Re-evaluating the transmission of the U.S. tuberculosis epidemic

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1 Introduction

Tuberculosis (TB) is one of the deadliest diseases in the world, with estimated eight million new cases and three million deaths from TB each year. However, the disparity of TB epidemics in developed and developing worlds has been observed long time back. In developed countries, major TB epidemics peaked and declined long before the treatment therapy for TB came out in the late 1940s. Several hypotheses have been proposed to explain this phenomenon, including those about the improvement in the living standard, the segregation of infectious cases in sanatoria or workhouse infirmaries, the attenuation of M. tuberculosis's virulence, or the increased host resistance.

To explain the sudden rise and the following dramatic decrease of major epidemics in developed counties, in 1995, Blower et al. (Blower et al., 1995) proposed a mathematical model of the intrinsic transmission dynamics of M. tuberculosis. In this report, I shall employed Blower's model to re-evaluate the usefulness of model as well as the transmission of TB in the U.S. after 27 years.

2 Methods

2.1 Data

Data of TB incidence in the U.S. from 1953 to 2020 were retrieved from the Centers for Disease Control and Prevention (CDC)

2.2 Model Description

The model consists of ordinary differential equations that represent the natural development of TB epidemics. Individuals are classified into five mutually exclusive epidemiological states: susceptible (S), latently infected (L), infectious TB (Ti), noninfectious TB (Tn), and recovered (R).

Individuals are assumed to develop disease by one of three mechanisms:

(1) progressive primary (active disease develops short after latency period),

(2) endogenous reactivation (disease develops after many years of dormant infection),

(3) exogenous reinfection (relapse after recovery from the disease)

The model captures key biological features of TB with three additional assumptions:

(1) only a certain proportion of cases are infectious,

(2) a case can be naturally cured and move to recovered compartment,

(3) a recovered individual may either relapse and develop TB or never relapse and die of any other causes.

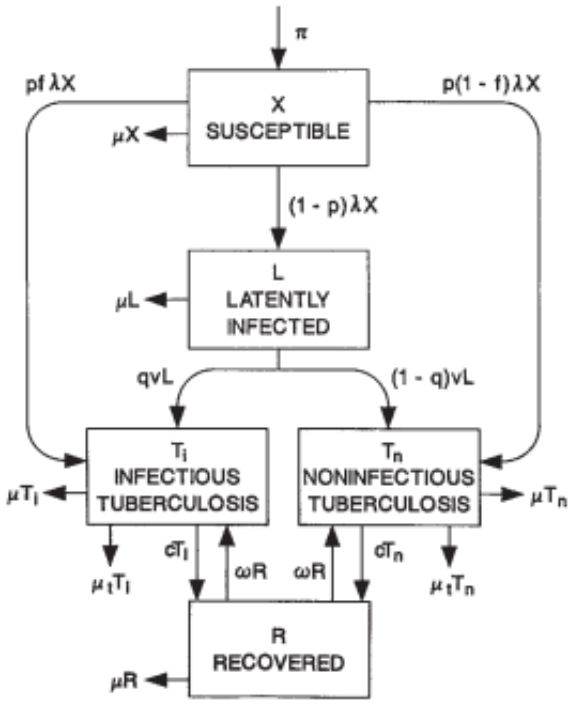

Figure 1: Compartment model of tuberculosis transmission (Reused from (Blower et al., 1995)).

Consequently, three types of TB are modeled: progressive primary TB, reactivation TB, relapse TB (hereafter referred as fast TB, slow TB, and relapse TB respectively).

The model also includes the dynamics of population. The birth rate and immigration rate are combined in recruitment rate Π. The disease-induced mortality rate is given by μ_T, and the mortality death rate from all other causes is μ.

A flow diagram of the model is provided in Figure 1, a detailed list of parameters is presented in Table 1, and initial conditions are given in Table 2.

Specification of differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \beta T_i S - \mu S \\
\frac{dL}{dt} &= (1-p)\beta T_i S - vL - \mu L \\
\frac{dT_i}{dt} &= pf\beta T_i S + qvL + \omega R - (\mu + \mu_T + c)T_i \\
\frac{dT_n}{dt} &= p(1-f)\beta T_i S + (1-q)vL + -(\mu + \mu_T + c)T_n \\
\frac{dR}{dt} &= c(T_i + T_n) - (2\omega + \mu)R
\end{aligned}$$

Data show a clear trend in TB incidence. In addition, with medical interventions introduced, it is reasonable to assume that the transmission rate and case-fatality rate decline over time. Therefore, I will consider 2 models:

- **Model 1**: Constant transmission rate β and case-fatality rate μ_T.
- **Model 2**: Time-dependent transmission rate $\beta(t)$ and case-fatality rate $\mu_T(t)$. $\beta(t)$ is assumed to follow a hyperbolic decline, and $\mu_T(t)$ to follow an harmonic decline.

$$\beta(t) = \frac{\beta_0}{(1 + bD_b t)^{\frac{1}{b}}}$$

$$\mu_T(t) = \frac{\mu_{T0}}{1 + D_m t}$$

Symbol	Biological Interpretation	Units	Prior Distribution	Note	Model 1 Est. (95% CrI)	Model 2 Est. (95% CrI)
$(\beta\Pi)/\mu$	Average number of infections caused by one case	/year	Triangular(0, 13, 7)		0.6370 (0.4484, 0.9633)	-
$(\beta_0\Pi)/\mu$	Baseline average number of infections caused by one case	/year	Triangular(0, 13, 7)		-	9.7356 (6.6853, 12.4480)
$1/\mu$	Average life expectancy	years	Uniform(60, 80)	Assumed based on U.S. life expectancy during study period	63.7189 (60.0867, 74.4922)	62.6033 (60.0784, 69.6758)
β	Transmission rate	/person/year		Derived from estimate of $(\beta\Pi)/\mu$	3.33e-9 (2.32e-9, 5.07e-9)	-
β_0	Baseline transmission rate	/person/year		Derived from estimate of $(\beta_0\Pi)/\mu$.	-	5.18e-8 (3.60e-8, 6.71e-8)
Π	Recruitment rate	people/year	3,000,000	Fixed by estimation of the US population growth	-	-
p	Proportion of new infections that develop TB within a year		Triangular(0, 0.05, 0.30)	See (Blower et al., 1995)	0.2263 (0.1354, 0.2885)	0.2685 (0.2230, 0.2951)
v	Progression rate to TB	/person/year	Uniform(0.00256, 0.00527)	Corresponds to a range of 5-10% progression in 20 years. See (Blower et al., 1995)	0.0035 (0.0026, 0.0051)	0.0034 (0.0026, 0.0051)
f	Probability of developing infectious TB (if one develops fast TB)		Triangular(0.50, 0.85, 0.70)	See (Blower et al., 1995)	0.5895 (0.5110, 0.7310)	0.6616 (0.5387, 0.7925)
q	Probability of developing infectious TB (if one develops slow TB)		Triangular(0.50, 1.00, 0.85)	See (Blower et al., 1995)	0.7096 (0.5326, 0.9208)	0.7671 (0.5504, 0.9394)
μ_T	TB case-fatality rate	/person/year	0.015	Fixed by estimation from U.S. data	-	-
μ_{T0}	Baseline case-fatality rate	/person/year	0.015	Assume μ_T follows exponential decline	-	-
2ω	Rate of relapse to active TB	/person/year	Triangular(0, 0.03, 0.01)	See (Blower et al., 1995)	0.0258 (0.0184, 0.0294)	0.0008 (0.0002, 0.0024)
c	Cure rate	/person/year	Triangular(0.021, 0.086, 0.058)	See (Blower et al., 1995)	0.0725 (0.0534, 0.0841)	0.0454 (0.0290, 0.0673)
D_m	Decline rate of μ_T		TruncatedNormal(0.5, 2, 1e-4, 10)	Noninformative prior	-	1.6247 (0.1565, 4.7861)
D_b	Decline rate of β		TruncatedNormal(0.5, 2, 1e-4, 10)	Noninformative prior	-	1.0507 (0.5930, 1.6367)
b	Constant in β's decline function		Uniform(0, 1)	Noninformative prior	-	0.8487 (0.7038, 0.9875)
ϕ^-	1/Scale parameter in Negative Binomial Distribution		TruncatedExponential(5, 0, 1e5)	Noninformative prior	1.0603 (0.7670, 1.4586)	0.0169 (0.0121, 0.0252)

Table 1: Model parameter specification and estimates

Symbol	Biological Interpretation	Value	Note
N	Population size	160,000,000	
S	Susceptible individuals	159494176	
L	Latently infected individuals	210760	Assume the number of latent TB cases is 2.5 times of that of active TB cases
T_i	Infectious TB cases	59013	Assume 70% of active TB cases are infectious
T_n	Non-infectious TB cases	25291	Assume 30% of active TB cases are noninfectious
R	Recovered individuals	210760	Assume the number of latent TB cases is 2.5 times of that of active TB cases

Table 2: Initial conditions

For likelihood, I specify:

$$y_i \sim NegativeBinominal(T_t, \phi)$$

where $T_t = T_i + T_n$, and $\phi = \frac{1}{\phi^-}$

Reproduction number R_t is given by:

$$R_t = R_t^{FAST} + R_t^{SLOW} + R_t^{RELAPSE}$$

where:

$$R_t^{FAST} = \left(\frac{\beta\Pi}{\mu}\right)\left(\frac{1}{\mu+\mu_T+c}\right)pf$$

$$R_t^{SLOW} = \left(\frac{\beta\Pi}{\mu}\right)\left(\frac{1}{\mu+\mu_T+c}\right)\left(\frac{q(1-p)v}{v+\mu}\right)$$

$$R_t^{RELAPSE} = \left(\frac{\beta\Pi}{\mu}\right)\left(\frac{1}{(\mu+\mu_T+c)^2-2\omega c/(2\omega+\mu)}\right)\left(p+\frac{(1-p)v}{v+\mu}\right)\left(\frac{\omega c}{2\omega+\mu}\right)$$

2.3 Model Estimation

Models are estimated using No-U-Turn Sampler (NUTS) sampler, with acceptance ratio 0.65. I run a model with 6 MCMC chains, with 3000 iterations each chains, and first 1000 warm-up iterations are discarded.

3 Results and Discussion

3.1 Model fitting

Parameter estimates are provided in the last two columns of Table 1. Model fitting are presented in Figure 2 and 3.

Figure 2 shows a very poor model fit of the model with constant β and μ_T. This is due to the inherent exponential growth assumption of compartment model with constant transmission rate. The number of active TB cases is forced to grow until the susceptible population is exhausted. As the size of susceptible is enormous to the active TB compartments, the model fails to capture the declining trend in data.

Figure 3, on the other hand, shows a relatively good fit to data.The fitted line follows closely to the trend of data, and 95% credible interval perfectly covers data. Therefore, in subsequent sections, I only consider Model 2's results.

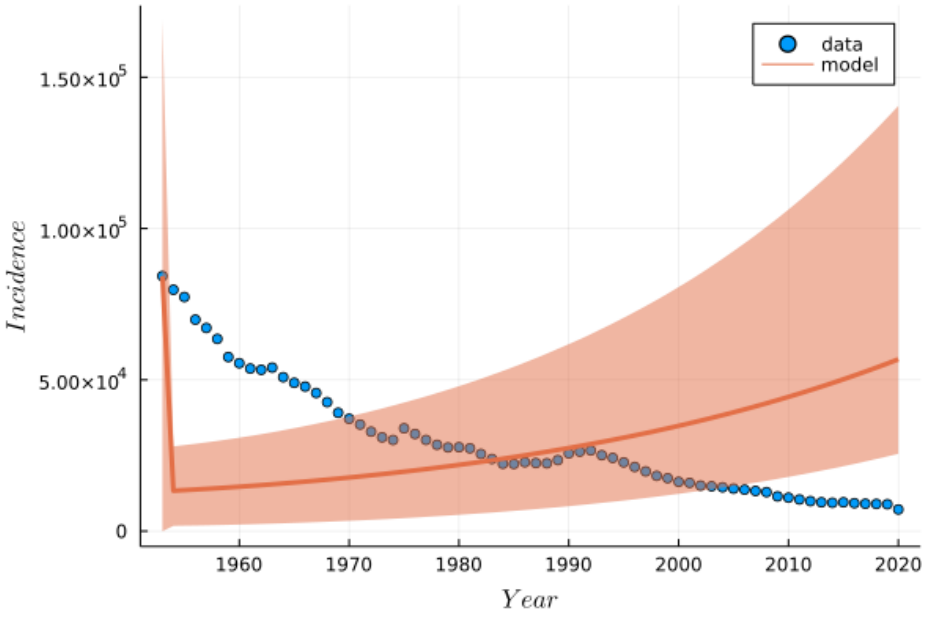

Figure 2: Model fitting with constant β and μ_T.

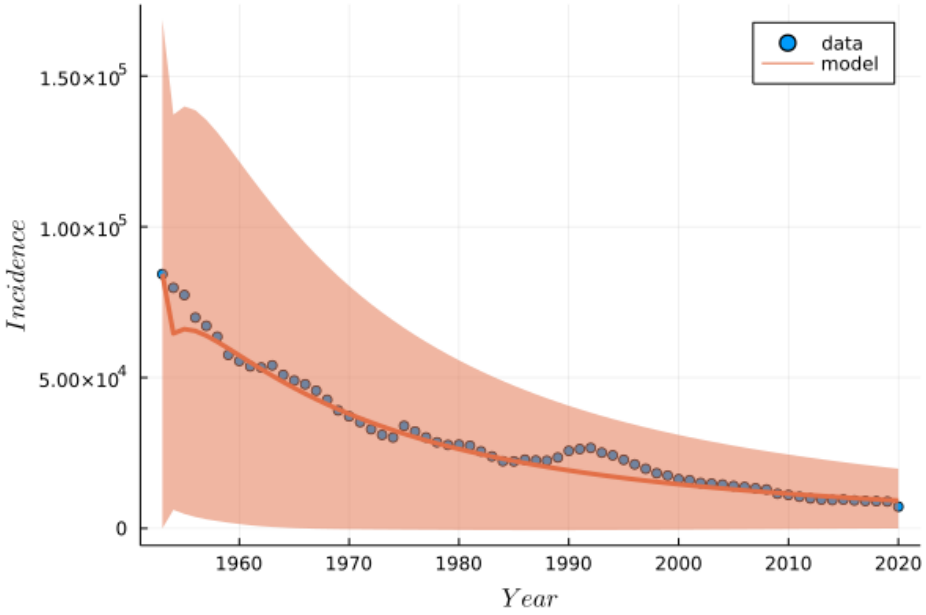

Figure 3: Model fitting with time-dependent β and μ_T.

3.2 Time-dependent function $\beta(t)$ and $\mu_T(t)$

The estimates of time-dependent $\beta(t)$ and $\mu_T(t)$ over time are displayed in Figure 4 and 5. A significant drop in both β and μ_T is observed until 1960, then slowing down, indicating the effectiveness of TB treatment and prevention interventions.

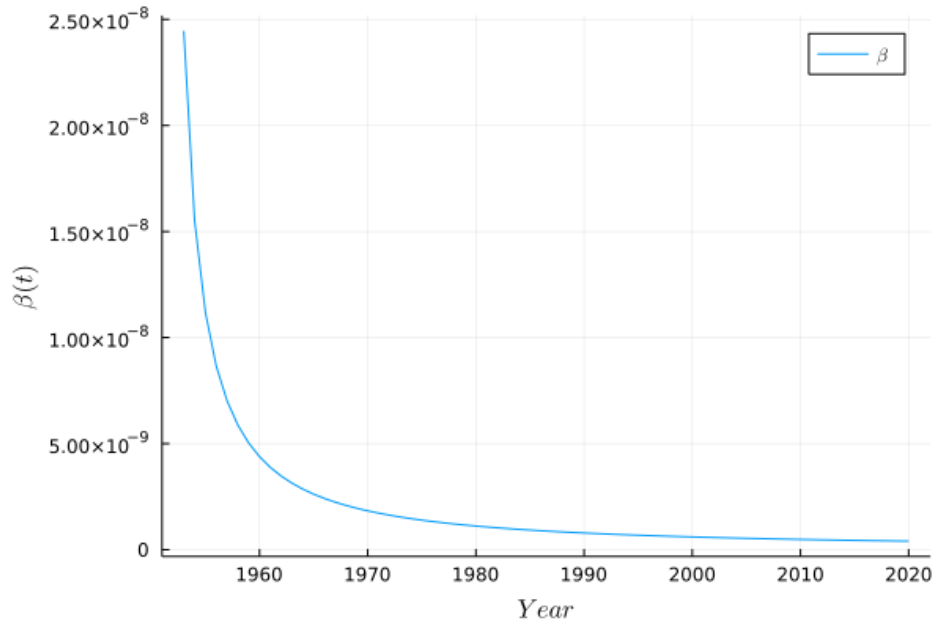

Figure 4: Mean estimate of time-dependent $\beta(t)$

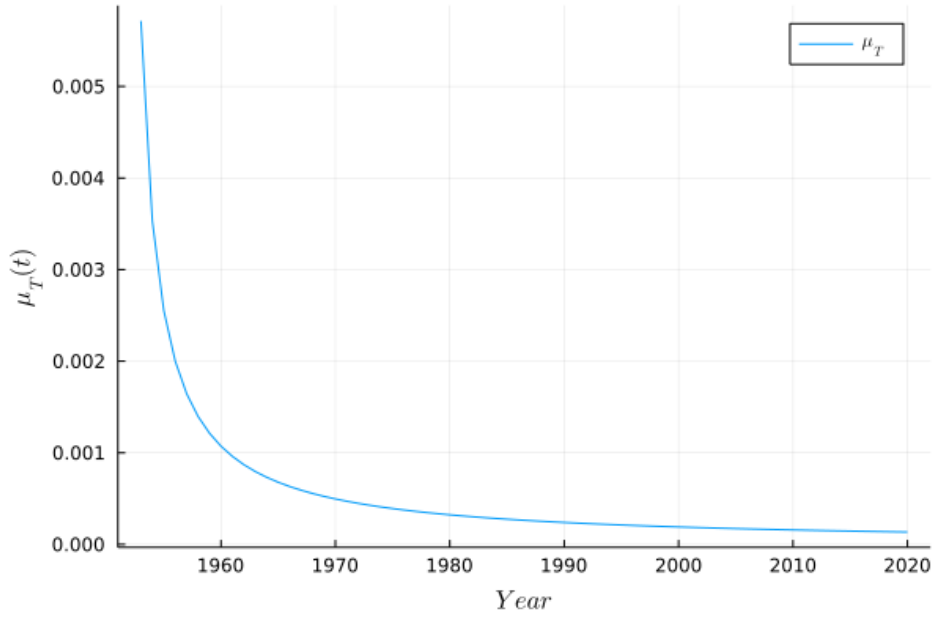

Figure 5: Mean estimate of time-dependent $\mu_T(t)$

3.3 Reproduction number

The estimate of reproduction number is presented in Figure 6. Throughout the study period (1953-2020), the reproduction number is significantly lower than 1, which is in line with the observation that TB epidemic in the U.S. (and other developed countries) has been declining long before TB become curable in 1940s. With declining R_t, the TB epidemic is expected to continue to decrease, and hopefully, will be eliminated in the near future. However, as TB is notorious for being latent in the population, elimination of TB requires great efforts from multiple stakeholders.

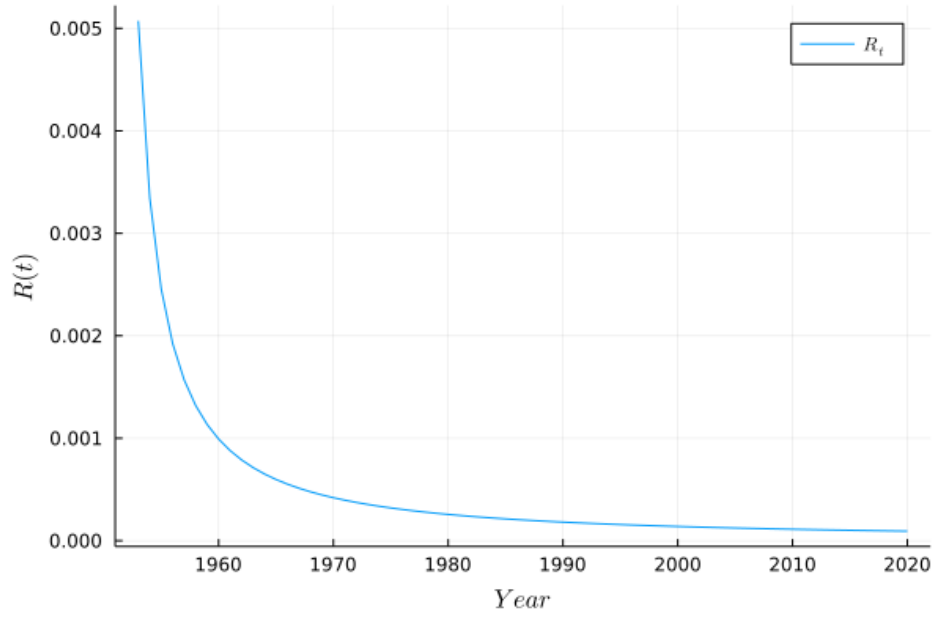

Figure 6: Mean estimate of reproduction number R_t

4 Conclusion

In this project report, I employed the transmission model proposed by (Blower et al., 1995) to re-evaluate the TB epidemic in the U.S., with 2 variations: (1) constant β and μ_T, and (2) time-dependent $\beta(t)$ and $\mu_T(t)$. Model with constant parameters shows extremely poor good fit to data, while time-dependent model has a good model fit. The time function of β and μ_T reflects the effectiveness of TB treatment and prevention programs.

The use of Bayesian approach allows me to flexibly estimate multiple parameters using informative priors (based on literature review) and/or non-informative priors. This poses a great benefit in comparison with the frequentist approach, where we either have to keep more parameters fixed or spend huge computational power in estimating many parameters as in time-dependent model.

However, interpretation of model results requires special attention at assumptions. Like other diseases, TB transmission mechanism is much more complicated in presented in the compartment model. In addition, the actual number of total active cases, latent cases and recovered cases are unknown and assumed.

5 Acknowledgment

Introduction section reused part of my own assignment in course Infectious Disease Epidemiology in 2016.

References

Blower, S., McLean, A., Porco, T., Small, P., Hopewell, P., Sanchez, M., & Moss, A. (1995, August). The intrinsic transmission dynamics of tuberculosis epidemics. *Nature medicine*, *1*(8), 815—821. Retrieved from https://doi.org/10.1038/nm0895-815 doi: 10.1038/nm0895-815