

EBOLA UPDATE

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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)



Country	Cases
Guinea	196
Liberia	378
Sierra Leone	307
Total	881



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



VEE Replicon and VLP



Profectus BioSciences, Inc.
rVSVN4CT1



HuAd26/MVA



Self-amplifying RNA vaccine



HuAd5 TRL3 agonist



Rabies EBOV



ChAd3



EBOV GP Nanoparticle

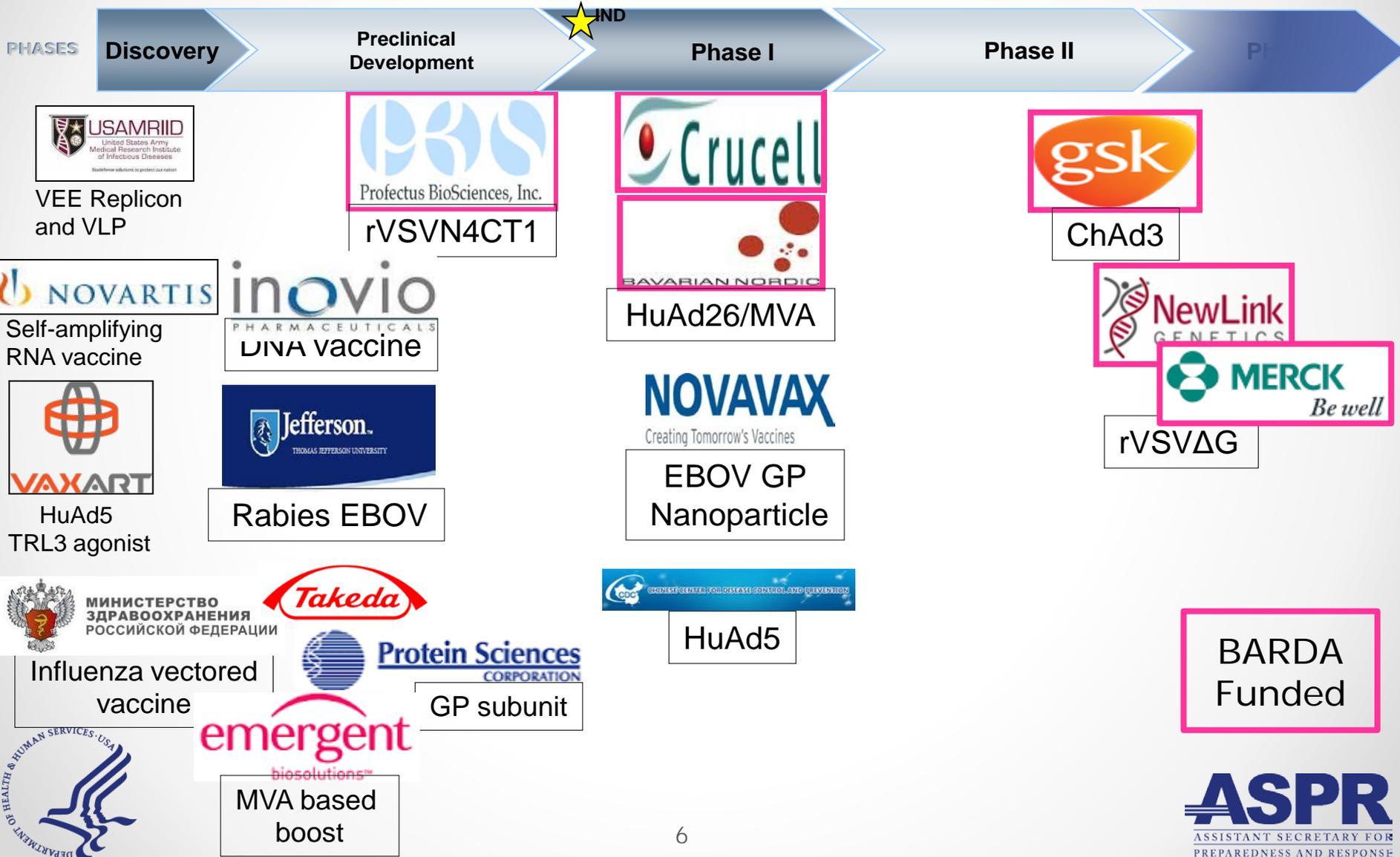


rVSVΔG



Ebola Vaccine Landscape

Current



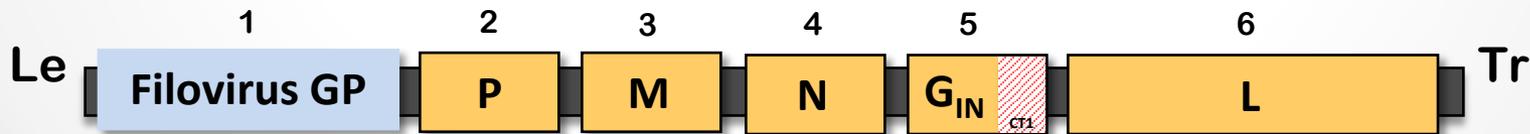
Vaccines

■ 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

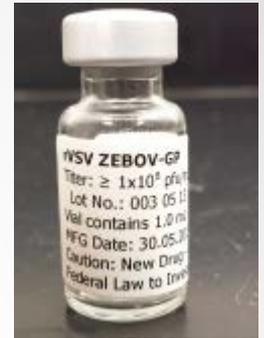
- Contract awarded in December
- ChAd3 vectored vaccine – bivalent against Zaire and Sudan and monovalent against Zaire – developed by VRC
- Duration of protection may be limited (<10 months) requiring MVA-vectored vaccine as boost for long-term protection
- Bivalent vaccine was shown to be safe and 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

- NewLink/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

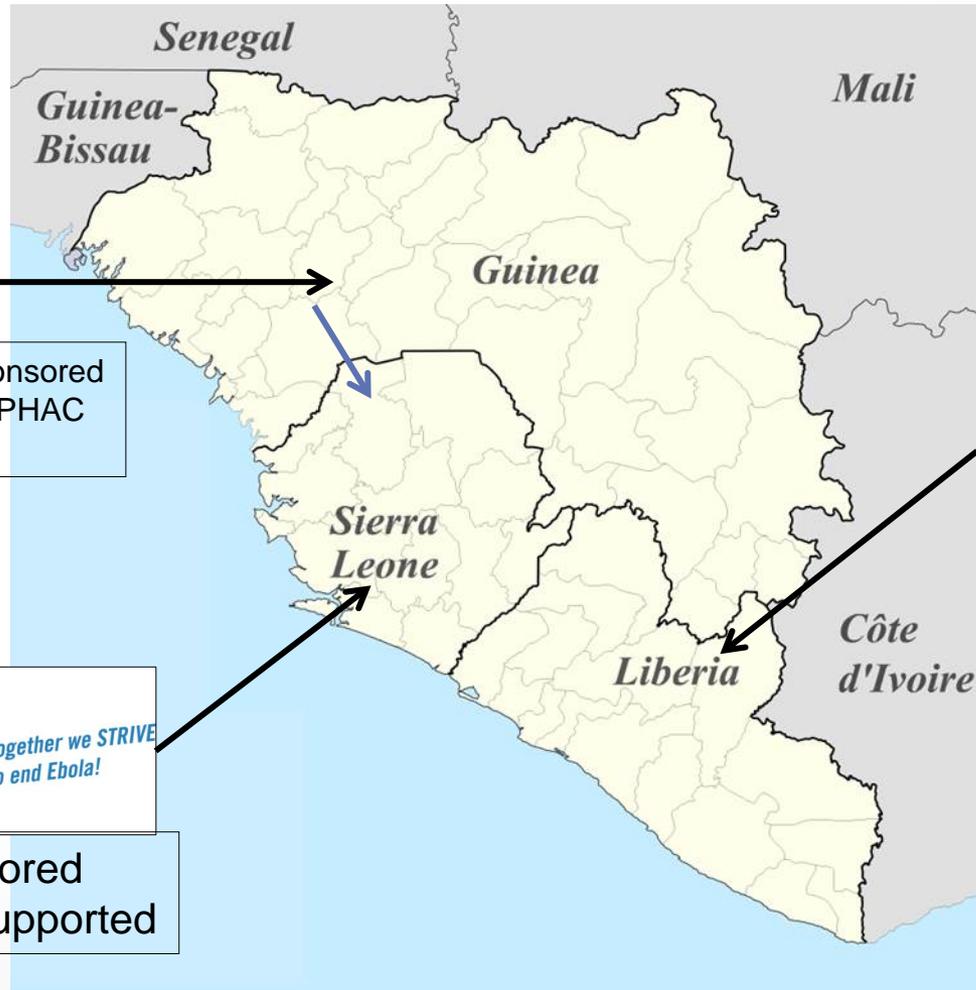


Vaccines

- 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



Campagne Ebola Ça Suffit

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



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)



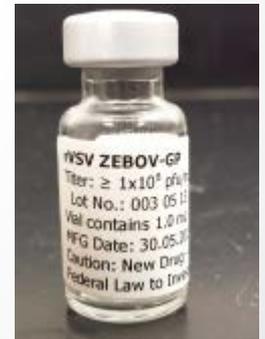
Vaccine Trial Liberia

- NewLink/Merck rVSV Δ G 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



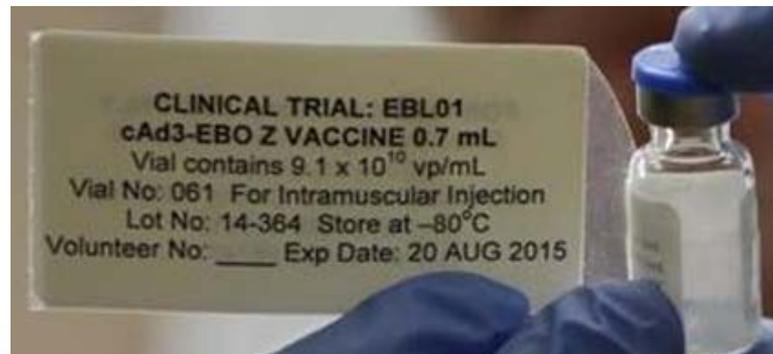
Safety and Immunogenicity

- NewLink/Merck rVSVΔG – 2×10^7
- In general, the vaccine appears to be safe and well tolerated
 - Multiple doses have been evaluated – 3×10^3 – 1×10^8
 - 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
 - Reports of arthralgia/arthritis 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 – 1×10^{11}
- In general, the vaccine appears to be safe and well tolerated
 - Multiple doses have been evaluated – 1×10^{10} – 2×10^{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



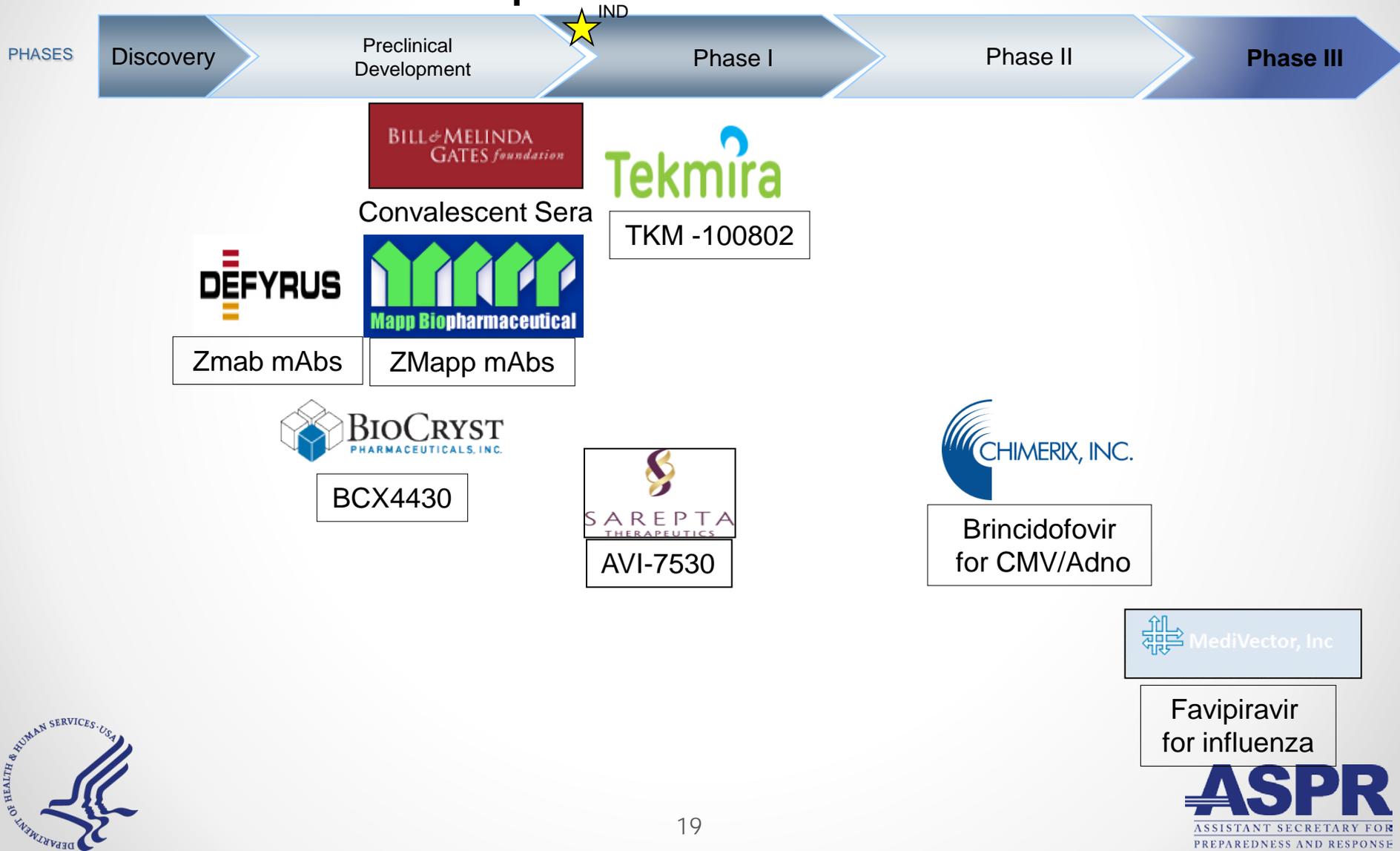
What's Next

- 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



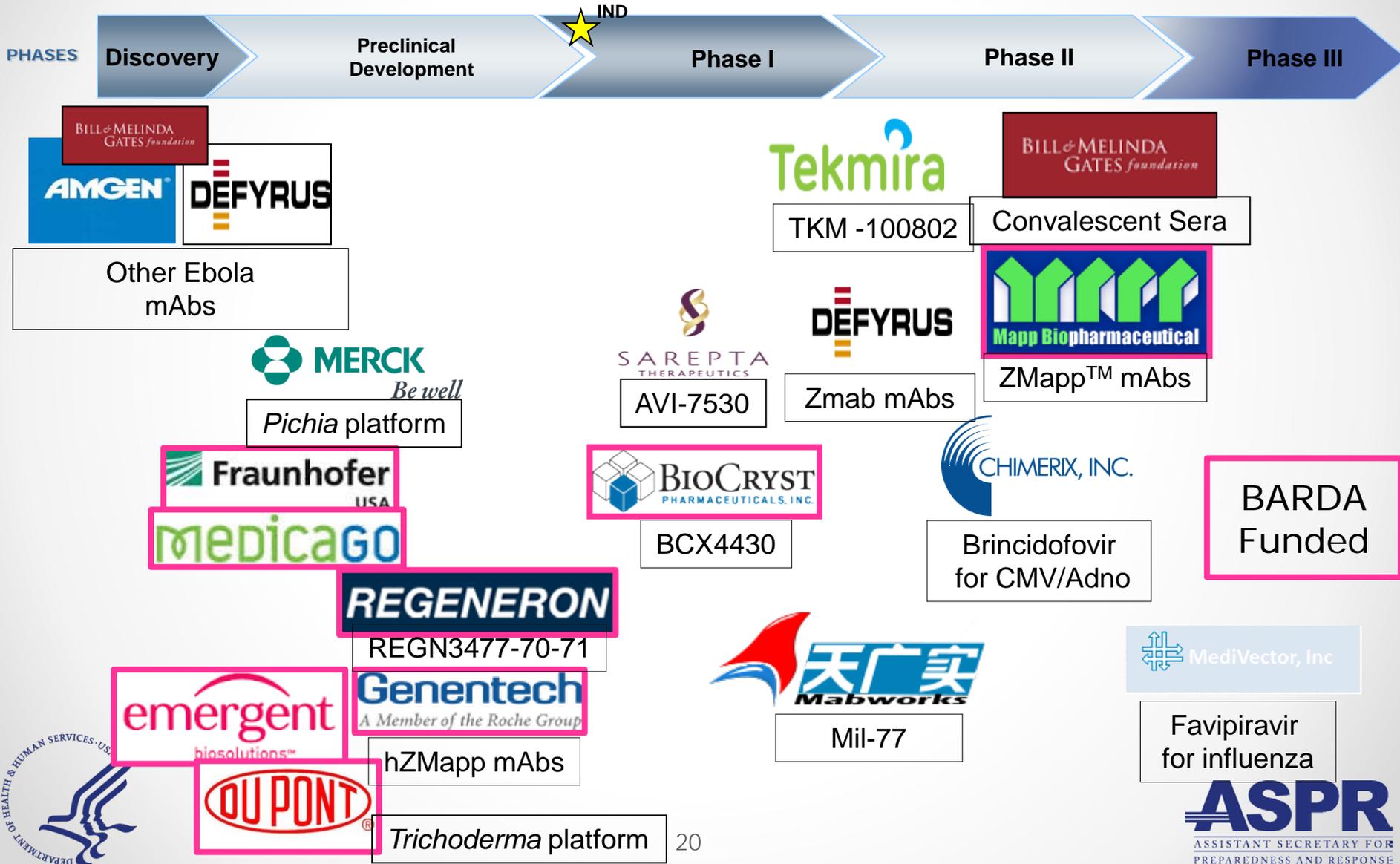
Ebola Therapeutics

Landscape Summer 2014



Ebola Therapeutics Landscape

Current

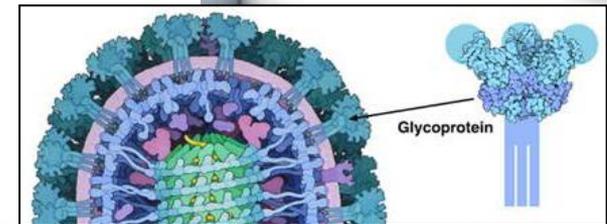
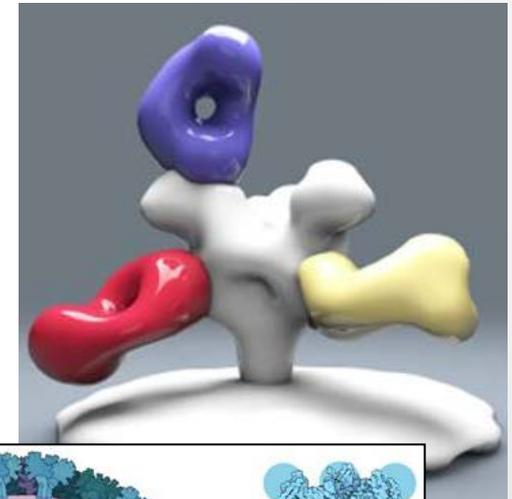


Expression of mAbs in Tobacco Plants

- 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



medicAGO



Fraunhofer
USA



BARDA's Efforts to Transition to Traditional Manufacturing Process



Recent photos from KBP



- 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



REGENERON

ASPR
ASSISTANT SECRETARY FOR
PREPAREDNESS AND RESPONSE



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

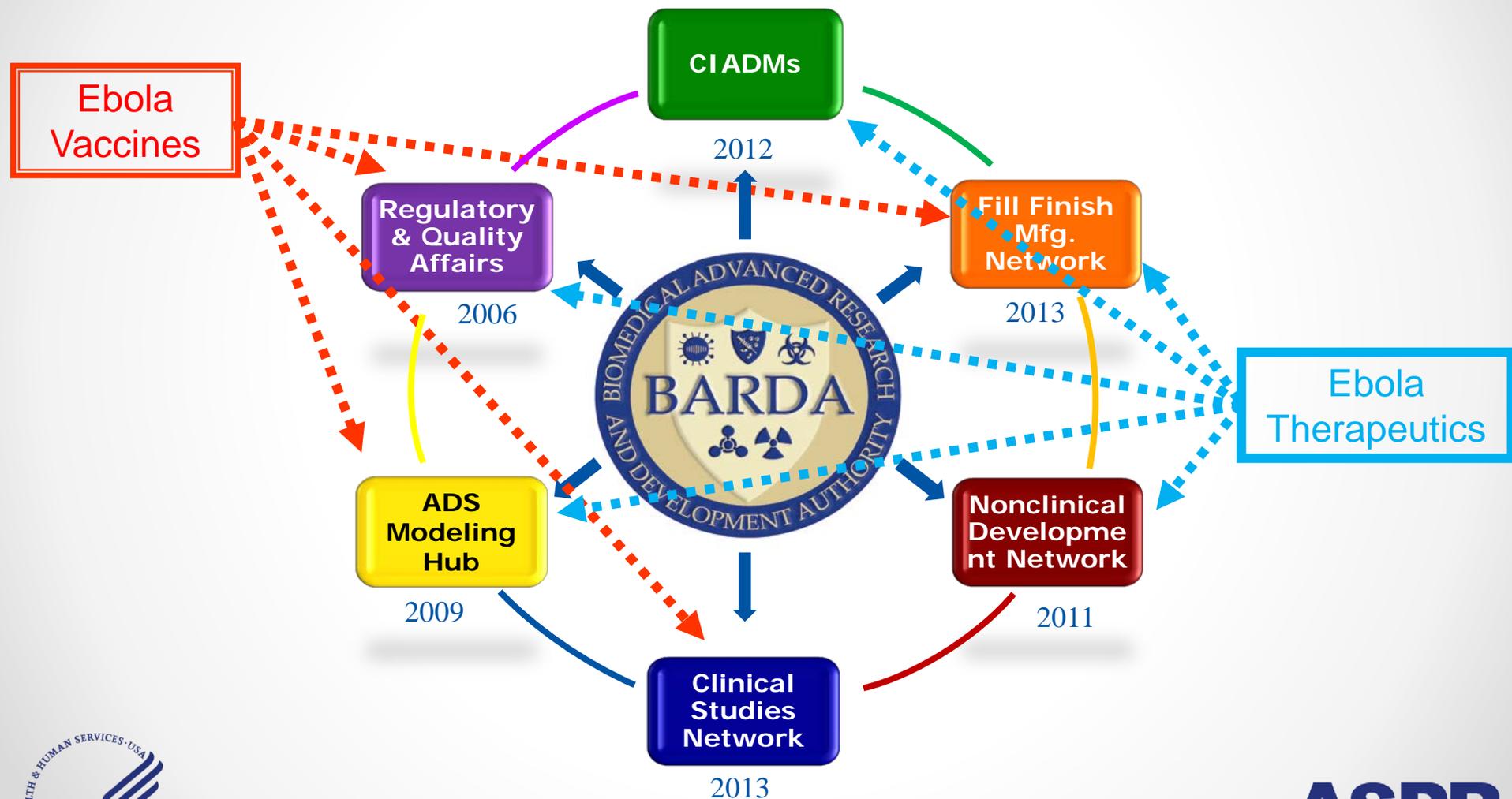


Ebola Diagnostics

- 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



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 an 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



Analytical Support

Division Representative analysis, results

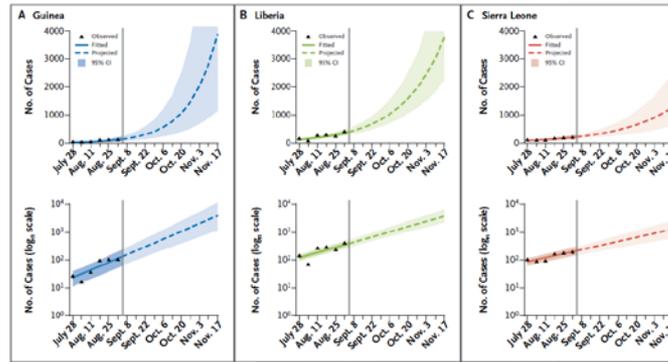
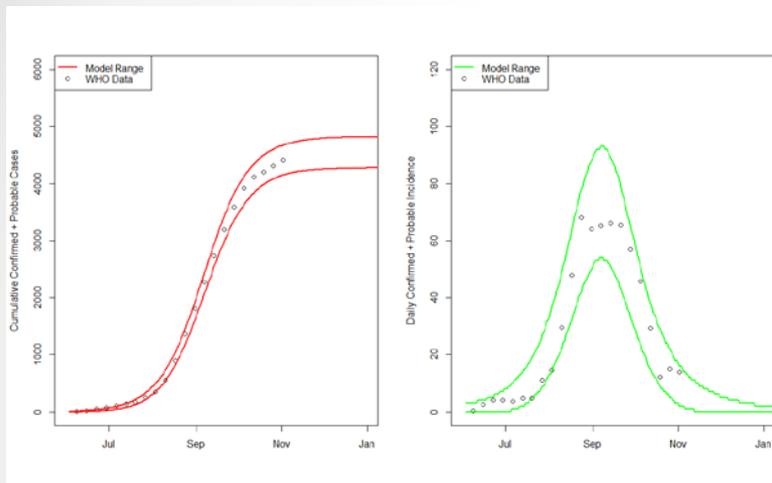
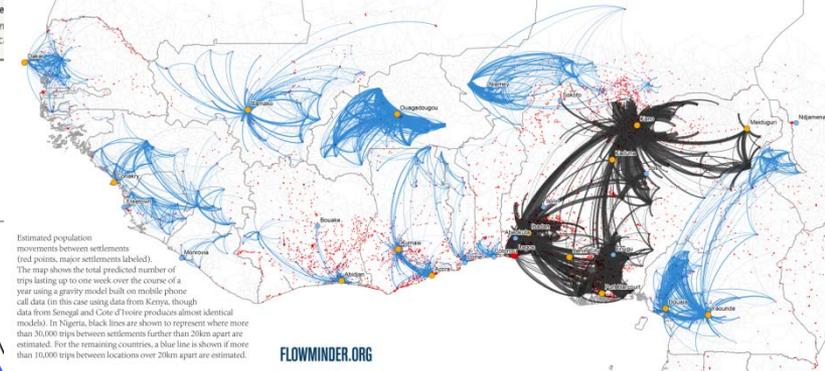
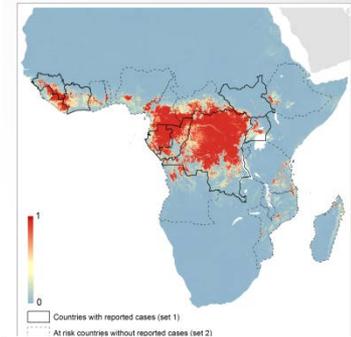


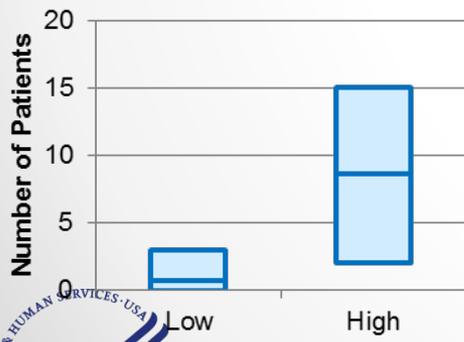
Figure 4. Observed and Projected Case Incidence
Observed and projected weekly case incidence in (upper panels) and logarithmic (lower panels) scale



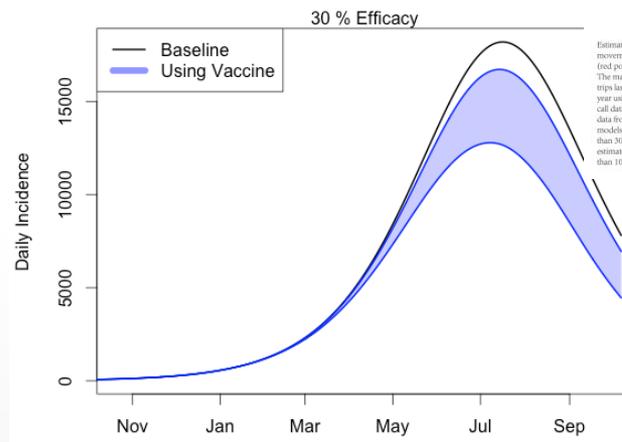
Estimated population movements between settlements (red points, major settlements labeled). The map shows the total predicted number of trips lasting up to one week over the course of a year using a gravity model built on mobile phone call data (in this case using data from Kenya, though data from Senegal and Congo D'ivoire produces almost identical models). In Nigeria, black lines are shown to represent where more than 30,000 trips between settlements further than 20km apart are estimated. For the remaining countries, a blue line is shown if more than 10,000 trips between locations over 20km apart are estimated.

FLOWMINDER.ORG

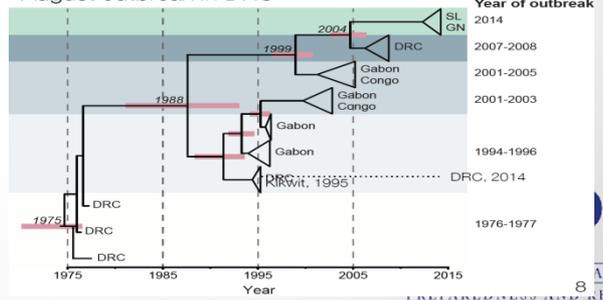
Estimated Number of Simultaneous Patients



Sierra Leone Impact of Vaccine



August outbreak in DRC



BARDA's Investments In Ebola

	Company	Funding (\$mm)	\$mm
Vaccines	Newlink/Merck	49.8	97.3 for vaccines (3 from FY2015 ARD)
	GSK	12.98	
	Janssen/BN	28.6	
	Profectus	5.9	
Therapeutics	MappBio	19.9	78.8 for therapeutics (25 from FY2014 ARD)
	BioCryst	17.8	
	Regeneron	17.1	
	CIADM - Genentech	19.8	
	CIADM - DuPont	0.4	
	Medicago	2.0	
	Faunhofer	1.8	
Fill/Finish Manufacturing	Nano/Baxter	7.0	
Diagnostic	OraSure	9.0	
Clinical Study	TRI/EMMES	18.9	
Non-clinical Studies	Various	2.8	(3 from FY2014/15 ARD)
Modeling	Leidos	1.2	
TOTAL INVESTMENT FROM CR and SUPPLEMENTAL		214.97	

BARDA's Response Has Been Global

