Zika Vaccine Development
Considering Endpoints

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Regulating vaccines at the FDA: development and licensure of Zika vaccines

Marion F. Gruber & Philip R. Krause

“In this regard, the clinical development program and regulatory strategy for a Zika vaccine must be tailored to the particular vaccine under investigation...it will be influenced by...characteristics of the vaccine, available nonclinical and clinical data for the particular vaccine and/or related vaccines, proposed indication, target population, and availability of an immune correlate of protection or a surrogate end point reasonably likely to predict clinical benefit.”
Zika Vaccine Development Goals

• Reduce clinical burden of infection
  – Congenital Zika Syndrome
  – Adverse outcomes

• Generate herd immunity

• Interrupt transmission
  – Mosquito, sexual, maternal

• Public benefit
  – Reduce suffering
  – Reduce health care resource utilization
  – Restore normalcy (travel, family planning, etc.)
Vaccine Trial Considerations

- Vaccine Efficacy (VE)
  - Expressed as a proportionate reduction in attack rate of the selected endpoint (AR) between the unvaccinated (ARU) and vaccinated (ARV) groups
  - Calculated from the relative risk (RR) of endpoint among the vaccinated group compared to the unvaccinated group

- $VE = \frac{(ARU - ARV)}{ARU} \times 100$

Assumption - The risk of meeting an efficacy endpoint in the unvaccinated group is the same as the vaccinated.
Choosing Efficacy Endpoints

- Equivalency of Risk
  - Where does exposure occur (home, school, etc.)?
  - What drives transmission (seasonality, travel, etc.)?
  - Who drives transmission (children, travelers, etc.)?
  - What reduces transmission (vector control, PPMs)?

*Risk of exposure must be equivalent between groups.*
Choosing Efficacy Endpoints

• Equivalency of Risk
  – What impacts exposure outcomes (infection, disease)?
    • Viral characteristics (genotype, tropisms)
    • Host characteristics (age, genetics, immunity)
    • Herd characteristics (collective immune profile)
  – What impacts data collection and quality?
    • Sociocultural considerations (stigma, reporting bias)
    • Standards of care (ability to modify outcomes)

Risk of exposure outcomes (infection vs. disease vs. severe/atypical disease) and ability to identify and report these outcomes must be equivalent between groups.
Choosing Efficacy Endpoints

• Additional Considerations for Endpoints
  – Ensure they are measurable and objective
  – Reduce variance in making measurements
  – Measure what represents the public health burden
  – What is affordable (time, logistics, money)

Endpoint selection is driven by the desire to measure impact against what is clinically relevant and representative of the public health burden but is impacted by numerous other factors and considerations.
Zika Endpoint - Infection

• Proposal
  – Measure prevention of infection in vaccine vs. control

• Methods
  – Routine sampling and testing of cohort / subgroup
  – Consider as a stand alone or secondary endpoint

• Practicalities
  – Which fluid will be sampled and how often?
  – Does the fluid represent true absence of infection?
  – Which assay (validation)?
  – Other confounders (assay cross-reactivity)?
Zika Endpoint – Zika Disease

• Proposal
  – Measure prevention of Zika disease in vaccine vs. P/C

• Methods
  – Establish a Zika disease case definition
  – Administer vaccine or P/C and surveil for disease

• Practicalities
  – Mild disease will occur with greater frequency but require a more sensitive surveillance system (active) to capture
  – Active case finding will capture more Zika (signal) but also more non-Zika (noise)
  – Mild disease does not represent the public health burden
Zika Endpoint – Atypical/Severe Disease

• Proposal
  – Measure prevention of atypical (GBS) and/or severe (CZS) Zika disease in vaccine vs. P/C

• Methods
  – Establish an atypical or severe Zika disease case definition
  – Administer vaccine or P/C and surveil for disease

• Practicalities
  – Severe disease will occur with less frequency but require a less sensitive surveillance system (passive?) to capture
  – Represents the public health burden and concern
  – May undervalue vaccine benefit (transmission impact)
Zika Endpoint – Secondary / Exploratory

• Reduction in viremia or RNAemia
  – Identify acute infections, compare replication kinetics
    • Associate with clinical outcomes
    • Hypothesize immuno-pathogenic mechanisms

• Disease attenuation
  – Track symptomatic infections, measure outcomes over time
    • Compare morbidity/disability between vaccine and P/C
    • Post-licensure?

• Vaccine performance against correlate / surrogate of protection
Dengue Exemplars - Variable Clinical Outcomes

- Dengue
  - Very few severe infections
  - Most infections not reported
  - Very few deaths

Understanding the occurrence and frequency of the various clinical outcomes is essential to developing an informed sample size.
Transmission and clinical outcomes may be focal occurring at the micro scale creating potential for missing transmission and disease.

Epidemiology of Inapparent and Symptomatic Acute Dengue Virus Infection: A Prospective Study of Primary School Children in Kamphaeng Phet, Thailand

*Am J Epidemiol* Vol. 156, No. 1, 2002

Incidence of inapparent: symptomatic dengue

Hospitalizations / 100 dengue infections

Dengue incidence / 100 students

Dengue disease severity by school and study year, Kamphaeng Phet, Thailand. 1998 (white bars), 1999 (single-hatched bars), and 2000 (double-hatched bars).
Different Endpoints = Different VE Outcomes

**VE against DENV1-4 by country:**
**CYD15 (9-16 years, ITT)**

<table>
<thead>
<tr>
<th>Country</th>
<th>N (% trial)</th>
<th>Baseline dengue seropositivity</th>
<th>Number of cases in placebo group</th>
<th>VE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>DENV-1</td>
<td>DENV-2</td>
</tr>
<tr>
<td>Mexico</td>
<td>3464 (17%)</td>
<td>53.1%</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>1315 (6%)</td>
<td>56.2%</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Brazil</td>
<td>3548 (17%)</td>
<td>73.5%</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Honduras</td>
<td>2799 (13%)</td>
<td>85.7%</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Colombia</td>
<td>9743 (47%)</td>
<td>92.2%</td>
<td>58</td>
<td>33</td>
</tr>
</tbody>
</table>

**VE against Severe or Hospitalized Dengue (ITT)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CYD14 (2-14 years)</th>
<th>CYD15 (9-16 years)</th>
<th>Pooled (2-16 years)</th>
<th>Pooled (9-16 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe VCD</td>
<td>70.0% (35.7-86.6)</td>
<td>95.5% (68.8-99.9)</td>
<td>79.1% (60.0-89.0)</td>
<td>93.2% (77.3-98.0)</td>
</tr>
<tr>
<td>Hospitalized VCD</td>
<td>67.4% (50.6-78.7)</td>
<td>80.3% (64.7-89.5)</td>
<td>72.7% (62.3-80.3)</td>
<td>80.8% (70.1-87.7)</td>
</tr>
</tbody>
</table>

**Hospitalised by serotype**

- **DENV1**
  - 71.5% (44.1-86.0)
  - 73.2% (27.8-91.0)
  - 72.1% (27.8-93.4)

- **DENV2**
  - 50.2% (12.7-78.0)
  - 80.1% (45.7-93.7)
  - 65.7% (39.3-80.6)

- **DENV3**
  - 73.2% (27.6-90.9)
  - 83.4% (33.6-97.1)
  - 77.4% (52.2-89.3)

- **DENV4**
  - 77.9% (20.8-95.0)
  - 91.7% (31.8-99.8)
  - 83.5% (54.5-94.0)

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**The Journal of Infectious Diseases® 2016;214:994-1000**

Table 3. CYD-TDV Vaccine Efficacy Against Both Virologically Confirmed Symptomatic Dengue and Asymptomatic Infection in the Immunogenicity Subset Among Individuals Aged 2-16 Years, by Age Group and Baseline Dengue Virus Serostatus

<table>
<thead>
<tr>
<th>Variable</th>
<th>Virologically Confirmed Symptomatic Dengue</th>
<th>Asymptomatic Infection</th>
<th>All Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall analysis, no.</td>
<td>3726</td>
<td>3669</td>
<td>3726</td>
</tr>
<tr>
<td>Vaccine group</td>
<td>25/2510 (1.0)</td>
<td>219/2488 (8.8)</td>
<td>244/2510 (9.7)</td>
</tr>
<tr>
<td>Placebo group</td>
<td>42/1226 (3.4)</td>
<td>157/1184 (13.3)</td>
<td>199/1226 (16.2)</td>
</tr>
<tr>
<td>Vaccine efficacy</td>
<td>70.9 (51.2-83.0)</td>
<td>33.5 (17.9-46.1)</td>
<td>40.1 (27.4-50.5)</td>
</tr>
</tbody>
</table>

Dengue VE varied by age, serostatus, infecting DENV type, country, symptomatic or asymptomatic, disease severity endpoint
ZCS is a Diverse Spectrum of Malformations

Zika Virus Infection in Pregnancy, Microcephaly, and Maternal and Fetal Health

What We Think, What We Know, and What We Think We Know

Maria Gabriela Alvarado, MD, MSPH; David A. Schwartz, MD, MS Hyg

(Arch Pathol Lab Med. doi: 10.5858/arpa.2016-0382-RA)

Definitive diagnosis is required for VE trials; diverse syndromes with numerous potential causes may complicate meeting this requirement.
Summary

• There are numerous factors which may impact disease transmission, infection dynamics, and subsequent clinical disease outcomes.
• These same factors make well-informed randomization strategies essential to ensuring volunteer cohorts share equal risk of reaching defined endpoints.
• The selected trial endpoints will impact all aspects of trial planning, execution, data collection, analyses and the likelihood of being able to determine VE.
• Desired TPPs for specific vaccine candidates guide endpoint proposals; regulatory agency counsel is key.