Considerations on Zika Vaccine Development

March 28, 2016
Vaccination for Congenital Infections: Lessons from Rubella

- Congenital Rubella Syndrome (CRS): Infants born with blindness, deafness, heart defects, often microcephaly
- Between 1964-1965, 50,000 pregnant women in U.S. exposed to Rubella
  - 20,000 infants born with CRS
- With MMR vaccine administered to general population, CRS has all but disappeared
Zika Vaccine Target Population

• Initially women of childbearing age
  - Target population at greatest risk

• General population
  - Herd immunity
  - Protect pregnant women and developing fetus
  - Rubella vaccination model
Flavivirus Vaccines

• Yellow Fever Vaccine
  - Effective against 7 genotypes
  - Protective titer ≥1:10
  - High efficacy rates

• JEV and TBE* Vaccines
  - Protective titer ≥1:10
  - High efficacy rates

• Investigational Dengue and WNV vaccines
  - Multiple platforms have been tested
  - E protein induced neutralizing antibody

• Protective immune response to vaccination (E protein)
  - Neutralizing Antibody
  - Structural considerations for antigen design

*not licensed for use in US
A West Nile Virus DNA Vaccine Utilizing a Modified Promoter Induces Neutralizing Antibody in Younger and Older Healthy Adults in a Phase I Clinical Trial.
Ledgerwood JE, the VRC 303 Study Team, et al.

NAb (EC50) by RVP neutralization assay responses at week 12 (4 weeks after 3rd vaccination)

Promoter: CMV          CMV/R
Cohort: All          All
18-50 yrs           51-65 yrs

West Nile Virus DNA Vaccine (Phase 1)

Phase I: Week 12 (4 weeks after 3rd vaccination)
Horses: 3 weeks after 1-mg dose WNV DNA vaccine

NAb was measured throughout the trial:
(A) 18–50-year-old    (B) 51–65-year-old

WNV reporter-virus particles (RVP) neutralization assay and plaque reduction neutralization (PRNT)

Martin et al. J Infect Dis. 2007;196:1732-1740
Zika Vaccine Clinical Development

• Research and down-selection of platform and antigen design
  - Role of prior Flavivirus vaccine research

• Preclinical assessment
  - Animal models needed to study pathogenesis and evaluate efficacy

• Phase 1 safety and immunogenicity
  - Zika naïve
  - Flavivirus naïve vs general population
  - Endemic vs nonendemic regions

• Phase 2 safety and immunogenicity for regimen and dose

• Human challenge efficacy data

• Phase 2B
  - Efficacy endpoint/design options
Zika VRC DNA Vaccine: Phase 1 Study

Phase I, randomized, multicenter clinical trial to evaluate the safety and immunogenicity of a Zika DNA vaccine in healthy adults 18-60 years old.

<table>
<thead>
<tr>
<th>Group</th>
<th>Subjects</th>
<th>Day 0</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 20</th>
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<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>Zika DNA</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>2</td>
<td>20</td>
<td>Zika DNA</td>
<td></td>
<td></td>
<td>Zika DNA</td>
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<tr>
<td>3</td>
<td>20</td>
<td>Zika DNA</td>
<td>Zika DNA</td>
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<tr>
<td>4</td>
<td>20</td>
<td>Zika DNA</td>
<td>Zika DNA</td>
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<tr>
<td>Total</td>
<td>80</td>
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</table>

*Zika DNA injections are 4 mg in 1 mL IM*
Zika Vaccine Phase 2B
Efficacy Trial Endpoint Options

• Option A: Diagnosis by seroconversion
  - Confounded by cross reactivity with Dengue, YF
  - Confounded by vaccine response to Env protein (PRNT or ELISA) and natural infection does not consistently induce responses to internal proteins
  - Is it possible to evaluate by T cell response to internal proteins

• Option B: Diagnosis by PCR of symptomatic cases only
  - Underestimates case count since 70%+ are subclinical or asymptomatic, and because of teratogenicity associated with asymptomatic infection, need to prevent all viremia

• Option C: Diagnosis by frequent urine PCR *plus* investigation of symptomatic cases
  - Advantages include more accurate case count and reduction of trial size
  - *Need additional data: urine PCR sensitivity in asymptomatic cases*
Assumptions:
• Double-blind, placebo-controlled, 1:1 randomized trial
• 5% Zika incidence in placebo group, 70% vaccine efficacy, 90% power
• 25% of Zika infections result in symptoms prompting evaluation

Option A (Seroconversion)
• No clear path forward in a vaccine trial unless T cell response to antigens not contained in vaccine could substitute

Option B (Plasma/Serum or Urine to Diagnose Symptomatic Cases Only)
• 2100 per group, n=4200 total

Option C (Urine PCR 3x Month, Goal to Diagnose All Cases)
• 525 per group, n=1050 total

*Trial size estimations include 20% overage to account for drop out
Zika Vaccine Efficacy Evaluation by Human Challenge

- Human challenge with Dengue is well established
- Zika virus causes relatively mild symptoms in adults
- Advantages
  - Demonstrate kinetics of virus clearance from all body compartments
  - Define clinical manifestations
  - Measure immune response patterns
  - Obtain clinical samples for reagents and generation of human mAbs
  - Evaluate diagnostics and efficacy of candidate vaccines and therapeutics
- Concerns
  - Guillain-Barre or other unexpected adverse events
  - Would need to avoid conception in women and sexual transmission by men
  - Direct challenge with needle and syringe may differ from mosquito transmission
- Other considerations
  - Could obtain efficacy data on prevention of viremia in small number of subjects
  - Would need to determine with regulatory authorities how this information would contribute to product development and licensure
Zika Vaccine
Development Approaches

<table>
<thead>
<tr>
<th>Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
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</thead>
<tbody>
<tr>
<td>Discovery and Preclinical</td>
<td>Phase 1</td>
<td>Human challenge</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>Phase 1</td>
<td>Phase 2/2B</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
<td>Phase 1</td>
<td>Phase 2</td>
<td></td>
</tr>
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</table>
Summary

• Prior flavivirus immunology and vaccine research is informative
• Animal models for immunogenicity and efficacy are needed
  – Understanding disease and data for evaluation of candidates
• Ongoing epidemiology and human disease research will inform vaccine trials design and target populations
• Data from phase 1 and human challenge could guide down-selection
• Further considerations on timing and endpoints of Phase 2/2B and human challenge data to assess efficacy and support broad use
Extra slides
Zika Vaccine Clinical Development

Phase I
- Phase II
- Phase IIb Trial
- Human Challenge
- Animal Rule

Phase III Trial
(Pre or Post Marketing?)
Zika Vaccine
Proposed Development Timeline

<table>
<thead>
<tr>
<th>Vaccine Candidate Type</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
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<tbody>
<tr>
<td>DNA vaccine candidate</td>
<td>Preclinical Discovery</td>
<td>Phase 1</td>
<td>Phase 2/2B</td>
</tr>
<tr>
<td>mRNA vaccine candidate</td>
<td>Preclinical Discovery</td>
<td>Phase 1</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Whole-inactivated virus</td>
<td>Preclinical Discovery</td>
<td>Phase 1</td>
<td>Phase 2/2B</td>
</tr>
<tr>
<td>Inactivated Zika chimera</td>
<td>Preclinical Discovery</td>
<td>Phase 1</td>
<td>Phase 2/2B</td>
</tr>
<tr>
<td>Live-attenuated Zika chimera</td>
<td>Preclinical Discovery</td>
<td>Phase 1</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Live-attenuated virus</td>
<td>Preclinical Discovery</td>
<td>Phase 1</td>
<td></td>
</tr>
<tr>
<td>Vector-based approaches</td>
<td>Preclinical Discovery</td>
<td>Phase 1</td>
<td></td>
</tr>
<tr>
<td>Subunit approaches</td>
<td>Preclinical Discovery</td>
<td>Phase 1</td>
<td></td>
</tr>
</tbody>
</table>

- **Intramural NIAID and partnerships**
- **Extramural NIAID and partnerships**
NIAID Vaccine Research

• Vaccine research – intramural candidates
  - DNA expressing preM and E (NIAID, VRC)
  - Live attenuated Dengue-Zika chimera (NIAID, LID)

• Vaccine research – extramural candidates
  (Academic and Industry collaborations)
  - Live attenuated or live chimeric virus
  - Whole inactivated virus or inactivated chimeric virus
  - mRNA platforms (SAM, others)
  - Replicating viral: VSV platform
  - Replication-defective Viral Vector: MVA
  - Subunit protein, VLP
## Special Populations: Pregnant Women

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Before pregnancy</th>
<th>During pregnancy</th>
<th>After pregnancy</th>
<th>Type of Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>Yes, if indicated</td>
<td>Yes, if indicated</td>
<td>Yes, if indicated</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Yes, if indicated</td>
<td>Yes, if indicated</td>
<td>Yes, if indicated</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Human Papillomavirus (HPV)</td>
<td>Yes, if indicated, through 26 years of age</td>
<td>No, under study</td>
<td>Yes, if indicated, through 26 years of age</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Influenza IV</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Influenza LAIV</td>
<td>Yes, if less than 50 years of age and healthy; avoid conception for 4 weeks</td>
<td>No</td>
<td>Yes, if less than 50 years of age and healthy; avoid conception for 4 weeks</td>
<td>Live</td>
</tr>
<tr>
<td>MMR</td>
<td>Yes, if indicated, avoid conception for 4 weeks</td>
<td>No</td>
<td>Yes, if indicated, give immediately postpartum if susceptible to rubella</td>
<td>Live</td>
</tr>
<tr>
<td>Meningococcal: • polysaccharide • conjugate</td>
<td>If indicated</td>
<td>If indicated</td>
<td>If indicated</td>
<td>Inactivated/inactivated</td>
</tr>
<tr>
<td>Pneumococcal Polysaccharide</td>
<td>If indicated</td>
<td>If indicated</td>
<td>If indicated</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Tdap</td>
<td>Yes, if indicated</td>
<td>Yes, vaccinate during each pregnancy ideally between 27 and 36 weeks of gestation</td>
<td>Yes, immediately postpartum, if not received previously</td>
<td>Toxoid/inactivated</td>
</tr>
<tr>
<td>Tetanus/Diphtheria Td</td>
<td>Yes, if indicated</td>
<td>Yes, if indicated, Tdap preferred</td>
<td>Yes, if indicated</td>
<td>Toxoid</td>
</tr>
<tr>
<td>Varicella</td>
<td>Yes, if indicated, avoid conception for 4 weeks</td>
<td>No</td>
<td>Yes, if indicated, give immediately postpartum if susceptible</td>
<td>Live</td>
</tr>
</tbody>
</table>

CDC, 2016
Vaccines Administered During Pregnancy

- Hepatitis A (if indicated)
- Hepatitis B (if indicated)
- Influenza IIV
- Meningococcal (if indicated)
- Pneumococcal (if indicated)
- Tdap (ideal between 27 and 36 weeks of gestation)
- Tetanus/Diptheria Td (if indicated, Tdap preferred)
# Phase 2/2B Potential Design

<table>
<thead>
<tr>
<th>Schema</th>
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</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>Part 1 (Non-endemic for Safety and Immunogenicity)</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>Part 2 (Endemic Population with Efficacy Endpoint)</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

**Note:**
- **Part 1**: Non-endemic group for safety and immunogenicity with 1,250 subjects divided into 1 and 2 groups.
- **Part 2**: Endemic population with efficacy endpoint with 1,200 subjects divided into 3 and 4 groups.
- **Total**: 2,450 subjects.
WNV DNA Vaccine References


• **Horse DNA Vaccine:** West Nile virus recombinant DNA vaccine protects mouse and horse from virus challenge and expresses in vitro a noninfectious recombinant antigen that can be used in enzyme-linked immunosorbent assays. Davis BS, Chang GJ, Cropp B, Roehrig JT, Martin DA, Mitchell CJ, Bowen R, Bunning ML. J Virol. 2001 May;75(9):4040-7.
