Lecture 10
Design and analysis of randomized vaccine trials for emerging infectious disease epidemics: The case of Ebola, COVID-19 and monkeypox

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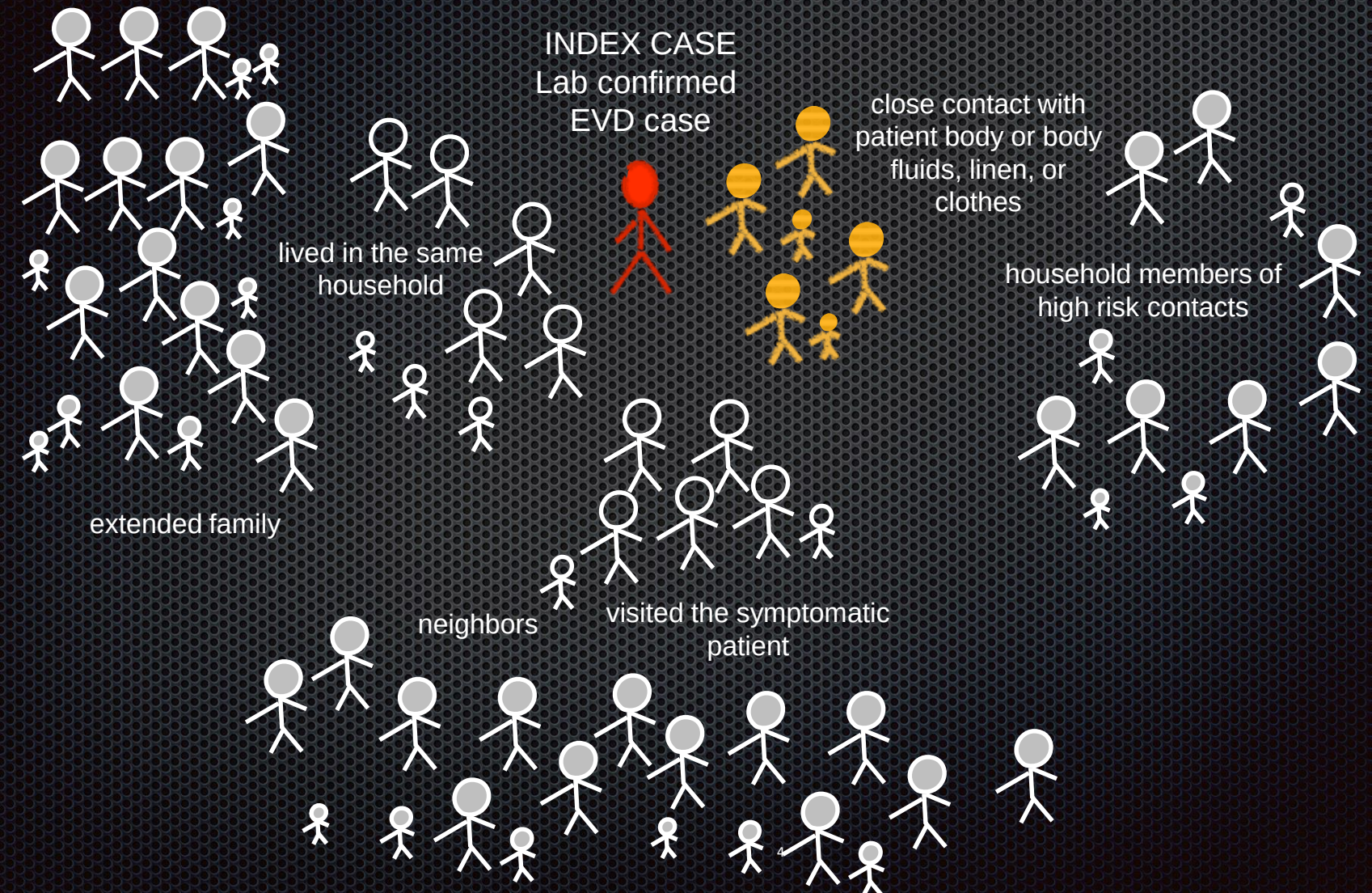
Phase III Ebola Vaccine Trial

Ring Vaccination

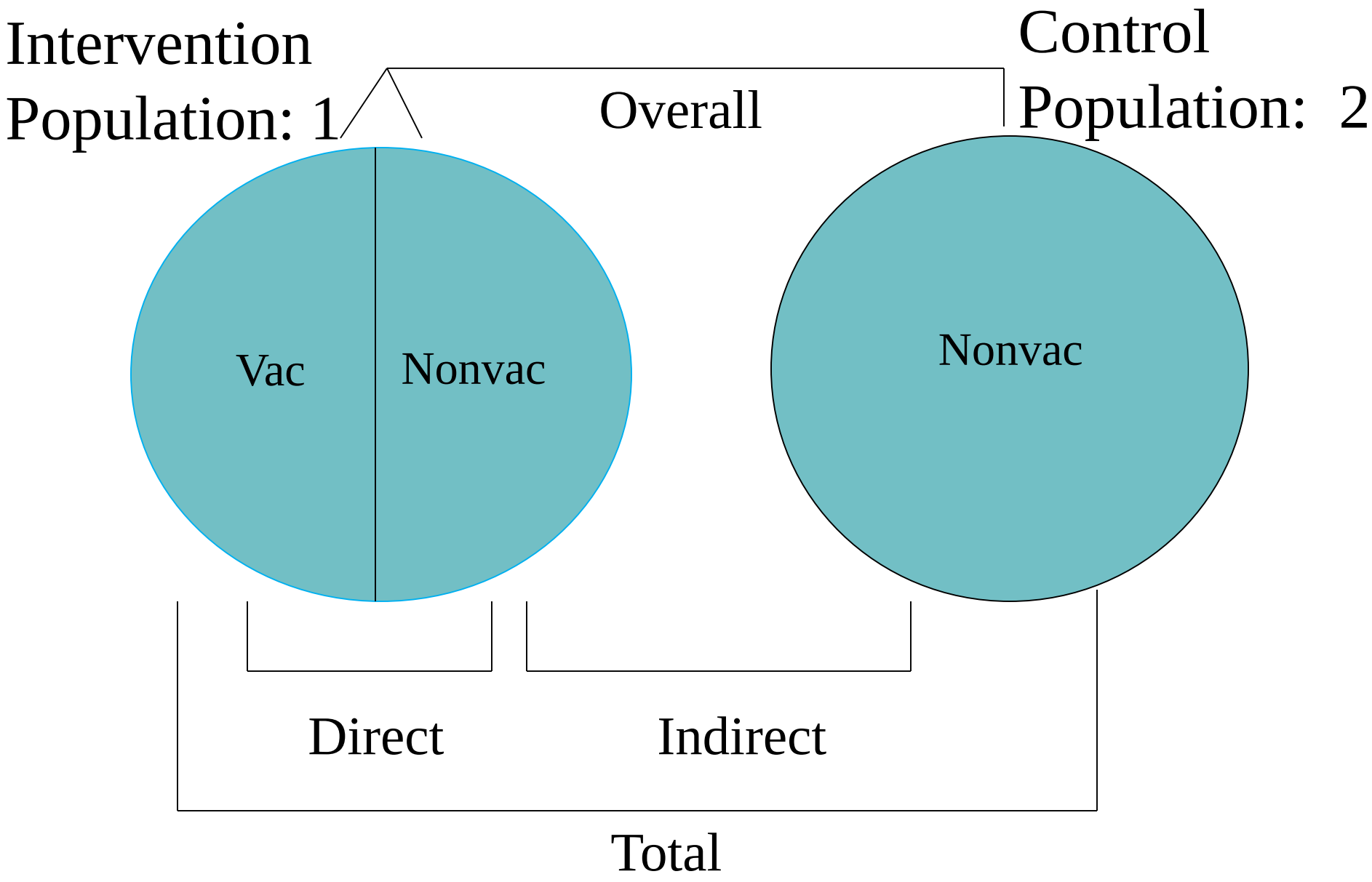
- First used during the consolidated phase of smallpox eradication in the 1970's
- Special case of surveillance and containment
  - Isolate cases
  - Quarantine contacts
- Instead of quarantine, vaccinate the contacts and contacts of contacts of index cases that are isolated

What is a vaccination ring?

Contacts and contacts of contacts

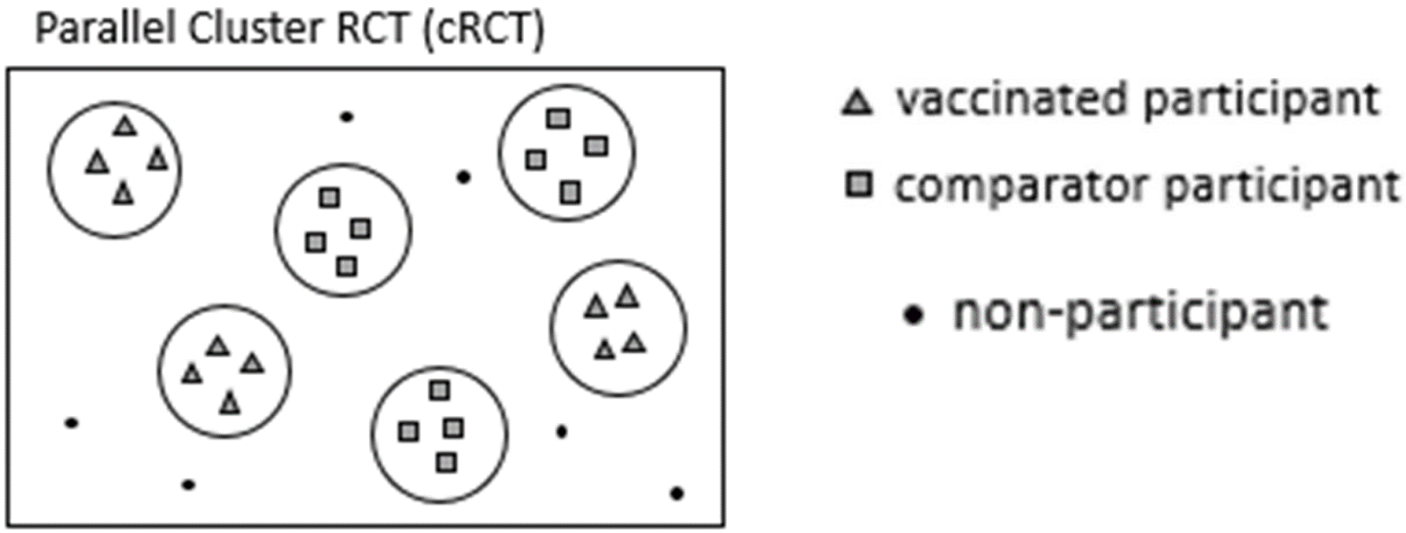


Vaccine Effectiveness



Ring vaccination randomization scheme

- Randomization across rings



Estimate total and overall effectiveness

Ebola vaccine trail in Guinea, West Africa: Case Study

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

thebmj

BMJ 2015;351:h3740 doi: 10.1136/bmj.h3740 (Published 27 July 2015)

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

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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*These authors contributed equally

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 Enwere, Rebecca Grais, Stephan Gunther, Pierre-Stéphane Gsell, Stefanie Hossmann, Sara Viksmoen Watle, Mandy Kader Kondé, Sakoba Keïta, 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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*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

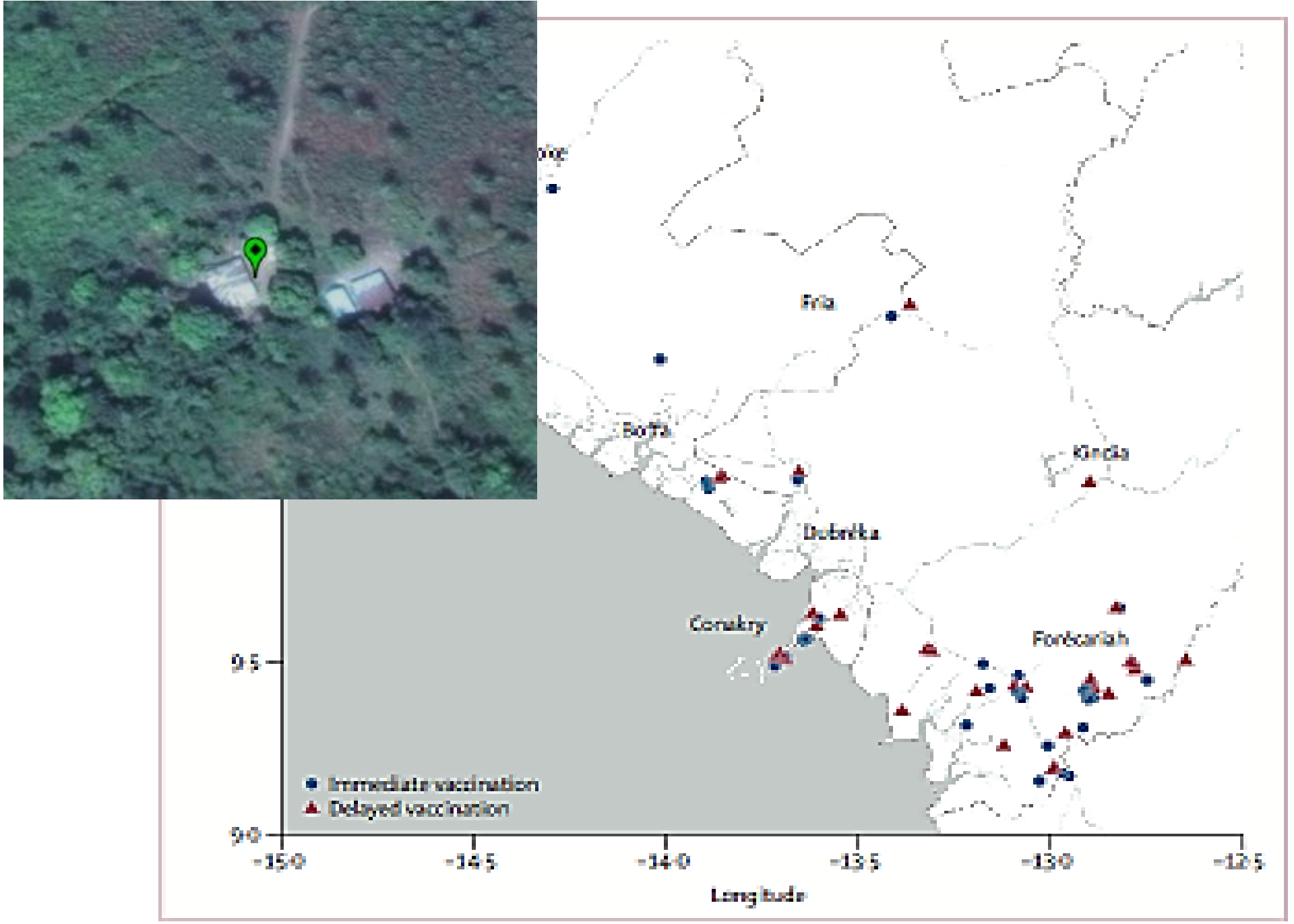
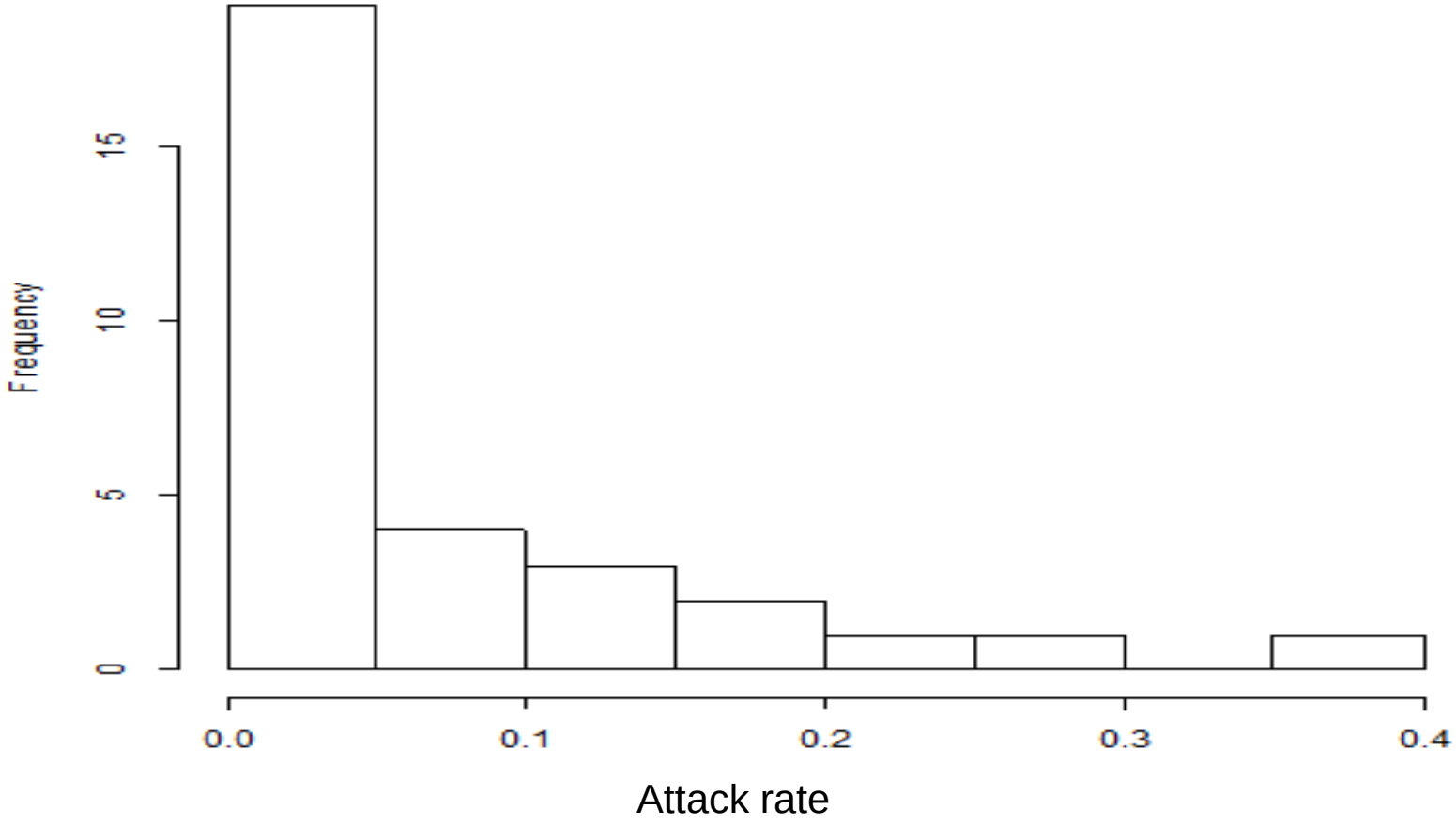


Figure 2: Study area of Ebola ça Suffit cluster vaccination trial in Basse-Guinée

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 ≈ 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, $\alpha = 0.05$ 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 where 4,394 people in the two arms, in 90 rings*

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

Challenge 2

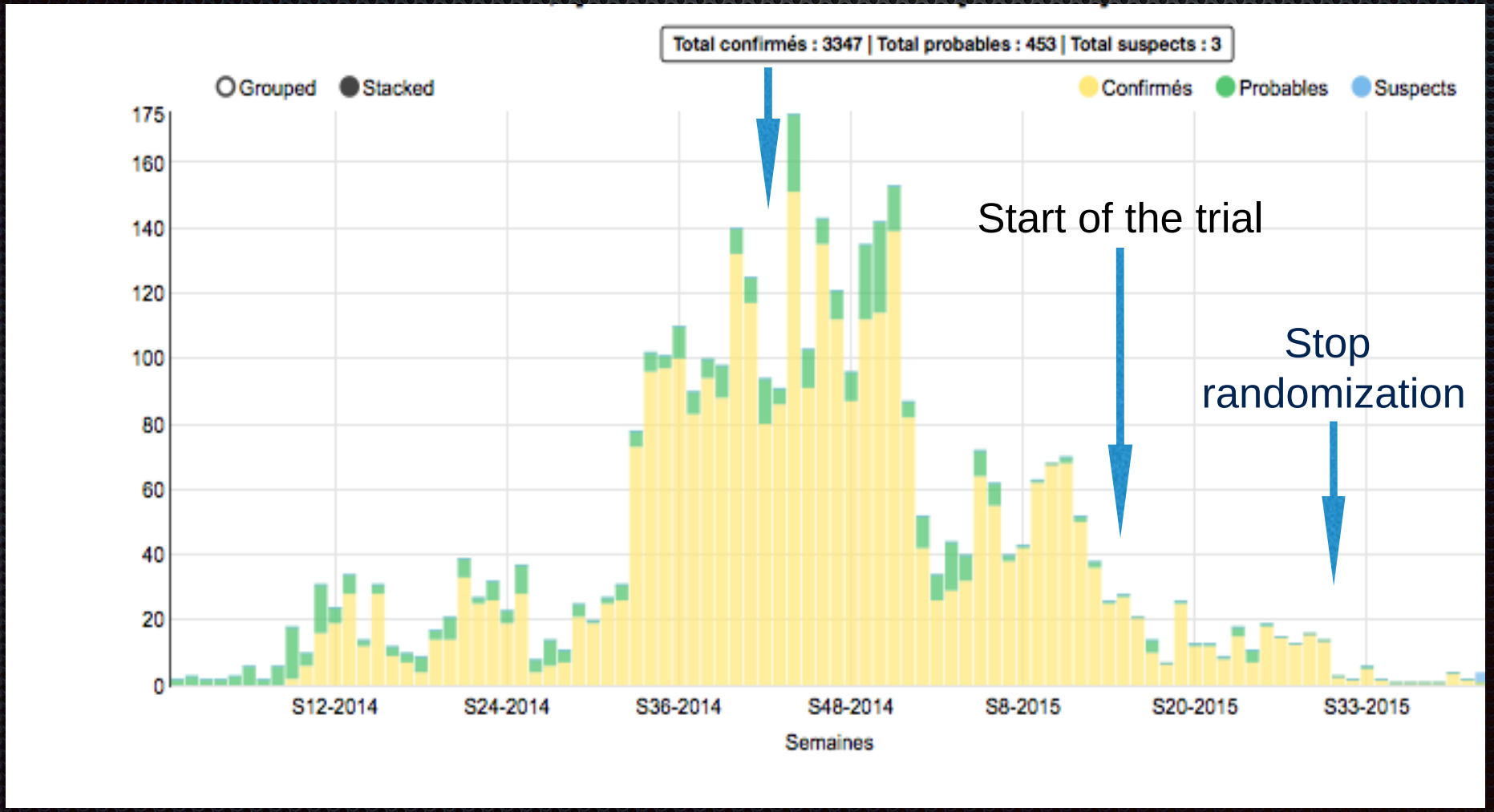
The unprecedented outbreak outpaced the speed with which clinical trials could be implemented

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

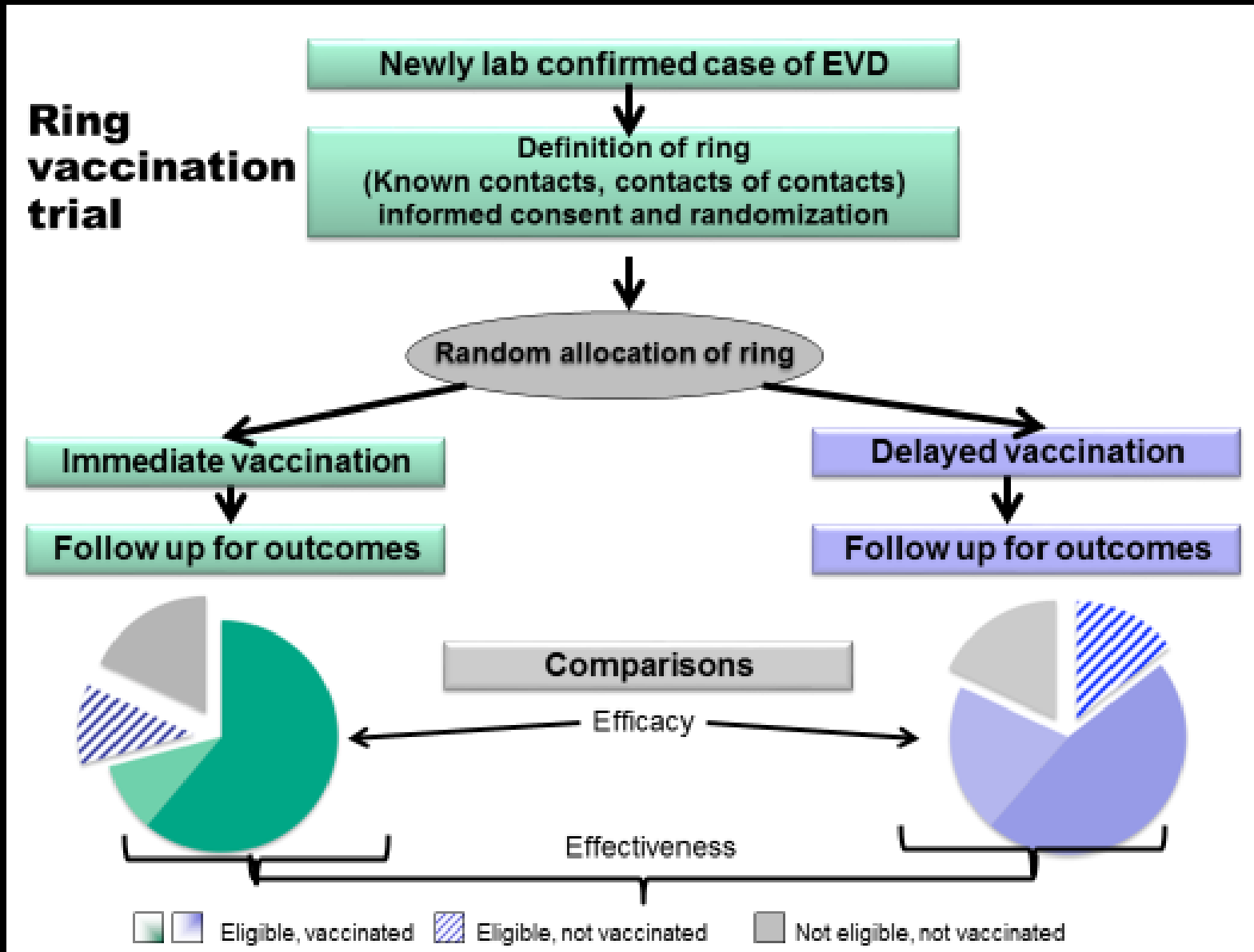


Challenge 3

The uncertainty in predicting future infection incidence

Fix 3

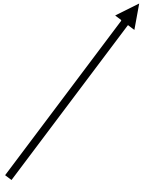
Adaptive design with real-time modifications, based on a predetermined interim analysis of study data.


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

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

Hazard function

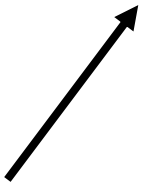
$$\lambda_{hvi}(t) = Z_h \, \lambda_0(t) \; Y_{hvi}(t) \, \theta^v \, e^{X_{hvi}(t)'\beta}$$



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

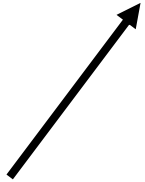
$$\lambda_{hvi}(t) = Z_h \, \lambda_0(t) \; Y_{hvi}(t) \, \theta^v \, e^{X_{hvi}(t)'\beta}$$

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: $\widehat{VE} = 1 - \widehat{\lambda_1}/\widehat{\lambda_0} = 1 - \hat{\theta}$

$\widehat{\lambda_1}$ = the estimated hazard of confirmed illness in the vaccinated

$\widehat{\lambda_0}$ = the estimated hazard confirmed illness in the unvaccinated

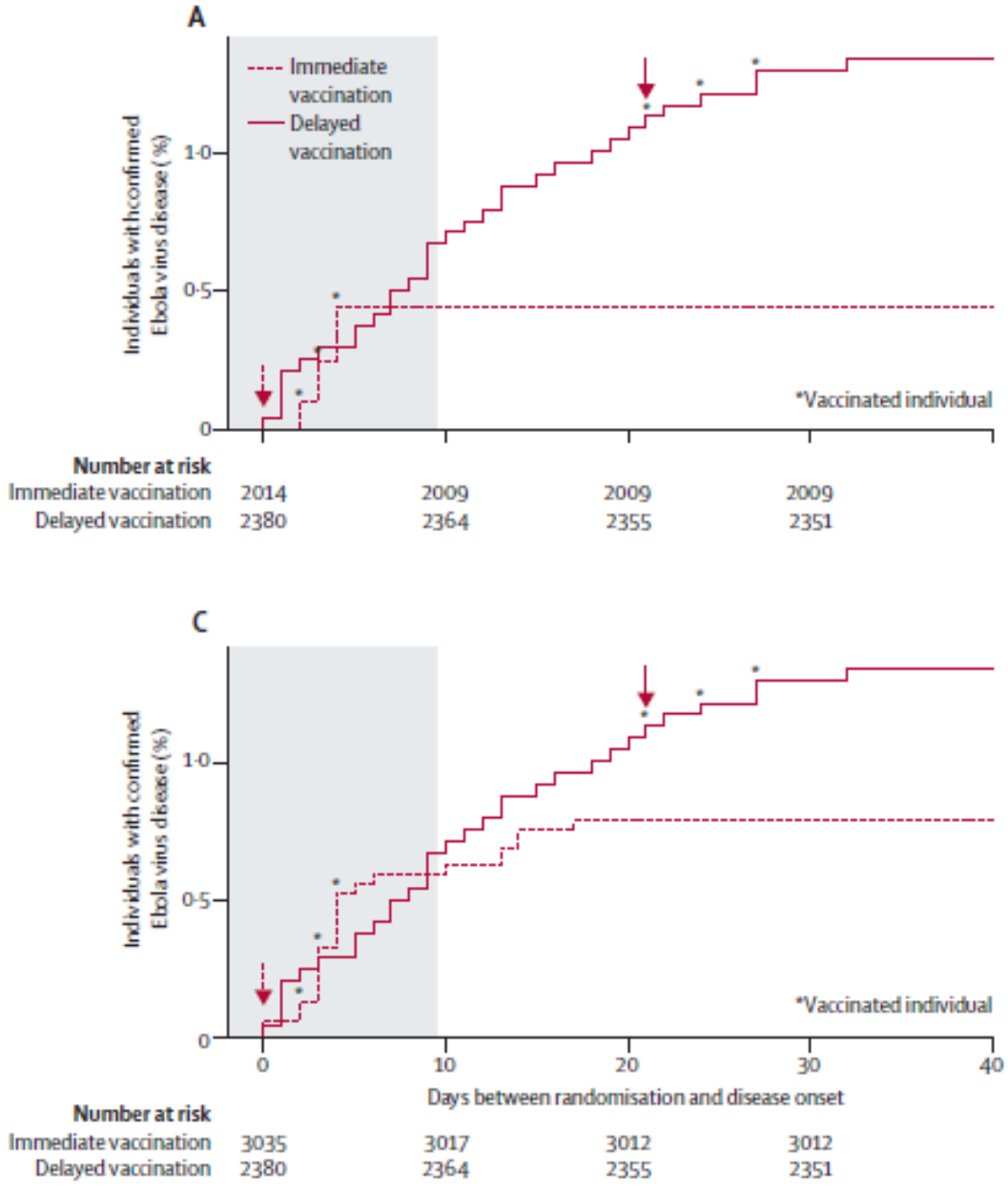
Model will be a mixed-effects, time-dependent, Cox regression model with a random effect (frailty) when there is clustering, or small sample equivalent using cumlative incidence (logist reg).

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)

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 is being used to contain and mitigate future Ebola introductions
- Over 450,000 people have been vaccinated in the 2019 - 2022 outbreaks of Ebola in the DRC

Ebola

Table: Chronology of previous Ebola virus disease outbreaks

Year	Country	EVD	Cases	Deaths	Case fatality
2020 -2022	Democratic Republic of the Congo	Zaire	Ongoing	Handful of cases	
2018-2020	Democratic Republic of the Congo	Zaire	3481	2299	66%
2018	Democratic Republic of the Congo	Zaire	54	33	61%
2017	Democratic Republic of the Congo	Zaire	8	4	50%
2015	Italy	Zaire	1	0	0%
2014	Spain	Zaire	1	0	0%
2014	UK	Zaire	1	0	0%
2014	USA	Zaire	4	1	25%
2014	Senegal	Zaire	1	0	0%
2014	Mali	Zaire	8	6	75%
2014	Nigeria	Zaire	20	8	40%
2014-2016	Sierra Leone	Zaire	14124*	3956*	28%
2014-2016	Liberia	Zaire	10675*	4809*	45%
2014-2016	Guinea	Zaire	3811*	2543*	67%

Ebola

Table: Chronology of previous Ebola virus disease outbreaks

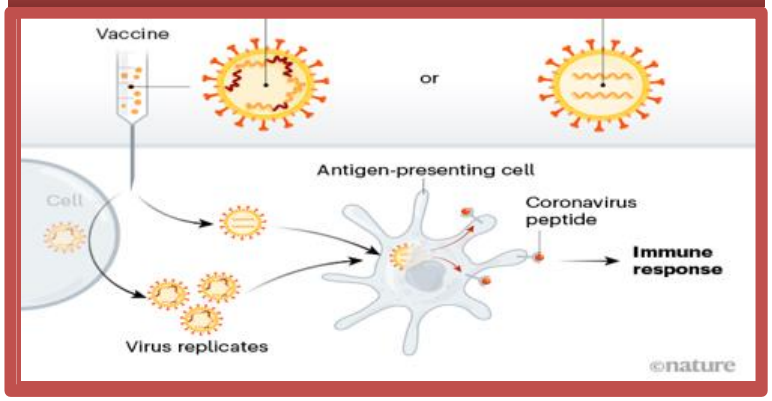
Year	Country	EVD	Cases	Deaths	Case fatality
2014	Democratic Republic of the Congo				
2012	Democratic Republic of the Congo	Bundibugyo	57	29	51%
2012	Uganda	Sudan	7	4	57%
2012	Uganda	Sudan	24	17	71%
2011	Uganda	Sudan	1	1	100%
2008	Democratic Republic of the Congo	Zaire	32	14	44%
2007	Uganda	Bundibugyo	149	37	25%
2007	Democratic Republic of the Congo	Zaire	264	187	71%
2005	Congo	Zaire	12	10	83%
2004	Sudan	Sudan	17	7	41%
2003 (Nov-Dec)	Congo	Zaire	35	29	83%
2003 (Jan-Apr)	Congo	Zaire	143	128	90%
2001-2002	Congo	Zaire	59	44	75%
2001-2002	Gabon	Zaire	65	53	82%
2000	Uganda	Sudan	425	224	53%
1996	South Africa (ex-Gabon)	Zaire	1	1	100%
1996 (Jul-Dec)	Gabon	Zaire	60	45	75%
1996 (Jan-Apr)	Gabon	Zaire	31	21	68%
1995	Democratic Republic of the Congo	Zaire	315	254	81%
1994	Côte d'Ivoire	Taï Forest	1	0	0%
1994	Gabon	Zaire	52	31	60%
1979	Sudan	Sudan	34	22	65%
1977	Democratic Republic of the Congo	Zaire	1	1	100%
1976	Sudan	Sudan	284	151	53%
1976	Democratic Republic of the Congo	Zaire	318	280	88%

The development and deployment of COVID-19 vaccines:

Types of COVID-19 vaccines

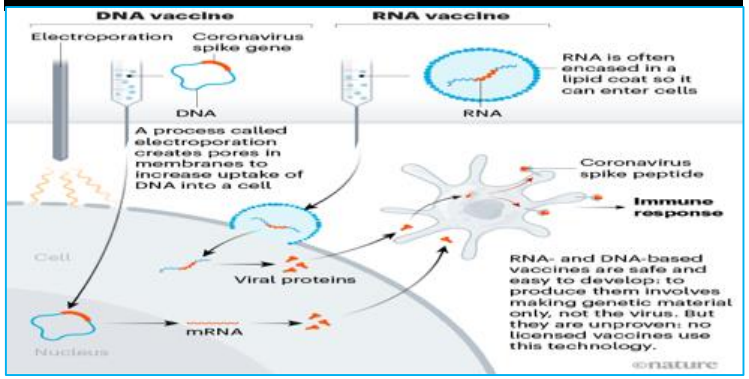
VIRUS VACCINES

Live-attenuated virus Inactivated virus



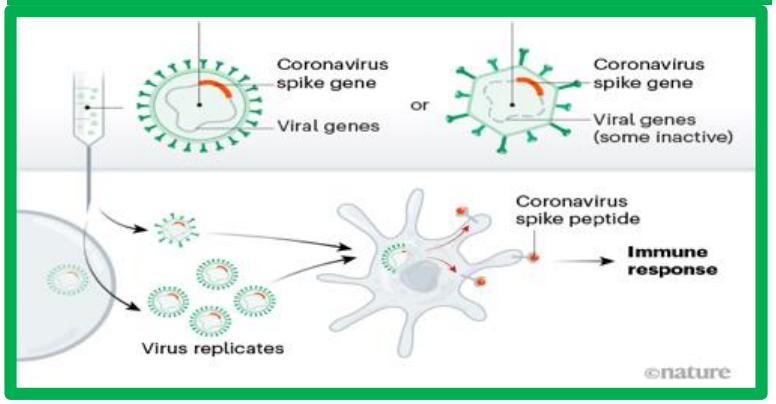
NUCLEIC ACID VACCINES

DNA and RNA vaccines



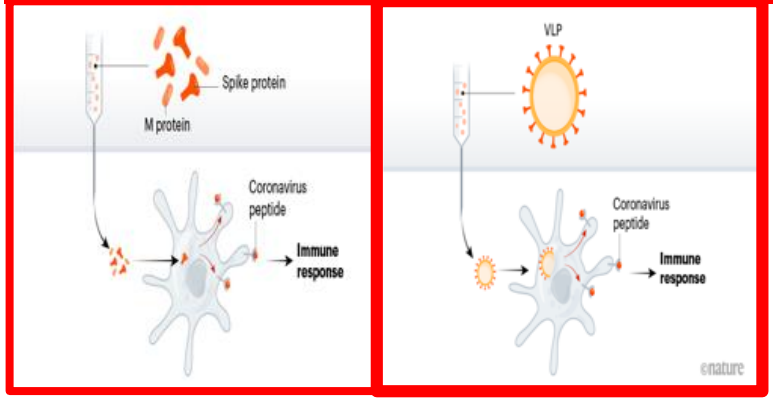
VIRAL VECTOR VACCINES

Replicating viral vector Non-replicating viral vector



PROTEIN-BASED VACCINES

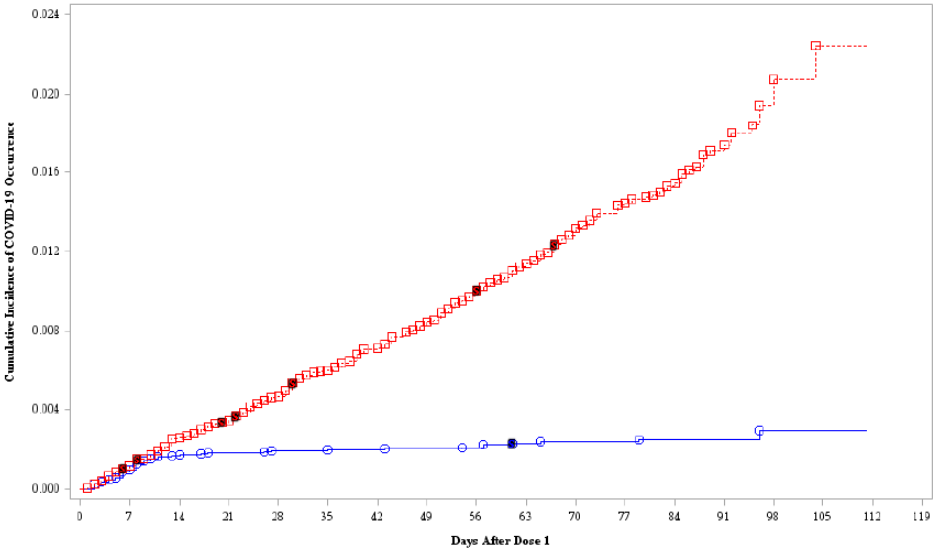
Protein subunits Virus-like particles



For example, phase III vaccine trail

- Sponsor Name: Pfizer
- Vaccine: BNT162b2 RNA vaccine
- **Final analysis carried out at 196 events**
  - **VE = 94.6% (95% CI 89.9 to 97.3)**
    - **Apparent VE severe disease and older adults**
    - **Safe so far, but more severe reaction in those with allergies**
    - **Licensed**

Figure 13 Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population



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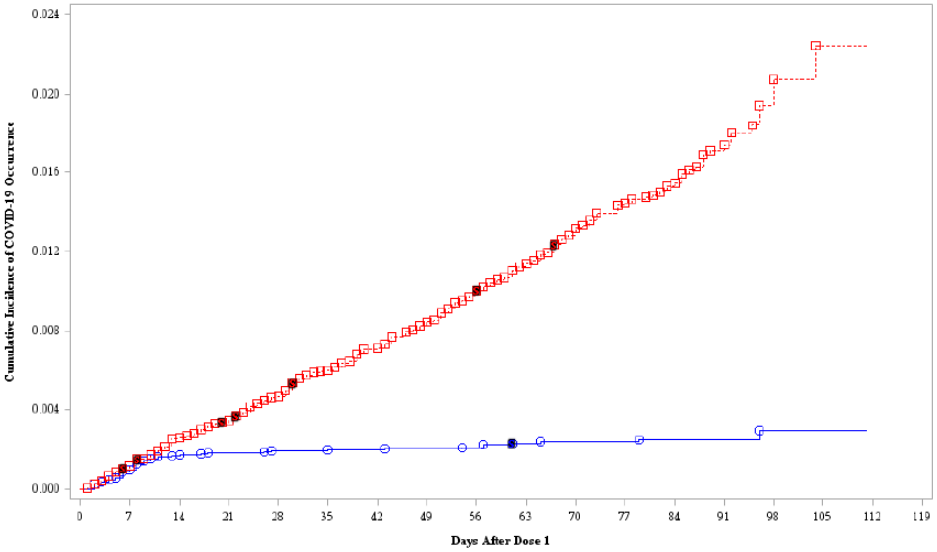

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Current COVID vaccines

- Most licensed vaccines started with VE > 90% against any COVID disease for the original strain, but are not protecting well against the Omicron variants, VE < 40%.
- Most started with VE > 95% against severe disease and have slipped a bit against the Omicron variants, VE ≈ 90%.
- We need an Omicron vaccine for primary series and boosters, or a live attenuated vaccine that stimulates mucosal immunity

WHO Solidarity vaccines trial

An international randomised trial of several candidate vaccines

- Prompt, efficient, and reliable evaluation of the several of the candidate SARS-CoV-2 vaccines under development
- Assessment of efficacy and safety
- Identification of those appropriate for deployment

Solidarity vaccines trial

An international randomised trial of several candidate vaccines

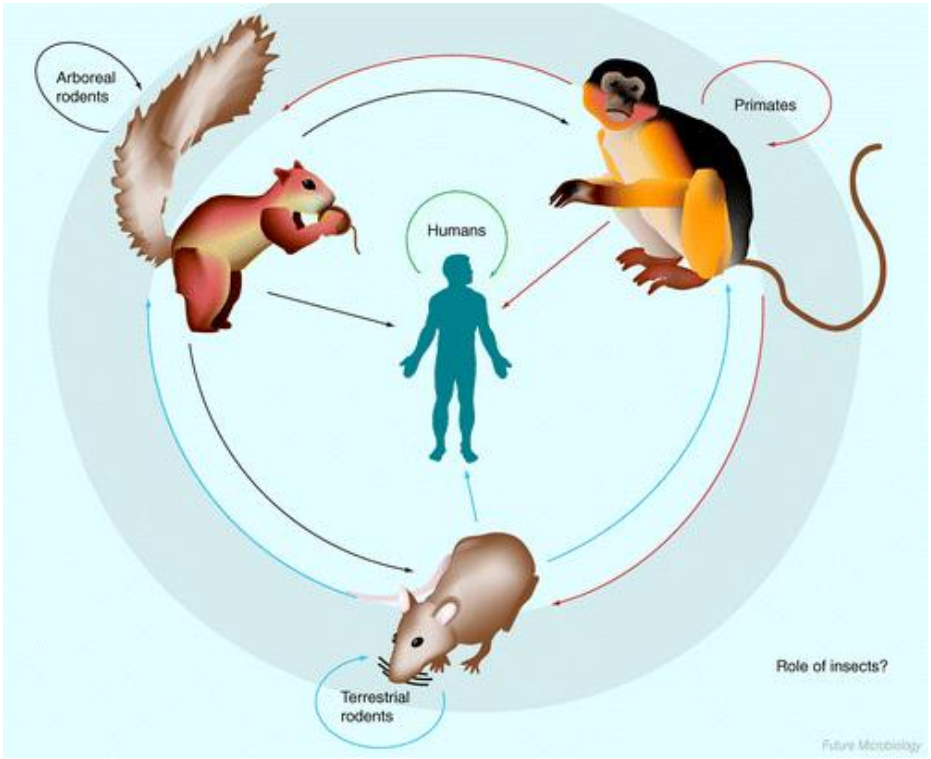
Evaluating several different candidate vaccines	Expeditiously enrolling participants at sites with high rates of COVID-19	Eliminating inefficiency of designing and conducting separate trials	International collaboration and countries' commitment
permitting selected vaccines to enter the trial whenever ready	flexible mix of fixed sites and pop-up sites	shared placebo group increases efficiency and attractiveness	fosters participation of sites with high COVID-19 rates
vaccines selection for trial assessed using a priori criteria	sufficient enrollment to assess efficacy and safety of all vaccines	If placebo can no longer be used, another vaccine becomes comparator	any effective vaccines will be tested at all sites
all vaccines selected for trial are eligible for testing at all sites	adaptive design accommodates unanticipated circumstances	ineffective vaccines don't much hinder evaluation of better vaccines	paves the way for international distribution of effective vaccines
INCREASING THE LIKELIHOOD OF FINDING SEVERAL EFFECTIVE VACCINES	**RAPID ACCUMULATION OF DATA TO SUPPORT RIGOROUS EVALUATION**	**RESULTS WITHIN 3-6 MONTHS AFTER EACH VACCINE IS READY FOR INCLUSION**	**FOSTERS INTERNATIONAL DEPLOYMENT WITH EQUITY OF ACCESS**

Current Solidarity Trial

- In the field in the Philippines, Colombia and Mali
  - Analyzing data for the first candidate: Medigen (protein-based) vaccine with adjuvant (aluminum hydroxide and CpG 1018)
  - Omicron vaccines going into the field soon
  - Live attenuated vaccine going into the field soon
- Identification of those appropriate for deployment

Monkeypox

- Origin: Rodents and (yes) monkeys in Central and West Africa 1958?



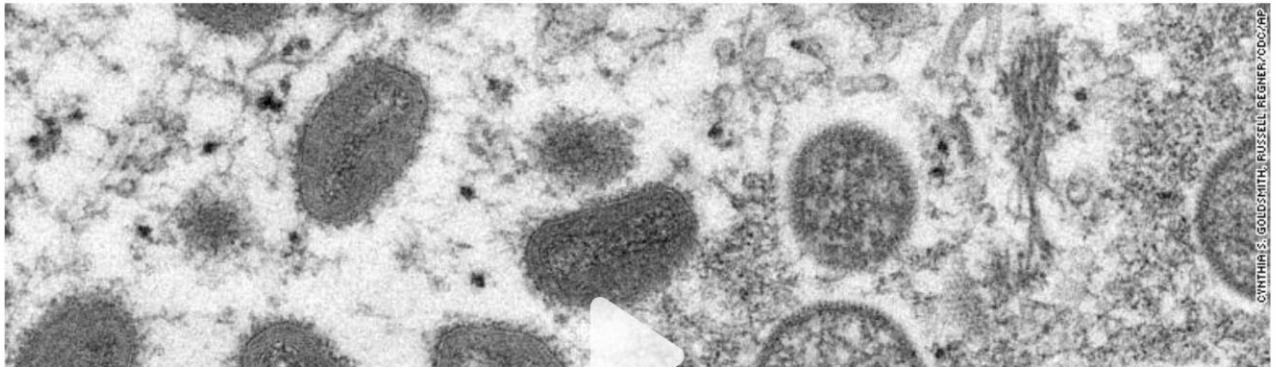
WHO: Monkeypox not a “Public Health Emergency of International Concern”

CNN health Life, But Better Fitness Food Sleep More Audio

WHO says monkeypox is not an international public health emergency, but it should continue to be monitored

By Carma Hassan, CNN

Updated 2155 GMT (0555 HKT) June 25, 2022



More From CNN

Johnson: Death of US democracy is 'grossly exaggerated'

Pfizer and BioNTech say updated Covid-19 boosters show increased...

World Health Organization

Ring vaccine trial for monkeypox (also containment)

- The similarity to smallpox points to ring vaccination as the best strategy for both a vaccine trial and for containing spread.
  - Ring vaccination was used to eradicate smallpox
- Index case is located and vaccinated with vaccine or comparator (also isolated if possible)
- The contacts and contacts of those contacts (or other contact tracing structure) of the index case are located, and randomized to either vaccine or comparator (also quarantined if possible)
- Any isolation or quarantined procedures are not part of the vaccine trial
- In addition, it is important to vaccine front-line health care workers who may come into contact with monkeypox cases with vaccine or comparator

Inspiration for trial design (lessons learned)

- WHO Ebola **ring VSV vaccine trial** in Guinea, 2015
  - Successful and rapid determination of the VE during and epidemic
  - rVSV-ZEBOV vaccine is now licensed and is used against Ebola Zaire (Ervebo)
  - Ring vaccination is used to contain Ebola outbreaks
- WHO Solidarity Trial Vaccines (STV) for COVID-19
  - An international, **multi center, multi vaccine, adaptive, shared placebo**, event driven, individually randomized controlled clinical trial that aims to evaluate the efficacy and safety of promising new COVID-19 vaccines
  - Currently in the field in 3 countries, with more to be soon added

Characteristics of vaccines relevant to a vaccine trial or vaccine use

- Most of the human information of VE and action is from smallpox
- Vaccine efficacy should be high, i.e., ≈ 85% against clinical disease, with waning
- Vaccine should have some protective effect during the prodromal period into the early stages of rash
- Vaccine should reduce transmission to others
- Licensed vaccines
  - JYNNEOS (Bavarian Nordic): Live, attenuated (non-replicating) vaccinia virus (MVA), 2 doses, believed to be safe, limited supply
  - ACAM2000 (Sanofi Pasteur): Live replication-competent vaccinia virus (MVA): like old smallpox vaccine, not very safe, less limited supply
- Several completely experimental vaccines

Basic trial design

- International, randomized clinical trial platform designed to rapidly evaluate the efficacy and safety of promising new candidate vaccines selected by an independent vaccine prioritization advisory group composed of leading scientists and experts
- Rapidly identify vaccines with worth-while efficacy using an adaptive design
- Vaccines and comparators will be individually randomized whenever possible
  - Populations at risk
  - Transmission clusters (rings, households, sexual contact networks)

Comparator

- Placebo (preferred)
- Delayed vaccination
- Other monkeypox vaccine (unlikely); noninferiority
- Other intervention such as antiviral agent (unlikely)

Primary Efficacy Endpoint

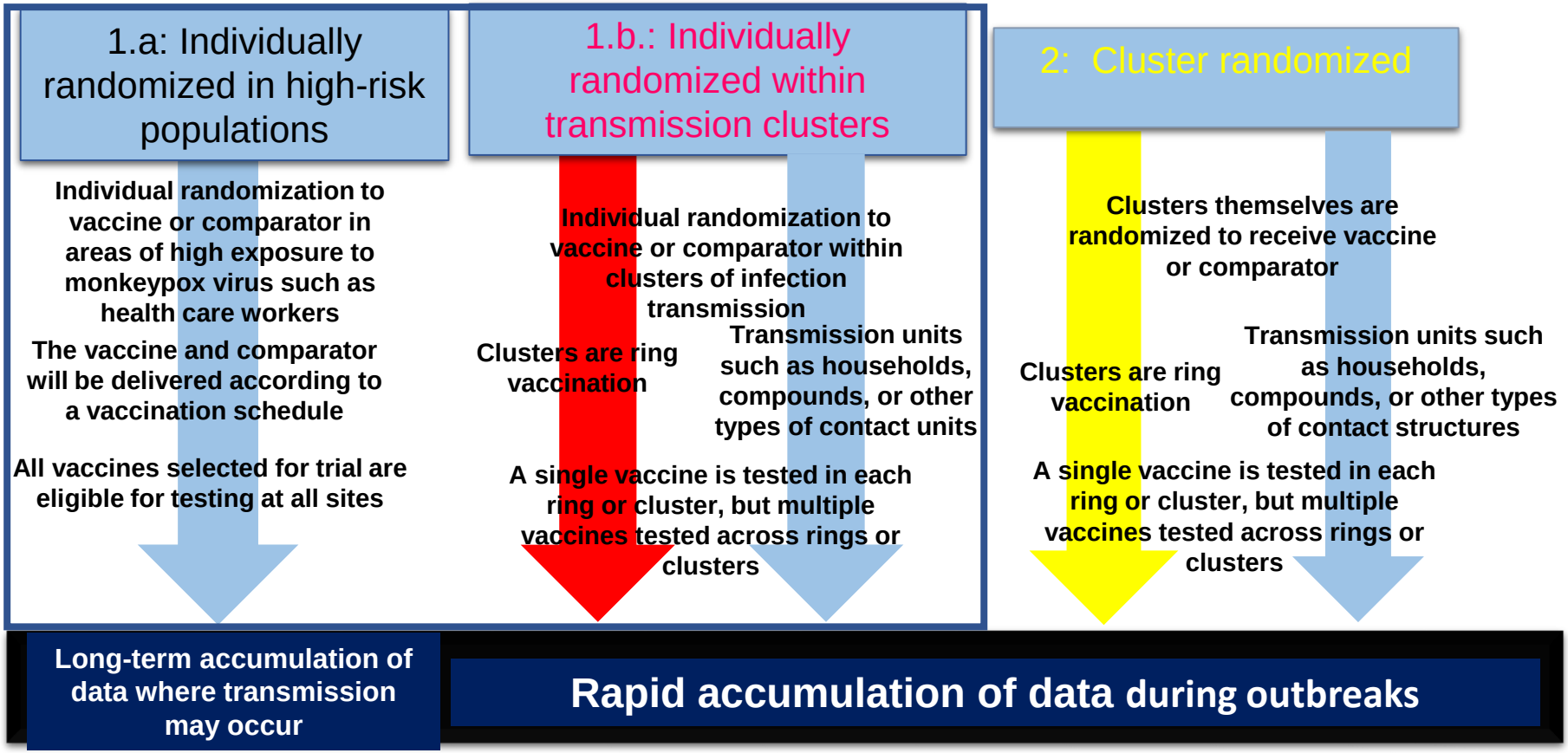
- To evaluate the effect of selected vaccines on the **rate of virologically confirmed monkeypox disease**, regardless of severity.
- Vaccine safety

Secondary Endpoints (partial list)

- **Protection against transmission to others**
- **Post-exposure prophylaxis against disease progression**
- **Protection against fatal disease**
- **Protection against infection**
- **Duration of efficacy**
  - Assessed by continuing blinded follow-up until some effective vaccine is actually deployed
- **Immune correlates of protection**

Monkeypox vaccines trial

An international randomized trial of several candidate vaccines



May the vaccines save us!

Thank You!