The ring trial design for the estimation of vaccine efficacy and effectiveness during infectious disease outbreaks

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Motivation: Assessing vaccine efficacy during an epidemic

2014-2016 West African Ebola epidemic

In late 2014, a decision was made to conduct Phase 3 vaccine trials for two promising candidate vaccines:

- rVSV-ZEBOV vaccine
- cAd3-ZEBOV vaccine



Challenge: Unpredictable temporal trends



West African epidemic was over an order of magnitude larger than any prior Ebola outbreak

425 cases in Uganda in 2000

In total, 28,616 reported Ebola virus disease cases

At the time the trials were being planned, there was substantial uncertainty about projected future disease incidence

Challenge: Unpredictable spatial spread



Large outbreaks occurred in urban centers, but were also distributed throughout the country, including in areas with lower population density

Statistical considerations for a trial:

- Total population 22 million
- Overall attack rate of 0.13%
- Lower if you exclude the early peak of the epidemic

Limited clinical trial infrastructure During a public health emergency

WHO Ebola Response Team (2016) NEJM, DOI: 10.1056/NEJMsr1513109

Insight: Ebola epidemiology

HOW DOES ONE GET EBOLA?

BY COMING INTO DIRECT CONTACT WITH: 2 Objects contaminated with the Body fluids of a person who is virus (needles, medical equipment) sick with or has died from Ebola





(blood, vomit, urine, feaces, sweat,

Infected fruit bats or primates

semen, saliva, etc)

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#PreventEbola

unicef 🚱 for every child Ebola virus spreads through direct contact with body fluids

Contact tracing coupled with isolation/quarantine is a key intervention

Contact tracing teams were active during the epidemic

Strategy: Ring vaccination

(The following article first appeared in: *Bulletin of the World Health Organization*, 1975, **52**: 209–222) Smallpox eradication in West and Central Africa*

WILLIAM H. FOEGE,1 J. D. MILLAR,2 & D. A. HENDERSON 3

In 1966, a programme to eradicate smallpox and control measles began in West and Central Africa. With WHO and US bilateral technical and financial assistance, the 20 countries mounted a coordinated campaign of mass vaccination, assessment, surveillance, and maintenance activities. The last cases of smallpox occurred in May 1970. The introduction of epidemiologically directed surveillance-containment activities and their rapid success resulted in interruption of smallpox transmission much sooner than anticipated. The area has remained free of smallpox. From 1966 to 1972, over 28 000 000 children 1–6 years of age also received measles vaccination. The campaign established or strengthened structures for preventive health care services in all the countries.



Innovation: Ring vaccination trial

Use the rings as the units in a cluster randomized trial

Trial design first described in BMJ 2015

Trial design first used in the *Ebola ça Suffit* trial in Guinea to test the efficacy and effectiveness of a single dose rVSV-ZEBOV vaccine



Design: Ebola ça Suffit trial

Initial inclusion criteria:

- Contacts and contacts of contacts of laboratory-confirmed Ebola virus disease (EVD) cases
- Age 18+ years (subsequently relaxed)

Exclusion criteria:

- History of EVD
- Pregnant or breastfeeding
- Significant immunodeficiency

Standard surveillance data collected on ineligible ring members

Intervention:

• Single dose of rVSV-ZEBOV vaccine immediately or 21 days later (unblinded)

Randomization:

• Block randomization by ring location (urban, rural) and ring size (≤ 20 , > 20)

Design: Ebola ça Suffit trial (2)

Primary endpoint:

Laboratory-confirmed EVD 10+ days after randomization

Primary analysis population:

- Vaccinated individuals in immediate rings, vs.
- Eligible individuals in the delayed rings

Secondary analysis population:

- All individuals (regardless of eligibility) in immediate rings, vs.
- All individuals (regardless of eligibility) in delayed rings

Design: Ebola ça Suffit trial (3)

Sample size:

- Assumed vaccine efficacy of 70%
- $\circ\,$ Two-sided lpha=0.05 test to rule out null hypothesis of 0%
- Average of 50 people per ring, 2% attack rate, ICC of 0.05
- 190 rings (95 per arm) required to achieve 90% power

Data monitoring:

- Truncated O'Brien-Fleming alpha spending function
- Single planned interim analysis at the half-way point

Results: Publications

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 Kieny*, John-Arne Røttingen*

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, Ira M Longini, Conall 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 Hossmann, Sara Viksmoen Watle, Mandy Kader Kondé, Sakoba Këita, Souleymane Kone, Eewa Kuisma, Myron M Levine, Serna Mandal, Thomas Mauget, Gunnstein Norheim, Ximena Riveros, Aboubacar Soumah, Sven Trelle, Andrea S Vicari, John-Arne Røttingen*, Marie-Paule Kieny* Interim analysis of 90 randomized rings in *The Lancet* July 31, 2015

Final analysis of 98 randomized and 19 non-randomized rings in *The Lancet* <u>December 22, 2016</u>

Impact: A fast-acting and efficacious vaccine

Estimated vaccine efficacy was 100% (95% CI: 68.9 to 100%)

- Interim analysis: 16 cases in 7 out of 42 delayed clusters, 0 cases in 48 immediate clusters
- No additional cases in the final randomized analysis

WHO Strategic Advisory Group of Experts on Immunization (SAGE) endorsed ring vaccination strategy for response to future Ebola Zaire outbreaks

Over 300,000 people vaccinated during subsequent outbreaks in the Democratic Republic of the Congo

Ervebo vaccine was licensed by the FDA in December 2019

Features of the Design

Practical features

Statistical features

Tailored to the outbreak context





Lancet 2015, DOI: 10.1016/S0140-6736(15)61117-5

Figure 1: Study area of Ebola ça Suffit cluster vaccination trial in Basse-Guinée

Feasible in challenging circumstances



Teams visit the rings on days 0, 3, 14, 21, 42, 63 and 84



- (+) Clustered design has logistical advantages
- (+) Stepped roll-out
- (+) Complements ongoing contact tracing

Images from AM Henao-Restrepo

Statistical feature #1: A bias/variance tradeoff



Statistical feature #1: A bias/variance tradeoff (2)

Per protocol analysis aims to exclude the early period before vaccines are fully protective But it should start as early as possible to maximize events

This trade-off is always present, but it is particularly acute in ring vaccination trials

- The period of peak transmission is shortly after the index case is identified
- Numbers may be smaller as cases are a rare event even in small networks

Creates a bias-variance tradeoff

- Want an unbiased estimate of the vaccine effect
- But, first and foremost, we want to show that the vaccine confers a benefit
- An overly restrictive analysis could jeopardize study power



FIG. 3. Arm 1 vaccinated on day $s_1 = 0$; Arm 0 never vaccinated ($b = \infty$). Constant background infection hazard rate $\lambda_W = 0.001$. Sample size n = 500 per arm. (Setting as in Figure 1.) Analysis period [d, 50) with length c = 50 - d; a range of d values are considered. (A) Apparent VE to assess bias, where the horizontal dotted line indicates $VE_0 = 90\%$. (B) Apparent power.

Dean et al. (2018) AOAS https://projecteuclid.org/euclid.aoas/1520564475

Statistical feature #2: Zero inflation

A large fraction of index cases do not result in secondary cases

Estimated household secondary attack rate:

- 12.5% (95% CI: 8.6 to 16.3%) from historical data
- 18% based on data from Sierra Leone

Common to see zero additional cases in a ring



Source: New York Times

Dean et al. (2016) CID, DOI: <u>10.1093/cid/ciw114</u> Glynn et al. (2017) JID, DOI: <u>10.1093/infdis/jix579</u>

Statistical feature #2: Zero inflation (2)

In the ring vaccination trial, considering all cases:

- 9 out of 48 immediate clusters had any subsequent cases
- 13 out of 42 delayed clusters had any subsequent cases

Even in delayed vaccination clusters, more than half of subsequent cases occurred within 10 days after randomization

For the primary analysis (≥10 days after randomization, vaccine-eligible):

- 0 out of 48 immediate clusters had any subsequent cases
- 7 out of 42 delayed clusters had any subsequent cases

	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 (lusters)					
mmediate	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)						
mmediate	9 (4)	10 (5)	18 (9)	21 (9)		
Delayed	16 (12)	6 (5)	16 (12)	25 (13)		
Number of cases at ≥10 da <u>ys (affecte</u> d clusters)						
mmediate	0 (0)	0 (0)	6* (3)	8* (4)		
Delayed	16† (7)	11† (5)	16†(7)	21†(7)		
/accine 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)		
o value§	0.0036	0.0194	0.1791	0.3351		

Ring vaccination trial analysis

Pre-specified Cox PH with a cluster-level random effect (frailty)

Analysis: For setting of 0 countable events in immediate arm:

• Two-sided Fisher's exact test on cluster-level data

	≥ 1 case (10+ days)	0 cases (10+ days)	TOTAL
IMMEDIATE	0 clusters	48 clusters	48 clusters
DELAYED	7 clusters	35 clusters	42 clusters

p = 0.0036* > OBF bound 0.0027

Henao-Restrepo, Longini, Egger, Dean *et al* (2015) *Lancet*. DOI: http://dx.doi.org/10.1016/S0140-6736(15)61117-5

Future role of ring vaccination trials

Preferred setting:

- Fast-acting vaccine
- Pathogen that moves through predictable contact networks
- Traditional vaccine trial not feasible

Extensions:

- Individual randomization
- Geographical/spatial/occupational ring e.g. work sites, care homes
- Use for other interventions (already similar to post-exposure prophylaxis trials)
- Interesting opportunities for analyses that integrate network features...

Dean et al. (2019) *Science Translational Medicine*, DOI: <u>10.1126/scitranslmed.aat0360</u> Bellan et al. (2019) *Vaccine*, DOI: <u>10.1016/j.vaccine.2019.06.019</u> RESEARCH ARTICLE

Containing Ebola at the Source with Ring Vaccination

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Merler et al. (2016) *PLoS Negl Trop Dis* Kucharski et al. (2016) *EID* DOI: <u>10.3201/eid2201.151410</u>

Conclusion

The ring vaccination trial design is a flexible strategy for evaluating vaccine efficacy and effectiveness

It has been shown to be feasible even in resource-limited settings during a public health emergency

It can be modified in various ways to make it suitable for other diseases or scientific questions

This approach has been demonstrated to be a valuable tool for unpredictable diseases

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THANK YOU!

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