Early Lessons from a Multi-Country Cluster-Randomized Stepped-Wedge Implementation Trial

Elizabeth Glaser Pediatric AIDS Foundation

Until no child has AIDS.

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Overview

- Background on pediatric HIV testing
- Background on POC EID project
- Study design
- Planned analyses
- Early lessons learned from implementation
- Discussion
Background

• HIV infected, untreated infants have rapid disease progression and high mortality
• Half of HIV infected infants will die by age 2 if untreated
• Survival of HIV-infected infants depends on a robust early infant diagnosis (EID) system
• The World Health Organization recommends that HIV-exposed infants (HEI) receive a virological diagnostic test at 6 weeks
Conventional EID:
1. Batch of samples gathered at facility before sending to central laboratory
2. Samples transported to central laboratory
3. Samples processed
4. Results transported by courier or delivered to requesting facility with SMS
5. Health care worker calls caregiver to facility
6. Caregiver is informed of result at next visit.
7. **Total turn around time approximately 30-90 days**

Point-of-Care EID:
1. Sample processed on site or transported from a spoke
2. Results transported by foot or courier service or delivered with SMS (from spoke)
3. Mothers wait on-site or return within 1 wk
4. Caregiver is informed of result on same day or next visit
5. **Total turn around time approximately 0 – 7 days**
POC EID Project

- Integration of point-of-care (POC) EID testing into a country’s existing laboratory network could improve EID system functioning.
- EGPAF received a grant from Unitaid to introduce routine POC EID testing in 9 countries in Africa (2015-2019)
- The impact evaluation is being conducted in Kenya and Zimbabwe
Impact Evaluation Objectives

- Estimate the effect of POC EID compared to Conventional EID on the following outcomes:
  - Percentage of HEI who receive the 4-6 week EID test result by 12 weeks of age
  - Proportion of HEI tested for HIV before 12 weeks of age
  - Turn-around time between collecting the sample to providing test result to caregivers for the first EID test
  - Time from sample collection to ART initiation in HIV-infected children
  - Proportion of HIV-infected children initiated on ART by 12 weeks of age
  - Retention of infants in care at 6 months
Why Stepped Wedge?

• Unethical to withhold the treatment (POC) when pilots have demonstrated effect
• Not logistically feasible to introduce POC at every site simultaneously
• Aligns with the operational plan for roll out
• WHO needs rigorous evidence to make recommendations (observational data is graded as ‘weak’)
Methods: Sample Size

- Effect size: at least a 50% increase in the proportion of caregivers receiving results by 12 weeks of infant age after introduction of POC
- Assumes a design effect of 2
- Block of 6 facilities of at least 22 exposed infants introduced to POC at each of 3 steps
- Complete design despite the 1 month transition period
- Stata’s steppedwedge function (Hemming K, Stata Journal 14:2, 2014)
Methods: Effect Size & Power

Sample Size - Power Curve

Proportion HEI receiving results @ 12 wks with SOC

Power (%)

Proportion HEI receiving results @ 12 wks with SOC

RR=1.5
RR=1.2
Methods: Sampling

• In each country, 18 health facilities were randomly selected from the list of project sites to serve as study sites
  • Out of 50 project sites in Zimbabwe and 45 in Kenya
• Sites include a testing site and any associated satellite sites (from which specimen are sent to the testing site)
• Data (all same variables) are collected from facility registers during conventional phase, and through new test request forms during intervention phase
Methods: Step Randomization

- Study sites were randomized to one of three steps for introduction of the intervention (POC EID)
- Each step lasts 4 months with a transition month in between to allow for changeover of each site from control to intervention

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<th>Step</th>
<th>Enroll Date</th>
<th>Transition Date</th>
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<tbody>
<tr>
<td>1</td>
<td>Sept-Dec 2017</td>
<td>Jan 2018</td>
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<tr>
<td>2</td>
<td>Feb-May 2018</td>
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<td>3</td>
<td>July-Oct 2018</td>
<td>Nov 2018</td>
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<tr>
<td>4</td>
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POC EID

Conventional

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POC EID

Conventional
Planned Statistical Analysis

• Estimate summary outcomes by block and step

• Estimating effect of POC:
  • generalized linear mixed effects models or GEE accounting for time trends and facility clustering

• Time to event outcomes: survival models with frailty

• Sub-analyses will compare hubs and spokes
Early lessons: Challenges

• Challenges
  • Design: Lack of data on ICC for SS estimation
  • Is it ethical to randomize introduction of the treatment rather than triage by need?
  • Slightly different data collection methods between the conventional and POC sites
  • Field teams lack of familiarity with study design
  • Coordination with the Ministries of Health to maintain the intervention introduction schedule in study sites
  • Coordination of timelines between two countries for logistical purposes
  • Supply side (programmatic) issues delayed start of timeline
Early lessons: Strengths

• Strengths
  • Historical data on testing closely predicted the testing demand and thus the number of observations per cluster
  • Political and ethical benefit of having all sites receive the intervention
  • Realistic timelines for introduction of intervention which better align with program realities (equipment acquisition and training)
  • Ideal for new innovations to start small and progressively introduce the treatment
Discussion

• Stepped wedge designs are feasible in the context of routine service delivery and program implementation.

• Despite challenges, it is possible to conduct multi-country trials using similar protocols and data collection methods.

• Clear political, ethical and analytic benefits.

• Need to carefully consider possibility of parallel designs.

• Stepped wedge designs are very promising for impact evaluation on introduction of new technologies.
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