OVERVIEW: ZIKA VACCINES IN DEVELOPMENT

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Office of the Assistant Secretary for Preparedness and Response (ASPR)
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National Vaccine Advisory Committee
Washington, DC

Resilient People. Healthy Communities. A Nation Prepared.
Zika Virus

Belongs to the family *Flaviviridae* (includes dengue, West Nile, Yellow Fever, Japanese encephalitis and St. Louis Encephalitis viruses)

**Brief history**

- First isolated in Zika forest in 1947 with limited human infections in Africa and SE Asia through 2006
- Emerged in Micronesia in 2007, and French Polynesia in 2008
- Most recent outbreak began in Brazil in 2015
- Currently found in over 80 countries and territories worldwide

**Disease**

- 80% asymptomatic
- 20% of patients present with rash, fever, conjunctivitis, and arthralgia
- Association with Congenital Zika Syndrome, Guillain-Barre Syndrome and many other neurological conditions
How Zika Spreads

Most people get Zika from a mosquito bite.

A mosquito bites a person infected with Zika virus.

The mosquito becomes infected.

A mosquito will often live in a single house during its lifetime.

More mosquitoes get infected and spread the virus.

The infected mosquito biting a family member or neighbor and infects them.

During pregnancy, a pregnant woman can pass Zika virus to her fetus during pregnancy. Zika causes microcephaly, a severe birth defect that is a sign of incomplete brain development.

Through sex, Zika virus can be passed through sex from a person who has Zika to his or her sex partners.

Through blood transfusion, there is a strong possibility that Zika virus can be spread through blood transfusions.
Congenital Syndrome

- Multi-faceted syndrome with broad-ranging neurological sequelae, unknown long-term health consequences
- Reported in 26 countries and territories in the Americas since Oct 2015
- 3,720 cases of microcephaly and/or CNS malformation reported (103 in North America; 3617 in Latin America)

Prevention of ZIKV Infection

There is currently no licensed ZIKV vaccine available, however...

- Vaccines for other flaviviruses have been developed and used for over 70 years
- Active development programs for Dengue and West Nile vaccines have been ongoing for over 30 years; however, knowledge of Zika virus was limited at the outset of the epidemic
- Past experience was leveraged for ZIKV vaccine development
- Zika R&D efforts accelerated greatly in 2016 by NIAID and WRAIR, followed by advanced development projects at BARDA
- A coordinated, interagency effort was established to oversee vaccine development and portfolio management
- BARDA has invested over $265 million in vaccine development
VACCINES IN CLINICAL DEVELOPMENT
Phase I Clinical Trials – 2 candidates: VRC 5288 and VRC 5283

- Interim data reported in Lancet, Dec. 2017 (Gaudinski et al)
- Zika neutralizing antibodies developed in 100% of subjects

Phase II/IIb Clinical Trial – VRC 5283

- Part A: Dose Escalation and Injection Number Study
  - Enrollment complete
  - Immunogenicity evaluation ongoing
- Part B: Efficacy Study
  - Regimen selected May 2017
  - Enrollment initiated 7/19/17, 248/2,400 enrolled as of Jan 30, 2017
  - 11/20 sites activated

Industry partner identified for commercialization
A Phase 2b, Randomized Trial to Evaluate the Safety and Immunogenicity of a Zika Virus ONA Vaccine

Healthy Volunteers Ages 15-35

20 sites in the US, Caribbean, Central and South America

Zika, is being reported in Peru, Mexico, and other areas that are 705 sites.

VRC 705: Phase 2/2b

<table>
<thead>
<tr>
<th>VRC 705 Phase 2b</th>
<th>Part A</th>
<th>Part B Regimen: 4mg Split Dose by PharmaJet: Vaccination at 0, 4, 8 weeks</th>
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<tbody>
<tr>
<td><strong>Group</strong></td>
<td><strong>n:</strong></td>
<td><strong>Total Dose</strong></td>
</tr>
<tr>
<td>1</td>
<td>30</td>
<td>4 mg</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>4 mg</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>5 mg</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>90</strong></td>
<td><strong>Part A Enrollment: Complete</strong></td>
</tr>
<tr>
<td>4</td>
<td>1200</td>
<td>4 mg</td>
</tr>
<tr>
<td>5</td>
<td>1200</td>
<td>N/A</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>2400</strong></td>
<td><strong>Blinded evaluation of case rates to increase sample size as needed</strong></td>
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</tbody>
</table>

Courtesy: G. Chen, VRC
Safety and Immunogenicity of an Anti–Zika Virus DNA Vaccine — Preliminary Report

Pablo Tebas et al.

- DNA plasmid vaccine expressing Zika prM-E
- Two groups of 20 received 1mg or 2 mg ID at 0, 4, 12 weeks w/electroporation
- No SAEs reported
- Anti-Zika antibodies detected in 100% in both groups
- Zika neutralizing antibodies developed in 62% of subjects
- Passive transfer of human vaccinee serum protected in a lethal mouse model
Live attenuated vaccine for DENV / ZIKV

Pentavalent DENV + ZIKV:

DEN1       DEN2       DEN3       DEN4 +

Δ3 0       Δ3 0       Δ3 0       Δ3 0       Δ3 0

5' - C prM E NS1 NS2A NS2B NS3 NS4A NS4B NS5 - 3' rDEN1Δ30

5' - C prM E NS1 NS2A NS2B NS3 NS4A NS4B NS5 - 3' rDEN2/4Δ30

5' - C prM E NS1 NS2A NS2B NS3 NS4A NS4B NS5 - 3' rDEN3Δ30/31

5' - C prM E NS1 NS2A NS2B NS3 NS4A NS4B NS5 - 3' rDEN4Δ30

5' - C prM E NS1 NS2A NS2B NS3 NS4A NS4B NS5 - 3' rZIKV/D4Δ30

Phase III underway

Pre-clinical development

NIAID Laboratory of Viral Diseases

Courtesy: S. Whitehead, LVD
<table>
<thead>
<tr>
<th>#</th>
<th>Deliverable</th>
<th>Timeline (CY)</th>
<th>DONE?</th>
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<tbody>
<tr>
<td>1</td>
<td>Virus construction, seed virus generation, pre-clinical evaluation</td>
<td>Q2 2017</td>
<td>✓</td>
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<tr>
<td>2</td>
<td>Manufacturing of Phase 1 and 2 CTM’s at Charles River Laboratories; Release testing</td>
<td>June – Nov 2017</td>
<td>✓</td>
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<tr>
<td>3</td>
<td>IND submission</td>
<td>Feb 2018</td>
<td>Initiated</td>
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<tr>
<td>4</td>
<td>Phase 1 - Monovalent</td>
<td>March 2018</td>
<td></td>
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<tr>
<td>5</td>
<td>Phase 2 - Pentavalent</td>
<td>May 2018</td>
<td></td>
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<tr>
<td>6</td>
<td>Phase 2a – Butantan Institute Bridging, Monovalent, Pentavalent</td>
<td>Pending Q4 2018</td>
<td></td>
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<tr>
<td>7</td>
<td>Phase 2b – Butantan Institute</td>
<td>Pending 2019</td>
<td></td>
</tr>
</tbody>
</table>

 Courtesy: S. Whitehead, LVD
Modern mRNA Vaccine

- Synthetic mRNA can be used to deliver virtually any gene
- Novel chemistry enables mRNA to elude intracellular innate host immune responses
- Once in cell, acts like a native mRNA to express foreign gene
- Robust, protective immunological responses in animal models
- Needle and syringe delivery
- Pre-clinical and clinical evaluation of multiple candidates ongoing
Inactivated Zika Vaccines

• “Proof-of-concept” clinical lot of Zika Purified Inactivated Vaccine (ZPIV) manufactured by WRAIR based on JEV vaccine technology
• Formalin-inactivated, alum-adjuvanted
• NIAID and WRAIR conducting five Phase I clinical trials to evaluate safety and immunogenicity
• BARDA awarded development contracts to Sanofi and Takeda to manufacture and license an inactivated Zika vaccine
  • Currently, only Takeda is continuing development of their Zika vaccine
  • Takeda Phase I safety and immunogenicity in naïve and Flavi-seropositive ongoing
  • Sanofi vaccine candidate no longer being pursued but company is conducting a case definition study that is still supported

Adapted from AS Fauci/NIAID
Preliminary aggregate safety and immunogenicity results from three trials of a purified inactivated Zika virus vaccine candidate: Phase 1, randomised, double-blind, placebo-controlled clinical trials

Kayvon Modjarrad, Leyi Line, Sarah George, Kathryn E. Stephenson, et al.

- Formalin-inactivated, alum-adjuvanted vaccine
- Administered on days 1 and 29
- Data from 68 subjects who received 5 ug IM
- Mild to moderate adverse events
- 92% seroconverted by day 57
- Peak MN titers at day 43 exceeding protective titers seen in animal studies
PRESS RELEASE

Zika Virus: Themis Bioscience Initiates Worldwide First Study With Live Attenuated Recombinant Vaccine

Vienna, Austria, 11-Apr-2017 – A promising vaccine for the Zika virus is now being tested by Themis Bioscience GmbH, a specialized biotech company developing prophylactic vaccines against emerging tropical infectious diseases. After recent progress with the development of a Chikungunya vaccine the company succeeded in swiftly adapting their proprietary vaccine technology for their Zika vaccine program. This program is based on a live attenuated recombinant vaccine that promises a fast and effective immune response.
Key Challenges/Questions

Regulatory/Clinical
- What if existing disease incidence does not support evaluation of vaccine efficacy?
- Will immunological responses prevent congenital infections?

Funding/Commercialization
- How will funding gaps be filled to support licensure?
- Will the commercial market sustain a Zika vaccine?
THANK YOU

Contact us
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