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

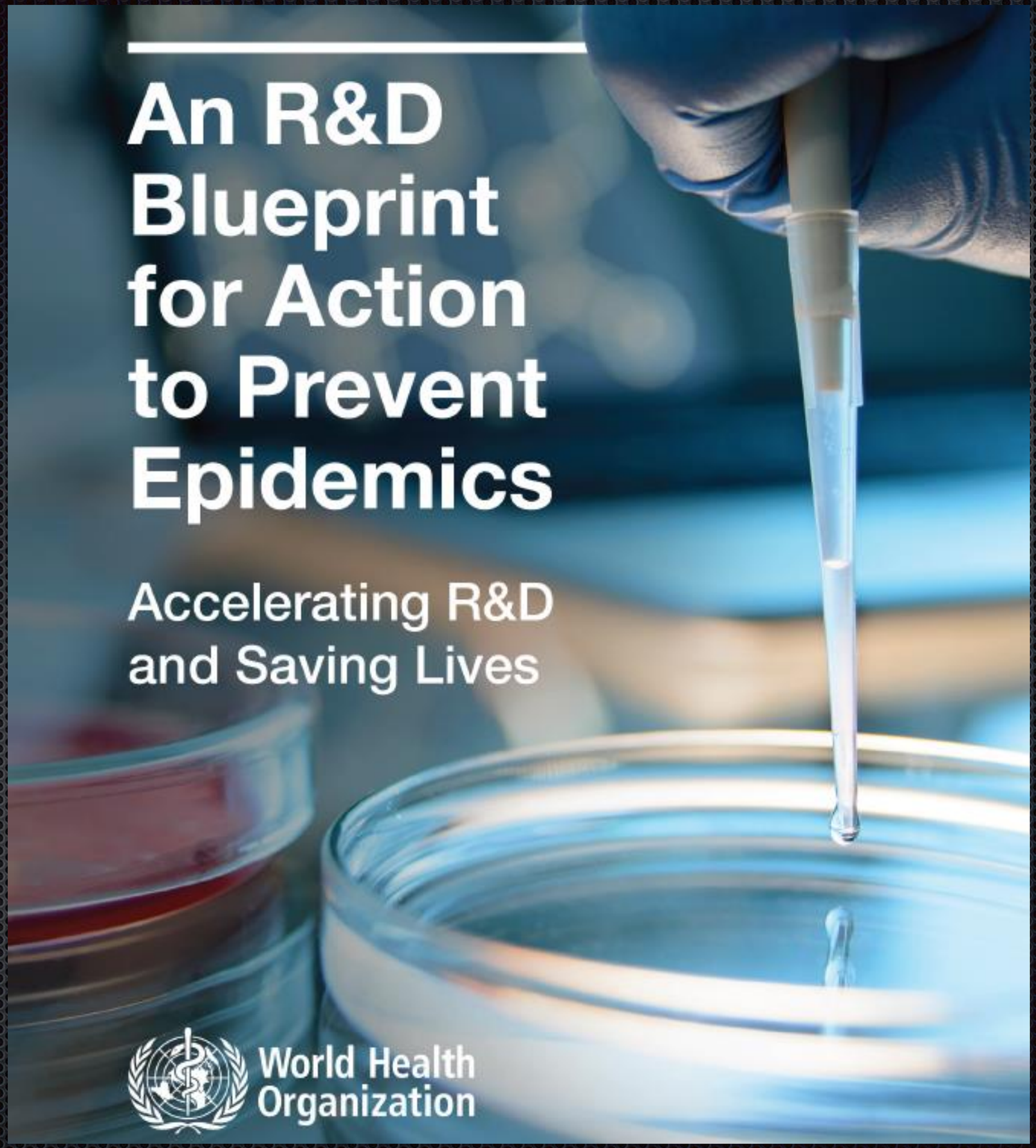
Ira Longini

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

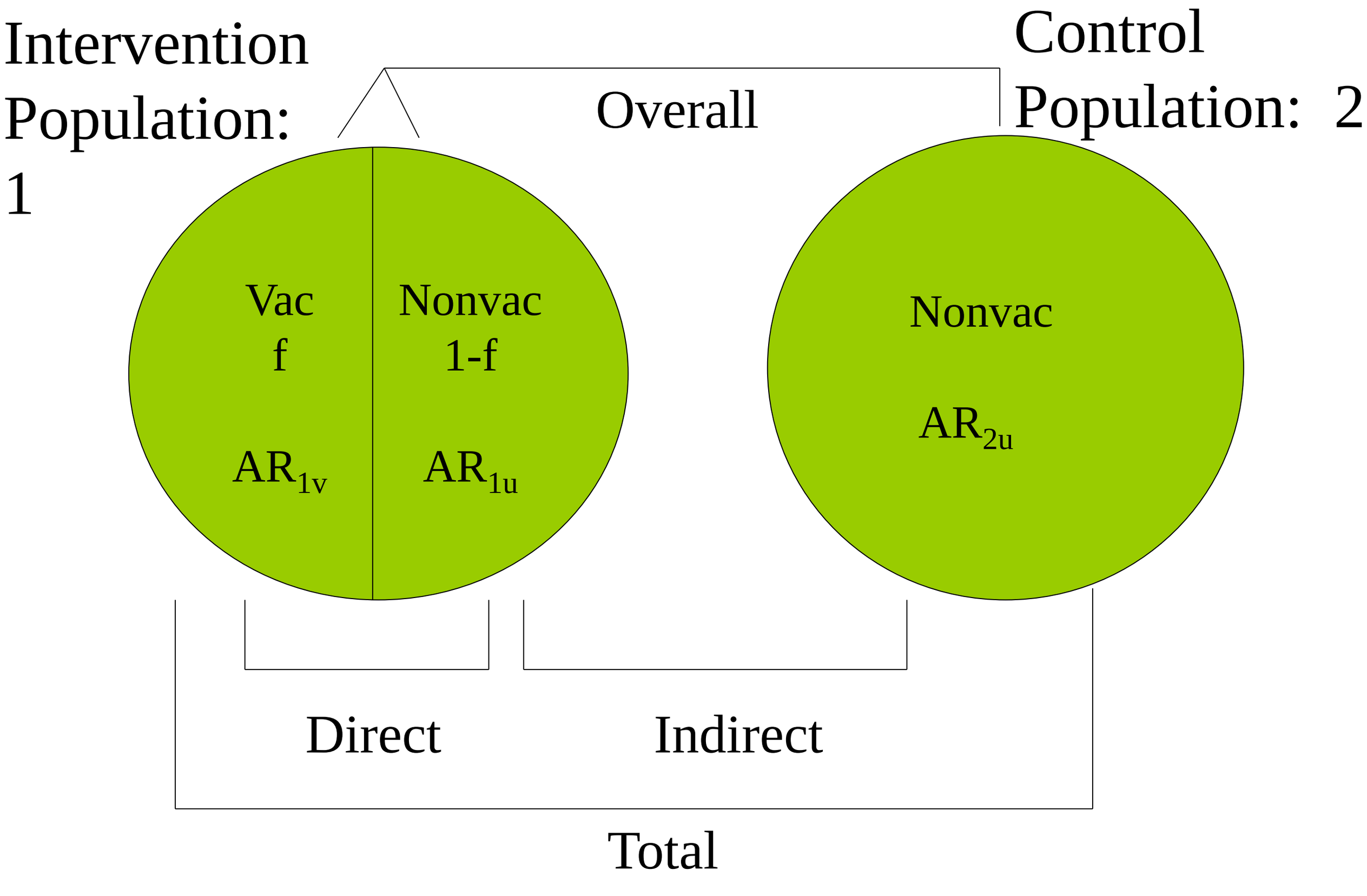
- WHO research and development blueprint: http://www.who.int/csr/research-and-development/en/
- Devise analytic and statistical methods for rapid estimation of the effectiveness of control measures
- Devise statistical and mathematical models for optimal control strategies



*http://www.who.int/csr/research-and-development/blueprint/en/

The design and analysis of vaccine trials for infectious disease emergencies

Vaccine Effectiveness



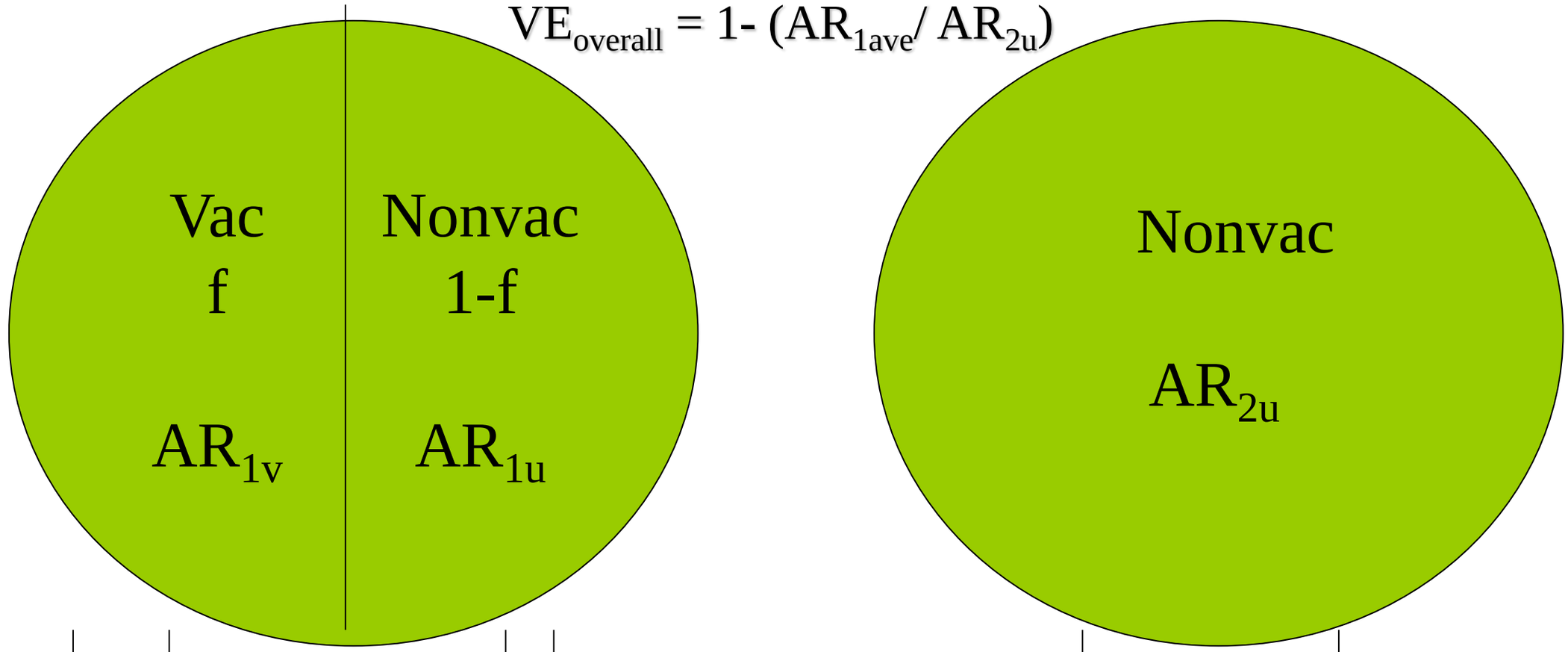
Vaccine Effectiveness

Intervention Population: 1

Control Population: 2

Overall

$VE_{overall} = 1- (AR_{1ave}/ AR_{2u})$



Direct

$VE_{direct} = 1- (AR_{1v} / AR_{1u})$

Indirect

$VE_{indirect} = 1- (AR_{1u} / AR_{2u})$

Total $VE_{total} = 1- (AR1v / AR2u)$

Vaccine Effectiveness

$$VE_{direct} = 1- (AR_{1v} / AR_{1u})$$

$$VE_{indirect} = 1- (AR_{1u} / AR_{2u})$$

$$VE_{total} = 1- (AR_{1v} / AR_{2u})$$

$$VE_{overall} = 1- (AR_{1ave} / AR_{2u})$$

where $AR_{1ave} = f\ AR_{1v} + (1 – f)\ AR_{1u}$

Halloran, *et al*., *Am J Epidemiol* **146,** 789-803 (1997)

Vaccine Effectiveness Gradient

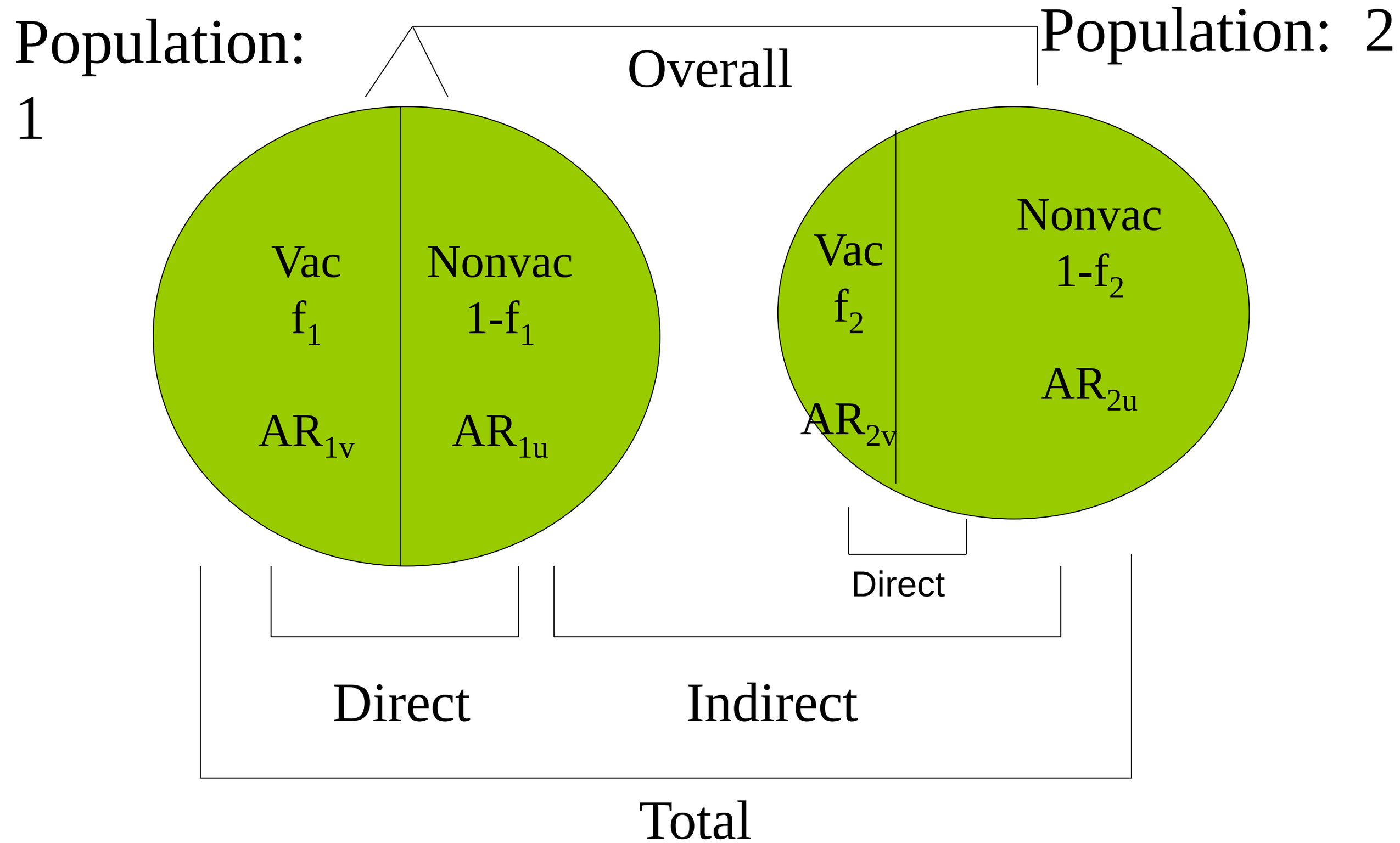


Table: Parameters used for measuring various effects of vaccination*

Level Parameter choice	Comparison groups and effect: Susceptibility	Infectiousness	Combined change in susceptibility and infectiousness
Conditional on exposure: I Transmission probability	$VE_{S,P}\dagger = 1 - \frac{p_{\cdot 1}}{p_{\cdot 0}}$	$VE_{I,P} = 1 - \frac{p_{1\cdot}}{p_{0\cdot}}$	$VE_{T,P} = 1 - \frac{p_{11}}{p_{00}}$

Study design: I direct	IIA indirect	IIB total	III overall
Unconditional: II Incidence or hazard rate, IR, λ	$VE_{S,IR} = 1 - \frac{IR_{A1}}{IR_{A0}}$	$VE_{IIA,IR} = 1 - \frac{IR_{A0}}{IR_{B0}}$	$VE_{IIB,IR} = 1 - \frac{IR_{A1}}{IR_{B0}}$	$VE_{III,IR} = 1 - \frac{IR_{A\cdot}}{IR_{B\cdot}}$
	$VE_{S,\lambda} = 1 - \frac{\lambda_{A1}}{\lambda_{A0}}$	$VE_{IIA,\lambda} = 1 - \frac{\lambda_{A0}}{\lambda_{B0}}$	$VE_{IIB,\lambda} = 1 - \frac{\lambda_{A1}}{\lambda_{B0}}$	$VE_{III,\lambda} = 1 - \frac{\lambda_{A\cdot}}{\lambda_{B\cdot}}$
III Proport. hazards, PH	$VE_{S,PH} = 1 - e^{\beta 1}$	NA	NA	NA
IV Cumulative incidence	$VE_{S,CI} = 1 - \frac{CI_{A1}}{CI_{A0}}$	$VE_{IIA,CI} = 1 - \frac{CI_{A0}}{CI_{B0}}$	$VE_{IIB,CI} = 1 - \frac{CI_{A1}}{CI_{B0}}$	$VE_{III,CI} = 1 - \frac{CI_{A\cdot}}{CI_{B\cdot}}$

* From Halloran, Struchiner, Longini, Am. J. Epidemiol 1997; 146;789–803.

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 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

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

Published Online
July 31, 2015
http://dx.doi.org/10.1016/S0140-6736(15)61117-5

See Online/Editorial
http://dx.doi.org/10.1016/S0140-6736(15)61177-1

*These authors contributed equally

World Health Organization, 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

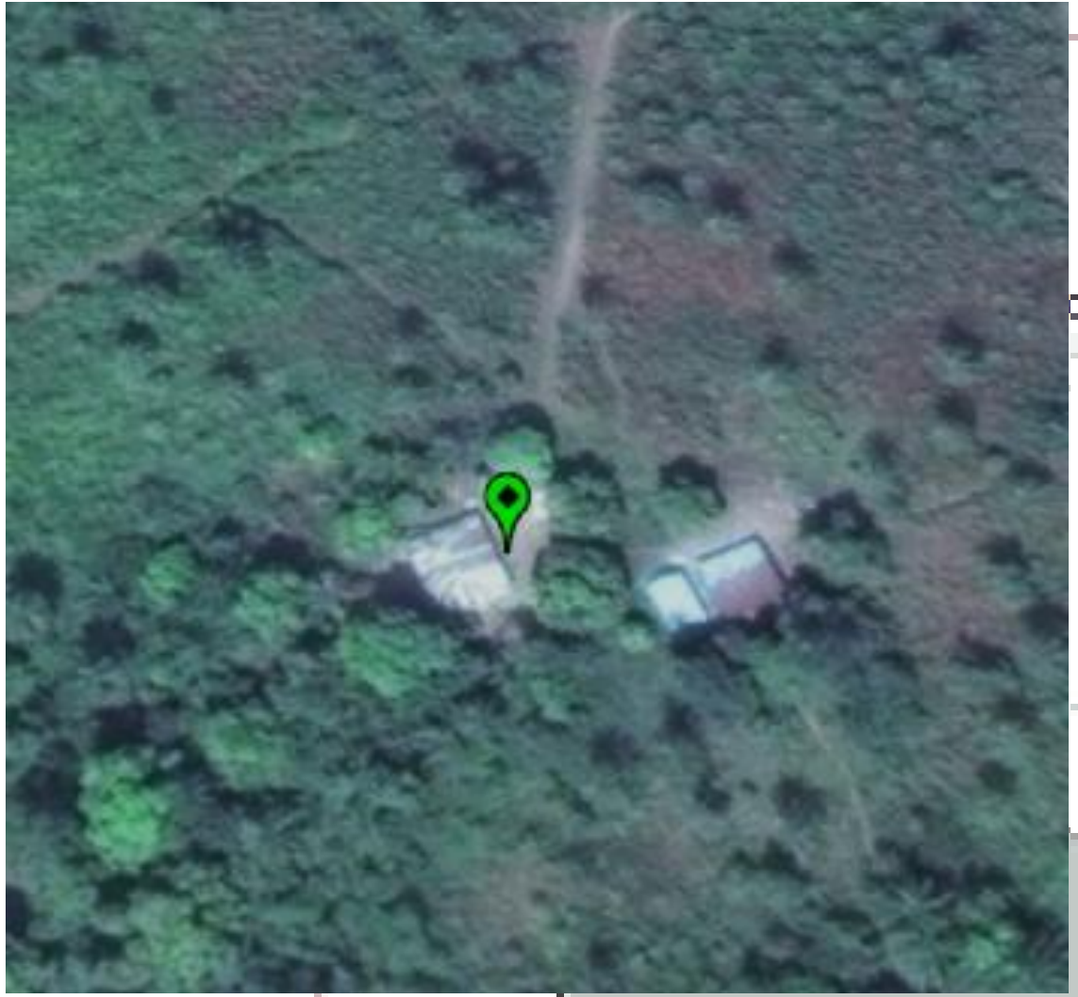
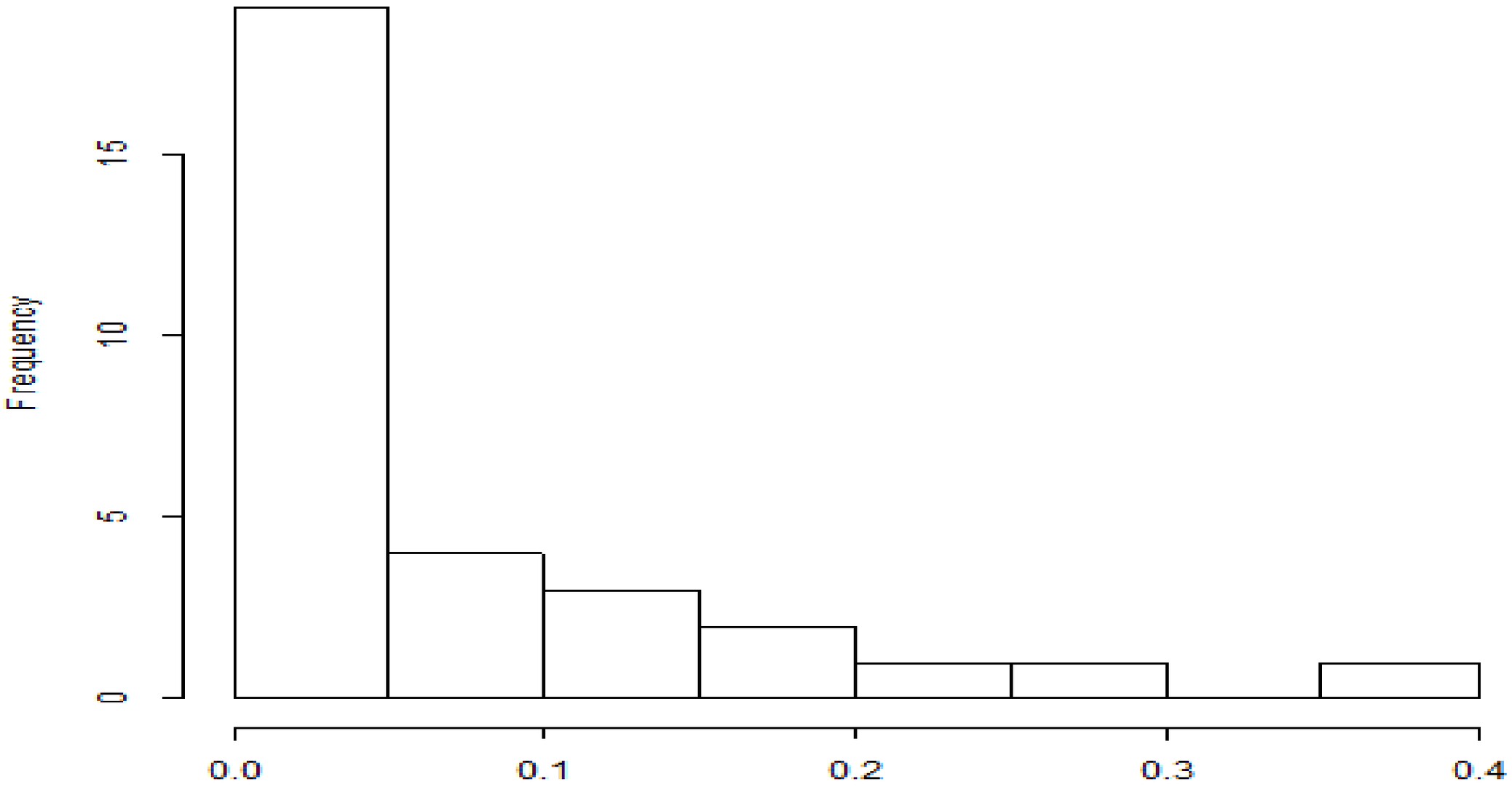


Figure 2: Study area of Ebola ça Suffit cluster vaccination trial in Basse-Guinée

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 ≈ 153,000

(VE = 0.7, power = 0.90, α = 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, $\alpha = 0.05$ 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

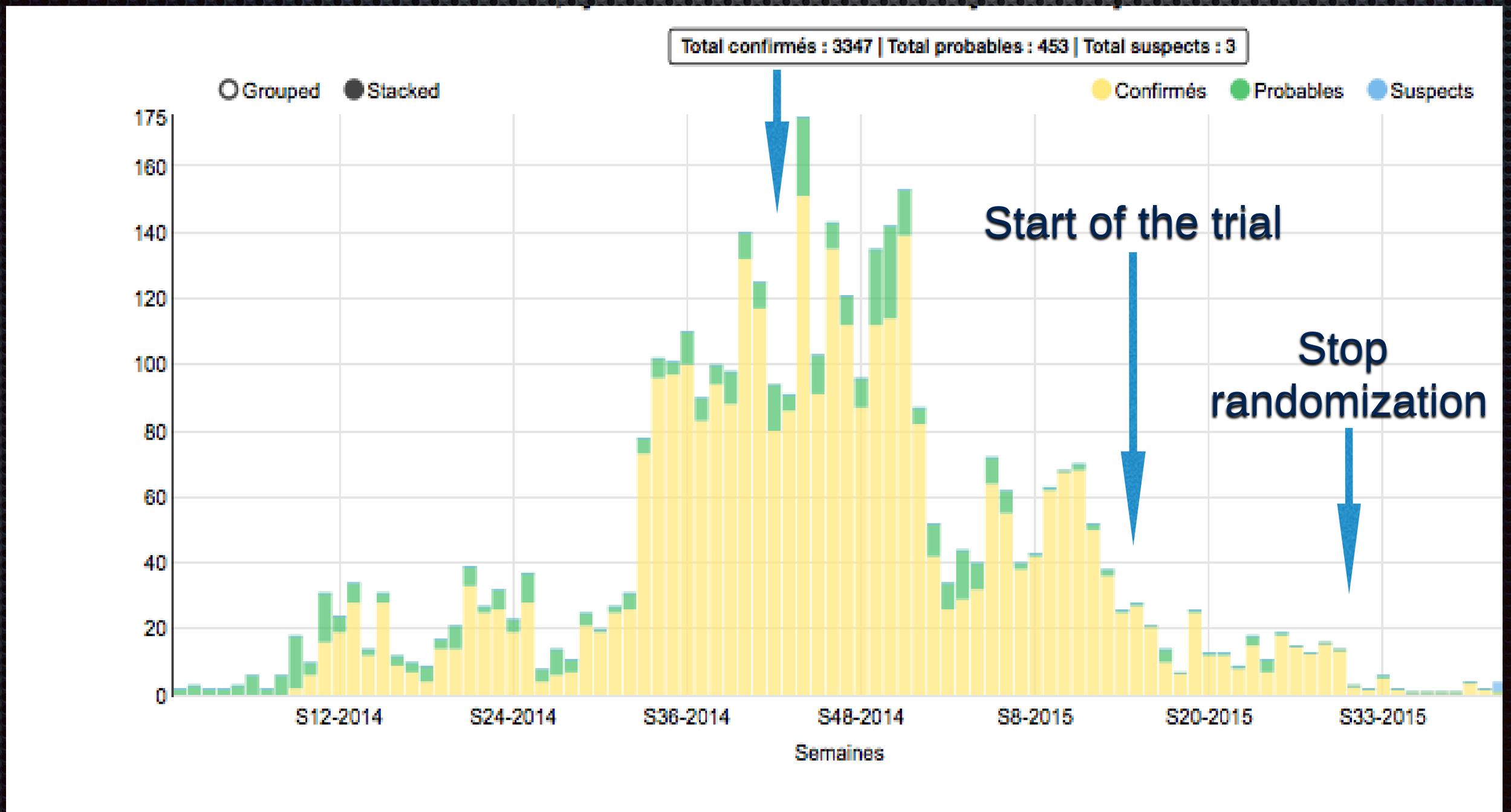
The unprecedented outbreak outpaced the speed with which clinical trials could be implemented

Fix 2

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



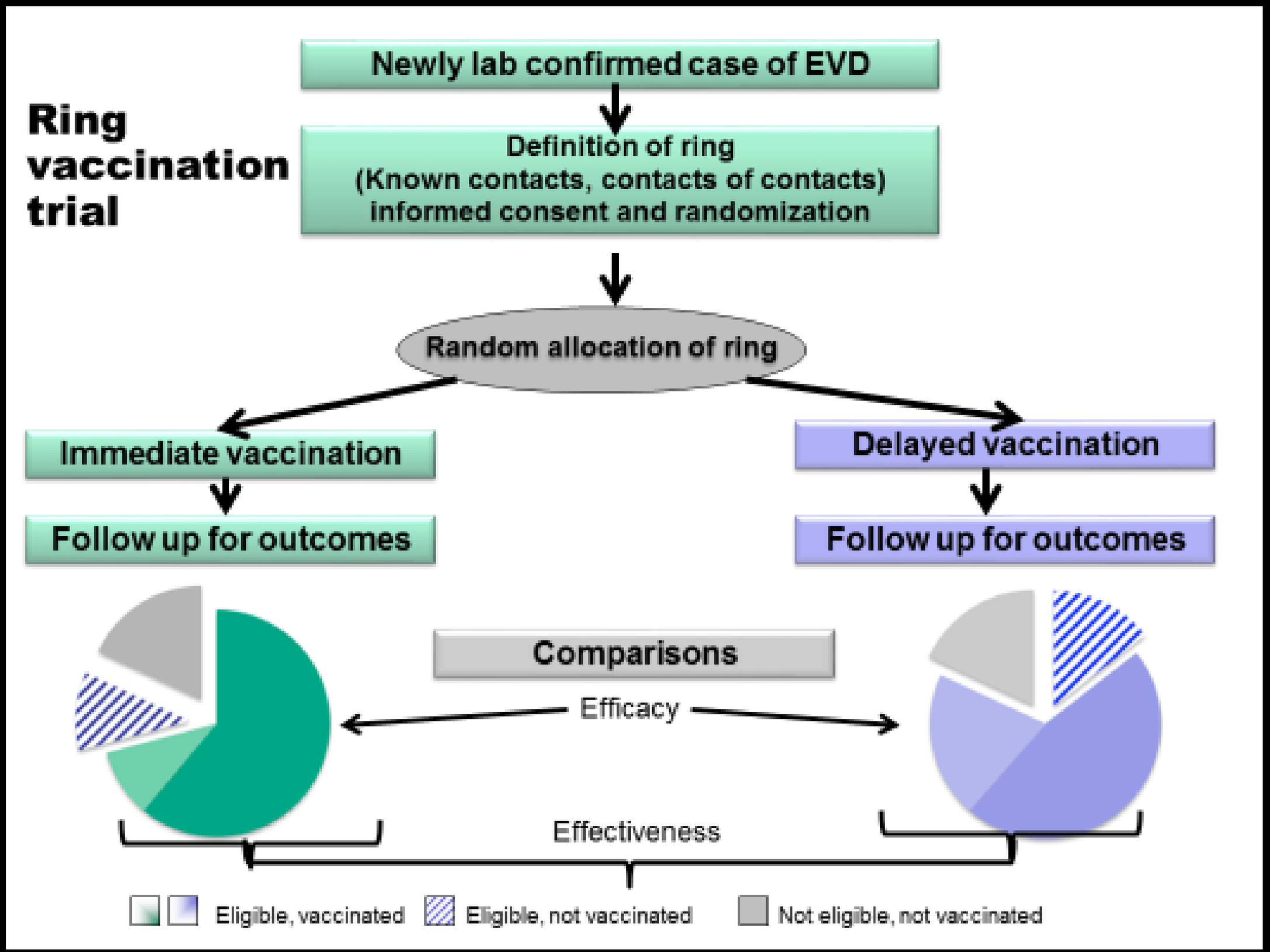
Challenge 3

The uncertainty in predicting future infection incidence

Fix 3

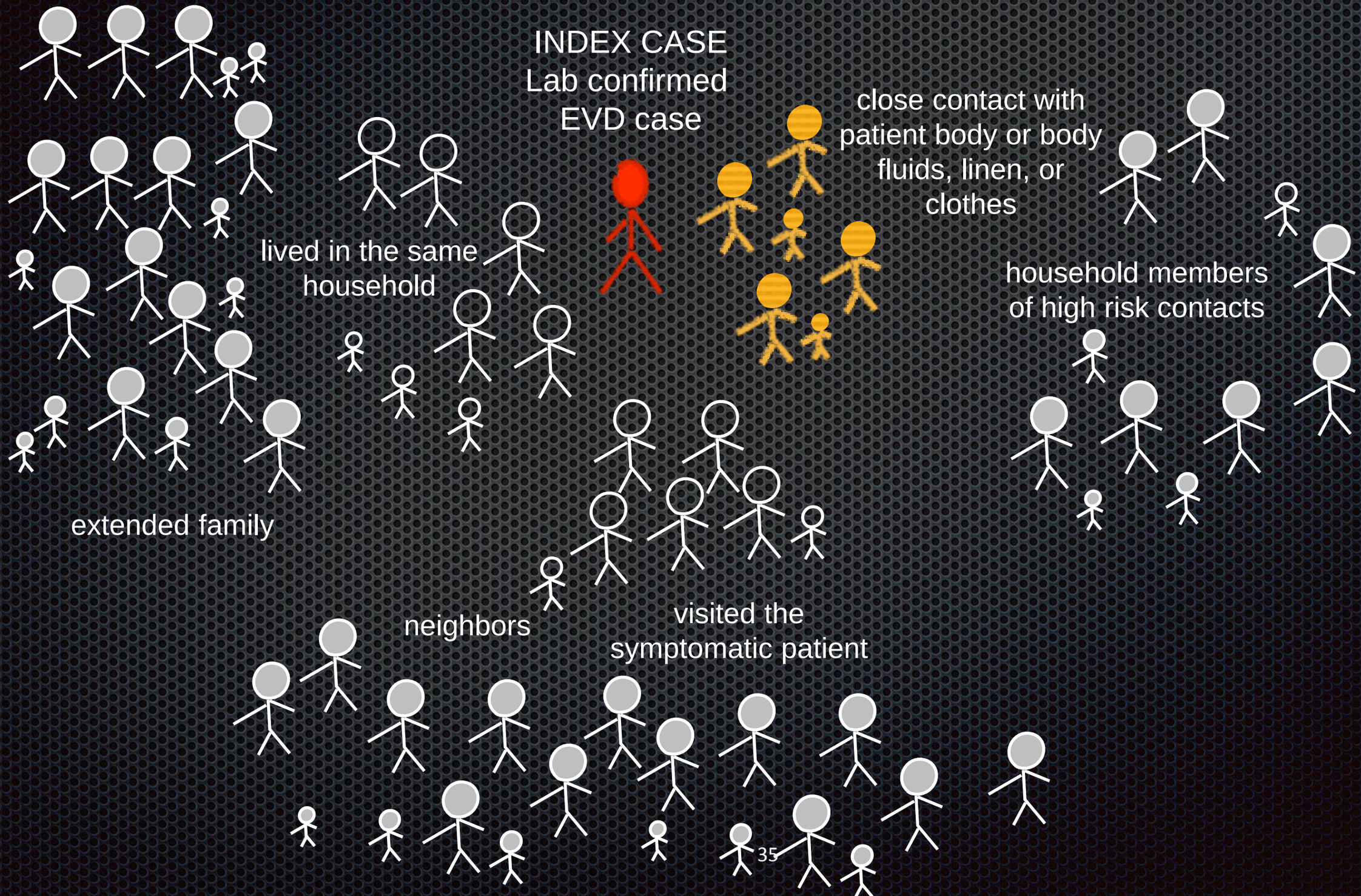
Adaptive design with real-time modifications, based on a predetermined interim analysis of study data.

Ring vaccination - cluster randomized trial



What is a vaccination ring?

Contacts and contacts of contacts



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

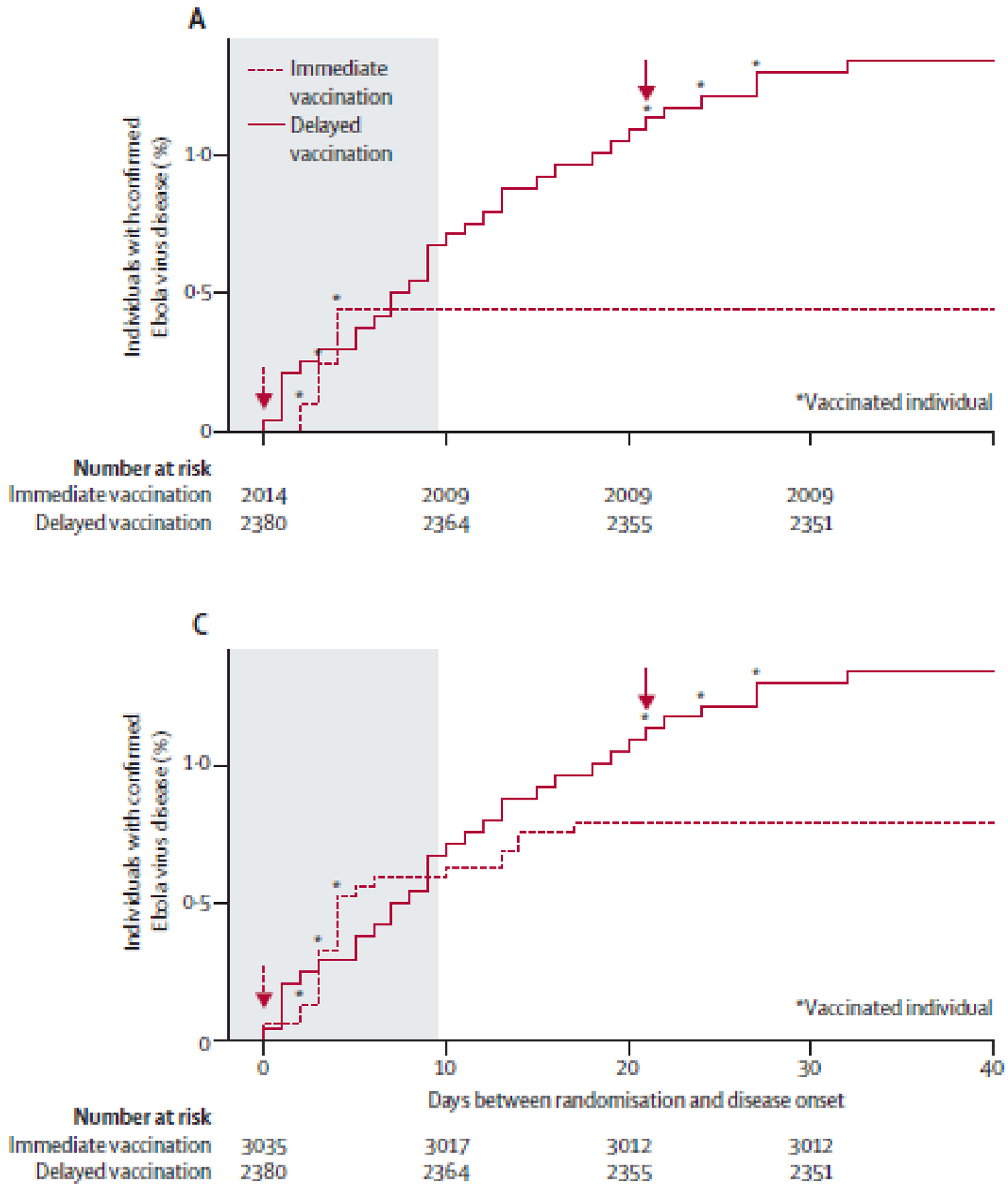
Model will be a mixed-effects, time-dependent, Cox regression model with a random effect (frailty) when there is clustering, or small sample equivalent using cumlative incidence (logist reg).

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)

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
IMMEDIATE	*0 clusters**	*48 clusters*	*48 clusters*
DELAYED	**7 clusters****	**35 clusters**	**42 clusters**
			p = 0.0036***

Time delays

We are dealing with an infectious disease

We only see confirmed EVD onsets, not infection times

- Incubation period

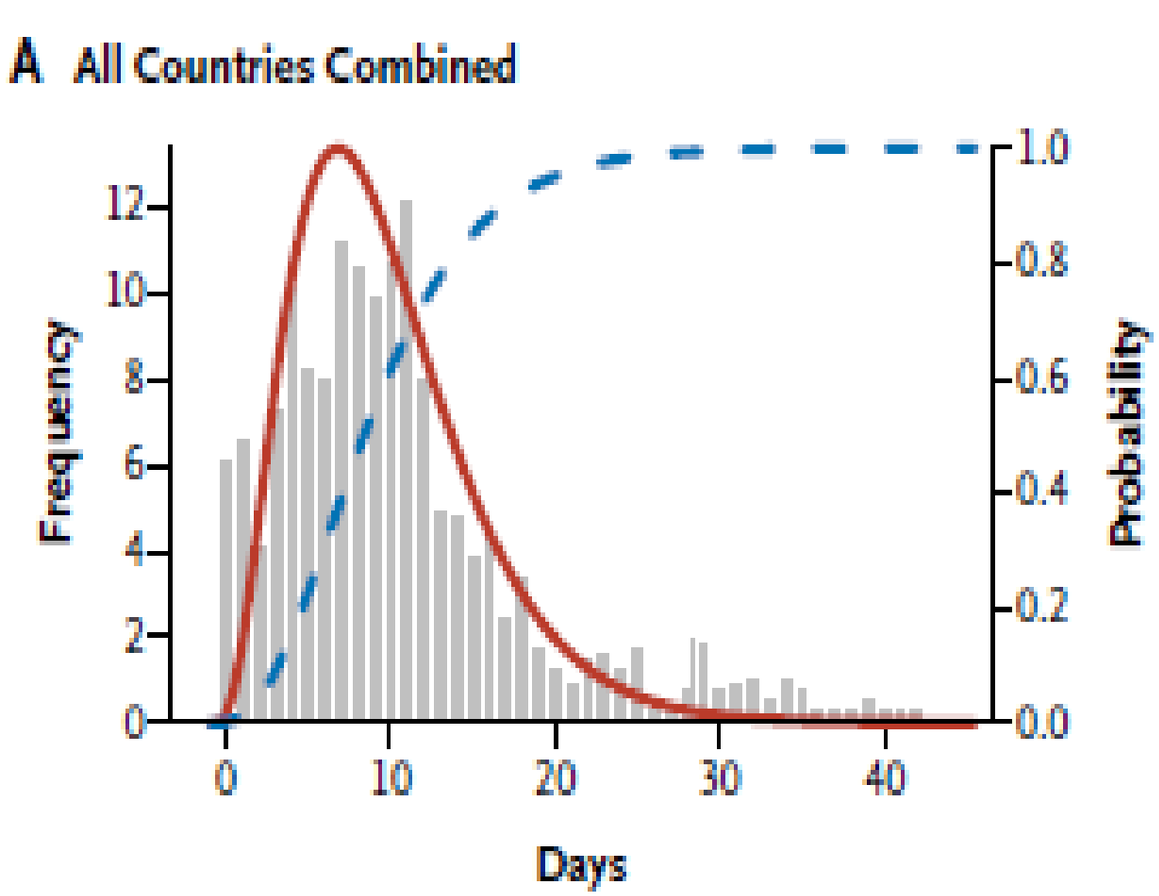
Time is needed for immunity to build after vaccination

- Immune ramp-up period

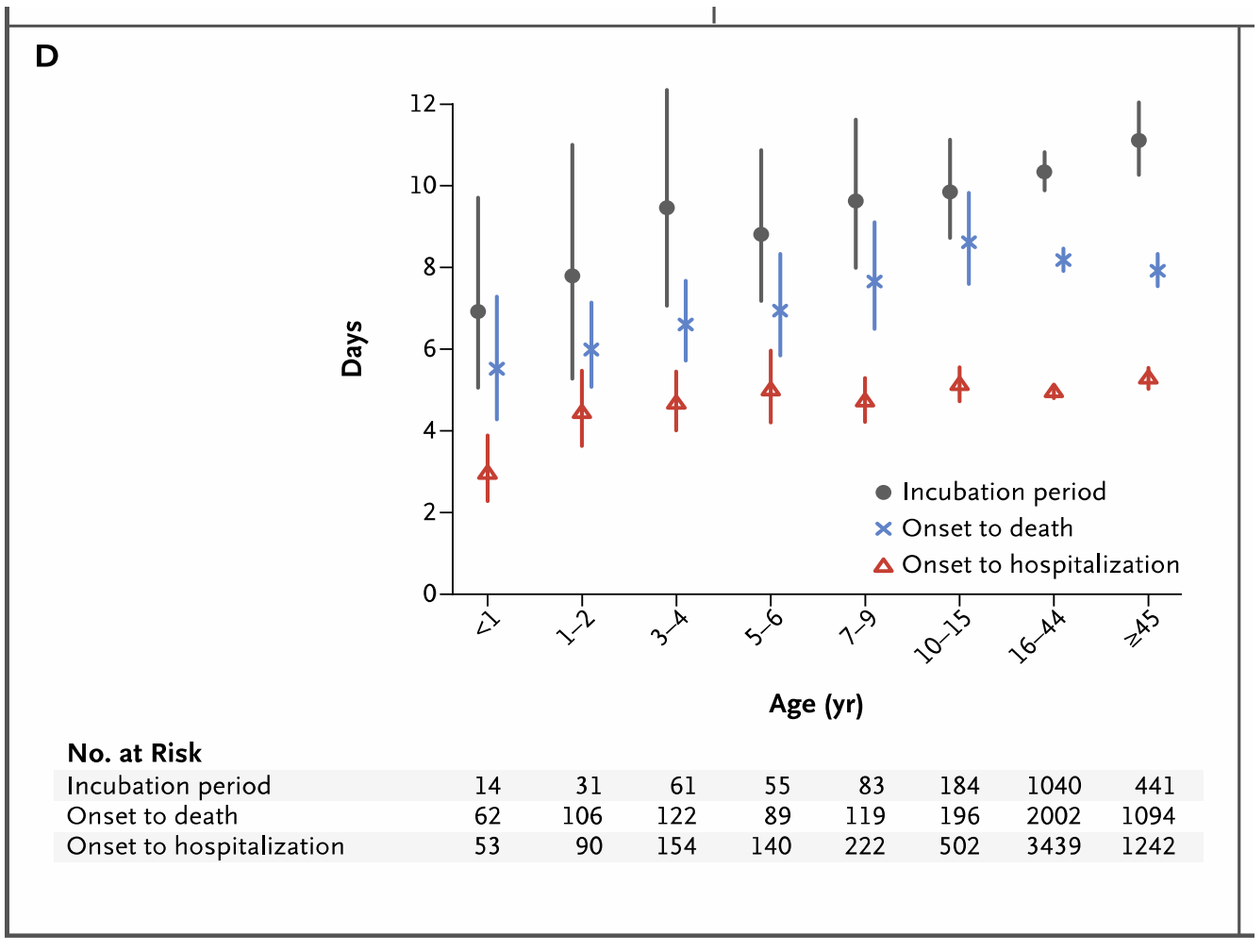
Analysis considerations:

Important intervals to incorporate into analysis

- Incubation period
  - Mean ≈ 10 days, but probably is more like 6 days



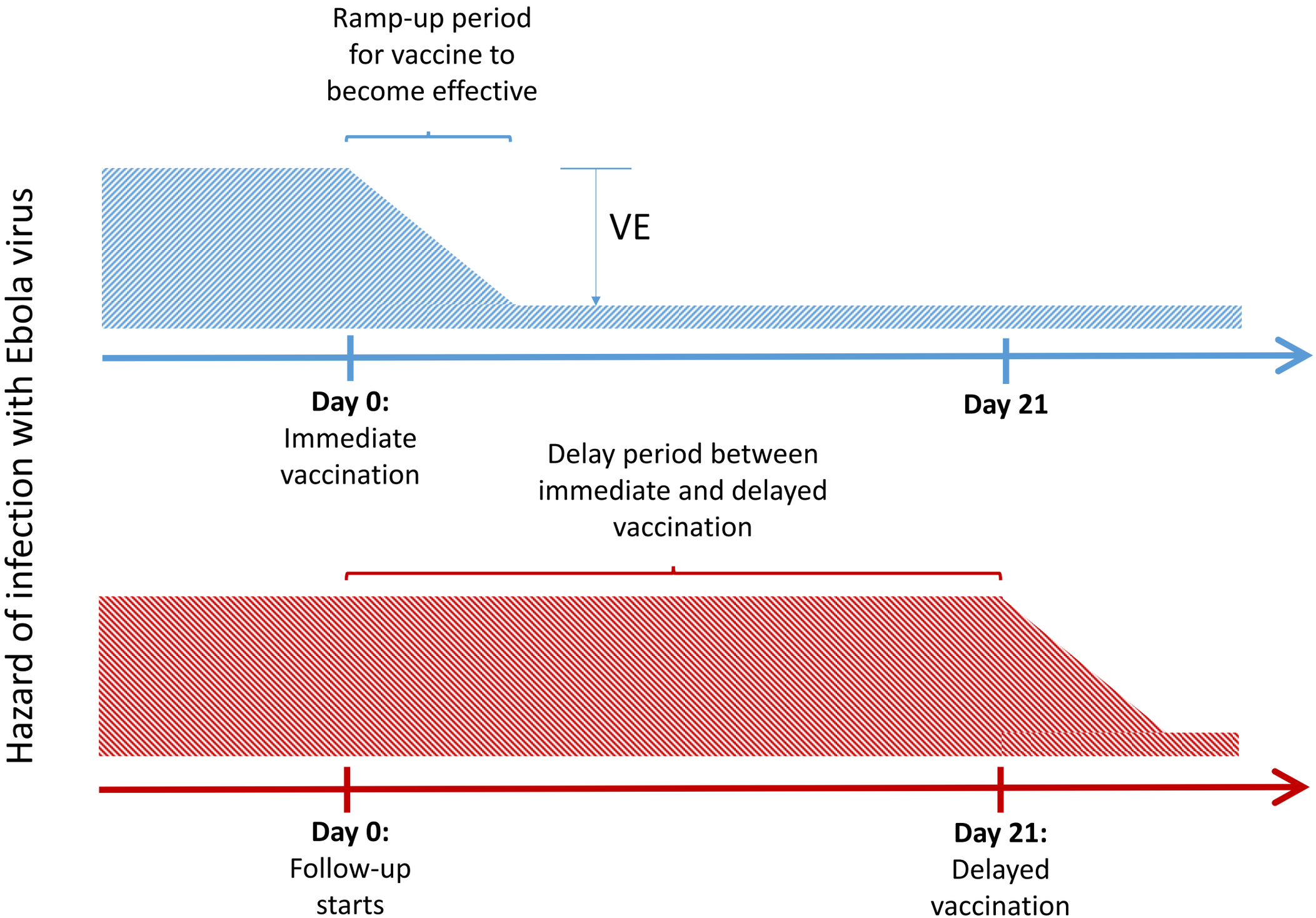
WHO Ebola Response Team, *NEJM* 2014

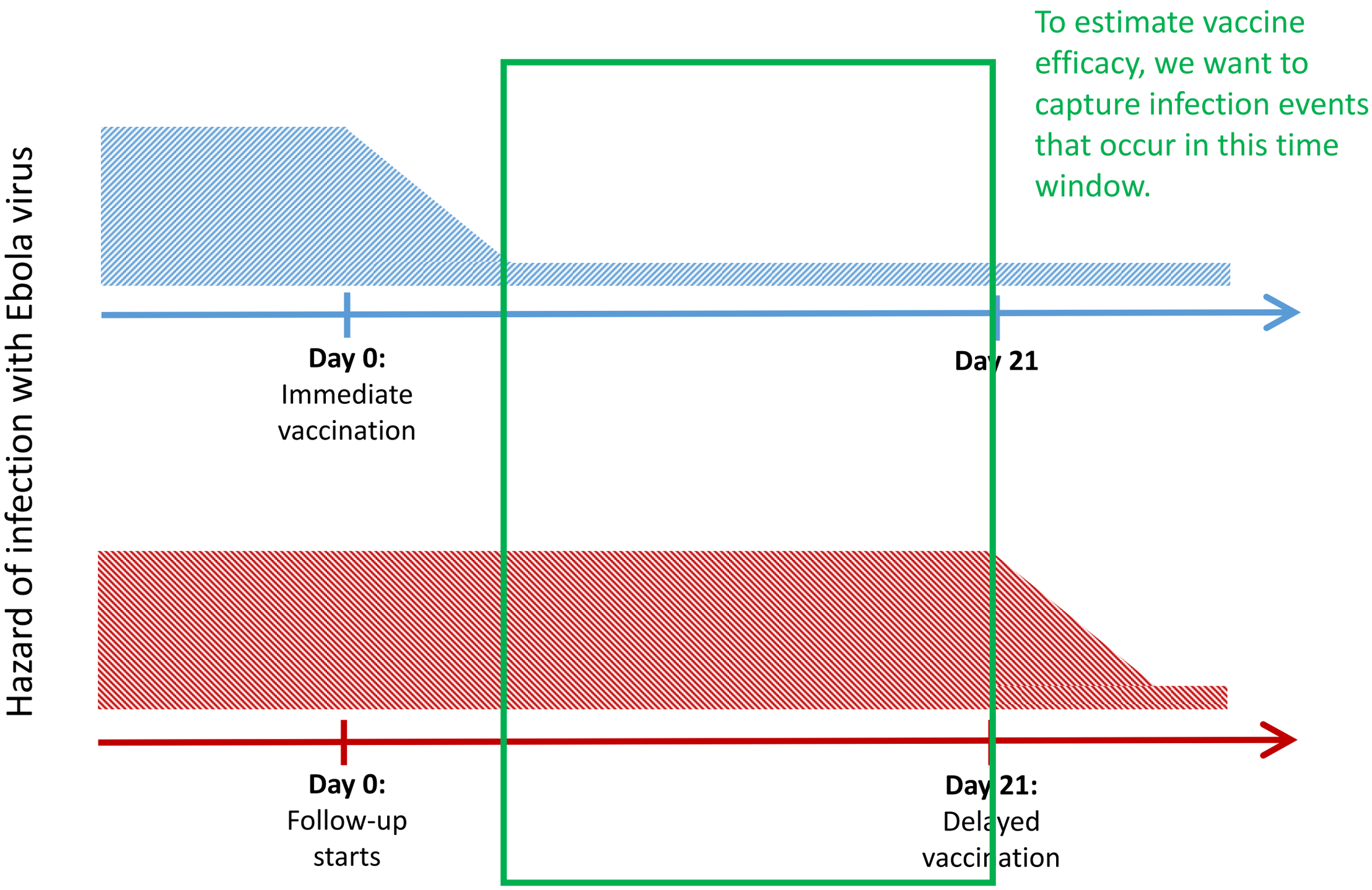


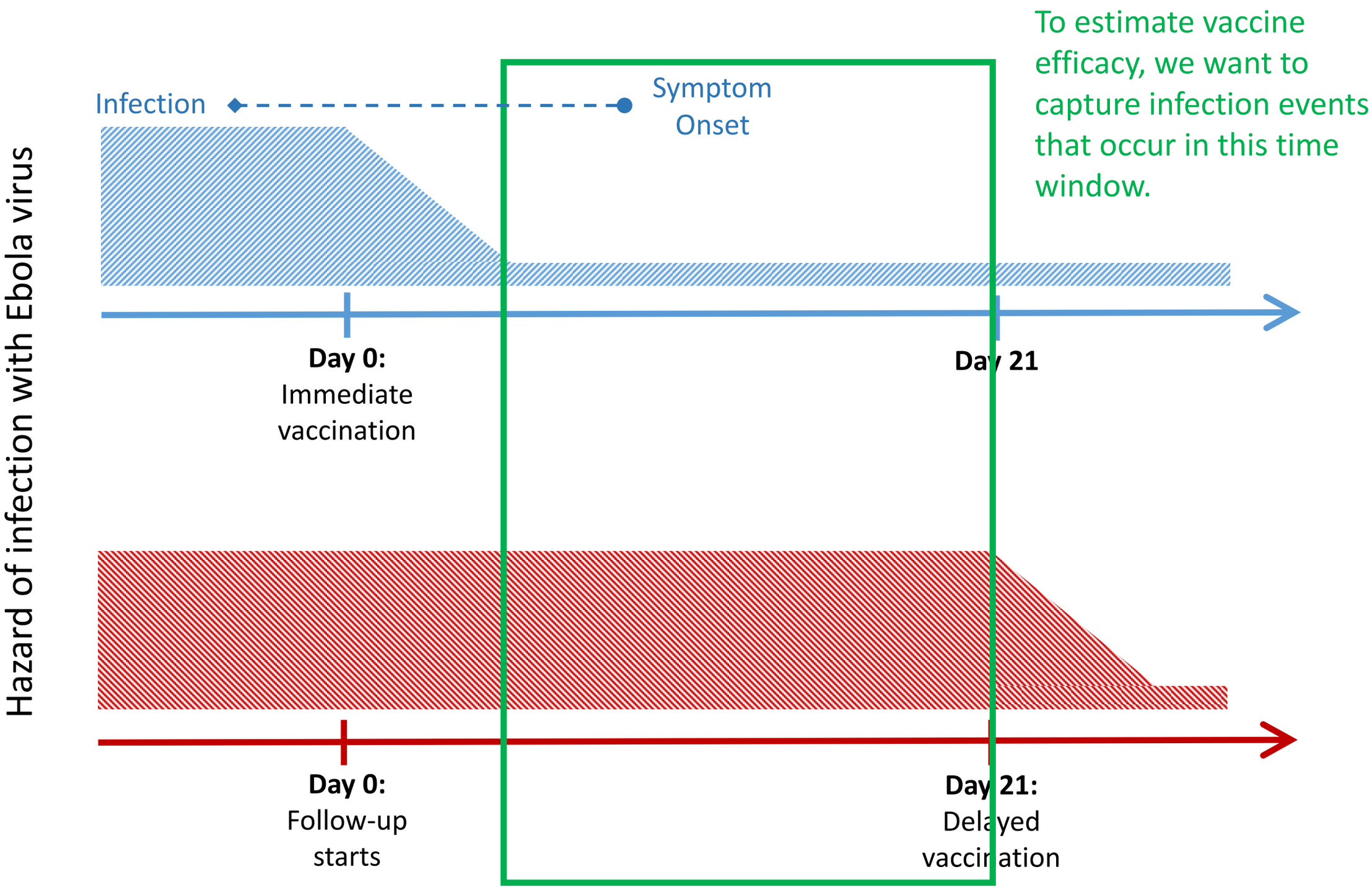
No. at Risk

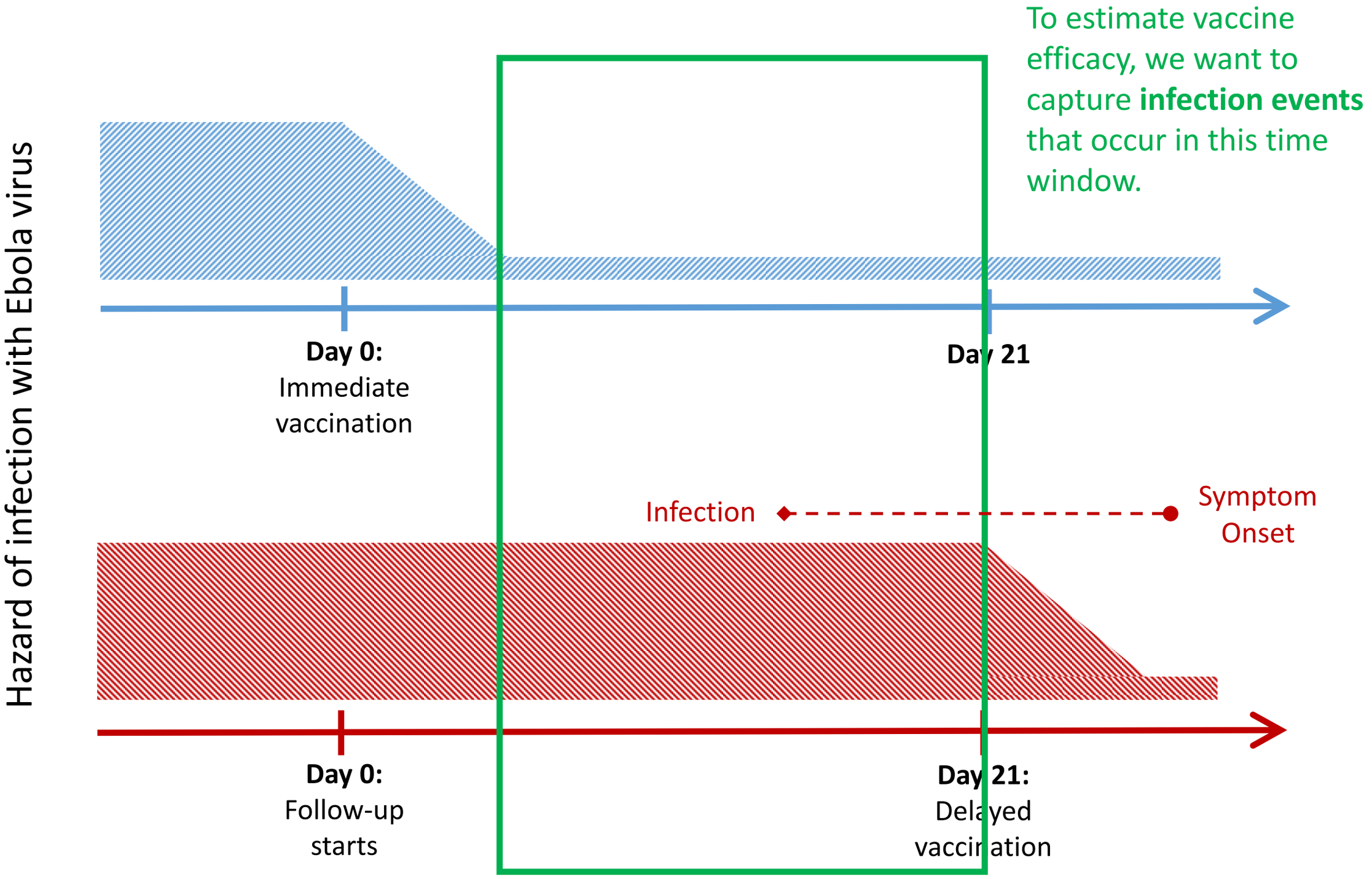
Incubation period	14	31	61	55	83	184	1040	441
Onset to death	62	106	122	89	119	196	2002	1094
Onset to hospitalization	53	90	154	140	222	502	3439	1242

N Engl J Med. 2015 Mar 26;372(13):1274-7. doi: 10.1056/NEJMc1415318.
Ebola virus disease among children in West Africa.
WHO Ebola Response Team, Agua-Agum J, Ariyarajah A, Blake IM, Cori A, Donnelly CA, Dorigatti I, Dye C, Eckmanns T, Ferguson NM, Fowler RA, Fraser C, Garske T, Hinsley W, Jombart T, Mills HL, Murthy S, Nedjati Gilani G, Nouvellet P, Pelletier L, Riley S, Schumacher D, Shah A, Van Kerkhove MD.

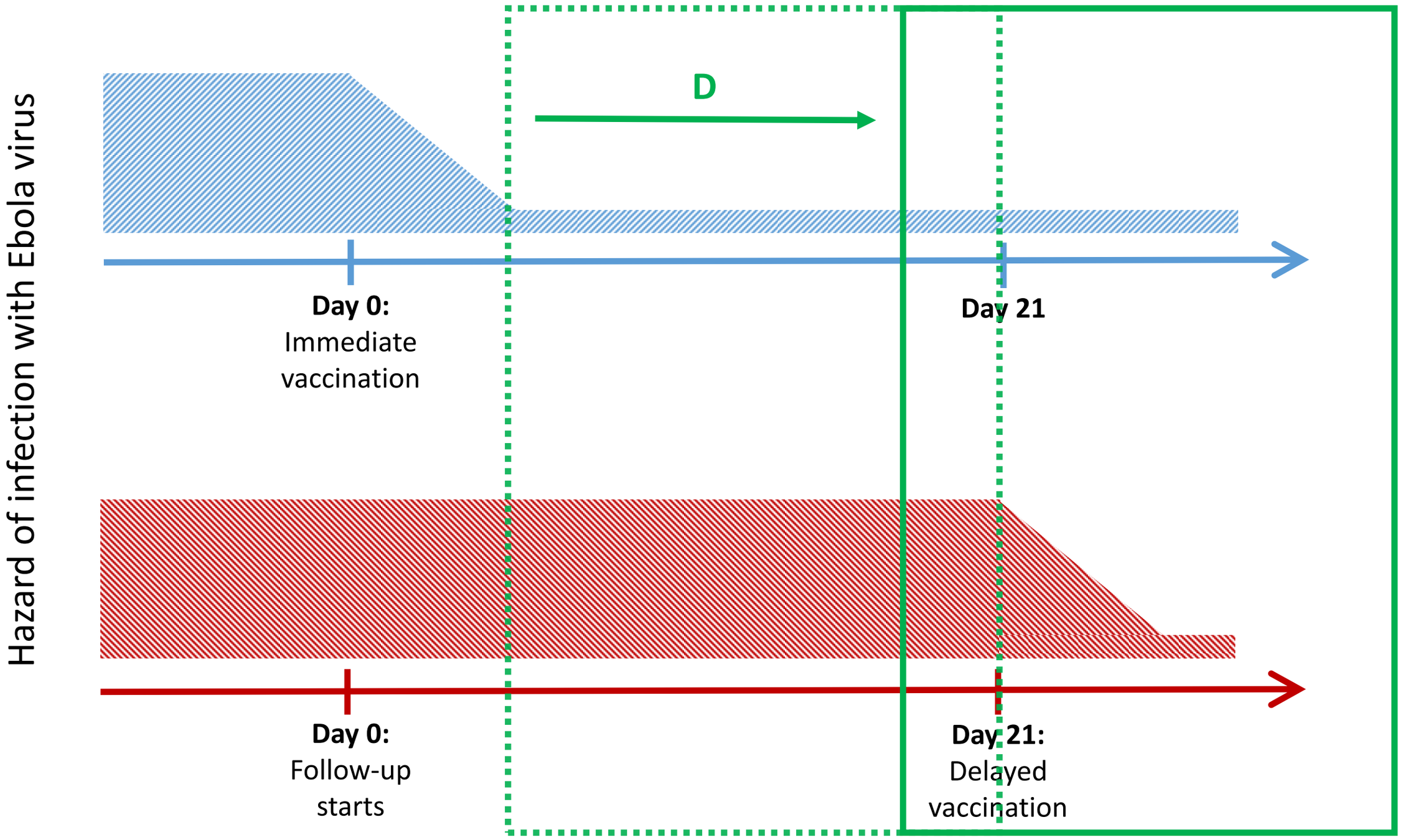

Ramp-up period
for vaccine to
become effective
VE
Hazard of infection with Ebola virus
Day 0:
Immediate
vaccination
Day 21
Delay period between
immediate and delayed
vaccination
Day 0:
Follow-up
starts
Day 21:
Delayed
vaccination


To estimate vaccine efficacy, we want to capture infection events that occur in this time window.
Hazard of infection with Ebola virus
Day 0:
Immediate vaccination
Day 21
Day 0:
Follow-up starts
Day 21:
Delayed vaccination


Hazard of infection with Ebola virus
Infection
Symptom Onset
To estimate vaccine efficacy, we want to capture infection events that occur in this time window.
Day 0:
Immediate vaccination
Day 21
Day 0:
Follow-up starts
Day 21:
Delayed vaccination


To estimate vaccine efficacy, we want to capture **infection events** that occur in this time window.
Hazard of infection with Ebola virus
Day 0:
Immediate vaccination
Day 21
Infection
Symptom Onset
Day 0:
Follow-up starts
Day 21:
Delayed vaccination

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



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

Hazard of infection with Ebola virus

Infection

Symptom Onset

Day 0:
Immediate vaccination

Day 21

Infection

Symptom Onset

Day 0:
Follow-up starts

Day 21:
Delayed vaccination

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*

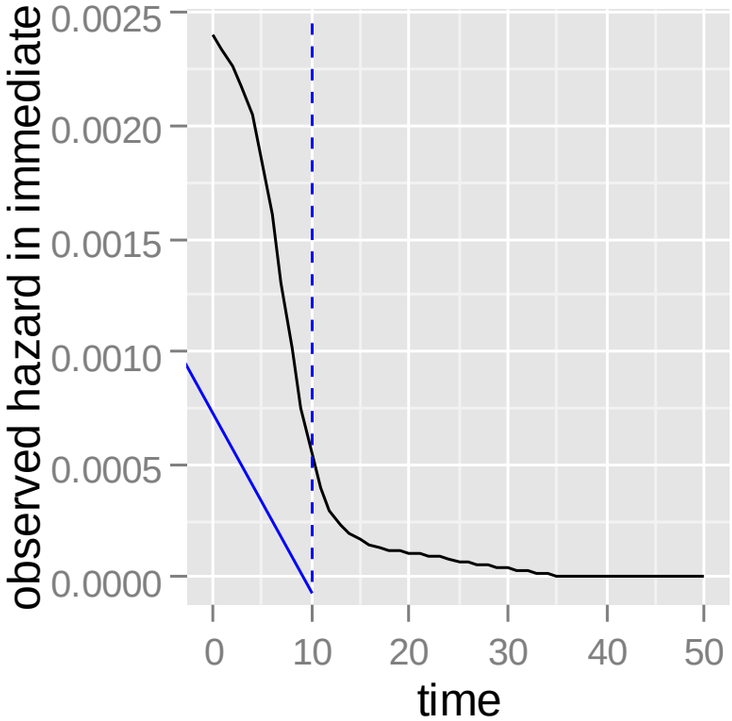
Decreasing Background Hazard

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

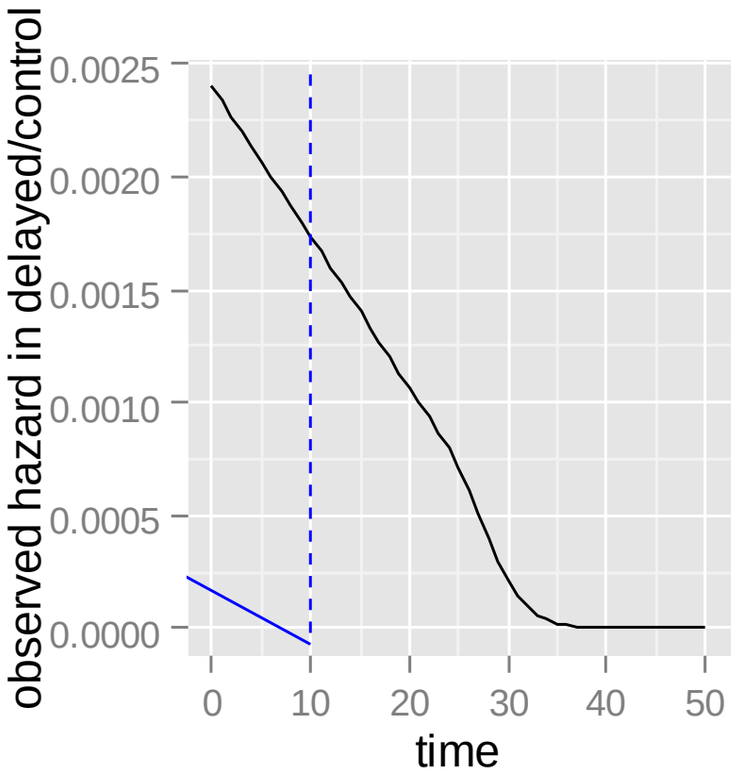
VE = 90%; **4 day ramp-up period** (gradually increases)

Incubation period gamma distributed with mean 6 days

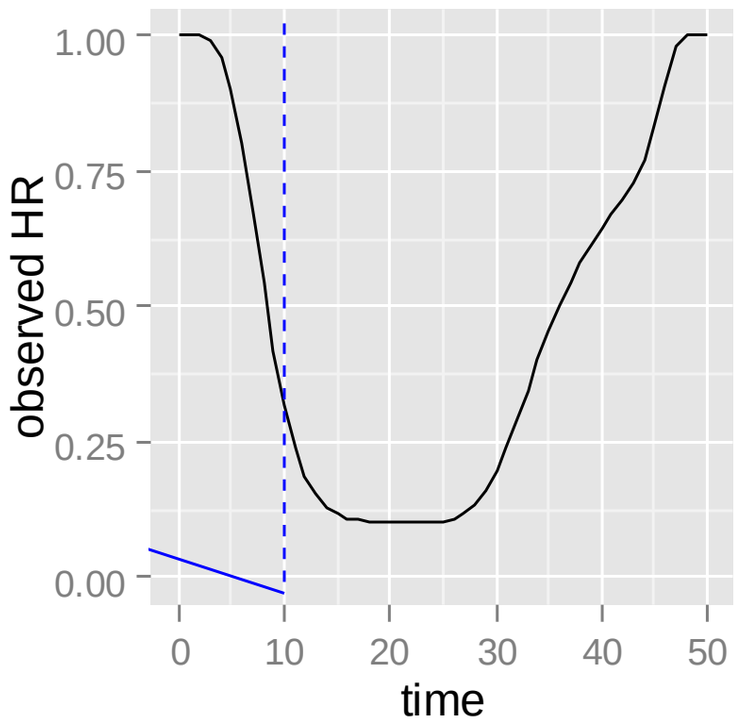
Decreasing background hazard that drops to 0 after 30 days



HAZARD OVER TIME IN IMMEDIATE ARM



HAZARD OVER TIME IN DELAYED ARM

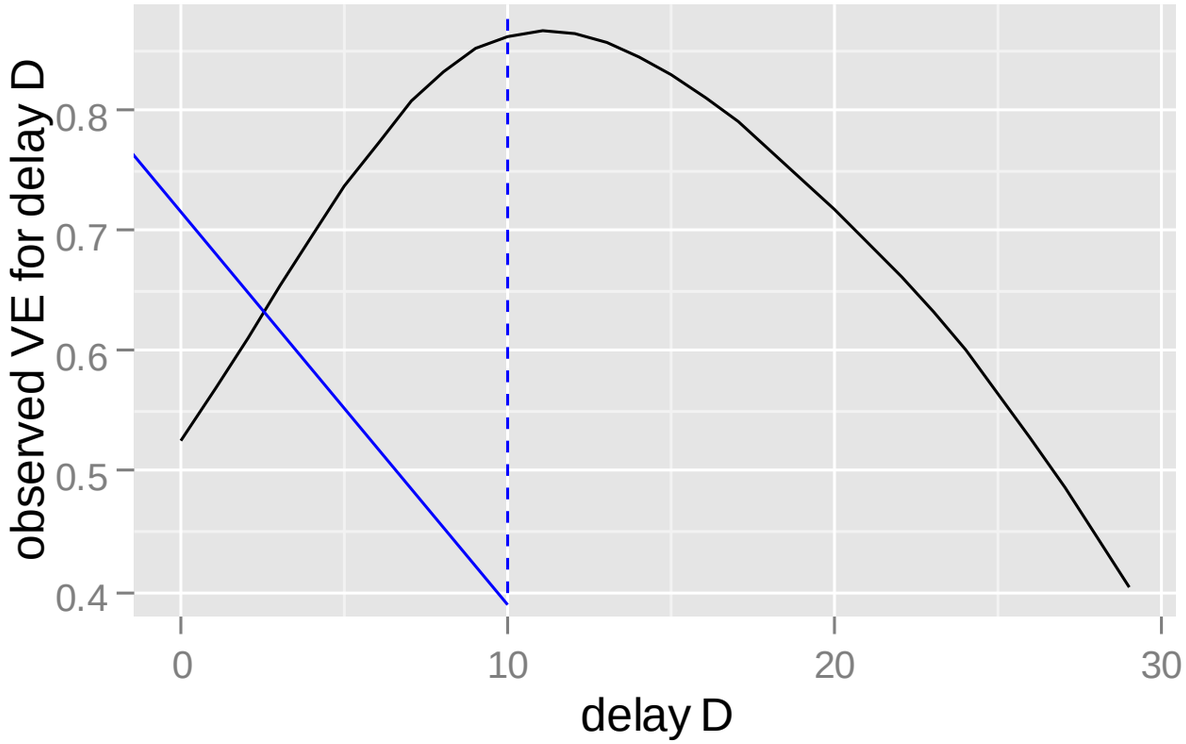


HAZARD RATIO OVER TIME

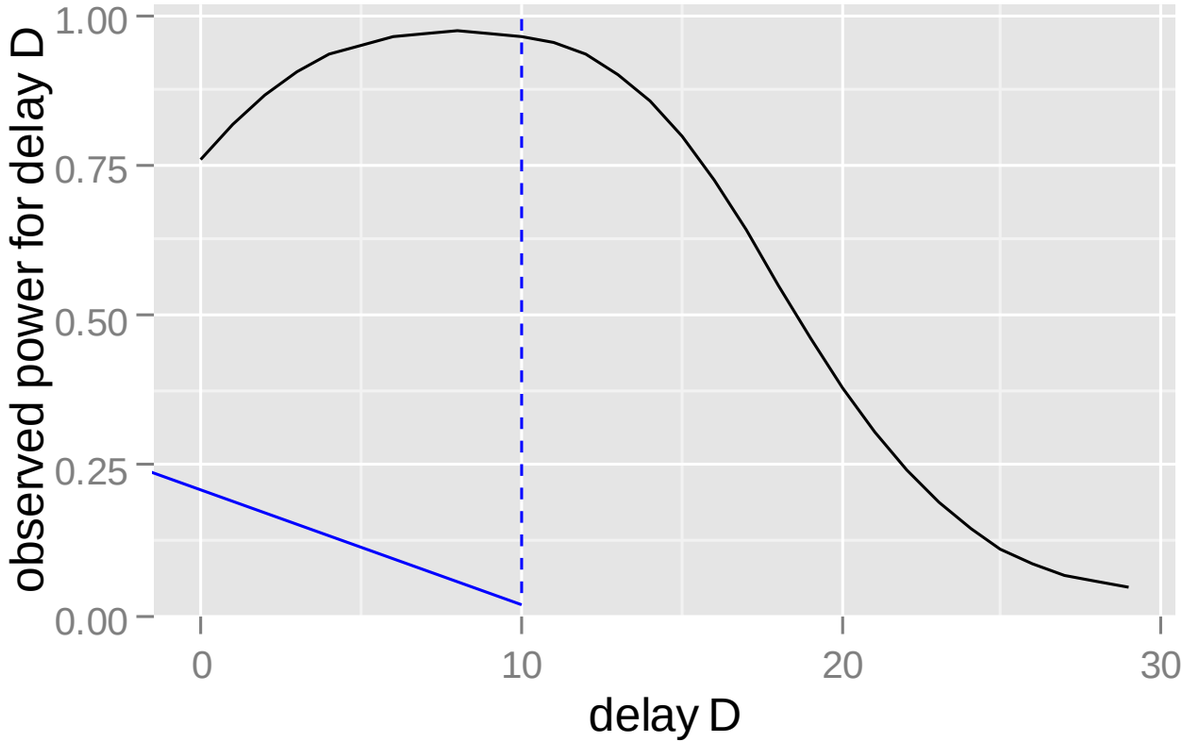
Decreasing Background Hazard

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…



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 use to contain and mitigate future Ebola introductions

Gavi Vaccine Alliance has pledged to purchase 300,000 doses of rVSVΔG-ZEBOV-GP for a mobile WHO stockpile

Science AAAS

Home | News | Journals | Topics | Careers

Latest News | ScienceInsider | ScienceShots | Sifter | From the Magazine | About News | Quizzes

SHARE

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

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

*http://www.sciencemag.org/news/2015/12/and-science-s-breakthrough-year

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

Parameter	Ebola	Zika
R_0	1.2-3.0	2.5-3.5?
Serial interval	I5 days	20 days
Pathogenicity	100%	20%

Acknowledgements

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

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

WHO and other funders for the trial

For statistical analysis and modeling:

NIH/NIAID, R37 AI32042
NIH/NIGMS, U54 GM11274

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

Source: http://www.theguardian.com/commentisfree/2015/aug/03/ebola-vaccine-trials-diseases