Latency in TB: Opportunities, challenges and the way forward

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Latent reservoirs are a hurdle for eradication in both TB and HIV.
Rationale for the treatment of latent TB (LTBI)

• INH X 9 months
• RIF/INH x 3 months

Sterling et al., NEJM 2011

LTBI treatment regimens

Aerosol infection → Active Disease

95% → 5%

Latent Infection → Reactivation

5%

~10 million active cases
~2 billion latent infections

global burden
Lessons for the field from the experience of treating latent TB
### Analysis 1.1. Comparison 1 Isoniazid versus placebo, Outcome 1 Active tuberculosis.

**Review:** Isoniazid for preventing tuberculosis in non-HIV infected persons

**Comparison:** 1 Isoniazid versus placebo

**Outcome:** 1 Active tuberculosis

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<td><strong>100.0%</strong></td>
<td><strong>0.40 [0.31, 0.52]</strong></td>
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Total events: 239 (Treatment), 557 (Control)

Heterogeneity: Tau² = 0.08; Chi² = 20.94, df = 10 (P = 0.02); P² = 52%
Test for overall effect: Z = 7.06 (P < 0.00001)
How well does treating LTBI work?

### Analysis 1.1. Comparison 1: Isoniazid versus placebo, Outcome 1: Active tuberculosis.

**Review:** Isoniazid for preventing tuberculosis in non-HIV infected persons

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**Total (95% CI)**

- Treatment: 40262 (239 events)
- Control: 33113 (557 events)

Total events: 239 (Treatment), 557 (Control)

Heterogeneity: $I^2 = 0.08$, $Ch^2 = 20.94$, df = 10 (P = 0.02); $I^2 = 52$

Test for overall effect: $Z = 7.06$ (P < 0.00001)
Success is context dependent
## Overall Effect of Community-wide Isoniazid Preventive Therapy: Tuberculosis Incidence and Prevalence

<table>
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<tr>
<th>Outcome</th>
<th>Control Clusters</th>
<th>Intervention Clusters</th>
<th>Rate Ratio (95% CI)*</th>
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<tr>
<td></td>
<td>Cases</td>
<td>Rate</td>
<td>Cases</td>
</tr>
<tr>
<td></td>
<td>no./no. of</td>
<td>per 100</td>
<td>no./no. of</td>
</tr>
<tr>
<td></td>
<td>person-yr</td>
<td>person-yr</td>
<td>person-yr</td>
</tr>
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<td>Primary outcome: tuberculosis incidence†</td>
<td>856/29,014</td>
<td>2.95</td>
<td>887/28,352</td>
</tr>
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<td></td>
<td>(0.75–1.34)</td>
<td>(0.76–1.21)</td>
<td>(0.73–1.48)</td>
</tr>
<tr>
<td></td>
<td>Definite or probable</td>
<td>656/29,014</td>
<td>2.26</td>
</tr>
<tr>
<td></td>
<td>(0.70–1.64)</td>
<td>(0.73–1.48)</td>
<td></td>
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<td>Prevalence Ratio (95% CI)†</td>
<td>1.05</td>
<td>0.86</td>
<td>0.98</td>
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<td>(0.60–1.82)</td>
<td>(0.65–1.48)</td>
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| Secondary outcome: tuberculosis prevalence‡ | 119/5557           | 2.14                  | 166/7049            | 2.35 | 1.05       | 0.86    | 0.98     | 0.90    |
|                                             | (0.60–1.82)       | (0.65–1.48)          | (0.66–1.55)        |       |            |         |          |         |
| Employees in workforce at the time of cluster enrollment | 97/4457            | 2.18                  | 128/5423           | 2.36 | 1.05       | 0.85    | 1.01     | 0.94    |
|                                              | (0.62–1.78)       | (0.66–1.55)          |                       |       |            |         |          |         |

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* Comparisons are for the intervention clusters versus the control clusters.
† Rate ratios were adjusted for individual-level variables (sex, age, and surface or underground work) and cluster-level variables (prevalence of silicosis and antiretroviral therapy, rate of tuberculosis case notification during the 12 months before cluster enrollment, and randomization strata).
‡ Rates per 100 person-years and percentages were calculated among all employees regardless of cluster.
§ The analysis of incidence during the 12-month measurement period for the primary outcome was restricted to employees who were in the cluster during the intervention enrollment period and the equivalent time for control clusters.
¶ The analysis of prevalence at the end of the study excluded employees with contaminated cultures, incomplete laboratory results, or both.

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Success does not reflect treatment of latent reservoirs

**Table 3. Direct Effect of Isoniazid Preventive Therapy as Shown by Tuberculosis Incidence, According to the Time Interval after Enrollment.**

<table>
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<tr>
<th>Time Interval</th>
<th>Control Cohort (N = 6263)</th>
<th>Isoniazid Cohort (N = 4646)</th>
<th>Rate Ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Rate†</td>
<td>Cases</td>
</tr>
<tr>
<td>Overall</td>
<td>382/13,776</td>
<td>2.77</td>
<td>175/9163</td>
</tr>
<tr>
<td>0–9 mo†</td>
<td>133/4,564</td>
<td>2.91</td>
<td>37/3358</td>
</tr>
<tr>
<td>&gt;9–18 mo</td>
<td>115/4,243</td>
<td>2.71</td>
<td>74/3,156</td>
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<tr>
<td>&gt;18 mo</td>
<td>134/4,970</td>
<td>2.70</td>
<td>64/2,649</td>
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**THIBELA TB: DURATION OF IPT EFFECT AT INDIVIDUAL LEVEL**

- **TB Incidence per 100 PYRS**
  - IPT arm
  - Control arm

- **58% reduction in TB incidence during 9m of IPT**

What can we learn about eradication?
Define the goal of eradication

**Eradication on the population level**
→ What is driving disease on a population level?
  - Transmission vs. reactivation of latent reservoirs
  - Shared opportunities—advanced molecular epidemiology
  - Mathematical modeling

**Eradication on the individual level**
→ What is driving disease in the infected individual?
How do we better understand what drives progression to TB disease?
Importance of experimental models to study latency and reactivation

Low dose infection by bronchoscopy

Primary infection

Replication & dissemination

Active disease

Latency

~10%

Reactivation

60%

40%

What is the path to active disease vs. latent infection?

What distinguishes animals with active disease vs. latent infection?

- Overlapping spectrum of pathologies
- Overlapping spectrum of lesional burdens
- Variability within a single host
- No single type of “active” or “latent” lesions
- Animals with active disease characterized by focal loss of control/immune pathology

- Microscopic Histopathology
  - Latent: Mineralized Granuloma, Caseous Granuloma, Non-necrotizing Granuloma, TB Pneumonia
  - Active

- Over 30 Weeks PI, 32 Weeks PI, 36 Weeks PI, and 40 Weeks PI

- CFU/lesion
  - four week, eleven week, Active, Latent

- Log scale from $10^0$ to $10^7$
Implications for understanding latent infection

- Variability in pathology, course and likely bacterial state
Can we target the organisms that will reactivate and cause disease?

Latency is a clinical diagnosis.

We infer the state of the pathogen—for TB, nonreplicating persistence. Probably not completely correct as isoniazid should not work.
Insights into reactivation

Low dose infection by bronchoscopy

Primary infection

Replication & dissemination

Active disease

Reactivation

Latency

60% ~10%

40% 71, 5831-5844 (2003), Infect Immun 77, 4631-4642 (2009)
How many latent organisms do you have to eliminate to lower the risk of disease?

Sterilization likely impossible.

Shared opportunity:
Quantitative framework to define the threshold for functional cure?

• in the presence of protective immunity?
• in the absence of protective immunity?

→ Convergence of HIV and TB
Opportunities

Paradigmatic similarities between strategies to target latent reservoirs in HIV and TB.

Opportunities to foster ties between HIV and TB eradication efforts:

• Synergistic efforts to define the force of ongoing transmission
• Efforts to develop experiment (NHP) models of the latent reservoirs relevant to reactivation
• Quantitative frameworks to define the threshold for cure and the effects of (partially) protective immunity

→ Importance of HIV/TB interactions and efforts to enhance immunity.