Statistical Methods for Infectious Diseases Assessing Indirect, Total, and Overall Effects Group-Randomized Studies Lecture 12

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February 17, 2009

Population Effects

Study Designs for Dependent Happenings

Group-Randomized Studies

Parallel Studies

Stepped wedge designs

Constrained randomization

Power and Sample Siize

Analysis

Study Designs for Dependent Happenings

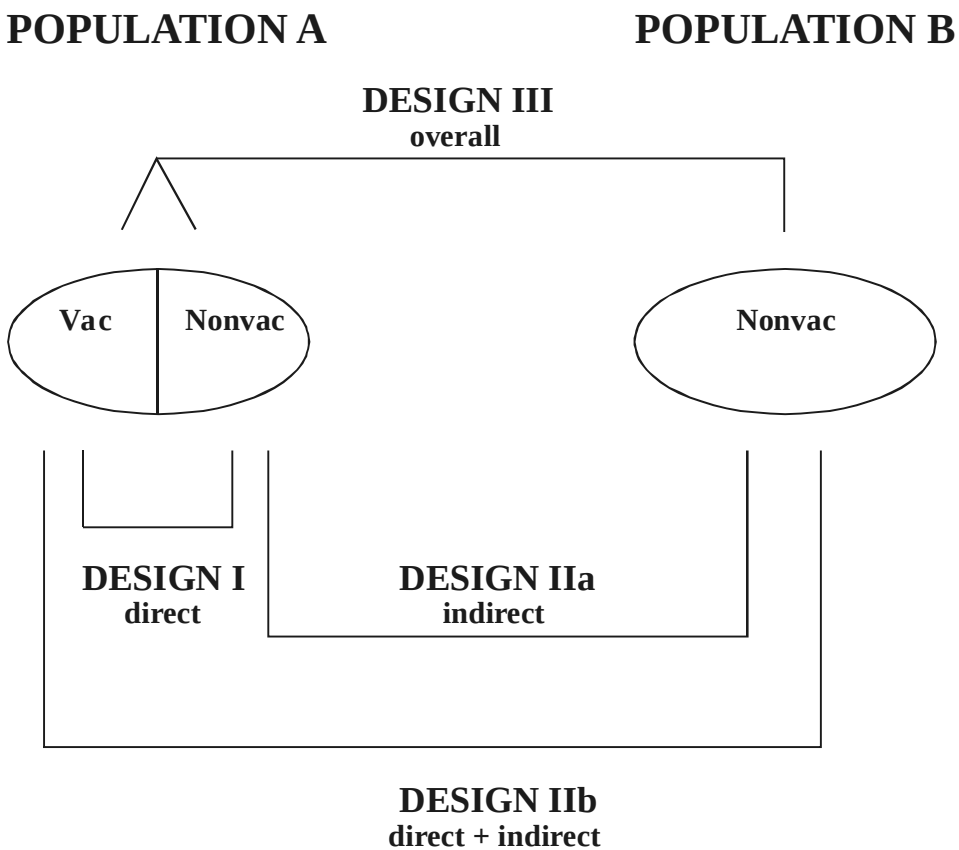

Figure: Halloran and Struchiner (1991)

Population-level Vaccine Effectiveness

- Indirect effects, VE_{IIa}
  - effects of widespread vaccination on someone who is not vaccinated
- Total Effects, VE_{IIb}
  - possibly synergistic effect of being vaccinated and widespread vaccination on someone who is vaccinated
- Overall effects, VE_{III}
  - overall population effect, say, reduction in incidence, (change of average of of first infection, R_0) 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	$VE_{S,p}\dagger = 1 - \frac{p_{\cdot 1}}{p_{\cdot 1}}$	$VE_{I,p} = 1 - \frac{p_{1\cdot}}{p_{0\cdot}}$	$VE_{T,p} = 1 - \frac{p_{11}}{p_{00}}$

Study design: Unconditional:	I direct	IIA indirect	IIB total	III overall
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.

Cluster-, group, community randomized studies

- intervention, or intervention strategy is randomized to groups of individuals.
- often conducted because it is not feasible to allocate the intervention individually, even though the effects on the individuals are of interest.
- Vaccination studies sometimes use a group-randomized design even when the direct protective effects are of interest because of practical or ethical consideration: polio trials.
- in household-based studies of vaccination where the parents or other household members might be unwilling to do a discordant, individual randomization.

Two levels of allocation

- Vaccination strategy or program at population level
- Individual allocation of vaccine within target population
- Both, either, or neither might be randomized

Definitions: potential outcomes

- The *direct effect* of vaccination in an individual is the difference between the outcome in the individual receiving the vaccine and what the outcome would have been if the individual had not been vaccinated, all other things being equal.

- The *indirect effect* of a vaccination program or strategy on an individual is the difference between what the outcome is in the individual *not* being vaccinated in a community with the vaccination program and what the outcome would have been in the individual, again not begin vaccinated, but in a comparable community with no vaccination program.

Definitions: potential outcomes

- The combined *total effect* in an individual of being vaccinated and the vaccination program in the community is the difference between the outcome in the individual being vaccinated in a community with the vaccination program and what the outcome would be if the individual were not vaccinated and the community did not have the vaccination program.

- The *overall effect* of a vaccination program is the difference in the outcome in an average individual in a community with the vaccination program compared to an average individual in a comparable population with no vaccination program.

Group-randomized studies

- Several populations needed for inference
- Should be comparable for characteristics related to transmission, covariates $\longrightarrow$ matching
- Effects of intervention possibly poorly defined: defined within
  - context of a particular intervention program
  - depends on level of coverage, distribution of vaccine, mixing patterns
  - Halloran and Struchiner (1995); Hudgens and Halloran (2008)
- subpopulations can also be compared

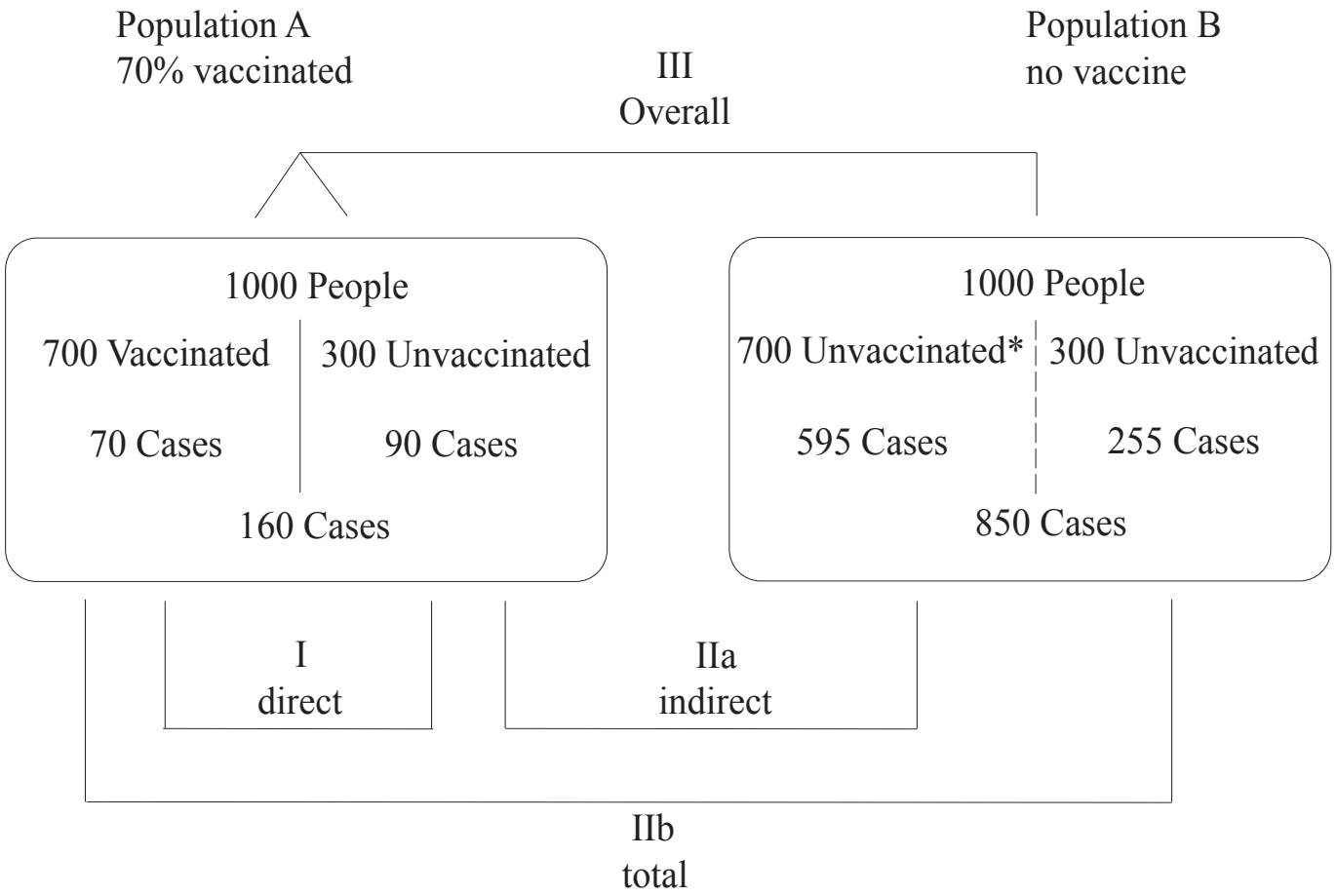

Figure: Comparison of two populations.

Simple Example, cont'd

- Direct effect: CI(A,unvac) − CI(A,vac)
  $= 90/300 - 70/700 = 0.30 - 0.10 = 0.20$
- Indirect effect: CI(B,unvac) − CI(A,unvac)
  $= 850/1000 - 90/300$ or
  $= 225/300 - 90/300 = 0.85 - 0.30 = 0.55$
- Total effect: CI(B,unvac) − CI(A,vac)
  $= 850/1000 - 70/700 = 0.85 - 0.10 = 0.75$
- Overall effect: CI(B) − CI(A)
  $= 850/1000 - 160/1000 = 0.85 - 0.16 = 0.69$
- Direct + Indirect = Total
- Overall essentially weighted average of pop B.

Different units to distinguish

- Unit of assignment: could be the unit that is assigned the allocation strategy, say a community is randomized to receive the vaccination strategy of interest, and another is assigned to receive a control vaccination strategy. With vaccines, additional unit of assignment is individual.
- Unit of intervention: health clinics, physician's practices, or nurse practitioner's office within a school.
- Unit of observation: cases is generally the individual; covariates individual or community
- Unit of analysis: assessed against the variation among those units.

Table: Design considerations in group-randomized studies to estimate indirect, total, or overall effects of vaccination strategies

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:
$\longrightarrow$ randomization or observational

Table: Community-randomized designs and randomization schemes

Design	Randomization scheme	Covariate constraints
Parallel	Completely randomized	Unconstrained
Stepped wedge	Stratified	Constrained
Cross-over	Matched-pairs	

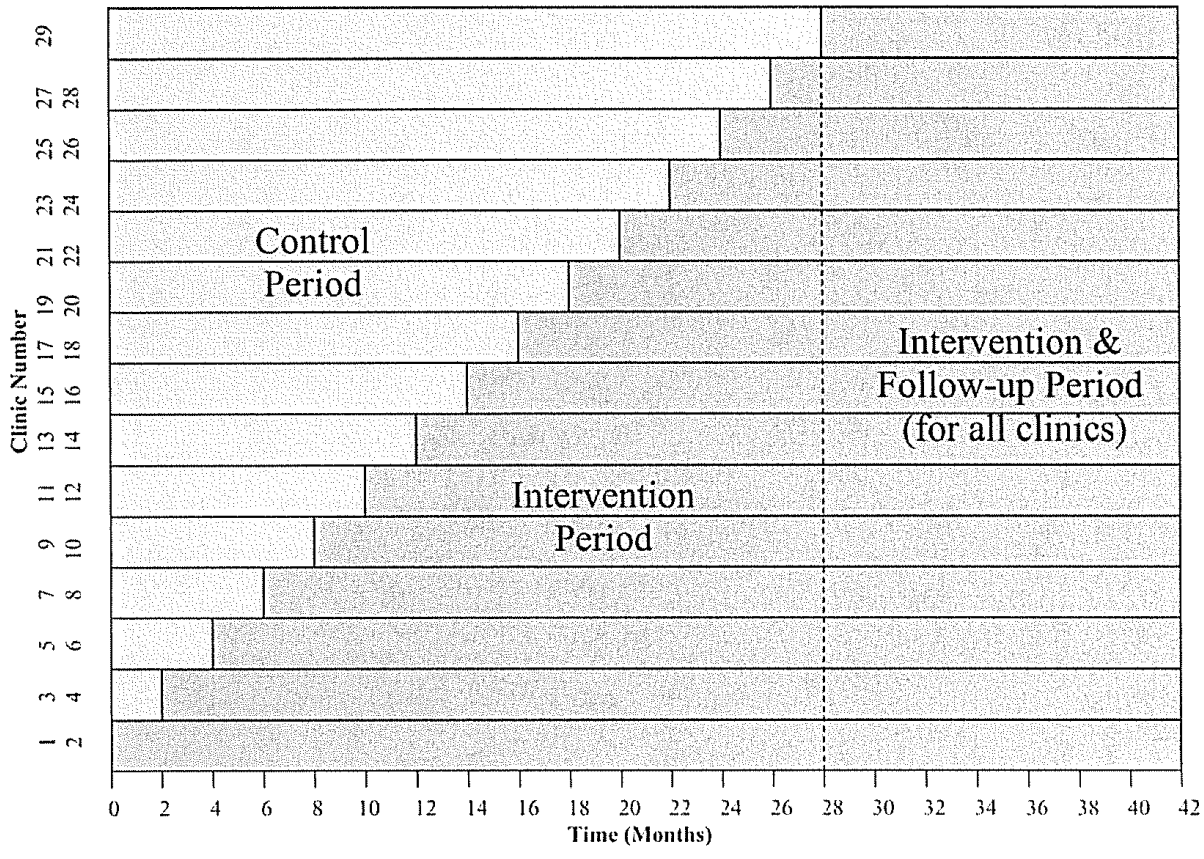

Figure: Example of a stepped wedge design (from Moulton et al 2007)

Parallel Pneumoccocal Vaccine Study

- Moulton et al (2001) designed a group-randomized, double-masked phase III trial of a seven-valent *Streptococcus pneumoniae* conjugate vaccine (PCV7) in American Indian populations in the U.S.

- Active control: a conjugate meningococcal group C vaccine (MnCC vaccine)
- Goal: evaluate the total effects of vaccination as well as the indirect effects, and at the same time to serve as a pivotal vaccine study.
- Goal: vaccinate as many children under 2 years of age as possible.

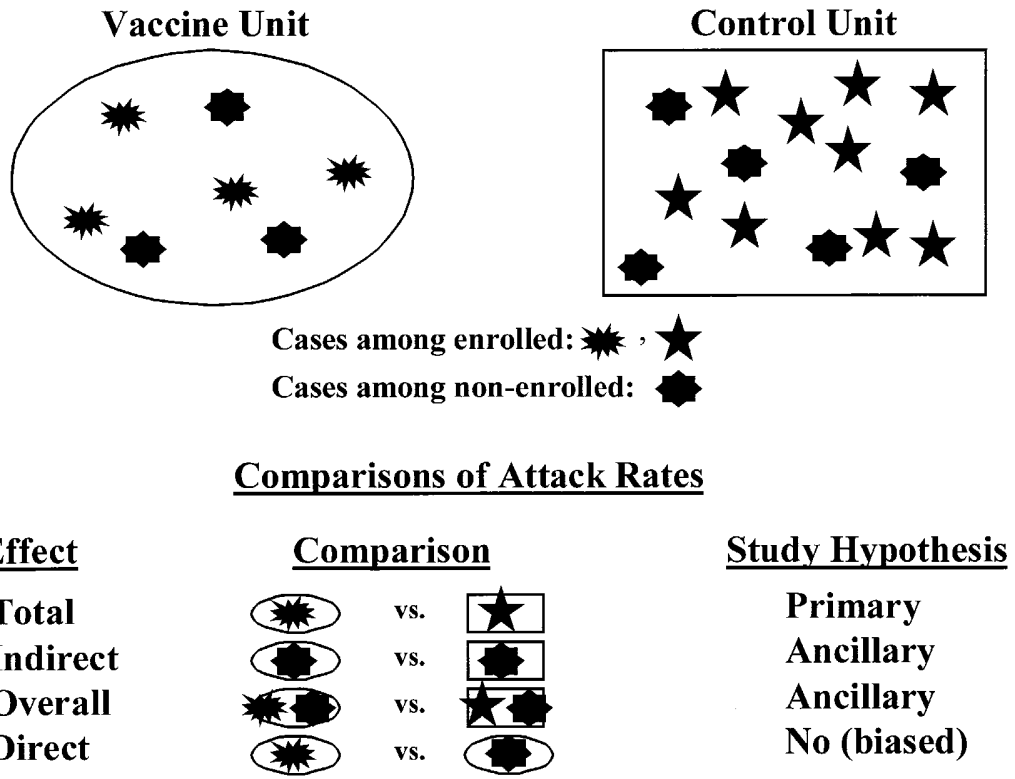

Figure: Schematic of the questions of interest in the pneumococcal vaccine trial in Native Americans. Participants in each vaccine unit receive PCV7 vaccine, and those in each control unit receive MnCC vaccine (from Moulton et al 2001).

Study

- 4,164 infants enrolled in the PCV7 communities and 3,926 in the MnCC communities between April 1997 and December 1999.
- 38 geographically defined randomization groups in consultation with the representatives with the Navajo Nation, and others to minimize mixing among the social and geographic units.
- Trial was designed to continue until 48 cases of invasive pneumococcal disease due to vaccine serotypes had accumulated.
- Discontinued due to licensing of vaccine: only 9 cases had accrued

Stepped wedge design

- Can be used when a parallel design is unfeasible either for practical or for ethical reasons.
- By the end of a trial using a stepped wedge design, all randomization units will have received the vaccination
- the time of the introduction of the vaccine intervention to each cluster is randomized
- Also referred to as phased implementation strategy.

Hepatitis B vaccine study in the Gambia

- Gambia Hepatitis Study Group (1987)
- Goal: to evaluate the effect of infant vaccination on preventing chronic liver disease and liver cancer later in life.
- 30 year followup planned
- Because at that time, four injections were required for full immunization, and the vaccine was to be administered along with the routine EPI vaccines, it was considered logistically unfeasible to do an individually randomized trial, as well as potentially ethically questionable.

Hepatitis B vaccine in The Gambia

- 7 EPI vaccination teams each assigned a portion of 104 delivery points that were visited at least once every two weeks.
- The study plan randomized one of the teams every 10 to 12 weeks to introduce the hepatitis B vaccine to the EPI schedule by vaccinating all newborns who reported to the vaccination points served by the team.
- This was to continue for a period of about four years, when all teams would be giving the vaccine, so that country-wide coverage would be achieved
- Followup planned

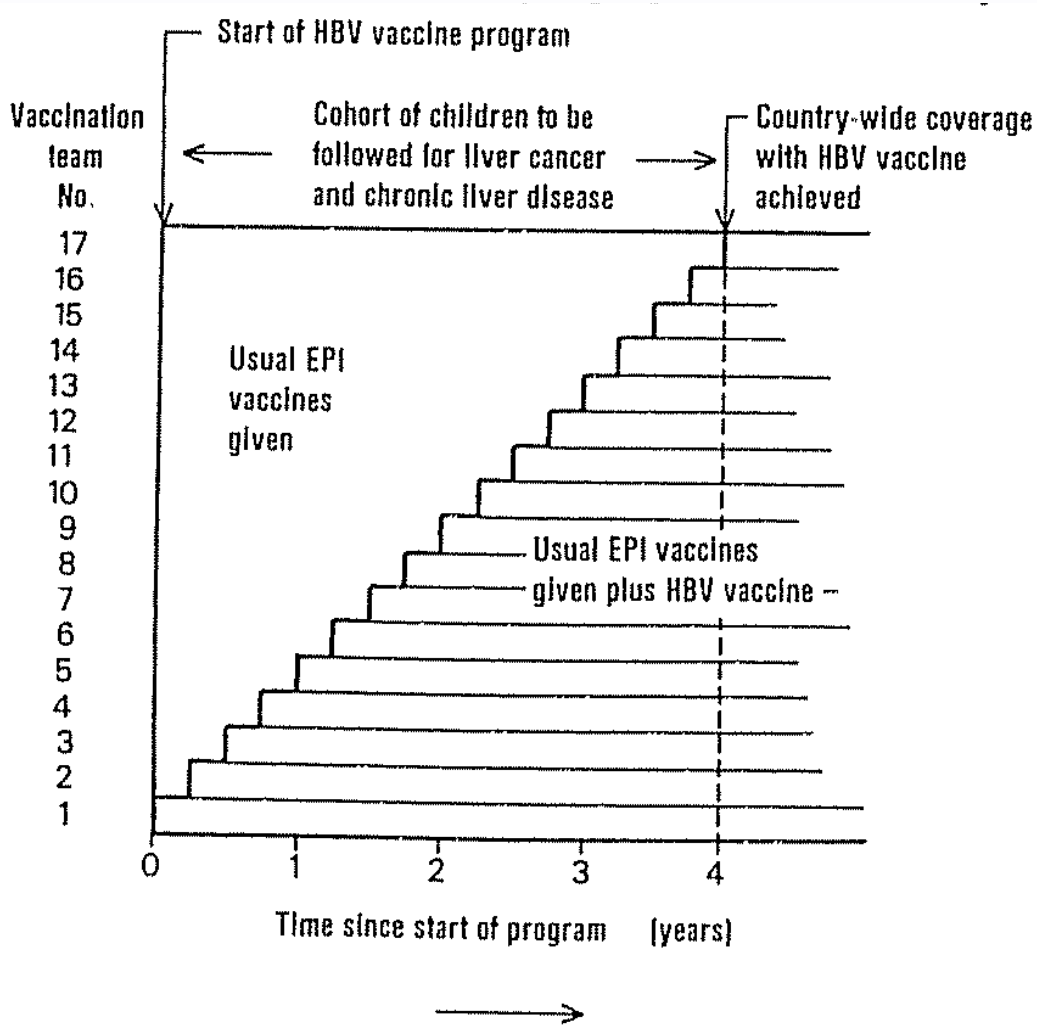

Figure: Stepped wedge design in the Gambia (from the Gambia Hepatitis Study Group 1987)

Covariate-constrained Randomization

- In the constrained, or restricted randomization, certain balancing criteria are determined before randomization that still retain validity of the design.
- Then the final randomization scheme is randomly chosen from among those that both satisfy the constraining criteria and are still valid.
- A completely randomized design is valid if each pair of randomization units has the same probability of being allocated the same treatment.

Constraints

- For continous covariates such as incidence rates, choose some measure based on the standard deviation or absolute mean difference.
- For dichotomous covariates, $\pm$ some percentage points might be appropriate.
- For example, suppose there was a difference in the incidence of disease between the north and south regions of the study area.
- Then one would not want all of the intervention sites in the north and control sites in the south.
- One could assign a 0,1 dummy variable for north and south and require that the difference between the intervention and control values be less than 10%.

Constraints

- Other important aspects, such as sources of water, proportion of the population with a certain educational level, health clinics, or roads within geographic areas can also be balanced within some specified range.
- Composite scores or more than one covariate can be used for defining the constraints that need to be satisfied.
- The constraining criteria can vary among the covariates.

Identify all possible allocations

- Form a list of all the possible allocations.
- For a design completely randomized at the group level, there will be $\binom{2N}{N}$ entries, where $2N$ is the total number of groups.
- For a pair-matched design, there will be 2^N entries, where N is the number of pairs.
- Making a pass through all of these entries, select those allocations that meet the specified criteria.

Check allocations for validity

- For example, some pairs of groups may always be in the same arm of the study, while others may never be in the same arm.
- To check the allocations, make a matrix whose elements are the number of times, from among those allocations satisifying the constraints, each pair is together.
- Examine the list for signs of over- or underrepresented pairs.
- If the allocations seem overly constrained, then relax one or more of the constraining criteria.
- Repeat until the allowable allocations seem appropriate.
- Then randomly select one of the allowable allocations.
- One can construct the matrix from a large number of acceptable designs, and choose one of them (SAS).

Table: Baseline average annual dengue incidence rate (percent) over the past three years in each of four communities to be included in the dengue vaccine trial. The balance of the randomization is measured by the mean difference in average annual incidence between the communities to receive vaccine and the control communities (adapted from Moulton (2004)).

	Communities				
Allocation	Vaccine		Control		Mean difference
A	3	5	11	13	−8
B	3	11	5	13	−2
C	3	13	5	11	0
D	5	11	3	13	0
E	5	13	3	11	2
F	11	13	3	5	8

Constraints in Stepped Wedge Design

- For example, it would be undesirable for all of the low-incidence communities to be randomized to introduce the vaccination strategy early in the stepped wedge study.
- One might want to aim for a balance on group-time spent in the control and vaccination program status with respect to the group-level covariates of interest..
- General idea: for each possible sequence of introduction of the vaccination strategies, the constraints are checked to see whether they are satisfied.
- If the number of groups is too large to enumerate all possible sequences, sequences are sampled randomly from all possible ones by random permutations of the group labels.

Ad hoc approach (Moulton et al 2007)

- For each jth covariate of the ith group, $i = 1, \ldots, N$, x_{ij}, and for a given time of entry t_i of group i into the vaccination strategy, $t = 1, \ldots, T$, let c_j be a proportional covariate-specific tolerance.
- The constraint can be expressed as

$$\frac{1}{1+c_j} < \frac{\sum_{i=1, t_i \neq T}^{N} (T - 1 - (t_i - 1)) x_{ij}}{\sum_{i=1, t_i \neq T}^{N} (t_i - 1) x_{ij}} < (1 + c_j).$$

- Then the sum of the covariate values weighted by the number of time units in the vaccine intervention must be within $c_j \times 100\%$ of that for the control status.

General Considerations

- The sample size calculation needs to take into account that randomization is by group rather than by individual.
- In general, group-randomized designs are less efficient than individually randomized studies due to the related factors of intra-group correlation and intergroup variability.
- That is, the more similar the individuals within each group are to each other and the more different the groups are from one another, the greater the group design effect on sample size will be.
- For a given sample size, a stepped wedge design will generally be less efficient than a parallel design.

Two measures used

- 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.
- The design effect D, or variance inflation factor, σ. For trials with equal numbers of individuals in each community,

$$D = \sigma = 1 + (n - 1)\rho,$$

  where n is the number of individuals per community, ρ is the intra-cluster correlation coefficient.
- D: factor by which the sample size needs to be increased above that required for an individually randomized trial to make up for randomization by cluster.

Analyzing Group-randomized Studies

- Key issue in analyzing group-randomized studies is to account for the clustering or group-randomization
- Two general approaches to analysis that account for potential within-cluster correlation:
  1. reduce the data for each cluster to a single observation and perform a standard two-sample analysis.
  2. do the analysis at the individual level but account for correlation somehow.
- Bootstrap, GEE, random effects....

Stepped wedge design

- Secular trends could be an issue
- Moulton et al (2006): the analysis is carried out by maximizing a partial likelihood function similar to a Cox proportional hazards model, then accounting for clustering

Pneumococcal vaccine study

- Estimating indirect effects: a non-homogeneous Poisson process in time and space (Moulton et al 2006).

- Let λ_{it} be the rate of disease among the individuals of interest in randomization unit i on day t. Let n_{it} be the person-days of exposure in the ith group on day t, α_t be the effect of the tth day, and γ be the log rate ratio comparing those in the vaccine intervention communities ($z_i = 1$) to those in the control unit ($z_i = 0$).
- A simple model for λ_{it} is given by

$$\lambda_{it} = n_{it} \exp(\alpha_t + \gamma z_i).$$

- The parameter α_t is a nuisance parameter that captures any secular trends specific to day t, such as seasonal or weekend effects.

Allow for different levels of coverage

- . Let Mnc_{it}^{25-49} be one for the ith unit on the tth day if it is a community randomized to MnCC vaccine, and if 25–49% of the children under age 2 on that day have received at least one immunization, otherwise it is zero.

$$\begin{aligned}\lambda_{it} &= n_{it}\exp(\alpha_t + \beta_1 Mnc_{it}^{25-49} + \beta_2 Mnc_{it}^{50+} \\ &\quad +\beta_3 Pnc_{it}^{0-24} + \beta_4 Pnc_{it}^{25-49} + \beta_5 Pnc_{it}^{50+})\end{aligned}$$

- One can compare across treatment arms within coverage levels. For example, if the difference $\beta_4 - \beta_1$ is negative, then it suggests presence of indirect effects at that level of coverage 25–49%.
- The rate ratio comparing the two treatment arms at above 50% coverage is given by $\exp(\beta_5 - \beta_2)$.

Eliminate nuisance parameter α_t

- Let T be the number of days in the study.
- Let δ_t be one if there is a case on the tth day and zero otherwise.
- Define $R(t)$ as the set of indices of those units at risk on day t. Let $\mathbf{x}_{jt}$ be the row vector of dummy variables for the jth unit on day t, with $j = i$ representing the community with a case on that day.
- The conditional likelihood function is

$$\prod_{t=1}^{t=T} \left[n_{it} \exp(\mathbf{x}_{it}\boldsymbol{\beta}) / \sum_{j \in R(t)} n_{jt} \exp(\mathbf{x}_{jt}\boldsymbol{\beta}) \right]^{\delta_t}.$$

Table: The reference category are units that received MnCC vaccine which on a given day had less than 25% of children enrolled in the study. The CMLEs are the log rate ratios comparing incidence in non-enrolled childrein in the given category in the reference category (from Moulton et al (2006)).

Dummy variable (arm/ % coverage)	CMLE	Robust SE	Bootstrap SE	Robust CI	Bootstrap percentile interval
MnCC 0–24%	0				
MnCC 25–49%	1.18	0.51	0.62	0.18, 2.17	0.12, 2.74
MnCC 50+%	1.93	0.66	0.81	0.64, 3.23	0.46, 4.25
PCV7 0–24%	1.09	0.49	0.60	0.14, 2.04	−0.07, 2.58
PCV7 25–49%	0.98	0.62	0.75	−0.24, 2.19	−1.05, 2.59
PCV7 50+%	1.96	0.71	0.85	0.56, 3.37	0.68, 4.37

Thank You!