Deciphering ethical assumptions about Stepped-Wedge Designs:
The case of Ebola vaccine research

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The views expressed are my own and do not represent the views of the NIH, DHHS, or any other US government agency

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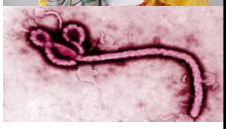
Ebola virus outbreak, 2014
- Public Health Crisis



- Deadly epidemic spreading
  - Limited health infrastructure
  - No preventive/curative treatment
- Placebo-Controlled Randomized trial

Gold standard for evaluating safety and efficacy

Joffe S, JAMA; Rid A, Emmanuel E, Lancet

Ethically questionable in health emergency like Ebola

Adebamowo C, et al. Lancet

  - Alternative designs considered (WHO, Oct 2014)
    - Stepped wedge design

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Stepped-wedge trial design to evaluate Ebola treatments

Piszczek and Partlow. Lancet Inf. Dis. 2015.

- Sequential roll-out of an intervention to participants (individuals or clusters) over several time periods

(Brown and Lilford. BMC Med Res Methodol 2006)

- Designs used for Ebola vaccines RCT

Trial	Arms
STRIVE Sierra Leone	Immediate vaccination, vs. 6 months waiting time
Ring trial "Ebola ca suffit" Guinea	Immediate vaccination, vs. 3 weeks waiting time
PREVAIL Liberia	Vaccine vs. placebo (double blind)

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Stepped wedge design: ethical rationale

- **All participants will have received the intervention**
  - -Preliminary data/belief that the intervention will do **more good than harm**
  - -**Logistical, practical or financial reasons**
    - -Impossible to deliver the intervention simultaneously to all participants

- Stepped-wedge trial design to evaluate Ebola treatments, Piszczek and Partlow. Lancet Inf. Dis. 2015. The stepped wedge trial design: a systematic review, Brown and Lilford. BMC Med Res Methodol 2006

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Ethics of stepped wedge design for Ebola vaccine research

- Objective: Examine ethics underlying rationale
  - A. More good than harm?
    - Is the SW design used to study experimental drugs/vaccines? Review
  - B. Do all participants receive intervention?
  - C. Logistics/practicality?

Methods: Review of SW design used to study experimental drugs/vaccines

- Data from published systematic reviews
  - Brown and Lilford, 2006
  - Mdege, Man et al., 2011
  - Beard et al., 2015
- Review of clinical trial registries: ongoing/unpublished trials (April 2014)
  1. ClinicalTrials.gov
  2. "International Standard Randomized Controlled Trial Number" (ISRCTN) registry
  3. European Union Clinical Trials Register
- Search terms: Step/stepped and wedge

Review of SW design used to study experimental drugs/vaccines (2)

- Intervention
  - Testing drugs/vaccines vs. other type of intervention
- Design
  - Cluster (intervention allocated by site) vs. Individual allocation
  - Recruitment/follow-up

Design	Features
Closed cohort	Each participant contribute to control and intervention Repeated measures on individuals
Repeated cross-sectional design / Continuous recruitment short exposure design	Participants contribute to control OR intervention
Mixed / open cohort	Participants contribute to control, intervention or BOTH

(Hemming K et al. BMJ 2015, Copas et al. Trials 2015)

SW in systematic reviews and registries

- 3 systematic reviews of SW (1987-2014)
  - 67 studies
- Trial registries : +73 SW studies
  - Clinicaltrials.gov N=51
  - ISRCTN N=22
- ➔ 140 SW studies/protocols since 1987

Results: Drug/vaccine SW studies

- 7 involved a drug or vaccine
  - Africa (Gambia, Senegal, Zambia, Uganda, South Africa); Brazil; USA
  - Implementation of interventions shown to be efficacious
  - Infectious disease

- **Hepatitis B** Vaccination - prevention liver cancer
- Preventive **malaria** treatment of children
- Expedited patient-delivered partner therapy for **chlamydia/gonorrhea**
- Provision antivirals to pregnant **HIV**+ women
- Cryptococcal screening + treatment (**HIV** patients entering antiretroviral therapy)
- Isoniazid preventive treatment for TB in **HIV**+ men

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Ethical analysis of SW designs (1/3)

A. More good than harm?

- Rarely used to study drugs or vaccines
  - Limited to drugs already shown to be efficacious

- Ethical considerations
  - Risk/Benefit
  - Social value of SW designs
    - 7 SW drug/vaccine trials: effectiveness/implementation
    - For Ebola vaccine: efficacy/safety

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Results: Design of drug/vaccine SW studies

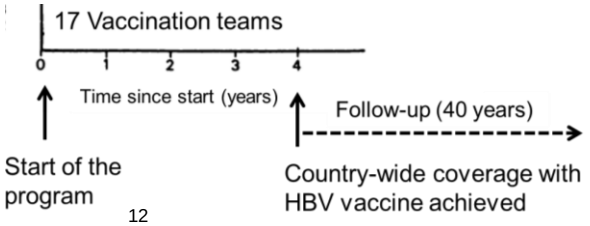
- 1/7 was individually randomized
  - Closed cohort
- 6/7 were cluster randomized trials
  - 3 repeated cross-sectional
  - 3 open cohorts

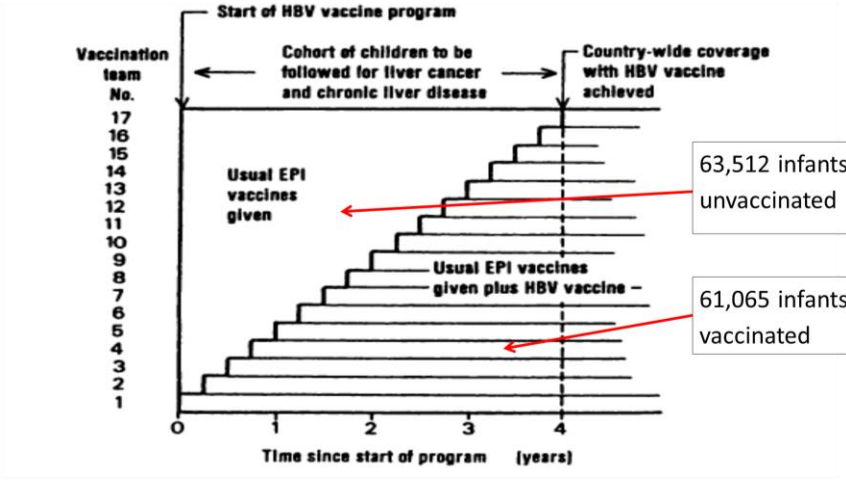
  Intervention ultimately implemented in all clusters, not all individuals
  - Example: The Gambia Hepatitis study

Example: The Gambia Hepatitis B Study (1987-ongoing)

- Vaccine: Evidence on acute HBV infection
- BUT
  - Durability of immunity ? Impact on liver cancer ?
  - Limited availability, cost

➔ Roll-out implementation over 4 years





The Gambia Hepatitis Study, Cancer research, 1987

Ethical analysis of SW designs (2/3)

B. Do all participants receive intervention?

No

- Fundamental distinctions underappreciated
  - Individual vs. cluster randomization; repeated cross sectional / open / closed cohort
    - Most often all clusters, but not all participants, will access the intervention
- Ethical considerations
  - IRB review - Consent

Conclusion / Ethical analysis of SW designs

C. Logistics/practicality?

- Balanced with complexity / scientific validity
  - Complex implementation (Prost et al., Trials 2015)
  - Analysis (Hemming, BMJ 2015)
  - Ebola outbreak: spatiotemporal variation (Bellan, Lancet inf dis 2015)
- Ethical considerations
  - Scientific Validity
  - Social value

- Thank you!