EBOLA UPDATE

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Resilient People. Healthy Communities. A Nation Prepared.
The Worst Ebola Outbreak On Record

- As of September 10, 2015
  - 28,147 cases (confirmed, probable, suspected)
  - 11,291 deaths

- Table below shows cases and deaths in healthcare and frontline workers (included in figures above)

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases</th>
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<tbody>
<tr>
<td>Guinea</td>
<td>196</td>
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<tr>
<td>Liberia</td>
<td>378</td>
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<tr>
<td>Sierra Leone</td>
<td>307</td>
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<tr>
<td>Total</td>
<td>881</td>
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Ebola is both an EID and a material threat to the United States
Development and Evaluation of Ebola Vaccines and Therapeutics 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
Ebola Vaccine Landscape

Summer 2014

Discovery

Preclinical Development

Phase I

Phase II

Phase III

VEE Replicon and VLP

rVSVN4CT1

Self-amplifying RNA vaccine

HuAd26/MVA

HuAd5 TRL3 agonist

Rabies EBOV

ChAd3

EBOV GP Nanoparticle

rVSVΔG
Ebola Vaccine Landscape

Current

Discovery

Preclinical Development

IND

Phase I

Phase II

Phase III

VEE Replicon and VLP

rVSVN4CT1

HuAd26/MVA

ChAd3

rVSVΔG

Self-amplifying RNA vaccine

DNA vaccine

Rabies EBOV

EBOV GP Nanoparticle

GP subunit

MVA based boost

BARDA Funded
Vaccines

- **Profectus BioSciences**
  - Recombinant vesicular stomatitis virus (rVSV) vectored monovalent vaccine against Ebola-Zaire
  - Contract awarded in October
    - Funding activities to support filing of investigational new drug (IND) and manufacture of clinical trial material
  - Vector has been evaluated in Phase I/II trials as an HIV vaccine
  - Recent pre-IND submission received favorable response from the FDA
    - Elimination of neurovirulence studies accelerates time to Phase 1 study
  - BARDA contract will provide material to DoD for use in potential clinical trials

rVSVN4CT1-FilovirusGP1
Vaccines

- **GlaxoSmithKline**
  - Contract awarded in December
  - ChAd3 vectored vaccine – bivalent against Zaire and Sudan and monovalent against Zaire – developed by VRC
  - Duration of protection may be limited (<10 months) requiring MVA-vectored vaccine as boost for long-term protection
  - Bivalent vaccine was shown to be safe and immunogenic in multiple Phase 1 studies
  - Currently being evaluated in a Phase II trial in Liberia - PREVAIL
  - BARDA contract is supporting manufacturing process improvements to support scale-up, formulation work, assay development and evaluation of alternative adenovirus vector(s)
Vaccines

- **NewlLink/Merck**
  - Contract awarded in December
  - rVSVΔG vectored vaccine – Ebola – developed by PHAC
  - Vaccine has been evaluated in multiple Phase I studies
  - Currently being evaluated in Phase II/III trials in Guinea (ring vaccination) and Sierra Leone (immediate vs delayed vaccination) - STRIVE
  - Merck is now the commercial partner with Newlink
  - BARDA contract is supporting manufacturing, process improvements to support scale-up, formulation work, assay development, and de-escalation Phase Ib study to support dose selection

**rVSVΔG-FilovirusGP4**
Vaccines

- **Crucell/Bavarian Nordic**
  - Contract awarded in September 2015
  - HuAd26Ebola/MVA trivalent heterologous prime/boost candidate
    - MVA targets Ebola, Sudan, and Marburg
    - Potential to offer long-term protection
  - Vaccines were evaluated in a Phase I study (Oxford) for safety and immunogenicity
    - Evaluated prime/boost order and timing between prime and boost
  - Vaccines were evaluated in a Phase II study (UK and France) for safety, tolerability, and immunogenicity
  - BARDA will support process development, assay development, and manufacturing activities
  - Phase II slated to begin in Sierra Leone
Three, Large, Phase II/III Vaccine Trials in West Africa

- NIH Sponsored and Supported
- SF, WHO, and Guinea Govt. Sponsored
- WHO, WT, MSF, RC of Norway, PHAC Supported
- CDC Sponsored
- CDC/BARDA Supported

Map showing locations in West Africa with relevant sponsorships and trials:

- Campagne Ebola Ça Suffit
- MSF, WHO, and Guinea Govt. Sponsored WHO, WT, MSF, RC of Norway, PHAC Supported
- STRIVE: Together we STRIVE to end Ebola! CDC Sponsored
- CDC/BARDA Supported

NIH Sponsored and Supported
Vaccine Trial-Guinea

- NewLink/Merck rVSVΔG vaccine
- Open-label, cluster randomized, ring vaccination trial
  - Randomized adult contacts and contacts of contacts of a laboratory confirmed case of Ebola into immediate vaccination or delayed vaccination (21 days), no placebo
  - Assessed Ebola virus disease with onset at least 10 days after randomization

- Preliminary analysis conducted:
  - 48 clusters (4123 individuals) immediate vaccination
    - 0 cases of Ebola
  - 42 clusters (3528 individuals) delayed vaccination
    - 16 cases of Ebola
  - Results suggest efficacy of vaccine and data will be reviewed by regulatory authorities

- Protocol has been modified to vaccinate all contacts and contacts-of-contacts immediately
  - Pediatrics are now included down to the age of 6
- Open-label phase IIb trial in healthcare workers evaluating safety and immunogenicity – target 1200 individuals
Vaccine Trial Sierra Leone

- NewLink/Merck rVSVΔG vaccine
- Unblinded, individually, randomized trial without a placebo arm
- Healthcare and front-line Ebola response workers
  - Randomized to immediate or deferred vaccination (6 months)
- Assessed laboratory confirmed Ebola virus disease, safety, and immunogenicity
  - Over 8700 individuals have been enrolled
  - Immediate vaccination – ~4,150 vaccinated in immediate arm
  - Delayed vaccination – will begin in September
    - Reactogenicity in subgroup (~400 patients/group)
    - Immunogenicity in subgroup (~500 patients)
Vaccine Trial Liberia

- NewLink/Merck rVSVΔG and GSK ChAd3 vaccines
- Randomized, double-blinded, placebo controlled trial
  - Evaluate safety, efficacy, and immunogenicity of the vaccine candidates
- Healthy adults or individuals at risk for EVD
  - 500 individuals in each of three arms
- Enrollment and vaccination is complete
  - Lack of Ebola disease – unable to evaluate efficacy of the vaccines
Safety and Immunogenicity

- NewLink/Merck rVSVΔG – 2 x 10⁷
- In general, the vaccine appears to be safe and well tolerated
  - Multiple doses have been evaluated – 3 x 10³ – 1 x 10⁸
  - Vaccine has been administered to ~14,000 individuals
    - Has been administered to 20 individuals 13-17 and 20 individuals 6-12 yrs of age (Gabon) with no reported SAEs
- Reports of arthralgia/arthritus resulted in pausing of a Phase I trial
- One vaccine related SAE reported in the Guinea trial
- Immunogenicity results will be forthcoming
Safety and Immunogenicity

- GSK ChAd3 – $1 \times 10^{11}$
- In general, the vaccine appears to be safe and well tolerated
  - Multiple doses have been evaluated – $1 \times 10^{10} – 2 \times 10^{11}$ (bivalent vaccine)
  - No reports of administration to pediatric patients
  - Immunogenicity results will be forthcoming
Vaccine Trial Challenges

- Balancing establishing/running a clinical trial during an international response to an epidemic
- Cold chain issues and lack of infrastructure
- There has been a rapid decrease in the number of Ebola cases
  - A good thing
- Adapting to cultural, educational, and language differences
- Lack of previous clinical trial experience in West Africa
  - Health care workers and volunteers are/were enthusiastic to help conduct the trials
- Follow-up and tracking of trial participants
What’s Next

- BARDA is currently supporting four vaccine candidates
  - Working in collaboration with DoD and NIH
- BARDA funding was provided under an Ebola CR and Supplemental
  - FY 2016 funding is uncertain above base ARD funding
  - Potential for vaccines/therapeutics to transition to PBS in FY16-17
- BARDA is supporting manufacturing for clinical trials, scale-up manufacturing, enhanced formulation
- Current vaccine candidates are monovalent, both DoD and HHS have an objective to develop trivalent vaccines
- Who will support manufacturing if a mass vaccination campaign is implemented?
- How will regulatory authorities license vaccines in the absence of definitive or sufficient efficacy data?
  - Animal rule
  - Accelerated approval pathway
Ebola Therapeutics

Landscape Summer 2014

**Discovery**
- Bill & Melinda Gates Foundation
- Tekmira
- Convalescent Sera
- Zmab mAbs
- ZMapp mAbs

**Preclinical Development**
- Biocryst Pharmaceuticals, Inc.
- BCX4430

**Phase I**
- Phase II
- Phase III
- IND
- TKM-100802

**Phase II**
- TKM-100802

**Phase III**
- AVI-7530
- ZMapp mAbs
- Brincidofovir for CMV/Adno

**Other**
- MediVector, Inc.
- Favipiravir for influenza
Ebola Therapeutics Landscape

Current

**IND**

**Discovery**

- Bill & Melinda Gates Foundation
- AMGEN®
- DEFYRUS

**Preclinical Development**

- Other Ebola mAbs
- Merck
- Fraunhofer USA
- Medicago

**Phase I**

- Regeneron
- Biocryst Pharmaceuticals, Inc.
- Emergent BioSolutions USA
- DuPont

**Phase II**

- Tekmira
- Defyrus

**Phase III**

- BARDA Funded
- Medivector, Inc.

**Other Ebola** mAbs

- ZMapp™ mAbs
- Avi-7530
- BCX4430
- Mil-77

**BRANDS**

- Brincidofovir for CMV/Adno
- Favipiravir for influenza

**COMPANIES**

- BARDA Funded
- Medivector, Inc.
Expression of mAbs in Tobacco Plants

- **ZMapp™** is supported via a partnership with Leaf/Mapp Bio
  - Manufactured in tobacco plants
  - Three, chimeric, monoclonal antibodies that bind to the Ebola glycoprotein
  - Was administered to several individuals under expanded access or eIND
  - Was the first product to show efficacy in NHPs when administered 5dpi
  - Six manufacturing campaigns were completed
  - Six additional campaigns underway
  - Currently being evaluated in a Phase II
    - Liberia, Sierra Leone, Guinea, and US
Expression of mAbs in Tobacco Plants

- BARDA is also supporting two additional companies that express proteins in tobacco plants
  - Evaluate expression levels in their expression system and proprietary plants
  - Product will be evaluated in non-clinical studies
BARDA’s Efforts to Transition to Traditional Manufacturing Process

- **Plant derived antibodies**
  - Limited capacity to scale-up
  - Limited number of CMOs
  - No approved products

- **CHO cell expression**
  - Enormous capacity to scale-up
  - Many CMOs
  - Many FDA approved products
Ebola Therapeutics

- **Regeneron**
  - Regeneron has a platform technology to quickly identify novel, mAbs in a murine system and convert to fully human antibodies
  - Regeneron identified 20 novel mAbs and selected a combination of 3 with activities similar to the antibodies in the ZMapp™ cocktail
  - BARDA awarded a contract to Regeneron in September 2015 to support manufacturing, assay development, IND enabling studies
  - BARDA has been supporting the evaluation of REGN3479-70-71 in non-clinical studies
    - Has shown efficacy in NHPs when administered 5dpi
  - Regeneron has their own manufacturing facility where they can manufacture at the 2000L scale
Ebola Therapeutics

- Centers for Innovation and Advanced Development and Manufacturing
- First awards under the CIADMs
  - Genentech humanized the three chimeric antibodies that comprise ZMapp™ and cloned them in their proprietary CHO cell line.
    - Under an agreement with BARDA/Emergent/Genentech, Emergent will perform process improvements at both the small and large manufacturing scale.
    - Product will be evaluated in non-clinical studies
  - DuPont has developed a platform technology to express proteins at very high levels based on Trichoderma reesei
    - Under an agreement with BARDA/Emergent/DuPont, Emergent will purify the three monoclonal antibodies that comprise ZMapp™ expressed in the DuPont fungal system
    - Product will be evaluated in non-clinical studies
Ebola Therapeutics

- BioCryst – developing BCX4430 as a potential Ebola therapeutic
  - Broad spectrum, small molecule, antiviral – adenosine analog
  - NIAID has support development of BCX4430 for Marburg
  - NIAID is supporting SAD and MAD Phase I studies in the UK
  - NIAID is supporting evaluation in NHPs for Ebola
  - BARDA is supporting manufacturing activities and some pre-IND enabling studies
Ebola Diagnostics

- Several diagnostics have received EUA
- BARDA is supporting OraSure for the development of a rapid, POC, diagnostic
  - Has EUA status
  - Utilizes blood or oral fluid
  - Quick – point of care, lateral flow
  - BARDA will support
    - Assay design/improvement
    - Process and product validation
    - Analytical and functional testing
    - Clinical trial to support 510(k) clearance
BARDA’s National Countermeasure Response Infrastructure

Ebola Vaccines

Regulatory & Quality Affairs
2006

CIADMs
2012

Fill Finish Mfg. Network
2013

 ADS Modeling Hub
2009

Nonclinical Development Network
2011

Clinical Studies Network
2013

Ebola Therapeutics
BARDA’s Clinical Studies Network

- Supported review and submission of INDs for both vaccines and therapeutic candidates
- Awarded contracts to conduct and support the CDC sponsored clinical trial in Sierra Leone
  - Provided personnel on the ground in SL to support the clinical study and establish a lab for analysis of samples
  - Provided liaison to the CDC in Atlanta for management of the CRO
  - Additional BARDA SMEs were on the ground in SL supporting logistics for shipment and distribution of vaccines and therapeutics
- Supported design of clinical studies for both vaccine and therapeutic candidates
- Liaison to WHO
Fill and Finish Manufacturing Network

- BARDA is supporting the fill/finish of ZMapp™
  - Contract was awarded in November 2014
  - Filled six lots of material
  - Stability studies
  - Shipped to sites in Liberia, SL, Guinea, US
  - Over-labeled product for use in Guinea
  - Will fill additional six lots currently being manufactured at KBP
Manufacturing Facilities and Engineering and Regulatory and Quality Affairs

- Provided review of regulatory documents
- Person in plant
- Audits and site visits of manufacturing facilities
- Import/Export document support
- Product storage
Analytical Support Division

- Modeling Coordination Group – collaboration/awareness of modeling efforts, results, and information sharing
  - Consists of representatives: HHS, CDC, NIH, DOD, VA, DHS, USAID, DoS, DoE, DNI, NOAA, World Bank, and academic partners
  - Weekly meetings beginning in August 2014 with ~30-50 participants

- Interagency collaboration with CDC, DoD, DHS, NSF, NIH, DoE – analytical review
  - Assess epidemiological situation
  - Project anticipated cases in West Africa and US
  - Assess impact of potential US outbreak
  - Estimate quantities of therapeutics, vaccines, diagnostics, and PPE
  - Evacuation planning/medevac estimates
  - Estimate US treatment capacity needs
  - Forecast implications for vaccine clinical trials
  - Supply chain analysis
Liberia forecast

Analysis and results

- Division Representative analysis, results

[Diagram images and charts related to Liberia forecast, vaccine impact, and outbreak in DRC]

- Estimated Number of Simultaneous Patients

- Sierra Leone Impact of Vaccine (30% Efficacy)

- August outbreak in DRC
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<th>Company</th>
<th>Funding ($mm)</th>
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<td><strong>Vaccines</strong></td>
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<td>97.3 for vaccines (3 from FY2015 ARD)</td>
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<td>Newlink/Merck</td>
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<td>Janssen/BN</td>
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<td>Profectus</td>
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<td><strong>Therapeutics</strong></td>
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<td>78.8 for therapeutics (25 from FY2014 ARD)</td>
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<td>MappBio</td>
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<td>BioCryst</td>
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<td><strong>Non-clinical Studies</strong></td>
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<td><strong>TOTAL INVESTMENT FROM CR and SUPPLEMENTAL</strong></td>
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BARDA’s Response Has Been Global