MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **1**, Number **1**, June **2004**

http://math.asu.edu/~mbe/

pp. **81–93**

INFLUENCE OF BACKWARD BIFURCATION ON INTERPRETATION OF R_0 IN A MODEL OF EPIDEMIC TUBERCULOSIS WITH REINFECTION

Benjamin H. Singer and Denise E. Kirschner

Department of Microbiology and Immunology
The University of Michigan Medical School
Ann Arbor, MI 48109-0620

(Communicated by Carlos Castillo-Chavez)

Abstract. There is significant disagreement in the epidemiological literature regarding the extent to which reinfection of latently infected individuals contributes to the dynamics of tuberculosis (TB) epidemics. In this study we present an epidemiological model of *Mycobacterium tuberculosis* infection that includes the process of reinfection. Using analysis and numerical simulations, we observe the effect that varying levels of reinfection has on the qualitative dynamics of the TB epidemic. We examine cases of the model both with and without treatment of actively infected individuals. Next, we consider a variation of the model describing a heterogeneous population, stratified by susceptibility to TB infection. Results show that a threshold level of reinfection exists in all cases of the model. Beyond this threshold, the dynamics of the model are described by a backward bifurcation. Uncertainty analysis of the parameters shows that this threshold is too high to be attained in a realistic epidemic. However, we show that even for sub-threshold levels of reinfection, including reinfection in the model changes dynamic behavior of the model. In particular, when reinfection is present the basic reproductive number, R_0, does not accurately describe the severity of an epidemic.

1. **Introduction.** Tuberculosis (TB), an infectious disease caused by the bacterium *Mycobacterium tuberculosis*, is estimated to infect one-third of the world's population and results in nearly 3 million deaths per year [1, 2, 3]. The high burden of TB infection in regions of Southeast Asia, Africa, and Russia has highlighted the need for global TB control [4, 5]. The emergence of drug-resistant strains of *M. tuberculosis* [5] and TB/HIV coinfection [6, 7, 8] will likely impact TB treatment and control strategies [9, 4].

The long period of latency in *M. tuberculosis* infection prior to the onset of active disease introduces additional ambiguity into understanding disease progression. Since initial infection is separated so dramatically in time from the development of disease, it is unclear whether the transition from latency to active disease is due to endogenous reactivation or exogenous reinfection [10, 11]. The relative importance of these two pathways to the development of active disease has significant

2000 *Mathematics Subject Classification.* 93D30, 34G20, 92D20.

Key words and phrases. TB, Epidemic, backward bifurcation, reinfection, R_0, heterogenous populations.

implications for treatment and control strategies, most notably in deciding whether latently infected and treated individuals are at risk of reinfection [12].

On the population level, epidemiological measurements of exogenous reinfection have proved extremely difficult. Effective treatment of tuberculosis with antibiotics makes studying reinfection on the individual level a tractable problem, since treatment can be considered a barrier to endogenous reactivation. However, several studies employing RFLP analysis of *M. tuberculosis* isolates from individuals with recurrent infection after treatment indicate that both reinfection and reactivation are possible, but offer conflicting views of their relative importance [13, 14, 15, 16]. The influence of local TB incidence on the probability of reinfection is unclear. While it seems natural to assume that reinfection will be found only in high incidence environments where latently infected individuals are constantly re-exposed to *M. tuberculosis*, some studies have found reinfection in low-incidence populations [15, 17].

Several authors have investigated the role of exogenous reinfection in TB and other epidemic diseases through the use of mathematical models. Vynnycky and Fine, by fitting an age-structured model to historical TB data in England and Wales, conclude that reinfection likely played an important role in that epidemic [18]. Several modeling studies have highlighted the bifurcation behavior of compartmental models when reinfection is considered [19, 20, 21]. Taking a more abstract approach, van den Driessche and colleagues have demonstrated the occurence of backward bifurcations in a number of general models describing infectious disease dynamics [19, 21]. This type of bifurcation behavior allows for the existence of multiple positive steady states, leading to different threshold conditions for the onset of an epidemic and its elimination. Here, we follow the method of Feng *et al.*, who construct a compartmental model for TB transmission with reinfection [20]. It has already been shown that models of this type do not demonstrate a backward bifurcation or multiple equilibria under realistic parameter values [**?**]. Our approach differs from this previous work, however, both in our model construction and analysis. We examine models describing the spread of TB in both homogeneous and heterogeneous populations. We demonstrate that the model of [22], like others, does not produce a backward bifurcation under realistic conditions. However, we explore not only bifurcation conditions of the model, but also the influence of reinfection on model behavior in the absence of a backward bifurcation. A key focus is whether the concept of R_0 is still valid in the context of backward bifurcations during a reinfection scenario.

2. **The Model.**

Our mathematical model of epidemic TB with reinfection is a direct extension of work on epidemic TB and HIV in populations stratified by genotype [23, 22, 24]. The model is specifically constructed to capture the behavior of epidemic TB in heterogeneous populations with two subgroups, one inherently more susceptible to infection with *M. tuberculosis* than the other. This model is used primarily to investigate the influence of various parameters on the steady-state of the TB epidemic, unlike work by others which explore the evolution of TB epidemics over time [25]. We now expand our model presented in [23] to study reinfection. Since reinfection in epidemic TB is not well characterized, including reinfection in the model allows us to study the influence of different levels of reinfection on the qualitative dynamics of a TB epidemic. In this study, we are not

concerned with inferring values for the reinfection parameters. Rather, we are interested in the different bifurcation patterns that occur when reinfection is present in the system, and the interplay of the reinfection parameter with the basic reproduction number, R_0. To this end, we define the level of reinfection in our system as the ratio of the transmission rate of *M. tuberculosis* between actively infected and latently infected individuals to the transmission rate between actively infected and unifected individuals. Specifically, we explore whether the levels of reinfection that are necessary to influence bifurcation behavior are consistent with those expected to occur in a real epidemic, and whether subthreshold levels of reinfection modify the interpretation of R_0.

We use a system of six nonlinear, ordinary differential equations to model the dynamics of *M. tuberculosis* infection within a heterogeneous population. As in [23] we divide the population in groups with neutral and susceptible phenotypes with respect to *M. tuberculosis* infection. We let $U_N(t)$ and $U_S(t)$ represent the number of uninfected individuals of neutral and susceptible phenotype, respectively. Similarly, $L_N(t)$ and $L_S(t)$ represent latently infected individuals, while $T_N(t)$ and $T_S(t)$ represent those with active infection. Suppressing the time dependence t of each variable and setting $P(t) = U_N(t) + U_S(t) + L_N(t) + L_S(t) + T_N(t) + T_S(t)$, the equations are as follows. Note that in the case $c_N = c_S = 0$, the model reduces to that of [22].

$$\frac{dU_N}{dt} = b\,(1-\nu) - \beta_w\,U_N\frac{T_N}{P} - \beta_x\,U_N\frac{T_S}{P} - \mu U_N \tag{1}$$

$$\frac{dU_S}{dt} = b\,\nu - \beta_y\,U_S\frac{T_N}{P} - \beta_z\,U_S\frac{T_S}{P} - \mu U_S \tag{2}$$

$$\begin{aligned}\frac{dL_N}{dt} = {} & (1-p_N)\beta_w\,U_N\frac{T_N}{P} + (1-p_N)\beta_x\,U_N\frac{T_S}{P} - c_N p_N\beta_w\,L_N\frac{T_N}{P} - \\ & c_N p_N\beta_x\,L_N\frac{T_S}{P} - (1-lt_N)\,r_n\,L_N + at_N\,T_N - \mu L_N\end{aligned} \tag{3}$$

$$\begin{aligned}\frac{dL_S}{dt} = {} & (1-p_S)\beta_y\,U_S\frac{T_N}{P} + (1-p_S)\beta_z\,U_S\frac{T_S}{P} - c_S p_S\beta_y\,L_S\frac{T_N}{P} - \\ & c_S p_S\beta_z\,L_S\frac{T_S}{P} - (1-lt_S)\,r_S\,L_S + at_S\,T_S - \mu L_S\end{aligned} \tag{4}$$

$$\begin{aligned}\frac{dT_N}{dt} = {} & p_N\beta_w\,U_N\frac{T_N}{P} + p_N\beta_x\,U_N\frac{T_S}{P} + c_N p_N\beta_w\,L_N\frac{T_N}{P} + \\ & c_N p_N\beta_x\,L_N\frac{T_S}{P} + (1-lt_N)\,r_n\,L_N - at_N\,T_N - (\mu+\mu_{tb})T_N\end{aligned} \tag{5}$$

$$\begin{aligned}\frac{dT_S}{dt} = {} & p_S\beta_y\,U_S\frac{T_N}{P} + p_S\beta_z\,U_S\frac{T_S}{P} + c_N p_S\beta_y\,L_S\frac{T_N}{P} + c_N p_S\beta_z\,L_S\frac{T_S}{P} \\ & +(1-lt_S)\,r_S\,L_S - at_S T_S - (\mu+\mu_{tb})T_S\end{aligned} \tag{6}$$

In previous work, we have distinguished between two sets of parameter values for the model (Table 1). One represented an epidemic in a population with high growth (HG) demographics of India, while the other represented low growth (LG) demographics of the United States[23, 22]. In order to provide results with the greatest generality, we have merged the intervals of these two parameter sets and

sample from the largest possible interval for the simulations presented here. For parameter values and derivations, see [22].

Param.	Definition	HG Values	LG Values
b	birth rate	25,567,802/yr	3,892,489
ν	frequency of susceptability allele	30%	10%
μ	non-TB death rate	0.01587/yr	0.01314
μ_{tb}	TB death rate	0.8 year^{-1}	0.8
β_w	# secondary infections ($UN \otimes TN$)	[5, 7] time^{-1}	[3, 5]
$\beta_x = \epsilon_x \beta_w$	# secondary infections ($UN \otimes TS$)	[7, 9] time^{-1}	[5, 7]
$\beta_y = \epsilon_y \beta_w$	# secondary infections ($US \otimes TN$)	[7, 9] time^{-1}	[5, 7]
$\beta_z = \epsilon_z \beta_w$	# secondary infections ($US \otimes TS$)	[9, 11] time^{-1}	[7, 9]
p_N	direct progression, neutral	5% – 10%	5% – 10%
$p_S = \epsilon_p p_N$	direct progression, susceptible	10% – 0.20%	10% – 0.20%
r_N	reactivation rate, neutral	0.00167 – 0.0033/yr	0.00125 – 0.0025/yr
$r_S = \epsilon_r r_N$	reactivation rate, susceptible	0.0033 – 0.0066/yr	0.0025 – 0.0050/yr
lt_N, lt_S	effective chemoprophylaxis, neutral	5 – 15%	5 – 15%
at_N, at_S	per capita therapy, neutral	0.342857 – 3.2/yr	0.342857 – 3.2/yr

TABLE 1. Parameters and values.

Fig. 1 shows the model diagram. The model follows a standard incidence-dependent model of transmission among infected individuals. These expressions are used to model nonlinear contact dynamics in large populations [26, 27].

To account for treatment, we follow our work on TB treatment in [22] and define lt_i as the fraction of the population receiving effective chemoprophylaxis, and at_i as the rate of effective per capita therapy ($i = N, S$). In the model, chemoprophylaxis of latently infected individuals (L_N, L_S) reduces their reactivation rate, and that initiation of therapeutics causes active infection to subside into latency. We do this since it is not known to what extent treated individuals are protected from subsequent infection or reactivation. Other models consider treatment by including a fourth population of 'treated individuals' into their compartmental model; however, most of the limited data available on this topic support that it is unlikely that treated individuals are removed from the SIR dynamics governing TB (c.f. [20, 28, 29]).

A detailed description of the baseline model for epidemic *M. tuberculosis* transmission can be found in [23] and [22].

3. **Bifurcation Behavior.** Many epidemiological models have defined a threshold condition that indicates whether an infection introduced into a population will be eliminated or become endemic [30]. The basic reproduction number, R_0, is defined as the average number of secondary infections produced by an infected individual in a completely susceptible population [27]. In models with only two steady states and a transcritical bifurcation, $R_0 > 1$ implies that the endemic state is stable (i.e the infection persists), and $R_0 \leq 1$ implies that the uninfected state is stable (i.e. the infection is eliminated).

We know both from the results of [20] and preliminary numerical experiments with the model given in equations (1) - (6) that models including reinfection may exhibit a backward, rather than a transcritical, bifurcation. Using the the same method for calculating R_0 as in [23], we find the expression for R_0 is unchanged by the presence of exogenous reinfection. That R_0 does not change when reinfection is included in the model is not entirely unexpected. The basic reproductive number,

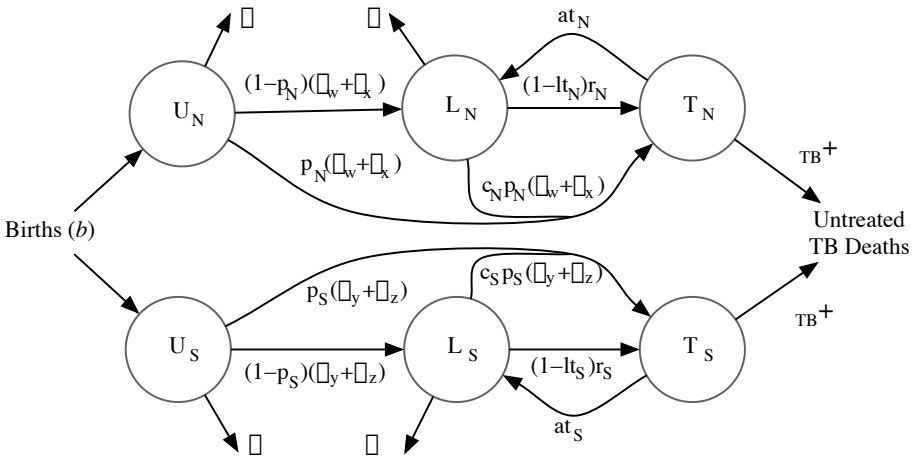

FIGURE 1. TB epidemic model including the genetically neutral (U_N, L_N, T_N) and genetically susceptible (U_S, L_S, T_S) populations. Births (b) occur at a constant rate with a fraction (ν) being genetically more susceptible to infection. Transmission/receipt of *M. tuberculosis* is represented by β_j $(j = w, x, y, z)$. Direct progression to active TB and the reactivation rate of latent infections are represented by p_i and r_i, respectively. We account for all-cause death μ, and death due to active TB, μ_{TB}. Treatment of latently and/or actively infected individuals is shown by lt_i and at_i, respectively. Reinfection transmission rates of *M. tuberculosis* are scaled by c_i. In all cases $i = N, S$.

as discussed in [30], expresses the number of secondary infections that will result when an infectious individual is introduced into an uninfected population. Since reinfection requires both latently infected and actively infectious individuals, we do not expect it to alter the dynamics of an uninfected population.

In the presence of reinfection, then, the value of R_0 does not completely describe the equilibrium behavior of the model. We analyze the existence of and threshold conditions for the onset of backward bifurcation, following the method of [20]. We first consider the case of a homogeneous population, or $\nu = 0$. Mathematically, the system of three ODEs (1), (3), and (5) has three steady state solutions. Because our model does not use a separate compartment for treated individuals, we can solve for these solutions explicitly, without limiting assumptions. These solutions are only epidemiologically meaningful, however, if they are finite and non-negative. Since a key characteristic of the backward bifurcation is the existence of three non-negative steady states, this allows us to specify a threshold condition on the reinfection parameter, c. Solving for the steady-state solutions using the method of [20] and suppressing the N, S notation, this condition is:

$$c \geq c_0 = \frac{at + \mu + \mu_{tb} + (1 - lt)\, r - \mu_{tb} p}{p(\beta - \mu - \mu_{tb})} \tag{7}$$

When $c \leq c_0$, the system can only realize two non-negative steady states, and thus has a single transcritical bifurcation at $R_0 = 1$. In the $c \leq c_0$ regime, the system has a single steady state solution, corresponding to zero prevalence and elimination of the TB epidemic, when $R_0 \leq 1$. When $R_0 > 1$, the system has two

steady states corresponding to endemic TB and zero prevalence. When $c > c_0$, the backward bifurcation has three steady state patterns. As in the transcritical bifurcation case, $R_0 > 1$ indicates the existence of both endemic and elimination states. In contrast to the transcritical bifurcation, there are three steady states when R_0 is immediately less than unity. If we fix a value of c, the upper and lower steady state curves meet at a single point: the limit point of the backward bifurcation. We refer to the limit point, as expressed on the R_0 scale, as R_c. For $R_0 \leq R_c$, there is only a single steady state corresponding to elimination of TB from the population.

Although we have derived a condition for the existence of various steady states of the system, we conduct no stability analysis for these steady states. Rather, we are concerned with determining if the conditions for the onset of a backward bifurcation in this model may be met under epidemiologically realistic conditions.

3.1. **Existence of the backward bifurcation.** The estimated value of R_0 is often used as an indicator for the severity of an epidemic, and forcing $R_0 < 1$ may be a goal for designing infection control and treatment measures for the elimination of an epidemic. The occurrence of a backward bifurcation, then, has important implications for the design of epidemiological control measures, since an epidemic may persist at steady state even if $R_0 < 1$ [12, 20, 18, 19].

Understanding whether our model predicts the occurrence of a backward bifurcation in the dynamics of an actual epidemic requires knowing both the backward bifurcation threshold, c_0, and the value of the reinfection parameter, c, in the given epidemic. Since reinfection has only been documented in small-scale studies, it is difficult to make precise estimates for c [31, 15, 13, 16]. However, using a method to determine uncertainty in a system due to parameters variation (Latin Hypercube Sampling, or LHS, c.f. [32, 33]), we can estimate a distribution for c_0.

Ranges for all parameters are given in [23, 22]. For the homogeneous population model, we merge the intervals estimated for high-growth and low-growth populations to give the broadest possible sample space for LHS. We then assume that each parameter range is uniformly distributed. By applying uncertainty analysis, we randomly sample the entire space of parameter value combinations in the model. each set by using equation (7). We construct a frequency histogram of the c_0 distribution over 20000 samples over two conditions (Fig. 2). First, we consider the distribution of c_0 in an untreated population ($at = 0$). Then, to visualize the influence of treatment on the bifurcation behavior of the model, we fix $at = 3$ (implies effective treatment of 79% of the population) to simulate the effect of highly effective therapy for active TB.

The estimated distributions for c_0 in the single population model have means of 2.1 and 10.6 for the $at = 0$ and $at = 3$ cases, respectively. Significantly, these distributions are bounded below. In the case without treatment, the distribution has a quick decaying tail. With the addition of treatment, the distribution shifts upward, with a slow decaying tail. However, the distribution is still sharply bounded below when treatment is included in the model (Fig. 2).

Analytical results for our model extend only to the simplified system of three equations for the homogeneous population. To investigate the possible influence of population heterogeneity on the threshold conditions for backward bifurcation, we study the behavior of the full system in equations (1) through (6).

To estimate the distribution of c_0 for the heterogeneous population model, we employ a straightforward iterative method. We first make the simplifying assumption

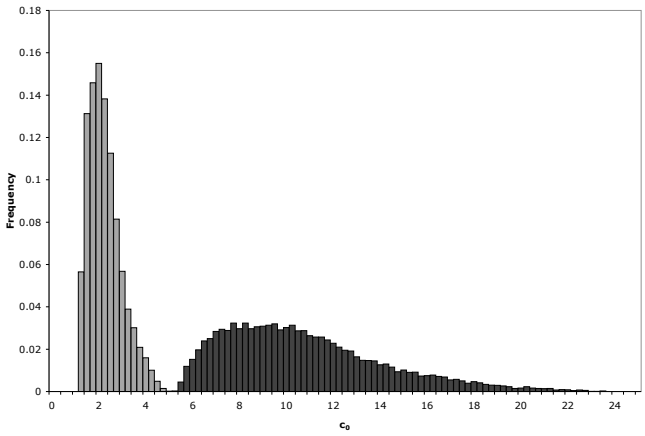

FIGURE 2. Distribution of values for c_0 under LHS in the single population model. Light gray: $at = 0$ (no treatment), dark gray: $at = 3$ (high treatment). Sample size $N = 20000$.

that the rate of reinfection is the same for both subpopulations (i.e. $c = c_N = c_S$), and therefore there is only a single bifurcation parameter associated with reinfection. The backward bifurcation is distinguished from the transcritical bifurcation by having three non-negative steady states in the region of parameter space where R_0 is less than unity but greater than the limit point of the backward bifurcation, R_p. Therefore, our procedure for determining the threshold value of c for the onset of backward bifurcation revolves around monitoring the number of steady states at a point in parameter space where R_0 is slightly less than unity. We sample parameter space with LHS, then solve $R_0 = 1 - \epsilon$ for a single parameter. The value of c is then incremented until three steady states appear at $R_0 = 1 - \epsilon$. This method of approximating the backward bifurcation threshold introduces several sources of error into the estimated distribution of c_0. However, these errors all lead to a broadening of the tail in the distribution of c_0 without affecting the distribution's lower bound (data not shown).

The estimated distributions for c_0 in the heterogeneous population model have means of 4.1 and 16.7 for the untreated and treated cases ($at = 0$ and $at = 3$ cases), respectively. As in the single population case, these distributions are bounded below. In the untreated case, the distribution has a quickly decaying tail. With the addition of treatment, the distribution shifts upward, with a slowly decaying tail. However, the distribution is still sharply bounded below when treatment is included in the model.

3.2. **Sub-threshold levels of reinfection.** Our results and the results of others show that the threshold level of reinfection (c_0) required for a backward bifurcation to occur is too high to be expected in a realistic epidemic [**?**]. However, the

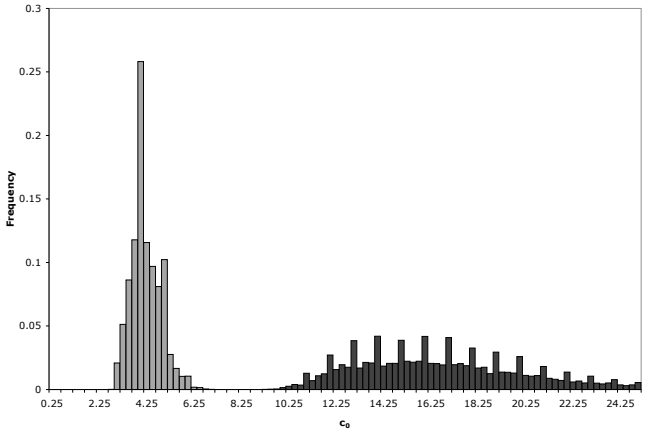

FIGURE 3. Distribution of values for c_0 under LHS in the heterogeneous population model. Light gray - $at = 0$, dark gray - $at = 3$. $N = 10000$, $\epsilon = .001$.

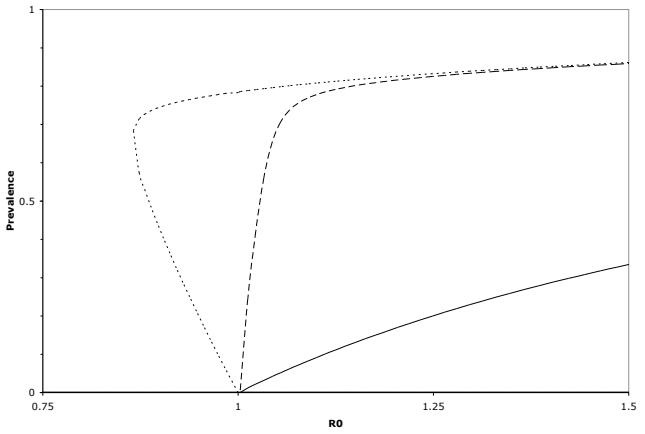

FIGURE 4. Onset of backward bifurcation with increasing reinfection. Solid curve: $c = 0$ (no reinfection). Dashed curve: $c < c_0$ (low level of reinfection). Dotted curve: $c > c_0$ (high level of reinfection).

sub-threshold behavior of the model still has important implications for the interpretation of epidemiological measures in the presence of reinfection. As can be seen

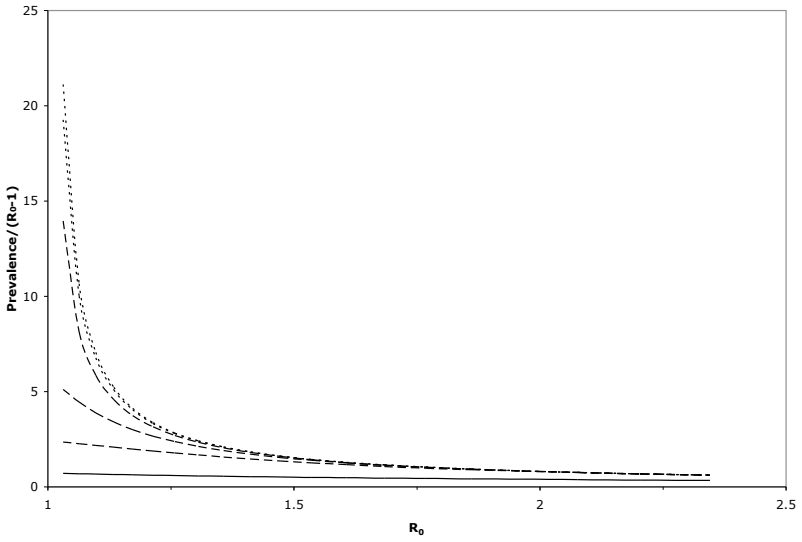

FIGURE 5. Plot of prevalen ce normalized by R_0 for multiple values of the reinfection threshold, c_0. For $c = 0$ (no reinfection), the line is nearly horizontal. For $c \geq c_0$ (superthreshold reinfection), dotted curves are overlapping and highly nonlinear. Dashed curves corresponding to $0 < c < c_0$ (subthreshold reinfection) show a continuum of nonlinearity between the no-reinfection case and the onset of backward bifurcation.

in Fig. 4, the transition from a transcritical to backward bifurcation at $R_0 = 1$ does not occur suddenly as c passes c_0. Rather, if steady-state prevalence is plotted as a function of R_0, the slope of the curve at the bifurcation point $R_0 = 1$ gradually increases as c increases. At $c = c_0$, the curve is vertical, and for $c \geq c_0$ the region of multiple steady states is apparent. For $R_0 >> 1$, however, all steady-state curves converge, regardless of the value of c.

The gradual transition from transcritical to backward bifurcation has important implications for model behavior. The behavior of the model in parameter regions that correspond to $R_0 > 1$ may be strikingly different the cases of $c = 0$ and $c_0 > c > 0$. In particular, a sub-threshold level of reinfection may dramatically increase prevalence even in the case of a single equilibrium. In Fig. 5, we plot $\frac{Prevalence}{R_0 - 1}$, the slope of the chord through the steady-state curve, as a function of R_0 for various values of c. For $c = 0$, the slope is nearly constant and R_0 is a good predictor of prevalence. For $c \geq c_0$, the slope approaches a constant as $R_0 \to \infty$ and approaches infinity as $R_0 \to 1$. This is expected, because after the onset of a backward bifurcation $R_0 = 1$ no longer corresponds to the elimination of epidemic disease in the model. However, it is important to note that for subthreshold levels of c, even those far below c_0, there is a several-fold change in the value of the slope

as $R_0 \to 1$. Therefore, in the presence of reinfection, the relationship between R_0 and prevalence is significantly nonlinear even for cases where the model exhibits only a transcritical bifurcation. This suggests that for a given epidemic, exogenous reinfection contributes significantly to prevalence and epidemic severity.

4. **Discussion.** The transmission and progression of TB infection has long been understood only on a population scale. With the advent of molecular fingerprinting for TB strains, the infection and transmission history of a single individual may be studied [34, 15, 35, 36, 17]. One of the principal aspects of TB transmission can be studied only in the context of this individual infection history. Our previous models of TB progression and transmission assume that once an individual is infected with TB, he or she is immune from further infection events [23, 22]. However, the availability of individual, strain-specific infection histories has made it clear that reinfection of latently or actively infected individuals does occur. It is unclear, though, whether reinfection occurs commonly enough to have an effect on the overall infection dynamics of the population [37].

Here, we extend our previous modeling framework for the transmission of TB in homogeneous and heterogeneous populations to include the process of reinfection of latently and actively infected individuals [22]. In the simplified case of a homogeneous population, we derive an analytical solution for steady states. Using this solution, we demonstrate that the model exhibits two distinct modes of bifurcation behavior. When the parameter c, which specifies the efficiency of reinfection relative to *de novo* infections, is small, the model has a transcritical bifurcation at the point in parameter space specified by $R_0 = 1$, as the model did in the absence of reinfection. Above a critical threshold value of reinfection, the system undergoes a backward bifurcation at $R_0 = 1$. We derive an expression for the critical value of the reinfection parameter, c_0 in terms of the other parameters of the system.

Using the LHS technique for uncertainty analysis, we then estimate a distribution for c_0 given plausible estimates for the values of the parameters of the simplified system. We also employ LHS and numerical computation of the steady states to estimate a distribution of c_0 in the heterogeneous population model.

Several groups have examined the influence of including reinfection in models of TB transmission or in more general models of infectious disease dynamics [19, 38, 20, 18]. They have found, as we have here, that the onset of backward bifurcation is tied to a threshold in the relative efficiency of reinfection. The existence of the backward bifurcation has important implications for the design of treatment protocols because it indicates that an epidemic cannot be eliminated from a population by simply reducing the value of the basic reproduction number, R_0, below 1.

Although our results here and the results of others indicate that the backward bifurcation is a possible description for the dynamics of epidemic TB, we find that the onset of the backward bifurcation is unlikely to occur in a realistic epidemic. In the homogeneous population model, the distribution of c_0 is bounded below at a value above 1. Therefore, the model predicts that a backward bifurcation will only occur when reinfection occurs at a rate which is actually higher than the initial infection rate. When treatment of actively infected individuals is added to the model, the distribution of c_0 shifts to the right, indicating that a backward bifurcation is even less likely to occur in a population with effective treatment. These results are not confined to the simplified, homogeneous population model. The results for the heterogeneous population model also indicate that reinfection

must be more efficient than initial infection for a backward bifurcation to occur, and that treatment only increases that value of c_0.

In the context of the homogeneous population model, we can easily derive analytical expressions for both R_0 and the steady-state solutions of the system, and so R_0 is primarily useful as an aggregate bifurcation parameter. However, in the heterogeneous population model such an analytical solution is not available and a numerical solution is obtained with difficulty. In this case, and indeed in many models for which R_0 is derived using different methods (such as the Next Generation Operator, Next Generation Kernel, or implicit [21, 38, 23] methods) in the absence of a steady-state solution, we look to R_0 not only as an aggregate of parameters but as an indicator of the severity of an epidemic.

In doing so, however, we make an implicit assumption of linearity in the relationship between R_0 and prevalence. We have shown, though, that in the presence of exogenous reinfection ($c > 0$) the relationship between R_0 and prevalence is far from linear. This demonstrated nonlinearity in the relationship between R_0 and prevalence in the presence of reinfection may serve as a caveat applicable in the modeling of other diseases. Recently, attention has been devoted to the possible role of reinfection in more generalized models than are considered here [38]. Even in situations where models do not bear out the presence of complex bifurcation behavior such as backward bifurcations in the behavior of an epidemic, this result demonstrates that the interpretation of R_0 and other indirect measures of an epidemic may be confounded by reinfection.

Acknowledgements: The authors wish to thank Dr. Carlos Castillo-Chavez for helpful discussions and Dr. Zhilan Feng for helpful suggestions on the manuscript. This work was supported by NIH grant # R01 HL62119 awarded to DEK.

REFERENCES

[1] D. Bleed, C. Watt, and C. Dye, "World Health Report 2001: Global Tuberculosis Control," tech. rep., World Health Organization, WHO/CDS/TB/2001.287, 2001. (http://www.who.int/gtb/publications/globrep01/index.html).

[2] B. Bloom, ed., *Tuberculosis: Pathogenesis, Protection and Control*. Washington D.C.: ASM Press, 1994.

[3] D. Snider Jr., M. Raviglione, and A. Kochi, *Global Burden of Tuberculosis*, pp. 3–11. In Bloom [2], 1994.

[4] K. Floyd, L. Blanc, M. Raviglione, and J. Lee, "Resources required for global Tuberculosis control," *Science*, vol. 295, pp. 2040–2041, 2002.

[5] L. Reichman and J. H. Tanne, *Timebomb: The Global Epidemic of Multi-Drug-Resistant Tuberculosis*. New York, NY: McGraw Hill, 2002.

[6] D. Kirschner, "Dynamics of co-infection with *Mycobacterium tuberculosis* and HIV-1," *Theoretical Population Biology*, vol. 55, pp. 94–109, 1999.

[7] T. Porco, P. Small, and S. Blower, "Amplification dynamics: predicting the effect of HIV on Tuberculosis outbreaks," *Journal of Acquired Immune Deficiency Syndromes*, vol. 28, pp. 437–444, 2001.

[8] Z. Toossi, J. Johnson, R. Kanost, W. Mianda, H. Luzze, P. Peters, A. Okwera, M. Joloba, P. Mugyenyi, R. Mugerwa, H. Aung, J. Ellner, and C. Hirsch, "Increased replication of HIV-1 at sites of *Mycobacterium tuberculosis* infection: potential mechanisms of viral activation," *Journal of Acquired Immune Deficiency Syndromes*, vol. 28, pp. 1–8, 2001.

[9] American Thoracic Society, "Treatment of Tuberculosis and Tuberculosis infection in adults and children," *American Journal of Respiratory and Critcal Care Medicine*, vol. 149, pp. 1359–1374, 1994.

[10] J. Romeyn, "Exogenous reinfection in tuberculosis," *American Review of Respiratory Diseases*, vol. 101, no. 6, pp. 923–927, 1970.

[11] W. Stead, "Pathogenesis of a first episode of chronic pulmonary tuberculosis in man: Recrudescence of residuals of the primary infection or exogenous reinfection?," *American Review of Respiratory Diseases*, vol. 95, pp. 729–???, 1967.

[12] P. Fine and P. Small, "Exogenous reinfection in Tuberculosis," *The New England Journal of Medicine*, vol. 341, pp. 1226–1227, 1999.

[13] A. van Rie, R. Warren, M. Richardson, T. Victor, R. Gie, D. Enarson, N. Beyers, and P. van Helden, "Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment," *New England Journal of Medicine*, vol. 341, no. 16, pp. 1174–1179, 1999.

[14] A. de Boer, R. van Soolingen, and M. Borgdorff, "Recurrent tuberculosis due to exogenous reinfection," *New England Journal of Medicine*, vol. 342, no. 14, pp. 1050–1051, 2000.

[15] A. Bandera, A. Gori, L. Catozzi, A. Eposti, G. Marchetti, C. Molteni, G. Ferrario, L. Codecasa, V. Penati, A. Matteelli, and F. Franzetti, "Molecular epidemiology study of exogenous reinfection in an area with low incidence of tuberculosis," *Journal of Clinical Microbiology*, vol. 39, no. 6, pp. 2213–2218, 2001.

[16] J. Caminero, M. Pena, M. Campos-Herrero, J. Rodriguez, O. Afonso, C. Martin, J. Pavon, M. Torres, M. Burgos, P. Cabrera, P. Small, and D. Enarson, "Exogenous reinfection with tuberculosis on a european island with moderate incidence of disease," *American Journal of Respiratory and Critical Care Medicine*, vol. 163, pp. 717–720, 2001.

[17] D. de Viedama, M. Marin, S. Harnangomez, M. Diaz, M. Serrrano, A. L, and E. Bouza, "Tuberculosis recurrences: Reinfection plays a role in a populations whose clinical/epidemiological characteristics do not favor reinfection," *Archives of Internal Medicine*, vol. 162, no. 16, pp. 1873–1879, 2002.

[18] E. Vynnycky and P. Fine, "The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection," *Epidemiology and Infection*, vol. 119, pp. 183–201, 1997.

[19] K. Hadeler and P. van den Driessche, "Backward birucation in epidemic control," *Mathematical Biosciences*, vol. 1997, no. 146, pp. 15–35, 1997.

[20] Z. Feng, C. Castillo-Chavez, and A. Capurro, "A model for tuberculosis with exogenous reinfection," *Theoretical Population Biology*, vol. 57, pp. 235–247, 2000.

[21] P. van den Driessche and J. Watmough, "Reproduction number and sub-threshold endemic equilibria for compartmental models of disease transmission," *Mathematical Biosciences*, 2002. Submitted.

[22] B. Murphy, B. Singer, and D. Kirschner, "On the treatment of tb in heterogenous populations,"

[23] B. Murphy, B. Singer, S. Anderson, and D. Kirschner, "Comparing epidemic tuberculosis in demographically distinct heterogeneous populations," *Mathematical Biosciences*, vol. 182, pp. 161–185, 2002.

[24] A. Sullivan, J. Wigginton, and D. Kirschner, "The coreceptor mutation CCR5Δ32 influences the dynamics of HIV epidemics and is selected for by HIV," *PNAS*, vol. 18, pp. 10214–10219, 2001.

[25] J. Aparicio, A. Capurro, and C. Castillo-Chávez, "Markers of disease evolution: the case of Tuberculosis," *Journal of Theoretical Biology*, vol. 215, no. 2, pp. 227–237, 2002.

[26] H. Hethcote, "Qualitative analysis of communicable disease models," *Mathematical Biosciences*, vol. 28, pp. 335–356, 1976.

[27] H. Hethcote, "The mathematics of infectious diseases," *SIAM Review*, vol. 42, no. 4, pp. 599–653, 2000.

[28] J. Aparicio, A. Capurro, and C. Castillo-Chávez, "On the fall and rise of Tuberculosis," tech. rep., Department of Biometrics, College of Agriculture and Life Sciences, Cornell University, 2000. http://www.biom.cornell.edu/.

[29] S. Blower and J. Gerberding, "Understanding, predicting, and controlling the emergence of drug-resistant tuberculosis: a theoretical framework," *Journal of Molecular Medicine*, vol. 76, pp. 624–636, 1998.

[30] F. Brauer and C. Castillo-Chávez, *Mathematical Models in Population Biology and Epidemiology*. Texts in Applied Mathematics, New York, NY: Springer-Verlag, 2001.

[31] M. Murray and E. Nardell, "Molecular epidemiology of tuberculosis: achievements and challenges to current knowledge," *Bulletin of the World Health Organization*, vol. 80, no. 6, pp. 477–480, 2002.

[32] S. Blower and H. Dowlatabadi, "Sensitivity and uncertainty analysis of complex models of disease transmission: an HIV model, as an example," *International Statistics Review*, vol. 62, no. 2, pp. 229–243, 1994.
[33] M. Sanchez and S. Blower, "Uncertainty and sensativity analysis of the basic reproductive rate," *American Journal of Epidemiology*, vol. 145, pp. 1127–1137, 1997.
[34] R. Sahavedan, C. Naranayan, C. Paramasivan, R. Prabhakar, and P. Naranayan, "Restriction length polymorphism typing of clinical isolates of *mycobacterium tuberculosis* from patients with pulmonary tuberculosis in madras, india but use of direct-repeat probe," *Journal of Clinical Microbiology*, vol. 33, no. 11, pp. 3037–3039, 1995.
[35] L. Fitzpatrick, A. Okwera, R. Megerwa, R. Rizdon, J. Ehiner, and I. Onorato, "An investigation of suspected exogenous reinfection in tuberculosis patients in kampala, uganda," *International Journal of Tuberculosis and Lung Diseases*, vol. 6, no. 6, pp. 550–552, 2002.
[36] A. Kruuner, L. Pehme, S. Ghebremichael, T. Koivula, S. Hoffner, and M. Mikelsaar, "Use of molucular techniques to distinguish between treatment failure and exogenous reinfection with mycobacterium tuberculosis," *Clinical Infectious Diseases*, vol. 35, pp. 146–155, 2002.
[37] P. van Helden, "Molecular epidemiology of tb: challenging dogmas and asking new questions," *IUBMB Life*, vol. 53, pp. 219–223, 2002.
[38] M. Martcheva and H. Thieme, "Progression age enhanced backward bifurcation in an epidemic model with super-infection," *Journal of Mathematical Biology*, vol. 46, no. 5, pp. 385–424, 2003.

Received on Feb. 28, 2004. Revised on March 5, 2004.

E-mail address: kirschne@umich.edu
E-mail address: singerb@umich.edu