

Vaccine Trial Designs

Dean Follmann

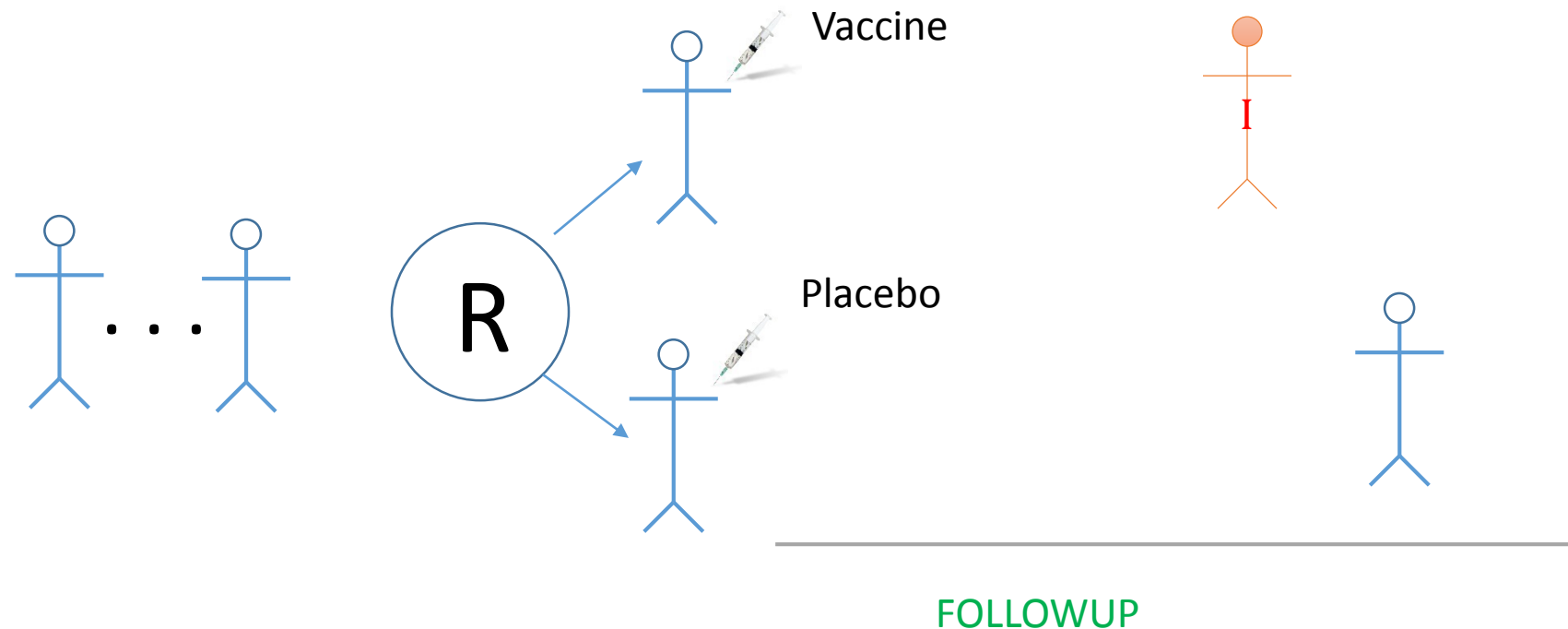
NIH

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 of influenza vaccine
 - 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

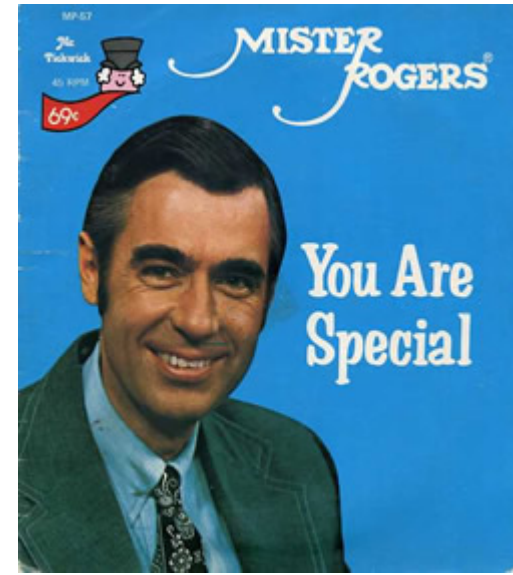
- Phase I: assess safety, immunogenicity $N \sim 20-30$
if promising proceed to
- Phase II: assess safety, immunogenicity $N \sim 100s$
if promising, proceed to
- Phase III: assess safety, immunogenicity, efficacy $N \sim 100s-1000s$
if successful, licensure

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 Guillain-Barre' syndrome
- Vaccination was suspended
- Rare events only detected with large studies

Guillain-Barré syndrome
Also called: GBS

ABOUT SYMPTOMS TREATMENTS

Damaged nerve cells cause ascending paralysis

Normal nerve cell

Damaged nerve cell

A condition in which the immune system attacks the nerves.

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 (true + rate) & high sensitivity (true – rate)
 - Low specificity dilutes VE (Lachenbruch 1998)
 - Low sensitivity reduces power (fewer events)
- 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

$$VE = 1 - (10/100)/(30/100) = 2/3 \text{ reduction in events}$$

Assessing VE: Conditional Binomial Method

- For low attack rate or unequal follow-up
- Assume $Y_v = \# \text{ disease on vaccine} \sim \text{Poisson}(N_v p_v)$
- Assume $Y_p = \# \text{ disease on placebo} \sim \text{Poisson}(N_p p_p)$
- $VE = (1 - p_v / p_p)$
 - If $N_p = N_v$
 $Y_v \mid Y_v + Y_p = M \sim \text{Binomial}(M, (1-VE)/(2-VE))$
- Unequal follow-up, replace N_z with total follow-up time in arm Z.
- Exact methods available based on binomial distribution

Assessing VE: Cox Regression

A model for the instantaneous risk of an event

$$h(t) = \omega(t) P(\text{event} | \text{exp}, Z=0) \quad \text{in placebo group}$$
$$h(t) = \omega(t) P(\text{event} | \text{exp}, Z=1) \quad \text{in vaccine group}$$

Risk of event

Risk of EXPOSURE
Same in both groups

Probability of infection, given exposure

The diagram consists of three blue arrows pointing upwards from labels to terms in the equations above. The first arrow points from 'Risk of event' to the $\omega(t)$ term in both equations. The second arrow points from 'Risk of EXPOSURE' to the 'exp' term in both equations. The third arrow points from 'Probability of infection, given exposure' to the $P(\text{event} | \text{exp}, Z=0)$ term in the placebo equation and the $P(\text{event} | \text{exp}, Z=1)$ term in the vaccine equation.

Cox Regression 2

$$h(t) = \omega(t) \underbrace{P(\text{event} \mid \text{exp}, Z=0)}_{h_0(t)} \exp\left\{ \log\left(\frac{P(\text{event} \mid \text{exp}, Z=0)}{P(\text{event} \mid \text{exp}, Z=1)} \right) Z \right\}$$
$$= h_0(t) \exp\{\beta Z\}$$

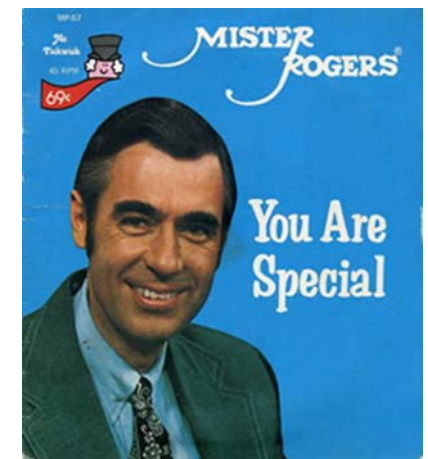
... $\exp(\beta)$ is the *per-exposure* reduction in the risk of event

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
- Lower bounds of .20 for Zika, .25 for HIV



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 under old and new manufacturing processes

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 of immune response

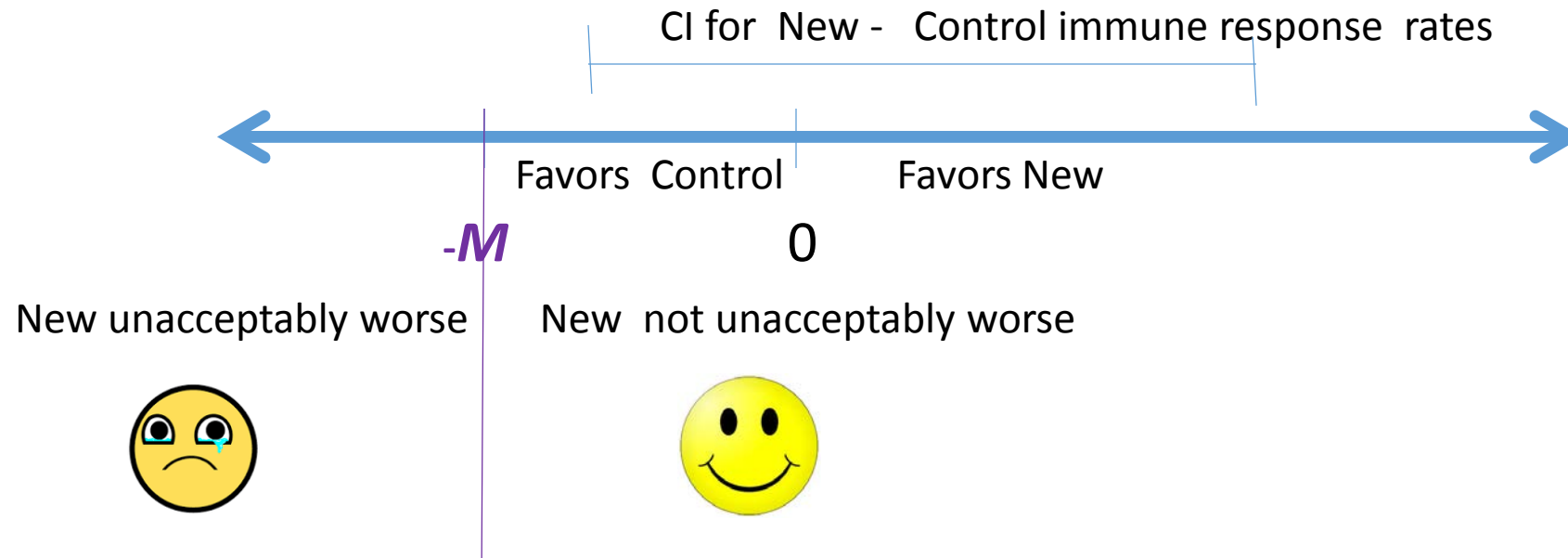
$$H_{\text{Null}}: P_{\text{New}} - P_{\text{Control}} \leq -0.10$$

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

where 0.10, the margin, represents the acceptable drop in the response rate 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*



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.



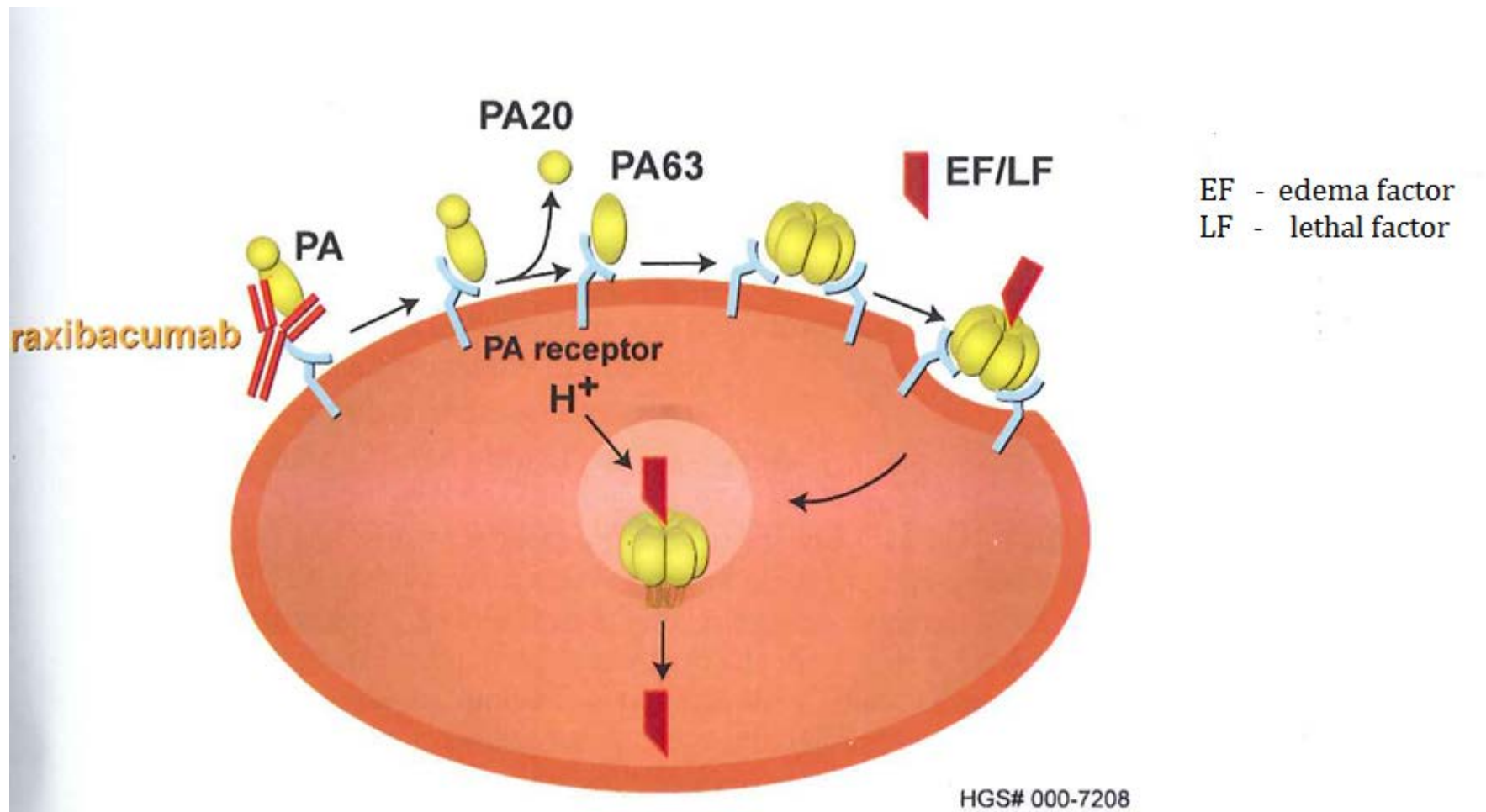


Figure 1-1

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

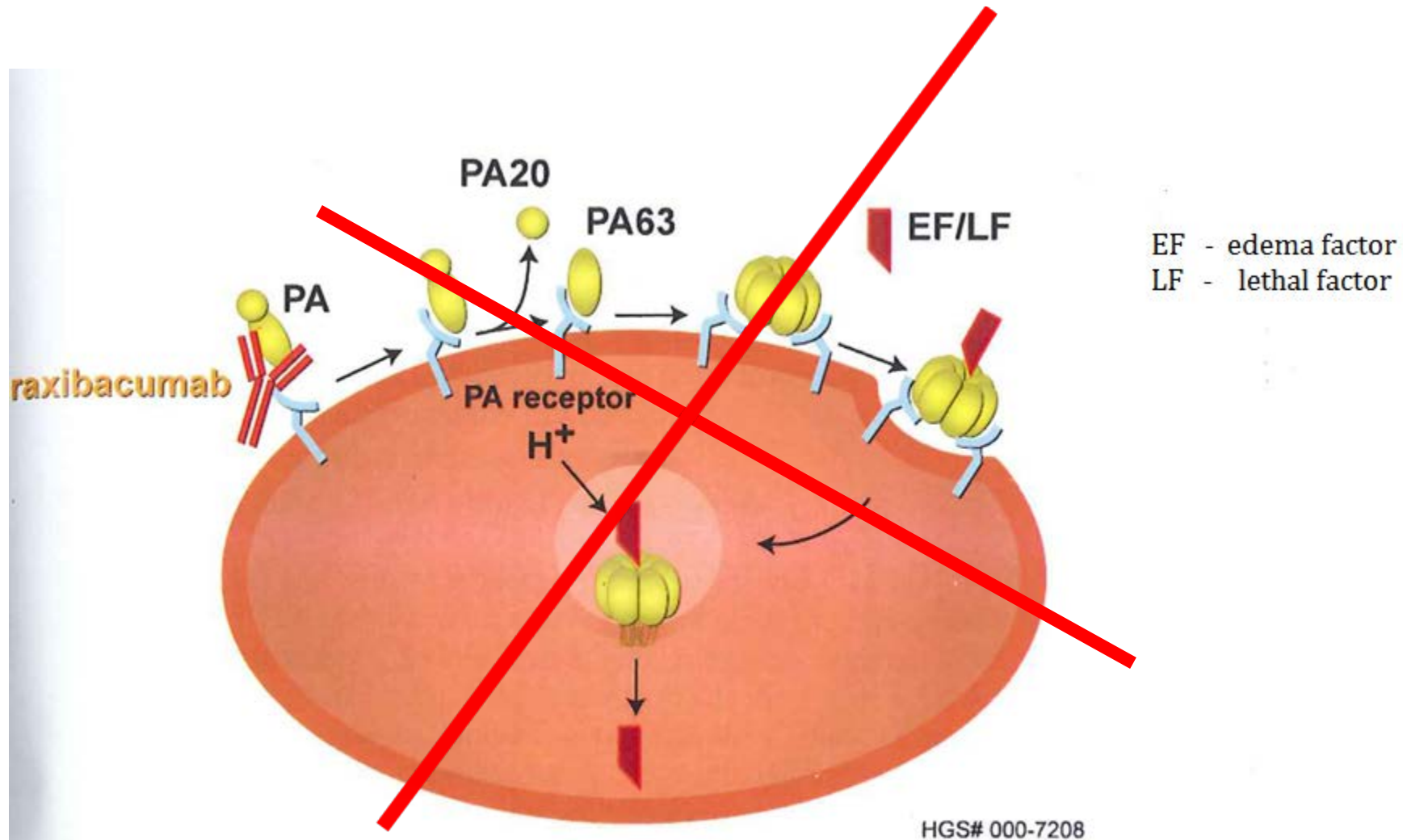
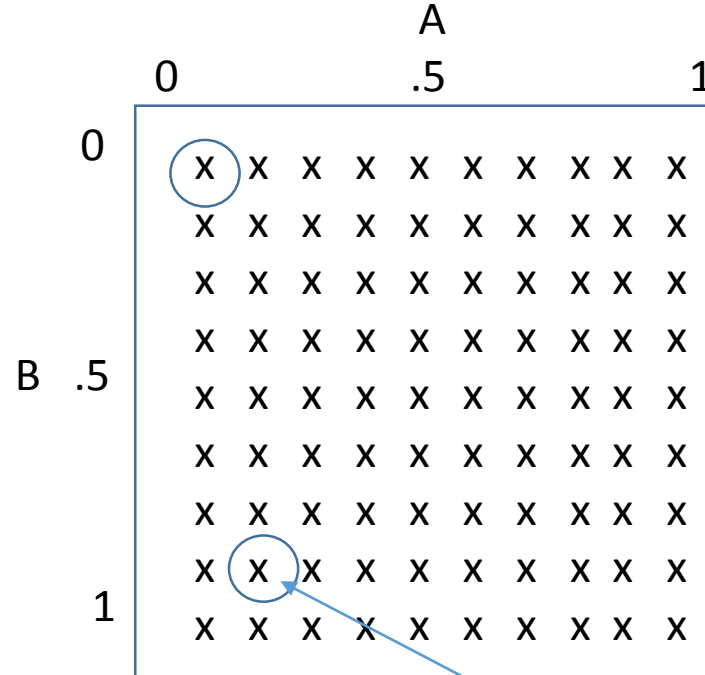


Figure 1-1

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'



$Y(.1,.9)$ yield when given $A=.1, B=.9$

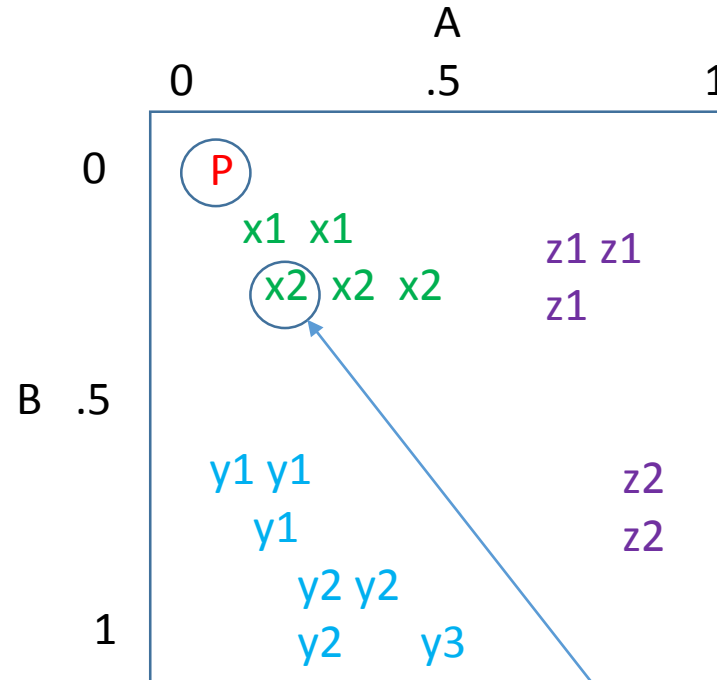
$$\Delta = \overline{Y(.1,.9)} - \overline{Y(0,0)}$$

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

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

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

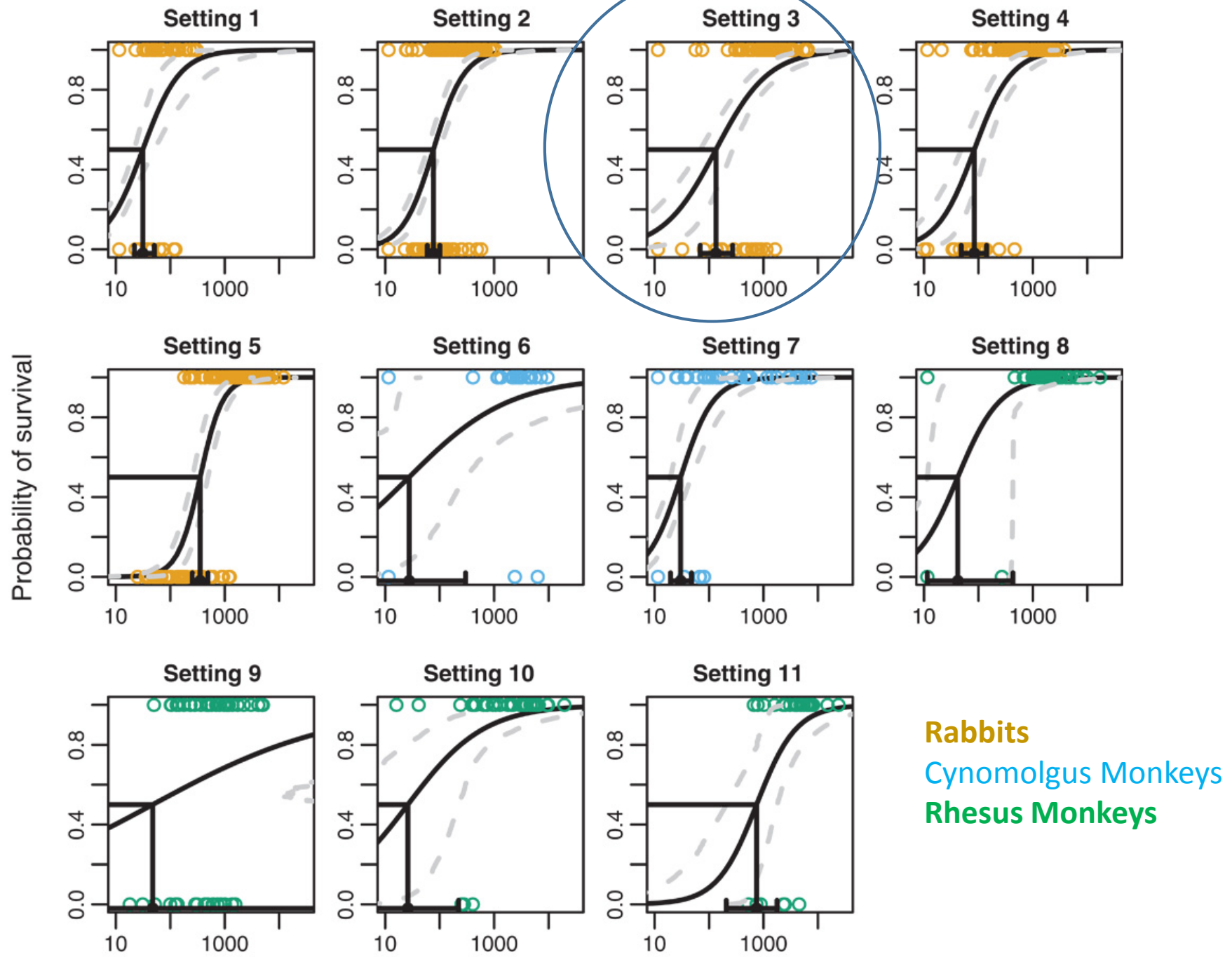
$Y(.1,.9)$ attack rate
in those who achieved $A=.1, B=.9$

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

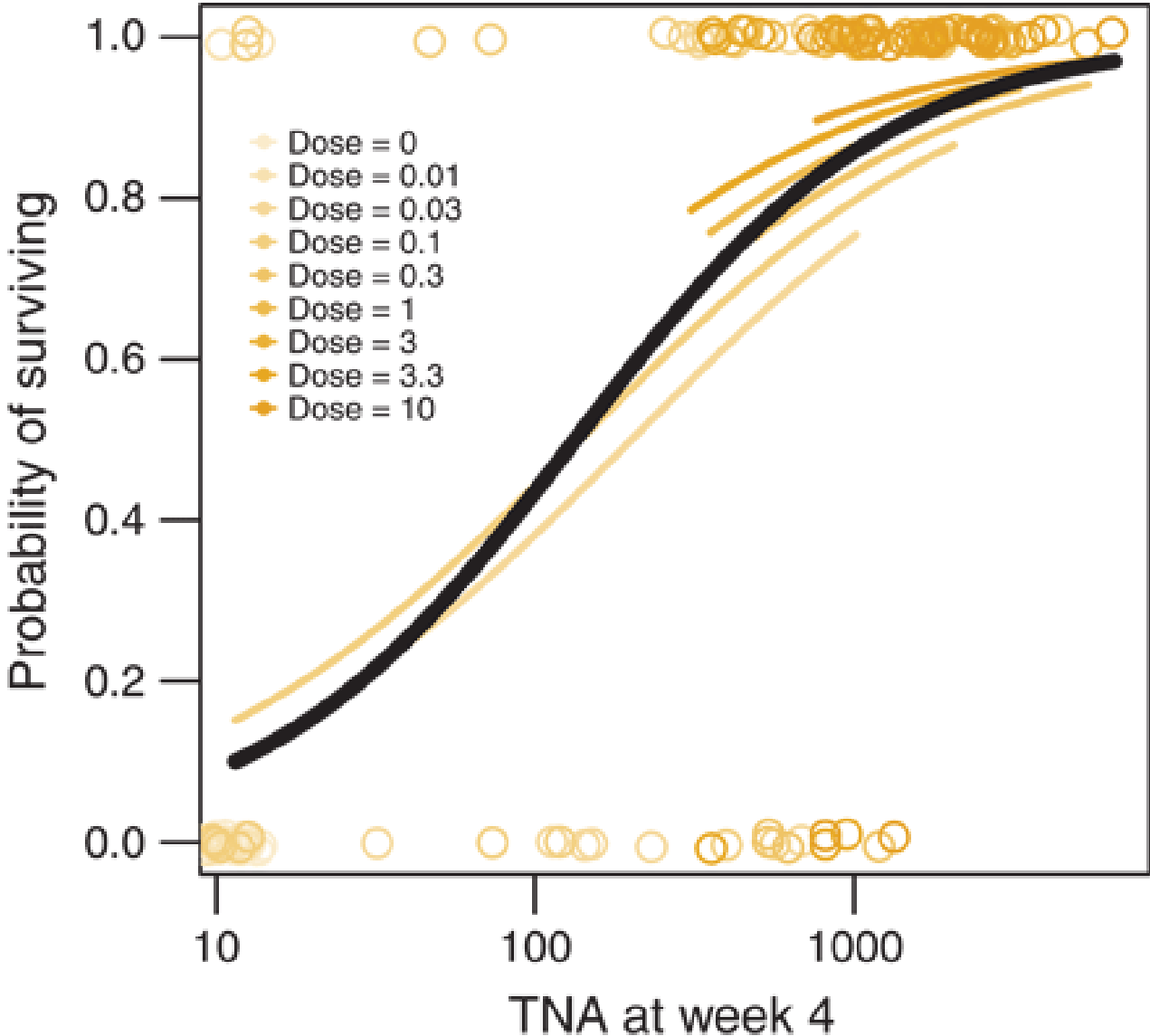
Δ Not necessarily the effect of $(A,B) = (.3,.3)$ relative to $(0,0)$

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 $A,B=.3,.3$



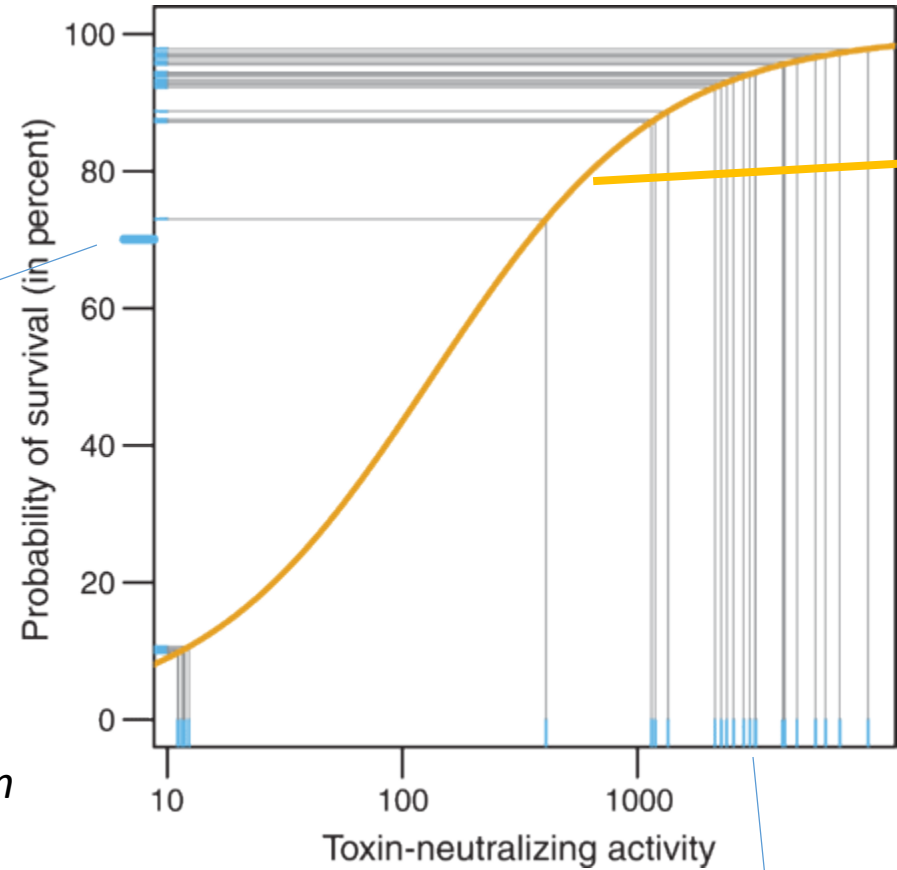
Setting 3: Little improvement in fit with dose in model supports Prentice criterion for surrogacy



From Rabbit to Monkey

Averaged
Predicted
Monkey Survival
Probability
70.1 (55.1,83.5)

*Observed Monkey
Survival Proportion*
75.9 (56.5, 89.7)



Rabbit Curve

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%

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

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

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

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

- Requires
 - Non-flu causes of ARI same for vaccinees/non-vaccinees
 - *But* elderly may have more non-flu ARI and get vaccinated more
 - VE does not vary with health seeking behavior
 - *But* VE may be worse for hypochondriacs



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 ----- 56% VE
 - Vaccinated in 2010-11 ----- 45% VE

| | 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 | |

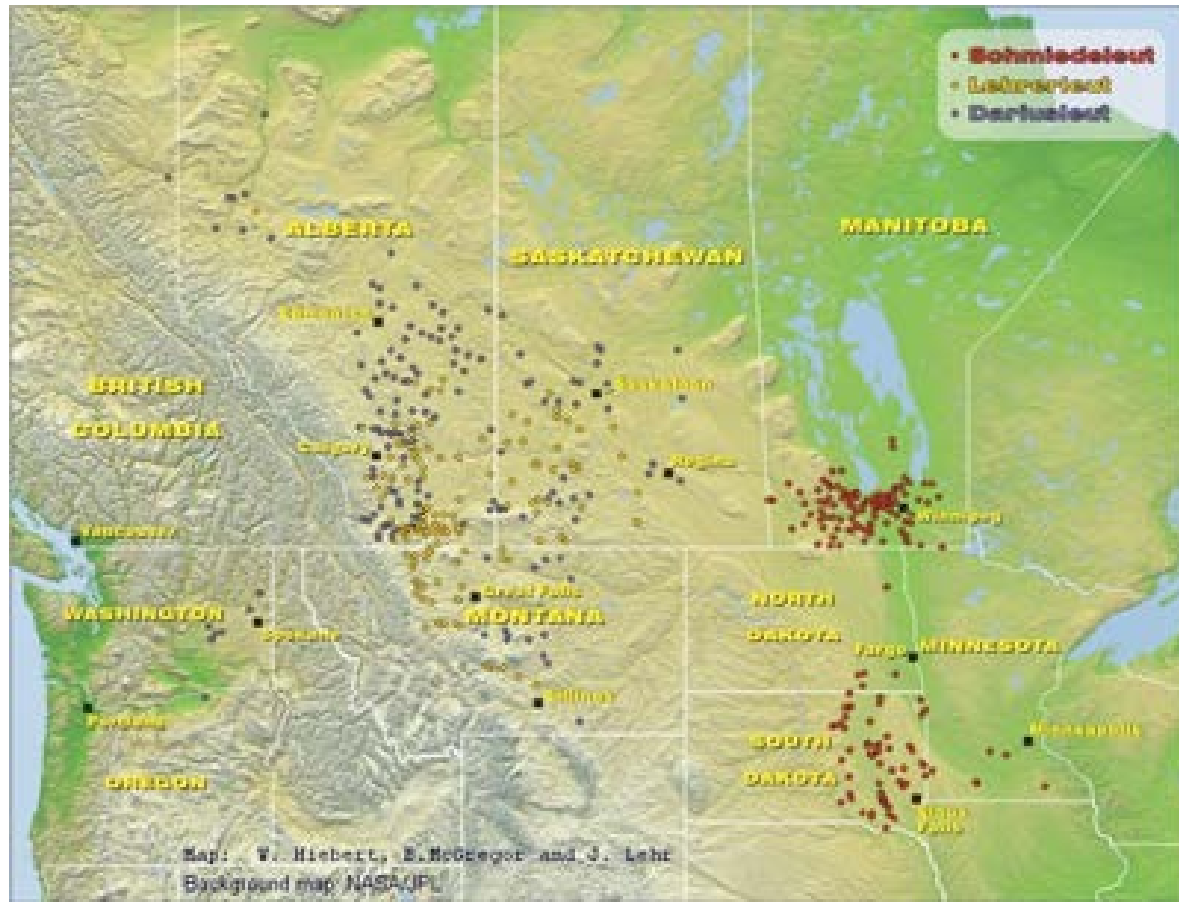
Cluster Randomized Vaccine Trials

- 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*)

Sir Roland Ross wrote about dependent happenings 1916



Hutterites



Hutterite Colonies in North America



One Hutterite colony

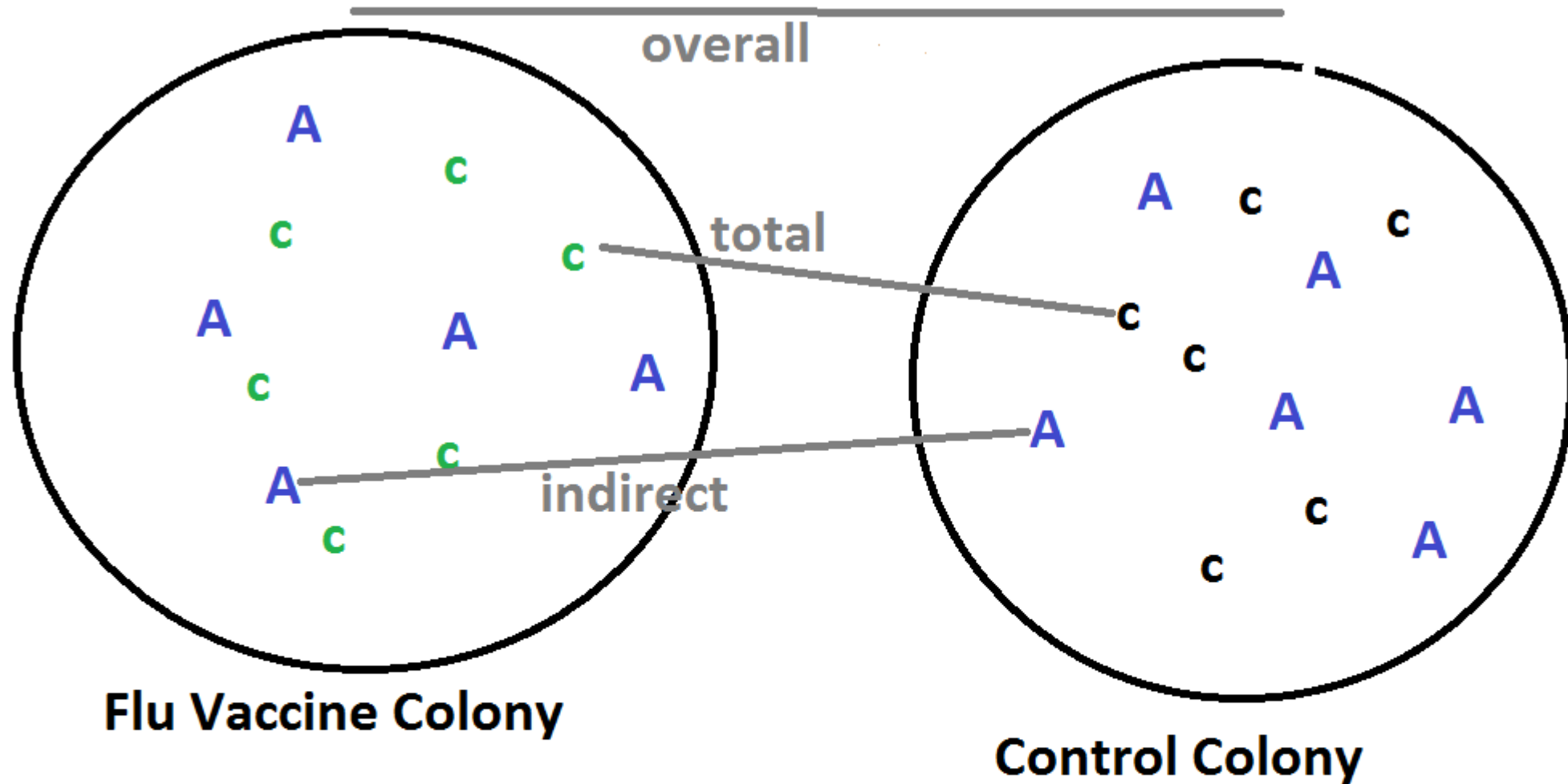


Hutterite Colony Trial

- 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



Flu Vaccine Colony

Control Colony

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 | |

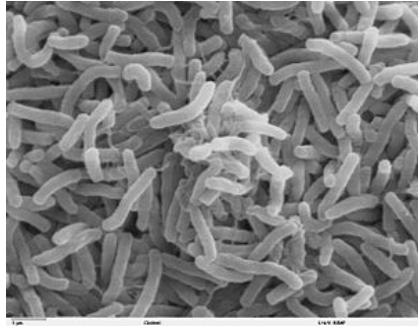
*VE estimated using a Cox Regression model with a sandwich estimate of variance

^VE estimated using 1 – ratio of infection rates

Human Challenge Studies

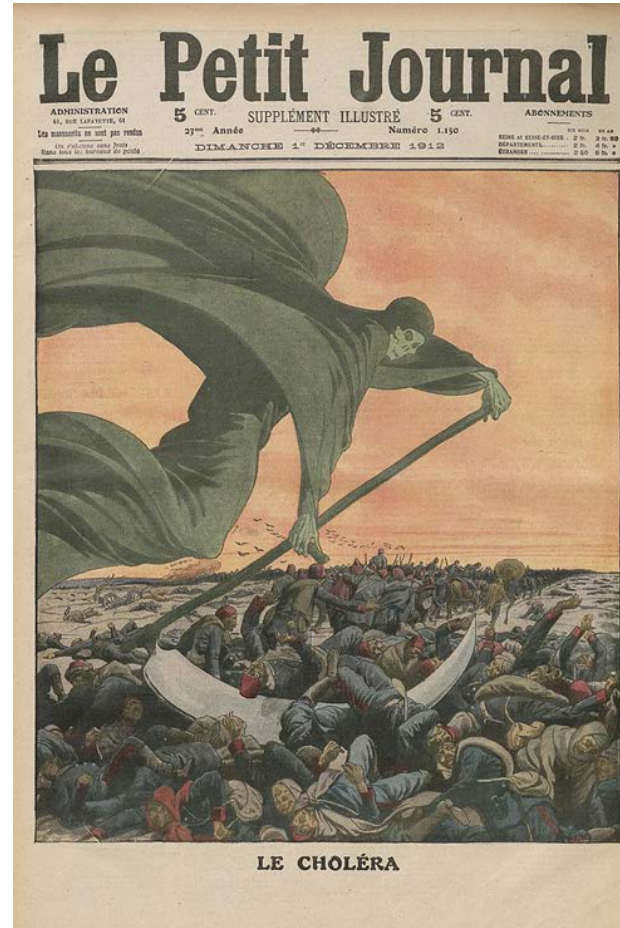
- Challenge a euphemism for giving enough germs to almost certainly cause infection in humans.
- Seem unethical but can be used if disease is controllable
 - Malaria parasites can be cleared by drugs
 - Can 'challenge' with a weakened pathogen (e.g. influenza, RSV)
 - Zika, probably not
- All proposed 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



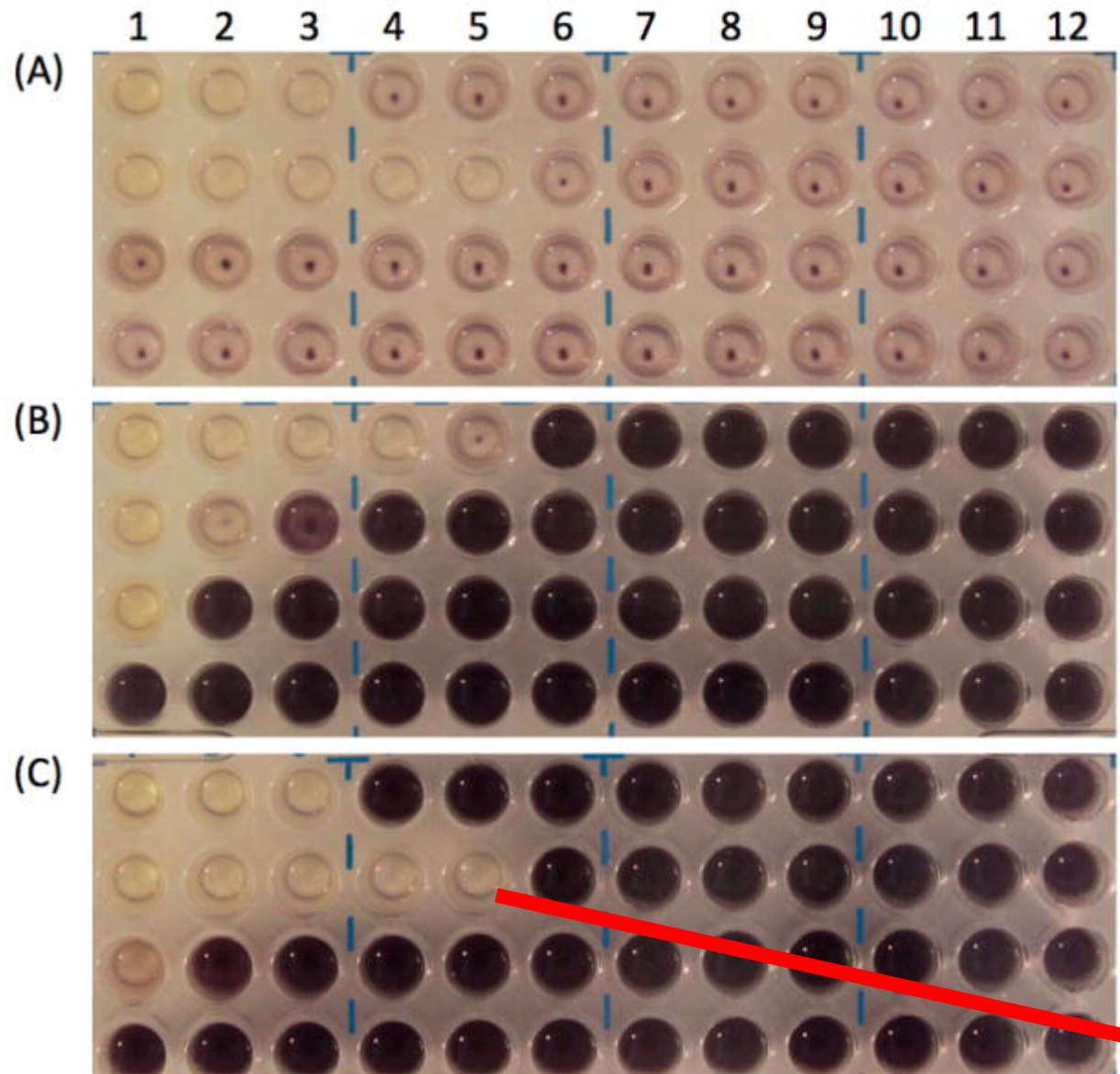
Human Challenge Trial for Cholera Vaccine

- 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% | |



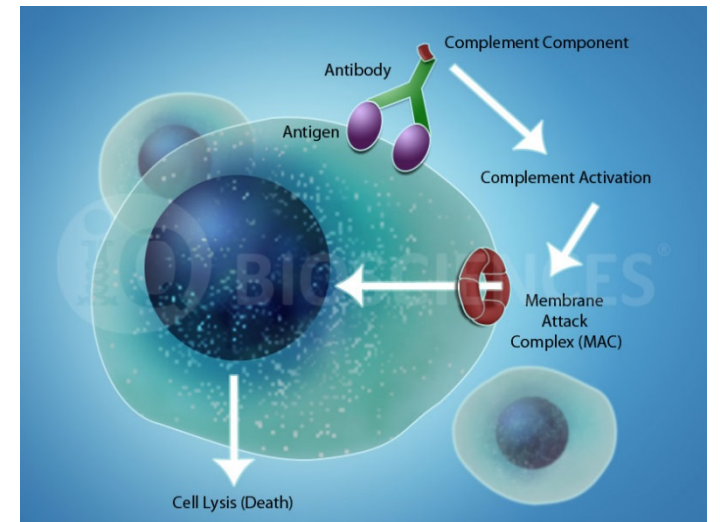
Subject 'A'



O395

N16961

BAA-2163



Bacteria Killed



Bacteria not killed

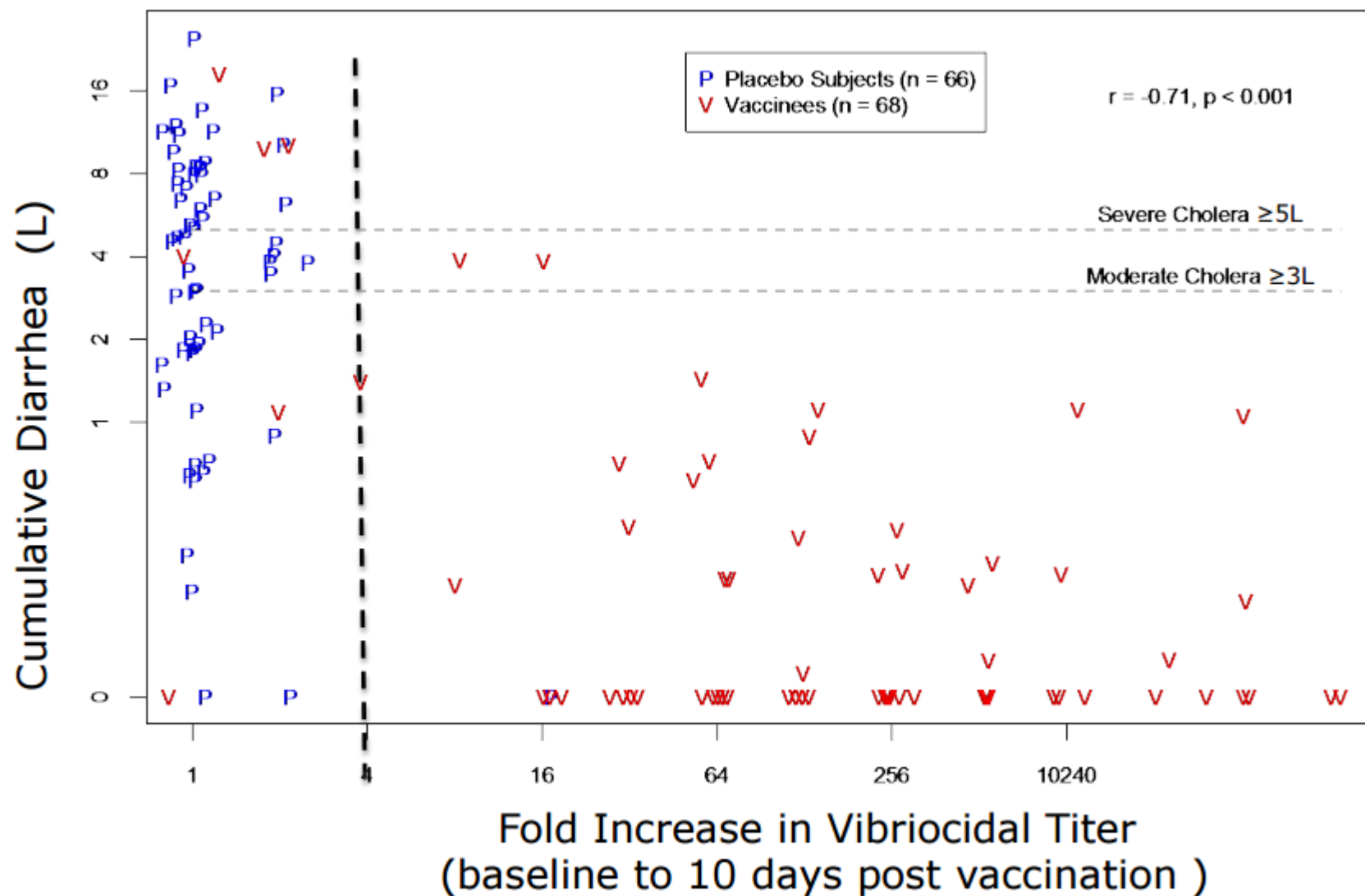
Undiluted

Son & Taylor 2011

1:2048 Dilution

Titer of 16

Cholera
WT Strain
N16861



PaxVax Presentation - ACIP 24 Feb 2016

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

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

$i = 1, \dots, 5$ (cluster) $j = 1, \dots, 4$ (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
 - *Often not appreciated!*
- Can use GEE with cluster=community (R-package `saw`)
- Permutation methods are attractive

| 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

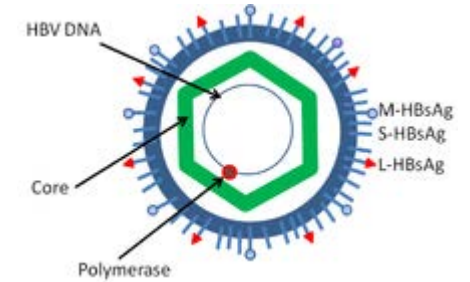
- For permutation p , fit model with permuted Z_{ij}

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

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)

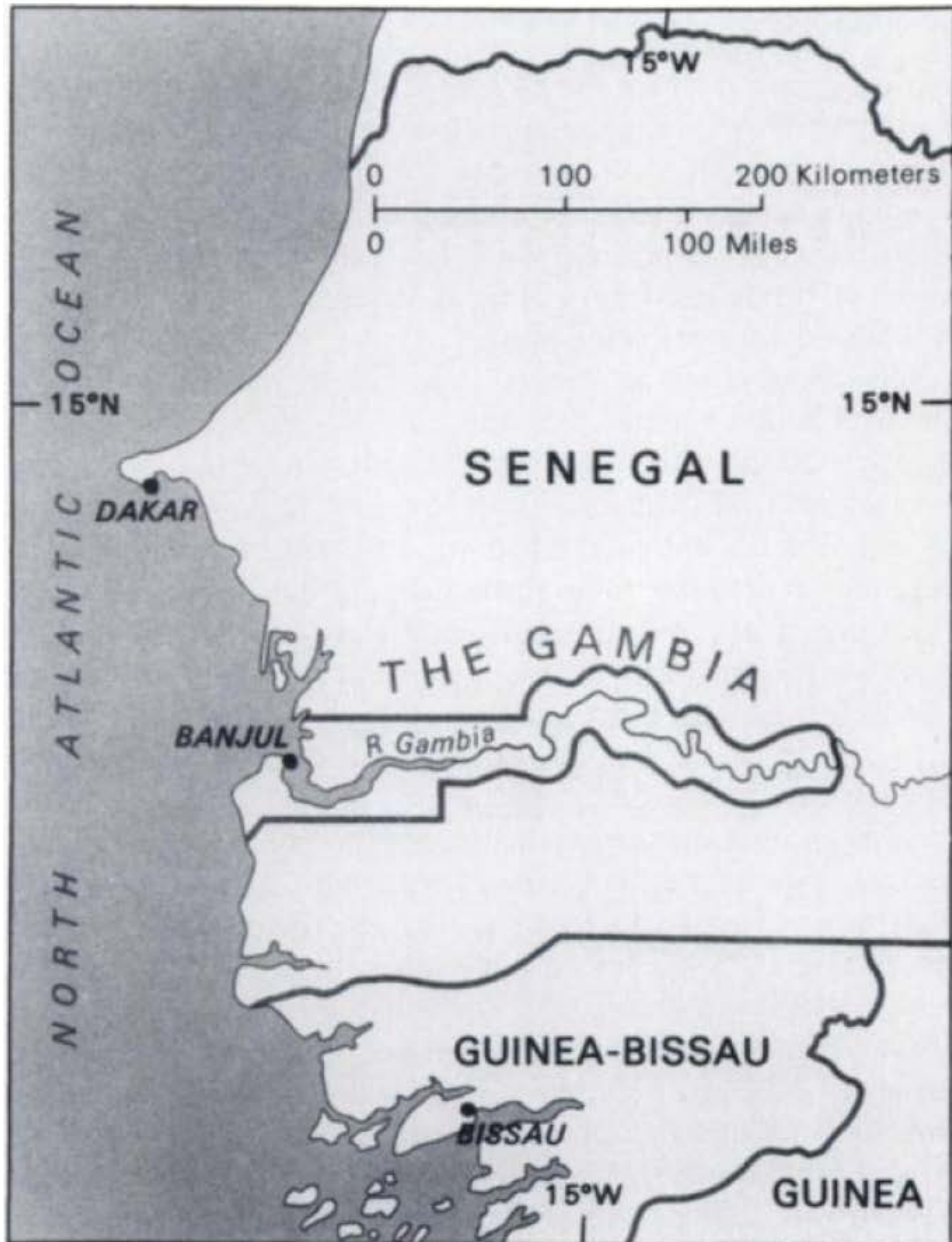
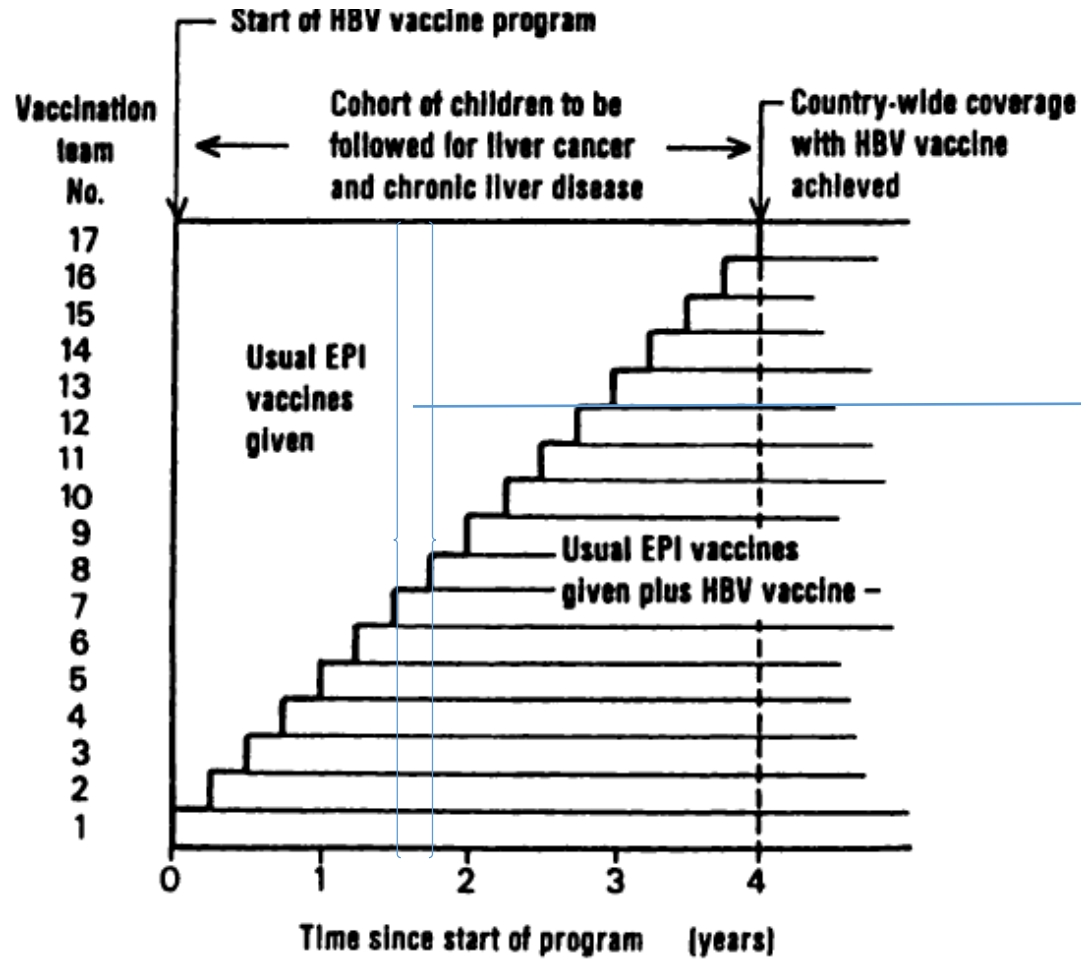


Fig. 1. The Gambia and neighboring countries.



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



Each Team is 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

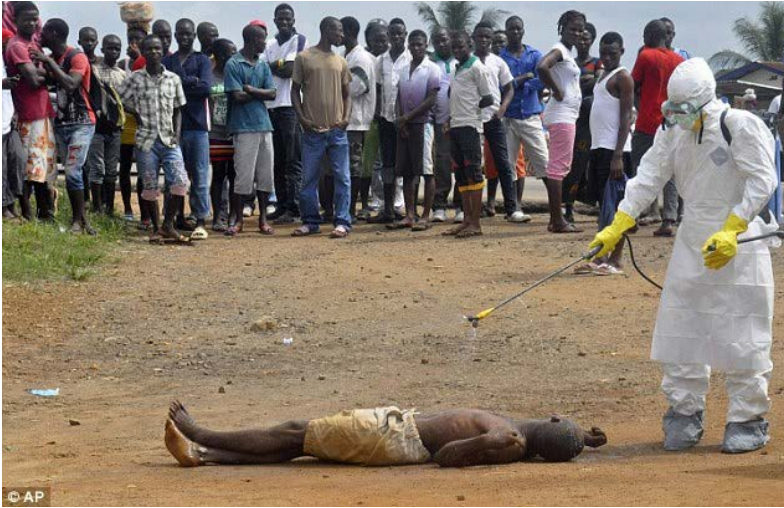
Fig. 2. Phased introduction of hepatitis B vaccination in The Gambia.

Simple Analysis

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



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

Ebola Virus



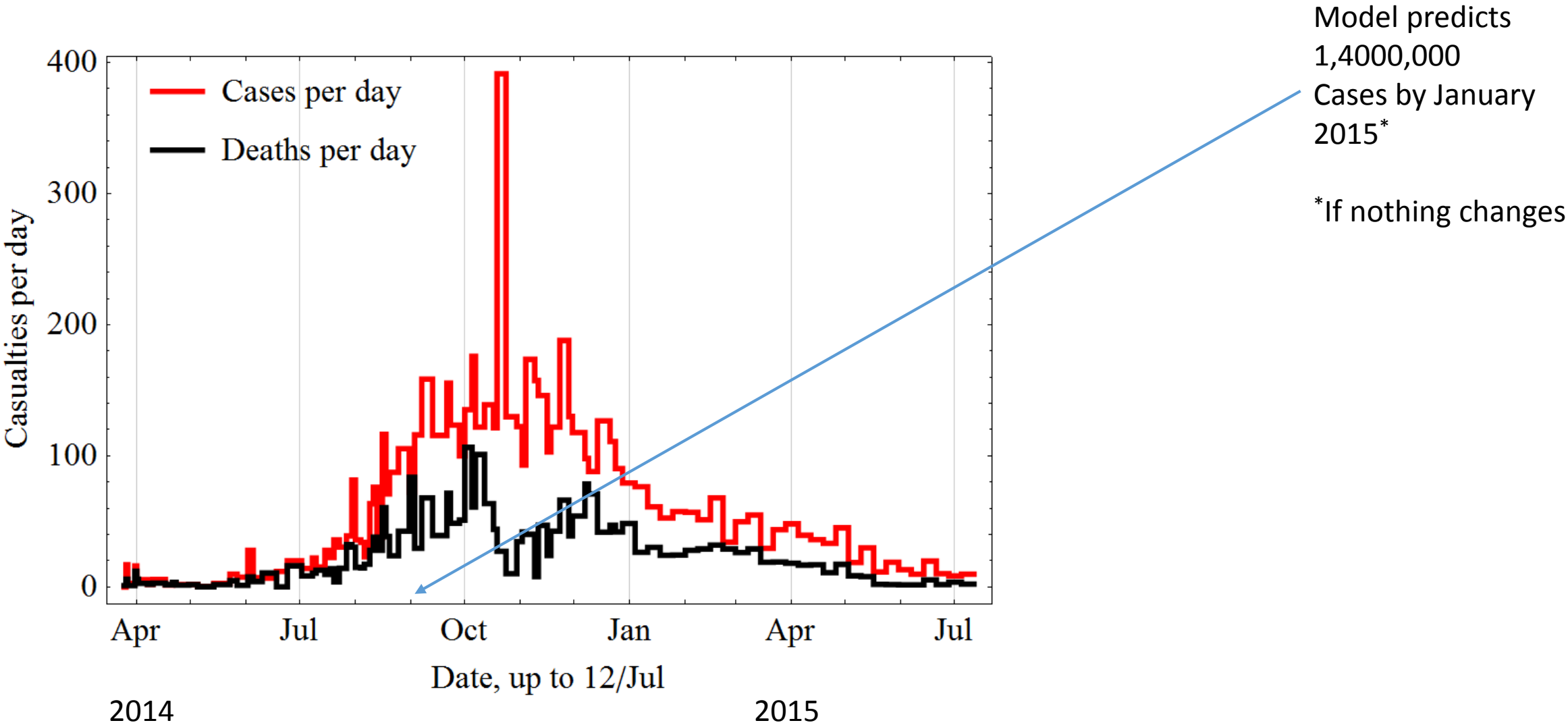
- Member of genus Filovirus, so-named for filament shape
- Like the other filovirus, Marburg virus, Ebola virus circulates in Africa causing outbreaks of hemorrhagic fever
- Fruit bats are the suspected reservoir

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



Ebola Vaccine Candidates

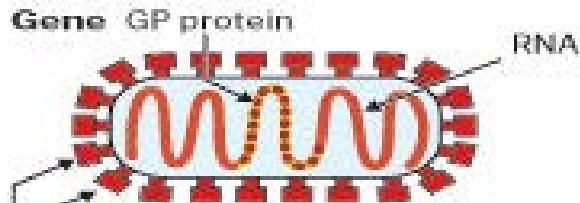
- ChAd3—replication incompetent Chimp adenovirus delivers outside (glycoprotein) of Ebola virus
 - 1 vector => 1 infected cell that alert immune system
 - several weeks to develop robust immune response
- VSV --- replication competent vesicular stomatitis virus (like rabies) modified to express Ebola 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, developed in Canada

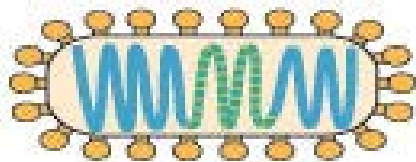
Ebola virus Zaire type



GP protein
The virus attacks human cells by locking on to them with the aid of this protein, which covers the virus

VSV

Vesicular stomatitis virus
(affects cattle)



This virus is weakened and will act as a vector for the vaccine

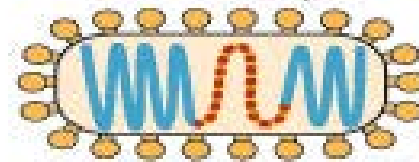
Sources: HUG, Geneva University, WHO

2

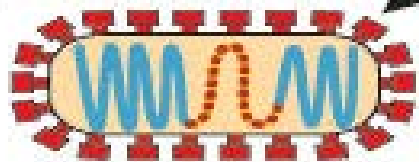


The GP protein's gene is taken from the Ebola virus

then transferred into the VSV virus

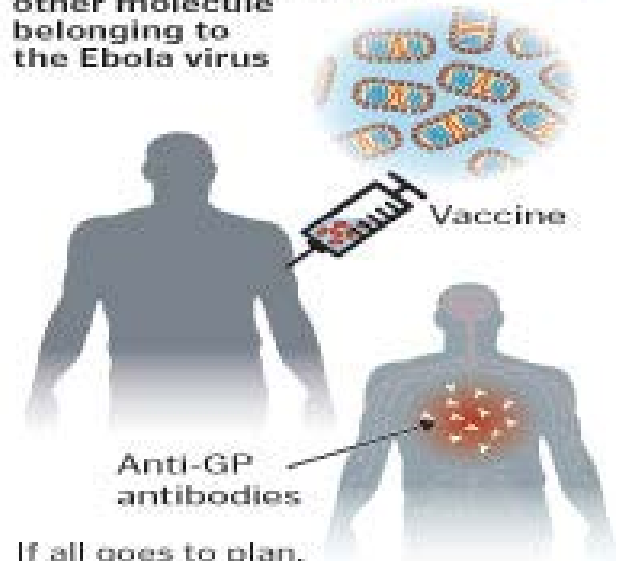


thereby replacing the VSV surface protein gene



3

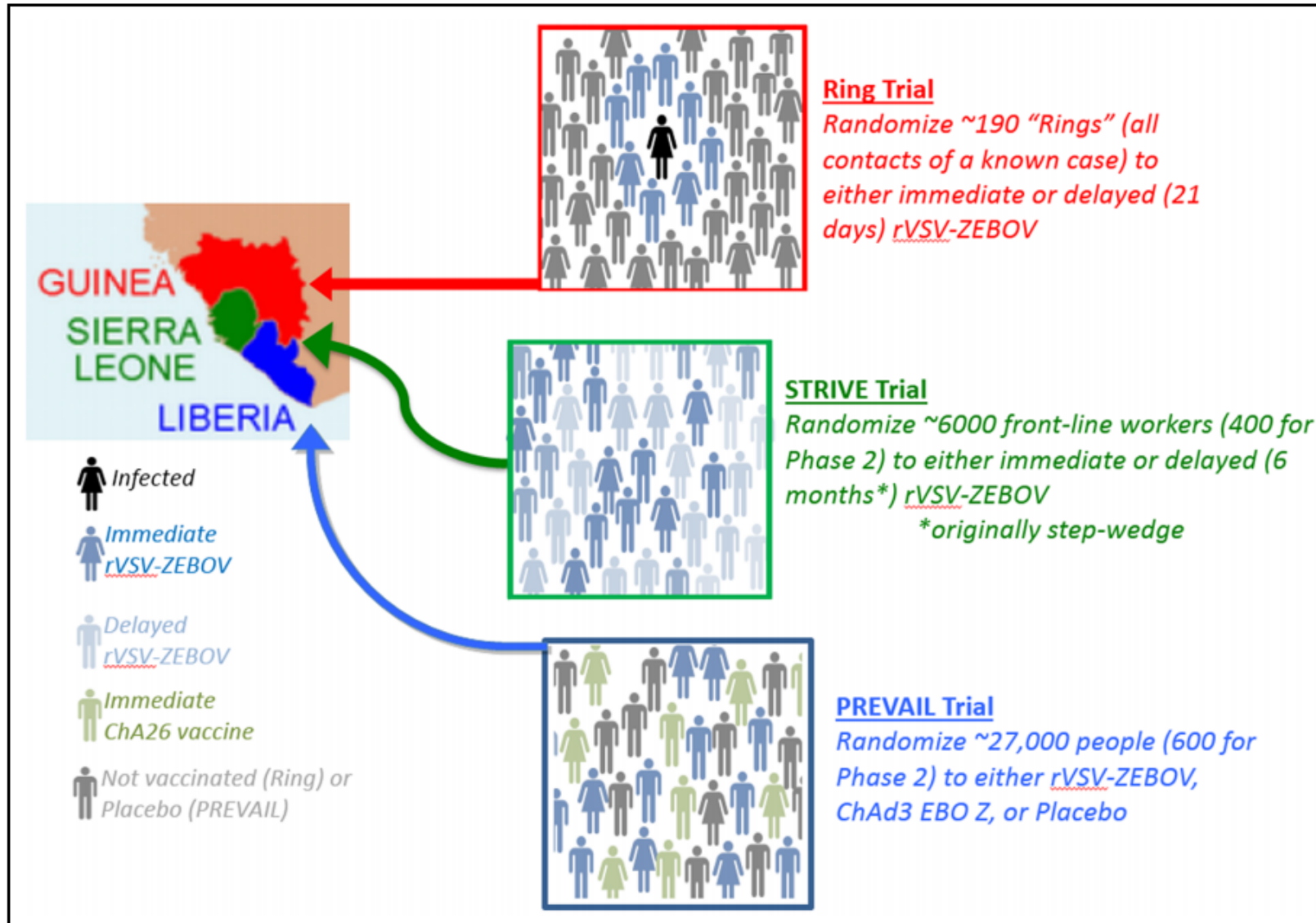
The vaccine therefore contains the modified VSV, but no other molecule belonging to the Ebola virus



Anti-GP antibodies

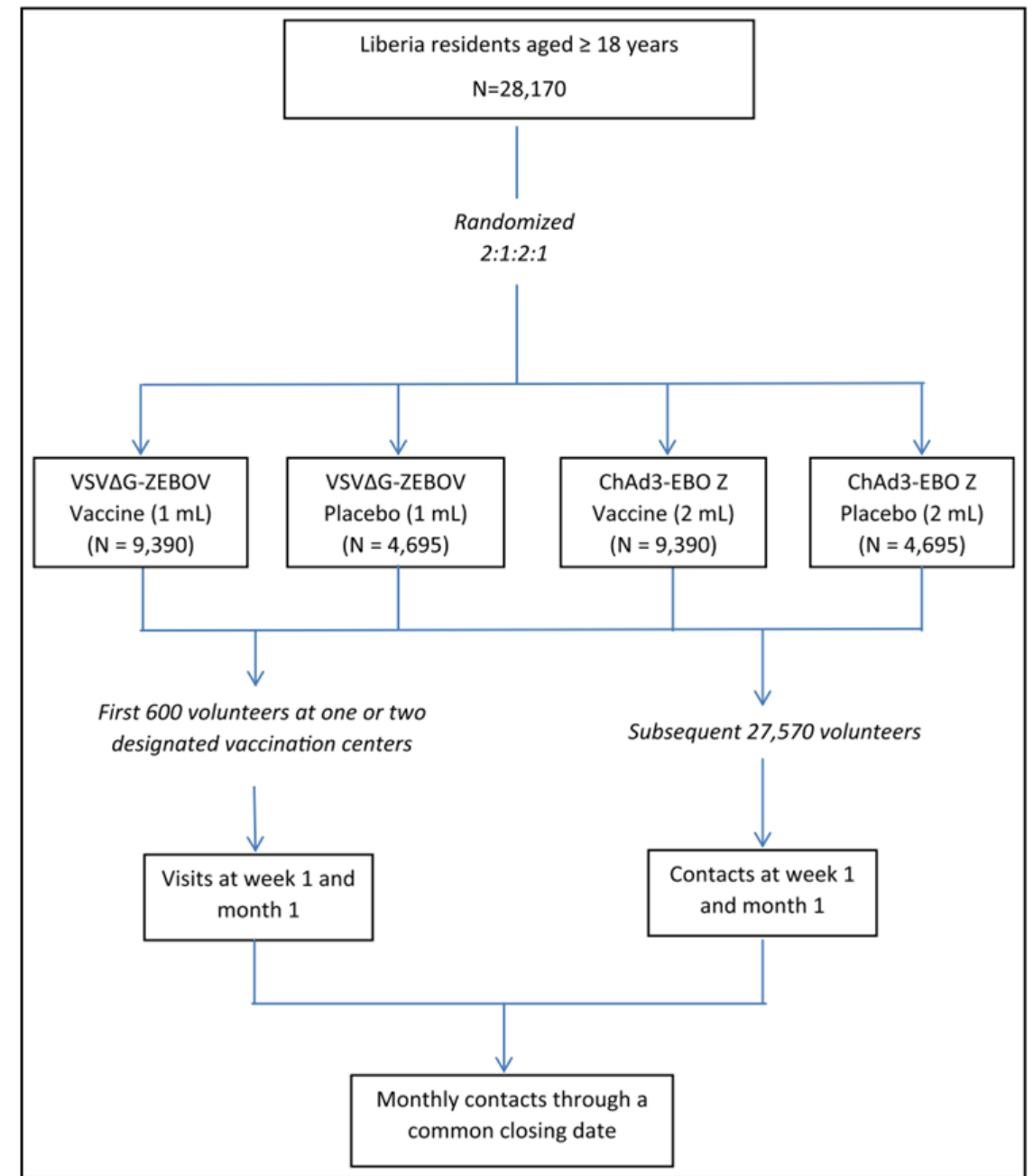
If all goes to plan, the vaccinated individual will produce antibodies neutralising GP proteins, thus ensuring protection against Ebola

TRIALS IN WEST AFRICA

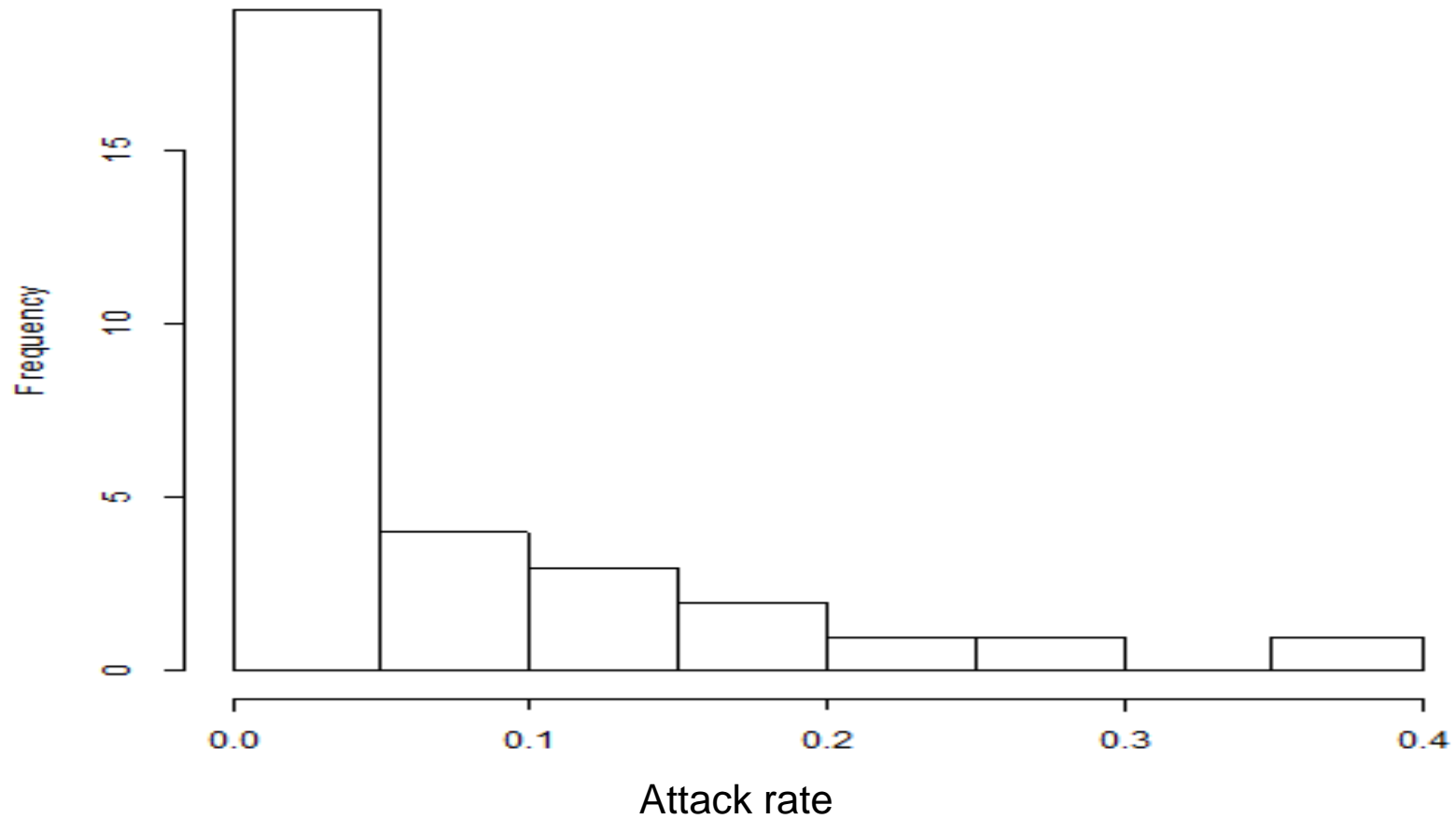


Prevail 1 Vaccine Trial

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



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

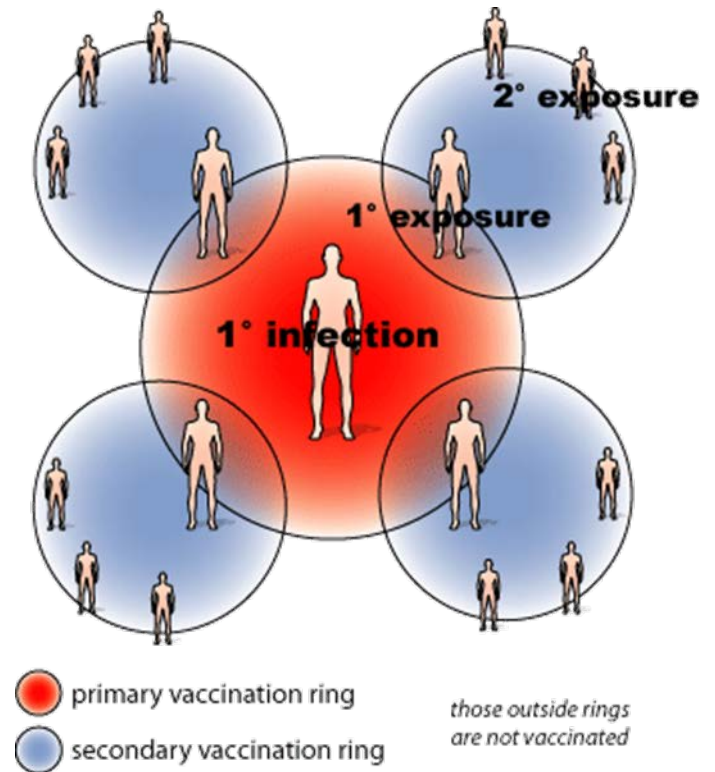


Median = 0.034, Mean = 0.065, Intraclass correlation = 0.065

*Source: WHO contact tracing teams in Guinea.

Ring Trial

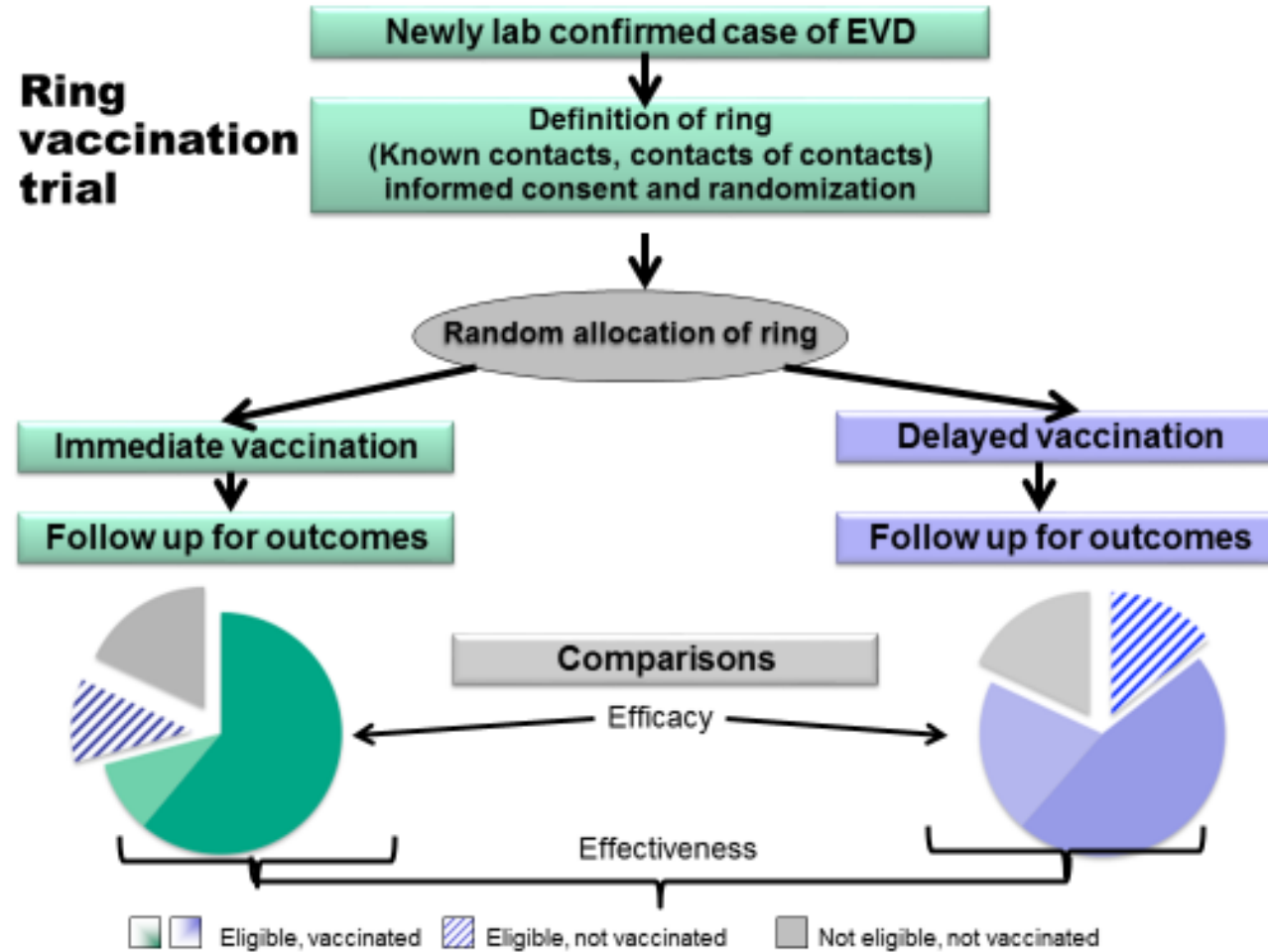
- Ring vaccination was used to eradicate smallpox
 - Like a firewall which aborts further spread
- WHO team proposed ring randomization
 - VSV – vaccine
 - Identify `rings' = contacts & contacts of contacts of Ebola cases
 - Randomize ring to immediate or 3 week delayed vaccination
 - (Cluster level 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 were 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, $E(Z_h) = 1$

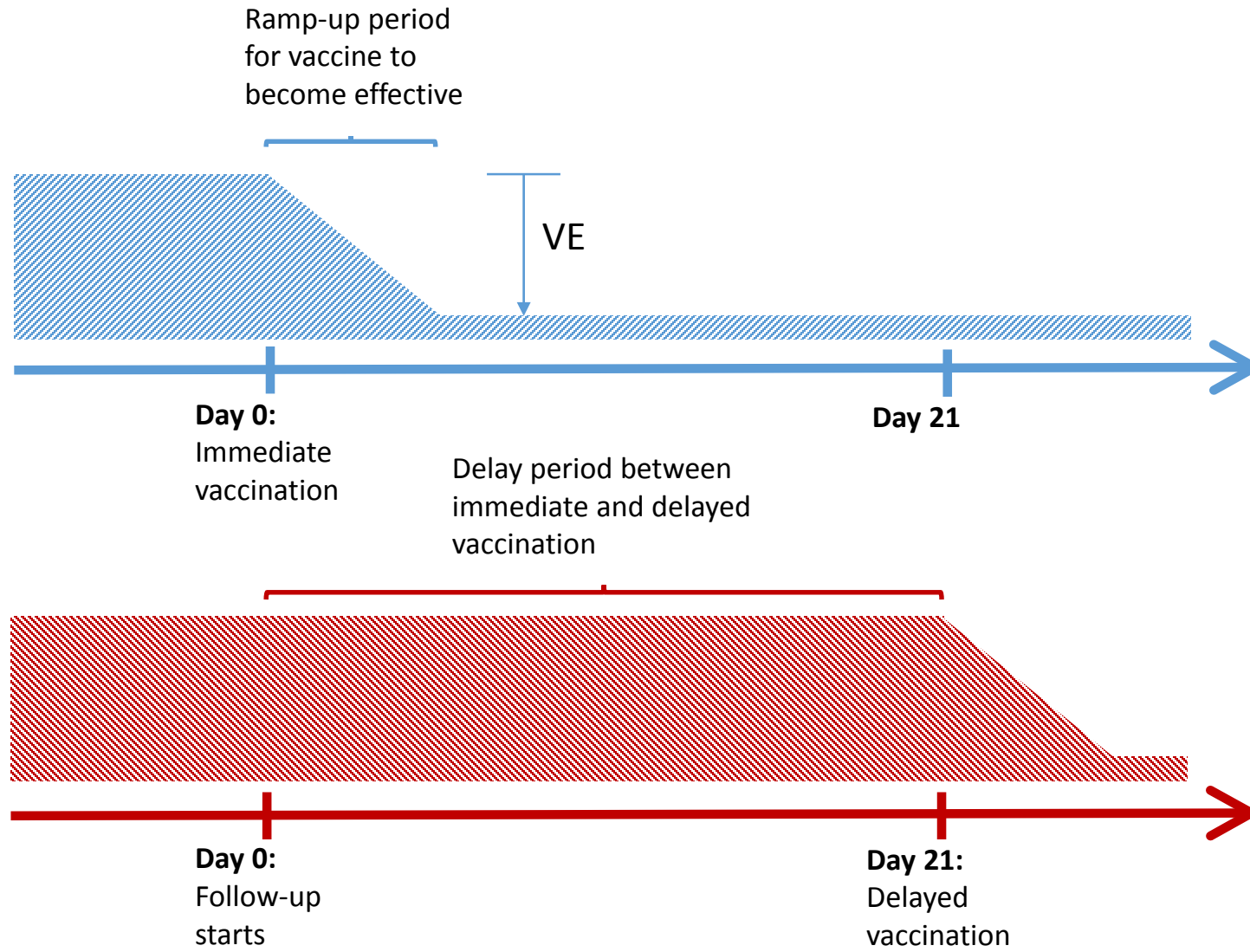
1 if past day 10
0 otherwise

Proportional hazards model with random effect for cluster (frailty)

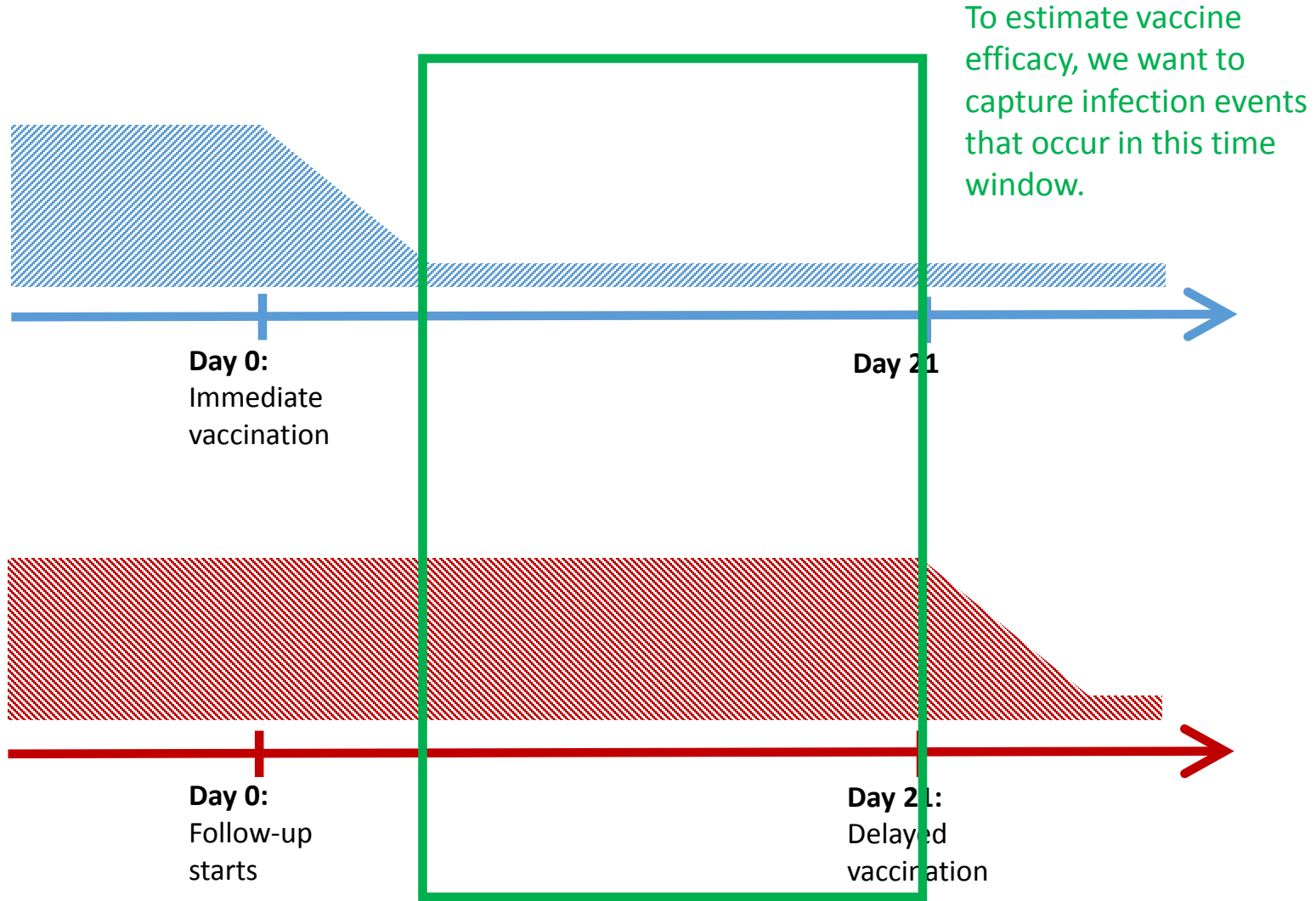
$$VE = 1 - \theta$$



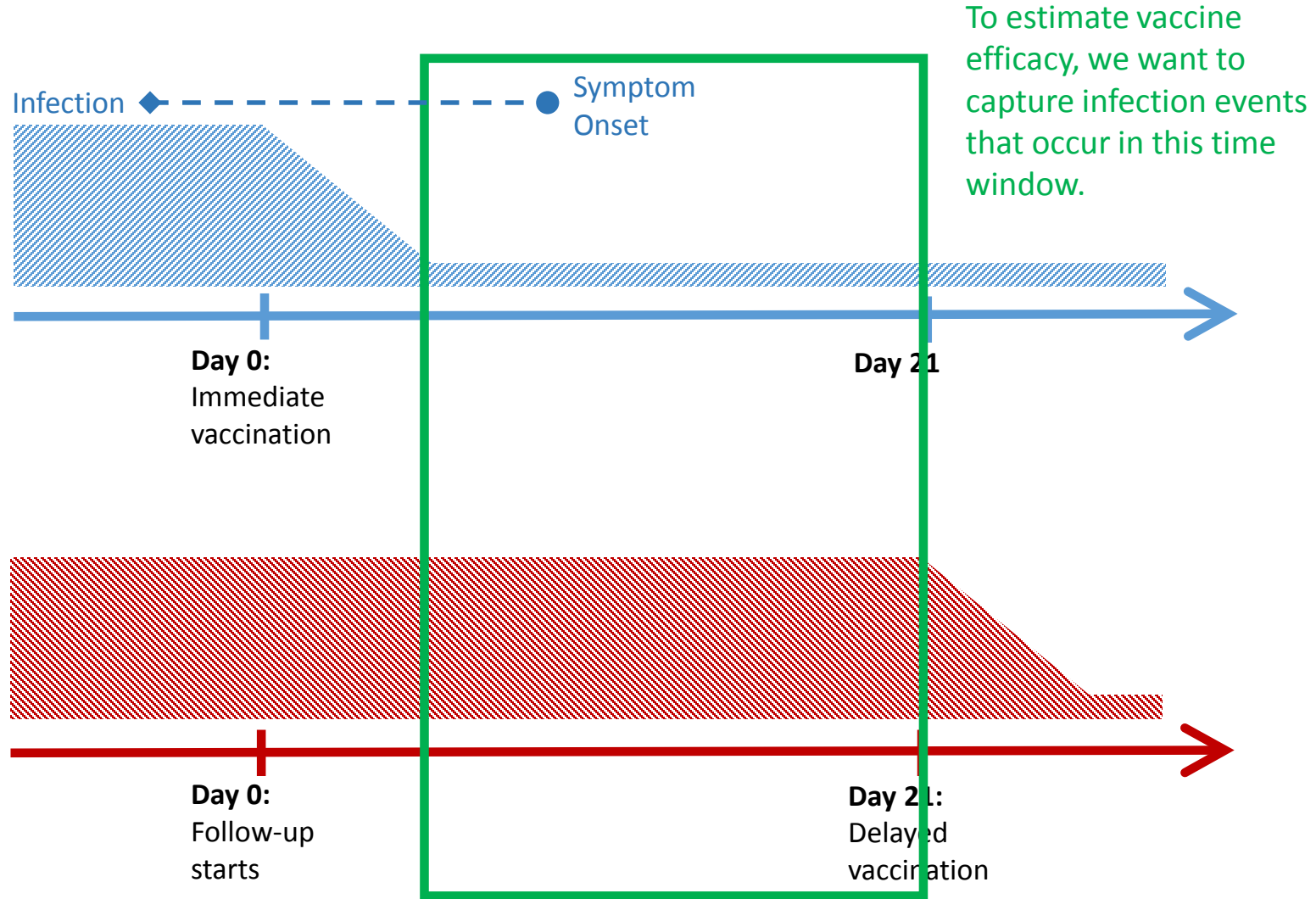
Hazard of infection with Ebola virus



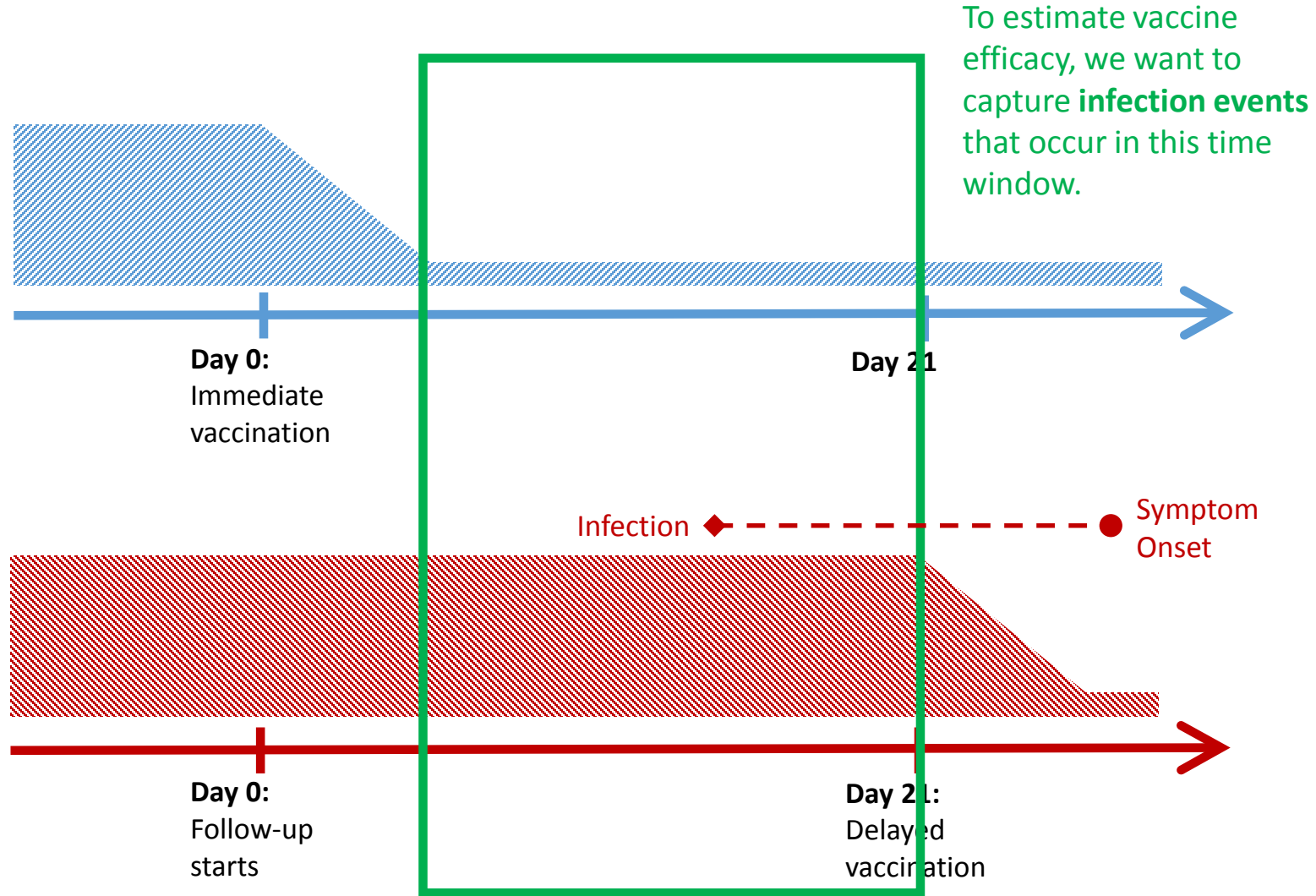
Hazard of infection with Ebola virus



Hazard of infection with Ebola virus

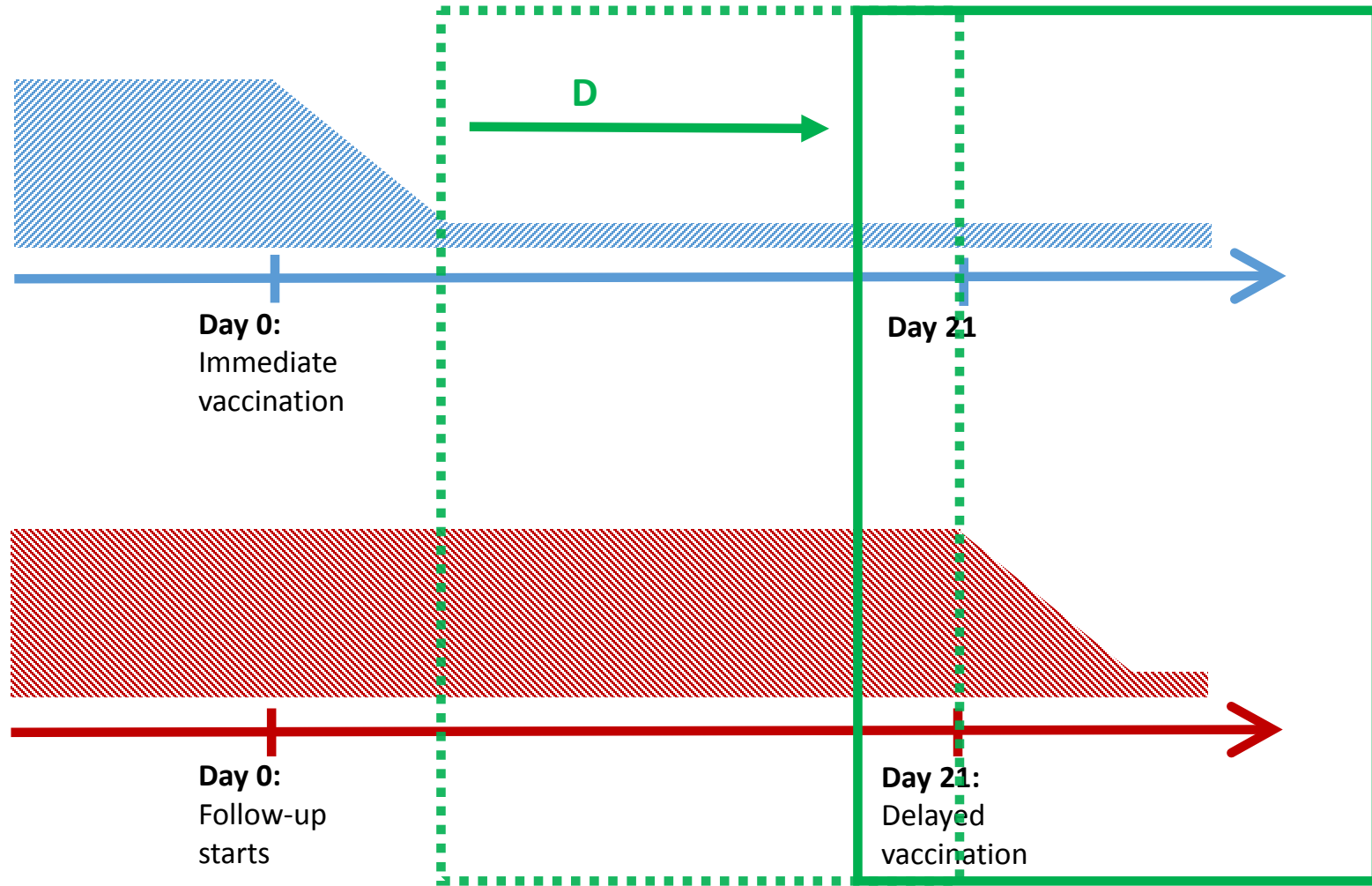


Hazard of infection with Ebola virus



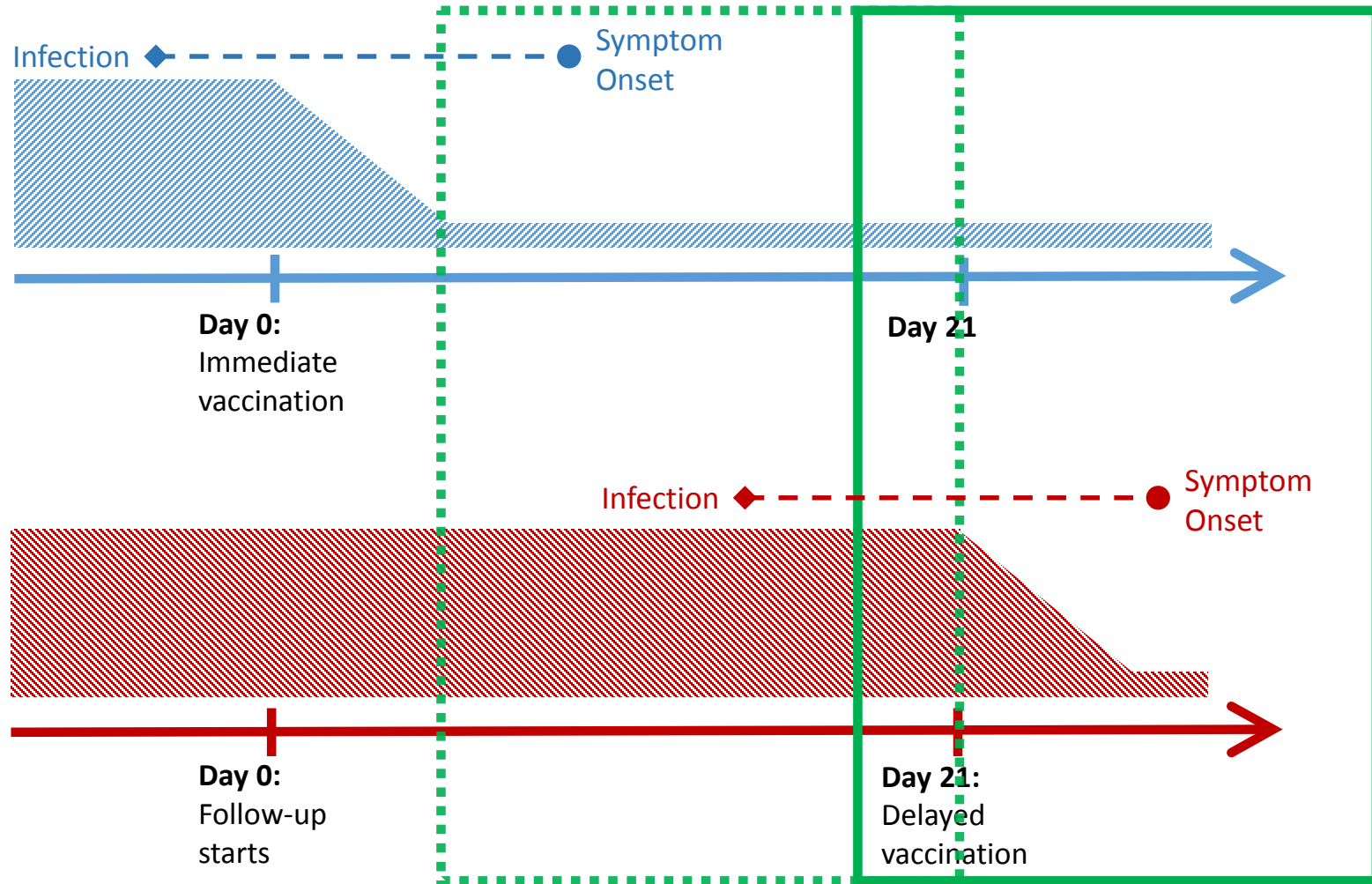
Hazard of infection with Ebola virus

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



Hazard of infection with Ebola virus

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



| | Randomised clusters† | | | |
|--|---|--|---|--|
| | 5 | 6 | 7 | 8 |
| | All vaccinated in immediate (group A) vs all eligible and consented on day 0 visit in delayed (group B) | All vaccinated in immediate (group A) vs all eligible in delayed (group B) | All eligible in immediate (group A) vs all eligible delayed (group B) | All contacts and contacts of contacts in immediate (group A) vs all contacts and contacts of contacts in delayed (group B) |
| Group A | | | | |
| Number of individuals (clusters) | 2108 (51) | 2108 (51) | 3212 (51) | 4513 (51) |
| Cases of Ebola virus disease (clusters affected) | 0 (0) | 0 (0) | 7 (4) | 10 (5) |
| Attack rate | 0% | 0% | 0.22% | 0.22% |
| Group B | | | | |
| Number of individuals (clusters) | 1429 (46) | 3075 (47) | 3075 (47) | 4529 (47) |
| Cases of Ebola virus disease (clusters affected) | 10 (4) | 16 (7) | 16 (7) | 22 (8) |
| Attack rate | 0.7% | 0.52% | 0.52% | 0.49% |
| Vaccine effect | | | | |
| Vaccine efficacy/ effectiveness‡ (%; 95% CI) | 100% (63.5 to 100.0) | 100% (68.9 to 100.0) | 64.6% (-46.5 to 91.4) | 64.6% (-44.2 to 91.3) |
| p value§ | 0.0471 | 0.0045 | 0.344 | 0.3761 |

NO CASES IN IMMEDIATE ARM & STUDY WAS STOPPED EARLY

Ebola was terrifying, placebo was felt unethical/unacceptable and trial was unblinded ----- thus multiple analysis groups

Analysis 5: all vaccinated in immediate vs all eligible/consented in delayed

| Clusters | Immediate | Delayed |
|----------|-----------|---------|
| No cases | 51 | 42 |
| 1+ cases | 0 | 4 |

SHARE



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

By [Science News Staff](#) | Dec. 17, 2015, 2:30 PM

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 - Slides
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- Michael Proschan (NIH)

Figure 1. Flow Diagram of Trial

