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# Clinical Trials in the Developing World and Ebola Vaccine Development

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Vaccinology Course

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# Objectives

- Review the roles of stakeholders in vaccine research and special considerations for work in developing countries
  - Trial design considerations when working in developing countries
  - Impact of research strategies on global immunization
  - Ebola vaccine development
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# Stakeholders in research

- Sponsor
  - Investigator
  - Regulatory agency
  - IRB/EC
  - Participant / Study population
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# Considerations of Sponsor

- Problem
  - Vaccine part of solution
  - Vaccine design plausible
  - Expect vaccine safe
  - Expect vaccine immunogenic
  - Expect vaccine works
  - Formulation practical
  - Manufacture possible
  - Market receptive
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# Responsibilities of Sponsor

- Compliance with multiple regulatory agencies
    - Local agency sensitive to manufacturer intentions to license vaccine locally
  - Protocol generation
  - Develop and maintain documentation similar to IND
  - Investigator selection
  - Investigator brochure
  - Monitoring
    - Safety
    - Data
  - Communication with regulatory agencies
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# Product Development Groups

- ❑ Meningitis Vaccine Project, partnership between WHO and PATH
    - Transfer of conjugate vaccine technology to SII
    - < 10 years to get a vaccine from bench to target population
  - ❑ Rotavirus Vaccine Project
  - ❑ Similar groups exist for vaccine development in other areas (e.g. malaria, HIV)
  - ❑ Ebola vaccine development
    - Consortium included WHO, investigators, manufacturers, regulatory agencies
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# Considerations of Investigators

- Assess if ethical to proceed
    - Safe?
      - More information is available in phase 3 than phase 1 trials
    - Likely to be efficacious?
    - Would give to self or family?
  - Know the study
    - Protocol
    - ICF
    - IB
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# Responsibilities of Investigators

- IRB approval - may be one of multiple sites
  - IRB/EC communication - may be difficult as EC is likely to have limited resources
  - Record keeping
  - Report AEs and SAEs - need to be aware of local, background frequency of AEs. Likely to be high mortality which is not related to vaccine
  - Perform trial: vaccinate and follow - population mobility, cultural considerations (e.g. gender)
  - Proof of Good Clinical Practice (GCP)
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# Responsibility of Sponsor and Investigators

- Ensure local capacity to complete study procedures
    - Personnel
      - Clinical and laboratory – trained and certified as appropriate
      - Regulatory
    - Informatics
    - Clinical/ Laboratory/ Vaccine storage space
    - Environmental considerations
      - Complete study activities
      - Records storage
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# Resources Required

- Clinic and office space, vaccine and specimen storage area
  - Emergency equipment
  - Experts
    - Clinical
    - Vaccines
    - Data
    - Regulatory affairs
    - Microbiology
    - Immunology
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# Considerations of Regulatory Agencies

- Often multiple agencies are involved
    - In manufacturing and trial population countries
    - Increase the rigor of review of the safety and efficacy data
  - There may be limited local expertise to review necessary documentation
  - Local agency considers the likelihood that the study vaccine would be licensed in their country
  - WHO prequalification
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# Considerations of the IRB

- Is the research feasible?
    - Insight into the population sensitivity
  - Does the investigator have adequate expertise?
  - Is the study scientifically sound?
    - Does it meet local needs?
  - Inclusion/exclusion justifiable?
  - Is consent obtained?
    - Review wording carefully
  - Is the risk appropriate and minimized?
    - Have specific local knowledge
    - May judge risks and benefits of research differently than other committees
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# Responsibilities of the IRB

- International/ developing country committees are held to the same international standards as US IRBs
    - FWA
  - Review and approve research
  - At least 5 people
  - At least 1 non-scientist
  - At least 1 not affiliated with the institution
  - May be difficult to find local experts that are NOT involved in the research
  - Due to fewer protocols reviewed, may have varying levels of expertise to review protocols
  - Time to review may be longer than expected
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# Considerations of study population and volunteers

- Community approval
  - Is the vaccine safe?
    - To others in my community
    - To me
  - Will there be any benefit to me?
    - Medical - may include the family
    - Financial - should not be coercive but must be reasonable and practical given local constraints
  - Will there be any benefit to my family/ community?
    - Well established that a community that has research ongoing has better outcomes than one that does not
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# Challenges of working with Investigators as Participants

- Target study population included first line workers
- Screening process
- Preserving confidentiality



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# Challenges of working with developing country populations

- Literacy is low in many countries (e.g. in Mali – 40%)
    - Consent process - audiotape
    - Need to witness
    - Difficulty in comprehension of research principles (e.g. placebo, randomization..)
    - Unable to perform self-monitoring
  - Role of women
    - Often not the primary decision makers
    - Lower literacy levels
  - Mobile populations (migrations for farming, pregnant women)
  - Role of head of household
    - Informal adoptions
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# Challenges to study design

- Background events – safety implications
    - High mortality rates
    - High rates of undiagnosed chronic conditions
    - Autopsies may not be performed
  - Efficacy definition
    - Ability to catch all cases with detection system
    - Case definitions need to be appropriate to the context
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# Conclusions

- By engaging all the appropriate stakeholders, it is possible to conduct high quality and relevant vaccine trials in resource poor settings in a timely fashion
  - Important to remain flexible and creative to address unexpected problems
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# **EBOLA VACCINE DEVELOPMENT**

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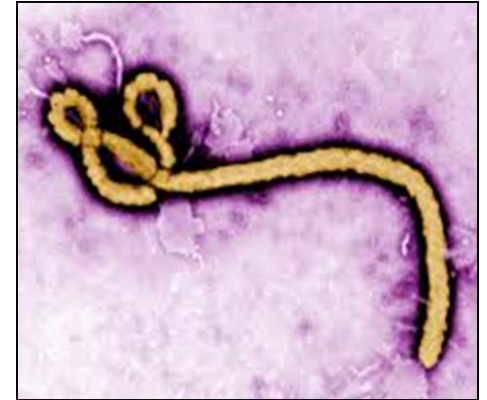
# Mali

- On March 21-22<sup>nd</sup> 2014, confirmation Ebola epidemic in Guinea
  - On March 23<sup>rd</sup> 2014, 1st emergency meeting in Mali
  - On April 1, 2014, the 3 suspected cases of Ebola virus disease had presented in Bamako, Mali. All arrived in from Guinea. Samples sent to CDC – negative.
  - Rapid intervention team – training, surveillance
  - In May 2014, NIH established a mobile, BSL3 laboratory at the medical school. Equipped to perform PCR testing.
  - By August 2014, many samples from suspect cases had been processed and none had been confirmed.
  - Concern among doctors in Bamako especially in neighborhoods that received those arriving from Guinea on buses and by private transport.
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# Race to develop a vaccine

- Prior to the 2014 outbreak
  - Vaccine candidates – 2 were well advanced
  - NHP model that seemed to predict efficacy
- On August 8, 2014, WHO declared a public health emergency of international concern.
- In recent years, there had been progress made on the development of a vaccine but no clinical trials yet. Funding? Regulatory pathway?
- On August 11, 2014, WHO convened a panel to discuss the ethics of using unregistered interventions
  - *Consensus that it's ethical to offer unproven interventions with as yet unknown efficacy and adverse effects as potential treatment or prevention*
  - *Moral duty to also evaluate these interventions (for treatment or prevention) in the best possible clinical trials under the circumstances in order to definitively prove their safety and efficacy or provide evidence to stop their utilization*

# Ebola vaccine candidates



Key antigen - wild type EBOV glycoprotein

- Single-dose vaccines
  - Replicating live viral vector
    - Vesicular stomatitis virus (VZV) expressing Zaire gp (Merck)
  - Non-replicating viral vector
    - Chimpanzee adenovirus 3 (NIH/GSK)
      - Monovalent Zaire -- ChAd3-EBO-Z
      - Bivalent – 1:1 mix of ChAd3-EBO-Z + ChAd3-EBO-S
- 2-dose/2-vaccine heterologous boost regimens
  - ChAd3-EBO prime followed by Modified Vaccinia Ankara (MVA) encoding EBOV glycoprotein boost (NIH/GSK)
  - Human Adeno 26-EBO priming dose followed by MVA-BN<sup>®</sup>-Filo (J&J and Bavarian Nordic)

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# Accelerated timelines

- Phase 1 trials would be launched first in countries with optimal facilities and followed as quickly as possible by phase 1-2 trials in Africa – safety, immunogenicity and dose-finding
  - Centralized laboratory testing to ensure comparability of data collected across studies of different vaccines in different populations
  - Trials would need to be monitored – DSMB and GCP
  - Data management support to accelerate availability of data to those responsible for licensure submissions and to enable adaptation of trials as quickly as possible
  - Deployment planning – prioritize those at highest risk, based on availability of doses, community engagement
  - Global Ebola Vaccine Implementation Team – develop plans and tools for use during deployment in emergency
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# Accelerated timelines

- 5 phase 1 trials of one candidate vaccine and 8 of another candidate were initiated between Sept and Dec 2014
  - Results became available by February 2015 and the data informed decisions for the 3 phase 2-3 trials.
  - By March 2015
    - PREVAIL in Liberia (rVSV-ZEBOV and ChAd3-EBO Z or placebo, individual)
    - STRIVE in Sierra Leone (rVSV-ZEBOV; individual, 6mos)
    - Ring vaccination (Ebola, ca suffit) in Guinea (rVSV-ZEBOV, cluster, 21d)
  - Interim results were available from Ca suffit in July 2015, <12 months since WHO had declared emergency
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# **Efficacy and effectiveness of an rVSV- vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial**

Ana Maria Henao-Restrepo, Ira M Longini, Matthias Egger, Natalie E Dean,  
W John Edmunds, Anton Camacha, Miles W Carroll, Moussa Doumbia,  
Bertrand Draguez, Sophie Duraffour, Godwin Enwere, Rebecca Grais,  
Stephan Gunther, Stefanie Hossmann, Many Kader Kondé, Souleymane Kone,  
Eeva Kuisma, Myron M Levine, Selma Mandal, Gunnstein Norheim,  
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Conall H Watson, Sakoba Keita, Marie Paule Kieny, John Arne Rottingen

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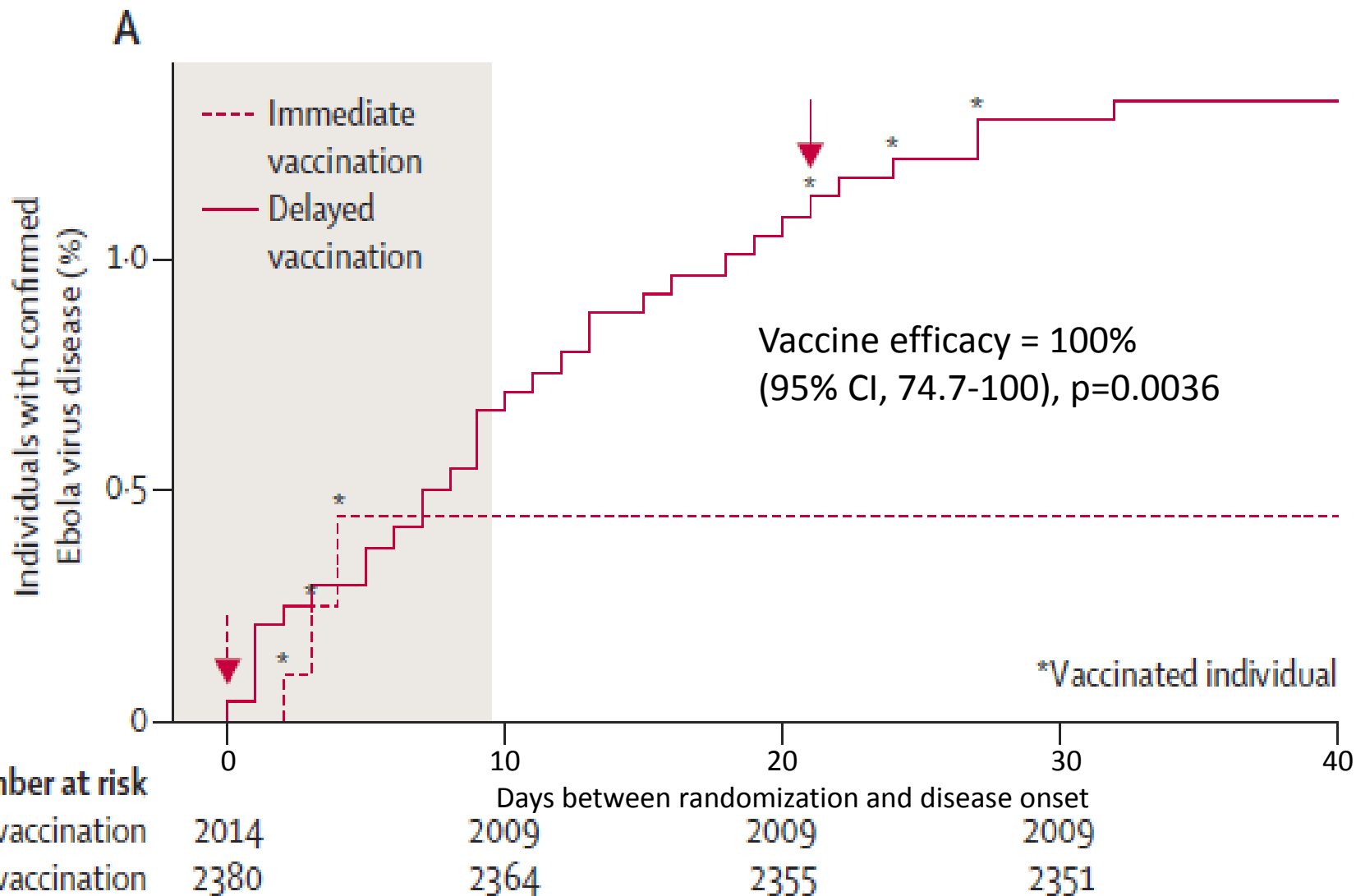
**[http://dx.doi.org/10.1016/S0140-6736\(15\)6117-5](http://dx.doi.org/10.1016/S0140-6736(15)6117-5)**

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# WHO Guinea ring vaccination efficacy trial

- Open-label, cluster-randomized, ring vaccination trial
  - EVD cases were identified by Ebola response teams
  - After lab confirmation, **clusters** of all contacts and contacts of contacts were defined
  - Clusters were randomly allocated 1:1 to immediate ring vaccination or 21-day delay before initiating vaccination
  - Block randomization with randomly varying blocks, stratified by location (urban vs rural) & ring size ( $\leq 20$  vs  $> 20$  persons).
  - **Primary outcome** was lab-confirmed **Ebola disease with onset at least 10 days after randomization** (assuming incubation of ~ 10 days)
  - Daily surveillance of contacts for signs & sx of Ebola illness
  - Enrollment began April 1, 2015; interim analysis at 90 rings
  - After interim review in July, DSMB stopped randomization
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***Primary analysis* – all individuals vaccinated in immediate vaccination group versus all individuals assigned to delayed vaccination**

	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)
<b>Number of individuals (clusters)</b>				
Immediate	2014 (48)	2048 (48)	3035 (48)	4123 (48)
Delayed	2380 (42)	1930 (42)	2380 (42)	3528 (42)
<b>Number of cases at &lt;10 days (affected clusters)</b>				
Immediate	9 (4)	10 (5)	18 (9)	21 (9)
Delayed	16 (12)	6 (5)	16 (12)	25 (13)
<b>Number of cases at ≥10 days (affected clusters)</b>				
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  $\beta$ -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**

	Eligible adults allocated immediate vaccination		All eligible adults allocated to delayed vaccination (n=2380)	Ineligible (not vaccinated; age <18 years, pregnant, or lactating)	
	Vaccinated immediately (n=2014)	Never vaccinated (n=1021)		Allocated to immediate vaccination (n=1088)	Allocated to delayed vaccination (n=1148)
Allocated delay (42 clusters)					
Cluster D1	..	..	6	..	1
Cluster D2	..	..	3	..	4
Cluster D3	..	..	2	..	0
Cluster D4	..	..	2	..	0
Cluster D5	..	..	1	..	0
Cluster D6	..	..	1	..	0
Cluster D7	..	..	1	..	0
35 clusters with 0 cases	..	..	..	..	..
Allocated immediate (48 clusters)					
Cluster I1	0	3	..	1	..
Cluster I2	0	2	..	0	..
Cluster I3	0	1	..	0	..
Cluster I4	0	0	..	1	..
44 clusters with 0 cases	..	..	..	..	..
Total	0/2014 (0.0%)	6/1021 (0.6%)	16/2380 (0.7%)	2/1088 (0.2%)	5/1148 (0.4%)

**Table 3: Distribution of confirmed Ebola virus disease cases in vaccinated and unvaccinated individuals in immediate and delayed clusters**

# Implications of the trial

- VSV-ZEBOV only vaccine candidate with efficacy data
- Ethical field trial design (everyone gets vaccine) but sufficient time between randomized groups for measuring efficacy
- Field trial assessed the way the vaccine would be used in public health (surveillance/containment)
- 11 months from Phase 1 trial to demonstrating efficacy in a Phase 3 field trial!!!
- Trial was carried out by workers (>90%) with no experience in clinical research. GCP training had to be given expeditiously.

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# Conclusions

- New model for the accelerated development, testing and approval of new interventions during similar emergencies
  - Adaptation of traditional R& D model
  - Compression of timelines
  - Unlikely partnerships
- *Public research institutes, private funders, civil society, countries, and industry have collaborated, in unprecedented ways, to defend the world against a deadly and deeply dreaded disease*