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

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The Threat

- Emerging infectious diseases are trying to kill, or at least, maim us.
- 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

- WHO research and development blueprint: http://www.who.int/blueprint/en/
- Devise analytic and statistical methods for rapid estimation of the effectiveness of control measures
- Devise statistical and mathematical models for optimal control strategies
A research and development Blueprint for action to prevent epidemics

Sharing biological samples and data during public health emergencies

WHO is developing a web-based tool to facilitate equitable sample and data sharing during public health emergencies. This document is now released for comments. It discusses in detail the possible approaches that can be used to share samples and benefits on the same footing, and provides concrete, real world examples of how these can be embedded in an MTA. Go to public consultation page.

Read more on biological samples and data sharing

Go to public consultation page.
The design and analysis of vaccine trials for infectious disease emergencies
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
Ebola vaccine trial 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
RESEARCH METHODS & REPORTING

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 ça 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 Kuiska, 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 $2 \times 10^7$ 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.
Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!)

Ana Maria Henao-Restrepo, Anton Camacho, Irina Longini, Conrad H Watson, W John Edmunds, Matthias Egger, Miles W Carroll, Natalie E Dean, Ibrahima Diatta, Moussa Doumbia, Bertrand Draguez, Sophie Duraffour, Godwin Enwere, Rebecca Grais, Stephan Gunther, Pierre-Stéphane Gsell, Stefanie Hessmann, Sara Viksmoen Watle, Mandy Kader Kondé, Sakoba Kéita, Souleymane Kone, Eeva Kuisma, Myron M Levine, Sema Mandal, Thomas Maugé, Gunnstein Norheim, Ximena Riveros, Aboubacar Soumah, Sven Trelle, Andrea S Vicari, John-Arne Røttingen*, Marie-Paule Kieny*

Summary
Background rVSV-ZEBOV is a recombinant, replication competent vesicular stomatitis virus-based candidate vaccine expressing a surface glycoprotein of Zaire Ebolavirus. We tested the effect of rVSV-ZEBOV in preventing Ebola virus disease in contacts and contacts of contacts of recently confirmed cases in Guinea, west Africa.

Methods We did an open-label, cluster-randomised ring vaccination trial (Ebola Ça Suffit!) in the communities of Conakry and eight surrounding prefectures in the Basse-Guinée region of Guinea, and in Tomkoli and Bombali in Sierra Leone. We assessed the efficacy of a single intramuscular dose of rVSV-ZEBOV (2×10^7 plaque-forming units administered in the deltoid muscle) in the prevention of laboratory confirmed Ebola virus disease. After confirmation of a case of Ebola virus disease, we definitively enumerated on a list a ring (cluster) of all their contacts and contacts...
“...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.
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 Suffix cluster vaccination trial in Basse-Guinée.
Clustering: Distribution of attack rates among known contacts of Ebola cases in Guinea

\[ \text{Median} = 0.034, \text{Mean} = 0.065, \text{Intraclass correlation} = 0.065 \]

*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 ≈ 21,000
(VE = 0.7, power = 0.90, α = 0.05 two sided)
Where do we do the trial?
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.
Randomization within small groups of people – that is, among small groups of people projected to have a similar risk of exposure to the virus
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
Adaptive design with real-time modifications, based on a predetermined interim analysis of study data.
Ring vaccination

Cluster randomized trial

**Advantages**

- 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

- Stepped wedge individual-level trial
  - As much vaccine as possible is being offered at every time
  - Adjustments possible during trial
  - With high coverage components of effectiveness can be estimated

**Immediate vaccination**

**Delayed vaccination (21 days)**

- Newly lab confirmed case of EVD
- Definition of ring (Known contacts, contacts of contacts) informed consent and randomization
- Random allocation of ring
- Immediate vaccination
- Follow up for outcomes
- Delayed vaccination
- Follow up for outcomes

**Comparisons**

- Efficacy
- Effectiveness

- Eligible, vaccinated
- Eligible, not vaccinated
- Not eligible, not vaccinated
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
- household members of high risk contacts

- lived in the same household

- extended family

- neighbors

- visited the symptomatic patient

- 31
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
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)
Cumulative risk, estimates, statistics

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

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<thead>
<tr>
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<th>Immediate</th>
<th>Delayed</th>
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<tbody>
<tr>
<td>≥ 1 case</td>
<td>0 clusters*</td>
<td>7 clusters**</td>
</tr>
<tr>
<td>(10+ days)</td>
<td>48 clusters</td>
<td>35 clusters</td>
</tr>
<tr>
<td>0 cases</td>
<td>48 clusters</td>
<td>42 clusters</td>
</tr>
<tr>
<td>(10+ days)</td>
<td>p = 0.0036***</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>48 clusters</td>
<td>42 clusters</td>
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* No case observed in vaccinated individuals more than 6 days after vaccination
** 16 cases (6, 3, 2, 2, 1, 1, 1 per cluster)
*** Truncated OBF threshold for 90/190 clusters is 0.0027

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 ≈ 10 days, but probably is more like 6 days

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WHO Ebola Response Team, *NEJM* 2014

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Day 0:
Immediate vaccination

Ramp-up period for vaccine to become effective

Day 0:
Follow-up starts

Delay period between immediate and delayed vaccination

Day 21:
Delayed vaccination

Hazard of infection with Ebola virus

VE
To estimate vaccine efficacy, we want to capture infection events that occur in this time window.
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

Day 21: Follow-up starts

Infection

To estimate vaccine efficacy, we want to capture infection events that occur in this time window.
Because we only observe symptom onset times, we shift the analysis period by a fixed delay, $D$. Day 0: Immediate vaccination. Day 21: Delayed vaccination. Day 0: Follow-up starts. Day 21: Follow-up starts.
Because we only observe symptom onset times, we shift the analysis period by a fixed delay, D.
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
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...

**OBSERVED VACCINE EFFICACY (BIAS) FOR EACH DELAY D**

**OBSERVED POWER FOR EACH DELAY D**
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
Ring vaccination contained
Ring vaccination not contained
April 2017  Meeting of the Strategic Advisory Group of Experts on Immunization (SAGE)*

For the next Ebola outbreak:

VSVΔG-ZEBOV-GP vaccine should be promptly deployed under appropriate conditions

i)  Ring vaccination

ii) Local and international health care and front line workers in the affected areas

iii) Health care and front line workers in areas at risk of expansion of the outbreak

And Science’s Breakthrough of the Year is...
Six-year-old Cecilia Kamara from Robertsport, Liberia holds up a sign after receiving news about the Ebola vaccine. Photograph: Alphanso Appleton
EBOLA VIRUS DISEASE
Democratic Republic of the Congo
External Situation Report 11

http://apps.who.int/iris/bitstream/handle/10665/272859/SITREP_EVD_DRC_20180619-eng.pdf?ua=1
EBOLA VIRUS DISEASE
Democratic Republic of the Congo

External Situation Report 11

Date of issue: 19 June 2018
Data as reported by: 17 June 2018

1. Situation update

The Ministry of Health and WHO continue to closely monitor the outbreak of Ebola virus disease (EVD) in the Democratic Republic of the Congo with cautious optimism. On 17 June 2018, one new suspected EVD case was reported in Itipo health area, Iboko Health Zone. Three laboratory specimens (from suspected cases reported previously) tested negative. Test results of nine suspected cases reported (previously) in Bikoro (4), Iboko (3) and Ingende (2) health zones are pending. Since 17 May 2018, no new confirmed EVD cases have been reported in Bikoro and Wangata health zones, while the last confirmed case-patient in Iboko Health Zone developed symptoms on 2 June 2018, was confirmed on 6 June 2018 and died on 9 June 2018.

Since the beginning of the outbreak (on 4 April 2018), a total of 62 EVD cases and 28 deaths have been reported, as of 17 June 2018. Of the 62 cases, 38 have been laboratory confirmed, 14 are probable (deaths for which it was not possible to collect laboratory specimens for testing) and 10 are suspected. Of the 52 confirmed and probable cases, 28 have died, giving a case fatality rate of 54%. Fifty-two percent (27) of the confirmed and probable cases are from Iboko, followed by 21 (40%) from Bikoro and four (8%) from Wangata health zones. A total of five healthcare workers have been affected, with four confirmed cases and two deaths.

The number of contacts requiring follow-up is progressively decreasing, with a total 1,417 completing the mandatory 21-day follow-up period. As of 17 June 2018, a total of 289 contacts were under follow up, of which 276 (96%) were reached on the reporting date.
Figure 1: Epidemic curve for Ebola virus disease outbreak in Equateur Province, Democratic Republic of the Congo, 17 June 2018 (n=52)

- Number of cases
- Date of illness onset (2018)
- Confirmed
- Probable

3,017 people vaccinated
Ring vaccination starts
Three foci of transmission
HOW DRC’S EBOLA OUTBREAK HAS BEEN CONTAINED

The Ebola outbreak in Congo has been closely tracked and, so far, well-contained, in stark contrast to the 2014 West Africa outbreak that killed thousands of people.

By SALEM SOLOMON | June 16, 2018

The Ebola outbreak in the Democratic Republic of the Congo appears to be in its waning days. Despite 28 deaths as of early June, health officials are cautiously optimistic that they are bringing the outbreak under control. So far, it’s a striking turnaround from the 2014 West Africa outbreak, which killed more than 11,000 people in Liberia, Sierra Leone and Guinea, and traveled as far as Glasgow, Scotland, and Dallas, Texas.

Despite difficult-to-traverse terrain and local communities’ skepticism of health care workers, from the start of the outbreak, officials got in front of the disease and kept it in check. Several factors made the DRC response markedly different than previous outbreaks, saving countless lives.

https://projects.voanews.com/drc-ebola-outbreak/
Here’s how

1. Long distances between villages and an underdeveloped infrastructure slowed the spread of the disease
2. The highly effective VSV vaccine was deployed almost immediately in the DRC
3. Local communities have been receptive to health care interventions
4. An improved international infrastructure to respond to disease outbreaks proved effective.

http://www.who.int/blueprint/en/
5. Maps, satellite imagery and other data sources armed responders with information to make timely, well-informed decisions.
Thank you