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Analysis of Cluster Randomized Trials

Fundamental Concepts

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Overview

- What are cluster randomized trials?
- Why do we do them?
- Implications for sample size and analysis
- Simple methods based on cluster summaries
- Adjusting for covariates
- Regression methods

Illustrations from HIV prevention trials

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What is a cluster randomized trial?

Groups (clusters) of individuals are randomly allocated to the different treatment conditions

The clusters might be:

- Towns, villages, cities
- Arbitrary geographical zones
- Schools
- Factories
- Clinics, hospitals, medical practices

Why use this design?

- Community-level interventions
- Logistical convenience/acceptability
- Avoid or reduce *contamination*

Also, for infectious disease interventions

- Capture effects on infectiousness as well as susceptibility
- Capture *mass effect* of intervening in entire population (*indirect* as well as *direct* effects)

Statistical implications of CRT design

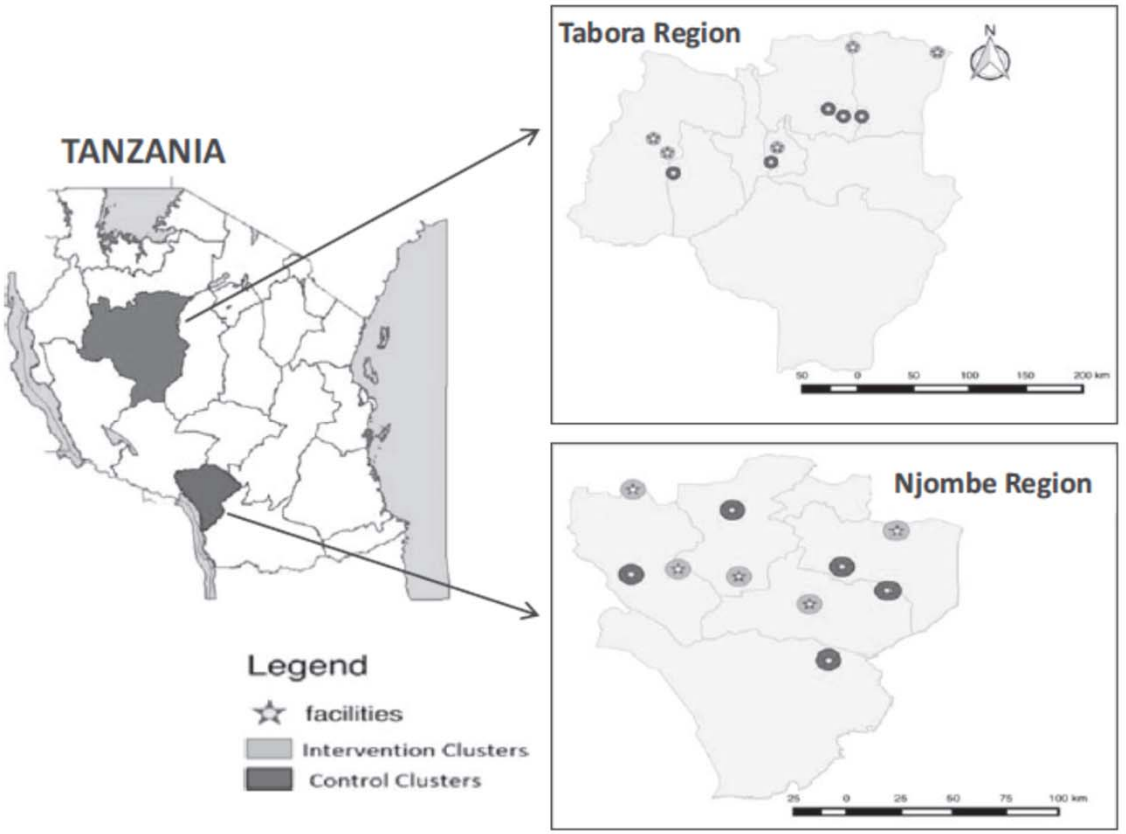
- Observations on individuals in the same cluster are *correlated*
- This correlation needs to be accounted for in the *design* and *analysis*
- Sample size needs to be increased
  - Design effect = $1 + (m - 1)\,\rho$
  - m = cluster size, ρ = ICC
- Need to use analysis methods that account for correlation
- Imbalance between study arms when small number of clusters

Approaches to analysis

- Analysis of cluster-level summaries
  - Compute summary measure for each cluster: e.g. a risk, rate or mean depending on outcome
  - Compare these cluster summaries between study arms using t-test or non-parametric test
- Regression methods on individual-level data
  - Use *random effects* models to account for correlation
  - Warning: Not robust when fewer than ~15 clusters per study arm

Example: Cluster-level summaries

- Trial to increase uptake of VMMC in adult men



Example: Cluster-level summaries

	Proportion aged 25-34	GM of proportions
Intervention clusters (10)	1462/6191	17.7%
Control clusters (10)	493/3926	13.0%

t-test on log(proportion)

RR: 1.36 (CI: 0.93-1.93)

p = 0.11

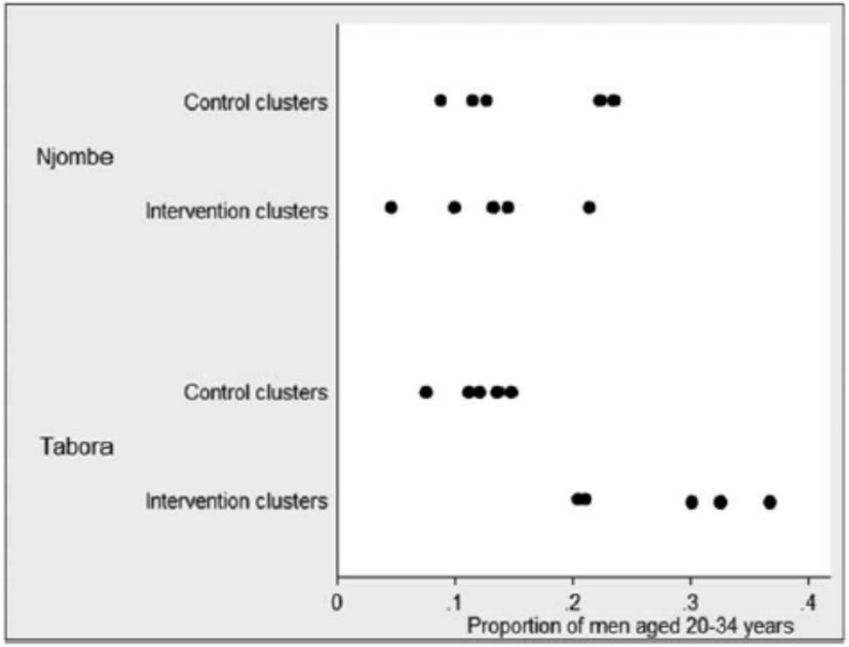
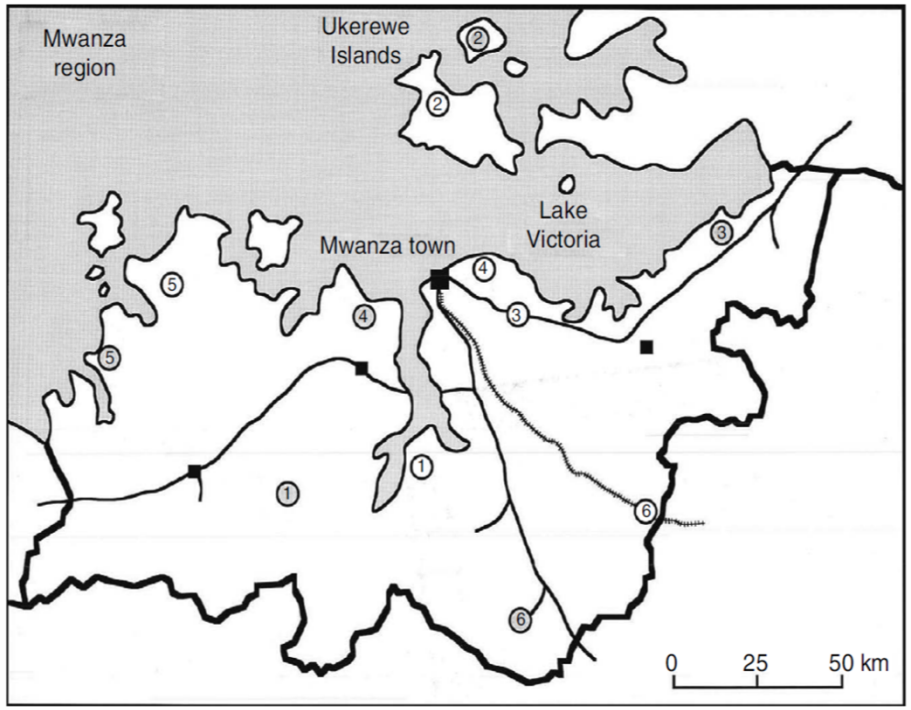


Fig. 3. Proportion of VMMC clients aged 20–34 years in each cluster, by arm and region. VMMC, voluntary medical male circumcision.

Wambura et al, AIDS 2017

Example: Matched pairs CRT

- Mwanza STD trial
- Paired design may help improve balance and reduce between-cluster variance
- 6 pairs of rural communities
- Intervention: improved STD treatment at clinic
- Measured impact on HIV incidence in randomly selected cohort of 1000 adults in each community
- Note: cohort selected from *general population*, not clinic patients



Grosskurth, Lancet 1995

Example: Matched pairs CRT

	HIV baseline prevalence (%)		HIV seroconversions		Crude RR (95% CI)
	Intervention	Comparison	Intervention	Comparison	
Matched pair/stratum					
1 Rural	3·9	3·0	5/568 (0·9%)	10/702 (1·4%)	0·62
2 Islands	2·0	1·6	4/766 (0·5%)	7/833 (0·8%)	0·62
3 Roadside	6·8	8·6	17/650 (2·6%)	20/630 (3·2%)	0·82
4 Lakeshore	5·4	4·3	13/734 (1·8%)	23/760 (3·0%)	0·59
5 Lakeshore	2·8	4·7	4/732 (0·5%)	12/782 (1·5%)	0·36
6 Rural	1·8	4·5	5/699 (0·7%)	10/693 (1·4%)	0·50
Overall	3·8	4·4	48/4149 (1·2%)	82/4400 (1·9%)	0·57† (0·42–0·76)

- RR computed in each matched pair
- Crude RR computed as geometric mean across pairs
  = 0.57 (CI: 0.42 – 0.76)
- Paired t-test gives p = 0.004
- Non-parametric sign test gives p = 0.03 (2-sided)
- Note: some imbalance in baseline HIV prevalence

Adjusting for covariates

- Can use 2-stage approach
- Stage 1:
  - Fit regression model to individual data including covariates but NOT study arm
  - Use model to obtain *Expected* number of events (e.g. HIV seroconversions) in each cluster under null hypothesis
  - Compute O/E for each cluster (*ratio residuals*)
- Stage 2:
  - Carry out t-test (paired or unpaired) on the O/E ratio residuals

Adjusting for covariates in paired CRT

Cluster	Intervention	Control	Adj RR
1	O_{I1}/E_{i1}	O_{C1}/E_{C1}	$(O_{I1}/E_{i1})/(O_{C1}/E_{C1})$
2	O_{I2}/E_{i2}	O_{C2}/E_{C2}	$(O_{I2}/E_{i2})/(O_{C2}/E_{C2})$
….	….	….	….

- Adjusting for age, sex and baseline HIV prevalence
- Adj RR = 0.39 (CI: 0.45-0.83)
- Paired t-test gives p = 0.009

Limitations of cluster summary methods

These methods have been shown to be highly robust but have a number of limitations:

- They are inconvenient as they generally involve a two-stage procedure
- They give equal weight to each cluster and so are not optimally efficient
- They do not allow the effects of intervention and other covariates (and their interactions) to be estimated together in the same regression model

Individual-level regression methods

- Random effects models and GEE are the most common approaches
- We focus on RE models here

Rates: $\log \lambda = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + u_i$

Binary: $\text{log-odds} = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + u_i$

Quantitative: $\mu = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + u_i$

where β_1 is intervention effect, $\beta_2, \ldots$ are covariate effects and u_i are random cluster effects (representing variation between clusters)

Example: Individual-level regression

- Comparison of two strategies of delivering HPV vaccine to schoolgirls in Tanzania
- Class-based (class 6) *vs* Age-based (12 years old)
- Primary outcome: HPV vaccine coverage by dose
- 134 primary schools randomly allocated to two strategies
- 3 private schools withdrew leaving 131 (67 class-based, 64 age-based)
- Analysed by Random Effects Logistic Regression

Example: Individual-level regression

	Age-based	Class-based
Dose 1	1788/2180 **82.0%**	2896/3352 **86.4%**
Dose 2	1695/2180 **77.8%**	2808/3352 **83.8%**
Dose 3	1572/2180 **72.1%**	2639/3352 **78.7%**

Dose 3

OR = 1.36 (CI: 1.02-1.82)

p = 0.04

ICC = 0.13

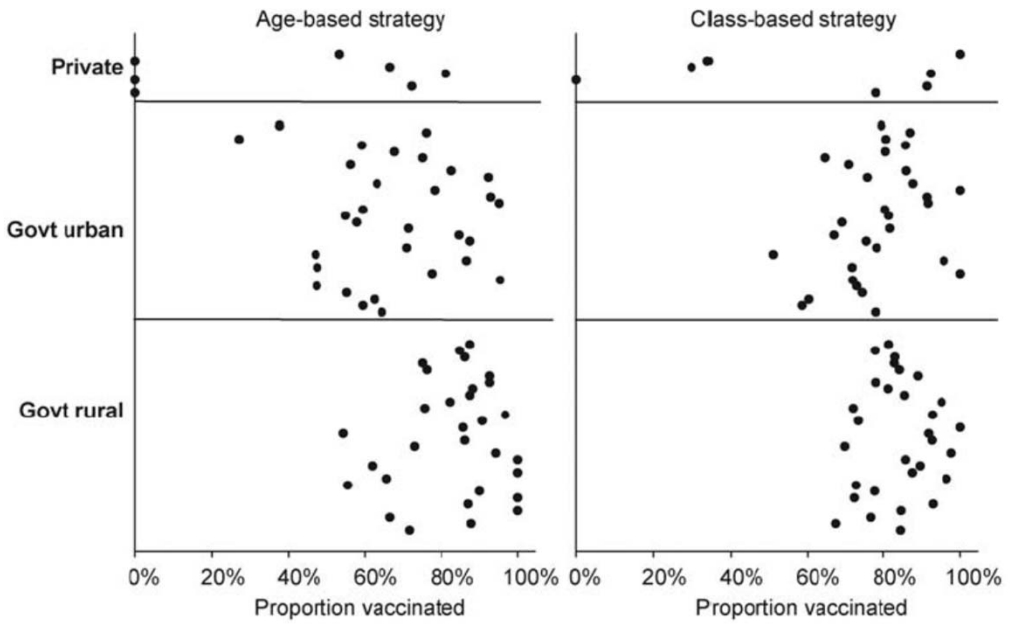


Figure 2. Coverage for dose 3 in each school, by school type and delivery strategy. Abbreviation: Govt, government.

Watson-Jones, JID 2012

Summary

- CRTs should be analyzed using methods that allow for correlated data
- Adjustment for covariates is often needed because balance not assured unless large number of clusters
- Regression methods are not robust for CRTs with small number of clusters
- CRTs different from conventional RCTs because study cohorts do not necessarily receive intervention – they are recruited to represent the general population of the community receiving the intervention

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