Lecture 10: Design and Analysis of Cluster Randomized Vaccine Trials for Emerging Infectious Disease Epidemics: The Case of Ring Vaccination for Ebola

Ira Longini
The Threat

- Emerging infectious diseases are trying to kill, or at least, maim use
- We can stop or mitigate them
  - Surveillance and containment
  - Vaccines
  - Therapies
- Current threats (examples)
  - Influenza, Zika, dengue, MERS, Ebola
  - and other hemorrhagic viruses, agent X
The Solution

- Devise analytic and statistical methods for rapid estimation of the effectiveness of control measures
- Devise statistical and mathematical models for optimal control strategies
An R&D Blueprint for Action to Prevent Epidemics

Accelerating R&D and Saving Lives

*http://www.who.int/csr/research-and-development/blueprint/en/*
The design and analysis of vaccine trials for infectious disease emergencies
Vaccine Effectiveness

Intervention Population: 1

- Vac f
- Nonvac 1-f
- AR_{1v}
- AR_{1u}

Overall

Control Population: 2

- Nonvac
- AR_{2u}

Total

Direct

Indirect
Vaccine Effectiveness

**Intervention Population:**
- Vac (1
- Nonvac (1-f

**Control Population:**
- Nonvac

**Overall**

\[ \text{VE}_{\text{overall}} = 1 - \left( \frac{\text{AR}_{1\text{ave}}}{\text{AR}_{2u}} \right) \]

**Direct**

\[ \text{VE}_{\text{direct}} = 1 - \left( \frac{\text{AR}_{1v}}{\text{AR}_{1u}} \right) \]

**Indirect**

\[ \text{VE}_{\text{indirect}} = 1 - \left( \frac{\text{AR}_{1u}}{\text{AR}_{2u}} \right) \]

**Total**

\[ \text{VE}_{\text{total}} = 1 - \left( \frac{\text{AR}_{1v}}{\text{AR}_{2u}} \right) \]
Vaccine Effectiveness

\[ V_{E\text{direct}} = 1 - \left( \frac{AR_{1v}}{AR_{1u}} \right) \]
\[ V_{E\text{indirect}} = 1 - \left( \frac{AR_{1u}}{AR_{2u}} \right) \]
\[ V_{E\text{total}} = 1 - \left( \frac{AR_{1v}}{AR_{2u}} \right) \]
\[ V_{E\text{overall}} = 1 - \left( \frac{AR_{1\text{ave}}}{AR_{2u}} \right) \]

where \( AR_{1\text{ave}} = f \cdot AR_{1v} + (1 - f) \cdot AR_{1u} \)

Vaccine Effectiveness Gradient

Population: 1

- Vac $f_1$
- Nonvac $1-f_1$

AR$_{1v}$
AR$_{1u}$

Overall

Population: 2

- Vac $f_2$
- Nonvac $1-f_2$

AR$_{2v}$
AR$_{2u}$

Direct

Indirect

Total
**Table:** Parameters used for measuring various effects of vaccination*

<table>
<thead>
<tr>
<th>Level Parameter choice</th>
<th>Susceptibility</th>
<th>Infectiousness</th>
<th>Combined change in susceptibility and infectiousness</th>
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</thead>
<tbody>
<tr>
<td><strong>Conditional on exposure:</strong></td>
<td></td>
<td></td>
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<tr>
<td>I Transmission probability</td>
<td></td>
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<tr>
<td>$\text{VE}_S, p^\dagger = 1 - \frac{p_1}{p_0}$</td>
<td>$\text{VE}_I, p = 1 - \frac{p_1}{p_0}$</td>
<td>$\text{VE}<em>T, p = 1 - \frac{p</em>{11}}{p_{00}}$</td>
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<tr>
<td><strong>Study design:</strong></td>
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<tr>
<td><strong>I</strong> direct</td>
<td></td>
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<tr>
<td>$\text{VE}<em>S, IR = 1 - \frac{\text{IR}</em>{A_1}}{\text{IR}_{A_0}}$</td>
<td>$\text{VE}<em>{IIA, IR} = 1 - \frac{\text{IR}</em>{A_0}}{\text{IR}_{B_0}}$</td>
<td>$\text{VE}<em>{IIB, IR} = 1 - \frac{\text{IR}</em>{A_1}}{\text{IR}_{B_0}}$</td>
<td>$\text{VE}<em>{III, IR} = 1 - \frac{\text{IR}</em>{A_1}}{\text{IR}_{B}}.$</td>
</tr>
<tr>
<td>$\text{VE}<em>S, \lambda = 1 - \frac{\lambda</em>{A_1}}{\lambda_{A_0}}$</td>
<td>$\text{VE}<em>{IIA, \lambda} = 1 - \frac{\lambda</em>{A_0}}{\lambda_{B_0}}$</td>
<td>$\text{VE}<em>{IIB, \lambda} = 1 - \frac{\lambda</em>{A_1}}{\lambda_{B_0}}$</td>
<td>$\text{VE}<em>{III, \lambda} = 1 - \frac{\lambda</em>{A_1}}{\lambda_{B}}.$</td>
</tr>
<tr>
<td><strong>II</strong> Incidence or hazard rate, IR, $\lambda$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>III</strong> Proport. hazards, PH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{VE}_S, PH = 1 - e^{\beta_1}$</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td><strong>IV</strong> Cumulative incidence</td>
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<td></td>
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<tr>
<td>$\text{VE}<em>S, CI = 1 - \frac{\text{CI}</em>{A_1}}{\text{CI}_{A_0}}$</td>
<td>$\text{VE}<em>{IIA, CI} = 1 - \frac{\text{CI}</em>{A_0}}{\text{CI}_{B_0}}$</td>
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<td>$\text{VE}<em>{III, CI} = 1 - \frac{\text{CI}</em>{A_1}}{\text{CI}_{B}}.$</td>
</tr>
</tbody>
</table>

Infectious disease factors to consider

- Transmissibility: $R_0$, other transmission parameters
- Speed of transmission: Serial interval, incubation, latent and infectious periods
- Type of contact
- Pathogenicity: Proportion asymptomatic
- Stage of epidemic
- Heterogeneity in transmission
Vaccine factors to consider

- Vaccine action: protection against infection, disease, transmission to others; leaky, all-or-none, mixture
- Number of doses
- Immunity ramp up period
Statistical factors

- Cluster randomized trail
- Estimate both efficacy and effectiveness within clusters
- Adaptive design on some level
- Stopping rules clearly defined

Challenge 1

Statistical factors
Ebola vaccine trail in Guinea, West Africa
Infectious disease factors for Ebola

• Transmissibility: $R_0 = 1.4 - 2.0$
• Speed of transmission: 10-12 days, incubation period 6 days
• Type of contact: direct to bodily fluids
• Pathogenicity: Close to 100%
• Stage of epidemic: Late
• Heterogeneity in transmission: close contact networks
Vesicular Stomatitis Virus vaccine (rVSV-ZEBOV) Merck

- Vaccine action: protection against disease; leaky
- Number of doses: one
- Immunity ramp up period: 4-7 day
  Non-human primate challenge studies
  Phase I and II human vaccine trials
The ring vaccination trial: a novel cluster randomised controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola

EBOLA ÇÀ SUFFIT RING VACCINATION TRIAL CONSORTIUM

Abstract

A World Health Organization expert meeting on Ebola vaccines proposed urgent safety and efficacy studies in response to the outbreak in West Africa. One approach to communicable disease control is ring vaccination of individuals at high risk of infection due to their social or geographical connection to a known case. This paper describes the protocol for a novel cluster randomised controlled trial design which uses ring vaccination.
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 Camacho, Miles W Carroll, Moussa Doumbia, Bertrand Draguez, Sophie Duraffour, Godwin Enwere, Rebecca Grais, Stephan Gunther, Stefanie Hossmann, Mandy Kader Kondé, Souleymane Kone, Eeva Kuisma, Myron M Levine, Sema Mandal, Gunnstein Norheim, Ximena Riveros, Aboubacar Soumah, Sven Trelle, Andrea S Vicari, Conall H Watson, Sakoba Kéita, Marie Paule Kiény*, John-Arne Røttingen*

Summary
Background A recombinant, replication-competent vesicular stomatitis virus-based vaccine expressing a surface glycoprotein of Zaire Ebolavirus (rVSV-ZEBOV) is a promising Ebola vaccine candidate. We report the results of an interim analysis of a trial of rVSV-ZEBOV in Guinea, west Africa.

Methods For this open-label, cluster-randomised ring vaccination trial, suspected cases of Ebola virus disease in Basse-Guinée (Guinea, west Africa) were independently ascertained by Ebola response teams as part of a national surveillance system. After laboratory confirmation of a new case, clusters of all contacts and contacts of contacts were defined and randomly allocated 1:1 to immediate vaccination or delayed (21 days later) vaccination with rVSV-ZEBOV (one dose of 2 x 10⁷ plaque-forming units, administered intramuscularly in the deltoid muscle). Adults (age ≥18 years) who were not pregnant or breastfeeding were eligible for vaccination. Block randomisation was used, with randomly varying blocks, stratified by location (urban vs rural) and size of rings (≤20 vs >20 individuals). The study is open label.
“...three challenges...

three fixes...”
Challenge 1

The way cases had surged in different geographic areas, thwarting efforts to design a randomized trial in which participants in each district faced the same infection risk.
Fix 1

Randomization within small groups of people – that is, among small groups of people projected to have a similar risk of exposure to the virus
Figure 2: Study area of Ebola 50 Suhit cluster vaccination trial in Basse-Guinée
Clustering: Distribution of attack rates among known contacts of Ebola cases in Guinea

Median = 0.034, Mean = 0.065, Intraclass correlation = 0.065

*Source: WHO contact tracing teams in Guinea.*
How was the ring vaccination trial implemented?
The social mobilization teams explain the trial and trial procedures to the community before any action starts.
Vaccination is administered immediately or after 3 weeks as defined by randomisation outcome.
Why “ring” vaccination trial for Ebola epidemics in terms of numbers?

Transmission can be intense but is usually clustered in transmission units, e.g., rings, households, contact networks

Ebola epidemic in West Africa

28,454 cases of EVD so far in a combined population of 22 million people: AR = 0.13%

For RCT: Sample size per arm ≈ 153,000
(VE = 0.7, power = 0.90, $\alpha = 0.05$ two sided)

Where do we do the trial?
Why ring vaccination trial for Ebola epidemics in terms of numbers?

Ring vaccination follows the transmission
For ring vaccination trial: AR in rings is 1-2% with a lot of variation, ICC = 0.05

Sample size per arm:
≈ 95 rings (5,000 people): two orders of magnitude smaller than RCT assuming VE = 0.7, power = 0.90, α = 0.05 two sided, ICC = 0.05)

≈ 36 rings (1,800 people) if VE = 1.00

Actual trial at interim analysis (half-way point): For the primary analysis, there where 4,394 people in the two arms, in 90 rings

Challenge 2

The unprecedented outbreak outpaced the speed with which clinical trials could be implemented
Vaccine trial concentrated vaccine and comparison arms where cases were in the last weeks of the main epidemic
Cases of Ebola by week of notification of cases, Guinea 2014-15

Decision to conduct trial

Start of the trial

Stop randomization
Challenge 3

The uncertainty in predicting future infection incidence
Fix 3

Adaptive design with real-time modifications, based on a predetermined interim analysis of study data.
Ring vaccination - cluster randomized trial

**Design**

**Randomized controlled trial (RCT)**

- «Gold standard»
- Low risk of bias
- Readily accepted by regulators

**Cluster randomized trial**

- Everyone in intervention clusters is offered vaccine immediately:
  - Enhanced compliance
  - Logistically easier

**Stepped wedge cluster trial**

- Every cluster is offered vaccine during follow-up:
  - Enhanced compliance/acceptability
  - Logistically easier
  - Adjustments possible during trial
  - More efficient than cluster trial

**Single-arm study with historical controls**

- Immediate vaccination
- Enhanced compliance/acceptability
- Logistically easy

- Delayed vaccination
- Follow up for outcomes

**Comparisons**

- Efficacy
- Effectiveness
What is a vaccination ring?

Contacts and contacts of contacts

INDEX CASE
Lab confirmed EVD case

close contact with patient body or body fluids, linen, or clothes

lived in the same household

household members of high risk contacts

extended family

neighbors

visited the symptomatic patient
In the ring vaccination trial, teams go to communities with a recently confirmed Ebola case.
Hazard function

\[ \lambda_{hvi}(t) = Z_h \lambda_0(t) Y_{hvi}(t) \theta^v e^{X_{hvi}(t)'} \beta \]

Random effect, \( E(Z_h) = 1 \)
Hazard function

$$\lambda_{hvi}(t) = Z_h \lambda_0(t) \ Y_{hvi}(t) \ \theta^v \ e^{X_{hvi}(t)'} \beta$$

Hazard rate to comparison group
Hazard function

\[ \lambda_{hvi}(t) = Z_h \lambda_0(t) Y_{hvi}(t) \theta^v e^{X_{hvi}(t)'} \beta \]

Participation indicator

Can be a function of time delays due to incubation period and immune ramp-up period.
Hazard function

\[ \lambda_{hvi}(t) = Z_h \lambda_0(t) \ Y_{hvi}(t) \ \theta^v \ e^{X_{hvi}(t)' \beta} \]

Vaccine effect, 1 - VE
Hazard function

$$\lambda_{hvi}(t) = Z_h \lambda_0(t) \ Y_{hvi}(t) \ \theta^v \ e^{X_{hvi}(t)' \beta}$$

Covariates if needed
Statistical approach for cluster-randomized trials or studies

Vaccine efficacy: $\hat{VE} = 1 - \frac{\hat{\lambda}_1}{\hat{\lambda}_0} = 1 - \hat{\theta}$

$\hat{\lambda}_1$ = the estimated hazard of confirmed illness in the vaccinated

$\hat{\lambda}_0$ = the estimated hazard confirmed illness in the unvaccinated

Model will be a mixed-effects, time-dependent, Cox regression model with a random effect (frailty) when there is clustering, or small sample equivalent using cumulative incidence (logist reg).

$H_0$: $VE = 0$ versus $H_{a}$: $VE \neq 0$.

Estimated $VE$ and 95% CI

Adaptive $\alpha$ spending boundaries (e.g., O’Brien-Fleming)
Primary outcome:
Vaccine efficacy = 100%
95%CI [75% - 100%]
p = 0.0036

Secondary outcome:
Overall Vaccine effectiveness = 75%
95%CI [7% - 94%]
p = 0.1791

Statistical Analysis

- Pre-specified Cox PH with a cluster-level random effect (frailty)
- For setting of 0 countable events in immediate arm:
  - Two-sided Fisher’s exact test on cluster-level data
  - Estimate 95% CI lower bound by fitting a beta-binomial distribution and using an inverted likelihood ratio test

<table>
<thead>
<tr>
<th></th>
<th>≥ 1 case (10+ days)</th>
<th>0 cases (10+ days)</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMMEDIATE</td>
<td>0 clusters*</td>
<td>48 clusters</td>
<td>48 clusters</td>
</tr>
<tr>
<td>DELAYED</td>
<td>7 clusters**</td>
<td>35 clusters</td>
<td>42 clusters</td>
</tr>
</tbody>
</table>

p = 0.0036***

Time delays

We are dealing with an infectious disease

We only see confirmed EVD onsets, not infection times
  * Incubation period

Time is needed for immunity to build after vaccination
  * Immune ramp-up period
Analysis considerations:
Important intervals to incorporate into analysis

- **Incubation period**
  - Mean $\approx$ 10 days, but probably is more like 6 days

WHO Ebola Response Team, *NEJM* 2014
Day 0:
Immediate vaccination

Ramp-up period for vaccine to become effective

VE

Day 0:
Follow-up starts

Delay period between immediate and delayed vaccination

Day 21:
Delayed vaccination

Day 21:
Delayed vaccination

Hazard of infection with Ebola virus
To estimate vaccine efficacy, we want to capture infection events that occur in this time window.
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To estimate vaccine efficacy, we want to capture infection events that occur in this time window.
Day 0: Immediate vaccination

Day 21: Delayed vaccination

Day 0: Follow-up starts

Because we only observe symptom onset times, we shift the analysis period by a fixed delay, $D$. 

Hazard of infection with Ebola virus
Because we only observe symptom onset times, we shift the analysis period by a fixed delay, $D$. 

Hazard of infection with Ebola virus
Delay period

• Misclassifications bias the estimate of vaccine efficacy towards the null
• More events, more power
• **Goal:** analytically quantify this bias and power and provide some guidance on how to select the delay period, $D$
Decreasing Background Hazard

Immediate arm vaccinated on day 0; control arm vaccinated after 21 days

VE = 90%; 4 day ramp-up period (gradually increases)

Incubation period gamma distributed with mean 6 days

Decreasing background hazard that drops to 0 after 30 days

HAZARD OVER TIME IN IMMEDIATE ARM

HAZARD OVER TIME IN DELAYED ARM

HAZARD RATIO OVER TIME
Decreasing Background Hazard

Immediate arm vaccinated on day 0; **control arm vaccinated after 21 days**

VE = 90%; **4 day ramp-up period** (gradually increases)

Incubation period gamma distributed with mean 6 days

Decreasing background hazard that drops to 0 after 30 days

*Count events between D and D+21. Consider a range of D values...*
Conclusions

• Optimal D is a compromise

• Consequence of misspecifying D is a downward bias leading to a loss in power

• Optimal D for minimizing bias is not necessarily equal to the optimal D for maximizing power
Conclusions

• Even if there is no delayed vaccination arm, this bias/variance tradeoff is relevant if the background hazard decreases over time
What does this mean?

Vaccine efficacy is high: 75 - 100%

Ring-level overall protection is 75% with about 50% coverage

Mobile stockpile of Ebola vaccine can be used to contain and mitigate future Ebola introductions

Gavi Vaccine Alliance has pledged to purchase 300,000 doses of rVSV∆G-ZEBOV-GP for a mobile WHO stockpile
And Science’s Breakthrough of the Year is...
Future outbreaks

Ring-intervention strategies can be used to deal with present and future disease threats -- WHO Roadmap

Zika virus threat: Vector control will not be uniformly effective.

No effective treatment, but significant severe morbidity.

A vaccine is needed and could be tested and deployed in a targeted strategy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ebola</th>
<th>Zika</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_0$</td>
<td>1.2-3.0</td>
<td>2.5-3.5?</td>
</tr>
<tr>
<td>Serial interval</td>
<td>15 days</td>
<td>20 days</td>
</tr>
<tr>
<td>Pathogenicity</td>
<td>100%</td>
<td>20%</td>
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</table>
Acknowledgements

Ana Maria Henao-Restrepo and the Ebola ça suffit essai clinique team

Natalie Dean (UF), Betz Halloran (Hutch/UW)

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NIH/NIGMS, U54 GM11274
Six-year-old Cecilia Kamara from Robertsport, Liberia holds up a sign after receiving news about the Ebola vaccine. Photograph: Alphonsio Appleton