What do we know (or don’t know) about Zika incidence and geographic spread that is critical for planning vaccine trials?

Laura C Rodrigues,
Prof Infectious Disease Epidemiology, LSHTM and Microcephaly Epidemic Research Group

No conflict of interest

WHO Workshop “Efficacy trials of ZIKV Vaccines: endpoints, trial design, site selection” - 1-2 June
What we know : The period of Zika spreading like wild fire in a new continent is over (introduced /susceptibles/ urban density/ mosquito)

What we don’t know: Pattern of transmission in the next few years: (i) Continued major outbreaks? (ii) No transmission until new susceptible cohort born and virus reintroduced? (iii) Continued transmission with occasional localized outbreaks ?

What we would like to know : Frequency/geographical distribution of immune/susceptible

The research we need: (i)Repeat, multi-site sero-prevalnce surveys (ii)Multi-site sero-conversion cohorts
Factors that might contribute to differences in speed of progression of Zika outbreaks

Introduction of the virus

Vector
- Which Aedes
- Quantity and density (Temperature, rainfall, Sanitation/breeding sites)
- Homogeneity

Humans
- Immunity
- Density/Social organization (Screens, air conditioning, outdoor living, clothing, mosquito repellent?)

Contribution of sexual transmission

Geography
- Clustering
- Isolation (islands or continents)
Dengue incidence by region and by year 1986-1999

Dengue incidence by month

Dengue incidence and areas with Aedes
How do we determine where we are in the course of any epidemic?

**DATA**

- **Cases**: Monitor incidence of disease (Ebola)

- **Complications**: Monitor the incidence of complications (polio/flaccid paralysis)

- **Sero-prevalence**: Serological surveys (measles, mumps)
How do we determine where we are in the course of Zika epidemics?

Challenges

- **Cases:** Monitor incidence of Zika disease
- **Complications:** Monitor the incidence of microcephaly
- **Sero-prevalence:** Serological surveys
How do we determine where we are in the course of the Zika epidemic?

**DATA**

- **Monitor incidence/notification** disease (clinical diagnosis difficult, many cases not symptomatic, and not all symptomatic present/are notified)

- **Monitor the incidence of microcephaly**: (different/changing diagnostic criteria, women avoiding or terminating pregnancy)

- **Serological surveys** (absence of reliable, cheap, available, specific serologic test for ZIKA IgM (CDC enzyme-linked immunosorbent assay ELISA for IgM antibodies)+ plaque reduction neutralization tests (PRNT))
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

Figure 2. Confirmed and Probable Cases of Zika Virus Disease on Yap among Persons Seeking Health Care, According to Week of Onset of Illness during the Period from April through July 2007.

Rate: 14.6% / 10,000 pop

Figure 3. Attack Rates for Confirmed and Probable Zika Virus Disease per 1000 Population According to Municipality on Yap during the Period from April through July 2007.
**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

**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

Duration of the outbreak: 4 months

Rate: 11.5 per 100 pop
Pernambuco

Continental 9 million inhabitants

Cases notified: 381 (!) since January 2016

**Microcephaly**, 408 cases confirmed + deaths

Prevalence of microcephaly 408/143489=2.8/1000

Sero-prevalence in Recife at end of outbreak: 56% (95% CI: 49-63)

198 mothers of normocephalic neonates tested by RT-PCR for ZIKV; 111 positive

Gross up @ 5 million cases (including subclinical)

Duration of the outbreak: 8 months
Sporadic: 10 months plus
## Summary of well documented 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>
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<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 +</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>
Number of cases of microcephaly/CNS notified, by month, by Brazilian region, Nov 2015-Mid Dez 2016

Fonte: Secretarias de Saúde dos Estados e Distrito Federal (dados atualizados até 17/12/2016)
Number of cases of microcephaly/CNS notified, by month, by Brazilian region, Nov 2015-Mid Dez 2016

28% (57 million) 8% (15 million) 9% (18 million) 42% 86 million 14% 29 million
<table>
<thead>
<tr>
<th>Country and when Zika presume to be introduced</th>
<th>Number of microcephaly</th>
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<td>Brazil 2014-2015</td>
<td>2205</td>
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Comparing prevalence of microcephaly in the cohorts of pregnant woman with Zika

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<th>RJ Cohort* risk % (95% CI)</th>
<th>CDC Cohort** risk % (95% CI)</th>
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<tr>
<td>CZS (including death)</td>
<td>46.4 (37 - 55)</td>
<td>11 (8.9 - 13)</td>
</tr>
<tr>
<td>CZS (live birth)</td>
<td>42 (36 - 48)</td>
<td>11 (8.9 - 13)</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>3.4%</td>
<td>4%</td>
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Cautious interpretation for other risks because differences in:

- Methodological
- Completeness of investigation
- Definitions of CZS
- Reporting of losses

*Brasil P et al. NEJM. 375;24; Dec.15, 2016.
Prevalence of microcephaly per live borns by month, and municipality  Pernambuco 2015-16
Prevalence of ZikV infection in Pernambuco/BR

Maternal PRNT for ZikV and DenV 1-4 in 173 mothers in the control group from the case control study

- Susceptible
- ZIKV positive: 5%
- ZIKV & DENV positive: 52%

Prevalence of Zika infection = 57%

Prevalence of microcephaly: 408/143,489 = 2.8/1000.

Data updated until the epidemiological week 39/2016

*Including cases classified as microcephaly (below - 2 SD) and the Severe microcephaly (below - 3dp)

Note: 71 cases without birthdate
What we can tell about the stage and speed of the Zika epidemic in Latin America

We do not know enough about the stage and speed of the Zika epidemics, outbreaks, sporadic transmission in Brazil & LA

Interpretation of microcephaly data difficult: differences in diagnostic criteria, pregnancy delays and terminations

But tentatively epidemics appear to progress at different speeds

Transmission likely to continue at lower levels
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The research we need: (i) repeat, multi-site sero-prevalence surveys (ii) Multi-site sero-conversion cohorts (iii) Mosquito density information
Priorities for research to inform vaccine trials

Repeat – age stratified repeated sero-prevalence surveys in different regions

Cohorts of seroconversion - (ZIP)

Test validation, sero-dynamics, mosquito density data, notifications of Zika- analysis integrating sero-prevalence data, mosquito surveys and microcephaly data
Thank you

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