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.

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

Ethically questionable in health emergency like Ebola

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

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

Adebamowo C, et al. Lancet

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

Designs used for Ebola vaccines RCT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arms</th>
</tr>
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<tbody>
<tr>
<td>STRIVE Sierra Leone</td>
<td>Immediate vaccination, vs. 6 months waiting time</td>
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<tr>
<td>Ring trial “Ebola ca suffit” Guinea</td>
<td>Immediate vaccination, vs. 3 weeks waiting time</td>
</tr>
<tr>
<td>PREVAIL Liberia</td>
<td>Vaccine vs. placebo (double blind)</td>
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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
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- Review of clinical trial registries: ongoing/unpublished trials (April 2014)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

<table>
<thead>
<tr>
<th>Design</th>
<th>Features</th>
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<tbody>
<tr>
<td>Closed cohort</td>
<td>Each participant contribute to control and intervention</td>
</tr>
<tr>
<td></td>
<td>Repeated measures on individuals</td>
</tr>
<tr>
<td>Repeated cross-sectional design</td>
<td>Participants contribute to control OR intervention</td>
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<tr>
<td>Continuous recruitment short exposure design</td>
<td></td>
</tr>
<tr>
<td>Mixed / open cohort</td>
<td>Participants contribute to control, intervention or BOTH</td>
</tr>
</tbody>
</table>

(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

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
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

\[ \text{17 Vaccination teams} \]
\[ \text{Time since start (years)} \]
\[ \text{Follow-up (40 years)} \]
\[ \text{Start of the program} \]
\[ \text{Country-wide coverage with HBV vaccine achieved} \]
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!