MODELING INTERVENTION STRATEGIES FOR UNITED STATES TB CONTROL

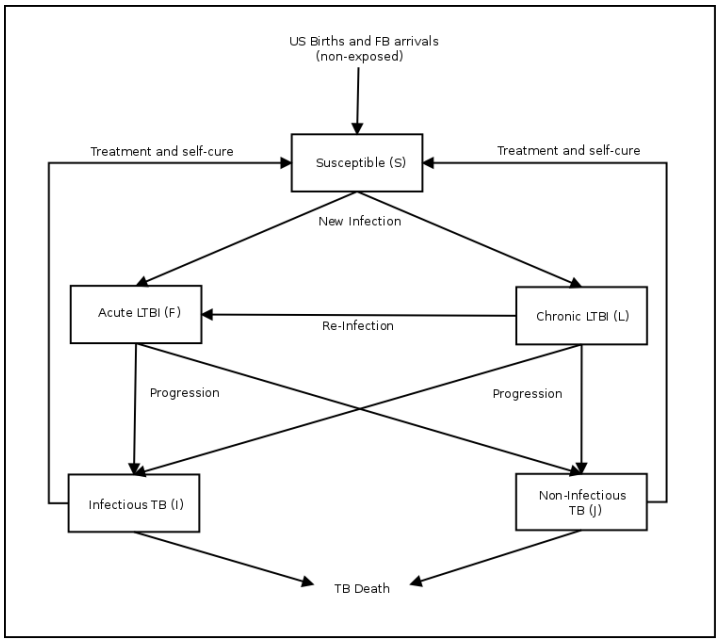
1. Introduction

Epidemiological models allow public health professionals to predict and analyze disease dynamics and intervention effectiveness. The most common examples of such models are compartmental differential equation models, in which the population is split between several possible health states, with flow between each state given according to deterministic differential equations. In 2012, Hill, Becerra, and Castro implemented a compartmental differential equaiton model of tuberculosis (TB) in the United States (US). Their model utilized five health states and two subpopulations, US-born (USB) and foreign-born (FB) for a total of 10 compartments. They used this model to evaluate several possible intervention strategies, and ultimately conclude that though increasing LTBI treatment was a good intervention strategy, the US was unlikely to meet their stated goal of elimination of TB in the US by 2100. In this work, the Hill model was extended in several key ways. First, additional tracking capabilities were added to the Hill model, such that it can now report further granularity in the disease dynamics. Further, economic components were added to the model in order to project the US health care system (HCS) costs due to TB given our current policy as well as for various interventions. Finally, a population level, agent based implementation of the Hill Model was created, in order to validate the Hill Model against the natural stochasticity present in real world disease spread.

2. Background

2.1. **The Hill Model.** A flowchart representation of the Hill Model is shown in Figure 1. Each compartment represents a different possible health state with respect to TB for every US-born or foreign-born individual, and arrows between different compartments represent possible transitions between states. Individuals also leave the model from all compartments due to natural death, which is left out of the figure for clarity.

The majority of USB and FB individuals fall into the Susceptible (S) category, which includes everyone who is uninfected and has not been exposed to TB. After exposure to an individual with TB, a person in the Susceptible compartment can develop Latent TB Infection (LTBI) and changes health states to either the Acute LTBI (F) or Chronic LTBI (L) compartment. Latently infected individuals are not infectious, but have some risk of developing active TB infection over time. However, the rates of disease progression are not equal, and individuals in the Acute LTBI compartment have a higher risk of developing active TB than those in the Chronic LTBI compartment. Individuals in the Chronic LTBI compartment may also be exogenously re-infected and transition to the Acute LTBI compartment.



Latently infected individuals may progress to one of two active TB states: Infectious TB (I) or Non-Infectious TB (J). Individuals in both compartments have an increased risk of death from active TB infection, but only individuals in the Infectious TB compartment are contagious. In addition, individuals in all of the infected compartments (F, L, I, J) may be treated or self-cure themselves of their respective TB health condition. However, in the model, treatment or self-cure from TB does not grant immunity, and all healthy individuals are grouped in the Susceptible compartment and may be re-infected at a later time.

3. Methods

3.1. **Basic Implementation.** Both the basic Hill Model and this extended Hill Model were implemented in `R` as a system of differential equations, which were solved via the `lsoda` routine. The systems of differential equations used in the Basic Hill Model and the extended Hill Model are shown below in Figure 2 and Figure 3 respectively.

The vector variables S_0, F_0, L_0, I_0, J_0 contain the number of US-born individuals in the S, F, L, I, J compartments respectively, and S_1, F_1, L_1, I_1, J_1 contain foreign-born individuals. N_0 and N_1 are the total populations of US-born and foreign-born individuals. The constants ρ and α are birth rates, while μ_i, and μ_d are death rates. A complete list and descriptions of all constants used in the model can be found in the appendix.

3.2. **Additional Tracking Capabilities.** In order to refine the tracking capabilities of the Hill Model, the original differential equations used to describe TB spread were separated into their component parts and each section was tracked separately. These components were made into compartments, tracked by differential equations

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\begin{aligned}
\dot{S}_0 &= \rho(N_0+N_1)+\sigma_0^F F_0+\sigma^L L_0+\varphi_0(I_0+J_0)-\lambda_0 S_0-\mu_0 S_0\\
\dot{F}_0 &= p\lambda_0 S_0+xp\lambda_0 L_0-(\mu_0+\nu^F+\sigma_0^F)F_0\\
\dot{L}_0 &= (1-p)\lambda_0 S_0-xp\lambda_0 L_0-(\mu_0+\nu_0^L+\sigma^L)L_0\\
\dot{I}_0 &= q(\nu^F F_0+\nu_0^L L_0)-(\mu_0+\mu^d+\varphi_0)I_0\\
\dot{J}_0 &= (1-q)(\nu^F F_0+\nu_0^L L_0)-(\mu_0+\mu^d+\varphi_0)J_0\\
\dot{S}_1 &= (1-f)\alpha(N_0+N_1)+\sigma_1^F F_1+\sigma^L L_1+\varphi_1(I_1+J_1)-\lambda_1 S_1-\mu_1 S_1\\
\dot{F}_1 &= gpf\alpha(N_0+N_1)+p\lambda_1 S_1+xp\lambda_1 L_1-(\mu_1+\nu^F+\sigma_1^F)F_1\\
\dot{L}_1 &= (1-gp)f\alpha(N_0+N_1)+(1-p)\lambda_1 S_1-xp\lambda_1 L_1-(\mu_1+\nu_1^L+\sigma^L)L_1\\
\dot{I}_1 &= q(\nu^F F_1+\nu_1^L L_1)-(\mu_1+\mu^d+\varphi_1)I_1\\
\dot{J}_1 &= (1-q)(\nu^F F_1+\nu_1^L L_1)-(\mu_1+\mu^d+\varphi_1)J_1
\end{aligned}
$$

EQUATION NUMBER SOMETHING TO SOMETHING, SORTED BY COMPARTMENT. In addition, estimations of the basic reproductive number of FB or USB active, infectious TB cases were made from a theoretical and an experimental perspective. Experimental data were calculated by reducing the initial population of FB or USB active, infectious TB cases by 1 and predicting the final number of cases seen in each case, in `R`.

3.3. **Economic Modeling.** Further, estimates for the cost of active TB treatment and for the cost of latent TB infection (LTBI) treatment were obtained from Dylan et. al. and So and So adherence effectivenss. CITE ME! Both these costs and any health state outcomes were discounted at a rate of 3% per year. From these estimated cost per treatment, total costs were obtained in the following way. It was assumed that every patient in the US with active TB is treated, not necessarily successfully, but further that every treatment costs exactly the average cost per treatment. Thus, active TB costs could be tracked simply by tracking the number of new active TB cases, and scaling by a discounted cost per treatment rate. Given the structure of the model, further granularity was obtained from the cost data by tracking separately the cost due to new cases that stemmed from activation of a chronic LTBI case, or activation of an acute LTBI case. These values give estimates for the US HCS TB cost due to exogenous infection of TB vs the US HCS TB cost due to activation of LTBI. Each of these components of the cost was a new differential equation tracked by the model, also solved by `lsoda`. For LTBI treatment cost, treatment was charged upon leaving the LTBI compartment due to the cumulative self-cure and treatment rate given in the Hill Model. The fraction of these indviduals who leave this compartment due to self cure was assumed to be zero. Given the uncertainty in measurments of LTBI treatment cost, extensive sensitivity analysis was performed on this parameter relative to final cost outcomes, which showed that it had an linear effect. In addition to US HCS cost, the system was implemented so as to also track projected intervention implementation cost, given user-inputted parameters relating to various possible intervention cost strategies. The extended Hill Model was used to track the effect of many interventions tested by the Hill Model as well as an additional intervention strategy of curing cases of immigrating LTBI prior to entry. This intervention strategy proved very promising and elimination year, final cost, and cost per case averted were tracked

for various levels of entering LTBI cure rate. The interventions were implemented so as to take effect during the year 2013 and run to 2100. The numerical DE solver `lsoda` used was run with a time step of 0.8. Sensitivity analysis was performed on this parameter and reducing the time step was shown to have minimal effect on final size or cost values.

3.4. **Agent Based.** The population level agent based model was implemented in several ways. Early implementations were built in `Netlogo` and `Java`, but final implementations were constructed in `C++`. An implementation was made that tracked the hill model exactly, up to still including the Acute Latent compartment in the model. Probabilites of agent progression between various health states were computed given rates in the hill model and a variety of approximations. The final size standard deviation and distribution data was collected via 2160 (MINUS SOME) runs with each agent in the model truly representing one individual and a time step of 0.01. These data were analyzed in *R*.

4. Results

4.1. **Basic Population Breakdown.** The additional tracking capabilities offered several key insights into US TB dynamics. Figure INSERT FIGURE HERE shows the yearly incidence of US TB, broken down into infection source. It can be seen that the majority of the US TB load is driven by activations of FB LTBI, followed by USB LTBI activations. This data further agrees with the conclusions drawn by Hill, Becerra, and Castro about the necessity of LTBI treatment in any valuable intervention strategy. Further, figure INSERT FIGURE HERE shows a similarly sourced plot, but analyzing the final US HCS costs due to TB. One can see that in this plot, roughly half of the US TB HCS costs are due to activations of LTBI. Note that both of these plots underestimate the impact LTBI activations play in the spread of TB, as every LTBI activation to infectious TB contributes not only to incidence and costs directly, but also indirectly by causing additional future cases, which is not captured in these graphs.

4.1.1. *Basic Reproduction Number.* The basic reproduction number of FB or USB cases of infectious TB was also estimated by this system. From a theoretical perspective, we can think of the total number of secondary infections over 100 years due to a FB or USB infectious TB case as describing a geometric series in a large population. Presuming there are no overlaps in infectious contacts, if a single case of infectious TB in either population infects p_f, p_u new cases in one year, respectively, then we can say that over the course of 100 years, the total number of cases infected will follow a geometric series. This analysis predicts that over 100 years, one USB infection will lead to 1.03 subsequent infections, whereas one FB infection will lead to .64 subsequent infections. These calculations are included in the appendix. Experimentally, these data were also analyzed, with results of 1.04 and .8, respectively.

4.2. **Intervention Analysis.** The primary interventions analyzed by the extended Hill were those that analyzed curing various percentages of entering LTBI cases. Four indicative percentages chosen were 20%, 35%, 50%, and 65%. Note that the hill model does not distinguish documented immigration from undocumented immigration, and as such estimates of entering LTBI cure rates higher than 65% become much more difficult to acheive.

4.3. **Agent Based Evaluation.**

4.4. **Sensitivity Analysis.**