

Cluster-randomized Trials: ¹ Infectious Diseases

WORKSHOP ON HERD EFFECTS ON VACCINE
EFFECTIVENESS

Bamako, Mali

Ira M. Longini, Jr.

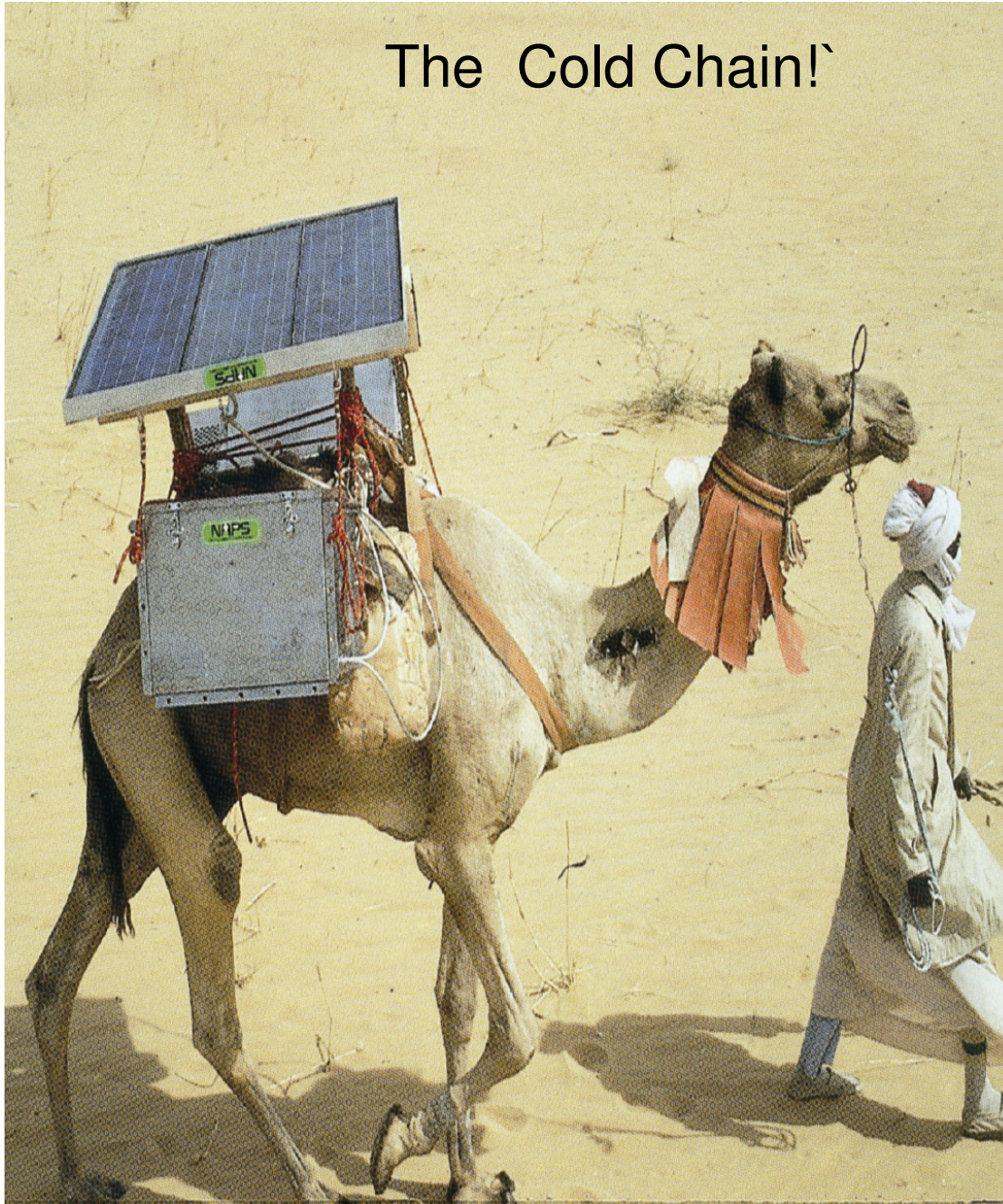
Center for Statistical and Quantitative Infectious Diseases
(**CSQUID**)

Vaccine and Infectious Disease Institute
Hutchinson Research Center

and

The University of Washington
Seattle Washington

The Cold Chain!



Camel with solar electricity powered refrigerator with vaccines being kept in the cold chain. Image courtesy of Naps Systems Oy, Finland, in Halloran, Longini and Struchiner (2009)

Statistics for Biology and Health

Statistics for Biology and Health

Halloran • Longini
Struchiner

M. Elizabeth Halloran • Ira M. Longini, Jr. • Claudio J. Struchiner
Design and Analysis of Vaccine Studies

M. Elizabeth Halloran
Ira M. Longini, Jr.
Claudio J. Struchiner

Widespread immunization has many different kinds of effects in individuals and populations, including in the unvaccinated individuals. The challenge is in understanding and estimating all of these effects. This book presents a unified conceptual framework of the different effects of vaccination at the individual and at the population level. The book covers many different vaccine effects, including vaccine efficacy for susceptibility, for disease, for post-infection outcomes, and for infectiousness. The book includes methods for evaluating indirect, total and overall effects of vaccination programs in populations. Topics include household studies, evaluating correlates of immune protection, and applications of casual inference. Material on concepts of infectious disease epidemiology, transmission models, casual inference, and vaccines provides background for the reader. This is the first book to present vaccine evaluation in this comprehensive conceptual framework.

This book is intended for colleagues and students in statistics, biostatistics, epidemiology, and infectious diseases. Most essential concepts are described in simple language accessible to epidemiologists, followed by technical material accessible to statisticians.

Elizabeth Halloran and Ira Longini are professors of biostatistics at the University of Washington and the Fred Hutchinson Cancer Research Center in Seattle. Claudio Struchiner is professor of epidemiology and biostatistics at the Brazilian School of Public Health of the Oswaldo Cruz Foundation in Rio de Janeiro. The authors are prominent researchers in the area. Halloran and Struchiner developed the study designs for dependent happenings to delineate indirect, total, and overall effects. Halloran has made contributions at the interface of epidemiological methods, causal inference, and transmission dynamics. Longini works in the area of stochastic processes applied to epidemiological infectious disease problems, specializing in the mathematical and statistical theory of epidemics. Struchiner has contributed to understanding the role of transmission in interpreting vaccine effects.

EPIDEMIOLOGY

ISBN 978-0-387-40313-7

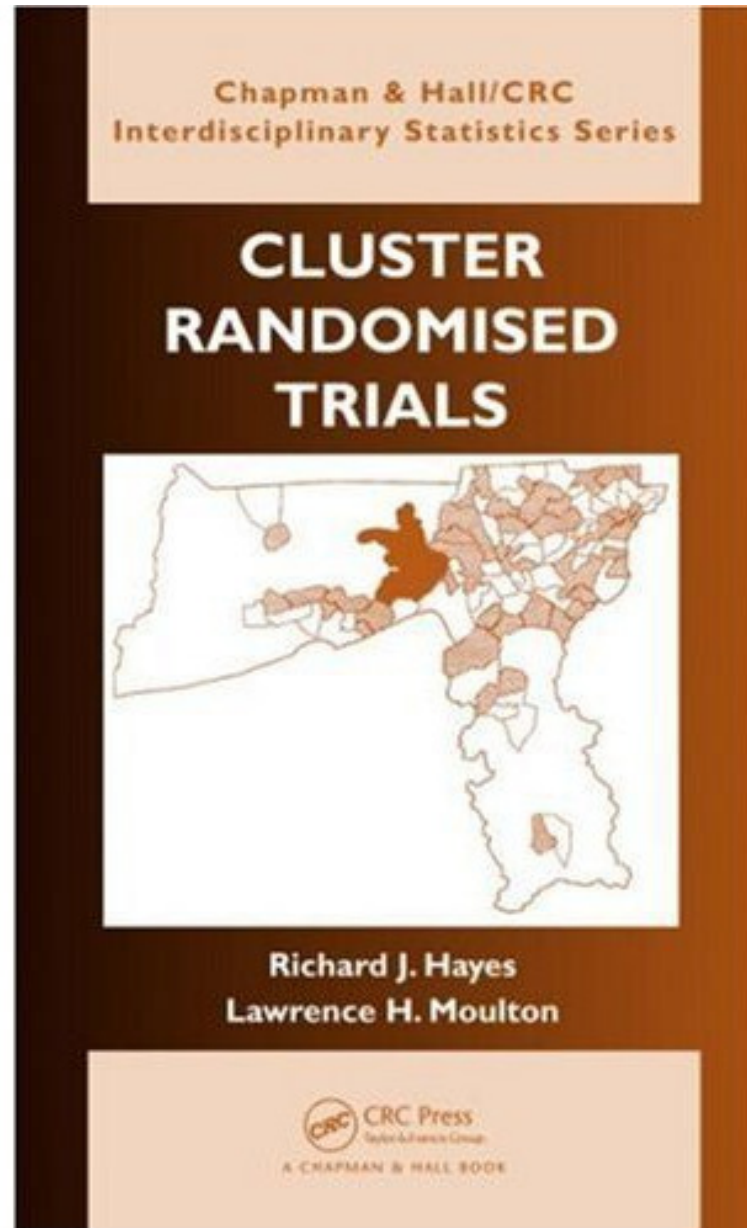
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Design and Analysis of Vaccine Studies

Design and Analysis of Vaccine Studies

Springer



1ST SUMMER INSTITUTE IN STATISTICS AND MODELING IN INFECTIOUS DISEASES



June 15 - July 1, 2009

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Supported by the National Institutes of Health

Today's Talk

- General design and analysis
- What is estimated and tested
- How to interpret estimated effects
- Examples

General Considerations

- Several populations needed for inference
- Should be comparable for characteristics related to transmission, covariates → matching
- Should be separated as much as possible with respect to transmission
- subpopulations within larger populations can also be compared

Design considerations in group-randomized studies

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Design consideration

Primary and secondary questions of interest

Vaccine and vaccination strategy, active control?

Clinical endpoints

Study population and subpopulations

Sources of transmission

Case ascertainment

Choice of randomization unit at the group level

Allocation mechanism at the individual level:

→ randomization or observational

What is Being Measured?

Vaccine efficacy and effectiveness

- Vaccine efficacy for susceptibility, VE_S :
 - direct protective effects
 - sometimes outcome is infection, sometimes disease
- Vaccine efficacy for progression, VE_P
 - after being infected, the effect on probability of developing symptoms (pathogenicity)
 - or after developing symptoms, probability of severe disease
- Vaccine efficacy for infectiousness, VE_I
 - the effect in reducing transmission from a vaccinated compared to an unvaccinated infected person.
- Vaccine efficacy if both are vaccinated, VE_T
 - the effect in reducing transmission if both infected and susceptible are vaccinated compared to if neither are vaccinated.

Vaccine efficacy and effectiveness

- Direct effects
 - direct protective effects in person who is vaccinated
- Indirect effects
 - effects of widespread vaccination on someone who is not vaccinated
- Total Effects
 - possibly synergistic effect of being vaccinated and widespread vaccination on someone who is vaccinated
- Overall effects
 - overall population effect, say, reduction in incidence, of widespread vaccination.

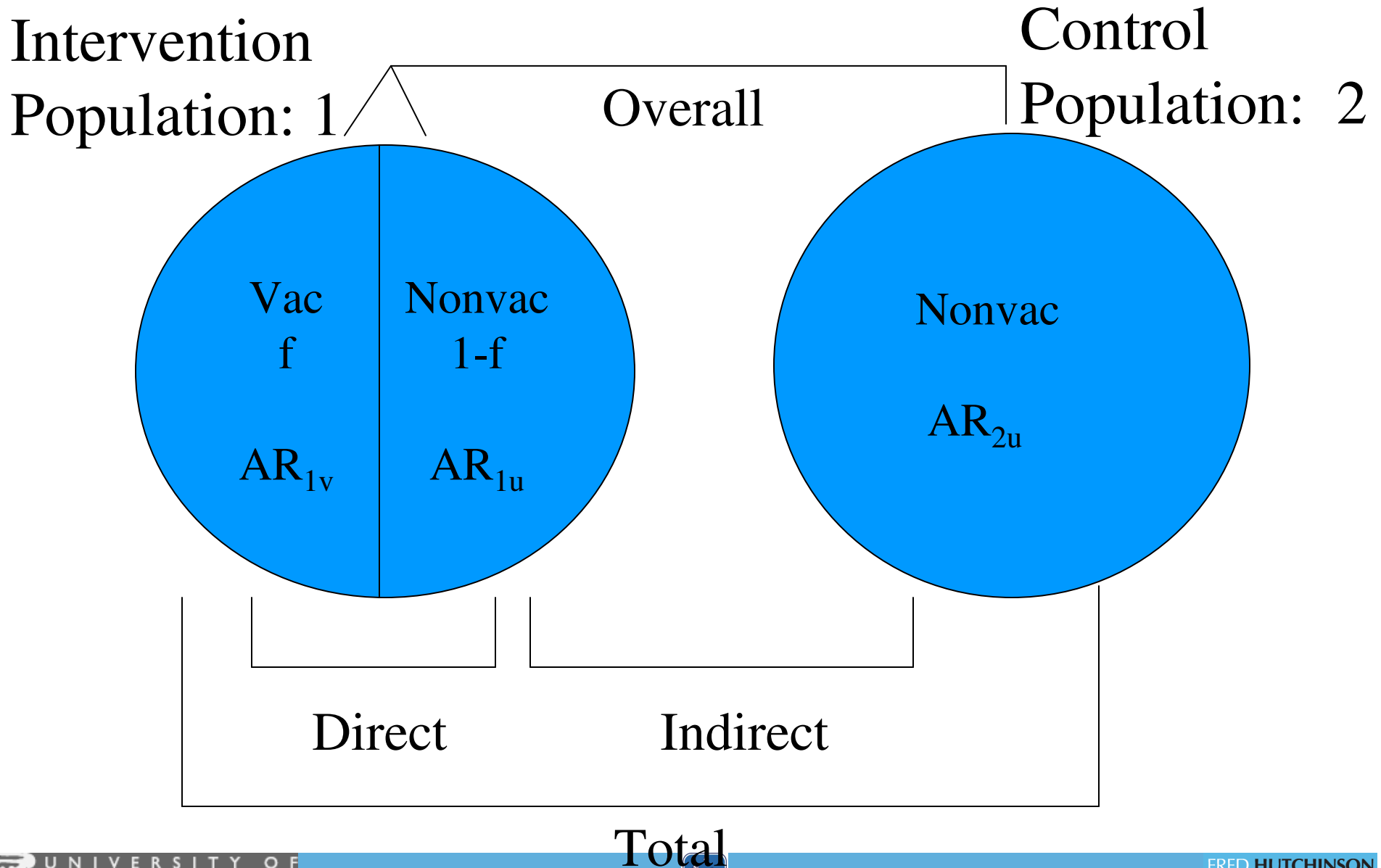
Table: Parameters used for measuring various effects of vaccination*

| Level Parameter choice | Comparison groups and effect | | | |
|--|--|--|--|--|
| | Susceptibility | Infectiousness | Combined change in susceptibility and infectiousness | |
| Conditional on exposure: | | | | |
| I Transmission probability | $VE_{S,p} = 1 - \frac{P_1}{P_0}$ | $VE_{I,p} = 1 - \frac{P_1}{P_0}$ | $VE_{T,p} = 1 - \frac{P_{11}}{P_{00}}$ | |
| | Study design | | | |
| | I direct | IIA indirect | IIB total | III overall |
| Unconditional: | | | | |
| II Incidence or hazard rate, IR, λ | $VE_{S,IR} = 1 - \frac{IR_{A1}}{IR_{A0}}$ | $VE_{IIA,IR} = 1 - \frac{IR_{A0}}{IR_{B0}}$ | $VE_{IIB,IR} = 1 - \frac{IR_{A1}}{IR_{B0}}$ | $VE_{III,IR} = 1 - \frac{IR_{A.}}{IR_{B.}}$ |
| | $VE_{S,\lambda} = 1 - \frac{\lambda_{A1}}{\lambda_{A0}}$ | $VE_{IIA,\lambda} = 1 - \frac{\lambda_{A0}}{\lambda_{B0}}$ | $VE_{IIB,\lambda} = 1 - \frac{\lambda_{A1}}{\lambda_{B0}}$ | $VE_{III,\lambda} = 1 - \frac{\lambda_{A.}}{\lambda_{B.}}$ |
| III Proport. hazards, PH | $VE_{S,PH} = 1 - e^{\beta_1}$ | NA | NA | NA |
| IV Cumulative incidence | $VE_{S,CI} = 1 - \frac{CI_{A1}}{CI_{A0}}$ | $VE_{IIA,CI} = 1 - \frac{CI_{A0}}{CI_{B0}}$ | $VE_{IIB,CI} = 1 - \frac{CI_{A1}}{CI_{B0}}$ | $VE_{III,CI} = 1 - \frac{CI_{A.}}{CI_{B.}}$ |

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

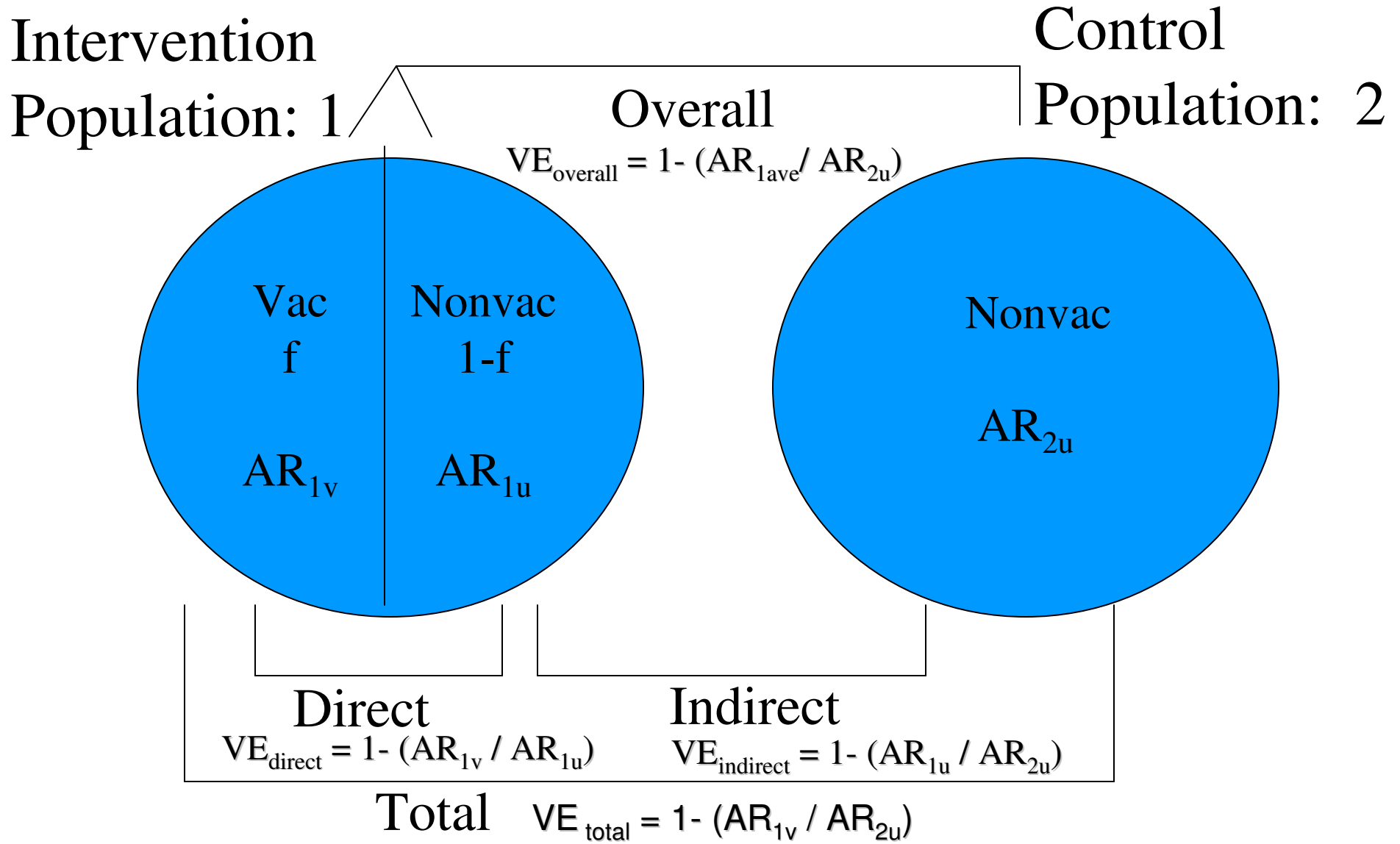
Vaccine Effectiveness

13

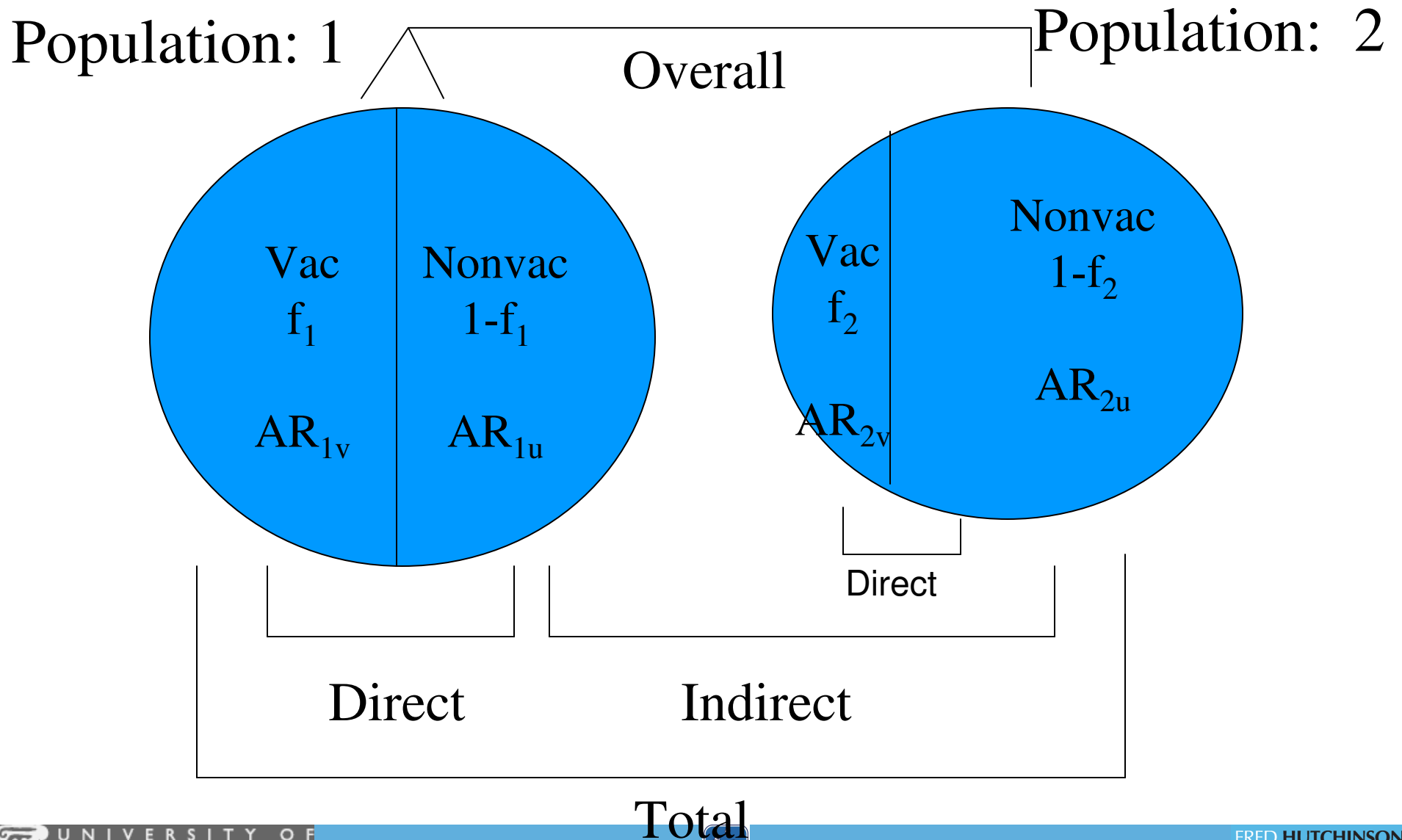


Vaccine Effectiveness

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Vaccine Effectiveness Gradient



| Vaccination Coverage (%) | | Mean Cases/1000 (95% CI) | | | | Mean Direct Effectiveness (%) (95% CI) | |
|--------------------------|--------------------|-----------------------------|--------------------|-------------------|-------------------|---|----------------|
| | | Placebo | | Vaccinated | | Observed | Simulated |
| Target Population | Overall Population | Observed | Simulated | Observed | Simulated | | |
| 14 | 9 | 7.0 (6.5, 7.5) | 7.8 (1.9, 14.8) | 2.7 (1.9, 3.5) | 2.8 (0.5, 6.1) | 62 | 65 (52, 77) |
| 31 | 20 | 5.9 (5.4, 6.4) | 4.7 (0.9, 10.2) | 2.5 (2.0, 3.0) | 1.7 (0.3, 3.8) | 58 | 65 (55, 76) |
| 38 | 25 | 4.7 (4.2, 5.2) | 3.8 (0.8, 8.6) | 1.6 (1.2, 2.0) | 1.3 (0.2, 3.4) | 67 | 65 (54, 77) |
| 46 | 30 | 4.7 (4.2, 5.2) | 2.8 (0.5, 6.8) | 2.3 (1.9, 2.7) | 1.0 (0.1, 2.5) | 52 | 66 (54, 79) |
| 58 | 38 | 1.5 (1.2, 1.8) | 1.8 (0.3, 4.8) | 1.3 (1.0, 1.6) | 0.6 (0.1, 1.8) | 14 | 66 (51, 80) |

χ^2 goodness-of-fit test for frequency data $p = 0.84$

Source: Longini, et al. PLoS, Medicine 4 (2007).

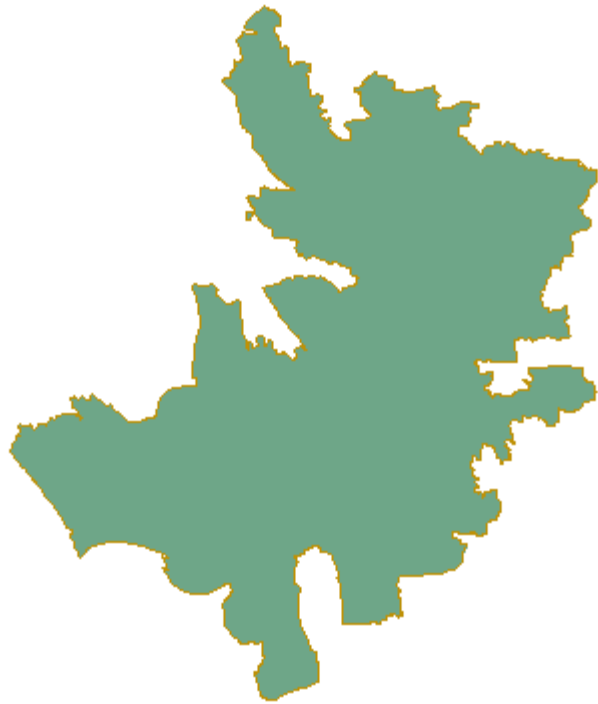
Average Indirect, Total and Overall Effectiveness of Vaccination,
and Cases Prevented 10,000 Per Doses

| Vaccination Coverage (%) | Mean Effectiveness (%) (95%CI) | | | Mean # Cases Prevented per 10,000 Doses |
|-----------------------------|-----------------------------------|------------------|------------------|--|
| | Indirect | Total | Overall | |
| 10 | 30 (-39, 83) | 76 (47, 95) | 34 (-30, 84) | 50 |
| 30 | 70 (31, 93) | 90 (76, 98) | 76 (44, 95) | 40 |
| 50 | 89 (72, 98) | 97 (91, 99) | 93 (82, 99) | 30 |
| 70 | 97 (91, 99) | 99 (97, 100) | 98 (95, 100) | 20 |
| 90 | 99 (98, 100) | 100 (99, 100) | 100 (99, 100) | 20 |

Source: Longini, et al. PLoS, Medicine 4 (2007).

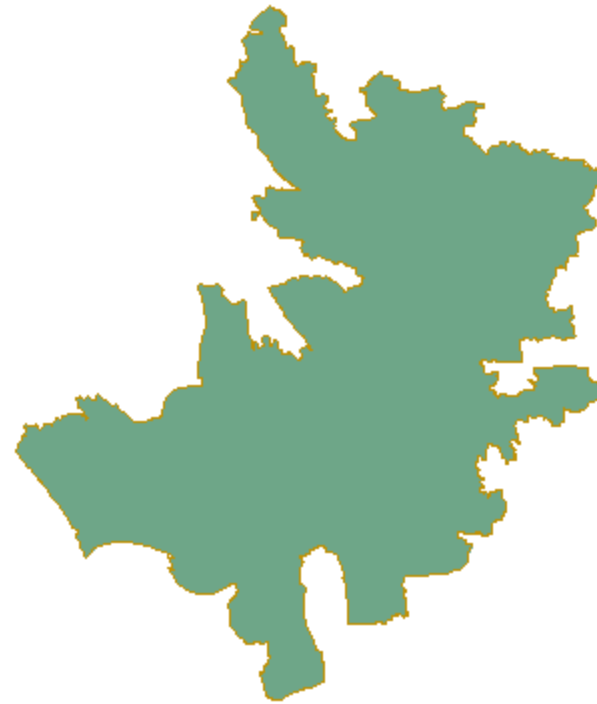
Mass Vaccination: 0 % Day 1

Red: Ill Yellow:Recovered

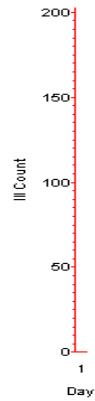


Mass Vaccination: 58 % Day 1

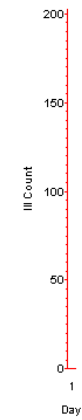
Red: Ill Yellow:Recovered



Epidemic curve: Day 1
Mass Vaccination:0%



Epidemic curve: Day 1
Mass Vaccination:58%



Sample Size and Power

Two Important Measures

- The coefficient of variation k :
- standard deviation divided by the mean of the incidence rate, or other outcome measure of interest such as proportions (attack rates) or mean of a continuous variable in the groups in the study.

Sample Size for Parallel Design ²¹

- If the outcome is based on person-time, let y denote the person-time of follow-up in each group.
- Then the number of groups required in each arm is

$$N = 1 + (z_{\alpha/2} + z_{\beta})^2 \frac{(\lambda_0 + \lambda_1)/y + k^2(\lambda_0^2 + \lambda_1^2)}{(\lambda_0 - \lambda_1)^2}.$$

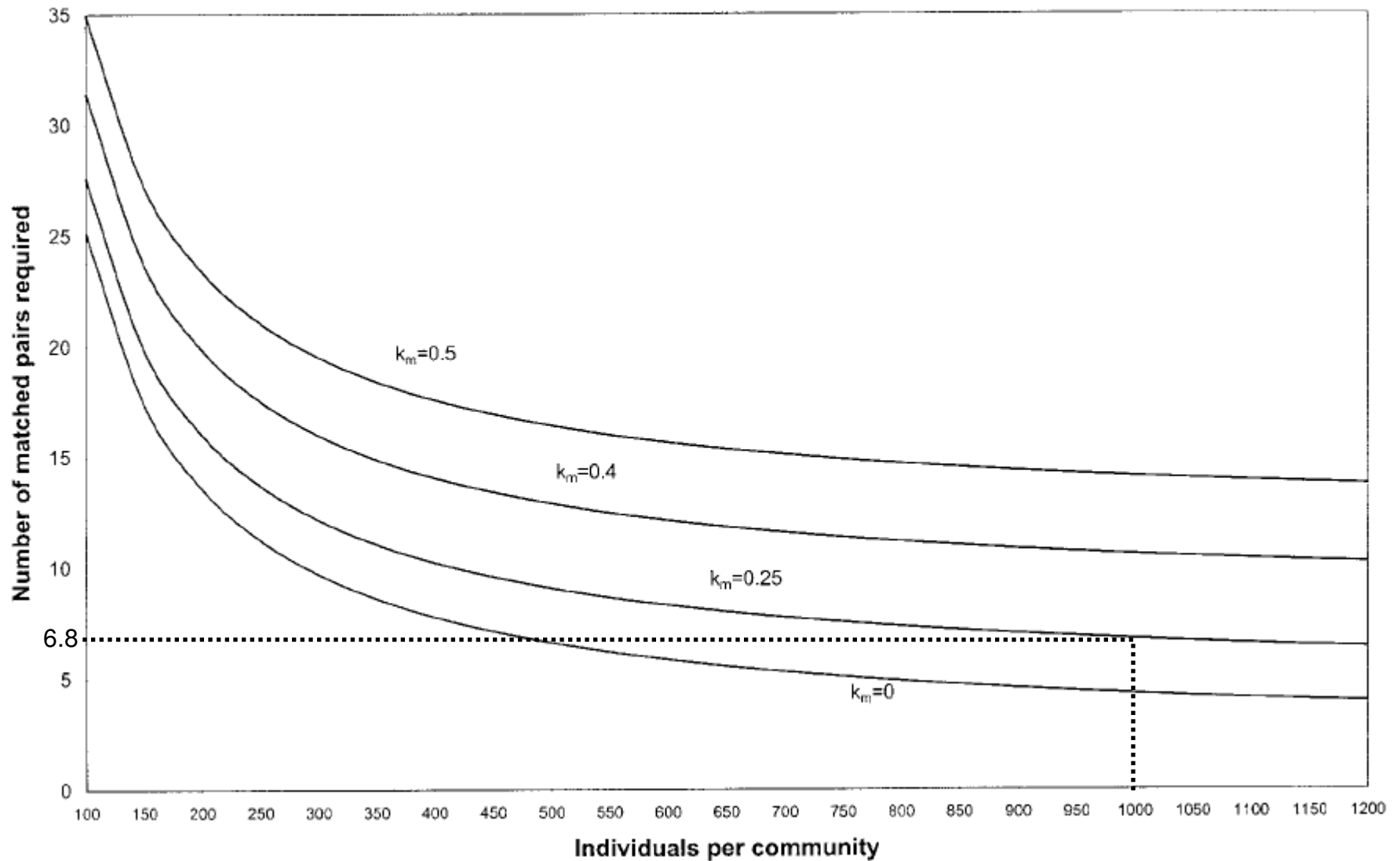
- The design effect on the sample size associated with the group-randomization can be estimated by dividing the equation by the corresponding equation for individual effects.

Source: Hayes and Bennett: Internat J Epidemiol **28**, 319-26 (1999)

Examples

- Cluster Randomized Influenza vaccine trial in Senegal
 - Monday, Session 1: Seasonal and pandemic influenza vaccines research and development, talk by Dr. Aldiouma Diallo
- HIV Reductions Due to STD Treatment in Mwanza, Tanzania, 1991-94
 - Grosskurth, et al., Lancet **346**, 530-36 (1995)
 - Hayes and Bennett: Internat J Epidemiol **28**, 319-26 (1999)

Sample Size Calculations for HIV Reductions Due to STD Treatment in Mwanza, Tanzania (power = 0.8, $\alpha = 0.05$)



Source: Hayes and Bennett: Internat J Epidemiol **28**, 319-26 (1999)

Study Area Matching

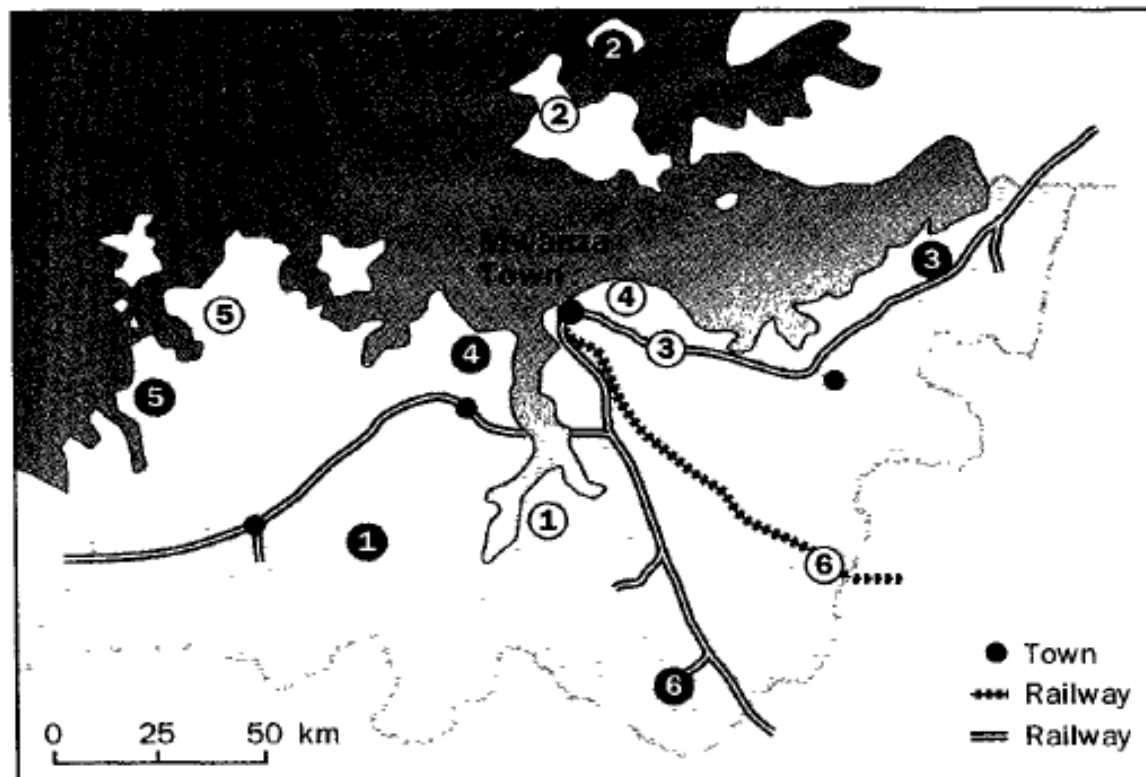


Figure 1: Map of Mwanza region

Numbered circles indicate location of six pairs of study communities; intervention communities are shown in black circles.

Source: Grosskurth, et al., Lancet **346**, 530-36 (1995)

HIV incidence over 2 years in intervention and comparison communities, and crude and adjusted risk ratios

| | Crude RR (95% CI) | Adjusted RR* (95% CI) |
|-----------------------------|------------------------------|----------------------------------|
| Matched pair/stratum | | |
| 1 Rural | 0.62 | 0.59 |
| 2 Islands | 0.62 | 0.65 |
| 3 Roadside | 0.82 | 0.88 |
| 4 Lakeshore | 0.59 | 0.62 |
| 5 Lakeshore | 0.36 | 0.35 |
| 6 Rural | 0.50 | 0.50 |
| Overall | 0.57† (0.42–0.76) | 0.58† (0.42–0.79) |

*Adjusted for potential confounders. †Geometric mean.

Source: Grosskurth, et al., Lancet **346**, 530-36 (1995)

Funding Sources

- National Institute of General Medical Sciences MIDAS grant U01-GM070749
- National Institute of Allergy and Infectious Diseases grant R01-AI32042

The End