TUBERCULOSIS CONTROL IN THE US: A STRATEGY TO MEET CDC'S GOAL

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Abstract

Non-autonomous systems of ordinary differential equations are introduced to model the transmission of dynamics of tuberculosis and to fit U.S. tuberculosis incidence over the past five decades. Tuberculosis may be controlled in the U.S. under the criterion given by CDC (one case per million) by the year 2020 if at least 20% of the latently-infected individuals are successfully treated. The effect of HIV/AIDS after 1983 is included in the analysis via a model that incorporates a function that accelerates TB progression. It is shown that TB's case rate may be eventually controlled despite increases in the rate of TB progression due to HIV. Sufficient conditions for TB extinction and persistence are derived in terms of upper limits and lower limits of the mortality functions.

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1 Introduction

Mycobacterium tuberculosis, the causative agent associated with the transmission of tuberculosis, was discovered by Robert Koch in 1882. Bacilli are spread in the air when infectious individuals sneeze, cough, speak or sing (American Thoracic Society, CDC, 1990). A susceptible individual may become infected with TB if he or she inhales bacilli from the air. The particles

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containing *Mycobacterium tuberculosis* are so small that normal air currents not only keep them airborne but also transport them throughout rooms or buildings (Wells, 1995). Individuals who regularly share space with those with active TB (the infectious stage of the disease) naturally have a higher risk of becoming infected than those who do not. Infections occur when susceptible persons inhale droplet nuclei containing *Mycobacterium tuberculosis.* The bacilli become established in the alveoli of the lungs from where they spread throughout the body. Hosts' immune response usually limits further bacilli multiplication and the spread that naturally follows initial infections. Only a small proportion of newly infected persons (usually less than 1%) develops active infections, that is, only a tiny proportion of those infected progresses rapidly towards active-TB. Between 5% and 10% of infecteds eventually develop active-TB but typically, they do it rather slowly. Most infected individuals remain as latently-infected carriers for their entire lifes. In general the distribution of progression times is skewed. The average length of the latent period (carrier at non-infectious stage) ranges from months to decades but the risk of progression, towards active-TB, increases markedly in the presence of co-infections that debilitate the immune system. In other words, the presence of co-infections alters the shape of the distribution of progression times. Persons with HIV co-infections progress faster towards the active (infectious) TB state than those without them (Selwyn *et al.*, 1989). However, impact from co-infections may be temporal if effective approaches are used against them.

Effective and widespread treatment for active and latently infected individuals has been available for about five decades. *Streptomycin*, an antibiotic, first discovered at Rutgers University in 1943, is still used but with *pyrazinamide.* Currently *Isoniazid* and *Rifampin* are most effective in the fight against *M. tuberculosis.* The widespread introduction of antibiotics reduced mortality by 70% from 1945 to 1955 in the U.S. but major reductions on TB mortality rates had already been achieved before their introduction (see

Aparicio *et al.*, 2000; Dubos and Dubos, 1952; Lowell *et al.*, 1969). Latent TB can be handled with a single drug *Isoniazid* but treatment is effective only if applied for at least six months. Active cases must be treated for nine months with multiple drugs (*Isoniazid, Rifampin, Pyrazinamide*) and complex regimens. Treatment in the U.S. covers over 95% of the cases (WHO, 2000b) despite its high cost. The expenses associated with treatment programs are so high that their effective implementation are pretty much out of reach in most developing nations. Antibiotic resistant strains may be easily generated if treatment is not completed and the consequences may be serious for such individuals (see Castillo-Chavez and Feng, 1997). Lack of treatment compliance has not only local but also global serious consequences that are not difficult to imagine in today's society (see Kolata, 1995).

In 1989, CDC and ACET (Advisory Council for the Elimination of Tuberculosis) set long term national goals for TB control that included specific national targets (CDC, 1989). CDC's goal was to reduce the case rate of TB to less than 3.5/100,000 by 2000 and to about 1/1,000,000 by 2010. Data suggest that these targets were optimistic. In this paper, we show that targeting a higher proportion of latently-infected individuals increases the likelihood that CDC's target may be reached. We illustrate the effect of treating a higher proportion of latently-infected individuals on CDC's target and show that meeting CDC's goal by 2020 is actually possible.

Our paper is organized as follows: Section 2 introduces the basic model structure for the study of the dynamics of TB transmission; the asymptotic behavior of the model of Section 2 is analyzed in Section 3; a function that captures the impact of HIV/AIDS on TB progression is introduced in Section 4; parameter values and parameter ranges are introduced and discussed in Section 5; Section 6 collects the results of simulations using estimated parameters and collects our conclusions; finally the Appendix includes two tables with a forecast of active TB cases by 2050 and the proof of the theorem on the asymptotic dynamics of our model.

2 Model structure

Tuberculosis, a slowly progressing disease, was one of the biggest contributors to human mortality in the past. TB's world prevalence of asymptomatics is huge (about one out of three persons may be infected with TB) but progression to active TB has slowed down (Aparicio *et al.*, 2000). In order to mimic the dynamics of TB over the past five decades, our model includes the U.S. population's demography. In addition, individuals are classified according to their TB epidemiological status: susceptible (S), latent/exposed (L) and (actively) infectious (I). We do not keep track of specific co-infections including HIV co-infections to keep the model as simple as possible. In fact, we do it in a practical way since our focus here is on TB control. Dynamical models for the transmission dynamics of tuberculosis have been developed in the recent past (Castillo-Chavez, 1997, 1998; Blower, 1995 and references therein). A similar approach leads to the following model:

$$\frac{dS}{dt} = F(N) - B(S,I,N) + r_2 L + r_1 I, \tag{1}$$

$$\frac{dL}{dt} = B(S,I,N) - (\mu + k + r_2)L, \tag{2}$$

$$\frac{dI}{dt} = kL - (\mu + d + r_1)I, \tag{3}$$

where $F(N)$ represents the recruitment rate as a function of total population size N; $B(N,I,S)$ denotes the incidence rate per unit time; $r_i (i = 1,2)$ denote treatment rates for actively and latently-infected individuals, respectively. The dynamics of the total population size $N(t) = S(t)+L(t)+I(t)$ is governed by the equation

$$\frac{dN}{dt} = F(N) - dI, \tag{4}$$

where d is the tuberculosis induced death rate, a very small rate when compared to the "natural" death rate (mortality rate due to all other causes). $F(N)$ will be assumed to be either a linear (exponential growth) or a nonlinear bounded function. This assumption covers most observed popula-

tion growth patterns on the time scale of TB epidemics (Song *et al.*, 2001). $B(N, I, S)$ will simply be taken as $\beta S\frac{I}{N}$ (*random mixing*).

In modeling "recent" (last five decades) tuberculosis transmission in the U.S. it is reasonable to disregard the impact of TB-induced mortality, that is, taking $d = 0$ is quite reasonable. Hence, the dynamics of TB in the U.S. over the past few decades can be reasonably modeled by a system where demography and epidemiology are uncoupled. Or equivalently, it can be modeled via a non-autonomous system since $N(t)$ can be "explicitly" computed from the demographic equation $\frac{dN}{dt} = F(N)$. Consequently, Equations (2) and (3) are enough to describe the transmission dynamics of tuberculosis, that is, our system reduces to the following non-autonomous system:

$$\frac{dL}{dt} = \beta\Big(N(t) - L - I\Big)\frac{I}{N(t)} - (\mu(t) + k + r_2)L, \tag{5}$$

$$\frac{dI}{dt} = kL - (\mu(t) + d(t) + r_1)I, \tag{6}$$

where $N(t)$, now assumed independent of the disease, is a known 'external' input to the epidemiological model. The values of $N(t)$ are inputted using published U.S. demographic data. The transmission rate,β, is assumed constant; k, TB's activation rate, is also assumed to be constant; r_i $(i = 1, 2)$, the treatment rates defined before, are also assumed to be constant. $\mu(t)$ and $d(t)$ are, in general, functions of time (see Aparicio *et al.*, 2000).

Age-structure and immigration (critical factors on TB persistence in the U.S.) can easily be incorporated into the modeling framework. However, data needs required by structured models can be huge and hence nearly impossible to meet.

If $n(t, a)$ denotes the age distribution of the population at time t per unit time then the corresponding age-structured demographic model is

$$\frac{\partial n}{\partial t} + \frac{\partial n}{\partial a} = -\mu(t, a) + m(t, a), \tag{7}$$

$$n(t, 0) = B(t) - \mu_0(t), \tag{8}$$

$$n(0, a) = n_0(a), \tag{9}$$

where $\mu(t,a)$ is the time-dependent age-specific death rate per unit time; $m(t,a)$ denotes the age-specific net immigration rate per unit time (for the U.S., $m(t,a)$ would be assumed to be positive for all ages); $n_0(a)$ denotes the initial distribution of the total population; $n(t,0)$ denotes the net birth rate, which equals $B(t)$, the total birth rate, minus $\mu_0(t)$, the death rate of newborns. The total population size is $N(t) = \int_0^\infty n(t,a)da$. System (5-9) is a mixture of demography and epidemiology that includes immigration. A study of the solutions $n(t,a)$ in System (7-9) can be found in (Iannelli, 1995 or Webb, 1985). Here, it is assumed that $N(t) = \int_0^\infty n(t,a)da$, $\mu(t)$ and $d(t)$ are bounded from below and from above. These assumptions guarantee that all solutions of the non-autonomous System (5-6) are bounded and nonnegative. Age-structure could also be incorporated in the epidemiology. We do not consider population structure explicitly in either the demography or the epidemiology because our general objectives fortunately can be met with the simpler system that requires less (and available) data.

3 Asymptotic behavior of solutions

An asymptotic analysis of Model (5-6) is carried out in the Appendix but the results are discussed in this section since they play a role in the parameterization of the model. The analysis helps establish a criterion for disease persistence, that is, a threshold condition, that must be met by our parameterized model. Such criterion also helps narrow down parameter ranges. Hence, the long term behavior of our system is determined by the asymptotic property of the functions $N(t)$, $\mu(t)$ and $d(t)$. The following theorem characterizes such behavior:

Theorem. *Assume* $\liminf_{t\to\infty}\mu(t) = \mu_\infty$, $\liminf_{t\to\infty} d(t) = d_\infty$, *and* $\limsup_{t\to\infty}\mu(t) = \mu^\infty$, $\limsup_{t\to\infty} d(t) = d^\infty$.

1. *If* $R_\infty = \left(\frac{k}{k+\mu_\infty+r_2}\right)\left(\frac{\beta}{\mu_\infty+d_\infty+r_1}\right) \leq 1$ *then* $\lim_{t\to\infty} L(t) = \lim_{t\to\infty} I(t) = 0$.

2. *If* $R^{\infty} = \left(\frac{k}{k+\mu^{\infty}+r_2}\right)\left(\frac{\beta}{\mu^{\infty}+d^{\infty}+r_1}\right) \geq 1$ *then* $\limsup_{t\to\infty} L(t) > 0$, *and* $\limsup_{t\to\infty} I(t) > 0$.

When $\mu(t) \equiv \mu$ and $d(t) \equiv d$ (both constant) then $R^{\infty} = R_{\infty} = \mathcal{R}_0$ gives the classical basic reproductive number, that is,

$$\mathcal{R}_0 = \beta\left(\frac{1}{\mu + d + r_1}\right)\left(\frac{k}{k+\mu+r_2}\right)$$

where β is the effective contact rate; $\frac{1}{r_1+\mu+d}$ is the effective infectious period; $\frac{k}{r_2+\mu+k}$ is the proportion of latently-infected individuals who make it to the active stage. In other words, $\mathcal{R}_0$ gives the average number of secondary infectious generated by a typical actively infected individual in a population of mostly susceptibles that is, in a population of susceptibles at a demographic steady state (autonomous system). This theorem provides a sharp classification for the two important biological states: disease elimination or persistence for non-autonomous systems. These thresholds help verify the reasonableness of published parameters. They are also helpful in the selection of reasonable ranges of unknown parameters. Our model generalizes the results established for related autonomous systems by Feng *et al.*(2001) and Song *et al.* (2001).

4 Impact of HIV/AIDS

Few infected individuals developed active tuberculosis since their immune's response is usually effective and fast. The immune system of infected individuals produces a thick waxy coat that almost immediately covers tuberculosis bacilli. This action prevents its activation. When the immune system of an infected person does not function well, for example, when an individual also faces a HIV/AIDS co-infection, the coat covering tuberculosis bacilli becomes more fragile and, hence it is more likely to break. Consequently, individuals with co-infections that enhance immune deficiencies, face a higher risk of

developing active TB infections. Hence, whenever a large pool of latently-infected TB individuals find themselves in the presence of such co-infections, the likelihood of an outbreak of active TB in such population increases.

Studies have shown that 15% of AIDS deaths are due to tuberculosis co-infections (WHO, 2000a). The risk of progression to active disease is markedly increased for persons with HIV co-infections (Selwyn, *et al.*, 1989). We incorporate the effects of AIDS co-infections from a single outbreak into our model in a rather simple and indirect way. A time-dependent function that enhances TB progression as a function of HIV risk during the time period when HIV had the most impact is used to modify the distributions of latent periods. Our assumption is based on the fact that HIV/AIDS increased tuberculosis incidence (and vice versa) during some identifiable window in time. We incorporate such a function in the following way:

$$\frac{dL}{dt} = \beta\left(N(t) - L - I\right)\frac{I}{N(t)} - (\mu(t) + k + r_2 + A(t))L, \tag{10}$$

$$\frac{dI}{dt} = (k + A(t))L - (\mu(t) + d(t) + r_1)I, \tag{11}$$

where

$$A(t) = \begin{cases} 0.05(t-1983)^{1.8}e^{-\sqrt{t-1983}} & \text{if } 1983 < t, \\ 0 & \text{otherwise.} \end{cases}$$

$A(t)$ models increased progression from latent to active TB beginning in 1983. This function has large values around the middle of the 1980's before HIV was identified and before any forms of treatment were available in the U.S.. It decreases dramatically afterwards (see Figure 1) in a way dictated by our desire to fit the data as close as possible. Mathematically, the addition of $A(t)$ does not change the asymptotic behavior of tuberculosis in the U.S. albeit it changes its quantitative dynamics over a relative short period of time. These changes fit observed patterns because $A(t)$ was chosen to make them fit. Hence, we have an epidemiological model that fits demographic and epidemiological data for the last five decades. AIDS has, naturally, delayed CDC's time table for TB "elimination" and our model explicitly

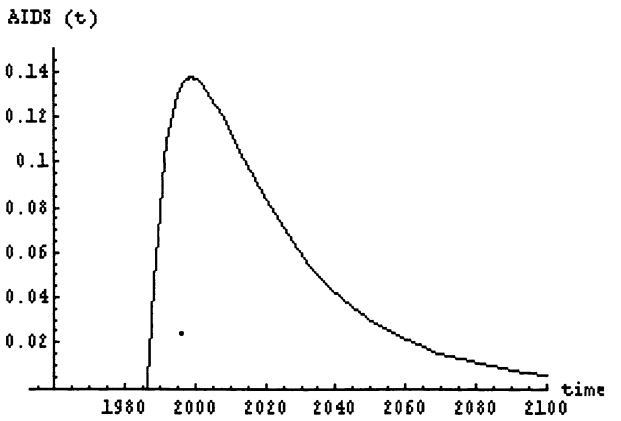

Figure 1: Shape of function of $A(t)$

takes account of this effect. The fact that there may be recurrent HIV/AIDS epidemics in the future that are not synchronized in time is likely to have important implications (recent increases in HIV in San Francisco may fit this category). Such temporal asynchrony could be modeled by

$$\frac{dL}{dt} = \beta\Big(N(t) - L - I\Big)\frac{I}{N(t)} - (\mu(t) + k + r_2 + \sum_{j=1}^{J} A_j(t))L, \tag{12}$$

$$\frac{dI}{dt} = (k + \sum_{j=1}^{J} A_j(t))L - (\mu(t) + d(t) + r_1)I, \tag{13}$$

where each function $A_j(t)$ would have a shape similar to that of A(t) but with a different support interval. System (5-6) and (12-13) has the asymptotic behavior predicted by our theorem in Section 3 but the time to CDC's 'TB elimination' may be radically changed if asynchronous epidemics are supported.

We observe that our model has only altered the distribution of progression times towards active TB due to the impact of a temporal co-infection, that is, a co-infection that impacts progression only for a short period of time. The growth of HIV co-infections and their strong impact on TB progression in the

1980's and 1990's changed the dynamics at least for a short period of time (before they return to their 'normal' or 'natural' dynamics). The fact that TB prevalence and incidence exhibited a prolonged downward trend before HIV implies that the time to meet CDC's target has been delayed by this HIV "perturbation". In summary, we have introduced a model that captures this phenomenon, that is an agreement with the data, and that incorporates demography and epidemiological interactions. It is in the context of this data-driven model that strategies to meet CDC's target in a reasonable period of time are discussed.

5 Parameter estimation

The parameter values and the asymptotic behavior of functions, like $\mu(t)$ and $N(t)$, determine the time to CDC's 'TB elimination'. We use the United States not only to illustrate the likelihood of meeting CDC's criterion but also to discuss the implications of future co-infection outbreaks. The selection of the required parameters in this setting is therefore difficult but literatures provide a reasonable start.

We use reasonable ranges and averages (from the literature) and use them in our extensive simulations. An explicit list of our parameter selection sources and assumptions is provided below:

1. The value of β (effective contact rate) is the product of the contact rate c and the transmission probability per contact. CDC has used an average contact rate of 9 (Etkind, 1993). Other studies have used estimates for c of the same order of magnitude (Shrestha-Kuwahara and Marks, 1999). Here, we take c to be around 10.

2. The value for the transmission probability per contact is around 0.2. CDC used 0.21 (Etkind, 1993). It is believed that this value has stabilized. It is believed that it has lived in the range of 0.21 to 0.23 since 1987 (National Tuberculosis Center, 2001).

3. The parameter k represents the per capita rate of progression from inactive-TB to active-TB. The exact distribution of the latent periods is unknown. Available information claims that 10% of inactive tuberculosis cases progress to active tuberculosis within 10 years. There is evidence that confirms the occurrence of cases 10 years after primary infections. Earlier work of Ferebee (1967) assumed that $k = \frac{1}{625}\text{year}^{-1}$. We shall assume that k is around 0.001

4. Our dynamic model for tuberculosis transmission is given by a system of ordinary differential equations whose solution curves are determined by initial conditions. There is no way for us to have a reasonable estimate of 'initial' levels of latently-infected individuals but it is reasonable to assume this number is of the order of 10^6 in the U.S.. Ferebee (1967) assumed that it was $25,000,000$ in the U.S. in 1967. More information on the number of active tuberculosis than inactive cases is available. The incidence rate multiplied by the case finding rate gives a rough estimate of the initial levels of active tuberculosis. We take 1953 as time zero and assume that $I(0) \approx 874230$ (10 times the number of cases in 1953).

5. Case reporting rates reflect the case finding rates which have a value of around 70%. The probability of successful treatment is greater than 95% in the U.S. (WHO, 2000). To be consistent with the data r_1 is assumed to take values around 0.65. The finding rate for inactive tuberculosis is about 10%. Latent tuberculosis treatment programs have a probability of success of about 0.90 in the U.S.. Treatment failure is mostly due to a patient's inability to complete treatment. To be consistent with the data r_2 is assumed to take values around 0.05.

6 Results and discussions

A discrete version of Model (7-9) for the demography was used by Bureau of the Census (Hollmann *et al.*, 2000) to fit and project the U.S. demography. The model looks like:

$$n_t(0) = B_{t-1,t} - \mu_{t-1,t}(0) + m_{t-1,t}(0), \tag{14}$$

$$n_t(a) = n_{t-1}(a-1) - \mu_{t-1,t}(a) + m_{t-1,t}(a), \tag{15}$$

where the total population (sum over all ages) is therefore given by

$$N_t = N_{t-1} + B_{t-1,t} - \bar{\mu}_{t-1,t} + M_{t-1,t}. \tag{16}$$

U.S. population projections by the Bureau of Census are available until 2100 (Census Bureau of U.S., 1999) from Model (14-16). We use the results of theses projections to input the $N(t)$ values required in our simulations. Of course, appropriate interpolations have to be made since we are using continuous time models. Data on mortality and TB induced death rates are available but only for the last one and half century (this is sufficient for us). In the implementation of our simulations, we interpolate from mortality data to obtain estimates for $\mu(t)$ and $d(t)$ when $t \leq 2000$ and when for $t > 2000$ we take them as constants by averaging the corresponding data for last 5-10 years. We conduct a sensitivity analysis to take into account the impact of variation on parameters. In some sense, we treat the parameters of the model as random variables from appropriate normal distributions. The values used as predictors of TB cases in the U.S. are the result of averaging 5,000 simulation runs.

Figure 2 shows that for the selected parameter ranges, the progression rate function $A(t)$ fits the data very well. That is, the fit successfully captures the past history of TB in the U.S.. A value of $r_2 = 0.05$ says that in the past only 5% of latently-infected individuals got treated per unit time. The treatment of 100% of active TB cases per unit time ($r_1 = 1$, instead of 0.65) is

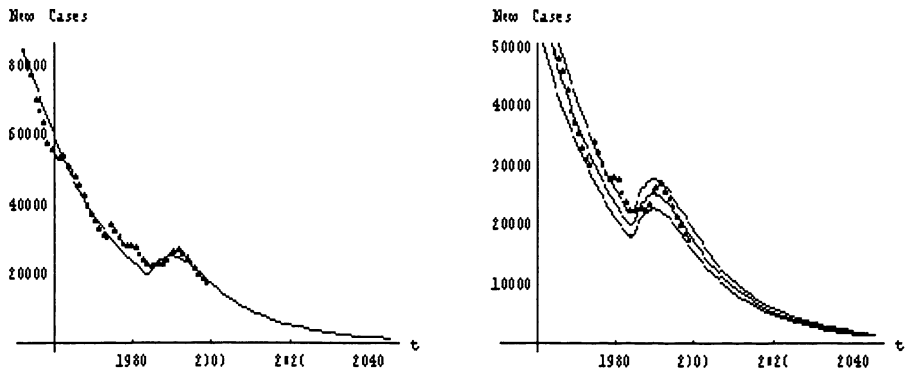

Figure 2: Left: New case of TB and data (dots). Right: 10% error bound of new cases and data

insufficient to reach CDC's goal (see Figure 3). However, treatment of more latently-infected individuals, for instance, raising r_2 to 20% per year, would help reach CDC's target of 1/1,000,000 in a more reasonable period of time (see Figure 3). Figure 4 illustrates the effect of HIV on the control of TB. It delays the achievement of CDC's goal but has no permanent impact on the

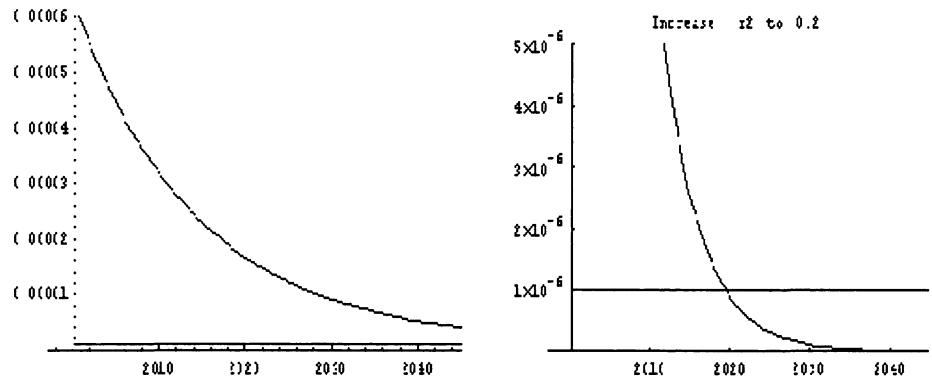

Figure 3: Left: $r_2 = 5\%$, no CDC 'TB elimination' by 2020. Right: $r_2 = 20\%$, CDC 'TB elimination' by 2020.

long-term persistence of TB. However, prolonging TB 'survival' enhances the likelihood of its evolution, a situation that is not explored here. We present two tables in the Appendix with a forecast of the number of new cases and

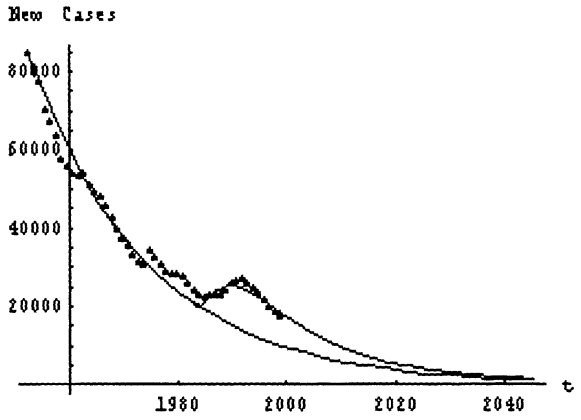

Figure 4: Impact of HIV. Lower curve represents no HIV effect; upper curve represents the case rate when HIV is included; both are the same before 1983. Dots represents real data

the number of latently-infected individuals in the U.S. over the next half century.

In this paper we have introduced the impact of HIV/AIDS on TB progression during the past two decades via the introduction of a temporary perturbation on the distribution of TB progression times. Our selection of this perturbation is driven by our desire to fit active-TB data since our primary goal is not to look at the coevolution of co-infections but rather at the impact of HIV/AIDS co-infections on the ability of the U.S. to meet CDC's target by 2010. Our model suggests that if emphasis is placed on treating at least 20% of the latently-infected individuals then CDC's target may be met by 2020. Our model also shows that re-emergence of diseases that compromise the immune system (or recurrent outbreaks) would make it very difficult to control TB unless treatment emphasis is put on the earlier (non-detectable) stages of TB diseases.

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References

1. American Thoracic Society, CDC. (1990). Diagnostic standards and classification of tuberculosis. *Am Rev Respir Dis.* **142:**725-735.

2. Aparicio J. P., Capurro A. F., and Castillo-Chavez C. (2000). On the fall and rise of tuberculosis. BU-1477-M, Department of Biometrics, Cornell University.

3. Blower S. M., McLean A.R., Porco T., Sanchez M., Small P.M., Hopewell P. C., Sanchez M. A., and Moss A. R. (1995). The intrinsic transmission dynamics of tuberculosis epidemics. *Nat. Med.* **1**:815-821.

4. Bureau of Census of U.S. (1999). Annual projections of the total residents population as of July 1: Middle, Lower, Highest and zero international population migration series, 1999 to 2100. Web sources, http://www.census.gov/population/www/projections/.

5. Castillo-Chavez C. and Feng Z. (1997). To treat or not to treat: the case of tuberculosis, *J. Math. Biol.*, **35**: 629-656.

6. Castillo-Chavez C. and Feng Z. (1998). Global stability of an age-structure model for TB and its application to optimal vaccination strategies, *Math. Biosci.*, **151**: 135-154.

7. CDC (1989). A strategic plan for the elimination of tuberculosis in the United states. *MMWR*, **38** (suppl. No S-3):1-25.

8. Dubos R. and Dubos J. (1952). The White Plague: Tuberculosis, Man and Society, Little and Brown, Boston.

9. Etkind S. C. (1993). Contact tracing in tuberculosis, In: *Tuberculosis: A comprehensive international approach*, Reichman L. B. and Hershfield E.S. Eds, New York, Basel, Hong Kong, pp.275.

10. Ferebee S.H. (1967). An epidemiological model of tuberculosis in the United States, *NTA Bulletin*, January 1967, 4-7.

11. Feng Z., Castillo-Chavez C., and Huang W. (2001). On the role of variable latent periods in mathematical models for tuberculosis, *Journal of Dynamics and Differential Equations,* **13** (In press).

12. Hirsch W. M., Hanisch H., and Gabriel J.P. (1985). Differential equation models for some parasitic infections; method for the study of asymptotic behavior, *Comm. Pure Appl. Math.* **38**:733-753.

13. Hollmann F. W., Mulder T. J., and Kallan J. E. (2000). Methodology and assumptions for the population projection of the United States: 1999 to 2100, Bureau of Census, Population Division working paper No 38. Web source http://www.census.gov/population/www/documentation/twps0038.html.

14. Iannelli M. (1995). *Mathematical Theory of Age-structured Population Dynamics*, Giardini Editori, E Stampatori, in Pisa.

15. Kolata G. (1995). First documented cases of TB passed on airliner is reported by U.S.. *New York Times*, March 3,1995.

16. Lowell A. *et al.* (1969). *Tuberculosis*, Harvard University Press, Cambridge MA.

17. National Tuberculosis Center (2001). Chapter Two, transmission and pathogenesis, in: *Core curriculum on tuberculosis*, web source: /http://www.umdnj.edu/ ntbcweb/corefr.htm.

18. Selwyn P. A., Hartel D., Lewis V.A., et al. (1989). A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N. Engl. J. Med.* **320**:545-550.

19. Shrestha-Kuwahara R. and Marks S. (1999). Preliminary findings from two contact investigations, In: *CDC, TB Notes No 2*, pp.11-15.

20. Song B., Castillo-Chavez, C., and Aparicio, J.P. (2001). Global dynamics of tuberculosis models with density dependent demography. In: *Mathematical Approaches for Emerging and Reemerging Infectious Diseases : Models, Methods and Theory*, Castillo-Chavez, C., S. Blower, P. van den Driessche, D. Kirschner, and A.A. Yakubu (eds), Springer-Verlag, New York (In press).

21. Thieme H.R. (1993). Persistence under relaxed point-dissipativity (with application to an endemic model), *SIAM J. Math. Anal.* **24**(2):407-435.

22. Wells W. F. (1955). Aerodynamics of droplet nuclei, *Airborne contagion and air hygiene.* Cambridge: Harvard University Press.

23. WHO (2000a). Tuberculosis, TB Fact Sheets, web source, http://www.who.int/inf-fs/en/fact104.html.

24. WHO (2000b). Global Tuberculosis Control: WHO report 2000. Geneva: World Health Organization.

25. Webb G. F. (1985). *Theory of nonlinear age-dependent population dynamics*, Marcel Dekker, New York.

A Tables

Prediction of TB Incidence of the U.S.

Year	Tuberculosis	Year	Tuberculosis
2001	26888.2	2026	6448.9
2002	25441.8	2027	6121.3
2003	24039.4	2028	5812.7
2004	22690.	2029	5522.3
2005	21397.3	2030	5248.7
2006	20166.6	2031	4990.4
2007	19000.6	2032	4746.3
2008	17895.9	2033	4516.0
2009	16855.7	2034	4298.4
2010	15877.9	2035	4092.1
2011	14959.4	2036	3896.3
2012	14097.3	2037	3710.9
2013	13287.8	2038	3535.6
2014	12530.3	2039	3369.5
2015	11822.2	2040	3211.6
2016	11158.8	2041	3061.7
2017	10538.3	2042	2919.6
2018	9957.7	2043	2784.4
2019	9414.6	2044	2655.8
2020	8905.6	2045	2533.7
2021	8427.4	2046	2417.7
2022	7979.6	2047	2307.2
2023	7559.8	2048	2202.1
2024	7166.2	2049	2101.9
2025	6796.8	2040	2006.3

Table 1: Number of active tuberculosis in the U.S. form 2001 through 2040

Prediction of Latent TB of the U.S.

Year	Latent TB	Year	Latent TB
2001	$1.998606832907533*10^6$	2026	708910.7866496837
2002	$1.923641943171843*10^6$	2027	678360.6672065898
2003	$1.851032791472061*10^6$	2028	649047.8934275835
2004	$1.780727957000281*10^6$	2029	620964.6129269843
2005	$1.712427328121379*10^6$	2030	594084.6524858062
2006	$1.646274943502753*10^6$	2031	568292.6894604814
2007	$1.582269278290167*10^6$	2032	543565.8952388513
2008	$1.520080645340529*10^6$	2033	519911.7440658233
2009	$1.459989683998999*10^6$	2034	497274.2113372126
2010	$1.401935871794004*10^6$	2035	475552.3255516171
2011	$1.345776986524634*10^6$	2036	454698.1230445390
2012	$1.291474406687125*10^6$	2037	434741.4368790902
2013	$1.238867122849632*10^6$	2038	415693.3226847585
2014	$1.188156782532186*10^6$	2039	397479.3322123775
2015	$1.139338047317955*10^6$	2040	380007.3759705960
2016	$1.092198664367019*10^6$	2041	363303.6546871724
2017	$1.046814234224803*10^6$	2042	347346.0655184661
2018	$1.003127238758086*10^6$	2043	332053.1078910177
2019	961123.3758838332	2044	317428.7300328113
2020	920677.5518493373	2045	303457.5335038745
2021	881654.2212026586	2046	290103.9100908917
2022	844202.9677817885	2047	277334.0112790820
2023	808252.6039557089	2048	265124.3304444849
2024	773771.6760658747	2049	253436.1904742842
2025	740708.6360752575	2050	242238.6155298132

Table 2: Number of Latent TB from 2001 though 2050

B Proof of theorem

Proof. We will use the following facts which are straightforward in real analysis.

$$\begin{aligned}
\limsup(A+B) &= \lim A + \limsup B, \text{ whenever } \lim A \text{ exists} \\
\liminf(A+B) &= \lim A + \liminf B, \text{ whenever } \lim A \text{ exists} \\
\limsup(AB) &= \lim A \limsup B, \text{ whenever } \lim A \text{ exists} \\
\liminf(AB) &= \lim A \liminf B, \text{ whenever } \lim A \text{ exists}
\end{aligned}$$

The proof is based on the Fluctuation Theorem (Hirsch, Hanisch and Gabriel, 1985) and its extension by Thieme (see Theorem 2.3 in Thieme 1993). Applying Theorem 2.3 from Thieme to Equations (5) and (6) directly, one obtains that $0 \leq \beta I^\infty - (\mu_\infty + k + r_2)L^\infty$ and $kL^\infty \leq (\mu_\infty + d_\infty + r_1)I^\infty$. Hence, it follows that $\beta I^\infty \geq \frac{\mu_\infty+k+r_2}{k}(\mu_\infty + d_\infty + r_1)I^\infty$, that is, $I^\infty\left(\frac{k}{k+\mu_\infty+r_2}\frac{\beta}{\mu_\infty+d_\infty+r_1} - 1\right) = I^\infty(R_\infty - 1) \geq 0$. Since $R_\infty < 1$ and $I(t)$ is bounded, it follows that $I^\infty = 0$. A similar argument results in $L^\infty = 0$. The first part of this theorem is proved. It is not difficult to show that $\limsup_{t\to\infty} L(t) = 0$ if and only if $\limsup_{t\to\infty} I(t) = 0$. For instance, the fact that $\limsup_{t\to\infty} I(t) = 0 \Rightarrow \limsup_{t\to\infty} L(t) = 0$ is verified below. From Equation (5)

$$\frac{dL}{dt} \leq \beta I - (\mu(t) + k + r_2)L.$$

It follows from the comparison principle that

$$L(t) \leq \frac{L_0 + \int_0^t \beta I(s) e^{\int_0^s (\mu(\tau)+k+r_2)d\tau} ds}{e^{\int_0^t (\mu(\tau)+k+r_2)d\tau}}.$$

Hence

$$\begin{aligned}
\limsup_{t\to\infty} L(t) &\leq \limsup_{t\to\infty} \frac{\beta I(t) e^{\int_0^t (\mu(\tau)+k+r_2)d\tau}}{(\mu(t)+k+r_2)e^{\int_0^t (\mu(\tau)+k+r_2)d\tau}} \\
&= \limsup_{t\to\infty} \frac{\beta I(t)}{\mu(t)+k+r_2} = 0.
\end{aligned}$$

The same argument gives $\limsup_{t\to\infty} L(t) = 0 \Rightarrow \limsup_{t\to\infty} I(t) = 0$.

Case 1: If $kL(t) \geq (\mu(t) + k + r_2)I(t)$ holds for all $t > 0$, then $\frac{dI}{dt} > 0$ directly implies $\limsup_{t\to\infty} I(t) > 0$;

Case 2: If $kL(t) < (\mu(t) + k + r_2)I(t)$ holds for all $t > 0$, then $\limsup_{t\to\infty} I(t) > 0$.

The proof of Case 2 is as follows: Suppose $\limsup_{t\to\infty} I(t) = 0$, then

$$\begin{aligned}
\frac{dL}{dt} &\geq \beta\frac{I(t)}{N(t)}\left(N(t) - \frac{\mu(t) + d(t) + r_1}{k}I - I\right) - \frac{(\mu(t) + d(t) + r_1)(\mu(t) + k + r_2)}{k}I \\
&= \left(\beta - \frac{(\mu(t) + d(t) + r_1)(\mu(t) + k + r_2)}{k}\right)I + o(I^2) \\
&\geq \left(\beta - \frac{(\mu^\infty + d^\infty) + r_1)(\mu^\infty + k + r_2)}{k}\right)I + o(I^2) \\
&= \frac{(\mu^\infty + d^\infty) + r_1)(\mu^\infty + k + r_2)}{k}(R^\infty - 1)I + o(I^2) > 0, \text{ for } t >> 1.
\end{aligned}$$

This implies that $\limsup_{t\to\infty} L(t) > 0$ which contradicts the assumption $\limsup_{t\to\infty} I(t) = 0$.

Trajectories of System (5-6) cannot intercept $kL(t) = (\mu(t)+d(t)+r_1)I(t)$ infinitely many times if $I(t) \to 0$ as $t \to \infty$ because $\frac{dL}{dt} > 0$ on $kL(t) = (\mu(t) + d(t) + r_1)I(t)$ whenever $R^\infty > 1$. Therefore, $\limsup_{t\to\infty} I(t) = 0$ implies that either $kL(t) > (\mu(t) + d(t) + r_1)I(t)$ or $kL(t) \leq (\mu(t) + d(t) + r_1)I(t)$ holds eventually. Hence, $\limsup_{t\to\infty} I(t) > 0$. □