014, with headache, fever, and a rash, 5 days after waking with a severe generalised headache, retro-orbital pain, weakness, and paraesthesia of the hands and feet. 2 days later she developed fever (axillary temperature 42°C), chills, and a pruritic rash on the face, abdomen, chest, and arms. By day 4, she was afebrile but had painful swelling of the hands (appendix) and feet, difficulty walking, and disseminated rash. She had had dengue 5 years previously, had not travelled recently, and did not recall any tick or mosquito bites.

On examination, she was alert and fully oriented. Axillary temperature was 36·7°C, pulse 90 beats per min, blood pressure 100/60 mm Hg, and respiratory rate 20 breaths per min. She had a diffuse erythematous macular rash, bilateral non-purulent conjunctival hyperaemia, enanthema of the palate, one enlarged painless cervical lymph node, and swelling of the hands and feet, but no signs of meningism. She had reduced strength in the legs, absent deep tendon reflexes at the knees and ankles, and both plantars were absent; sensation to light touch was reduced in the legs, but she had no urinary retention or ataxia. Examination, including neurological examination of the arms, was otherwise normal. Lumbar puncture (day 6), nerve conduction studies and an electromyogram (day 10), and a non-enhanced MRI (day 13) were normal. From day 10 the rash and swelling began to resolve with supportive treatment. By day 13 she was fully mobile and could be discharged. At follow-up on day 41, her only remaining symptom was persistent headache.

We investigated her serum and cerebrospinal fluid (CSF) for dengue, chikungunya, and Zika viruses. Real-time PCR for dengue and chikungunya was negative, but PCR was positive for Zika virus[1] in serum (day 5), CSF (day 6), saliva (day 10), and urine (day 11). The CSF and acute and convalescent serum were negative for dengue and chikungunya by IgM-capture ELISA. Zika ELISA was not available. To identify the Zika virus genotype we sequenced 327 base pair amplicons encompassing the envelope protein, and identified the Asian lineage of Zika in the CSF (figure).

Like dengue and chikungunya, Zika virus causes a febrile illness with rash. During the 2013 outbreak of Zika virus in French Polynesia[2] an apparent increase in Guillain-Barré syndrome incidence was noted but with no baseline data for comparison. One case[3] had antibodies against Zika and dengue viruses (which can also trigger Guillain-Barré syndrome),[4] but no virus was detected.

Our patient had no evidence of dengue or chikungunya infection, but Zika was found in the CSF by PCR, and unusually she also had high grade fever and clinical features consistent with paraparetic Guillain-Barré syndrome, a rare atypical presentation.[5] CSF and neurophysiological investigations were normal, as is often found early in Guillain-Barré syndrome. She met Level III of diagnostic certainty for Guillain-Barré syndrome in the Brighton classification (consistent clinical features, but no supporting CSF or neurophysiology evidence).

Our case highlights the potential for neurotropism of Zika virus, and the need to consider this emerging virus as a mosquito-borne cause of fever, rash, and neurological disease.

Summary

Zika causes other birth defects and is a trigger for Guillain Barré syndrome

What's the exact risk? Why so many birth defects in Brazil? Are there other factors involved?

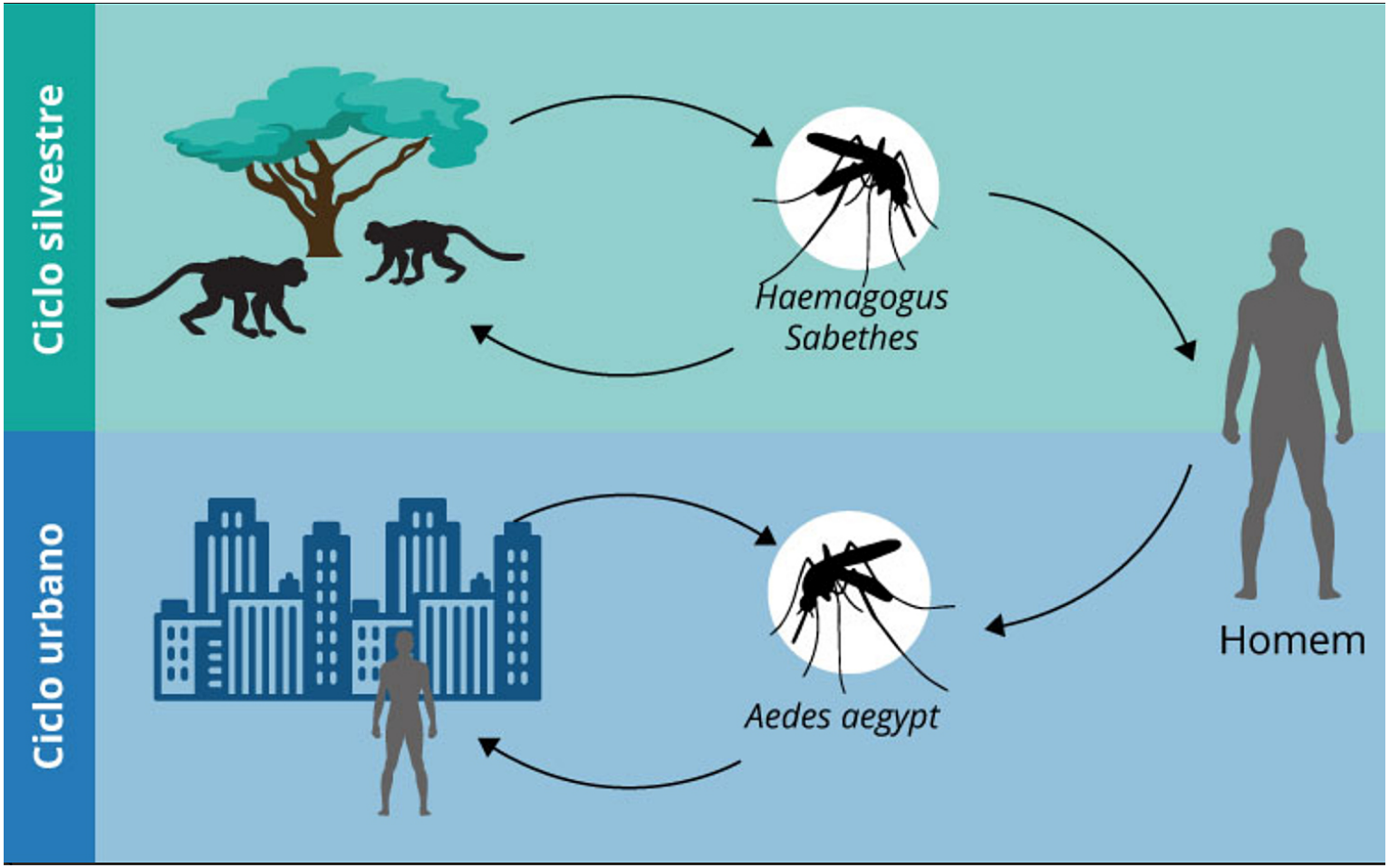
Several vaccines are under development and will likely be available in the next few years

The role of cross-reactive immune responses in clinical disease remains to be determined

Yellow fever

- Flavivirus
- *Aedes* mosquitoes
- Biphasic illness, early mild
- Late deterioration in 15% with high mortality (liver failure etc)
- Effective vaccine (lifelong immunity)
- Huge historical significance in “European” colonisation of other continents, trade and military

Life cycle yellow fever



http://portalms.saude.gov.br/saude-de-a-z/febre-amarela-sintomas-transmissao-e-prevencao

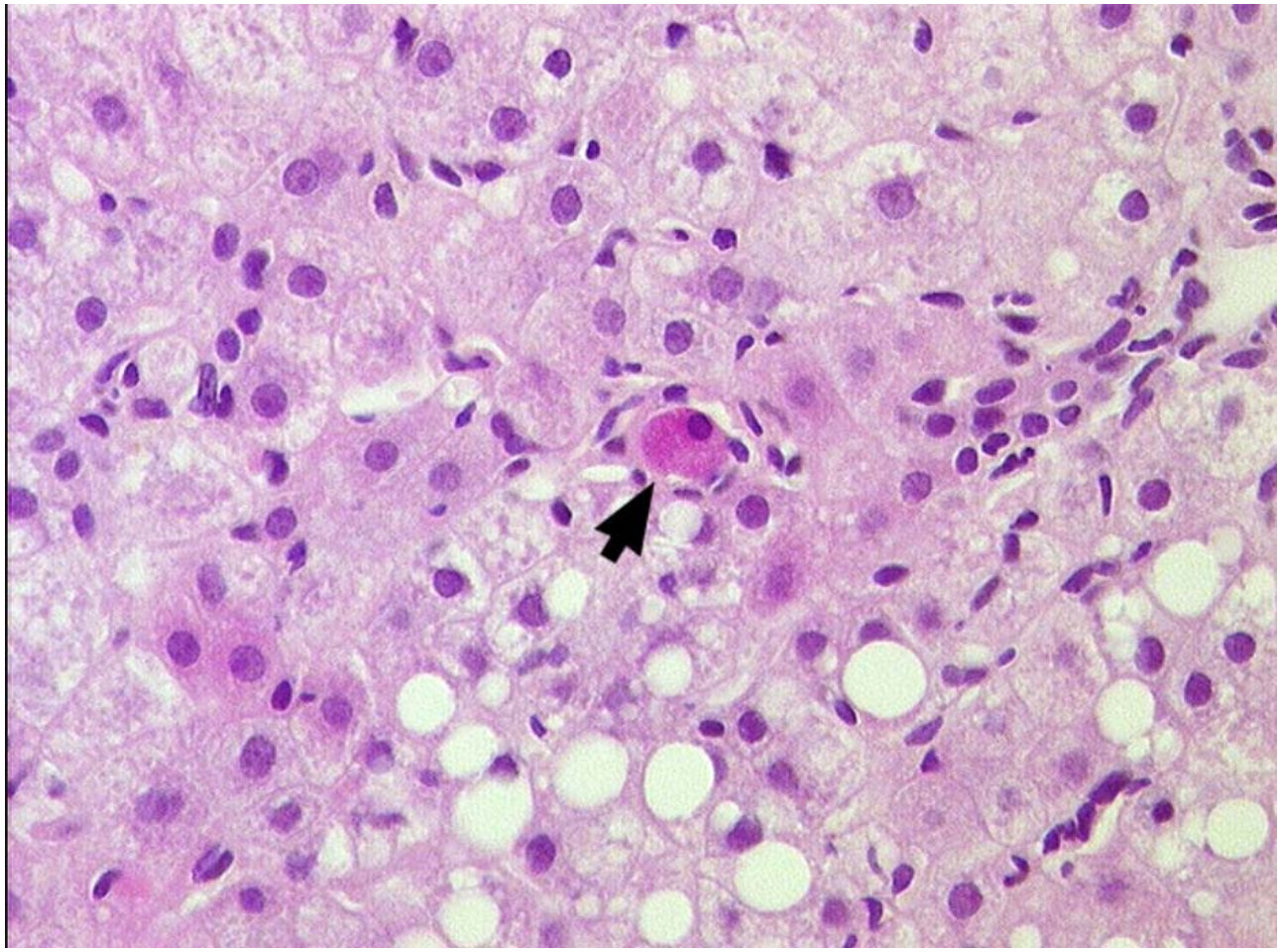
Symptoms

Brazilian Ministry of Health

http://portalms.saude.gov.br/saude-de-a-z/febre-amarela-sintomas-transmissao-e-prevencao

Councilman bodies in liver

Eosinophilic body of apoptotic hepatocyte

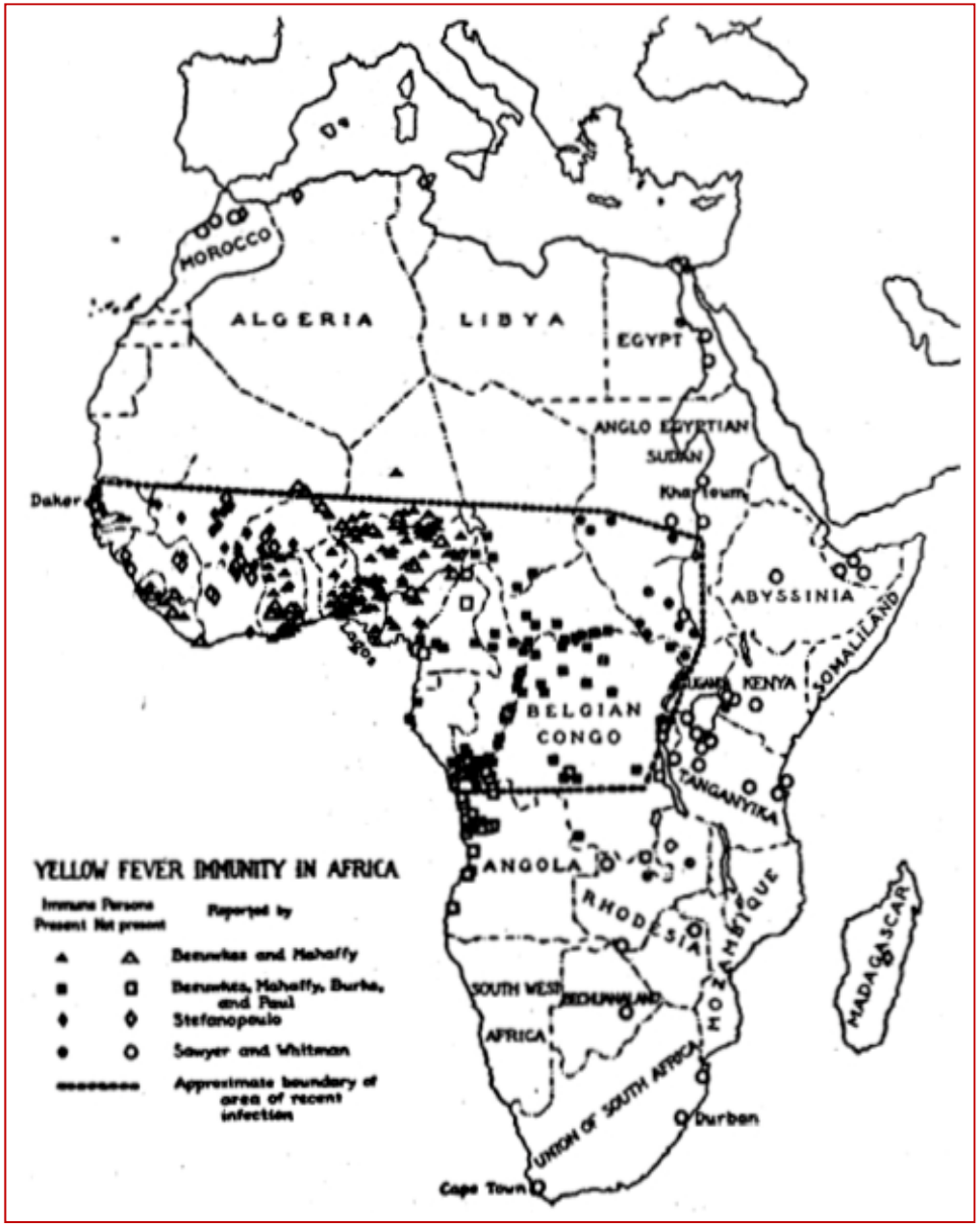


https://www.pinterest.com/pin/325736985530048998/

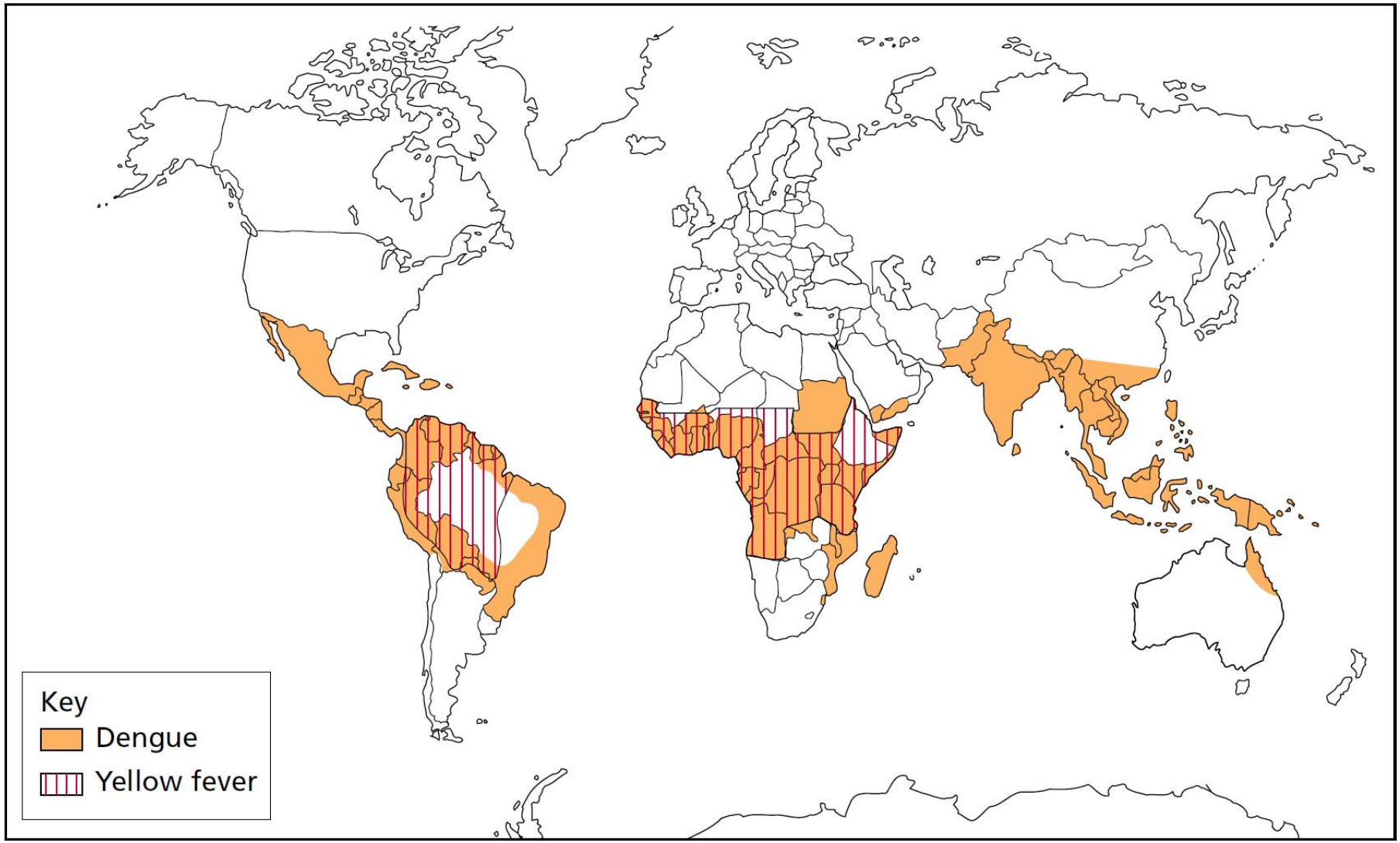
THE PRESENT GEOGRAPHIC DISTRIBUTION OF YELLOW FEVER AND ITS SIGNIFICANCE[1]

DR. WILBUR A. SAWYER

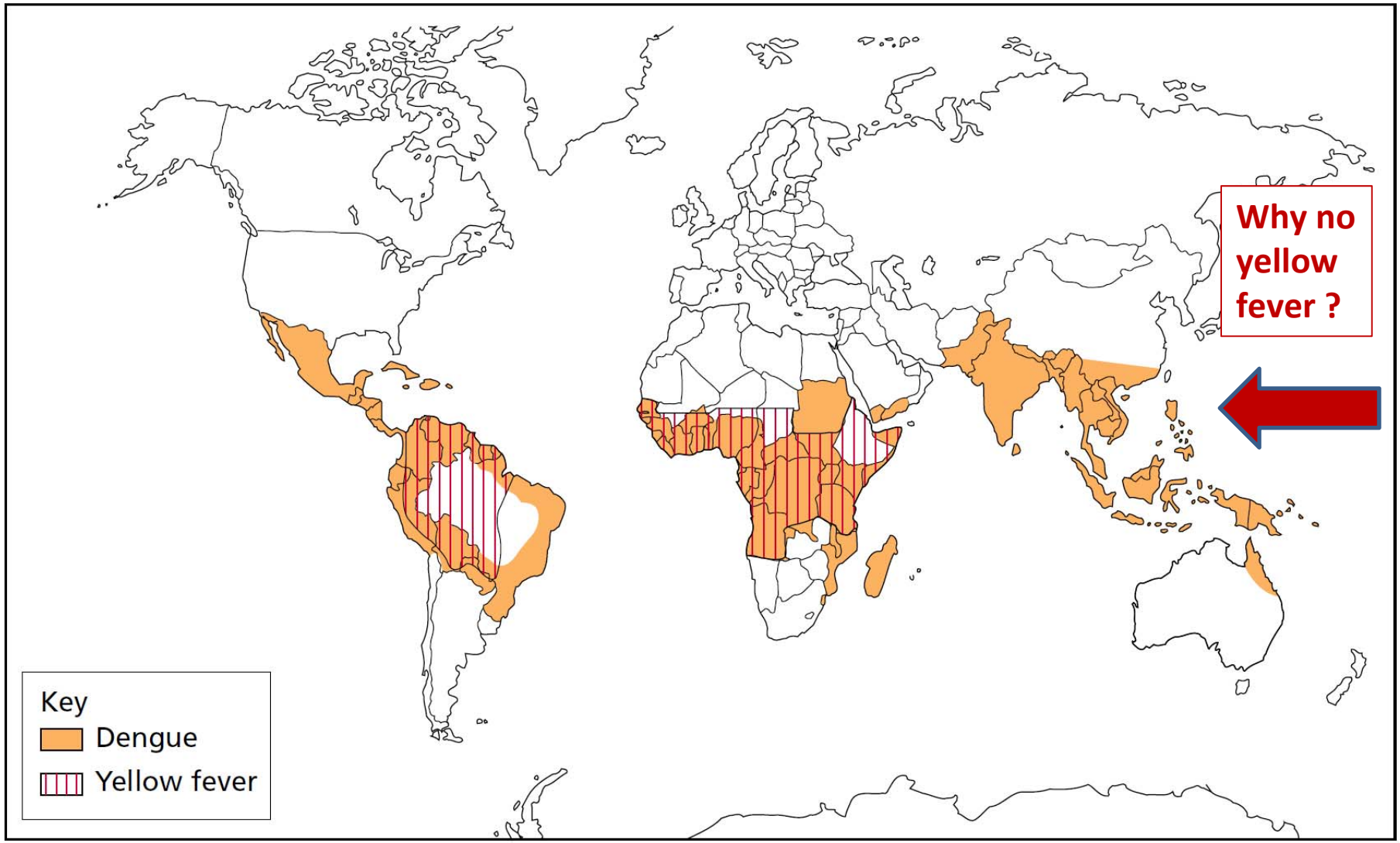
Associate Director, International Health Division, Rockefeller Foundation New York



Harvey Lectures: 1932-1934
c/o David Hill



Solomon T. Ch 42 in *Lecture Notes Tropical Medicine* 2014



Solomon T. Ch 42 in *Lecture Notes Tropical Medicine* 2014

RAPID RISK ASSESSMENT

Outbreaks of yellow fever in Angola, Democratic Republic of Congo and Uganda

First update, 27 May 2016

Main conclusions and options for response

In the EU/EEA, the risk of yellow fever virus being introduced is limited to unvaccinated viraemic travellers coming from epidemic areas. Given that outbreaks of yellow fever in urban settings have the potential for rapid spread and that significant yellow fever epidemics are ongoing in Angola, DRC and Uganda, EU/EEA Member States should consider a range of options for response.

Information for travellers to and EU citizens residing in areas with active transmission

break

response operations

duction

Yellow Fever – China

Disease Outbreak News
22 April 2016

Between 4 and 12 April 2016, the National IHR Focal Point of China notified WHO of 2 additional imported cases of yellow fever (YF). To date, a total of 11 laboratory-confirmed YF cases imported from Angola have been reported in China.

The tenth imported case is an 18-year-old male from Fujian Province, China, who had been living in Angola. On 12 March, he had onset of fever and other symptoms, and visited a local hospital in Angola. On 27 March 2016, the patient travelled to Fuzhou City, Fujian Province, China via Dubai, United Arab Emirates and Beijing, China. He was afebrile on arrival in China. On 28 March, the patient sought medical care. Yellow fever infection was confirmed by polymerase chain reaction (PCR) at the Fujian International Travel Health Centre. Test results were corroborated by the Fujian Centers for Disease Control (CDC). The patient was hospitalised in Fuzhou and remains under treatment.

Related links

More on yellow fever
Yellow fever fact sheet
Yellow fever health topic
More yellow fever outbreak
China country profile

Pan American Health Organization
World Health Organization
Americas

Epidemiological Update
Yellow Fever

20 March 2018

Situation summary in the Americas

Between January 2016 and 13 March 2018, seven countries and territories of the Region of the Americas reported confirmed cases of yellow fever: the Plurinational State of Bolivia, Brazil, Colombia, Ecuador, French Guiana, Peru, and Suriname. The number of human cases and epizootics collectively reported in this period in the Region of the Americas is the highest observed in decades.

Since the 16 February 2018 Epidemiological Update on Yellow Fever[1] published by the Pan American Health Organization / World Health Organization (PAHO/WHO), **Brazil** and **Peru** had reported new yellow fever cases; following is a summary of the situation in both countries.

Brazil Jul 2017-13 Mar 2018 920 confirmed cases 300 deaths

Peru 22 cases

Exported 12 cases in international travellers

Yellow fever risks travellers

- 2 week trip to Illness Death

West Africa	1/2,000	1/10,000
S or C America	1/20,000	1/100,000

- Vaccine risk ?1/1,000,000

Monath TP, Cetron M. *CID* 2002; 34: 1369-78

Research letters

Lancet 2001

Hepatitis and death following vaccination with 17D-204 yellow fever vaccine

Raymond C Chan, David J Penney, Dianne Little, Ian W Carter, Jason A Roberts, William D Rawlinson

We describe a man vaccinated with the 17D204 strain of yellow fever virus, who subsequently died of yellow fever. Sequencing of the NS5-3′ untranslated region showed that the virus isolated from the patient was identical to the vaccine strain of the same batch, and different from wild-type virus. Both viruses contained a mutation, although the association of this mutation with virulence is unknown. Severe, rapidly progressive, and ultimately fatal disease can follow use of the 17D204 vaccine strain. There is need for renewed discussion as to the safety of the vaccine and the indications for its use.

Lancet 2001; **358:** 121–22

See Commentary page 84

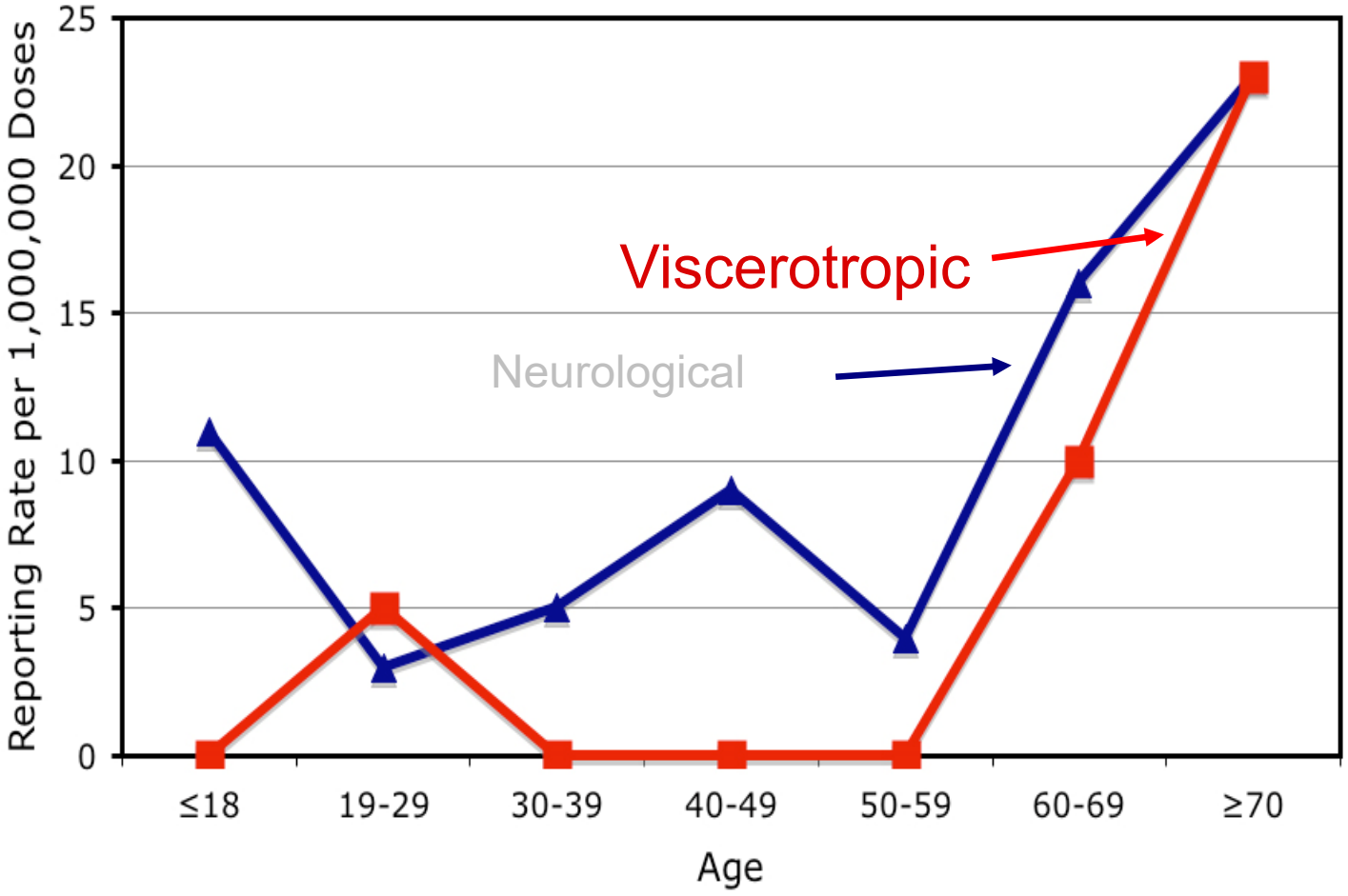
Serology for hepatitis A virus, hepatitis B virus, hepatitis C virus, HIV, *Coxiella burnetii*, *Chlamydia* spp, *Rickettsia* spp, and *Leptospira* spp were negative. Serum paracetamol concentrations were not in the toxic range.

On Feb 2, despite aggressive fluid treatment, he remained febrile, hypotensive, anuric, and had became increasingly acidotic. Continuous venovenous haemodialysis was begun but he continued to deteriorate (creatinine 336 μmol/L, aspartate aminotransferase 6750 U/L, alanine aminotransferase 1550 U/L). In consultation with the patient's family, supportive treatment was withdrawn on Feb 3.

A necropsy was done 36 h after death. He had petechial haemorrhages over the lateral aspects of the trunk. There

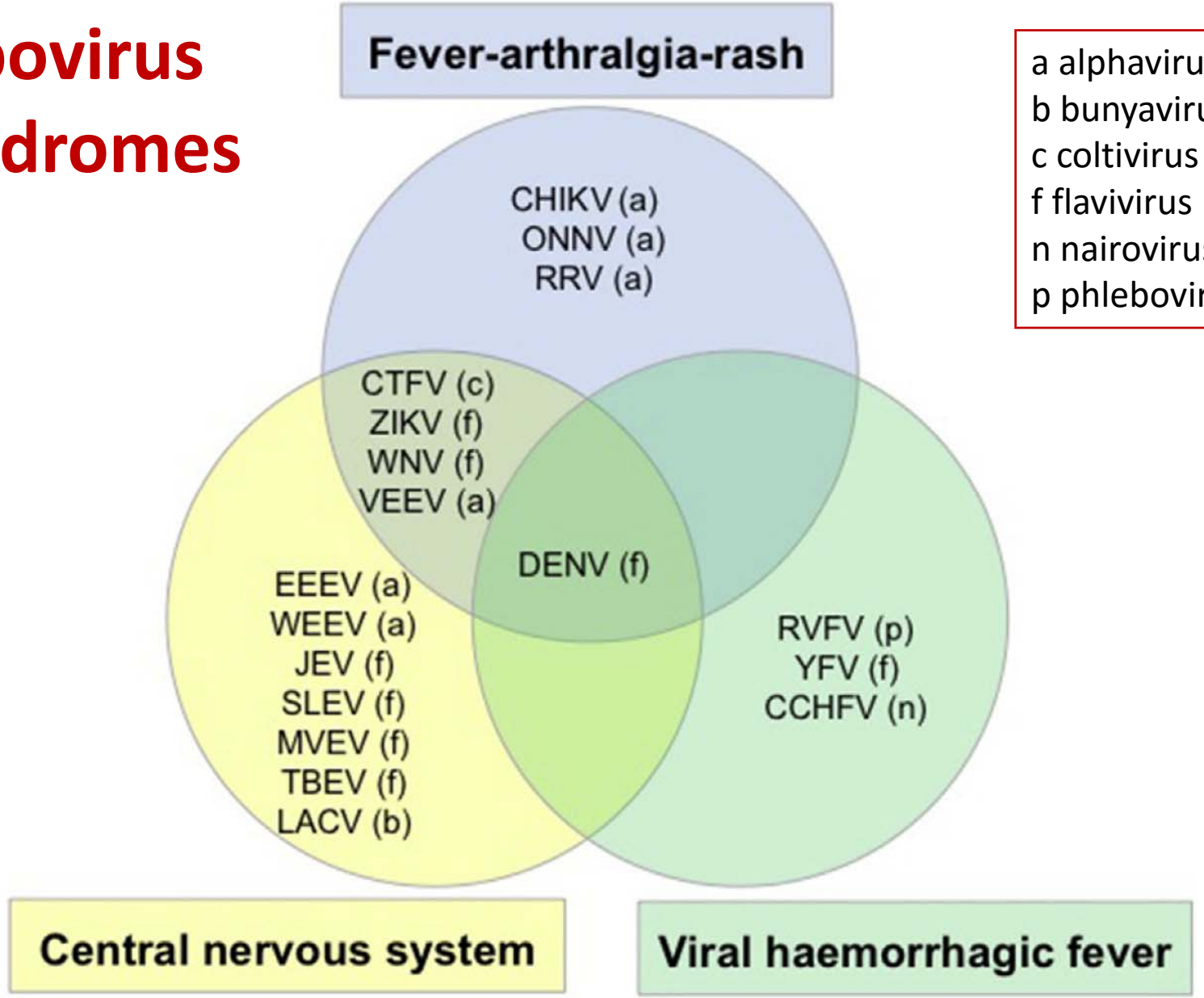
Viscerotropic & Neurological: 1/250,000 doses

Viscerotropic & neurological adverse events
US Passive Reporting Rates (VAERS)



Lindsey NP, et al. *Vaccine* 2008; 26: 6077 c/o David Hill

Arbovirus syndromes



a alphavirus
b bunyavirus
c coltivirus
f flavivirus
n nairovirus
p phlebovirus

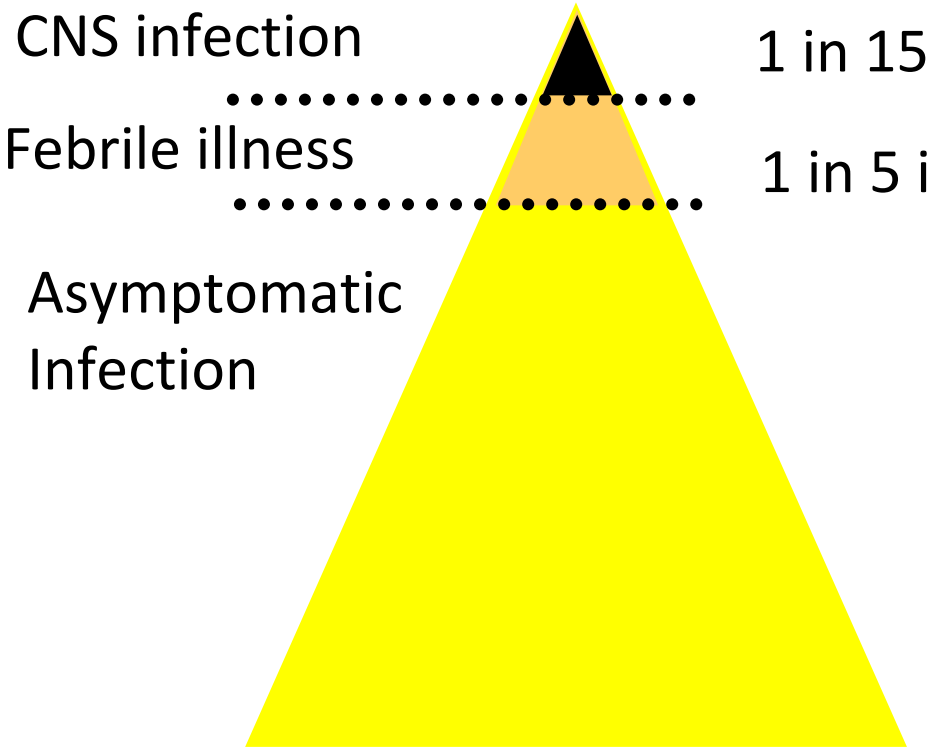
Eckerle I *et al. Clin Microbiol Infect* 2018; 24: 240-5

West Nile Fever virus

- Uganda, 1937
- Fever, arthralgia, rash
- Africa, Middle East, southwest Asia
- Epidemics
  - Israel 1950s
  - South Africa 1970s

c/o Tom Solomon

West Nile virus: clinical epidemiology



1 in 150 infections

1 in 5 infections

Increased risk of severe disease in:

Elderly

Immunocompromised

(other chronic illness)

Transmission risk: blood products, organs

Mostashair, NEJM 2001

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

Flavivirus Encephalitis

Tom Solomon, M.D., Ph.D.

DURING THE SUMMERS OF 2002 AND 2003, NORTH AMERICA WAS AFfected by its largest-ever outbreaks of arboviral encephalitis. West Nile virus caused 2942 cases of meningitis or encephalitis in 2002, with 276 deaths, and 2866 cases in 2003, with 246 deaths.[1,2] West Nile virus, which in the United States was first detected in New York in 1999, is one of several mosquito-borne neurotropic members of the Japanese encephalitis (JE) serogroup of the genus flavivirus, family Flaviviridae, that cause similar disease patterns across the globe (Fig. 1 and Table 1). These include St. Louis encephalitis virus in the United States, Rocio virus, which has caused encephalitis outbreaks in Brazil, and Murray Valley encephalitis virus in Australia, New Guinea, and New Zealand. Kunjin virus, which also circulates in Australia, recently has been reclassified as a subtype of West Nile virus. In terms of numbers, the most important member of the group is Japanese encephalitis virus, which causes an

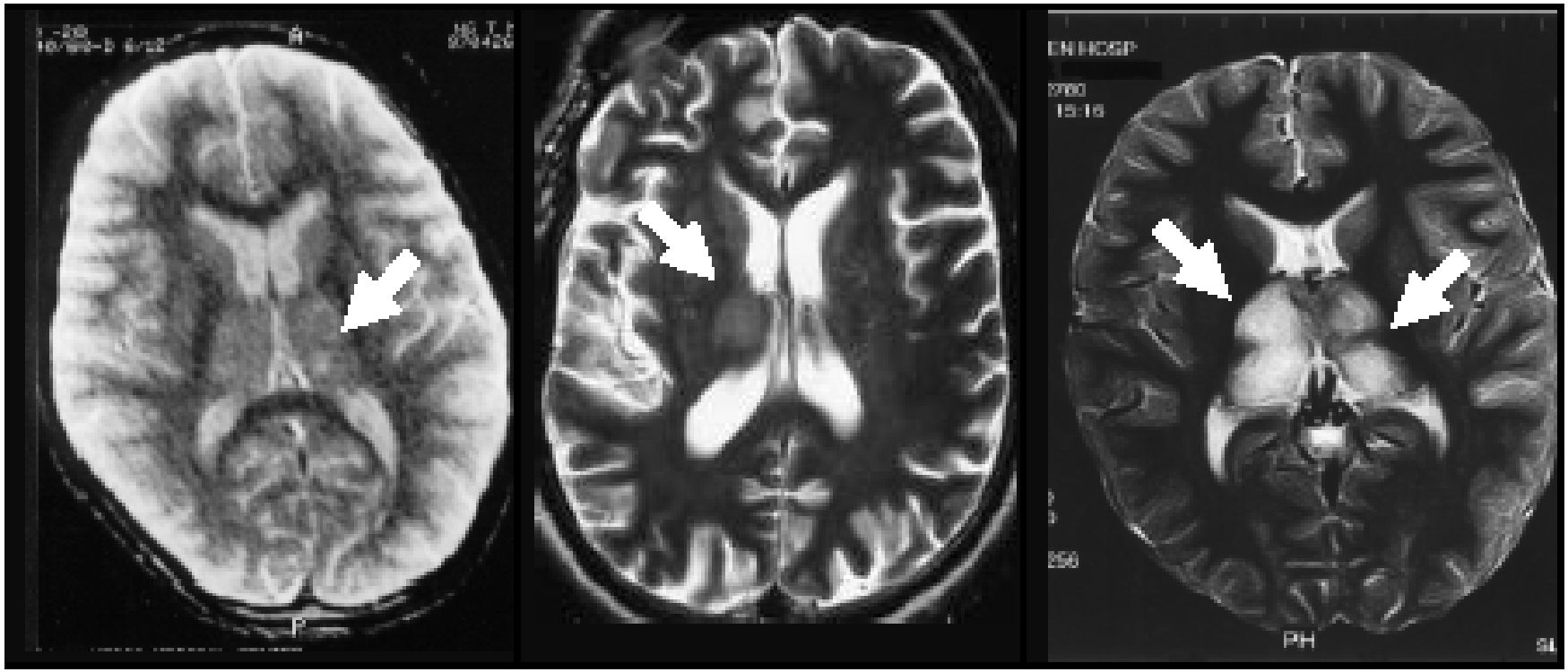
Clinical features of JE Serogroup Flavivirus Encephalitis

	JEV	WNV	SLEV	MVEV
Presenting with encephalitis (%)	60-75	58-62	58-85	50
Presenting with meningitis (%)	5-10	15-40	5-40	50
Flaccid Paralysis (%)	20-40	30		20-40
Seizures (%)	85	10		85
Parkinsonism	++	+	++	+
Case fatality rate (%)	20-30	4-14	3-30	15-30

Solomon T. Flavivirus Encephalitis *NEJM* 2004

“Parkinsonism” in flavivirus infections

- Rigidity, cogwheel; resting tremors; mask-like facies **Solomon T. Flavivirus Encephalitis *NEJM* 2004**
- Bruxism, choreoathetosis, orofacial dyskinesias



Japanese encephalitis West Nile encephalitis Murray Valley encephalitis

Confusion in 87 Year old man Leicester, UK

Presented in June 2016 with 3 days:

- Confusion
- Lethargy
- Ataxia
- Fever to 38˚

Generally well

Recent 2 week holiday in Alicante, Spain

Frequent trips, active, had been working on family shed

Findings

T 37.7˚

Confused and flat but blood pressure and pulse normal

Hallucinating

Hyperaesthesia to blood taking

Doubly incontinent

No neck stiffness

No focal neurological signs

No rash, lymphadenopathy, bleeding, joint involvement

Tests

C reactive protein 5 mg/L (normal <7)

White count 5 x 10^9/L

- Neutrophils 3.73 x 10^9/L
- Lymphocytes 1.07 x 10^9/L

Platelets 134 x 10^9/L

Biochemistry normal

Chest X ray normal

Lumbar puncture not possible

MR and CT head and EEG normal

Progress

Treated with ceftriaxone and aciclovir for 2 weeks

Doxycycline not given

Improved after 72 hours

Made full recovery (except amnesia)

Bacterial and other cultures, bacterial antigen tests etc all negative

What is your diagnosis?

A. Herpes simplex encephalitis
B. Rickettsial infection (spotted fever)
C. Sandfly fever
D. Tick borne encephalitis
E. West Nile Virus
F. Something else

How would you confirm the diagnosis ?

A. PCR for virus in blood
B. PCR for virus in cerebrospinal fluid
C. Rapid antigen test for sandfly fever group antigen in serum
D. Serology in paired acute and convalescent sera for phleboviruses
E. Serum IgM for phleboviruses
F. Something else

National reference laboratory and Imported Fever service
PHE Porton/Liverpool/HTD London

Convalescent serum (21 days)

IFA for Naples and Toscana virus IgG > 1/10 000

Other sandfly groups (Phleboviruses: Bunyaviridae) non reactive

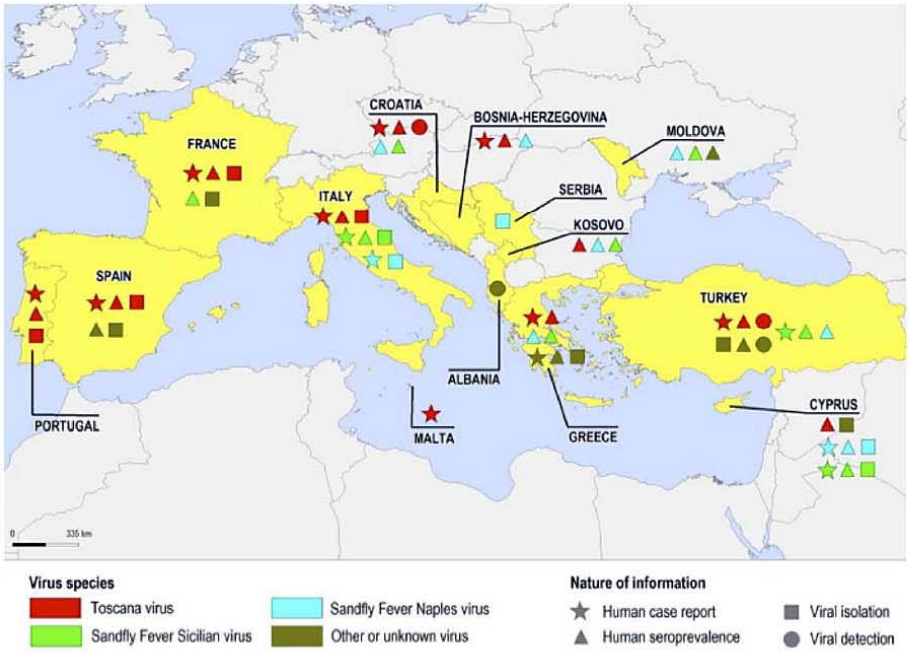
PCR on plasma from day 5 - negative for RNA

Diagnosis = Toscana virus

- Only neuroinvasive phlebovirus
- Hyperaesthesia has been documented
- Clue is thrombocytopenia

Toscana virus (sandfly fevers) (Bunyaviridae, Phlebovirus

c/o Chantal Reusken



Osborne et al., 2015

Toscana virus

- Leading cause of aseptic meningitis and flu like illness during summer season – Italy (80% in childeren; 50% adults), Turkey (16% aseptic meningitis) areas in S. France and Spain – emerging pathogen around the Mediterranean
- Widely variable seroprevalence (3% Torino – 50% Ionian islands)
- Symptoms: aseptic meningitis, encephalitis or mild fever and rash.
- Hosts/life-cycle not well studied/known
- Limited studies available
- No specific treatment or vaccine available

Phlebotomus spp **(Sand fly)**

c/o Chantal Reusken

Courtesy of Louise Sigfrid

Charrel RN, *et al. Emerg Infect Dis.* 2005; 11: 1657-63
Papa A, *et al. Emerg Infect Dis*. 2014; 20: 1417-9

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Veater *et al. BMC Geriatrics* (2017) 17:193
DOI 10.1186/s12877-017-0593-2

BMC Geriatrics

CASE REPORT Open Access

Toscana virus meningo-encephalitis: an important differential diagnosis for elderly travellers returning from Mediterranean countries

James Veater[1], Farhan Mehedi[2], Chee Kay Cheung[3,6], Laura Nabarro[4], Jane Osborne[4], Nicholas Wong[1], Martin Wiselka[1] and Julian W Tang[5,6*]

***BMC Geriatr.* 2017; 17: 193**

Lessons

- Older people travel, expect more strange diagnoses in this group
- Travel history essential (not initially available here)
- Consider arbovirus infections (and rickettsial)
- Toscana virus rarely diagnosed in UK
- Increasingly diagnosed across Mediterranean countries
- Role of reference laboratories and national clinical expertise and advice

Summary - Diagnostic approach

- History
- More history
- Detail of geography, timing
- Occupational and recreational exposures
- Compliance with protection
- Physical signs (rash, eschar etc)
- Knowledge of prevailing infections

- Tests ordered and interpreted in light of
  - Pretest probability
  - Quality of tests

Don’t forget

- Think malaria
- Exclude VHF
- Blood film – thrombocytopenia, eosinophilia
- Think about antimicrobial resistance
- If malaria is excluded, is empirical therapy indicated while awaiting results?
  - Doxycycline (leptospirosis, tick/scrub typhus)
  - Azithromycin or ceftriaxone (enteric fever)