MODELING INTERVENTION STRATEGIES FOR UNITED STATES TB CONTROL

List of results

1. Abstract

An epidemiological and economic model for tuberculosis in the United States was developed, extending a model developed in 2012 by the Centers for Disease Control and Prevention. Sensitivity analysis of this model reveals that the percentage of foreign-born immigrants with LTBI is a highly influential parameter. Various intervention strategies, particularly those that reduced LTBI among foreign-born arrivals, were evaluated, and cost per case averted estimates were found. Additionally, a population-level, stochastic, agent-based model was built. This model demonstrated the feasibility of using agent-based modeling in the context of minimal population heterogeneity and provided statistical characterization of the results of the compartmental model. The distributions of the final population sizes and incidence rates projected by the stochastic model were found to be approximately normal, with means centered at the results of compartmental model.

2. Introduction

Epidemiological models allow public health professionals to predict and analyze disease dynamics and intervention effectiveness. The most common examples of such models are detereministic, compartmental, differential equation models. In these models, the population is split between several possible health states, or compartments, and a system of differential equations governs population flow between the various compartments. In 2012, Hill, Becerra, and Castro implemented a compartmental differential equaiton model of tuberculosis (TB) in the United States (US). Their model characterized five health states across 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 concluded that though increasing LTBI treatment was an effective intervention strategy, the US was unlikely to meet their stated goal of elimination of TB in the US by 2100. Here, we present an extended Hill model with additional tracking capabilities, such that it can now report further granularity in the disease dynamics. Furthermore, this model also tracks economic data in order to project the US health care system (HCS) costs due to TB given our current policy as well as in the context of various interventions.

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Though compartmental, differential equation models are the most common strategy when modeling large-scale diseases at the population level, an alternative approach is to use an agent-based model. Agent based models provide a more nuanced view of disease spread as they provide a more biologically accurate modeling framework; however, they are often considered to be computationally infeasible at population level. In order to challenge this assumption of infeasibility and provide

statistical verification of the results of the compartmental model, we implemented a stochastic, agent-based model of US TB dynamics at the population level.

3. Background

3.1. **Tuberculosis.** Add background info about TB. Latent phase, etc. I think it makes sense to give it its own section. COLIN

3.2. **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.

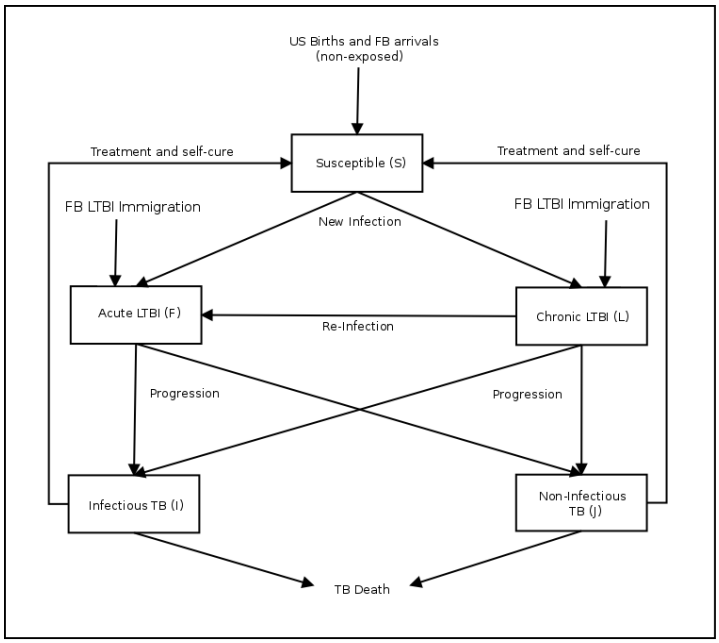

Figure 1. Schematic of the Hill Model.

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). Latently infected individuals are asymptomatic and non-infectious, but have some risk of developing active TB infection over time. To reflect the fact that real LTBI patients have a much higher risk of developing active TB within two years of exposure, the Hill Model splits the LTBI compartment into Acute LTBI (fast progressors) and Chronic LTBI (slow progressors). Accordingly, individuals in the Acute LTBI compartment have a higher risk

Make this not a figure. This should definitely just be tex.

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

FIGURE 2. System of Differential Equations given in the Hill Model.

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.

4. METHODS

4.1. **Basic Structure.** Both the Hill Model (Basic Hill Model) and our extended Model (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 to capture basic disease dynamics in the Basic Hill Model are shown in Figure 2. In the Extended Hill Model, each flow rate equation from the Basic Hill Model was separated into its component part and these were tracked separately. In other words, rather than tracking net flow into various compartments, the Extended Hill Model tracks flow between all pairs of compartments separately. Furthermore, these equations were each also supplemented to also estimate their corresponding US HCS costs. These equations are detailed in the

Add extended Hill equations to the appendix.

appendix, section 7.2. Historical data from 2000-2008 was used to initialize the model, which was then run up to the year 2100.

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, whereas S_1, F_1, L_1, I_1, J_1 contain the number of 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, Section 7.1.

4.2. **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 detailed in the appendix. Progressions into active TB due to activations of LTBI or exogenous infection were tracked, allowing for sourced incidence data to be generated. These equations allowed the model to track the sourced number of TB cases, TB deaths, and natural deaths. Furthermore, the model also tracks the sourced cost on the US HCS. The immigrating cases of LTBI (acute or chronic) were also tracked. In the case of intervention testing, the number of cured and untreated cases of entering LTBI were both tracked. Cured cases of LTBI entering, TB deaths, total TB cases, and total cost were also tracked discounted at 3% annually. This discounting was converted to a continuous differential equation for use within the model. In general, incidence data is calculated in the same way in the Extended Hill Model as it was in the Basic Hill Model.

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 FB or USB infectious TB populations by one and allowing the model to progress otherwise as normal. The decreased number of total TB cases seen details how many infections can be thought to be due to one infected individual in the given population. In the agent-based model, this *one* was a true model agent whereas in the compartmental model, this decrease of *one* was a proportional decrease based on the scaled population level.

From a theoretical perspective, the spread of TB was thought to be a geometric series. If one infectious individual infects x people annually, over the course of N years the total number of infections caused by this individual can be approximated by the geometric series of N terms with rate x and initial term 1. In this case, $N = 100$, and the ratios for FB infectious individuals and USB infectious individuals were obtained from ¡+RATIO CITATION COLIN+¿

4.3. **Economic Modeling.** In order to track the US HCS economic load given the TB rates, we made the following treatment cost assumptions. A single case of active TB was assumed to yield a $14,000 US HCS cost, charged immediately upon disease contraction. This cost is the weighted mean of the costs of cases requiring hospitalization (happening 49% of the time) and cases not requiring hospitalization (51%). These cost estimates were found in ¡+DYLAN COST STUDY CITATION+¿. LTBI treatment costs were given by $468.00 US HCS cost, charged immediately upon successful treatment. These estimates were calculated based on the cost of a successfull treatment, and the typical adherence and efficacy of said treatment ¡+DYLAN COST STUDY CITATION, ADHERENCE CITATION+¿. It is important to note that the charging assumptions are different for treatment of active TB as opposed to treatment of latent TB. In particular, cases of active

TB imply a cost immediately upon disease contraction, whereas latent TB costs are charged only upon successful treatment. The motivation for this distinction is that active TB treatment is mandated by the US for all known cases and, further, most treatment costs are incurred at the beginning of the treatment cycle. As such, charging for every known case, immediately at contraction is a well motivated assumption. On the other hand, latent TB is only rarely treated in discovered cases and the costs are more evenly distributed. Furthermore, the choice to charge only upon successful treatment yields a more conservative estimate of the success of any intervention analyzed.

Cost data were separately tracked due to incoming active TB costs stemming from activation of LTBI vs exogenous reinfection. These data were modelled as additional compartments and also solved by `lsoda`. Given the uncertainty in measurments of LTBI treatment cost, extensive sensitivity analysis was performed on this parameter relative to final cost outcomes. 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. In particular, the intervention strategy of curing entering cases of LTBI 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.

4.4. **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++`. Probabilites of agent progression between various health states were computed given rates in the hill model and a variety of integration approximations. The model maintained individual records for every individual with LTBI or active TB. Susceptible individuals were not modelled as agents; instead, a binomial distribution was used to probabilistically determine the number of new infections each time step. Similarlly, the number of new immigrants each time step was chosen from a probability distribution. We collected final population distribution data via ¡+NUMBER OF RUNS 2160+¿ runs with each agent in the model truly representing one infected individual and a time step of 0.01. These data were analyzed in R. This model was also made to track deaths, total TB cases, and infection sources, as well as economic data. These data were consistently normal and matched the deterministic model.

Further implementations of the `C++` model were made that deviated from the basic Hill Model. Specifically, the acute latent compartment in the basic Hill Model is a vestigal necessity of compartmental modeling and not reflective of the biology of tuberculosis. As such, an agent based model was implemented that more closely respects the biology of tuberculosis. Results from this model were also normal and did not differ significantly from the strict Hill model.

5. Results

5.1. **Basic Population Breakdown.** The additional tracking capabilities offered several key insights into US TB dynamics. Figure 3 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 effective intervention strategy. Further, figure 4 shows a similarly sourced plot, but analyzing the final US

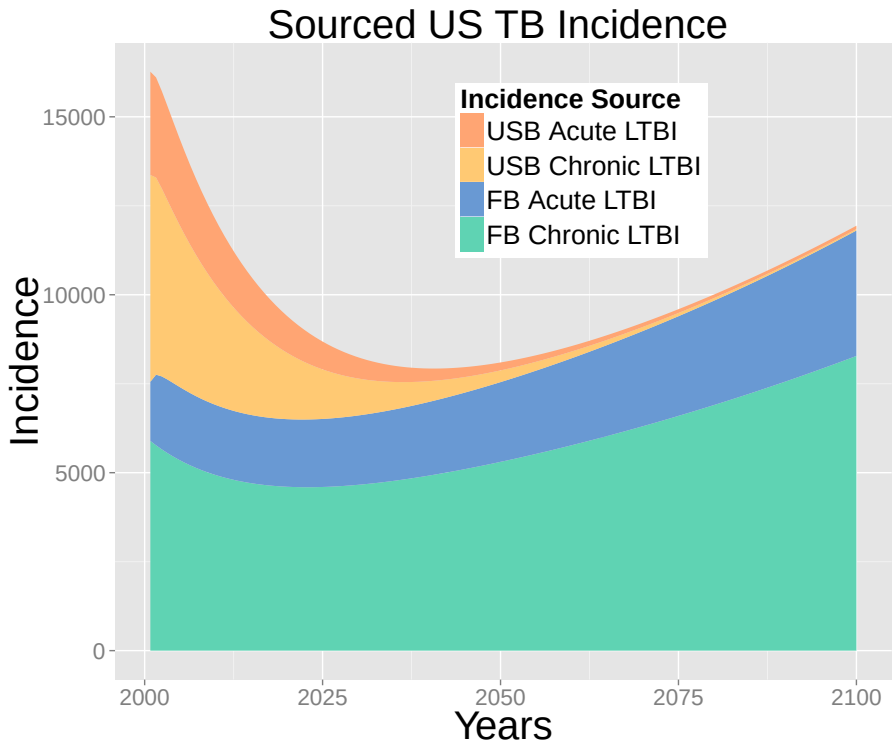

FIGURE 3. Sourced yearly incidence data generated by the extended Hill Model.

HCS costs due to active TB. One can see that in this plot, roughly half of the US TB HCS costs are due to activations of LTBI. Note that In this data, it is appropriate to think of the costs due to acute LTBI as costs due to exogenous re-inection, whereas active TB costs due to chronic LTBI are activations of long standing latent infections into active TB. 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. Further, there are also US HCS costs due to LTBI treatment, which is not illustrated in these graphs.

5.1.1. *Basic Reproduction Number.* The basic reproduction number of FB or USB cases of infectious TB was also estimated by this system. Using the best-fit values of parameters from the Hill model, we found the average number of secondary infections arising from a single case of infectious TB to be 0.423 and 0.370 for USB and FB populations respectively. These values differ because in the model,

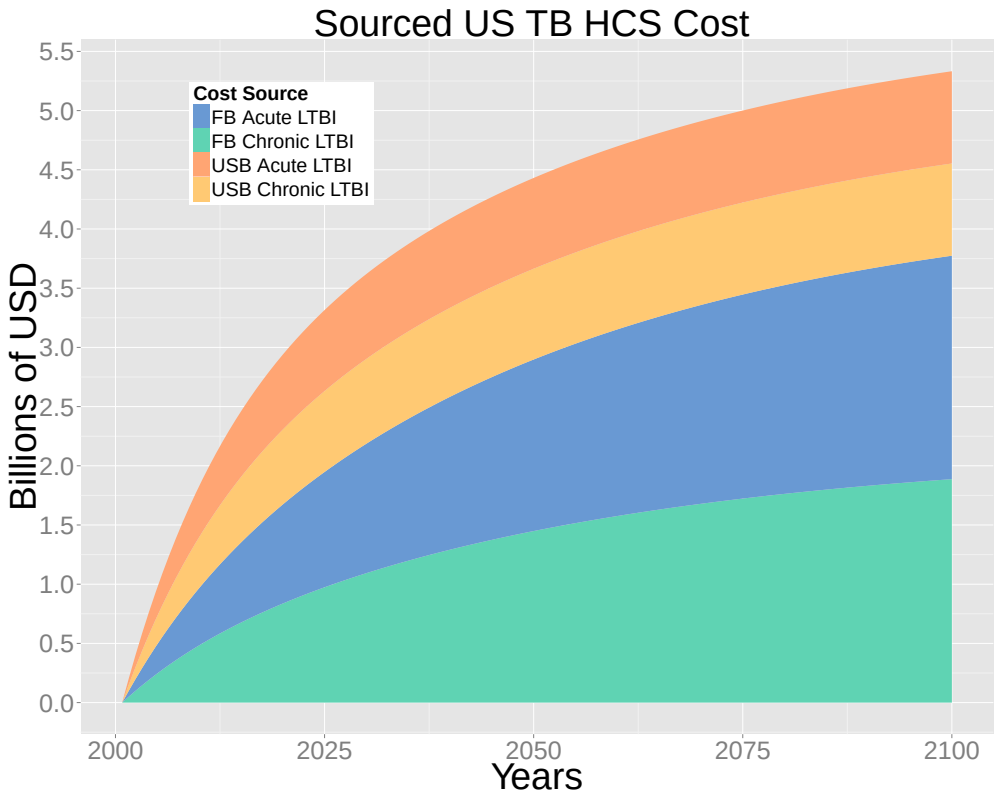

FIGURE 4. Sourced US HCS economic TB load. Note that this data only illustrates the load due to treating active TB, but illustrates where the infections driving this cost come from.

there are different estimates for death rates and the rate of TB treatment and self-cure in the USB and FB populations, so the average infectious period differs between the two populations. Extrapolating these results, 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, 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 1.04 subsequent infections, whereas one FB infection will lead to .83 subsequent infections. Experimentally, these data were also analyzed, with results of 1.03 and .64, respectively. Full calculations are included in the Appendix.

5.2. **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 5%, 10%, 25%, and 50%. Note that the Hill model does not distinguish documented immigration from undocumented immigration, and as such estimates of entering LTBI cure rates higher than 50% become

	red5	red10	red25	red50
2025	67908.81	67855.46	67654.07	67332.53
2050	28938.23	28878.70	28699.15	28404.13
2075	21044.88	20989.16	20820.53	20541.77
2100	18130.11	18076.11	17912.95	17642.64

TABLE 1. Cost Per Case Averted by Reducing Incoming LTBI by X percent (in dollar per case)

much more difficult to achieve. It was seen that in this model as well as in the basic Hill, no analyzed intervention predicted elimination by 2100. In order to obtain elimination by 2100, at least 95% of entering LTBI cases had to be cured, which is practically impossible. However, it was seen that curing entering cases of LTBI resulted in a net US HCS cost per case averted of $67,654.07 at 2025, $28,699.15 at 2050, and $17,912.95 at 2100 (assuming 25% reduction with each cure costing $800; see Table 1 for other percentages). Given the variable nature of LTBI treatment cost, the model code is extendible such that a user can adjust these costs themselves to explore more specific methods of curing entering LTBI. Further, it was also found that the relationship between total incidence at 2100 and percentage of incoming LTBI cases cured was linear, and from this estimates were made of the yearly average US HCS savings garnered by curing one case of entering LTBI over the time scale 2000 to 2025, 2000 to 2050, and 2000 to 2100. This value peaked at $1.283 billion at 2100 (25% reduction). This illustrates that it would be cost saving to cure cases of LTBI at the cost of $1.283 billion "2000" dollars over the time period 2000-2100. These intervention strategies also resulted in 11,900; 29,880; and 60,189 fewer cases of TB seen in the US, and 1,025; 2,573; and 5,185 fewer TB deaths, for 10%, 25%, and 50% reduction, respectively.

Several other intervention strategies analyzed by the Hill Model were refined with the Extended Hill, and economic properties about each of them were tracked. The results for these interventions, which are less effective than curing entering LTBI cases across the board, are given in the appendix.

5.3. **Sensitivity Analysis.** To account for uncertainty of input parameter values and to gain insight about the most influential parameters in the model, we used Latin Hypercube Sampling to analyze the deterministic model, implemented with the `lhs` package in `R`. We varied the 16 parameters from the original Hill model according to triangular distributions centered around their best-fit values, and two additional treatment cost parameters according to uniform distributions. We obtained similar results to the Hill model analyzing non-economic outcomes, as expected for validation. For economic outcomes, we found the parameter f, the fraction of FB arrivals with LTBI, to be highly correlated with the projected overall cost burden of TB in the United States over the next 100 years. Another highly influential parameter in the model was σ^L, the treatment rate for chronic LTBI. However, while increasing σ^L significantly decreases the cost burden due to Active TB treatment, it increases the cost burden due to Latent TB treatment by a greater amount, given the model estimates that Latent TB treament and Active TB treatment health care costs are approximately $700 and $14,000 per case cured

respectively. A full description of the Latin Hypercube Sampling analysis and tables of Partial Rank Correlation Coefficient (PRCC) results for all parameters are given in the Appendix, Section 7.6.

5.4. **Agent Based Evaluation.** The agent-based model allowed the statistical properties of the system to be analyzed and verified. In particular, it illustrated that the deterministic Hill model provides a robust and consistent statistical measure of TB epidemic behavior in the US conditions. We found that the distribution of incidence and final population sizes were normal, with mean accurate to the deterministic model and standard deviations given in table X, in the Appendix. Additionally, the agent-based model provided a computational framework to produce meaningful intervention results. On lab-grade, student hardware, a statistically meaningful experiment could be run overnight, producing data in a day. This demonstrates that this modeling strategy is feasible in this general case.

6. Discussion

These results confirm the hypothesis that curing incoming LTBI rates is a necessary step towards elimination and indicate that it is a cost effective option.
Where did we show it was cost effective relative to other interventions? Also, the section below (future work) might be better just directly included in the discussion. Also, if we want to make this claim here we need to include other interventions in the main body.
In addition, beyond demonstrating quantitatively that this intervention strategy is a necessary step towards US elimination, we also obtained qualitative indications that this is the case. In every intervention we tested (see, for example, Intervention ¡+ADD ME+¿ and ¡+ADD ME+¿ in section ¡+ADD ME+¿) we observed a plateauing effect, where the incidence per million stabilized after some time and resisted further change. In particular, even when transmission was reduced to 0%, we still observed this plateauing effect, which implies that something other than active transmission was generating enough incidence to sustain TB in an endemic state in the US population. However, when the FB LTBI immigration was cut, this effect vanished. These results therefore support the argument that the USB LTBI population is sufficiently large to sustain a sizable, endemic TB-disease state in the United States provided it is continually refueled via the entering LTBI immigrants. Thus, there is no intervention that can ignore the LTBI population that can hope to eliminate TB in the United States. Among those interventions that treat cases of LTBI, targeting the immigrating LTBI requires no additional US HCS dollars beyond what is spent now to identify the LTBI population and is therefore extremely efficient. Additionally, our analysis shows that paying for the treatment of these individuals is extremely cost effective TODO: Show this.

6.1. **Future Work.** This work could be extended by examining different classes of interventions or more accurately estimating intervention cost with the deterministic extended Hill. Further work could also be done with the agent-based Hill Model,

by using it to examine the effect contact structure plays on US TB incidence levels or to examine the effects drug-resistant TB will have on US TB dynamics.

7. Appendix

7.1. **Hill Constants.** Below, we detail some of the relevant constants in the Basic Hill Model, and their best-fit values. A full listing of constants used in the original Hill Model can be found in ¡+CITATION HERE+¿.
(USB = US born, FB = Foriegn born)

$\sigma^L = 0.057$	(Treatment rate for chronic LTBI)
$v_0^L = 0.0014$	(Progression rate for reactivation in the USB population)
$v_1^L = 0.0010$	(Progression rate for reactivation in the FB population)
$f = 0.187$	(Fraction of FB arrivals with LTBI)
$p = 0.103$	(Fraction of new infections which are acute)
$ARI_0 = 0.00030$	(2000 Annual Risk of Infection, USB)
$q = 0.708$	(Fraction of infections progressing to infectious disease)
$g = 0.0047$	(Fraction of FB arrivals with LTBI who are fast progressors)
$\sigma^F = 0.461$	(Cumulative fraction of treatment for acute infection)
$r_0 = 0.667$	(Fraction of cases due to reactivation in USB population)
$r_1 = 0.780$	(Fraction of cases due to reactivation in FB population)
$\mu^d = 0.115$	(Mortality rate due to TB)
$x = 0.111$	(Fraction of re-infected chronic LTBI moving to acute infection)
$\phi = 0.897$	(Cumulative fraction self-cure and treatment of active disease)
$e_0 = 0.965$	(Fraction of preferred contacts within own population for USB)
$e_1 = 0.985$	(Fraction of preferred contacts within own population for FB)

7.2. **The Extended Hill Equations.** Below, we detail some of the relevant equations used in the extended hill model. In many cases, the equations of the Hill model were split into their component parts, which could then be tracked separately.

TODO: What equations should be put in here?

Here, a continuous discounting approximation is used to a discount rate of 3% yearly, found via $discV$. In many of the differential equations, a small c is used to denote *cost of*.

7.3. **Estimations for Infectious Rates of FB and USB.**

7.4. **Statistical Qualities of the Agent Based Model.** Results for USB Incidence, FB Incidence, USB Population, and FB Population in the year 2100 shown, overlayed with linear (normal) fit are shown in figure 5. These plots demonstrate the normality of the Stochastic data.

7.5. **Finer Intervention Analysis.**

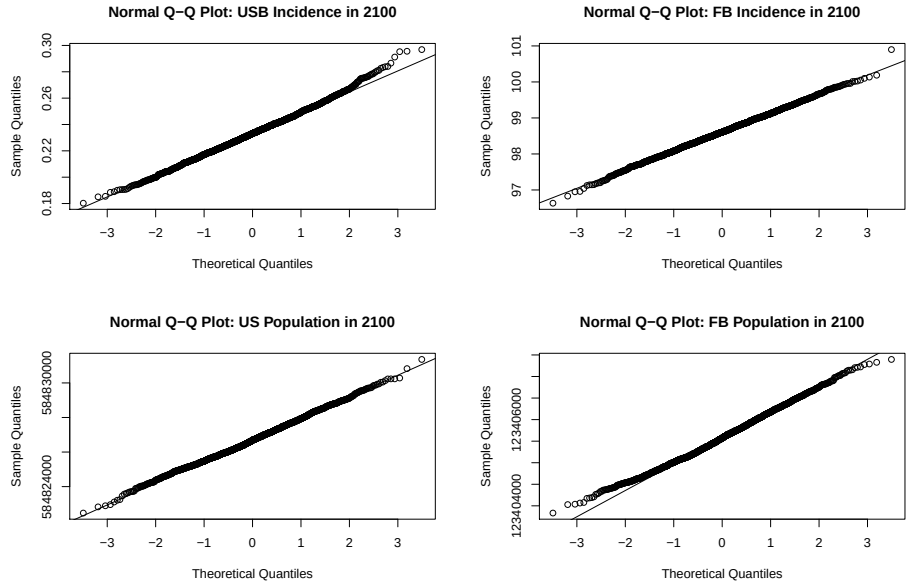

FIGURE 5. Normal Q-Q Plots for 2103 runs of the Stochastic Model with population constant = 1.

	red5	red10	red25	red50
2025	1115.12	2231.70	5592.43	11227.57
2050	3406.41	6821.27	17117.18	34447.71
2075	4976.77	9967.15	25021.33	50389.58
2100	5942.02	11900.90	29880.03	60189.49

TABLE 2. Cases of TB Averted by Reducing Incoming LTBI by various percentages (Cure=$800)

	red5	red10	red25	red50
2025	67908.81	67855.46	67654.07	67332.53
2050	28938.23	28878.70	28699.15	28404.13
2075	21044.88	20989.16	20820.53	20541.77
2100	18130.11	18076.11	17912.95	17642.64

TABLE 3. Cost Per Case Averted by Reducing Incoming LTBI by various percent (in dollars per case, Cure=$800)

7.6. **Latin Hypercube Sampling.** Following the example of the Hill model, we generated a Latin Hypercube Sample varying 18 of the input parameters. From these parameters, 16 are identical to the input parameters varied in the sensitivity analysis of the original Hill model, and the remaining two parameters, C_A and C_L, detailed below, are variables for the average cost of Active and Latent TB treatment in the US. Probability distributions for the original 16 parameters of the Hill model were all set to be Triangular, with mode at the best fit value and end

points at the 2.5 and 97.5 percentile values reported in the Hill model. Probability distributions for C_A and C_L were set to be Uniform, with range +/- 10% of the estimated value. All probabilty distributions used to generate the Latin Hypercube are listed in Table 1.

Additional Cost Parameters

$C_A = \$14,014.50$ (Cost per Active TB treatment)

$C_L = \$700$ (Cost per Latent TB treatment)

Parameter	Distribution
σ_L	Tri(0.015,0.057,0.086)
v_1^L	Tri(0.0009,0.0010,0.0014)
f	Tri(0.157,0.187,0.232)
p	Tri(0.053,0.103,0.137)
ARI_0	Tri(0.00021,0.00030,0.00030)
q	Tri(0.569,0.708,0.825)
g	Tri(0.0008,0.0047,0.0815)
σ_F	Tri(0.419,0.461,0.574)
r_1	Tri(0.759,0.780,0.831)
r_0	Tri(0.623,0.667,0.694)
μ^d	Tri(0.071,0.115,0.231)
x	Tri(0.088,0.111,0.860)
v_0^L	Tri(0.0011,0.0014,0.0015)
ϕ	Tri(0.861,0.897,0.938)
e_0	Tri(0.853,0.965,0.995)
e_1	Tri(0.877,0.985,0.999)
C_A	Uniform(12613,15416)
C_L	Uniform(630,770)

Table 1. Probability distributions for model parameters, where Tri(x,y,z) denotes the Triangular distribution with endpoints (x,z) and mode y.

With a random Latin Hypercube Sample of size n=100,000, we computed partial rank correlation coefficients (PRCC) for each of the initial parameters and treatment costs, according to four different outcomes: 1) projected annual incidence in 2100 in the overall population, 2) projected cumulative cost of Latent TB treatments by 2100, 3) projected cumulative cost of Active TB treatments by 2100, 4) projected cumulative total cost of TB treatments by 2100. For outcome 1, PRCC values are shown alongside PRCC values computed in the original Hill model for the same outcome in Table 2, showing the closeness of our findings to the sensitivity results of the original Hill model. PRCC values for the remaining outcomes are reported in Table 3.

Parameter	Extended Hill Model	Original Hill model
σ^L	-0.9303	-0.9381
v_1^L	0.7871	0.8309
f	0.7050	0.8072
p	0.8369	0.6100
ARI_0	0.5950	0.4939
q	0.5797	0.4543
g	0.6122	0.4517
σ^F	-0.4911	-0.3772
r_1	0.0028	-0.1109
r_0	0.0018	0.0760
μ^d	0.0923	0.0513
x	0.0999	0.0345
v_0^L	0.0133	0.0266
ϕ	0.0082	0.0177
e_0	0.0178	-0.0072
e_1	0.1154	0.0046
C_A	-0.0023	N/A
C_L	0.0009	N/A

Table 2. PRCC values for projected annual incidence in 2100 in the overall population, alongside corresponding values from the original Hill model.

From Table 2, we see that the PRCC values in the Extended Hill Model and the Original Hill Model match up reasonably well. In both cases, σ^L is the most influential parameter, with PRCC values around -0.93. The cost parameters C_A and C_L have PRCC values close to zero, which is expected because varying the treatment costs should not affect the incidence rate of TB. Parameters in the original Hill model with small PRCC magnitudes (less than 0.15) also have small PRCC values in the extended model, while parameters with larger PRCC magnitudes (greater than 0.35) similarly have large PRCC values in the extended model. This validates the non-economic components of our model against the original Hill model.

In Table 3, we see that the cost parameters C_A and C_L are highly correlated with Active treatment costs and Latent treatment costs respectively. These high PRCC values are expected because there is a linear relationship between C_A and the cumulative Active treatment cost, and similarly for C_L and the cumulative Latent treatment cost. In addition, we note that both C_A and C_L are influential in the total overall cost, with PRCC values of 0.6385 and 0.7598 respectively. Because the PRCC value for C_L is greater here, despite the fact that $C_A > C_L$, we can infer that cumulative Latent TB treatment costs are projected to be greater than cumulative Active TB costs with these estimates for cost parameters, so C_L is a more influential parameter for total cumulative treatment costs.

Other variables with significant PRCC magnitudes (greater than 0.5) in Table 3 include σ^L, v_1^L, f, p, ARI_0, q, g, and σ^F. Two of these parameters, σ^L and v_1^L, have relatively large PRCC magnitudes for both Latent and Active Costs, but

Parameter	Latent Costs	Active Costs	Total Costs
σ^L	0.9612	-0.9284	0.4169
v_1^L	-0.4190	0.6470	0.3533
f	0.7467	0.5493	0.8083
p	0.3371	0.8810	0.8776
ARI_0	0.3920	0.6728	0.7337
q	0.3837	0.6573	0.7200
g	0.1120	0.5369	0.5182
σ^F	-0.1138	-0.5631	-0.5435
r_1	0.1253	0.0658	0.1401
r_0	0.1325	0.0878	0.1658
μ_d	0.0249	0.0560	0.0613
x	0.0214	0.1282	0.1253
v_0^L	-0.3103	0.0502	-0.1867
ϕ	-0.0023	-0.0102	-0.0107
e_0	0.0081	0.0253	0.0269
e_1	0.0804	0.1653	0.1926
C_A	0.0011	0.7024	0.6385
C_L	0.8515	0.0013	0.7598

Table 3. PRCC values for cumulative US Health Care system costs from Latent TB treatment, Active TB treatment, and Total treatment costs

smaller PRCC magnitudes for Total Costs. Because their PRCC values for each of these two outcomes is different in sign, the net change to the total cost is partially cancelled out, so these parameters have a reduced influence on final US healthcare system costs. On the other hand, parameters such as f and p have large positive PRCC values for both Latent Costs and Active Costs, and we observe large positive PRCC values for Total Costs as well.

To gain insight about strategies to reduce the cost burden for TB in the US, we focus on the parameters with the greatest PRCC magnitudes for Total Cost aside from C_A and C_L, namely f, p, ARI_0, and q. All these parameters have PRCC magnitudes above 0.7, and are highly correlated with the total cost burden of TB borne by the US projected over the next 100 years. Out of these, ARI_0 is based on a historical fixed value, the Annual Risk of Infection among the US born population in the year 2000, and therefore is unchangeable under any intervention strategy. The parameters p (the fraction of new infections which are acute) and q (the fraction of infections progressing to infectious disease) are variables which depend on physiological disease dynamics, and may be altered with advances in medicine or mutations in the bacterial strains of TB. The parameter f is the fraction of FB arrivals with LTBI, which may vary depending on US immigration policies and medical practices. These results suggest that treating cases of LTBI among new FB arrivals may be the most cost efficient intervention strategy to reduce the disease burden for TB in the US, under the assumptions of the Hill model.