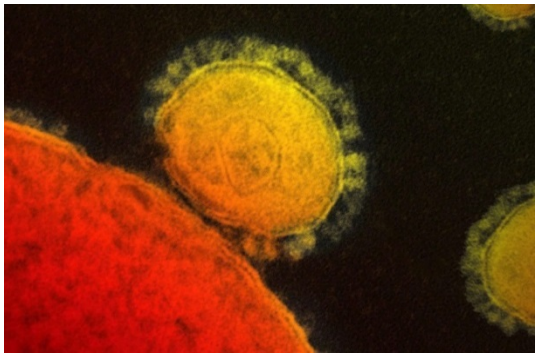
TACKLING EMERGING AND RE-EMERGING INFECTIOUS DISEASES



Rick Bright, PhD

Director
Influenza and Emerging Diseases
Biomedical Advanced Research and Development Authority
Assistant Secretary for Preparedness and Response
US Department of Health and Human Services

Developing Countries Vaccine Manufacturing Network Meeting
Buenos Aires, Argentina
25 October 2016

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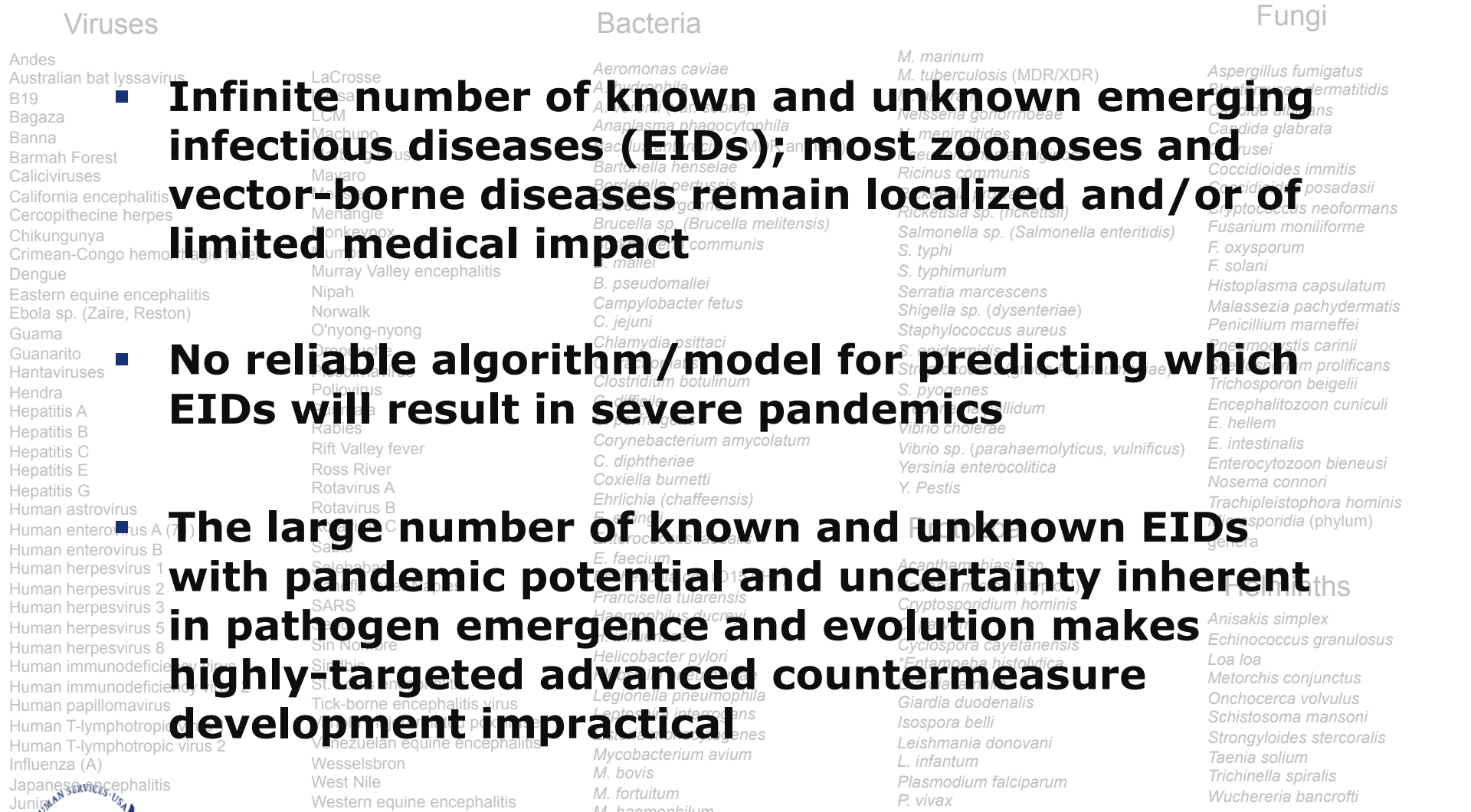
Emerging Infectious Diseases



- **Infinite number of known and unknown emerging infectious diseases (EIDs); most zoonoses and vector-borne diseases remain localized and/or of limited medical impact**
- **No reliable algorithm/model for predicting which EIDs will result in severe pandemics**
- **The large number of known and unknown EIDs with pandemic potential and uncertainty inherent in pathogen emergence and evolution makes highly-targeted advanced countermeasure development impractical**

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Emerging Infectious Disease: Charge to BARDA

- The Pandemic and All-Hazards Preparedness Act- Title IV, sec. 401 calls for the Secretary to "**integrate … emerging infectious disease requirements with the advanced research and development strategic initiatives for innovation, and the procurement of qualified countermeasures and qualified pandemic and epidemic products**"

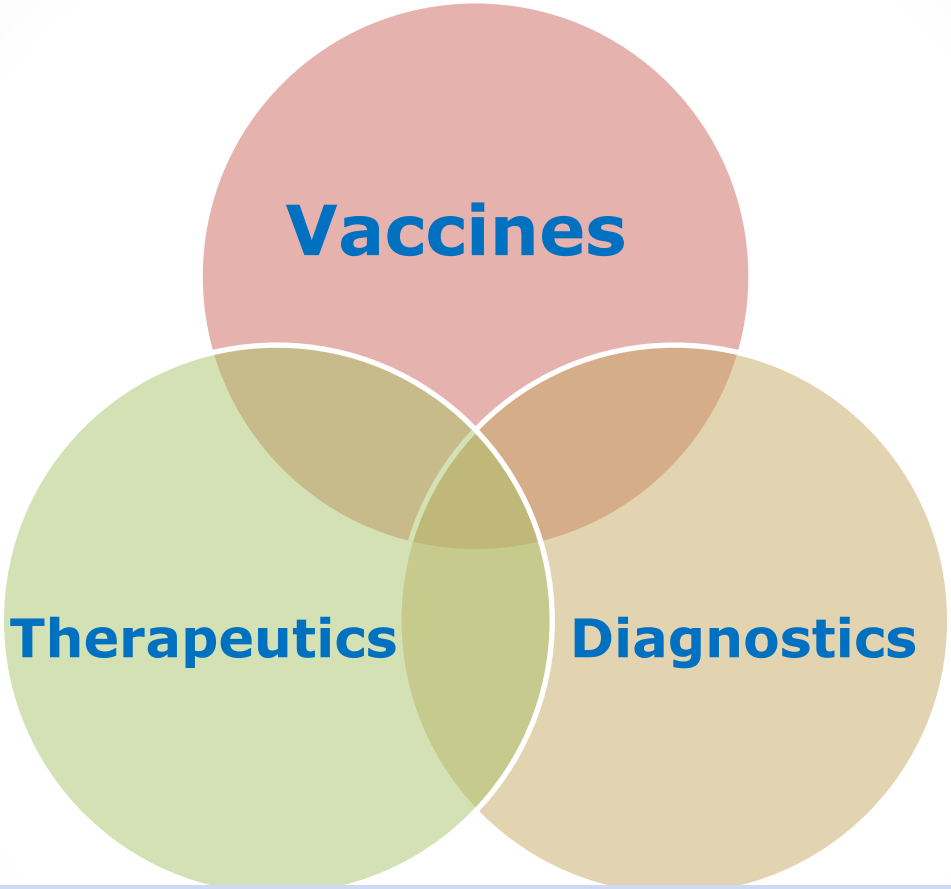
- Emerging infectious diseases fall within the charge of the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE)

- BARDA has assembled the staff, gathered the expertise, and built the program structure for dealing with Pan Flu and CBRN threat preparedness, and is well-positioned to apply this knowledge base to EID threat preparedness

Multi-hazard advanced development strategies

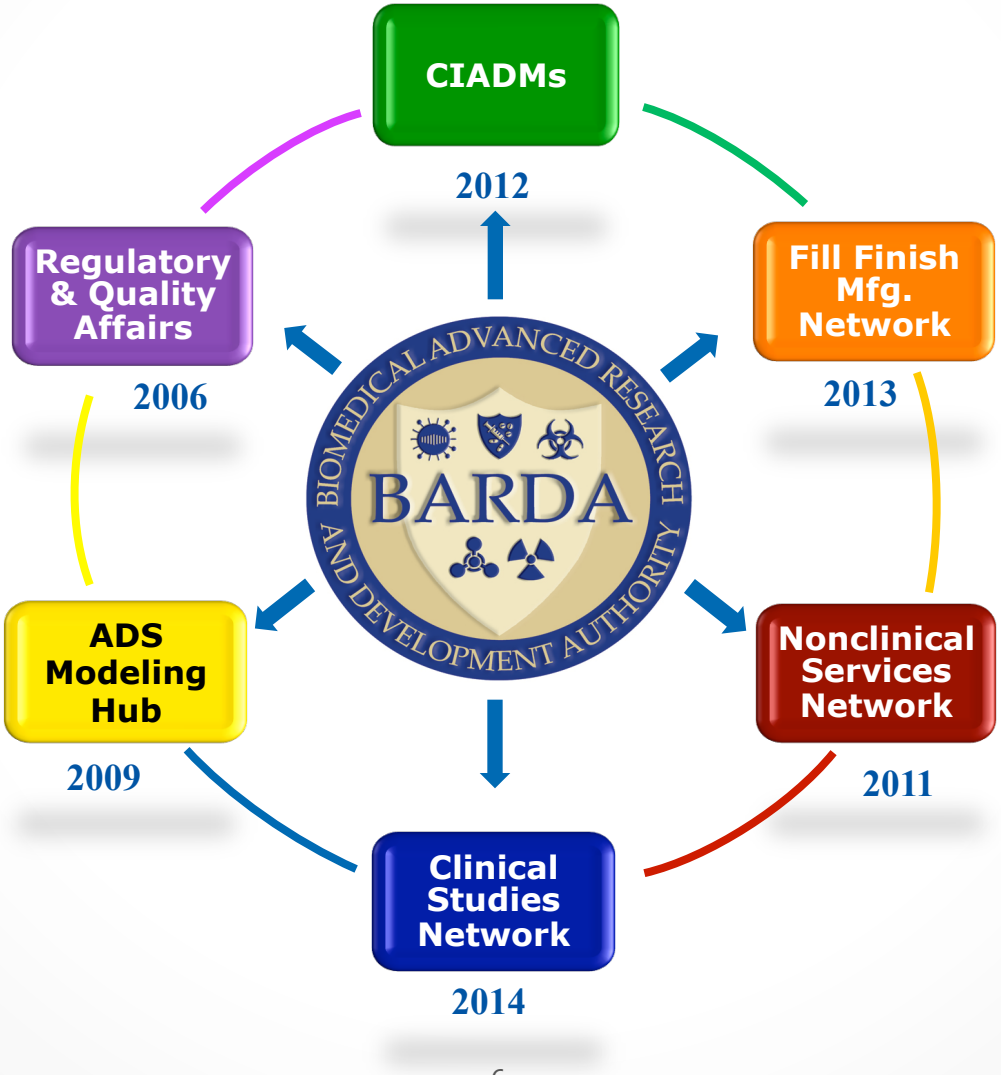
- Approach preparedness against unpredictable disease threats through multi-hazard strategies
- Within multi-hazard strategies, particular focus can be given to pathogens which currently pose a high threat (quantifiable assessment)
- Complements and strengthens current BARDA programs, initiatives, and capabilities

Emerging Threats Require An Integrated Response

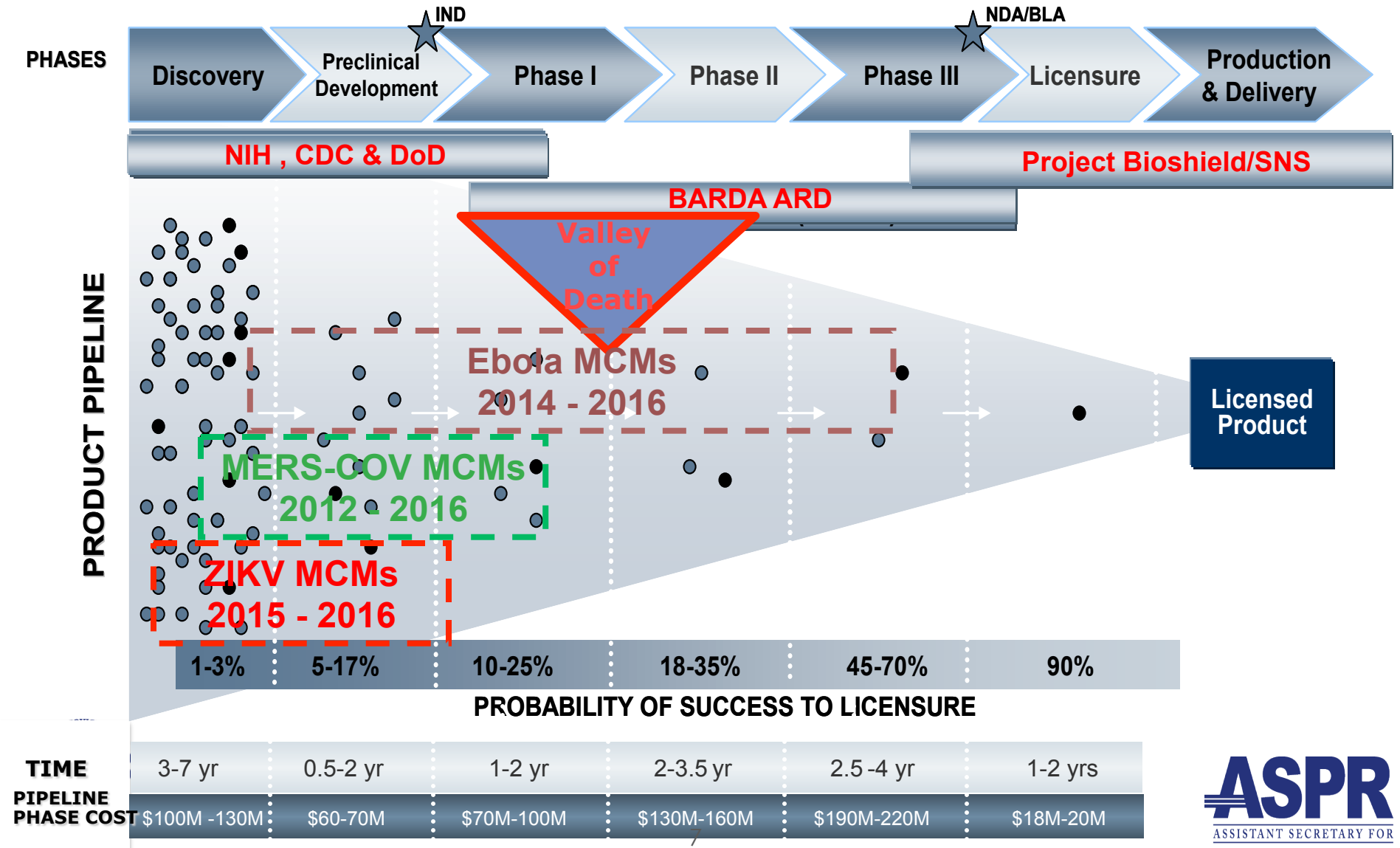


Early Detection → Early Response → Saving Lives

Emerging Threats Require a Coordinated Response of Supporting Systems



Vaccine & Drug Development is Expensive, Risky and Lengthy



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BARDA EID Consideration Framework

Threat-Based Criteria:

Is the pathogen / pathogen group capable of being a *public health threat* to the U.S.?
-documented threat of emergence
-highly transmissible
-rapid and uncontrollable spread
-high morbidity/mortality rates

Yes

Countermeasure-Based Criteria:

No or few developed, licensed, and highly effective MCMs already on the market?

Need for additional incentive for Industry to rapidly develop MCMs?

Need for advanced development MCM support (BARDA/CBRN, Global Health NGOs)?

Yes

CONTINUAL RE-ASSESSMENT OF THREATS, COUNTERMEASURES, AND STATE OF THE SCIENCE

Scientific criteria:

Is the level of basic MCM research, proof of concept, and basic development sufficient to progress to advanced development?

Public Health need for BARDA expertise, resources, and capabilities?

Yes

CANDIDATE EIDs FOR BARDA ADVANCED DEVELOPMENT

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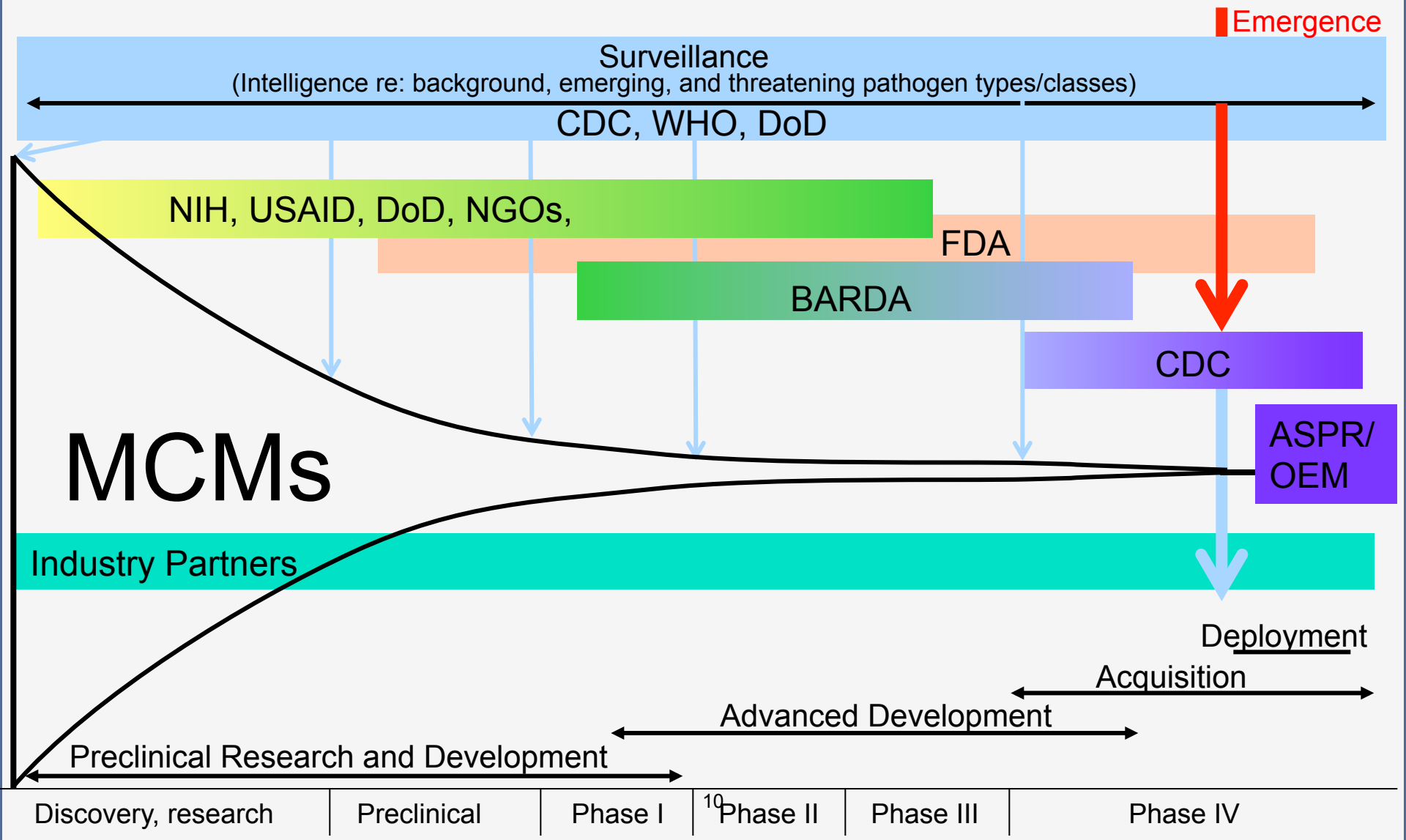
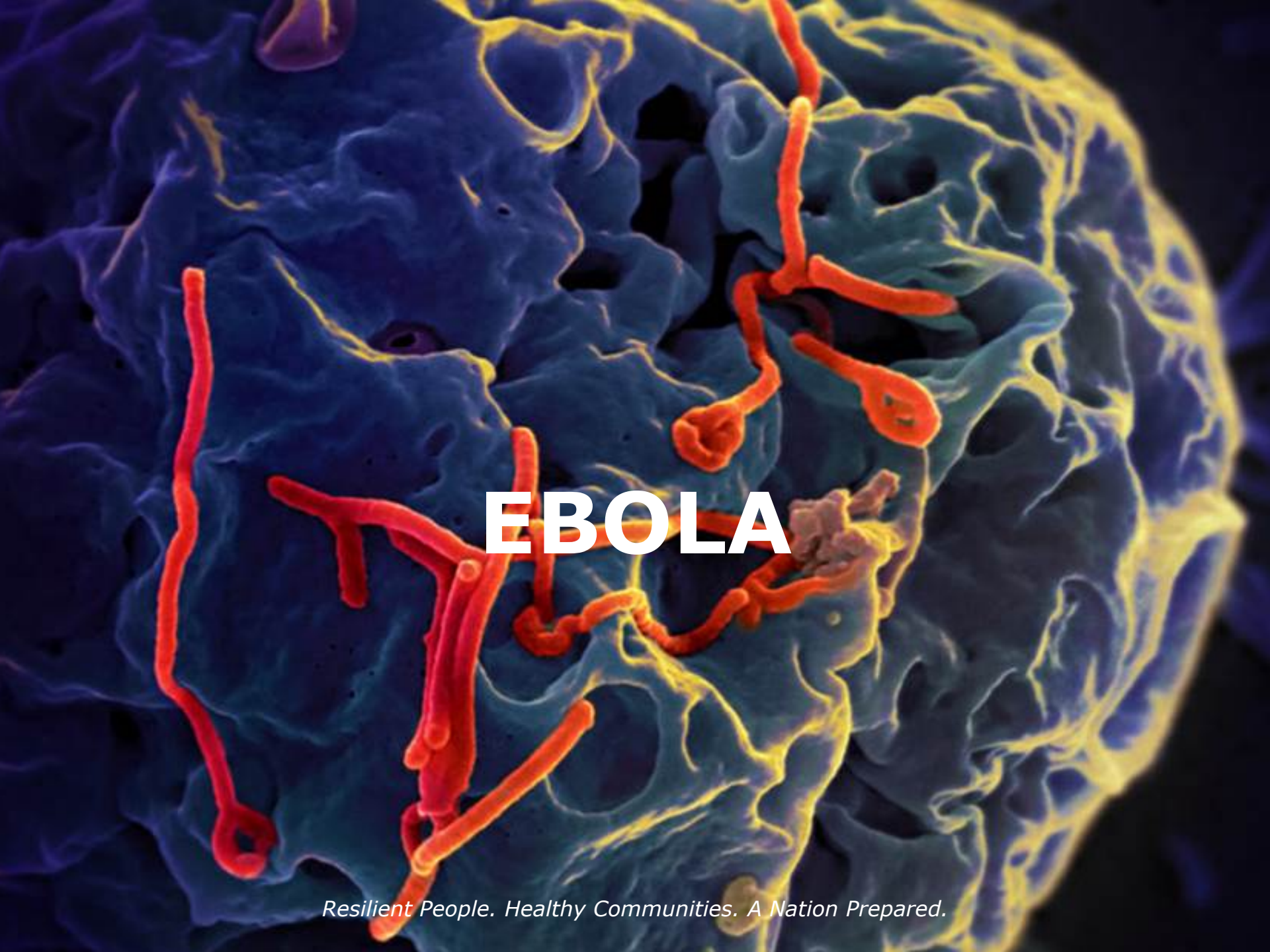
Emerging Infectious Diseases Program Align with Broad BARDA Initiatives

- Build Emerging Disease requirements into solicitations for general, flexible, or adaptive technologies and countermeasures, including:
  - Personal Protective Equipment
  - Broad-spectrum Therapeutics
  - Platform Technologies
    - Vaccines
    - Diagnostics
  - Enhancing Manufacturing Capacity

Emerging Infectious Disease MCM Continuum





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The Worst Ebola Outbreak On Record

Total Cases	Confirmed Cases	Deaths
28,652	15,261	11,325

Table above includes 513 deaths of healthcare and frontline workers

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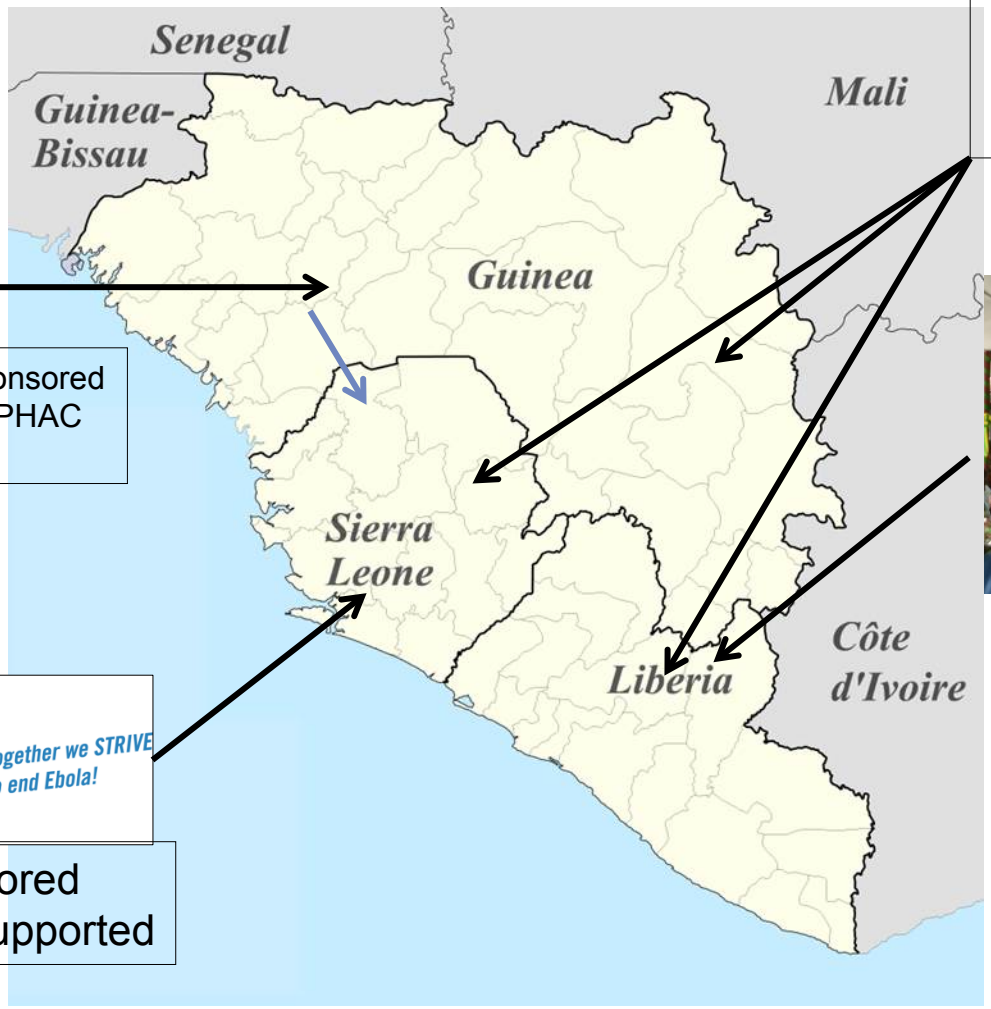
Development and Evaluation of Ebola MCMs Has Been a Coordinated Effort

- Development
  - NIH
  - DoD
  - BARDA
  - FDA
  - PHAC
  - Industry partners
- Evaluation
  - NIH
  - DoD
  - CDC/OID/NCIRD
  - FDA
  - BARDA
  - WHO
  - NGOs
  - Industry partners
  - Liberia, Sierra Leone, and Guinea regulatory authorities

Three, Large, Phase II/III Vaccine Trials and One Therapeutic Trial



Prevail II
NIH Sponsored and Supported

Campagne Ebola Ça Suffit

MSF, WHO, and Guinea Govt. Sponsored
WHO, WT, MSF, RC of Norway, PHAC Supported

NIH Sponsored and Supported

STRIVE
Together we STRIVE to end Ebola!
Sierra Leone Trial to Introduce a Vaccine against Ebola

CDC Sponsored
CDC/BARDA Supported

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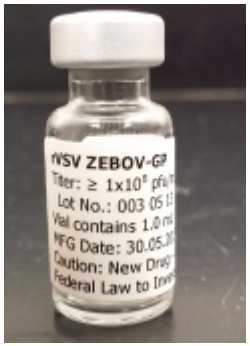
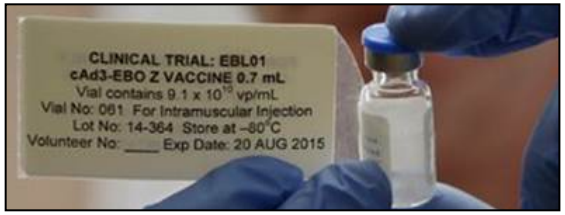
Ebola Vaccines

- Profectus BioSciences
  - Recombinant vesicular stomatitis virus (rVSV) vectored monovalent vaccine against Ebola-Zaire
    - Currently in Phase I and program will transition to DoD

- NewLink/Merck
  - Recombinant vesicular stomatitis virus vectored monovalent vaccine against Ebola
    - Has been evaluated in Phase II/III studies in Liberia, Sierra Leone and Guinea
- GlaxoSmithKline
  - Chimp Ad3 vectored monovalent vaccine against Ebola
    - One of the first Ebola vaccines to enter clinical trials
    - Has been evaluated in a Phase II/III study in Liberia



- Crucell/Bavarian Nordic
  - HuAd26 prime with MVA trivalent, heterologous boost
    - Has been evaluated in Phase I study – Oxford
    - Multiple Phase II studies



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Ebola Therapeutics

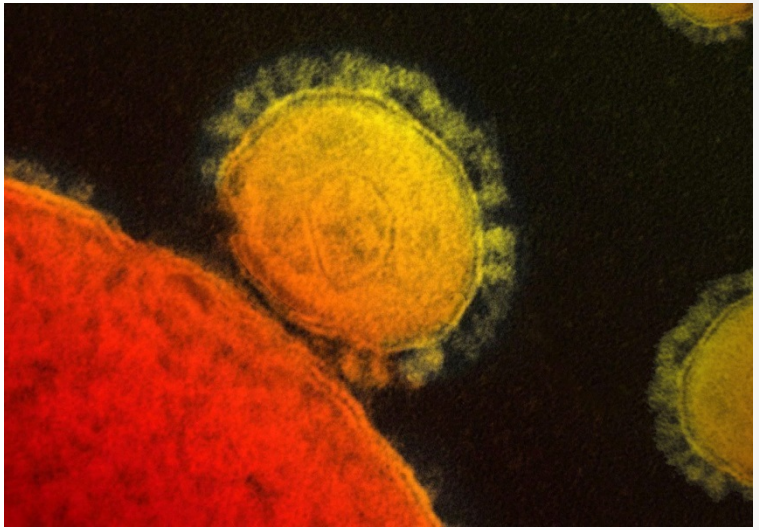
- Mapp Bio
  - Developing a cocktail of chimeric monoclonal antibodies (ZMapp)
    - Has been evaluated in a Phase II/III efficacy trial (PREVAIL II)
    - Trial was halted – trend toward efficacy but failed to meet endpoints
- Regeneron
  - Developing a cocktail of fully human monoclonal antibodies
    - Currently in Phase I
- BioCryst
  - Developing a small molecule drug (BCX4430) – potential broad spectrum
    - Currently in Phase I
- Genentech/Emergent (CIADM)
  - Developing a cocktail of humanized ZMapp clones in CHO cells
    - Currently being evaluated in non-clinical studies
- BARDA supported small-scale efforts with Medicago and Fraunhofer


MERS CORONAVIRUS

Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

- MERS-CoV belongs to the family Coronaviridae
- Other coronaviruses include:
  - SARS-CoV
  - Human coronavirus 229E & OC43
- Enveloped viruses containing nonsegmented, positive-strand RNA genome
- Two outbreaks of novel coronaviruses causing acute respiratory distress syndrome and high death rates this century

MERS-CoV

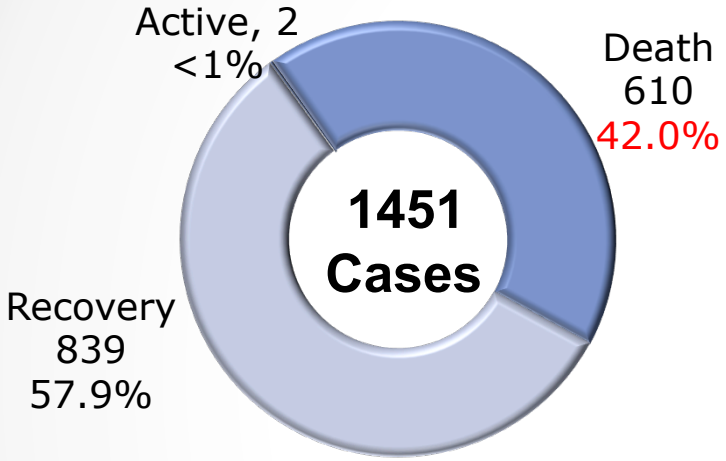


South Korea Wedding during the MERS outbreak

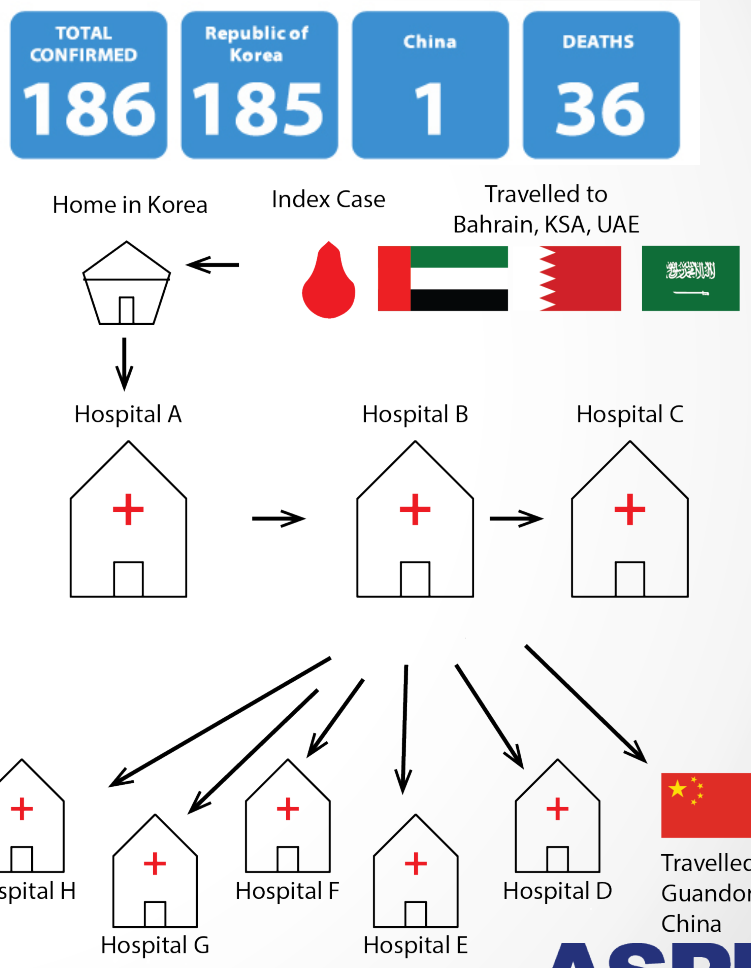
There are currently no licensed or approved vaccines or treatments for Coronaviruses

MERS-CoV Outbreaks in Saudi Arabia and South Korea

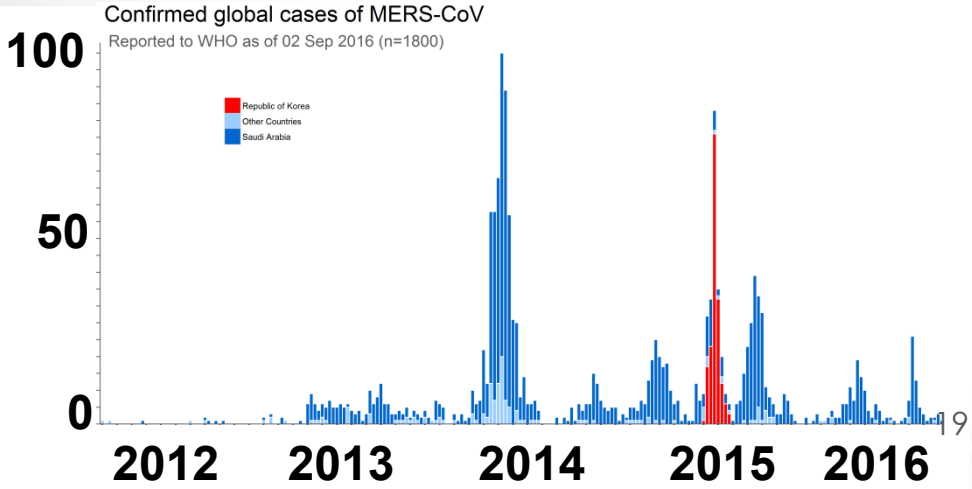
Saudi Arabia since 2012



South Korea, 2015



Global cases per week



http://www.jidc.org/index.php/journal/article/view/7278
http://www.who.int/emergencies/mers-cov/epi-2-september-2016.png?ua=1 http://www.moh.gov.sa/en/CCC/PressReleases/Pages/statistics-2016-09-11-001.aspx

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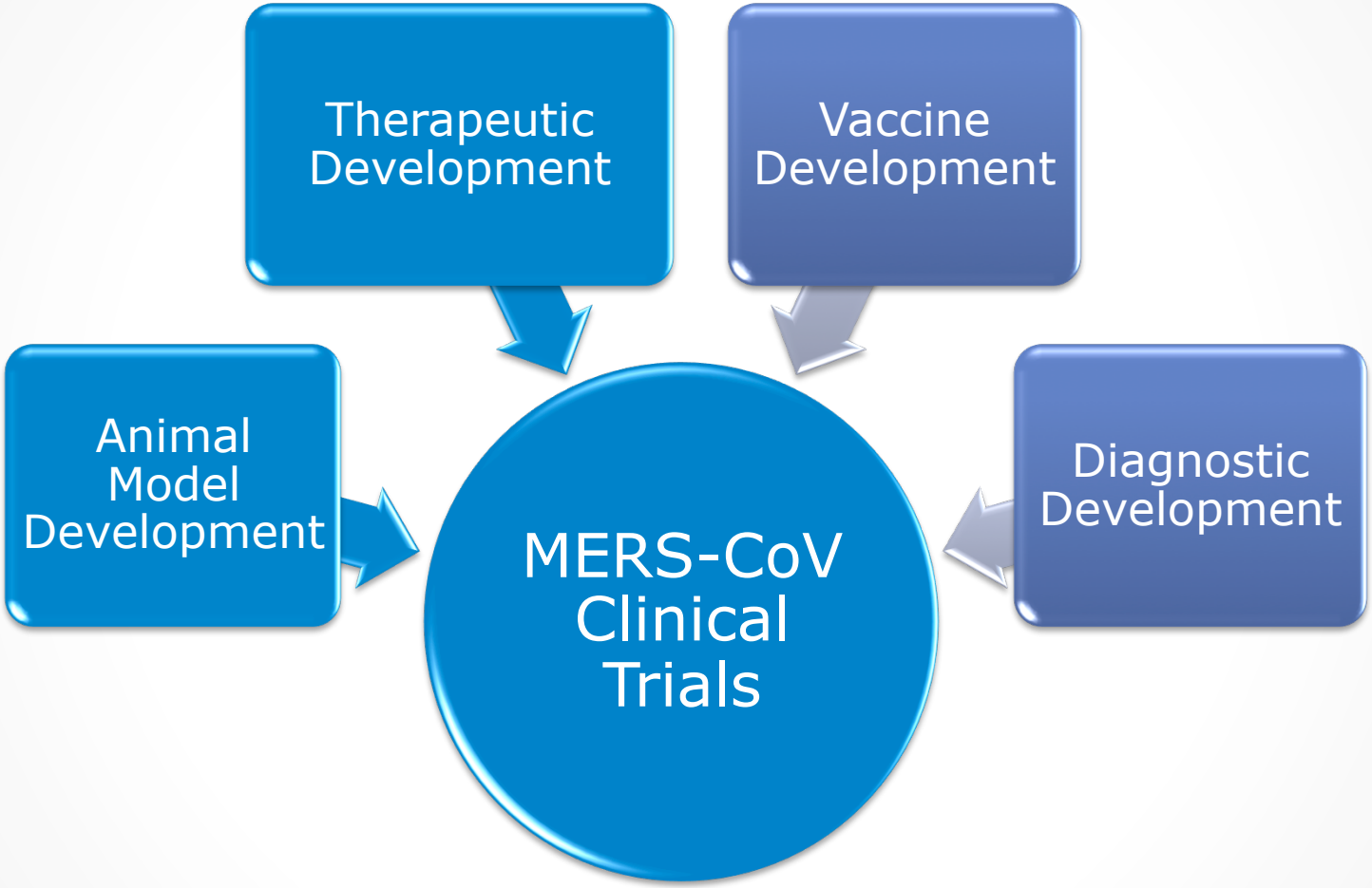
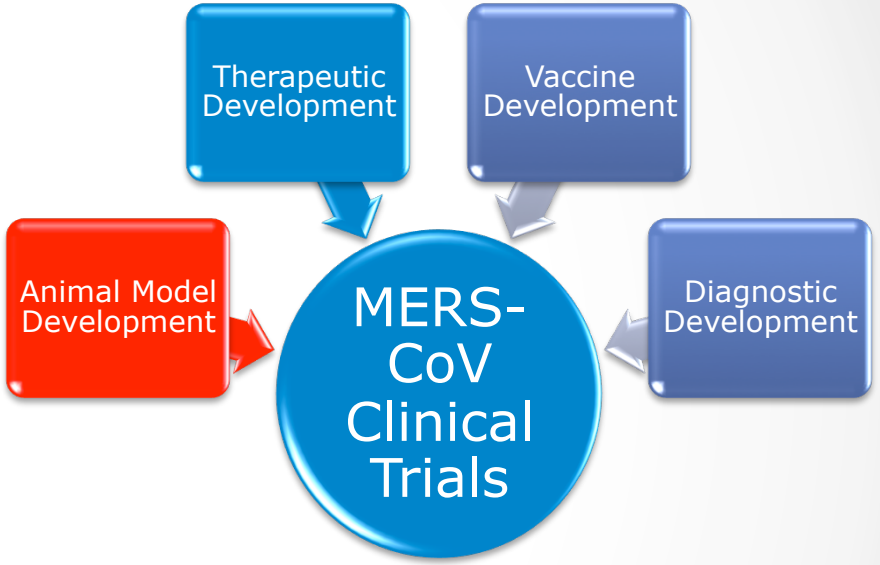
BARDA Priorities



Priorities: Animal Model Development

- Mouse studies at University of Maryland School of Medicine
- NHP studies at NIAID Rocky Mountain Laboratories
- Utilize the BARDA Nonclinical Development Network to standardize models
- NIH MERS Animal Model Standardization Workshop



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Priorities: Therapeutic Development

- Funnel all early stage drugs through the mouse models
- If there is POC efficacy in the mouse, then test the drug in the NHP model
- Positive data from the NHP is the trigger for Phase 1 clinical trials

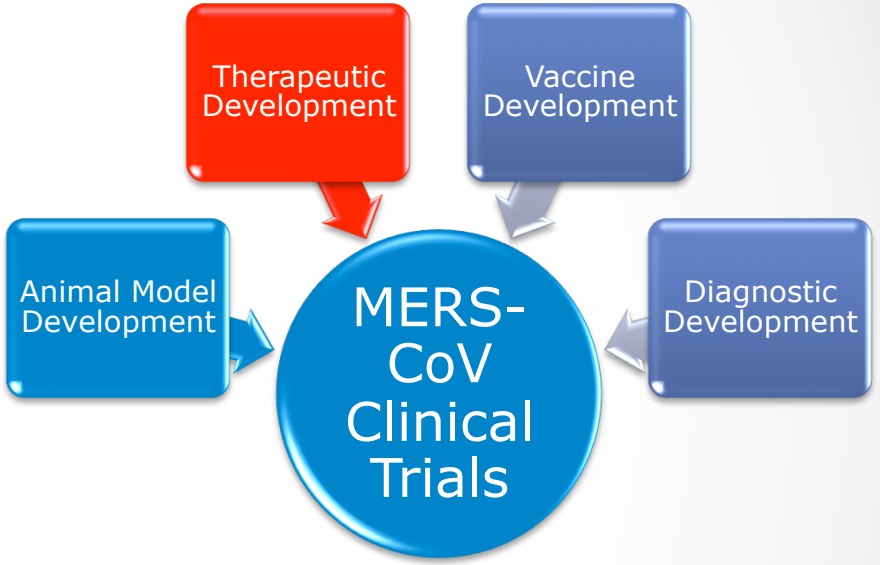

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Photo credit: CDC/James Gathany

Zika Virus

- Zika virus (ZIKV) belongs to the family Flaviviridae (Dengue, West Nile, Yellow Fever, Japanese encephalitis)
- 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
  - Current outbreak began in Brazil in 2015
  - Currently found in over 60 countries and territories worldwide
  - WHO declared a PHEIC on February 1, 2016
  - HHS Secretary declared a public health emergency in Puerto Rico (8/12)

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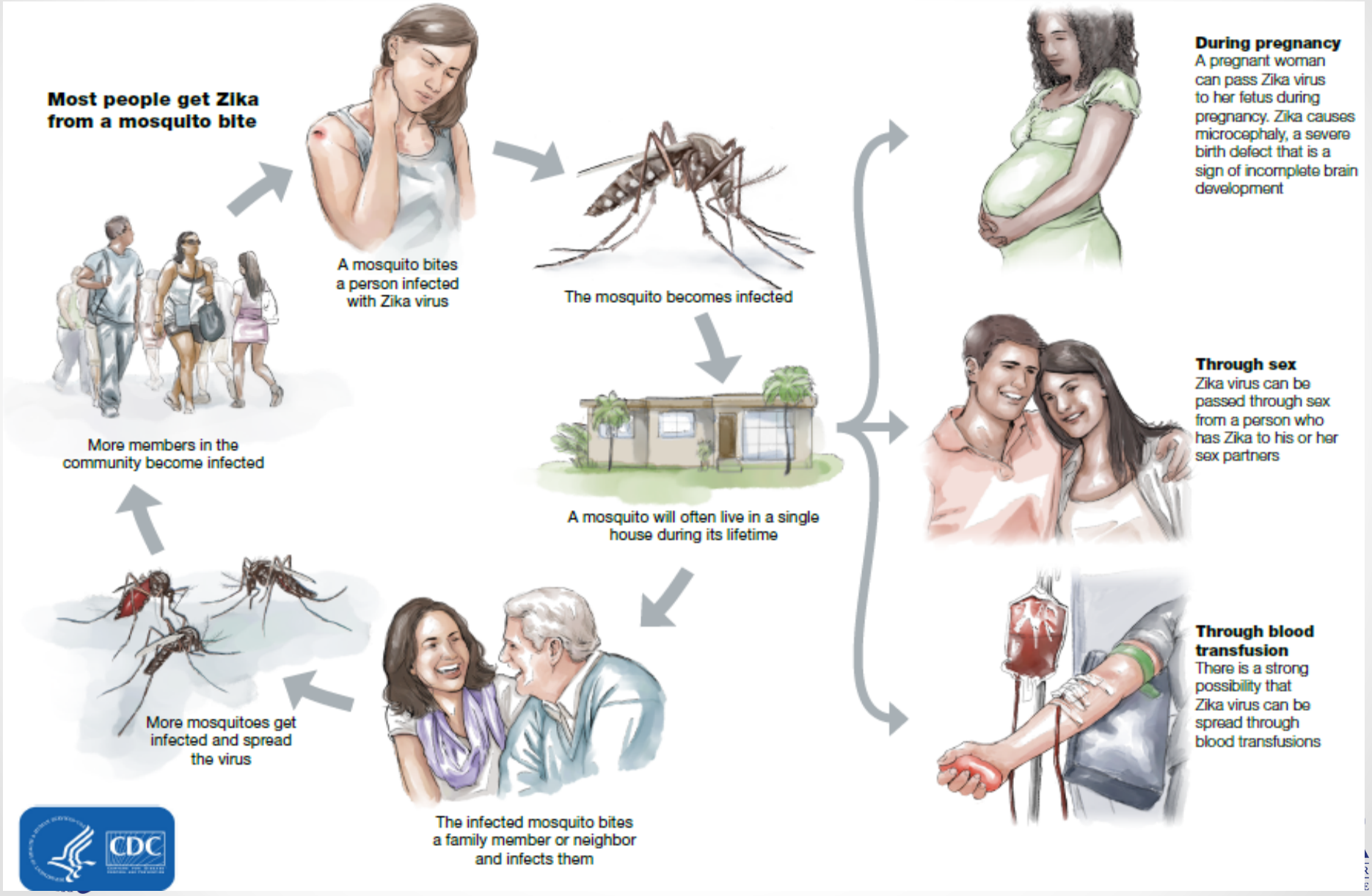
How Zika Spreads



Congenital Syndrome

- Multi-faceted syndrome with broad-ranging neurological sequelae, unknown long-term health consequences
- Reported in 15 countries throughout North and South America
- As of 8/26, over 1,928 cases reported (1,845 in Brazil)

BARDA Priorities for Zika

BARDA will work with PHEMCE partners to address medical countermeasure needs for the Zika response both domestically and globally.

Prevent Zika virus infection through new vaccines

Detect acute and previous Zika virus infections through new rapid diagnostics

Ensure a blood supply safe from Zika virus through use of screening tests for donated blood and virus inactivation in blood products

Activate our National Medical Countermeasure Response Infrastructure to help medical countermeasure developers

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Priority 1: Prevent ZIKV Infection

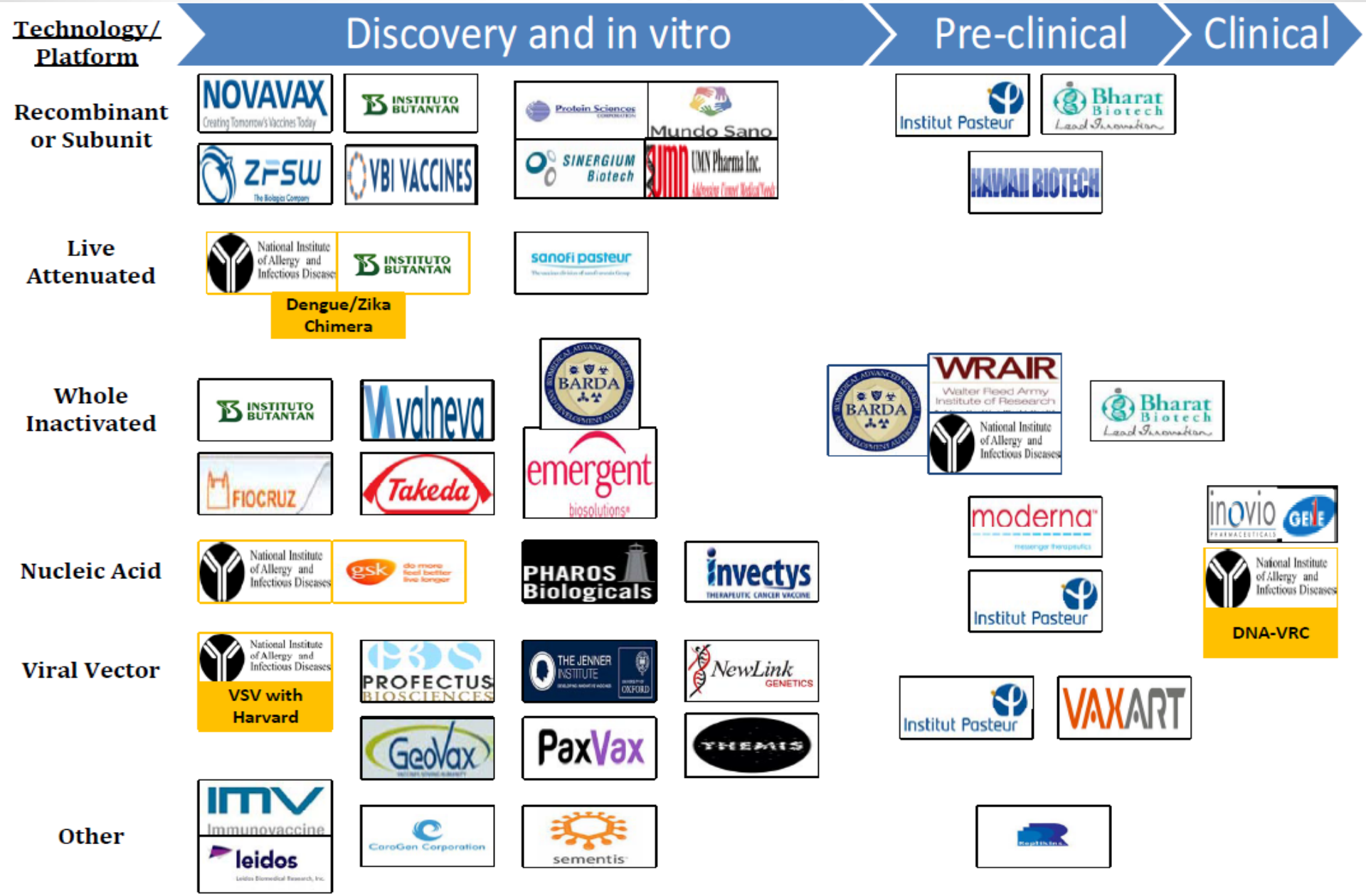
There is currently no licensed ZIKV vaccine available, however…

- Vaccine 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, 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 ZIKV vaccine development

USG ZIKV Vaccine Goals

- Vaccine Candidate(s) available to address immediate U.S. response needs by 2018
  - Protection of key at-risk populations
  - Potential suppression of transmission in active disease sites
  - Reduction of disease
- Vaccine candidate(s) approved for general use and commercial distribution by 2020
  - Marketed for personal protection and general public heath use to control transmission and endemic / epidemic disease
  - Potential for global distribution
  - Broad coverage across age groups
  - Limited contraindications

Zika Vaccines Landscape September 7, 2016

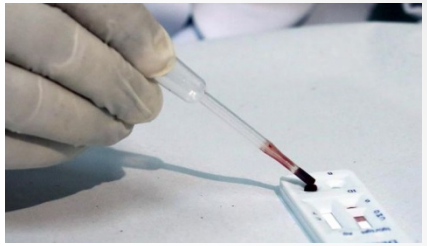


HHS Vaccines in Development

- **DNA vaccine** – based on West Nile vaccine (NIAID/VRC), currently enrolling Phase I, Phase II in Nov/Dec 2016
- **Whole-particle inactivated vaccines**
  - WRAIR/NIAID/BARDA - Phase I in Oct 2016
  - BARDA/Emergent CIADM – Phase I in April 2017
  - **BARDA/Butantan – Phase I in 2017**
  - BARDA/Takeda – Phase I in Sept. 2017
  - BARDA/Sanofi – Phase I/II in 2018
- **mRNA vaccines**
  - NIAID/GSK – self replicating replicon RNA
  - BARDA/Moderna – mRNA, Phase I in Dec. 2016
- **Live-attenuated dengue/ZIKV chimeric** – vaccine (for non-obstetric population) – based on NIAID dengue vaccine candidate, collaboration with Butantan
- **Vesicular stomatitis virus** (VSV) – vectored vaccine (Harvard)

Priority 2: Detect Zika Infection

There is currently no FDA-cleared *in vitro* diagnostic for the detection of ZIKV infection, however…



- On February 26, 2016, HHS Secretary declared a potential public health emergency due to ZIKV that allowed FDA to issue an emergency use authorization (EUA) for CDC's Zika IgM Antibody Capture ELISA (Zika MAC-ELISA)
- Declaration allows FDA to issue additional EUAs for commercial tests that meet specific criteria for performance validation

HHS Zika Diagnostics Strategic Goals

- Expand testing capacity in public health/LRN and commercial laboratories
- Advance the development of more specific and sensitive tests for use in the U.S. and elsewhere
- Provide reagents (viruses, antigens, clinical samples) and reference panels for test development and validation
- Develop high throughput assays to detect Zika virus in the blood supply
- Define and communicate to developers the FDA regulatory pathways for Zika assays

Priority 3: Secure and Protect Blood Supply

- Unexpected involvement in movement of blood products to Puerto Rico (PR)
- Assist in development of pathogen reduction technologies (PRT) for processing of blood products

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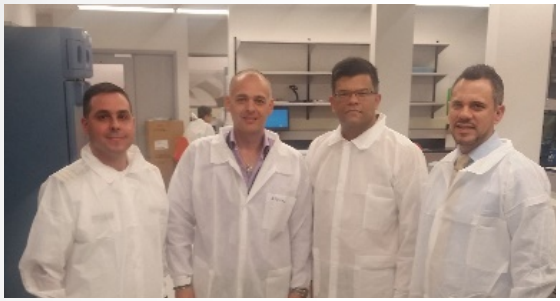
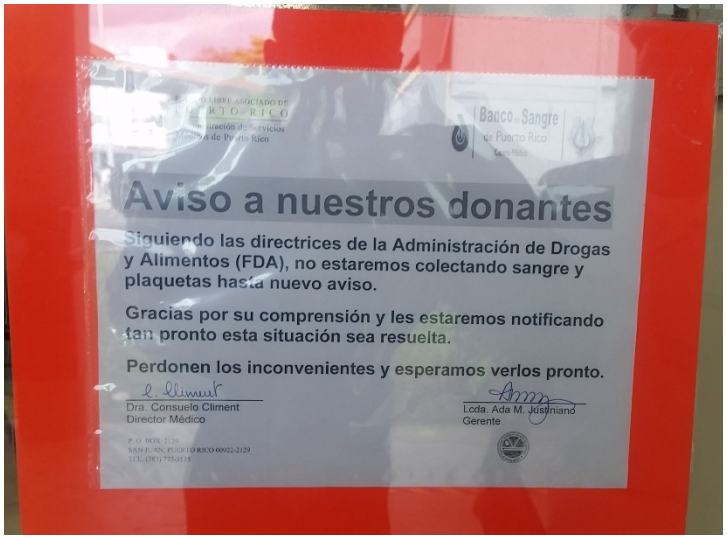
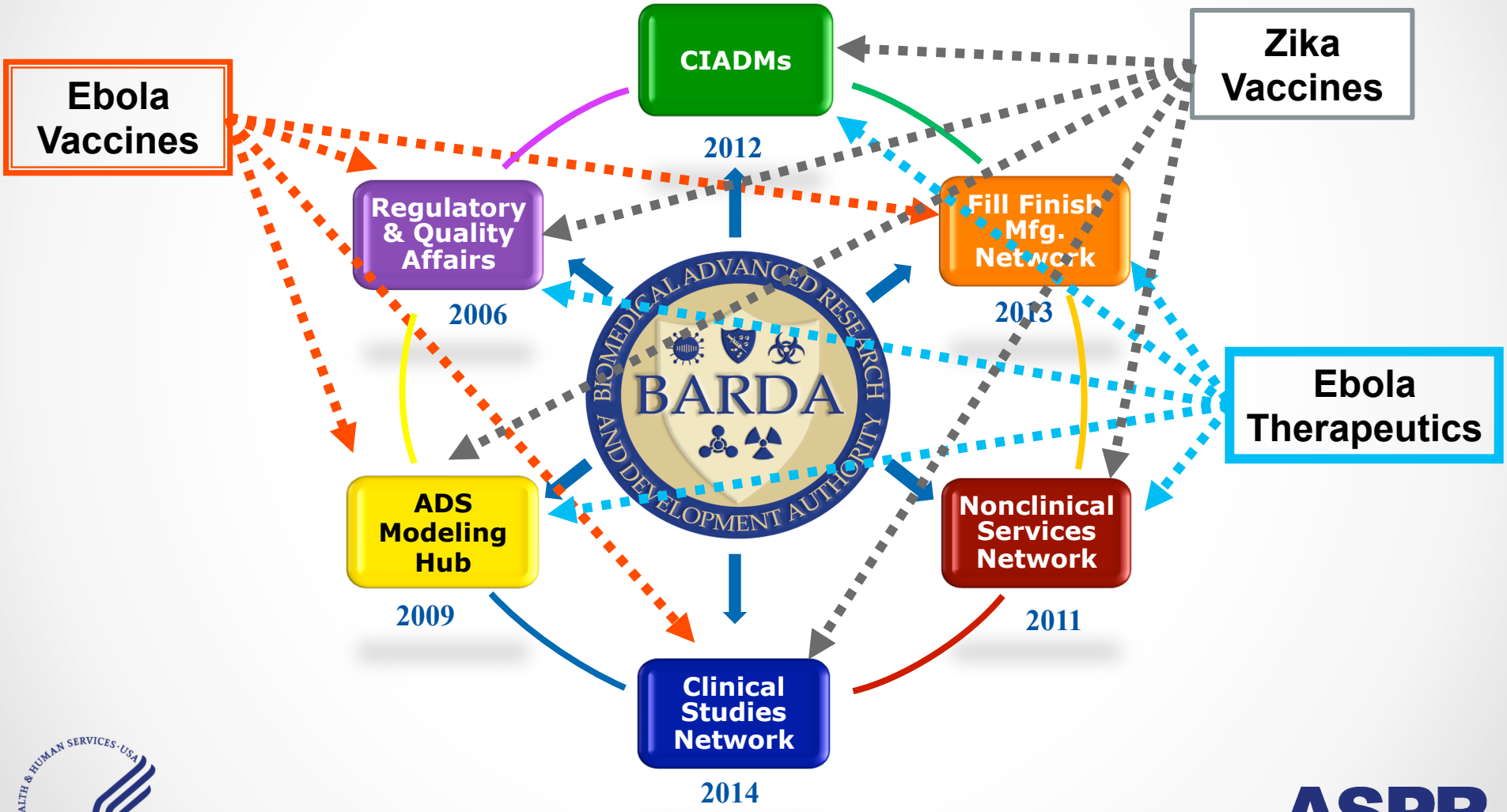
Puerto Rico Blood Supply





Coordination of BARDA's National MCM Response Infrastructure



New Models of Collaboration are Required to Tackle EIDs

- Priority disease targets are no longer only those that are important to high income countries
  - Collaboration with developing countries is necessary
- Vaccines for emerging diseases require more complex science and the ideal candidate vaccine is no longer immediately identifiable
  - Collaboration with multiple groups developing and evaluating vaccines is necessary
- Public sector investment is essential in the form or public-private partnerships
  - Additional and new business and funding models are increasingly necessary

Boston Globe
Silvia Izquierdo/AP