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MDR-TB Treatment as Prevention:
Modeling the Population-Level Impact of Expanded Treatment for Multidrug-Resistant Tuberculosis

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Abstract

Background: In 2013, approximately 480,000 people developed new active multidrug-resistant tuberculosis (MDR-TB), while only 97,000 people started treatment for MDR-TB. Individuals with untreated MDR-TB are infectious The contribution of insufficient treatment to ongoing transmission of MDR-TB remains poorly defined.

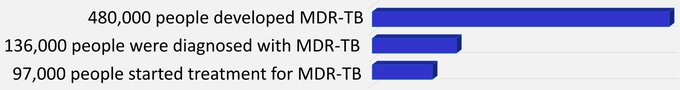
Methods: We constructed a dynamic transmission model of an MDR-TB epidemic in a representative East/Southeast Asian setting, calibrated using a country (Vietnam) with high-quality TB data. Using approximate Bayesian computation, we investigated a wide array of potential epidemic trajectories consistent with current notification data and known TB epidemiology. Within these data-consistent trajectories, we investigated the impact of improving access to MDR-TB diagnosis and treatment on ten-year projections of MDR-TB incidence and mortality.

Results: Data-consistent simulations projected an overall decline in TB incidence but an increase in MDR-TB incidence by 17% (95% Uncertainty Range [UR] -38% to +137%) between 2015 and 2025 under continued 2013 treatment practices. But if, by 2017, all patients with previously-treated TB could be tested for drug susceptibility, and 85% of those with MDR-TB could be placed on second-line treatment, then our model projects that MDR-TB incidence in 2025 could be reduced by 26% (95% UR 4-52%) relative to projections under continued current practice. If this treatment could be implemented via a novel second-line regimen with similar effectiveness and tolerability as current first-line therapy, a 52% (95% UR 19-72%) reduction in MDR-TB incidence could be achieved by 2025.

Conclusion: Diagnosing and treating MDR-TB reduces transmission and therefore decreases MDR-TB incidence. Focusing MDR diagnostic efforts on previously-treated cases is an efficient and effective approach.

Introduction

Worldwide, most MDR-TB goes undiagnosed and untreated. In 2013[1]:



The resulting unchecked MDR-TB epidemics hamper global TB control and imperil the financial solvency of national TB programs. Therefore, **MDR-TB may be an opportunity for "treatment as prevention."**

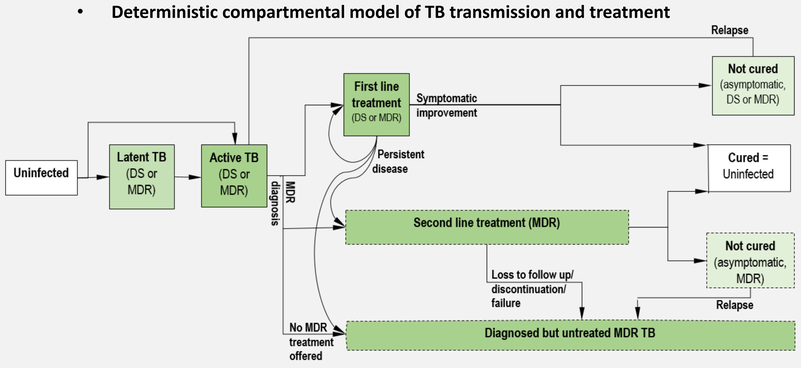
What impact could expanded MDR-TB diagnosis and treatment have?

What patients should we target given limited resources?

The difficulties of directly documenting TB transmission (due to casual airborne contacts and long latency periods) make a mechanistic mathematical model useful here.

Methods

- **Deterministic compartmental model of TB transmission and treatment**



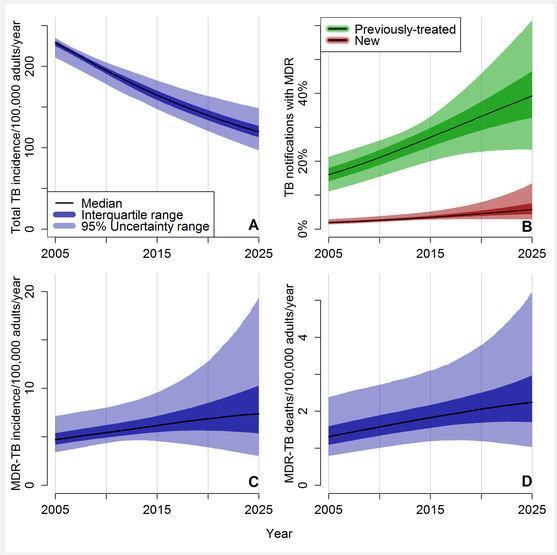
- **Drug-susceptible (DS) & MDR-TB strains** circulate in the population
- MDR can be selected during DS TB treatment; we assume a fitness cost of this drug resistance.[2]
- Approximate Bayesian computation approach to calibration: Sample (Latin hypercubes) wide **plausible parameter ranges** (see last Figure at right). Reject simulations inconsistent with **2013 TB notification data for a representative Southeast Asian setting, Vietnam** (WHO[1]).
- Among remaining data-consistent simulations, evaluate trends in TB and MDR-TB incidence and mortality, without and with improvements in MDR-TB diagnosis and treatment practices.

Results: TB and MDR-TB epidemic under continued current practice

Decline in total TB continues, but **MDR-TB increases (**as a % of all TB cases, and likely also in absolute incident MDR-TB cases).

Due to poor treatment availability and outcomes, the average MDR-TB case (2013):

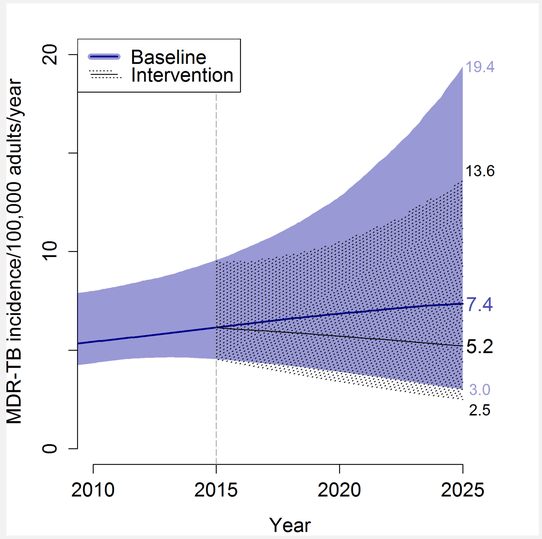
- Is **infectious** 1.9x (95% uncertainty range [UR] 1.5-2.6x) **longer** than a DS case
- Produces **2.6** (95% UR 1.1-5.5) **secondary cases** of active MDR-TB



Results: Projected impact of expanding MDR diagnosis and treatment

Primary modeled intervention:
Suppose we **diagnose all MDR-TB in previously-treated TB patients** (before retreating them), and **start MDR-appropriate treatment for at least 85% of them**, by 2017.
We'll conservatively assume continued use of current lengthy, toxic, insufficiently-effective MDR regimens, which cure only ~50% of patients.

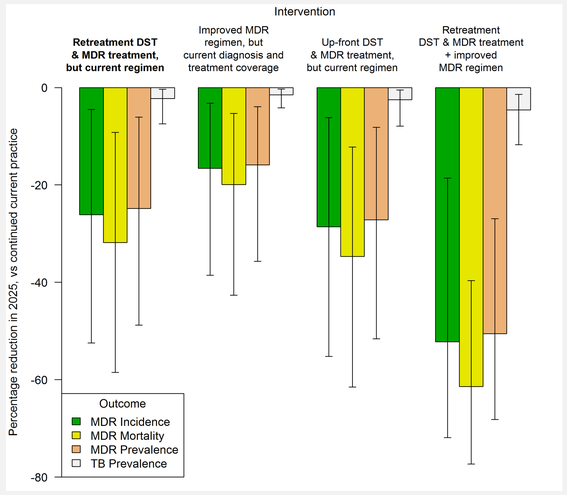
Primary result: 26% (95% UR 4-52%) reduction in MDR-TB incidence in 2025, relative to projected incidence under continued current practice



Results: Impacts of Alternative Interventions

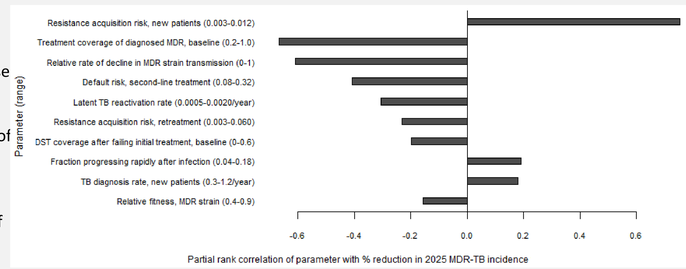
Up-front DST for all TB patients before initial treatment only **marginally improves impact**

A new, **potent, all-oral, short-course regimen** (assuming adherence, tolerability, and efficacy comparable to the current standard first-line regimen) has modest impact at current low treatment coverage, but **doubles the expected impact of expanded MDR diagnosis and treatment**



Results: Sensitivity analysis for individual model parameters

Improving these estimates' uncertainty would require more precise knowledge of the **transmission efficiency** (fitness) of MDR strains, of the balance of **primary TB vs latent reactivation**, and of MDR-TB treatment outcomes.



Conclusions

- **Testing all previous-treated TB patients** (~10% of all TB patients) for drug susceptibility, and **providing MDR therapy** to diagnosed MDR-TB cases (even with 15% initial loss to follow up and existing poor treatment success rates), **could prevent 1/4 of MDR-TB cases in 2025.**
- A **novel MDR-TB treatment regimen** as effective and tolerable as the current first-line regimen[3] could double these expected gains.
- **Limitations** of our estimates include wide parameter **uncertainty**, **assumed homogeneity** of individuals and MDR strains, and no explicit emergence and transmission of **second-line drug resistance**.[4]

References: 1. "Global Tuberculosis Report 2014" (World Health Organization, Geneva, 2014). 2. J. M. Trauer, J. T. Denholm, E. S. McBryde, Construction of a mathematical model for tuberculosis transmission in highly endemic regions of the Asia-Pacific. *J. Theor. Biol.* **358**, 74–84 (2014). 3. R. Tasneen *et al.*, Contribution of the Nitroimidazoles PA-824 and TBA-354 to the Activity of Novel Regimens in Murine Models of Tuberculosis. *Antimicrob. Agents Chemother.* **59**, 129–135 (2015). 4. J. P. Cegielski *et al.*, Extensive drug resistance acquired during treatment of multidrug-resistant tuberculosis. *Clin. Infect. Dis.* **59**, 1049–1063 (2014).

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