Development, Manufacturing and Supply of Ebola Vaccine

Jeffrey T. Blue

Director, Vaccine Drug Product Development

Merck & Co. Inc

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Presentation Outline

- **Ebola Background**
  - 2014 Outbreak
  - Clinical Candidates During Outbreak
    - Merck's Candidate
  - WHO Guinea Ring Efficacy Results
- **Merck's Commitment to Ebola**
  - Merck's Approach to Develop an Ebola Vaccine
  - Typical Vaccine Development
  - Merck's Ebola Vaccine Development Timeline
- **Process Development**
  - Scope of Work
  - Vaccine Path to PPQ
    - Upstream
    - Downstream
    - Drug Product
    - Site Readiness
- **Program Challenges**
- **Applicability to Other Vaccines and Biologics**
- **Conclusions**
- **Partners, Alliances, and Acknowledgements**

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2016 PDA Annual Meeting | March 14-16, 2016 | JW Marriott San Antonio Hill Country | San Antonio, TX

Ebola Virus

- **Member of the filoviridae family of viruses, first discovered in 1976 in the Ebola river (Zaire, now, Democratic Republic of Congo)**
- **Hemorrhagic fever and deadly disease caused by infection with one of the Ebola virus strains (Human: Zaire, Sudan, Ivory Coast, Bundibugyo; non-human primates: Reston)**
- **Animal-borne virus, with fruit bats as most likely reservoir**
  - Natural reservoir host not yet identified
- **Transmission by direct contact (through broken skin or mucous membranes) with blood or body fluids of infected individual or contaminated objects, and infected fruit bats or primates**

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2014 – 2016 Ebola Virus Outbreak

- **First case in Guinea March 2014 and peaked in Aug–Oct '14**
  - WHO declaration of Public Health Emergency on International Concern (PHEIC) on August 8th
- **Zaire ebolavirus species**
- **Cumulatively 28,000+ cases and 11,000+ deaths by January 2016**
  - > 10 times more cases during the current epidemic than in all previous outbreaks combined
  - Impacted: Guinea, Liberia, Sierra Leone
    - A few cases reported in Nigeria, Mali, Senegal, Spain, US, UK, and Italy
- **WHO declares outbreak over on January 14th, 2016**
  - New cases have been detected in Sierra Leone since

Latest Ebola outbreak over in Liberia; West Africa is at zero, but new flare-ups are likely to occur

News release

14 JANUARY 2016 | LIBERIA - Today, WHO declares the end of the most recent outbreak of Ebola virus disease in Liberia and says all known chains of transmission have been stopped in West Africa. But the Organization says the job is not over, more flare-ups are expected and that strong surveillance and response systems will be critical in the months to come.

Liberia was first declared free of Ebola transmission in May 2015, but the virus was re-introduced twice since then, with the latest flare-up in November. Today's announcement comes 42 days (two 21-day incubation cycles of the virus) after the last confirmed patient in Liberia tested negative for the disease 2 times.

http://who.int/mediacentre/news/releases/2016/ebola-zero-liberia/en/

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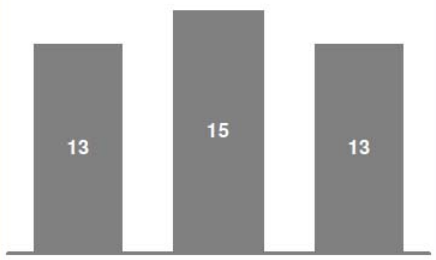
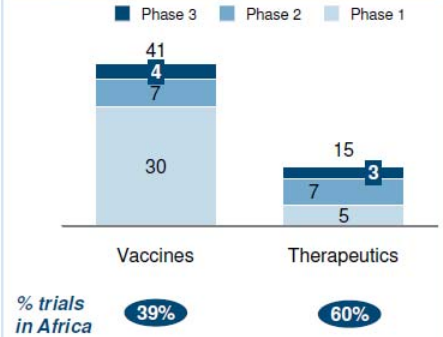
Ebola Clinical Candidates During 2014 – 2016 Western African Outbreak

Ebola vaccine, therapeutic, and diagnostic candidates in clinical development (2014-2015)



Clinical trials for Ebola vaccines and therapeutics[4] (2014-2015)



1 Considering different vaccine combinations/variants as distinct
2 Including therapies only given under compassionate use
3 Products that have received FDA or WHO emergency use listing; up to 80 are in some stage of development
4 Based on triangulation from public sources and stakeholder interviews. If a trial spans multiple phases or is unclassified, classification here is based on the highest phase or the trial's primary outcomes

SOURCE: Clinicaltrials.gov (September 2015), WHO ICTRP portal, Pan-African Trial Registry, Stakeholder interviews, WHO categorization of drugs for Ebola, WHO Diagnostics, FDA Emergency Use Authorizations

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Taken from WHO Report on Ebola R&D Landscape of Official Candidates and Trials (October 2015)

Development History for Merck's Ebola Vaccine Candidate

- **Application of the rVSV technology and initial development of the candidate Ebola vaccine was accomplished by Public Health Agency of Canada (PHAC)**
- **PHAC licensed the filovirus vaccine technology to NewLink Genetics to further development and initiate clinical development**
- **The initial PHAC clinical lot was manufactured in 2013 by a German CMO and utilized in most clinical trials**
  - NewLink Genetics filed IND and started Phase I trials (3 sites) and oversaw the clinical development
  - Funding to support development and clinical lots completed by multiple partners
    - BARDA, DTRA, Wellcome Trust, NIH, NIAID and WHO
  - PHAC lot utilized to support Phase II/III in West Africa (Liberia, Guinea, Sierra Leone)
  - NewLink Genetics continued to work with German CMO for additional clinical lots and process development
- **Towards the end of 2014, Merck and NewLink Genetics Corp. entered into an exclusive worldwide license agreement**
  - Merck assumed responsibility to research, develop, manufacture, and distribute the investigational Ebola vaccine candidate (rVSV- ΔG-ZEBOV-GP) and other filovirus based vaccines based on rVSV technology
- **Merck, NewLink Genetics and a global network of partners are collaborating in unprecedented ways with the singular focus on speeding the research, development and deployment of a well-tolerated and effective Ebola vaccine**

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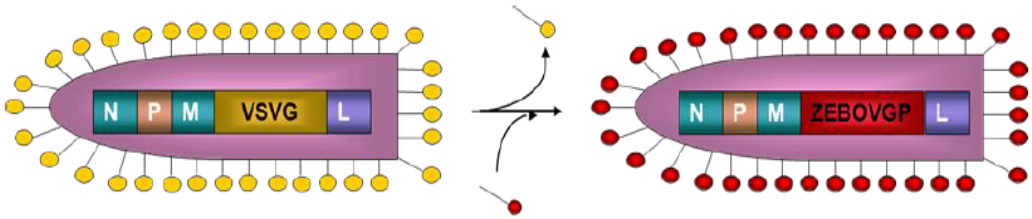
Composition of Merck's Ebola Vaccine Candidate (rVSV-ZEBOV-GP)

- **Vector = live attenuated recombinant vesicular stomatitis virus (rVSV)**
  - Antigen = Zaire Ebola virus (ZEBOV) glycoprotein (GP)
    - VSV G (envelope) GP replaced with Ebola-Zaire envelope GP
    - Eliminates VSV GP toxicity and changes host range
      - VSV is further attenuated by the GP substitution



VSV WT Glycoproteins switched VSVΔG/ZEBOVGP

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WHO Guinea Ring Vaccination Trial: Interim Analysis Efficacy Results

	All vaccinated in immediate versus all eligible in delayed (primary analysis)	All eligible and consented	All eligible (eligible adults, contacts and contacts of contacts)	All (all contacts and contacts of contacts)
Number of individuals (clusters)				
Immediate	2014 (48)	2048 (48)	3035 (48)	4123 (48)
Delayed	2380 (42)	1930 (42)	2380 (42)	3528 (42)
Number of cases at <10 days (affected clusters)				
Immediate	9 (4)	10 (5)	18 (9)	21 (9)
Delayed	16 (12)	6 (5)	16 (12)	25 (13)
Number of cases at ≥10 days (affected clusters)				
Immediate	0 (0)	0 (0)	6* (3)	8* (4)
Delayed	16† (7)	11† (5)	16† (7)	21† (7)
Vaccine efficacy/ effectiveness‡ (%; 95% CI)	100% (74·7 to 100)	100% (70·8 to 100)	75·1% (−7·1 to 94·2)	76·3% (−15·5 to 95·1)
p value§	0·0036	0·0194	0·1791	0·3351

*All cases occurred in unvaccinated individuals. †Four cases were vaccinated and developed symptoms on day 0, 2, 6, or 6 after vaccination. ‡From fitting a β-binomial distribution to the cluster-level numerators and denominators and using an inverted likelihood ratio test to identify the lower bound for vaccine efficacy (first two columns); from Cox proportional hazards model to estimate vaccine effectiveness (last two columns). §From Fisher's exact test (two-sided).

Table 2: Calculations of vaccine efficacy and vaccine effectiveness based on different study populations

Lancet publication of Interim Analysis on July 31st 2015

- **First evidence of efficacy in human subjects for any Ebola vaccine**
- **No EVD cases in either immediate or delayed arm from Day 6 post dose onward**
- **Study expanded into Sierra Leone with all additional subjects vaccinated upon enrollment (no delayed arm)**
- **Enrolling adolescents and children > 6 years old**

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Merck's Approach to Address Potential Vaccine Needs and Vaccine Availability

- **Move monovalent frozen product forward for licensure as efficiently as possible**
  - Complete clinical development to produce required safety database, demonstrate evidence of clinical benefit, and manufacturing consistency
  - Prepare commercial manufacturing facility and execute on manufacturing scale-up and PPQ activities
- **Collaborate with current dose owners and stakeholders to align on best use of existing doses of vaccine (~150 – 170K currently exist)**
  - Through expanded ring vaccination trials, new/expanded trials for at-risk US-based and ex-US populations, trials in special populations etc.
- **Ramp up Merck manufacturing capabilities (Pilot Plant) to produce additional doses that could be deployed in the case of expanded or new outbreak (not commercial doses; only for clinical trials or emergency use)**
  - Ethical obligation to ensure vaccine available in the event of another epidemic
- **Kick off early development of thermostable product(s) to protect against key Filoviruses**

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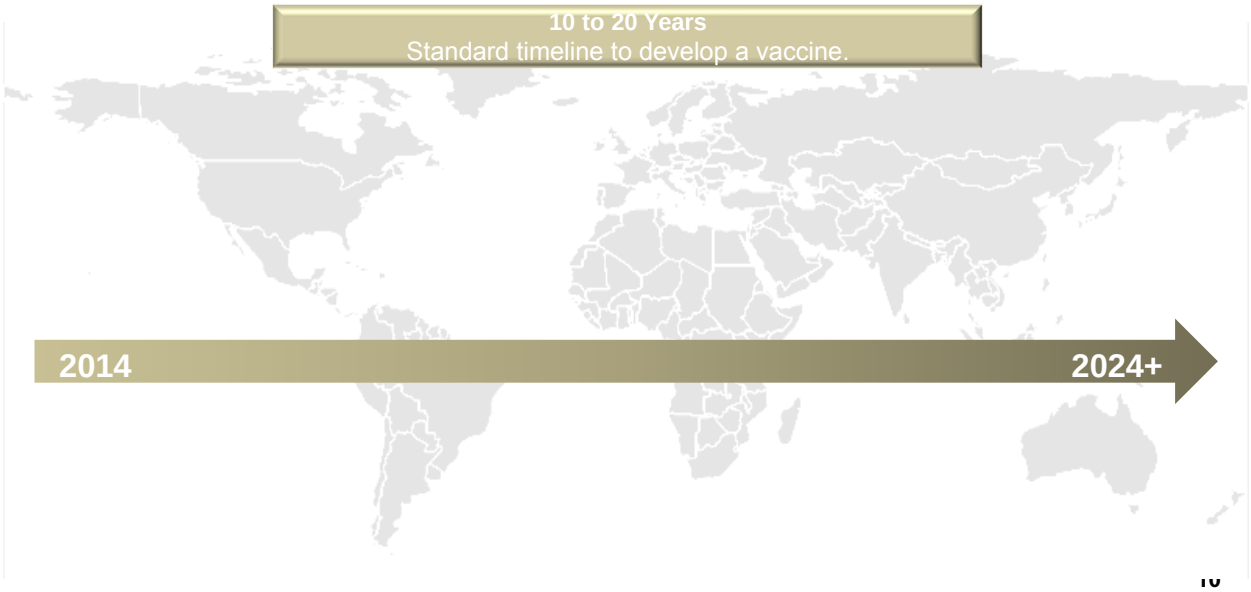
Typical Timeline for Vaccine Development



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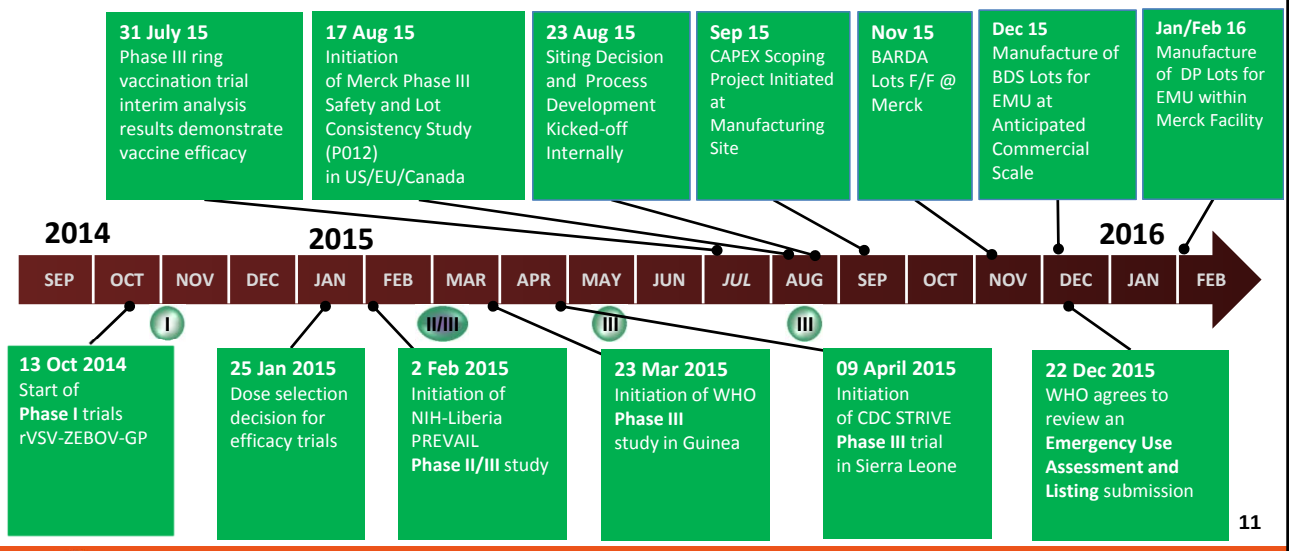
Merck's Vaccine Milestones and Accelerated Timeline to Develop the Ebola Vaccine

Over 18,000 volunteers vaccinated to date



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Process Development

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Scope of Process Development

- **Obtain data to support BLA filing**
  - Generate necessary lab-scale development data to support critical ranges
  - Generate comparison data of clinical and commercial processes
- **Develop commercial scale-up process and move from existing clinical process**
  - Show comparability between clinical and expected commercial process
  - Minimize changes to existing process to shorten timelines and accelerate program
  - Utilize knowledge gained through EMU manufacturing for scale-up development
- **QbD Risk based approach to parameter studies**
  - Gain process knowledge and explore processing surface to ensure process parameters are in a stable zone
  - Team not investigating all areas of process, but rather focused on key areas
    - Expedites process development and increases team's efficiency in delivering a commercial process
  - Utilizing clinical scale targets
    - Only adjusting unit operations necessary to ensure a robust manufacturing process is achieved (i.e. TFF)

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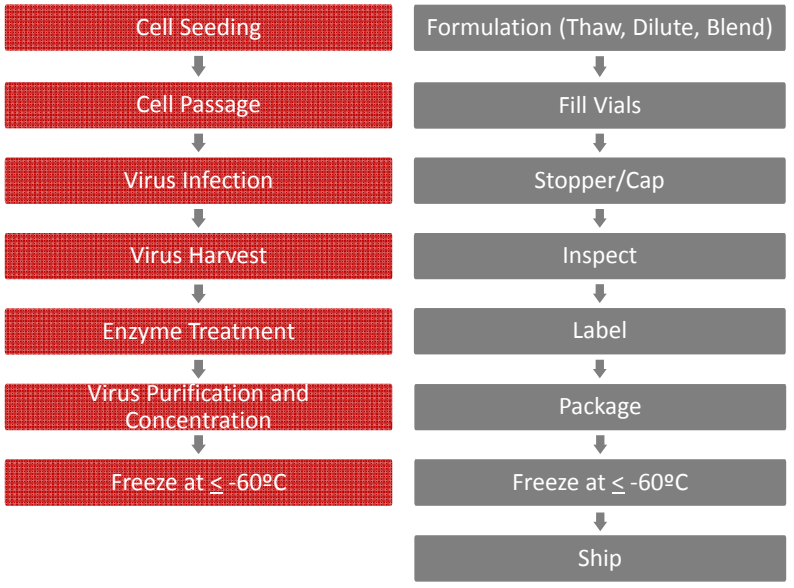
Vaccine Process Flow



- **DS and DP is stored and kept at ≤ -60C**
- **Preliminary data indicates DP stable at 2-8ºC for 3 – 4 weeks**
- **Next generation vaccine to explore a more thermostable formulation**

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Vaccine Path to PPQ (Upstream and Downstream Drug Substance Development)

Process Development Kicked Off [Aug2015] → Reviewed and scored prelim FMEA → Identified key experiments to support PPQ ranges

- **Upstream Development**
  - MOI
  - Plant density
  - Day of Infection
  - Harvest Time
  - PBS Rinse
  - Medium Age
- **Downstream Development**
  - Depth Filtration Pmax Studies
  - Enzyme Rxn
    - DOE
    - Time course studies
  - TFF
    - DOE
    - Impact of Loading
- **Other DS Studies**
  - Hold time studies
    - Stock seed
    - HVF
    - CH
    - RVH
  - Investigate various RB sizes

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Impact of MOI and Harvest Time: Finalized Response Surface Design

Factor	Levels
MOI (1 PFU: viable cell)	MOIs examined over 100-fold range
Harvest Timing (HPI)	Examined harvesting over multiple days post infection

JMP 11 design including replicates and 6 center points

30 conditions

Experiment 1	***Replicate experiment***	Experiment 2
Conditions 1-30		Conditions 1-30

Same design used in both experiments, replicate to gain confidence around results

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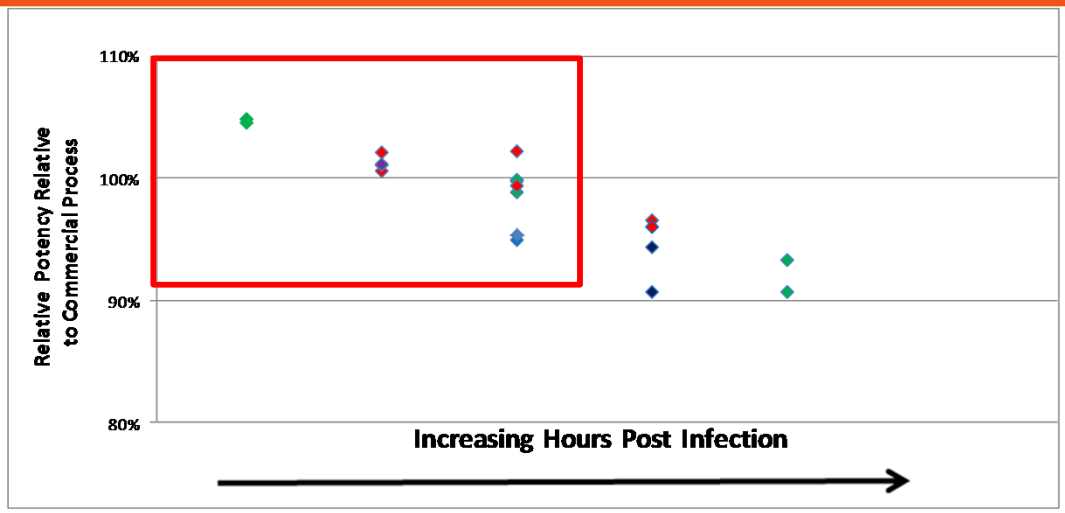
Relative Impact of MOI and Relative Harvest Time on Potency



- **Proposed operating space highlighted in red box**
  - Large operation window for Harvest time and MOI
- **Additional data pending from 3rd & 4th DOE at lower MOI**

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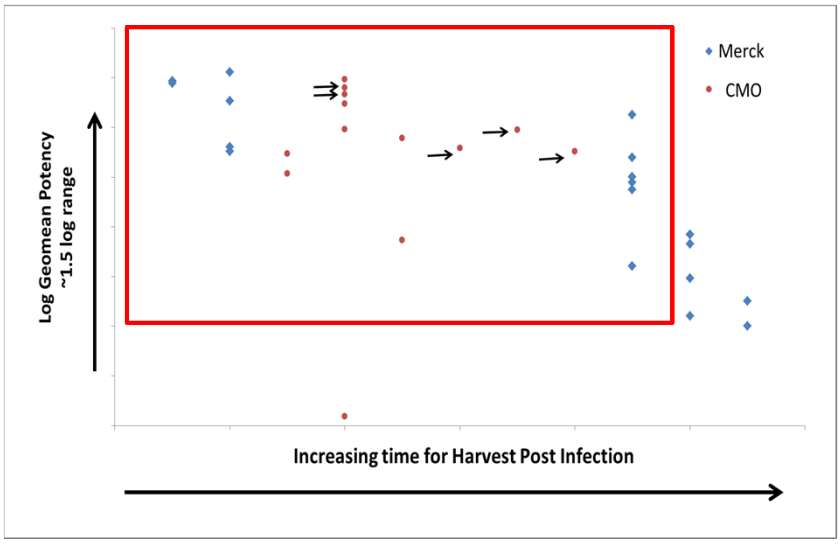
Comparison of the Expected Merck Commercial Process with Clinical Process



- **Data presented are for Harvested Viral Fluids**
- **Lab-scale results (blue diamonds) compared to clinical process (red circles)**
  - Arrows indicate lots utilized in clinical trials
- **Lab-scale and clinical processes comparable for potency and harvest times**
  - Development fits well into operating space

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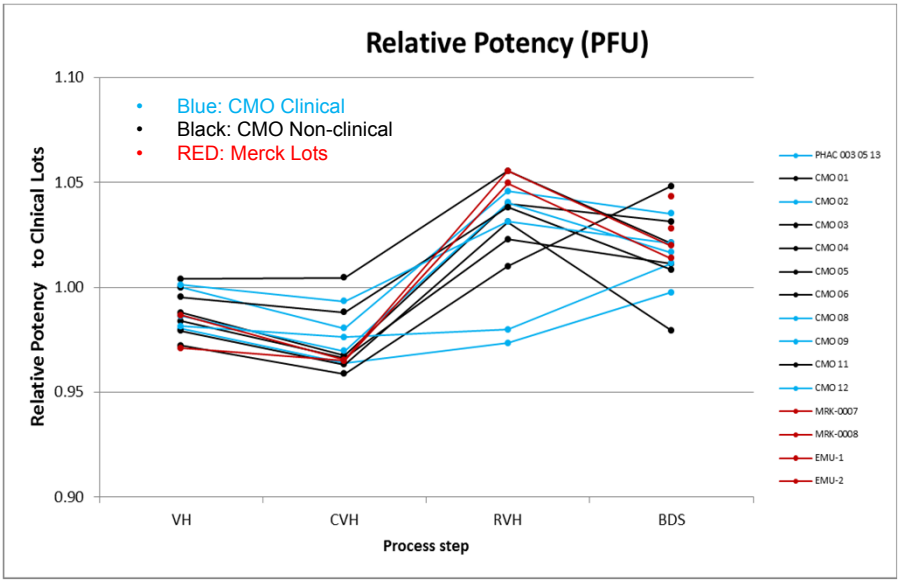
Process Comparability: Clinical/ Emergency Use / Commercial Scale



- **Commercial process is comparable to EMU and clinical process**
  - No significant differences in final BDS potencies
- **Final yields within clinical experience range**

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Expected Process Parameters (Comparison of Clinical and Commercial Process)

	Clinical Process (CMO)	Commercial Process
Harvesting Time	No Expected Changes	
MOI		
Reaction Temperature		
Reaction Time		
Reactor	GE Wave Bioreactor	200L SU Jacketed Vessel
Mixing Process	Rocking	Bottom Mounted Magnetic Stirrer

- **No significant changes across the process expected**
  - Goal is to minimize changes, only modify steps necessary for scale-up

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Vaccine Path to PPQ (DP Development)

- **Impact of shear and mixing on final formulated bulk (FFB)**
- **Short-term stability studies to investigate the impact of normal manufacturing times and temperatures on drug product potency**
  - 2-8C
  - TOR
- **Impact of freezing and thawing**
- **BDS dilutability studies to target a final DP potency**
- **Materials of contact experiments and examination of CCI for the final DP image**
  - SD and MD vials
  - Examination of different formulation vessels (i.e., SS, Glass, SUT)
- **Long-term stability studies for DP stability studies**

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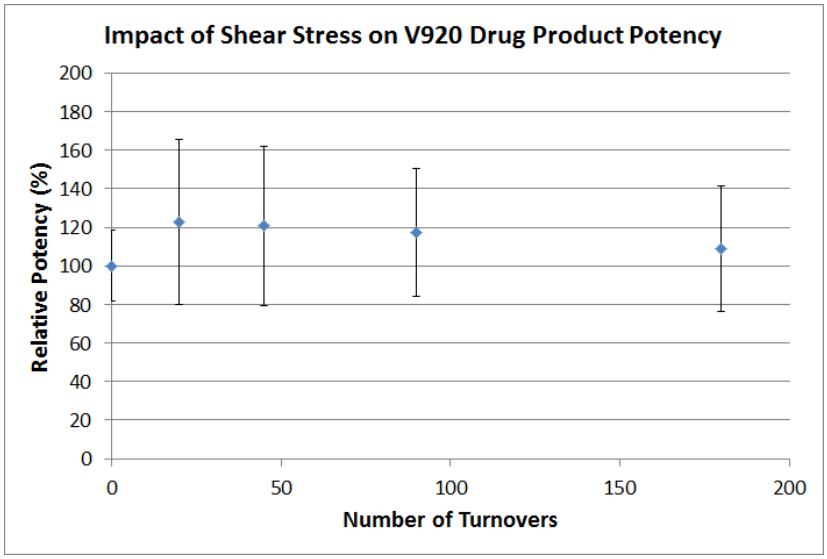
DP Results: Impact of Vaccine to Shear



- **DP not impacted by shear stress**
  - DP was exposed to 180 turnovers in an experimental shear cell

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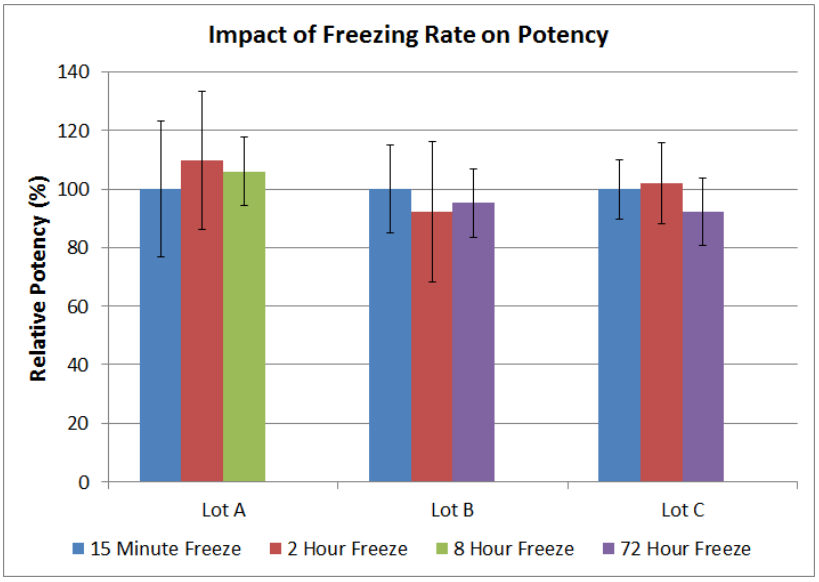
Impact of Freezing Rate of Ebola DP stability



- **Evaluated impact of freezing rate on DP**
  - Quick freezing in LN2 blast freezer (15min)
  - Slow freezing in -70C freezer (2 & 8hr)
  - 72hr freeze controlled in Lyophilization cabinet
    - Mimics expected large lot freezing time
- **Method of freezing does not appear to impact potency**
  - Allows flexibility for manufacturing and freeze process

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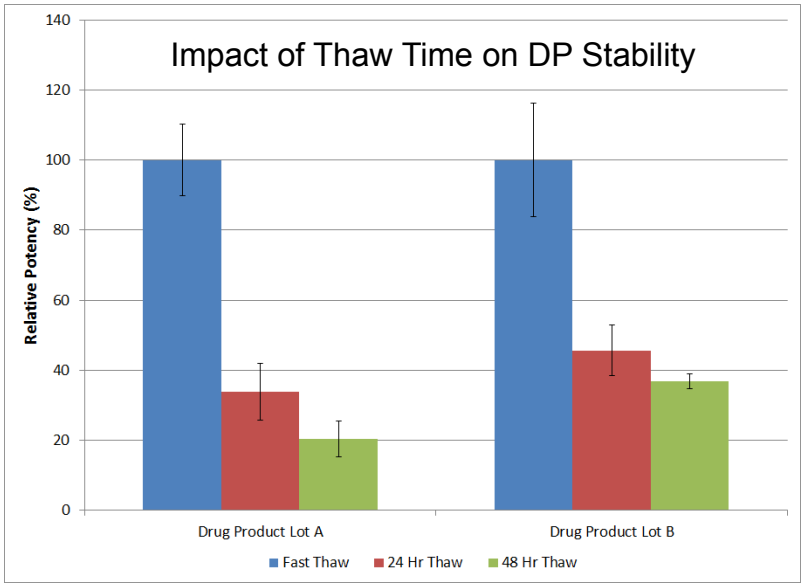
Impact to Thawing Rate on Ebola DP Potency (10D image)



- **Thaw rate impacts DP potency in 10D image**
  - Studies underway to examine single dose image
- **Thawing protocol important for vaccine field use**
  - Thaw at RT to minimize the thaw time

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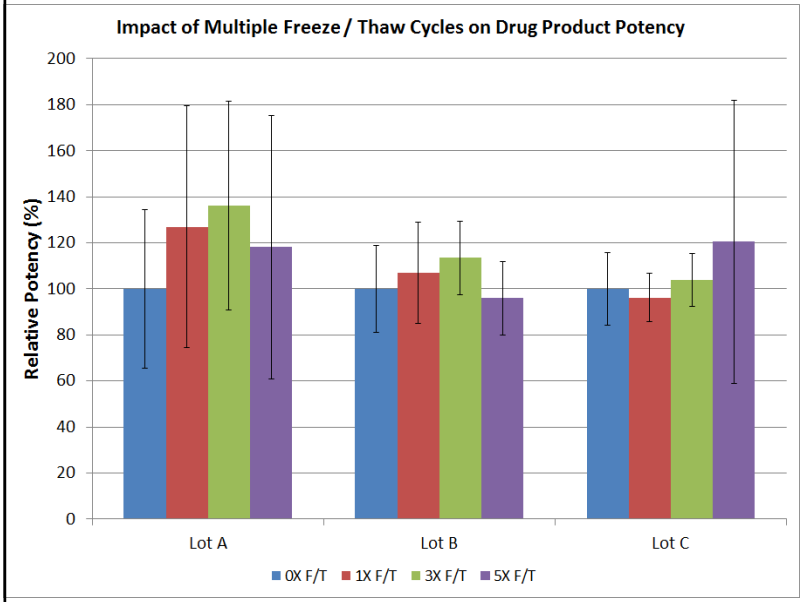
Ebola DP Freeze / Thaw Stability



- **Vaccine appears stable through 5 Freeze-thaw cycles**
  - Flexibility in manufacturing for packaging and labelling
  - Vials frozen in -70ºC freezer and thawed at room temperature

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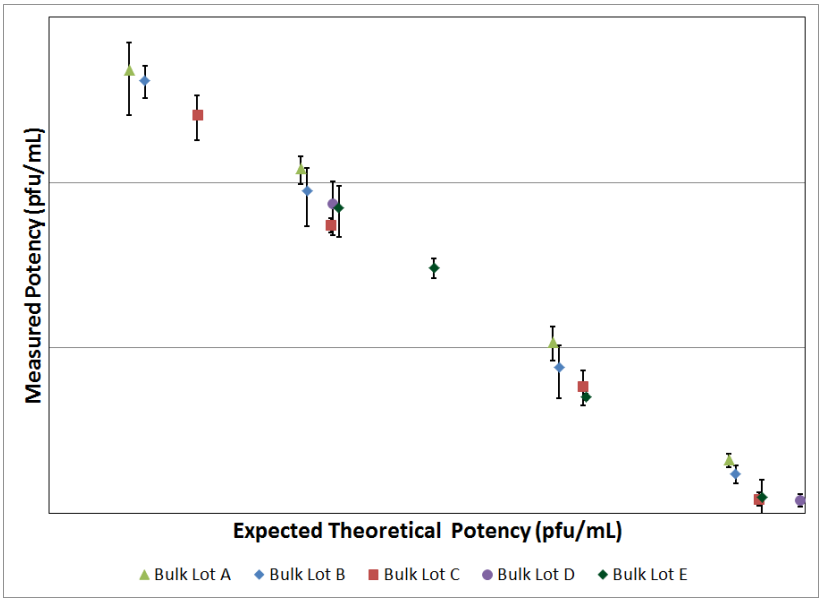
Dilutability of Ebola BDS to DP Target Potency



- **BDS can be diluted to specified DP potency**
  - Increased confidence in achieving formulation and filling targets
    - Examined both clinical and commercial processes

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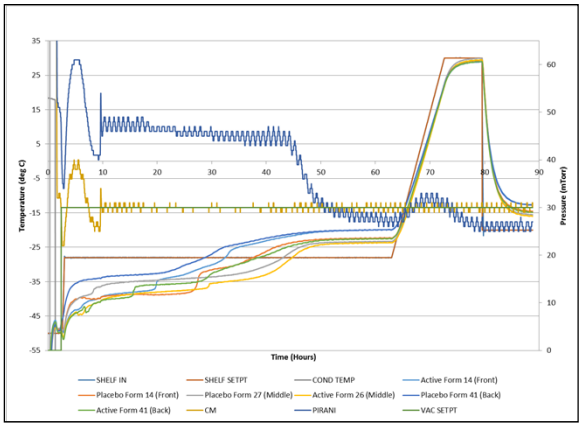
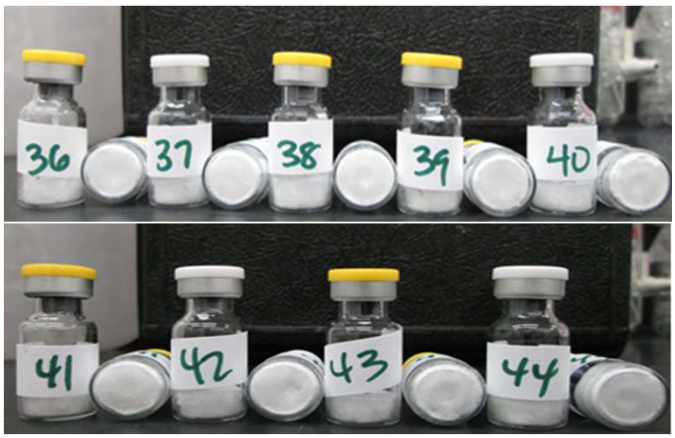
Initial Development of Lyophilized Formulation for Potential Ebola Next Gen Product





- **All formulations examined achieve acceptable cake appearance with non-optimized cycle**
- **Initial formulation development focused on lyophilization yields and accelerated stability**
  - Utilize accelerated stability to identify lead formulations for long-term stability studies

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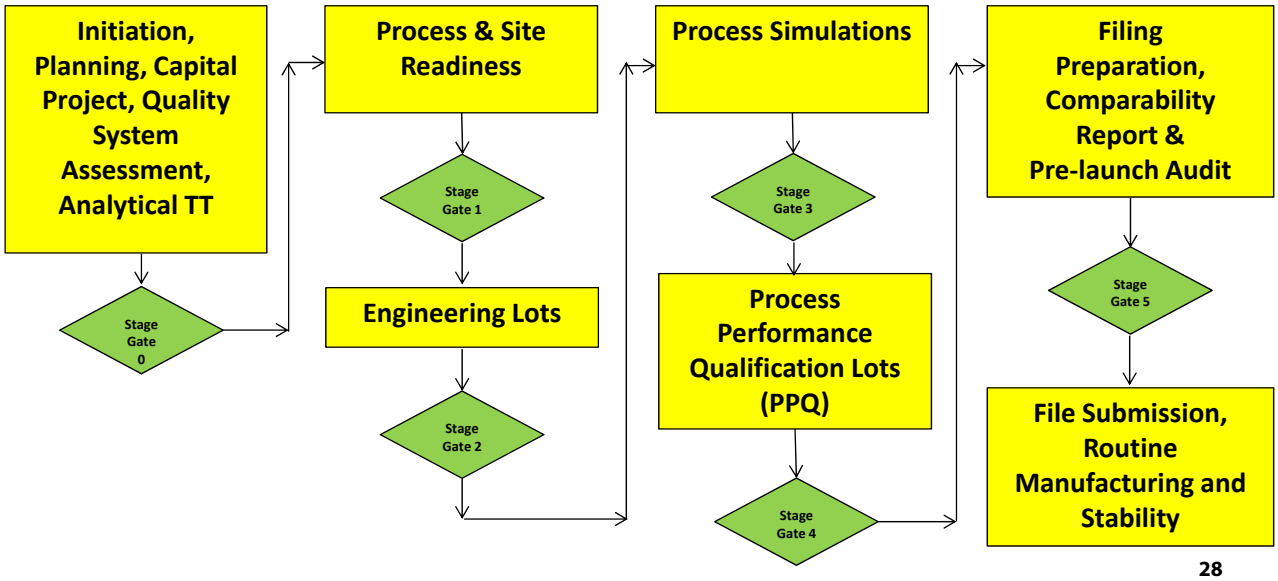
Tech Transfer Site Readiness Roadmap



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Program Challenges

- **Three parallel activities within Merck to drive program forward and inability to sequence**
  - Develop Scale-up process for Commercial Manufacturing
    - Site and Tech Transfer strategy and CapEx project to ready the facility as soon as possible
    - Process not fully assessed and design space not understood, required development in-lab to fit to facility and better understand process
  - Manufacture Emergency Use Material to Support a Potential Future Zaire Ebola Outbreak
    - Ensure doses available prior to licensed product in an emergency / clinical setting
  - Development efforts initiated for next generation vaccine candidate
    - Thermostable lyophilized product
- **Different approaches to risk based decision making**
  - Team not investigating all areas of process, but rather focused on key areas
    - Expedites process development and increases team's efficiency in delivering a commercial process
- **Rapidly evolving external environment**
  - Aug. 2015: Ebola Outbreak in progress; Jan. 2016; WHO declares Ebola outbreak over
  - Numerous points to interact with during development for both development and funding
    - WHO, GAVI, BARDA, DTRA, DOD, Wellcome Trust, NewLink/BPS, NIH, NIAID

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Applicability of Strategy Applied for Merck's Ebola Vaccine to Other Programs

- **Examination of changes in scale and bulk process for later stage development**
  - Changing scale
    - Moving from clinical scale to commercial scale
  - Moving to different platform for production
    - RB process to cell stacks or microcarriers for BDS production
  - Moving from transient transfectants in early stage development to stable clones
- **Formulation changes during development**
  - Biologics utilizing "platform" formulations in early phase programs and later moving to commercial formulation
  - Moving from frozen liquid formulations to improved refrigerator stable and lyophilized formulations as move into Phase II and beyond
- **Building strong analytical comparability to minimize clinical studies**

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Summary, Conclusions, and Successes

- **Merck committed to move the vaccine forward to licensure as quickly as possible and ensure vaccine availability for at-risk populations in advance of product licensure**
  - Merck has successfully manufactured clinical trial/EMU supplies
    - Filed necessary EUAL with WHO
- **Strong preclinical data, including evidence of protection after single dose**
  - Positioned the vaccine to be an important vaccine candidate in response to recent Ebola outbreak
- **Merck has shown ability to scale process from clinical to commercial process**
  - Comparability assessment underway between processes
- **Initial efforts underway to examine next generation product**
  - Thermostable / lyophilized product
- **Merck and NewLink working in collaboration with a large number of partners**
  - Regulators, Academia, International Health Agencies, NGOs, US Military, and other US and ex-US government agencies have moved the vaccine forward at an unprecedented pace

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Partnerships and Alliances

Public Health Agency of Canada (PHAC)

NewLink Genetics (Bio-Protection Systems Corporation)

Phase I Studies

WHO Clinical Consortium/ Wellcome Trust

- **Switzerland**: University Hospitals of Geneva
- **Germany:** University Medical Center Hamburg/Clinical Trial Center North
- **Gabon:** Centre de Recherches Medicales de Lambarene/University of Tuebingen
- **Kenya:** Kenya Medical Research Institute
- Marburg Laboratory

- CCV – Halifax, Canada
- US Department of Defense (WRAIR, JVAP, USAMRIID, DTRA)
- NIAID/NIH
- BARDA

Phase II/III Studies

- **Liberia:** Liberia – NIH Partnership (NIAID)
- **Sierra Leone:** CDC/ Sierra Leone Medical School, BARDA
- **Guinea:** WHO/Norwegian Institute of Public Health//MSF/Health Canada
- US Department of Defense (WRAIR, JVAP, USAMRIID, DTRA)

Acknowledgements

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- Kim Hassis
- Kay Hunsberger
- Lynne Isopi
- Risat Jannat
- Maggie Keane
- Tom Monath (NewLink Genetics)
- Richard Peluso
- Erica Strable
- Francis Torres
- Julie Waterbury
- Merck-NewLink Joint Steering Committee
- V920 IDST and PDT
- Merck Senior Leaders across the company
- Multiple external partners and collaborators
- Multiple external funding organizations

- Elements of this program has been funded in whole or in part with Federal Funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response; Biomedical Advanced Research and Development Authority under Contract Number: HHSO100201500002C

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Thank You!!

V920 Merck's selection of the NewLink rVSVΔG-ZEBOV-GP LVV live attenuated candidate was validated with extremely positive efficacy results

QUESTIONS?

The V920 internal Merck team is highly functioning, motivated and dedicated. They have accomplished an extraordinary amount of work with external partners in a relatively short time frame. "Best team I've ever worked with in my career"

Back-ups

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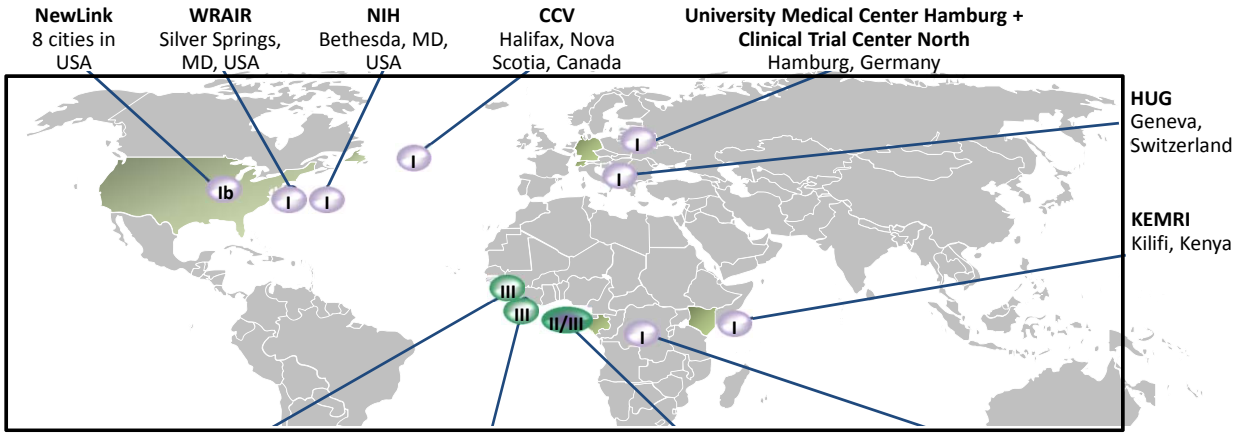
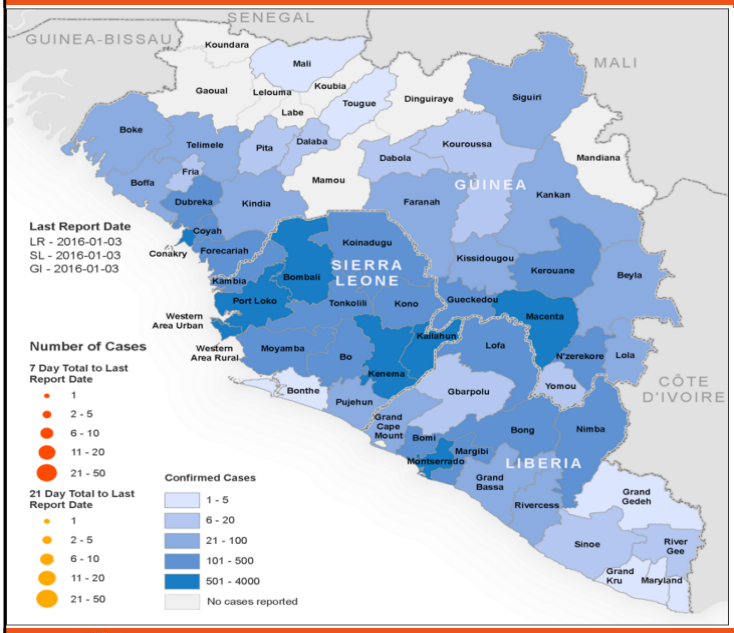
The International Partnership Facilitating rVSV-ZEBOV Clinical Trial Evaluation



- Supported by the WHO, NewLink, Merck, and the Public Health Agency of Canada. Funding from the US Department of Defense, NIAID, BMGF, Wellcome Trust, and the European Commission.

In 2014-5, the Zaire Ebola outbreak spread throughout all three countries most heavily impacted by Ebola.



- From a single case identified in Liberia in May 2014, all prefactures within Sierra Leone and Liberia and 70% of prefactures in Guinea were touched by Ebola.
- Geographical distribution of new and total confirmed cases, 03-Jan-2016, by WHO

- http://apps.who.int/ebola/current-situation/ebola-situation-report-6-january-2016

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Chronology of Ebola Outbreaks sine 1976

Year	Country	Virus	Cases	Deaths
1976	Zaire (DRC)	Zaire	318	280 (88%)
1976	Sudan (South Sudan)	Sudan	284	151 (53%)
1979	Susan (South Sudan)	Sudan	34	22 (65%)
1994	Gabon	Zaire	52	31 (60%)
1994	Ivory Coast	Ivory Coast	1	0
1995	DRC	Zaire	315	250 (81%)
1996	Gabon	Zaire	37	21 (57%)
1996-7	Gabon	Zaire	60	45 (74%)
2000-1	Uganda	Sudan	425	224 (53%)
2001-2	Gabon	Zaire	65	53 (82%)
2001-2	Rep of Congo	Zaire	57	43 (75%)
2002-3	Rep of Congo	Zaire	143	128 (89%)

Year	Country	Virus	Cases	Deaths
2003	Rep of Congo	Zaire	35	29 (83%)
2004	Susan (South Sudan)	Sudan	17	7 (41%)
2007	DRC	Zaire	264	187 (71%)
2007-8	Uganda	Bundi-bugyo	149	37 (25%)
2008-9	DRC	Zaire	32	15 (47%)
2011	Uganda	Sudan	1	1 (100%)
2012	Uganda	Sudan	11	4 (36%)
2012	DRC	Bundi-bugyo	36	13 (36%)
2012-3	Uganda	Sudan	6	3 (50%)
2014-Present	Multiple	Zaire	28287	11309 (39%)
2014	DRC	Zaire	66	49 (74%)

*Exclude Reston outbreaks, isolated laboratory infections

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