Ebola Prevention Vaccine Evaluation in Sierra Leone

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Sierra Leone – CDC Collaboration

World Health Organization, Geneva
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Principal Partners

Sierra Leone
- College of Medicine and Allied Health Sciences
  (Co-PI Dr Samai)
- Ministry of Health and Sanitation

United States
- Centers for Disease Control and Prevention
- Biomedical Advanced Research and Development Authority (BARDA)

World Health Organisation

Vaccine Manufacturers
Overview

- Study design and sample size
- Safety
- Regulatory
- Implementation
- Next steps
Study Design and Sample Size
Study Objectives

Overarching goal is to accelerate introduction of an Ebola vaccine among high-risk individuals while concurrently evaluating efficacy and safety.

Primary scientific objectives are to:
1. Estimate the efficacy of the vaccine in preventing laboratory-confirmed Ebola virus disease (EVD) > 21 days post-vaccination
2. Assess serious adverse events (SAEs) following administration of the vaccine

Secondary scientific objectives are to:
1. Estimate the efficacy of the vaccine in preventing death due to laboratory-confirmed EVD
2. Estimate the efficacy of the vaccine in preventing laboratory-confirmed EVD at earlier time points post-vaccination (>7 days, >14 days)
3. [Subgroup] Assess reactogenicity and unsolicited adverse events (AEs) in approximately the first 200 study participants to be vaccinated with the vaccine
Study Population

- Healthcare and frontline workers in Sierra Leone
  - 18 years of age and older
  - HCWs in an Ebola care, holding, or treatment center
  - Other HCWs providing non-Ebola-related healthcare
  - Front line workers (e.g., surveillance officers, ambulance workers, burial teams)
  - Both nationals and expatriates are eligible if they anticipate working in a response role during the full study vaccination period
Proposed Districts in Sierra Leone for Vaccine Evaluation

First choice

Extra if needed

1 - Western Area Urban
2 - Western Area Rural
Confirmed Ebola Cases 22 December - 04 January 2015

Confirmed Cases Reported:
- 300+
- 150 - 299
- 50 - 149
- 5 - 49
- 0 - 4

District Name
2 Week Total (Outbreak Total)
# Confirmed Cases  # Total Confirmed Cases
22 Dec - 04 Jan 2015  23 May - 04 Jan 2015

Confirmed Cases:
- Since 22 December 2014: 589
- Since 23 May 2014: 7,606

These maps have been produced by CDC on behalf of the Sierra Leone Ministry of Health and Sanitation. They do not express an official view of the Ministry of Health and Sanitation, the CDC, or the United States Government.
Stepped Wedge Design

- Allows for evaluation of vaccine efficacy (VE) using a phased vaccine introduction period
- Accelerates time to vaccination of all participants
- Clusters of the target population (e.g., hospitals/clinics, Ebola Treatment Units, burial teams, etc.) are randomized to receive vaccine over different weeks
- Follow-up of the cohort begins at week 0 for all participants, regardless of when they have been randomized to receive vaccine
- A participant’s status will cross over from unvaccinated to vaccinated during his/her randomly assigned vaccination week
### Example Vaccination Groups:

1. Facility HCW such as doctors, nurses, phlebotomists
2. Facility support such as cooking and food delivery, housekeeping, sanitation
3. Ambulance teams
4. Burial teams

Each of 3 shifts is a treated as a different Vaccination Group. Vaccination Groups and shifts are distributed evenly across Vaccination Weeks, with a vaccination weeks assigned at random.
Sample Roster of Vaccination Cluster Types: Western District

<table>
<thead>
<tr>
<th>Cluster Type</th>
<th>No. Clusters</th>
<th>Workers per Cluster</th>
<th>Total no. Workers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community Health Clinic</td>
<td>30</td>
<td>30</td>
<td>900</td>
</tr>
<tr>
<td>Clinic</td>
<td>21</td>
<td>15</td>
<td>315</td>
</tr>
<tr>
<td>Community Health Post</td>
<td>23</td>
<td>10</td>
<td>230</td>
</tr>
<tr>
<td>Maternal and Child Health Post</td>
<td>30</td>
<td>5</td>
<td>150</td>
</tr>
<tr>
<td>Secondary Hospital</td>
<td>10</td>
<td>100</td>
<td>1000</td>
</tr>
<tr>
<td>Burial Teams</td>
<td>20</td>
<td>12</td>
<td>240</td>
</tr>
<tr>
<td>District Surveillance Officer</td>
<td>24</td>
<td>3</td>
<td>72</td>
</tr>
<tr>
<td>Ambulance Teams</td>
<td>22</td>
<td>2</td>
<td>44</td>
</tr>
<tr>
<td>Quarantine</td>
<td>1</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Nutrition</td>
<td>2</td>
<td>18</td>
<td>36</td>
</tr>
<tr>
<td>Tertiary Hospital</td>
<td>3</td>
<td>250</td>
<td>750</td>
</tr>
<tr>
<td>Contact Tracers</td>
<td>46</td>
<td>10</td>
<td>460</td>
</tr>
<tr>
<td>EHCs</td>
<td>8</td>
<td>50</td>
<td>400</td>
</tr>
<tr>
<td>ETUs</td>
<td>2</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>EHC/ETUs</td>
<td>3</td>
<td>160</td>
<td>480</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>245</strong></td>
<td></td>
<td><strong>5202</strong></td>
</tr>
</tbody>
</table>
Estimation of Vaccine Efficacy

- Participants followed for EVD outcomes; symptom onset dates of laboratory-confirmed cases recorded

- Cox proportional hazards regression used to estimate a hazard ratio with time-varying vaccination status and implicit stratification on time to control for confounding by time and survivor bias

- The hazard ratio can be interpreted as an incidence density ratio, defined as incidence rates of infection within vaccinated versus unvaccinated follow-up time.

- Vaccine effectiveness or VE = (1-IDR) · 100%
Safety
Exclusion criteria

- Pertinent exclusion criteria *
  - Pregnancy – will test for pregnancy with kit
  - Immunocompromised – clinical evidence - no HIV testing
  - History of EVD or under quarantine for exposure
  - Previous receipt of investigational Ebola or Marburg vaccine
  - Allergy to prior vaccine of vaccine component
  - Known research agent or other vaccine within previous 28 days
  - Fever $\geq 38^\circ$C at time of vaccination

* Details presented using vaccination with cAd3-ZEBOV as an example.
Safety Component *

- Enrollment period, vaccination Day 0 in AM, vaccinee stays home for rest of Day 0
- Monthly telephone call follow-up for SAE ** monitoring for all 6,000 people for 6 months
- Reactogenicity in 200 people subset on Days 1-7 mainly looking for fever and severe local and systemic reactions
- Will track pregnancies exposures that come to attention for outcome (if pregnant on Day 0 or within 1 month of vaccination)

* Monitoring plan presented using vaccination with cAd3-ZEBOV as an example.

** SAE: Death, event that is life-threatening, hospitalization, prolongation of existing hospitalization, significant disability, congenital anomalies, other medically important events that may require intervention to prevent one the above outcomes, excluding EVD.
Site Enrollment

Roster Development

Recruitment & Sensitization

Eligibility Screening

Consent to vaccination

Enrollment of participant

Randomization to vaccination week

Phased vaccination period

Subgroup (n=200)

Interim monitoring

AEFI Monitoring
- SAE: active & passive monitoring for 6 months in all subjects
- Other AE: enhanced safety monitoring for 1 month in subset (n=200)

Final study call: 6 months post-vaccination

VE & Safety Analysis

Provision of care for study participants

Ongoing Site Surveillance for EVD

Recruitment & Sensitization
Data Safety Monitoring Board

- Data Safety Monitoring Board will be convened
  - Review protocol before initiation
  - Monitor study conduct during the study, including safety & efficacy
  - Powered to detect *increased* risk of Ebola Disease

- Will include representation and expertise of:
  - Ebola virus disease
  - Vectored vaccines
  - Bioethics
  - Clinician
  - Adult immunization safety
  - Statistics
  - Sierra Leone

- AE causality assessment by Sierra Leone Committee for Adverse Events Following Immunization
  - Immediate report of Serious and Unexpected Adverse Events
Ethical Review (IRB)

- Ethical review will be conducted by both CDC IRB & Sierra Leone Ethics and Scientific Review Committee
- CDC IRB submission December 5th, initial review complete; approval pending resolution of comments
- Sierra Leone IRB initial submission complete; pending resubmission with response to comments
- Future amendments are possible and will be submitted to both for re-review and approval as protocol is finalized
Pre-Investigational New Drug (IND) meeting

- Completed in December 2014

- Discussed the proposed study plan with FDA to identify and resolve significant issues prior to IND submission to ensure generation of meaningful data supportive of expanded use and/or licensure
Investigational New Drug (IND) Submission

- Obtain U.S. Food and Drug Administration (FDA) “safe-to-proceed” to conduct clinical study with unapproved (investigational) product

- Intention of the IND to support expanded access and/or licensure of the vaccine

- Submission to the Pharmacy Board of Sierra Leone (FDA equivalent regulatory body) planned in parallel
Submission to the Pharmacy Board of Sierra Leone

- IRB approved protocol and study forms
- Letter of agreement between COMAHS and US CDC
- DSMB members including at least one Sierra Leonean
- Documentation of registration with Pan African Clinical Trials Registry
- Declaration that study investigators will comply with GCP principles
- Investigators Brochure and CMC
- Application for approval for importing study vaccine
Implementation
Clinical Research Organization (CRO) Support

- Identifying CRO to assist with clinical trial functions through engagement of BARDA’s existing clinical studies network contract

- CRO tasks may include:
  - Data Management
  - Site Monitoring
  - GCP and GCLP Training
  - Project management
  - Administrative support
Critical Implementation Needs

- Cold chain
- Vaccination
- Surveillance
- Care for study subjects
  - EVD
  - AEFI
- Laboratory testing and EVD confirmation
- Communications and sensitization
- Logistics
- Project management
- Space, transport, security
Next steps for vaccine selection

- Monitor safety and immunogenicity data from ongoing vaccine trials as they become available
- Decide on which vaccine (and dose)
- Primary criteria:
  - At least moderate short term effectiveness likely
  - No serious safety signal from data
  - Sufficient data and vaccine to start in early 2015
  - Capacity to ramp up production
  - Practical regimen
Next steps

- IRB approval of final protocol
- File regulatory approval
- Clinical Trial Agreements with companies
- Hire and train personnel
- Finalize study logistics
- Begin enrollment
Communication and sensitization, ongoing discussion with partners

Timeline

October 2014
- Share plans and coordinate with partners
- Determine roles and responsibilities
- Estimate needs in staff, infrastructure, funding

November 2014
- Continue work on study protocol, SOPs, data collection forms

Dec 2014-Feb 2015
- Review Phase 1 data
- Finalize protocol
- Obtain ethical and regulatory approvals
- Setup sites
- Hire & train staff
- Launch communications

First quarter 2015
- Start recruiting, training, and hiring

Second-Third quarter 2015
- Begin data collection
- Establish communication channels with partners
- Monitor progress and adapt plans as necessary
Thank you

Questions?

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Study power with constant and declining background incidence*

<table>
<thead>
<tr>
<th>VE</th>
<th>Constant incidence 1%/m</th>
<th>Declining incidence 1%/m -&gt; 0.5%/m</th>
<th>Declining incidence 1%/m -&gt; 0%/m</th>
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</thead>
<tbody>
<tr>
<td>50</td>
<td>0.81</td>
<td>0.54</td>
<td>0.12</td>
</tr>
<tr>
<td>60</td>
<td>0.95</td>
<td>0.72</td>
<td>0.16</td>
</tr>
<tr>
<td>70</td>
<td>&gt;0.99</td>
<td>0.88</td>
<td>0.23</td>
</tr>
<tr>
<td>80</td>
<td>&gt;0.99</td>
<td>0.97</td>
<td>0.31</td>
</tr>
<tr>
<td>90</td>
<td>&gt;0.99</td>
<td>0.99</td>
<td>0.35</td>
</tr>
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</table>

*Alpha = 0.025
100 simulations (more will be done)
4475 participants, no loss to follow-up
30 week study duration
28 weeks of vaccine rollout (wedges)
11 weeks to full sero-conversion from prime + boost
The following table contain sample sizes required for 80% power to detect selected vaccine effectiveness (VE) or higher, for decreased risk of Ebola infection during vaccinated compared with unvaccinated follow-up time (alpha=0.025, see note at bottom). Sample sizes are calculated for background infection rates of 0.5%, 0.75%, 1.0% per month. Design Effect (DEFF) is assumed = 1.1, and is used to inflated sample sizes to account for clustering of subjects within clinics or other facilities. A loss to follow-up (LTFU) rate of 20% is assumed. 50% of follow-up time is vaccinated, 50% of follow-up time is unvaccinated. Tables also show incidence density ratios (IDR) or higher that can be detected when using the sample sizes required for detecting selected VE% or higher.

<table>
<thead>
<tr>
<th>Power</th>
<th>alpha</th>
<th>VE% or higher</th>
<th>Background rate of infection per month</th>
<th>Total cases</th>
<th>Required Combined vaccinated and unvaccinated follow-up time (person-months)</th>
<th>Total persons followed up for 18 week study duration (with DEFF=1.1)</th>
<th>Total persons followed up for 18 week study duration (with LTFU=20%)</th>
<th>Total persons followed up for 18 week study duration (with LTFU=20%)</th>
<th>IDR or higher that is detectable with sample size for VE</th>
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<tbody>
<tr>
<td>80</td>
<td>0.025</td>
<td>80</td>
<td>0.50</td>
<td>17.9</td>
<td>5,980</td>
<td>2,044</td>
<td>2,248</td>
<td>2,810</td>
<td>2.36</td>
</tr>
<tr>
<td>80</td>
<td>0.025</td>
<td>80</td>
<td>0.75</td>
<td>17.9</td>
<td>3,990</td>
<td>1,363</td>
<td>1,499</td>
<td>1,874</td>
<td>2.36</td>
</tr>
<tr>
<td>80</td>
<td>0.025</td>
<td>80</td>
<td>1.00</td>
<td>17.9</td>
<td>2,990</td>
<td>1,022</td>
<td>1,124</td>
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<td>2.36</td>
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<tr>
<td>80</td>
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<td>70</td>
<td>0.50</td>
<td>28.2</td>
<td>8,670</td>
<td>2,963</td>
<td>3,259</td>
<td>4,074</td>
<td>2.08</td>
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<td>70</td>
<td>0.75</td>
<td>28.2</td>
<td>5,780</td>
<td>1,975</td>
<td>2,173</td>
<td>2,716</td>
<td>2.08</td>
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<tr>
<td>80</td>
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<td>70</td>
<td>1.00</td>
<td>28.2</td>
<td>4,330</td>
<td>1,481</td>
<td>1,629</td>
<td>2,037</td>
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<tr>
<td>80</td>
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<td>60</td>
<td>0.50</td>
<td>44.8</td>
<td>12,810</td>
<td>4,380</td>
<td>4,818</td>
<td>6,022</td>
<td>1.86</td>
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<td>80</td>
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<td>0.75</td>
<td>44.8</td>
<td>8,540</td>
<td>2,920</td>
<td>3,212</td>
<td>4,015</td>
<td>1.86</td>
</tr>
<tr>
<td>80</td>
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<td>60</td>
<td>1.00</td>
<td>44.8</td>
<td>6,410</td>
<td>2,190</td>
<td>2,409</td>
<td>3,011</td>
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<tr>
<td>80</td>
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<td>0.50</td>
<td>74.1</td>
<td>19,760</td>
<td>6,757</td>
<td>7,432</td>
<td>9,290</td>
<td>1.66</td>
</tr>
<tr>
<td>80</td>
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<td>50</td>
<td>0.75</td>
<td>74.1</td>
<td>13,180</td>
<td>4,504</td>
<td>4,955</td>
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<td>1.66</td>
</tr>
<tr>
<td>80</td>
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<td>50</td>
<td>1.00</td>
<td>74.1</td>
<td>9,880</td>
<td>3,378</td>
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