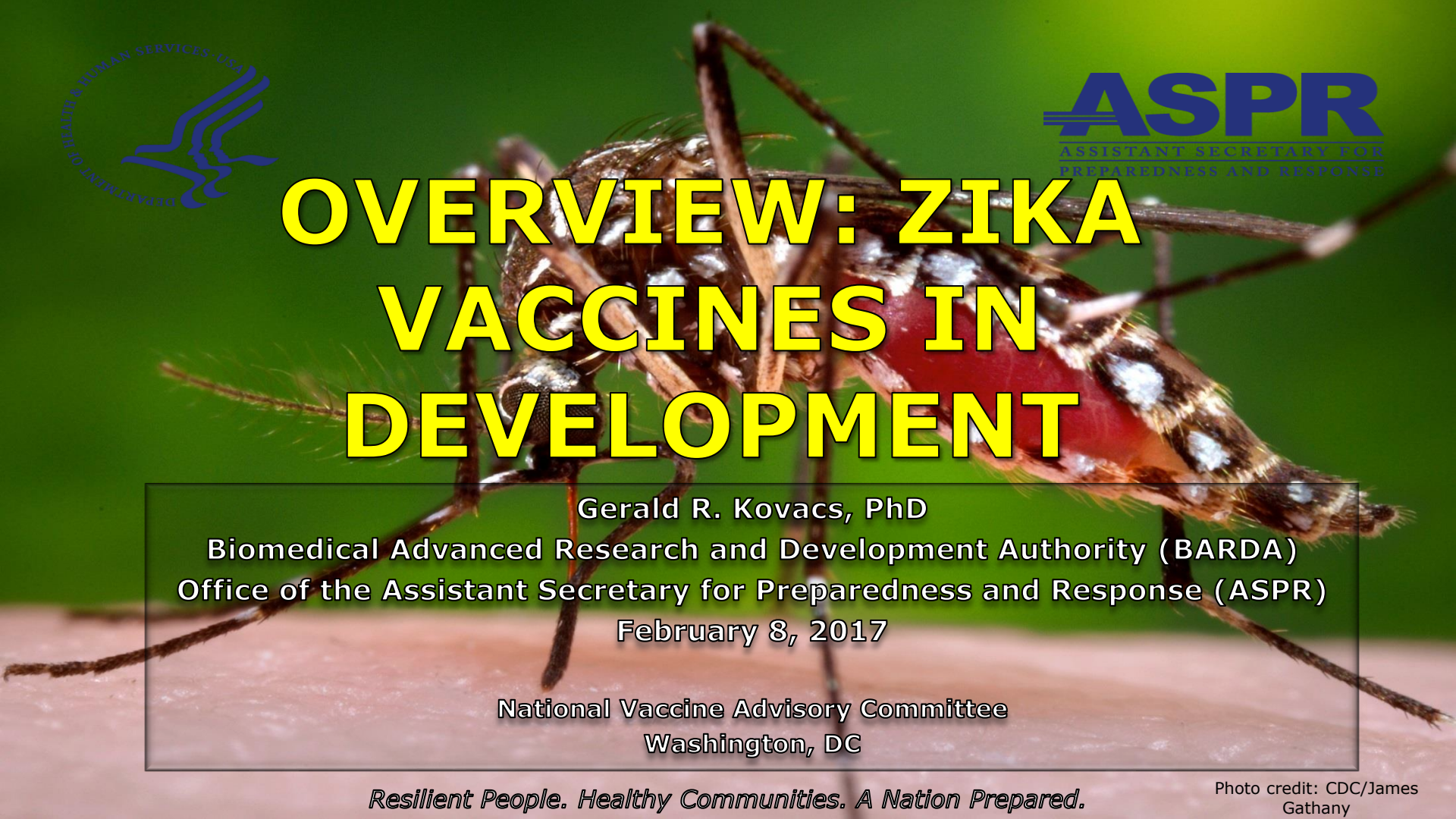


OVERVIEW: ZIKA VACCINES IN DEVELOPMENT

Gerald R. Kovacs, PhD
Biomedical Advanced Research and Development Authority (BARDA)
Office of the Assistant Secretary for Preparedness and Response (ASPR)
February 8, 2017

National Vaccine Advisory Committee
Washington, DC

Resilient People. Healthy Communities. A Nation Prepared.

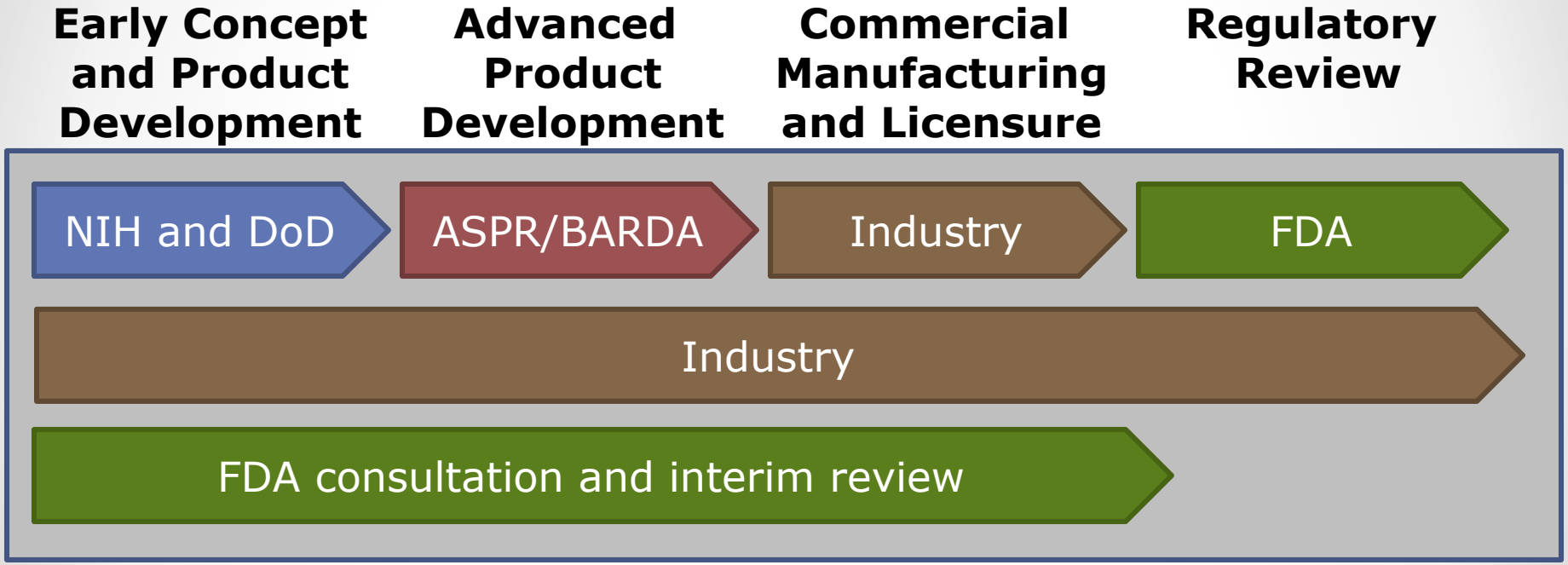
Photo credit: CDC/James Gathany

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



Adapted from AS Fauci/NIAID

Vaccine Landscape Feb 2016

Platform	Research & Discovery	Preclinical	Phase 1
Recombinant or Subunit	NOVAVAX Creating Tomorrow's Vaccines Today; HAWAII BIOTECH		
Live Attenuated	National Institute of Allergy and Infectious Diseases; INSTITUTO BUTANTAN		
Whole Virus Inactivated			
Nucleic Acid	National Institute of Allergy and Infectious Diseases; DNA-VRC		
Viral Vector	PROFECTUS BIOSCIENCES		
Other			

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

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

Alignment of USG Candidates

Primary Aim	Current USG Candidates		
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		

Note: Candidates from Aim 2 can be used to address Aim 3

ASPR
ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

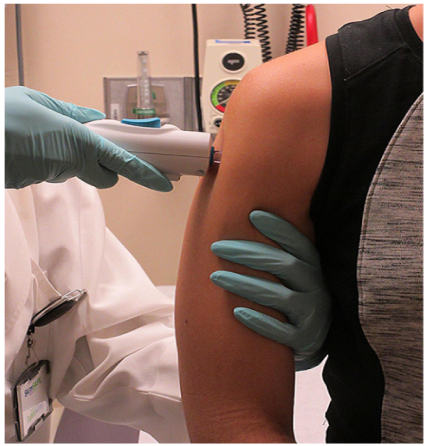
Nucleic Acid Vaccines

National Institutes of Health
Turning Discovery Into Health

FOR IMMEDIATE RELEASE
Wednesday, August 3, 2016

News Release

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

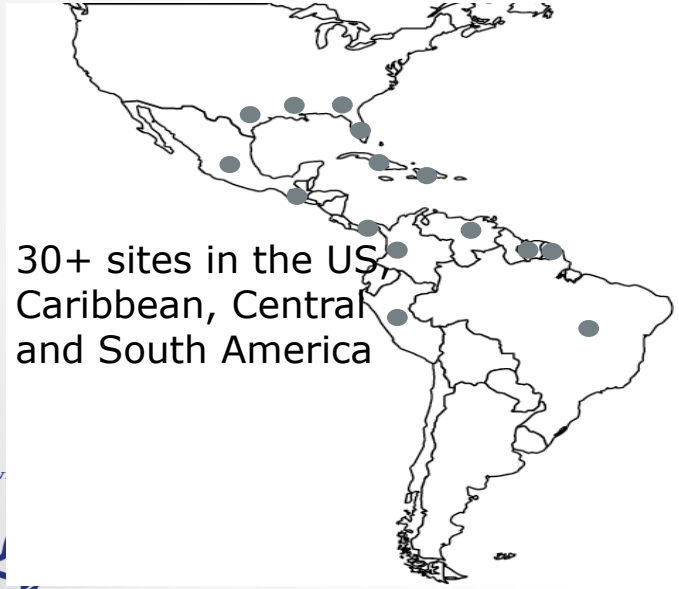
AS Fauci/NIAID

Link to Web Page

ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

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



Study Schema			
Group	Subjects	Day 0	Week 4
1	1200	ZIKV DNA	ZIKV DNA
2	1200	Placebo	Placebo
Total	2400	ZIKV DNA (4 mg/1 mL) and placebo injections (1 mL) are administered IM * Final interval pending NHP data.	

Target start date: Jan 2017

AS Fauci/NIAID

ASPR
ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

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

ASPR
ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

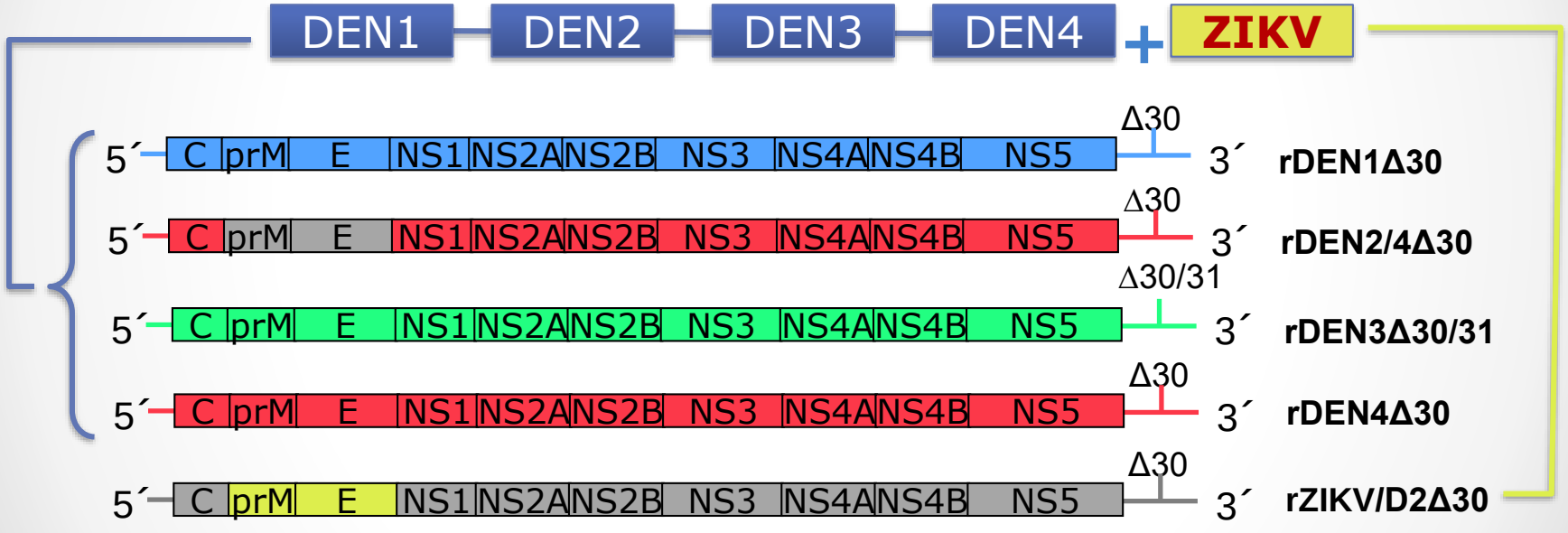
ZPIV Phase I Clinical Trials

- 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

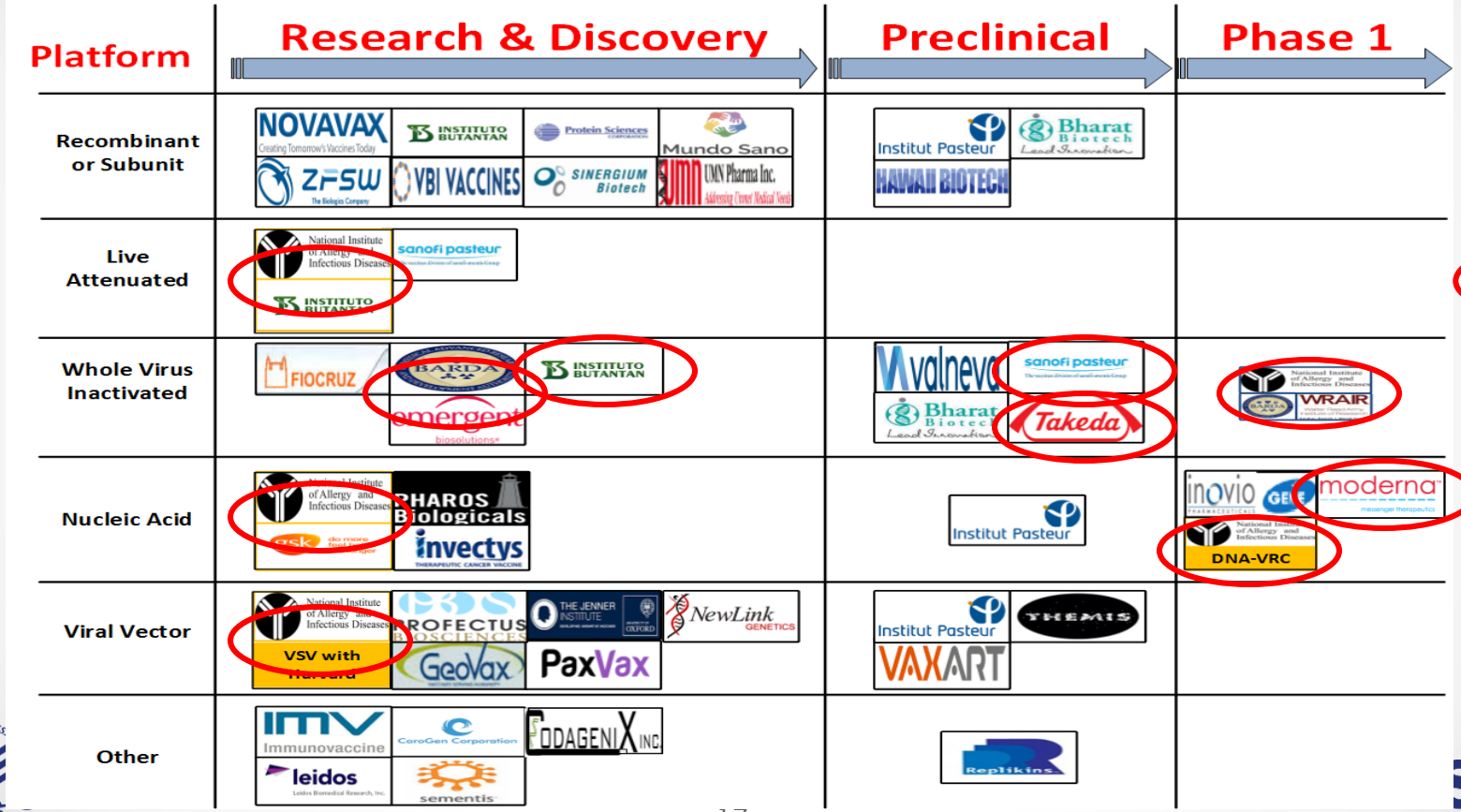
Live Attenuated DV/ZIKV Vaccine
(NIAID Laboratory of Infectious Diseases)

Pentavalent DENV + ZIKV:

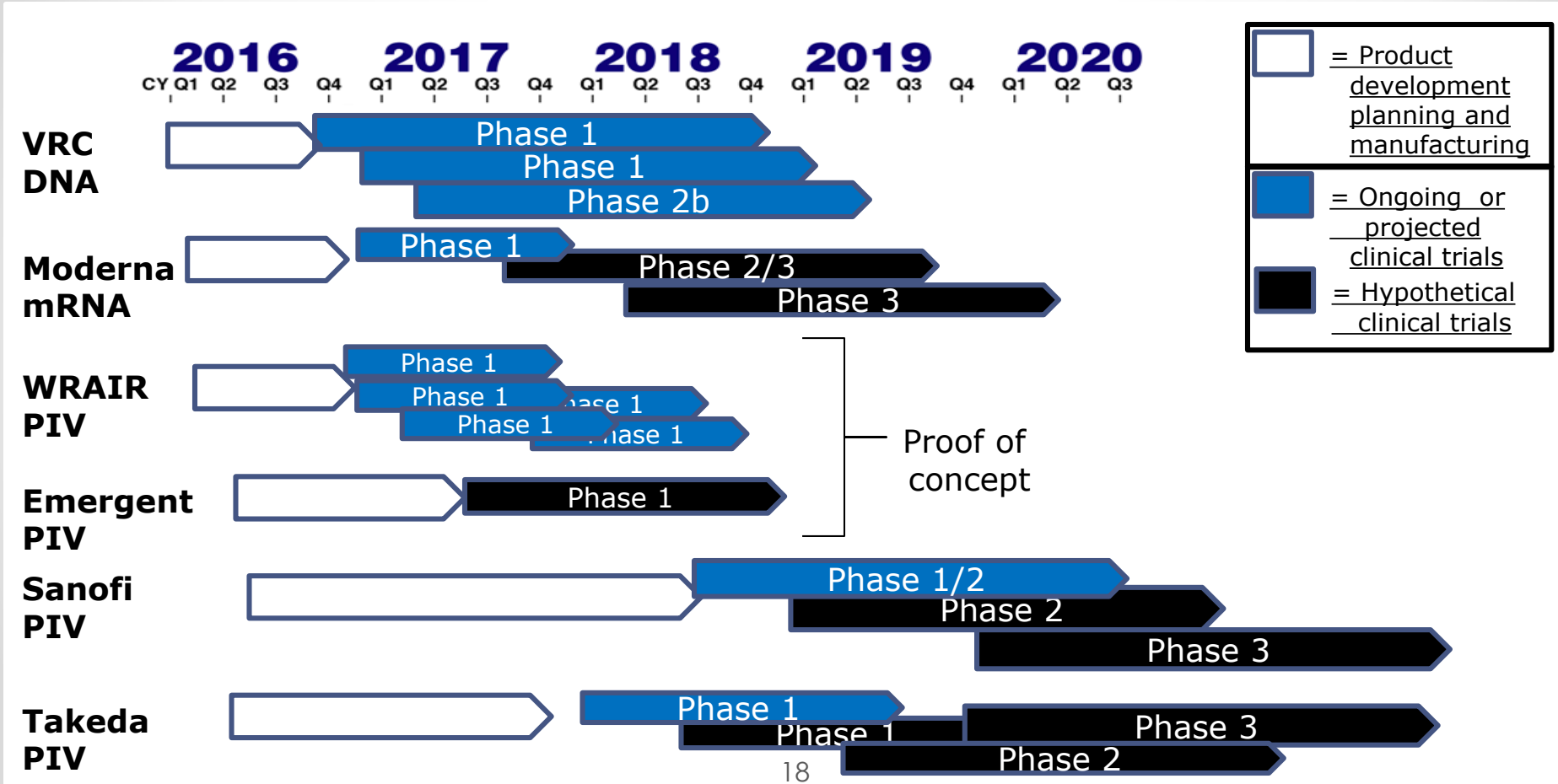


- Addition of this ZIKV component provides an immunological advantage for DENV
- ZIKV component may also be suitable as stand-alone vaccine

Vaccine Landscape Jan. 2017



USG Zika Vaccines Trials



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?