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Practical aspects of backward bifurcation in a mathematical model for tuberculosis

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HIGHLIGHTS

- We examine practical aspects of backward bifurcation for a model of tuberculosis.
- We identify the aspects of TB that make backward bifurcation more likely to occur.
- We consider the magnitude and sensitivity of the resulting backward bifurcations.
- Resulting bifurcations may be too small to have noticeable epidemiological impact.

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ABSTRACT

In this work, we examine practical aspects of backward bifurcation for a data-based model of tuberculosis that incorporates multiple features which have previously been shown to produce backward bifurcation (e.g. exogenous reinfection and imperfect vaccination) and new considerations such as the treatment of latent TB infection (LTBI) and the BCG vaccine's interference with detecting LTBI. Understanding the interplay between these multiple factors and backward bifurcation is particularly timely given that new diagnostic tests for LTBI detection could dramatically increase rates of both LTBI detection and vaccination in the coming decades.

By establishing analytic thresholds for the existence of backward bifurcation, we identify those aspects of TB's complicated pathology that make backward bifurcation more or less likely to occur. We also examine the magnitude of the backward bifurcation produced by the model and its sensitivity to various model parameters. We find that backward bifurcation is unlikely to occur. While increased vaccine coverage and/or increased detection and treatment of LTBI can push the threshold for backward bifurcation into the region of biological plausibility, the resulting bifurcations may still be too small to have any noticeable epidemiological impact.

1. Introduction

Tuberculosis (TB) infection has been present throughout much of human history. In fact, evidence of TB has even been found in 500,000 year-old hominin fossils (Kappelman et al., 2008). Despite this long history and the fact that successful treatment therapies for TB have been known for decades, it is currently estimated that a third of the world's population is infected with TB. Tuberculosis remains one of the three deadliest infectious diseases in the world; HIV/AIDS, TB and malaria are often referred to as "The Big 3." One reason for TB's stubborn persistence is the lack of an ideal vaccine for tuberculosis. The Bacille Calmette-Guérin (BCG) vaccine is one of the world's safest and least expensive vaccines, but hundreds of clinical trials have estimated its efficacy in preventing infection everywhere from 0 to 84% (Centers for Disease Control and Prevention, 1996; Hart and Sutherland, 1977). Complicating matters further, BCG can interfere with the ability to detect latent tuberculosis infection (LTBI) as vaccination can cause positive tuberculin skin test (TST) results (used to detect LTBI) in uninfected individuals. Consequently, policies regarding the use of BCG vary throughout the international community (World Health Organization, 2004; Centers for Disease Control and Prevention, 1996; Infuso and Falzon, 2006; Gerberry and Milner, 2012) and many countries are currently considering changes to their BCG policies (Infuso and Falzon, 2006).

Beyond its public health impact, the unique pathogenesis of TB has made the disease particularly interesting and rewarding to study using mathematical models (Castillo-Chavez and Song,

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2004). One characteristic is an extended period of latency in which the infected individual is asymptomatic and noninfectious. The vast majority of those infected with TB will remain latently infected for life and never develop infectious TB. However, during this extended latent period, an individual can be reinfected with a new external strain of the disease through a process known as exogenous reinfection. Another complex feature of TB is that evidence suggests that recovery from infectious TB can make one more susceptible to subsequent infection (Verver et al., 2005).

One topic of particular interest to mathematical modelers of TB has been backward bifurcation; the situation in which reducing the basic reproductive number below 1 is not sufficient to eradicate infection (Feng et al., 2000). Theoretically, this phenomenon has been linked to several central characteristics of TB epidemiology, including imperfect intervention strategies, incomplete immunity, vaccination and limited treatment resources.In this work, we investigate a mathematical model for TB based on that of Gerberry and Milner (2012) and Gerberry (2009) that includes the major pathogenesis of TB as well as imperfect vaccination (through multiple modes of protection), vaccine waning, detection and treatment of LTBI and the interference between vaccination and LTBI treatment. In doing so, we illustrate the impact of these characteristics on both the existence of backward bifurcation and the magnitude of the backward bifurcation if it occurs. The results have policy implications in the coming decades as improved detection technologies for LTBI known as interferon-gamma release assays (IGRAs) become more readily available (Lalvani and Pareek, 2010; Al-Orainey, 2009; Oxlade et al., 2007). IGRAs are more accurate than TST in detecting LTBI and are not confounded by previous BCG vaccination. Therefore, the potential exists for these new technologies to push TB towards eradication by dramatically increasing rates of both LTBI detection and vaccination.

The structure of our paper is as follows: in Section 2, we discuss backward bifurcation and summarize the relevant literature. In Section 3, we formulate a mathematical model for the epidemiology of tuberculosis. In Section 5, we characterize the disease-free equilibrium, basic reproductive number and the average duration of infectious TB. In Section 4 we establish biologically reasonable parameter values for the model. In Section 6, we establish analytic conditions for the existence of backward bifurcation and in Section 7, we examine the magnitude of the resulting backward bifurcation using numerical techniques.

2. Background

The basic reproductive number $\mathcal{R}_0$ is defined as the average number of secondary infections caused by a single infection introduced into a completely susceptible population. In most compartmental models for infectious disease, $\mathcal{R}_0$ determines whether an infection can persist in a population. If $\mathcal{R}_0 > 1$, the average infected individual can replace their own infection as well as contribute additional infection into the population and the disease can invade the population. If $\mathcal{R}_0 < 1$, the average infected individual cannot replace their own infection and the disease consequently dies out. Mathematically, this is realized through a forward, or supercritical, bifurcation at $\mathcal{R}_0 = 1$ (see Fig. 1a). In this situation, asymptotic stability is exchange between the disease-free equilibrium (DFE), which is asymptotically stable for $\mathcal{R}_0 < 1$, and the endemic equilibrium, which exists for $\mathcal{R}_0 > 1$.

For some models of infectious disease, the relationship between $\mathcal{R}_0$ and the persistence of infection is more complicated. In the situation of a backward, or subcritical, bifurcation, it is possible for an asymptotically stable endemic equilibrium to exist despite having $\mathcal{R}_0 < 1$. As illustrated in Fig. 1b, the asymptotic stability of the DFE is the same (i.e. asymptotically stable for $\mathcal{R}_0 < 1$ and unstable for $\mathcal{R}_0 > 1$) as with forward bifurcation. The difference is that the endemic equilibrium that appears at $\mathcal{R}_0 = 1$ is unstable, exists for values of $\mathcal{R}_0 < 1$ and is accompanied by a larger asymptotically stable endemic equilibrium.

The epidemiological implications for backward bifurcation are considerable and have been nicely described by Dushoff et al. (1998) and Brauer (2004). Summarizing their discussions, backward bifurcation is important in at least three critical ways:

- For fixed model parameters, it is possible for a disease to persist even if $\mathcal{R}_0 < 1$. Specifically, this occurs if the initial prevalence of infection is greater than the prevalence at the unstable endemic equilibrium.
- For an endemic setting in which control measures are reducing the reproductive number, the condition that $\mathcal{R}_0 < 1$ is not sufficient to eradicate the disease. Rather, the reproductive number must be reduced beyond an eradication threshold, which we denote $\mathcal{R}_0^*$ (see Fig. 1b), in order to eliminate the disease.
- For a setting in which $\mathcal{R}_0$ increases across the threshold of $\mathcal{R}_0 = 1$, the equilibrium prevalence is discontinuous as a function of $\mathcal{R}_0$. As the reproductive number crosses 1 from below, the introduction of an arbitrarily small number of infected individuals results in an endemic equilibrium prevalence $P^* > 0$ (see Fig. 1b).

While several mechanisms have been shown to be capable of producing the behavior, a general framework for thinking about backward bifurcation is to consider the infectious potential of an average infected individual, which we refer to as Patient A. In the standard case of forward bifurcation, Patient A's infectious potential is maximized when the rest of the population is uninfected (i.e. Patient A's maximum infectious potential is equal to $\mathcal{R}_0$). If other

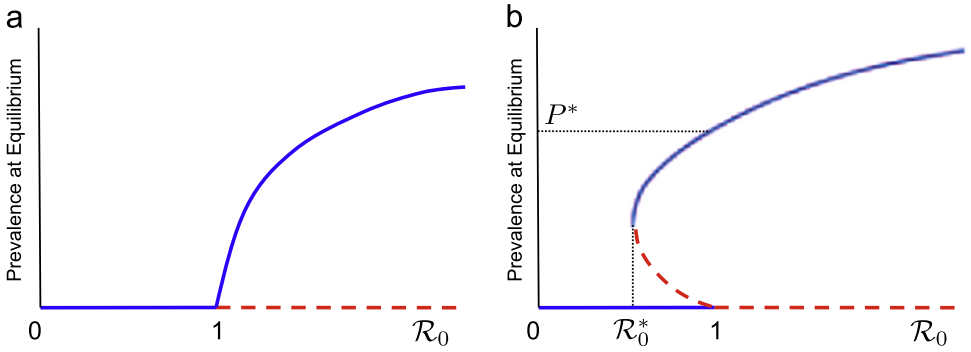

Fig. 1. Bifurcation curves illustrating forward and backward bifurcation at $\mathcal{R}_0 = 1$. Solid blue lines represent asymptotically stable equilibria. Red dashed lines represent unstable equilibria. We refer to $\mathcal{R}_0^*$ as the eradication threshold and P^* as the endemic prevalence at $\mathcal{R}_0 = 1$. (a) Forward bifurcation at $\mathcal{R}_0 = 1$. (b) Backward bifurcation at $\mathcal{R}_0 = 1$. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)