

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 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](#)



ABOUT R&D BLUEPRINT



WHAT THE BLUEPRINT DOES



PRIORITY DISEASES

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 trial
- 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

 OPEN ACCESS

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

disease within a few weeks. When implemented as a targeted programmatic public health measure, such an approach is described as “ring vaccination.”

A surveillance-containment strategy using ring vaccination was central to smallpox eradication in the 1970s. This contributed to the interruption of transmission in Africa, South America, and Asia.² Ring vaccination with an efficacious vaccine might similarly help to control other communicable diseases by

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 Kéïta, Marie Paule Kieny*, 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 2×10^7 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

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World Health Organization,
Geneva, Switzerland
(A M Henao-Restrepo MD,

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 Emwere, Rebecca Grais, Stephan Gunther, Pierre-Stéphane Gsell, Stefanie Hossmann, Sara Viksmoen Wattle, Mandy Kader Kondé, Sakoba Kéita, Souleymane Kone, Eewa Kuisma, Myron M Levine, Sema Mandal, Thomas Mauget, 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 Tomkolili 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

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See Online/Comment

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*Contributed equally

WHO, Geneva, Switzerland
(A M Henao-Restrepo MD,

“...**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

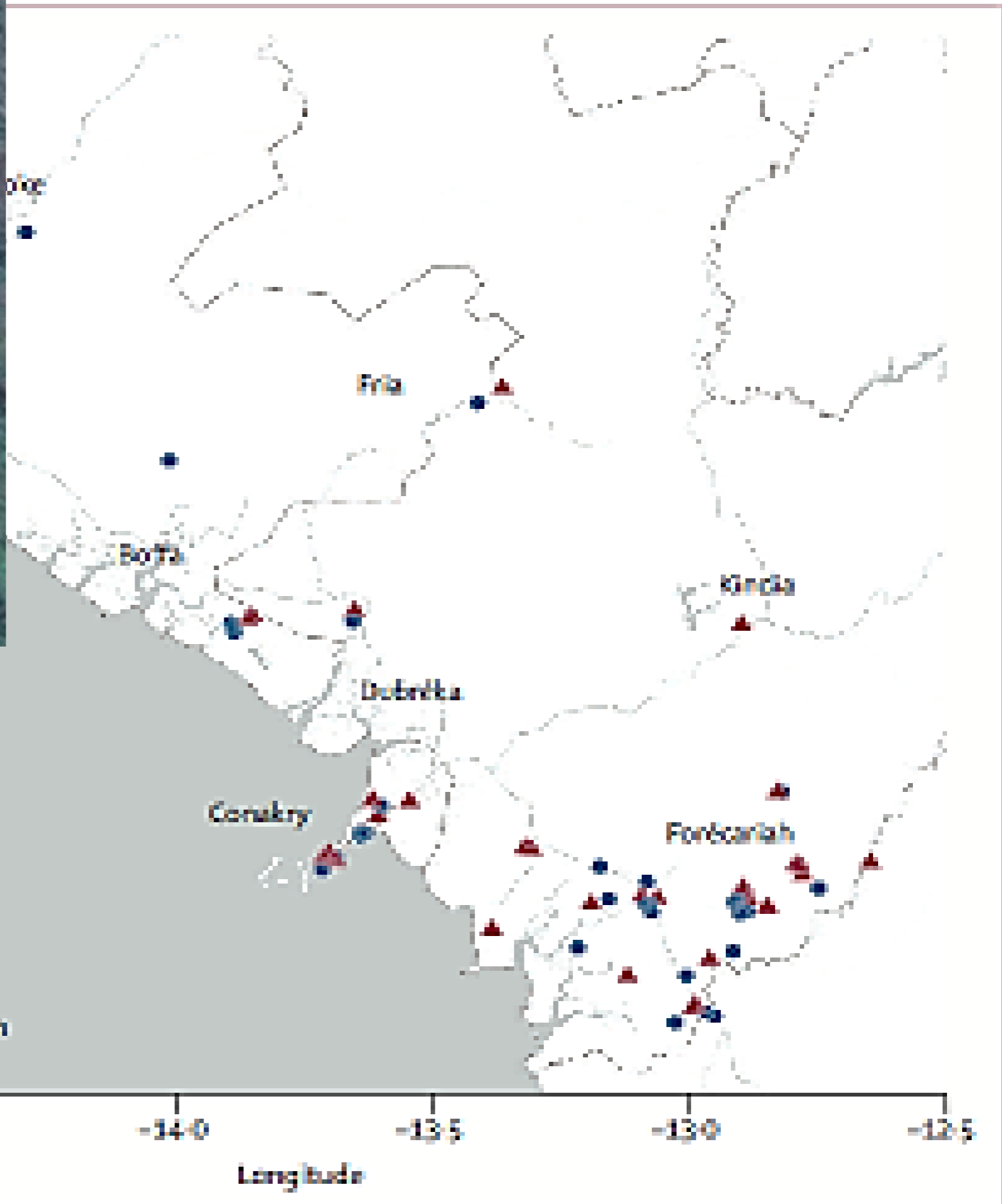
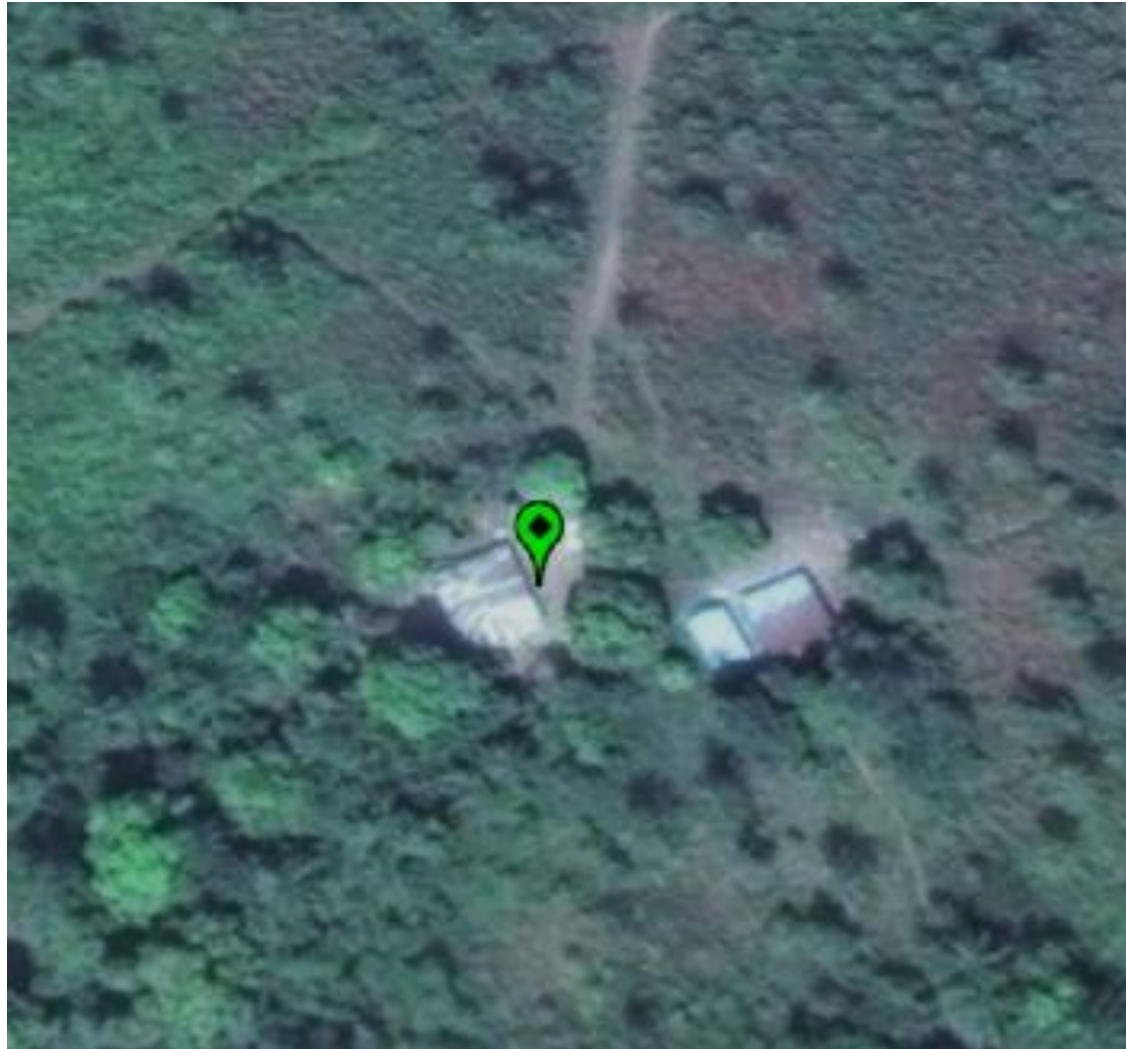
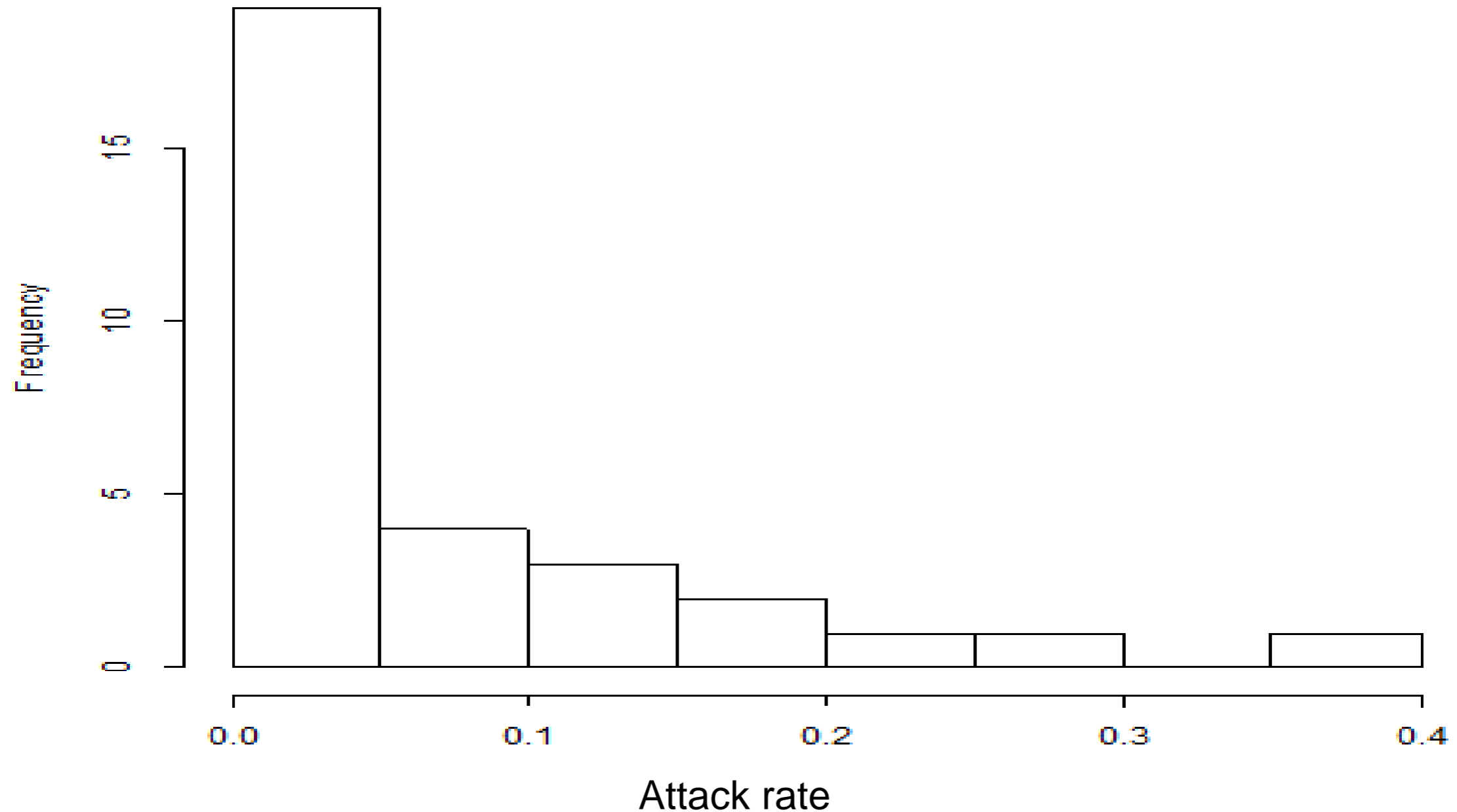


Figure 1: Study area of Ebola *z*o Soffit cluster vaccination trial in Basra-Guinée

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 $\approx 21,000$

($VE = 0.7$, power = 0.90, $\alpha = 0.05$ 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, $\alpha = 0.05$ 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 were 4,394 people in the two arms, in 90 rings*

*Henao-Restrepo, Longini, Egger, Dean, et al. Lancet (2015)

Challenge 2

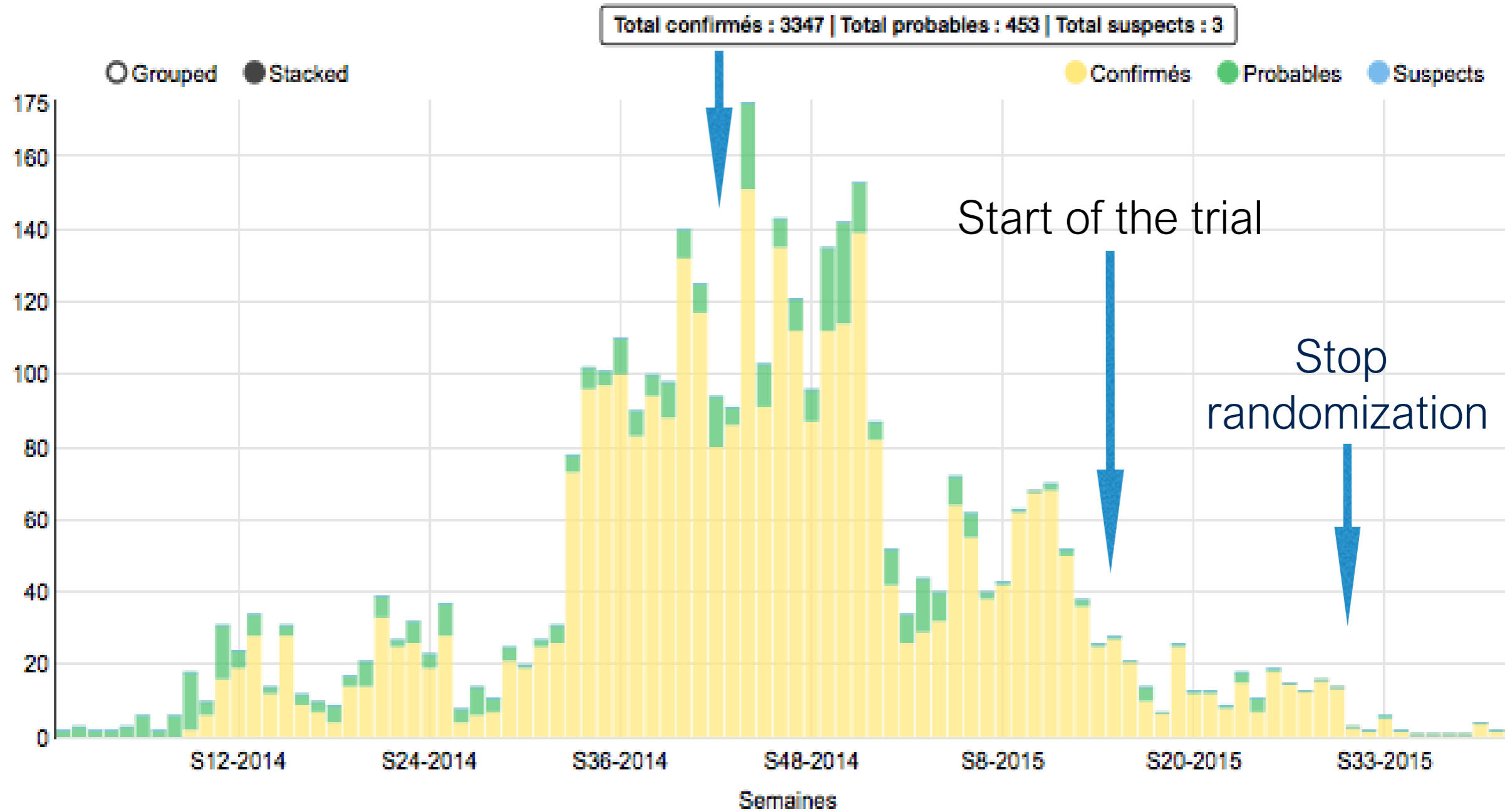
The unprecedented outbreak outpaced the speed with which clinical trials could be implemented

Fix 2

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



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 trial

Newly lab confirmed case of EVD

Definition of ring
(Known contacts, contacts of contacts)
informed consent and randomization

Random allocation of ring

Immediate vaccination

Delayed vaccination

Follow up for outcomes

Follow up for outcomes

Comparisons

Efficacy

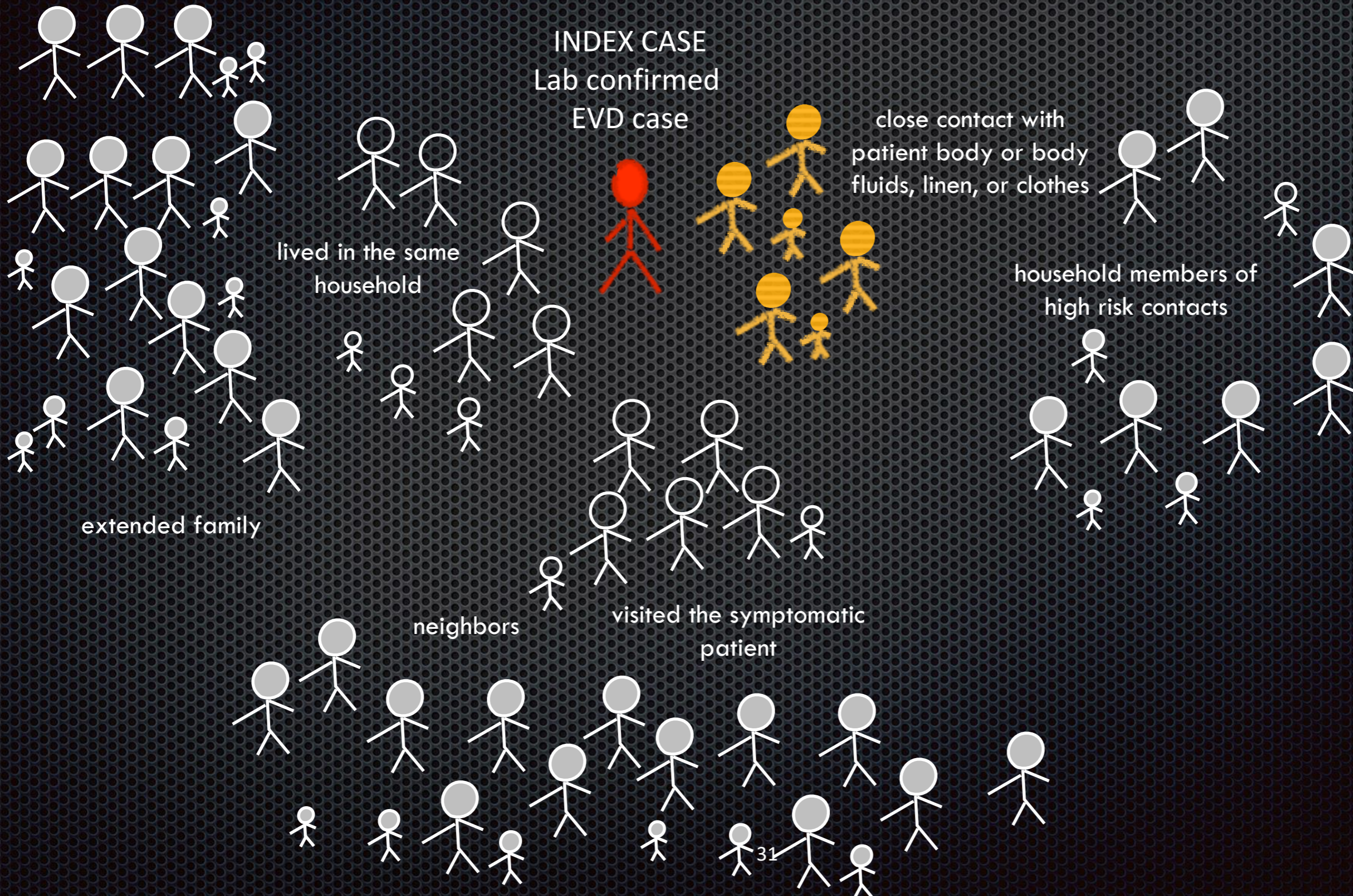
Effectiveness



Eligible, vaccinated Eligible, not vaccinated Not eligible, not vaccinated

What is a vaccination ring?

Contacts and contacts of contacts

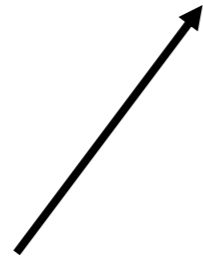




In the ring vaccination trial, teams go to communities with a recently confirmed Ebola case

Hazard function

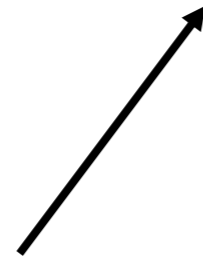
$$\lambda_{hvi}(t) = Z_h \lambda_0(t) Y_{hvi}(t) \theta^v e^{X_{hvi}(t)' \beta}$$



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

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

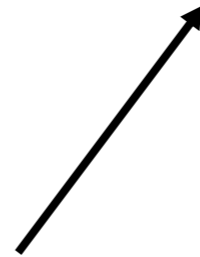


Participation indicator

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

Hazard function

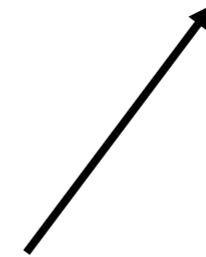
$$\lambda_{hvi}(t) = Z_h \lambda_0(t) Y_{hvi}(t) \theta^v e^{X_{hvi}(t)' \beta}$$



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: $\widehat{VE} = 1 - \widehat{\lambda}_1 / \widehat{\lambda}_0 = 1 - \widehat{\theta}$

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

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

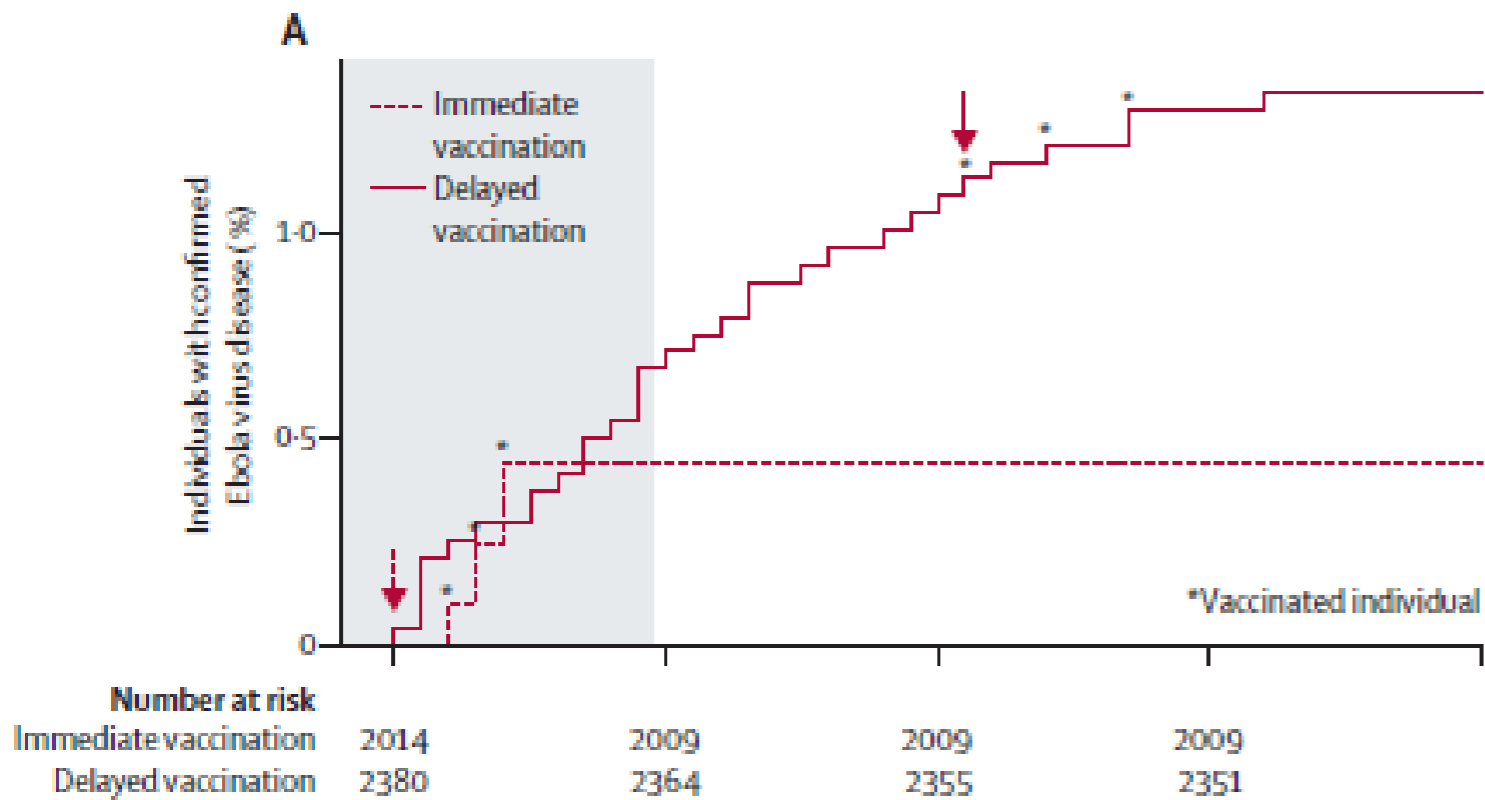
Model will be a mixed-effects, time-dependent, Cox regression model with a random effect (frailty) when there is clustering, or small sample equivalent using cumulative incidence (logist reg).

$H_0: VE = 0$ versus $H_a: VE \neq 0$.

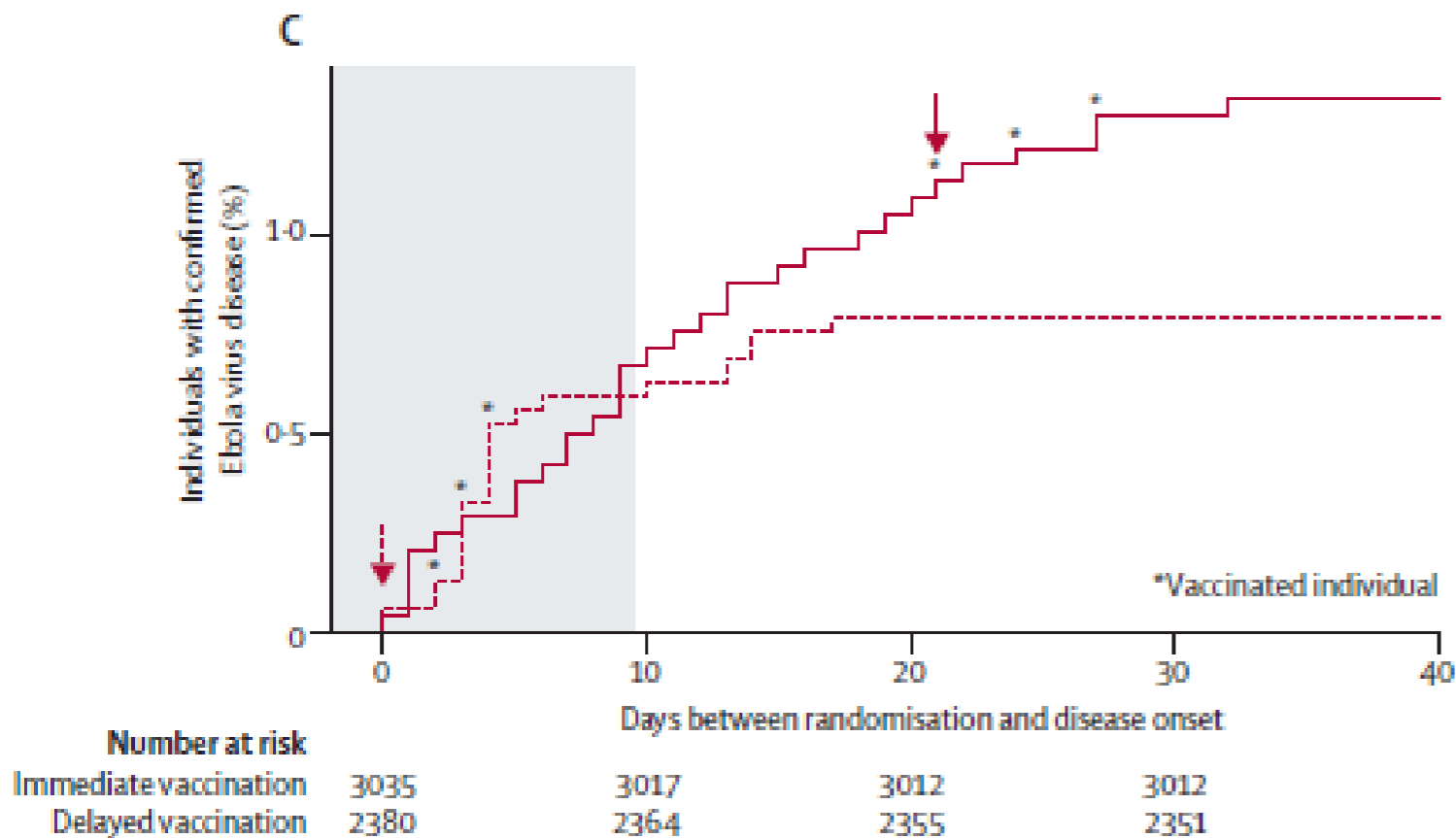
Estimated VE and 95% CI

Adaptive α 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

Source: Henao-Restrepo, Longini, Egger, Dean, *et al. Lancet* (2015)

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

	≥ 1 case (10+ days)	0 cases (10+ days)	TOTAL
<i>IMMEDIATE</i>	<i>0 clusters*</i>	<i>48 clusters</i>	<i>48 clusters</i>
DELAYED	7 clusters**	35 clusters	42 clusters
			p = 0.0036***

What does this mean?

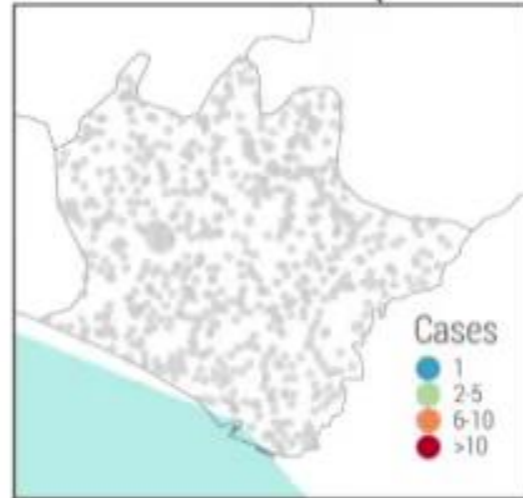
Vaccine efficacy is high: 75 - 100%

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

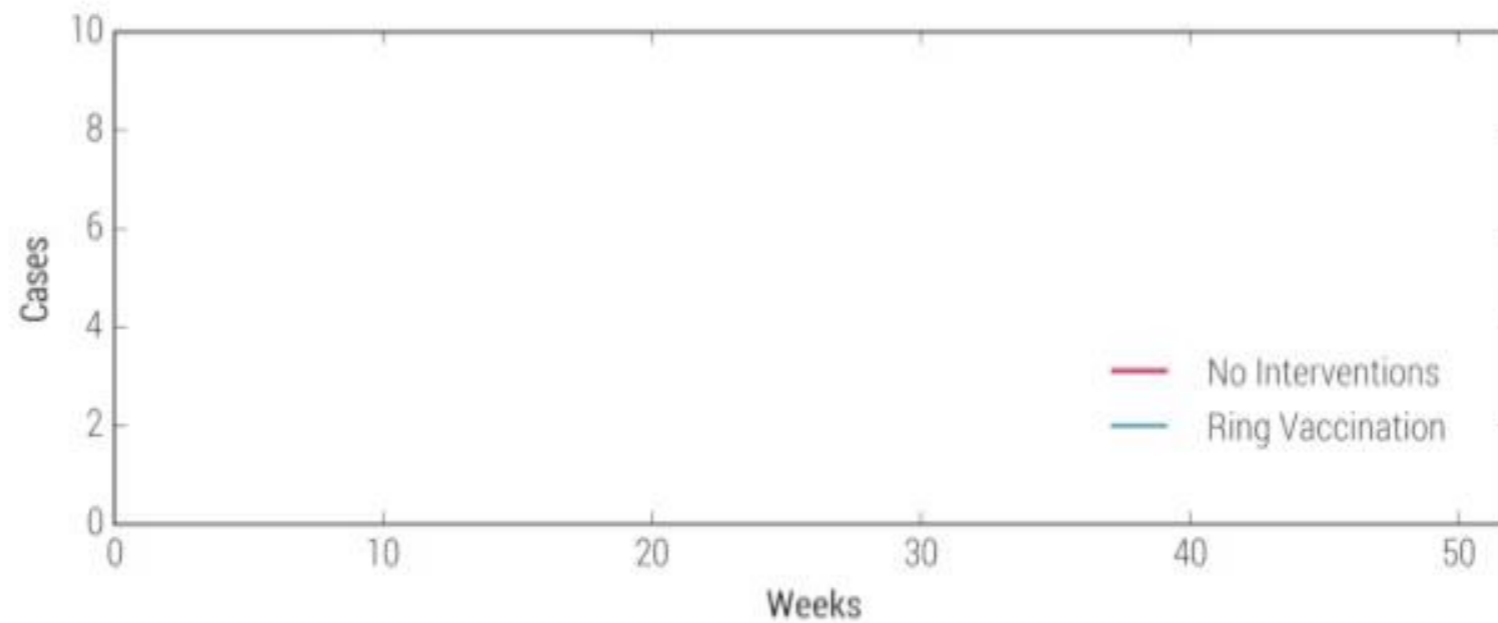
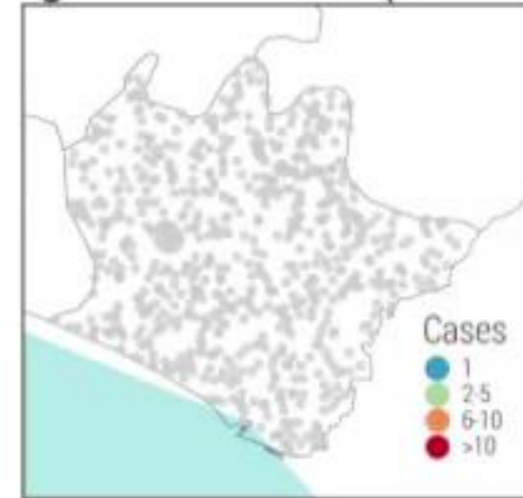
Mobile stockpile of Ebola vaccine can be use to contain and mitigate future Ebola introductions

Ring vaccination contained

No interventions (week : 1)

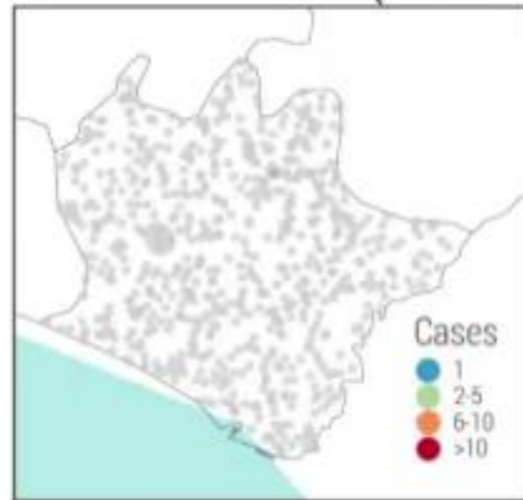


Ring vaccination (week : 1)

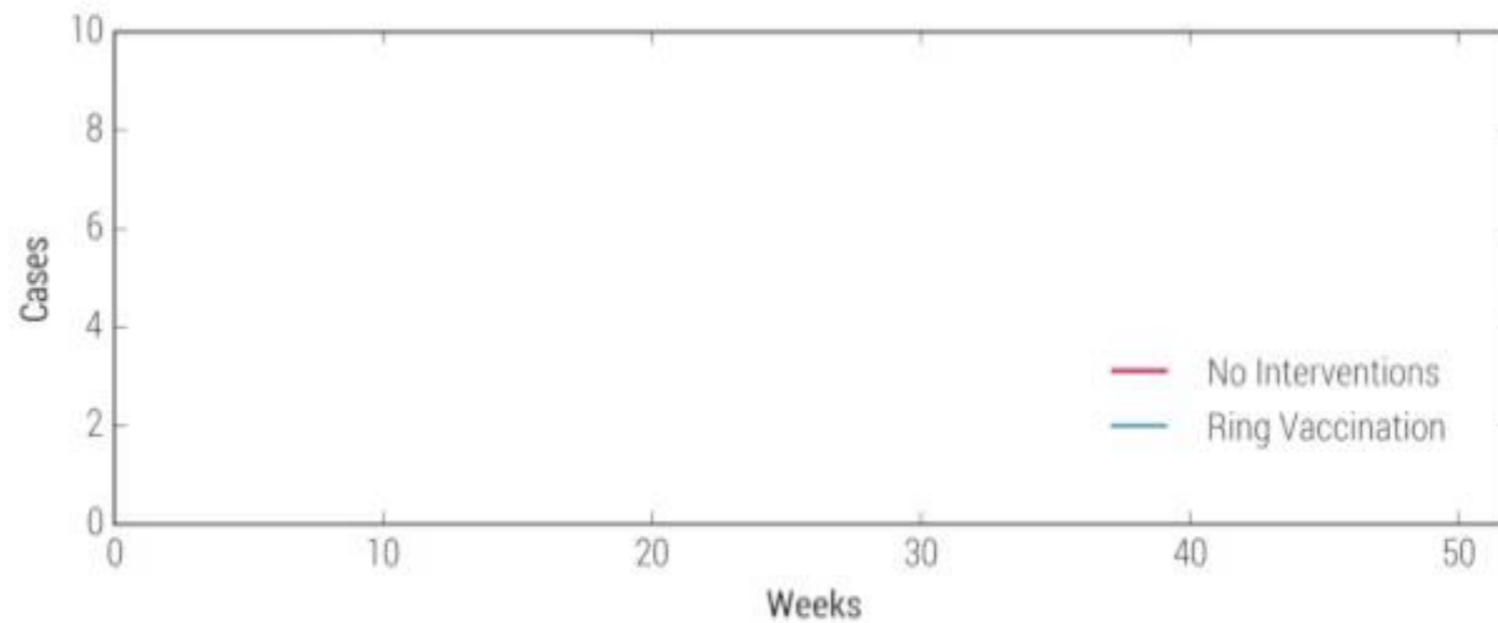
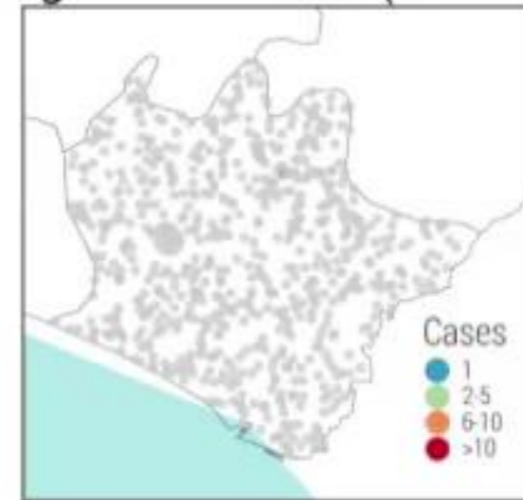


Ring vaccination not contained

No interventions (week : 1)



Ring vaccination (week : 1)



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And Science's Breakthrough of the Year is...

By Science News Staff | Dec. 17, 2015, 2:30 PM



📷 Six-year-old Cecilia Kamara from Robertsport, Liberia holds up a sign after receiving news about the Ebola vaccine. Photograph: Alphanso Appleton

Current epidemic in the DRC

June 29, 2019

- 2,312 confirmed cases
- 1,559 deaths, crude CFR 68%
- 145,445 people vaccinated with rVSV-ZEBOV vaccine in a ring vaccination strategy
- Cases are concentrated in the provinces of North Kivu and Ituri
- Significant violence and instability in many of the affected areas

Vaccine Efficacy

- Vaccine is delivered under a protocol with consent, and follow-up
- Ring vaccination + vaccination of HCWs + some additional targeted groups*
- VE is estimated by comparing the Ebola illness attack rate for confirmed cases for vaccinated people in vaccinated rings, compared to unvaccinated people in appropriate comparison groups.

*https://www.who.int/immunization/policy/position_papers/interim_ebola_recommendations_may_2019.pdf?ua=1<https://www.google.com>

Vaccine Efficacy Estimates*

- For those vaccinated 10 days or more before their illness onset: VE = 97.5%, 95% CI [95.8 –98.5%]
- For HCWs vaccinated 10 days or more before their illness onset: VE = 97.5%, 95% CI [92.4 –99.1]
regardless of time vaccinated VE = 88.1%, 95% CI [79.9-92.9]
- High VE against death given illness

*<https://www.who.int/csr/resources/publications/ebola/ebola-ring-vaccination-results-12-april-2019.pdf>

Ebola model structure, estimation and analysis

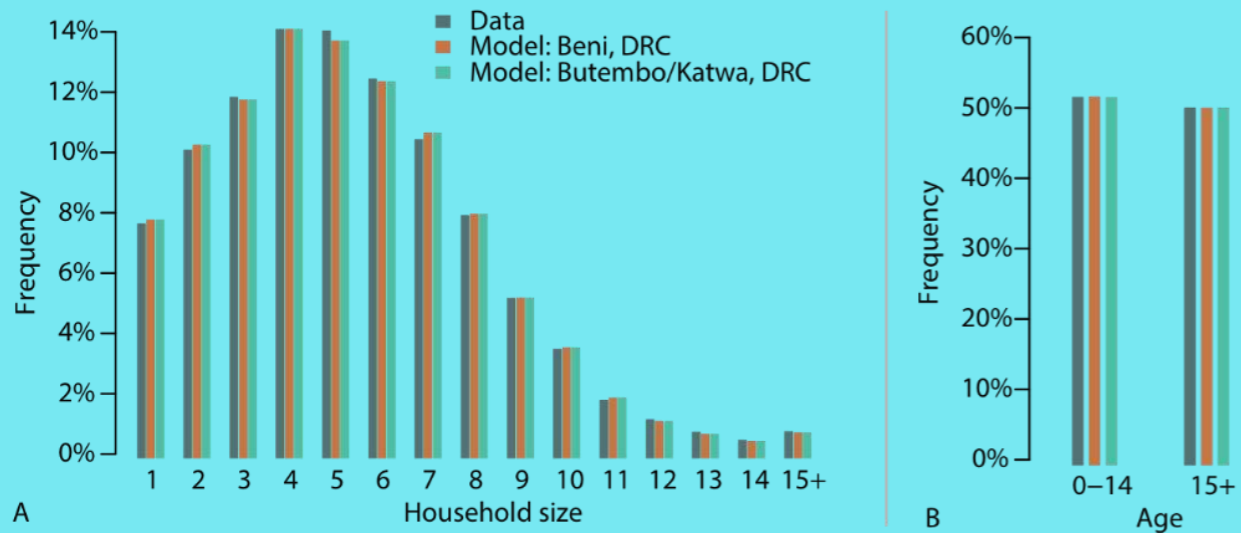
Modeling Methodology

Spatially structured population model

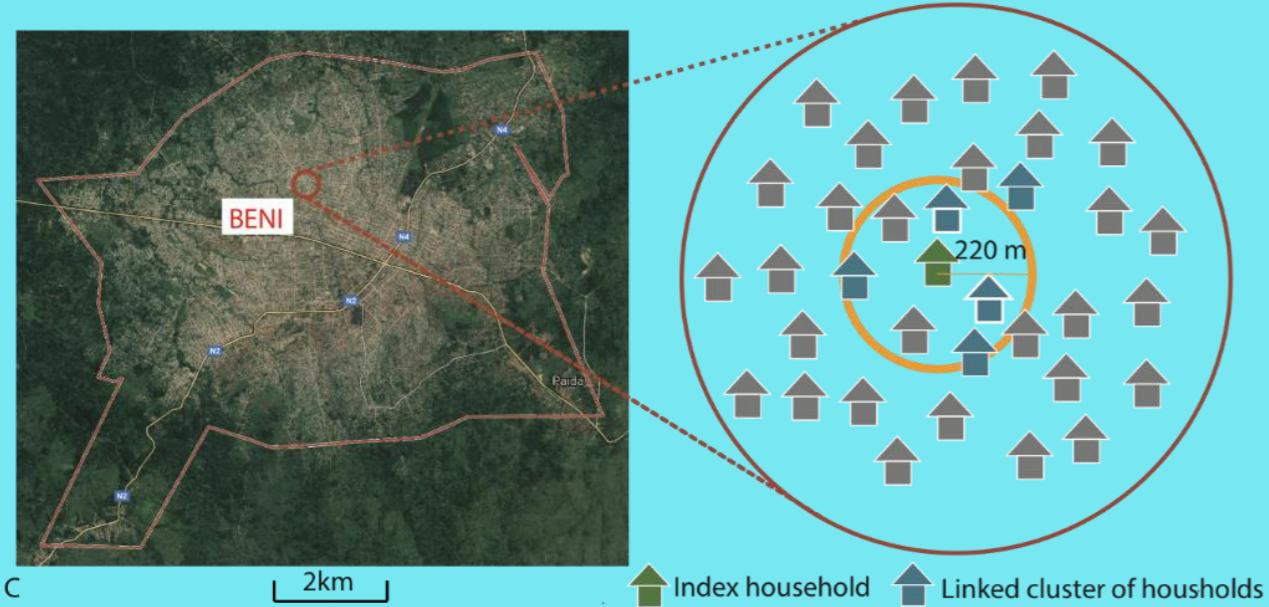
Each individual in the population model is explicitly simulated. Individuals are assigned to specific households. Each household is geolocated and linked to other households to create clusters of households.

Individual Based Transmission & Vaccine strategy simulation

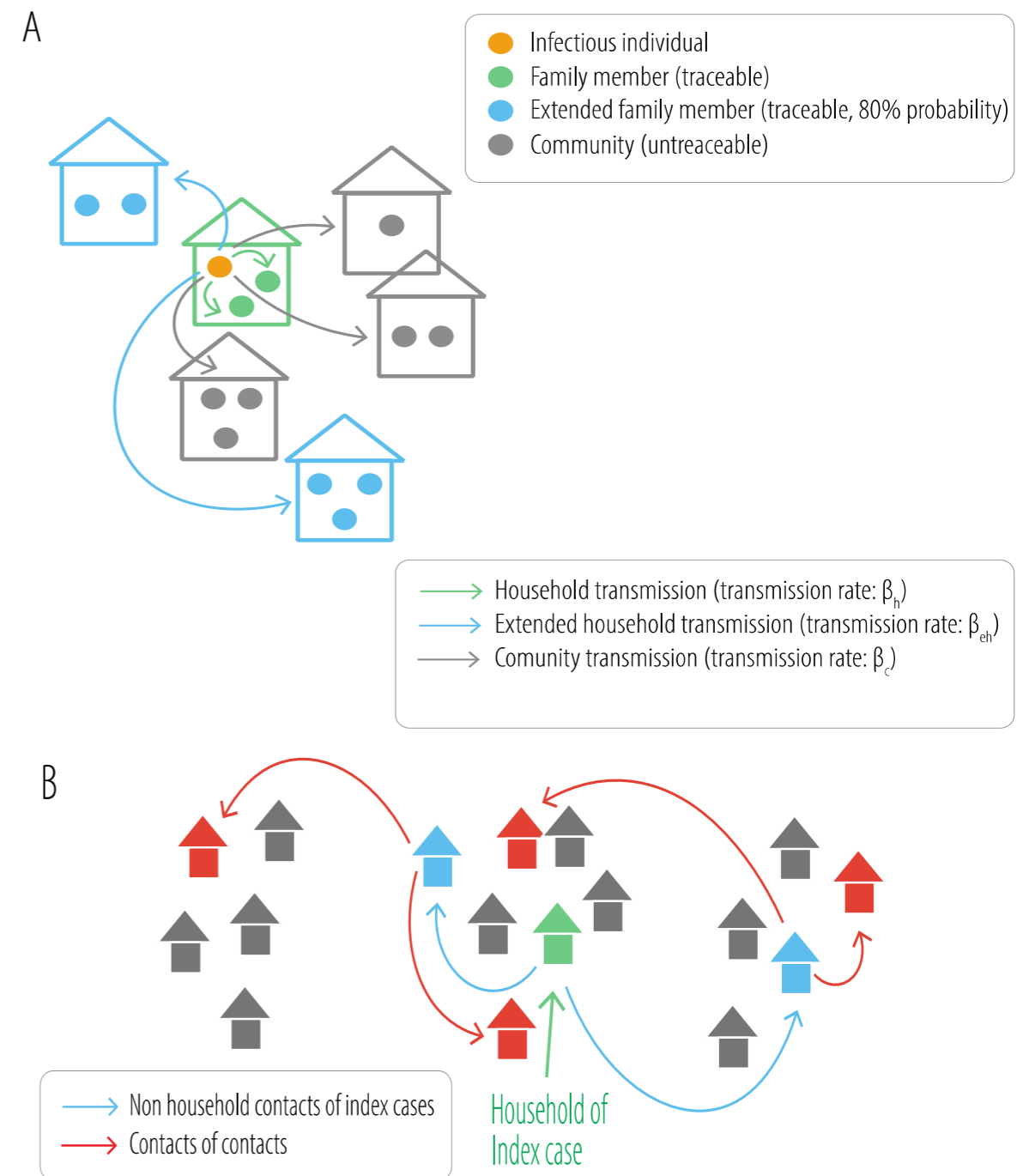
The resulting population structure allows the explicit simulation of interventions (e.g. contact tracing and ring vaccination operations with the rVSV vaccine) targeting contacts of cases – individuals living in the same household of cases, e.g. relatives, or in the linked cluster of households, other relatives, non-relative known contacts , and of the contacts of contacts.



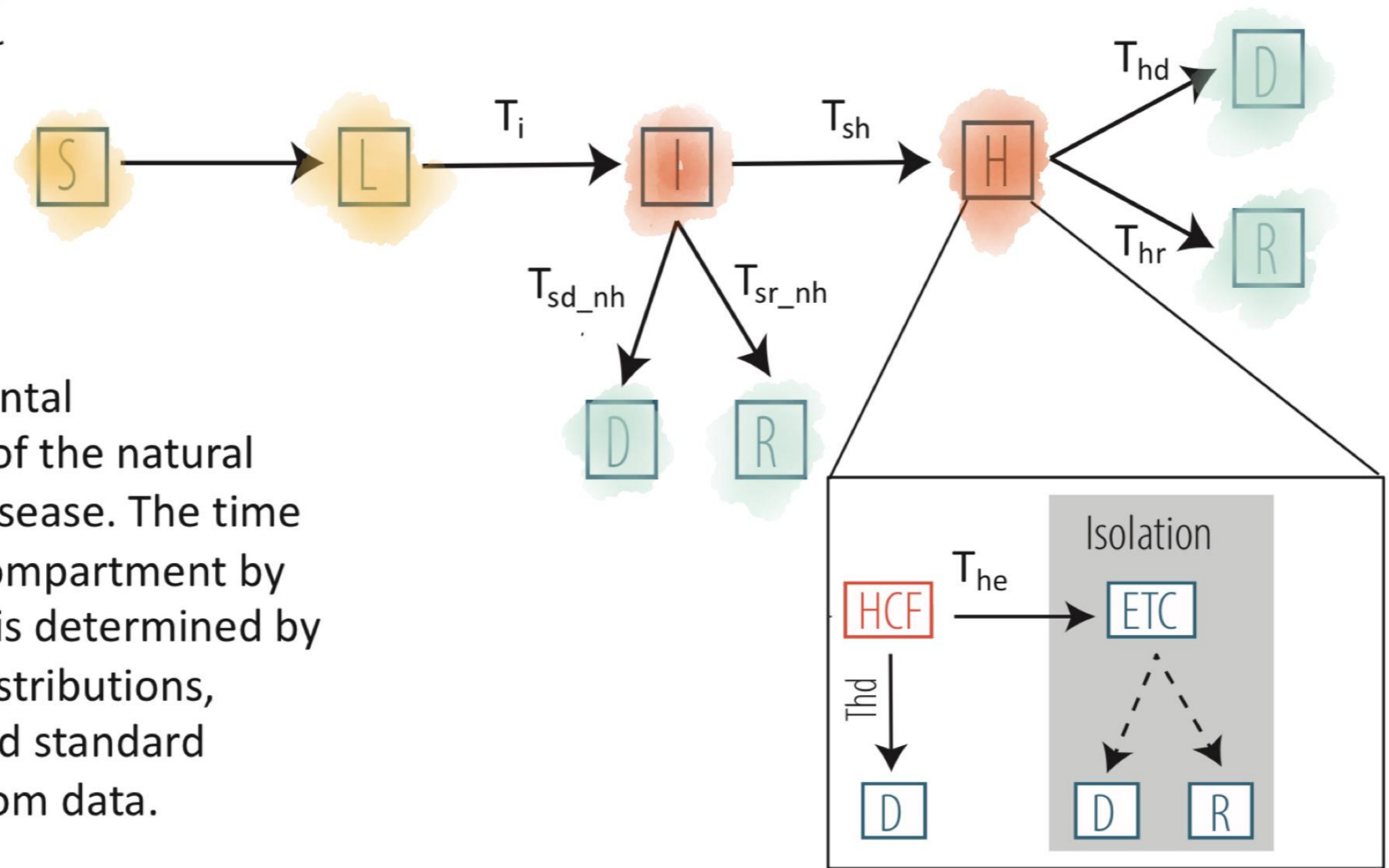
- DRC demographic data: population size, distribution of household size, age distribution of household members. Data on household size and age distribution of household members were taken from the Demographic and Health Surveys (DHS) program. Data on population size of Beni and Butembo/Katwa.
- Google maps images, OpenStreetMap images, and WFP Logistics Cluster maps.
- Ring vaccination data: geographical distance among contacts (and contact of contacts) in the vaccination rings, ring size.



A kernel function of the distance was used to define the set of households generating known contacts. Specifically, for each household i , we define a set of weights $k_{ij} = \frac{1}{(a+d_{ij})^b}$, where d_{ij} is the distance of household i from all households j in the population (expressed in Km); parameter a is an offset and parameter b regulates the decrease of the weight with distance. The values of parameters a and b were selected in such a way that the mean distance between members of the cluster of households is equal to the mean distance among contacts in vaccination rings during the current outbreak in DRC.



Disease Natural History



The compartmental representation of the natural history of the disease. The time spent in each compartment by each individual is determined by using gamma distributions, whose mean and standard deviation are from data.

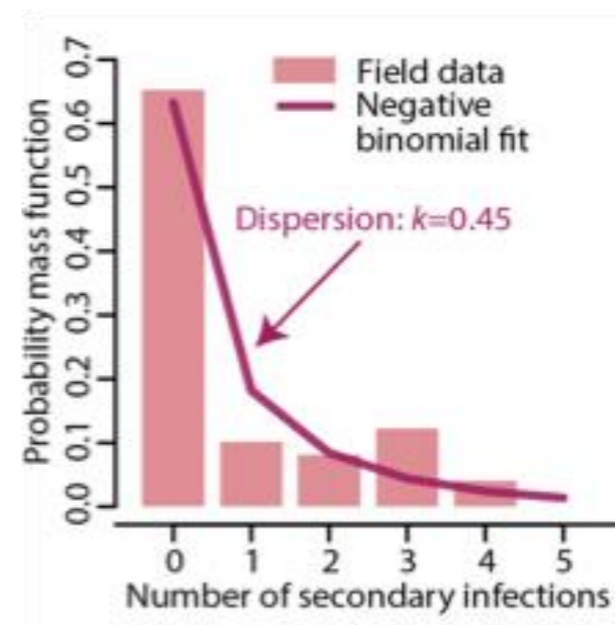
Transmission Dynamics

The transmission process is simulated for each infectious individual.

At the end of the latent period the index case can transmit the infection through contacts in the household, with members of the linked cluster of households and in the general community (three different transmissibility parameters β_h , β_{eh} and β_c).

Each individual in the specific setting

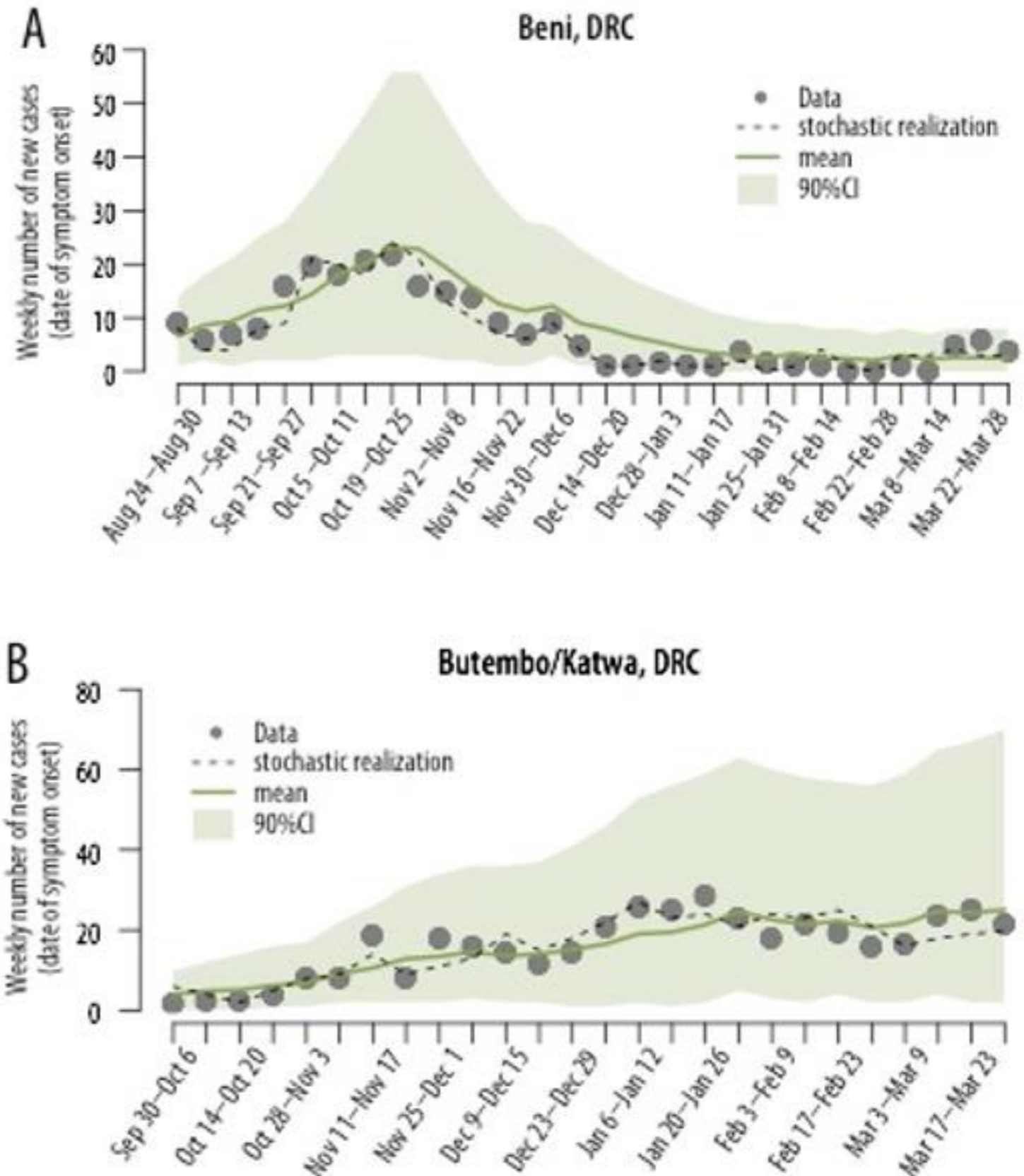
feels a force of infection $\lambda_j = \alpha_j \beta_x \rho_i / N_x$ where α_j is the susceptibility and ρ_i is the infectiousness of the index case i .



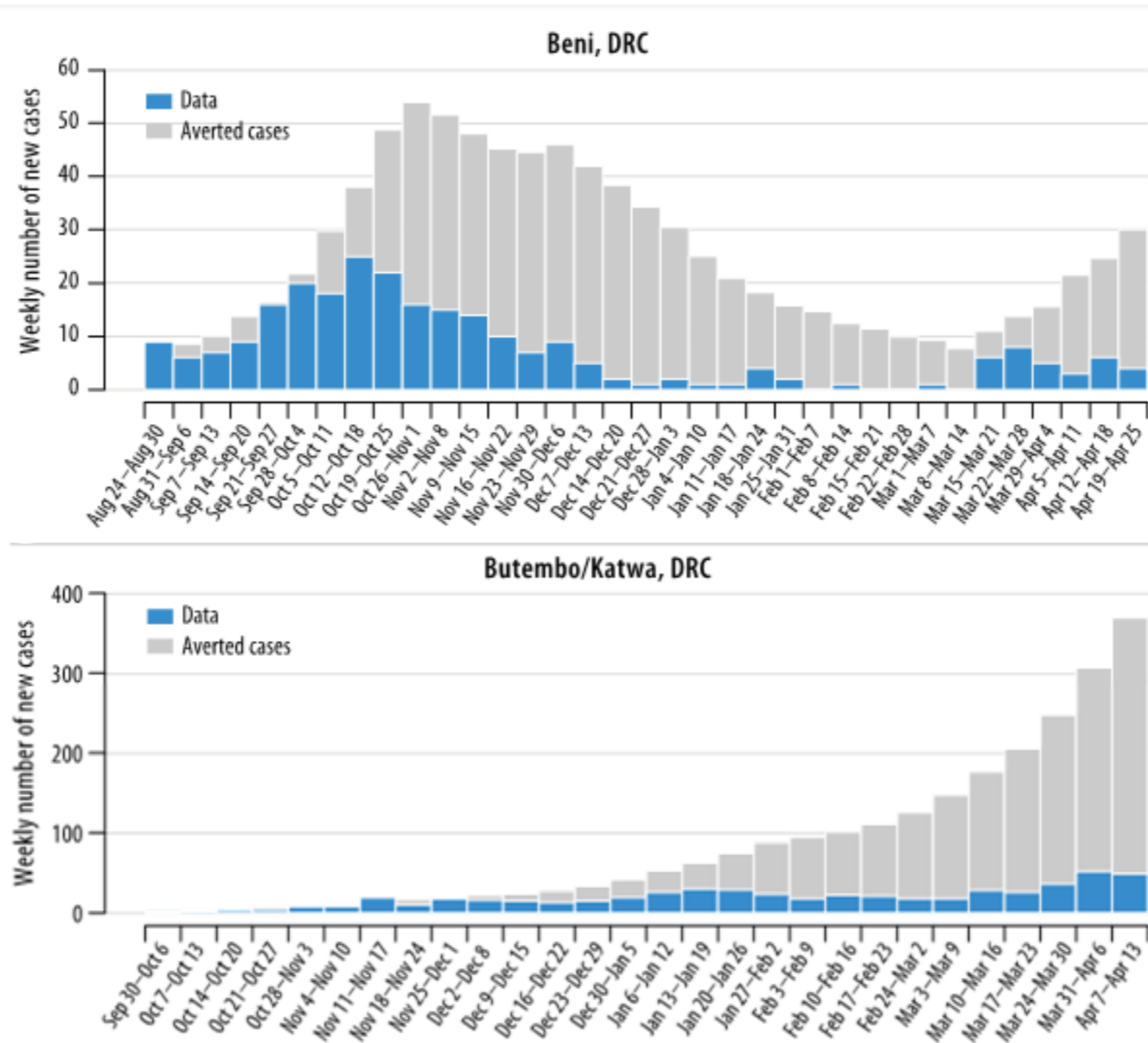
Model calibration

Model calibration

To estimate the four key transmission rates, we used a Markov chain Monte Carlo (MCMC) approach exploring the likelihood of the recorded number of confirmed cases by symptoms onset in each setting.



Cases averted by ring vaccination



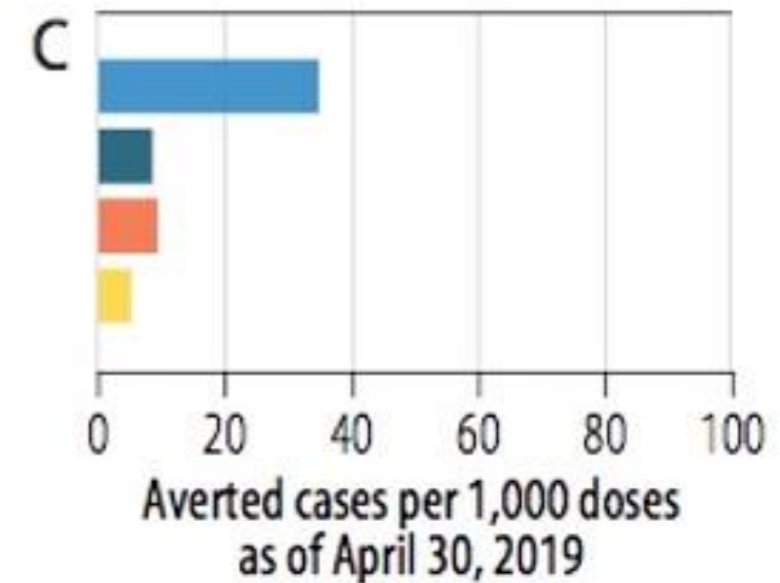
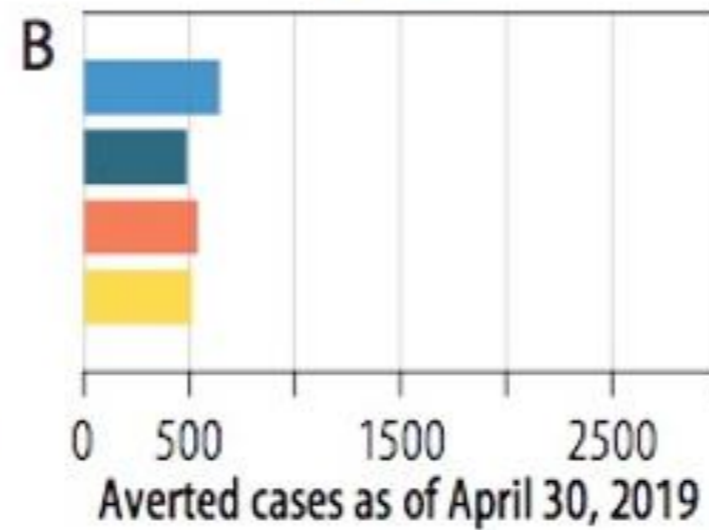
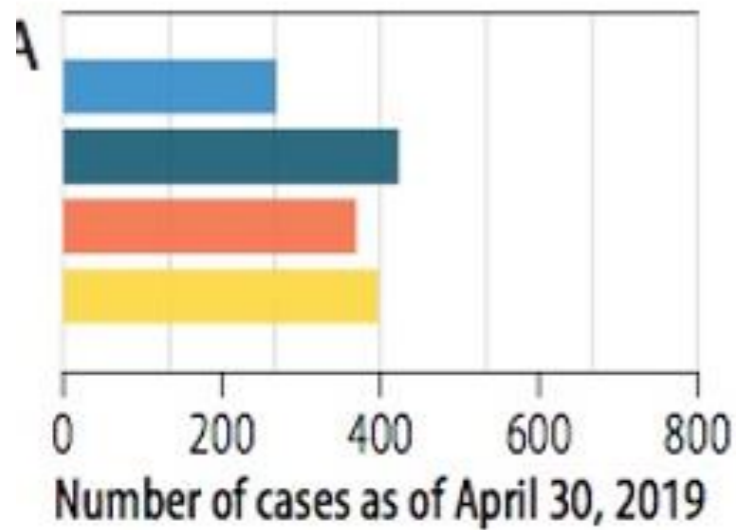
Ring vaccination prevents 5 out of 6 Ebola cases for a large part of the epidemic

Evaluation of different vaccination strategies

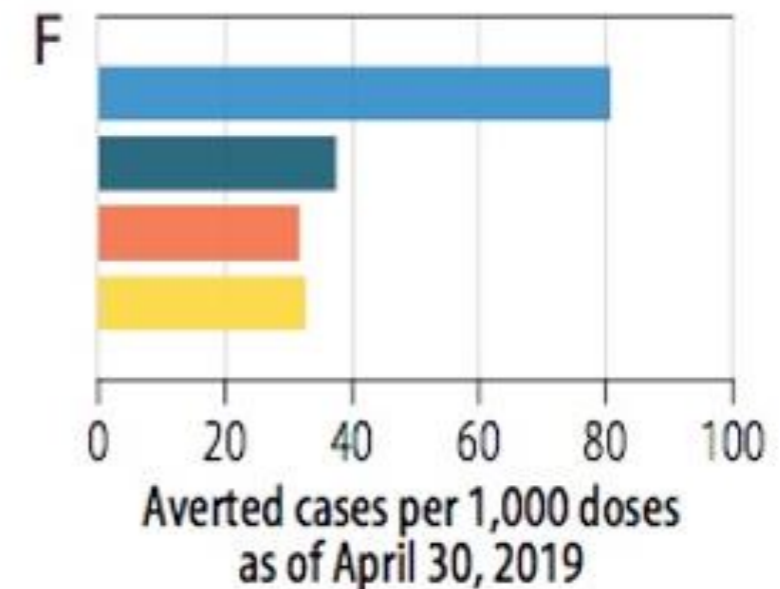
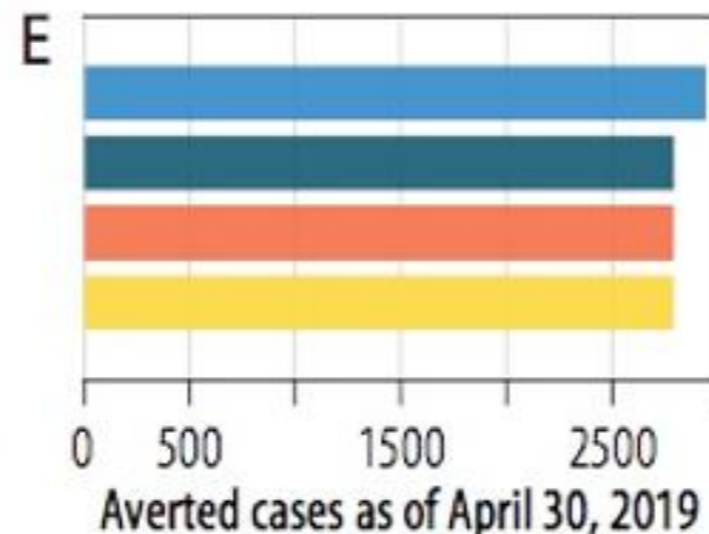
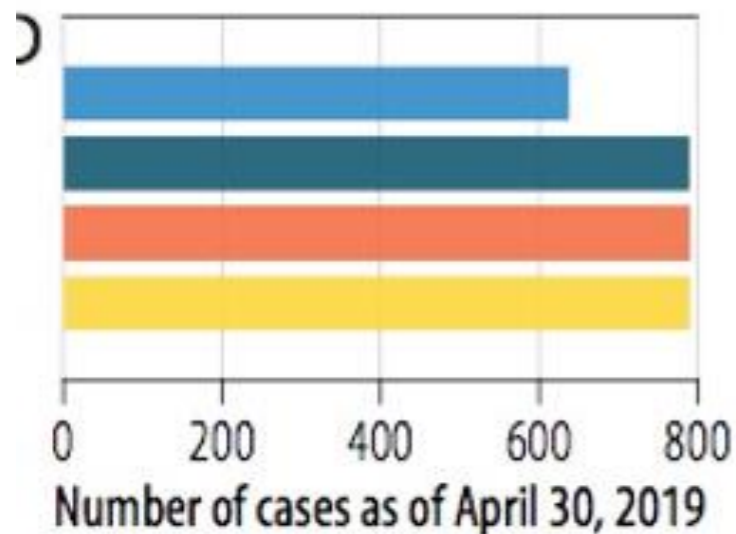
- **Mass vaccination:** Random vaccination 400 doses deliver daily in each affected health zone.
- **Targeted geographic vaccination:** Vaccination of contacts and contacts of contacts plus persons living around the place of residence of a case (i.e., in a radius of **100 meters**) from a newly detected EVD case; Same number of vaccination teams as in the case of ring vaccination, but assume that they can vaccinate up to 80 persons per day.
- **Ring+:** Extending ring vaccination, with the same number of operating teams and administered vaccine doses, by offering the vaccine also to individuals living in the neighborhoods around health care facilities where EVD patients consulted/were admitted

Impact of different vaccination

Beni, DRC



Butembo/Katwa, DRC



SAGE on Immunization

Interim Recommendations on Vaccination against EVD*

1. Implementation of innovative operational strategies
2. Revised vaccination strategy to adjust the target population for ring vaccination to include a second and third barrier of immunized individuals around each incident case
3. Alternative dosing for the rVSV-ZEBOV-GP vaccine.
4. Proposal to further adjust the protocol to incorporate alternative individual informed consent forms.
5. Implementation of a mass communication campaign.

*https://www.who.int/immunization/policy/position_papers/interimEbola_recommendations_may_2019.pdf?ua=1<https://>

Conclusions

- Ring vaccination with rVSV vaccine is the most effective vaccination strategy to control the Ebola outbreak in the DRC.
- The implementation of the vaccination strategy is the main reason that the epidemic is not rapidly growing in several health zones and sustaining its implementation is critical to eliminate Ebola in DRC.

Thank you