# Cluster-randomized trials

## Including cluster-crossover designs

**Sven Trelle**

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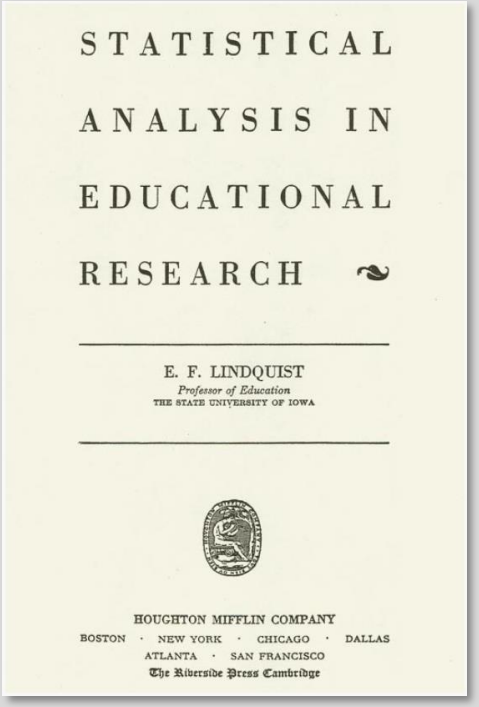
# Cluster-randomized trials

## An old design experiences a revival …



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**Cluster Randomized Clinical Trials (CRTs): Opportunities and Challenges**

**April 29, 2020**
**(7:30 Breakfast - 4:30pm)**

13th Annual Conference on Statistical Issues in Clinical Trials
Rubenstein Auditorium
UPenn School of Medicine
Philadelphia, PA 19104

DEPARTMENT of BIOSTATISTICS EPIDEMIOLOGY & INFORMATICS

| METHODS |
| --- |
| David Murray, PhD (NIH) |
| Overview: *Innovations in the Design and Analysis of Group- or Cluster- Randomized Trials* |
| Victor DeGruttola, ScD (Harvard) |
| *Using Network- and Individual-Level Information in Design and Analysis of Clustered Trials* |
| Luke J. Keele, PhD (University of Pennsylvania) |
| *Complexities Caused by Noncompliance in Cluster Randomized Trials* |
| James P. Hughes, PhD (University of Washington) |
| *Current Issues in the Design and Analysis of Stepped Wedge Trials* |
| **APPLICATIONS** |
| Lawrence H. Moulton, PhD (Johns Hopkins University) |
| Randomization: Beyond the Closurization Principle |
| Ira Longini, PhD (University of Florida) |
| *The Ring Vaccine Trial Design for the Estimation of Vaccine Efficacy and Effectiveness During Infectious Disease Outbreaks* |
| Deborah J. Donnell, PhD (University of Washington) |
| *Challenges in Implementing CRTs: From Hawthorne Effect to Measurement Bias* |
| Weili He, PhD (AbbVie) |
| *Practical Considerations in Utilizing Cluster Randomized Trials in Medical Research* |
| **PANEL DISCUSSIONS** |
| Karla Hemming, PhD (University of Birmingham) |
| David Murray, PhD (National Institutes of Health) |
| Michael Proschan, PhD (National Institutes of Health) |
| Jeffrey Roberts, MD (US Food and Drug Administration) |
| Alisa Shields-Stephens, PhD (University of Pennsylvania) |
| Monica Taljaard, PhD (Ottawa Hospital Research Institute) |

# Outline

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1. Cluster-randomized trials
   a. Definition
   b. Applications and examples
   c. Main advantages/rationale
   d. Main pitfalls and disadvantages
   e. Sample size and analysis
2. Cluster cross-over trials
3. A note on the stepped wedge design
4. Ethical aspects and informed consent

Note: This presentation is only a teaser, as all the others in this course …

# The key message

## As starter

Generally speaking:

Only do a cluster trial if absolutely necessary – otherwise do an individually randomized-controlled trial

→ Cluster design requires good justification

# Definition

## Cluster-randomized trial

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- The unit of outcome measurement/analysis is nested within the unit of randomization (and therefore different)
  - All units within a cluster receive the same intervention but clusters are randomly allocated to an intervention
- Some relation to hierarchical/multi-level modelling
- Other forms of clustering in health research (which have no direct relation to cluster trials):
  - Center-effects in multicenter trials
  - Therapist (e.g. surgeon) effects in trials of non-drug (complex) interventions
  - …

# Types of clusters

## Examples from practice

- Wards
- (General) practices
- Hospitals
- Physicians/health-care providers
- Geographical regions
- Not necessarily «health service research» → patients as clusters
  - Teeth
  - Joints
  - Eyes
  - …

# Types of interventions

## Some examples

- Very often
  - Educational interventions
  - Complex interventions in general
  - Expensive machines
  - Health policy/service interventions (e.g. insurance models)
- More rarely (at least in the past)
  - Pharmaceutical products
  - Medical devices

  i.e. classical health-care interventions

# Clustering and the intervention

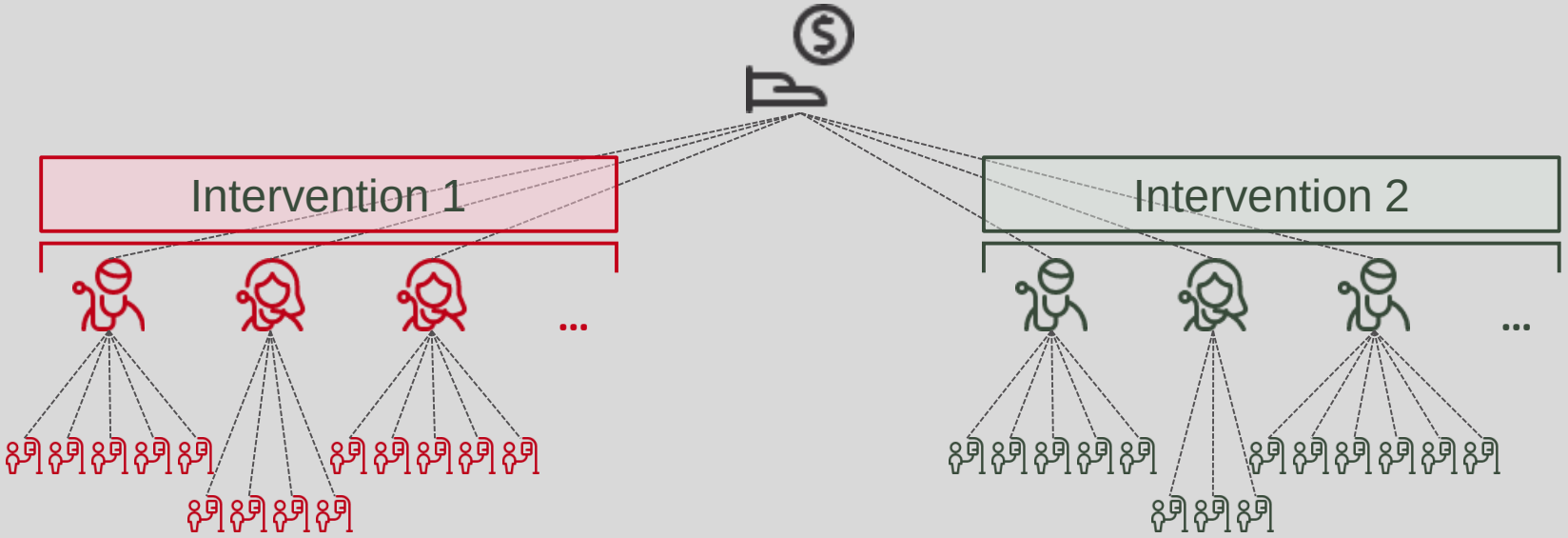
## Sometimes causing confusion

– The unit of randomization is not **necessarily** the unit at which the intervention is applied i.e. the cluster unit might not be the direct recipient of the intervention

# Intervention administered at cluster and nested level

## Clustering and the intervention

– The unit of randomization is not **necessarily** the unit at which the intervention is applied i.e. the direct recipient of the intervention



# Intervention administered at cluster level

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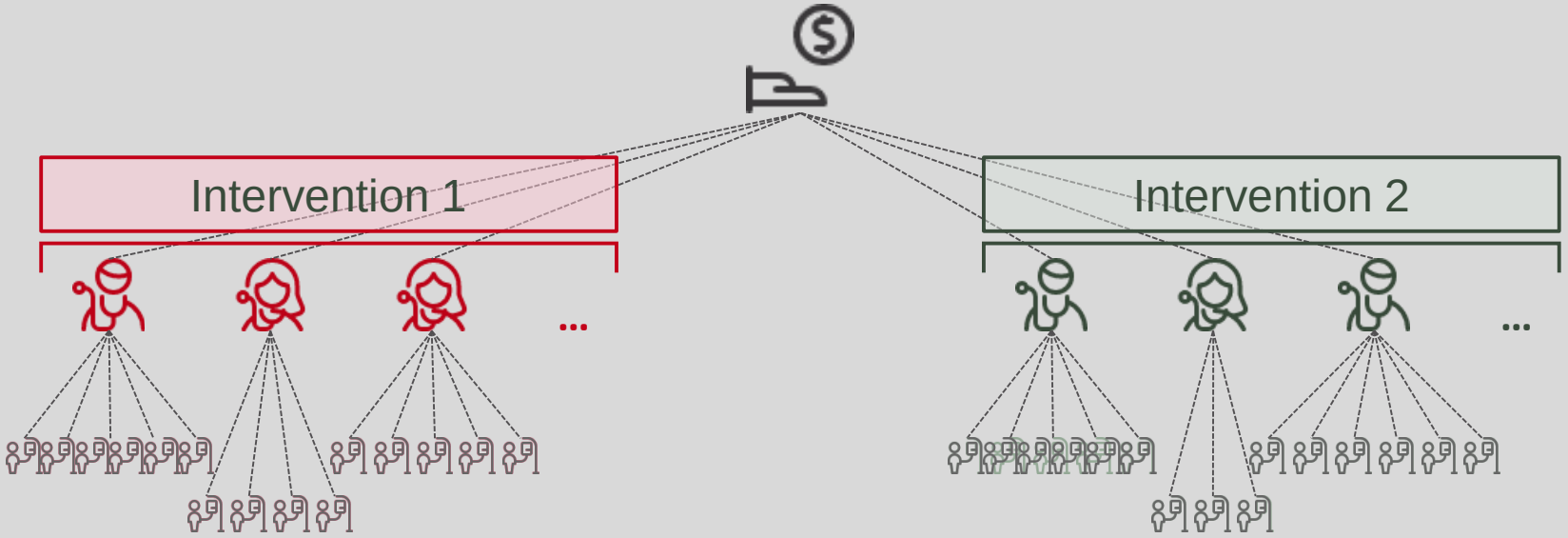

# Intervention administered at nested level

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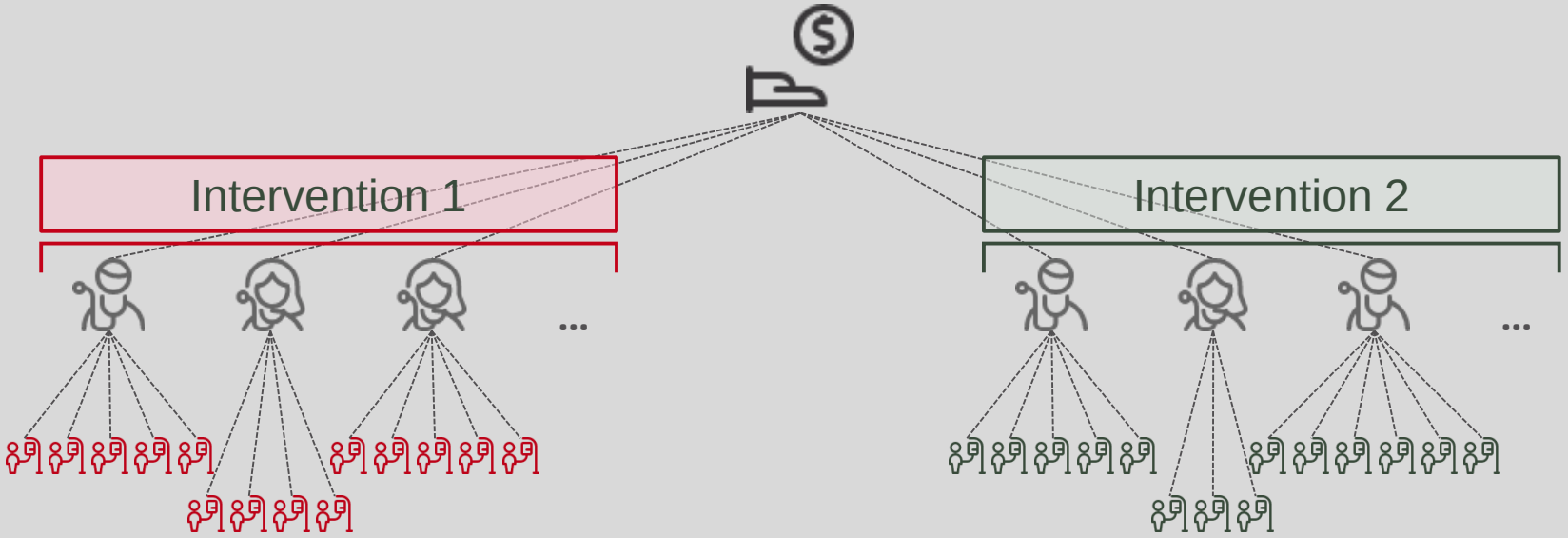
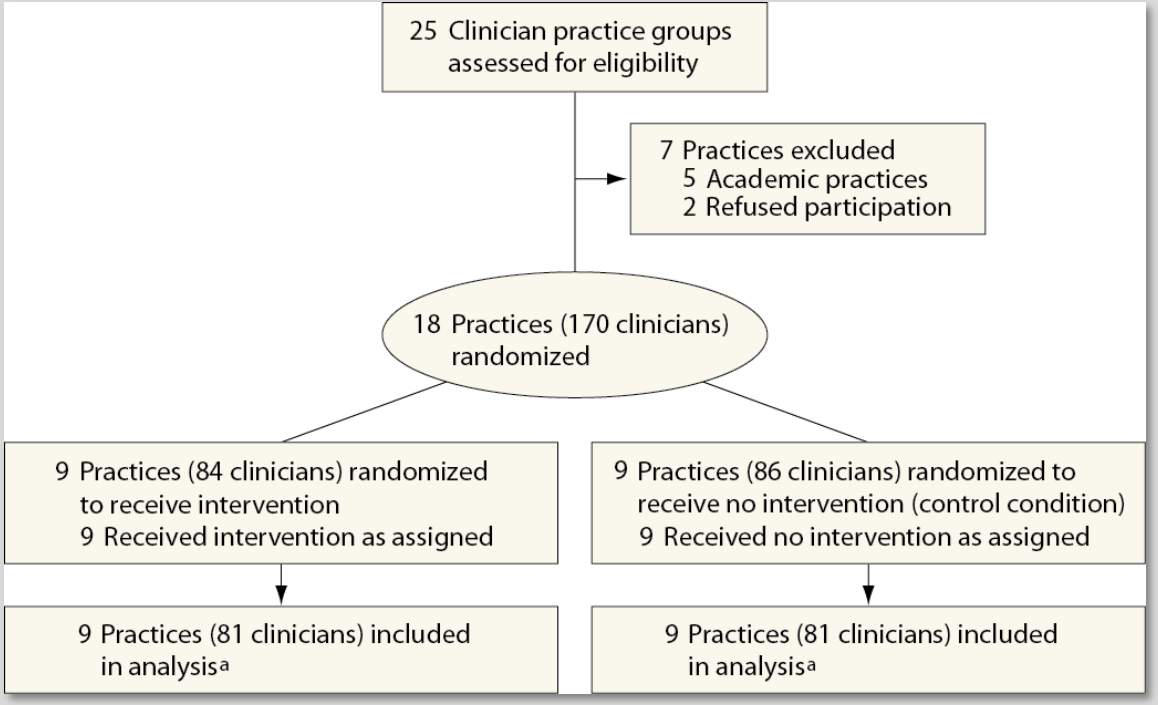


# Applications and examples

# Antibiotic stewardship as a classical type of trial

## Gerber JS et al. 2013



# Antibiotic stewardship as a classical type of trial

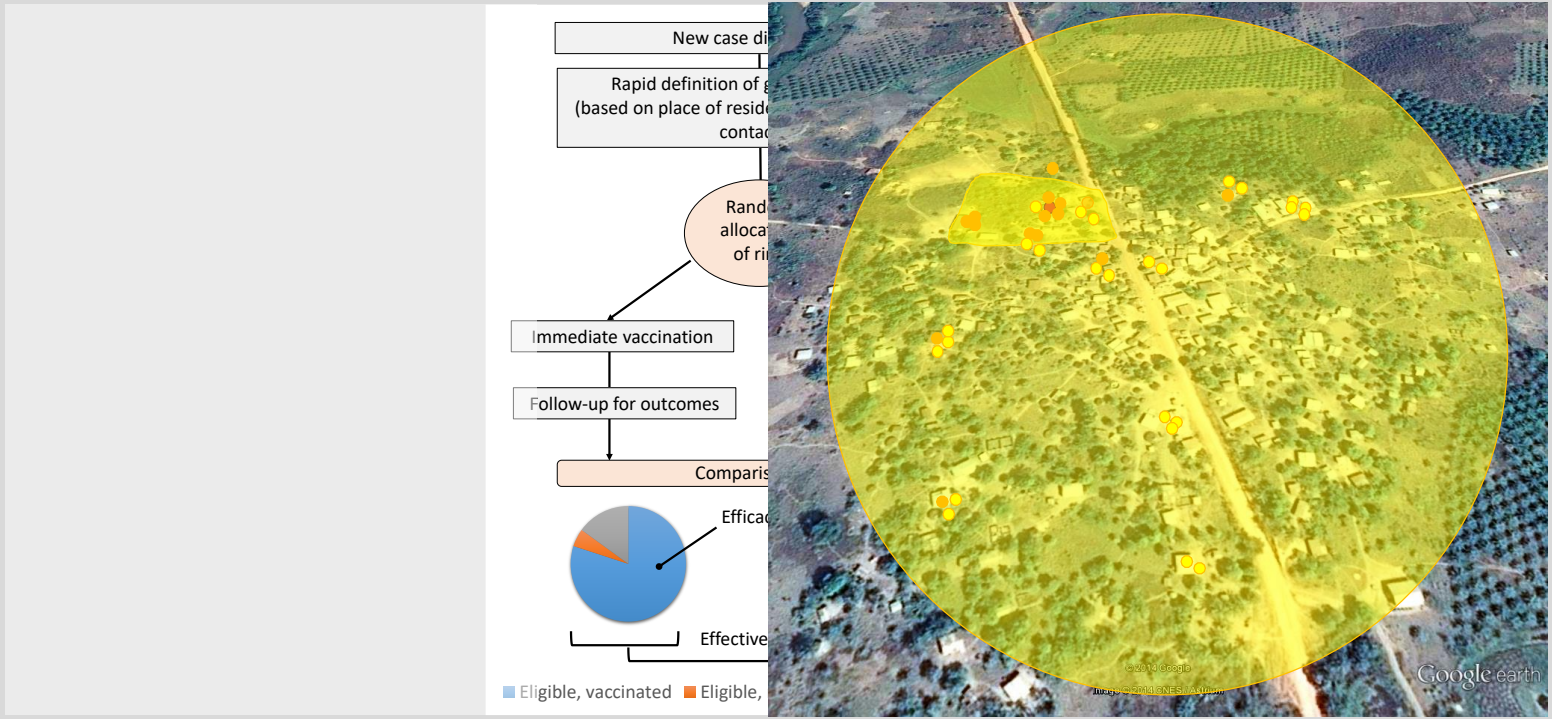
## Gerber JS et al. 2013

- Intervention
  - On-site education session
  - Personalized, quarterly audit and prescription feedback (1 year)
- Control
  - Standard of care i.e. no education, no audit or feedback
- Main outcome
  - Broad-spectrum (off-guideline) antibiotic prescription (per patient)

→ Intervention administered at cluster-level i.e. indirect effect measured

# Public health intervention (vaccination)

## Ebola ça suffit!



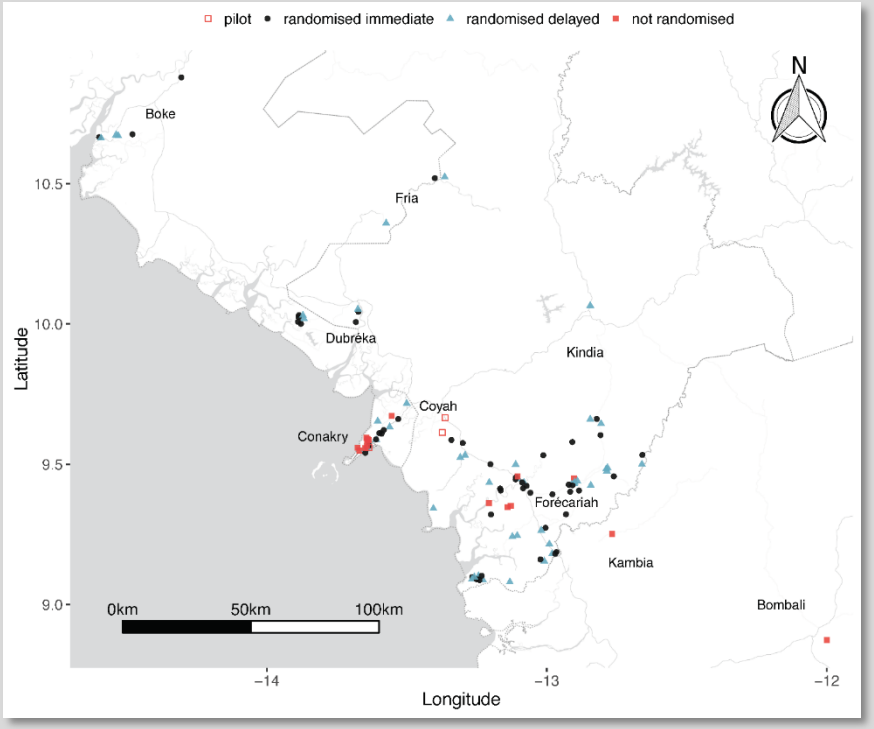

*Ebola ça Suffit Ring Vaccination Trial Consortium 2015*

# Ebola ça suffit!

## Rationale for cluster design

- Cluster design not uncommon in vaccine trials (usually geographically defined)
- Also driven by feasibility

→ Intervention administered at nested level i.e. direct effect measured




*Ebola ça Suffit Ring Vaccination Trial Consortium 2015*

# Improving the Quality of Dentistry (IQuaD)

## Specific design features

- A cluster factorial randomised controlled trial comparing
  - oral hygiene advice and(/or) periodontal instrumentation
  - with routine care
  - for the prevention and management of periodontal disease
  - in adults
- Almost all design features of individually randomized trials can be applied to cluster trials e.g. stratification, matched-pairs randomization, factorial, cross-over designs (later in talk)

*Ramsay CR et al. 2018*

# Matched pairs randomization

## Mexican universal health insurance programme trial

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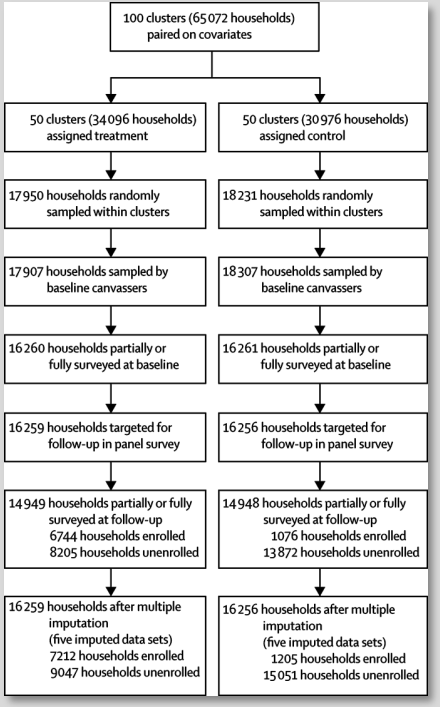
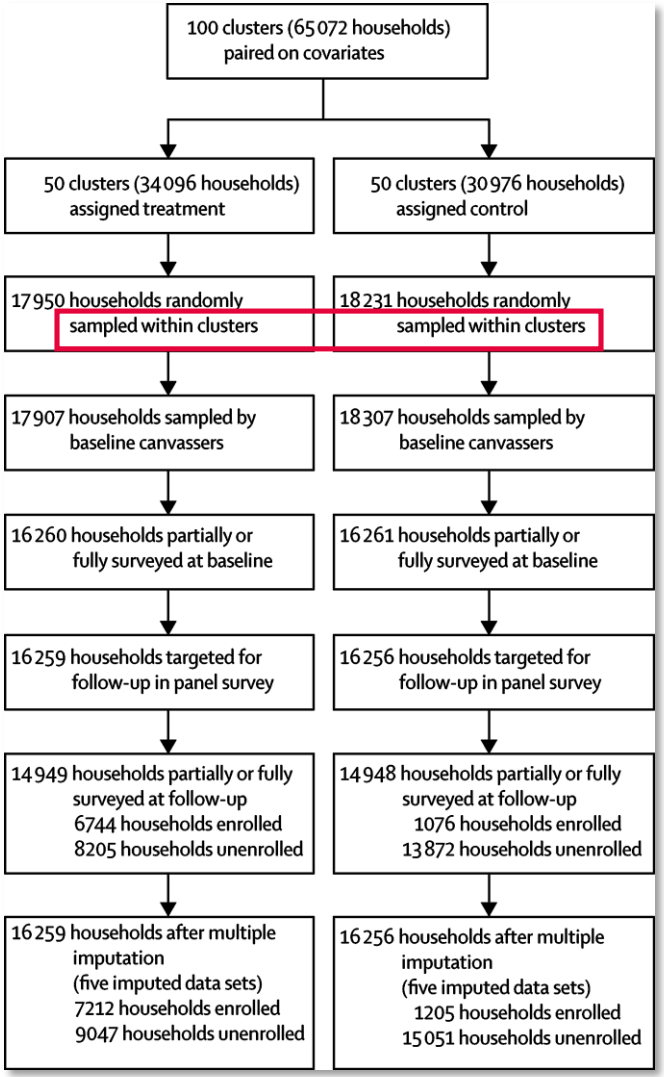
- To evaluate aspects of Seguro Popular, a program with
  - health insurance,
  - regular and preventive medical care,
  - medicines, and
  - health facilities

  to 50 million uninsured Mexicans.
- Clusters: 148 **health facility catchment areas** (74 matched pairs)
- Nested units: households
- Outcome (1st): **catastrophic (health) expenditures**




*King G et al. 2009*


100 clusters (65 072 households) paired on covariates
50 clusters (34 096 households) assigned treatment
50 clusters (30 976 households) assigned control
17 950 households randomly sampled within clusters
18 231 households randomly sampled within clusters
17 907 households sampled by baseline canvassers
18 307 households sampled by baseline canvassers
16 260 households partially or fully surveyed at baseline
16 261 households partially or fully surveyed at baseline
16 259 households targeted for follow-up in panel survey
16 256 households targeted for follow-up in panel survey
14 949 households partially or fully surveyed at follow-up
6744 households enrolled
8205 households unenrolled
14 948 households partially or fully surveyed at follow-up
1076 households enrolled
13 872 households unenrolled
16 259 households after multiple imputation
(five imputed data sets)
7212 households enrolled
9047 households unenrolled
16 256 households after multiple imputation
(five imputed data sets)
1205 households enrolled
15 051 households unenrolled

# Households as cluster units

## Home Injury Prevention Intervention (HIPI)

- Assessor-blind, cluster-randomised controlled trial of 842 **households** comparing
- immediate home modifications (treatment group)
- with 3-year wait before modifications (control group)
- for **falls** at home that needed medical treatment.

*Keall MD et al. 2015*

# Individuals as cluster unit

## Watthanasaen S et al. 2017

- This cluster randomised controlled trial evaluated
- a school-based xylitol chewing-gum programme
- on caries onset rate measured as the change in caries onset on **tooth** surfaces
- among 174 **students** with visual or hearing impairment.

Nested units (‘individuals’)

Clusters

# Advantages and rationale for design choice

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# Type of intervention

## As a driver for cluster design

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- Intervention can only be applied at cluster level but (main) outcome of interest is on nested level
- Examples
  - Smoking bans
  - Insurance models
  - …

→ Implicitly, the underlying reason is actually contamination

# Type of intervention

## Really a cluster trial?

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- Just because an intervention is applied at a ‘clustering’ units does not make a trial (necessarily) a cluster trial
- It needs to satisfy also the second condition: outcome measured at nested units
- Can sometimes be difficult to see especially with binary outcomes (flag: only cluster-level analyses planned)
  - But sometimes also tricky the other way round: an individual randomized trial that is actually a cluster trial …
- Depends on the research question
- Antibiotic stewardship trial as example
  - Alternatives: overall costs for antibiotics, antibiotic prescriptions per practice, …

*See also Donner A and Klar N 2004*

# Contamination

## Main rationale for design

- Individuals (nested units) randomized to one intervention exposed to the comparison intervention
- Either experimental OR control i.e. contamination can be in both directions

→ When defining the cluster unit, carefully check mechanism of contamination

- Some contamination is acceptable (see Hewitt CE etal. 2008)

# Other arguments

## Broad forward

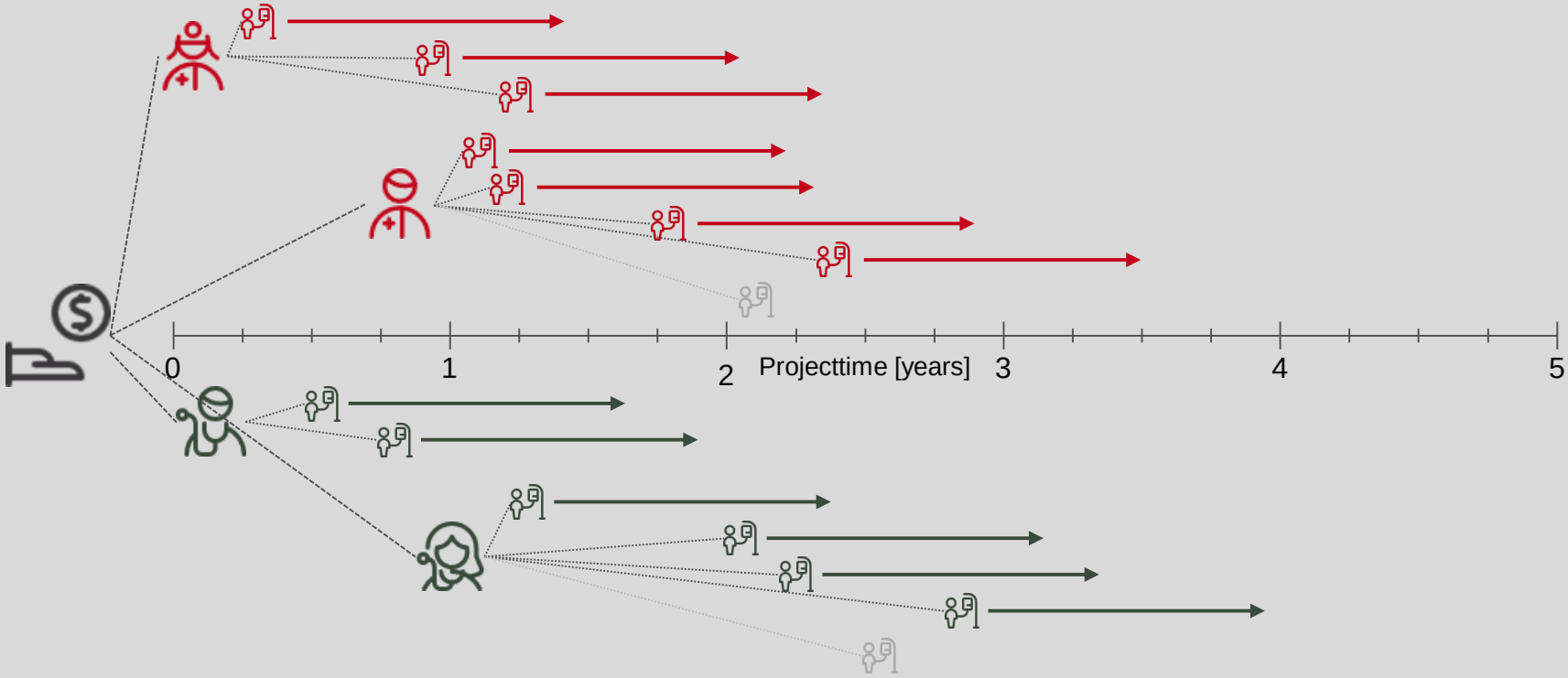
- Logistical convenience
- Reduced costs
- More pragmatic
- Consent easier (sometimes not needed at all)

*Crespi CM 2016; see also Goldstein CE et al. 2018*

# Pitfalls and disadvantages

# Selection bias

## The major methodological challenge



# Selection bias

## Two types of mechanisms

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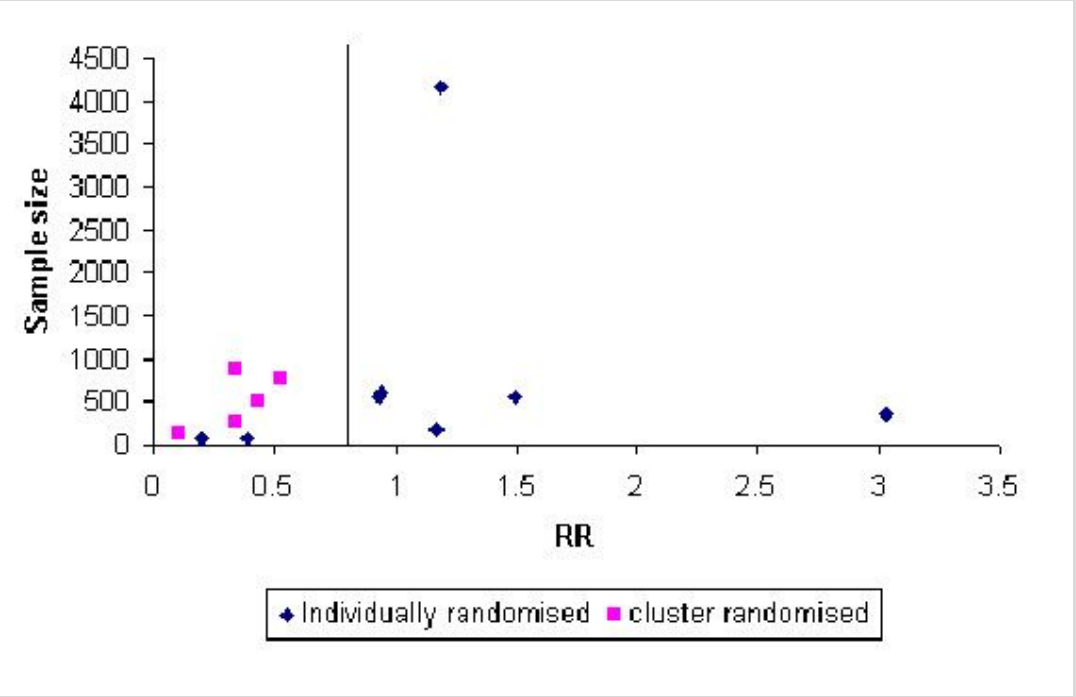
- Foreknowledge of allocation leads to
  - selective enrollment (Schulz K et al.1994, Jordhoy MS et al. 2002)
  - selective participation
    - by not showing up at the cluster unit at all
    - differential consent (Molloy DW et al. 2000)

*Han S et al. 2005*

# Selection bias

## Empirical data

- Trials evaluating hip protectors for prevention of hip fractures




*Hahn S et al. 2005*

# Sidenote: baseline imbalance

## In cluster trials

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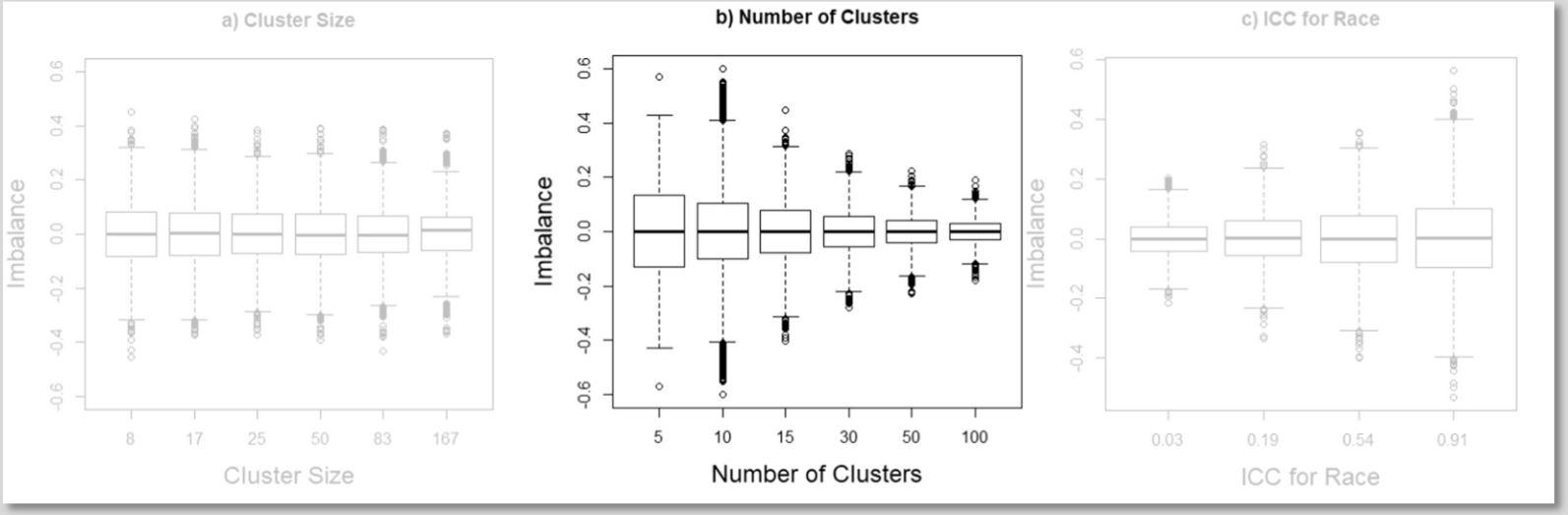
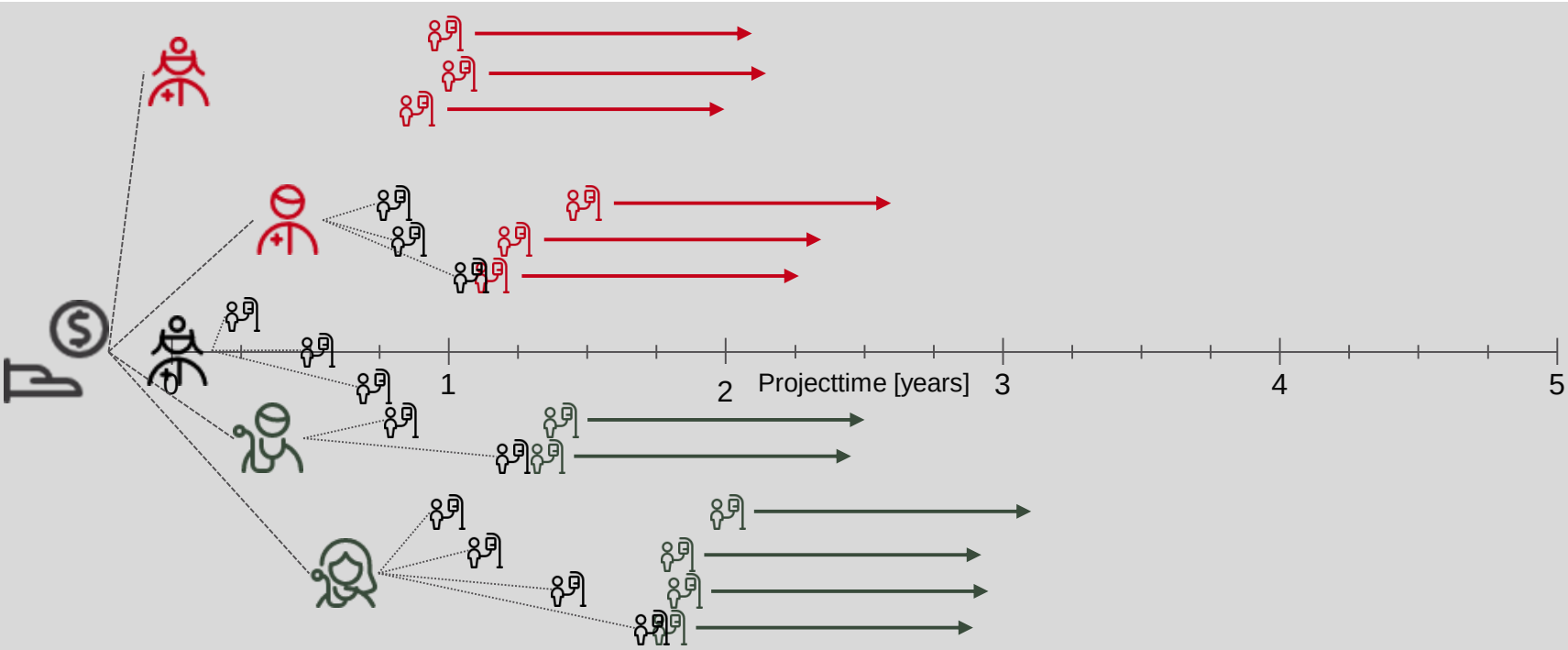
- Selection bias or random chance
- More frequent in cluster trials than in individually randomized trials




*Yang S et al.2020*

# Selection bias

Allocation in batches to achieve concealment of allocation



# Sample size and analysis

# Sample size

## General comments

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- Power is affected by the (statistical) correlation of nested units within clusters i.e. observations within the same cluster tend to vary less than randomly selected observations from the overall population
- Correlation is quantified by the Intraclass/-cluster Correlation Coefficient (ICC)
- Fixing the intraclass correlation coefficient for sample size calculation most challenging (often unknown)
- Estimates of intraclass correlation coefficients from studies < ca. 40 cluster units highly uncertain, even more pronounced for binary outcomes (Ukoumunne OC 2004)

# Sample size

## Design factor

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- Typical intraclass correlation coefficients range from 0.01 to 0.05 but might go up to 0.1 and can be considerably larger than anticipated (e.g. $ICC_{assumed}$ 0.022 → $ICC_{observed}$ 0.11 (Vitiello MV et al. 2013))
- This, and the large uncertainty in estimates → be conservative i.e. round up rather down
- Calculate sample size for an individually randomized trial and inflate by variance inflation (design) factor
- Formula: $VIF = 1 + (m - 1)\rho$

  $VIF$, Variance Inflation Factor (design factor)

  $m$, (weighted) average cluster size, check formula (extension: allowance for variable cluster size)

  $\rho$, intraclass correlation coefficient

# Sample size

## Design factor

- Typical intraclass correlation co
  might go up to 0.1 and can be
  (e.g. $ICC_{assumed}$ 0.022 → $ICC_{obs}$
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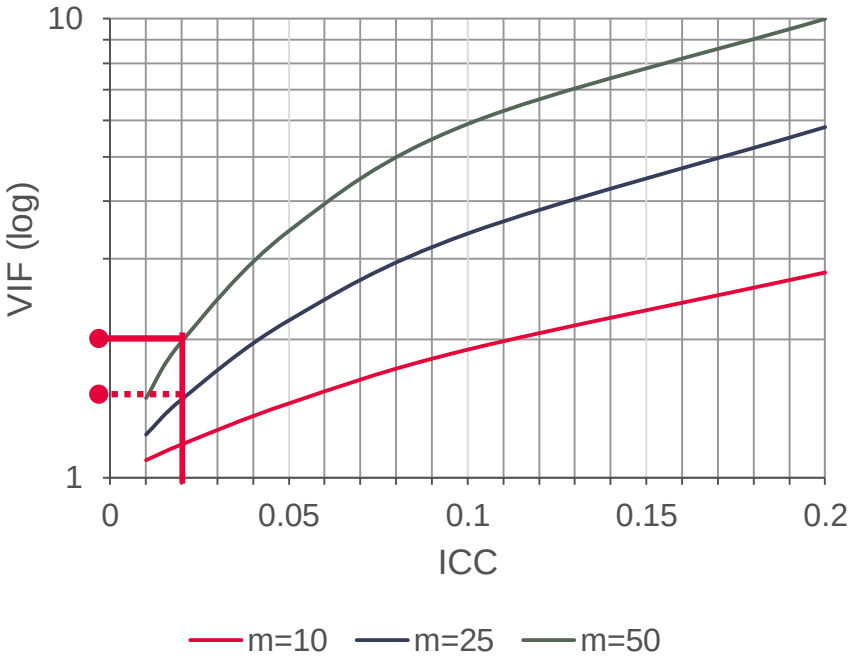


# Analysis

## See references

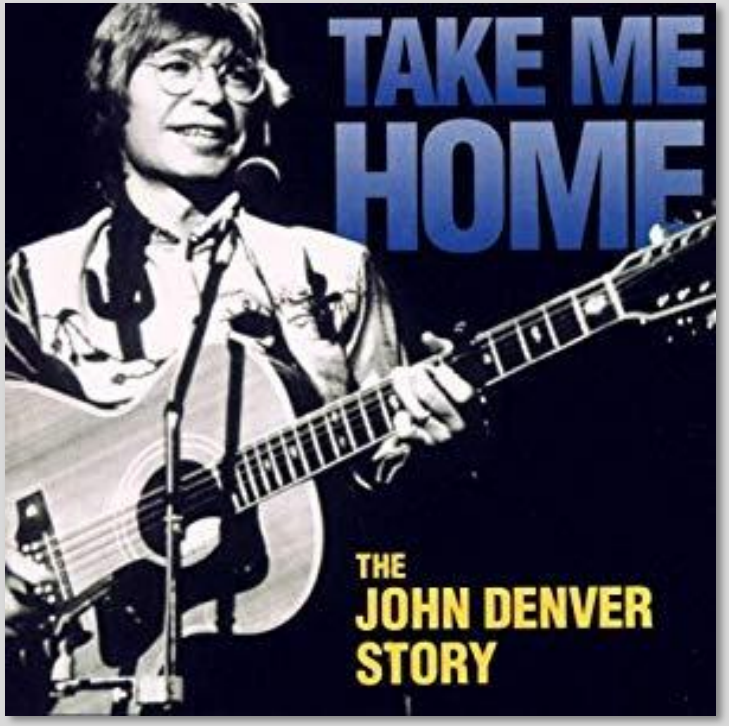
- Usually individual- AND cluster-level outcome data
- Think about baseline adjustment (also characteristics of nested units)
- Clustering must be taken into account (otherwise (highly) anti-conservative i.e. type I error inflated)
- May allow for changes over time of intracluster correlation (Grantham KL et al. 2019)
- Main choices for individual-level analysis
  - Standard regression models with robust standard errors
  - Generalized Estimating Equations (GEE) with ‘exchangable’ correlation matrix with robust standard errors (< ca. 80-90 clusters, Kahan BC et al. 2016)
  - Random (mixed) effects regression
- Difference between random-effects and population-averaged estimators → https://www.stata.com/support/faqs/statistics/random-effects-versus-population-averaged/

*Peter TJ et al. 2003, Ma J et al. 2013*

# Take home messages



- Stick to individually randomized designs if possible
- Identify the cluster and nested unit
- Take all (statistical) correlations into account in the design and analysis
- Analyses can easily get very complex



# Thank you

# for your attention!

**Sven Trelle**

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