What has stopped MDR-TB sweeping to dominance? a fitness cost or protective latency effects?

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Contents

1 Abstract / Background / Introduction

Rough thoughts...

- MDR-TB is bad... how long around / treatment etc
- Prevalence of MDR-TB at 5
- Fitness cost detected in vitro, epidemiologically (clusters) and in situ (my Peru work). Perhaps this stops spread?
- OR Protective effect of DS-TB carriage. Immunity. Perhaps this stops it?
- Explored changing demography, latency assumptions and fitness cost levels
- Removed latency protection, allowing for coinfection or just remove? and compare levels of MDR-TB
- Also, explored impact of reduced DS-TB LTBI due to LTBI therapy - does this allow MDR to dominate?

2 Questions / Thoughts

- Should we include a fitness cost distribution? (as in my previous work). This would increase our predicted levels of MDR-TB. Could include by exploring a mean and variance combination. ut I don't think it helps to answer the theoretical question here
- Should we include strain immunity (Basu, 2008 work)?
- Should we include mixed infections to explore immnunity / interaction effects? started to build but many unknowns. Key thing is to capture that treatment of MDR-TB can happen at a higher rate than the stats on confirmed MDR-TB receiving treatment. Could include cross-immunity. As in not just vary protection from latency, but also let DS LTBI be less likely to become DR? kinda include this with the fitness cost to transmission...

3 Methods

3.1 Overview

3.2 Model

We built a deterministic transmission model using a standard natural history framework with two strains (DS-TB and MDR-TB). Uninfected, go to Latent, got to active disease. Treatment slightly different: track time on treatment, with fail / cure outcomes are end of each timestep. Previous treatment (any) is tracked in order to match statistics on levels of MDR-TB Fitness cost applied to transmission or progression Treatment of MDR-TB higher than just CDR as misdiagnosis / think they are DS-TB: reason for higher level of MDR in re-treatment. Use "case detection of TB"

3.3 Equations

There are 7 basic subpopulations, stratified by naive and previously treated (with subscript "p"). The natural history states are uninfected (U), latently infected with drug susceptible (L_S) or MDR-TB (L_R), active disease with drug susceptible (A_S) or MDR-TB (A_R). There are also two treatment states: on treatment and previously infected with DS-TB (T_S) or with MDR-TB (T_R). We assumed that the false positive rate for those uninfected with *M.tb.* was negligible (i.e. we did not have a previously treated uninfected sub-population).

We modelled the population as a discrete time, single age stratified population. People could be aged 0 - 100 (j). Those uninfected come from new births.

$$U[i,1] = b \tag{1}$$

where $b = birth_{rate} * p_{size}[i-1] * dt$, the product of the annual birth rate (from UN data), the population size in the previous time step ($p_{size}[i-1]$) and the timestep (dt).

The force of infection at time step i ($\lambda_S[i]$,$\lambda_R[i]$) for DS-TB or MDR-TB respectively is calculated as the rate of transmission (β) divided by the population size (p_size), multiplied by the number with active TB (naive and previously treated).

$$\lambda_S[i-1] = \frac{\beta}{p_{size}[i-1]} \sum_j p_i(A_S[i-1] + A_{Sp}[i-1]) \tag{2}$$

$$\lambda_R[i-1] = \frac{\beta}{p_{size}[i-1]} \sum_j p_i(A_R[i-1] + A_{Rp}[i-1]) \tag{3}$$

Those who are uninfected transition to carrying *M.tb.*. The background death rate is m which varies by age as determined by UN population data.

$$U[i,2:100] = U[i-1,1:99] - (m[1:99] + \lambda_S[i-1] + \lambda_R[i-1])U[i-1,1:99] \tag{4}$$

Those with latent *M.tb* infection can progress to active disease at a rate σ, or be reinfected. A proportion p of all those that are (re-)infected progress immediately to active TB disease. The protective effect of being latently infected is x.

$$
\begin{aligned}
L_S[i, 2:100] &= L_S[i-1, 1:99] + \lambda_S[i-1](1-p)(U[i-1, 1:99] + xL_R[i-1, 1:99]) \\
&\quad - (\sigma + m[1:99] + x(\lambda_S[i-1]p + \lambda_R[i-1]))L_S[i-1, 1:99] \\
L_R[i, 2:100] &= L_R[i-1, 1:99] \\
&\quad + \lambda_R[i-1](1-p)(U[i-1, 1:99] + xL_S[i-1, 1:99]) \\
&\quad - (\sigma + m[1:99] + x(\lambda_R[i-1]p + \lambda_S[i-1]))L_R[i-1, 1:99]
\end{aligned} \tag{5}
$$

Those with active TB disease can be detected and receive treatment at an aggregated rate $w_s[i], w_r[i]$ for DS-TB or MDR-TB respectively. There is a additional mortality rate for those with active TB (m_a) which is not age dependent.

$$
\begin{aligned}
A_R[i, 2:100] &= A_R[i-1, 1:99] + \lambda_R[i-1]p(U[i-1, 1:99] + x(L_S[i-1, 1:99] + L_R[i-1, 1:99])) \\
&\quad + \sigma L_R[i-1, 1:99] - (w_r[i-1] + m[1:99] + m_a)A_R[i-1, 1:99] \\
A_S[i, 2:100] &= A_S[i-1, 1:99] + \lambda_S[i-1]p(U[i-1, 1:99] + x(L_S[i-1, 1:99] + L_R[i-1, 1:99])) \\
&\quad + \sigma L_S[i-1, 1:99] - (w_s[i-1] + m[1:99] + m_a)A_S[i-1, 1:99]
\end{aligned} \tag{6}
$$

Those in the previously treated stratification transition through the treatment sub-populations, but otherwise have the same natural history dynamics. For those latently infected and previously treated the dynamics are:

$$
\begin{aligned}
L_{Sp}[i, 2:100] &= L_{Sp}[i-1, 1:99] + \lambda_S[i-1](1-p)(xL_{Rp}[i-1, 1:99]) \\
&\quad + new_L S_f rom_r x + new_L S_f rom_r x_p \\
&\quad - (\sigma + m[1:99] + x(\lambda_S[i-1]p + \lambda_R[i-1]))L_{Sp}[i-1, 1:99] \\
L_{Rp}[i, 2:100] &= L_{Rp}[i-1, 1:99] + \lambda_R[i-1](1-p)(xL_{Sp}[i-1, 1:99]) \\
&\quad + new_L R_f rom_r x + new_L R_f rom_r x_p \\
&\quad - (\sigma + m[1:99] + x(\lambda_R[i-1]p + \lambda_S[i-1]))L_{Rp}[i-1, 1:99]
\end{aligned} \tag{7}
$$