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Design and analysis of cluster-randomized trials with examples in infectious diseases

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with examples in infectious diseases

Paul Milligan

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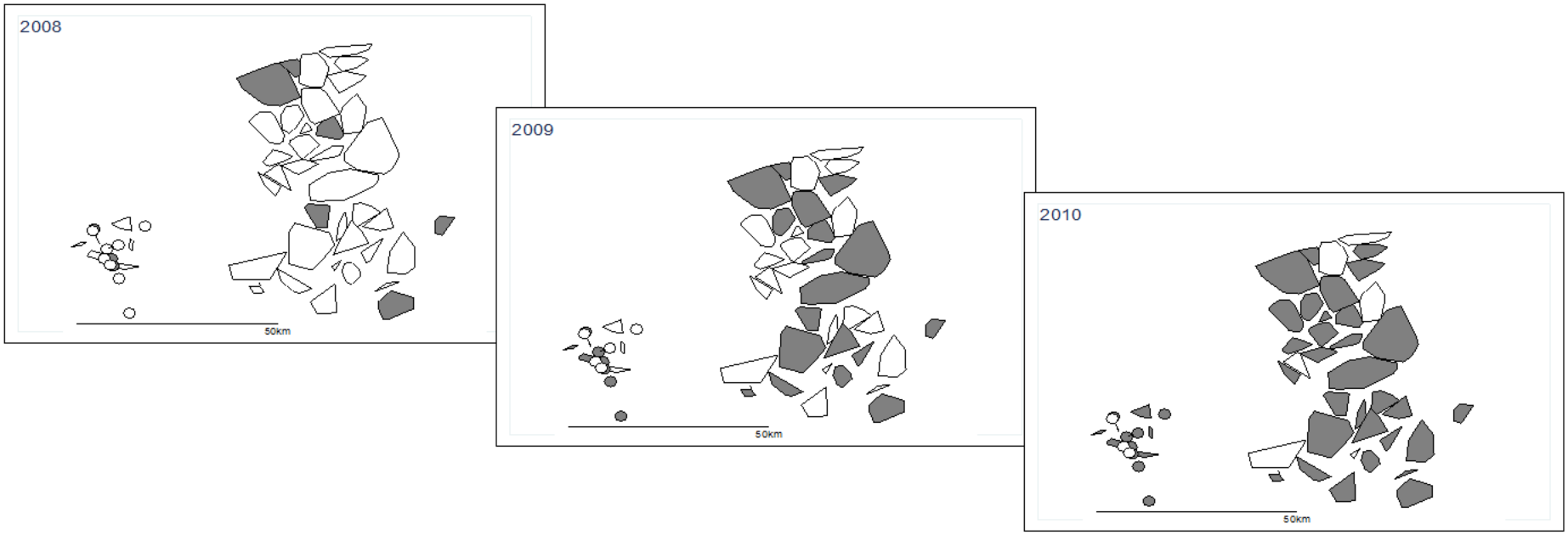
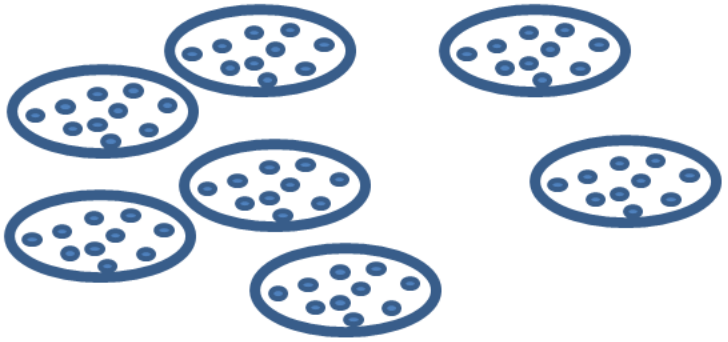


Cluster randomized trials

- In clinical trials it is usual to randomize participants *individually*
- Some interventions can be delivered, or assessed, only at *group* or *area* level



- Household
- Village or community
- Medical practitioner
- School
- Hospital
- District

Outline of the session:

- Reasons for cluster randomization
- Some examples
- Statistical issues
- Design
- Analysis
- Ethics

- Further reading

Reasons for cluster randomization

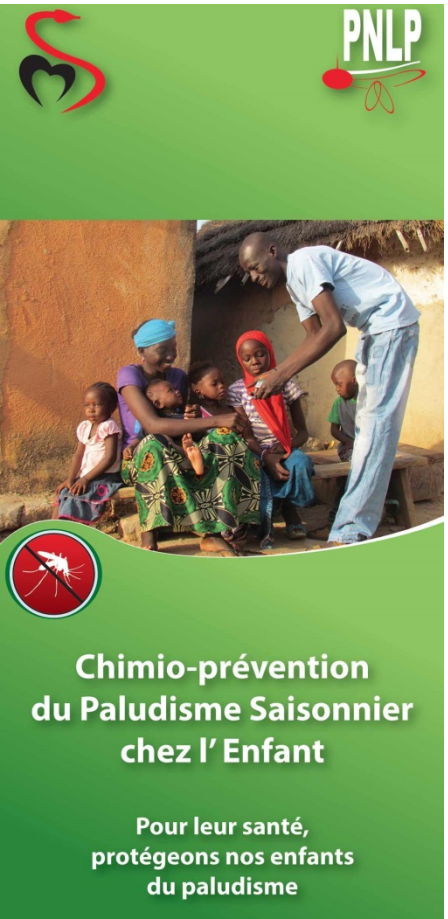
- the intervention is naturally delivered to groups rather than individually, (or it is more convenient or acceptable to do so)
- to capture indirect effects
- to allow operational factors in a real-life setting to be taken into account (e.g. cost effectiveness)
- to reduce contamination

Example 1

OPEN ACCESS Freely available online PLOS MEDICINE

Two Strategies for the Delivery of IPTc in an Area of Seasonal Malaria Transmission in The Gambia: A Randomised Controlled Trial

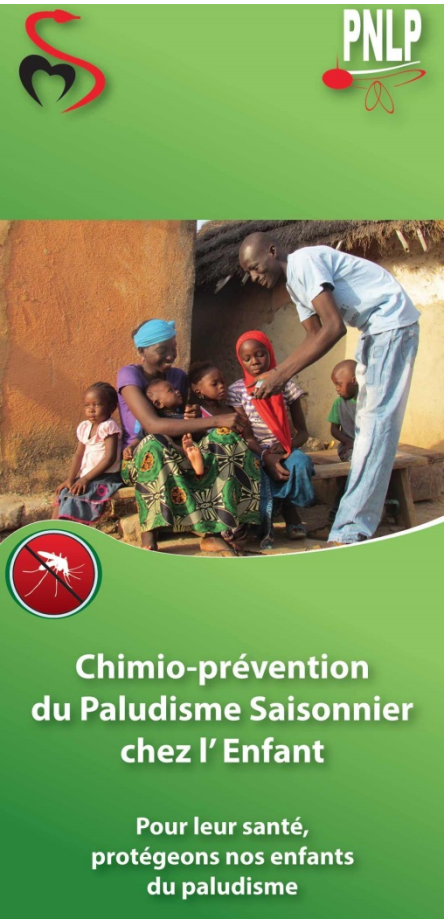
Bojang et al. 2010 Plos Med 8(2)



- In the community by village health workers

- At the clinic

Example 1



Intervention:

monthly antimalarial treatment to prevent malaria

Primary outcome:

malaria cases in children, diagnosed at the health centre

Unit of randomization:

immunisation outreach clinics

Design:

cluster randomized trial with 2 intervention groups

Sample size:

26 clusters (2x13), about total of about 12000 children

Results

- Baseline comparability

	Clinic	Village
No. of children	6076	6250
No. of clusters	13	13
Mean distance to health centre, km	14.2	13.9
Slept under a bednet	51%	64%
Children >1yr fully vaccinated	69%	79%

- Main outcomes

	Clinic	Village	Difference (95%CI)
Coverage*	48%	74%	27% (16% to 38%)
Malaria incidence cases/1000 child months	8.2/1000	4.5/1000	3.7 (-0.7 to 8.1)
Mean haemoglobin concentration*	10.2	10.4	0.16 (-0.22 to 0.54)
Financial cost per child fully protected	$2.97	$1.23	$1.74

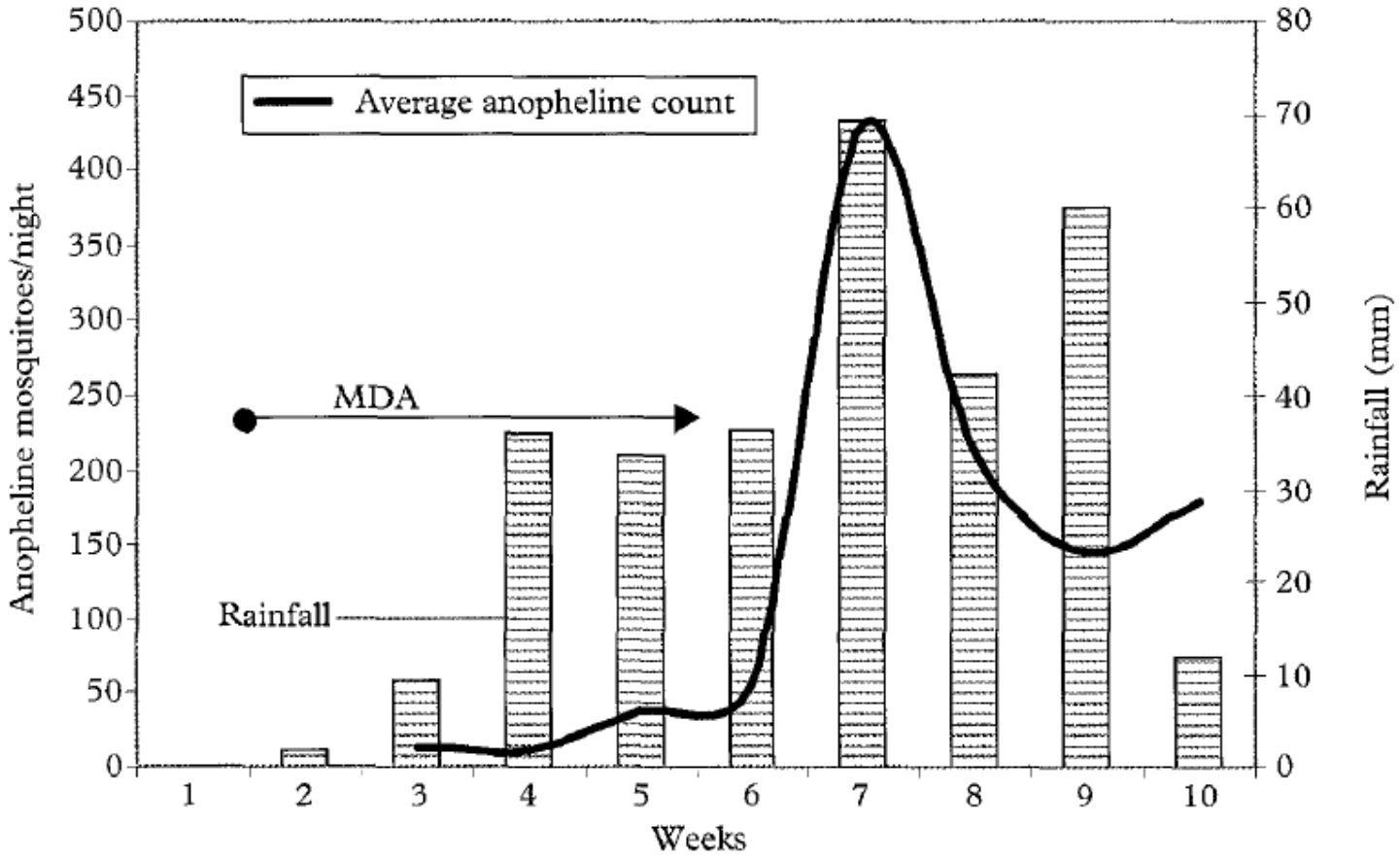
*evaluated in survey of 1200 children

Example 2

TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE (2003) 97, 217–225

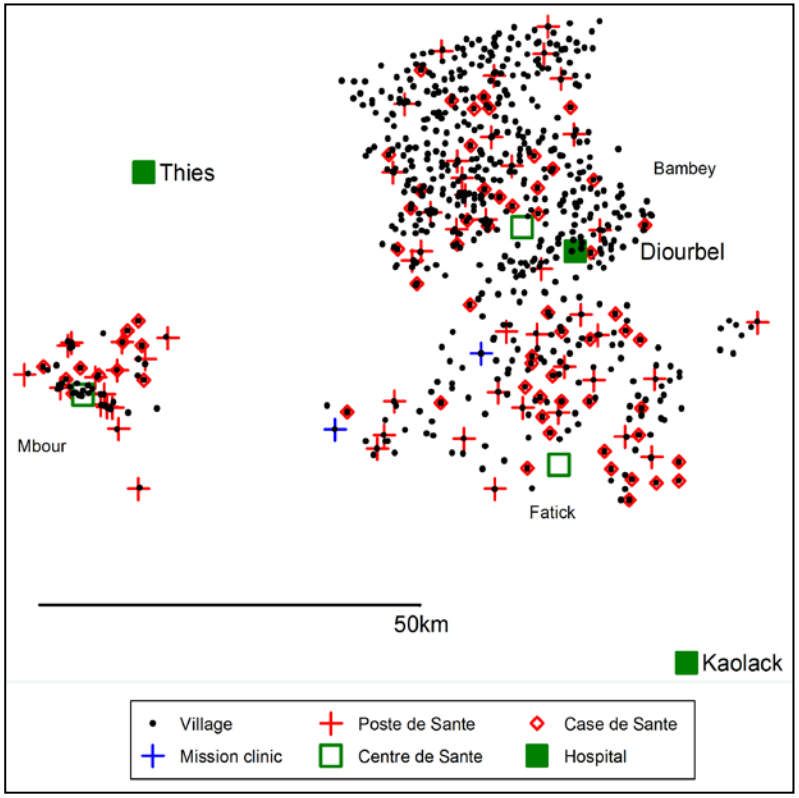
The effect of mass administration of sulfadoxine–pyrimethamine combined with artesunate on malaria incidence: a double-blind, community-randomized, placebo-controlled trial in The Gambia

von Seidlein et al.



Example 3

	Area 1	Area 2	Area 3	Area 4
Year 1				
Year 2				
Year 3				
Year 4				



Phased introduction of malaria chemoprevention in a stepped wedge design

Four key issues:

1. The effect of clustering
   has to be taken into account when calculating sample size, and in the analysis of results

2. Care needed during randomization to make sure the groups are well balanced

3. Selection of individuals within clusters may take place after randomization, care is therefore needed to avoid selection bias

4. To separate direct from indirect effects requires evaluation in untreated individuals within treated clusters

Clustered data

Every group or cluster of individuals has its own characteristics. Individuals within a cluster tend to be more similar to each other than to members of another cluster.

“Randomization by cluster accompanied by an analysis appropriate to randomization by individual is an exercise in *self-deception”* (*Cornfield*, 1978).

Clustered data

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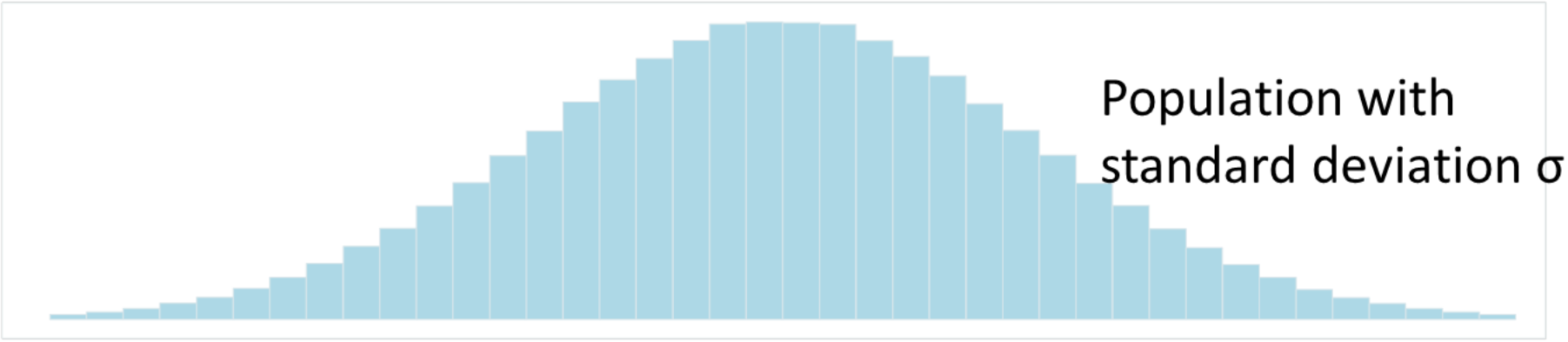
Confidence intervals *are too narrow*

P-values *are too small*

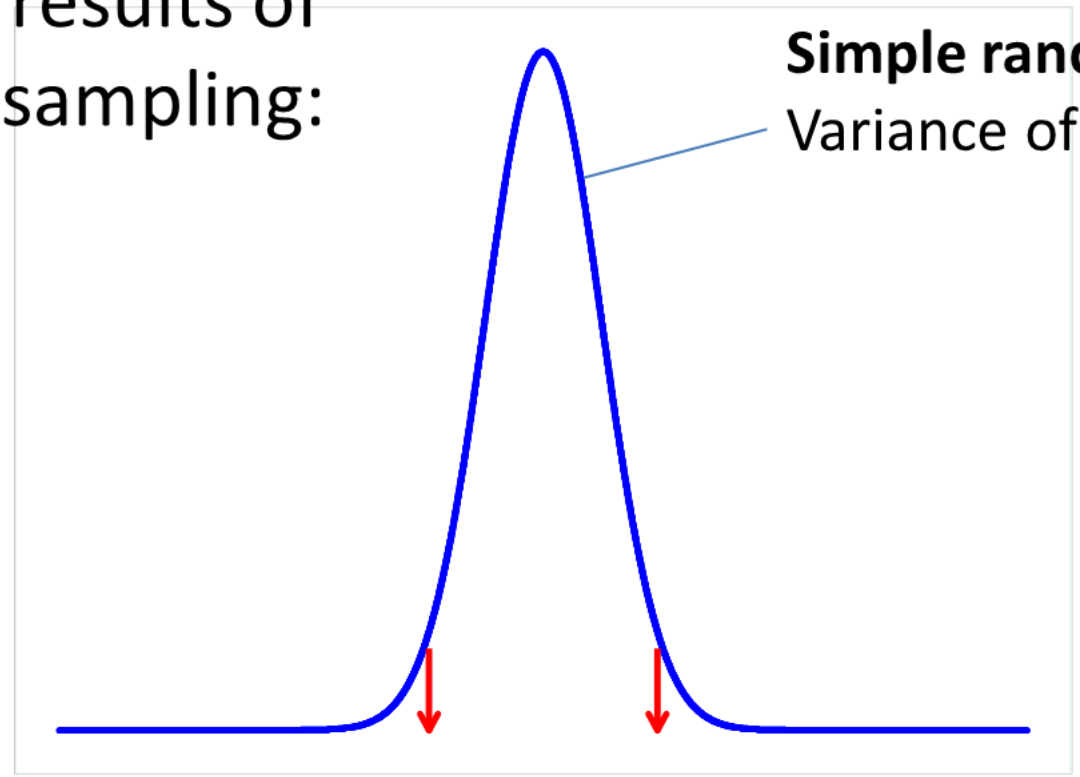
Simple random sampling

Cluster sampling

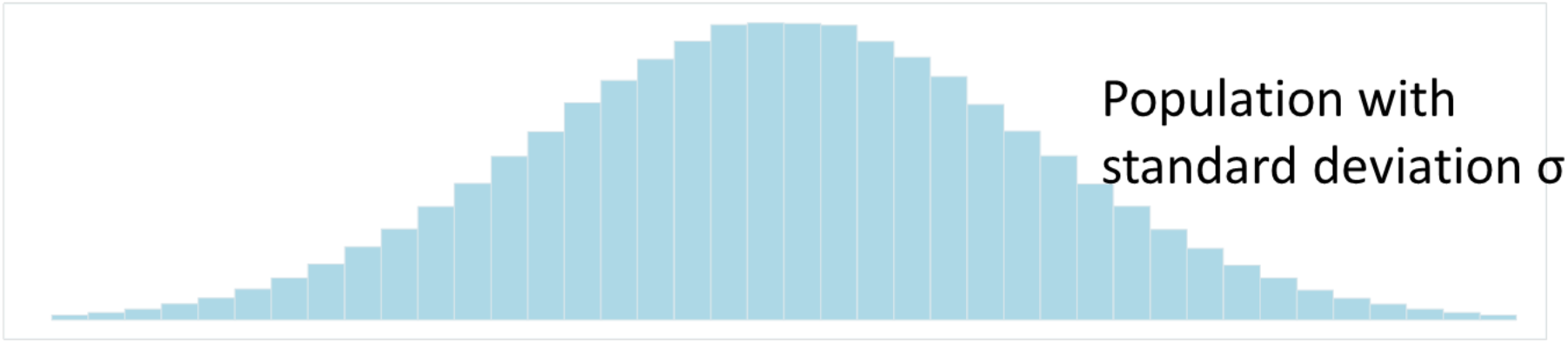
Understanding the effects of clustering



Expected results of repeated sampling:



Understanding the effects of clustering



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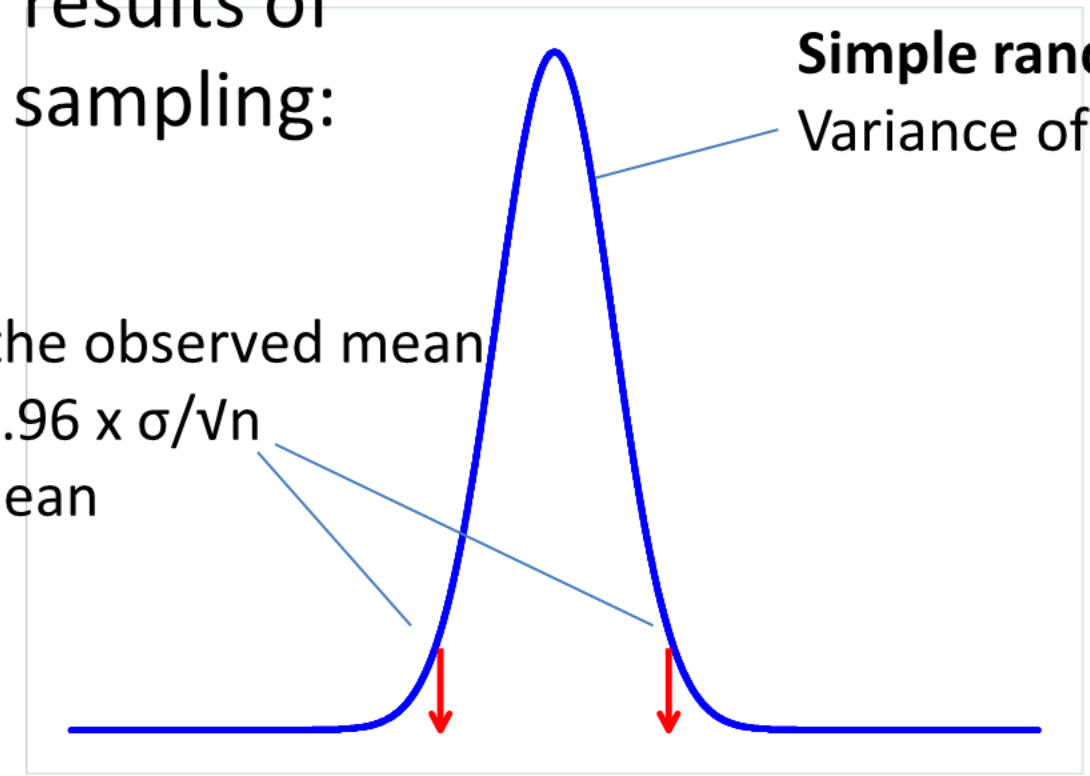
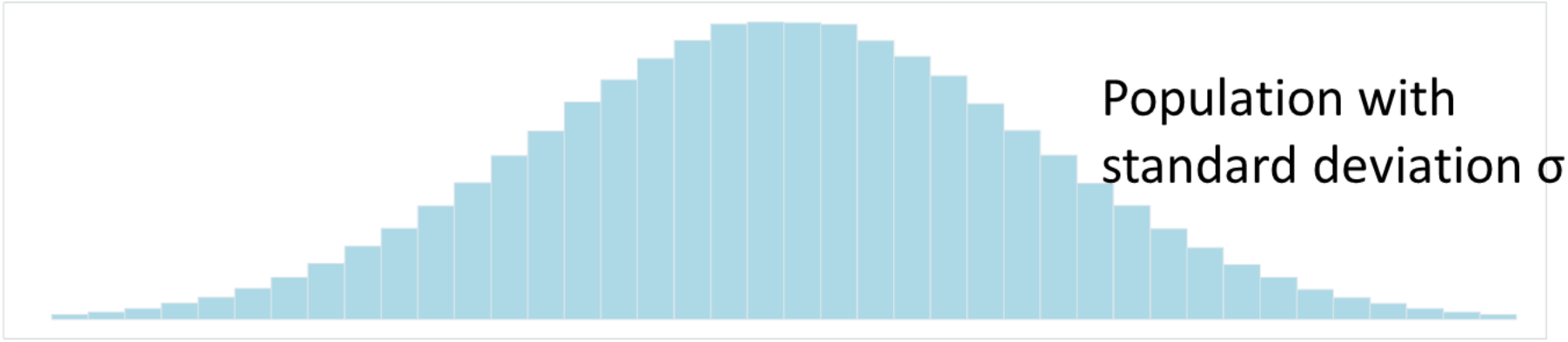


Understanding the effects of clustering



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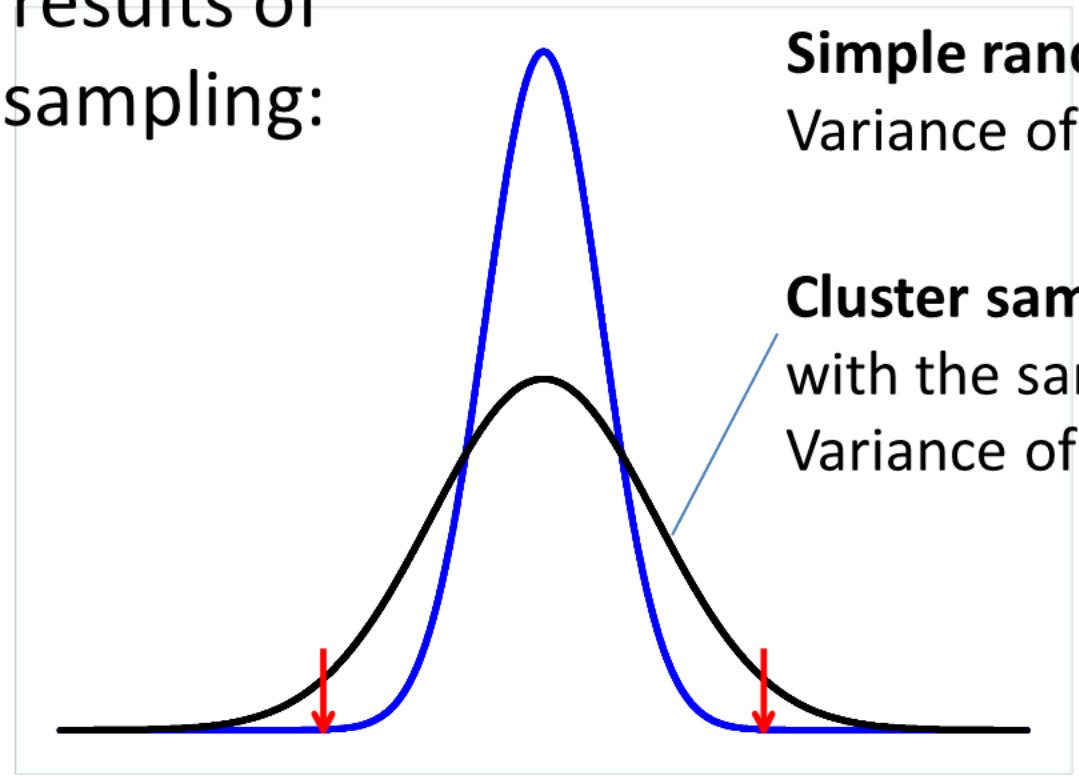
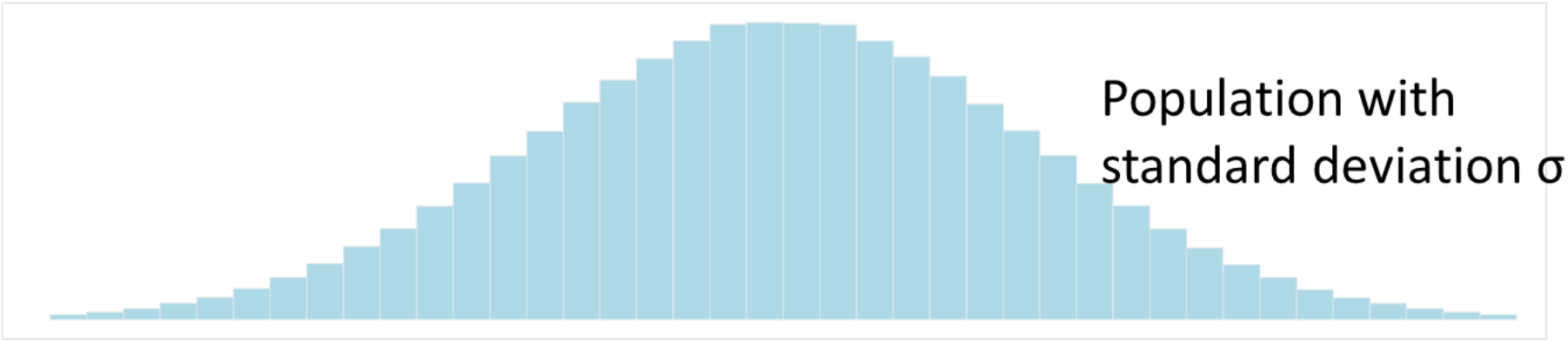


Simple random sampling
Variance of the mean: σ^2/n

Cluster sampling
with the same sample size
Variance of the mean:
$\sigma^2/n \times VIF$

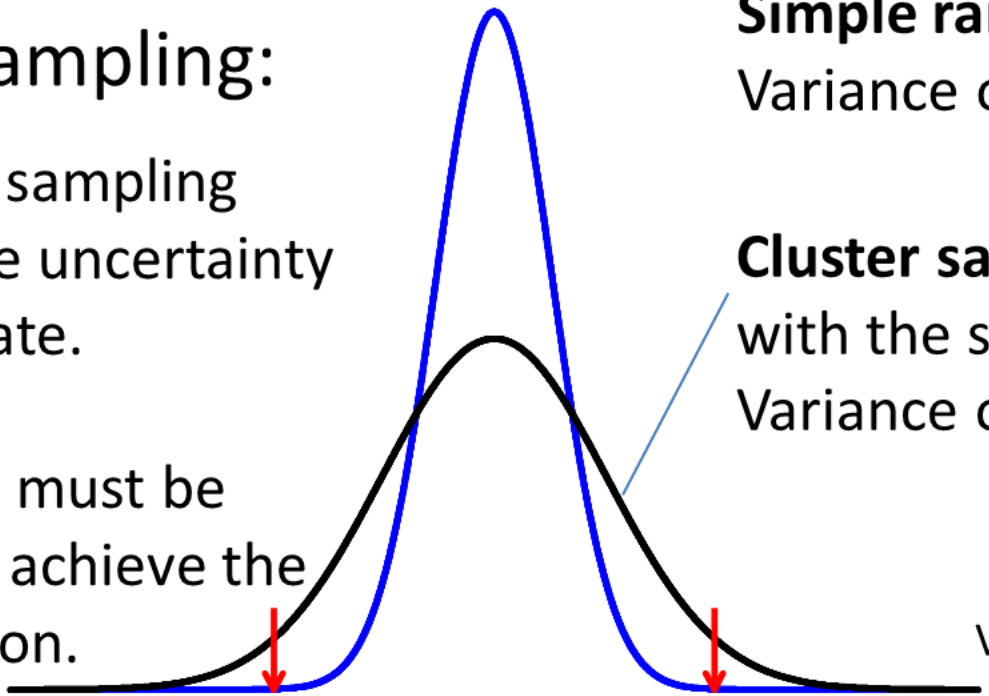
Understanding the effects of clustering



Expected results of repeated sampling:

With cluster sampling there is more uncertainty in our estimate.

Sample sizes must be increased to achieve the same precision.



Simple random sampling
Variance of the mean: σ^2/n

Cluster sampling
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Variance of the mean:
$\sigma^2/n \times VIF$

Variance Inflation Factor

VIF depends on:

the degree of clustering

the size of the clusters

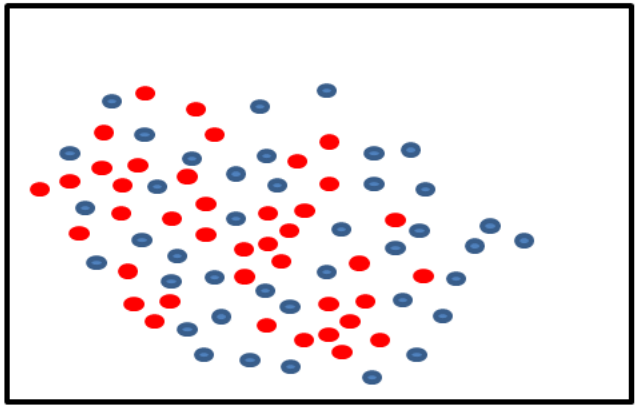
$$VIF = 1 + (b-1)\rho$$

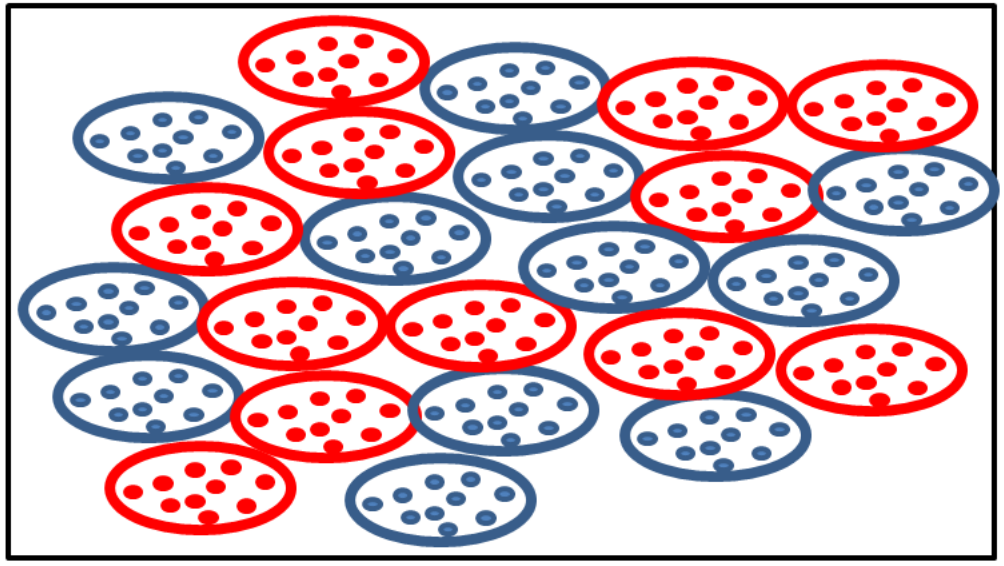
cluster size

intra-class correlation

Example: Cluster size b=50, ρ=0.04 => VIF=2.96

we need a 3-fold increase in sample size compared to an individually randomized trial



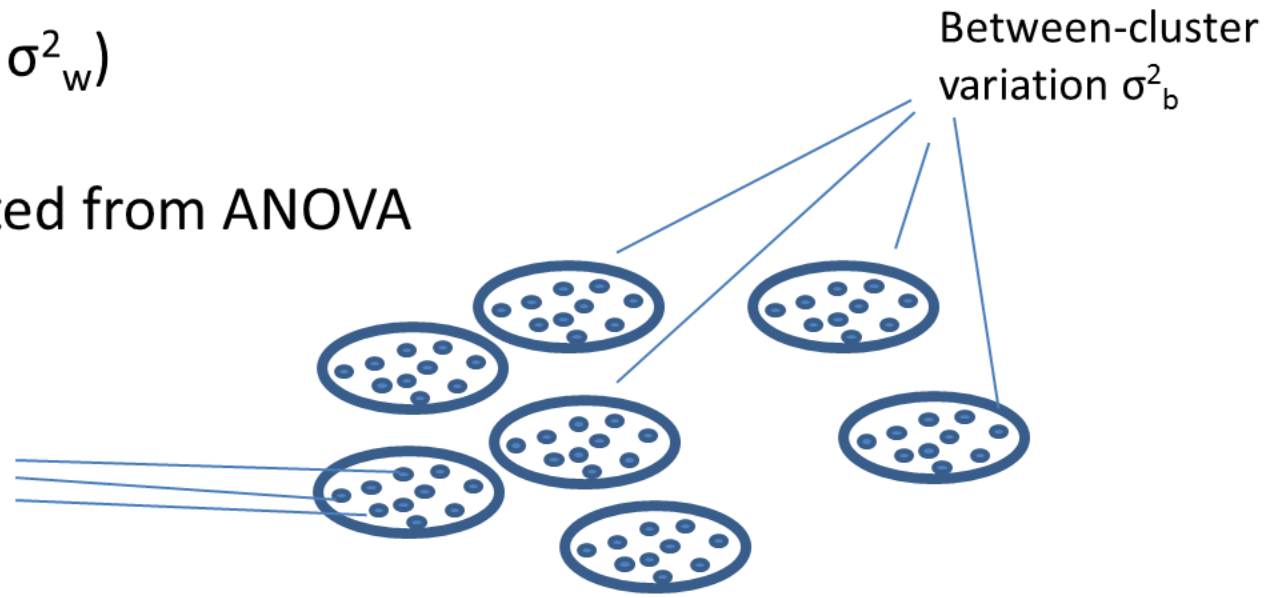


Estimating ρ:

- published studies
- pilot studies
- routine data from the study area
- informed guesswork

$\rho = \sigma^2_b / (\sigma^2_b + \sigma^2_w)$

can be estimated from ANOVA



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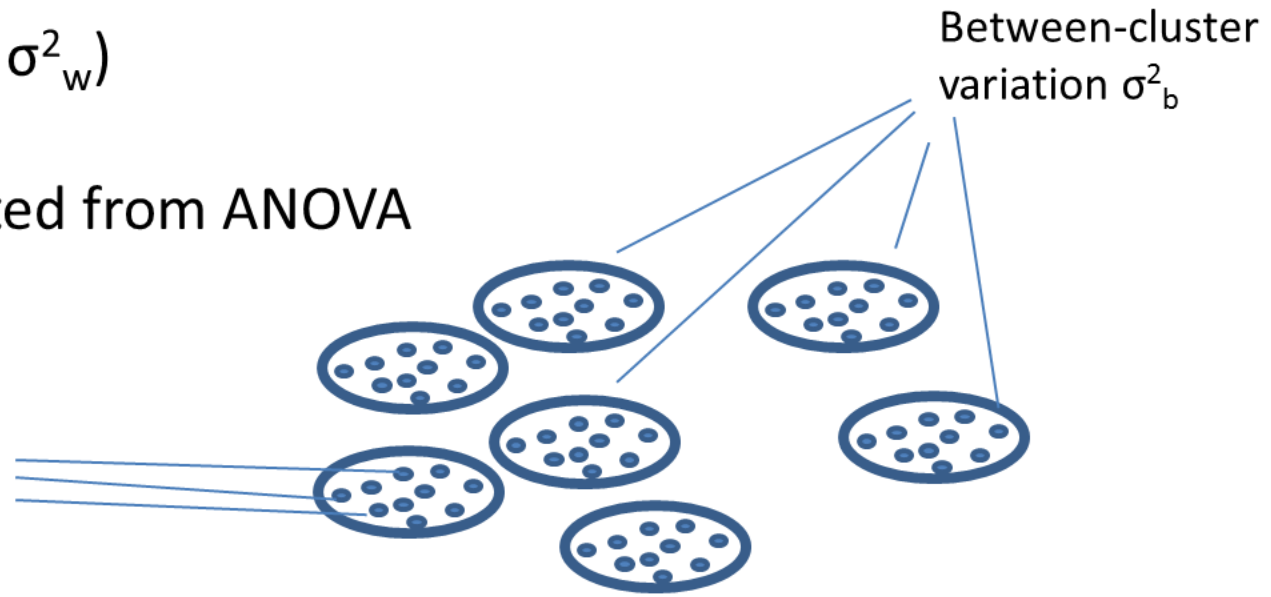


Methods for binary outcomes, and for incidence rates are described in:

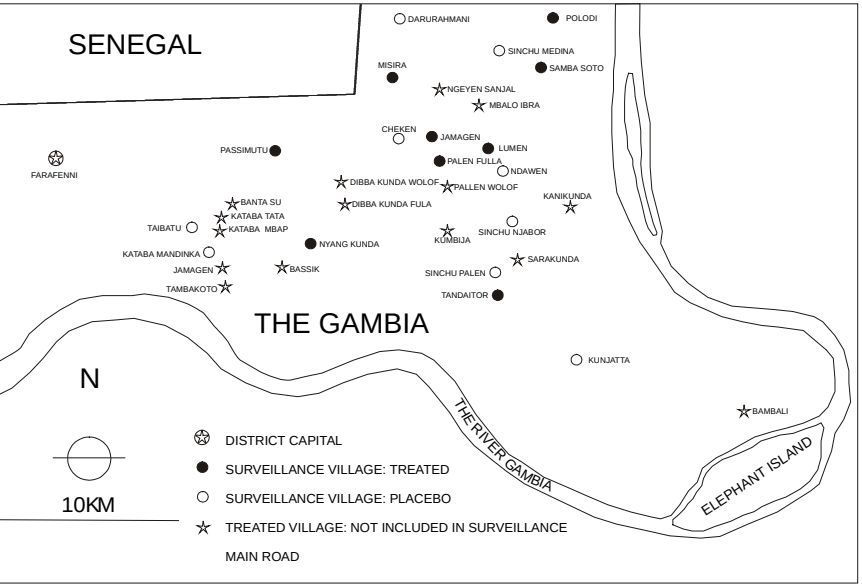
Hayes&Bennett(1999) *International Journal of Epidemiology* 28:319-326

Defining the clusters

- May be determined by:
  - the nature of the intervention
  - logistics of delivery
  - the need to minimize contamination
  - statistical considerations:
    - for a given total sample size, smaller clusters give better power
    - for some endpoints we may subsample the individuals within a cluster. The VIF depends on the *number sampled*, not the total size

Some examples:

Houses screened to prevent mosquito entry.
Trial endpoint: anaemia in children.
500 houses, mean number of children 2.2 per house.



Mass drug administration in the dry season to remove the source of infection to mosquitoes.
Trial endpoint: incidence of malaria in children.
18 clusters in matched pairs. Mean 213 children per cluster.
All surrounding areas were treated to reduce contamination effects from the wider population.

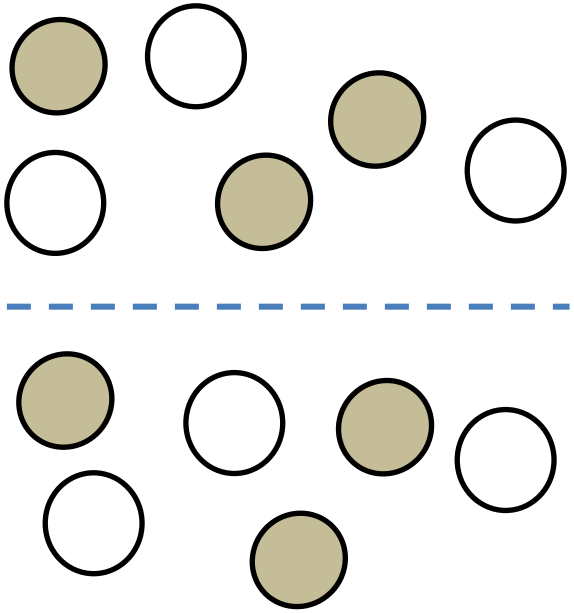
Stepped-wedge evaluation of SMC effectiveness

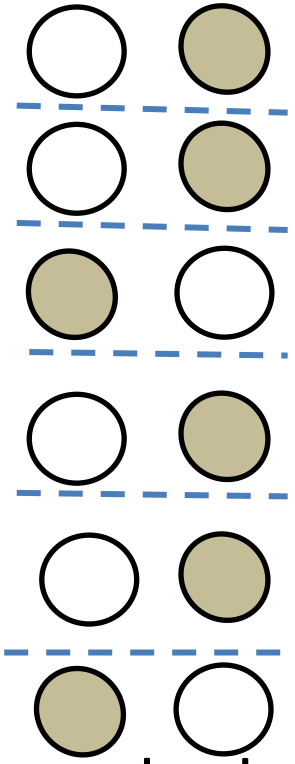
- phased introduction by health posts
- 54 clusters mean size 3000 children but only a subset used in each cluster in surveys
- cases linked to cluster of residence

	Area 1	Area 2	Area 3	Area 4
Year 1				
Year 2				
Year 3				
Year 4				

Matching vs stratification

Stratified design





Pair-matched design

Pair-matched designs can be inefficient if the matching is not strongly associated with trial outcome.
Stratified designs, with 2 or 3 strata, are often preferred.

Analysis of a pair-matched study

	Rate/100 person-weeks		
Village pair	MDA	Placebo	Rate ratio
1	3.6	2.83	0.79
2	1.34	2.05	1.53
3	2.35	3.22	1.37
4	3.16	2.15	0.68
5	0.74	1.81	2.42
6	1.39	1.44	1.04
7	0.97	0.62	0.64
8	3.19	2.05	0.64
9	1.2	1.6	1.33

Geometric mean 1.05
(95%CI 0.73,1.5)

Design to improve power and precision

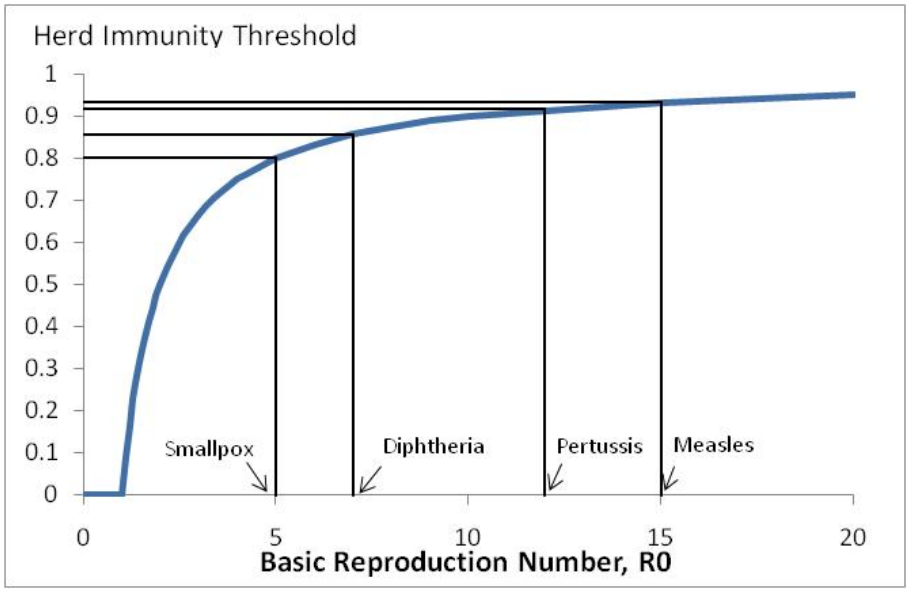
- Stratification
- Increase the number of clusters

o Constrained randomization

o Pre-intervention measurement of the outcome (or of prognostic variables)

Indirect effects

- Indirect effects depend on:
  - efficacy in reducing infectiousness
  - coverage of the intervention
  - basic reproduction number, R0, in the study population
  - transmission patterns (who infects whom)



DL Smith et al
PLoS Biol 5(3): e42.

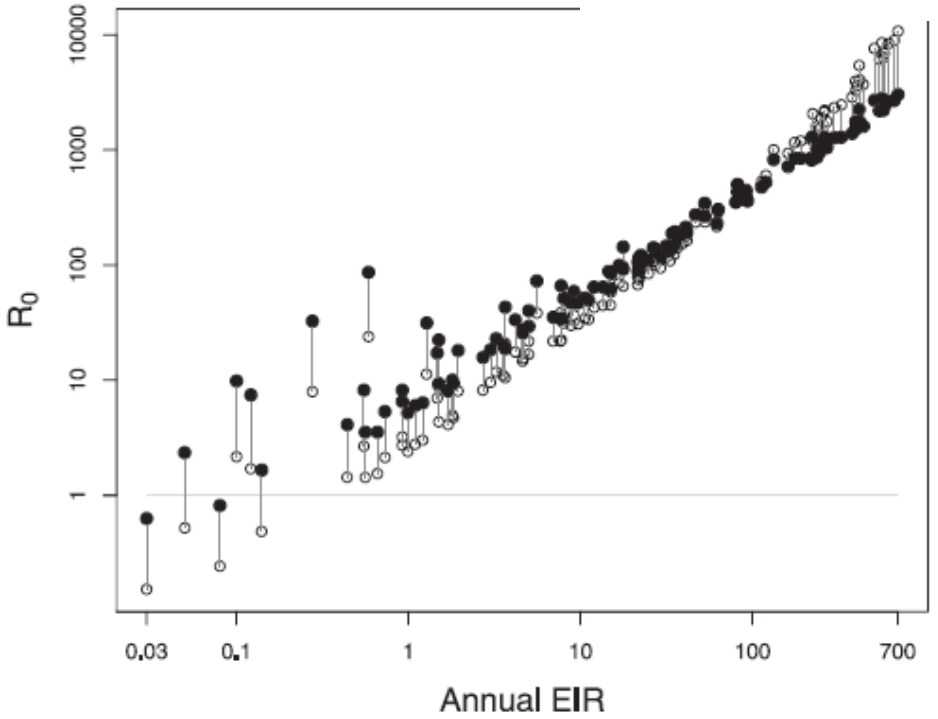
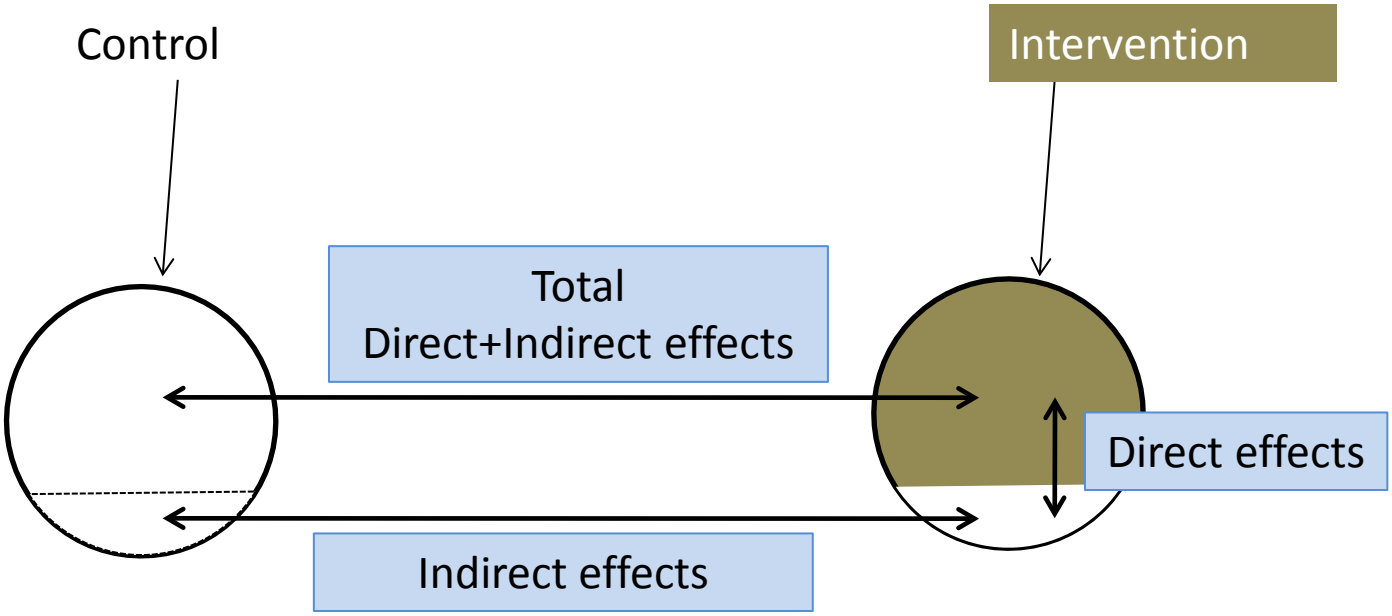


Figure 2. R_0 Estimates for 121 African Populations

Here, we show two different sets of estimates, plotted as a function of the estimated EIR. The first set of estimates assumes that none of the parameter estimates are biased by immunity or heterogeneous biting at the equilibrium (solid circles). The second set of estimates assumes that heterogeneous biting and transmission-blocking immunity bias parameters (open circles); σ is as illustrated by Figure 3. Corrections for this potential bias substantially increase the range of R_0 estimates.

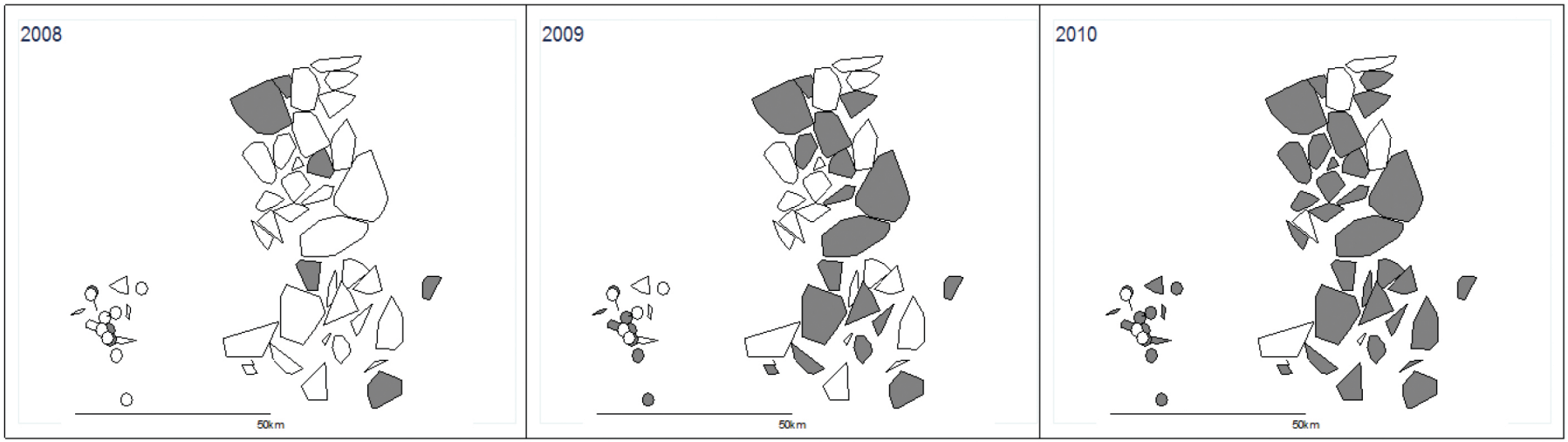
doi:10.1371/journal.pbio.0050042.g002

Separating Direct and Indirect Effects



+ overall effect comparing intervention and control clusters

Stepped wedge evaluation of SMC



- 54 health posts (constrained) randomization:
  Year1=9; Year2 = 9+18; Year3 = 9+18+18; Year 4 = 9+18+18+9
- SMC provided for all children under 10 yrs of age
- Incidence of malaria in all age groups recorded in health posts:
  - Incidence in children (for assessment of direct effects)
  - Incidence in older age groups (for assessment of indirect effects)
- Population at risk determined from demographic surveillance

analysis of stepped-wedge trial

Incidence rate = observed no. of events/time at risk

log (incidence rate) = log(no. of events) – log(time at risk)

The expected number of events is assumed to follow a log linear model:

$$\log(\mu_{ij}) = \text{constant} + TREAT \times X_{ij} + YEAR_j + \log(T_{ij}) + \alpha_i,$$

Expected number of events in cluster i in year j

Intervention effect, to be estimated

X_{ij}=0 (no intervention) =1 (intervention) in cluster i in year j

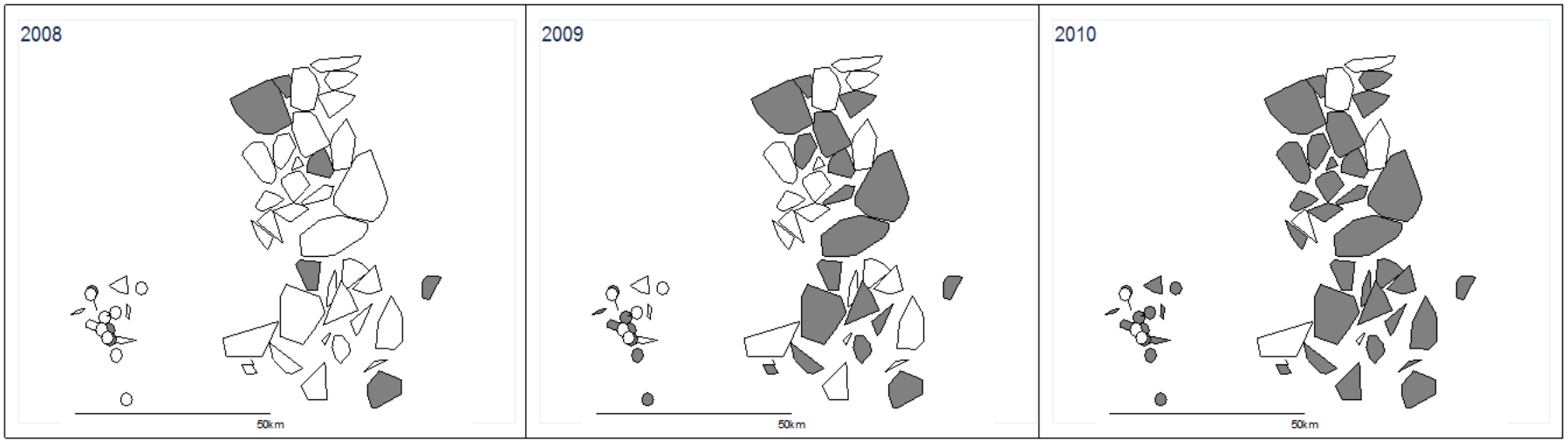
Total person years at risk in cluster i in year j

Cluster effect, estimated as a random effect with a normal or gamma distribution

% efficacy = 100x[1-exp(TREAT)]

This *Poisson regression model* is fitted to the observed data for each cluster, to obtain estimates of the intervention effect, for example using the **xtpoisson** command in Stata.

Stepped wedge evaluation of SMC



- Effectiveness against malaria (SMC age groups): 60% (95% CI 54%,64%)
  [c.f. 86% in individually RCT Cisse et al (2006)]
- Effectiveness against malaria (too old for SMC): 26% (95% CI 18%, 33%)

Analysis methods

- Analysis of cluster-level summaries
  - treatment effects estimated from analysis of cluster means
  - compared using t-test

- Analysis of individual-level data
  - need to allow for dependence among observations in the same cluster using:
    - random effect models, or
    - GEE models with robust standard errors, or
    - robust standard errors
  - not recommended if the no. of clusters is small (<20 per arm)

Ethical issues in cluster trials

- Two levels of consent:
  - Consent to randomization: Community leaders or 'Gatekeepers' give approval on behalf of the community. May not be feasible to obtain individual consent before randomization.
  - Individual consent to intervention and outcome assessment.
- In some interventions, avoiding the intervention may be impossible, meaningful consent can occur only at group level (e.g. mass media campaigns)
- Consent after randomization - possibility of selection bias

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Guidelines and Guidance

The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials

Charles Weijer[1,2,3*], Jeremy M. Grimshaw[1,4,5], Martin P. Eccles[6], Andrew D. McRae[1,3,7], Angela White[1], Jamie C. Brehaut[4,8], Monica Taljaard[1,4,8], the Ottawa Ethics of Cluster Randomized Trials Consensus Group[¶]

Further reading

- Bennett et al. (2002) Methods for the analysis of incidence rates in cluster randomized trials. International Journal of Epidemiology 31:839-846

- Hayes and Moulton (2009) Cluster randomized trials. Chapman and Hall.

- Weijer *et al.* (2011) Ethical issues posed by cluster randomized trials in health research. Trials 12:100 http://www.trialsjournal.com/content/12/1/100

- ***Consort 2010 statement: extension to cluster randomised trials. BMJ 2012***
- ***http://www.bmj.com/content/345/bmj.e5661***