Community-based Intervention Trials "the concept "

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Overview (1)

- Introduction
- Study designs: internal validity
- Historical tribulations of C-QE & Cluster RCT
- Methodological issues in C-RCT
  1. The concept of "community", various designs, analyses and reporting issues
  2. Units of randomization, appropriate comparisons, units of analysis, intra-class correlation and power
  3. Ethics
  4. Challenges

Overview (2)

- How are change effects brought about? Interpreting complex pathways
- External validity and generalizability

Introduction

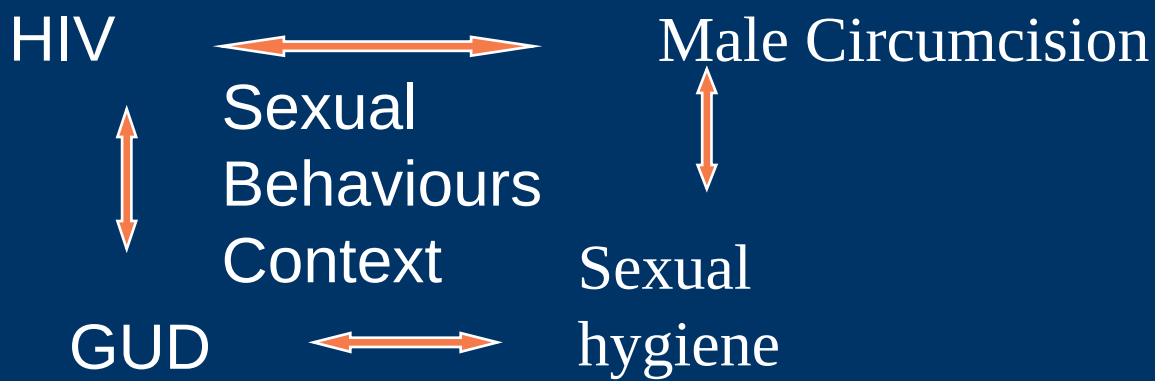
- Galileo Galilei to Claude Bernard
- Hypothesis submitted to ordeal "Cimento". If test fails fresh experiment.
- 1747, Lind runs a controlled trial on scurvey.
- Framing the question

Internal validity

- **Chance:** ***random error***
- **Bias:** ***systematic error (non-random) distorting estimates/results of study***
  - **Selection**
  - **Measurement and misclassification**
  - **Confounding**
  - **Information**

Sources of Biases

Measurement **Selection**



Confounding **Temporal sequence**

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Study Designs (internal validity)

OBSERVATIONAL — *Exposure NOT manipulated by Investigator*

Analytic

- Cohort
- Case-control

Descriptive

- Case-series
- Cross-sectional
- Ecological

EXPERIMENTAL — *Exposure manipulated by Investigator*

- **Quasi-experimental and Randomized trials**
  - Individuals
  - Clusters

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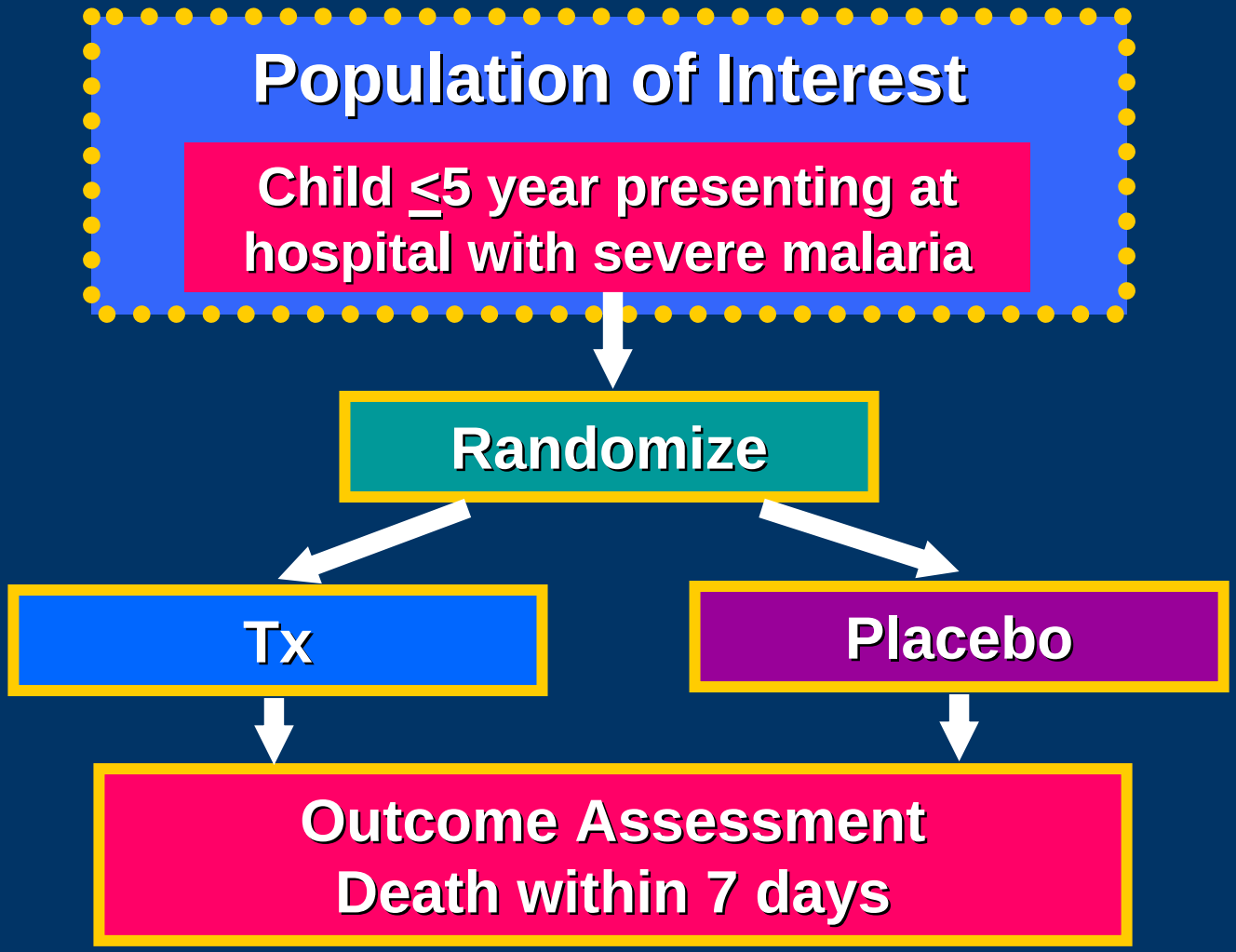
Definition of levels of evidence and grading of recommendation for internal validity

Level	Type of evidence available from	Grade
I a	Meta-analysis of RCTs	A
I b	At least one RCT	
I I a	At least one well-designed controlled study without randomization	B
I I b	At least one other type of well-designed quasi-experimental study	
III	Well-designed non-experimental descriptive studies	
IV	Expert committee reports or opinions and/or clinical experience of respected authorities	C

RCT Paradigm



Advantages of Randomized Trials

- The only effective method known to control selection bias
- Controls confounding bias without adjustment
- Many statistical methods assume random assignment
- Maintains advantages (time sequence) of cohort studies
- Vigour (tests limits of applicability), precision (Silverman)

Disadvantages of Randomized Trials

- Impracticality if inborn attribute cannot be manipulated, risk of intervention too big, too complex and expensive
- Reductionism: focus on one independent variable
- May lack representativeness - volunteers may differ from population of interest. Generalizability issues
- Ethical challenges of experimental research
- True effect may not be ascertained for many years
- Study power is dependent on number of events observed during the study
- Prohibitively difficult with low incidence outcomes

Classification of RCT

Based on	Classification
Type of intervention	Therapeutic; Preventive
Unit of randomization	Individual ;Community
Design	Parallel; Cross-over; Factorial
Sample Size	Fixed; Sequential
Randomization	Fixed; Adaptive (Number, Baseline, Outcome); Blocking
Masking	Single, Double, Triple,…

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Tribulations of Community Quasi-experimental (QE) studies & RCT in Health

- Two traditions: therapeutic individual RCT and population/community level (preventive) health interventions. Little cross-over with education field.
- First therapeutic, individual, RCT: MRC on streptomycin and TB (1948)
- QE: Longitudinal (cohort) study of community nutrition interventions (Guatemala,1969-1977)

Tribulations of Community Quasi-experimental (QE) studies & RCT(2)

- QE: North Karelia Project (Finland, collective behaviours & cardio-vascular diseases (CVD), 1976)
- QE: Stanford five city project (CVD), USA, 1985 and Pawtucket & Minnesota Heart Health Programmes (1990s): decline in risk factors in intervention communities comparable to secular trend in control communities.

Tribulations of Community quasi-experimental studies & RCT (3)

- C-RCT: Vitamin A supplements effectiveness on childhood mortality in 450 villages in Indonesia. One year mortality rates compared. Sommer et al., Lancet, 1986
- Stanton and Clements randomize families to explore the effect of hand-washing on diarrhoeal diseases, 1987.

Tribulations of Community Quasi-experimental (QE) studies and RCT (4)

- Mertens, Hayes & Smith propose to assess the effect of STI treatment on HIV incidence, using a community-based randomized design, 1990.
- C-RCT: 6 paired communities, with one of each pair randomly assigned to STI treatment. Outcome assessed on HIV incidence (Grosskurth et al, Hayes et al, 1995).

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Tribulations of Community Quasi-experimental (QE) studies and RCT(5)

- C-RCT: COMMIT Research Group. 11 paired communities with one of pairs randomly assigned to the intervention group. 5-year smoking cessation rates compared. Smoking rates declined along with similar secular trends in control communities (A.J. P. H., 1995).
- C-RCTs multiply and methodological challenges become more precise. E.g. Ghana Vast (Vit A), Rakai, Fontanet, Masaka, RIPPLE, some circumcision trials etc.
- Murray D. publishes "Design and analysis of community trials in 1998". Hayes & Bennett paper on sample size for C-RCT. Donner and Klar publish book on C-RCT(2000)

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Randomizing individuals or "communities"?

- Level at which change is expected: drug, vaccine (individual versus herd immunity), behaviours.
- Model of change process: e.g. peer influence on behaviours, services coverage, e.g. fluoridation of water supply, transmission dynamics of infectious diseases, susceptibility and infectiousness.
- Avoiding "contamination" effects of interventions (e.g. IEC)
- Practical and Ethical considerations

Why not "before and after" and "one to one" comparisons to establish causality?

- **Before and after not sufficient because variations in disease rates over time are likely to be unrelated to the intervention under study (**Mertens et al, 1990**).**
- **One intervention and one control community also inadequate because any difference between the two communities may be due to underlying differences in risk between them rather than the effect of the intervention (**Mertens et al, 1990**).**

Unit of Randomization vs. Unit of Analysis

- Inferences are frequently intended to apply at the individual level while randomization is at the cluster or group level. Thus the unit of randomization may be different from the unit of analysis.
- Lack of independence among individuals in the same cluster (intracluster or intraclass correlation), creates special methodological challenges in both design and analysis.

Presence of between-cluster variation implies:

I. **Reduction in effective sample size.**

- **Extent depends on degree of within-cluster correlation and on average cluster size.**

II. **Standard approaches for sample size estimation and statistical analysis do not apply.**

- **Hayes and Bennet detail simple sample size calculations (1999)**
- **Recommended use generalized linear MIXED models AFTER appropriate specification of the pathways for change (see below).** See Donner & Klar, 2000 for detailed discussions.

Possible Reasons for Between-Cluster Variation

1. Subjects may select the clusters to which they belong; e.g. patients using a categorical STI clinic may share characteristics related to age or sex
2. Covariates may affect all individuals within the cluster who share exposure to a common environment
3. Individuals within clusters frequently interact and, as a result, may respond similarly
4. Tendency of some infectious diseases to spread more rapidly within communities.

Donner & Klar, 2000

Design effect

- Both the number of clusters and the size of the cluster play a role in the power of the study and the sample size.
- Between-cluster component of variance and within-cluster component of variance need to be considered.

Factors Influencing Loss of Precision

1. Interventions often applied on a group basis with little or no attention given to individual study participants.
2. Immigration of new subjects after baseline.
3. Parts of clusters, rather than just a few individuals, may be lost to follow-up.
4. Optimistic expectations regarding effect size.

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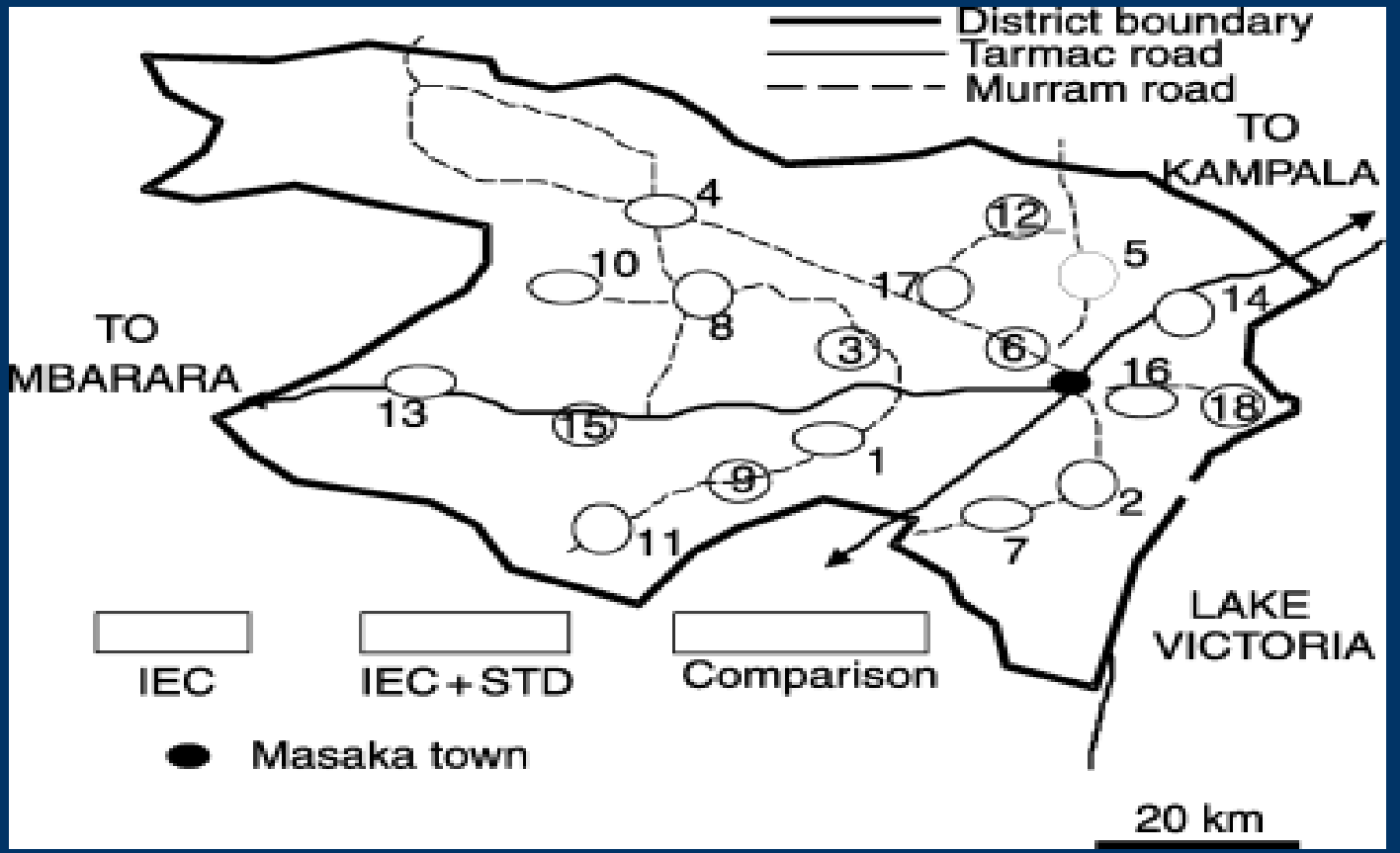
Community concepts

- Geographical
- Demographic
- Social
- Cultural
- Sexual networks
- "Adopters, non-adopters"

Example of geographic boundaries of "Communities"



Kamali et al,
TM&IH, 2002

Reporting study results:

- Number of clusters randomized, average cluster size and number of subjects selected for study from each cluster.
- Values of the intra-cluster correlation coefficient for the primary outcome variables.
- Statistical analyses to account for between-cluster variations.

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Ethical issues

- **First no harm**
- **Alternative intervention as a control: when is it too late to withdraw intervention from control? "Stepped wedge"strategy from Gambia Hep. Study Group (1987). Adding proven effective interventions that decrease outcome incidence, thereby reducing power (e.g. condoms in HIV prevention).**
- **Informed consent:** procedures to be performed must be clearly explained. Persons or "communities" free to refuse to participate or withdraw
- **Stopping rule explicit before start**

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Some challenges in C-RCT

- Masking, Adherence, Dropouts, Missing Data,
- Cohort vs cross-sectional surveys. Measurement of Covariates, Sub-group analyses
- Interim analysis (Termination)
- Analytical tools to be used
- Logistics
- RCT is often not possible: well established intervention, efficacious in ideal circumstances, complex pathways, efficacy against one outcome not known. Observational methods need improving (see TREND statement, Des Jarlais et al, 2004 and discussion below).

Challenges in C-RCT

- A step back: many (C)-RCTs conducted in last 15 years. Few conclusive results.
- Example: in the field of HIV prevention, 33 RCTs completed (behavioural change, diaphragm, microbicides, STI Tx, vaccines, circumcision) with 4 suggesting conclusive evidence of efficacy (Wasserheit, 2006). Assuming minimum average cost of US$ 7 million/RCT leads to a total of :

US$ 230 million.

Overview (2)

- How are change effects brought about? Interpreting complex pathways
- External validity and generalizability

Specification of the Process for effecting change

- **Evaluation of mechanisms responsible for community change is critical to both internal and external validity of C-RCT** (Atienza & King, 2002)
- **Understanding how social, physical environment & collective/indiv. behaviours intersect to influence health key to developing enduring & effective programmes.**
- **Demand and supply side issues to be considered in intervention designs (increase "adopters")**

Specification of the Process for effecting change

- **Interaction between researchers and communities** (shared responsibility, trust, mutual benefit and accountability)
- **Participatory learning rather than instructions in training and community "empowerment"(e.g.** Manandhar et al, 2004**)**
- **Caution with temptation to search for a single magic technical solution to address complex socially rooted problems.**

External validity

- **Generalizability: "the essence of knowledge is generalization" (Reichenbach, 1965) – Time, place, populations and their context.**

Probability, plausibility and adquacy

- **Probability statement: RCT**
- **Plausibility statement: observational studies with comparison**
- **Adequacy statement: trends in process and/or impact indicators suggesting important effect.**

Victora et al, 2004

Causal chains, efficacy and effectiveness

- **Efficacy: effect under "ideal circumstances";**
- **Effectiveness: "normal, routine conditions";**
- **Causal chain short & simple: strong internal and external validity for RCT & C-RCT**
- **Many public health (& social) interventions, delivered under routine conditions, involve complex pathways, making RCT results subject to effect modification in different populations.**
- **Evaluation of large-scale interventions more often calls for plausibility designs rather than RCT** (Victora et al, 2004)

Types of Effect Modification Affecting the Generalizability of Findings From RCT

- Presence of other factors reduces the dose–response slope (antagonism)
- Presence of other factors increases the dose–response slope (synergism)
- Curvilinear dose–response
- Limited scope for improvement in the impact E. Intervention is inappropriate because a critical cofactor is missing
- Intervention is addressing a determinant that is not important

Victora et al, 2004

Are parachutes effective in preventing death and major injury after gravitational challenge?

- Parachute use is associated with adverse effects due to failure of the intervention. Studies of free fall do not show 100% mortality
- No randomised controlled trials of parachute use have been undertaken
- The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect.
- Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump (BMJ, 2003)