MODELING INTERVENTION STRATEGIES FOR UNITED STATES TB CONTROL

1. Abstract

An extended epidemiological model for Tuberculosis in the US was developed, based on an existing epidemiological model developed in 2012 by the Centers for Disease Control and Prevention. Economic parameters to track the cost burden of TB for the US health care system were added. The sensitivity of the extended model to changes in parameters was analyzed, and the percentage of foreign-born immigrants with LTBI appears to be a highly influential parameter in the model. Intervention strategies to reduce LTBI among foreign-born arrivals were evaluated, and estimates of the cost per case averted were found. Additionally, a population-level, stochastic, agent-based model was built to provide statistical verification of the results of the deterministic model and to demonstrate feasibility of agent-based modeling even on such large population scales.

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 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.

Though compartmental, differential equation models are the most common strategy when modeling large-scale diseases at the population level with minimal age stratification, 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 reasonable framework; however, they are often considered to be computationally infeasible at population level. In this work, a stochastic, agent-based model of US TB was implemented which was used at the population level to both provide statistical verification of the Hill Model and to demonstrate the computational feasibility of an agent-based modeling framework for general disease modeling.

3. Background

3.1. **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.

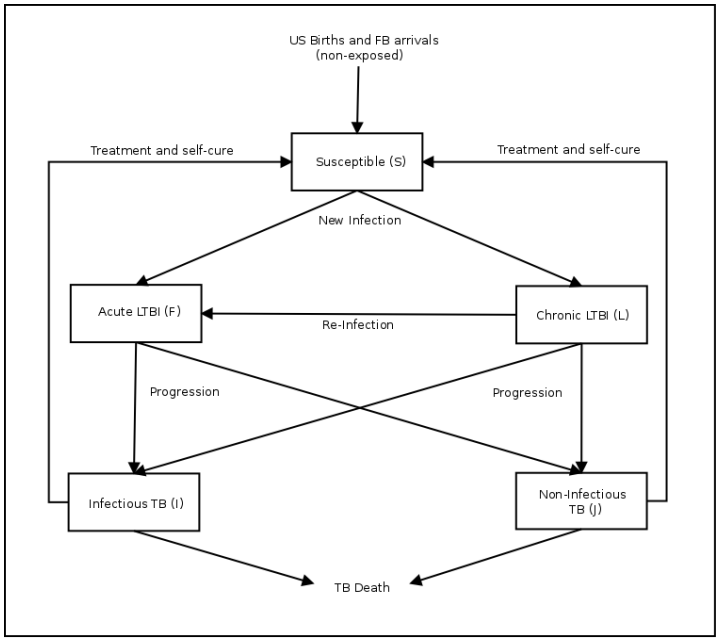

Figure 1. Schematic of the Hill Model.

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 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

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

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

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 an extended version of the Hill 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, more differential equations were implemented to add additional tracking and economic modeling. These equations are detailed in the 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 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. These equations allowed the model to track the total number of TB cases, TB deaths, and natural deaths. Further, the model tracks, the sourced cost on the US HCS. Progressions into active TB due to activations of LTBI or exogenous infection were tracked, allowing for sourced incidence data to be generated. The entering 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 population of FB or USB active, infectious TB cases 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.

From an experimental 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.** When tracking the economic implications of current US TB load and various intervention strategies, active TB costs were given by $14,000. 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 data were found in DYLAN COST STUDY CITATION. LTBI treatment costs were given by $468.00. These data were based on the cost of a successfull treatment, given by DYLAN COST STUDY CITATION, as well as adherence and efficacy data found in ADHERENCE CITATION.

From these estimated cost per treatment, total costs were obtained by assuming that every patient with active TB in the US is treated at full price, though the treatment may fail. As individuals with active TB are charged upon entry to the active TB compartment, the model can also accurately estimate sourced US HCS cost data. 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`. 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. 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++`. 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 model maintained scaled individual records for every individual with LTBI, with susceptible individuals not modelled as agents. Instead, a binomial distribution was used to probabilistically pick the number of new infections each time step. Similarlly, immigration was also handeled outside of the agent-based modelling. The final size standard deviation and distribution data was collected via 2160 (MINUS SOME) 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. This data were consistent with the deterministic model, and not reproduced in this write-up.

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, and an agent based model was implemented that more closely respects the biology of tuberculosis. Results from this model or the strict Hill model did not differ significantly.

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 valuable intervention strategy. Further, figure 4 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. In this data, it is appropriate to think of the costs due to acute LTBI are due to exogenous re-inection, whereas active TB costs due to chronic LTBI are activations of LTBI 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 is also US HCS costs due to treating LTBI, 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, 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

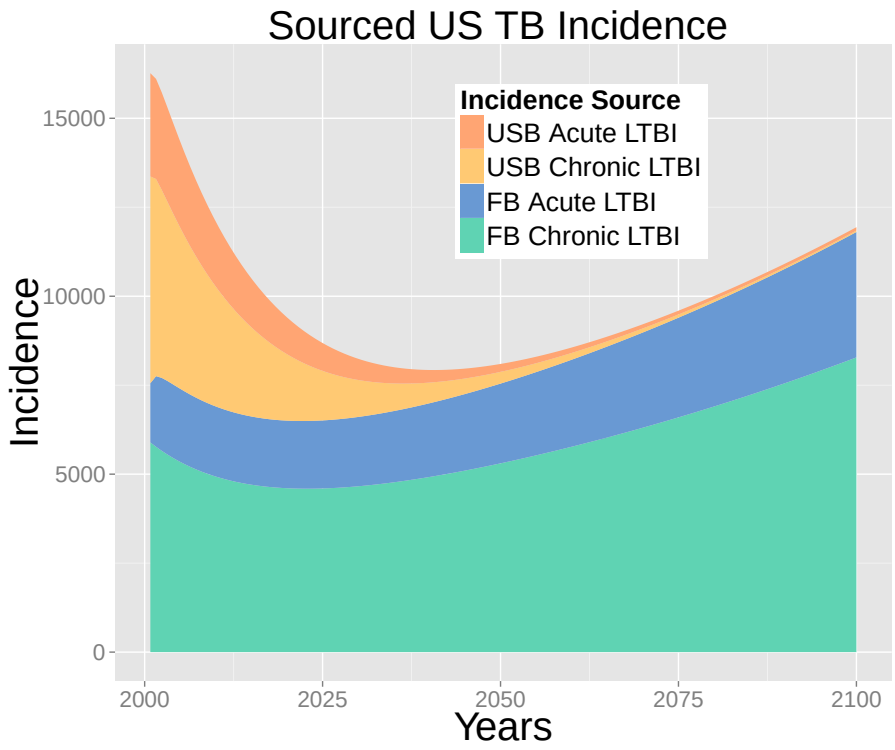

FIGURE 3. Sourced yearly incidence data generated by the extended Hill Model.

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 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;

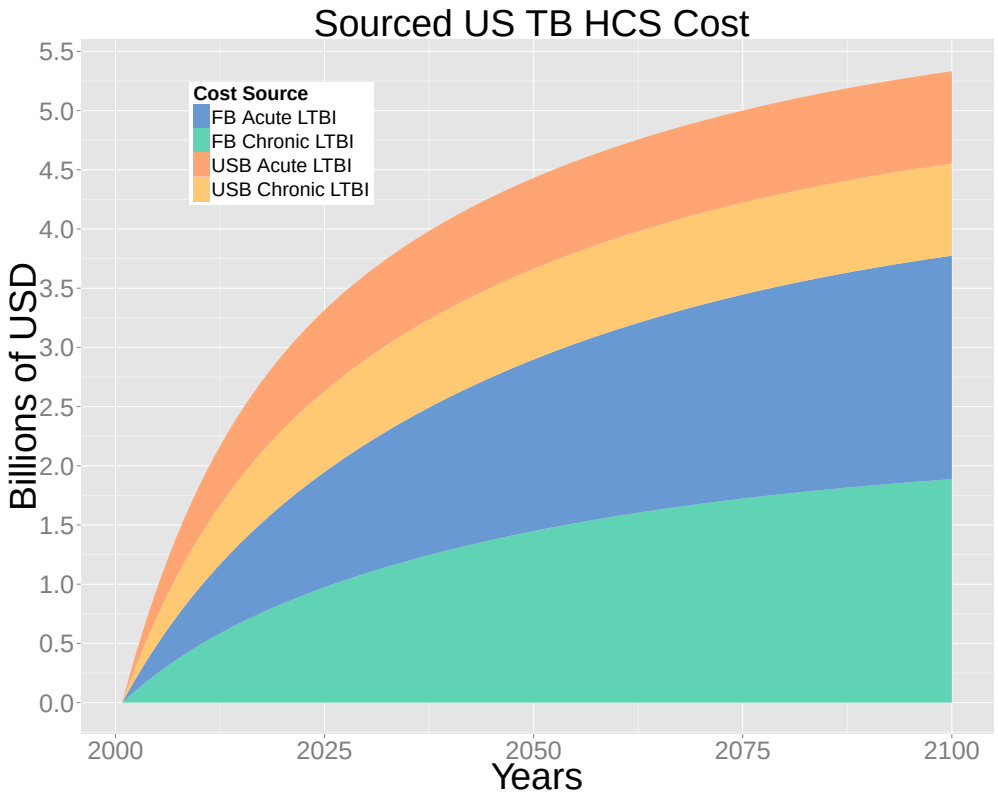

FIGURE 4. Sourced US HCS economic TB load. Note that this data only illustrates the load due to treating active TB, but illustrates where the infections driving this cost come from.

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.

	red5	red10	red25	red50
2000	ND	ND	ND	ND
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)

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

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¿

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

```
sigmaLBase  <- 0.057
fBase       <- 0.187
transBase   <- 1
incLTBIBase <- 1


#Treatment Effectiveness Data:
probHosp      <- .49 #Probability of hospitalization for active TB treatment
efficacyLTBI  <- .9  #LTBI treatement efficacy
adherenceLTBI <- .64 #LTBI treatment adherence
probLTBItreatsuccess <- efficacyLTBI*adherenceLTBI

#Cost Parameter Values:
costtb   <- 2985   #TB treatment cost w/o hopsitalization <- Dylan supp. p.11-12
costhosp <- 25495  #TB treatment cost w/ hospitalization  <- Dylan supp. p.10
costLTBI <- 403.45 #LTBI treatment cost
Ct       <- costtb*(1-probHosp) + costhosp*probHosp #Cost of active TB treatment
Cl       <- costLTBI/probLTBItreatsuccess           #Cost of LTBI treatment

parms <- c(
mu0   = 1/78,      #Natural mortality rate USB per year
mu1   = 1/53,      #Natural mortality rate FB per year
ro    = 0.018,     #USB birth rate per year
alpha = 0.005,     #FB arrival rate per year
p     = 0.103,     #Fraction of new infections which are acute (fast
progressors)
vF    = 1.5,       #Progression rate of acute infection per year
l0    = 0.015,     #Prevalence of LTBI in the USB population in 2000
l1    = 0.211,     #Prevalence of LTBI in the FB population in 2000:
r0    = 0.667,     #Fraction of cases due to reactivation in the USB population
r1    = 0.780,     #Fraction of cases due to reactivation in the FB population
vL0   = 0.0014,    #Progression rate for reactivation (chronic LTBI) in the USB
population per year
vL1   = 0.0010,    #Progression rate for reactivation (chronic LTBI) in the FB
population per year
q     = 0.708,     #Fraction of infections progressing to infectious disease
mud   = 0.115,     #Mortality rate due to TB per year
x     = 0.111,     #Fraction of re-infected chronic LTBI moving to acute
infection
ARI0  = 0.030/100, #Annual risk of infection for USB in 2000
beta  = 10.39,     #Effective contact rate per year
e0    = 0.965,     #Fraction of preferred contacts with own population for USB
e1    = 0.985,     #Fraction of preferred contacts with own population for FB
g     = 0.0047,    #Fraction of FB arrivals with LTBI who are fast progressors
phi0  = 1.114,     #Cumulative fraction self-cure and treatment of active
disease for both populations pre year RATES (USB)
phi1  = 1.167,     #Cumulative fraction self-cure and treatment of active
disease for both populations pre year RATES (FB)
sigmaF0 = 1.296,   #Cumulative fraction of treatment for acute infection for
both populations per year RATES (USB)
sigmaF1 = 1.301,   #Cumulative fraction of treatment for acute infection for
both populations per year RATES (FB)
sigmaLBase = sigmaLBase, #Treatment rate for chronic LTBI per year
fBase = fBase,      #Fraction of FB arrivals with LTBI

#2010 New Cases in Population i (millions)
#source: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5105a3.htm
newCases0 = .008714,  #US-born
newCases1 = .007554,  #Foreign-born

CtBase = Ct,
ClBase = Cl
)
```

FIGURE 5. A list of relevant constants in the Basic & Extended Hill Model

```
discV   <- 1/(1.03^t)  #amount costs, health states discount constant

#parameter values initialized for each time step
c01          <- (1-e0)*((1-e1)*N1)/((1-e0)*N0 + (1-e1)*N1)       #proportion of contacts made with FB individuals  (USB)
c00          <- 1 - c01                                          #proportion of contacts made with USB individuals (USB)
c10          <- (1-e1)*((1-e0)*N0)/((1-e0)*N0 + (1-e1)*N1)       #proportion of contacts made with USB individuals (FB)
c11          <- 1 - c10                                          #proportion of contacts made with FB individuals  (FB)
dLTBIEn      <- f*alpha*(N0+N1)                                  #FB arrivals with LTBI entering
dnatdeath0   <- mu0 * N0                                         #Natural deaths (USB)
dnatdeath1   <- mu1 * N1                                         #Natural deaths (FB)
dtbdeath0    <- mud * (I0 + J0)                                  #TB deaths (USB)
dtbdeath1    <- mud * (I1 + J1)                                  #TB deaths (FB)
dtbdeathD0   <- discV * dtbdeath0                                #TB deaths with discounting (USB)
dtbdeathD1   <- discV * dtbdeath1                                #TB deaths with discounting (FB)
dprogAcute0  <- vF*F0                                            #Acute LTBI progressions to Active TB disease (USB)
dprogAcute1  <- vF*F1                                            #Acute LTBI progressions to Active TB disease (FB)
dprogChron0  <- vL0*L0                                           #Chronic LTBI progressions to Active TB disease (USB)
dprogChron1  <- vL1*L1                                           #Chronic LTBI progressions to Active TB disease (FB)
dprogTotal0  <- dprogAcute0 + dprogChron0                        #Progression to Active TB (USB)
dprogTotal1  <- dprogAcute1 + dprogChron1                        #Progression to Active TB (FB)
dprogTotalD0 <- discV * dprogTotal0                              #Progression to Active TB with discounting (USB)
dprogTotalD1 <- discV * dprogTotal1                              #Progression to Active TB with discounting (FB)
lambda0      <- transmission*(beta*(c00*(I0/N0) + c01*(I1/N1)))  #Forces of Infection (USB)
lambda1      <- transmission*(beta*(c10*(I0/N0) + c11*(I1/N1)))  #Forces of Infection (FB)
dexogenous0  <- x*p*lambda0*L0                                   #Exogenous re-infections of Chronic LTBI to Acute LTBI (USB)
dexogenous1  <- x*p*lambda1*L1                                   #Exogenous re-infections of Chronic LTBI to Acute LTBI (FB)
dInterventionCost <- discV * (iCnewCases*1e6*(dprogTotal0+dprogTotal1) + iCtotPop*1e6*(N0+N1) + iCLTBIEn*1e6*dLTBIEn*(1-incLTBI))

#Difference Equations (USB)
dS0 <- ro*(N0+N1) + sigmaF0*F0 + sigmaL*L0 + phi0*(I0+J0) - lambda0*S0 - mu0*S0
dF0 <- p*lambda0*S0 + dexogenous0 - (mu0 + vF + sigmaF0)*F0
dL0 <- (1-p)*lambda0*S0 - dexogenous0 - (mu0 + vL0 + sigmaL)*L0
dI0 <- q*(dprogAcute0 + dprogChron0) - (mu0 + mud + phi0)*I0
dJ0 <- (1-q)*(dprogAcute0 + dprogChron0) - (mu0 + mud + phi0)*J0

#Difference Equations (FB)
dS1 <- (1-incLTBI)*dLTBIEn+(1-f)*alpha*(N0+N1) + sigmaF1*F1 + sigmaL*L1 + phi1*(I1 + J1) - lambda1*S1 - mu1*S1
dF1 <- g*p*dLTBIEn*incLTBI + p*lambda1*S1 + dexogenous1 - (mu1 + vF + sigmaF1)*F1
dL1 <- (1-g*p)*dLTBIEn*incLTBI + (1-p)*lambda1*S1 - dexogenous1 - (mu1 + vL1 +sigmaL)*L1
dI1 <- q*(dprogAcute1 + dprogChron1) - (mu1 + mud + phi1)*I1
dJ1 <- (1-q)*(dprogAcute1 + dprogChron1) - (mu1 + mud + phi1)*J1

dN0 <- dS0 + dF0 + dL0 + dI0 + dJ0
dN1 <- dS1 + dF1 + dL1 + dI1 + dJ1

#Cost calculations
dcL0 <- discV * Cl * sigmaL  * 1e6 * L0                   #cost for Chronic LTBI cures      (USB)
dcF0 <- discV * Cl * sigmaF0 * 1e6 * F0                   #cost for Acute LTBI cures        (USB)
dcI0 <- discV * Ct * q*(dprogAcute0 + dprogChron0) * 1e6     #cost for Infectious TB cures     (USB)
dcJ0 <- discV * Ct * (1-q)*(dprogAcute0 + dprogChron0) * 1e6 #cost for Non-Infectious TB cures (USB)
dcI0dL0 <- discV * Ct * q*(dprogChron0) * 1e6     #cost for Infectious TB cures     (USB)
dcI0dF0 <- discV * Ct * q*(dprogChron0) * 1e6     #cost for Infectious TB cures     (USB)
dcJ0dL0 <- discV * Ct * (1-q)*(dprogAcute0) * 1e6 #cost for Non-Infectious TB cures (USB)
dcJ0dF0 <- discV * Ct * (1-q)*(dprogAcute0) * 1e6 #cost for Non-Infectious TB cures (USB)
dcL1 <- discV * Cl * sigmaL  * 1e6 * L1                   #cost for Chronic LTBI cures      (FB)
dcF1 <- discV * Cl * sigmaF1 * 1e6 * F1                   #cost for Acute LTBI cures        (FB)
dcI1 <- discV * Ct * q*(dprogAcute1 + dprogChron1) * 1e6     #cost for Infectious TB cures     (FB)
dcJ1 <- discV * Ct * (1-q)*(dprogAcute1 + dprogChron1) * 1e6 #cost for Non-Infectious TB cures (FB)
dcI1dL1 <- discV * Ct * q*(dprogChron1) * 1e6     #cost for Infectious TB cures     (USB)
dcI1dF1 <- discV * Ct * q*(dprogChron1) * 1e6     #cost for Infectious TB cures     (USB)
dcJ1dL1 <- discV * Ct * (1-q)*(dprogAcute1) * 1e6 #cost for Non-Infectious TB cures (USB)
dcJ1dF1 <- discV * Ct * (1-q)*(dprogAcute1) * 1e6 #cost for Non-Infectious TB cures (USB)
dcN0 <- dcF0 + dcL0 + dcI0 + dcJ0                          #Total cost for all treatments (USB)
dcN1 <- dcF1 + dcL1 + dcI1 + dcJ1                          #Total cost for all treatments (FB)
```

FIGURE 6. The equations defining the Extended Hill Model, shown in `R` syntax. In this model, compartments share the same names as they did in the Hill Model, *i.e.* `S1` is the Foreign Born susceptible population.

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 7. These plots demonstrate the normality of the Stocahstic Data.

7.5. **Finer Intervention Analysis.**

7.6. **Latin Hypercube Sampling.** The model parameters and variable names referred to in this analysis are listed below, along with best-fit or estimated values. 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, are variables for the average cost of Active and Latent TB treatment in the US. Probability distributions for the

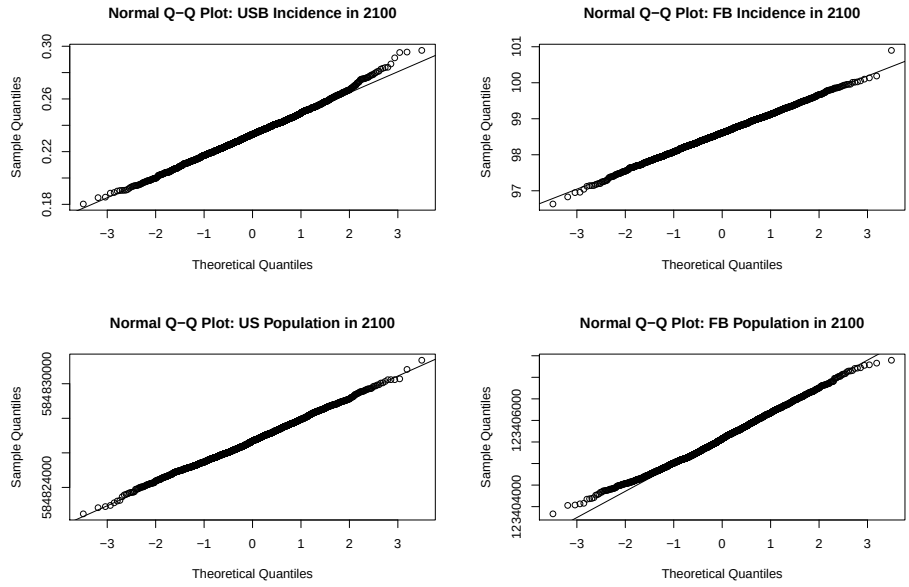

FIGURE 7. Normal Q-Q Plots for 2103 runs of the Stochastic Model with population constant = 1.

	red5	red10	red25	red50
2000	0.00	0.00	0.00	0.00
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 X percent (Cure=$800)

	red5	red10	red25	red50
2000	ND	ND	ND	ND
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 X percent (in dollar per case, Cure=$800)

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.

Original Hill Model Parameters (USB = US born, FB = Foriegn born)

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

Additional Cost Parameters

1. C_A = $14,014.50 (Cost per Active TB treatment)
2. C_L = $700 (Cost per Latent TB treatment)

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

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.

reported in Table 3.

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.

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.

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 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

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

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.