Role of a ZIKV CHIM in vaccine evaluation

Anna Durbin
Johns Hopkins Bloomberg School of Public Health
WHO Zika Workshop, Geneva
2 June 2017
ZIKV congenital syndrome

• There is increasing evidence from ZIKV outbreak in Latin America that congenital ZIKV syndrome can occur regardless of the timing of maternal infection

• Severity of disease in the mother is not associated with the occurrence of ZIKV congenital syndrome in the infant (ZIKV congenital syndrome can occur regardless of whether or not the mother had a symptomatic ZIKV infection)
  – This may indicate any level of viremia in the mother may cause adverse outcomes in the fetus
  – Prevention of symptomatic illness in the mother may not be sufficient to prevent CZS in the fetus; prevention of infection may be required
ZIKV CHIM in vaccine development

• Down-selection of candidate vaccines
  – Currently 45 candidate ZIKV vaccines have been described as under development
  – Limited financial and human resources are available to evaluate all these candidates
  – Down-select candidates early to ensure resources are utilized for development of candidates that demonstrate the highest likelihood of success

• Assess vaccine efficacy if circulation of ZIKV diminishes such that true field efficacy trials cannot be done
**ZIKV CHIM in vaccine development**

- Assess the ability to induce sterilizing immunity and its duration – very difficult to do in field studies
- Assess the effect of pre-existing flavivirus immunity on vaccine immunogenicity / protection
- Assess the ability of passively-transferred antibody to protect against ZIKV infection and the durability of that protection
- Identify correlate(s) of protection
Secondary advantages of a ZIKV CHIM

• Characterize ZIKV infection in humans
  – Determine how long replicating ZIKV is shed in blood, urine, semen, vaginal secretions to better determine the risk of sexual transmission
  – Determine if viral load affects duration of shedding
  – Determine if viral load affects symptom presentation
  – Determine if inoculum affects peak viral load/duration of shedding

• Data from well-designed ZIKV CHIM could be used in the development of public health guidelines related to transmission of ZIKV

• Characterize the effect of pre-existing DENV antibody (or other flavivirus antibody) on ZIKV infection
Conclusions from an ethical review of Zika human challenge convened by US NIH December 2016


Key Question: Are the risks reasonable, minimized, and justified by the potential social value of the trial?

Conclusion:

• There is substantial uncertainty about the risks to potential volunteers in Zika virus human challenge study.

• Particular concern about possible risks to third parties (foetuses, members of the community)

• Absence of a strong argument and evidence that a challenge study will accelerate vaccine development

• Absence of an indication that field trials will be prohibitively difficult to conduct

• The committee concluded that it is premature to proceed with a Zika virus human challenge trial
Use of CHIM in vaccine development

- RTS,S
  - CHIM studies first used to evaluate efficacy of RTS,S
  - Later used to refine the formulation and dosing regimen
- PfSPZ
  - Used to evaluate efficacy
  - Used to define the most effective route of administration and dosing regimen
- The malaria CHIM is now a standard step in the development of malaria vaccines
- Dengue CHIM determined which formulation of the NIH LATV dengue vaccine would be evaluated in Phase 3 clinical trial in Brazil
Use of the CHIM in vaccine licensure

- The live attenuated cholera vaccine Vaxchora (PaxVax) was licensed based on efficacy data from the cholera CHIM.

- The CHIM was critical because:
  - *The low incidence of cholera infection in travelers made a traditional field efficacy trial non-feasible*
  - The trial established an immunologic correlate of protection that could be used as a regulatory criterion for immunologic bridging.

- CHIMs used to determine vaccine efficacy do not negate the need for large trials to assess vaccine safety
Risks of ZIKV CHIM

• ZIKV illness
  – ZIKV infection is generally described as a mild transient illness with the most common physical sign/symptom being rash

• Congenital ZIKV syndrome if infected in utero

• Guillian-Barré syndrome or other reported neurological complications

• Transmission of ZIKV
  – Vector-borne transmission
  – Sexual transmission
Sexual transmission of ZIKV

• CDC has confirmed 48 cases of sexual transmission
  – Most are male-to-female (including transmission from a vasectomized male)
  – 1 male-to-male
  – 1 Female-to-male transmission

• All but one of the travelers had symptoms consistent with ZIKV

• All cases of documented sexual transmission occurred within 21 days of return from ZIKV-endemic area
  – One case occurred ~ 40 days after return but both partners traveled to ZIKV-endemic area
Sexual Transmission

- 48 documented cases of sexually-transmitted ZIKV infection resulting from 5,026 travel-associated ZIKV cases (fewer than 1%)
- ZIKV has been detected by PCR in semen out to 6 months after symptoms have developed
- The longest interval replicating ZIKV has been detected in semen by tissue culture is 69 days
- To date, there is only 1 prospective longitudinal study that has evaluated ZIKV shedding in body fluids, including semen
  - 31/58 (53%) men had Zika detected by PCR in semen
  - On 6/20 (30%) PCR-positive samples had virus detected by culture
Guillain-Barré Syndrome (GBS) and ZIKV

- Current CDC research suggests GBS is associated with ZIKV; however CDC states only a small proportion of people with recent ZIKV get GBS
- Most studies describing GBS and ZIKV are observational
- Onset of GBS following ZIKV quite early in many of these studies
- Diagnosis of ZIKV in many of these studies by history of rash/fever
ZIKV and GBS – Cao Lormeau study

• Strongest evidence of association presented in retrospective case-control study from French Polynesia

• 42 patients admitted with GBS between November 2013 & February 2014
  – Presented with neurological symptoms a median of 6 days after onset viral syndrome
  – All negative for ZIKV by RT-PCR
  – Multiple serological tests were performed out to 3 months post-hospitalization (IgG, IgM, or PRNT)
  – Were diagnosed with ZIKV if any one of the serological tests was positive

• Compared with control group of 98 patients admitted for non-febrile disease
  – Controls were tested once within 7 days of admission

• Estimated rate of GBS to be 0.24/1,000
  – Less than rate of GBS with Campylobacter jejuni: 0.25 – 0.65/1,000
Cao-Lormeau study - critiques

- OR of GBS with ZIKV if use only IgG from first blood sample = 1.33 [95% CI 0.65 – 2.78]; p=0.4\(^1\)
  - (compared with Cao-Lormeau estimated OR 59.7, [non-estimable 95% CI])
- Restricting controls to non-febrile patients and patients from referral hospital may have caused an artifact by diminishing the probability of exposure of the controls to ZIKV

Overall, the number of persons with suspected GBS and evidence of ZIKV or flavivirus infection was 2.5 times greater than the number of persons with suspected GBS and no evidence of ZIKV infection.

Median interval from antecedent acute illness to onset of neurologic signs was 5 days (range 0 – 17 days).

Median age of patients was 55 (range 21 – 88)
  – Higher incidence of women with GBS
Risk Mitigation in ZIKV CHIM

- Risk of congenital ZIKV syndrome
  - Pregnancy and breast-feeding would exclude participation
  - Pregnant partner would be exclusionary criterion
  - Mandatory use of highly effective contraception (oral or implantable hormonal, IUD)

- Risk of transmission
  - Conduct the study as an inpatient study (inpatient for about 14 days post-infection)
  - Educate subjects on the risk of sexual transmission
  - Require all subjects to agree to use barrier contraception for the duration of the study
  - Partners could be voluntarily monitored

- Risk of GBS (or other neurological complication)
  - Enroll younger subjects (≤ 40)
  - Ensure subjects are fully educated regarding the risk of GBS
  - Ensure diagnosis and treatment of GBS are available to all subjects
  - Indemnify trial such that subjects are not responsible for cost of care
Summary

• ZIKV CHIM provides the opportunity to down-select candidate vaccines such that only those that meet specified efficacy criteria would proceed to larger field trials in endemic areas
  – Sterilizing immunity
  – Efficacy evaluation if unable to be done in the field
• ZIKV CHIM can be used to fully characterize the replication/shedding of ZIKV in humans
  – Possibly inform public health policy
• Risks associated with a ZIKV CHIM are being evaluated and scientific evidence suggests that risk mitigation will allow the study to proceed in a safe and ethical manner
  – Narrow pathway forward
Transmission of ZIKV

• *Aedes* mosquitoes thought to be the primary mosquito vector for ZIKV with ZIKV cases reported primarily during mosquito-transmission season in affected areas

• Sexual transmission of ZIKV
  – CDC has reported 48 cases of sexual transmission from a total of 5,026 ZIKV cases occurring in the U.S. (imported & local transmission, as of 12/28/16)
  – Most cases have been from a symptomatic partner, although transmission from an asymptomatic partner has been reported
  – ZIKV can be found by PCR in the semen for up to 6 months post-infection however, *in all cases of sexual transmission reported to date, the non-traveler partner has become symptomatic within 21 days of exposure*
GBS & ZIKV – Puerto Rico

• The PRDH & CDC implemented the GBS Passive Surveillance System (GBPSS) in Feb. 2016
• Reported 56 suspected cases of GBS with onset during the period Jan. 1, 2016 – July 31, 2016
  – 37% had no evidence of ZIKV infection
  – 29% had presumptive ZIKV infection (14% had presumptive flavivirus infection)
  – Median age was 55 years (range 21 – 88)
  – Median interval from antecedent illness to onset of neurological signs was 5 days (range 0 – 17 days)
• The number of persons with suspected GBS and evidence of ZIKV or flavivirus infection was 2.5 times greater than the number of persons with GBS and no evidence of ZIKV infection
## ZIKV vaccines in development

<table>
<thead>
<tr>
<th>Developers</th>
<th>Type of vaccine</th>
<th>Antigen</th>
<th>Development/Phase</th>
<th>Registration No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLS-5700</td>
<td>GeneOne / Inovio</td>
<td>DNA</td>
<td>prM &amp; E</td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NCT02809443, NCT02887482</td>
</tr>
<tr>
<td>VRC ZIKV DNA</td>
<td>VRC/NIAID</td>
<td>DNA</td>
<td>PrM &amp; E</td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NCT02840487, NCT02996461, NCT03110770</td>
</tr>
<tr>
<td>BioManguinhos/Fiocruz</td>
<td>VLP</td>
<td>E protein</td>
<td>Non-clinical</td>
<td></td>
</tr>
<tr>
<td>ZIKVLP</td>
<td>Institut Pasteur</td>
<td>VLP</td>
<td>Non-clinical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shanghai</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NewLink Genetics</td>
<td>VLP</td>
<td>PrM &amp; E</td>
<td>Non-clinical</td>
<td></td>
</tr>
<tr>
<td>Bharat</td>
<td>PIV</td>
<td>Whole virus</td>
<td>Phase 1</td>
<td>(registration # not known)</td>
</tr>
<tr>
<td>BioManguinhos/Fiocruz</td>
<td>PIV</td>
<td>Whole virus</td>
<td>Non-clinical</td>
<td></td>
</tr>
<tr>
<td>Butantan ZIKV</td>
<td>Butantan</td>
<td>PIV</td>
<td>Whole virus</td>
<td>Non-clinical</td>
</tr>
<tr>
<td>NewLink Genetics</td>
<td>PIV</td>
<td>Whole virus</td>
<td>Non-clinical</td>
<td></td>
</tr>
<tr>
<td>Valneva</td>
<td>PIV</td>
<td>Whole virus</td>
<td>Non-clinical</td>
<td></td>
</tr>
</tbody>
</table>
# ZIKV vaccines (con’t)

<table>
<thead>
<tr>
<th>Developers</th>
<th>Type of vaccine</th>
<th>Antigen</th>
<th>Development/Phase</th>
<th>Registration No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butantan attenuated ZIKV</td>
<td>Butantan</td>
<td>LAV</td>
<td>Whole virus</td>
<td>Non-clinical</td>
</tr>
<tr>
<td>rZIKV/DEN2Δ30</td>
<td>NIAID Intramural</td>
<td>LAV</td>
<td>Whole virus</td>
<td>Non-clinical</td>
</tr>
<tr>
<td>rZIKV/DEN4Δ30</td>
<td>NIAID Intramural</td>
<td>LAV</td>
<td>Whole virus</td>
<td>Non-clinical</td>
</tr>
<tr>
<td>rZIKV-3’/DEN4Δ30</td>
<td>NIAID Intramural</td>
<td>LAV</td>
<td>Whole virus</td>
<td>Non-clinical</td>
</tr>
<tr>
<td>rZIKVΔ30</td>
<td>NIAID Intramural</td>
<td>LAV</td>
<td>Whole virus</td>
<td>Non-clinical</td>
</tr>
<tr>
<td>Bharat</td>
<td>PIV</td>
<td>Whole virus</td>
<td>Non-clinical</td>
<td></td>
</tr>
<tr>
<td>BioManguinhos/ Fiocruz</td>
<td>PIV</td>
<td>Whole virus</td>
<td>Non-clinical</td>
<td></td>
</tr>
<tr>
<td>Butantan ZIKV</td>
<td>Butantan</td>
<td>PIV</td>
<td>Whole virus</td>
<td>Non-clinical</td>
</tr>
<tr>
<td>NewLink Genetics</td>
<td>PIV</td>
<td>Whole virus</td>
<td>Non-clinical</td>
<td></td>
</tr>
<tr>
<td>Valneva</td>
<td>PIV</td>
<td>Whole virus</td>
<td>Non-clinical</td>
<td></td>
</tr>
<tr>
<td>ZIKV PIV</td>
<td>WRAIR/Harvard/ NIAID/Sanofi Pasteur</td>
<td>PIV</td>
<td>Whole virus</td>
<td>Non-clinical</td>
</tr>
</tbody>
</table>

NCT02952833, NCT02937233, NCT02963909, NCT03008122
# ZIKV vaccines (con’t)

<table>
<thead>
<tr>
<th>Developers</th>
<th>Type of vaccine</th>
<th>Antigen</th>
<th>Development/Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>BioManguinhos/Fiocruz</td>
<td>Recombinant viral vector</td>
<td>PrM/E &amp; NS1 proteins</td>
<td>Non-clinical</td>
</tr>
<tr>
<td>BioManguinhos/Fiocruz</td>
<td>Recombinant viral vector</td>
<td>E protein</td>
<td>Non-clinical</td>
</tr>
<tr>
<td>GEO-ZM05</td>
<td>GeoVax/ UGA/CDC</td>
<td>Recombinant viral vector</td>
<td>Non-clinical</td>
</tr>
<tr>
<td>NiLV-ZK</td>
<td>Institut Pasteur France</td>
<td>Recombinant viral vector</td>
<td>Non-clinical</td>
</tr>
<tr>
<td>ChAdOx1-Zk</td>
<td>Zika structural proteins</td>
<td>Recombinant viral vector</td>
<td>Non-clinical</td>
</tr>
<tr>
<td>Chimeravax-Zika</td>
<td>Sanofi Pasteur</td>
<td>Recombinant viral vector</td>
<td>Zika structural</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>proteins</td>
</tr>
<tr>
<td>SCV-CHIKV+ZIKV+YF</td>
<td>Sementis Ltd</td>
<td>Recombinant viral vector</td>
<td>ZIKV, CHIK, YF</td>
</tr>
<tr>
<td>MV-Zika</td>
<td>Themis Bioscience GmbH</td>
<td>Recombinant viral vector</td>
<td>prM-E</td>
</tr>
<tr>
<td>VXA-Zikavax</td>
<td>Vaxart</td>
<td>Recombinant viral vector</td>
<td>Env+</td>
</tr>
<tr>
<td>Replikins Zika Vaccine</td>
<td>Replikins, Ltd and LLC</td>
<td>Peptide</td>
<td>Synthetic peptides</td>
</tr>
<tr>
<td>mRNA-1325</td>
<td>Valera (Moderna)</td>
<td>mRNA</td>
<td>prM-E</td>
</tr>
</tbody>
</table>

**References:**
- NCT02996890
- NCT03014089

---

**CIR**

*Advancing Vaccine Science*