Evaluation of Public Health Interventions: Recent Developments in Cluster Randomized Trials and Related Designs

Department of Epidemiology & Biostatistics, GWU, March 26 2018

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Overview

1. Motivating example
2. Clustering
3. Small # clusters & baseline covariate imbalance
4. Stepped wedge designs

Cluster randomized trials

Motivating example

Background and motivation

Health and Literacy Intervention (HALI) cluster randomized trial (CRT)

- 101 schools: 51 intervention and 50 control
  - ~ 5000 children → ~ 50/school
- Intervention: screen & treat 1/term for 2 years
- Primary endpoint: malaria (yes vs. no) at 24 months

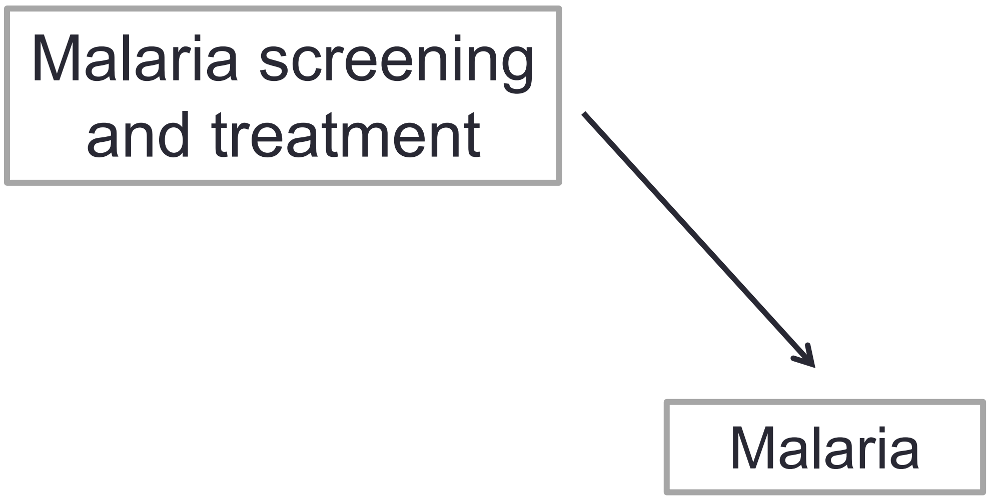
London School of Hygiene & Tropical Medicine

Health and Literacy Intervention Project

International Initiative for Impact Evaluation

Background and motivation

Health and Literacy Intervention (HALI) cluster randomized trial (CRT)



Hypothesis: screening and treating children for malaria will lead to reduced <u>prevalence</u> of malaria

Background and motivation

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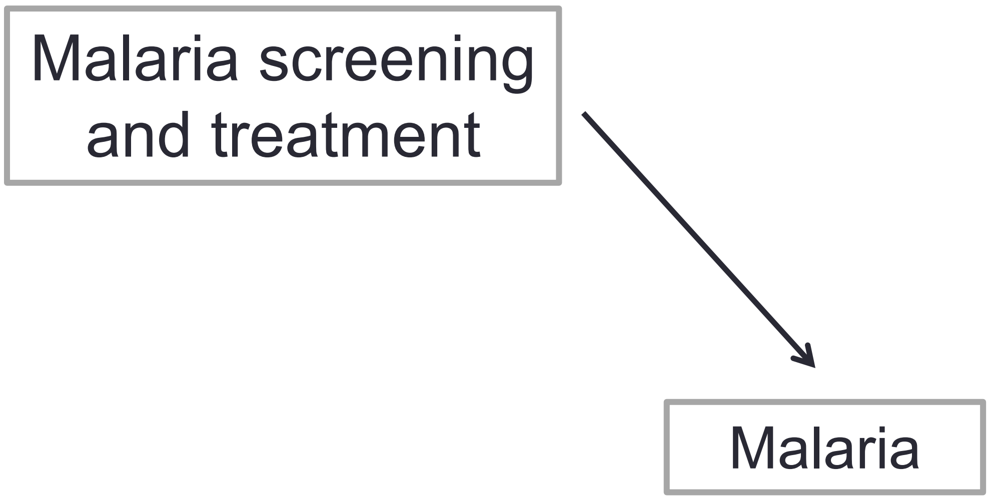

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Factors related to malaria: age, geographic location, bed-net use etc.

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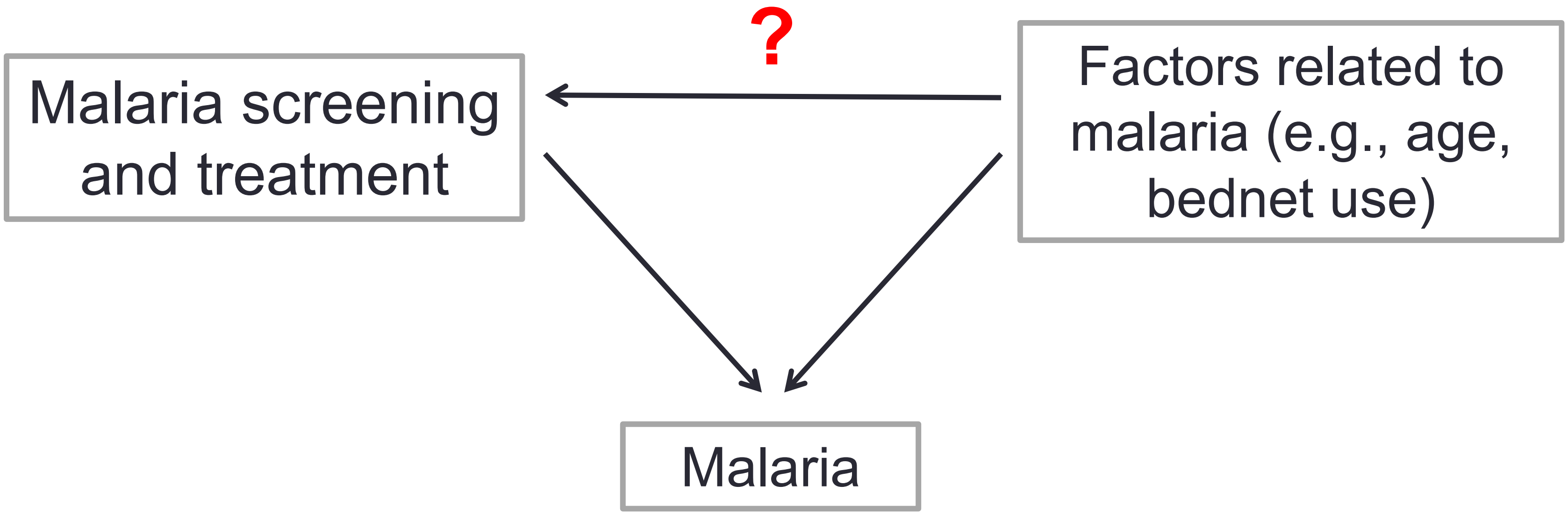

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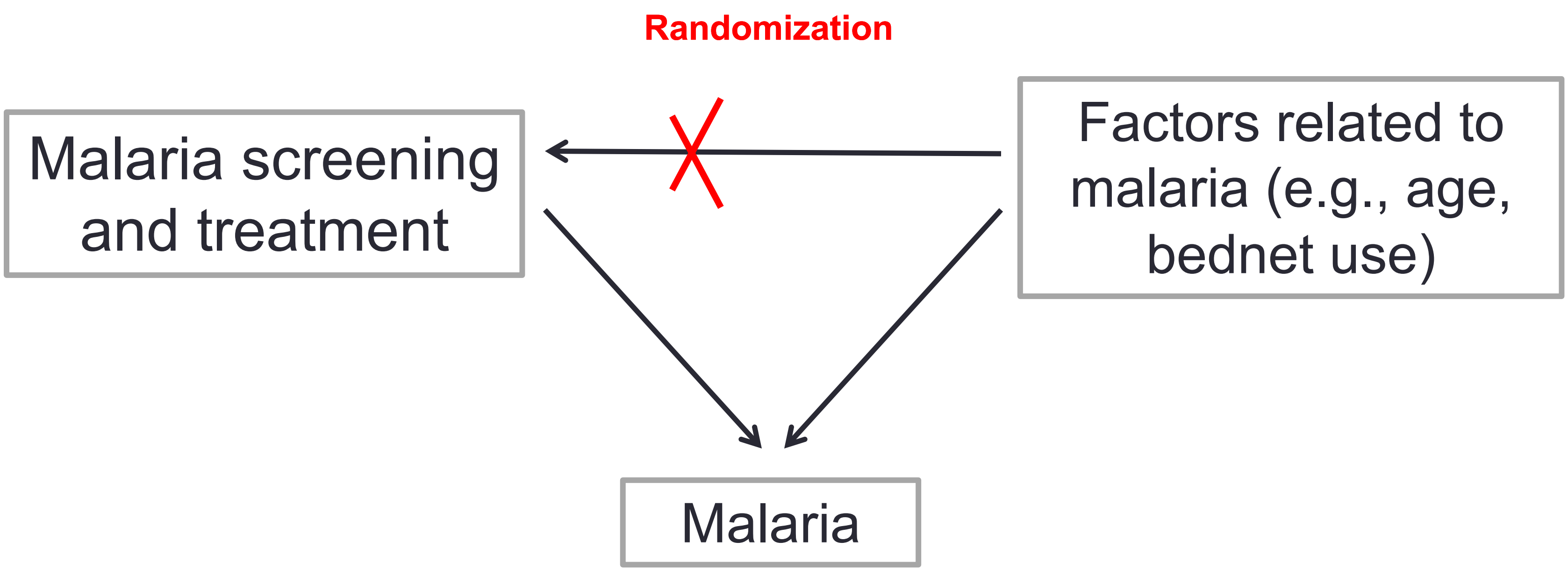

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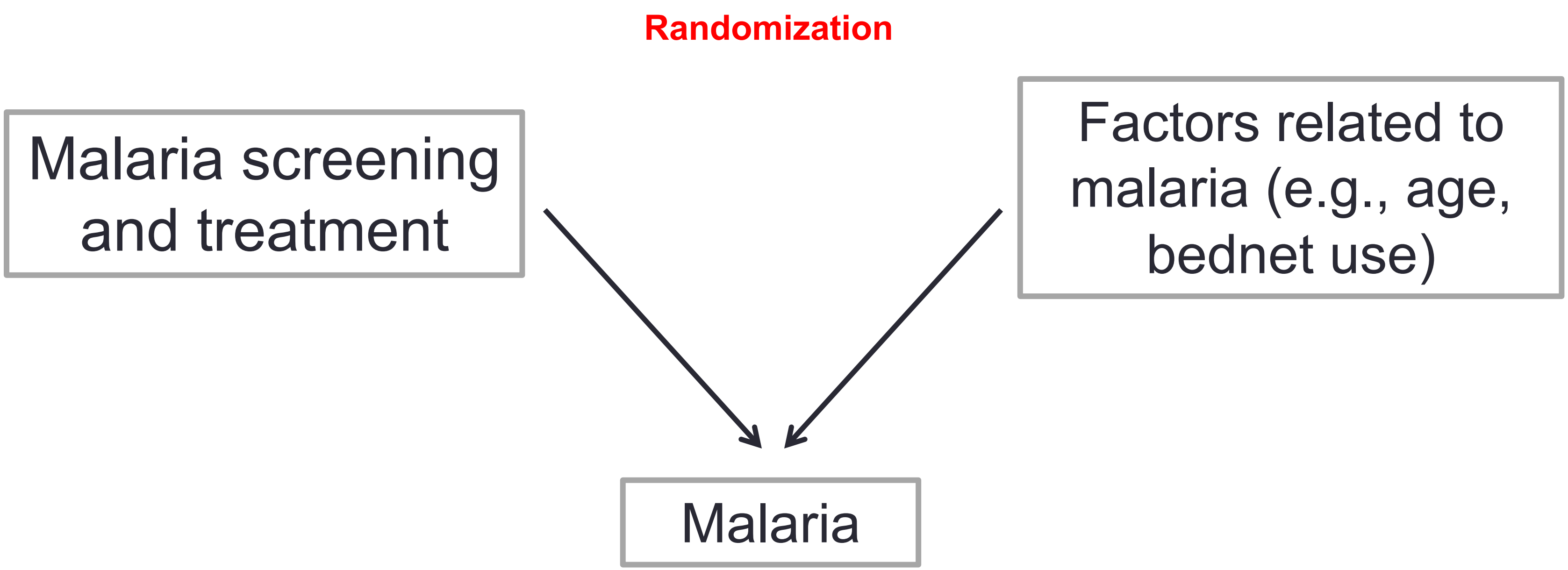

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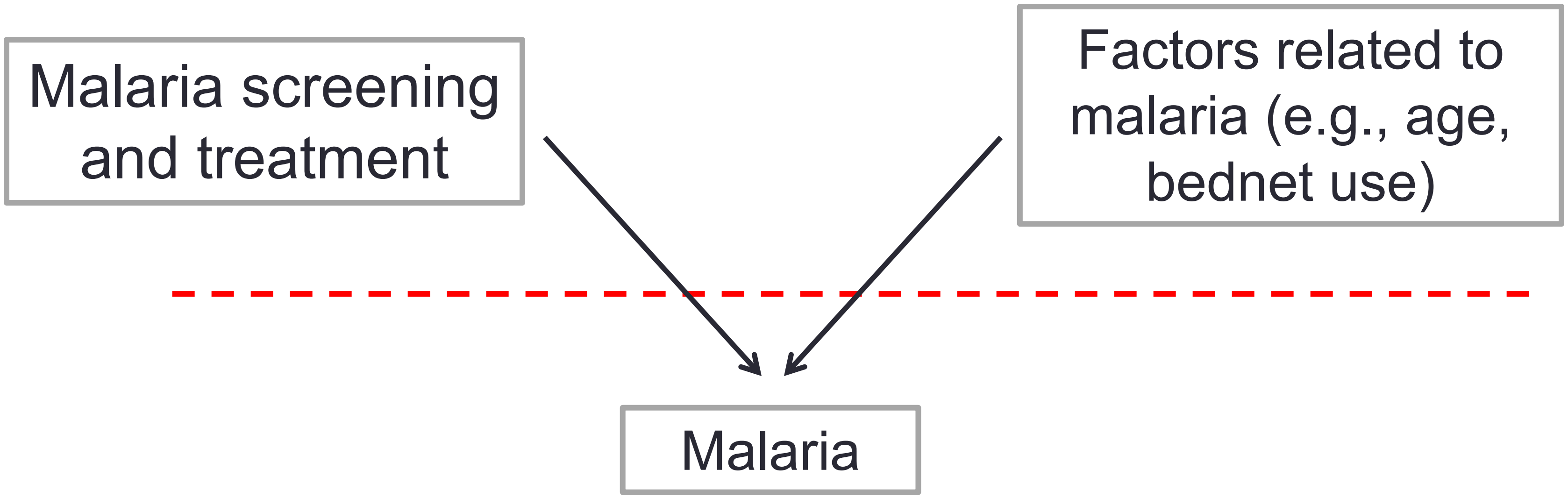
Health and Literacy Intervention (HALI) cluster randomized trial (CRT)

Level 2: Randomization at clinic (i.e., cluster) level

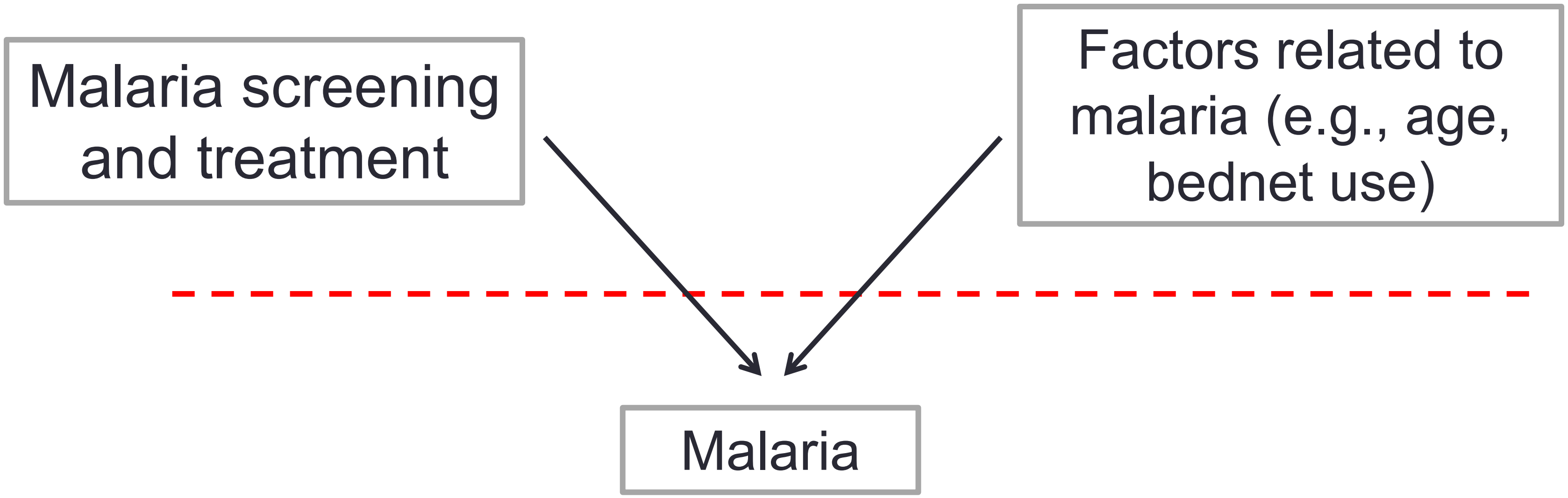


Level 1: Individual-level outcomes nested in schools

Background and motivation

Health and Literacy Intervention (HALI) cluster randomized trial (CRT)

Level 2: Randomization at clinic (i.e., cluster) level



Level 1: Individual-level outcomes nested in schools

Child-level outcomes within same school expected to be correlated with each other (ie, to *cluster*)

Background and motivation

Health and Literacy Intervention (HALI) cluster randomized trial (CRT)

Level 2: Randomization at clinic (i.e., cluster) level

Malaria screening and treatment

Factors related to malaria (e.g., age, bednet use)

Malaria

Level 1: Individual-level outcomes nested in schools

Child-level outcomes within same school expected to be correlated with each other (ie, to *cluster*)

Reduces power to detect treatment effect if same sample size used as under individual randomization

Implications of using CRT design

- CRT (statistical) price to pay
  - Lower power for same total sample size under individual randomization
  - Harder to detect an intervention effect
- So why use CRT design?
  - Intervention at cluster level (e.g., pump in village)
  - To avoid treatment contamination under individual randomization (e.g., HALI trial)
  - Logistically easier to implement trial

HALI trial

Two published outcomes papers

OPEN ACCESS Freely available online — PLOS MEDICINE

Impact of Intermittent Screening and Treatment for Malaria among School Children in Kenya: A Cluster Randomised Trial

Katherine E. Halliday[1]*, George Okello[2], Elizabeth L. Turner[3], Kiambo Njagi[4], Carlos Mcharo[5], Juddy Kengo[5], Elizabeth Allen[6], Margaret M. Dubeck[7], Matthew C. H. Jukes[8], Simon J. Brooker[1,9]

JOURNAL OF RESEARCH ON EDUCATIONAL EFFECTIVENESS
http://dx.doi.org/10.1080/19345747.2016.1221487

Improving Literacy Instruction in Kenya Through Teacher Professional Development and Text Messages Support: A Cluster Randomized Trial

Matthew C. H. Jukes[a,b], Elizabeth L. Turner[c], Margaret M. Dubeck[a,b,d], Katherine E. Halliday[e], Hellen N. Inyega[f], Sharon Wolf[g], Stephanie Simmons Zuilkowski[h], and Simon J. Brooker[e]

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Note: no evidence of an effect of intervention on malaria prevalence

HALI trial

Two published outcomes papers

Evidence of an effect on literacy outcomes due to a teacher intervention evaluated in same trial

JOURNAL OF RESEARCH ON EDUCATIONAL EFFECTIVENESS
http://dx.doi.org/10.1080/19345747.2016.1221487

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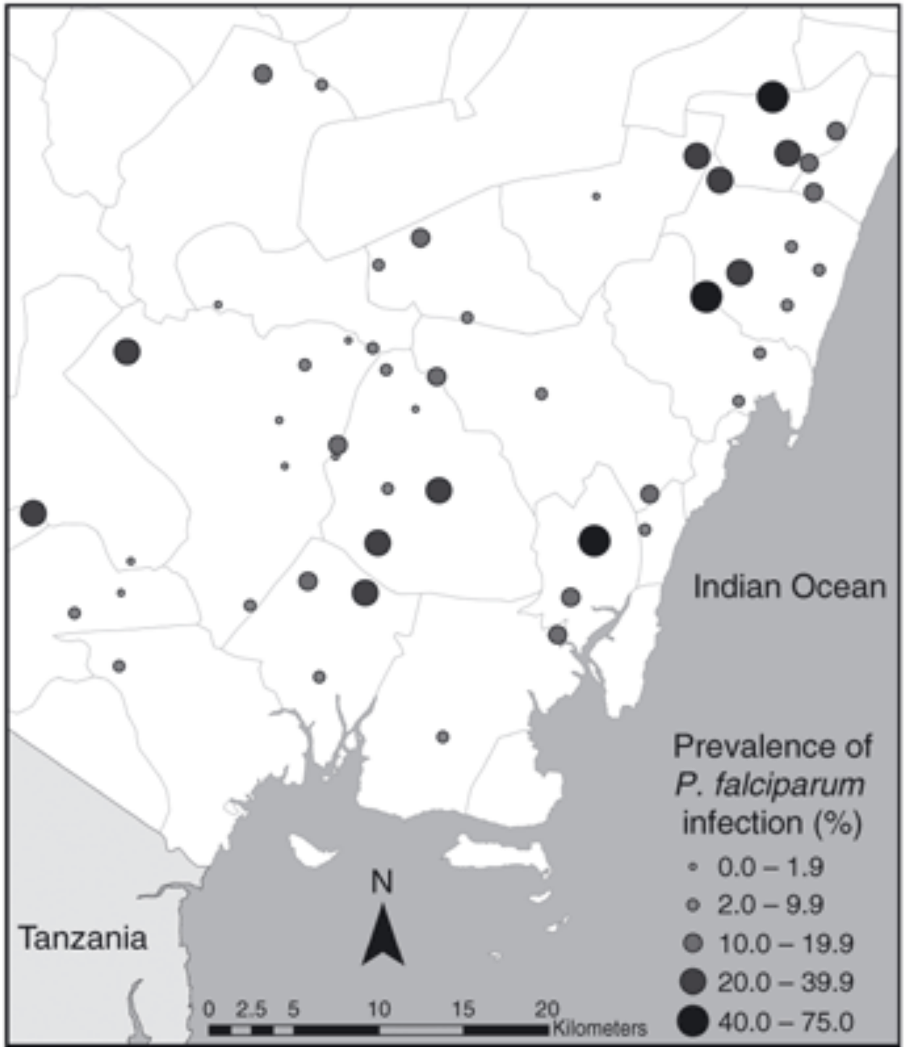
Cluster randomized trials

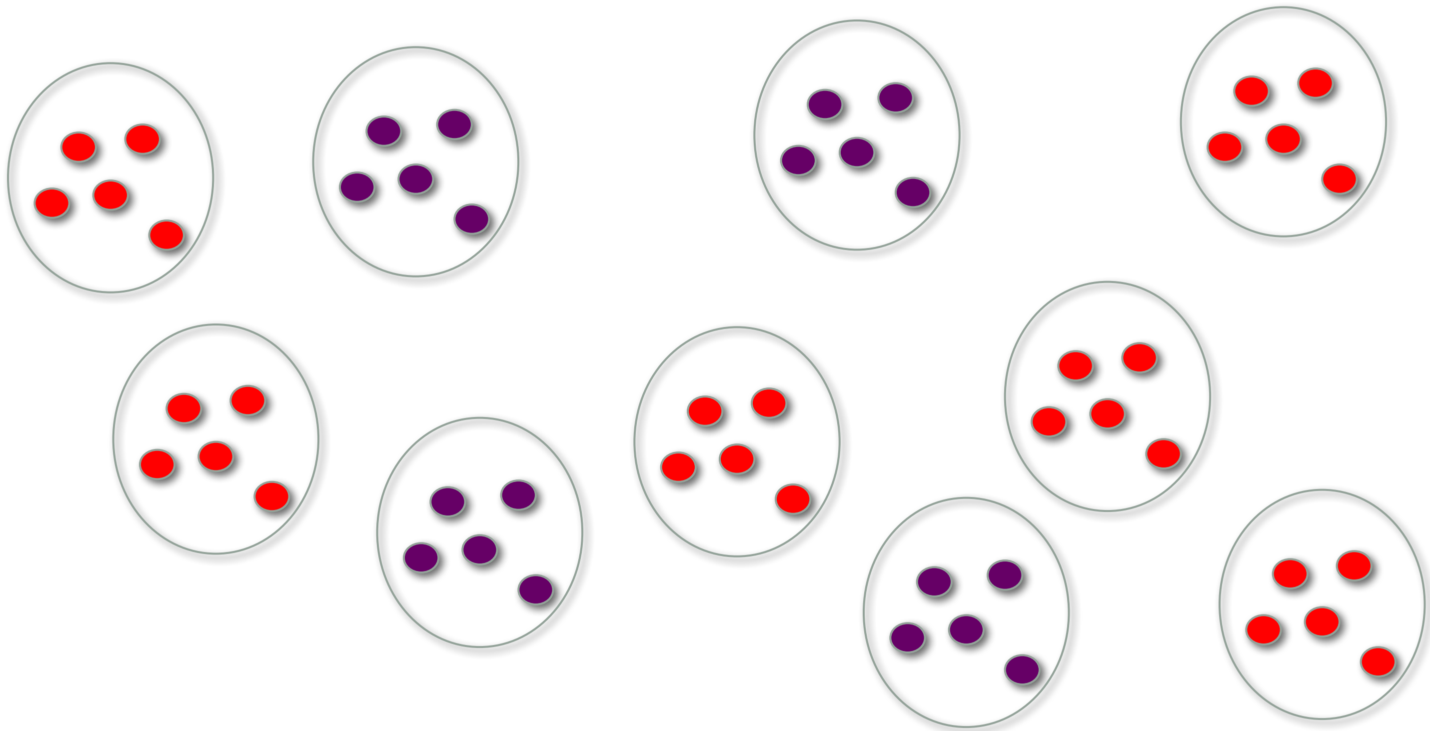
Design challenge: clustering

Baseline clustering: malaria prevalence by school



Halliday, Karanja, Turner et al. (2012), Tropical Medicine & International Health, 17(5): 532-549

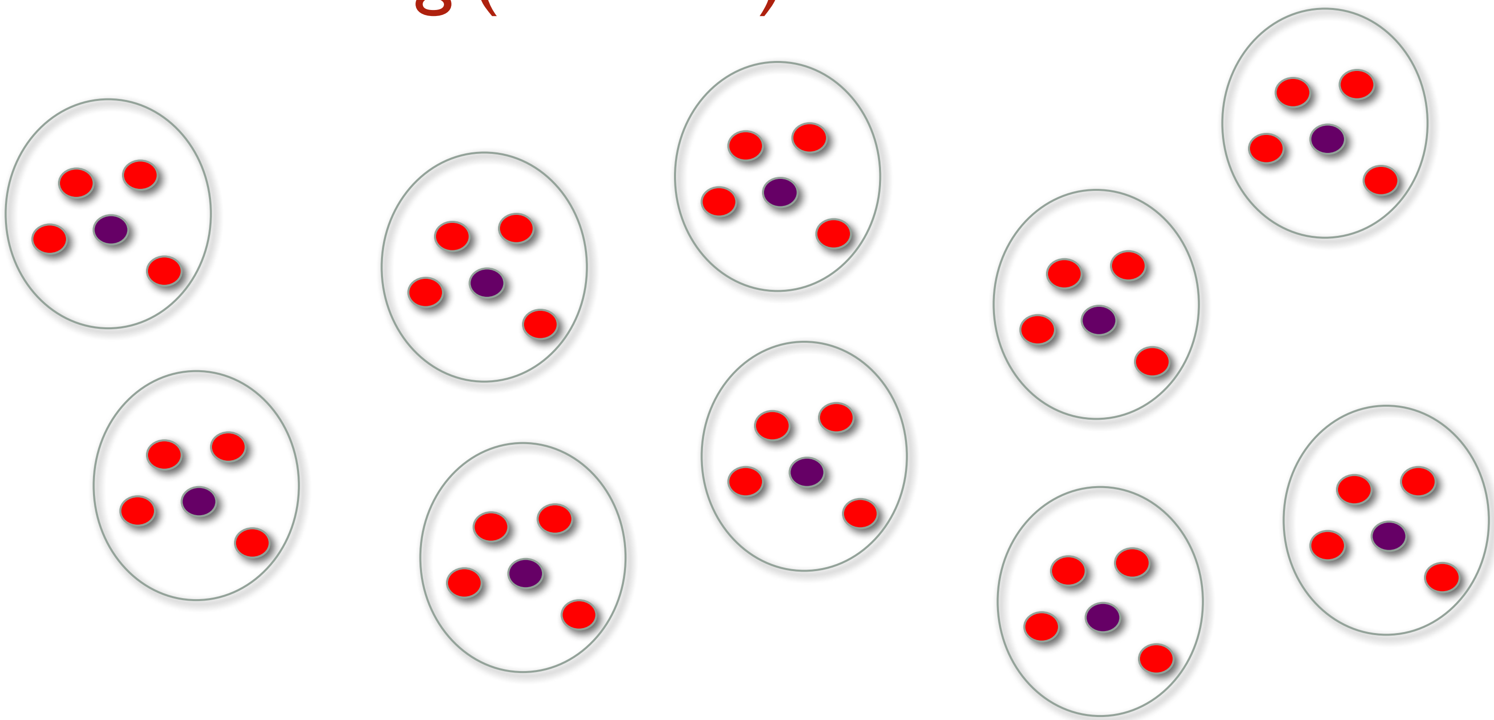
Complete clustering (ICC = 1)



Malaria
No malaria

>1 child /school gives no more information than 1 child/school since every child in a given school has the same outcome

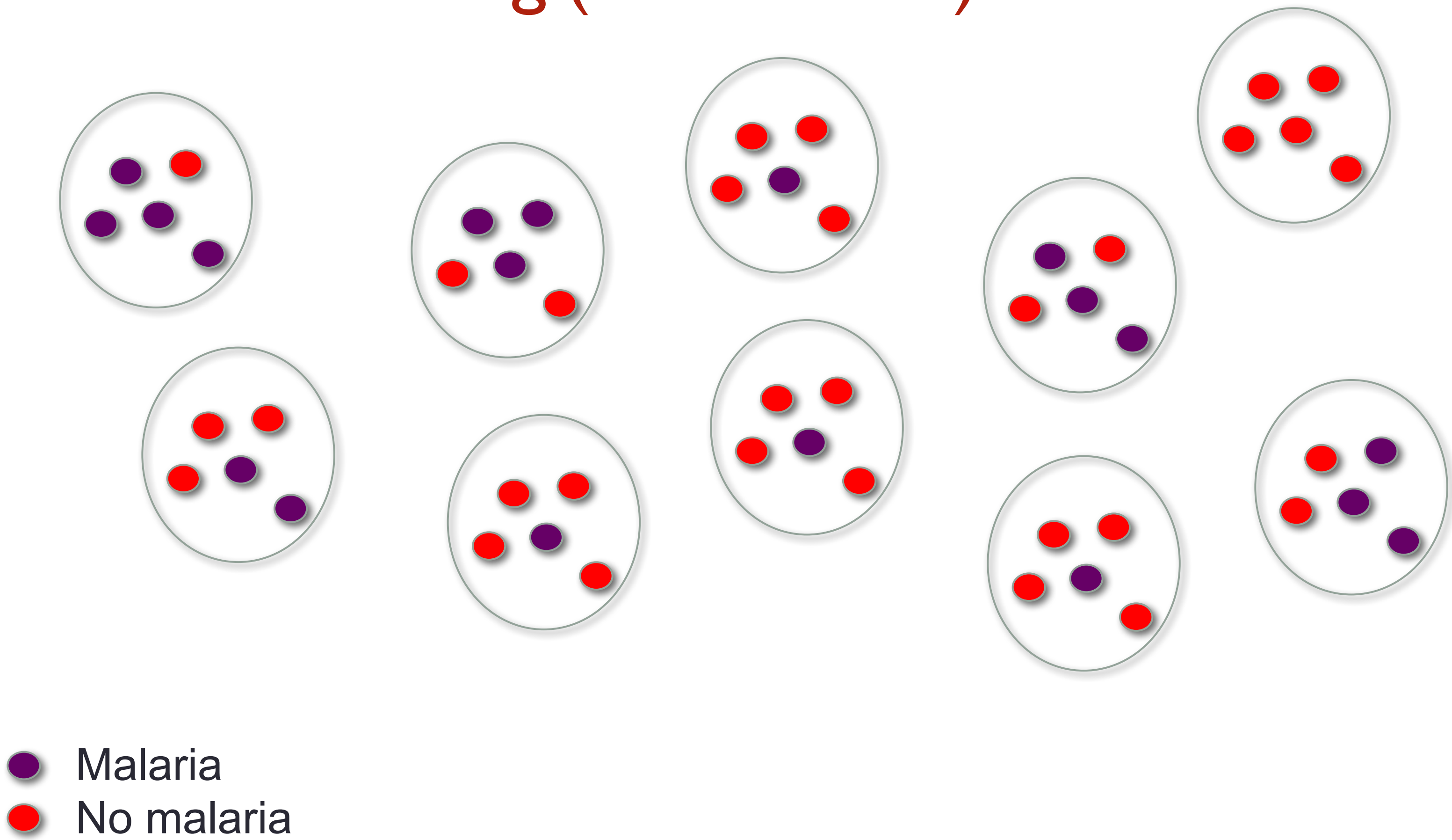
No clustering (ICC = 0)



- Malaria
- No malaria

20% prevalence of malaria in each school
No structure by school - more like a random sample of children

Some clustering (0 < ICC < 1)



A more typical situation: e.g., cluster-prevalence 0% - 80%

Clustering in CRTs

- Outcomes in same clusters more similar to each other than to those in other clusters
- Previous example
  - 50 children in 10 schools
  - Effective sample size between 10 – 50
- Implications for statistical inference
- Major challenge in design & analysis

Measure of clustering: ICC

Intra-cluster correlation coefficient (ICC, ρ)

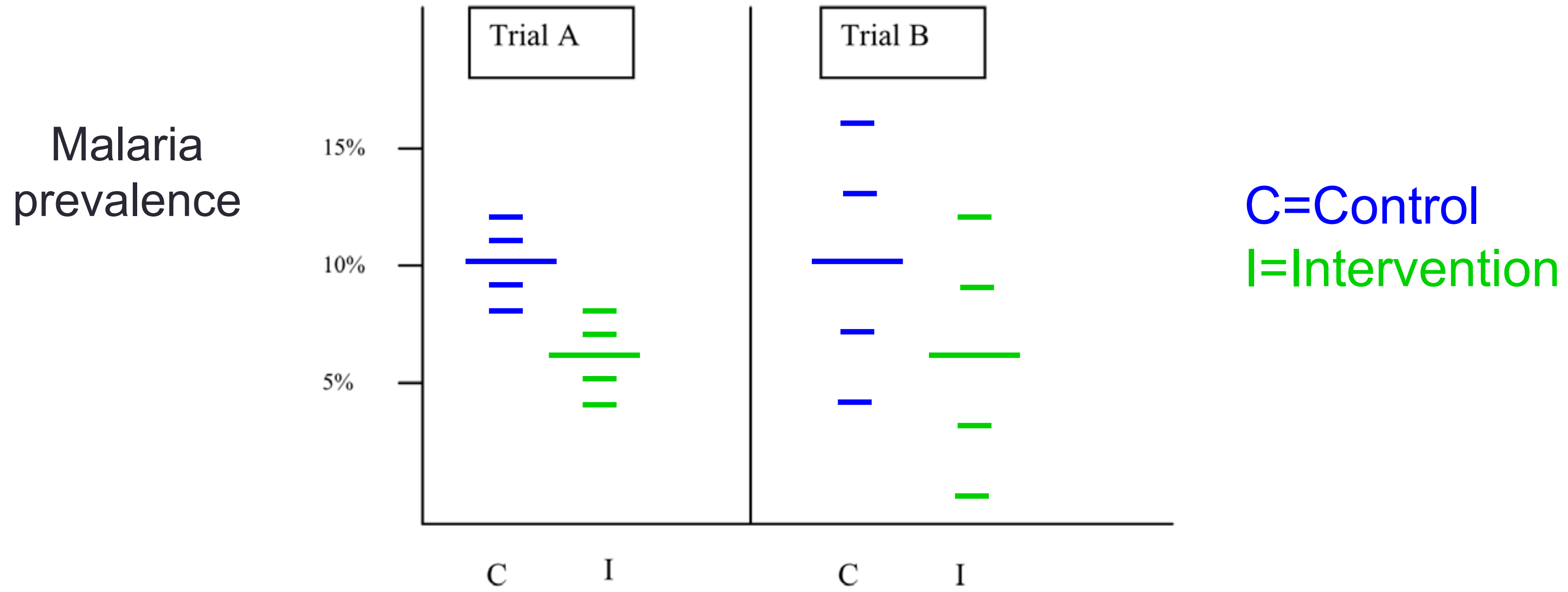
- Most commonly used measure of clustering
- Ranges: 0-1; 0= no clustering; 1= total clustering
- Typically < 0.2, commonly around 0.01 - 0.05

ICC for continuous outcomes:

$$\rho = \frac{\sigma_B^2}{\sigma_B^2 + \sigma_W^2} = \frac{\sigma_B^2}{\sigma_{Total}^2}$$

- Involves both Between-cluster & Within-cluster variance

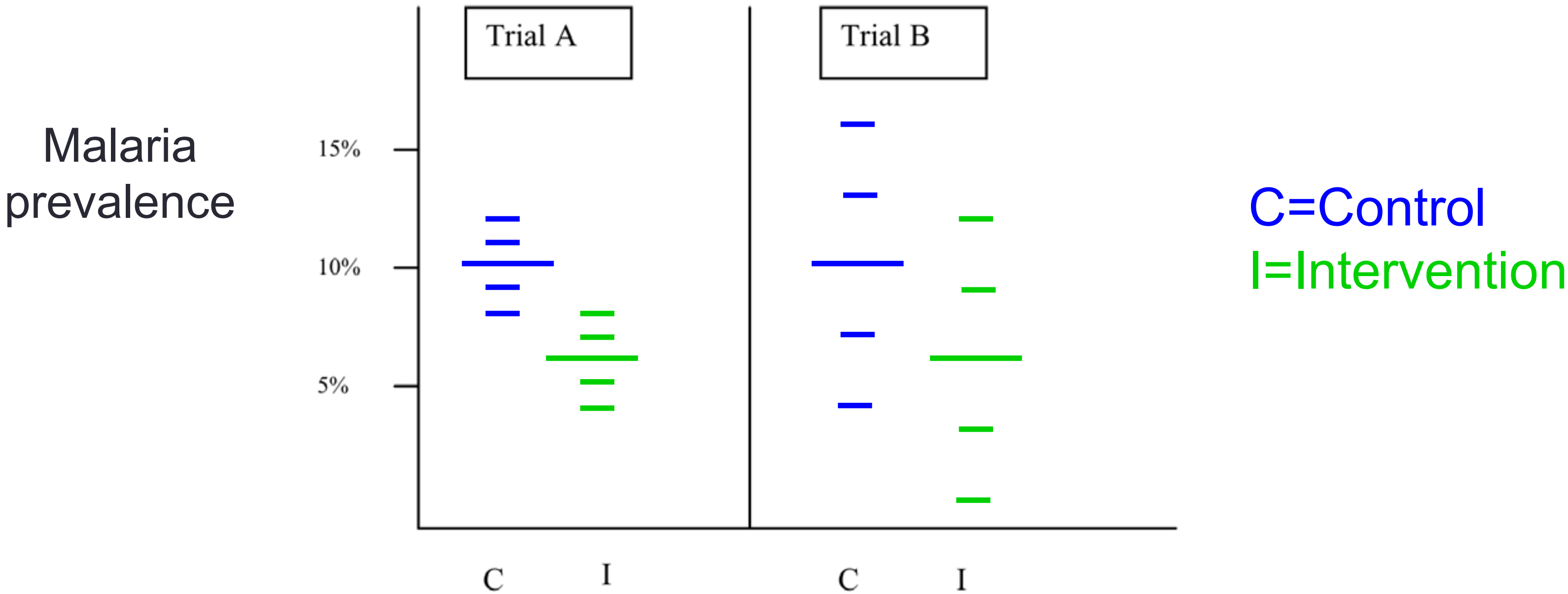
Clustering in CRTs: implications for analysis



- 5 schools each randomized to control and intervention
- 100 eligible participants per clinic measured

Example from Hayes & Moulton (2009)

Clustering in CRTs: implications for analysis



- 5 schools each randomized to control and intervention
- 100 eligible participants per clinic measured

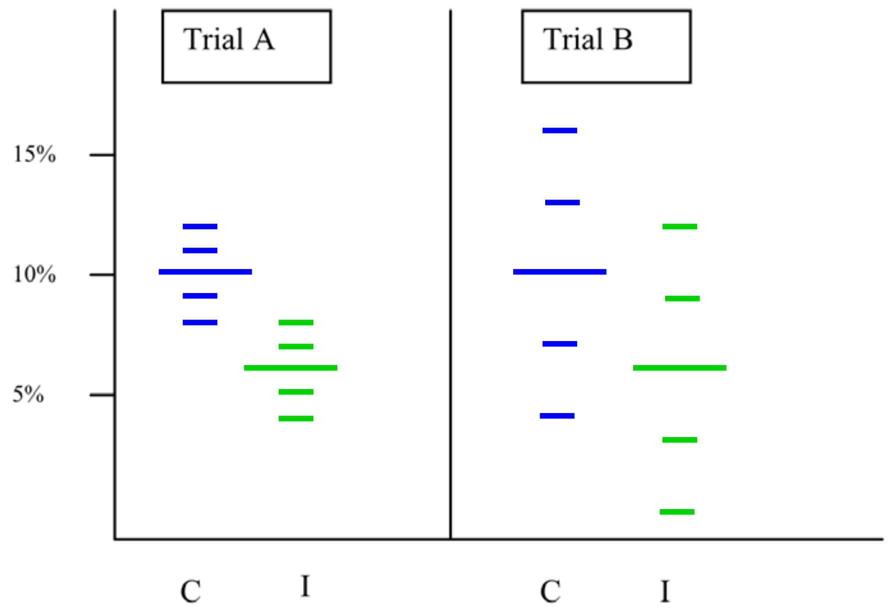
Overall malaria prevalence in each trial: 10% vs 6%

Question: is intervention effective?

Example from Hayes & Moulton (2009)

Clustering in CRTs: implications for analysis

Malaria prevalence



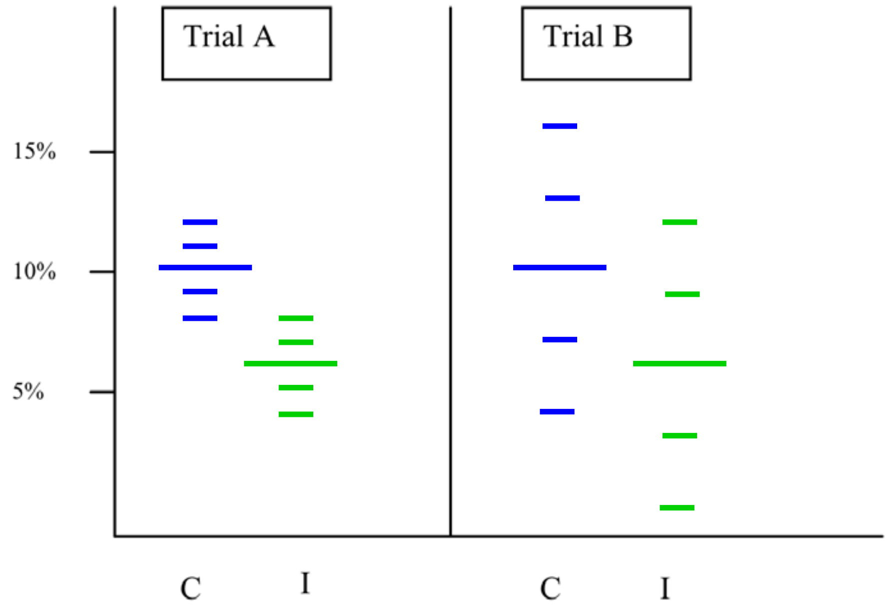
C=Control
I=Intervention

Which trial shows more evidence of benefit?

Example from Hayes & Moulton (2009)

Clustering in CRTs: implications for analysis

Malaria prevalence



C=Control
I=Intervention

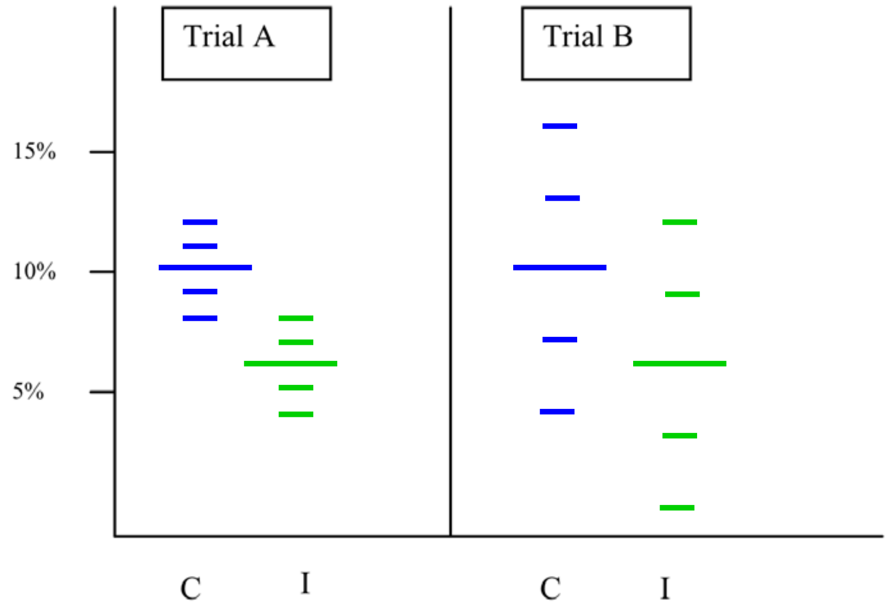
Study features

?

Example from Hayes & Moulton (2009)

Clustering in CRTs: implications for analysis

Malaria prevalence



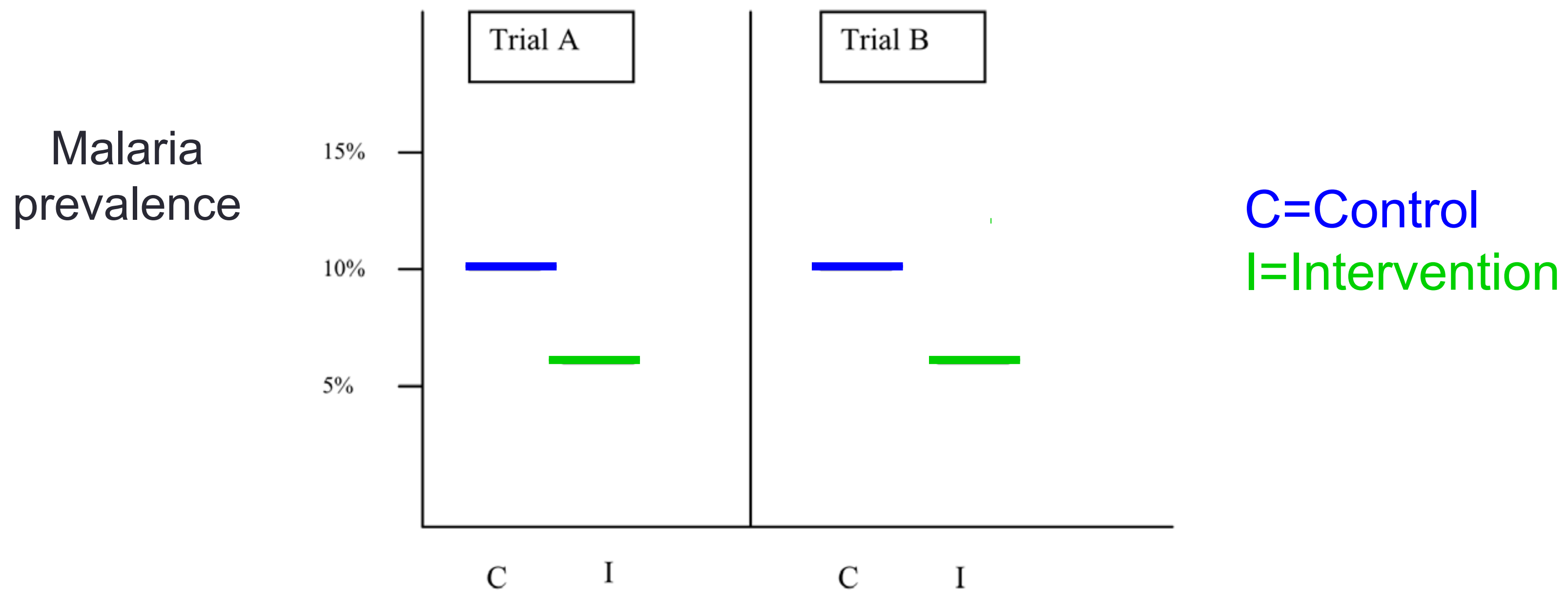
C=Control
I=Intervention

Study features

- Trial A:
  - Lower between-school variability
  - Little overlap of I & C clinic-level proportions
- Trial B: overlap of I & C school-level proportions

Example from Hayes & Moulton (2009)

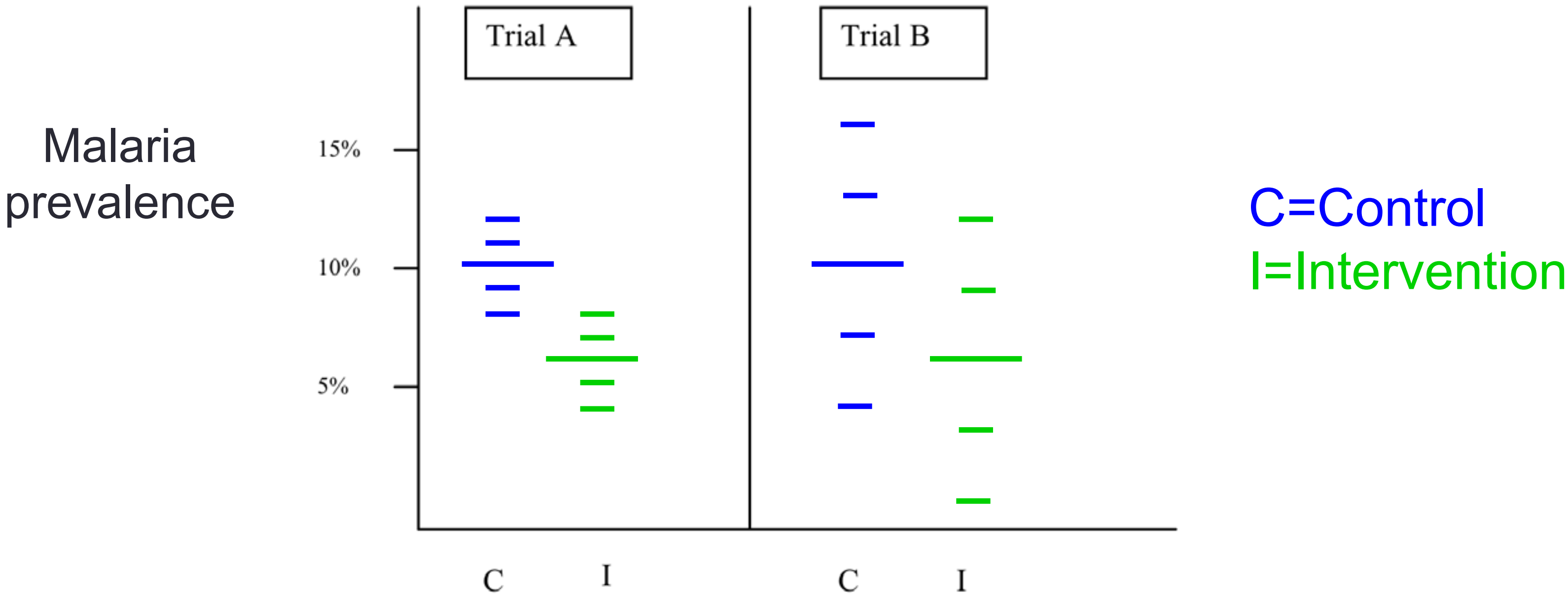
Clustering in CRTs: implications for analysis



- If ignore clustering: p-value = **0.02** for both trials
- Comparison of 10% (50/500) vs 6% (30/500) by chi-sq. test

Example from Hayes & Moulton (2009)

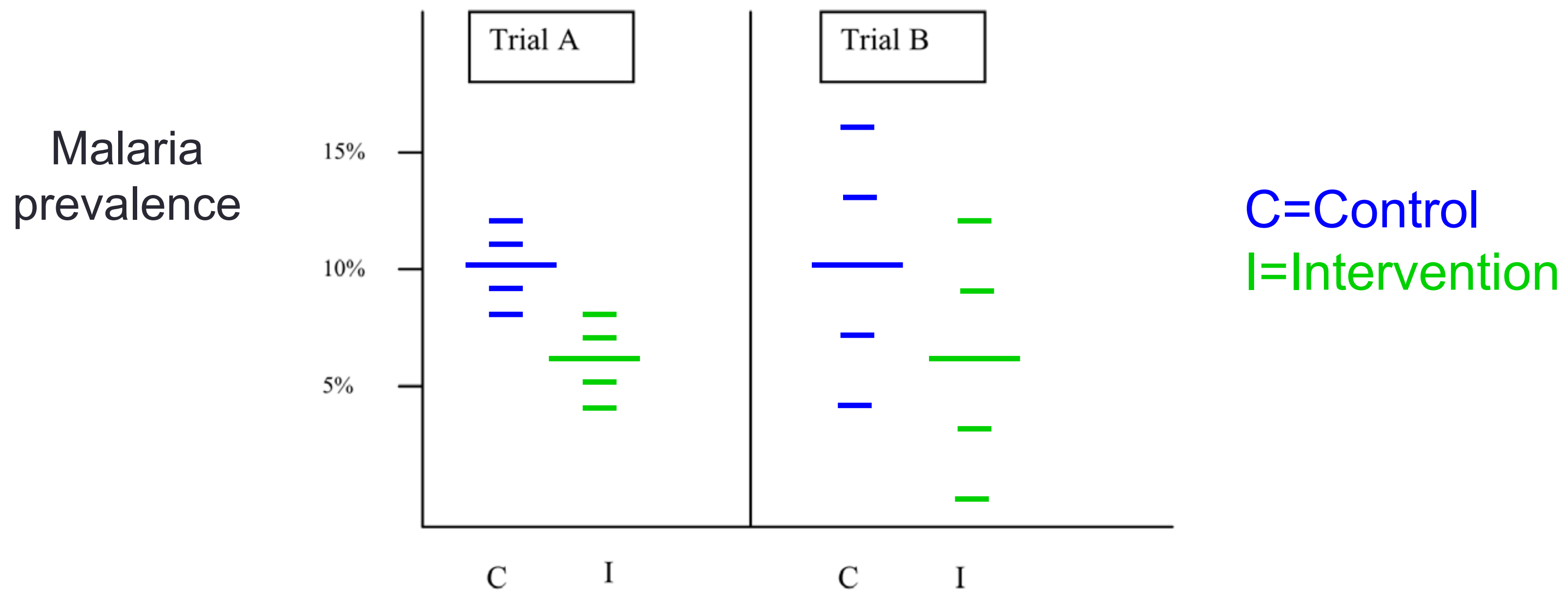
Clustering in CRTs: implications for analysis



- Trial B p-value accounting for clustered design = ?
- If ignore clustering: p-value = **0.02**

Example from Hayes & Moulton (2009)

Clustering in CRTs: implications for analysis

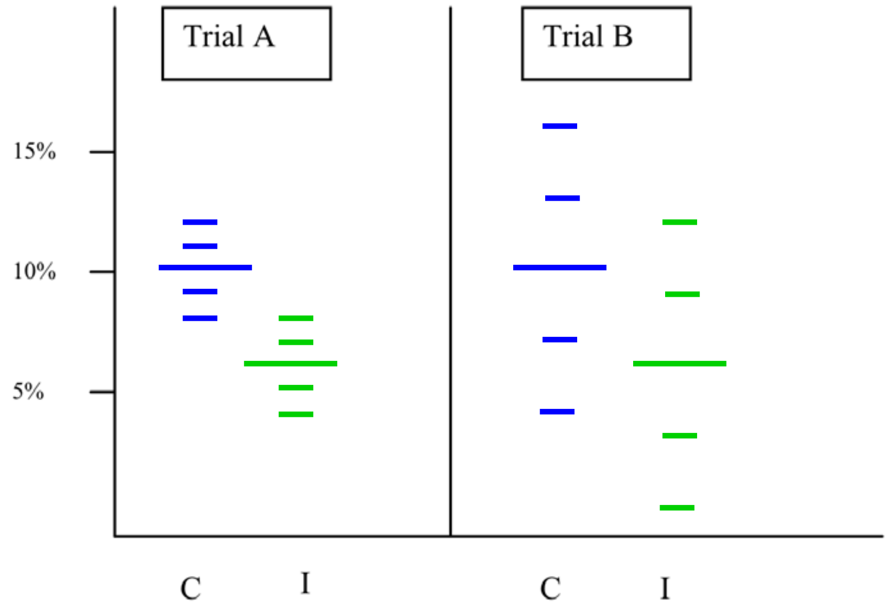


- Trial B p-value accounting for clustered design = **0.17**
- If ignore clustering: p-value = **0.02**

Example from Hayes & Moulton (2009)

Clustering in CRTs: implications for analysis

Malaria prevalence



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I=Intervention

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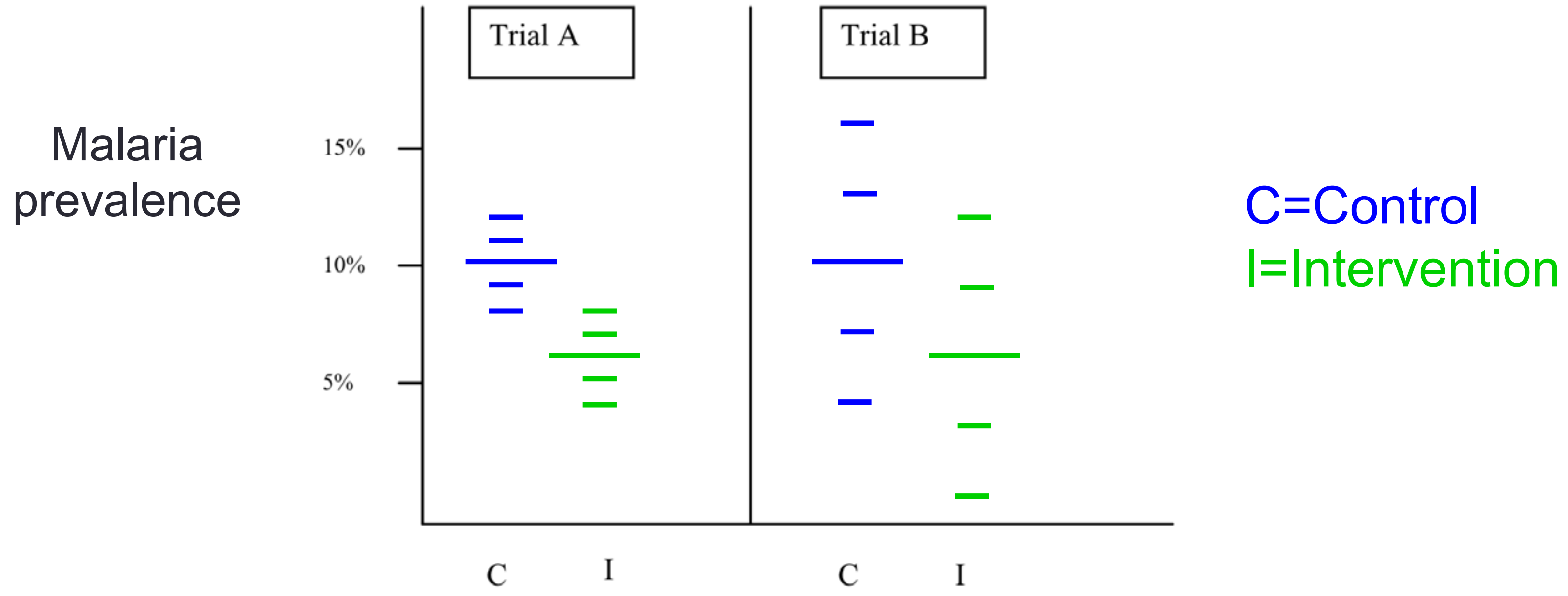
Clustering in CRTs: implications for analysis

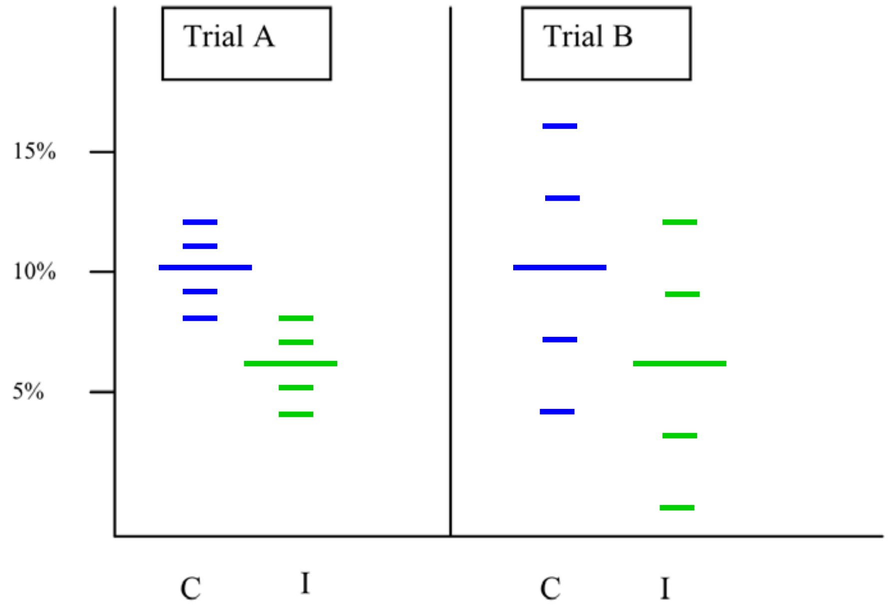


- Trial A p-value accounting for clustered design = **0.01**
- If ignore clustering: p-value = **0.02**

Example from Hayes & Moulton (2009)

Clustering in CRTs: implications for analysis

Malaria prevalence



C=Control
I=Intervention

- Trial A p-value accounting for clustered design* = **0.01**
- Trial B p-value accounting for clustered design* = **0.17**

*By using a cluster-level analysis where the 10 cluster-level proportions (5 per arm) are treated as continuous variables and analyzed with Wilcoxon rank sum test

Example from Hayes & Moulton (2009)

Summary: clustering & analysis

- Two example trials
  - Analyzed with cluster-level analysis
  - Overall sample size (# schools/trial) =10
- Both trials had same signal (10% vs 6%)
  - Totally different conclusions from each trial
  - Between-cluster variability Trial A < Trial B
  - *P*-value Trial A < *P*-value Trial B
- Important: If ignore clustered design, could claim ‘significant’ when not (eg, Trial B)

Summary: clustering & analysis

- Cluster-level analysis rarely used
- Typically use regression methods
  - Random effects / mixed effects models
  - Generalized estimating equations (GEE)
  - Analyze individual-level data
    - e.g., N=1000 participants/trial not N=10 schools

Recent examples from my research

CRT methods

AJPH METHODS

Review of Recent Methodological Developments in Group-Randomized Trials: Part 1—Design

In 2004, Murray et al. reviewed

Elizabeth L. Turner, PhD, Fan Li, MSc, John A. Gallis, ScM, Melanie Prague, PhD, and David M. Murray, PhD

AJPH METHODS

Review of Recent Methodological Developments in Group-Randomized Trials: Part 2—Analysis

In 2004, Murray et al. reviewed methodological developments

Elizabeth L. Turner, PhD, Melanie Prague, PhD, John A. Gallis, ScM, Fan Li, MSc, and David M. Murray, PhD

Recent examples from my research

CRT design

BMJ Open

Innovative public–private partnership to target subsidised antimalarials: a study protocol for a cluster randomised controlled trial to evaluate a community intervention in Western Kenya

Jeremiah Laktabai,[1] Adriane Lesser,[2] Alyssa Platt,[2,3] Elisa Maffioli,[2,4] Manoj Mohanan,[2,4,5] Diana Menya,[6] Wendy Prudhomme O'Meara,[2,6,7] Elizabeth L Turner[2,3]

STUDY PROTOCOL

Reducing stigma among healthcare providers to improve mental health services (RESHAPE): protocol for a pilot cluster randomized controlled trial of a stigma reduction intervention for training primary healthcare workers in Nepal

Brandon A. Kohrt[1,2,3*], Mark J. D. Jordans[2,4], Elizabeth L. Turner[1,5], Kathleen J. Sikkema[1,6], Nagend
Sauharda Rai[1,2,3], Daisy R. Singla[7,8], Jagannath Lamichhane[9], Crick Lund[4,10] and Vikram Patel[11,12,

Cluster randomized trials

Design challenge: clustering

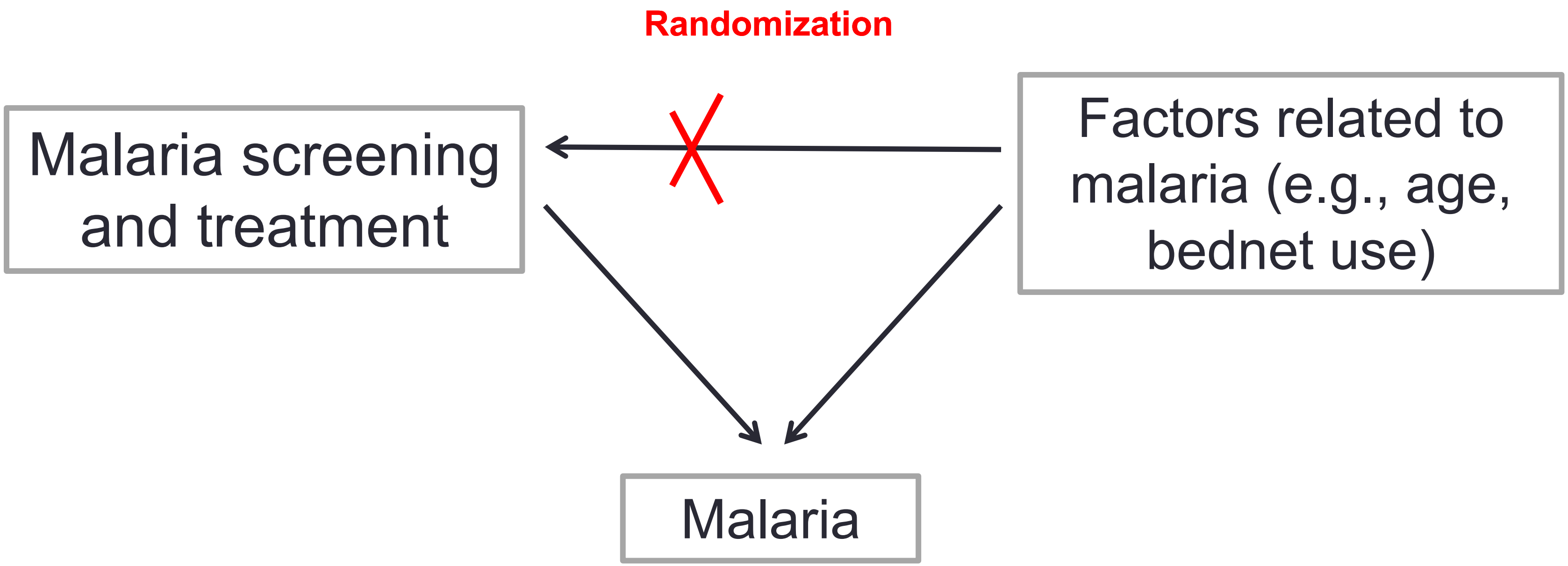
Solution:
design & analyze accounting for it

Cluster randomized trials

Design challenge: baseline imbalance

Motivating example CRT

Health and Literacy Intervention (HALI)



Goal: randomization → baseline balance of covariates

Check: baseline tables for 101 clusters (schools)

Table 1. Baseline characteristics of 5,233 study children in the 50 control and 51 IST intervention schools.

Characteristics; *n* (%)[a]	Measure/Subcharacteristic	Control	Intervention
School characteristics[b]		**50 schools**	**51 schools**
Exam score	Mean (SD)	223.4 (27.7)	225.8 (29.0)
School size	Median (IQR) [min, max]	505 (308, 961) [85, 4,891]	568 (389, 692) [2
Enrolled class 1	Mean (SD) [min, max]	24.4 (3.3) [10,30]	25.8 (1.5) [23,30]
Enrolled class 5	Mean (SD) [min, max]	26.0 (4.6) [8,30]	27.3 (3.3) [16,32]
School programmes	Feeding	22 (44.0)	27 (52.9)
	De-worming	50 (100.0)	49 (96.1)
	Malaria control	9 (18.4)	12 (23.5)
Child characteristics[b]		**2,523 children**	**2,710 children**
Age[c]	Mean (SD)	10.1 (2.8)	10.3 (2.8)
	5–9	1,041 (41.2)	1,069 (39.5)
	10–12	877 (34.8)	925 (34.1)
	13–20	605 (24.0)	716 (26.4)
Sex	Male	1,257 (49.8)	1,319 (48.7)
Child sleeps under net	Usually	1,668 (67.3)	1,682 (63.1)
	Treated net[d]	1,357 (83.3)	1,308 (80.5)
	Last night[d]	1,606 (96.3)	1,609 (95.7)

Halliday (2014), PLOS Medicine, 11(1) e1001594
http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001594

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Good balance of age

http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001594

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Some imbalance of bednet use

http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001594

PLOS MEDICINE

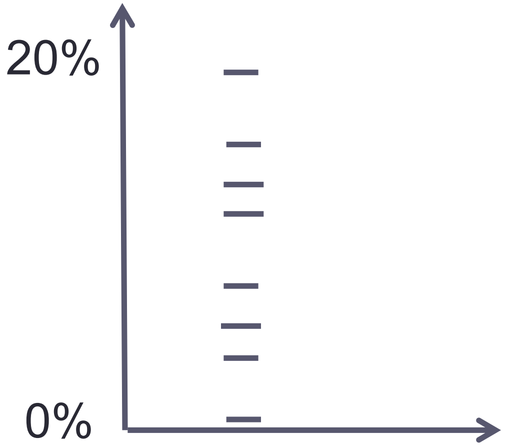
Small # of clusters & baseline imbalance

- CRTs often enroll small # (<40) clusters
- Randomization may not balance baseline covariates
- Baseline imbalance threatens internal validity
- Could address with adjusted analysis
- Better to use design strategy: 'Restricted randomization'
  - Pair-matching
  - Stratification
  - Covariate-constrained randomization

Baseline covariate imbalance

Example: 8 schools (clusters)

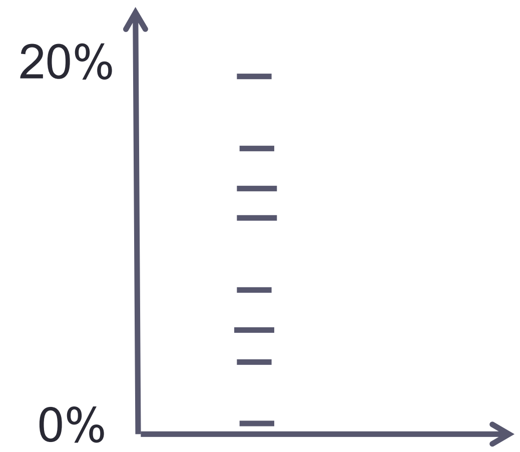
Baseline malaria prevalence



Baseline covariate imbalance

Example: 8 schools (clusters)

Baseline malaria prevalence



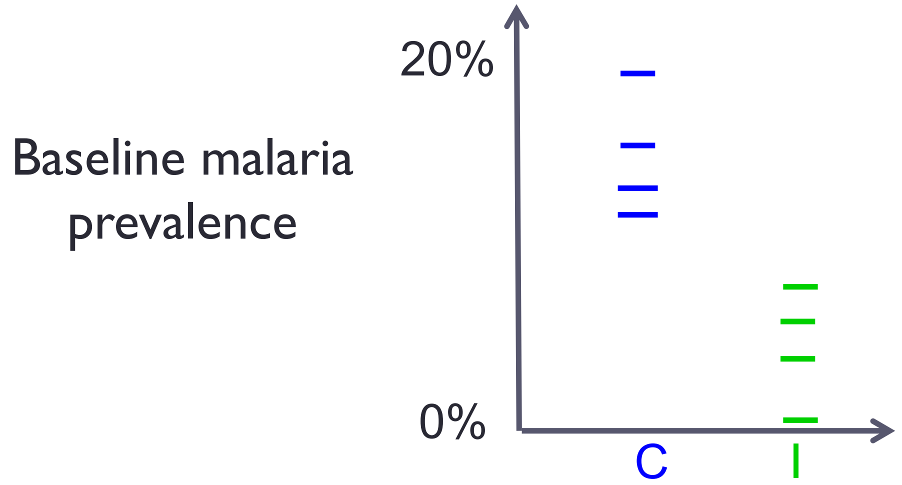
Question: Why do we care about getting balance between treatment arms on school-level malaria prevalence?

It might be related to prevalence in future!

Baseline covariate imbalance

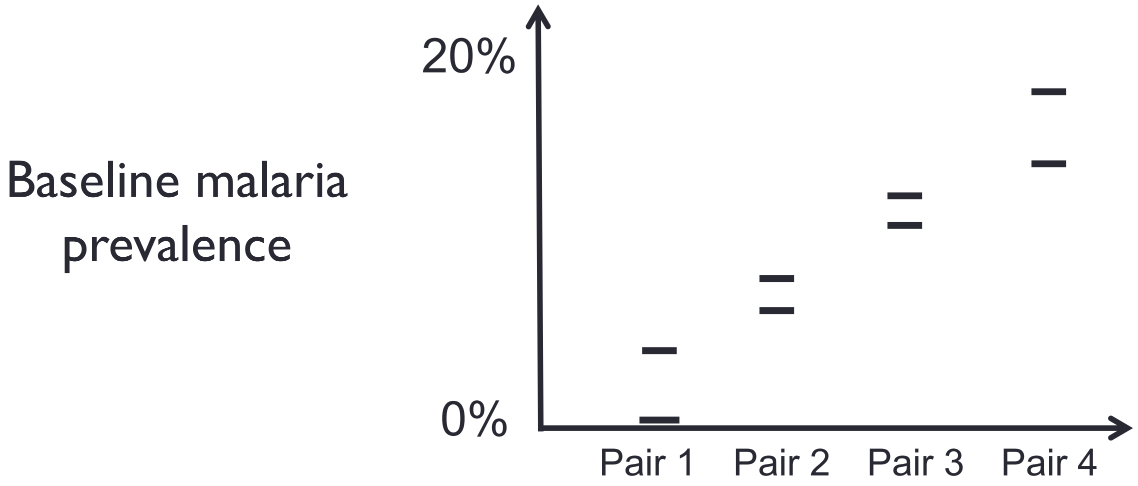
Example: 8 schools (clusters)

Example of extreme baseline imbalance using simple (ie, regular) randomization



Baseline covariate imbalance

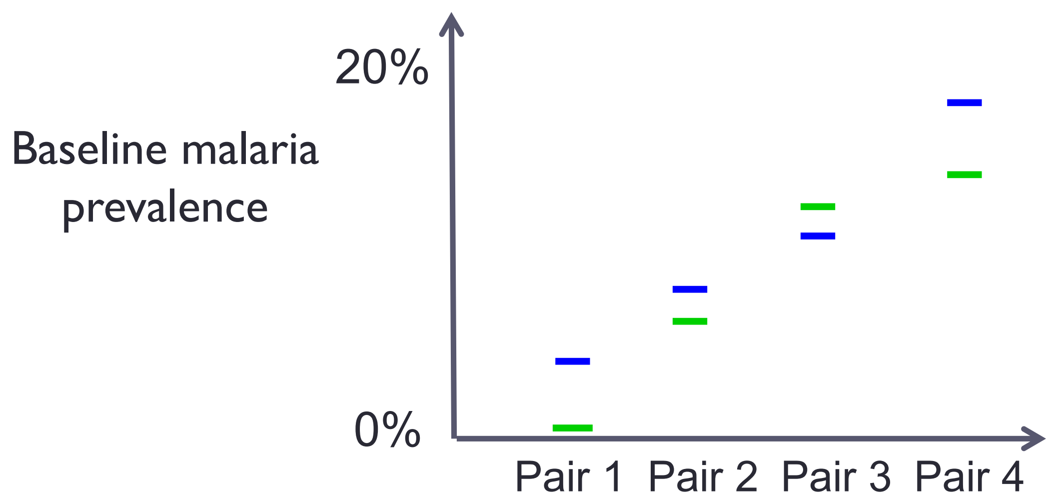
Possible design solution 1: pair-matching



Baseline covariate imbalance

Possible design solution 1: pair-matching

One example of pair-matched randomization to control & intervention arms



Important: account for paired design in the analysis
(eg, paired t-test or Wilcoxon signed rank test for cluster-level analysis or matched regression model)

Pair-matching in practice

Example from my research: published CRT outcomes paper

Efficacy of iron-supplement bars to reduce anemia in urban Indian women: a cluster-randomized controlled trial[1,2]

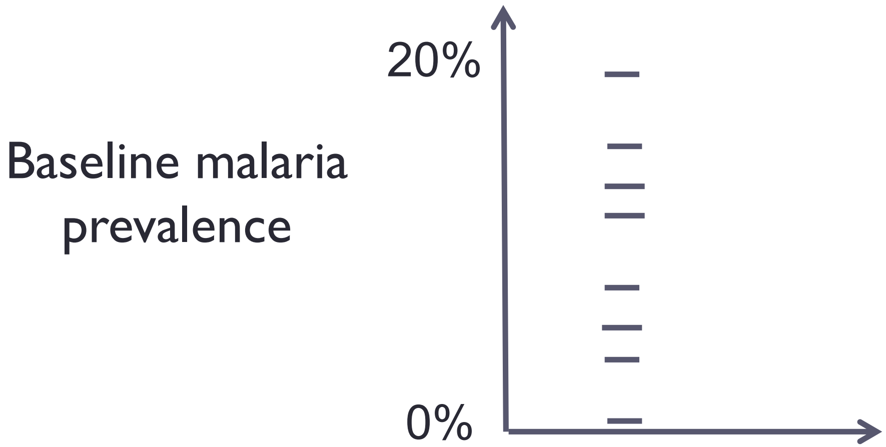
*Rajvi Mehta,[3] Alyssa C Platt,[4,6] Xizi Sun,[4] Mukesh Desai,[7] Dennis Clements,[5,6] and Elizabeth L Turner[4,6]**

[3]Duke University School of Medicine, Departments of [4]Biostatistics and Bioinformatics and [5]Pediatrics, and [6]Duke Global Health Institute, Duke University, Durham, NC; and [7]Department of Hematology and Immunology, B.J. Wadia Hospital, Mumbai, Maharashtra, India

Am J Clin Nutr 2017;105:746–57. Printed in USA.

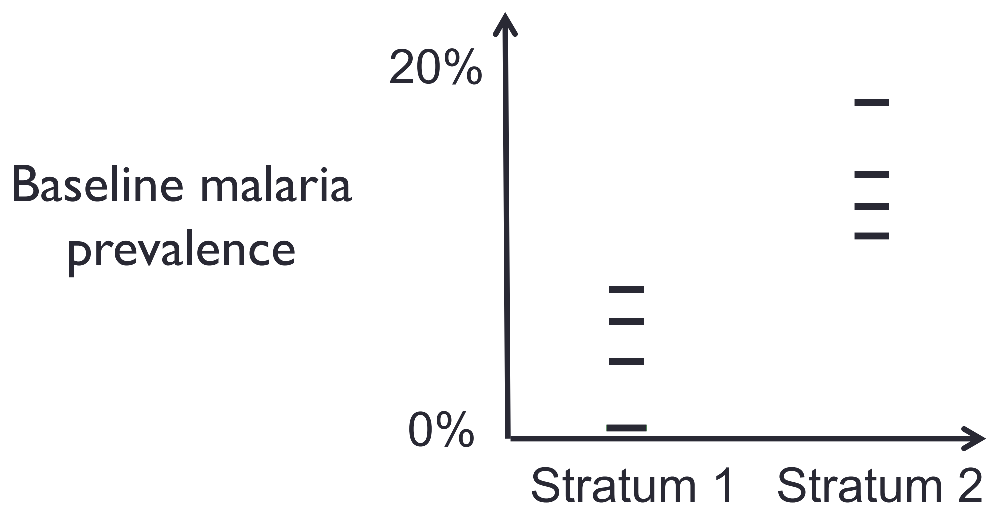
Baseline covariate imbalance

Example: 8 schools (clusters)



Baseline covariate imbalance

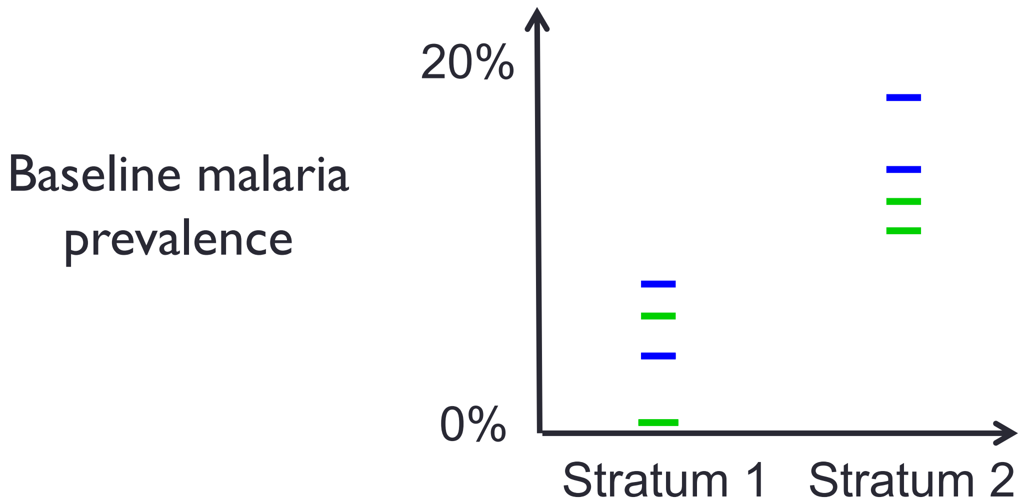
Possible design solution 2: stratification



Baseline covariate imbalance

Possible design solution 2: stratification

An example of stratified randomization to control & intervention arms



Important: account for stratified design in the analysis
(eg, stratified permutation test or fixed effect for strata in model-based analysis)

Stratification in practice

Example from my research: published CRT protocol paper

Turner *et al. Trials* (2016) 17:442
DOI 10.1186/s13063-016-1530-y

Trials

STUDY PROTOCOL Open Access

CrossMark

The effectiveness of the peer delivered Thinking Healthy Plus (THPP+) Programme for maternal depression and child socio-emotional development in Pakistan: study protocol for a three-year cluster randomized controlled trial

Elizabeth L. Turner[1,2], Siham Sikander[3], Omer Bangash[3], Ahmed Zaidi[3], Lisa Bates[4], John Gallis[1,2], Nima Ganga[1], Karen O'Donnell[1], Atif Rahman[5*] and Joanna Maselko[6*]

Baseline covariate imbalance

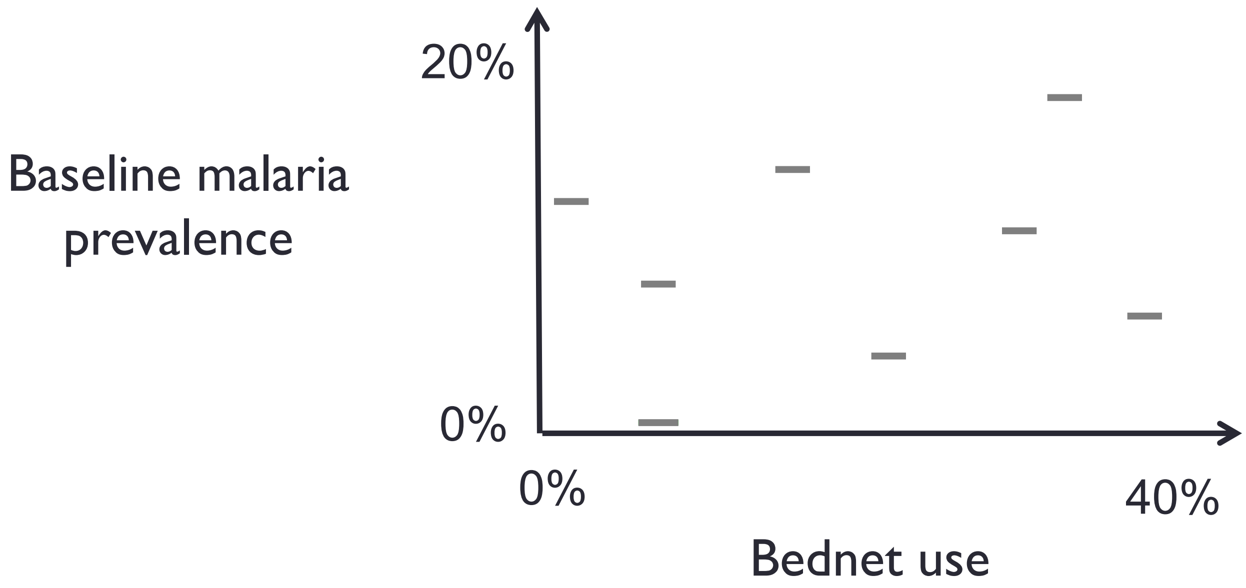
Possible design solution 3: Constrained randomization

- Previous examples – only one school-level covariate
  - i.e., baseline malaria prevalence
- Often have multiple school-level covariates
  - Categorical & continuous
  - Pair-matching & stratification cannot easily handle this
- Need more general form of restricted randomization
  - Covariate-constrained randomization

Baseline covariate imbalance

Possible design solution 3: Constrained randomization

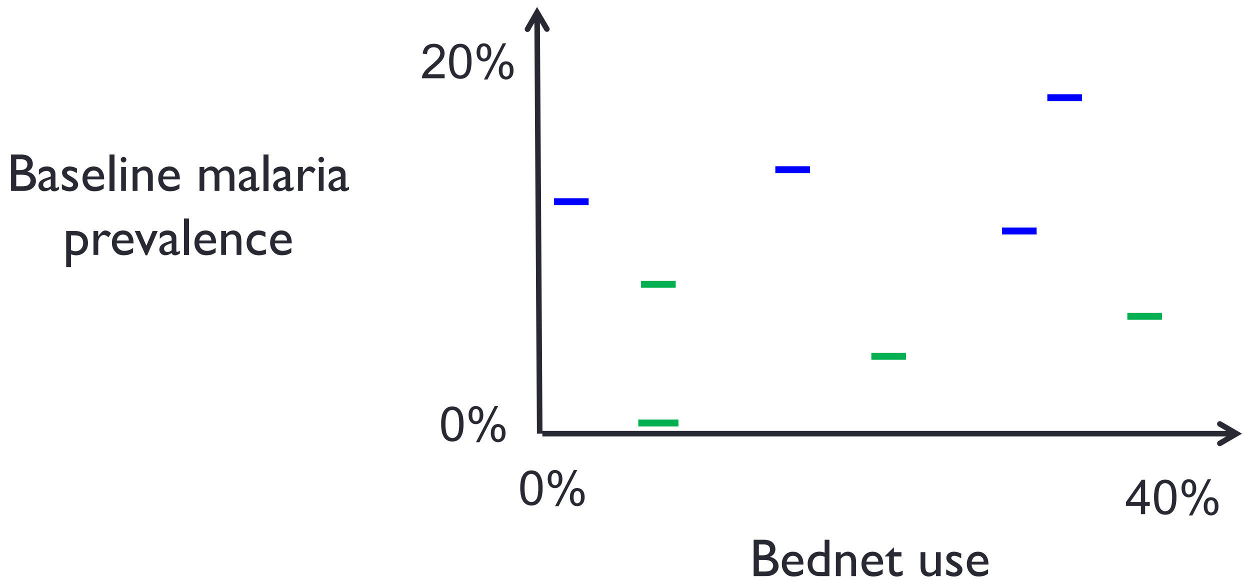
Example: balance two continuous cluster covariates



Baseline covariate imbalance

Possible design solution 3: Constrained randomization

An example of simple randomization to control & intervention arms

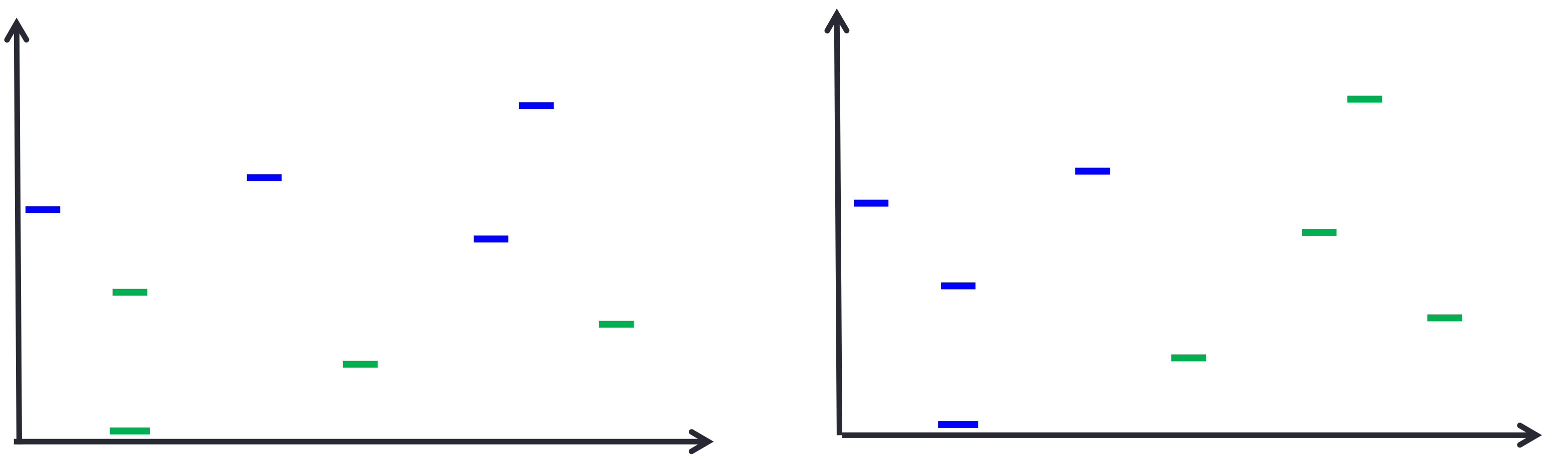


Not well-balanced on baseline malaria prevalence but reasonable balance on bednet use

Baseline covariate imbalance

Possible design solution 3: Constrained randomization

Neither randomization has good balance of both covariates across trial arms.

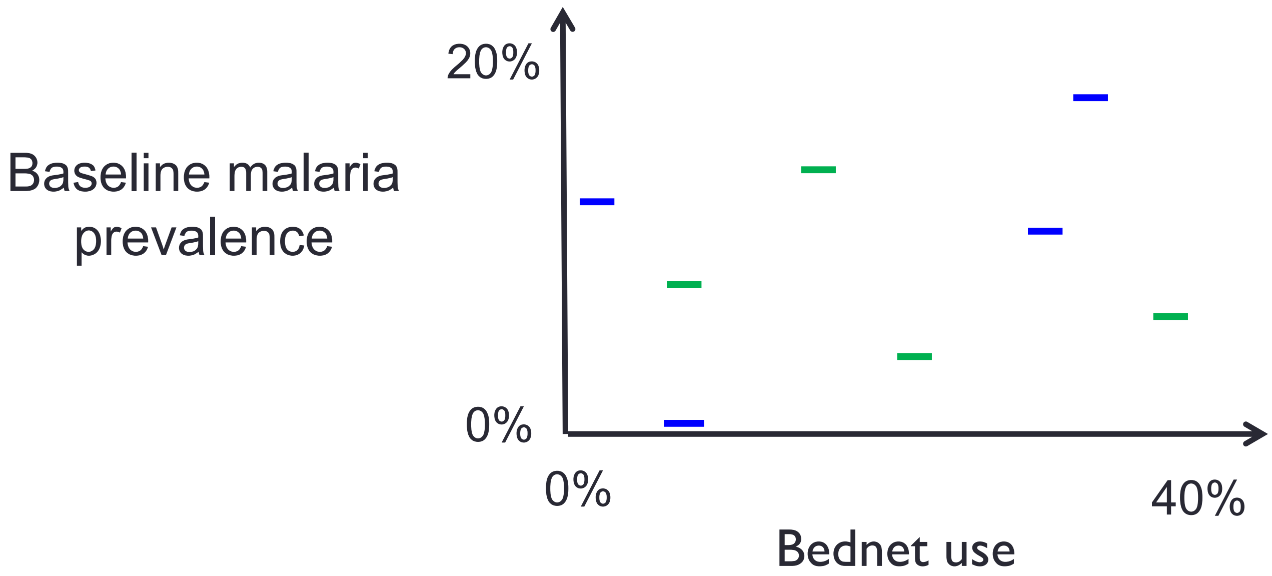


Solution: only allow randomizations that are "balanced enough" as measured by a "balance score"
i.e., use covariate-constrained randomization

Baseline covariate imbalance

Possible design solution 3: Constrained randomization

This randomization could be "balanced enough"



Must account for constrained randomization design in the analysis

Covariate constrained randomization

Example from my research - methods

RESEARCH ARTICLE

WILEY Statistics in Medicine

An evaluation of constrained randomization for the design and analysis of group-randomized trials with binary outcomes

Fan Li[1,2] | Elizabeth L. Turner[1,3] | Patrick J. Heagerty[4] | David M. Murray[5] | William M. Vollmer[6] | Elizabeth R. DeLong[1,2]

Covariate constrained randomization

Example from my research – software implementation

The Stata Journal (*yyyy*) *vv*, Number *ii*, pp. 1–23

cvcrand and cptest: Efficient design and analysis of cluster randomized trials

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cvcrand: Efficient Design and Analysis of Cluster Randomized Tria

Constrained randomization by Raab and Butcher (2001) <doi:10.1002/1097-0258(20010215)20:3
suitable for cluster randomized trials (CRTs) with a small number of clusters (e.g., 20 or fewer). T
based on the baseline values of some cluster-level covariates specified. The intervention effect on
through clustered permutation test introduced by Gail, et al. (1996) <doi:10.1002/(SICI)1097-025
SIM220%3E3.0.CO;2-Q>. Motivated from Li, et al. (2016) <doi:10.1002/sim.7410>, the packag
baseline values of cluster-level covariates and cluster permutation test on the individual-level out

Version:	0.0.1
Depends:	R (≥ 3.3.1)
Imports:	tableone
Suggests:	knitr, rmarkdown
Published:	2017-11-28
Author:	Hengshi Yu [aut, cre], John A. Gallis [aut], Fan Li [aut], Elizabeth L. Turner
Maintainer:	Hengshi Yu <hengshi at umich.edu>
License:	GPL-2 | GPL-3 [expanded from: GPL (≥ 2)]

Cluster randomized trials

Design challenge: baseline imbalance

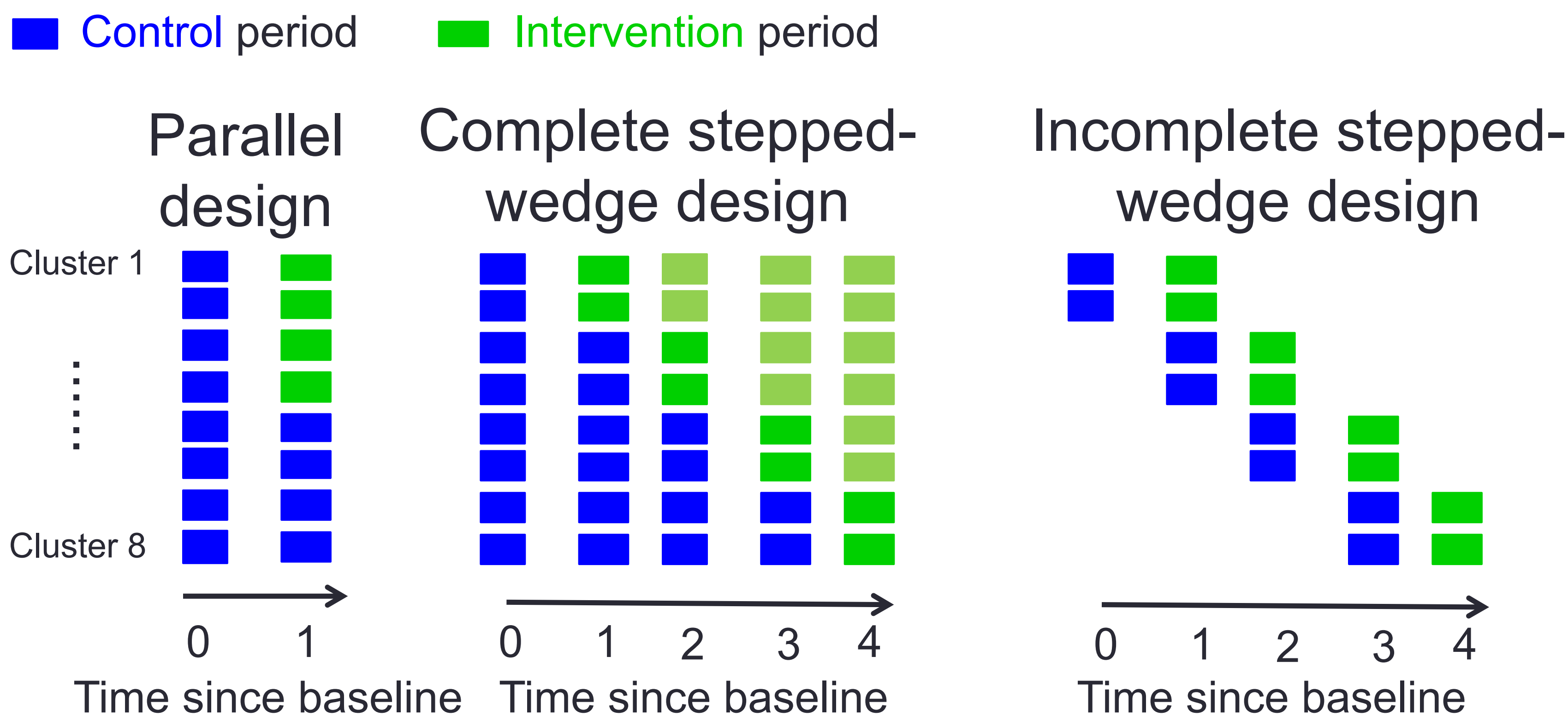
Solution:
use restricted randomization

Cluster randomized trials

Stepped-wedge designs

Parallel CRT vs. SW-CRT

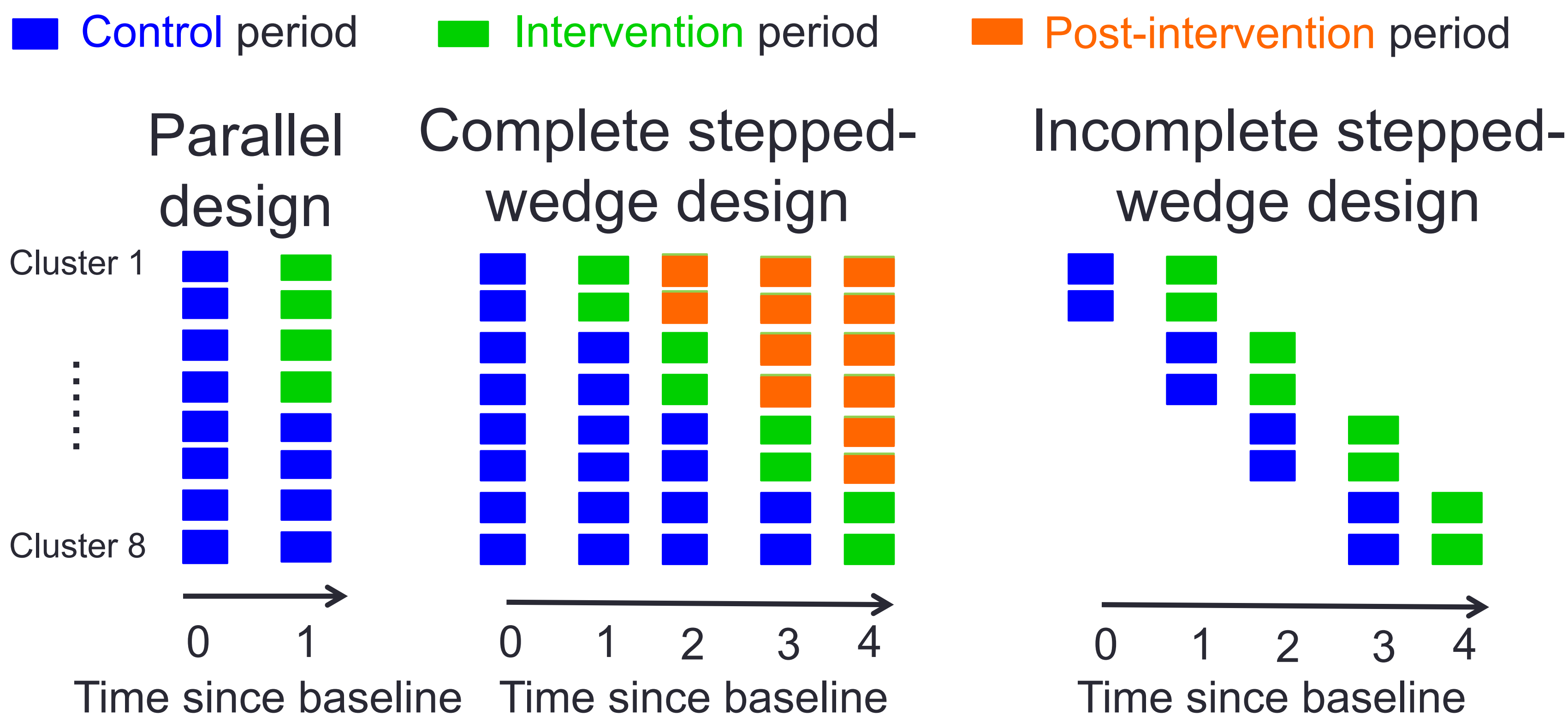
Examples with 8 clusters: 1-year intervention



Based on: Hemming (2015) Stat Med

Parallel CRT vs. SW-CRT

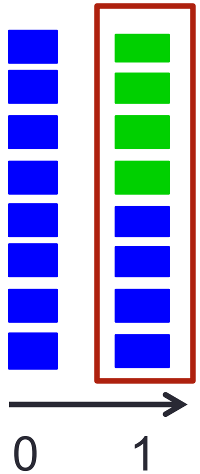
Examples with 8 clusters: 1-year intervention



Based on: Hemming (2015) Stat Med

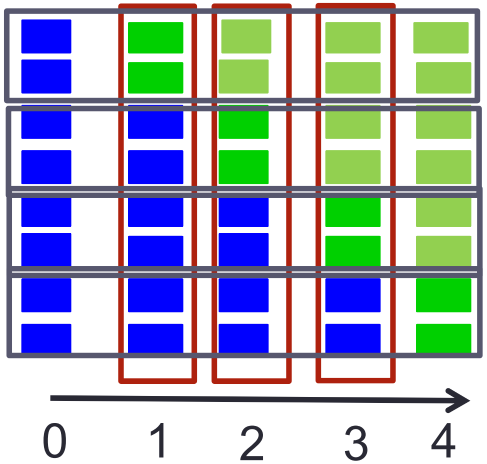
CRT analysis: treatment effects

Estimated (primarily) using between- cluster ie, **vertical** information



Parallel design

Estimated using both **vertical** & **horizontal** (ie, within-cluster) information



Complete SW design

Control period   Intervention period

Based on: Hemming (2015) Stat Med

SW-CRT design and analysis

Examples from my research

Sample size determination for GEE analyses of SW-CRTs

Li F, **Turner EL**, Preisser J. Under review.

Optimal allocation of clusters in cohort SW designs

Li F, **Turner EL**, Preisser J. To appear in *Statistics & Prob. Letters*

Covariate constrained randomization for the design of parallel and SW-CRTs

- Invited session at *Society of Clinical Trials Annual Meeting*, May 2018
- Joint work with Karla Hemming (University of Birmingham), Andrew Copas (University College London) and Fan Li (Duke)

Summary

Evaluation of Public Health Interventions:

Recent Developments in Cluster Randomized Trials and Related Designs

Summary

- Recent developments in CRTs

  1. Motivating example
  2. Clustering
  3. Small # clusters & baseline covariate imbalance
  4. Stepped wedge designs

References - Statistical

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References – Motivating example

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