Community-wide isoniazid preventive therapy among gold miners in South Africa: the Thibela TB study

Chihota VN, Popane F, Churchyard GJ, Lewis JJ, Fielding KL, Vynnycky E, White RG, Grant AD

on behalf of the Thibela TB team
Background

- TB case notification rates in South African gold mines are extremely high (<5%/yr by 2001) due to
  - High prevalence of silicosis
  - Exacerbated by rising HIV prevalence (~30% in 2000)
TB case notification rates in South African gold mines are extremely high (<5%/yr by 2001)

Failure of “standard” control measures that includes
- DOTS
- active case finding
- targeted IPT
- HIV testing & ART
Background

• TB case notification rates in South African gold mines are extremely high (<5%/yr by 2001)

<table>
<thead>
<tr>
<th>Year</th>
<th>HIV Pos</th>
<th>HIV Neg</th>
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<tbody>
<tr>
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More needs to be done to control TB in the mines
Targeted vs. community-wide IPT

High TB risk: TB contact
HIV+
Targeted vs. community-wide IPT

High TB risk: TB contact 🌟
HIV+ 🌟
Offered IPT 🌟
Targeted vs. community-wide IPT

High TB risk: TB contact
HIV+
Offered IPT

High TB risk: everyone
Targeted vs. community-wide IPT

High TB risk: TB contact
- HIV+
Offered IPT:

High TB risk: everyone
Offered IPT: everyone
**Aim**

To compare the effectiveness of

- isoniazid preventive therapy (IPT) given on a community-wide basis
- to current standard of care on TB among gold miners in South Africa
Methods
Study design

- Cluster-randomised intervention study

- Cluster defined as all employees & contractors at mine shaft(s) and associated hostels
Study design

- Cluster-randomised intervention study

15 clusters:

5,366  11,892  6,124  6,586  3,665  8,756  6,091  2,279

3,025  5,187  3,200  3,296  9,173  2,690  1,266
Study design

- Cluster-randomised intervention study

15 clusters: 8 intervention and 7 control

<table>
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<tr>
<th>Intervention</th>
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**Study design**

- Cluster-randomised intervention study

**15 clusters: 8 intervention and 7 control**

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<th>Intervention Sample</th>
<th>Control Sample</th>
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<td>3,296</td>
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<td>5</td>
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<td>9,173</td>
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<td>6</td>
<td>8,756</td>
<td>2,690</td>
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<tr>
<td>15</td>
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</table>

**Notes:**
- The sample sizes for intervention and control groups are shown above. Each cluster is represented by a sample.
Study design

- Outcomes measured
  - only in employees
  - among all employees, regardless of whether they took IPT or not
- HIV testing not done, as requested by labour
Intervention

• Community education and mobilisation
  • Intervention offered to entire workforce

• TB screening: symptoms and chest X-ray
  • Persons with suspected TB investigated by collecting one sputum specimen for microscopy, culture, speciation & drug sensitivity testing
  • Persons with suspected TB referred for investigation and treatment

• If eligible, 9 months of isoniazid preventive therapy

• Monthly follow-up visits for dispensing & screening for TB (symptom) & possible side effects
Study activity timeline

Intervention clusters

Baseline Survey

Intervention enrolment 3-16 months

Intervention follow-up 9 months

Primary outcome measurement 12 months

Final Survey

TB episodes:
data collection
Study activity timeline

Control clusters

Baseline Survey

Nominal follow-up time

Primary outcome measurement 12 months

TB episodes: data collection

Final Survey

TB episodes: data collection
Primary endpoint

- TB incidence (all cases) among employees measured over 12 months from last person enrolled completing therapy
Secondary endpoints: TB prevalence

• TB prevalence (sputum culture) among a sample of employees at the end of the study

Fielding et al Contemporary Clinical Trials 2011 32:382-92
Flora Popane

Implementation
Human resources and infrastructure

- 200+ Thibela staff members
- 20 study implementation sites
  - 35 containers converted
  - 180 tons equipment moved
Data Management

Study centre

- 15 million data points
- 8 million consistency checks

Production server

HR data 2.7 million records

Central server
Community mobilisation

- Communication underpins community mobilisation
- Communication requires
  - multiple strategies
  - strong brand identity
  - simple key messages
  - to be repeated frequently
Community mobilisation – Education

- All materials in 8 languages
- >30,000 booklets and posters distributed
- >70,000 one to one contacts
- Banners, flipcharts, pamphlets
- TB & Thibela education DVDs
- Peer educator & CAG training
Community mobilisation

7 launches
800 stakeholder briefing sessions
>2000 radio announcements
>1500 video showings
Community mobilisation
Community mobilisation
Markinor survey

“I wish all people can understand the importance of preventing TB rather than treating it.”

“TB is an enemy that needs to be annihilated everywhere.”
September 2007

GCPj award for “Most innovative patient recruitment strategy”

Nomination for “Clinical trial which best promoted access to treatment”
Results
Population-level effect of isoniazid preventive therapy on tuberculosis in the Thibela TB study

Gavin Churchyard
Participant flow

Total population
78,744

Intervention clusters
40,981

Consented
27,126 (66.2%)

Started IPT
23,659 (87.2%)

Control clusters
37,763

Ineligible
1,455 TB suspect
2,012 Ineligible for IPT
## Results

**Baseline characteristics** *(N=15,607)*

- Median age 45 years
- Male 95.9%
- Silicosis 2.7%
- History of TB 12.5%
- HIV positive (self report) 12%
- Prior IPT usage 0.6%
- Current ART 2.7%

* Results were similar by study arm
Uptake to the intervention

Uptake in last four clusters = 78.7%

Uptake in first four clusters = 58.0%
% population taking IPT by study month

% of cluster dispensed IPT per month

month from start of intervention
Effectiveness

TB incidence

Among employees in the primary outcome measurement

<table>
<thead>
<tr>
<th></th>
<th>TB</th>
<th>Person years</th>
<th>Rate/100 pyo</th>
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</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>887</td>
<td>29,352</td>
<td>3.02</td>
</tr>
<tr>
<td>Control</td>
<td>856</td>
<td>29,015</td>
<td>2.95</td>
</tr>
</tbody>
</table>

Incidence rate ratio

Unadjusted       1.00 (95% CI 0.75-1.34)
Adjusted*        0.96 (95% CI 0.76-1.21)

*Adjusted for individual level variables gender, age, surface/underground work, and cluster level variables of silicosis and ART prevalences TB case notification rate 12-months prior to cluster enrolment and pre-randomisation strata
Effectiveness

TB prevalence

Among a sample of employees at study end

<table>
<thead>
<tr>
<th></th>
<th>TB (n)</th>
<th>Total (N)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>166</td>
<td>7,049</td>
<td>2.35</td>
</tr>
<tr>
<td>Control</td>
<td>119</td>
<td>5,557</td>
<td>2.14</td>
</tr>
</tbody>
</table>

Prevalence ratio

Unadjusted       1.05 (95% CI 0.60-1.82)
Adjusted*        0.98 (95% CI 0.65-1.48)

*Adjusted for individual level variables gender, age, surface/underground work, and cluster level variables of silicosis and ART prevalences TB case notification rate 12-months prior to cluster enrolment and pre-randomisation strata
Conclusion

- Community-wide IPT did not improve TB control at a population level
- In the following 2 presentations we present data on factors that may have influenced the effectiveness of community-wide IPT
  - Retention and adherence
  - Time to treatment start
  - In and out migration
  - ART uptake
  - Individual level effectiveness of IPT
Additional analyses to understand lack of population-level effect

James Lewis
Retention varied by cluster

Kaplan-Meier plot of time to early withdrawal from the intervention – each line is for a cluster
Retention varied by cluster

- 6m retention in first four clusters = 48.2%
- 6m retention in last four clusters = 68.3%

Days since first dispensed INH
Retention varied by cluster

Variation by cluster largely driven by differences in retention at first follow-up visit
Adherence was assessed at monthly follow-up visits by:

- self-reported pill taking in last three days;
- urine test on random selection of participants;
- return for visits;
- pill counts.

At monthly follow-up visits, 88.8% reported missing no tablets in last three days (varied by cluster from 81.8% to 92.6%)
Adherence: urine test

Random selection at 3m, 6m and 9m visits had urine tested for INH metabolites
Adherence: urine test

Initial default and time to treatment

- Initial default (sputum positive but not on Rx) is an emerging concern for TB programmes ¹
- 17% initial default in 13 clinics in WC ²
- We combined data from three sources:
  - People with suspected TB identified through intervention or mine health services
  - Data abstracted from medical records for all TB patients
  - Human Resources data on workforce terminations

¹ Harries et al. IJTLID 2009; ² Botha et al. IJTLID 2008
TB suspects identified through mine health services started treatment quicker, but ultimately were no more likely to start treatment than those identified through Thibela screening.
TB suspects identified through mine health services started treatment quicker, but ultimately were no more likely to start treatment than those identified through Thibela screening.
Out-migration is number in employment at A, but not at B, as % of workforce size at A
In-migration is number in employment at B, but not at A, as % of workforce size at A
Migration

Out-migration: 21% in intervention arm, 19% in control arm.
In-migration: 23% in intervention arm, 21% in control arm.

Out-migration: 16% in employees, 45% in contractors.
In-migration: 17% in employees, 55% in contractors.
Increasing ART coverage by time

ART coverage defined as number dispensed ART at least once in 6m period divided by workforce size
Individual-level effect of isoniazid preventive therapy on risk of tuberculosis in the Thibela TB study

Katherine Fielding
Background and objectives

- Community-wide IPT did not reduce TB incidence or prevalence at a population level

- We investigate the effect of IPT on TB incidence in
  - individuals starting IPT in intervention clusters vs.
  - individuals in control clusters
Study design

Control clusters (7)

Baseline Sample
Baseline Sample
Baseline Sample

Baseline survey participants from control clusters (7)

Intervention clusters (8)

Baseline Sample
Baseline Sample
Baseline Sample

Baseline survey participants from intervention clusters (8)
Study design

Baseline survey participants from control clusters (7)
Excluded
Not employee
Excluded
TB / IPT
Employees
Control arm
Currently not on TB treatment or IPT

Baseline survey participants from intervention clusters (8)
Excluded
Not employee
Employees
IPT arm
Started IPT (regardless of TST or HIV status)
Methods – time at risk in control arm

- **Control arm** - time at risk measured
  - from recruitment into baseline survey
  - to the earliest of starting TB treatment, leaving workforce, end of cluster follow-up

- **IPT arm** - time at risk measured
  - from first dispensed IPT
  - to the earliest of starting TB treatment, leaving workforce, end of cluster follow-up
Methods – time at risk in IPT arm

- **Control arm** - time at risk measured
  - from recruitment into baseline survey
  - to the earliest of starting TB treatment, leaving workforce, end of cluster follow-up

- **IPT arm** - time at risk measured
  - from first dispensed IPT
  - to the earliest of starting TB treatment, leaving workforce, end of cluster follow-up
Methods – during IPT treatment period

• Compared TB incidence in these cohorts, stratified by time interval
  • 0-9 months after cohort entry; representing the intended *IPT treatment period*
  • 9-18 months; >18 months, after cohort entry; representing time following the IPT treatment period
Methods – following IPT treatment period

• Compared TB incidence in these cohorts, stratified by time interval
  • 0-9 months after cohort entry; representing the intended *IPT treatment period*
  • 9-18 months; >18 months, after cohort entry; representing time following the IPT treatment period
Case definition for TB

- Starting on TB treatment by mine health services

- Excluded cases where only non tuberculosis mycobacteria were identified
Results – flow diagram

Baseline survey (n=15,609, 15 clusters)

Employees (n=14,005, 15 clusters)

Control clusters (n=6,397, 7 clusters)

Excluded TB / IPT (n=134)

Control arm (n=6,263, 7 clusters)

Intervention clusters (n=7,608, 8 clusters)

Excluded Did not start IPT (n=2,963)

IPT arm (Started IPT) (n=4,646, 8 clusters)

Excluded Not employees (n=1,604)
## Summary at baseline, and follow-up in years

<table>
<thead>
<tr>
<th></th>
<th>Control arm n=6263</th>
<th>IPT arm n=4646</th>
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</thead>
<tbody>
<tr>
<td><strong>Age, years – median (IQR)</strong></td>
<td>43 (36-48)</td>
<td>44 (37-49)</td>
</tr>
<tr>
<td><strong>Male, %</strong></td>
<td>97.7</td>
<td>97.6</td>
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<tr>
<td><strong>Previous TB, %</strong></td>
<td>10.6</td>
<td>12.1</td>
</tr>
<tr>
<td><strong>Current ART use, %</strong></td>
<td>1.7</td>
<td>3.1</td>
</tr>
<tr>
<td><strong>Lives in hostel, %</strong></td>
<td>59.9</td>
<td>61.1</td>
</tr>
<tr>
<td><strong>South African, %</strong></td>
<td>55.2</td>
<td>55.6</td>
</tr>
<tr>
<td><strong>Previous TB on CXR, %</strong></td>
<td>15.6</td>
<td>14.7</td>
</tr>
<tr>
<td><strong>Silicosis - CXR, %</strong></td>
<td>3.2</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>Follow-up, years – median (IQR)</strong></td>
<td>2.4 (1.8-2.8)</td>
<td>2.0 (1.8-2.3)</td>
</tr>
</tbody>
</table>

IQR interquartile range; CXR chest radiograph
TB incidence over entire follow-up period

- 557 TB episodes over 22,939 person years of follow-up (pyrs)

- Control arm
  - 382 TB episodes over 13,776 pyrs
  - TB incidence of 2.77/100 pyrs

- IPT arm
  - 175 TB episodes over 9,163 pyrs
  - TB incidence of 1.91/100 pyrs
## Effect of IPT during the IPT period

<table>
<thead>
<tr>
<th>Interval</th>
<th>Arm</th>
<th>Rate, per 100pyrs</th>
<th>Unadjusted IRR (95% CI)</th>
<th>Adjusted IRR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>0-9mth</td>
<td>IPT</td>
<td>1.10</td>
<td>0.38 (0.19-0.75)</td>
<td>0.37 (0.19-0.72)</td>
</tr>
<tr>
<td>(IPT period)</td>
<td>Control</td>
<td>2.91</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>9-18mths</td>
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<tr>
<td></td>
<td>Control</td>
<td>2.71</td>
<td>1</td>
<td>1</td>
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<tr>
<td>&gt;18mths</td>
<td>IPT</td>
<td>2.42</td>
<td>0.83 (0.54-1.27)</td>
<td>0.79 (0.54-1.17)</td>
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<tr>
<td></td>
<td>Control</td>
<td>2.70</td>
<td>1</td>
<td>1</td>
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IRR incidence rate ratio; CI confidence interval

* adjusted for age, sex, previous TB, ART, country, residence

### During the IPT treatment period: 63% reduction in TB incidence

**Baseline Survey**

- **IPT arm:**
  - IPT
  - Control

- **Control arm:**
  - IPT
  - Control

End of cluster follow-up
## Effect of IPT following the IPT period

<table>
<thead>
<tr>
<th>Interval</th>
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**IRR incidence rate ratio; CI confidence interval**

* adjusted for age, sex, previous TB, ART, country, residence

### Following the IPT treatment period: TB incidence similar in the two arms

**Baseline Survey**

**End of cluster follow-up**
Conclusions

• During the IPT treatment period TB incidence was reduced by nearly two-thirds, among those who started IPT

• But this effect was not durable

• Consistent with data from the IPT trial among HIV+, in Botswana (late breaker CROI 2012)
  • In 36 month IPT arm, among TST+, following cessation of IPT, cumulative TB incidence increased by 90%

• Need to disentangle effects of ART
Conclusions (2)

• Suggests that in these settings the rate of reinfection is high

• To explore this need to understand what the risk of infection is likely to be
  • difficult to measure directly

• Mathematical modelling can help investigate this
Why did we see no detectable impact in Thibela and what can we do to control TB in the mines?

Emilia Vynnycky,
Tom Sumner, Andy Cox, Richard G White
Outline

1. Why did we get no detectable impact in Thibela?
   a. Description of the model
   b. Model results

2. How much bigger could the impact have been, given the technology available?

3. What might control TB in the mines?
**Key definitions**

**Measured incidence:** incidence of TB disease, as observed in Thibela TB

**True incidence:** incidence of TB disease that would be seen if all cases could be detected

**ARI:** annual risk of *M tuberculosis* infection i.e. risk of a person acquiring a new *Mtb* infection per year

**“Cure” of latent infection:** the infection in an individual is cleared and the person can only develop disease if they get a new infection
Overview of the model

• Model describes the epidemiology of TB in each intervention cluster, incorporating directly measured data and assumptions

• Controls taken to be perfectly matched, i.e. identical to intervention clusters, but without the intervention

• Model considers only culture-positive TB
Model diagram - pre-intervention

- Latent infection
- Reinfected
- Undetected s-c+ disease
- Detected s-c+ disease
- Undetected s+c+ disease
- On TB treatment
- Recovered

- In or out-migration
- Death
- Disease
Key default model assumptions

• 30% HIV prevalence

• 20% average annual risk of *M. tuberculosis* infection

• TB disease occurs either through reactivation or following reinfection at estimated rates

• Increased risk of disease if HIV+ and/or silicotic

• IPT protection against disease through reactivation/after reinfection, whilst on IPT:
  - 63%: HIV- or HIV+ not on ART
  - 80%: HIV+ and on ART
  - no protection once stop IPT

• 6 months of IPT cures an estimated fraction of latent infections
Modelling used trial data on:

- In and out migration
- ART coverage
- Silicosis prevalence
- Delays to detection & TB treatment
- Initial default
- IPT uptake & retention
- Case-screening on recruitment
- Contact with the outside community
Model diagram – with the intervention

- **Latent (not protected by IPT)**
- **Latent (on IPT)**
- **Cleared infection**
- **Reinfected (not protected by IPT)**
- **Reinfected (on IPT)**
- **Undetected s-c+ disease**
- **Undetected s+c+ disease**
- **Detected s-c+ disease**
- **Detected s+c+ disease**
- **On TB treatment**
- **Recovered**

- In or out-migration
- Death
- Disease whilst not protected by IPT
- Disease whilst protected by IPT

- <6 mths IPT
- ≥6 mths IPT

Model diagram with the intervention.
Model-fitting and parameter estimation

• Unknown parameters
  • Risks of disease through reactivation & after reinfection
  • Proportion of latent infections that are cured by 6 months of IPT

• Model was fitted to prevalence & incidence data for all clusters to estimate unknown parameters, for two IPT scenarios in which:
  • IPT cures all reinfections
  • IPT cures an estimated fraction of all infections

• Best-fitting parameters: those resulting in the smallest impact of IPT on the incidence and prevalence
Results
To match low impact observed, model needed to assume 6 months IPT did not cure latent infections.

Assuming 6m IPT cures latent infections.

Allowing model to assume 6m IPT might not cure.

Best-fitting: % cleared = 0%
Assuming an increased annual risk of *M. tuberculosis* infection could not explain lack of trial impact.

<table>
<thead>
<tr>
<th>% impact on TB incidence</th>
<th>Non-curing model</th>
<th>Fully-curing model</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
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<tr>
<td>30%</td>
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<tr>
<td>40%</td>
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<tr>
<td>50%</td>
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Assumed annual risk of infection (%)
Outline

1. Why did we get no detectable impact in Thibela?
   a. Description of the model
   b. Model results

2. How much bigger could the impact have been, given the technology available?

3. What might control TB in the mines?
Even optimal implementation of Thibela TB would have led to modest additional impact (under 20%)
Outline

1. Why did we get no detectable impact in Thibela?
   a. Description of the model
   b. Model results

2. How much bigger could the impact have been, given the technology available?

3. What might control TB in the mines?
3. What intervention might work in the mines?

Decreased treatment delay

• ↓ initial default to 5%
• ↓ time to treatment:
  • 90% of s+ starting in 1 month;
  • 90% of s- starting in 3 months
Reduced treatment delay has a modest impact on the TB incidence.

Number of cases/100,000/year (true incidence)

Year


No intervention
Decreased treatment delay
3. What intervention might work in the mines?

**Decreased treatment delay + IPT interventions**

1. Coverage increased to highest levels seen
2. Continuous community-wide IPT for ~50% of individuals
3. 3 month regimen curing latent infection
Continuous community-wide IPT or a 3 month fully-curing regimen would have a bigger impact than 9 months of IPT

- **Initial round with 9 months IPT, with coverage at highest levels seen in Thibela**, followed by continuous community-wide IPT with 50% coverage.

- **Single round with a 3 month fully-curing regimen**, coverage at highest levels seen in Thibela, no community-wide IPT.

* Year

** Year

*** Year

---

* Initial round with 9 months IPT, with coverage at highest levels seen in Thibela

** Initial round with 9 months IPT, with coverage at highest levels seen in Thibela, followed by continuous community-wide IPT with 50% coverage.

*** Single round with a 3 month fully-curing regimen, coverage at highest levels seen in Thibela, no community-wide IPT.

---

- **No intervention**
- **Decreased treatment delay**
- **Increased IPT uptake***
- **Continuous community-wide IPT**
- **3 month regimen cures latent infns***
3. What intervention might work in the mines?

Decreased treatment delay + ART coverage

↑ to 80% in 1 year in various HIV+ groups:

• <350 cells/mL
• <500 cells/mL
• all HIV-positives (not just those diagnosed)
ART scale-up could result in large reductions in the TB incidence

* ART coverage increased to 80% by 2009
3. What intervention might work in the mines?

**Decreased treatment delay + Xpert**

1. Screen with Xray in annual occupational health checks, use Xpert for people with suspected TB
2. Screen with Xpert in annual occupational health checks
Using Xpert leads to a modest impact on the TB incidence.

![Graph showing the impact of Xpert on TB incidence]

- **No intervention**
- **Decreased treatment delay**

**Number of cases/100,000/year** (true incidence)

- Year range from 2003 to 2017
- The graph illustrates the decline in TB incidence over these years, with a significant drop in the no intervention scenario compared to the decreased treatment delay scenario.
Using Xpert leads to a modest impact on the TB incidence

Number of cases/100,000/year (true incidence)

Year


- No intervention
- Decreased treatment delay*
- Screen with Xray at annual occupational health checks and Xpert for people with suspected TB*

* The lines for these two scenarios are on top of each other
Using Xpert leads to a modest impact on the TB incidence

- No intervention
- Decreased treatment delay*
- Screen with Xray at annual occupational health checks and Xpert for people with suspected TB*
- Screen with Xpert at annual occupational health checks

* The lines for these two scenarios are on top of each other
BUT... using Xpert without reducing time to treatment is likely to have a similar impact to reducing treatment delay in existing services.
3. What intervention might work in the mines?

Dust control

Calculate the proportion of the TB incidence that is due to silicosis and HIV
Dust control has the potential to lead to some reductions in incidence

- Assuming an HIV prevalence of 30%, proportion of TB incidence attributable to:
  - Silicosis: about 10%
  - HIV: about 70%

- Therefore, if no miners had silicosis, the incidence could be about 10% lower than it is at present

- However, a much greater proportion of the TB incidence is attributable to HIV than to silicosis
Combining interventions could reduce the TB incidence by over 50%
Combining interventions could reduce the TB incidence by over 50%

*Screen with Xpert in annual occupational health screening
Combining interventions could reduce the TB incidence by over 50%

*Screen with Xpert in annual occupational health screening

**ART coverage increased to 80% by 2009
Combining interventions could reduce the TB incidence by over 50%

Number of cases/100,000/year (true incidence)

Year


Reduced treatment delay
Screen with Xpert*
ART for 80% HIV+**
IPT for 50% of all individuals***

*Screen with Xpert in annual occupational health screening
**ART coverage increased to 80% by 2009
***Initial round with 9 months IPT, with coverage at highest levels seen in Thibela, followed by continuous community-wide IPT with 50% coverage
Limitations

• Some uncertainty in model parameters and model structure (as in all models)

• Of particular note
  • Lack of trial impact could instead be explained by:
    • Other (unknown) factors?
      – Possible?
    • Undetected imbalance between trial arms?
      – Unlikely?
  • We had to assume HIV prevalence and annual risk of MTB infection
  • But results robust to plausible variation in these assumptions
Conclusions – why did we get no detectable impact in Thibela?

- Due to several factors including lower uptake, coverage and retention than expected and migration

- However, the modelling also supports the conclusion that 6-9 months of IPT did not cure many latent infections in this setting

- Given this, even optimal implementation of Thibela TB would only have led to a modest additional impact (under 20%)
Conclusions – what might control TB in the mines?

• An intensive “combination-prevention” approach is needed to control TB in the mines, including:
  • improved diagnostic tests
  • effective improvement of health systems to minimise time to treatment
  • increased and improved ART coverage
  • more effective preventive therapy regimens
The Thibela TB study: implications for policy and practice

Alison Grant
Thibela TB: main results

- At the individual level, community-wide IPT reduced TB incidence among gold miners
- At the population level, community-wide IPT did not improve TB control in gold mines
## Thibela TB: why didn't it improve TB control?

<table>
<thead>
<tr>
<th>Was it that:</th>
<th>Results suggest:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention coverage too low?</td>
<td>yes, but even if optimised, impact wouldn't last long</td>
</tr>
<tr>
<td>Migration in and out of mines too high?</td>
<td>not a major factor</td>
</tr>
<tr>
<td>IPT didn't protect individuals against TB?</td>
<td>no</td>
</tr>
<tr>
<td>IPT effect didn't last long enough</td>
<td>yes.....</td>
</tr>
</tbody>
</table>
Thibela TB: was IPT effect brief because risk of reinfection very high?
Thibela TB: was IPT effect brief because risk of reinfection very high?

- Assuming IPT cures latent infection and protects against disease following reinfection, only during the IPT course
Thibela TB: was IPT effect brief because risk of reinfection very high?

- Assuming IPT cures latent infection and protects against disease following reinfection, only during the IPT course
- Durability of IPT depends on risk of new TB infection
- Risk of new TB infection hard to measure
- Model suggests that big variation in estimated risk of new infection (in plausible range for mines) did not greatly affect impact of Thibela TB
Thibela TB: was IPT effect brief because IPT does not cure latent infection?
Thibela TB: was IPT effect brief because IPT does not cure latent infection?

• Assuming IPT does not cure latent infection, but protects vs. reactivation and reinfection, only during the IPT course
• Where risk of new infection low, durability of IPT primarily depends on efficacy of regimen to cure latent TB
• Cure of latent infection very difficult to measure
• Model suggests that cure vs. not of latent infection made a big difference to population-level impact of Thibela TB
Thibela TB: implications for TB control in gold mines

- Even if optimally implemented, community-wide IPT for 6-9 months would not be a long term solution to TB control in mines

![Graph showing TB cases over time with interventions](image-url)
Thibela TB: what will it take to control TB in gold mines?

- Model suggests we need:
  - to FIND TB:
    - better case finding - e.g. Xpert MTB/RIF, find more cases earlier AND
  - to TREAT TB:
    - reduce treatment delay among sputum pos cases (regardless of diagnostic system)
Thibela TB: what will it take to control TB in gold mines?

- Model suggests we need:
  - to FIND TB, to TREAT TB:
  - to PREVENT TB:
    - continuous IPT - supported by Botswana IPT study
    - better drug regimens to cure latent infection
Thibela TB: what will it take to control TB in gold mines?

- Model suggests we need:
  - to FIND TB, to TREAT TB:
  - to PREVENT TB with better regimens:
  - to PREVENT TB by reducing susceptibility:
    - better ART coverage (~70% TB cases are attributable to HIV)
    - better dust control (~10% TB cases are attributable to silicosis)
Thibela TB: what will it take to control TB in gold mines?

- To make a real difference, we need combination TB prevention:
Thibela TB: implications for research

- Limited durability of IPT consistent with data from Botswana
- To tailor TB control strategies to local epidemiology, need to understand why:
  - ?high risk of reinfection leading to recurrent disease among highly susceptible people
  - ?failure to cure latent infection in susceptible people
  - ?or (probably) a bit of both
Thibela TB: priorities for TB control outside the mines

- FIND TB:
  - reduce time to diagnosis:
    - active case finding (clinics, households, communities)
    - Xpert MTB/RIF......
Thibela TB: priorities for TB control outside the mines

- **FIND TB**
- **TREAT TB:**
  - ensure people with positive sputum results, diagnosed by whatever method, start treatment promptly
Thibela TB: priorities for TB control outside the mines

- FIND TB
- TREAT TB
- PREVENT TB
  - better regimens:
    - continuous IPT
    - alternative regimens with higher cure potential
  - address susceptibility:
    - maximise ART coverage
    - ensure retention in care
Targeted IPT

Community-wide IPT x 9m

Yes please!

No thanks!
# Combination prevention for TB in gold mines

<table>
<thead>
<tr>
<th>Better diagnosis</th>
<th>✔️</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce treatment delay</td>
<td>✔️</td>
</tr>
<tr>
<td>Maximise ART coverage</td>
<td>✔️</td>
</tr>
<tr>
<td>Better preventive therapy</td>
<td>✔️</td>
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</tbody>
</table>
Thanks to the thousands of participants & the Thibela TB team

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