AMR AND EMERGING DISEASE DIAGNOSTICS

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Resilient People. Healthy Communities. A Nation Prepared.
CARB: AMR Diagnostics

- National Action Plan For Combating Antibiotic-resistant Bacteria
  - Diagnostics Objectives
    - 3.1 Develop and validate new diagnostics—including tests that rapidly distinguish between viral and bacterial pathogens and tests that detect antibiotic-resistance—that can be implemented in a wide range of settings.
    - 3.2 Expand the availability and use of diagnostics to improve treatment of antibiotic-resistant bacteria, enhance infection control, and facilitate outbreak detection and response in healthcare and community settings.
BAA Area of Interest

- 6.8 diagnostic tests to detect/identify drug resistant priority public health bacterial pathogens and characterize their resistance profiles, and to support enrollment in clinical trials of new antibiotics.
  - improved, rapid platforms and assays.
  - multiplex molecular assays to tests to enable antibiotic clinical trials
  - sample to result sequencing solutions
  - novel phenotypic technologies and assays that shorten the time required to detect or confirm resistance.
  - tests to distinguish viral vs. bacterial infections
AMR Projects

- First Light Biosciences Anthrax MDR test aims to determine antimicrobial susceptibility of *B. anthracis* directly from venous whole blood within 5 hours.
  - Challenges:
    - Low bacterial load in whole blood
    - Select agent biosecurity/biosafety
    - No naturally resistant strains

- DNAe simplified next generation nucleotide sequencing platform
  - Applications:
    - Influenza
    - AMR
Develop new, innovative, accurate, and cost-effective *in vitro* diagnostic tests that would rapidly inform clinical treatment decisions and be of significant clinical and public health utility to combat the development and spread of antibiotic resistant bacteria.
Antimicrobial Resistance Diagnostic Challenge

- **Step 1**
  - Up to $50,000 per semi-finalist
  - Maximum 20 semi-finalists
  - Submissions due: January 9, 2017

- **Step 2**
  - Eligibility is not dependent on participation in Step 1
  - Up to $100,000 per semi-finalist
  - Maximum 10 semi-finalists
  - Submissions due September 4, 2018

- **Step 3**
  - Selected diagnostic devices/assays will be evaluated by USG in independent laboratory using specimen panels provided by the Challenge sponsors.
  - $18,000,000 to be divided among up to 3 winners
  - Submissions due: January 3, 2020

  Judges will determine the number of prizes for each phase.
Antimicrobial Resistance Diagnostic Challenge

- Improve antibiotic decision making by healthcare providers and be effective in reducing inappropriate use of antibiotics
- Applicable in inpatient and/or outpatient settings
- Demonstrate a clinically significant advance in diagnostic test performance and address gaps or deficiencies in current capabilities such as
  - ease of use
  - time to result
  - significant advances in sensitivity and specificity
  - ability to process a broad range of specimen types
Antimicrobial Resistance Diagnostic Challenge

- Examples of breakthroughs:
  - More rapidly identify/detect the specific etiology of infection caused by any of the 18 drug-resistant bacteria of highest concern
  - More rapidly identify/detect pathogens, and characterize antibiotic susceptibility
  - Detect biomarkers that would inform patient management decisions such as need for antibiotics or severity of infection

CDC Drug Resistance Threat Report 2013
Emerging Disease Diagnostics

- Ebola
- MERS-CoV
- Zika
- ???
What determines the success of a diagnostic test?

**Exposed**
- Infected (Rule-in/Rule-out)
- Early Disease
- Rx Utility/Impact

**Disease Progression**
- Surveillance (e.g., scope, health risk)
- Individual patient management

**Technical Factors**
- Clinically Valid Analyte (specific/non-specific, host/agent)
  - Specimen type (when and where analyte is present)
  - Specimen Collection and Processing
  - Assay (Method, reagents)
  - Platform

**Operational Factors**
- Regulatory
  - Manufacturing, Stockpiling, Distribution
  - Operational Framework
  - User Expertise, Proficiency Testing
  - Results Interpretation, Predictive Value, Management Decision
- Data Management
Lessons from Ebola

- Knowledge gaps
- No specifications/requirements
- Lack of access to viruses and positive specimens
- CONOPS
- US vs. International event
- Regulatory (EUA, WHO EUAL)
- Clinical studies in outbreak settings with minimal infrastructure
- Biosafety in testing settings
- Need for USG support to advance commercial assays
  - USG Support- 13 Molecular, 11 Rapid Ag
PHEMCE VHF Panels for assay advanced development

- Inactivated virus panels
- Available to developers
  - with preliminary sensitivity and specificity data demonstrating
  - held preliminary meeting with FDA

Order: BEI
Order criteria: rosemary.humes@hhs.gov

VHF Panel includes:
- Ebolavirus Zaire 2014
- Ebola Zaire Luebo
- Ebola Zaire Booue
- Ebola Tai Forest (Ivory Coast)
- Ebola Reston
- Ebola Sudan - Gulu
- Ebola Uganda-Bunidbugyo
- Marburg Angola
- Marburg Musoke
- Rift Valley Fever virus
- Crimean Congo Hemorrhagic Fever
- Lassa virus (Josiah)
- Lassa virus (Pinneo)
- Lassa virus (Macenta)
- Dengue 1 (WP74)
- Dengue 2 (16803)
- Dengue 3 (CH53489)
- Dengue 4 (341750)
- Yellow fever (Asibi)
MERS-CoV
Potential Public Health Emergency

- May 29, 2013: HHS Secretary Declaration
- “MERS-CoV has significant potential to affect national security or the health and security of US citizens living abroad. Circumstances exist to justify the emergency use authorization (EUA) of *in-vitro* diagnostic tests”

- 2014: 2 US cases (IN, FL, both imported)
MERS-CoV Commercial Assays

- Challenges for developers:
  - Sample availability
  - Live virus studies require BSL-3
  - Standard Panel availability
  - Market Uptake
  - Individual country requirements

- EUA Regulatory Pathway
  - FDA recommends pre-submission meeting
MERS Virus Availability

- USG (CDC, BARDA, FDA) collaboration
- Inactivated viruses:
  - MERS CoV high concentration for LOD
  - Panel for analytic sensitivity and specificity
    - MERS CoV
    - Coronavirus 229E
    - Coronavirus OC43
    - Coronavirus NL63
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 virus assays.
BARDA Zika Dx Activities

- Market research
- Rapid performance evaluation of early candidates
  - Collaboration with CDC
- BAA
  - point-of-care and laboratory based serology assays for Zika virus
  - serologic assays to discriminate Zika, dengue and chikungunya virus infections
- Connect developers to flavivirus researchers
  - Collaboration with NIH
- Specimens for test evaluation
- Role of diagnostics for vaccine trials
# Zika Diagnostic Assays

<table>
<thead>
<tr>
<th>Indication</th>
<th>Diagnostic Technology</th>
<th>Useful Period (Post Onset)</th>
<th>EUA/IND</th>
<th>BARDA Role</th>
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</thead>
<tbody>
<tr>
<td>Identify persons with active Zika infection (active symptoms)</td>
<td>Molecular (PCR-like) tests</td>
<td>Up to 7 days</td>
<td>CDC and 6 commercial</td>
<td>Small Zika PCR positive validation panels (plasma)</td>
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<tr>
<td>Identify persons previously infected with Zika virus, particularly women infected during pregnancy.</td>
<td>Serologic/Antibody (IgM) tests</td>
<td>~3 days to &gt;&gt; 3months</td>
<td>CDC and 1 commercial</td>
<td>ARD funding, Serum panels</td>
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<tr>
<td>Ensure safety of the blood supply.</td>
<td>Molecular assays, high-throughput platforms</td>
<td>Active infection in asymptomatic individuals</td>
<td>2 commercial (IND)</td>
<td>ARD funding, validation panels</td>
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Antibody Test Challenges

- Sensitivity/Specificity
  - Flavivirus cross-reactivity
  - ↑ specificity may result in ↓ sensitivity
  - Need for IgM positive clinical specimens (can’t contrive samples)
  - Need to have convalescent serum (serial bleeds) from PCR positive cases to validate clinical truth.
  - Diagnostic reliability of detecting Zika specific IgM/IgG response in primary and secondary infection.
  - Best antigen to use is still a research question
IgM positive Specimens

1. BARDA contract with ClinicalRM (CRO)
   Collect convalescent serum from individuals confirmed to have Zika infection by PCR or IgM/PRNT

2. CDC – performs MAC-ELISA and PRNT on convalescent serum to confirm presence of Zika IgM.

3. BARDA-CDC create blinded panels for developers

4. Developer shares results with BARDA, CDC, FDA

5. Unblinded key sent to developer
Clinical Specimen Panels

- **Serology Panels**
  - 10-15 IgM positive specimens
  - ~0.5 ml/specimen
  - Convalescent serum from PCR +, or IgM PRNT + individuals
  - Collected under IRB approved protocol
  - Serum retested to confirm IgM positive
  - Available now

- **Molecular Panels**
  - 10-15 PCR positive specimens
  - ~1 ml/specimen
  - PCR positive plasma from donor units collected in PR, collected under IND protocol
  - Available now

Contact: rosemary.humes@hhs.gov
Interfacing with BARDA

- Website: medicalcountermeasures.gov
  - Information on open influenza BAAs and RFPs
  - Request a TechWatch meeting with BARDA

- Technical POC for BAA
  rodney.wallace@hhs.gov 202-205-3983
QUESTIONS?