OVERVIEW: ZIKA VACCINES IN DEVELOPMENT

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Biomedical Advanced Research and Development Authority (BARDA)

Office of the Assistant Secretary for Preparedness and Response (ASPR)

February 8, 2018

National Vaccine Advisory Committee

Washington, DC

Resilient People. Healthy Communities. A Nation Prepared.

Photo credit: CDC/James Gathany

Zika Virus

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

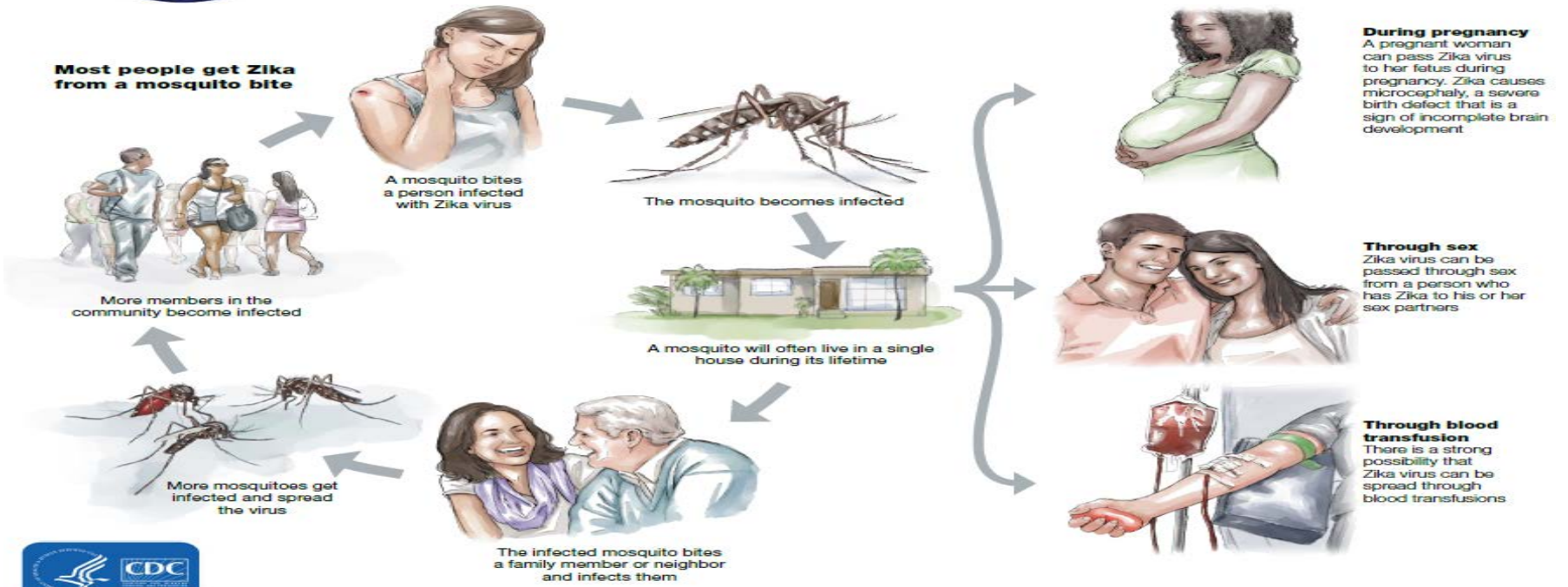
Brief history

- 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



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)**

- https://www.cdc.gov/pregnancy/zika/testing-follow-up/zika-syndrome-birth-defects.html
- http://www.paho.org/hq/index.php?option=com_content&view=article&id=12390&Itemid=42090&lang=en

Prevention of ZIKV Infection

There is currently no licensed ZIKV vaccine available, however…

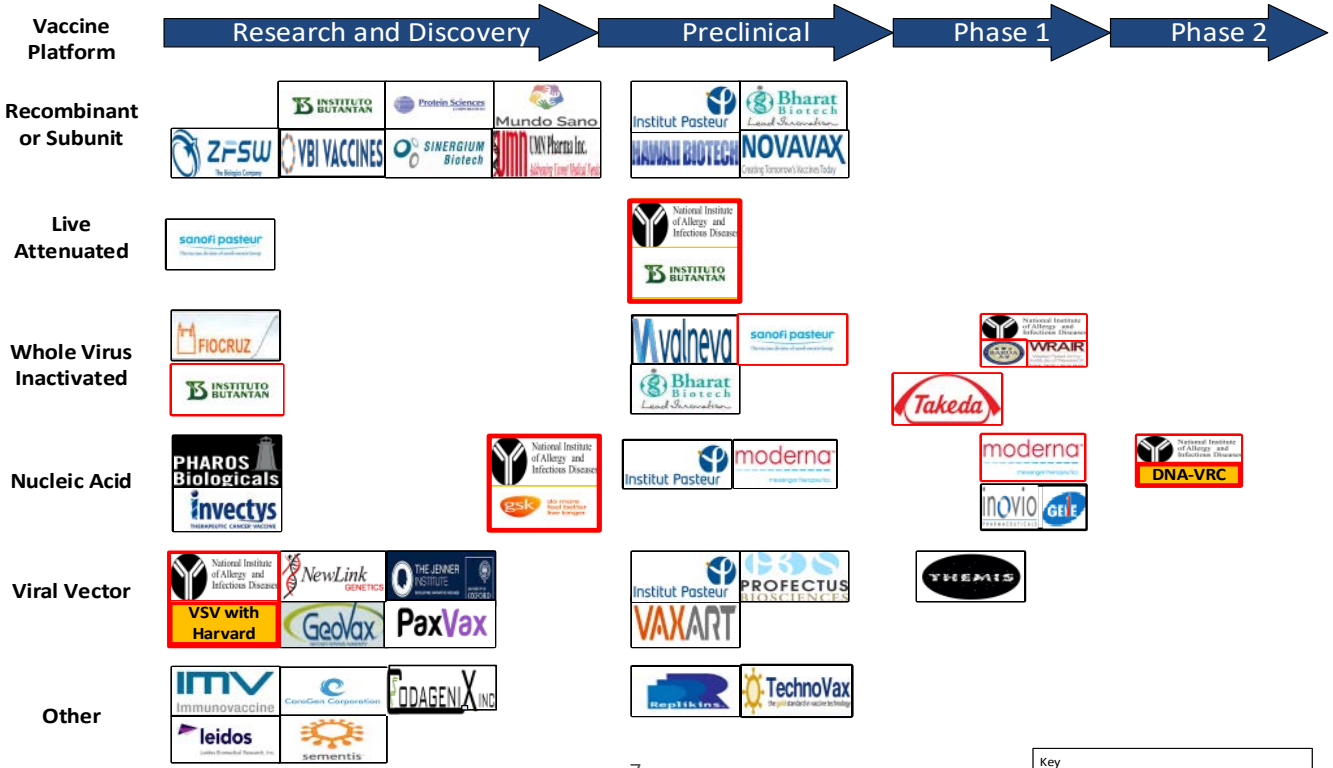
- Vaccines for other flaviviruses have been developed and used for over 70 years
- Active development programs for Dengue and West Nile vaccines have been ongoing for over 30 years; however, knowledge of Zika virus was limited at the outset of the epidemic
- Past experience was leveraged for ZIKV vaccine 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

Vaccine Landscape
Feb. 2016

Vaccine Platform	Research and Discovery → Preclinical → Phase 1 → Phase 2
Recombinant or Subunit	NOVAVAX; HAWAII BIOTECH
Live Attenuated	National Institute of Allergy and Infectious Disease; INSTITUTO BUTANTAN
Whole Virus Inactivated	
Nucleic Acid	National Institute of Allergy and Infectious Disease; DNA-VRC
Viral Vector	PROFECTUS BIOSCIENCES
Other	

Key
Supported by USG
Version: 1-17-18, 2016

Vaccine Landscape
Jan. 2018

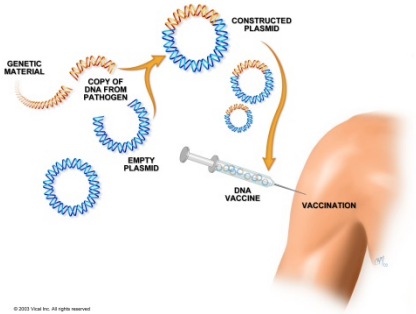


VACCINES IN CLINICAL DEVELOPMENT

VRC DNA Vaccine Milestones

Phase I Clinical Trials – 2 candidates: VRC 5288 and VRC 5283

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



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 3017
  - 11/20 sites activated

Industry partner identified for commercialization

VRC 705: Phase 2/2b

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 2b							
Part A							
Group	**n:**	**Total Dose**	**Number of Injections**	**Number of limbs**	**Day 0**	**Week 4**	**Week 8**
1	30	4 mg	2	2 limbs (both arms)	DNA	DNA	DNA
2	30	4mg	4	4 limbs (arms and legs)	DNA	DNA	DNA
3	30	5 mg	4	4 limbs (arms and legs)	DNA	DNA	DNA
Total	**90**	**Part A Enrollment: Complete**					
Part B **Regimen: 4mg Split Dose by PharmaJet:** Vaccination at 0, **4, 8 weeks**							
Group	**n=**	**Total Dose**	**Number of Injections**	**Number of limbs**	**Day 0**	**Week 4**	**Week 8**
4	1200	4 mg	2	2 limbs (both arms)	DNA	DNA	DNA
5	1200	N/A	2	2 limbs (both arms)	Placebo	Placebo	Placebo
Total	**2400**	***Blinded evaluation of case rates to increase sample size as needed***					

Part B Enrollment as of 1/30: 248

Courtesy: G. Chen, VRC

Inovio Pharmaceuticals
DNA Vaccine

The NEW ENGLAND JOURNAL of MEDICINE

October 4, 2017

Safety and Immunogenicity of an Anti–Zika Virus DNA Vaccine — Preliminary Report

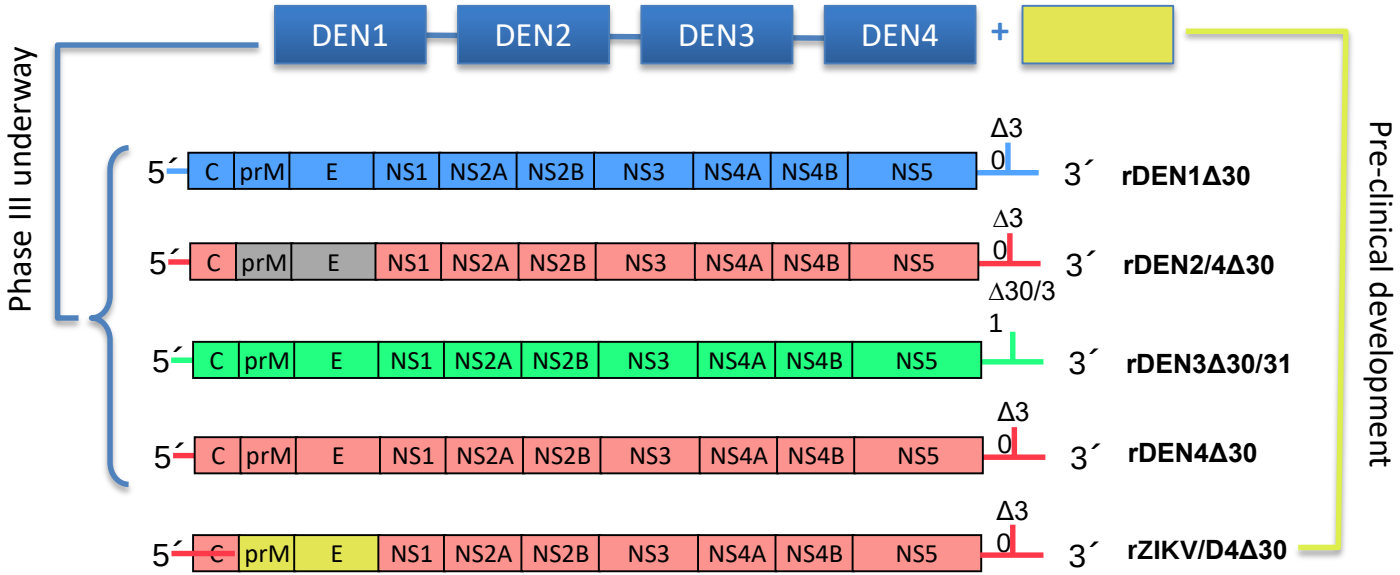
Pablo Tebas et al.

- 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

NIAID Laboratory of Viral Diseases

Pentavalent DENV + ZIKV:



Courtesy: S. Whitehead, LVD

LAV Candidate

NIAID Laboratory of Viral Diseases

#	Deliverable	Timeline (CY)	DONE? √
1	Virus construction, seed virus generation, pre-clinical evaluation	Q2 2017	✓
2	Manufacturing of Phase 1 and 2 CTM's at Charles River Laboratories; Release testing	June – Nov 2017	✓
3	IND submission	Feb 2018	Initiated
4	Phase 1 - Monovalent	March 2018	
5	Phase 2 - Pentavalent	May 2018	
6	Phase 2a – Butantan Institute Bridging, Monovalent, Pentavalent	Pending Q4 2018	
7	Phase 2b – Butantan Institute	Pending 2019	

Courtesy: S. Whitehead, LVD

Moderna 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

ASPR Assistant Secretary for Preparedness and Response | WRAIR Walter Reed Army Institute of Research | NIH National Institute of Allergy and Infectious Diseases

Adapted from AS Fauci/NIAID

ZPIV Phase I Clinical Trials

THE LANCET

Published Online Dec. 4, 2017

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

Themis Measles Recombinant Vector

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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www.Medicalcountermeasures.gov