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.
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
Product Development Pipeline

Early Concept and Product Development
- NIH and DoD

Advanced Product Development
- ASPR/BARDA

Commercial Manufacturing and Licensure
- Industry

Regulatory Review
- FDA

Industry
- FDA consultation and interim review

Adapted from AS Fauci/NIAID
# Vaccine Landscape Feb 2016

<table>
<thead>
<tr>
<th>Platform</th>
<th>Research &amp; Discovery</th>
<th>Preclinical</th>
<th>Phase 1</th>
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<tbody>
<tr>
<td>Recombinant or Subunit</td>
<td><strong>NOVAVAX</strong></td>
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<tr>
<td>Live Attenuated</td>
<td><strong>VLA INSITUTO</strong></td>
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<td>Whole Virus Inactivated</td>
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<td>Nucleic Acid</td>
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<tr>
<td>Viral Vector</td>
<td><strong>PROFECTUS BIOSCIENCE</strong></td>
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<td>Other</td>
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US Zika Vaccine Goals

2016-2018

**Aim #1:** Evaluate available vaccine candidates to assess safety, efficacy, and immunogenicity and identify protective immune correlates during the time of highest disease incidence.

**By 2018**

**Aim #2:** Deploy an available vaccine under an appropriate regulatory mechanism to US populations at high risk of exposure.

**By 2020**

**Aim #3:** Work with industry partners to commercialize vaccine(s) for broad distribution.
### General Considerations on Vaccine Technologies

<table>
<thead>
<tr>
<th>Technology</th>
<th>Pros</th>
<th>Cons</th>
<th>Licensed Human Flavivirus Vaccines</th>
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</thead>
<tbody>
<tr>
<td>Nucleic Acid (DNA, mRNA)</td>
<td>Simple process development/mfg. Potential for rapid response capability.</td>
<td>No DNA or mRNA vaccines licensed for human use. Limited experience at commercial scale.</td>
<td>No</td>
</tr>
<tr>
<td>Whole Virus Inactivated</td>
<td>Likely straightforward. Commercial platforms exist. Inactivated vaccines are approved for other indications.</td>
<td>May need several doses and adjuvant. Need large production requirement.</td>
<td>Japanese Encephalitis, Tick Borne Encephalitis</td>
</tr>
<tr>
<td>Live Attenuated (including flavi-chimeras)</td>
<td>Commercial platforms exist.</td>
<td>Generally contraindicated in pregnant women and very young children.</td>
<td>Yellow fever, Dengue, Japanese Encephalitis</td>
</tr>
<tr>
<td>Viral Vectors</td>
<td>Viral-vectored vaccines in advanced trials for other diseases. Commercial platforms exist.</td>
<td>Safety concerns in pregnant women, depending on replication competency.</td>
<td>No</td>
</tr>
<tr>
<td>Recombinant/Subunit</td>
<td>Low risk. Several commercial platforms exist.</td>
<td>Some difficulty depending on the platform, e.g. protein folding. Use of adjuvants may increase concerns.</td>
<td>No</td>
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</table>

**General Considerations on Vaccine Technologies**
# Alignment of USG Candidates

<table>
<thead>
<tr>
<th>Primary Aim</th>
<th>Current USG Candidates</th>
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</table>
| **Aim #1:** Evaluation of candidates to obtain correlate | DNA  
VRC, Partner TBD | mRNA  
VRC, BARDA, Moderna | PIV  
WRAIR, NIAID, BARDA |
| **Aim #2:** Deploy vaccine to “at risk” US population | DNA  
VRC, Partner TBD | mRNA  
BARDA, Moderna |  |
| **Aim #3:** Commercialization of global, durable vaccine | PIV  
WRAIR, NIAID, BARDA, Sanofi | PIV  
BARDA, Takeda | Live Attenuated Zika Chimera  
LID, Butantan |
| **Additional Candidates In Development** | VSV Vectored Vaccine  
NIAID, Harvard, No Partner | Chimera  
CDC, No Partner | VLP  
CDC, No Partner |
| | mRNA  
VRC, GSK | PIV  
BARDA, Butantan |  |

*Other additional candidates are under early development*

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**Note:** Candidates from Aim 2 can be used to address Aim 3
Nucleic Acid Vaccines
NIH Begins Testing Investigational Zika Vaccine in Humans

- DNA vaccine developed by VRC
- Phase I trial to enroll 80 vols ages 18-35 yo
- Initial results expected by the end of 2016
Zika DNA Phase 2b Vaccine Trial Design

A Phase 2b, Randomized, Placebo-Controlled Trial to Evaluate the Safety and Immunogenicity of a Zika Virus DNA Vaccine, VRC-ZKADNA085-00-VP

30+ sites in the US, Caribbean, Central and South America

Target start date: Jan 2017

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<th>Study Schema</th>
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<tr>
<td>Group</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>Total</td>
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* Final interval pending NHP data.
mRNA Vaccine

- Manufactured by Moderna Therapeutics
- Can be used to deliver virtually any gene
- Flexible, rapid manufacturing platform – “plug and play”
- Novel chemistry enables mRNA to elude intracellular innate 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
- Phase I initiated in December 2016
Purified Inactivated Vaccines
Inactivated Zika Vaccines (ZPIV)

- Two candidates in development: Sanofi Pasteur and Takeda
- Formalin-inactivated Zika virus, alum-adjuvanted
- “Proof-of-concept” lot manufactured by WRAIR based on technology used for JEV vaccine
- Vaccine is fully protective in mice and NHP models
- NIAID and WRAIR will conduct five Phase I clinical trials to evaluate safety and immunogenicity
- WRAIR transferring technology to Sanofi Pasteur – accelerating development
- BARDA awarded large development contracts to Sanofi and Takeda to manufacture and license an inactivated Zika vaccine

Adapted from AS Fauci/NIAID
ZPIV Phase I Clinical Trials

- 5 clinical trials planned with ZPIV (Q4 2016-Q1 2017)
  - Four single-site trials testing ZPIV alone
    - St. Louis University (NIAID/VTEU) – Dose sparing, ongoing
    - WRAIR – Prior vaccination with other flavivirus vaccines (YF, JE), ongoing
    - BIDMC (WRAIR) – Alternate dose schedule
    - Puerto Rico (NIAID/VTEU) – Population previously exposed to flavivirus infection
  - One trial testing ZPIV in combination with Zika DNA vaccine prime (VRC)
Live
Attenuated/Chimeric Vaccine
Live Attenuated DV/ZIKV Vaccine
(NIAID Laboratory of Infectious Diseases)

Pentavalent DENV + ZIKV:

- Addition of this ZIKV component provides an immunological advantage for DENV
- ZIKV component may also be suitable as stand-alone vaccine

Pre-clinical development

Phase III underway
# Vaccine Landscape Jan. 2017

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<td>Live Attenuated</td>
<td>Sanofi Pasteur, Institut Pasteur</td>
<td>Valneva, Takeda, Sanofi Pasteur</td>
<td>USG Funded</td>
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<td>Fiocruz, Emergent Biosolutions, Instituto Butantan</td>
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<td>Pharos Biologicals, Invectys</td>
<td>Institut Pasteur</td>
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<td>Viral Vector</td>
<td>VSV with Harvard, Geovax, PaxVax</td>
<td>NewLink Genetics, Themis</td>
<td></td>
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<td>Other</td>
<td>IMV Immunovaccine, Leidos, Codagenix</td>
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USG Funded
Key Challenges/Questions

- **Regulatory/Clinical**
  - Will future disease incidence support evaluation of vaccine efficacy?
  - Which regulatory path will be most feasible?
  - Will human challenge and/or accelerated approval (correlate of protection) facilitate/accelerate evaluation?
  - Will an animal model(s) provide us with sufficient data to support efficacy determinations in humans?
  - Will pre-immunity to other flaviviruses affect Zika vaccine take, and vice versa?

- **Manufacturing**
  - Will manufacturers be able to develop a vaccine fast enough to impact the epidemic?
  - Will previous flavivirus vaccine platforms work well enough to prevent congenital infections?
  - Will the market sustain more than one vaccine?