"How can definitions and data from surveillance, clinical case definitions for Zika illness, complications, and manifestations help inform trial designs?"

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Clinical endpoints in Zika trial design: realistic and meaningful?

1) To measure efficacy against symptomatic disease
   • Do we have a good case definition of 'symptomatic' Zika?
   • Is there any evidence or reason to believe that symptomatic Zika is associated with a higher risk of complications (e.g. neurological / congenital) compared to 'asymptomatic' Zika?

2) To measure efficacy against severe disease?
   • What is the frequency of severe manifestations?
   • Do we know if there are any „intermediate severity manifestations“?
What do we know about candidate endpoints?

- **Frequent**
  - Rash plus 2 (PAHO Def.) ~ 95% of any symptoms?
  - Any clinical symptoms – 20% of infected individuals?

- **Rare**
  - Microcephaly 1-3%?
  - Congenital Zika Syndrome ~ 5-10%? 42%?
  - Of what – infected, symptomatic...?
  - Guillain-Barré Syndrome 1-5 / 10,000
  - GBS and other Severe Neurological Manifestations 5-10 per 10,000?
<table>
<thead>
<tr>
<th>Clinical and laboriatl findings</th>
<th>Dengue</th>
<th>Zika</th>
<th>Chikungunya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Above 38°C (100.4F)</td>
<td>Afebrile or mild fever [≤ 38.5°C (101.3F)]</td>
<td>Above 38°C (100.4F)</td>
</tr>
<tr>
<td></td>
<td>Intense (several times a day)</td>
<td>Sporadic fever (1-2 times a day)</td>
<td>Intense (1-2 times a day)</td>
</tr>
<tr>
<td>Fever duration</td>
<td>4 to 7 days</td>
<td>1 - 2 days</td>
<td>2 - 3 days</td>
</tr>
<tr>
<td>Exanthema</td>
<td>Starts on the 4th day</td>
<td>Starts on the 1st or 2nd day</td>
<td>Starts on the 2nd or 5th day</td>
</tr>
<tr>
<td>Exanthema frequency</td>
<td>30 - 50 % of cases</td>
<td>90 - 100 % of cases</td>
<td>50 % of cases</td>
</tr>
<tr>
<td>Myalgia (Frequency)</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Arthralgia (Frequency)</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Joint pain intensity</td>
<td>Light</td>
<td>Light/Moderate</td>
<td>Moderate/Intense</td>
</tr>
<tr>
<td>Joint edema</td>
<td>Rare</td>
<td>Frequent and of light intensity</td>
<td>Frequent and moderate to intense</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>Rare</td>
<td>50 - 90 % of cases</td>
<td>30 % of cases</td>
</tr>
<tr>
<td>Headache</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Ganglion hypertrophy</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Hemorrhagic dyscrasia</td>
<td>++</td>
<td>Absent</td>
<td>+</td>
</tr>
<tr>
<td>Risk of death</td>
<td>+++</td>
<td>Not known</td>
<td>+</td>
</tr>
<tr>
<td>Neurologic damage</td>
<td>++</td>
<td>+++</td>
<td>+ (mostly in neonates)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>Not common</td>
<td>Not common</td>
<td>Frequent</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>+++</td>
<td>Absent</td>
<td>+</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

- Are clinical endpoints discriminatory?
IDAMS clinical sites superimposed on a heat map showing the global distribution and burden of dengue – Bhatt et al, Nature 2013
Intermediate Summary

• Clinical picture not discriminatory
• Severe endpoints rare, intermediate endpoints feasible?

BUT

• ... how can the ongoing large cohort studies inform trial design?
What can we learn from dengue research?

• Standardized clinical endpoints for dengue intervention studies
• Effort moderated by National Institutes of Health (NIH), Partnership for Dengue Control (PDC), and supported by WHO
• Two-level strategy:
  • Standardized severe dengue (severe vascular leakage, severe bleeding, severe organ manifestation etc...), rare endpoints
  • Intermediate severity endpoints – need to be ON THE CAUSAL PATHWAY to severe, and validated in prospective data sets
Other manifestations...? Intermediate severity?

Patient came to our clinic in Heidelberg after travel to Malaysian Borneo
Tappe et al., EID 2015

1 Patient out of ~ 100 confirmed patients in Rio with peripheral nerve manifestation
Brasil et al., PLoS NTDs 2016
Strong signals for microcephaly risk variability within Brazil – need to better understand and standardize!

What can ongoing cohorts contribute?

- Multicentre cohort studies in Latin America and the Caribbean (N=5-10,000)
- Pregnant women / children cohorts (asymptomatic), but also in symptomatic patients (general population)
- Harmonization and Data Sharing with ZIKAPlan and ZIKAction
- Harmonization and Data Sharing beyond – WHO moderated IPD-MA

Summary / Points for discussion

What can the ongoing cohorts contribute towards clinical endpoints?

• Network of clinical sites, harmonization & standardization of tools (clinical and diagnostic), data sharing

• Clinical characterization of symptomatic disease (without fever/rash trigger) – CASE DEFINITIONS

• Comparison of risk for complications between symptomatic and asymptomatic (oligosymptomatic) in pregnant women cohorts

• Intermediate severity endpoints?

• Standardization of severe endpoints:
  • Congenital Zika Syndrome, overall frequency, co-factors, effect modifiers!?  
  • Congenital Zika Syndrome, relative frequency of components  
  • Imaging Definitions (Ultrasound?)