DetectTB

Impact of periodic case-finding for symptomatic smear-positive disease on community control of prevalent infectious tuberculosis:

A cluster randomised trial of two delivery strategies in Harare, Zimbabwe

ISRCTN 84352452
African TB control: now or never?

- Reasons to be hopeful
  - Major investment
  - Evidence based interventions

But...

- Infectious TB remains highly prevalence despite “DOTS”
- MDR and XDR-TB
- Strengthening of association between TB & HIV regionally
- ½ million HIV+TB deaths p.a.
  - Quarter of all global TB deaths
  - 90% in Africa
  - revised sharply *upwards* in 2007

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Potential high impact TB control strategies

- Case-finding
  - Most TB disease due to recent transmission to casual contacts

- Direct protection of healthy HIV+ individuals
  - Treatment of latent TB infection (isoniazid)
  - Antiretroviral Treatment ("ART")

ACF trade-offs

More resource intensive & costly to sustain but potential for higher impact

>70% TB case detection, but may fall if repeated in same community

≈20% to ≈70% TB case detection

<5% to >25% case detection reported from different models

≈10% all TB patients report recent close contact with infectious TB. % of TB due to other individual risk factors varies widely by setting.

Screen whole groups or communities for TB disease (e.g. CXR)

Screen whole groups or communities for TB symptoms (further investigate symptomatics)

Provide whole groups or communities with the opportunity to be screened for TB in community

Targeted ACF aimed at individuals or groups with known risk factors for TB infection or disease

Most readily sustainable
Cumulative impact of periodic case-finding, according to rate at which infectious cases are replenished between rounds, assuming 25% of prevalent cases are diagnosed each round.
Intervention aimed primarily at HIV-ve TB

- **HIV+ve TB**
- **HIV-ve TB**

**6-monthly intervention**

- **Corbett 2009 (10k Zim)**
- **Wood 2007 (1k S.Africa)**
- **Corbett 2007 (5k Zim)**
- **Corbett 2004 (2k S.Africa)**

- **Routine program for incidence estimates**
- **Cohort study for incidence estimates**

**Weeks of infectiousness (smr+ve) before diagnosis**

**Messages**

- TB infectious / spread by coughing
- Infectious for months or years with mild symptoms, esp if HIV-ve
- Undiagnosed TB puts family & friends at risk
- TB can be cured

**Intensified case-finding in community**

↓ TB transmission (cluster size)

Health seeking

Smear+ve days averted

**DETECTB: trial design**

**Household enumeration**

**Prevalence survey 1**

**Cluster 1**

**干预循环：主要结果**

**Prevalence survey 2**

**Time**

PS1 (12% HHds)

PS2 (12% HHds)
2 arms: no standard of care
6 rounds spaced every 6 mos
- Community workers
- Sputum microscopy

DOOR TO DOOR (team of 6)

- Cough for $\geq 2$ wks
- Also accept:
  - unintentional weight loss
  - drenching night sweats
  - Haemoptysis

MOBILE VAN (team of 3)
Study population at start of intervention

Clusters
TB case notification rate (s+)
2005/6
  # of households
  # adults

2005/6 survey
Cult+ TB
HIV
Age
Past TB treatment
Current smoker
Visits beerhalls

Second household survey (2007)

Mobile

Door-to-door

<table>
<thead>
<tr>
<th></th>
<th>Mobile</th>
<th>Door-to-door</th>
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</thead>
<tbody>
<tr>
<td>Clusters</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>TB case notification rate (s+)</td>
<td>309 per 100k</td>
<td>249 per 100k</td>
</tr>
<tr>
<td>2005/6</td>
<td></td>
<td></td>
</tr>
<tr>
<td># of households</td>
<td>20,700</td>
<td>20,719</td>
</tr>
<tr>
<td># adults(^1)</td>
<td>55,741</td>
<td>54,691</td>
</tr>
<tr>
<td>2005/6 survey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cult+ TB</td>
<td>65 per 1000</td>
<td>65 per 1000</td>
</tr>
<tr>
<td>HIV</td>
<td>22%</td>
<td>21%</td>
</tr>
<tr>
<td>Age</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Past TB treatment</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Visits beerhalls</td>
<td>19%</td>
<td>20%</td>
</tr>
</tbody>
</table>

12% increase in # HHds
13% increase in # adults
HIV prevalence 19%

Corbett et al. IJTL (2009)
Intervention
Primary outcome:
Cumulative rate of smear+ve TB from community

<table>
<thead>
<tr>
<th>Comparison of 2 arms</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate ratio</td>
<td>1.7</td>
<td>1.3 to 2.3</td>
</tr>
<tr>
<td>Adjusted RR</td>
<td>1.5</td>
<td>1.1 to 2.0</td>
</tr>
</tbody>
</table>

Mobile substantially outperformed door-to-door strategy
- Contrary to universal pre-trial expectations

10,177 participants
- 4.7% smear+ve in mobile arm
- 2.9% smear+ve in door-to-door arm

41% of all smear+ve TB diagnosed by DETECTB
Case-notifications per 100,000 pop per round of ICF by service provider

Period average for Harare (annual CNR 200 per 100k)

ICF: 34% to 47% all smr+ve patients

Routine DOTS registrations
DETECTB FU of smr-ve suspects
DETECTB ICF smrs+ve
Health seeking behaviour

All TB patients, smear-ve TB suspects seeking further investigations

- 78% No previous health seeking
- 15% TB suspects
  - 75% mobile
  - 81% door-to-door
- 2% TB patients
  - 70%

Despite a well developed and respected primary care network in Harare
Mobile more effective in high HIV prevalence, crowded neighbourhoods

Cluster-level HIV prevalence and cumulative Rd 1 to 6 per capita yield of TB

Increasing per capita TB yield

Cluster HIV prevalence

HIV prevalence (%) in pre-intervention survey

Mobile ● Door to door X
Secondary outcome: impact on TB control?

Measured at *start* of Round 6

<table>
<thead>
<tr>
<th>Prevalent</th>
<th>Before</th>
<th>By Round 6</th>
<th>% reduction</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n = 10092</td>
<td>n = 11,037</td>
<td></td>
</tr>
<tr>
<td>Cult+TB</td>
<td>N: 65, prev: 0.64</td>
<td>N: 41, prev: 0.37</td>
<td>43%</td>
</tr>
<tr>
<td>Smear+TB</td>
<td>N: 40, prev: 0.40</td>
<td>N: 25, prev: 0.22</td>
<td>44%</td>
</tr>
<tr>
<td>All TB cases</td>
<td>N: 91, prev: 0.90</td>
<td>N: 62, prev: 0.56</td>
<td>38%</td>
</tr>
<tr>
<td>All cult+ isolates</td>
<td>N: 88, prev: 0.87</td>
<td>N: 55, prev: 0.49</td>
<td>44%</td>
</tr>
</tbody>
</table>

Before: n = 10092
By Round 6: n = 11,037

95% CI
DETECTB secondary outcome

Less good reduction in undiagnosed TB in HIV+ and men

% reduction (1-RR) in culture+ve TB

All participants

Unadjusted

Adjusted*

Subgroup analyses

HIV+

HIV-

Male

Female

* DETECTB secondary outcome

Less good reduction in undiagnosed TB in HIV+ and men

Overall

By HIV status

By Gender

By Arm

% reduction (1-RR) in culture+ve TB

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Participation and case-detection in Round 1

HIV-ve   HIV+ve

Cough > 2wks
Smr+ TB with cough
TB with cough
All TB
Smr+ TB

-100% -80% -60% -40% -20% 0% 20% 40% 60% 80% 100%
Summary: DETECTB

**Primary outcome**
- High numbers of participants in both arms
- But only ~ 25% detection of s+ participants per round
- Mobile substantially more effective at detecting smear+ve TB
- Mobile especially good in crowded high HIV communities
- Difference in smear+ve rate not participation rate
- Most cases no previous contact with Health system

**Secondary outcome**
- Substantial decline in undiagnosed culture+ TB
  - HIV- 59% reduction
  - HIV+ 25% reduction
- Reduction to low rates regionally
- Major improvement in TB control in a high HIV setting
- Likely to correspond with equivalent reduction in TB transmission rates
Broader lessons

- Undiagnosed s+ & c+ TB highly prevalent in African communities
  - So is undiagnosed / untreated HIV
  - Killer combination for PLWHA
  - Major inconsistency in investing in IPT/HIV care scale up while tolerating active TB prevalence of 1-2% in the community

- “Active-passive” ACF very well received
  - Strong public health message
  - Reduction in all forms of TB from s+ case-detection

- Impact mainly through *direct* or *indirect* effects?
  - Try to maximise both!
  - Indirect dependant on functional adequacy of DOTS & primary care network
  - Direct effect dependant on CHW network & capacity for community mobilisation

- Much easier to deliver to “working-class” Harare than the slums of urban Blantyre: roads / competing noise and hawkers
Kaplan-Meier plot: days of smear-positivity before diagnosis of smr+ve TB in HIV+ve patients

Interval censoring:
- best fit: loglogistic distribution
- median 15 days
- geometric mean 6 weeks
DETECTB Collaborators

Trial steering committee
- Rob Wilkinson
- Anthony Butterworth
- Frances Cowan

Harare
- BRTI
  - Field, Lab & data teams
    - Ethel Dauya
    - Beauty Makamure
    - Tsitsi Bandason
  - Peter Mason
- NIHR / BRTI: Shungu Munyati
- City Health: Stan Mungofa
- MoHCW: Owen Mugurungi
- IUATLD and Regional WHO
- CDC-Zimbabwe, DfID
- PSI, Zimbabwe

UK
- LSHTM
  - Liz Corbett
  - Richard Hayes
  - Trinh Duong & Yin Bun Cheung
  - David Mabey
  - Peter Godfrey-Faussett
  - Tamara Hurst & Fiona Marquet

WHO Geneva
- Brian Williams

South Africa
- Gavin Churchyard
Intervention area: NW Blantyre
1/3rd of Blantyre City: HIV prevalence 19%
- 78 CHW areas: active TB case-finding
- 28 clusters randomised to +/- HIV/TB prevention
Anticipated TB outcomes

- Active case-finding
  - Program data (routine notifications)
  - Compare neighbouring time trends

- Cluster randomised trial
  - TB incidence between arms over 2 year period
Blantyre Malawi
Combined TB prevention: active case-finding plus nested cluster-randomised trial of intensified HIV/TB prevention

Interventions
1. Active TB case-finding (ACF)
2. Nested cluster-randomised trial
   - ACF +/- “Test-and-treat” for HIV/TB
     - HIV self-testing
     - Isoniazid preventive therapy +/- ART

Cluster randomised trial outcomes
- TB case-notification rates
  - Enhanced M&E
- Undiagnosed HIV infection
- Adult mortality (KPS system)

Qualitative & cost-effectiveness
<table>
<thead>
<tr>
<th>ACTIVE CASE-FINDING</th>
<th>PASSIVE CASE-FINDING</th>
</tr>
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<tbody>
<tr>
<td>1. <strong>TB suspects</strong> defined through</td>
<td>1. <strong>TB suspects</strong> defined through</td>
</tr>
<tr>
<td>A individual-level risk factors for TB disease or infection (e.g. HIV infection,</td>
<td>Self-presentation to a health facility with ill-health</td>
</tr>
<tr>
<td>recent immigration, IVDU, or</td>
<td></td>
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<tr>
<td>b Contract tracing (e.g. household member of TB patient), <em>or</em></td>
<td></td>
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<tr>
<td>c living in a “high risk community” known to have a high prevalence or incidence</td>
<td></td>
</tr>
<tr>
<td>of TB disease, e.g.</td>
<td></td>
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<tr>
<td>- urban residential suburbs/slums</td>
<td></td>
</tr>
<tr>
<td>- remote communities</td>
<td></td>
</tr>
<tr>
<td>- prisoners, miners</td>
<td></td>
</tr>
<tr>
<td>2. <strong>Screening strategy</strong> can target chronic cough, or include asymptomatic</td>
<td>2. <strong>Screening strategy</strong>: cough for 2 to 3 weeks or longer for pulmonary TB</td>
</tr>
<tr>
<td>individuals</td>
<td></td>
</tr>
<tr>
<td>3. <strong>Investigation algorithm</strong> may include CXR, smear, culture, tuberculin skin</td>
<td>3. <strong>Investigation algorithm</strong> defined by NTP</td>
</tr>
<tr>
<td>test (if isoniazid preventive therapy being considered), and newer diagnostics</td>
<td></td>
</tr>
<tr>
<td>4. <strong>Implementation</strong> may be community-directed, integrated into the schedule of</td>
<td>4. <strong>Implementation</strong> through routine health services</td>
</tr>
<tr>
<td>community health workers, or via dedicated TB outreach teams</td>
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African TB control: now or never?

- Major global commitment to improving control
- Tangible gains, including new diagnostics

But...

- MDR and XDR-TB
- Prolonged infectiousness of both HIV and TB
- Control of HIV-related TB becoming more difficult
  - Incidence of TB in HIV+ves 3-4-fold higher than 10 yrs ago
  - MTB strain replacement in South Africa

![Notified TB cases per 100,000 pop. 1980-2008](chart.png)