Randomization-Based Inference for Cluster Randomized Trials

Dustin J. Rabideau

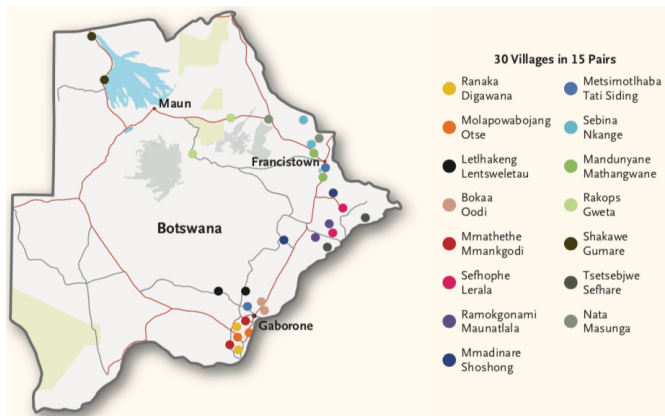November 20, 2023

Cluster Randomized Trial (CRT)

Individually-randomized trial: individuals are randomized

CRT: **groups/clusters of people** are randomized

Example: The Botswana Combination Prevention Project

30 Villages in 15 Pairs

Ranaka Digawana · Metsimotlhaba Tati Siding · Molapowabojang Otse · Sebina Nkange · Letlhakeng Lentsweletau · Mandunyane Mathangwane · Bokaa Oodi · Rakops Gweta · Mmathethe Mmankgodi · Shakawe Gumare · Sefhophe Lerala · Tsetsebjwe Sefhare · Ramokgonami Maunatlala · Nata Masunga · Mmadinare Shoshong

Makhema et al. (2019). Universal Testing, Expanded Treatment, and Incidence of HIV Infection in Botswana. *NEJM*.

Large HIV prevention CRT

- 30 communities, 8,551 individuals in HIV-incidence cohort
- Intervention: combination prevention package vs. standard-care
- Outcome: HIV infection, annual study visits (interval-censored)

Reasons to Conduct a CRT

1. Intervention is more naturally/feasibly applied at cluster level

2. Avoid treatment contamination

3. Capture population-level (indirect) effects of intervention

Statistical Analysis of a CRT

Statistical challenges in CRTs

- individual-level outcomes within a cluster are **correlated**
- small sample setting (only 30 clusters, 15/group)
- design features (pair-matched randomization)

Typical regression approaches for CRTs:

- **mixed effects model** (random effects/maximum likelihood)
- **marginal model via GEE** (generalized estimating equation)

Distributional assumptions not met or a small # of clusters

- **inaccurate** p-values and confidence intervals
- $\implies$ **Wrong conclusions could be drawn from the study!**

Randomization-Based Inference

(A.k.a. permutation methods, re-randomization tests)

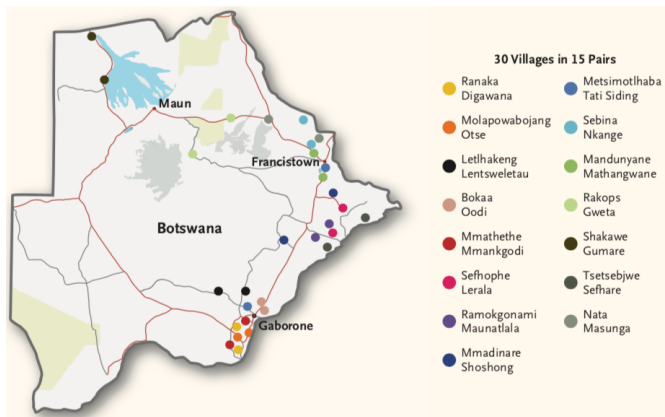Recent resurgence of interest in randomization-based inference for CRTs

Advantages:

- Distribution-free (outcome, correlation)
- Exact (small # clusters)

Challenges

- Less common, less familiar
- More computational time required
- Focus on tests/p-values; **confidence interval methods are limited**

Example: The Botswana Combination Prevention Project

Makhema et al. (2019). Universal Testing, Expanded Treatment, and Incidence of HIV Infection in Botswana. *NEJM*.

"The unadjusted HIV incidence ratio in the intervention group as compared with the standard-care group was 0.69 (**p=0.09**) by [randomization] test (95% confidence interval [CI], **0.46 to 0.90** by pair-stratified Cox model)."

Learning Objectives

1. Learn how to conduct a randomization test

2. Learn how to calculate a randomization-based confidence interval

3. Reinforce concepts by applying these methods to the Botswana Combination Prevention Project

Setting and Notation

Parallel CRT with 2 treatment groups

- # of individuals per cluster can vary
- Y_{ki} is outcome for the ith individual, kth cluster
- $X_k = 1$ (intervention group)
- $X_k = 0$ (control group)

Randomization Test

Quantity of interest: marginal effect of treatment (X) on outcome (Y)

$$\theta = g\{E(Y_{ki}|X_k = 1)\} - g\{E(Y_{ki}|X_k = 0)\}$$

- continuous Y (ignore g), θ represents **difference in means**
- binary Y and "logit" g, θ represents **(log) odds ratio**

To conduct a randomization test of no treatment effect $(H_0 : \theta = 0)$:

1. Fit regression model with **observed** data, get observed $\widehat{\theta}$
2. **Shuffle** treatment assignments, re-fit model, get $\widehat{\theta}^{(2)}$; Ditto $\widehat{\theta}^{(3)}$; ...
3. Calculate % of permuted estimates "as or more extreme" than $\widehat{\theta}$

Randomization Test

1. Fit regression model with **observed** treatment vector $\boldsymbol{x} = (x_1, \ldots, x_K)$ to get $\widehat{\theta}^{(1)} = \widehat{\theta}$

$$g\{E(Y_{ki}|X_k)\} = \mu + \theta x_k$$

```
> fit <- glm(y ~ x, data = ds)
> coef(fit)["x"] # thetaHat
```

⋆⋆ Note, we are fitting a model (GLM) typically used in the **independent data** (i.e., non-clustered) setting

Randomization Test

2. Shuffle treatment assignments and re-fit model with **permuted** treatment vector $\boldsymbol{X}^{(p)}$ to get $\widehat{\theta}^{(p)}$ (and repeat this step for $p = 2, \ldots, P$)
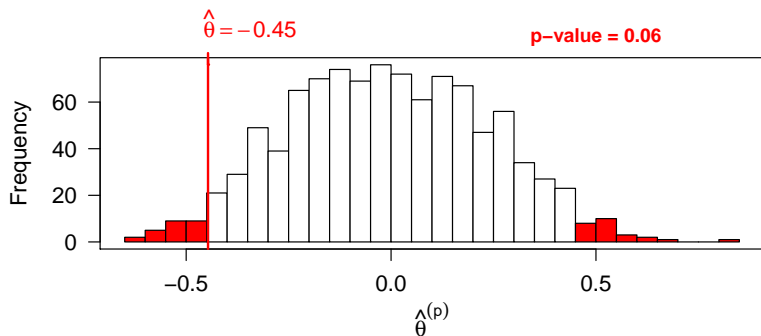
$$g\{E(Y_{ki}|X_k)\} = \mu + \theta X_k^{(p)}$$

```
> for (p in 2:P) {
>     ds$xp <- permute(ds$x) # special function
>     fit <- glm(y ~ xp, data = ds)
>     coef(fit)["xp"]} # thetaHat_p
```

| | Cluster | |
$\boldsymbol{X}^{(p)}$	1	2	3	4	5	6	$\widehat{\theta}^{(p)}$
$\boldsymbol{X}^{(1)} = \boldsymbol{x}$	1	1	1	0	0	0	$\widehat{\theta}^{(1)} = \widehat{\theta}$
$\boldsymbol{X}^{(2)}$	1	0	0	1	0	1	$\widehat{\theta}^{(2)}$
$\boldsymbol{X}^{(3)}$	0	1	1	1	0	0	$\widehat{\theta}^{(3)}$
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
$\boldsymbol{X}^{(P)}$	0	0	1	0	1	1	$\widehat{\theta}^{(P)}$

Randomization Test

3. Calculate p-value = proportion of $\{\widehat{\theta}^{(1)}, \widehat{\theta}^{(2)}, \ldots, \widehat{\theta}^{(P)}\}$ that are "as or more extreme" than (observed) $\widehat{\theta}^{(1)} = \widehat{\theta}$

Randomization-Based Confidence Interval

Need to "invert" randomization test to calculate a confidence interval (CI)

- Conduct **many** randomization tests to see which θs are "reasonable"

To calculate a randomization-based confidence interval for θ:

1. Conduct randomization test for a non-zero null value ($H_0 : \theta = \theta_0$)
2. Repeat across many different θ_0
3. Collect all θ_0 **not** rejected by this test; bounds form CI

Randomization-Based Confidence Interval

1. Conduct randomization test for a non-zero null value ($H_0 : \theta = \theta_0$)

Mathematically equivalent to $H_0 : \tau = (\theta - \theta_0) = 0$ (zero null)

$$g\{E(Y_{ki}|X_k^{(p)})\} = \mu + \theta_0 x_k + \tau X_k^{(p)}$$

- **Permuted** treatment $\boldsymbol{X}^{(p)}$ for offset-adjusted term $\tau X_k^{(p)}$
- **Observed** treatment $\boldsymbol{x}$ for **offset** $\theta_0 x_k$ (fixed across all permutations)

```
> fit <- glm(y ~offset(theta0 * x) + xp, data = ds)
> coef(fit)["xp"] # tauHat_p
```

⋆⋆ Note, this boils down to conducting a randomization test the same way as before, **but now with a fixed offset term in your model**
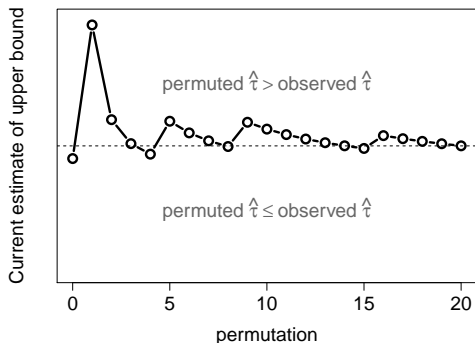
Randomization-Based Confidence Interval

2. Repeat across many different θ_0
3. Collect all θ_0 **not** rejected by this test; bounds form CI
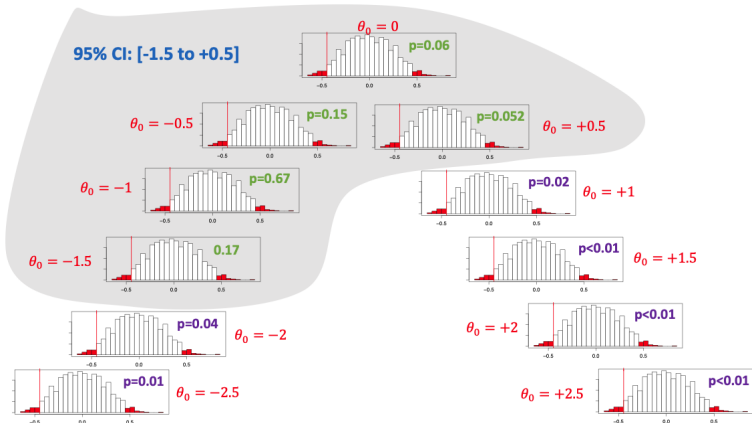
Fast CI Computation

Grid/binary search $= (P$ perms$) \times ($many $\theta_0) \quad \approx$ hours to days

Efficient search[1] $= (P$ perms$) \qquad\qquad\qquad \approx$ **seconds to minutes**

[1] Adapted from: (1) Garthwaite (1996). Confidence intervals from randomization tests. *Biometrics*. (2) Garthwaite and Jones (2009). A Stochastic Approximation Method and Its Application to Confidence Intervals. *J. Comput. Graph. Stat.*

Introduction   Test   **Confidence Interval**   Example   Appendix   drabideau@mgh.harvard.edu   17 / 27

Accounting for Study Design Features

E.g. stratified, pair-matched, restricted randomization

Typical solution: include additional term(s) in model
- can change value/interpretation of the targeted parameter
- can exacerbate GEE small-sample bias (or result in overcorrection)

Accounting for Study Design Features

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Typical solution: include additional term(s) in model
- can change value/interpretation of the targeted parameter
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Randomization-based solution: restrict $\boldsymbol{X}^{(p)}$ based on design
- E.g. BCPP: 30 communities, pair-matched randomization
  $\implies$ sample $\boldsymbol{X}^{(p)}$ from among $2^{15} \approx 33\text{K}$ (not $\frac{30!}{15!15!} \approx 155\text{M}$)
- maintain target of inference and parsimonious nonstratified model

R Package on Github: permuter

 My R package makes this all **very easy** to implement!

```
> devtools::install_github("djrabideau/permuter")

> fit <- glm(y ~ x, data = ds)
> permtest(fit, data = ds, ...)
> permci(fit, data = ds, ...)

> ?permtest
> ?permci
```
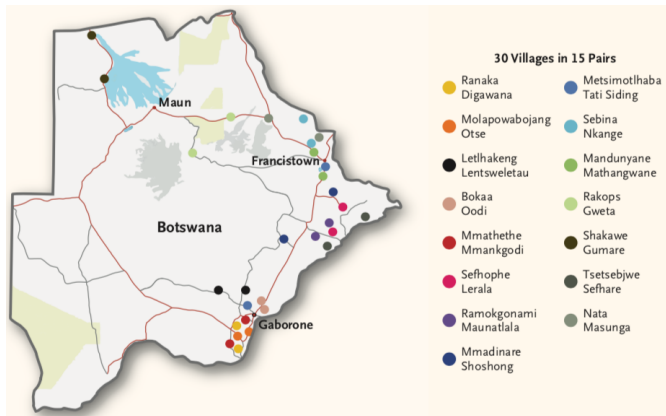
R package link: https://github.com/djrabideau/permuter

Example: The Botswana Combination Prevention Project

30 Villages in 15 Pairs

Ranaka Digawana
Molapowabojang Otse
Letlhakeng Lentsweletau
Bokaa Oodi
Mmathethe Mmankgodi
Sefhophe Lerala
Ramokgonami Maunatlala
Mmadinare Shoshong

Metsimotlhaba Tati Siding
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"The unadjusted HIV incidence ratio in the intervention group as compared with the standard-care group was 0.69 (**p=0.09**) by [randomization] test (95% confidence interval [CI], **0.46 to 0.90** by pair-stratified Cox model)."

BCPP Data

Primary outcome: HIV infection measured at annual study visits

- interval-censored time-to-event outcome

pid	community	pair	trt	hiv	left	right
01-001	1	1	Intervention	0	754	Inf
01-002	1	1	Intervention	1	681	765
01-003	1	1	Intervention	0	404	Inf
02-001	2	1	Standard	0	702	Inf
02-002	2	1	Standard	1	404	668
03-001	3	2	Intervention	0	354	Inf
⋮	⋮	⋮	⋮	⋮	⋮	
30-282	30	15	Intervention	0	689	Inf

BCPP randomization test

```
> fit <- survreg(Surv(left, right, type = "interval2") ~ trt)
> test <- permtest(fit, trtname = "trt", runit = "community",
                   strat = "pair", nperm = 5000)
> plot(ptest)
```


Randomization Distribution
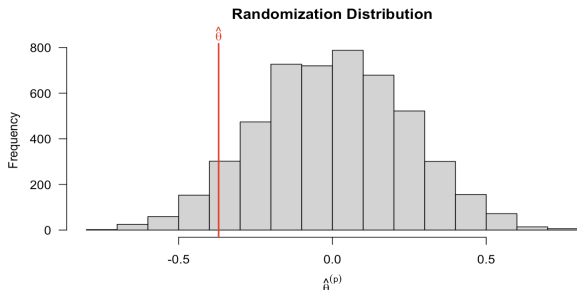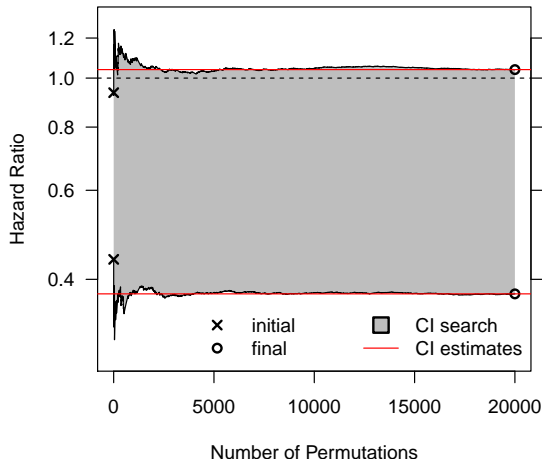
$\widehat{\theta} = -0.37$

Hazard Ratio $= 0.69$

Randomization **p=0.09**

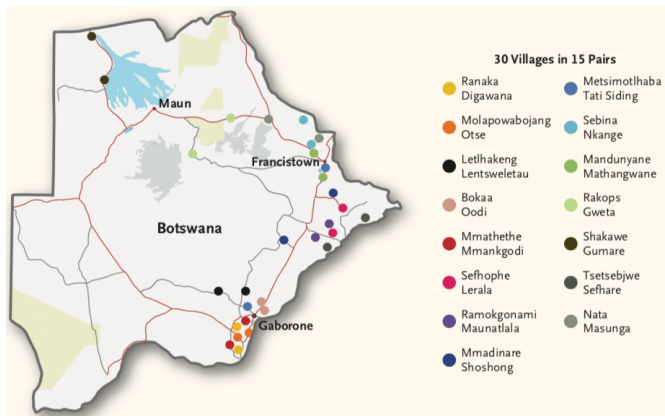⏱ 2 minutes on laptop

BCPP randomization-based confidence interval

```
> pci <- permci(fit, trtname = "trt", runit = "community",
                strat = "pair", nperm = 20000)
> plot(pci)
```


Randomization-based
95% CI: **0.37 to 1.04**

⏱ 40 minutes on laptop

Example: The Botswana Combination Prevention Project

30 Villages in 15 Pairs

- Ranaka Digawana
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"The unadjusted HIV incidence ratio in the intervention group as compared with the standard-care group was 0.69 (**p=0.09**) by [randomization] test (95% confidence interval [CI], **0.46 to 0.90** by pair-stratified Cox model))."

Now, we get 0.69 (**p=0.09**) with 95% CI, **0.37 to 1.04** ✓

Summary

Randomization-based inference is a robust analysis strategy for CRTs

- Distribution-free (outcome, correlation)
- Exact (small # clusters)

To conduct a randomization **test** of no treatment effect ($H_0 : \theta = 0$):

1. Fit regression model with **observed** data, get observed $\widehat{\theta}$
2. **Shuffle** treatment assignments, re-fit model, get $\widehat{\theta}^{(2)}$; Ditto $\widehat{\theta}^{(3)}$; ...
3. Calculate % of permuted estimates "as or more extreme" than $\widehat{\theta}$

To calculate a randomization-based **confidence interval** for θ:

1. Conduct randomization test for non-zero null ($H_0 : \theta = \theta_0$) via **offset**
2. Repeat across many different θ_0
3. Collect all θ_0 **not** rejected by this test; bounds form CI

To Dive Deeper. . .

Recommended papers

- Rabideau and Wang (2021). Randomization-based confidence intervals for cluster randomized trials. *Biostatistics.*
- Rabideau and Wang (2021). Randomization-based inference for a marginal treatment effect in stepped wedge cluster randomized trials. *Stat. Med.*
- Ernst (2004). Permutation Methods: A Basis for Exact Inference. *Stat. Sci.*

Try out my R package

- https://github.com/djrabideau/permuter

Thanks!

| Method	HR	95% CI	p-value
Randomization, Marginal	0.640	[0.374, 1.039]	0.064
Randomization, Pair-Stratified	0.646	[0.369, 1.054]	0.068
Weibull, Frailty-Cluster	0.640	[0.432, 0.947]	0.025
Weibull, Frailty-Pair	0.641	[0.453, 0.905]	0.012
Weibull, Pair-Stratified	0.646	[0.457, 0.913]	0.013

The Botswana Combination Prevention Project
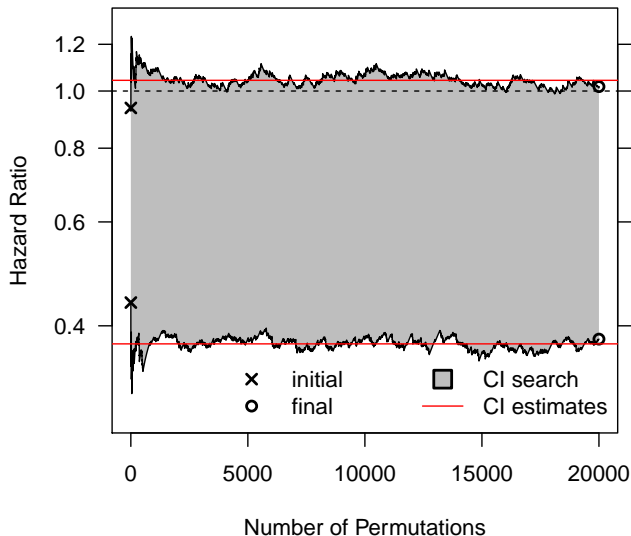
Monitoring 4 separate chains using different starting values
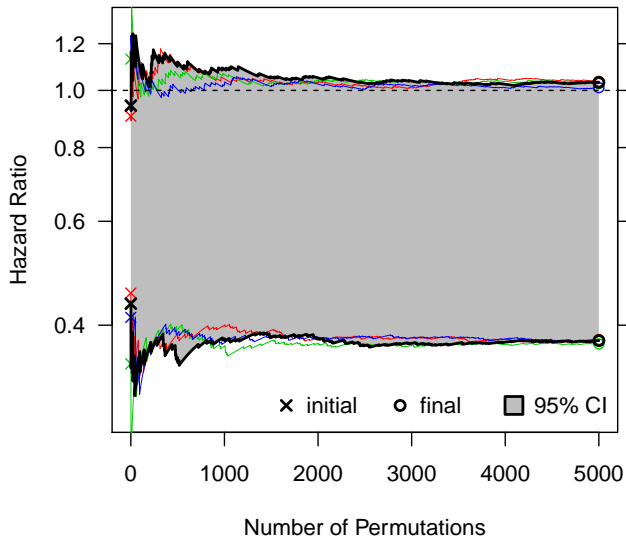
The Botswana Combination Prevention Project

Search procedure adapted from Garthwaite (1996)
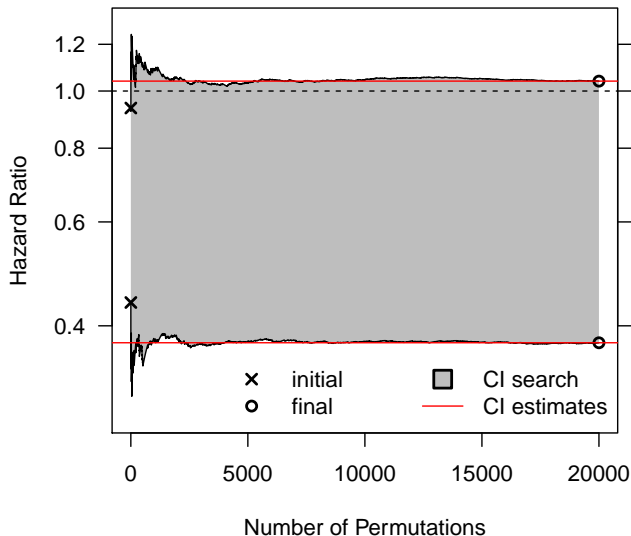
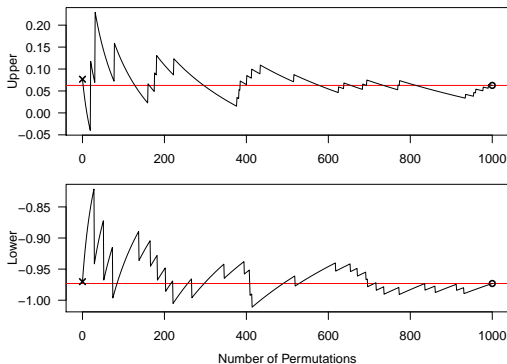# The Botswana Combination Prevention Project

Search procedure adapted from Garthwaite and Jones (2009)

R package
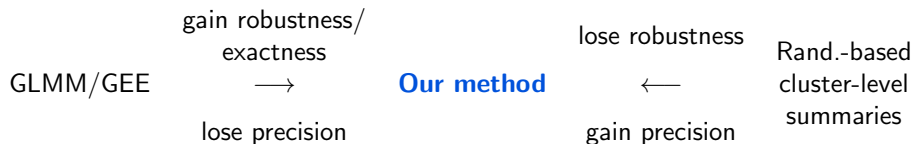
```
> m1 <- glm(bpepisodes ~ spnvac, family = poisson, data = pneumovac)
> ci <- permci(m1, trtname = "spnvac",
               runit = "randunit", data = pneumovac,
               nperm = 1000, ncores = 2, seed = 445, level = 0.95)
> print(ci$ci)
      lower       upper
-0.97314014   0.06265964
> plot(ci)
```

Our method **provides a compromise** between existing approaches:

	gain robustness/ exactness		lose robustness	
GLMM/GEE	$\longrightarrow$	**Our method**	$\longleftarrow$	Rand.-based cluster-level summaries
	lose precision		gain precision	

Randomization-Based CI for SWTs

Population model

$$(\boldsymbol{Y}_i | \boldsymbol{X}_i = \boldsymbol{x}_*) \sim F(\boldsymbol{\eta}_{\boldsymbol{x}_*}, \phi), \quad \boldsymbol{\eta}_{\boldsymbol{x}_*} = (\eta_{1x_1}, \ldots, \eta_{Jx_J})^T,$$
$$\eta_{jx} = g\{E(Y_{ijk} | X_{ij} = x)\} = \mu + \beta_j + \theta x$$

- constant treatment effect (θ) across clusters and time
- common **average** secular trend across clusters (i.e. same β_j for all i)
- correlation not impacted by treatment, but otherwise **unspecified**

Comply:
- Exchangeable correlation structure (Hussey and Hughes, 2007)
- Nested exchangeable (Hooper et al, 2015; Hemming et al, 2017)
- Exponential decay (Kasza et al, 2019)

Do not comply:
- Treatment heterogeneous correlation structure (Hughes et al, 2015)
- Treatment effect heterogeneity (models C-E in Hemming et al, 2017)

Simulations: Different Target Parameters

Marginal model: **cluster-average** treatment effect

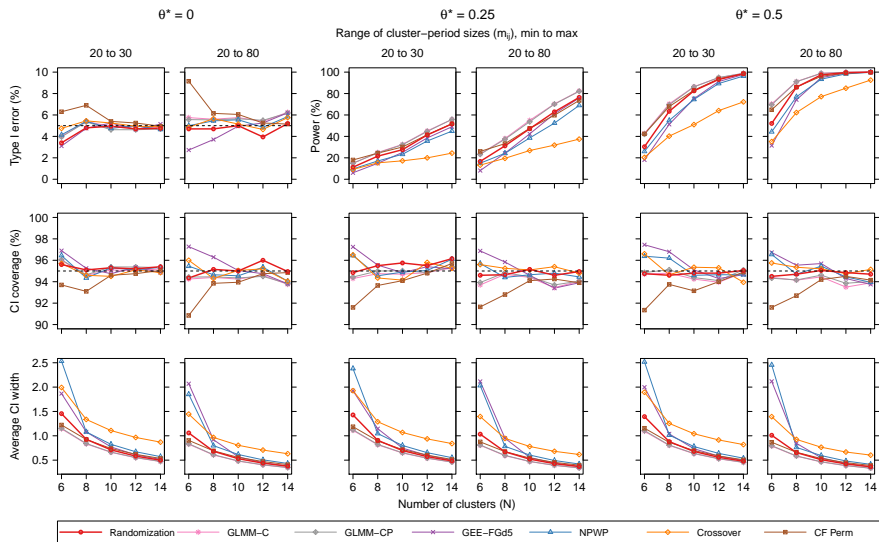- $\theta = g\{E(Y_{ki}|X_k = 1)\} - g\{E(Y_{ki}|X_k = 0)\}$

Mixed model: **cluster-specific** treatment effect

- $\theta^* = g\{E(Y_{ki}|X_k = 1, \gamma_k)\} - g\{E(Y_{ki}|X_k = 0, \gamma_k)\}$
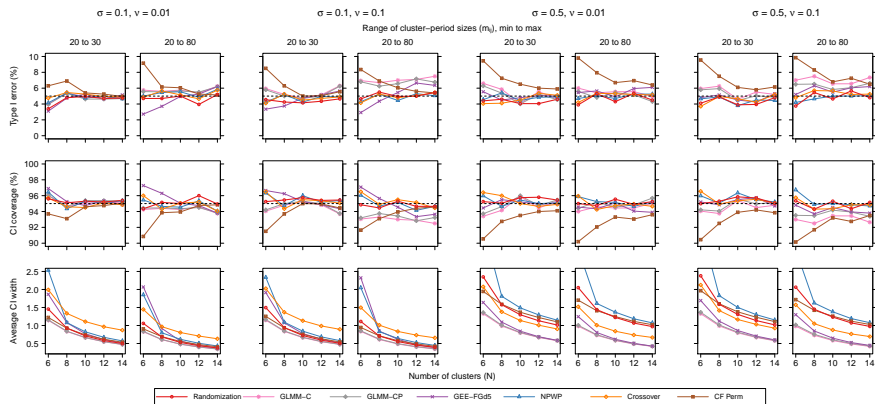- relation to marginal θ: integrate over random effects

Cluster-Level Analysis:

- (weighted) average of cluster(-period) summaries
- relation to marginal θ can be **complex**
  - contrast function (e.g. nonlinear)
  - weights
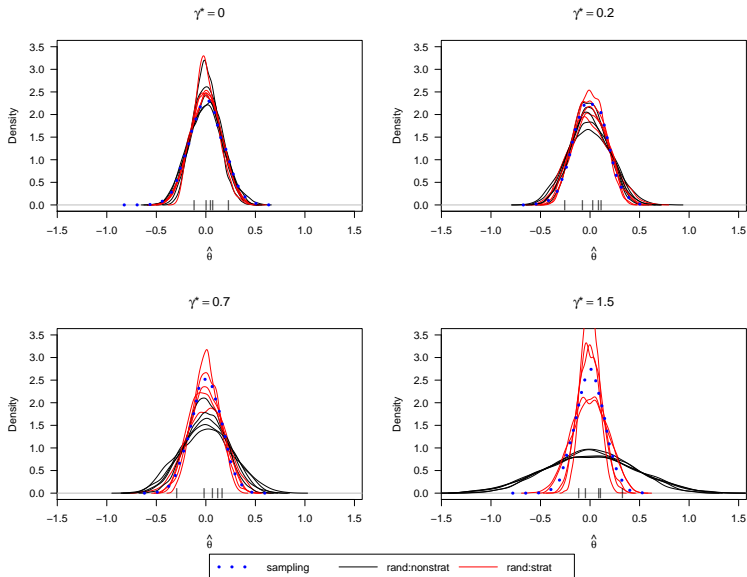 - cluster-period sizes
  - heuristic adjustments

# Simulations: Accounting for Study Design Features

Simulations: Stratified SWT with a Binary Outcome

- single binary stratification factor Z
- larger γ^* $\implies$ larger Y-Z association
- both nonstratified (-ns) and stratified analysis

Method	γ^*	CI coverage (%)			Average CI width		
				N			
		6	10	14	6	10	14
	0	94	95	96	1.67	0.72	0.50
Randomization	1.5	95	95	96	1.46	0.61	0.43
	1.5-ns	100	100	100	4.73	2.10	1.58
	0	94	93	95	1.12	0.65	0.47
GLMM-C	1.5	95	95	94	1.08	0.63	0.45
	1.5-ns	96	95	95	1.29	0.77	0.56
	0	98	94	95	2.11	0.77	0.51
GEE-FGd5	1.5	98	95	95	2.13	0.74	0.49
	1.5-ns	96	95	96	1.49	0.76	0.52
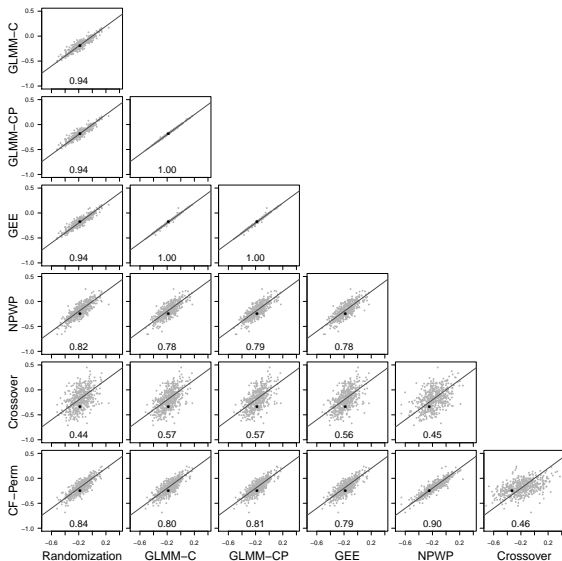
The XpertMTB/RIF Trial

SWT assessing 2 diagnostic tests of tuberculosis (TB)

- XpertMTB/RIF rapid test ($X = 1$) vs. smear microscopy ($X = 0$)
- 14 laboratories, 8 periods, 3,926 individuals diagnosed with TB
- composite binary outcome (death, dropout, drug failure/resistance)
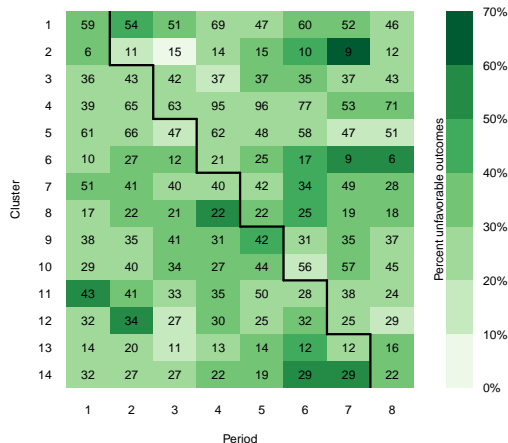
The XpertMTB/RIF Trial

Analysis type	Method	OR	95% CI	p-value
	Randomization	**0.84**	**[0.64, 1.07]**	**0.13**
Individual-level	GLMM-C	0.84	[0.68, 1.03]	0.09
	GEE-FGd5	0.83	[0.57, 1.21]	0.31
	NPWP	0.78	[0.61, 0.97]	0.02
Cluster-period	Crossover	0.72	[0.52, 1.01]	0.05
	CF-Perm	0.78	[0.61, 1.01]	0.06