VACCINE DEVELOPMENT FOR ZIKA VIRUS

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BARDA
NVAC February 02, 2016

Photo credit: CDC/James Gathany
Zika virus

- Zika virus belongs to the family Flaviviridae
- Other flaviviruses include:
  - Dengue, West Nile, yellow fever, Japanese encephalitis
- Enveloped viruses containing positive-strand RNA genome
- First isolated in Zika forest in 1947 with limited human infections in Africa and SE Asia through 2006
- 2007 emerged in Micronesia
- 2013-14 emerged in French Polynesia (>30,000)
Spread of Zika virus in 2015-2016
Travellers from Brazil

Risk of local transmission of Zika virus
- Seasonal
- Year-round

Cities with >1,000 travellers from Brazil, Sep 2014-Aug 2015

Source: Dr K Khan, St Michael’s Hospital, Toronto

Economist.com
Clinical symptoms of Zika virus

- ~80% of cases could be asymptomatic
- Disease symptoms are similar to dengue and chikungunya including a fever, rash, conjunctivitis, and joint pain
- Severe disease outcomes requiring hospitalization and fatalities are rare
- Duration is ~4-7 days
Microcephaly in Brazil

Brazil saw 20 times more microcephaly cases in 2015 than normal.

SOURCE: Brazil Ministry of Health
Zika vaccine need

- There is evidence suggesting Zika virus causal association with GBS in adults, microcephaly, and other central nervous system malformations in fetuses
- There is growing evidence of potential complications attributable to Zika virus infection in pregnant woman
  - Cases of miscarriage and stillbirth with evidence of Zika virus infection in the fetus and newborn
  - Evidence of Zika virus passing the placenta to infect the fetus
- There is evidence of Zika virus in donated blood
- This is potential for sexual transmission of Zika
- Zika virus has demonstrated high attack rates and rapid global spread

There is currently no vaccine available to prevent infection from Zika virus
There is currently no vaccine available to prevent infection from Zika virus, however,

- Vaccine for other flaviviruses have been developed and used for over 70 years
  - Japanese encephalitis vaccine have been available since 1930s and have been made in numerous forms, including live attenuated virus, whole inactivated virus, recombinant and chimeric viruses
  - Yellow fever vaccine was licensed over 60 years ago – 17D live attenuated virus that is still in use today

- Active development programs for dengue and West Nile vaccines have been ongoing for over 30 years, exploring a variety of vaccine platforms to develop vaccines for these flaviviruses

- Experiences gained and vaccine platforms developed for other flaviviruses could be leveraged for Zika vaccine development
## Dengue Vaccine Candidates in Clinical Development

<table>
<thead>
<tr>
<th>Developer</th>
<th>Preclinical development</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Licensure</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK and WRAIR(^1)</td>
<td>TDENV/PIV: purified inactivated vaccine developed using formalin inactivated</td>
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<tr>
<td>Merck</td>
<td>V180: recombinant subunit vaccine developed using wildtype premembrane and truncated envelope protein via expression in the Drosophila S2 cell expression system</td>
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<tr>
<td>NIAID(^2)</td>
<td>TV003/TV005: live attenuated vaccine using wild type strains with genetic mutations</td>
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<tr>
<td>Butantan Institute</td>
<td>TV005: live attenuated vaccine developed using wild type strains with genetic mutations</td>
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<tr>
<td>Panacea Biotec(^3)</td>
<td>DIME100: DNA vaccine developed using premembrane and envelope proteins of DENV1 expressed under control of the human cytomegalovirus promoter/enhancer of the plasmid vector VR1012</td>
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<tr>
<td>NMRC(^4)</td>
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<tr>
<td>Sanofi Pasteur</td>
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<td>Takeda</td>
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</tbody>
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\(^{1}\) GlaxoSmithKline and Walter Reed Army Institute Research.

\(^{2}\) National Institute of Allergy and Infectious Diseases, US NIH: National Institutes of Health. NIAID licensed its strains to several developing country manufacturers on a non-exclusive basis.

\(^{3}\) Both Butantan Institute and Panacea Biotec use NIAID vaccine formulation.

\(^{4}\) US Navy Medical Research and Development.

\(^{5}\) Dengvaxia has been approved by Mexico, the Philippines and Brazil for 9 to 45 year olds living in dengue endemic areas.

*Table last updated January 4, 2016

Courtesy of the Dengue Vaccine Initiative
Zika Virus Vaccine Landscape

Vaccine Platform

**Recombinant Subunit**
- **NOVAVAX**
  - Glycoprotein E Nanoparticle
- **HAWAII BIOTECH**
  - Recomb E Protein in Drosophila S2 cells

**Live Attenuated**
- [National Institute of Allergy and Infectious Diseases](#)
  - Chimeric (S Whitehead) LID

**Plasmid DNA**
- [inovio](#)
- [GENE](#)
  - DNA
- [National Institute of Allergy and Infectious Disease](#)
  - DNA VRC

**Viral Vector**
- [PROFECTUS BIOSCIENCES](#)
  - VSV

Discovery/in vitro  Pre-Clinical  Clinical

Non-Clinical Studies

An accessible version can be found on page 17

February 01, 2016
Vaccine & Drug Development is still Expensive, Risky and Lengthy

**PHASES**
- Discovery
- Preclinical Development
- Phase I
- Phase II
- Phase III
- Licensure
- Production & Delivery

**PROBABILITY OF SUCCESS TO LICENSURE**

- Licensed Product
  - 1-3%
  - 5-17%
  - 10-25%
  - 18-35%
  - 45-70%
  - 90%

**PRODUCT PIPELINE**

- Valley of Death
- Ebola MCMs 2014 - 2016
- MERS-COV MCMs 2012 - 2016
- ZIKV MCMs 2015 - 2016

**TIME & PHASE COST**

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<tr>
<td>3-7 yr</td>
<td>$100M - 130M</td>
</tr>
<tr>
<td>0.5-2 yr</td>
<td>$60 - 70M</td>
</tr>
<tr>
<td>1-2 yr</td>
<td>$70M - 100M</td>
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<tr>
<td>2-3.5 yr</td>
<td>$130M - 160M</td>
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<tr>
<td>2.5-4 yr</td>
<td>$190M - 220M</td>
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<td>1-2 yrs</td>
<td>$18M - 20M</td>
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*Project BioShield: $11.8B, BARDA: $540M, Project BioShield: $5.6B*
Zika virus vaccines R&D
Key Questions/Concerns

- Safety Concerns
  - Pre-existing immunity to Zika, Yellow Fever, Dengue, and vaccine platforms
  - Is there a potential for antibody dependent enhancement?

- Intended Usage
  - General usage (GUP) and post-exposure (PEP) prophylaxis
  - Special populations – Pregnant women, WoCBA, infants, children

- Vaccine Properties
  - Vaccine components (e.g. E protein, whole virus, adjuvants, other viruses)
  - Level and type of elicited immunity
  - Kinetics of vaccine immunity
  - Duration of immunity (Heterologous Prime/Boost Approach)
  - Routes of administration
  - Platform technology maturity
  - Manufacturing process maturity (potency assays, vaccine stability)

- Zika virus natural and adaptive immunity in animals and humans
  - Correlates of protective immunity
  - Immunogenicity and protection study design

Assays & reagents
Upcoming workshops

- 2-5 February 2016, Nicaragua: Sub-regional Laboratory Training Workshop for Zika detection and sub-regional training workshop on Aedes aegypti control
- 15 February 2016, Puerto Rico: Experts Meeting on Zika regional laboratory surveillance
- 16-17 February 2016, Puerto Rico: WHO Dengue Collaborating Centers Meeting
- 18-19 February 2016, Puerto Rico: Meeting of the Latin American Network on Arboviruses Diagnostic (RELDA)
- 1-2 March 2016, Washington DC: PAHO Meeting on the Zika virus research agenda and its public health implications in the Americas
- 28-29 March 2016, Washington DC: HHS Stakeholders meeting on Zika virus and Medical Countermeasures
Summary

- We are at the forefront of this outbreak situation and many questions remain unanswered
  - Careful prioritization and coordination is needed to address these questions
  - International collaborations will be critical to accelerating the response

- Zika viruses will continue to spread throughout the Americas and remain a human health threat

- WHO declared a Public Health Emergency of International Concern on February 1, 2016
  - Urgent Priority must be considered to better understand the potential link between Zika virus and congenital malformations and other neurological disorders
  - Diagnostics must be developed to be able to detect Zika virus infection to contribute to surveillance and disease mitigation
  - Systems must be developed and validated to ensure safety of blood supply
  - Risk communications must be developed and disseminated

- There are currently no commercially approved vaccines or therapeutics for Zika

- Vaccines development for other flaviviruses should be leveraged to potentially accelerate the Zika virus vaccine
  - Caution should be given to safety concerns observed from other flavivirus vaccine efforts
  - Careful consideration should be given to the development of vaccines indicated for pregnant women, women of childbearing age, neonates and children
Contact us

- Request a Tech Watch meeting through [www.medicalcountermeasures.gov](http://www.medicalcountermeasures.gov)
  - Contact Jonathan Seals, Director Strategic Science and Technology Division, [jonathan.seals@hhs.gov](mailto:jonathan.seals@hhs.gov)

- BARDA Broad Agency Announcement
  - [BAA-16-100-SOL-00003](https://www.medicalcountermeasures.gov) will support innovation through development of platform technologies that enhance capabilities for development and manufacturing of MCMs.
  - Technical Point of Contact: Mark Craven; [mark.craven@hhs.gov](mailto:mark.craven@hhs.gov)

- NIH Federal Funding Opportunity
  - [NOT-AI-16-026](https://www.medicalcountermeasures.gov) will support high-priority Zika virus research areas detailed in the solicitation
Xó, ZIKA!!

Boston Globe
Silvia Izquierdo/AP
# Zika Virus Vaccine Landscape

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