Dr Didier Musso
Unit of emerging infectious diseases
Institut Louis Malardé, Tahiti, French Polynesia

Zika virus, following the same path as dengue and chikungunya.

French Polynesia

Zika Virus

Discovered in 1947 in Uganda, Africa

- Rhesus monkeys (1947)
- Mosquitoes (1948)

First human infection in Nigeria (1954)

Seroprevalence studies in Africa and Asia: detection of ZIKV antibodies in humans and animal but seroprevalence studies difficult to interpret

- Cross-reactions with other flavivirus (dengue, yellow fever …)

Zika Virus 1947 - 2007

From 1947 to 2007 : only 14 human infections confirmed (Africa and Asia)!

Zika Virus 2007: Yap

2007: Outbreak in Yap, Federated Sates of Micronesia

- About 5.000 estimated infection (75% population)
- First outbreak, first detection out of Asia and Africa
- Only mild disease
- No hospitalizations
- No death
- No complications

Zika virus 2007 - 2013

2007 to 2013 : nothing to declare (1 infection in Philippe from retrospective study)

What happens in French Polynesia in October 2013 ?

Same beginning as in Yap: **patients presenting atypical dengue symptoms and testing negative for DENV:**

- No fever or only mild fever (acute onset of high fever in dengue) +++
- Conjunctivitis
- No acute onset of symptoms +++
- Laboratory tests negative for dengue (molecular diagnosis)

- We tested samples for other arboviruses with potential to emerge in FP
  - WNV, endemic in the USA
  - ZIKV that circulated in the Pacific in 2007
  - CHIKV that circulated in the New Caledonia since 2011 we were prepared for CHIKV

Laboratory test positive for ZIKV. Confirmation by sequencing.

Conclusion: ZIKV

Zika Virus outbreak in French Polynesia 2013 - 2014

2013 - 2014: French Polynesia

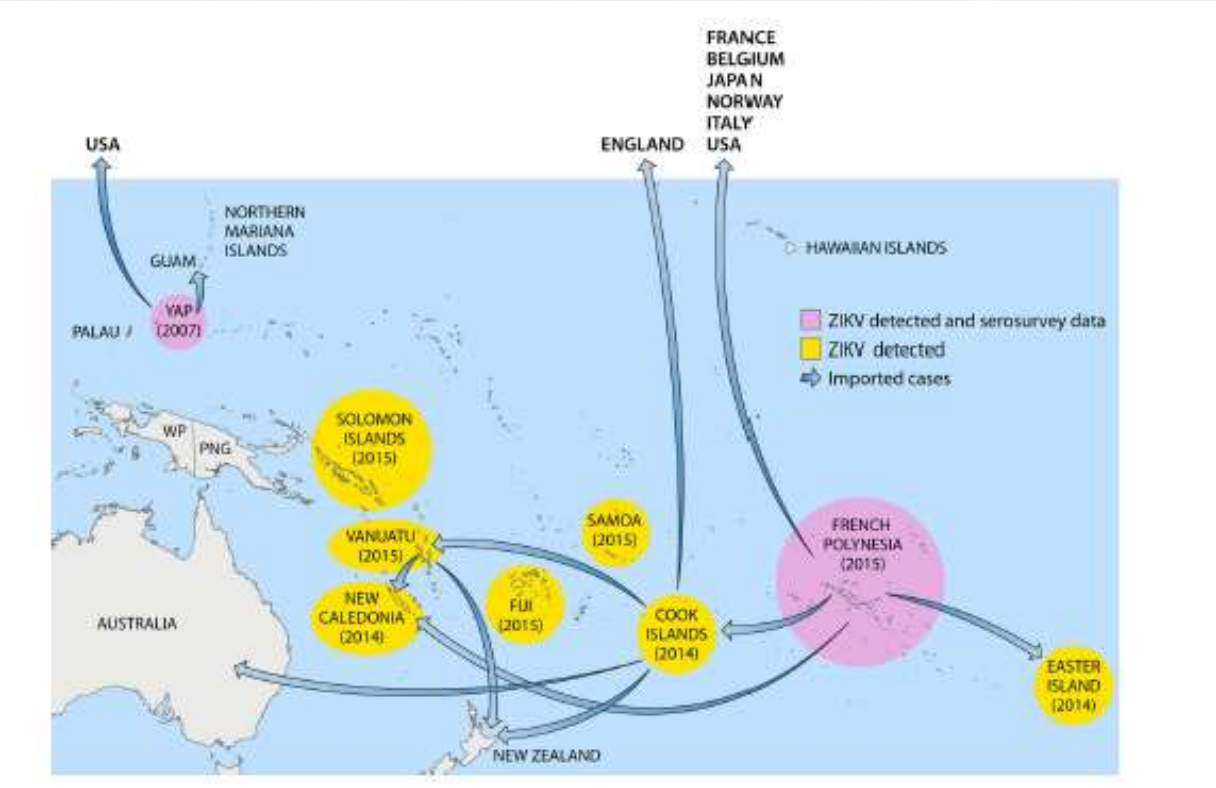
- About 30.000 symptomatic cases (11.5 % population)
- Serosurvey
  - < 1% before the outbreak
  - More than 60% after
- **Severe neurological complications (Guillain-Barré Syndrôme)**

+++, 20 fold increase

- Non vector borne transmission
  - Materno-fetal
  - Potential for sexual transmission
  - Potential for transmission by blood transfusion

Zika Virus in the Pacific

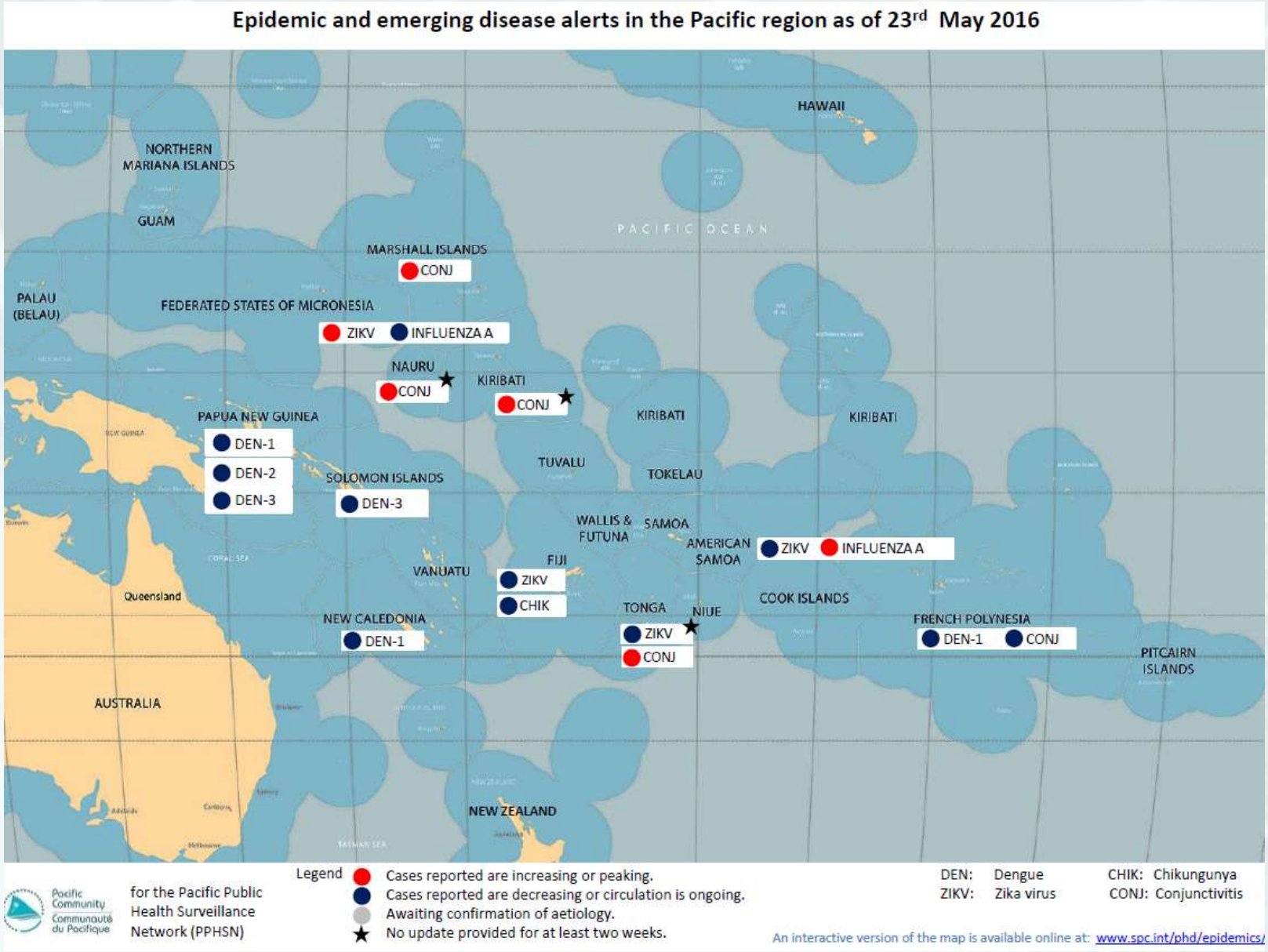
From 2014: spread in the Pacific



(Musso and Gubler al. CMR. 2016;29:487-524)

2016:

- ZIKV is still circulating in the Pacific


Epidemic and emerging disease alerts in the Pacific region as of 23rd May 2016
HAWAII
NORTHERN MARIANA ISLANDS
GUAM
PACIFIC OCEAN
MARSHALL ISLANDS
CONJ
PALAU (BELAU)
FEDERATED STATES OF MICRONESIA
ZIKV
INFLUENZA A
NAURU
CONJ
KIRIBATI
CONJ
KIRIBATI
KIRIBATI
PAPUA NEW GUINEA
DEN-1
DEN-2
DEN-3
TUVALU
TOKELAU
SOLOMON ISLANDS
DEN-3
WALLIS & FUTUNA
SAMOA
AMERICAN SAMOA
ZIKV
INFLUENZA A
FIJI
VANUATU
ZIKV
CHIK
Queensland
COOK ISLANDS
TONGA
NIUE
NEW CALEDONIA
DEN-1
ZIKV
CONJ
FRENCH POLYNESIA
DEN-1
CONJ
PITCAIRN ISLANDS
AUSTRALIA
NEW ZEALAND
Pacific Community Communauté du Pacifique
for the Pacific Public Health Surveillance Network (PPHSN)
Legend
Cases reported are increasing or peaking.
Cases reported are decreasing or circulation is ongoing.
Awaiting confirmation of aetiology.
No update provided for at least two weeks.
DEN: Dengue
ZIKV: Zika virus
CHIK: Chikungunya
CONJ: Conjunctivitis
An interactive version of the map is available online at: www.spc.int/phd/epidemics/

Zika virus in the Americas, from 2015

- Epidemic of “exanthematic disease” of unknown origin in late 2014 in Brazil
- Problem in Brazil: **co-circulation** of several arbovirus: dengue, chikungunya, yellow fever, Oropouche fever, St Louis encephalitis, Mayoro fever in addition to bacterial and parasitic diseases (Malaria) … Difficult to diagnose a new pathogen
- ZIKV circulation confirmed on May 2015 (Bahía)
- Spread very fast:

Common features of ZIKV and other arboviruses (DENV, CHIKV, WNV)

Classification

(Arbovirus = Arthropod-borne viruses)

CLASSIFICATION				
	ZIKV	CHIKV	WNV	DENV
Family	*Flaviviridae*	*Togaviridae*	*Flaviviridae*	*Flaviviridae*
Genus	*Flavivirus*	*Alphavirus*	*Flavivirus*	*Flavivirus*

Place of discovery

Uganda

- Bwamba fever 1937
- West Nile virus 1937
- Semliki forest 1942
- Bunyamwera 1943
- Uganda S 1947
- Zika virus 1947
- Mengo 1946

Tanzania

- CHIKV 1952*

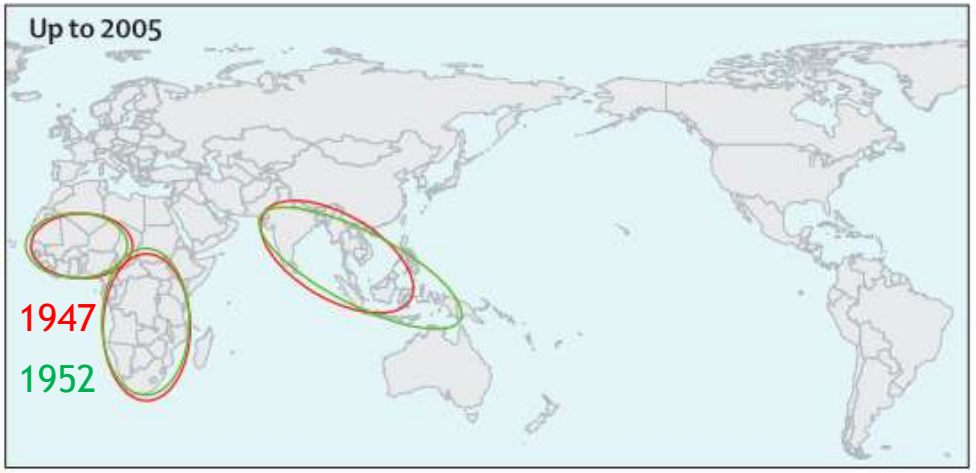
CHIKV older disease:
Ki denga pego

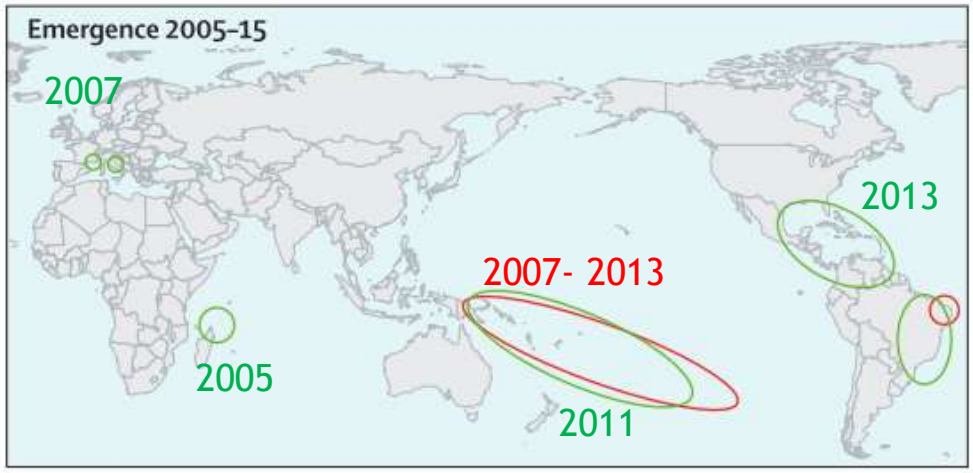
DENV old disease (> 250 Y)
Described during World War II

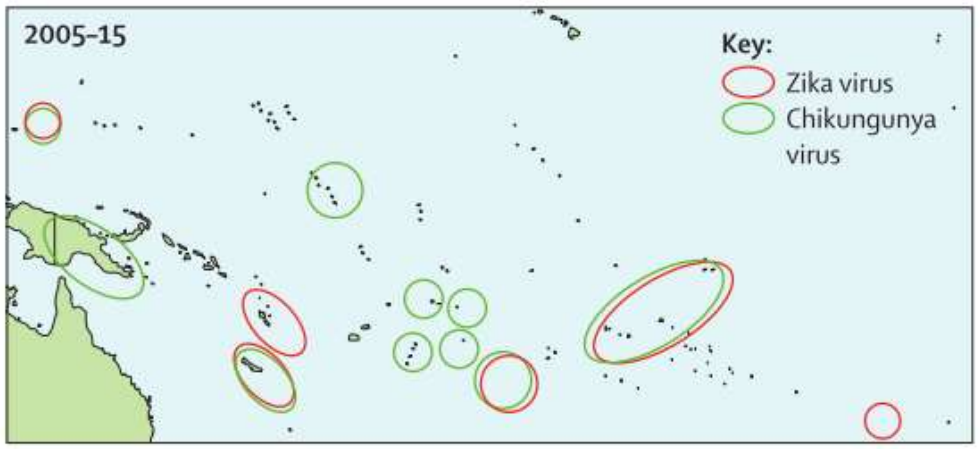
Emergence : ZIKV compared to CHIKV

ZIKV

CHIKV

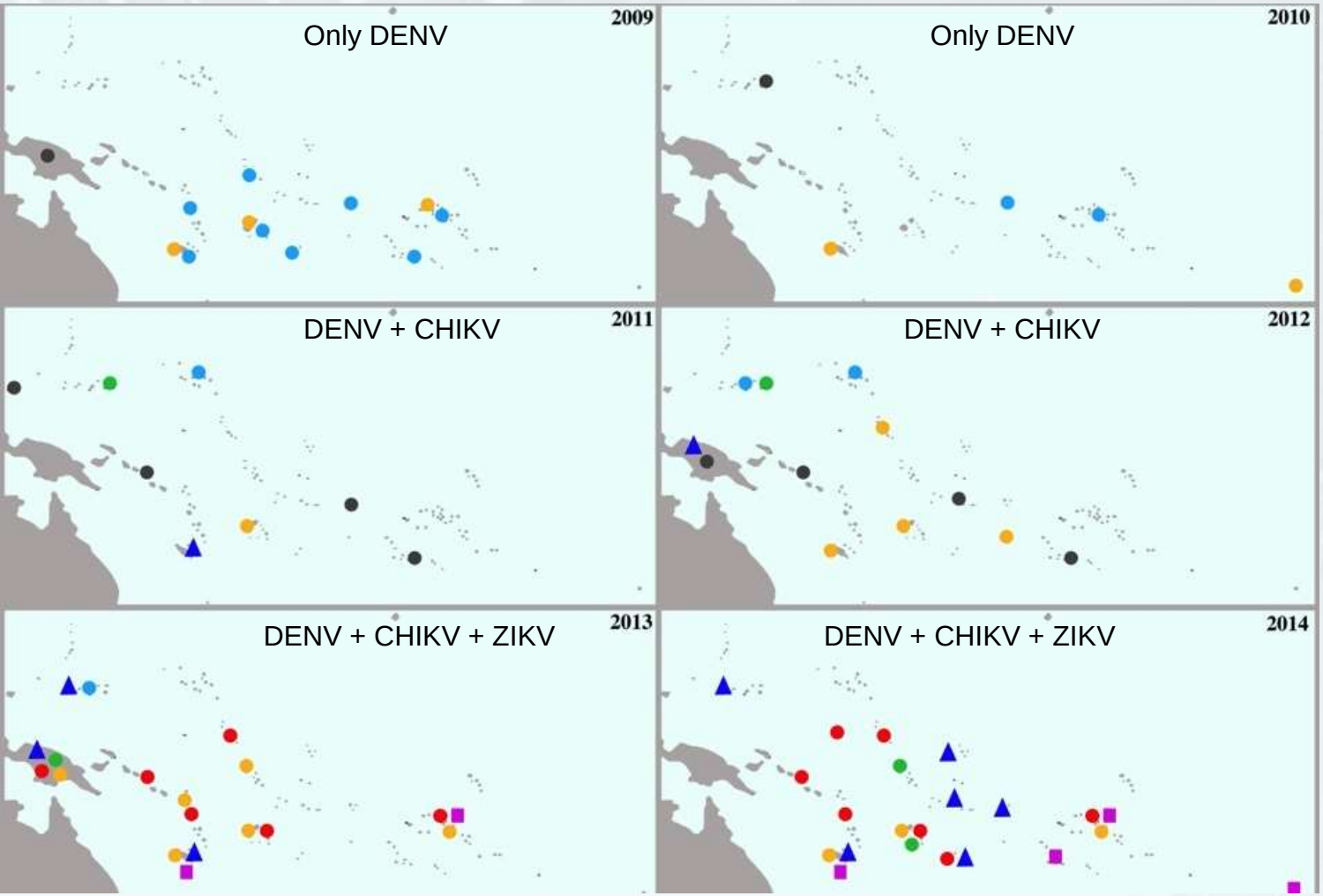






Musso and Gubler. Zika virus following the path of dengue and chikungunya. The Lancet. 2015;386:243-244

Emergence and co-circulation of ZIKV CHIKV DENV in the Pacific



Cao-Lormeau VM, Musso D. The Lancet 2014

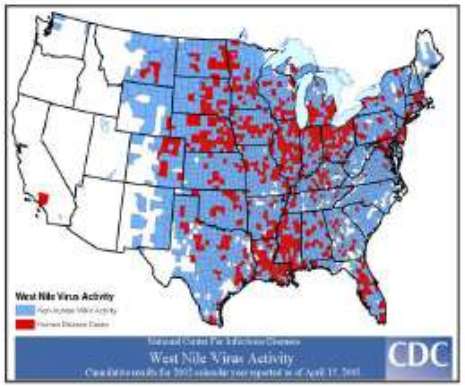
Emergence of WNV

Romania 1996
Russia 1999
America 1999

1999

2000

2001



2002

WNV in the USA 1999-2002

Geographic distribution

GEOGRAPHIC DISTRIBUTION				
	ZIKV	CHIKV	WNV	DENV
Africa	+	+	+	+
Asia	+	+	+	+
Americas	+	+	+	+
Oceania	+	+	potential	+
Europe	potential	+	+	+

Clinical presentation

MAIN CLINICAL PRESENTATION				
	ZIKV	CHIKV	WNV	DENV
Main clinical presentation	Mild disease	Mild disease Severe arthralgia and relapsing arthralgia	Mild disease	Dengue fever Severe dengue
Symptomatic	1/5 – 1/6	8.5 /10	1 / 4	1/4 – 1/9

Severe complications

SEVERE COMPLICATIONS			
	ZIKV	CHIKV	WNV
First description	2013 (FP) 2015 (Brazil)	2005 (Reunion Island)	1996 (Romania)
Years after discovery	66	53	59
Description of complications associated with emergence	+++	+++	+++
Complications	Neurologic (GBS) CNS malformation	Neurologic	Neurologic

Non vector borne transmission associated with emergence

Non vector borne transmission				
	ZIKV	CHIKV	WNV	DENV
Materno fetal	+++	+	+	+
Blood transfusion / transplant	+	potential	+++	+
Sexual	++	-	-	-

The potential for ZIKV emergence +++

ZIKV and other arbovirus need:

- Reservoir / host (vertebrate) in which the virus multiply
- Vector (mosquito, tick) to transmit the virus between vertebrates

The potential for ZIKV emergence +++

Adaptation of ZIKV +++ (same for DENV)

ZIKV can adapt to new vectors and hosts +++++

- From a sylvatic cycle in Africa involving feral mosquitoes as vectors (*Ae africanus*) and primates (Rhesus monkeys) as reservoirs

- To an urban / periurban cycle involving *Ae. aegypti and Ae. albopictus* as vectors and humans as reservoir (Pacific: no primates in Yap, French Polynesia, New Caledonia …)

The potential for ZIKV emergence +++

In the wild ZIKV has been isolated only from primates (human and monkeys), antibodies detected in several other species

Mosquitoes competent vectors: ZIKV, transmission has been demonstrated for

- *Ae. africanus* (African mosquito)
- *Ae. hensilii* (Pacific mosquito, potential vector in Yap)
- *Ae. aegypti* (widespread)
- *Ae. albopictus* (widespread)

- Culex ???

Transmission can be different within the same specie (Some *Ae. aegypti* and *Ae. albopictus* strains are low competent)

Adaptation of ZIKV

Petersen et al. NEJM. 2016;374:1552-63

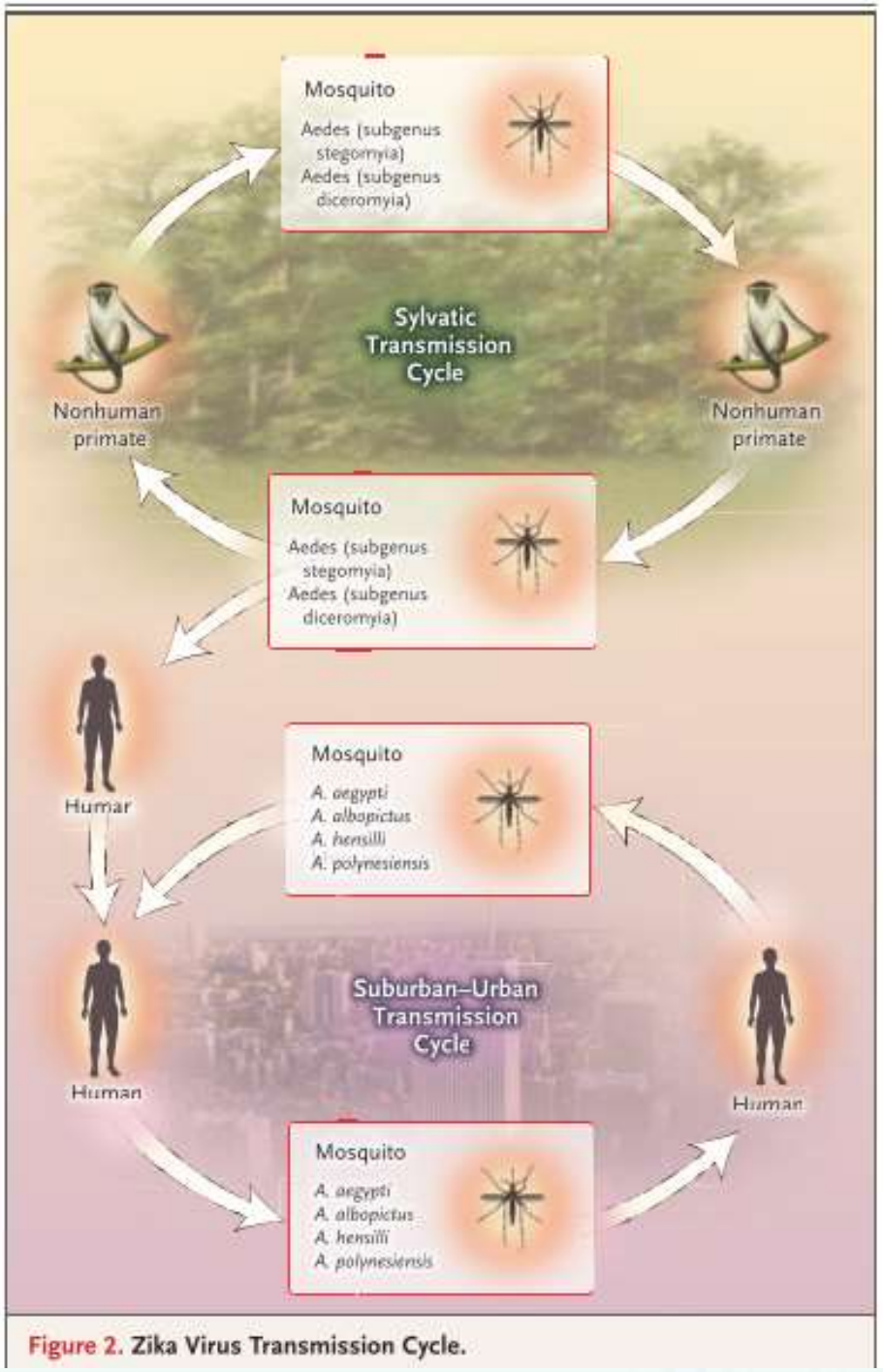


Figure 2. Zika Virus Transmission Cycle.

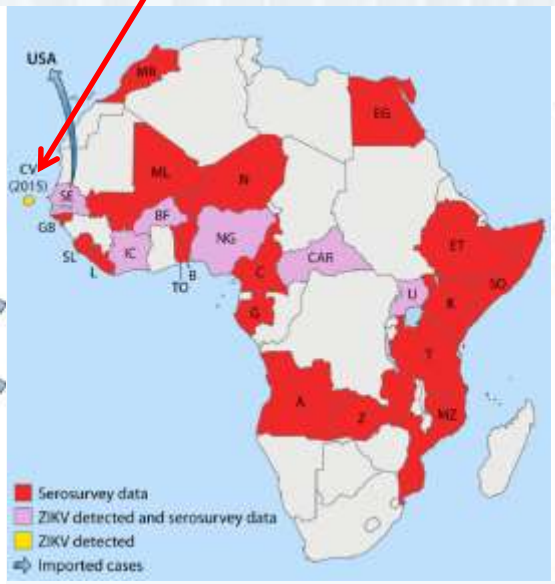
Zika virus : 3 important evens

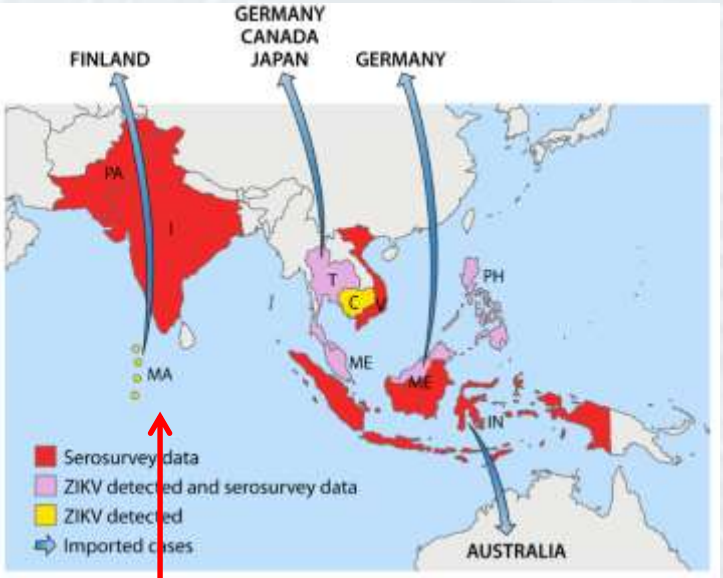
Retrospective detection of ZIKV from 3 infants in December 2014, Haiti

Outbreak in Africa: Cape Verde (Senegal) , November 2015: ZIKV return to its origins ?

Circulation in Maldives demonstrated by detection of ZIKV in a returning traveler

ZIKV circulates undetected +++

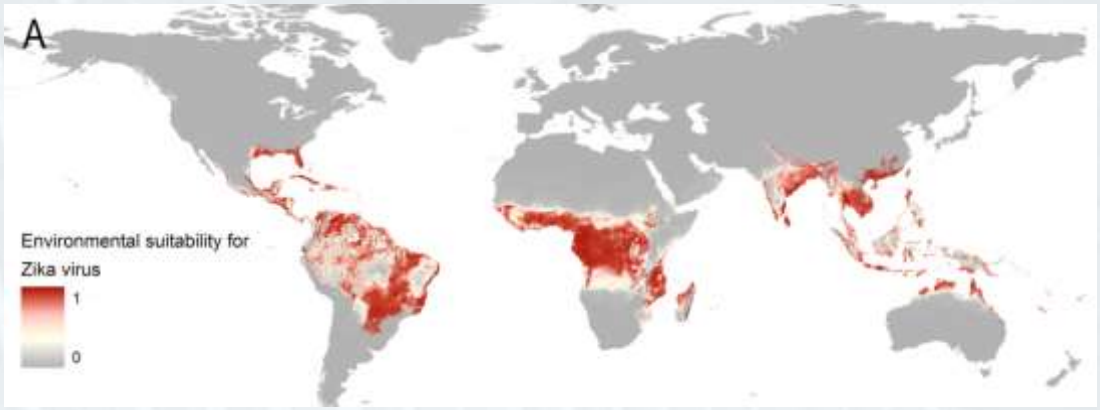




(Musso and Gubler al. CMR. 2016;29:487-524)

The potential area of emergence of ZIKV overlap the area of distribution of *Ae. aegypti* and *Ae. albopictus*

Aedes aegypti and *Ae. albopictus*



ZIKV

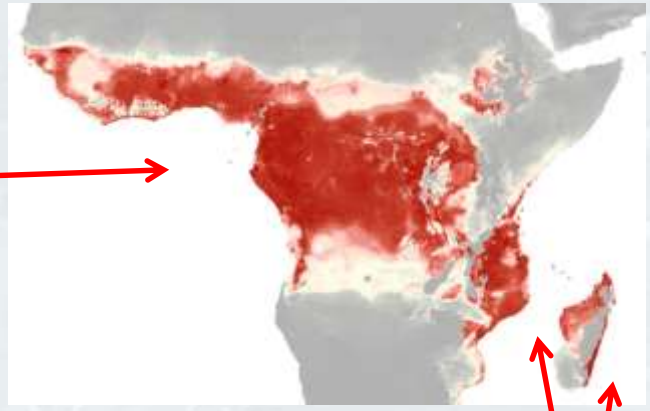
DENV 1-4

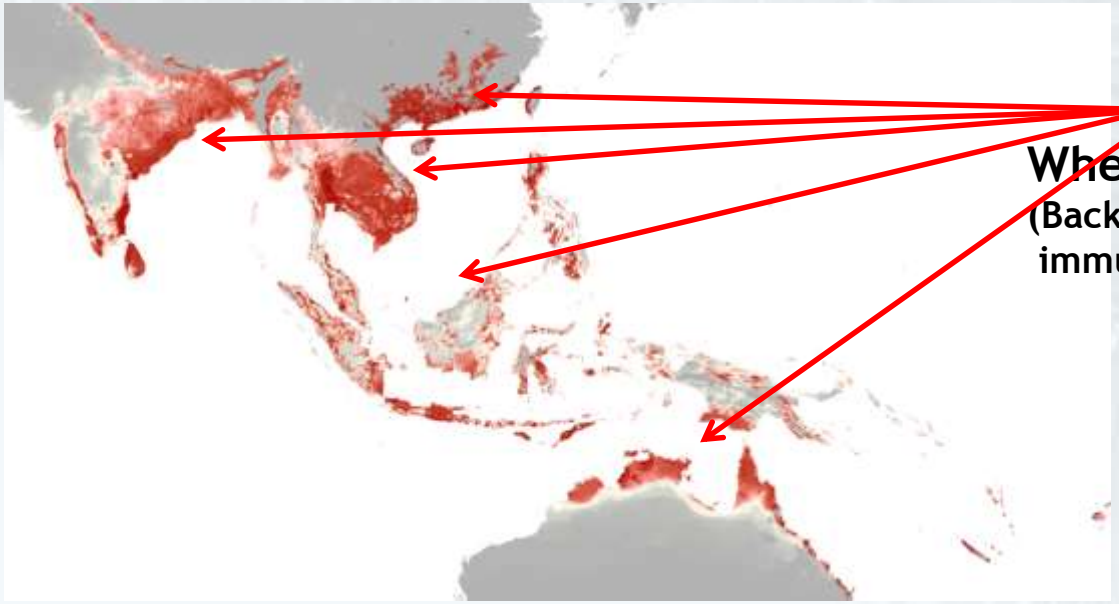
CHIKV

Focus on Zika

Done

Why no large outbreaks ? (African lineage)





When ? (Background immunity ?)

Messina et al. eLife. 2016:5: doi: 10.7554/eLife.15272.

The potential area of emergence of ZIKV overlap the area of distribution of *Ae. aegypti* and *Ae. albopictus*

Populations exposed to vectors of ZIKV (Messina et al. eLife. 2016:5: doi: 10.7554/eLife.15272.)

Region/Country	Population living in areas suitable for ZIKV transmission (millions)
Africa	**452.58**
Nigeria	111.97
Democratic Republic of the Congo	68.95
Uganda	33.43
United Republic of Tanzania	22.70
Americas	**298.36**
Brazil	120.65
Mexico	32.22
Colombia	29.54
Venezuela	22.22
Asia	**1,422.13**
India	413.19
Indonesia	226.04
China	213.84
Bangladesh	133.29
World	***2,173.27***

Table 1. Population living in areas suitable for ZIKV transmission within each major world region and top four countries contributing to these populations at risk.

Why ZIKV is emerging ? Why severe complications ?

Mutation associated with emergence / virulence		
ZIKV	CHIKV	WNV
? Not yet demonstrated	Reunion Island Mutation envelope gene (impact on CHIKV infectivity)	USA NY 99 prototype strains replaced by a new dominant genotype (WN 02)

Why ZIKV is emerging ? Why severe complications ?

Description of severe complication can also be related only to increase transmission:

- Example GBS
  - French Polynesia 42 cases = 1 / 6.500 inhabitants
  - Population of Yap: 7.500: 1 case expected, impossible to detect an increased incidence

- Example microcephaly
  - FP Increase in incidence reported retrospectively (8 cases)

The future of ZIKV, and other arboviruses, is difficult to predict

ZIKV: same pathogen, different outcomes

Example 1 : GBS

- Highest increase reported in French Polynesia (20 fold)
- Brazil + 19% (1439 to 1708), El Salvador + 5% (169 to 178),

Suriname 2.5 fold (4 to 10)(WHO)

Example 2 : outbreaks profile in French Polynesia and New Caledonia

2 French oversea territories of the South Pacific

- Same strain (introduced in New Caledonia from French Polynesia)
- Population: 270,000 in both countries
- *Ae. aegypti* in both countries
- But: **FP 11.5 % population, NC 0.8%** had clinical ZIKV infection

Why ?

- *Ae. polynesiensis* in FP
- Mid cold season in NC
- Different vector control strategies
- Melanesian in NC, Polynesian in FP

- **Same for CHIKV**

Emergence is unpredictable

DENV 1-4

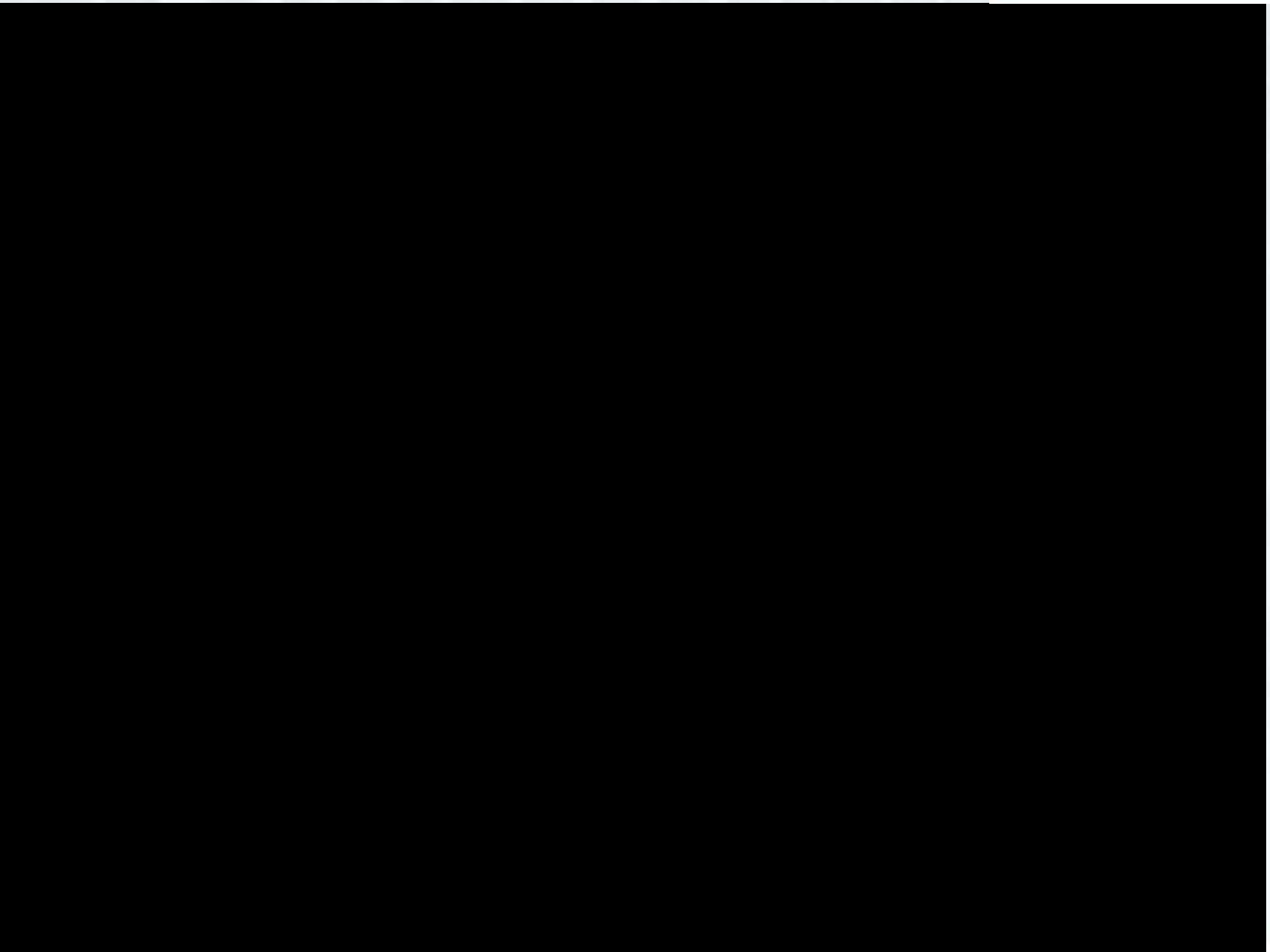
ZIKV, WHO 2016, update April 14

CHIKV

YFV, however transmitted by *Aedes aegypti*

Emergence is unpredictable

Daily flights in the word



Non vector borne transmission of ZIKV: transfusion

ZIKV is a new challenge for blood transfusion (Musso Stramer Bush). The Lancet. 2016: ahead of print)

- Potential for transmission demonstrated during the French Polynesia outbreak (2.8% blood donors tested positive)
- 2 suspected cases of ZIKV infection post transfusion reported in Brazil
- Confirmed cases after transfusion of platelet: 1 donor, 2 recipients (submitted for publication)
- Recommendations issued by WHO and FDA
  - Temporary deferral of blood donors
  - Donor self-reporting of ZIKV symptoms post-donation
  - Quarantine of blood components
  - Supplying epidemic regions with blood collected from non-endemic areas
  - Testing blood donations
  - Pathogen inactivation of blood products
  - If limited capacities: focus on at risk recipients (intrauterine and pregnant women transfusion)

Thank you / Merci / Maururu for your attention