Vaccine Trial Designs

Dean Follmann

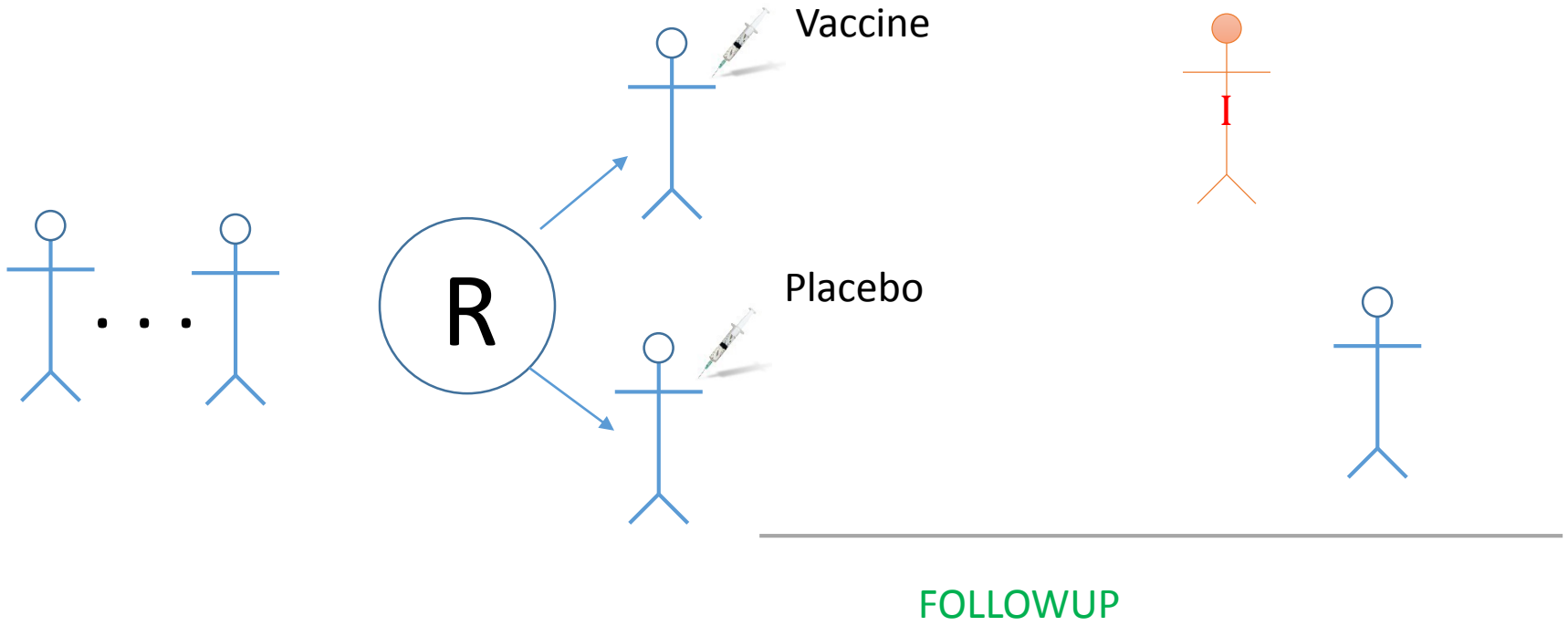
NIH

Outline: Vaccines Trial Designs

- Randomized Vaccine Designs for Licensure
  - Phase I - Phase III
- Animal Rule for Licensure
  - Inhalational Anthrax
- Observational Vaccine Designs for Effectiveness
  - Screening studies Influenza
  - Test-negative Influenza
- Novel Randomized Designs
  - Cluster randomized trials for indirect effects influenza
  - Challenge studies Cholera
  - Stepped Wedge Design
  - Ring Design Ebola

Vaccine Trials

- Randomize volunteers to vaccine or placebo
- Follow them for safety, immune response +/- infection/disease



Traditional Licensure Path Phase I-III

- Phase I: assess safety, immunogenicity N ~ 20-30

  if promising proceed to

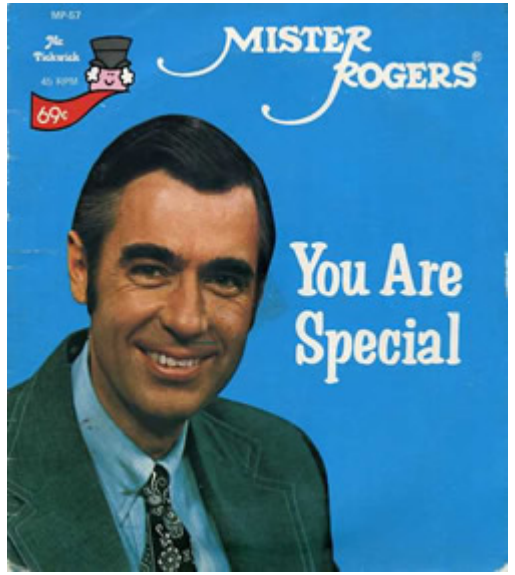
- Phase II: assess safety, immunogenicity N ~ 100s

  if promising, proceed to

- Phase III: assess safety, immunogenicity, efficacy N~ 100s-1000s

  if successful, licensure

Vaccines are *special*



Preventive vaccines usually given to healthy individuals

- usually higher level of efficacy desired than for therapeutics
- stricter toxicity criteria for discontinuing further vaccinations
- major public health impact

Ref: Chan, Wang, & Heyse, 2003

Vaccine Metrics

3 types of endpoints

- Safety (adverse events)
- Immune response (e.g., responders, antibody titers)
- Clinical disease or infection

Safety

- Phase 1 Main goal is careful assessment of safety before giving vaccine to larger numbers of subjects
- Phase 2 and 3 more of the same
- With larger studies, can pick up less common safety signals.
  - But there’s a limit.

1976 Swine Flu

- Jan 1976: Fort Dix recruits got sick with `swine flu’ H1N1 influenza
  - Similar to 1918 strain that killed 50-100 million
- Public Health Officials were alarmed & argued for massive vaccination campaign
  - 40 million vaccinated Oct-Dec 1976
  - 54 cases of Guillian-Barre’ syndrome
- Vaccination was suspended
- Rare events only detected with large studies

Immune Response

- Phase 1 & 2
  - Want a vaccine to be safe, but also need evidence the vaccine

    is invoking an immune response
  - Will measure immune response, typically antibodies to the vaccine.
    - Helps guide dose, formulation, timing of injections
  - Based on an assumption or evidence that the measured immune response is relevant for such decisions
- Phase 3
  - Immune response can be correlated with infection/disease

Assessing Vaccine Efficacy (VE): disease or infection

- Want high specificity & high sensitivity
  - Low specificity dilutes VE (Lachenbruch 1998)
  - Low sensitivity reduces power
- May be able to use expensive diagnostic in a subset
  - Validation sets (Halloran & Longini 2001)
- VE = 1 – R

  where R is a ratio of proportions, incidence rates, hazards, or odds of disease in vaccinated relative to control subjects

Assess VE: Proportion getting event

- When R is a ratio of proportions having event:

  - assumes equal follow-up for all subjects

  - likelihood score method for confidence intervals , usually gives tail probabilities closer to nominal levels

(Gart, 1985; Farrington & Manning, 1990; Blackwelder, 1993)

Assessing VE: Conditional Binomial Method

- For low attack rate or unequal follow-up
- Assume Y_v = # disease on vaccine ~ Poisson($N_v p_v$)
- Assume Y_P = # disease on placebo ~ Poisson($N_p p_p$)
- VE = $(1 - p_v / p_p)$
  - If $N_p = N_v$

    $Y_v \mid Y_v + Y_P = M \sim \text{Binomial}(M, (1\text{-VE})/(2\text{-VE}))$
- Unequal follow-up, replace N_z with total follow-up time in arm Z.
- Exact methods available based on binomial distribution

Chan Bohidar 1998

Assessing VE: Cox Regression

A model for the instantaneous risk of an event . . . .

$h(t) = \omega(t)\, P(\text{event} \mid \text{exp}, Z=0)$ in placebo group

$h(t) = \omega(t)\, P(\text{event} \mid \text{exp}, Z=1)$ in vaccine group

Probability of infection, given exposure

Risk of event

Risk of EXPOSURE
Same in both groups

Cox Regression 2

$$h(t)=\omega(t)P(\text{event} \mid \text{exp}, Z=0)\ \exp\left\{ \log\left(\frac{P(\text{event}|\text{exp}, Z=0)}{P(\text{event}|\text{exp}, Z=1)} \right) Z \right\}$$

$$= \quad h_0(t) \quad \text{xp}\{\beta Z\}$$

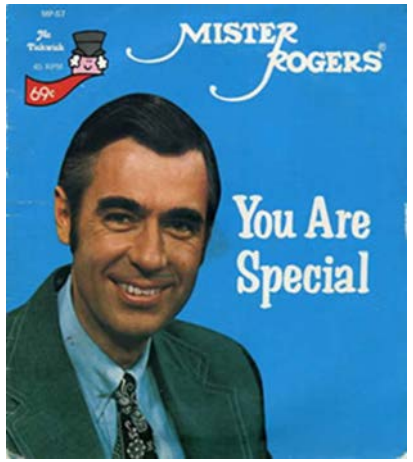
. . . exp(β) is the *per-exposure* reduction in the risk of event

Inference for VE = 1 - R

- Focus on estimation, not hypothesis testing *per se*
- Significantly better than placebo: necessary but usually not sufficient for widespread use in healthy humans
- Appropriate question: How much better than placebo?
- Addressed by a confidence interval

  e.g., 95% CI on VE (.05, .50)

  - significantly better than placebo
  - but problematic for routine childhood immunization
  - lower bound on VE > .60 often anticipated for childhood vaccines



Immune Response Trials: Non-inferiority

- Suppose it is accepted that an immune response readout is a valid proxy for efficacy for a given vaccine
- Then use immune response as the only readout
  - New vaccine for same disease indication as previously licensed vaccine
  - Combination vaccines: combined version compared to separately administered components
  - Bridging studies: comparison of a vaccine to a changed version of itself (e.g., change in manufacturing, dose, formulation, population, etc.)
    - e.g., comparison of vaccines with and without thimerosal

Immune Response Trials: Noninferiority

- May not expect new vaccine to have better immune response
- Show vaccine (combination, version, etc.) is not inferior to the comparator by an amount M called the margin

Immune Response: Noninferiority of rates

Typical hypothesis: difference between 2 rates

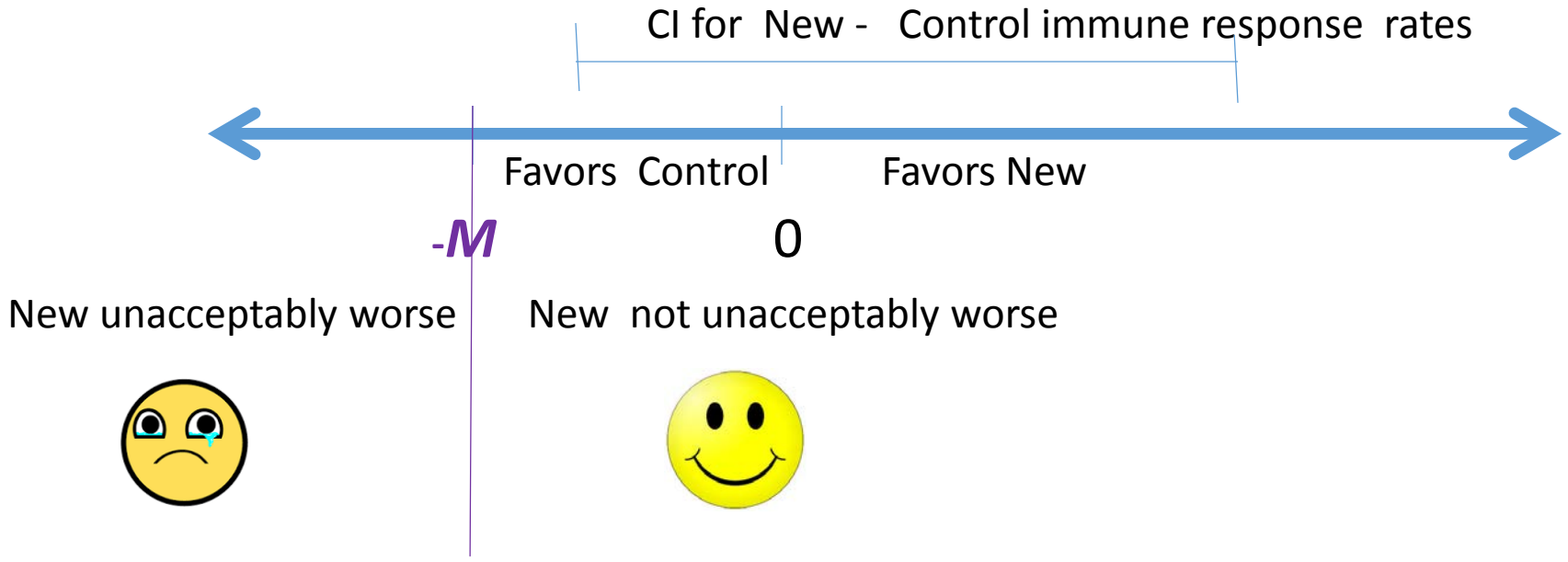
H_{Null}: $P_{New} - P_{Control} \leq -0.10$

$H_{Alternative}$: $P_{New} - P_{Control} > -0.10$

where 0.10 represents the acceptable drop in
Rate responding among those receiving
the new vaccine relative to the control vaccine

Immune Response: Noninferiority of rates

- Noninferiority Trial: New Vaccine versus Control Vaccine
- CI of difference in immune response rates needs to exceed a ***margin***



Analysis of NI Trials

- Estimate rates under the null
- Form test statistic $Z = \frac{\hat{P}_{New} - \hat{P}_{Control} + M}{\hat{\sigma}}$

  $\hat{\sigma}$ = standard deviation estimated under the null
- Reject Null in favor of non-inferiority if Z > 1.96

Wang, Mehrotra et al 2006

Immune Response Trials: Concerns

Multiplicity

- Combination or multivalent vaccines
  - 21 CFR 601.25 (d) (4) (ii)

    "A biological product may combine two or more safe and effective active components: . . . (ii) when combining of the active ingredients does not decrease the purity, potency, safety, or effectiveness of any of the individual active components. . . ."

  - Passage implies that a separate non-inferiority evaluation must be successfully met for every individual component: alpha but not power controlled

  - Must increase power of individual tests in order to maintain adequate overall power. Consequently, total sample size must be increased..

Sample Sizes Required for Overall 80% Power to Compare Two Proportions*

by Number of Components

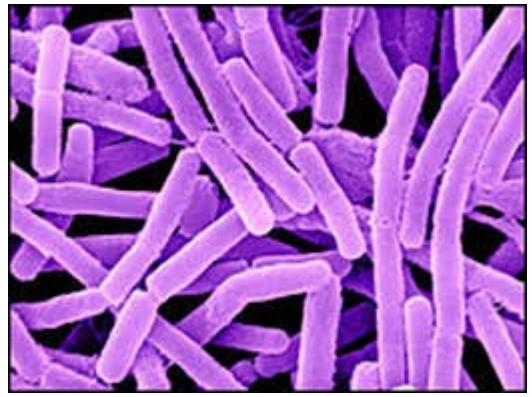
Number of Components	Individual Test Power	Individual Test Type 1 Error (α)	Total Sample Size **
1	0.800	0.05	244
5	0.956	0.05	432
10	0.978	0.05	512

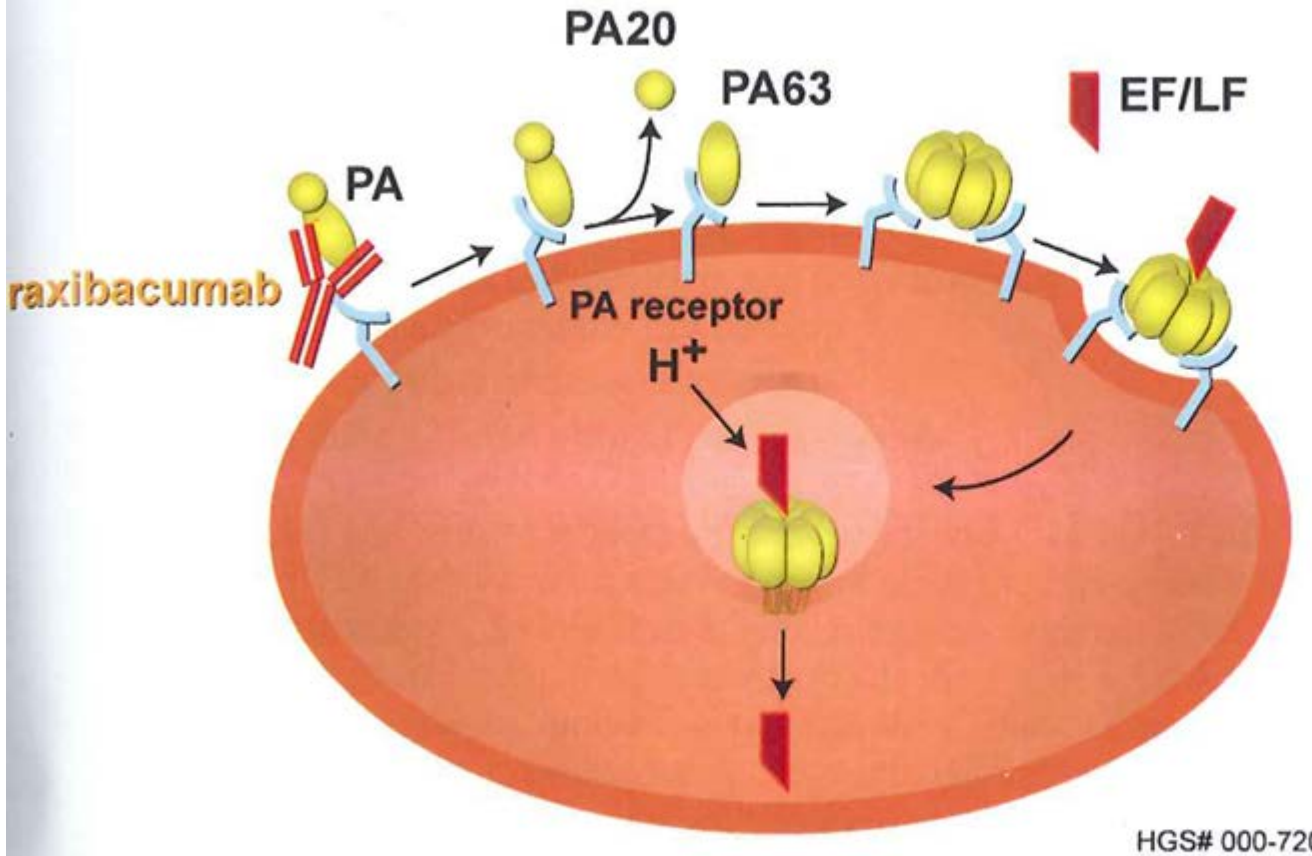
* Assuming a non-inferiority margin of – 0.10, true proportion responding among new and control vaccine recipients is 0.90, and tests are independent.

** Calculated using likelihood score method.

Animal Rule for Anthrax Vaccine

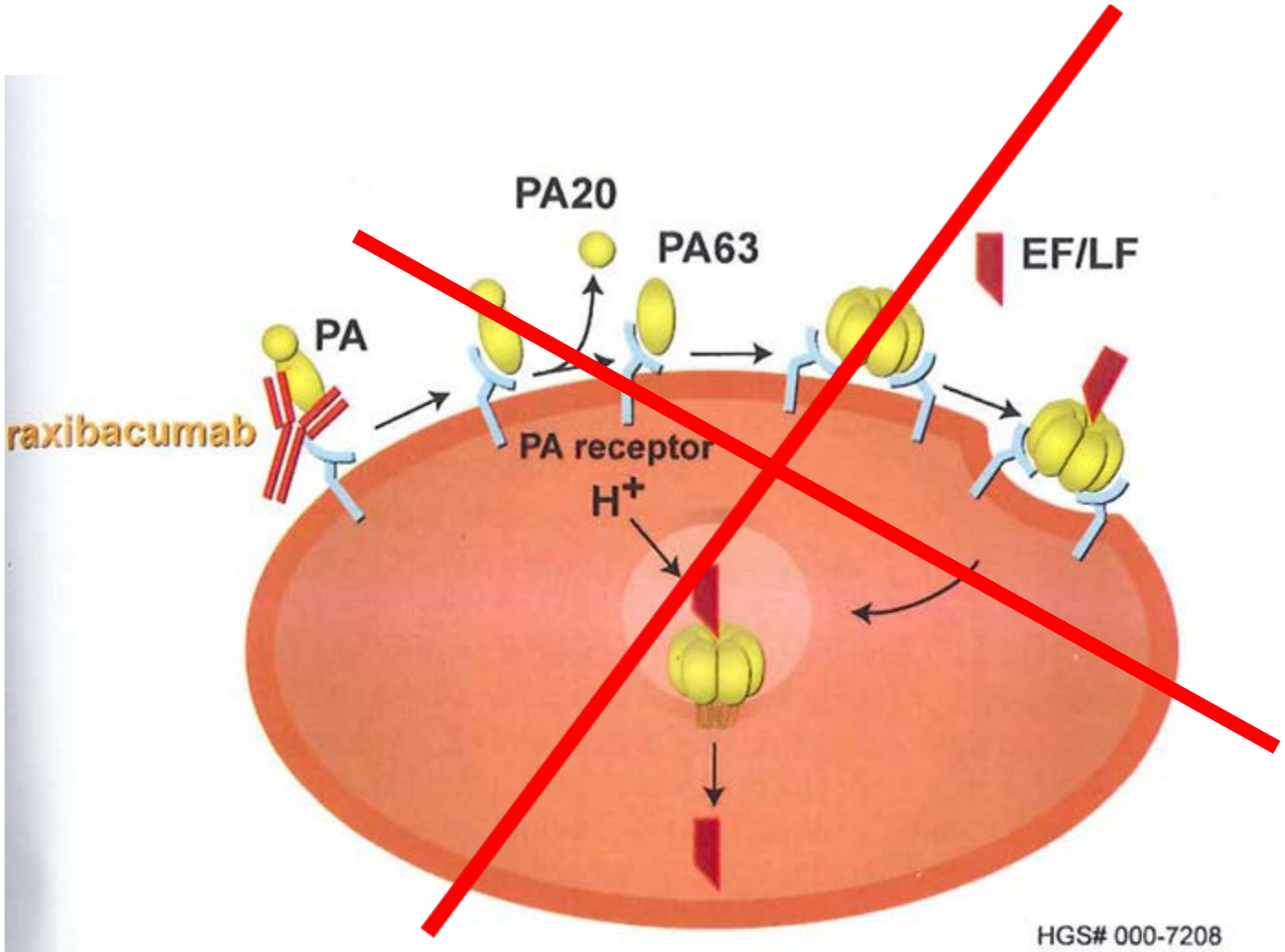
- Inhalation anthrax doesn't naturally occur
- FDA allows licensure based on animal models
  - Animal model recapitulates key aspects of human disease
- Passive immunization shows sufficient anthrax antibody protects
- Build a model for VE in animals using antibody
  - Vary vaccine dose to induce variation in antibody
  - See if antibody alone predicts well.
- Make the leap from Monkey to Man
  - Check the leap from Rabbit to Monkey etc.





EF - edema factor
LF - lethal factor

Figure 1-1 **Mechanism of action of anthrax toxins and inhibition by anti-PA antibody**

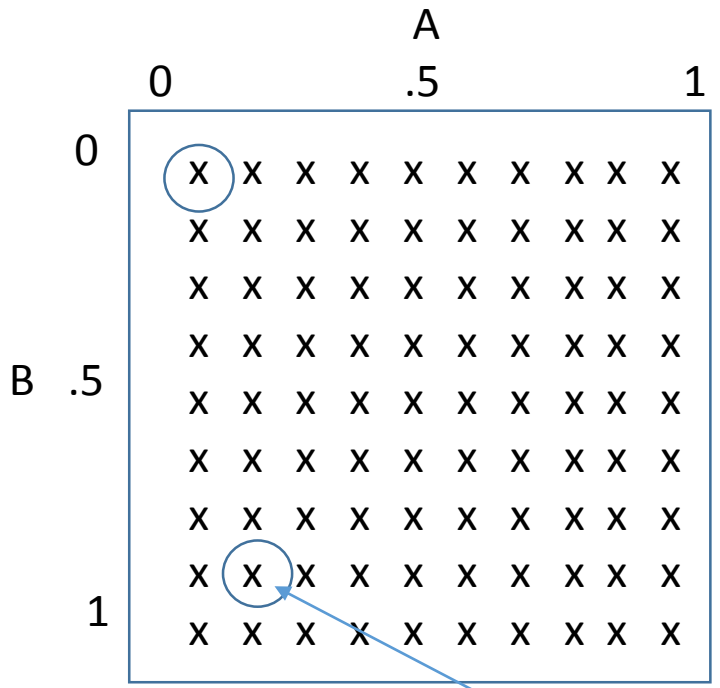


EF - edema factor
LF - lethal factor

Figure 1-1 **Mechanism of action of anthrax toxins and inhibition by anti-PA antibody**

Farmers: Randomize to A=a, B=b

A = Fertilizer type ‘A’
B = Fertilizer type ‘B’



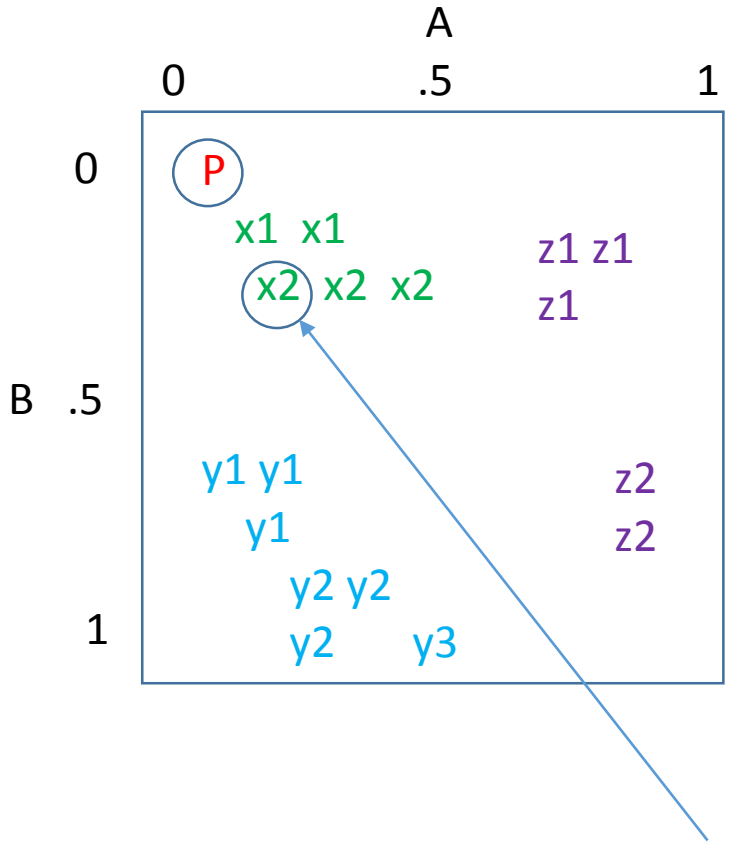
Dial B=.9 A= .1
Observe Y(.1,.9) – yield in many fields

$\Delta = \overline{Y(.1,.9)} - \overline{Y(0,0)}$

Δ =Effect of (A,B) = (.1,.9) relative to (A,B)=(0,0)

Vaccinologists: Randomize dose, see A=a, B=b

A = T cell response
B = Antibody response



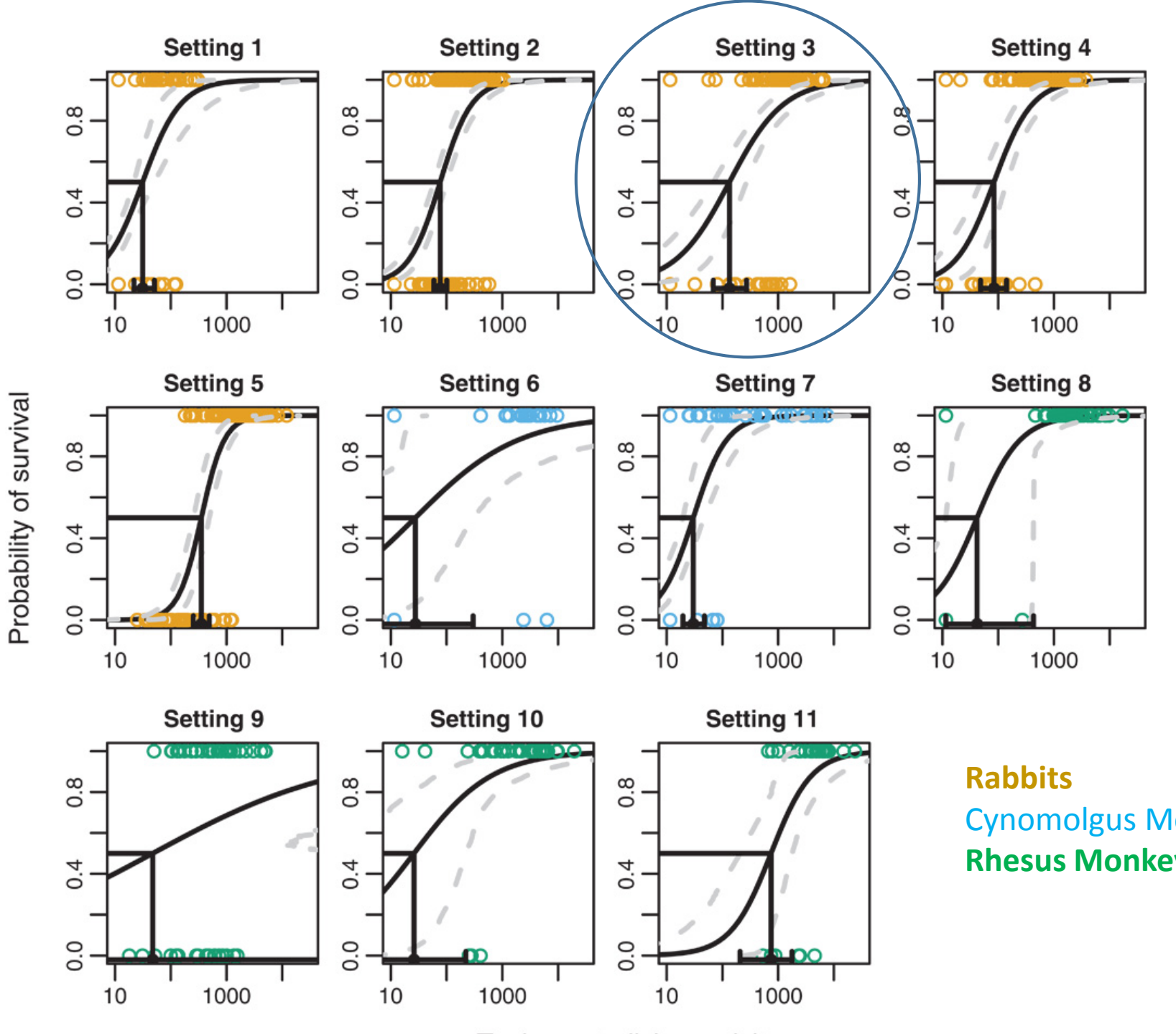
x1 dose 1 of green vaccine
z2 dose 2 of purple vaccine
y3 dose 3 of blue vaccine

$\Delta = \overline{Y(.3,.3)} - \overline{Y(0,0)}$

Δ Not necessarily the effect of (A,B) = (.3,.3) relative to (0,0)

Feel better if similar Δ achieved at (.3,.3) from multiple vaccines

Dial in dose 3 of green vaccine
Observe Y--attack rate--in green vaccinees who achieved A,B=.3,.3

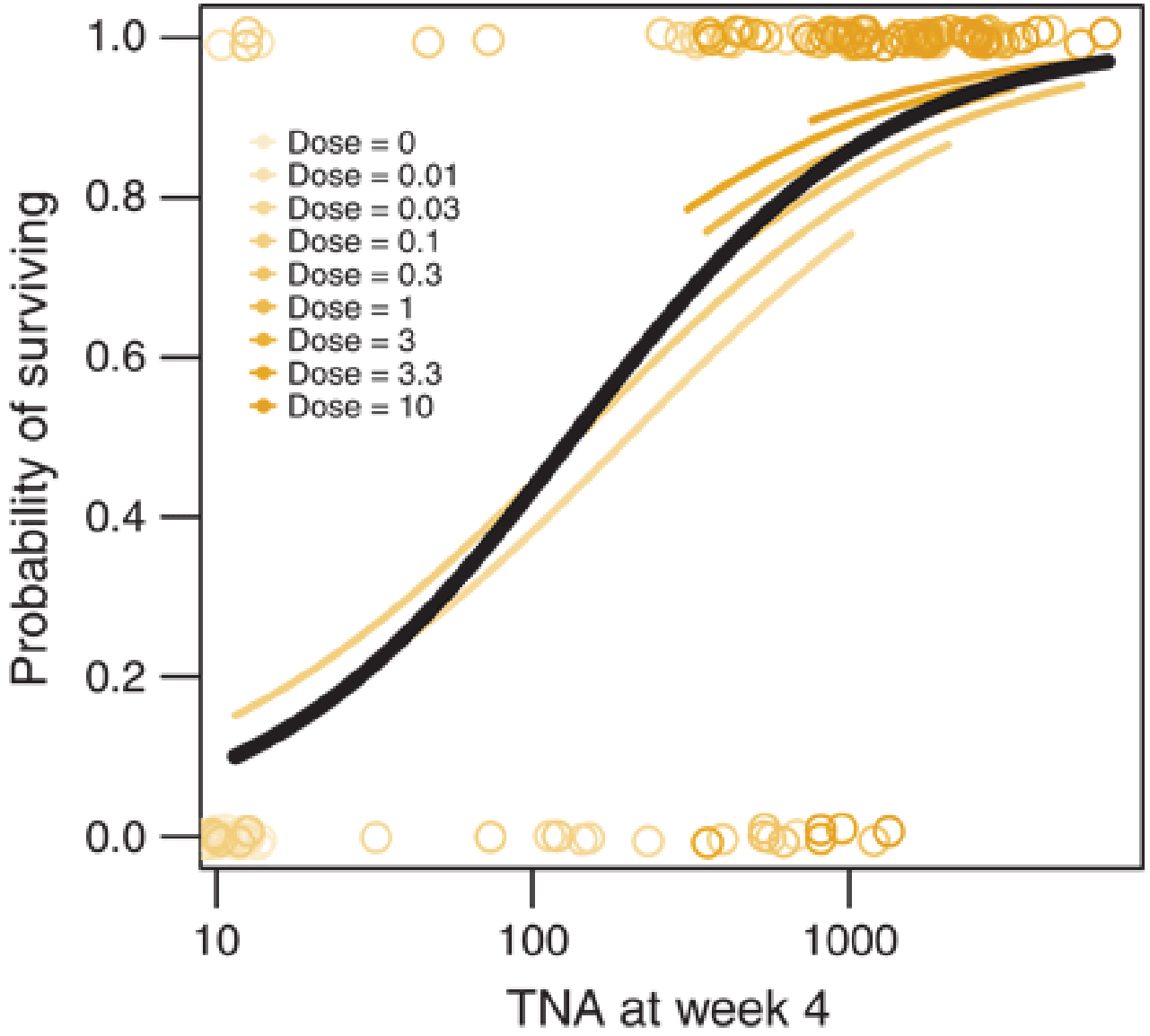


Rabbits

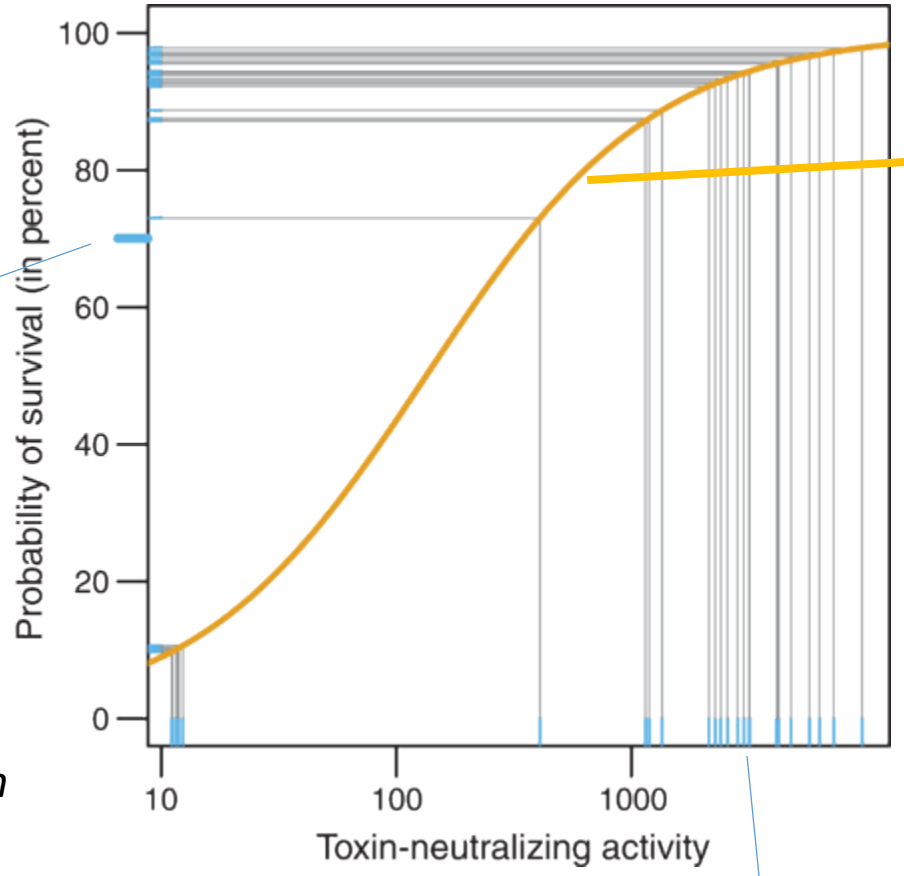
Cynomolgus Monkeys

Rhesus Monkeys

Setting 3: Little improvement in fit with dose in model supports Prentice criterion for surrogacy



From Rabbit to Monkey

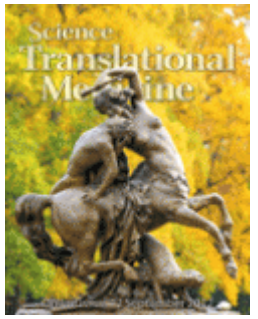


Rabbit Curve

Averaged Predicted Monkey Survival Probability
70.1 (55.1,83.5)

Observed Monkey Survival Proportion
75.9 (56.5, 89.7)

Monkey Antibody Values



Fay et al 2012

Vaccine Effectiveness: Screening Method

- For vaccines that are deployed, how to estimate `real-world' effectiveness?
- Identify *all or a random sample* of those with severe acute respiratory illness (ARI) positive for influenza
  - Find out 40% vaccinated for influenza
- Suppose vaccine coverage in population is 65%

$$VE = 1 - \frac{Odds\ of\ flu\ vaccine\ in\ cases}{Odds\ of\ flu\ vaccine\ in\ population} = 1 - \frac{.40/.60}{.65/.35} = .64$$

- In practice identify those who go to hospital for ARI
  - Likely those with health care access, health concerns & *not random*

Farrington 1993

Vaccine Effectiveness: Test Negative

- Control for health seeking behavior
- Identify those who are hospitalized for ARI
  - 'cases' --- those who are positive for influenza virus
  - 'controls' – those who are negative for influenza virus
- Estimate of vaccine effectiveness

$$VE = 1 - \frac{Odds\ of\ flu\ vaccine\ in\ cases}{Odds\ of\ flu\ vaccine\ in\ controls}$$

- Requires
  - Non-flu causes of ARI same for vaccinees/non-vaccinees
    - e.g. Elderly may have more non-flu ARI and get vaccinated more
  - VE does not vary with health seeking behavior
    - e.g. VE worse for hypochondriacs

Jackson Nelson 2013

Flu Vaccine Effectiveness of 2011-12

- Test negative design employed
- Patients with ARI <= 7 days were enrolled in 5 out-patient clinics over the 2010-11 season
  - Test for flu virus + = case - = control
- Influenza Vaccination status based on documentation > 14 days before illness onset
- Logistic Regression adjustment
  - Demographic, health status, calendar time
  - Current season vaccination, Prior season vaccination & interaction

Results

- Vaccine effectiveness for 2011-12 similar for those
  - Not vaccinated in 2010-11 (but vaccinated in 2010-11)
  - Vaccinated in 2010-11 (and vaccinated in 2010-11)

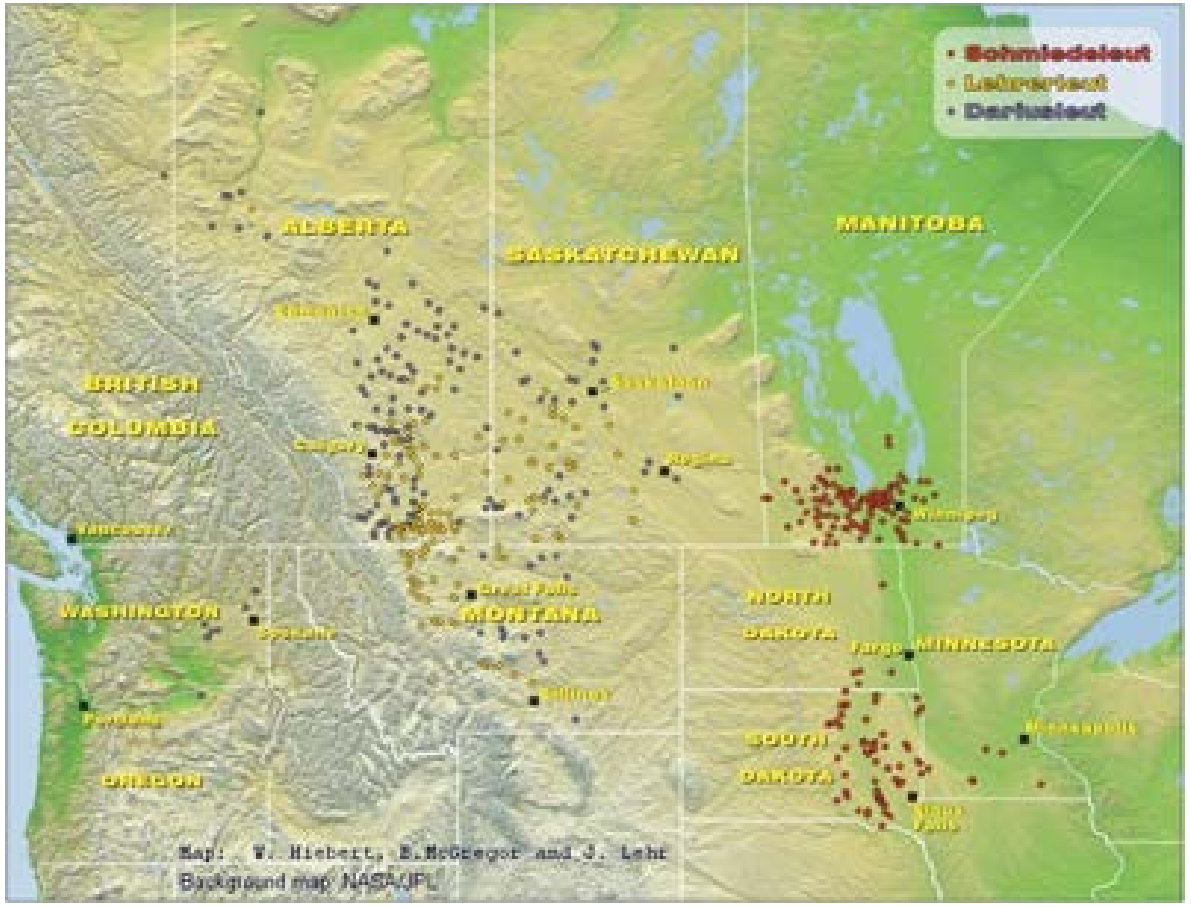
	Influenza-Positive Cases		Influenza-Negative Controls		Unadjusted		Adjusted[a]	
	No. Cases/ Row Total	Row %	No. Controls/ Row Total	Row %	VE %	(95% CI)	VE %	(95% CI)
Vaccinated current 2011–2012[b] only	42/512	8.2	470/512	91.8	61	(45 to 72)	56	(37 to 69)
Vaccinated current 2011–2012[b] and prior 2010–2011[c]	106/895	11.8	789/895	88.2	41	(26 to 54)	45	(27 to 58)
Vaccinated prior 2010–2011[c] only	45/277	16.3	232/277	83.8	15	(–19 to 40)	18	(–20 to 43)
Not vaccinated either 2010–2011 or 2011–2012	298/1597	18.7	1299/1597	81.3	Reference		Reference	

Cluster Randomized Vaccine Trials

- Infection *happenings* can be *dependent*
  - Fewer infections among vaccinated *yields*
  - Fewer exposures/infections among unvaccinated
- Also known as the indirect effect of vaccination or herd immunity
- To assess can compare vaccinated clusters to unvaccinated clusters
- Need the right sorts of clusters
  - Relatively isolated (*so indirect effects can be substantial)*
  - Not completely isolated *(so exposure is possible)*

Ross 1916 wrote about dependent happenings

Hutterites



Hutterite Colonies in North America

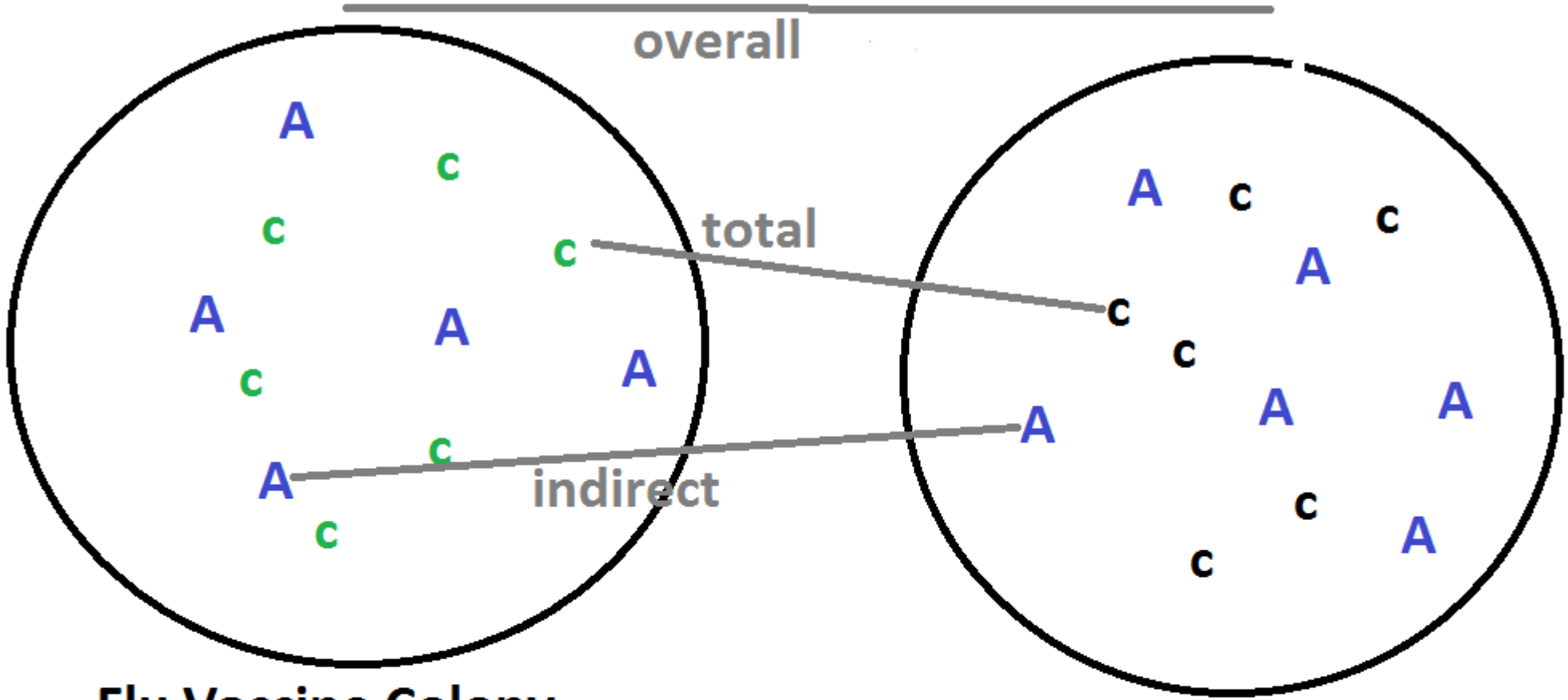
One Hutterite colony

Hutterite Colony Trial

- Children 3-15 years old a major source of influenza transmission
- Vaccinate children
  - Indirect effects measured on adults
  - Overall effects measured on everyone
- 25 colonies Influenza vaccine (median size 78)
- 24 colonies Hepatitis A vaccine (median size 62)

Details

- Statistical modeling suggested 70% coverage of vaccinated children would impact adults
- Vaccination was blinded
  - <9 y.o. naïve: two shots H--------S or F-------F
  - >9 y.o. : one shot H or F
    - H-hepatitis vaccine S-saline F-flu vaccine
- Evaluation
  - 28 December 2008 through 23 June 2009
  - Laboratory confirmed influenza:
    - 2+ symptoms and PCR+ respiratory sample



A - adult

c - child influenza flu vaccine

c - child Hepatitis A vaccine

Hutterite Colony Trial

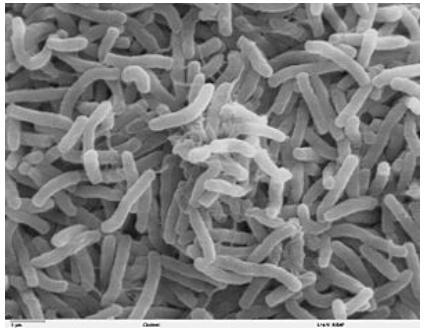
	Flu Vaccine Colony	Hep A Vaccine Colony	VE
Non-recipients ADULTS	1271	1055	61% VE-Indirect*
# FLU	39	80	p=.03
All Participants Colony	1773	1500	59% VE-Overall
# FLU	80	159	p=.04
Intended Recipients Children	502	445	54% VE-Total^
# FLU	41	79	

*VE estimated using a Cox Regression model with a sandwich estimate of variance
^VE estimated using 1 – ratio of infection rates

Human Challenge Studies

- Challenge a euphemism for giving enough germs to almost certainly cause infection in humans.
- Seem unethical but can be used if disease is controllable
  - Malaria parasites can be cleared by drugs
  - Can ‘challenge’ with a weakened pathogen (e.g. influenza, RSV)
  - Zika?
- All proposed human trials must undergo ethical review

Cholera



Vibrio cholerae

- Waterborne bacterium that causes severe diarrhea disease
  - Vomiting
  - Severe dehydration
  - Fecal – Oral Transmission
- Problem in the developing world with unclean water
- Outbreaks occur
  - Current Haitian outbreak caused by Nepalese UN troops to help with 2010 earthquake. Spread to Cuba, DR

Cholera

- Celebrated example of epidemiology
- John Snow mapped cases of diarrhea
  - Clustered around a pump
- Removed handle
- Outbreak stopped

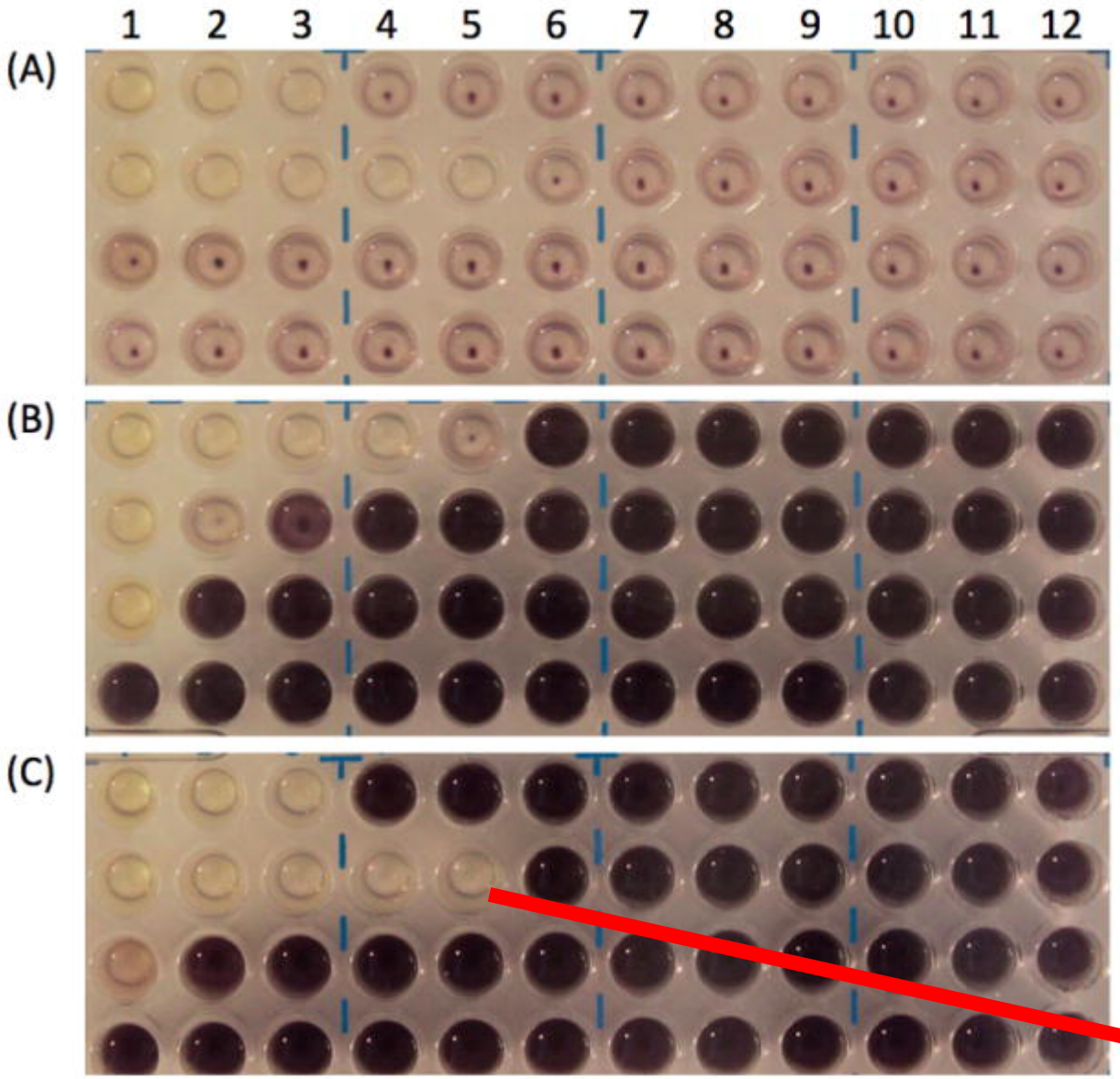
Human Challenge Trial for Cholera Vaccine

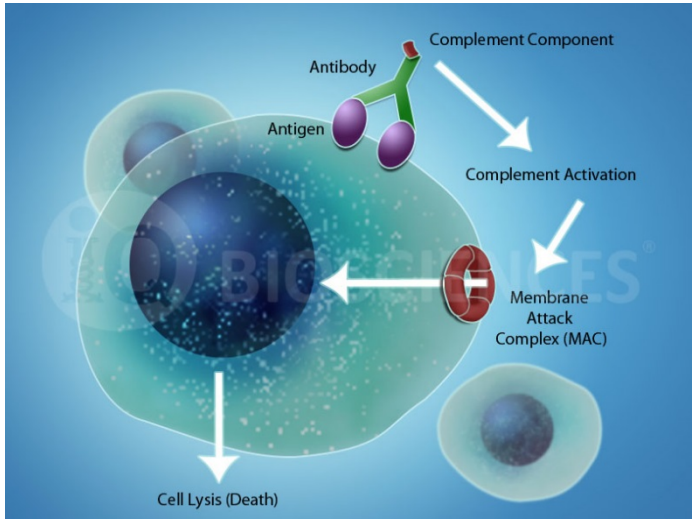
- Market for a travelers vaccine
- VaxChora an oral live-attenuated single dose vaccine
- Randomized 210 volunteers 1:1 Vaccine/Placebo
  - Primary endpoint > 3L liquid stool during course of illness
  - Challenge cohort & safety cohort

Measure	Vaccine 10 day challenge N=35	Vaccine 3 month challenge N=33	Placebo N=66
>3L liquid stool	6%	12%	59%
Vaccine Efficacy	90%	80%	
Lower CI	63%	50%	

http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2016-02/cholera-02-danzig.pdf

Subject ‘A’





Bacteria Killed

Bacteria not killed

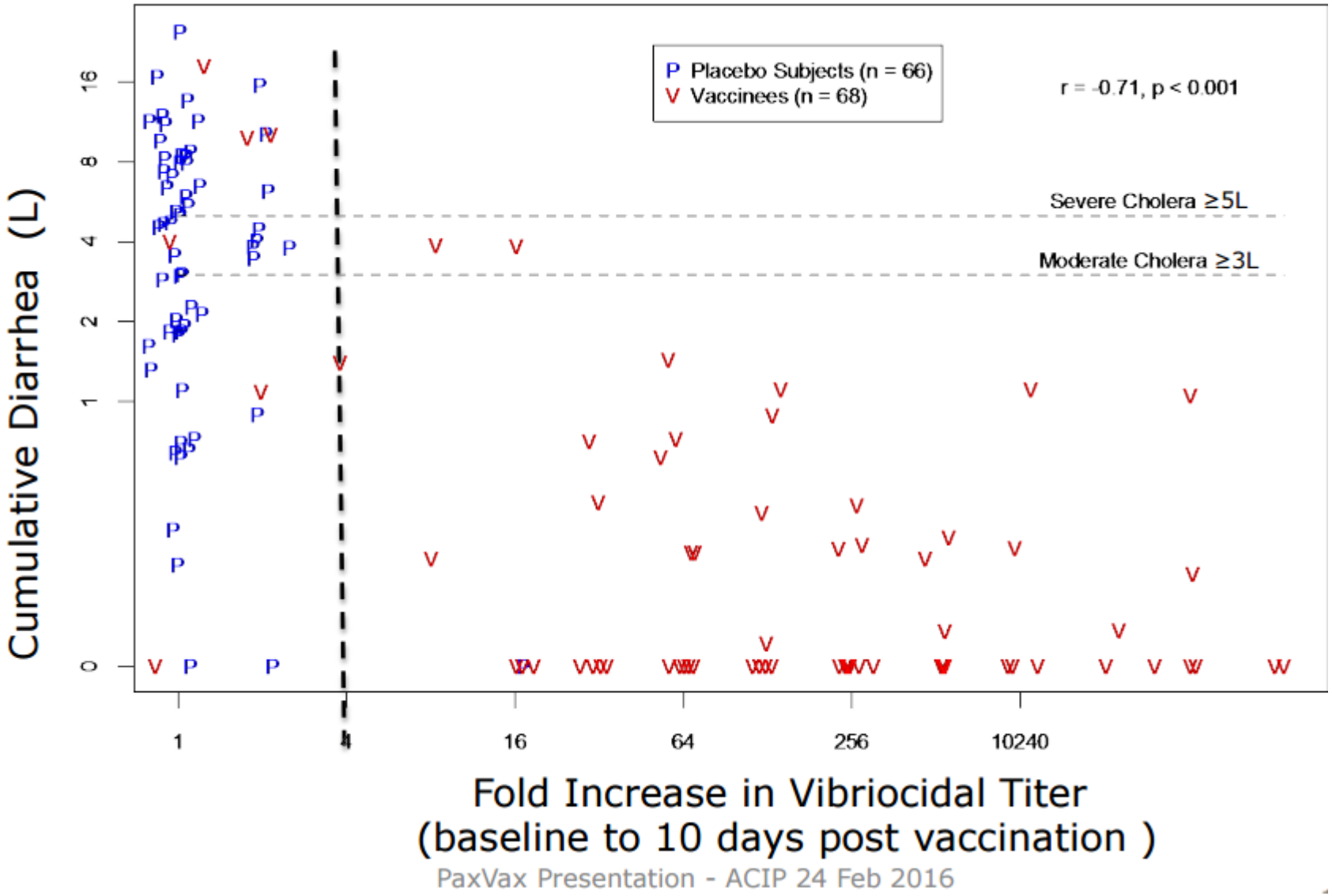
Undiluted

Son & Taylor 2011

1:2048 Dilution

Titer of 16

Cholera
WT Strain
N16861



http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2016-02/cholera-02-danzig.pdf

Stepped Wedge Design

- A kind of community randomized trial
  - Effective sample size is # communities not # of people in a community
- Can roll out vaccine at 1 site per month
- Randomize order of rollout

Community	Period 1	Period 2	Period 3	Period 4
1				
2				Vaccine
3			Vaccine	Vaccine
4		Vaccine	Vaccine	Vaccine
5	Vaccine	Vaccine	Vaccine	Vaccine

Community	Period 1	Period 2	Period 3	Period 4
1	$\alpha_1+\beta_1$	$\alpha_1+\beta_2$	$\alpha_1+\beta_3$	$\alpha_1+\beta_4$
2	$\alpha_2+\beta_1$	$\alpha_2+\beta_2$	$\alpha_2+\beta_3$	$\alpha_2+\beta_4+\theta$
3	$\alpha_3+\beta_1$	$\alpha_3+\beta_2$	$\alpha_3+\beta_3+\theta$	$\alpha_3+\beta_4+\theta$
4	$\alpha_4+\beta_1$	$\alpha_4+\beta_2+\theta$	$\alpha_4+\beta_3+\theta$	$\alpha_4+\beta_4+\theta$
5	$\alpha_5+\beta_1+\theta$	$\alpha_5+\beta_2+\theta$	$\alpha_5+\beta_3+\theta$	$\alpha_5+\beta_4+\theta$

Analysis

- Simple Model with cluster α and time β effects

$$Y_{ij} = \alpha_i + \beta_j + \theta Z_{ij} + e_{ij}$$

$i = 1,\ldots,5$ (cluster) $j=1,\ldots4$ (period)

$Z_{ij} = 1$ if vaccination occurring 0 otherwise

Y_{ij} = infection rate

- A trial with 5 clusters and 4 periods is like a trial with 5 subjects and 4 repeated measures
- Can use GEE with cluster=community (R-package saws)
- Permutation methods are attractive

Hussey and Hughes 2007
Fay & Graubard 2001

Community	Period 1	Period 2	Period 3	Period 4
1		Vaccine	Vaccine	Vaccine
2				Vaccine
3			Vaccine	Vaccine
4				
5	Vaccine	Vaccine	Vaccine	Vaccine

Community	Period 1	Period 2	Period 3	Period 4
1	Vaccine	Vaccine	Vaccine	Vaccine
2				
3				Vaccine
4		Vaccine	Vaccine	Vaccine
5			Vaccine	Vaccine

Permutation Analysis

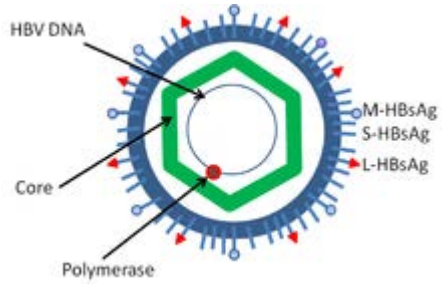
- For permutation p, fit model with permuted Z_{ij}

$$Y_{ij} = \alpha_i + \beta_j + \theta Z^p_{ij} + e_{ij}$$

Estimate θ^p

- See how extreme the original estimate of θ is in terms of permutation distribution of θ^p s

Hepatitis B Vaccine



- Hepatitis B--- a virus spread by sex, contact with blood, needle
- West Africa 1980s: Nearly everyone is infected with HBV during childhood
- HBV leads to liver disease and liver cancer in middle age
- Vaccine immunogen uses HBsAB protein (part of virion's outer shell)

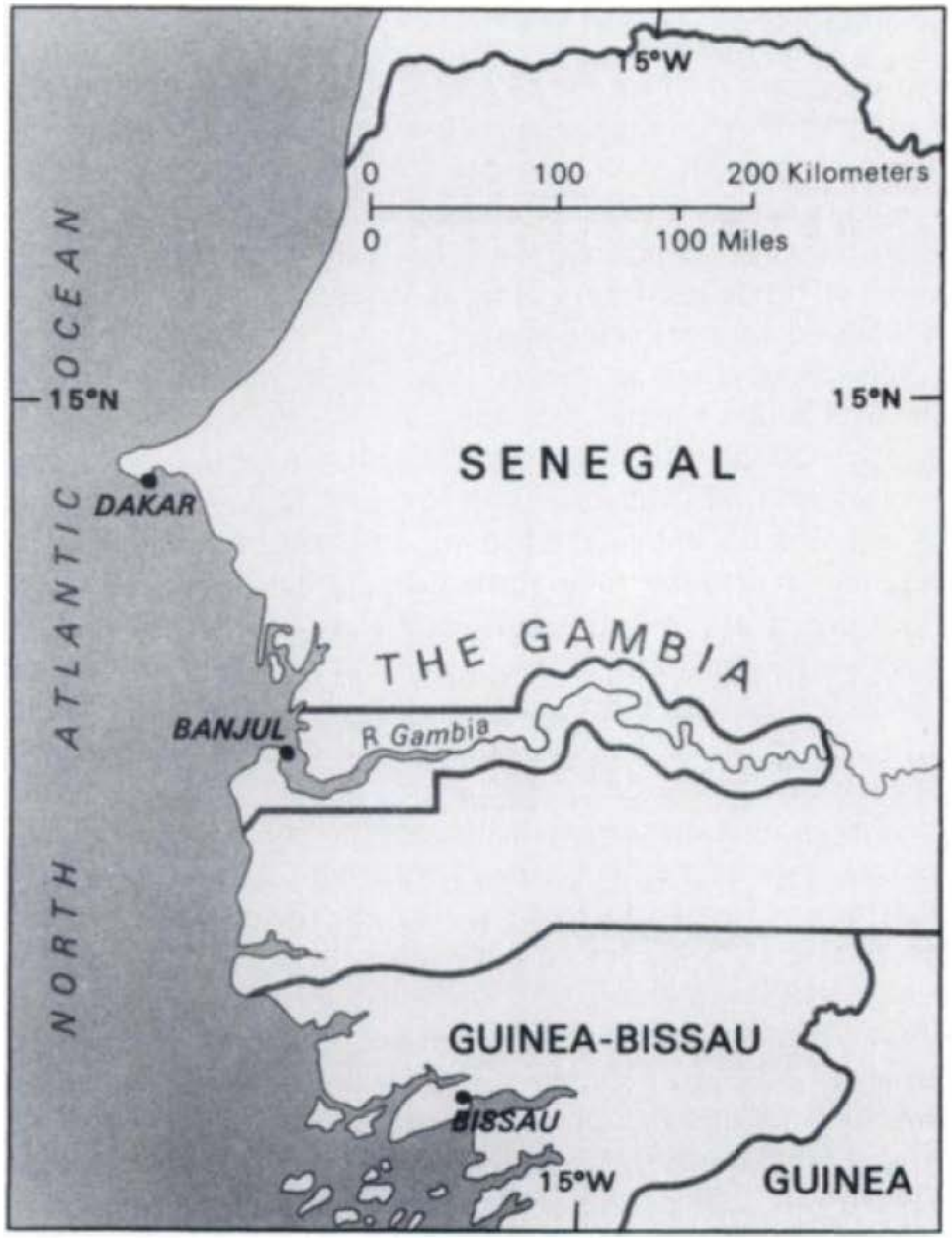


Fig. 1. The Gambia and neighboring countries.

The British Navy made The Gambia a British colony
- range of naval guns was about 10 miles

Small dense country covered by 17 geographically
Dispersed health centers

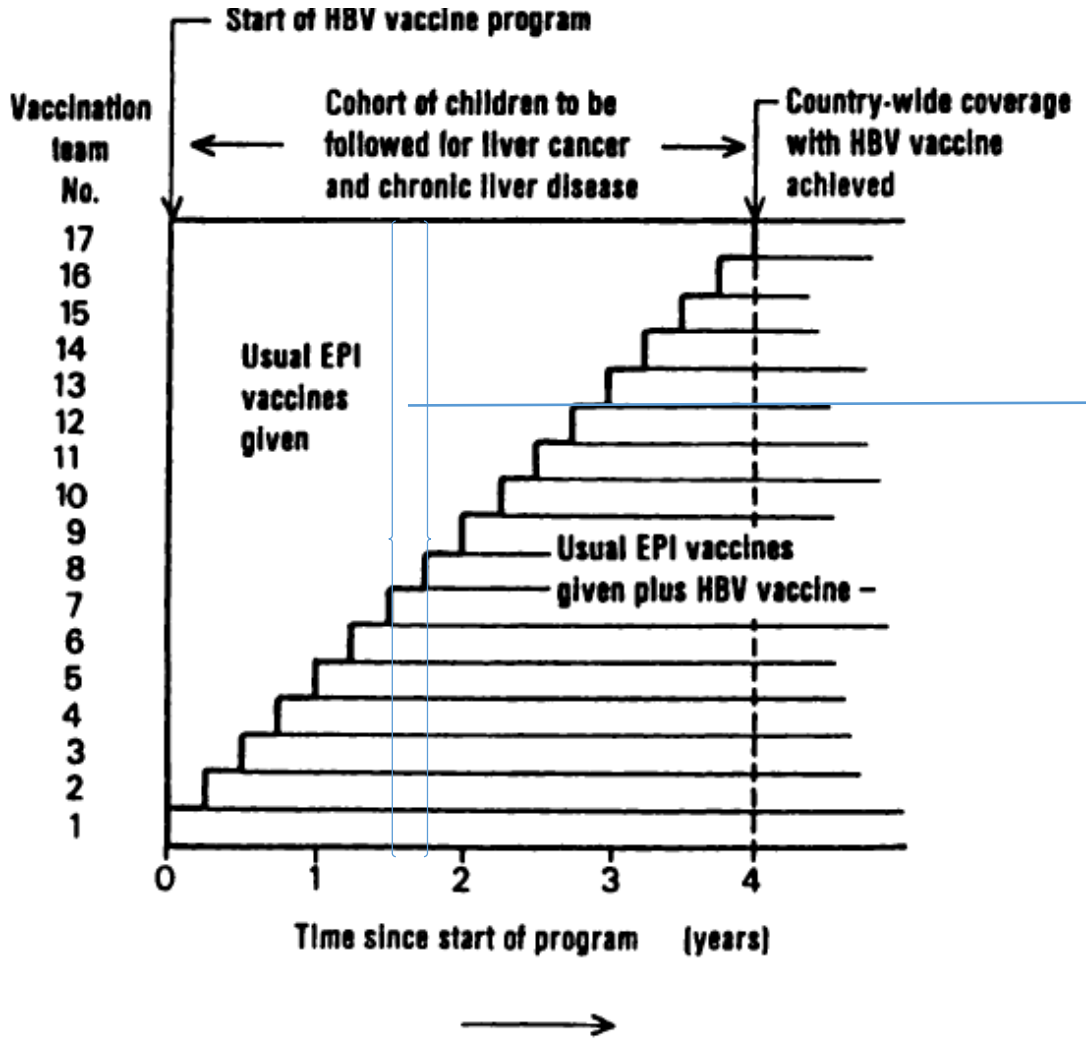


Fig. 2. Phased introduction of hepatitis B vaccination in The Gambia.

Each time responsible for an area

Teams vaccinate newborns with usual vaccines (DPT polio, yellow fever, measles) +/- Hepatitis B

Compare rates of HCC in vaccinated to unvaccinated children

Table 3 *Cumulative incidence of liver cancer up to age 50 years in The Gambia*

Age group (yr)	Annual incidence of liver cancer/ 10^5 males[a]	Cumulative no. of cases in group of 30,000 newborn males (to end of each age group) assuming[b]		
		No attrition	30% attrition	50% attrition
0–4	0	0	0	0
5–9	0	0	0	0
10–14	2	3	2	1
15–19	3	7	5	4
20–24	5	15	10	7
25–29	8	27	19	13
30–34	11	43	30	22
35–39	18	70	49	35
40–44	38	127	89	64
45–49	52	205	144	102

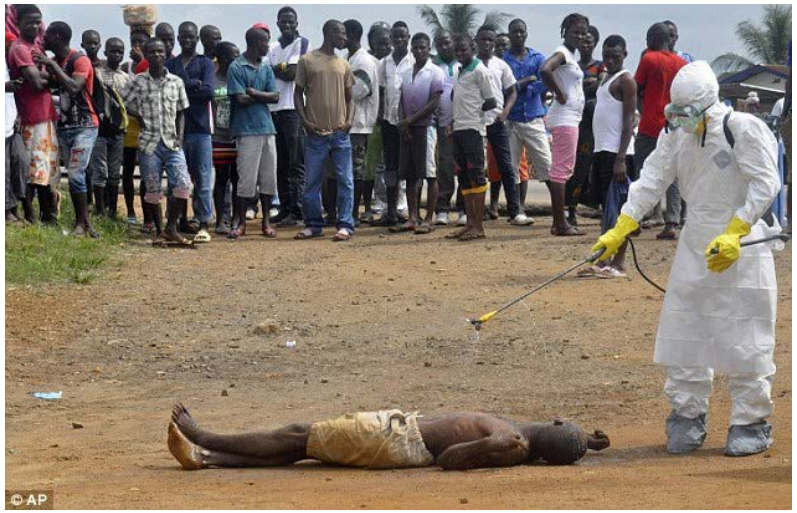
[a] Data from 1981–1982 Gambian case-control study (12).
[b] Estimates based on data for males.

Simple Analysis

- Clusters were randomized so analysis at cluster level
- Y_{ij} ~ # of cases in hepatic cellular carcinoma over 50 years from region i from birth period j. i=1,…,17 j=1,…,16.
- Z_{ij}= 1 if cohort received vaccine 0 otherwise
- N_{ij} = number of children vaccinated
- Set E(Y_{ij}) = exp($\alpha_i + \beta_j + \theta Z_{ij}$) = N_{ij} exp($\alpha + \theta Z_{ij}$) ~ Poisson model
- VE = 1 - exp(θ)
- Could use Poisson model or permutation for inference

Ebola Vaccine Trials

- 2014-2015 Ebola outbreak in West Africa was terrifying



- And sensationalized

The New York Times

Ebola Cases Could Reach 1.4 Million Within Four Months, C.D.C. Estimates

THE WALL STREET JOURNAL.

New Ebola Cases May Rise to 10,000 a Week by December

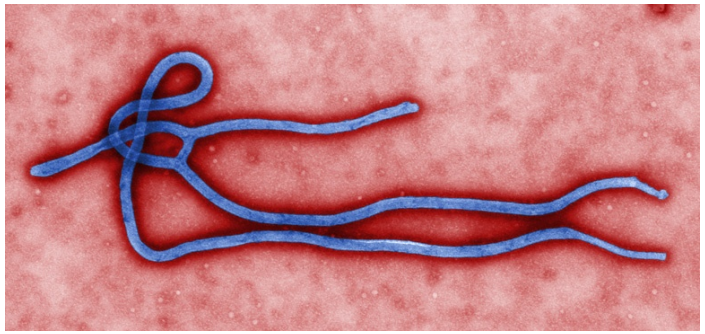
The Washington Post

Ebola could infect 500,000 by end of January, according to CDC projection

AP Associated Press

Ebola in America: Scientists try to predict number of US cases

Ebola Virus

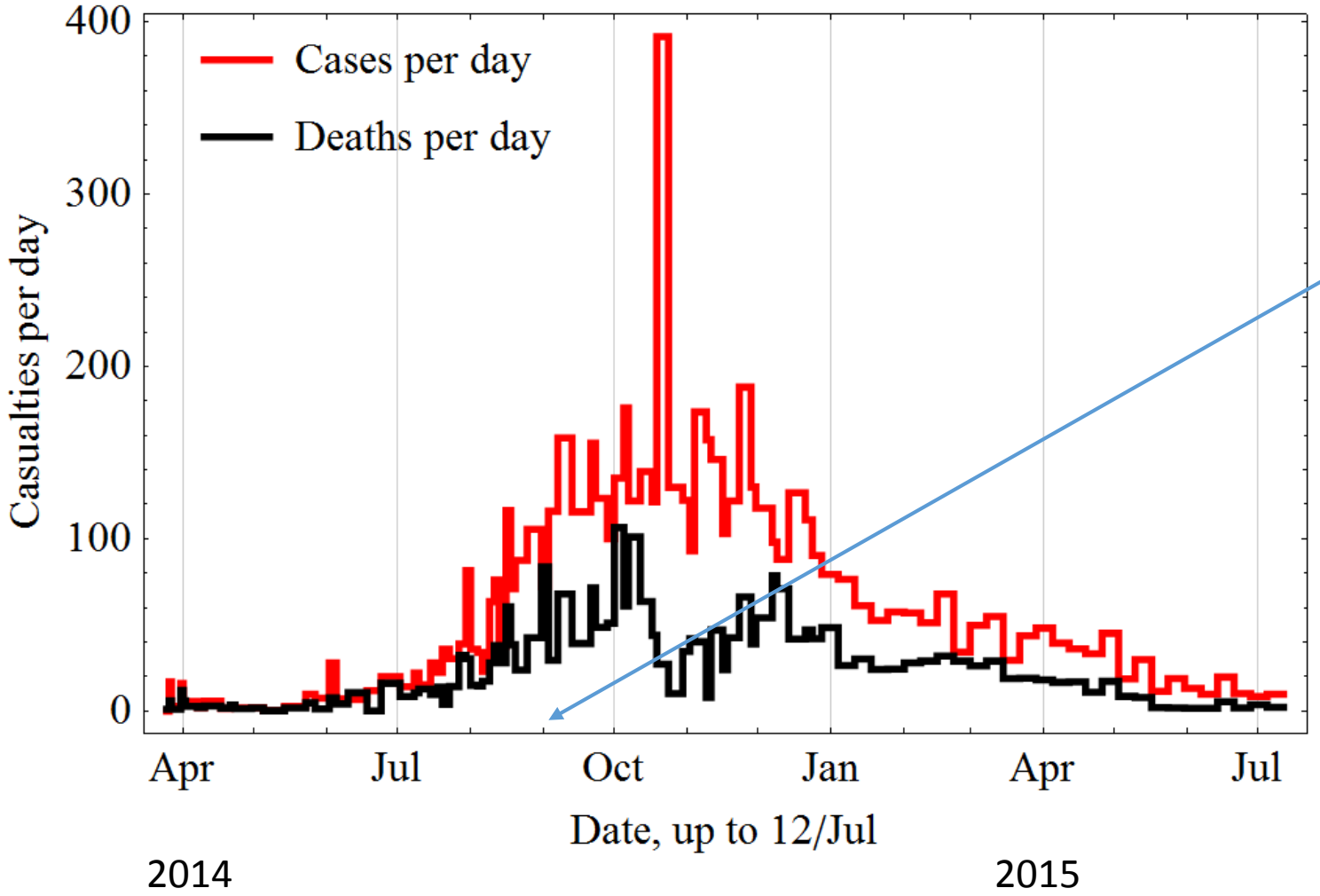


- Member of genus Filovirus, so-named for filament shape
- Like the other filovirus, Marburg virus, Ebola virus circulates in Africa causing outbreaks of hemorrhagic fever
- Fruit bats are the suspected reservoir

Ebola Virus Disease Outbreak in West Africa

Appears to have emerged in small town in southern Guinea, Guéckédou, near the border of Sierra Leone and Liberia, in December 2013,
N Engl J Med 2014; 371:1418-1425.

Ebola over time



Model predicts 1,4000,000 Cases by January 2015*

*If nothing changes

Ebola Vaccine Candidates

- ChAd3—replication incompetent Chimp adenovirus delivers outside (glycoprotein) of Ebola virus

  1 vector => 1 infected cell that alert immune system

  several weeks to develop robust immune response

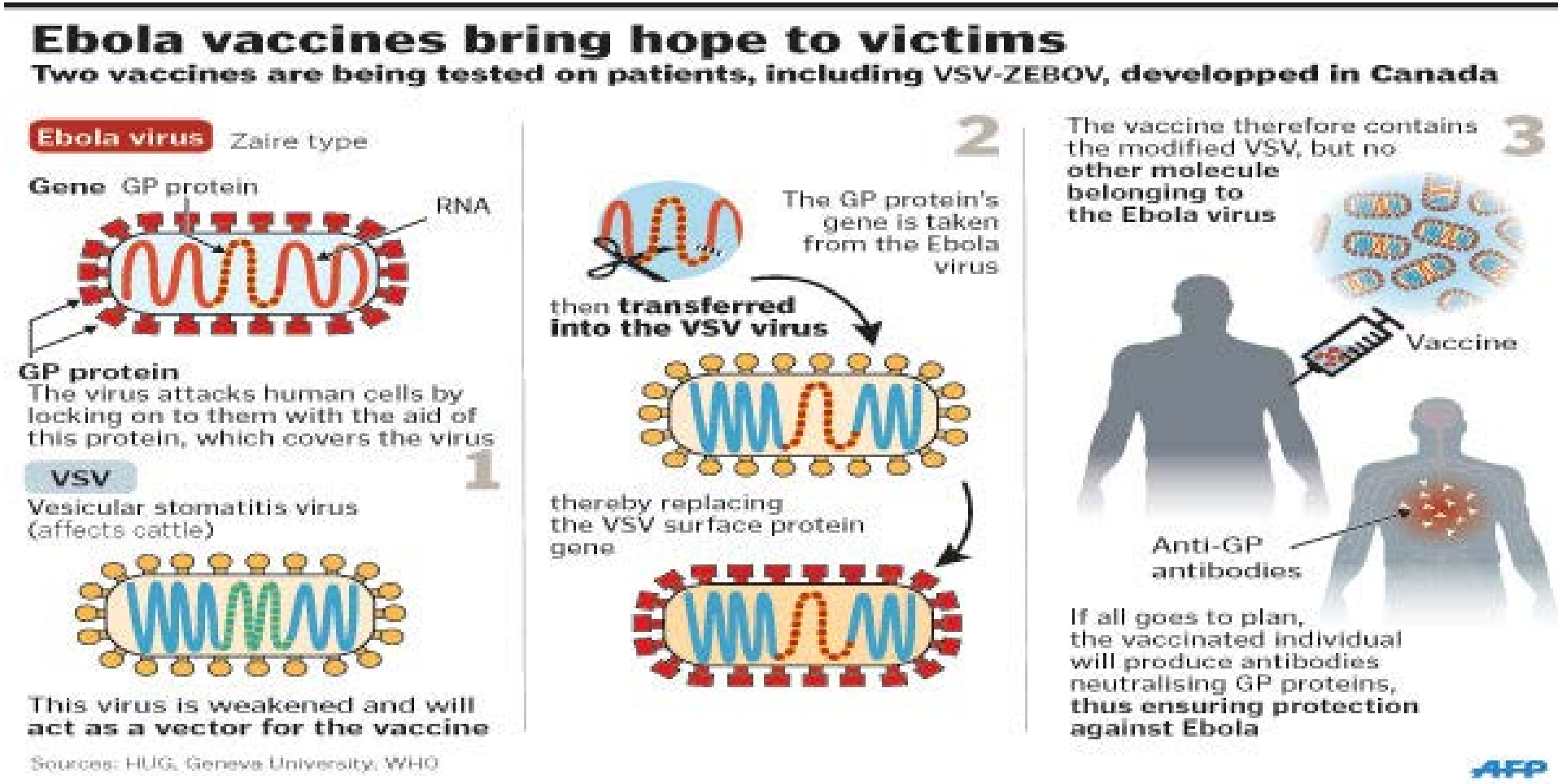
- VSV --- replication competent vesicular stomatitis virus (like rabies) modified to express ebola glycoprotein

  1 vector => multiple infected cells that alert immune system

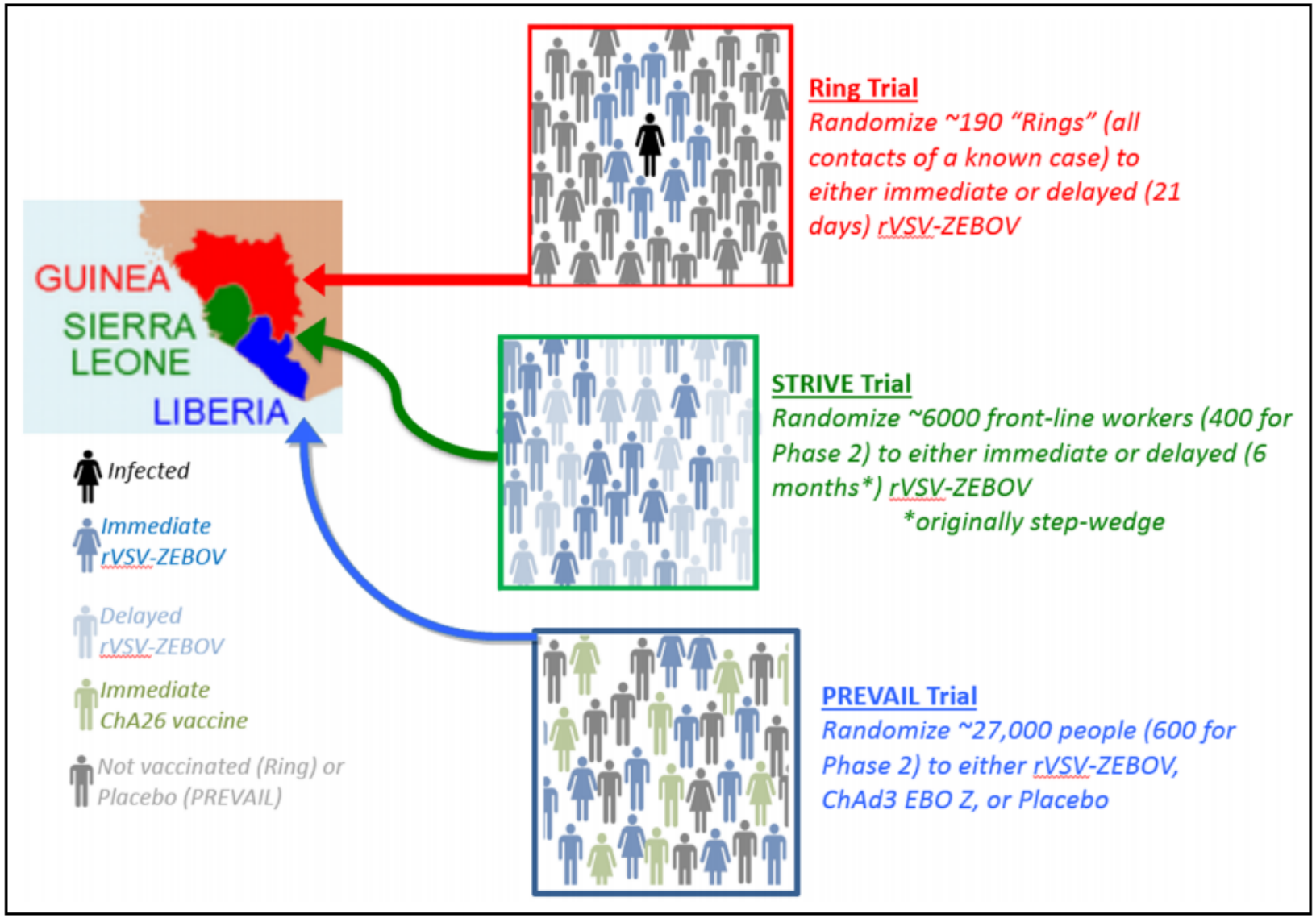
  rapid development of immune response

  NHP studies show some protection *after* challenge

VSV vaccine

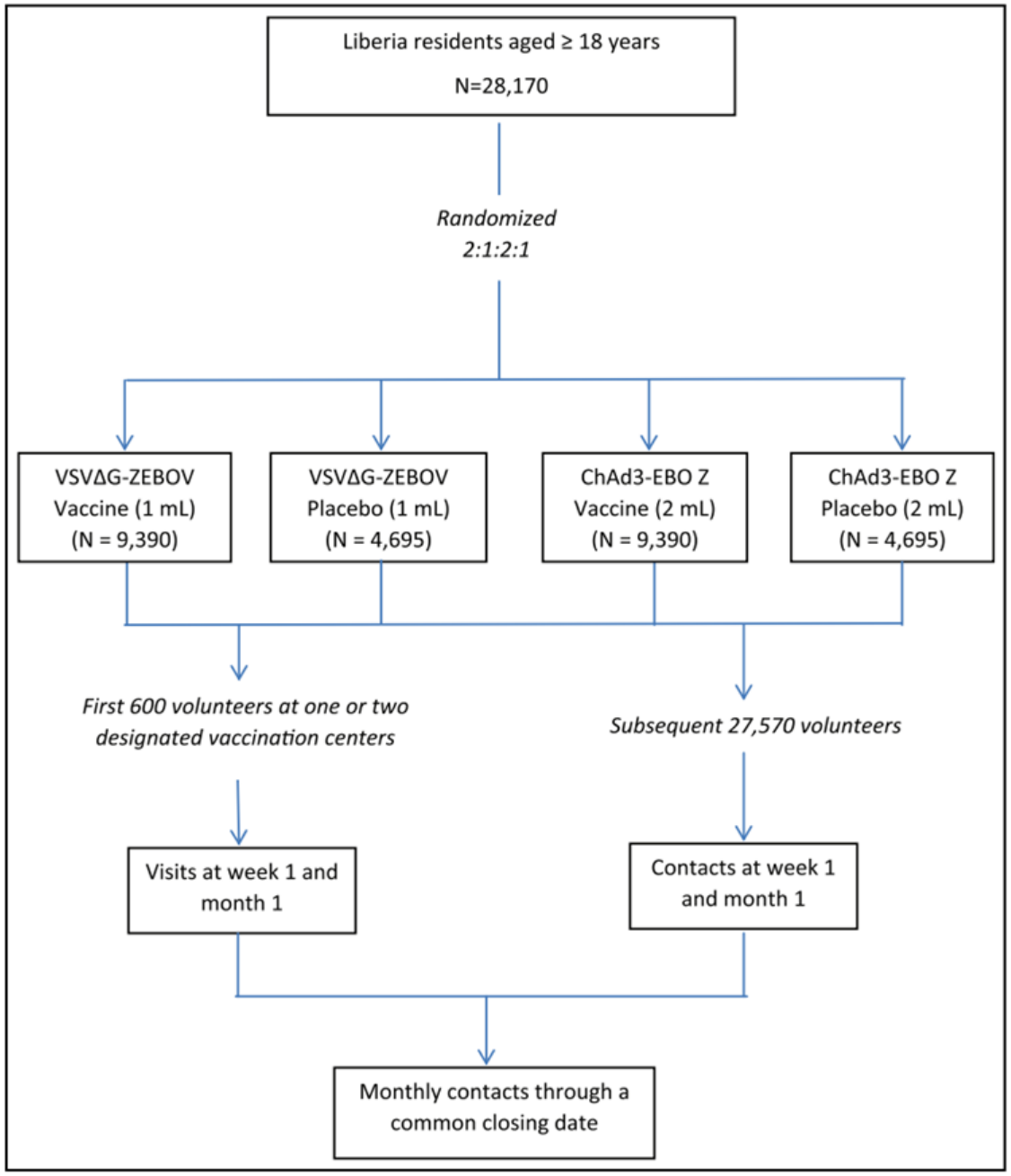

Ebola vaccines bring hope to victims
Two vaccines are being tested on patients, including VSV-ZEBOV, developped in Canada
Ebola virus
Zaire type
Gene
GP protein
RNA
GP protein
The virus attacks human cells by locking on to them with the aid of this protein, which covers the virus
1
VSV
Vesicular stomatitis virus
(affects cattle)
This virus is weakened and will act as a vector for the vaccine
2
The GP protein's gene is taken from the Ebola virus
then transferred into the VSV virus
thereby replacing the VSV surface protein gene
3
The vaccine therefore contains the modified VSV, but no other molecule belonging to the Ebola virus
Vaccine
Anti-GP antibodies
If all goes to plan, the vaccinated individual will produce antibodies neutralising GP proteins, thus ensuring protection against Ebola
Sources: HUG, Geneva University, WHO
AFP

TRIALS IN WEST AFRICA



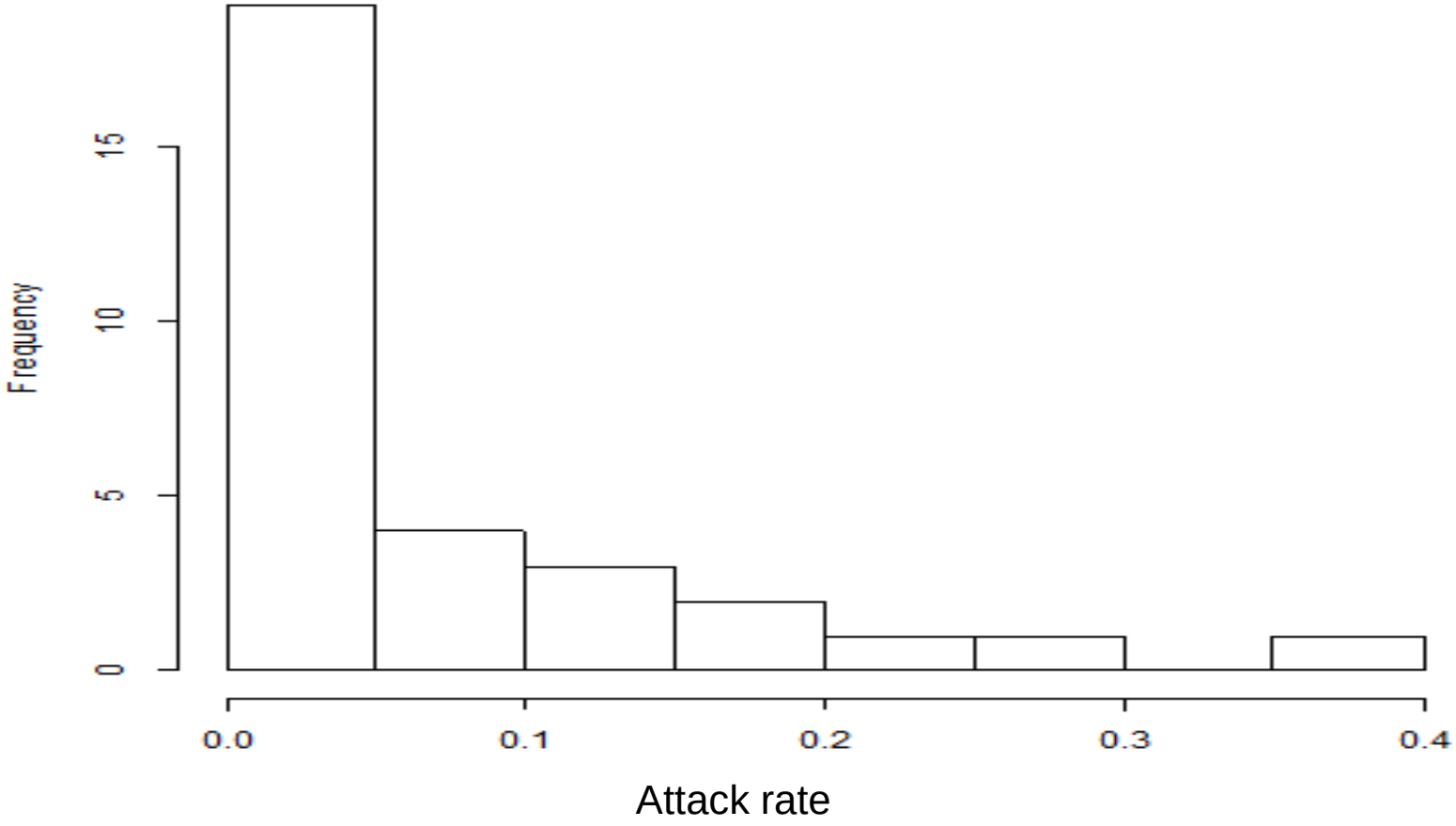
Prevail 1 Vaccine Trial

- Study stopped when epidemic in Liberia stopped
- Randomized around 2000 volunteers
- Effectively a blinded phase II study of safety and immunogenicity



Study design overview: organogram describing the recruitment of subjects and study design in PREVAIL I.

Clustering: Distribution of attack rates among known contacts of Ebola cases in Guinea



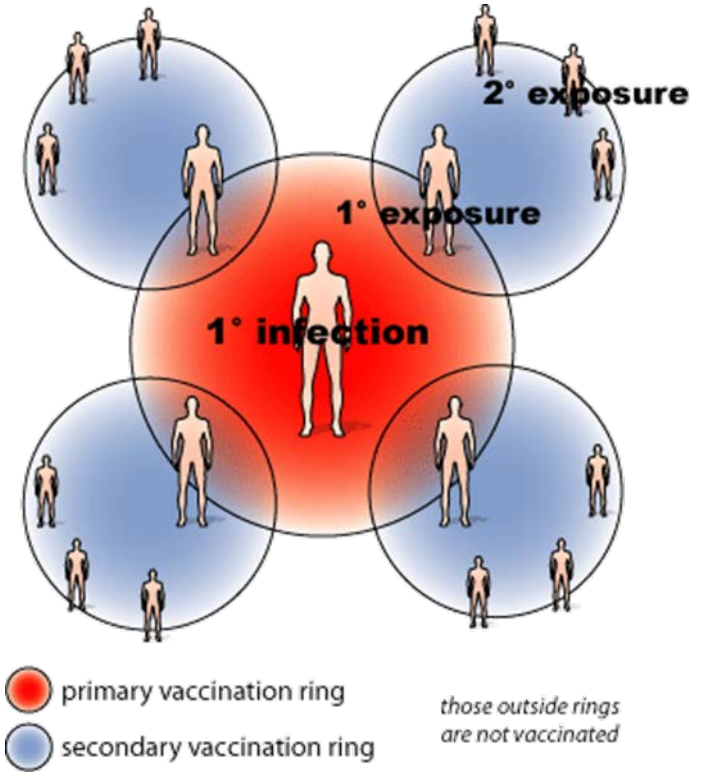
Median = 0.034, Mean = 0.065, Intraclass correlation = 0.065

*Source: WHO contact tracing teams in Guinea.

Ring Trial

- Ring vaccination was used to eradicate smallpox
  - Like a firewall which aborts further spread

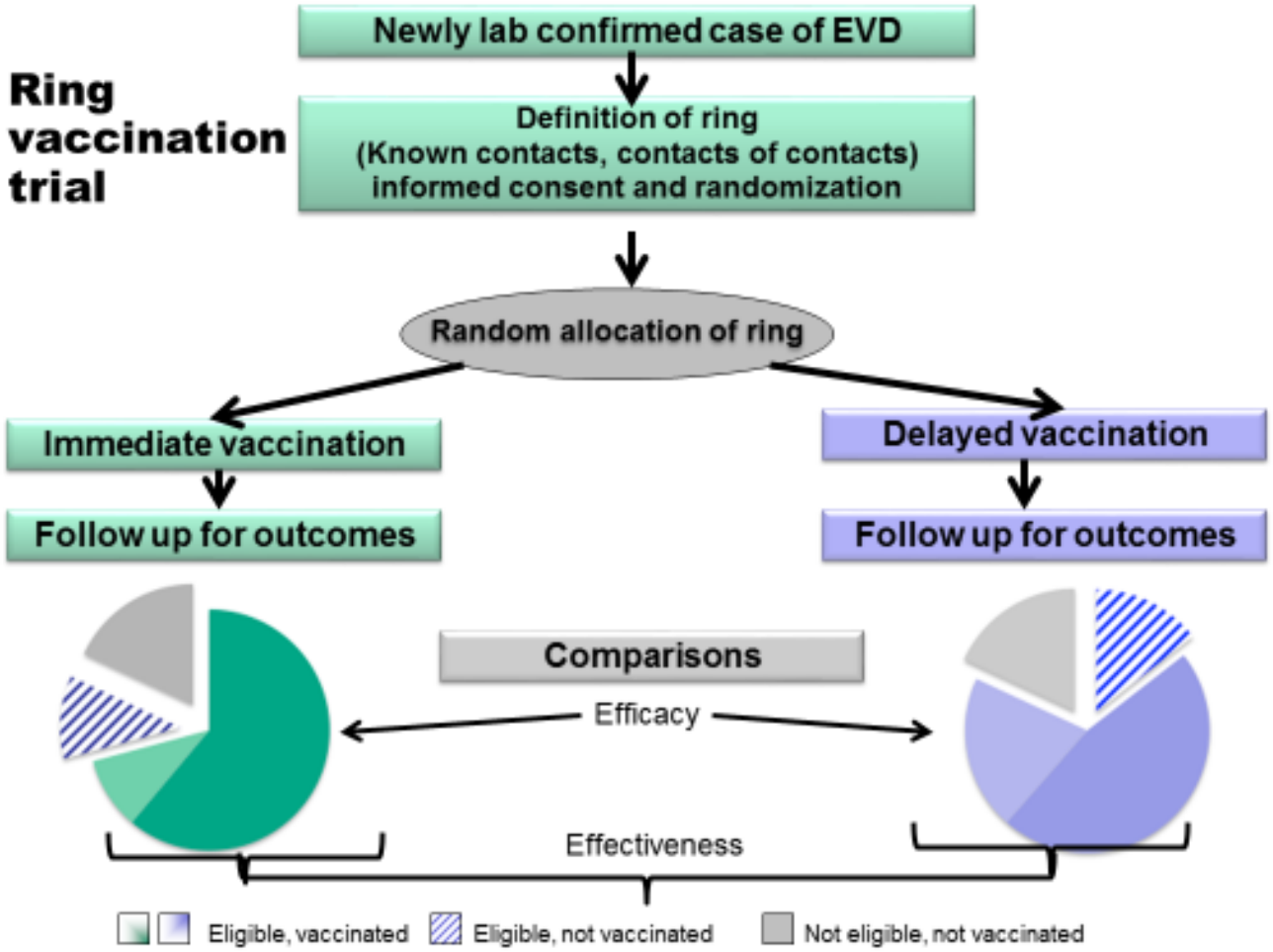
- WHO team proposed ring randomization
  - VSV – vaccine
  - Identify `rings' = contacts & contacts of contacts of Ebola cases
  - Randomize ring to immediate or 3 week delayed vaccination
  - (Cluster level randomization gets at direct + indirect effects of vaccination)



Design considerations

- For ring vaccination trial: Attack rate in rings is 1-2% with a lot of variation, Intra class correlation (ICC = 0.05)
- Need about 190 rings of size 50 to have 90% power to detect a VE of .70.
- Start counting events 10 days after randomization
  - Allows vaccine ramp-up
  - Avoids infections detected after randomization but caused before randomization
- Actual trial at interim analysis (half-way point): For the primary analysis, there where 4,394 people in the two arms, in 90 rings*

Ring strategy



Hazard function

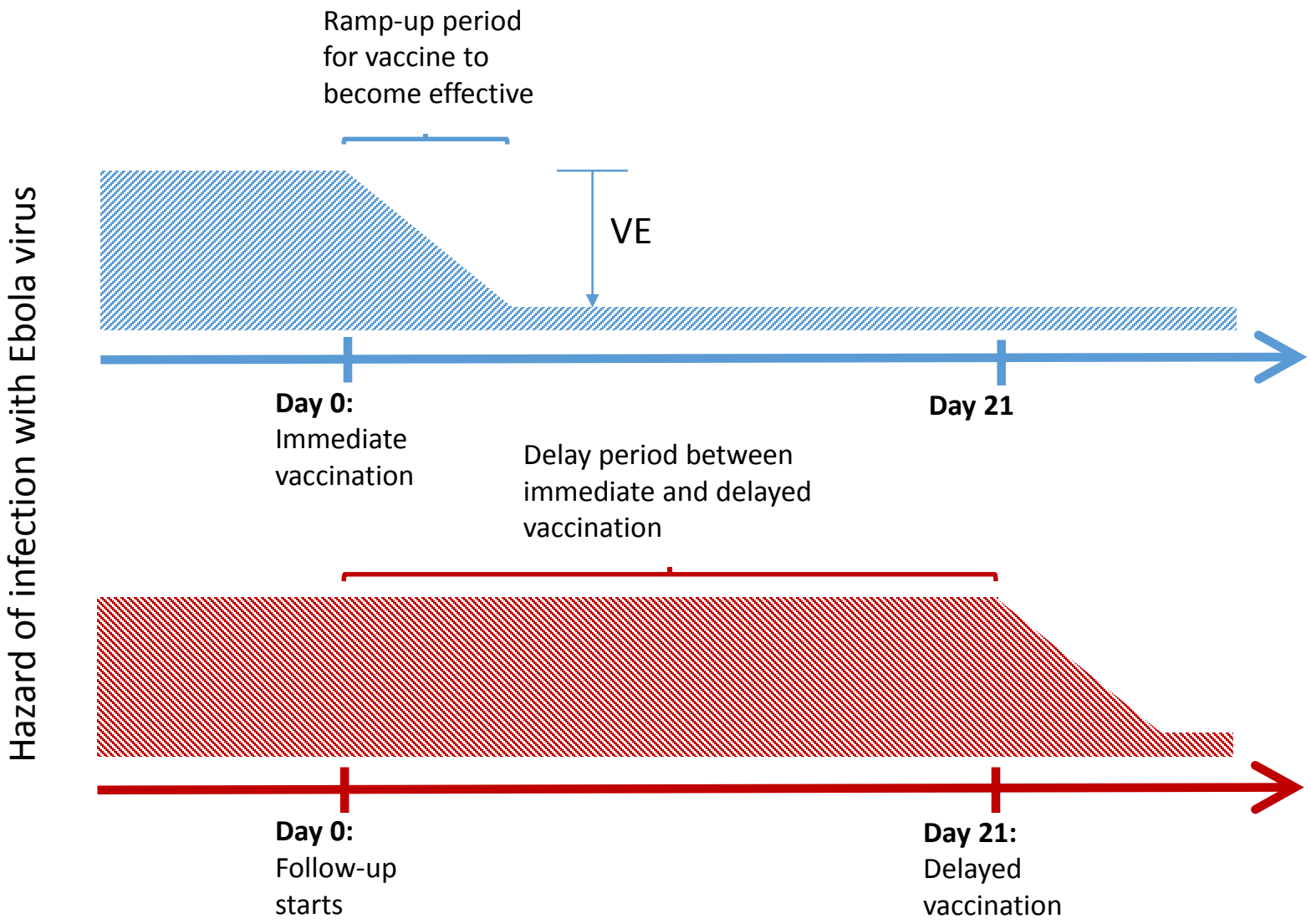
$$\lambda_{hvi}(t) = Z_h \, \lambda_0(t) \; Y_{hvi}(t) \, \theta^v \, e^{X_{hvi}(t)'\beta}$$

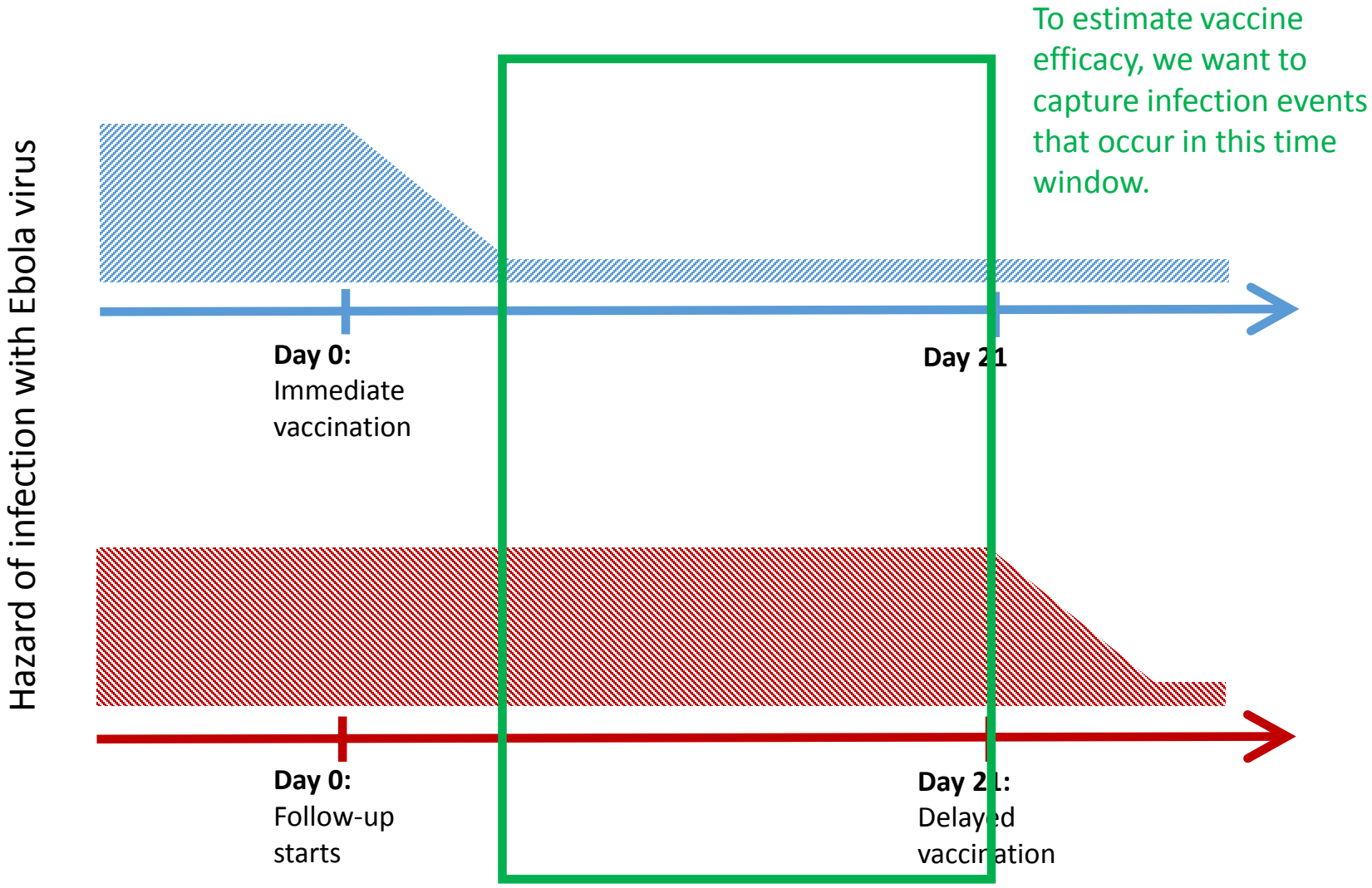
Random effect, E(Z_h) = 1

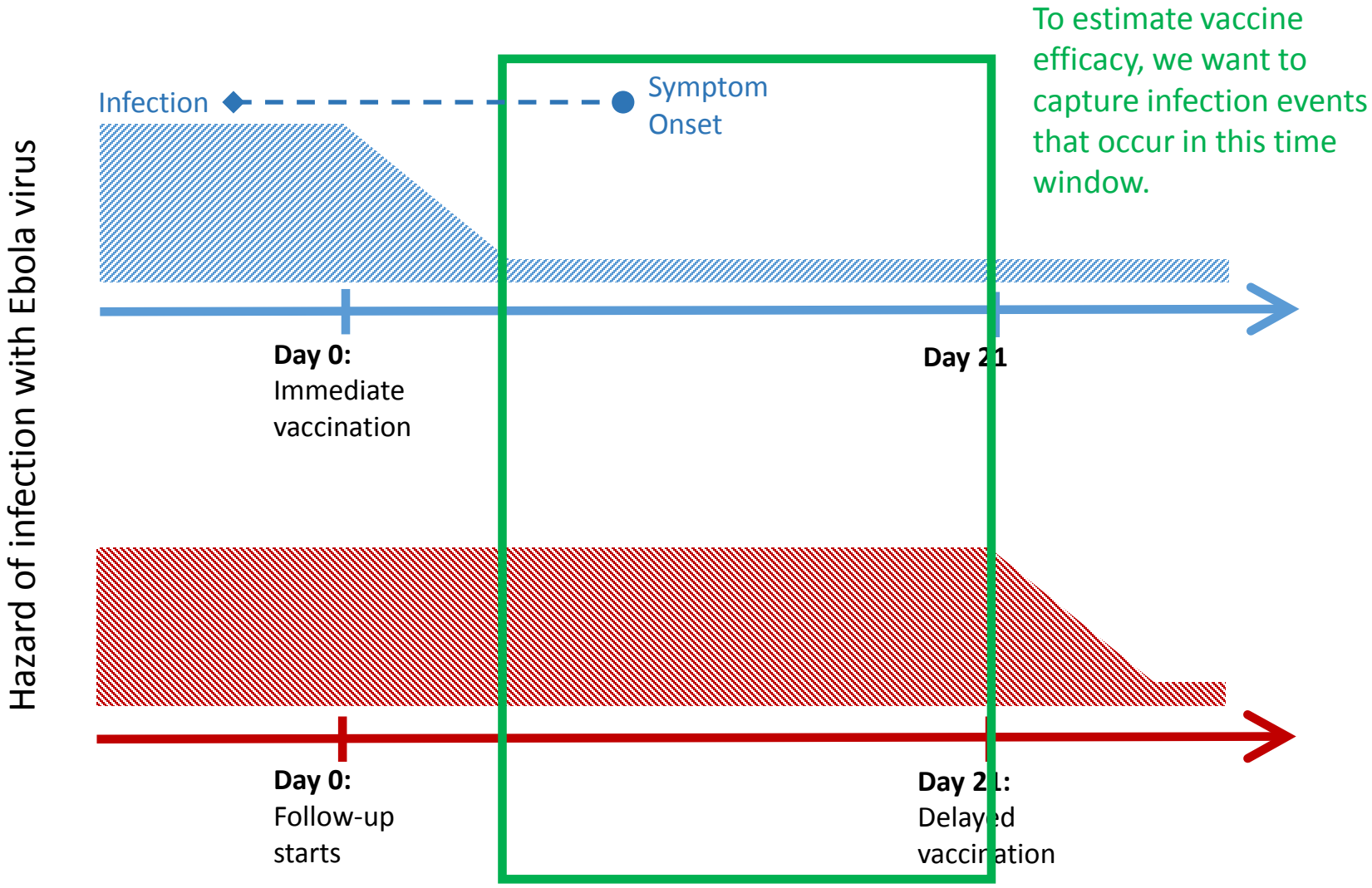
1 if past day 10
0 otherwise

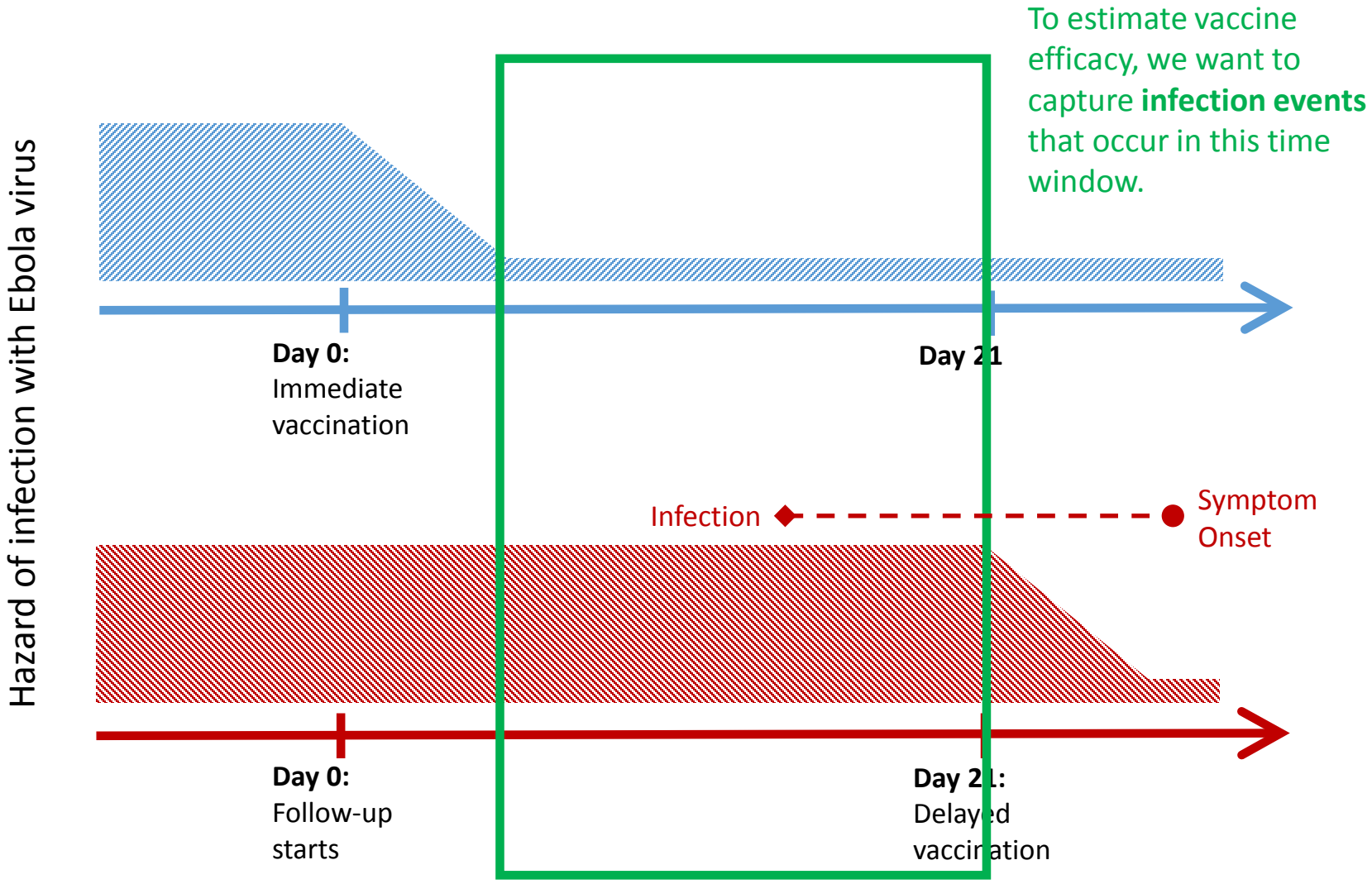
Proportional hazards model with random effect for cluster (frailty)

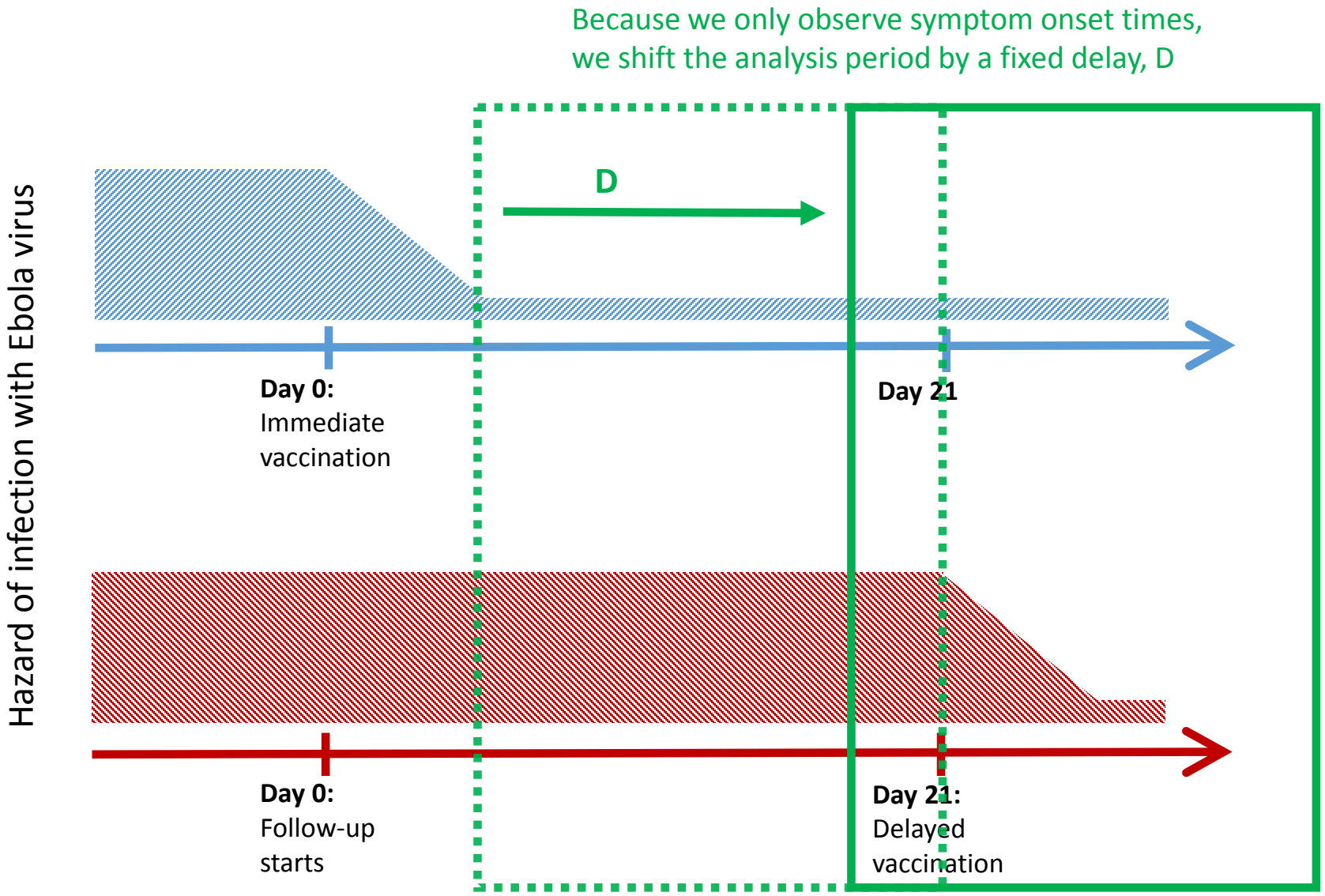
VE = 1 - θ

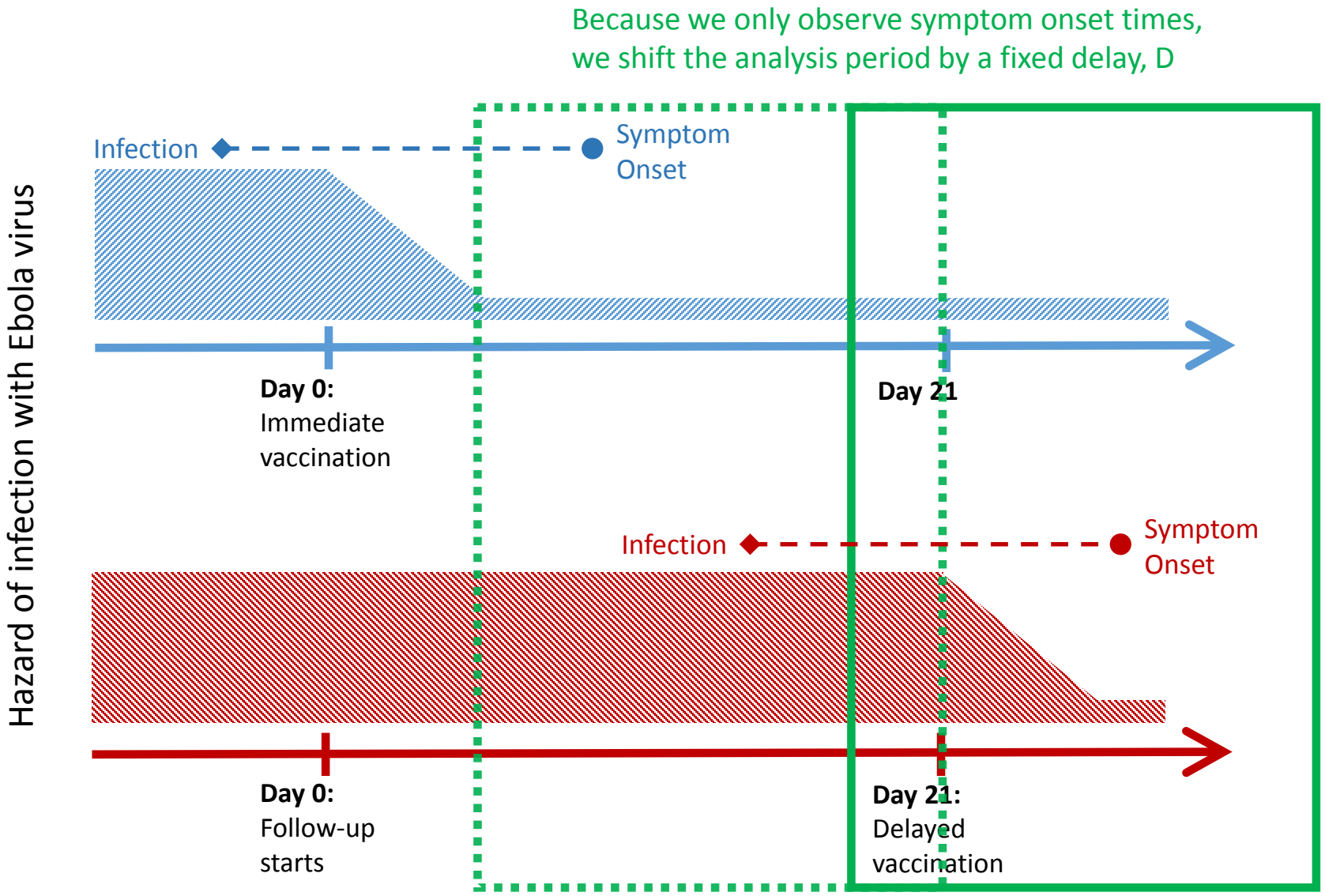

Ramp-up period
for vaccine to
become effective
VE
Hazard of infection with Ebola virus
Day 0:
Immediate
vaccination
Day 21
Delay period between
immediate and delayed
vaccination
Day 0:
Follow-up
starts
Day 21:
Delayed
vaccination


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


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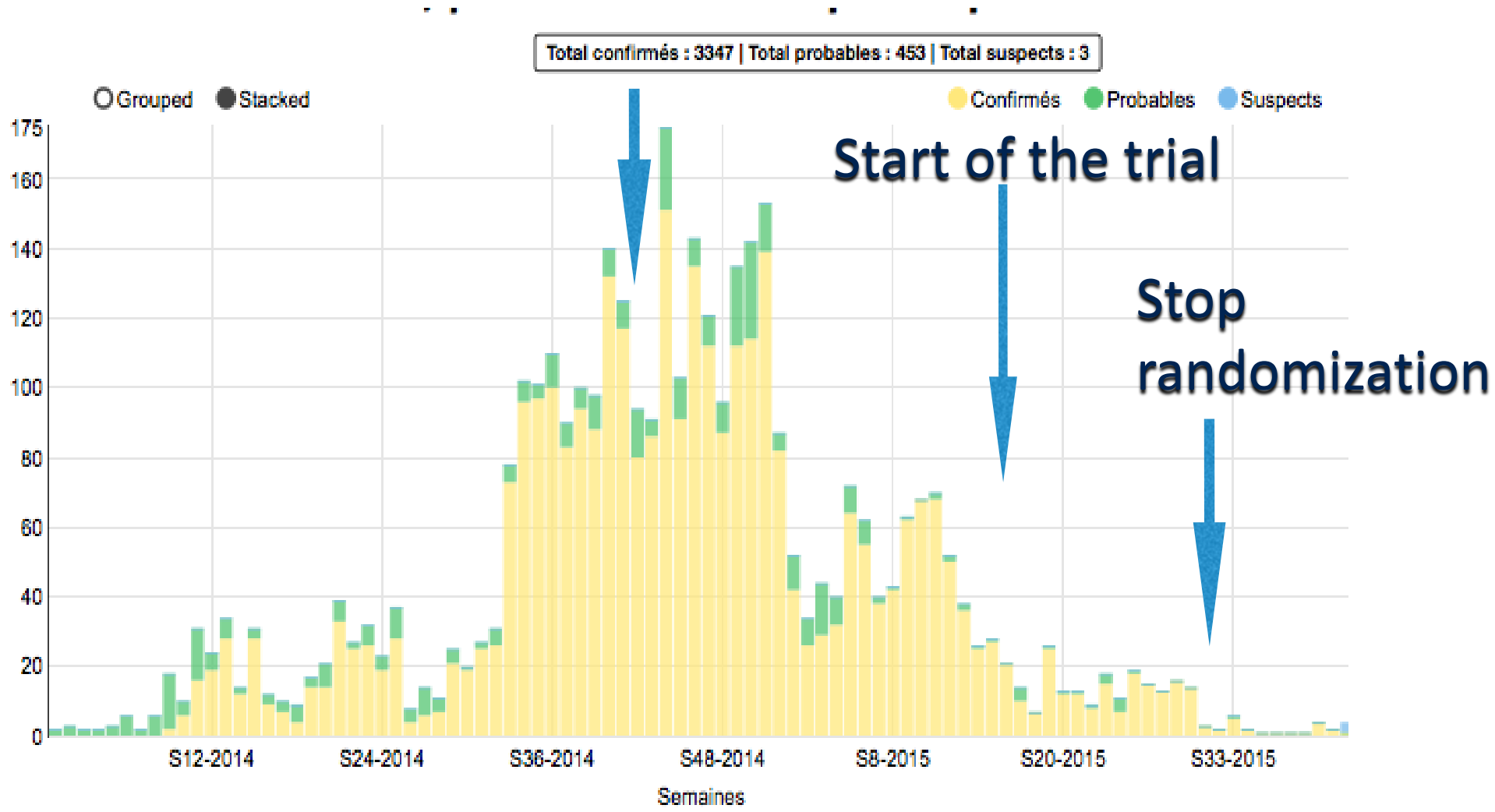
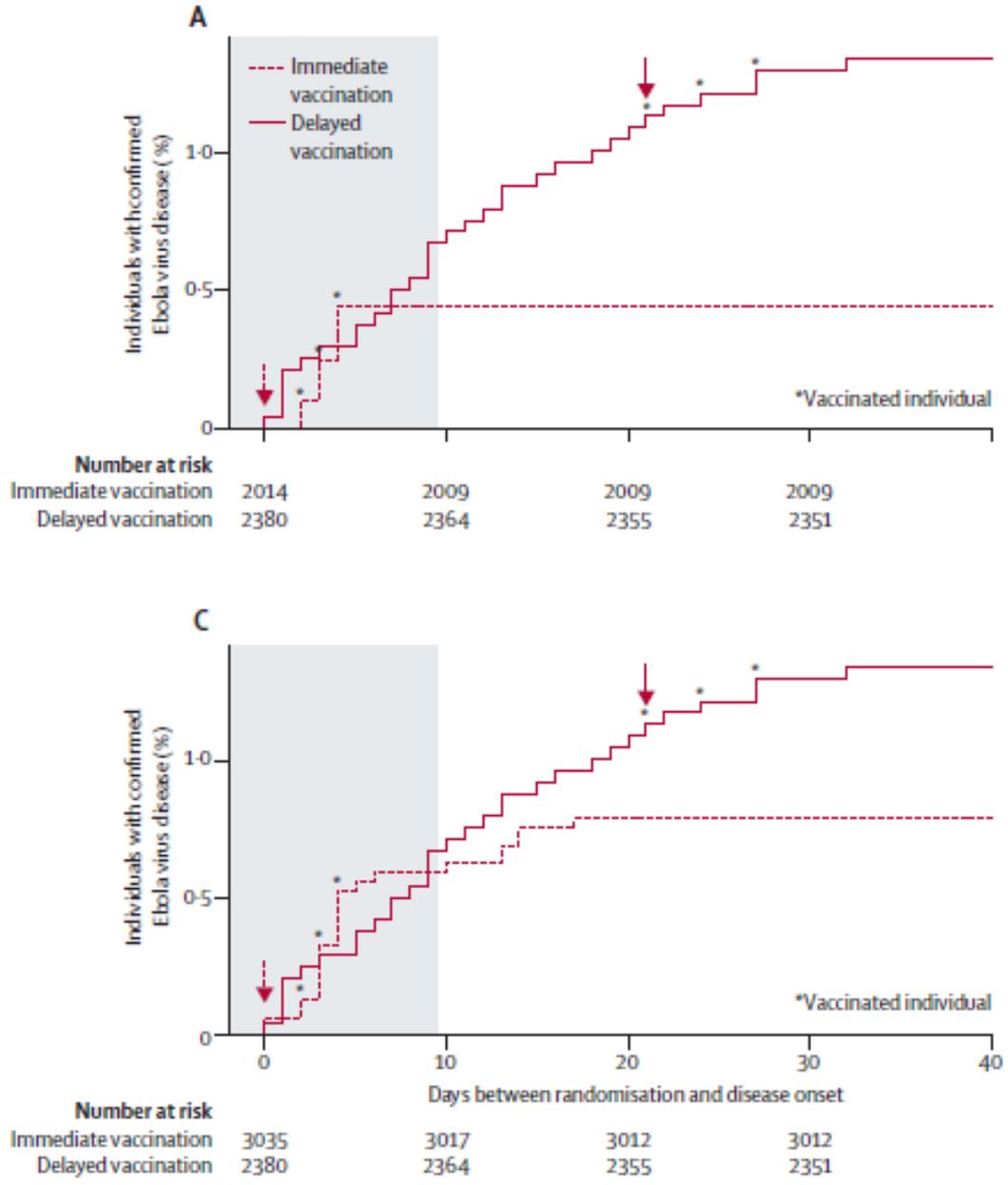
Hazard of infection with Ebola virus
Infection
Symptom Onset
Day 0:
Immediate vaccination
Day 21
Infection
Symptom Onset
Day 0:
Follow-up starts
Day 21:
Delayed vaccination

Cases of Ebola by week Guinea 2014-15



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**

* 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

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

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

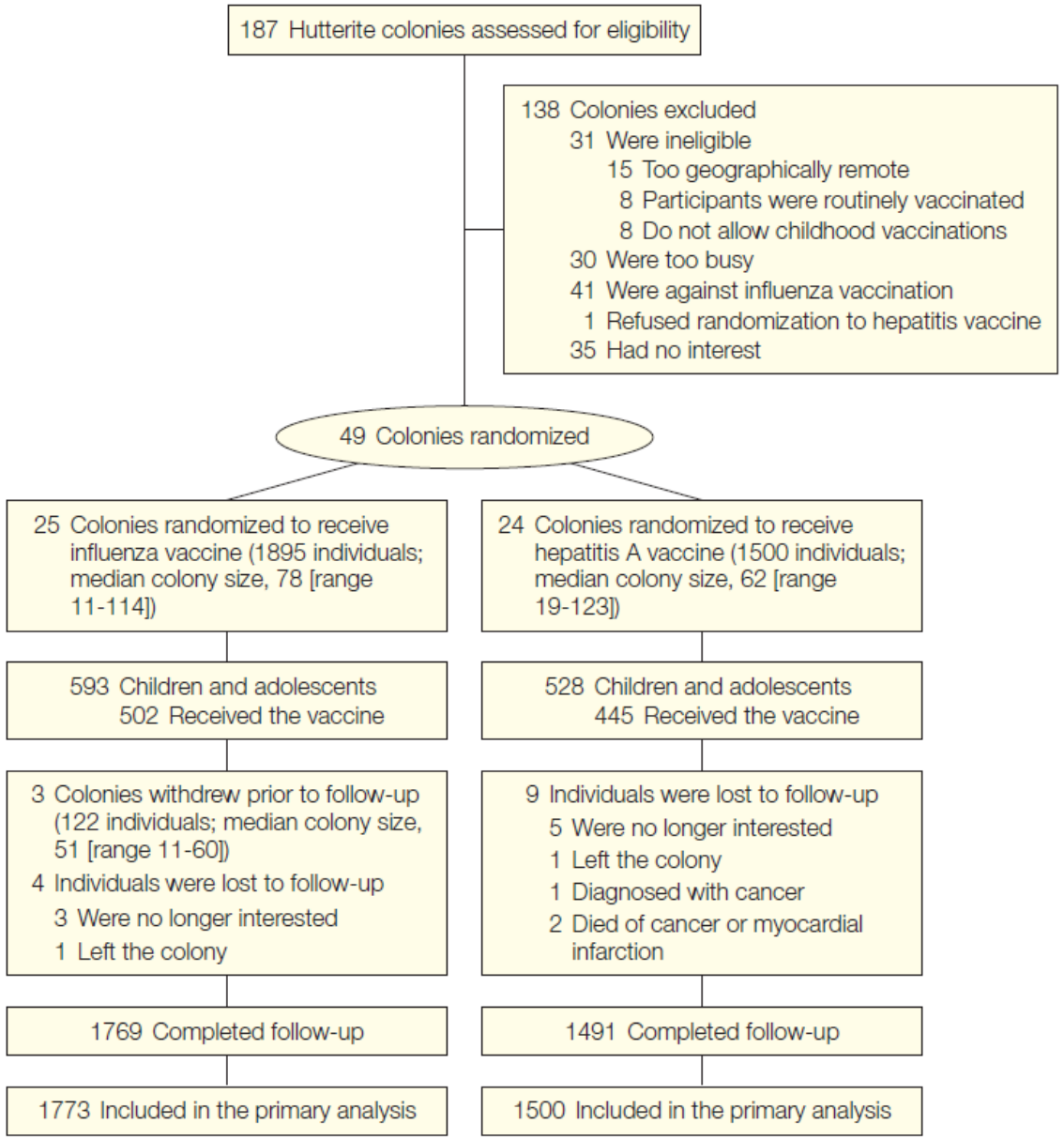
By Science News Staff | Dec. 17, 2015 , 2:30 PM

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

Acknowledgements

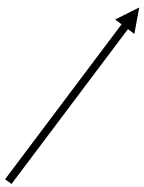
- Betz Halloran, Peter Gilbert, Michael Sachs, Erin Gabriel
- Dale Horne (FDA)
  - slides
- Ira Longini (UF)
  - Ring trial
  - Slides
- Michael Fay (NIH)
- Michael Proschan (NIH)

Figure 1. Flow Diagram of Trial



Hazard function

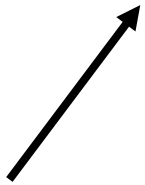
$$\lambda_{hvi}(t) = Z_h \, \lambda_0(t) \; Y_{hvi}(t) \, \theta^v \, e^{X_{hvi}(t)'\beta}$$



Random effect, E(Z_h) = 1

Hazard function

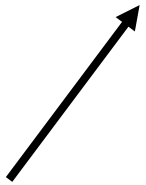
$$\lambda_{hvi}(t) = Z_h \, \lambda_0(t) \; Y_{hvi}(t) \, \theta^v \, e^{X_{hvi}(t)'\beta}$$



Hazard rate to comparison group

Hazard function

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

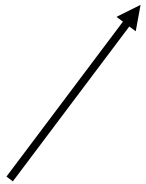


Participation indicator

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

Hazard function

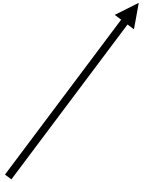
$$\lambda_{hvi}(t) = Z_h \, \lambda_0(t) \; Y_{hvi}(t) \, \theta^v \, e^{X_{hvi}(t)'\beta}$$



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

The test-negative design for estimating influenza vaccine effectiveness

Michael L. Jackson[a,*], Jennifer C. Nelson[a]

Influenza Vaccine Effectiveness in the 2011–2012 Season: Protection Against Each Circulating Virus and the Effect of Prior Vaccination on Estimates

Suzanne E. Ohmit,1 Mark G. Thompson,2 Joshua G. Petrie,1 Swathi N. Thaker,2 Michael L. Jackson,3 Edward A. Belongia,4 Richard K. Zimmerman,5 Manjusha Gaglani,7,8 Lois Lamerato,9 Sarah M. Spencer,2 Lisa Jackson,3 Jennifer K. Meece,4 Mary Patricia Nowalk,5 Jungbee Song,7,8 Marcus Zervos,9 Po-