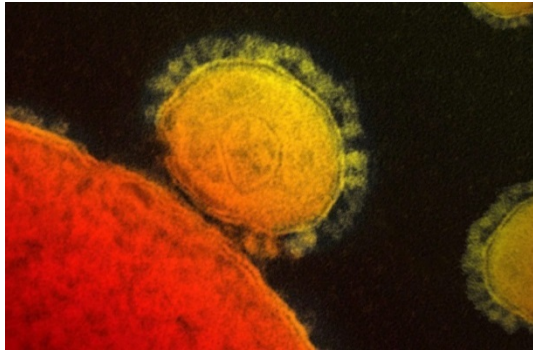




# TACKLING EMERGING AND RE-EMERGING INFECTIOUS DISEASES



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

*Resilient People. Healthy Communities. A Nation Prepared.*

# Emerging Infectious Diseases

## Viruses

## Bacteria

## Fungi

**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**

Andes  
Australian bat lyssavirus  
B19  
Bagaza  
Banna  
Barmah Forest  
Caliciviruses  
California encephalitis  
Cercopithecine herpes  
Chikungunya  
Crimean-Congo hemorrhagic fever  
Dengue  
Eastern equine encephalitis  
Ebola sp. (Zaire, Reston)  
Guama  
Guanarito  
Hantaviruses  
Hendra  
Hepatitis A  
Hepatitis B  
Hepatitis C  
Hepatitis E  
Hepatitis G  
Human astrovirus  
Human enterovirus A (70)  
Human enterovirus B  
Human herpesvirus 1  
Human herpesvirus 2  
Human herpesvirus 3  
Human herpesvirus 5  
Human herpesvirus 8  
Human immunodeficiency virus  
Human immunodeficiency virus 2  
Human papillomavirus  
Human T-lymphotropic virus  
Human T-lymphotropic virus 2  
Influenza (A)  
Japanese encephalitis  
Junin  
Kyasanur Forest disease  
Lassa fever

LaCrosse  
Lassa  
LCM  
Machupo  
Marburg virus  
Mayaro  
Menangle  
Monkeypox  
Murray Valley encephalitis  
Nipah  
Norwalk  
O'nyong-nyong  
Poliovirus  
Rabies  
Rift Valley fever  
Ross River  
Rotavirus A  
Rotavirus B  
Rotavirus C  
SARS  
SARS-CoV-2  
Sindbis  
St Louis encephalitis  
Tick-borne encephalitis virus  
Venezuelan equine encephalitis  
Wesselsbron  
West Nile  
Western equine encephalitis  
Yellow fever  
Zika

Aeromonas caviae  
Anthrax  
Anaplasma phagocytophilum  
Bacillus anthracis  
Bartonella henselae  
Bordetella pertussis  
Brucella sp. (Brucella melitensis)  
Brucella sp. (Brucella abortus)  
B. pseudomallei  
Campylobacter fetus  
C. jejuni  
Chlamydia psittaci  
Clostridium botulinum  
C. difficile  
C. perfringens  
Corynebacterium amycolatum  
C. diphtheriae  
Coxiella burnetii  
Ehrlichia (chaffeensis)  
E. coli  
E. faecium  
E. coli O157  
Francisella tularensis  
Haemophilus ducreyi  
Helicobacter pylori  
Legionella pneumophila  
Listeria monocytogenes  
Mycobacterium avium  
M. bovis  
M. fortuitum  
M. haemophilum  
M. leprae

M. marinum  
M. tuberculosis (MDR/XDR)  
Neisseria gonorrhoeae  
N. meningitidis  
Ricin  
Ricin communis  
Rickettsia sp. (Rickettsia)  
Salmonella sp. (Salmonella enteritidis)  
S. typhi  
S. typhimurium  
Serratia marcescens  
Shigella sp. (dysenteriae)  
Staphylococcus aureus  
S. epidermidis  
Streptococcus pneumoniae  
S. pyogenes  
Staphylococcus aureus  
Vibrio cholerae  
Vibrio sp. (parahaemolyticus, vulnificus)  
Yersinia enterocolitica  
Y. Pestis

Aspergillus fumigatus  
Aspergillus dermatitidis  
Candida albicans  
Candida glabrata  
Coccidioides immitis  
Cryptosporidium parvum  
Fusarium moniliforme  
F. oxysporum  
F. solani  
Histoplasma capsulatum  
Malassezia pachydermatis  
Penicillium marneffei  
Pneumocystis carinii  
Trichosporon beigeli  
Encephalitozoon cuniculi  
E. hellem  
E. intestinalis  
Enterocytozoon bieneusi  
Nosema connori  
Trachipleistophora hominis  
Microsporidia (phylum)

Anisakis simplex  
Echinococcus granulosus  
Loa loa  
Metorchis conjunctus  
Onchocerca volvulus  
Schistosoma mansoni  
Strongyloides stercoralis  
Taenia solium  
Trichinella spiralis  
Wuchereria bancrofti



# 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

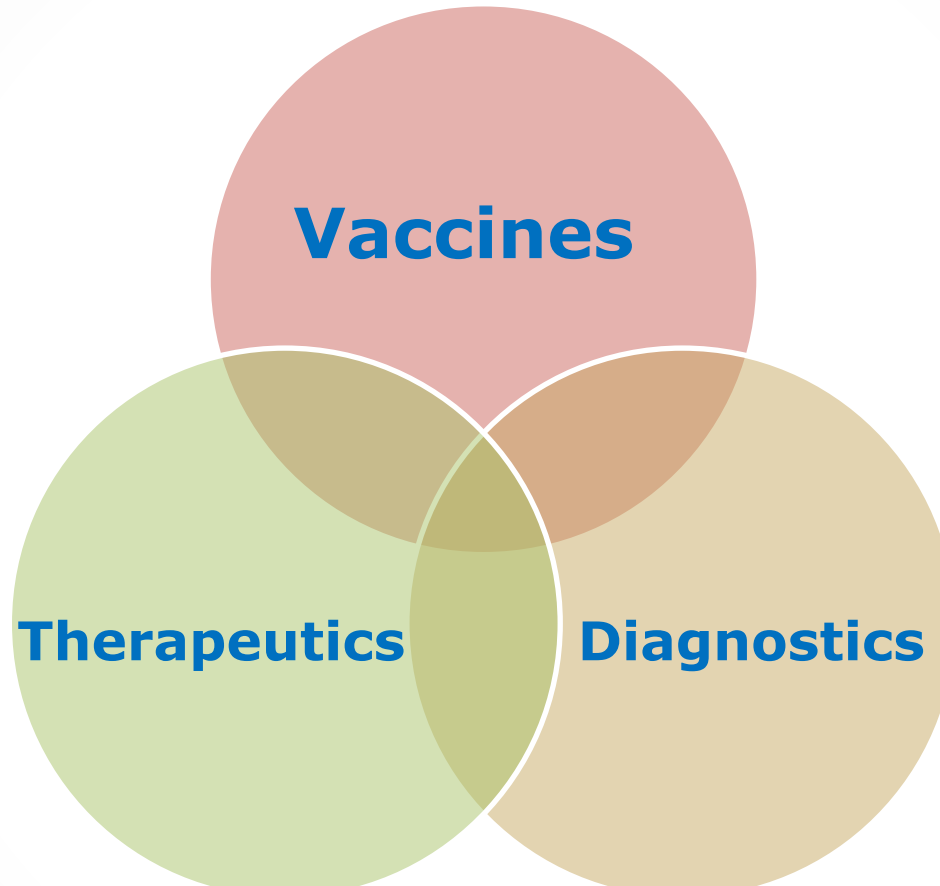
# Multi-hazard advanced development strategies

- 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



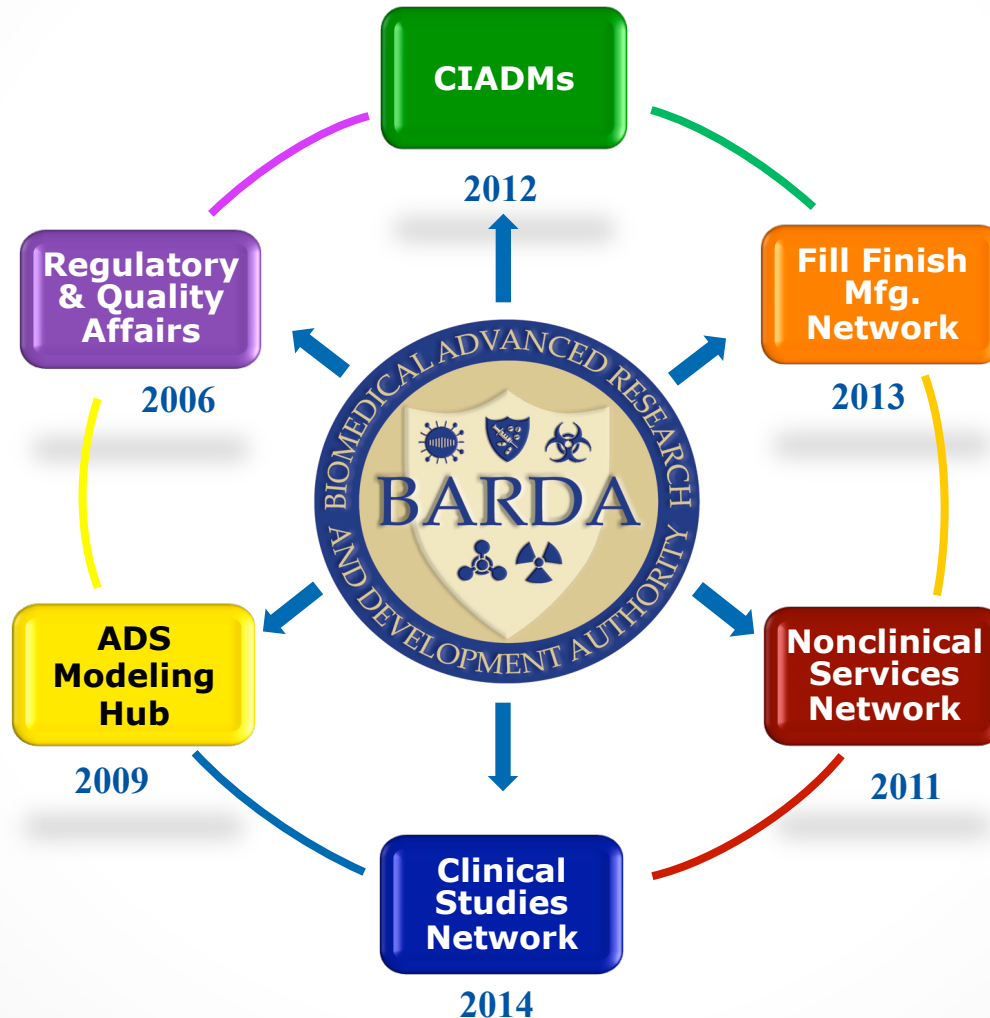


# Emerging Threats Require An Integrated Response

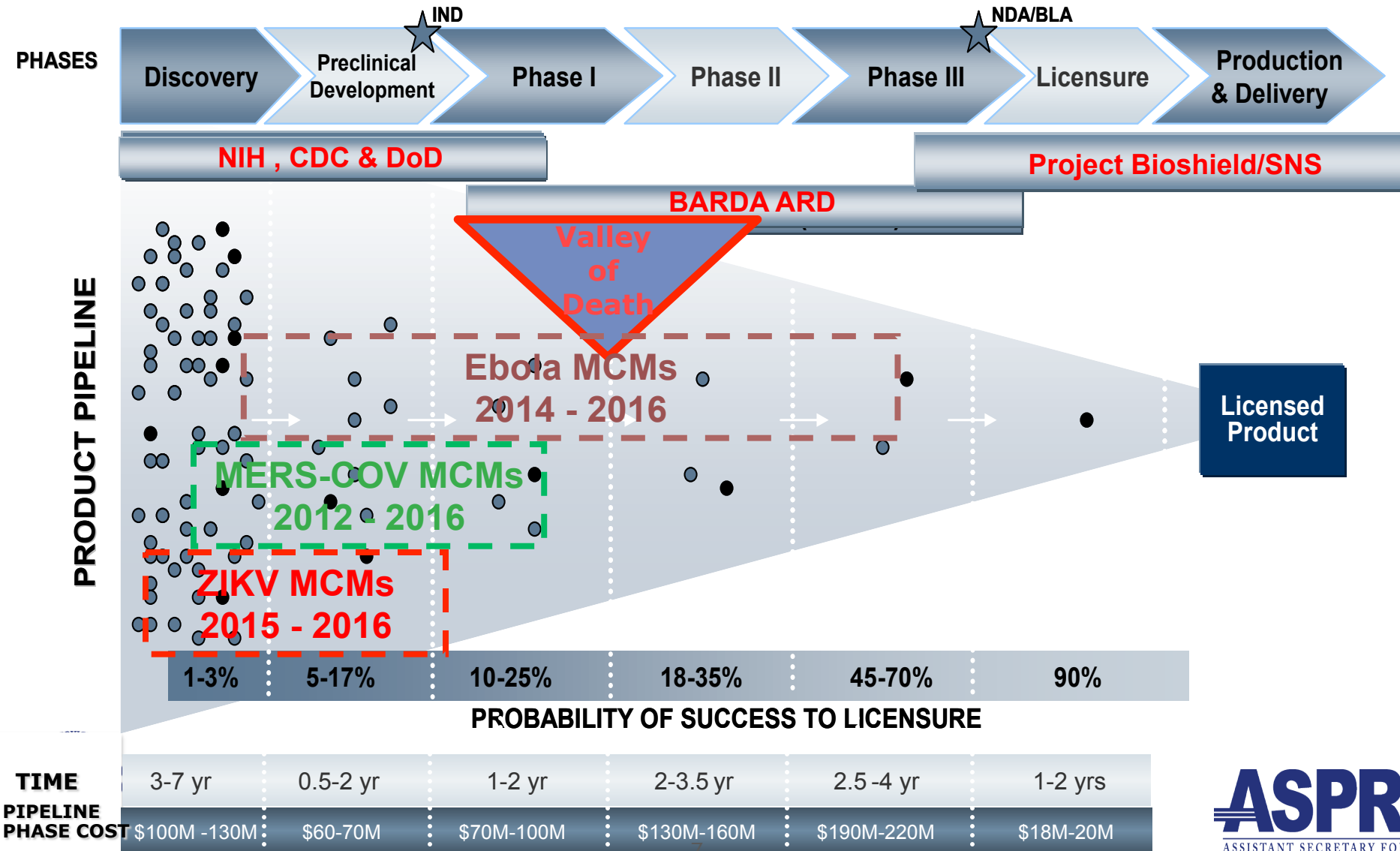


Early Detection → Early Response → Saving Lives

# Emerging Threats Require a Coordinated Response of Supporting Systems



# Vaccine & Drug Development is Expensive, Risky and Lengthy



# 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

CANDIDATE  
EIDs FOR BARDA  
ADVANCED  
DEVELOPMENT

## Scientific criteria:

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

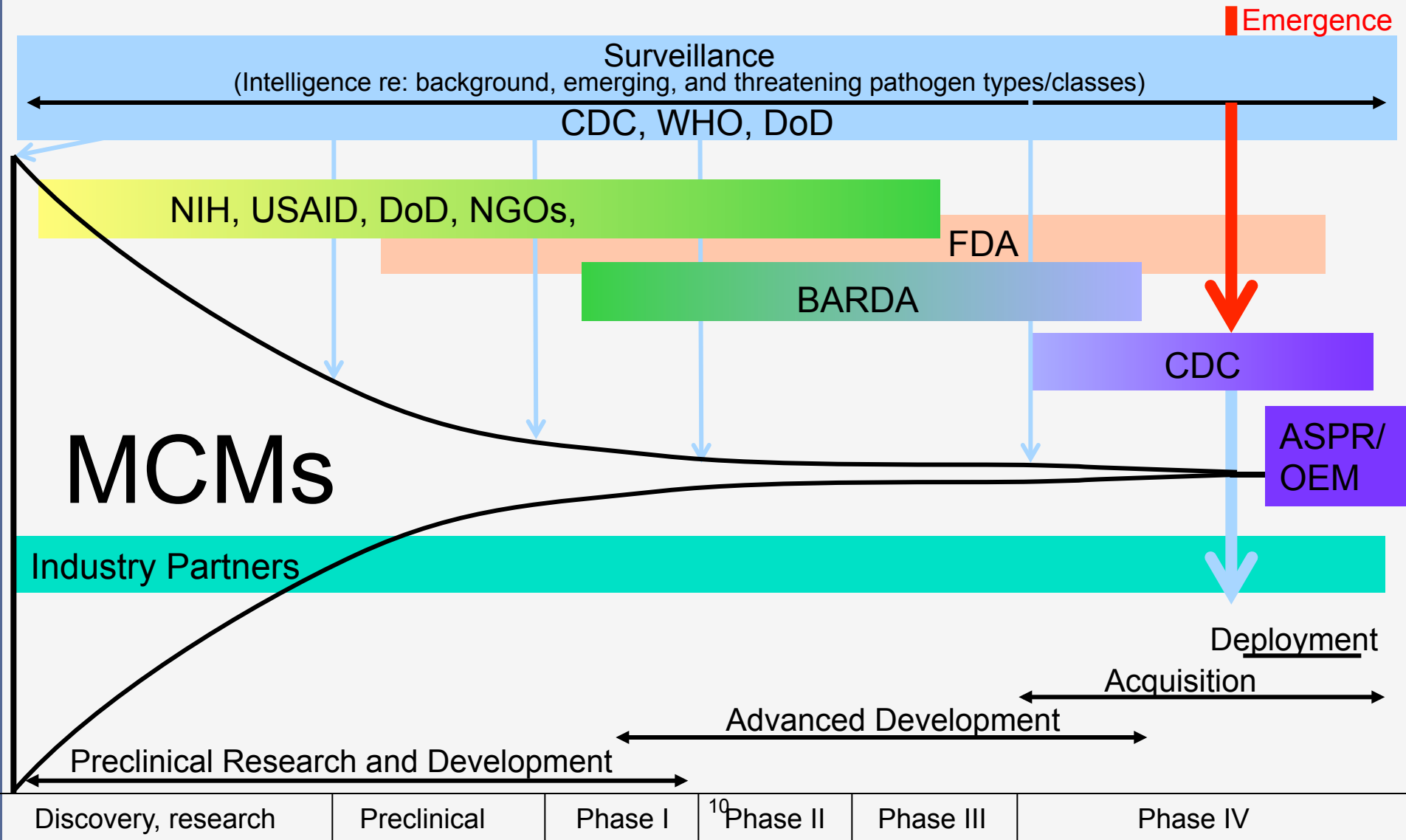
Public Health need for BARDA expertise, resources, and capabilities?

Yes

# 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





A stylized map of the African continent is shown in shades of blue and yellow. Overlaid on the map are numerous red, thread-like structures that represent Ebola virus particles. These structures are of varying lengths and some have small circular protrusions at their ends. The word "EBOLA" is written in large, white, bold, sans-serif capital letters across the center of the map.

# EBOLA

*Resilient People. Healthy Communities. A Nation Prepared.*



# The Worst Ebola Outbreak On Record

Total Cases

28,652

Confirmed Cases

15,261

Deaths

11,325

Table above includes 513 deaths of healthcare and frontline workers



# Development and Evaluation of Ebola MCMs Has Been a Coordinated Effort

## ■ Development

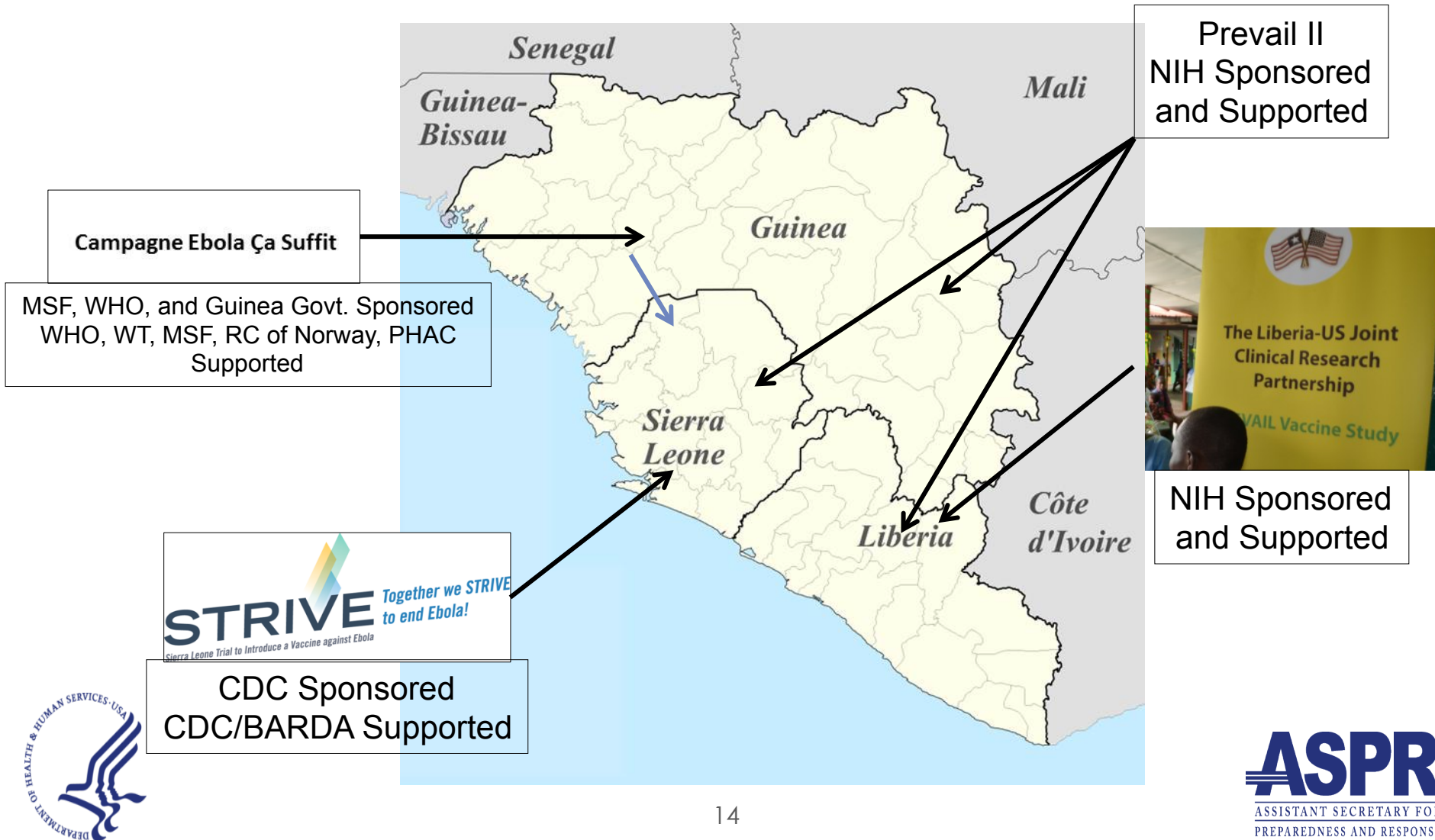
- NIH
- DoD
- BARDA
- FDA
- PHAC
- Industry partners

## ■ 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



# 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

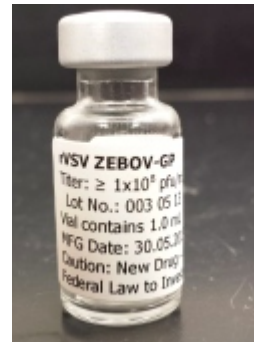


## ■ NewLink/Merck

- 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



# 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





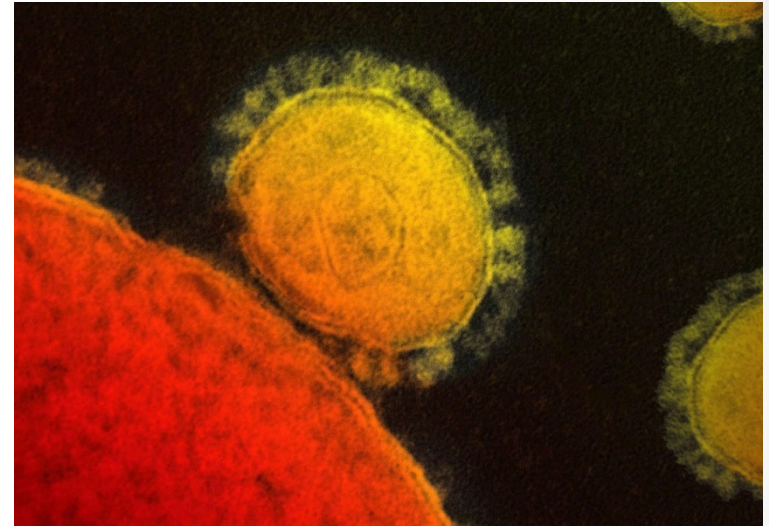
# MERS CORONAVIRUS



# 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

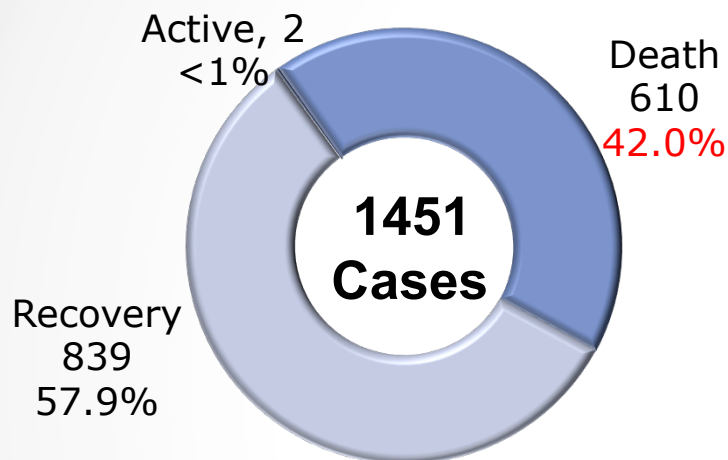


**There are currently no licensed or approved vaccines or treatments for Coronaviruses**



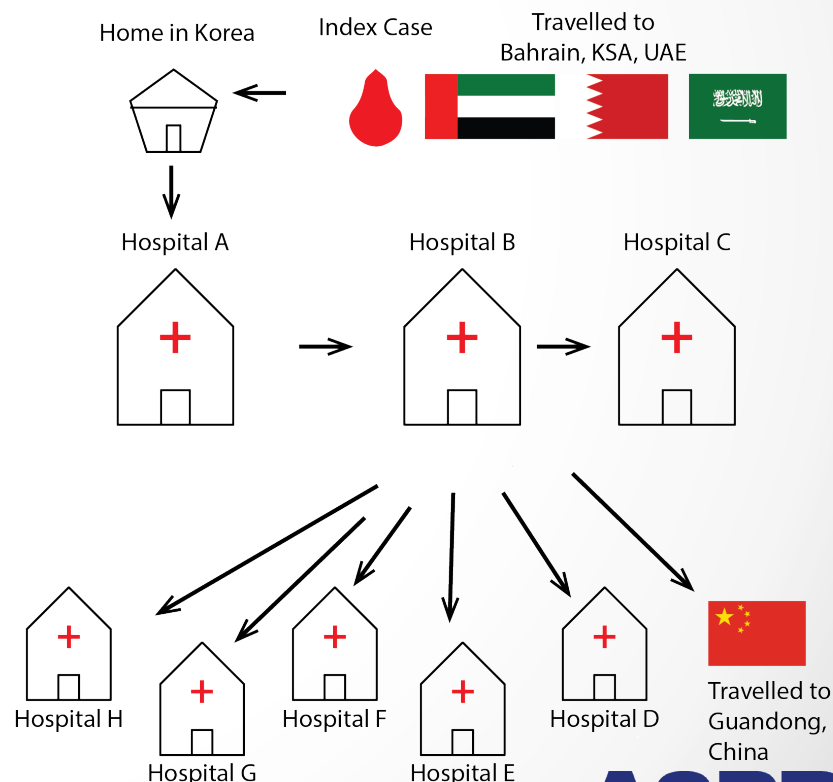
# MERS-CoV Outbreaks in Saudi Arabia and South Korea

## Saudi Arabia since 2012

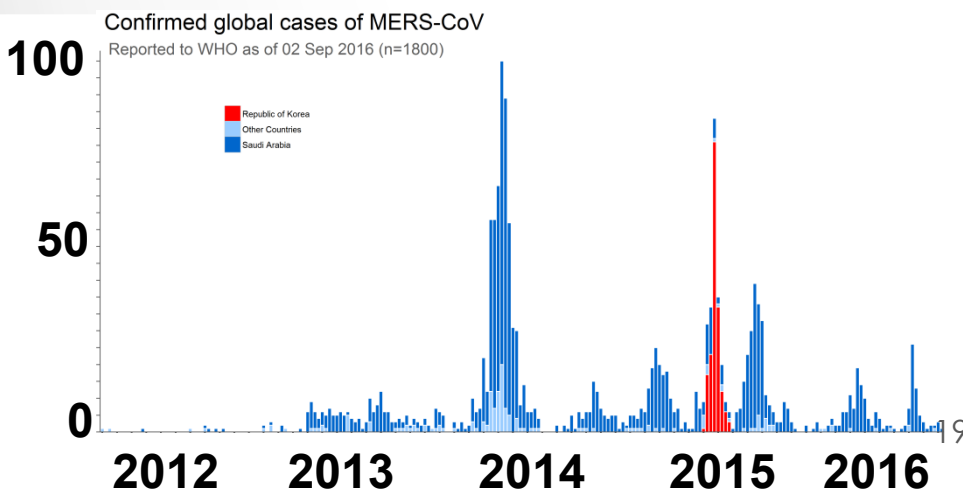


## South Korea, 2015

TOTAL CONFIRMED	Republic of Korea	China	DEATHS
186	185	1	36



## Global cases per week



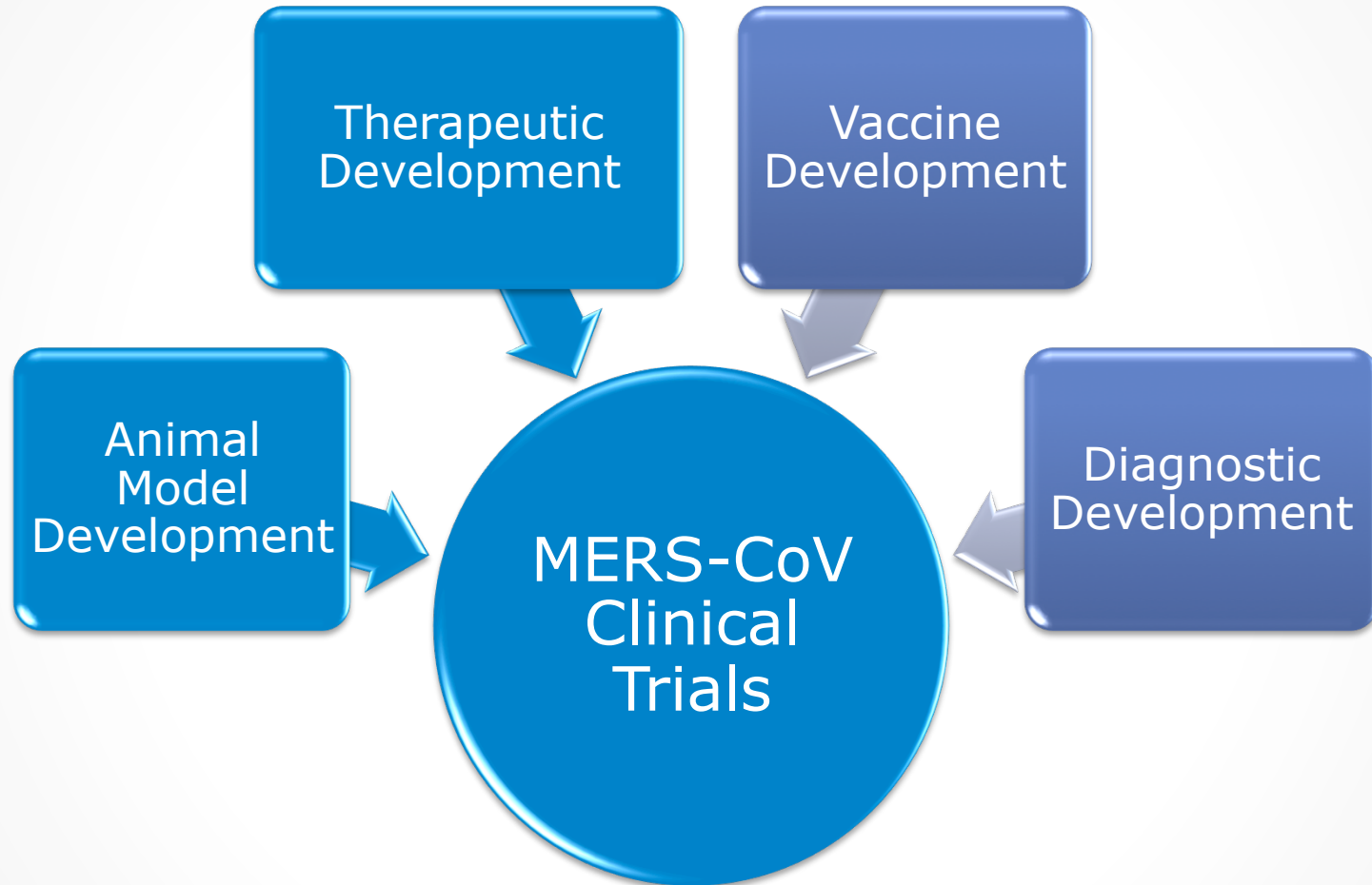
<http://www.jidc.org/index.php/journal/article/view/7278>

<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>

**ASPR**  
ASSISTANT SECRETARY FOR  
PREPAREDNESS AND RESPONSE

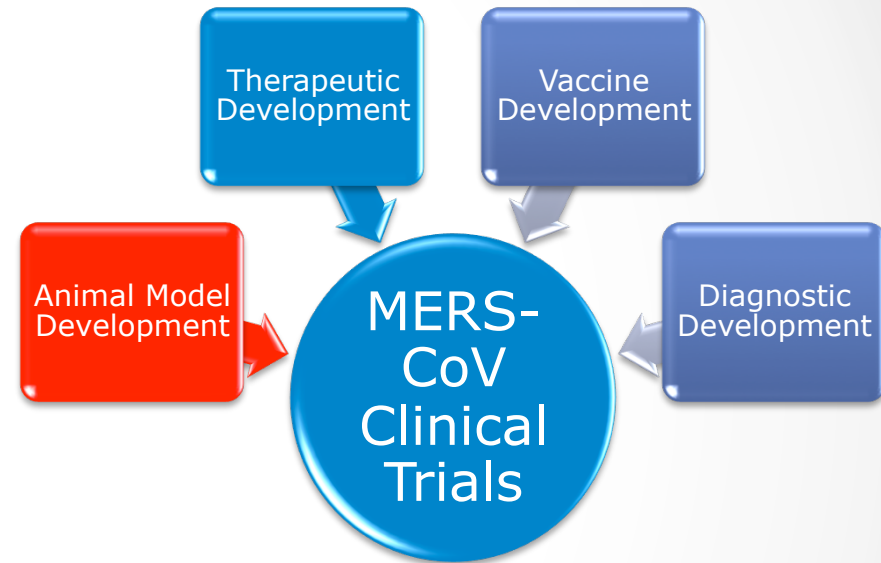
# BARDA Priorities



# Priorities:

## Animal Model Development

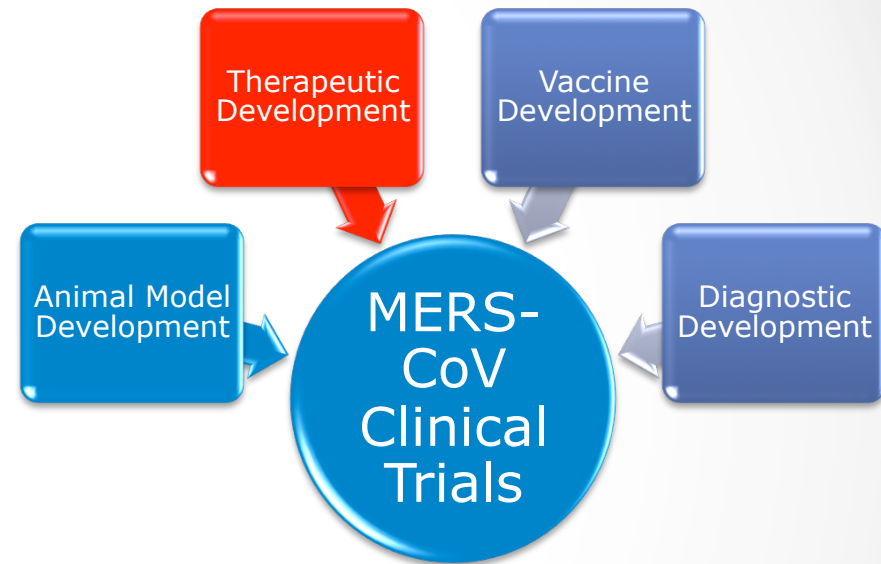
- Mouse studies at University of Maryland School of Medicine
- NHP studies at NIAID Rocky Mountain Laboratories
- Utilize the BARDA Nonclinical Development Network to standardize models
- NIH MERS Animal Model Standardization Workshop



UNIVERSITY of MARYLAND  
SCHOOL OF MEDICINE

# 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



UNIVERSITY of MARYLAND  
SCHOOL OF MEDICINE





# USG ZIKA RESPONSE

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)





# How Zika Spreads

**Most people get Zika from a mosquito bite**



More members in the community become infected



A mosquito bites a person infected with Zika virus



The mosquito becomes infected



A mosquito will often live in a single house during its lifetime



More mosquitoes get infected and spread the virus



The infected mosquito bites a family member or neighbor and infects them



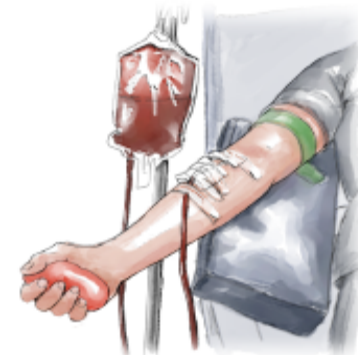
## **During pregnancy**

A pregnant woman can pass Zika virus to her fetus during pregnancy. Zika causes microcephaly, a severe birth defect that is a sign of incomplete brain development



## **Through sex**

Zika virus can be passed through sex from a person who has Zika to his or her sex partners

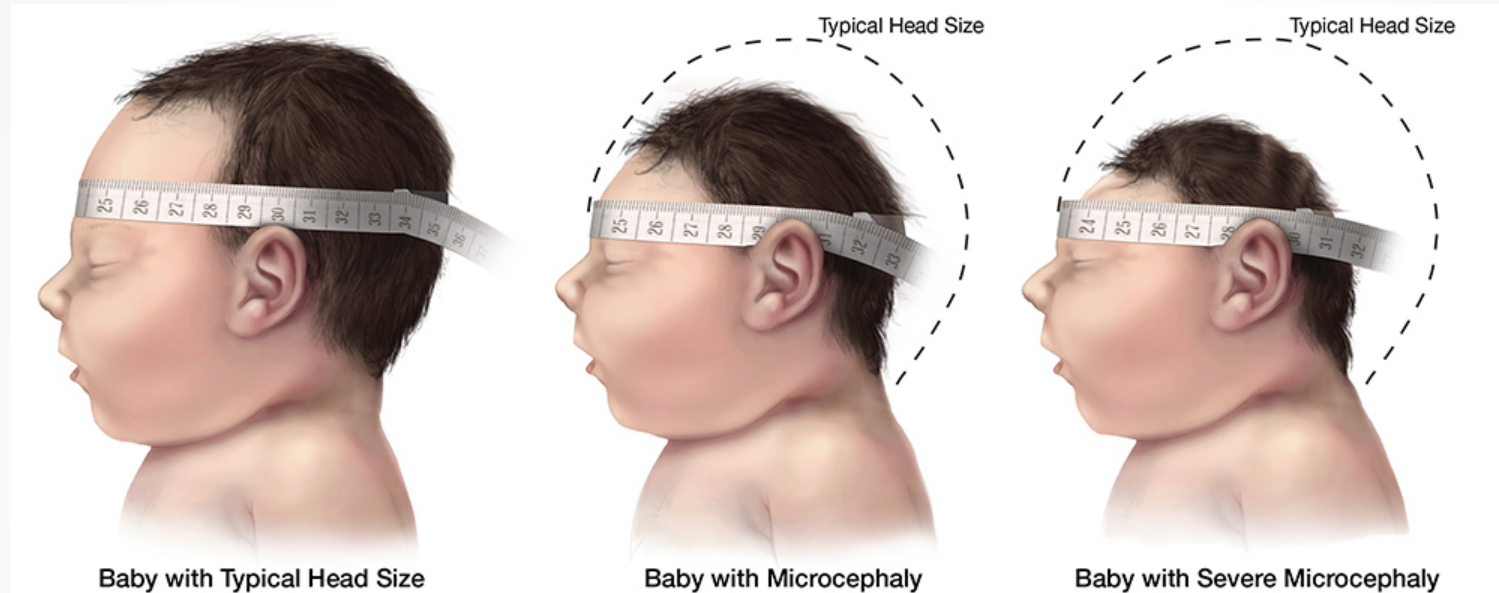


## **Through blood transfusion**

There is a strong possibility that Zika virus can be spread through blood transfusions



# 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

# 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 health 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

## Technology/ Platform

Discovery and in vitro

Pre-clinical

Clinical

## Recombinant or Subunit



## Live Attenuated



Dengue/Zika  
Chimera

## Whole Inactivated



## Nucleic Acid



## Viral Vector



VSV with  
Harvard



DNA-VRC



## Other



# 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

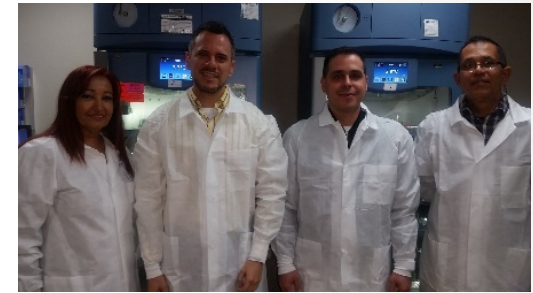
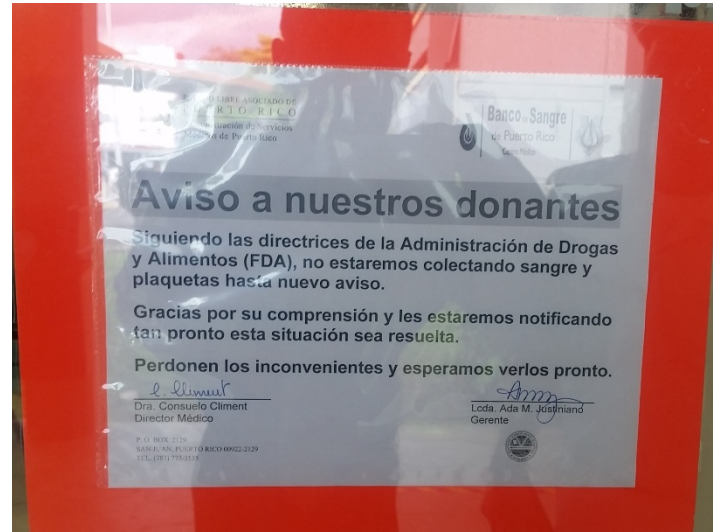


# Priority 3: Secure and Protect Blood Supply

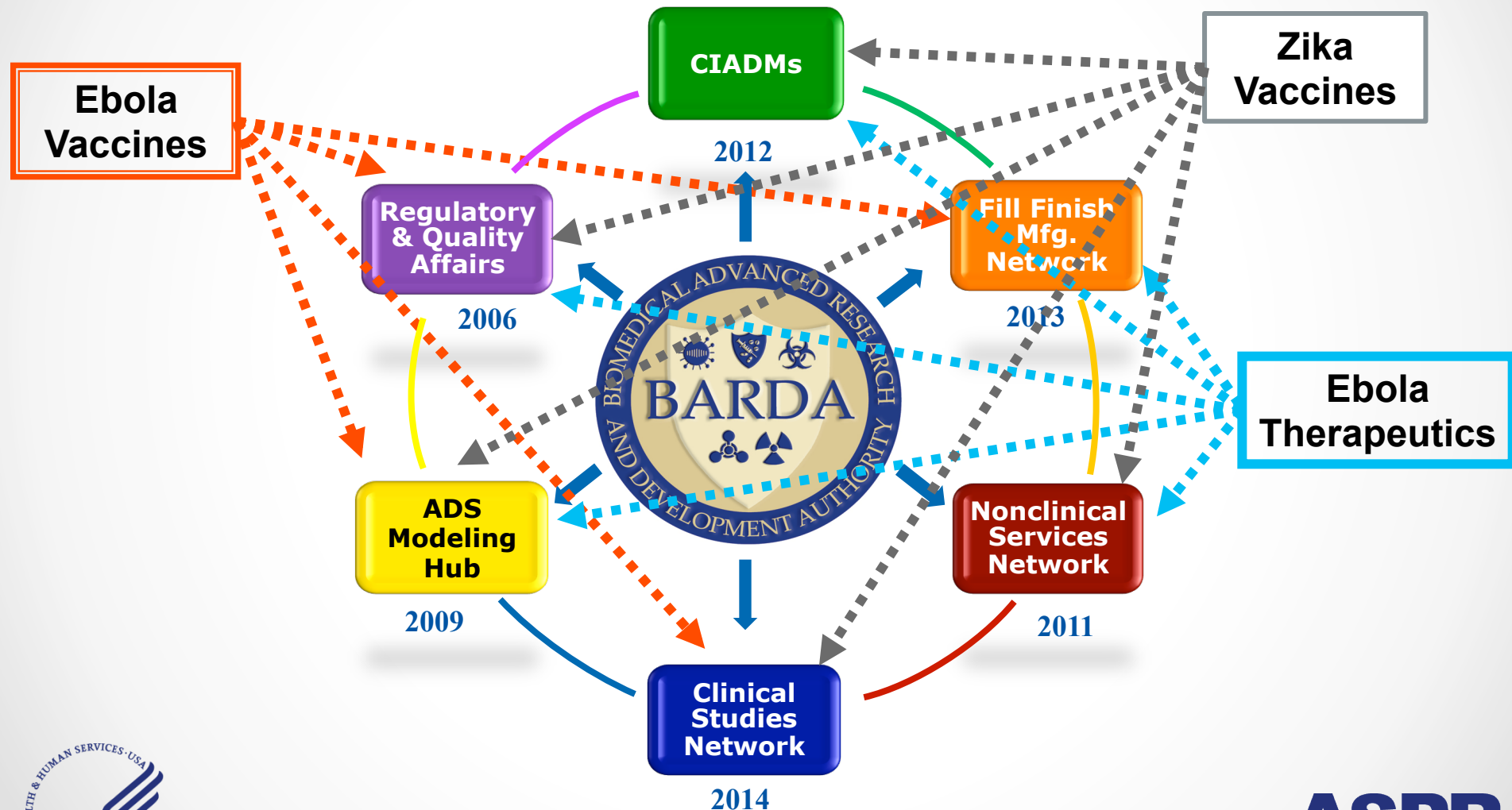
- Unexpected involvement in movement of blood products to Puerto Rico (PR)
- Assist in development of pathogen reduction technologies (PRT) for processing of blood products



# 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 of public-private partnerships
  - Additional and new business and funding models are increasingly necessary





Boston Globe  
Silvia Izquierdo/AP