EVOLUTION OF THE ZIKA OUTBREAK

Professor Annelies Wilder-Smith MD PhD
ZikaPLAN Scientific Coordinator
President of the International Society of Travel Medicine
Quartet of enzootic arboviruses in West Africa with history of urban emergence: yellow fever, dengue, chikungunya and Zika

A. furcifer
A. taylori
A. luteocephalus

A. aegypti
A. albopictus

Patas, African green monkeys
Guinea baboon

Sylvatic cycle
Rural areas
Human cycle

Zone of emergence

TOT?
Zika virus: a brief history

Discovery: 1947, Rhesus macaque, Zika forest, Uganda
Discovered by Alexander John Haddow, Professor at the University of Glasgow

Alexander Haddow papers at the University of Glasgow
Haddow Collection, University of Glasgow Archives & Special Collections

Washington 2017
**Zika discovery in Haddow’s research volumes, 1948**

Haddow Collection, University of Glasgow Archives & Special Collections
Historical timelines of Zika virus spread (1947-2016)
### Countries and territories showing historical time-line of Zika virus spread (1947 - 2016)

**Summary of recent (2010–present) cases of Zika virus infection in Southeast Asia.**

<table>
<thead>
<tr>
<th>Country</th>
<th>Case year</th>
<th>Diagnosis method</th>
<th>Cases</th>
<th>Resident/tourist</th>
<th>References</th>
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<tbody>
<tr>
<td>Cambodia</td>
<td>2010</td>
<td>RT-PCR, sequencing</td>
<td>1</td>
<td>Resident</td>
<td>[5]</td>
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<tr>
<td>Indonesia</td>
<td>2013&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RT-PCR, sequencing</td>
<td>1</td>
<td>Tourist</td>
<td>[11]</td>
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<td></td>
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<td>1</td>
<td>Tourist</td>
<td>[12]</td>
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<tr>
<td></td>
<td>2014/2015</td>
<td>Virus culture/RT-PCR sequencing</td>
<td>1</td>
<td>Resident</td>
<td>[8]</td>
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<tr>
<td>Malaysia</td>
<td>2014</td>
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<td>Tourist</td>
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<tr>
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<td>RT-PCR, virus recovery and sequencing</td>
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<td>Resident</td>
<td>[6]</td>
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<td>1</td>
<td>Tourist</td>
<td>[10]</td>
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<td></td>
<td>2014</td>
<td>RT-PCR, serology</td>
<td>1</td>
<td>Tourist</td>
<td>[14]</td>
</tr>
</tbody>
</table>
Historical timelines of Zika virus spread (1947-2016)

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Yap in Micronesia

Very small – 4 Islands, (7391 inhabitants)

Cases presenting to health care: 185

(108 confirmed or probable by Zika IgM/PRNT)

Microcephaly, GBS: none reported

Sero-prevalence after the outbreak: 73% (95% CI 68 to 77)

557 people interviewed, and tested for anti Zika IgM + PRNT

Of those, 38% or 19% reported illness during the outbreak period

Duration of the outbreak: 3 months
French Polynesia

Islands 268 270 inhabitants

Cases 8750 (presenting to health care several islands) 383 confirmed by PCR, Grossing up, 32 000 estimated presented, 6400 with symptoms

Microcephaly, 8 cases GBS: 42, another 30 neurological complications? Prevalence of microcephaly 8/4182 births 2/1000 livebirths

Sero-prevalence after the outbreak: 66% (95% CI: 62, 70) 584 patients; RT-PCR for ZIKV; 294 positive.

Corresponding to an estimated 174 400 infections
Uma nova epidemia

AUGUST/2015

Washington 2017
Microcephaly

**Aug – Sep**
Increased awareness of neonates with microcephaly

**Oct**
- SES-PE receives notifications from doctors
- Picture suggestive of congenital infection

**Oct**
Beginning of investigation of SES-PE¹, SVS/MS² and OPAS

**11th Nov**
Declaration of National Public Health Emergency

**1st Feb**
Public Health Emergency of International Concern (PHEIC) WHO

**18 Feb**
Notification of Zika virus cases – SINAN Brazil

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1 Health Secretary of Pernambuco State
2 Health Surveillance Secretary of the Ministry of Health

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Public Health Emergency of International concern (PHEIC)

• an extraordinary event which is determined, as provided in these Regulations:

i. to constitute a public health risk to other States through the international spread of disease; and

ii. to potentially require a coordinated international response”. This definition implies a situation that: is serious, unusual or unexpected; carries implications for public health beyond the affected State’s national border; and may require immediate international action.
Causality?

• Case control study: crude OR: 55.5 (Lancet 2016)
• Pyriproxyfen theory disproven in case control (Mem Inst Oswaldo Cruz. 2016)
• Evidence of ZIKV in amniotic fluid and fetus’ brain in a traveller (NEJM 2016)
• Experimental animal studies
• Systematic review (PLOS Medicine 2017)
Zika PLAN

MERCG Cohort of pregnant women

PREGNANT WOMEN WITH RASH

RT-PCR and IgM (MAC-ELISA)

PCR or IgM POSITIVE

ZIKA CONFIRMED

PCR and IgM NEGATIVE

TORCH, CHIKV, DENV

NEGATIVE

ZIKA PROBABLE

POSITIVE

*Protocol harmonization meeting of Brazilian and Latin American researchers with the support of OPAS/WHO was held in Recife, Brazil, March 2016

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Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians

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

A  Lateral view of skull irregularities  B  Excessive scalp with folds  C  Lateral skull radiograph

D  MRI at 29 wk gestation  E  3-Dimensional skull reconstruction  F  3-Dimensional skull reconstruction
Figure 2. Brain Findings in Infants With Presumed Congenital Zika Syndrome

A. Calcifications and shallow sulci
B. Punctate calcifications and ventriculomegaly
C. Calcifications and skull collapse

D. Decreased cranial vault and small cerebellum
E. Shallow sulci and calcifications
F. Irregular cortex
Calcifications
Figure 3. Wide-Angle Fundus Images (RetCam) of a Male Infant With Congenital Zika Infection

A  Right eye

B  Left eye
A. Newborn infant with bilateral contractures of the hips and knees, bilateral talipes calcaneovalgus, and anterior dislocation of the knees. Hips are bilaterally dislocated. B. Newborn infant with bilateral contractures of the shoulders, elbows, wrists, hips, knees, and right talipes equinovarus. Hips are bilaterally dislocated.
Virus Zika Infection & Neurological Disease
Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study


Summary  
Background Between October, 2013, and April, 2014, French Polynesia experienced the largest Zika virus outbreak ever described at that time. During the same period, an increase in Guillain-Barré syndrome was reported, suggesting a possible association between Zika virus and Guillain-Barré syndrome. We aimed to assess the role of Zika virus and dengue virus infection in developing Guillain-Barré syndrome.

Figure: Weekly cases of suspected Zika virus infections and Guillain-Barré syndrome in French Polynesia between October, 2013, and April, 2014
GBS during outbreak of Zika Infection in French Polynesia (2013-2014)

[Population census 2012: 268,270 inhabitants]
Lancet February 29, 2016

- Risk of GBS was 0.24 per 1000 Zika infections (1 per 4000 infected patients)
- Mean Age 42 ys (IQR 36-56)
- 31 Men (74%)
- History of viral illness in 88%
- Median of 6 days [IQR 4-10] before onset of GBS
- Median Progression of neuro symptoms to nadir was 4 days [IQR 4-9]
- Plateau phase 4 days [IQR 3-10]
- Clinical outcome 3 months after:
  - 24 (57%) patients were able to walk without assistance

Clinical Features
- Generalized muscle weakness 74%
- Inability to walk 44%
- Facial palsy 64%
- Admission to ICU 38%
- Respiratory support 29%
- Neurophysiology (37 cases) consistent with Acute Motor Axonal Neuropathy (AMAN)
2016: GBS in times of Zika

Source: WHO website
Neurological Problems Presumed to be Associated with Zika Infection

Peripheral Nervous System Involvement:
- Guillain-Barre Syndrome
  - Acute Demyelinating Polyneuropathy
  - Acute Motor Axonal Neuropathy
  - Miller-Fisher variant
- Neuropathies

Central Nervous System Involvement:
- Encephalitis
- Myelitis
- Optic neuritis

January 13, 2017

Immune Mediated Pathogenesis vs Direct Viral Neuropathogenicity or Both
What is the true risk?

Pathogenesis

D

20-25%
Symptomatic
Guillain-Barré syndrome
0.24/1,000
3-10%
Death
>6 month disability

75-80%
Asymptomatic

30%
Adverse fetal outcomes

25%
Microcephaly
Fetal demise, IUGR, intracranial calcifications, ventriculomegaly, etc.

??%
Mother symptomatic

30%
Mother asymptomatic

??%

>75%
Funded by the Horizon 2020 Framework Programme of the European Union

Zika
Preparedness Latin American Network

16 June 2016
Prof. Dr. med. Annelies Wilder-Smith
WHO convened ZIKV-IPD Consortium: Research Questions

• What is the absolute risk of microcephaly and other birth defects by gestational age, rash, viremia, and other co-factors?

• Are there significant co-factors or effect modifiers?
Table 1. Pregnancy Outcomes for 442 Women With Completed Pregnancies With Laboratory Evidence of Possible Zika Virus Infection by Maternal Symptom Status and Timing of Symptom Onset or Exposure, US Zika Pregnancy Registry, December 2015–September 2016

<table>
<thead>
<tr>
<th>No. of Pregnancies</th>
<th>Brain Abnormalities and/or Microcephaly&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Neural Tube Defects, Eye Abnormalities, and Consequences of Central Nervous System Dysfunction&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Total With ≥1 Birth Defect</th>
<th>Total Completed Pregnancies</th>
<th>Preliminary Estimates of Pregnancies With Birth Defects, % (95% CI)&lt;sup&gt;d&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>By maternal symptom status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal symptoms of Zika virus infection</td>
<td>8</td>
<td>2</td>
<td>10</td>
<td>167</td>
<td>6 (3-11)</td>
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<tr>
<td>No reported maternal symptoms of Zika virus infection</td>
<td>14</td>
<td>2</td>
<td>16</td>
<td>271</td>
<td>6 (4-9)</td>
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<tr>
<td>Unknown symptom status</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>By timing of symptoms or exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First trimester</td>
<td>8</td>
<td>1</td>
<td>9</td>
<td>85</td>
<td>11 (6-19)</td>
</tr>
<tr>
<td>Multiple trimesters including first trimester</td>
<td>13</td>
<td>2</td>
<td>15</td>
<td>211</td>
<td>7 (4-11)</td>
</tr>
<tr>
<td>Second trimester only</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>76</td>
<td>0 (0-5)</td>
</tr>
<tr>
<td>Multiple trimesters including second and third trimester</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Third trimester only</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>31</td>
<td>0 (0-11)</td>
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<tr>
<td>Periconceptional</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td></td>
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<tr>
<td>Unknown or missing data</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>4</td>
<td>26</td>
<td>442</td>
<td>6 (4-8)</td>
</tr>
</tbody>
</table>
Immediate Interventions?
Latin American countries that have declared delaying pregnancy as a strategy

<table>
<thead>
<tr>
<th>Country</th>
<th>Started</th>
<th>Proposed end date</th>
<th>Source reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jamaica</td>
<td>18-Jan-2016</td>
<td>31-Dec-2016</td>
<td>(39)</td>
</tr>
<tr>
<td>El Salvador</td>
<td>20-Jan-2016</td>
<td>01-Jan-2018</td>
<td>(40)</td>
</tr>
<tr>
<td>Ecuador</td>
<td>20-Jan-2016</td>
<td>Not clear</td>
<td>(4)</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>20-Jan-2016</td>
<td>31-Dec-2016</td>
<td>(41)</td>
</tr>
<tr>
<td>Colombia</td>
<td>07-Jan-2016</td>
<td>01-Jul-2016</td>
<td>(42)</td>
</tr>
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</table>
How will the ZIKV outbreak evolve further?
## Summary of these outbreaks

<table>
<thead>
<tr>
<th></th>
<th>Population</th>
<th>Duration of outbreak</th>
<th>Sporadic cases after outbreak</th>
<th>Sero-prevalence at end of outbreak</th>
<th>Prevalence of microcephaly per annual 1000 livebirths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yap</td>
<td>7391</td>
<td>3 months</td>
<td>no</td>
<td>73%</td>
<td>n/a</td>
</tr>
<tr>
<td>French Polynesia</td>
<td>268 270</td>
<td>4 months</td>
<td>no</td>
<td>66%</td>
<td>2/1000</td>
</tr>
<tr>
<td>Pernambuco State</td>
<td>9 278 000</td>
<td>8 months</td>
<td>10 months + 56% (Recife)</td>
<td>56% (Recife)</td>
<td>2.8/1000</td>
</tr>
<tr>
<td>All Brazil</td>
<td>210 431 965</td>
<td>Outbreaks</td>
<td>Not over</td>
<td>Not over and no data</td>
<td>0.8/1000</td>
</tr>
</tbody>
</table>
Cases of microcephaly according to epidemiological birth week. Pernambuco, 2015-2016

Brazil >200,000 by Dec 2016
2,366 confirmed CZS

Note: 71 cases without birthdate

Source: CIEVS/GIEVE/DGIAEVE/SEVS/SES-PE
Data updated until the epidemiological week 39/2016
*Including cases classified as microcephaly (below - 2 SD) and the Severe microcephaly (below - 3 dp)
What will drive the epidemic?

• Climate and ecological factors
• Herd immunity (1- 1/R0)
• Viral mutations, new introductions

• Relative contribution of sexual transmission?
• Co-factors?
• Role of preceding flavivirus infections? (ZikaPLAN: cohort of 17,000 subjects in 14 different geographic locations in Brazil with information on previous dengue infection)
How relevant is sexual transmission in outbreak propagation?

Sexual transmission contributes 3% to the overall R0; Sexual transmission cannot sustain an outbreak; Althaus et al

The New England Journal of Medicine

Persistence of Zika Virus in Body Fluids — Preliminary Report

What does the future hold?

- Ferguson’s analysis suggests that once the current epidemic is over, herd immunity will lead to a delay of at least a decade before large epidemics may recur.

Future scenarios

Dynamics

A Zika ‘free’
Introduction of Zika
- $R < 1$
- $R > 1$

B Epidemic

C Endemic

$R > 1$
Sylvatic
Local extinction

Prevalence in non-human primates
Human cases

Washington 2017
Timeline Zika virus outbreak / WHO response

- **Apr 2015**: First cases of Zika in Brazil
- **Oct 2015**: Report of significant increase in number of microcephaly in Brazil
- **Feb 2016**: WHO declares Zika as PHEIC
- **Sep 2016**: WHO declares end of Zika PHEIC
- **Oct 2016**: WHO Zika causality statement
- **Nov 2016**: WHO Zika causality statement
Nov 2016: no more a PHEIC

WHO Statement on the Fifth meeting of the Emergency Committee under the International Health Regulations (2005) regarding microcephaly, other neurological disorders and Zika virus

Announcement Displayed From:
Friday, November 18, 2016 - 19:13

“We are sending the message that Zika is here to stay and WHO’s response is here to stay.”
Case counts in the US as of 1 Feb 2017

US States
- Locally acquired mosquito-borne cases reported: 220
- Travel-associated cases reported: 4,752
- Laboratory acquired cases reported: 1
- Total: 4,973
  - Sexually transmitted: 41
  - Guillain-Barré syndrome: 13

US Territories
- Locally acquired cases reported: 36,274
- Travel-associated cases reported: 140
- Total: 36,414*
  - Guillain-Barré syndrome: 52

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Travel associated cases into Europe (2016)

Netherlands – 89, Belgium – 102, Luxembourg – 2

UK – 188

Denmark – 8

Norway – 8

Sweden – 35

Finland – 1

Czech Republic – 13, Austria – 22, Slovenia – 7

Slovakia – 3, Hungary – 2

Romania – 3

Portugal – 17

Spain – 292

Italy – 92

Malta – 2

Greece – 2