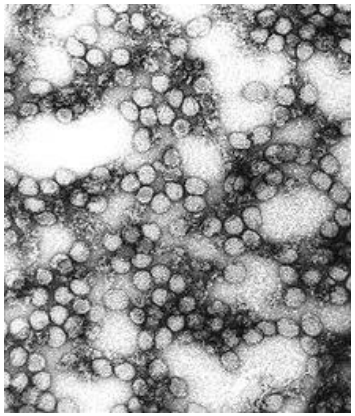
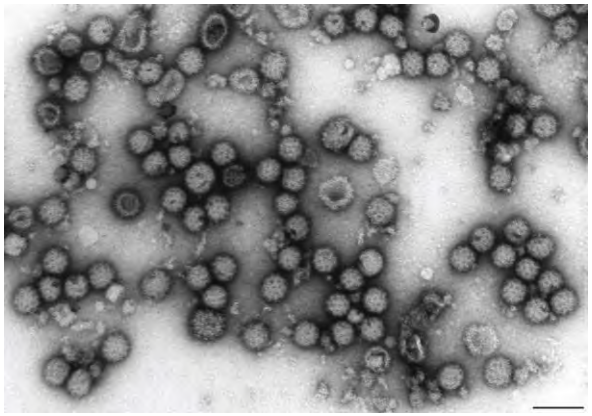
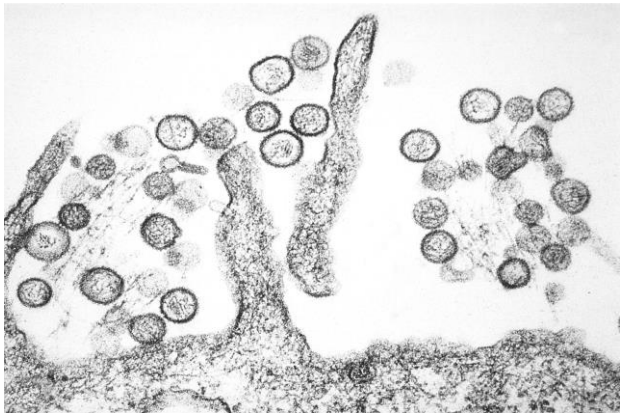




Arboviroses au retour des Tropiques
7 juin 2018

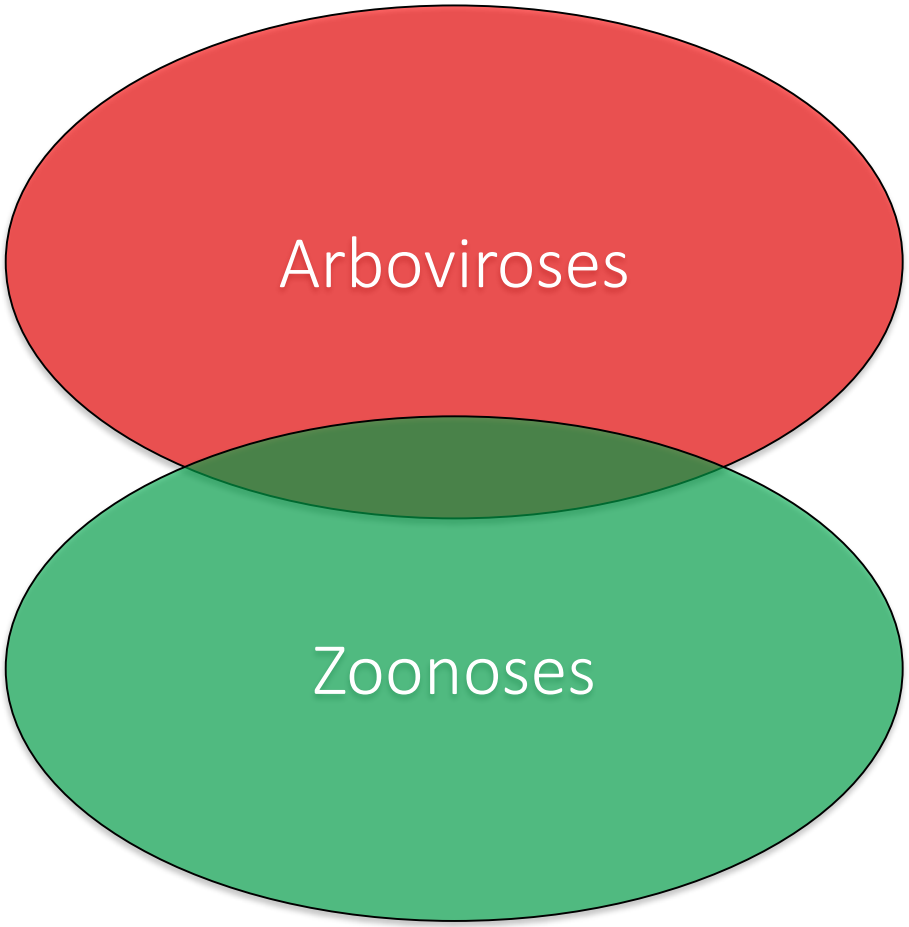
Manuel Schibler, Laboratoire de virologie et Service des maladies infectieuses, HUG

UNIVERSITÉ DE GENÈVE

Hôpitaux Universitaires Genève

L'ESSENTIEL, C'EST VOUS.

Terminologie



Virus transmis par un vecteur arthropode
ARthropod-**BO**rne virus

Virus transmis par un animal vertébré
zôon « animal » et *nosos* « maladie »

Arboviroses

Fièvre jaune

Zika

Dengue

West nile

Aedes aegypti

Aedes albopictus

Culex spp

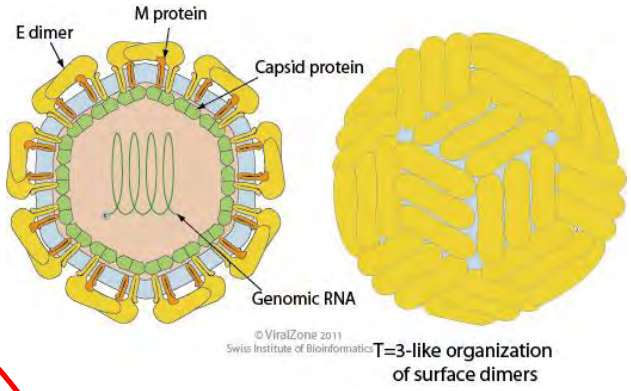
Chikungunya

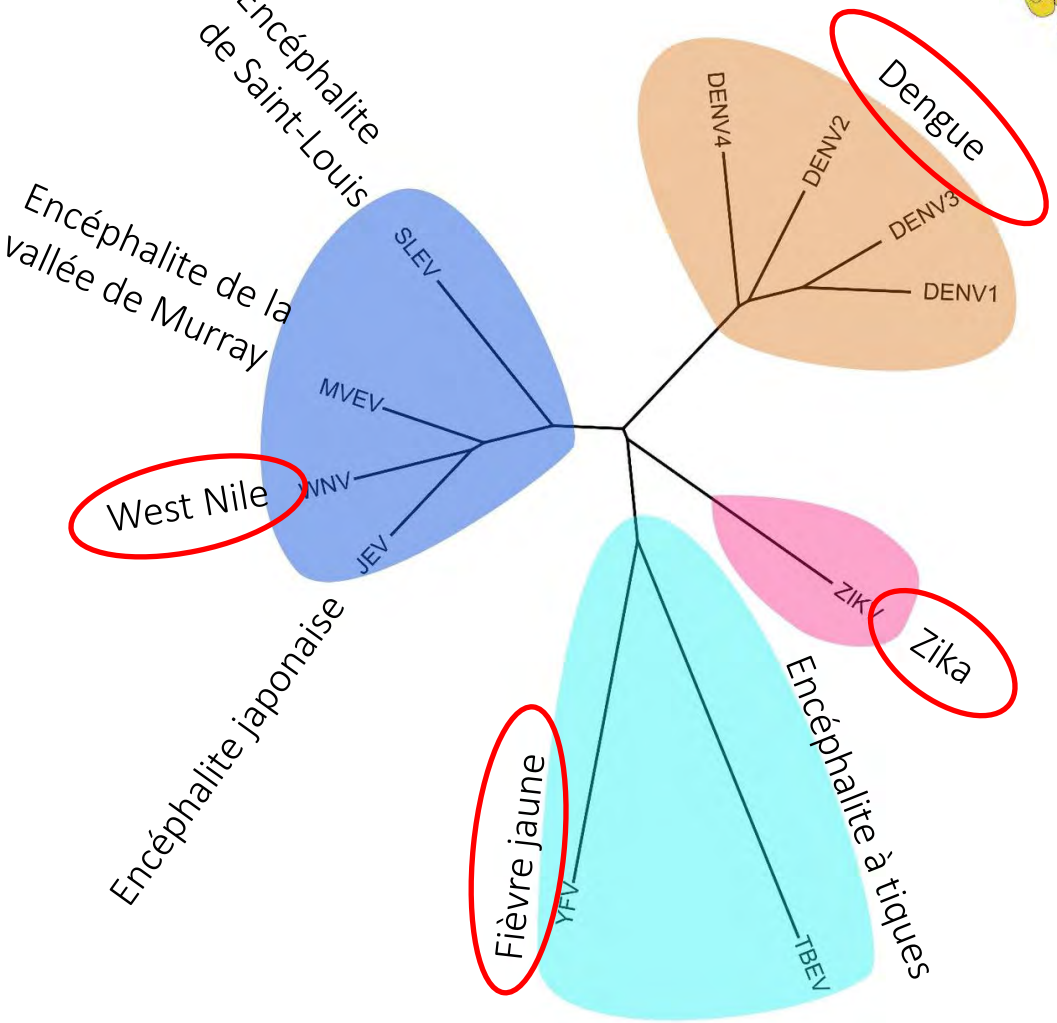
Images: CDC et wikipédia

On les classe comment?

- Par famille de virus?
- Par type de vecteur?
- Par région géographique?

Famille des Flavivirus





Arboviroses

Flaviviridae

Fièvre jaune

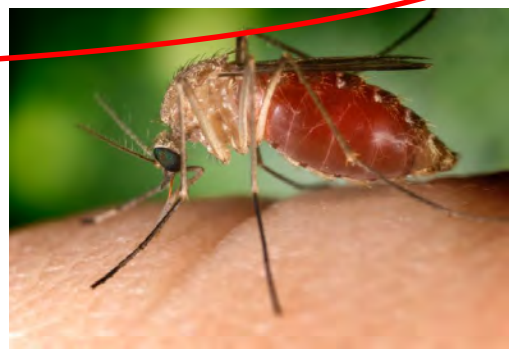
Dengue

Zika

West nile

Aedes aegypti

Aedes albopictus

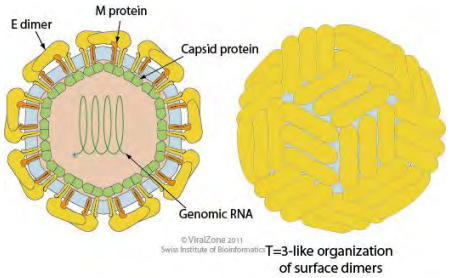


Culex spp

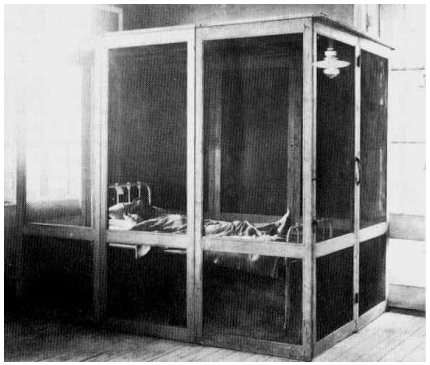
Chikungunya

Images: CDC et wikipédia

Fièvre jaune



Carlos J Finlay



Walter Reed 1901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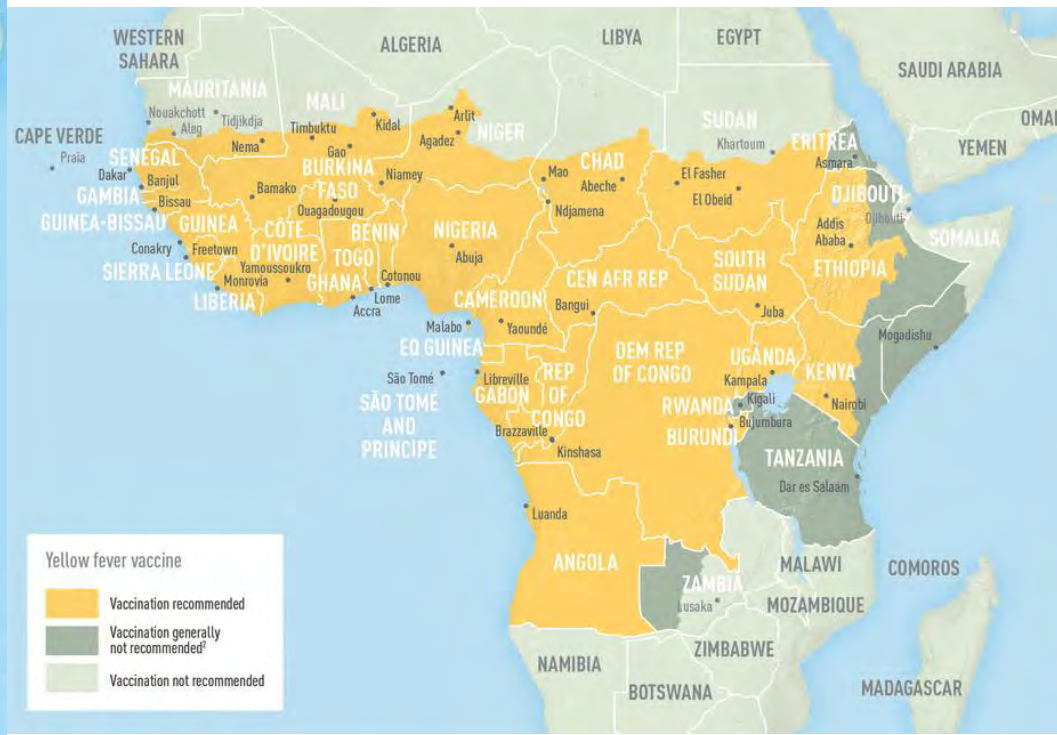
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El Fasher
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Banjul
Niamey
Abeche
DJIBOUTI
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Bissau
Bamako
BURKINA FASO
El Obeid
Ouagadougou
Ndjamena
Addis Ababa
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Freetown
Abuja
SOMALIA
TOGO
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SIERRA LEONE
Yamoussoukro
Monrovia
Cotonou
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CEN AFR REP
LIBERIA
Lome
Accra
CAMEROON
Bangui
Juba
Malabo
Yaoundé
Mogadishu
EQ GUINEA
DEM REP OF CONGO
UGANDA
São Tomé
Libreville
REP OF CONGO
KENYA
Kampala
GABON
Kigali
SÃO TOMÉ AND PRINCIPE
RWANDA
Nairobi
Brazzaville
Bujumbura
BURUNDI
Kinshasa
TANZANIA
Dar es Salaam
Luanda
ANGOLA
MALAWI
COMOROS
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Yellow fever vaccine
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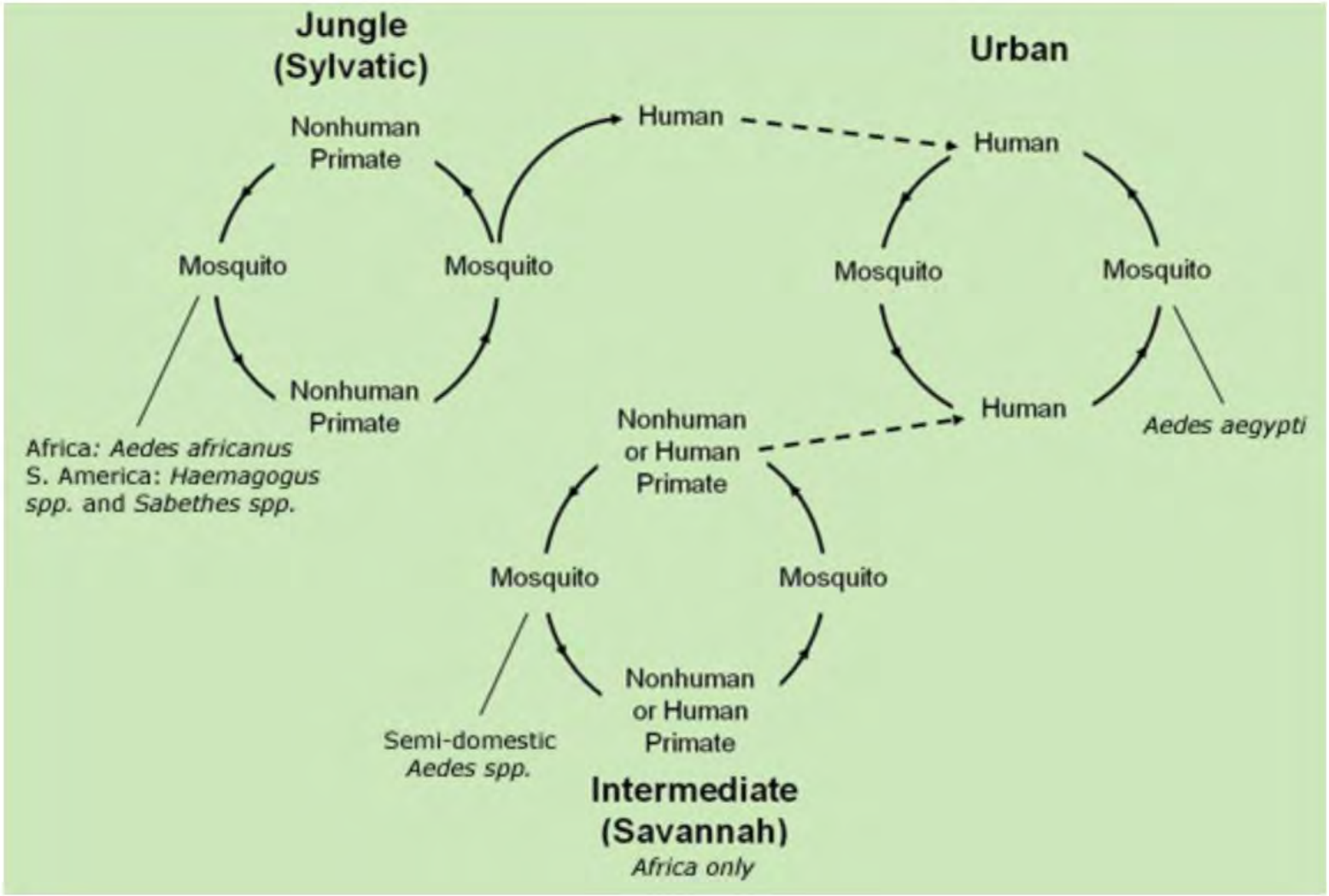
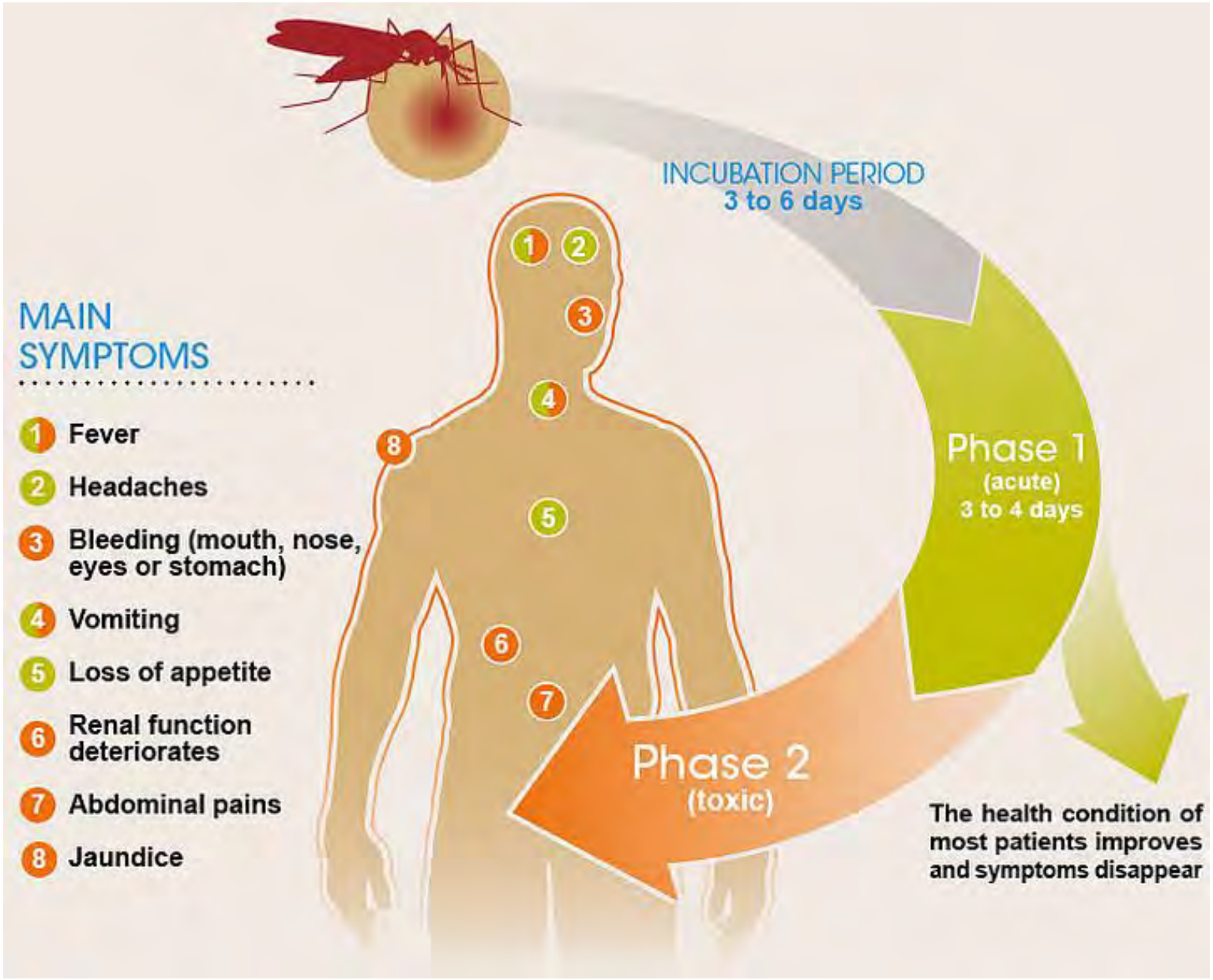
Images: CDC

Cycle de transmission



Déroulement de l'infection

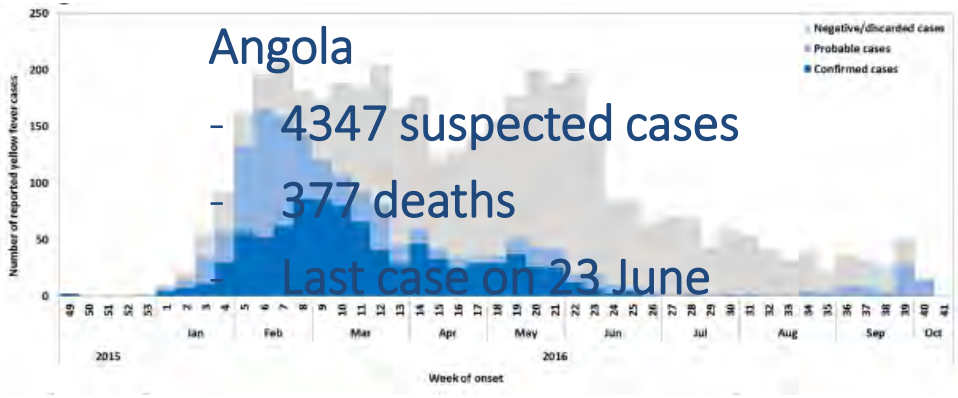
- Asymptomatique ou paucisymptomatique la plupart du temps
- Incubation de 3 à 6 jours avant l'apparition des premiers symptômes: état grippal avec fièvre, céphalées, vomissements, douleurs musculaires et articulaires
- Guérison la plupart du temps, lente
- Dans 15% des cas, après une rémission de quelques heures à 1 jour, maladie plus sévère avec:
  - Fièvre importante
  - Ictère
  - Hémorragies
  - Dysfonction d'organes multiple

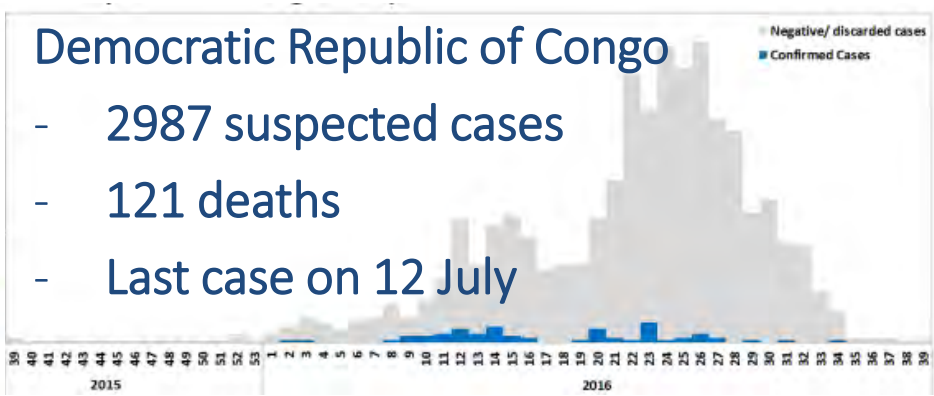


https://pgporg.wordpress.com/2016/08/17/yellow-fever-key-facts/

Epidémies récentes

2016

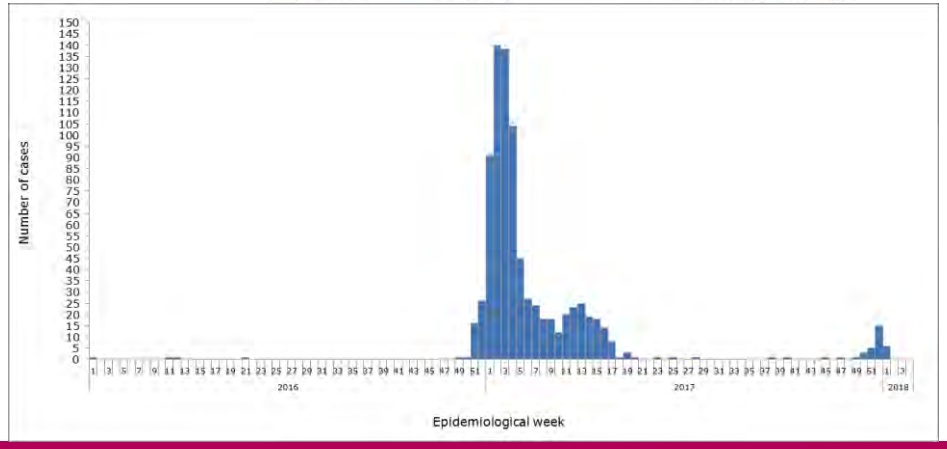




7.5 millions de gens vaccinés avec 1/5 de la dose habituelle

WHO report update as of 20 Oct 2016 ; Elachola H Lancet 2016

Brésil 2017-18

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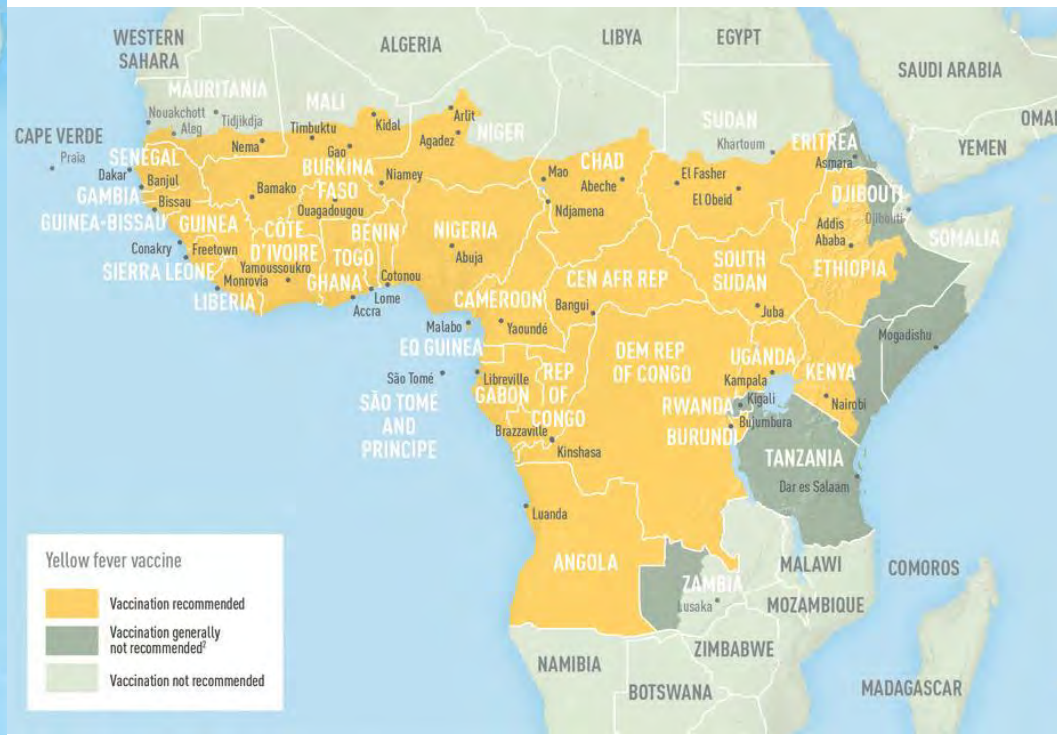
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ERITREA
CAPE VERDE
Aleg
Nema
Gao
Asmara
Praia
SENEGAL
CHAD
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El Fasher
Dakar
Banjul
Niamey
Abeche
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Bamako
BURKINA FASO
El Obeid
Ouagadougou
Ndjamena
Addis Ababa
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GUINEA
CÔTE D'IVOIRE
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TOGO
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LIBERIA
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Malabo
Yaoundé
Mogadishu
EQ GUINEA
DEM REP OF CONGO
UGANDA
São Tomé
Libreville
REP OF CONGO
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RWANDA
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Images: CDC

International Journal of Infectious Diseases 48 (2016) 98–103

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Review

Yellow fever cases in Asia: primed for an epidemic

Sean Wasserman [a,*], Paul Anantharajah Tambyah [b], Poh Lian Lim [c,d]

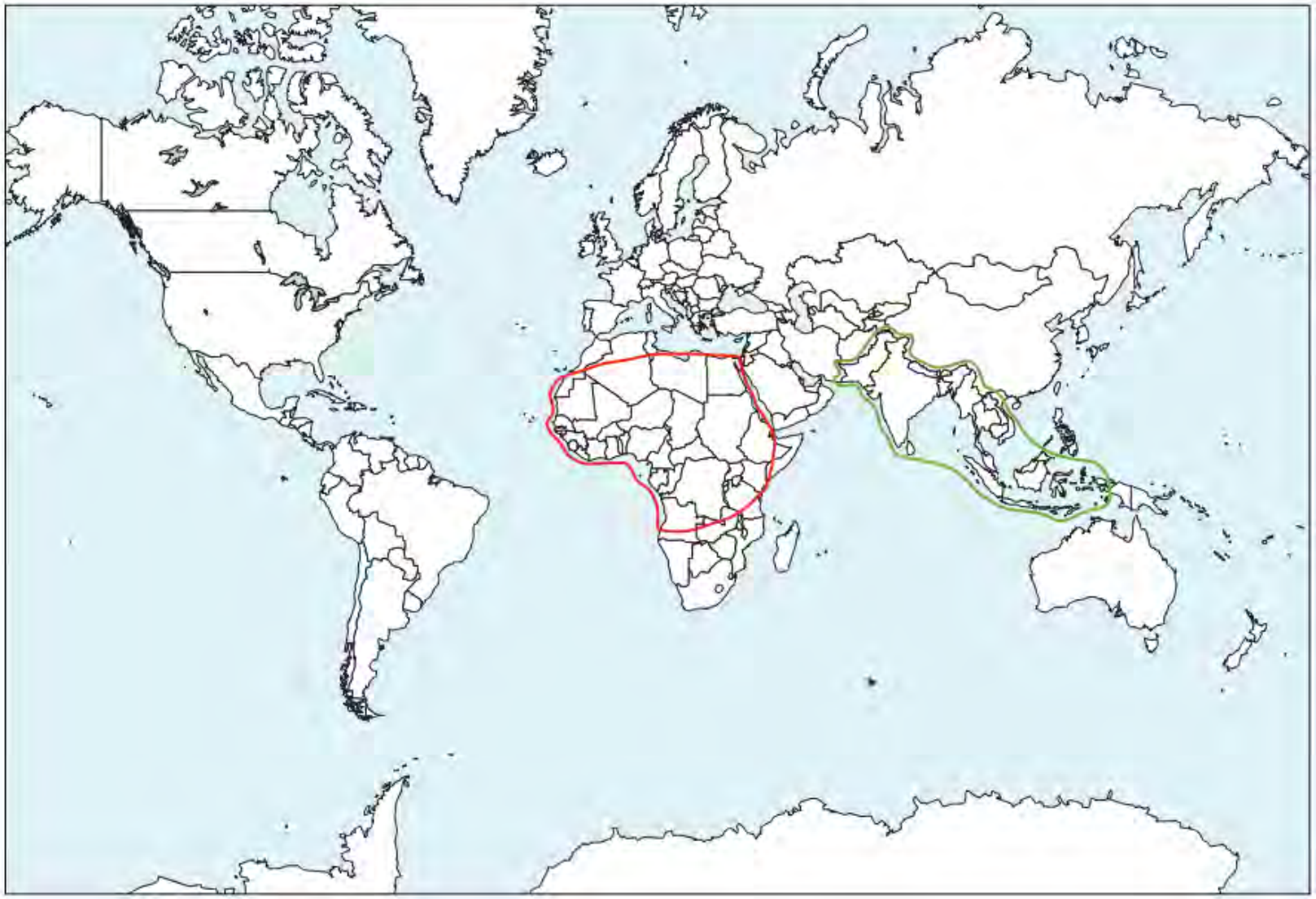
[a] Division of Infectious Diseases and HIV Medicine, Department of Medicine, University of Cape Town, Cape Town, South Africa
[b] Division of Infectious Diseases, National University of Singapore, Singapore
[c] Department of Infectious Diseases, Institute of Infectious Diseases and Epidemiology, Tan Tock Seng Hospital, Singapore
[d] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

2015…

Virus Zika

- Ouganda 1947, macaque Rhésus
- Ouganda 1964,
  - 1er cas humain documenté
- Avant 2007:
  - cas humains sporadiques en Afrique et en Asie du Sud-Est
    - Nigeria: 3 cas (virus isolé: TRSTMH 1954)
    - Malaisie: 1 cas (AMJTMH 1969)
    - Nigeria: 2 cas (J Hyg Camb 1979)
    - Indonésie (Java): 7 cas (TRSTMH 1981)
    - Cambodge : 1 cas (EID 2012)

Zika avant 2007…



Wikan N, Smith DR. Lancet Infect Dis. 2016 Jul;16(7):e119-e126.

Zika avant 2007…

- 2007 : Yap, 1’000 habitants
  73% de la population infectée

- 2013-2014 : Polynésie française, 270’000 habitants
  Estimation de 66% de la population infectée

- 2014 : Île de Pâques, 3’860 habitants

Duffy et al, NEJM 2009 Jun 11;360(24):2536-43.
Cao Lormeau, Emerg Infect Dis. 2014 Nov;20(11):1960.
Tognarelli J. et al, Arch Virol 2016; 161: 665-8

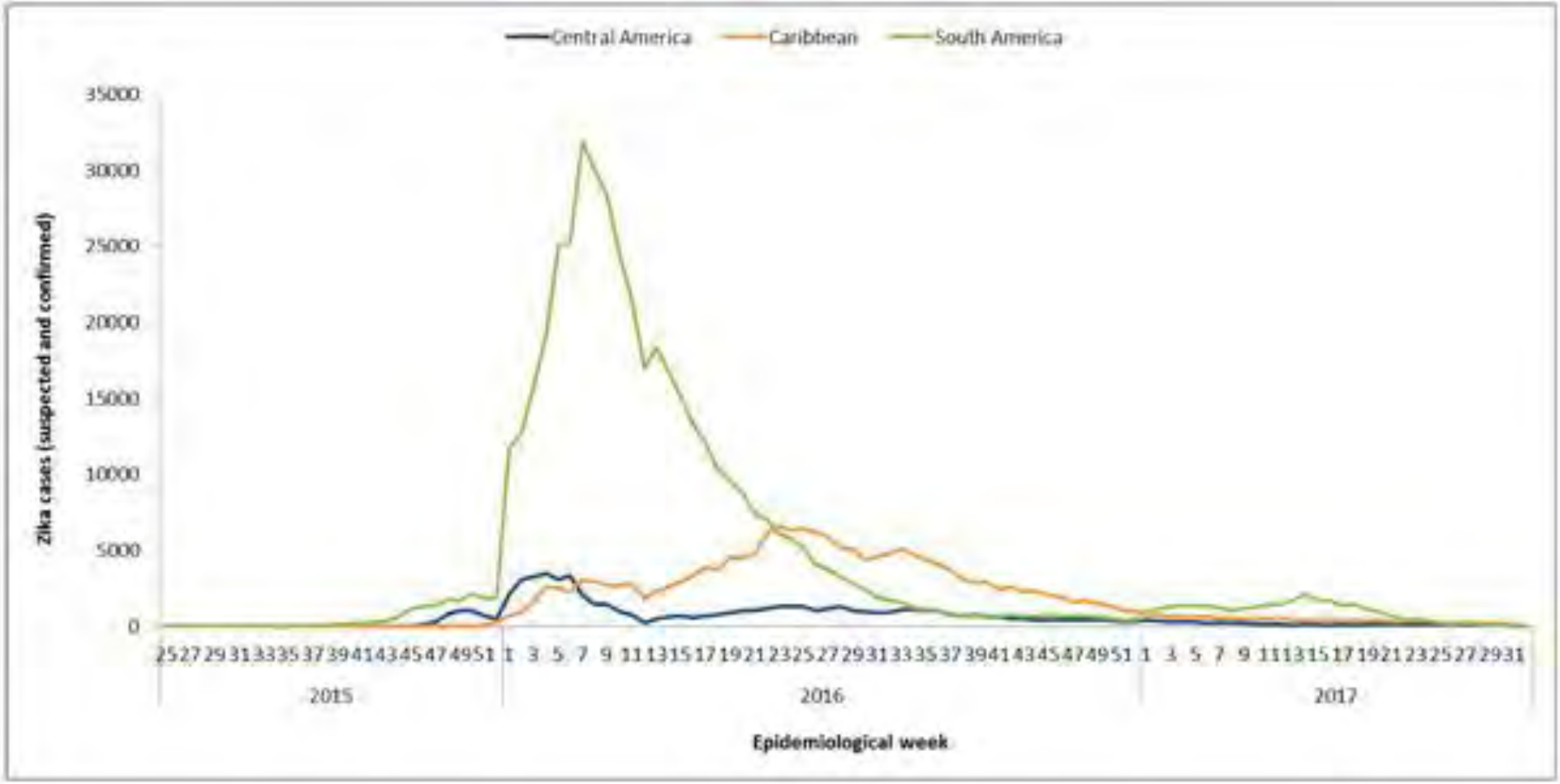
2015…

- Avril 2015: Nordeste, Brésil

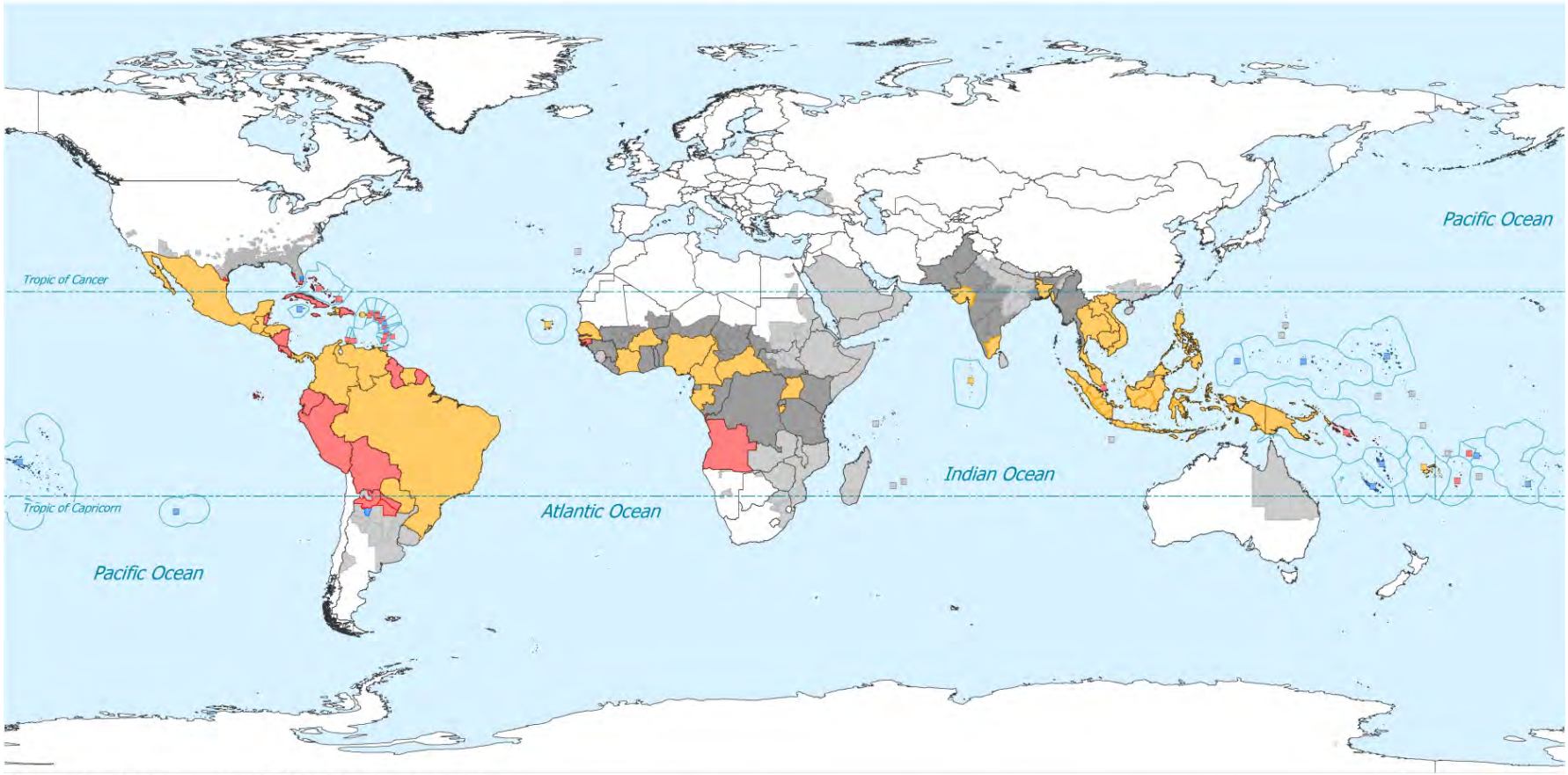
  + 20 pays en Amérique du Sud et centrale

- 200 millions d'habitants
- 2.9 millions de naissances par an

Enfissi A. et al. Lancet 2016;387 : 227-8
Musso D. Emerg Infect Dis 2015;21(10): 1887
Wkly Epidemiol Rec.2016 Feb 19;91(7):73-81.



PAHO_WHO 25.08.2017

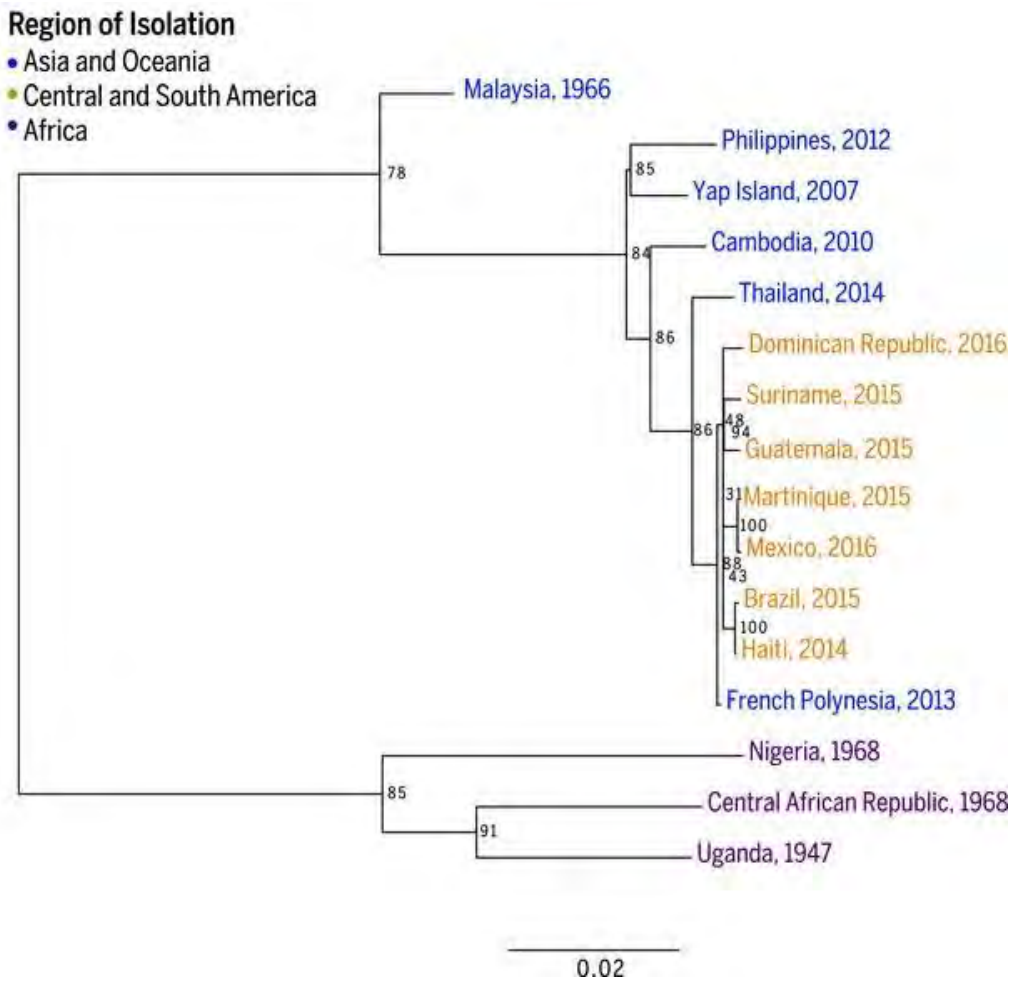


Country classification category (Cat.) for Zika virus transmission

- Areas with virus transmission following virus new/re introduction (WHO Cat. 1)
- Areas with virus transmission following previous virus circulation (WHO Cat. 2)
- Areas with interrupted transmission (WHO Cat. 3)
- Areas bordering a WHO Cat. 2 area (sub-category of WHO Cat. 4)
- Areas with potential for transmission (sub-category of WHO Cat. 4)
- Maritime Exclusive Economic Zones for non-visible areas

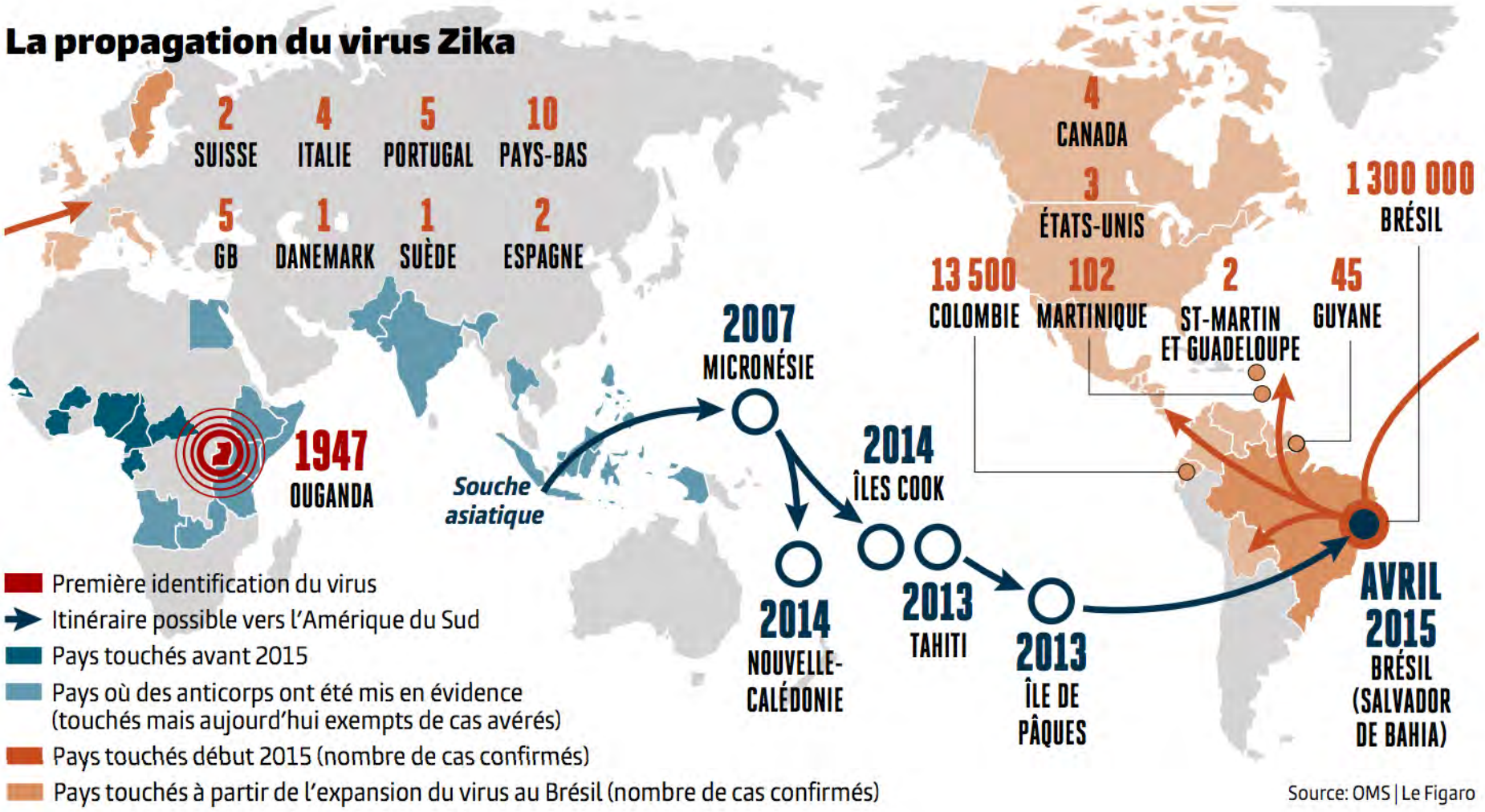
ECDC. Map produced on 19 Dec 2017.
Map your data at: https://emma.ecdc.europa.eu

Zika virus: 2 lignées (Asiatique et Africaine)



Iles du Pacifique et Amérique latine: lignée asiatique

Lessier J Science 2016, Pettersson J H-O Mbio 2016


La propagation du virus Zika
2 SUISSE
4 ITALIE
5 PORTUGAL
10 PAYS-BAS
5 GB
1 DANEMARK
1 SUÈDE
2 ESPAGNE
1947 OUGANDA
Souche asiatique
2007 MICRONÉSIE
2014 NOUVELLE-CALÉDONIE
2014 ÎLES COOK
2013 TAHITI
2013 ÎLE DE PÂQUES
4 CANADA
3 ÉTATS-UNIS
13 500 COLOMBIE
102 MARTINIQUE
2 ST-MARTIN ET GUADELOUPE
45 GUYANE
1 300 000 BRÉSIL
AVRIL 2015 BRÉSIL (SALVADOR DE BAHIA)
Première identification du virus
Itinéraire possible vers l'Amérique du Sud
Pays touchés avant 2015
Pays où des anticorps ont été mis en évidence (touchés mais aujourd'hui exempts de cas avérés)
Pays touchés début 2015 (nombre de cas confirmés)
Pays touchés à partir de l'expansion du virus au Brésil (nombre de cas confirmés)
Source: OMS | Le Figaro

Transmission

- **Vectorielle**: moustiques Aedes aegypti > albopictus (cycle urbain)
- **Materno-fœtale**
- **Sexuelle:**
  - Homme → Femme (persistance ARN dans sperme → 188j)
  - Homme → Homme
  - Femme → Homme
  - Infection symptomatique >>> asymptomatique (2 cas rapportés)
- Pas de transmission par le lait maternel rapportée

Clinique

Symptôme	Dengue	Chikungunya	Zika
Asymptomatique	35-50%	5%	75-80%
Fièvre	+++	+++	+
Arthralgie	++	+++	++
Rash	++	++	+++
Conjonctivite	+	+	+++
Leucopénie/ thrombopénie	+++	++	+

- **Fièvre discrète/modérée**
- Rash maculo-papulaire **prurigineux**
- **Conjonctivite**
- Douleurs rétro-orbitales
- Myalgie, arthralgie
- Symptômes digestifs

Clinique

Bébé atteint de microcéphalie

Complications foetales

- Octobre 2015, augmentation microcéphalies dans Etat de Pernambuco (nord-est Brésil)
  - 2014: Prévalence microcéphalie au Brésil : 5.7 cas/100'000 naissances
  - 30 November 2015: 99.7/100'000 naissances → 4074 cas
- Transmission materno-foetale: ZIKV RNA dans les restes de fœtus perdus et dans les enfants avec microcéphalies
- Polynésie française: augmentation de malformations cérébrales foetus/n-nés 2014-2015
- Tous les trimestres à risque (max fin 1er - début 2ème trimestre)
- Risque mal quantifié: 1 – 29%

Brasil et al. *New Engl J Med* 2016

Complications foetales

Clinical Feature	Findings in Infants With Confirmed Congenital ZIKV Infection
Cranial morphology	FBDS: severe microcephaly, overlapping cranial sutures, prominent occipital bone, redundant scalp skin, and neurologic impairment
Brain anomalies	Cerebral cortex thinning; abnormal gyral patterns; increased fluid spaces (ventriculomegaly or extra-axial); subcortical calcifications; corpus callosum anomalies; decreased white matter; and cerebellar (vermis) hypoplasia
Ocular anomalies	Structural anomalies (microphthalmia, coloboma); cataracts; and posterior anomalies: chorioretinal atrophy, focal pigmentary mottling, and optic nerve hypoplasia/atrophy
Congenital contractures	Unilateral or bilateral clubfoot and arthrogryposis multiplex congenita
Neurologic sequelae	Motor disabilities; cognitive disabilities; hypertonia/spasticity; hypotonia; irritability/excessive crying; tremors and extrapyramidal symptoms; swallowing dysfunction; vision impairment; hearing impairment; and epilepsy

Abbreviations: FBDS, fetal brain disruption sequence; ZIKV, Zika virus.

Figure 1. Cranial Morphology Supporting Fetal Brain Disruption Sequence Phenotype in Congenital Zika Syndrome

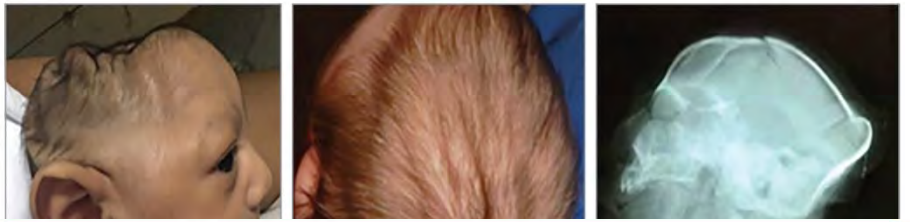
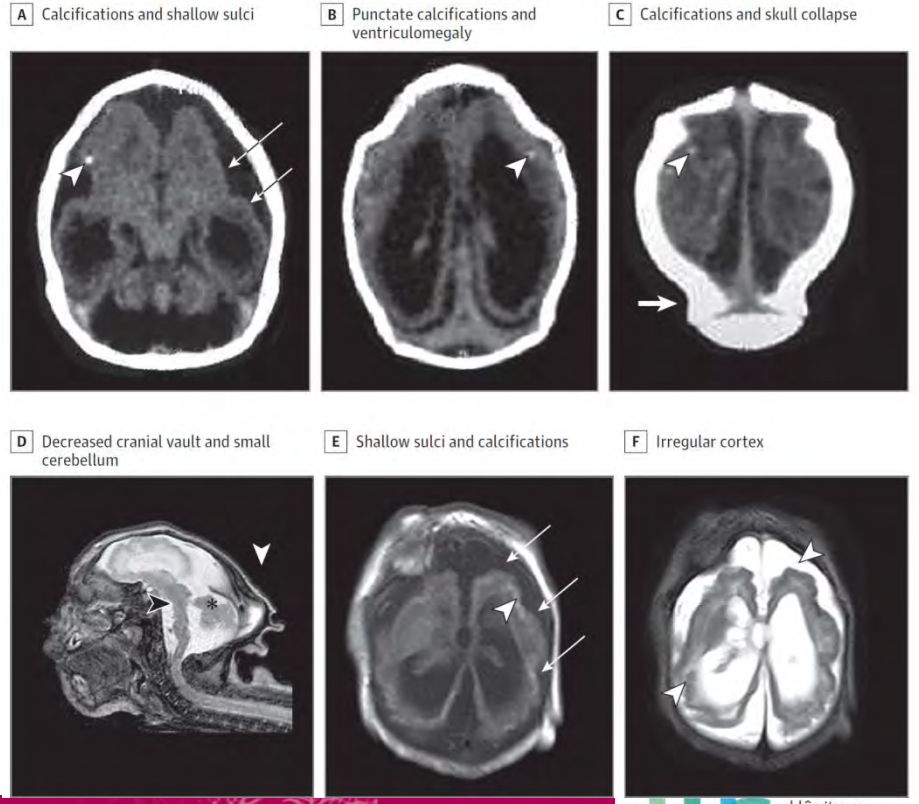


Figure 2. Brain Findings in Infants With Presumed Congenital Zika Syndrome



Moore et al. JAMA pediatrics 2016

Complications foetales

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Abbreviations: FBDS, fetal brain disruption sequence; ZIKV, Zika virus.

Figure 3. Wide-Angle Fundus Images (RetCam) of a Male Infant With Congenital Zika Infection

Figure 4. Infants With Congenital Zika Infection, Microcephaly, and Arthrogryposis

A Multiple contractures with knee dislocation

B Multiple contractures including right talipes equinovarus

Moore et al. JAMA pediatrics 2016

Complications neurologiques

- Syndrome de Guillain-Barré
  - Incidence x 20 en Polynésie française
  - ≈ 1/4000 infections symptomatiques
  - Pathogénie (inf/imm) à clarifier
- Méningo-encéphalite
- Myélite transverse
- Paralysie faciale

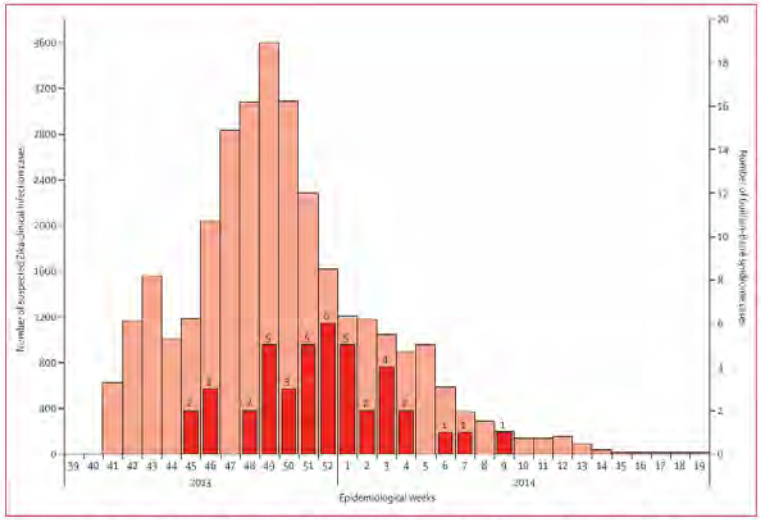
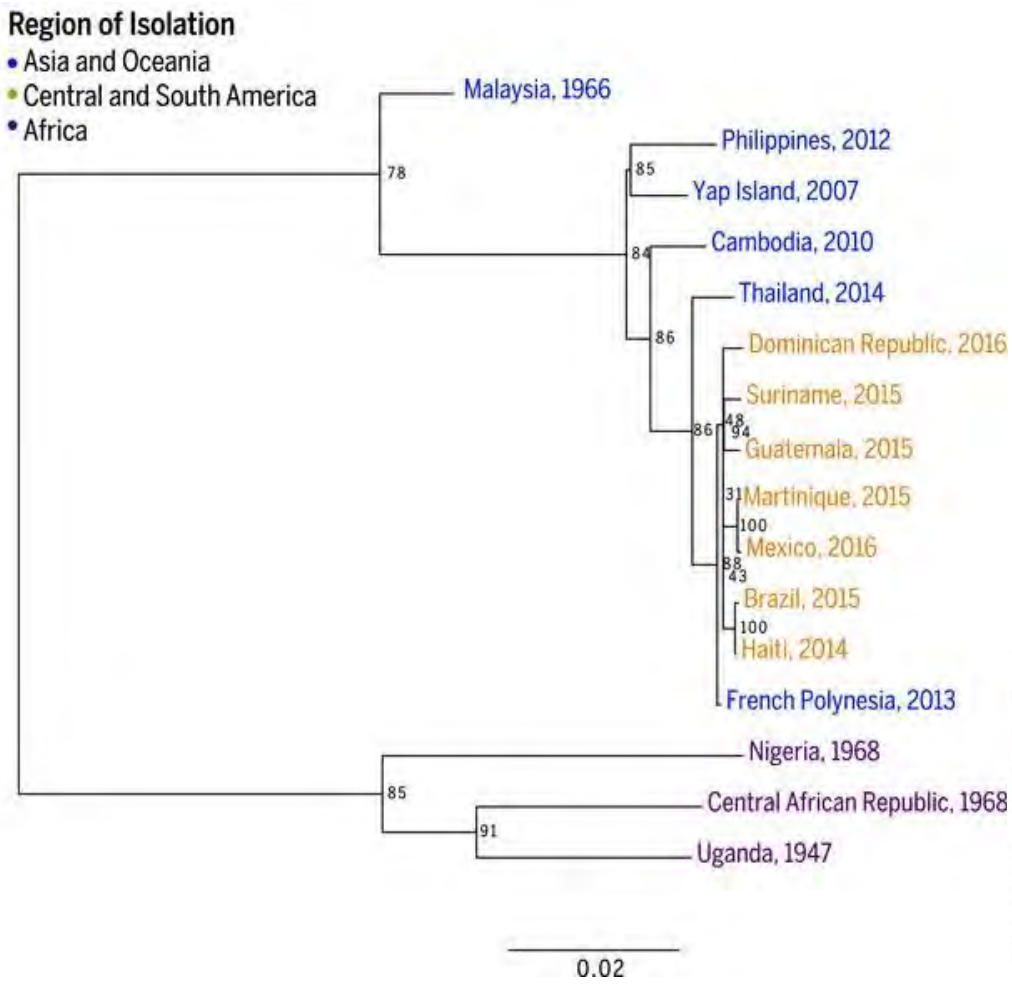


Figure: Weekly cases of suspected Zika virus infections and Guillain-Barré syndrome in French Polynesia between October, 2013, and April, 2014

www.thelancet.com Published online February 29, 2016 http://dx.doi.org/10.1016/S0140-6736(16)00562-6

Musso et al. Clin Microbiol Infect 2014
Cao Lormeau et al. Lancet 2016

Zika virus: 2 lignées (Asiatique et Africain)



- Iles du Pacifique et Amérique latine: lignée asiatique
- Le neurotropisme est-il spécifique à la lignée asiatique?

A single mutation in the prM protein of Zika virus contributes to fetal microcephaly

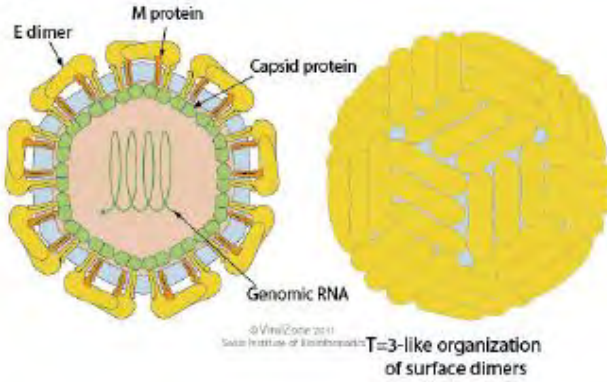
Ling Yuan,[1,2*] Xing-Yao Huang,[3*] Zhong-Yu Liu,[3*] Feng Zhang,[1,2*] Xing-Liang Zhu,[1,2*] Jiu-Yang Yu,[3*] Xue Ji,[3] Yan-Peng Xu,[3] Guanghui Li,[1,2] Cui Li,[1,2] Hong-Jiang Wang,[3] Yong-Qiang Deng,[3] Menghua Wu,[4] Meng-Li Cheng,[3,5] Qing Ye,[3] Dong-Yang Xie,[3,5] Xiao-Feng Li,[3] Xiangxi Wang,[6] Weifeng Shi,[7] Baoyang Hu,[4] Pei-Yong Shi,[8] Zhiheng Xu,[1,2,9]† Cheng-Feng Qin[3]†

Lessier J Science 2016, Pettersson J H-O Mbio 2016

Science. 2017 Nov 17;358(6365):933-936

Diagnostic & traitement

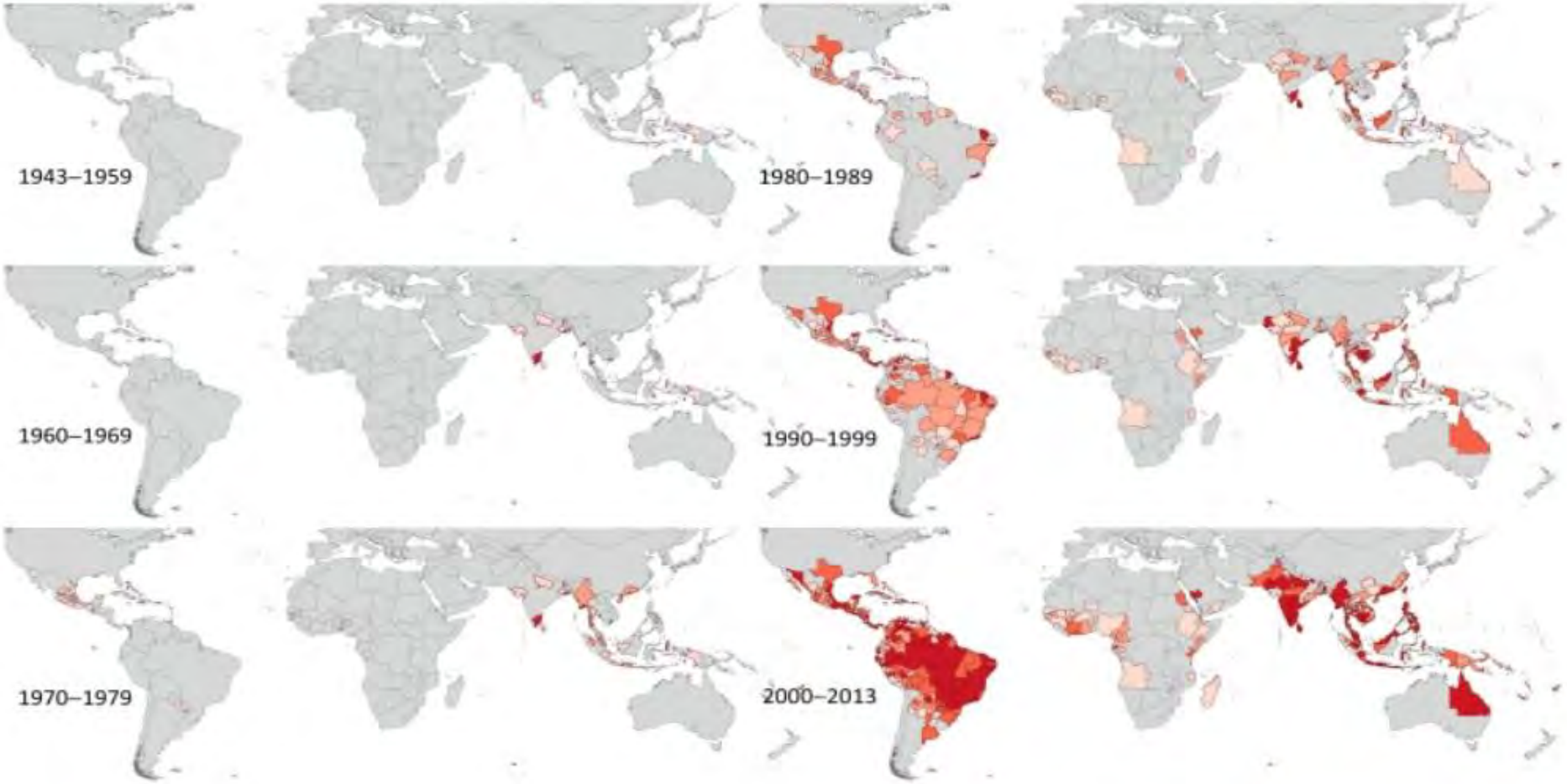
- **Détection du RNA viral par real-time RT- PCR**
  - Dans plasma (salive) → J6 (virémie courte et faible)
  - Dans l'urine → J15
  - Dans sperme, plus long
- Chez femme enceinte, RT-PCR plasma peut être positive >50j
- **Sérologie IgM (ELISA)**
  - Positive dès J5-7, persistance plusieurs mois
  - Réactions croisées avec d'autres flavivirus (ex: dengue)
  - Plaque reduction neutralization test (PRNT) dans cas douteux mais pas disponible en Suisse
  - Si IgM et IgG négatifs en cas de suspicion d'infection aiguë, répéter les sérologies 10-14 jours plus tard afin d'observer la cinétique
- Traitement: pas de traitement antiviral, traitement symptomatique



DENGUE

https://la1ere.francetvinfo.fr/polynesie/tahiti/polynesie-francaise/deux-personnes-atteintes-dengue-type-2-polynesie-443567.html

Dengue: 4 sérotypes co-circulants



DENV Co-circulation. Cumulative number of DENV types reported by decade since 1943.

Remerciements à la Dre C. Plumettaz

Cas de dengue en Amérique latine

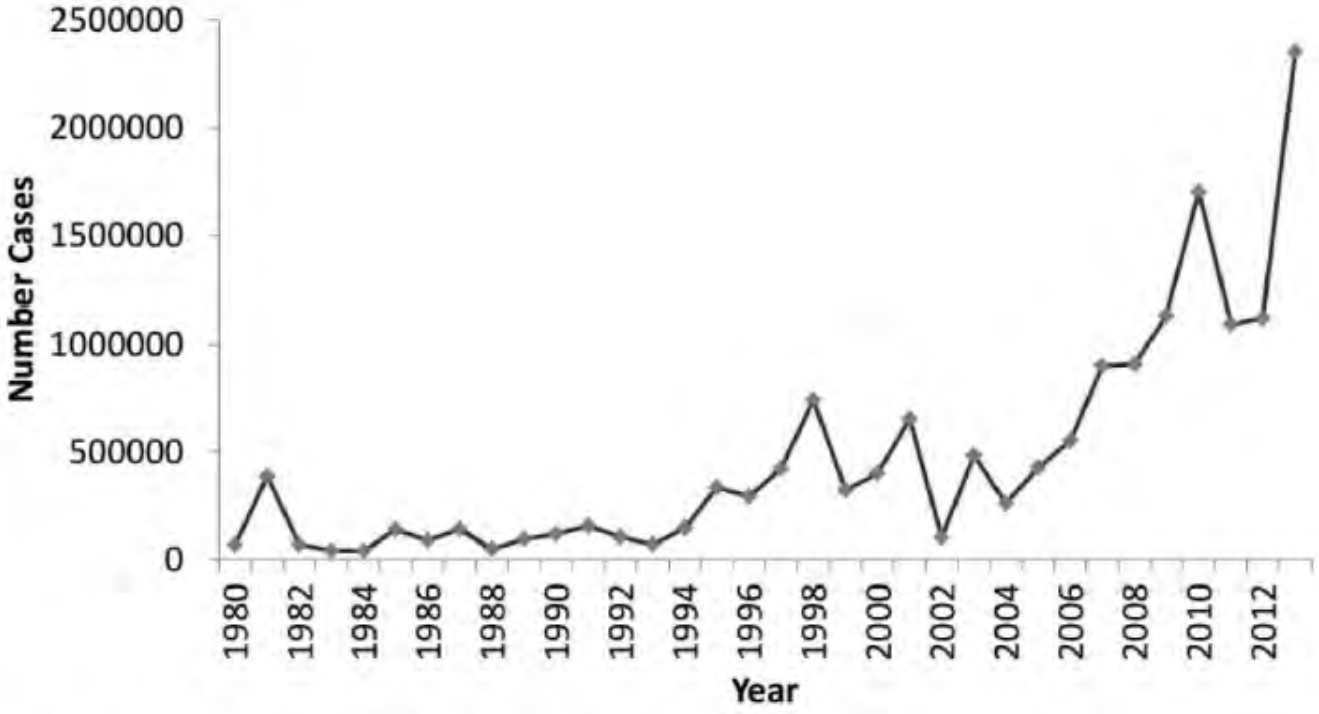
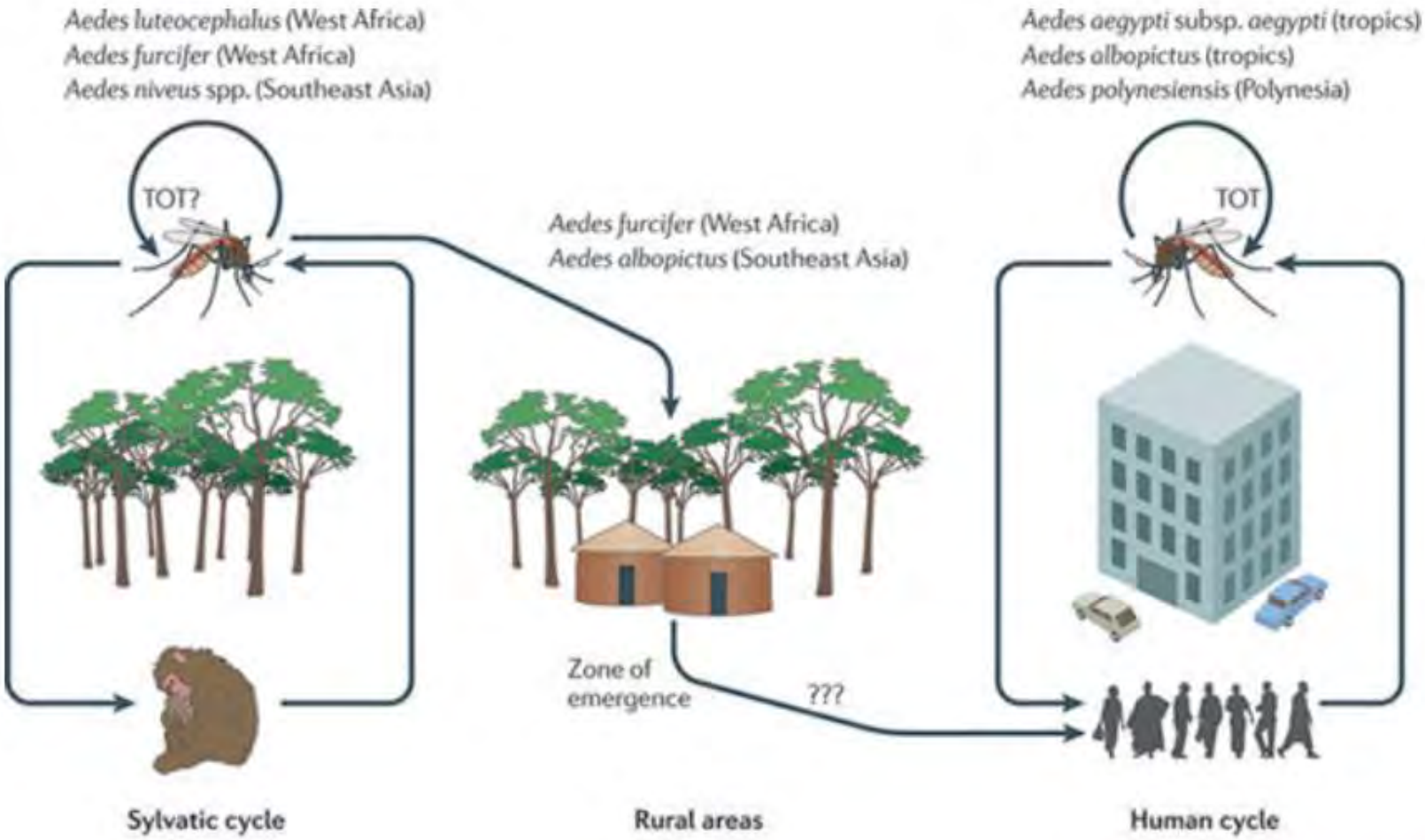


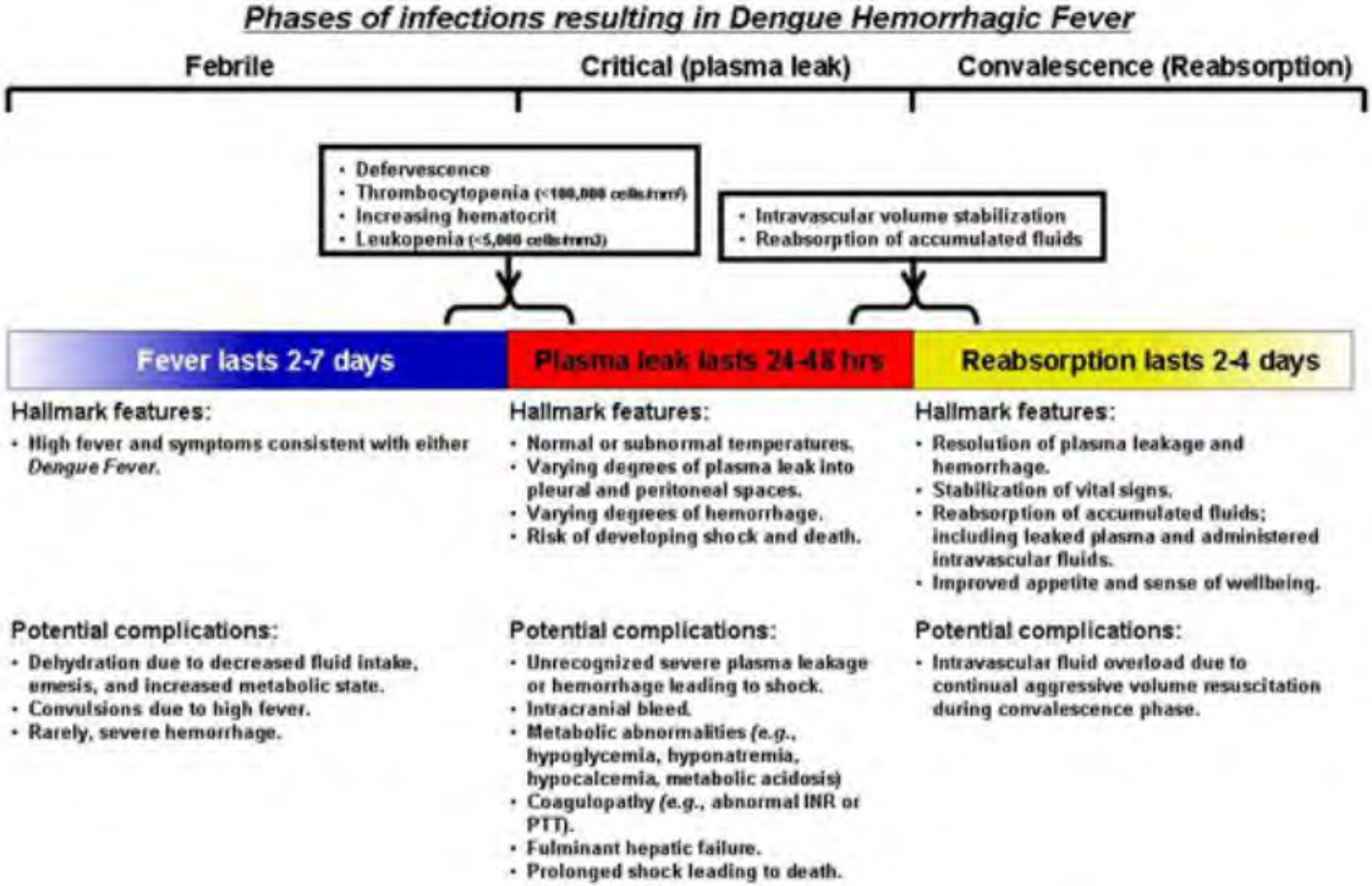
FIGURE WO-7 Dengue incidence is rapidly increasing in the Americas.
SOURCES: As presented by Lyle Petersen on September 16, 2014. Data from Pan American Health Organization.

Cycles de transmission

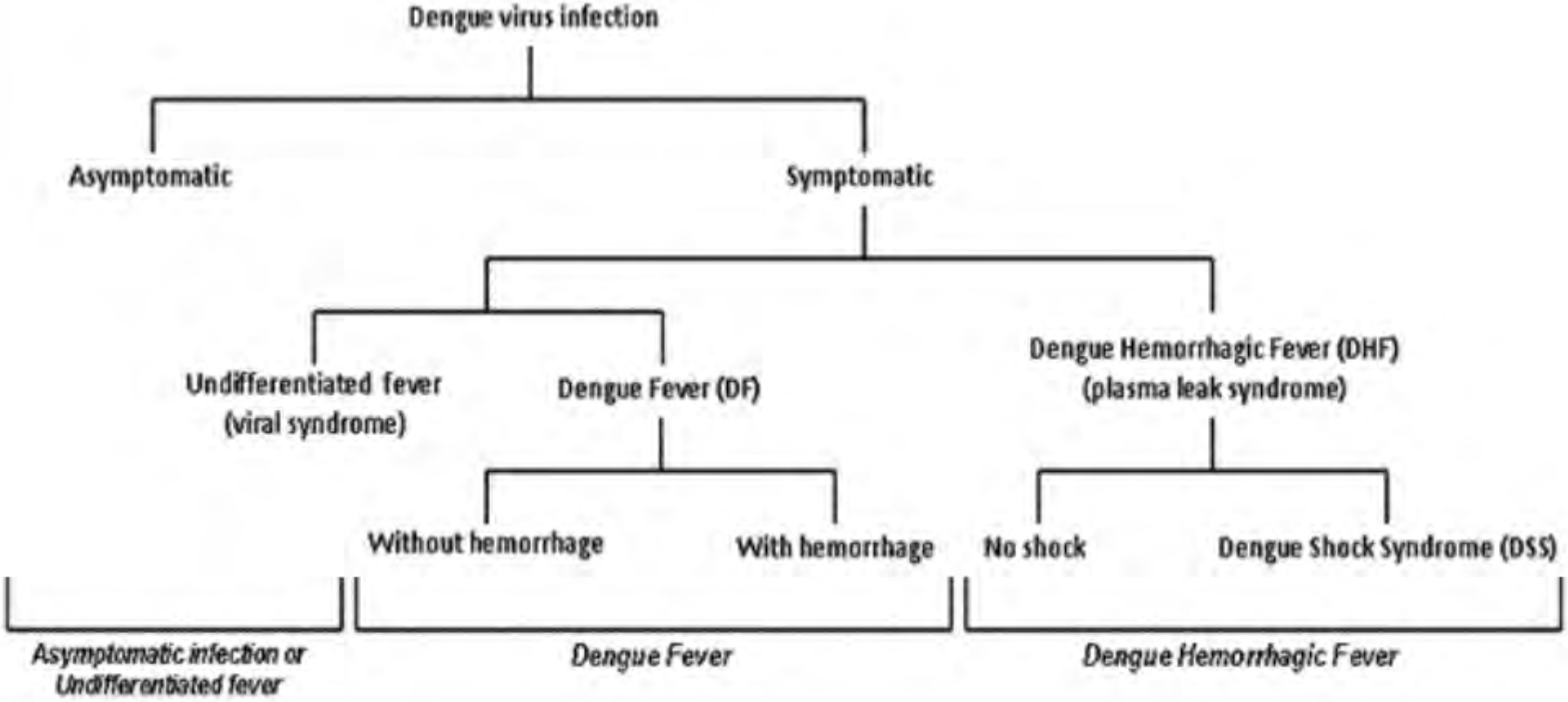


Nature Reviews | Microbiology

Caractéristiques cliniques



Caractéristiques cliniques



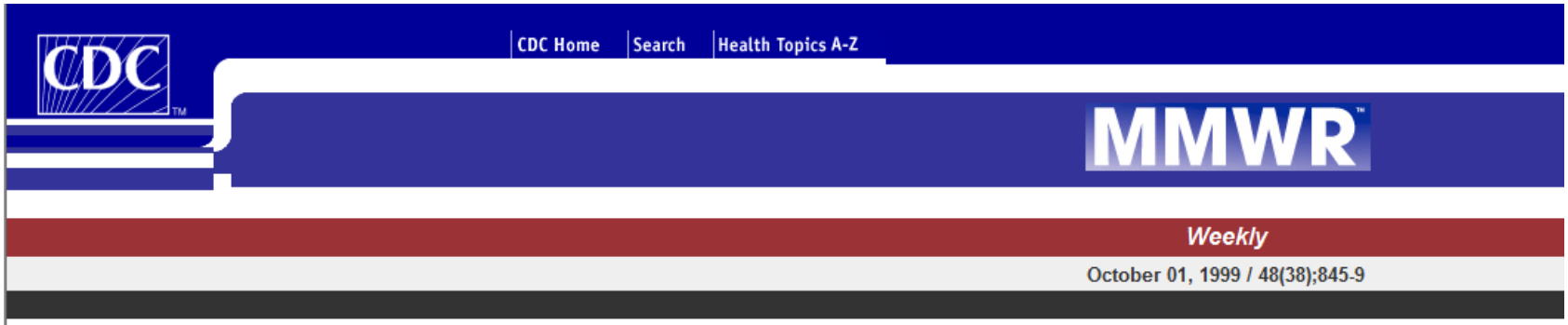
*Adapted from *Dengue Hoemorrhagic Fever: Diagnosis, Treatment, Prevention and Control. 2nd edition.* WHO, Geneva, 1997

« théorie des anticorps facilitants »

Dengue: 4 sérotypes

Personne infectée par la dengue pour la 2ème fois, mais par un sérotype différent

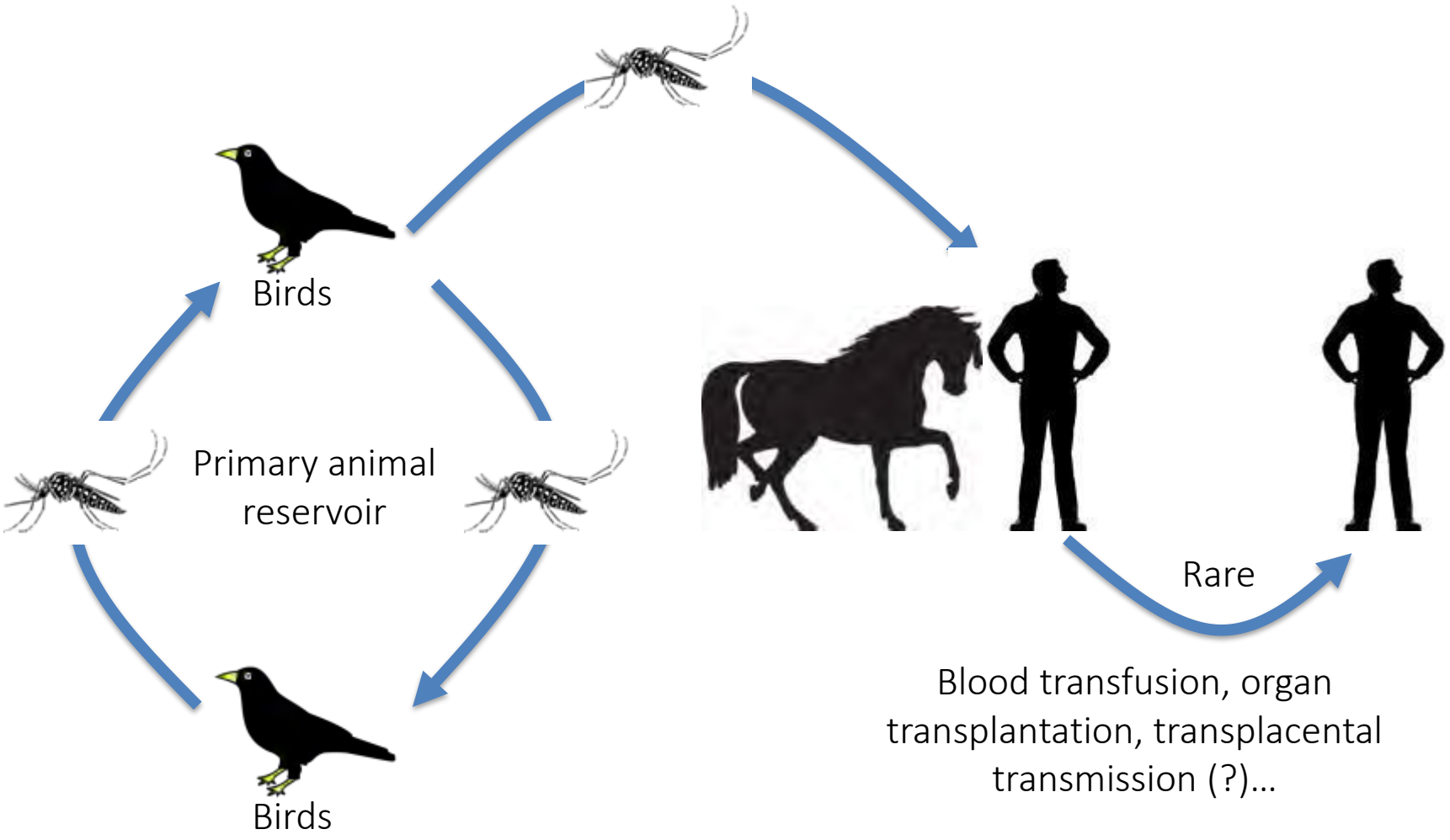
Certains anticorps induits par la première infection faciliteraient l'infection des monocytes lors de l'infection subséquente par un virus d'un autre sérotype

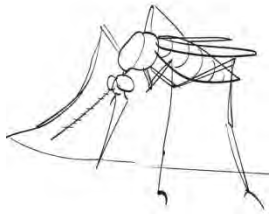


On August 23, 1999, an infectious disease physician from a hospital in northern Queens contacted the New York City Department of Health (NYCDOH) to report two patients with encephalitis. On investigation, NYCDOH initially identified a cluster of six patients with encephalitis…

Before and concurrent with this outbreak, local health officials observed increased fatalities among New York City birds, especially crows…

West Nile cycle





WEST NILE VIRUS

Neurotropic flavivirus

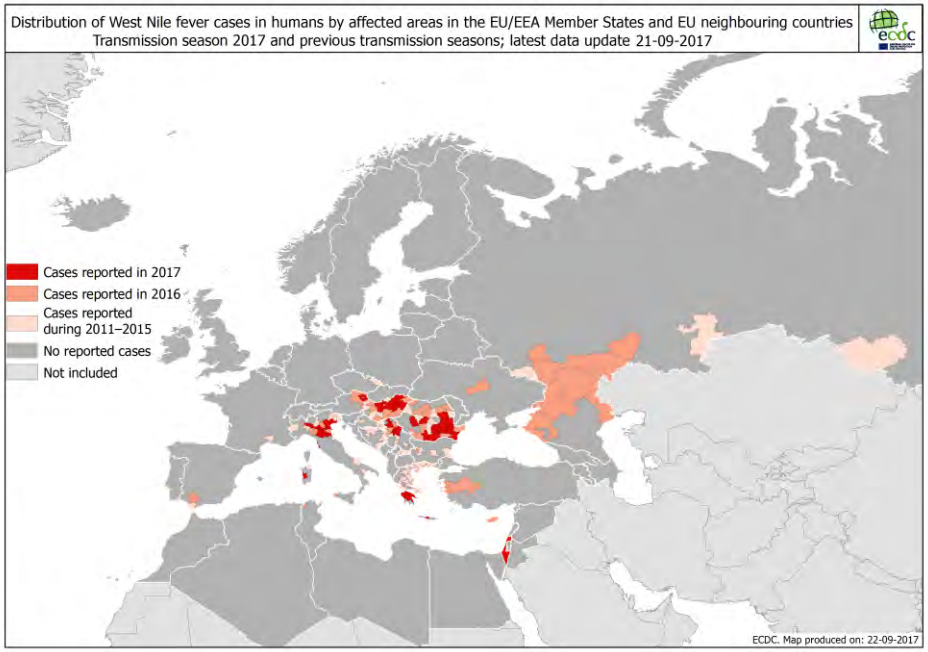
ASYMPTOMATIC
70-80%

WEST NILE FEVER
20-25%

NEURO-INVASIVE DISEASE
1%

West Nile cases in Europe 2017

- Italy 47 cases
- Greece 45 cases
- Romania 39 cases
- Hungary 14 cases
- Austria 2 cases.
- Serbia 28 cases
- Israel nine cases



Neuroinvasive West Nile in the USA since 1999

Average incidence

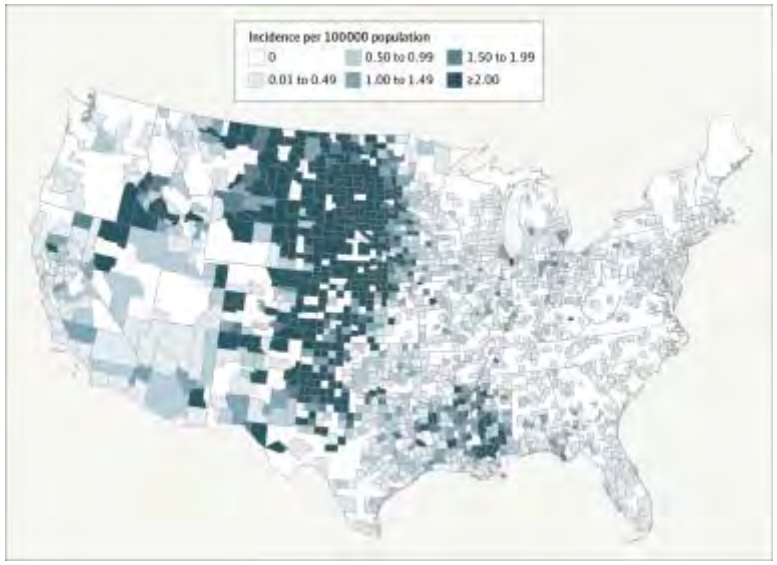


Figure 3. Map of Average Annual Human Neuroinvasive Disease Incidence in the United States, 1999-2012

Cumulative numbers

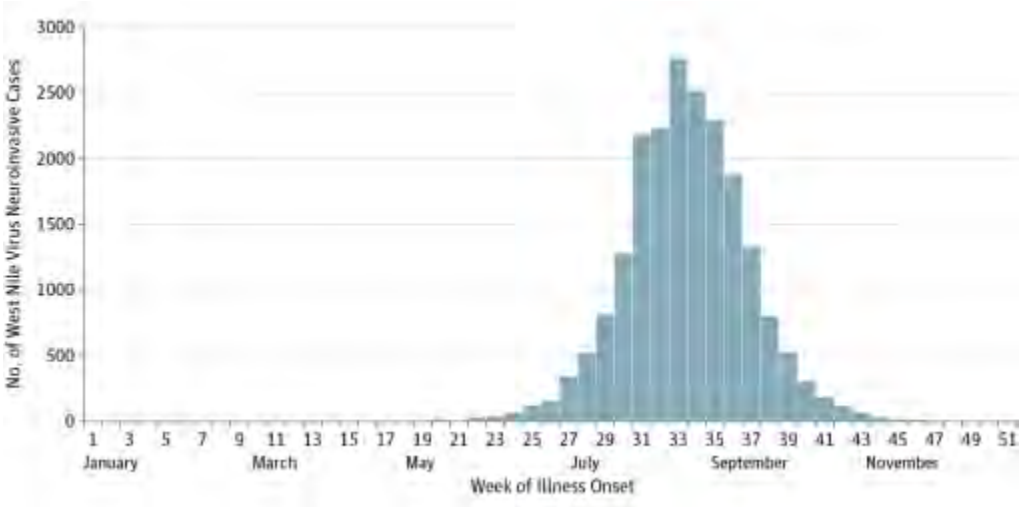
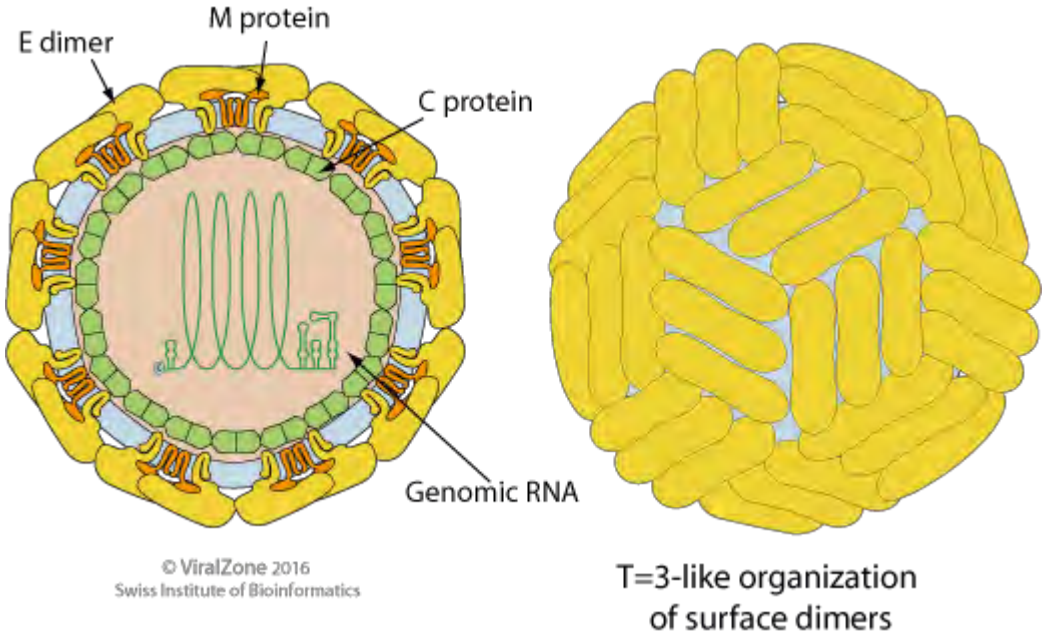


Figure 4. Cumulative Number of Human West Nile Virus Neuroinvasive Disease Cases by Week of Onset, 1999-2012

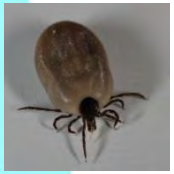
- All blood donors screened by RT-PCR

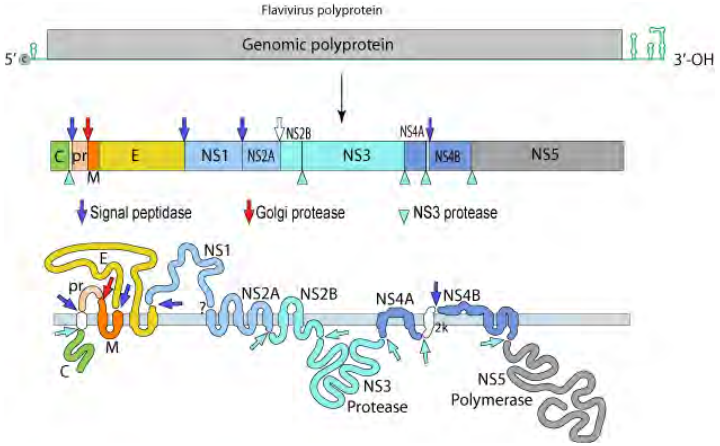


Encéphalite japonaise

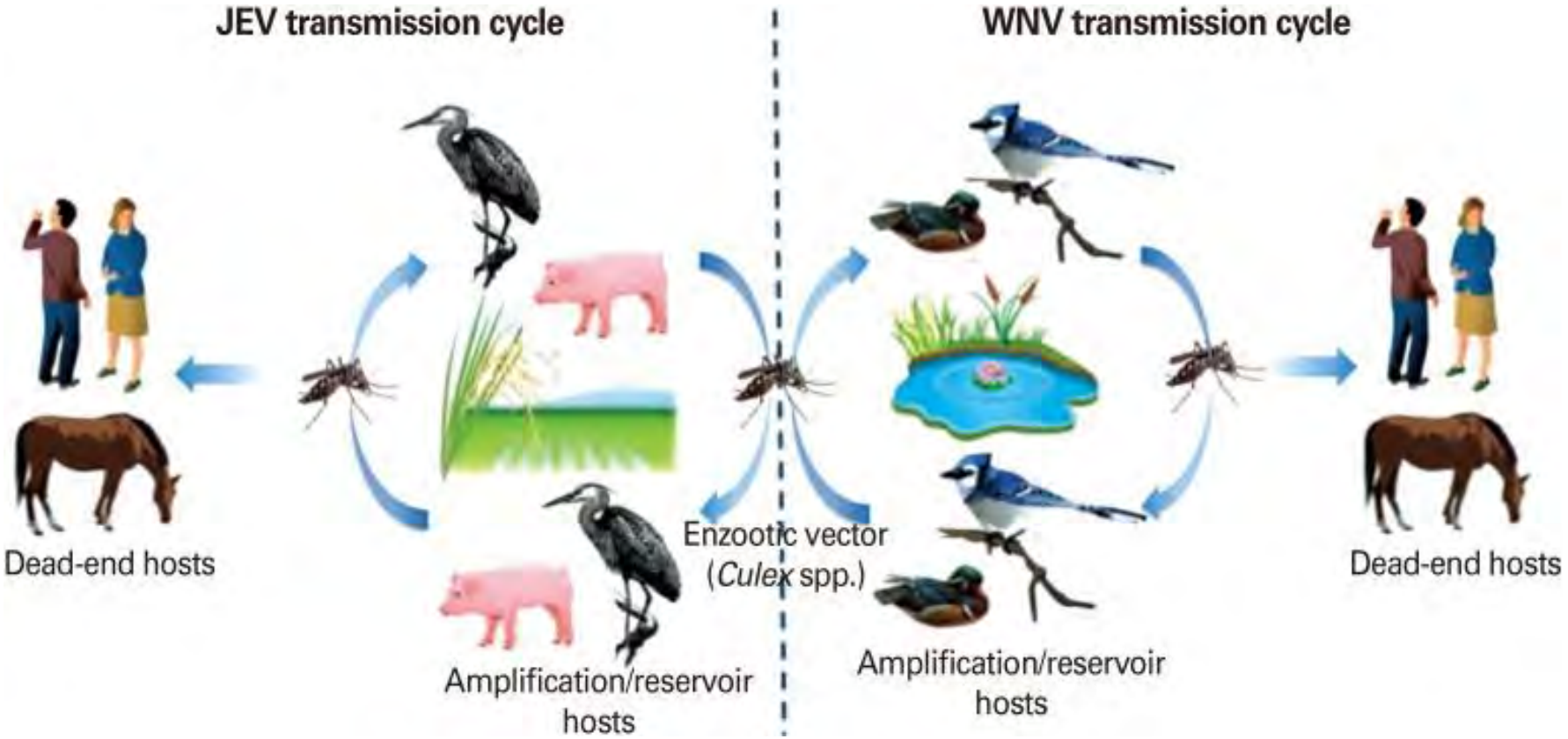
Based on the E gene sequence or the complete genome, JEV can be further divided into five genotypes (GI–GV)

Phylogenetic analysis of NS1 proteins from different flaviviruses.





Song H et al. Nature Structural & Molecular Biology 23, 456–458 (2016)



Go YY et al. Clin Exp Vaccine Res. 2014 Jan;3(1):58-77.

Clinical manifestations of JEV

- febrile illness
- aseptic meningitis
- acute encephalitis → death

JEV Vaccine

- The inactivated mouse brain-derived (IMB) vaccine is now commonly replaced by cell culture-based vaccines

- A live attenuated vaccine based on the SA 14-14-2 strain of the JE virus is widely used in China and in an increasing number of countries within the Asian region, including India, the Republic of Korea, Sri Lanka, and Thailand

- A Vero cell-derived, inactivated and alum-adjuvanted JE vaccine based on the SA 14-14-2 strain was approved in 2009 in North America, Australia and various European countries. The primary two doses are administered 4 weeks apart. A booster dose is recommended 1–2 years after the primary immunization.

World Health Organization

Joint pains. The pain was frightening in its severity, completely immobilizing many patients and preventing sleep in the first few days of illness. It was intensified by movement and localized in the large joints. In some cases there was also severe backache. Morphia was the only analgesic which was found to modify the pain. In two cases the pain was mainly localized in a joint which had sustained a previous injury. There were usually no localizing

The pain was frightening in its severity,
nting sleep in the first few days of illness.

and no inhabitant can remember a similar epidemic. Owing to the distinctive severity of the joint pains and the sudden onset a local name was rapidly applied ; the disease became known as *chikungunya*, meaning — " that which bends up".

the disease became
known as *chikungunya*, meaning — " that which bends up".

COMMUNICATIONS

AN EPIDEMIC OF VIRUS DISEASE IN SOUTHERN PROVINCE, TANGANYIKA TERRITORY, IN 1952-53

I. Clinical Features

BY

MARION C. ROBINSON*

(*From Lulindi Hospital, Universities Mission to Central Africa*)

TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.
Vol. 49. No. 1. January, 1955.

THE NEWALA EPIDEMIC

THE VIRUS: ISOLATION, PATHOGENIC PROPERTIES AND RELATIONSHIP TO THE EPIDEMIC

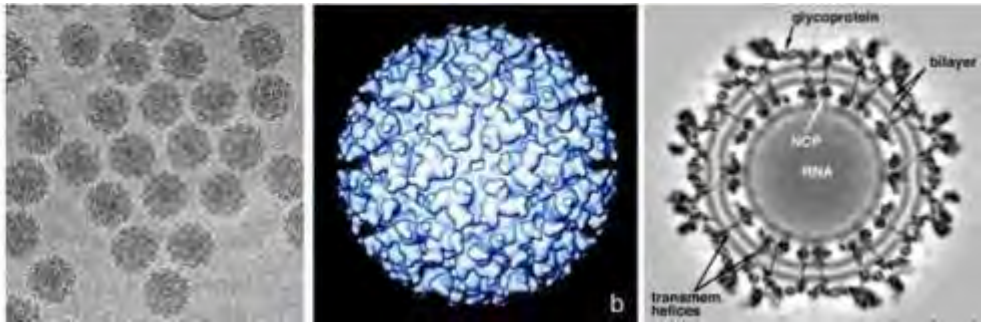
BY R. W. ROSS*

From the Virus Research Institute, Entebbe

CONTENTS

J Hyg (Lond). 1956 June; 54(2): 177–191

Chikungunya: αvirus, Togaviridae: ss+ RNA virus



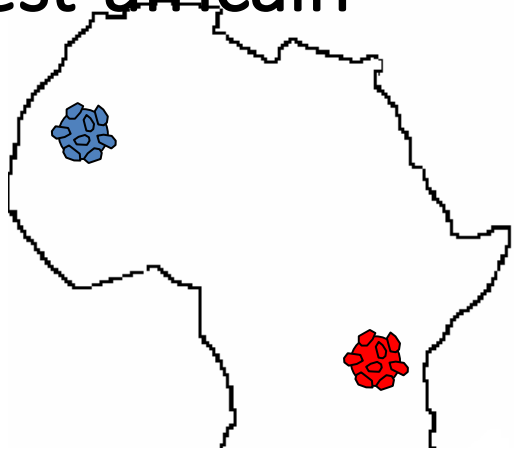
Transmission

- **Vectorielle:** moustiques *Aedes (aegypti, albopictus)*
- Pas de transmission inter-humaine directe rapportée

Chikungunya: lignées virales et vecteur avant 2007

Vecteur: Aedes aegypti

Ouest-africain



Asiatique

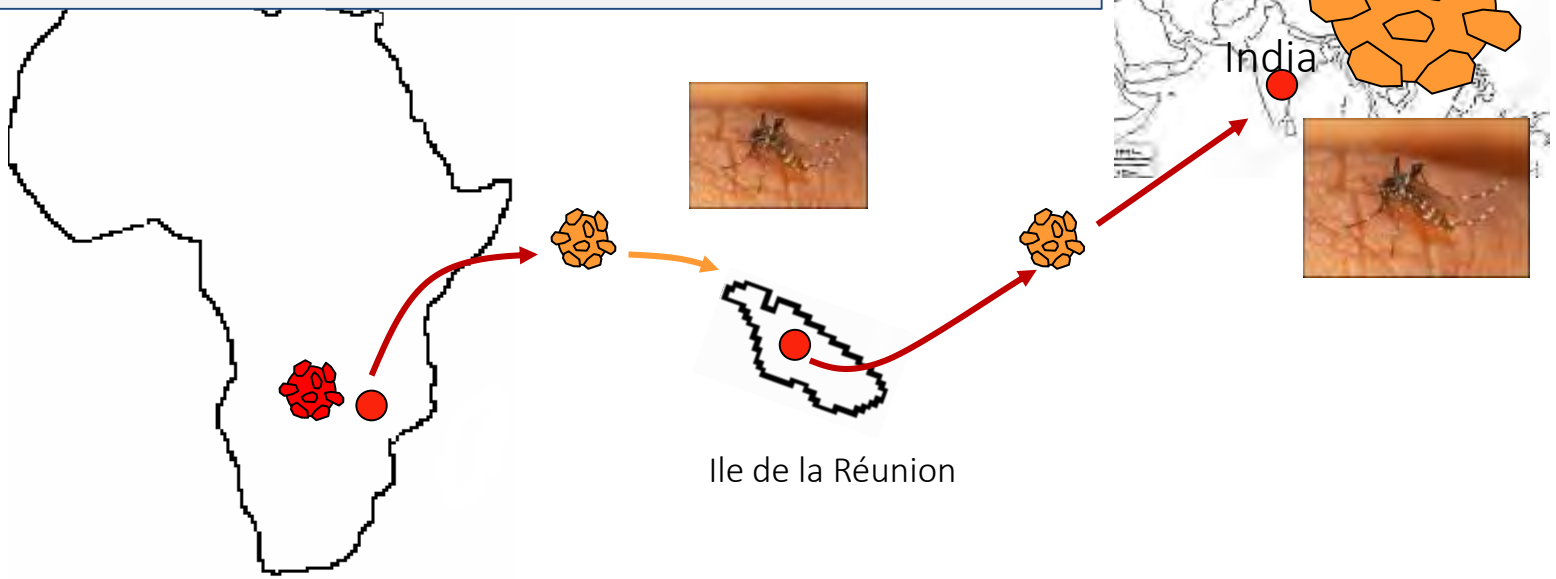
Peu fréquent et sporadique

Est-sud-africain

Quelques épidémies documentées

2007: chikungunya & *A. albopictus*

Manifestations principales
Fièvre - athralgies (> 90% des cas) - myalgies (50%) – éruption curanée (50%) – symptômes digestifs (<50%)

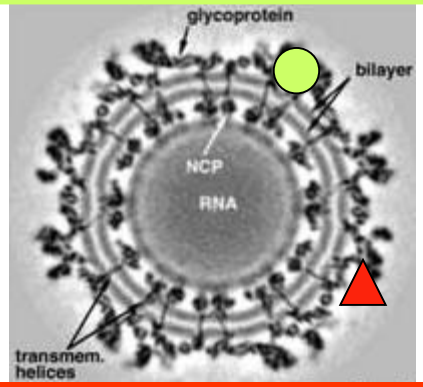


Country	Cases (2005-2006)	Mortality/100'000
La Réunion (777'000)	258'000 cases (38%)	91.8
India full estimate	6'5 mio cases	276

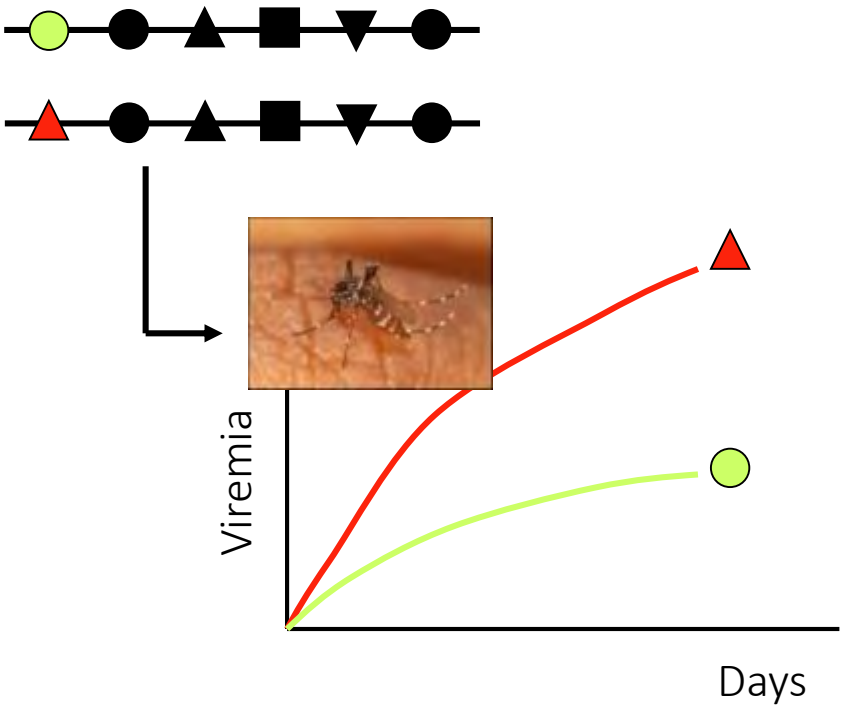
Chikungunya: mutations et adaptation à un nouveau vecteur *(A. albopictus)*

E1 glycoprotein

Mars 2005:
100% des souches A226



Avril 2006: 90% A226V



L'Amérique latine, les moustiques et les virus…

Continent infesté par les moustiques

Aedes aegypti et *Aedes albopictus*

Virus CHIK, DEN et Zika:
mêmes vecteurs
même répartition
mêmes symptômes…

Complication post-Chikungunya

- **Arthralgies/arthrite persistantes**
  - **~ 20 to 60% des cases après 12 mois**

    Thiberville et al. Antiviral Reserach 2013
- Grossesse
  - Transmission verticale péripartum (49% des cas) et maladie sévère dans 53% des nouveaux-nés

    Gerardin Plos Med 2008
- Complications neurologiques
  - Encéphalite, Guillain-Barré

Diagnostic & traitement

- **Détection du RNA viral par real-time RT- PCR**
  - Dans plasma, dans la première semaine qui suit le début des symptômes

- **Sérologie (ELISA)**
  - **IgM:** Positive dès J5-7, persistance plusieurs mois
  - Si IgM et IgG négatifs en cas de suspicion d'infection aiguë, répéter les sérologies 10-14 jours plus tard afin d'observer la cinétique

- Traitement: pas de traitement antiviral, traitement symptomatique

En résumé

- Arboviroses tropicales: penser Flavivirus + Chikungunya… et moustiques!
- Flavivirus:
  - Fièvre jaune
  - Zika
  - Dengue
  - West Nile
  - Encéphalite japonaise
- Infections aiguës, parfois bénignes, parfois sévères
- Diagnostic sérologique, attention aux réactions croisées pour les flavivirus
- Pas de ttt spécifique, vaccins

Merci pour votre attention!