Complications of Zika virus infections: experience in French Polynesia

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

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French Polynesia, South Pacific

- French oversea territory
- 5 archipelagoes
- About 100 inhabited Islands
- Population 270,000 inhabitants

Zika virus history

1947
- Discovery, Uganda, Africa

1962/63
- First human infection, Uganda, Africa

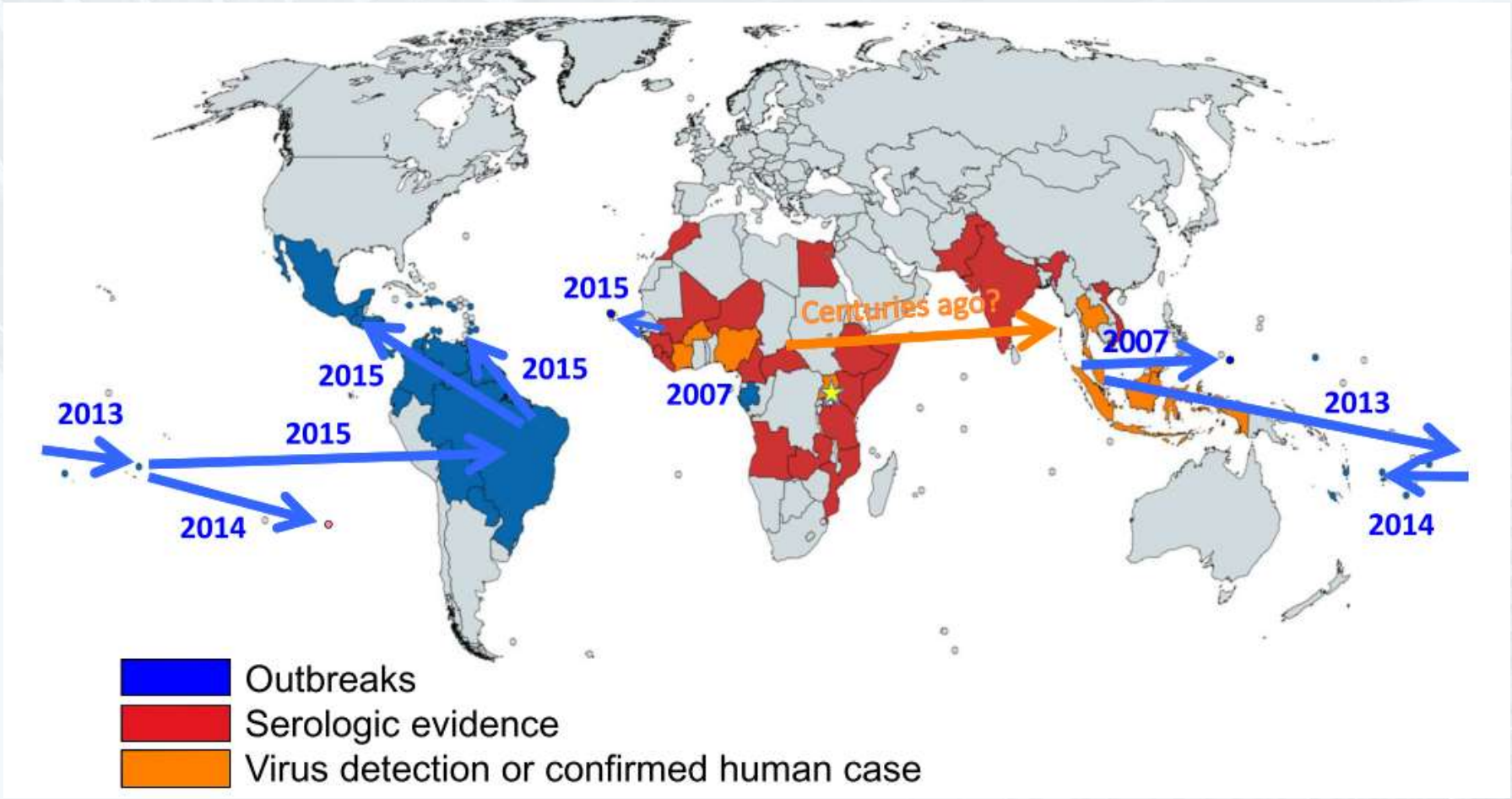
2007
- First outbreak, Yap State, Western Pacific

2013-2014
- Second outbreak, French Polynesia, South Pacific. Description of
  - First severe complications potentially associated to ZIKV: GBS
  - Potential for non-vector borne transmission: sexual, materno-fetal and transfusion

2015
- Spread in the Pacific
- Emergence in Brazil and spread in the Americas and Caribeans
- Description of microcephaly and other congenital central nervous system (CNS) malformation potentially associated to ZIKV
- First outbreak in Africa (Cabo Verde)

2016
- February: WHO declare ZIKV a public health emergency of international concern (PHEIC), detection of ZIKV RNA in amniotic fluid
- May: ZIKV infected, replicate and damage human neural progenitor cells, confirmation of ZIKV transfusion transmission and of the link between ZIKV and GBS
- April: confirmation of ZIKV sexual transmission
- July: first outbreak in continental US
- August: first outbreak in Asia (Singapore), DNA ZIKV vaccine entered phase 1 clinical trial
- November: WHO declare ZIKV is no longer a PHEIC
- December: demonstration of heterologous protection against ZIKV in Rhesus macaques

2017
- Over the past 10 years
  - About 80 countries or territories have reported active ZIKV circulation
  - 13 countries or territories have reported person to person ZIKV transmission
  - 23 countries or territories have reported an increase of GBS potentially associated to ZIKV
  - 31 countries or territories have reported an increase of microcephaly and other congenital central nervous system (CBS) potentially associated to ZIKV



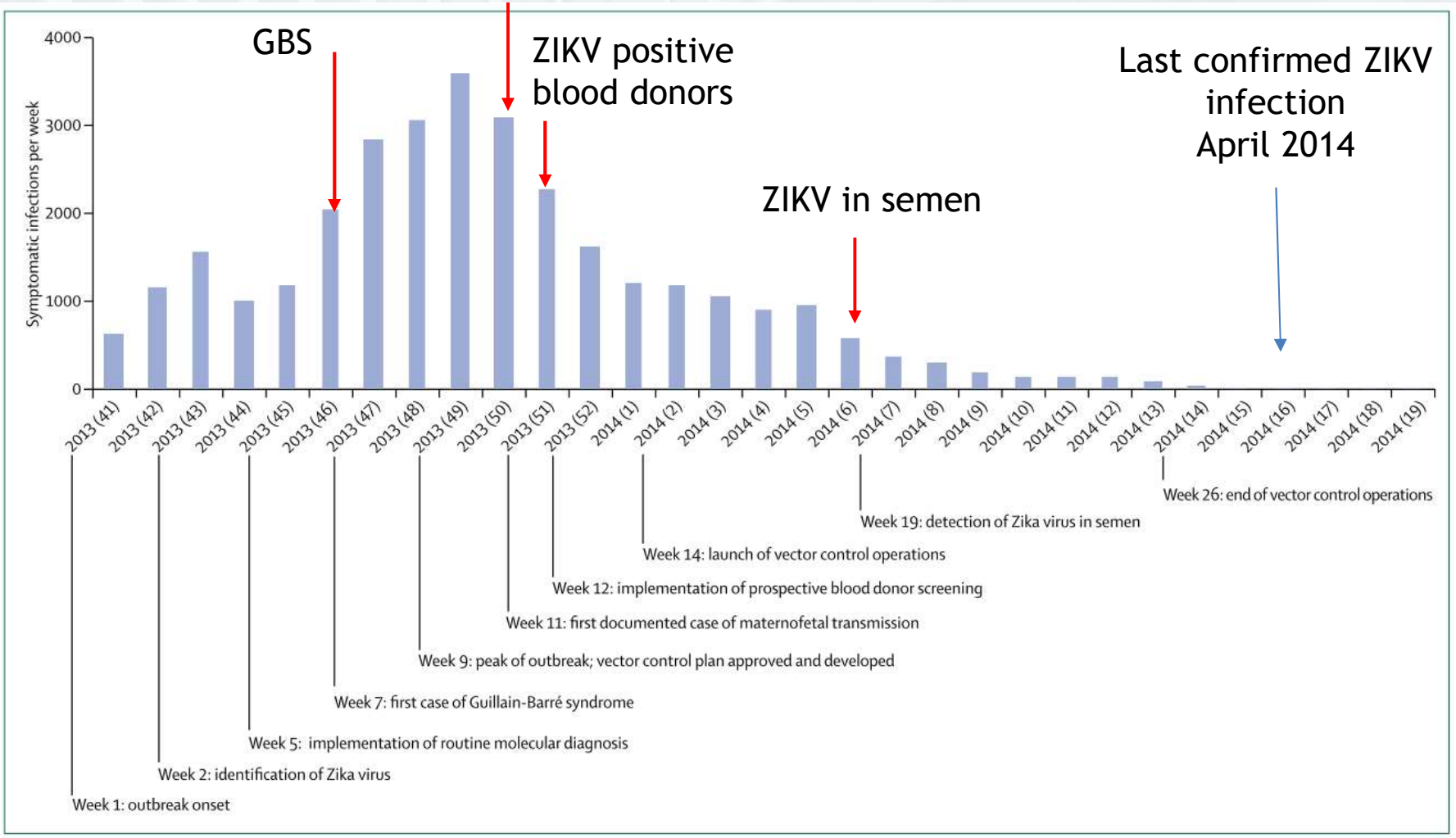
Weaver et al, 2016, Antivir Research

French Polynesia (FP): October 2013 – April 2014

30,000 symptomatic cases, over 50% of the population infected

Materno-fetal transmission

Musso et al, Lancet ID, 2017



What was known about neurological complication of arboviruses when ZIKV emerged in FP

Flavivirus						*Alphavirus*
	ZIKV	DENV	WNV	YVF	JEV	CHIKV
Nonvector borne transmission						
Materno fetal	Yes	Yes	No	Yes[a]	No	Yes
Sexual	Yes	No	No	No	No	No
Transfusion	Yes	Yes	Yes	Yes[a]	No	No
Main complication in newborn						
Microcephaly	Yes	No	No	No	No	No
Other CNS malformation	Yes	No	No	No	No	No
Main complications in infants and adults						
Bleeding	No	Yes	Yes	Yes	No	Yes
Plasma leakage	No	Yes	No	Yes	No	No
Severe organ involvement	No	Yes	Yes	Yes	No	No
Chronic arthralgia	No	No	No	No	No	Yes
Main complications in adults						
Guillain-Barré syndrome	Yes	Yes	Yes	Yes[a]	Yes	Yes
Meningoencephalitis	Yes	Yes	Yes	Yes[a]	Yes	Yes
Myelitis	Yes	Yes	No	Yes[a]	Yes	Yes
Meningitis	No	No	Yes	Yes[a]	Yes	No
Prevention and treatment						
Vaccine	No	Yes	No	Yes	Yes	No
Specific treatment	No	No	No	No	No	No

Gubler et al, JID, 2017

Arboviruses are neurotropic, especially those of the *Flavivirus* genus

Neurological complications differs

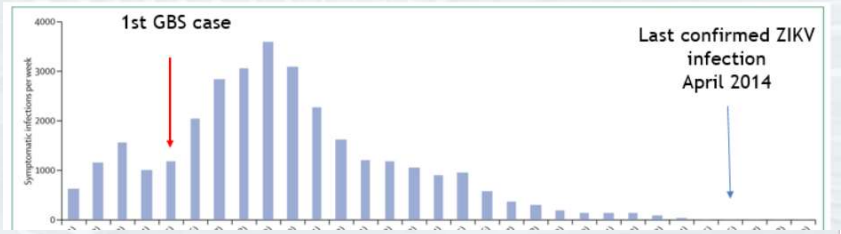
- WNV: meningoencephalitis
- JEV: encephalitis

GBS post arboviruses infections already reported

What was known about neurological complications of ZIKV when it emerged in FP

Nothing !

FIRST GBS related ZIKV case in French Polynesia



First GBS case in late 2013, published in March 2014

- Woman, 40y/o
- Myalgia, low grade fever, and conjunctivitis 7 D before GBS onset.

RAPID COMMUNICATIONS

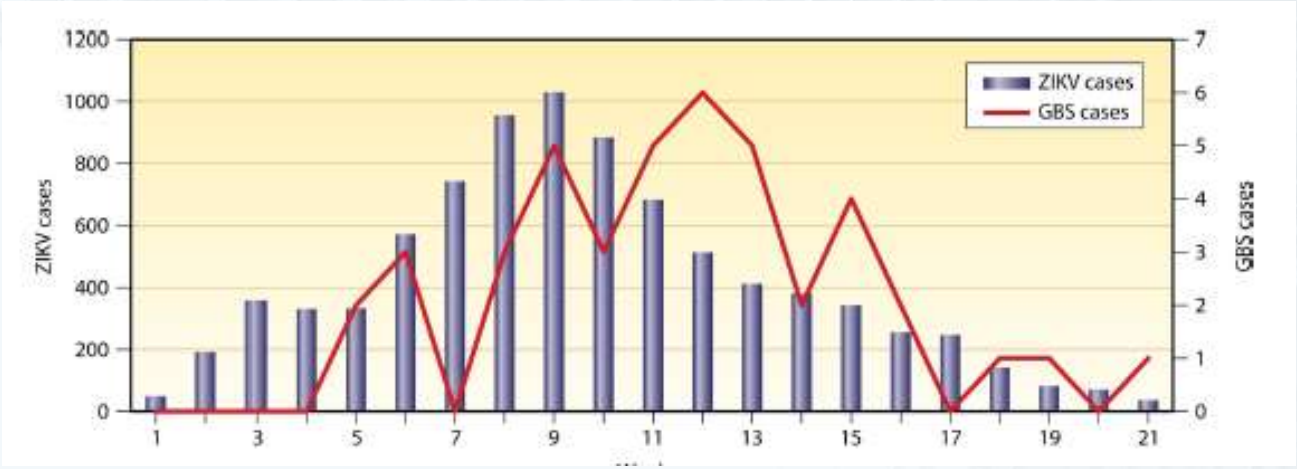
Zika virus infection complicated by Guillain-Barré syndrome – case report, French Polynesia, December 2013

E Oehler (erwan.oehler@cht.pf)[1], L Watrin[2], P Larre[2], I Leparc-Goffart[3], S Lastère[4], F Valour[1], L Baudouin[5], H P Mallet[6], D Musso[7], F Ghawche[2]

CLUSTER OF GBS in French Polynesia

Spatio-temporal correlation between GBS cases and ZIKV outbreak

42 GBS cases or a 20 fold increase in incidence during the outbreak +++



Musso et al, CMR, 2016

GBS in French Polynesia

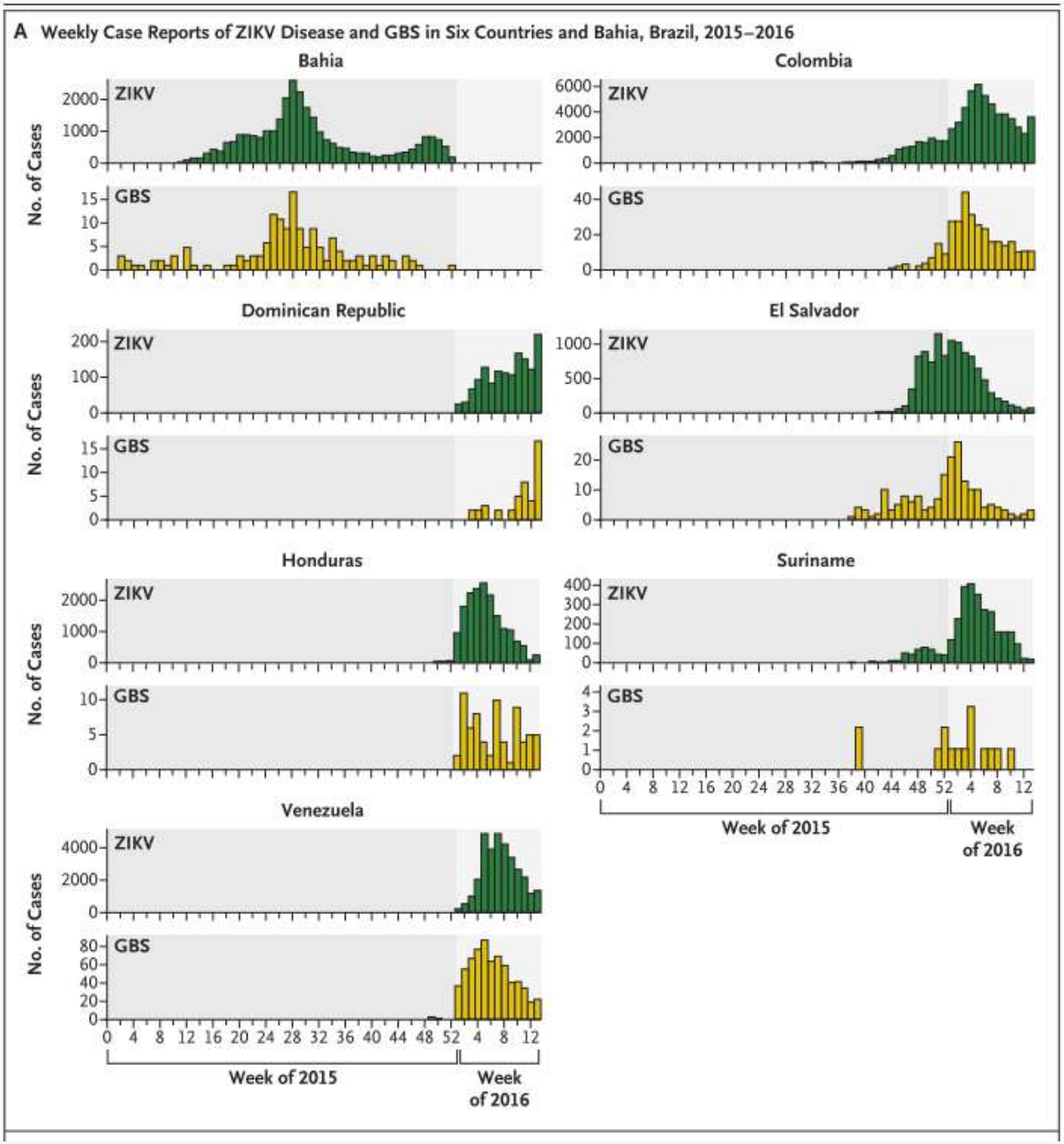
Link between ZIKV and GBS demonstrated in a case control study

- 42 cases (20 fold increase of incidence)
- 100% had neutralizing antibodies against ZIKV
- 88% had transient illness with a median of 6 (2-23) D before onset of GBS
- Median duration of plateau phase 6 D
- 38% hospitalized in ICU, 29% required respiratory assistance
- Overload of the ICU +++, public health issue +++
- No patients died
- 3 months after discharge, 57% were able to walk without assistance
- GBS of AMAN type
- 31% had anti-ganglioside antibodies (low for AMAN type)
- No difference in past dengue history between cases and controls
- No risk factors identified

Cao-Lormeau et al, Lancet 2016

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**



SIMILAR CLUSTERS WILL BE OBSERVED IN LATIN AMERICA AND CARRIBEANS

Dos Santos et al, NEJM, 2016

ZIKV RELATED GBS / OTHER PATHOGENS RELATED GBS

Common features of ZIKV related GBS (*Monsalve et al, Autoimmunity reveiw, 2017*), *(Muñoz et al, JID, 2017)*

- GBS classification
  - Acute inflammatory demyelinating polyneuropathy (AIDP) (75.7%) (Colombia, Brazil, Puerto Rico)
  - Acute motor axonal neuropathy (AMAN) (20%) (French Polynesia) (GBS related *C. jejuni*)
  - Acute motor and sensory axonal neuropathy (AMSAN) (4.3%)
- Onset of GBS is 5-10 days post ZIKV symptoms / 2-4 weeks for other GBS. Suggesting a parainfectious (direct neurotropism or hyper acute immune response) rather than a post infectious (molecular mimicry) mechanism
- Severity similar to other GBS
- ZIKV: global increase in GBS incidence: 2 to 10 fold (*dos Santos et al, NEJM, 2016*)

OTHER ZIKV COMPLICATIONS REPORTED IN ADULTS IN FRENCH POLYNESIA

- **N**eurologic complications: (link not demonstrated)
  - 9 encephalitis and meningo-encephalitis
  - 4 acute myelitis
  - 1 optic neuritis

- Other complications
  - 4 thrombocytopenic purpura

- All this complication will be subsequently reported in Latin America

ZIKA COMPLICATIONS IN NEWBORNS IN FRENCH POLYNESIA

First ZIKV materno (perinatal transmission, contamination occurred probably in the last stages of pregnancy)

Eurosurveillance, Volume 19, Issue 13, 03 April 2014

Rapid communications

EVIDENCE OF PERINATAL TRANSMISSION OF ZIKA VIRUS, FRENCH POLYNESIA, DECEMBER 2013 AND FEBRUARY 2014

M Besnard[1], S Lastère[1], A Teissier[2], V M Cao-Lormeau[2], D Musso (dmusso@ilm.pf)[2]

RETROSPECTIVELY we reported 19 CNS malformations (*Besnard et al, Eurosurveil 2016*)

- 8 major brain lesions with severe microcephaly
- 6 severe brain lesions without microcephaly
- 5 brainstem dysfunctions without visible malformations
- 14 fold increase in microcephaly and 31 fold increase in brainstem dysfunction

Risk of microcephaly in French Polynesia: 1% in the first trimester (*Cauchemaz et al, Lancet, 2016*)

OTHER UNEXPECTED EVENTS IN FRENCH POLYNESIA

Potential for ZIKV sexual transmission

- Sexual transmission of arboviruses had never reported before
- ZIKV (RNA and isolation of ZIKV in culture) isolated in the semen (*EID 2014*)
- Sexual will be further confirmed

Potential Sexual Transmission of Zika Virus

Didier Musso, Claudine Roche, Emilie Robin, Tuxuan Nhan, Anita Teissier, Van-Mai Cao-Lormeau

OTHER UNEXPECTED EVENTS IN FRENCH POLYNESIA

Potential for post transfusion transmission

- Post transfusion arbovirus infections already reported for close related viruses (WNV +++, DENV)
- Post transfusion transmission of ZIKV confirmed in Brasil

Eurosurveillance, Volume 19, Issue 14, 10 April 2014

Rapid communications

POTENTIAL FOR ZIKA VIRUS TRANSMISSION THROUGH BLOOD TRANSFUSION DEMONSTRATED DURING AN OUTBREAK IN FRENCH POLYNESIA, NOVEMBER 2013 TO FEBRUARY 2014

D Musso (dmusso@ilm.pf)[1], T Nhan[1], E Robin[1], C Roche[1], D Bierlaire[2], K Zisou[1], A Shan Yan[1], V M Cao-Lormeau[1], J Broult[2]

LONG TERM COMPLICATIONS OF ZIKV INFECTIONS IN FRENCH POLYNESIA

?

Number of infections was probably too low (30-32,000 estimated cases) to detect unusual long term complications

Even is long term complications are suspected it will not be possible to demonstrate the link with ZIKV several years after the outbreak.

EMERGENCE OF ZIKV IN FRENCH POLYNESIA

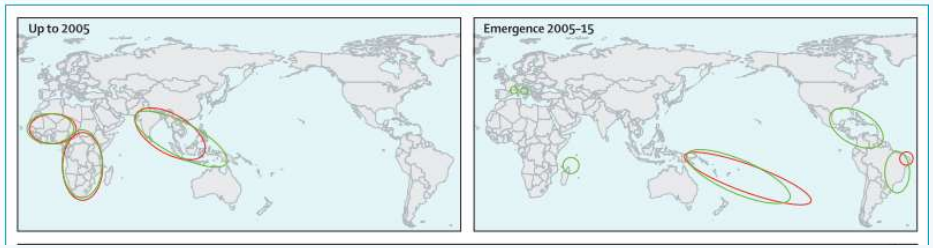
Lessons learned from our experience

What was unexpected

- Emergence of ZIKV in FP
- Burden of ZIKV
- Cluster of GBS
- Description of materno fetal transmission
- Potential for sexual transmission
- Potential for blood transfusion transmission

Expected after the emergence in French Polynesia

- Spread in other countries in the Pacific and potentially in the Americas
- But: timing, magnitude and severe complication that occurred in Latin America were totally unpredictable +++



(*Musso et al, Lancet, 2015*)

EMERGENCE OF ZIKV IN FRENCH POLYNESIA

Lessons learned from our experience

- When a new pathogen emerge:
  - If the priority is the management of cases, surveillance and research should be implemented whenever possible
  - Be curious
  - Explore all unexpected events
  - Collect all specimens you can and store them
  - Implement follow up of patients
  - Do not listen people that say “it is only a mild disease”
  - Do not solely relying on data available for closely related pathogens
  - Be prepared for the worst case scenario +++
  - If possible: do not wait for international support (problem for low and middle income countries)

WHAT IS THE FUTURE OF ZIKV

?

WHICH IS THE NEXT EMERGING PATHOGEN

?

EMERGENCE OF ARBOVIRUSES IS UNPREDICTABLE

EPIDEMIOLOGICAL NOTES ON SOME VIRUSES ISOLATED IN UGANDA
(Yellow fever, Rift Valley fever, Bwamba fever, West Nile, Mengo, Semliki forest, Bunyamwera, Ntaya, Uganda S and Zika viruses)

BY

G. W. A. DICK, M.D., B.SC., M.R.C.P. (Edin.), M.P.H. (Johns Hopkins).

National Institute for Medical Research, London.

Over 10 years (1937 to 1947) the Yellow fever research institute, Uganda discovered 7 new viruses

- **West Nile virus in 1937**
- Bwamba virus in 1937
- Semliki forest virus in 1942
- Bunyamvera virus in 1943
- Ntaya virus in 1943
- Uganda S virus in 1947
- **Zika virus in 1947**

- **WNV and ZIKV emerged, what is the future of the others ?**

IF A NEW PATHOGEN EMERGE

Lessons learned from our experience

The unpredictability of the emergence of arboviruses underscores the need for improving laboratory and surveillance capacity, and reinforces the need for global preparedness for the worst-case scenario

Thank you and come to French Polynesia:

We have more than Zika virus…