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Emergent heterogeneity in declining tuberculosis epidemics

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Abstract

Tuberculosis is a disease of global importance: over 2 million deaths are attributed to this infectious disease each year. Even in areas where tuberculosis is in decline, there are sporadic outbreaks which are often attributed either to increased host susceptibility or increased strain transmissibility and virulence. Using two mathematical models, we explore the role of the contact structure of the population, and find that in declining epidemics, localized outbreaks may occur as a result of contact heterogeneity even in the absence of host or strain variability. We discuss the implications of this finding for tuberculosis control in low incidence settings.

Keywords: Epidemiology; Networks; Mathematical model; Delay model; Reinfection

1. Introduction

Tuberculosis (TB) is caused by infection with the bacterium *Mycobacterium tuberculosis*. The bacilli spread through the respiratory route: individuals with active disease may transmit infection if the airborne particles produced when they cough, talk, and sing are inhaled by others. Once infected, individuals enter a period of latency during which they exhibit no symptoms and are not infectious to others. While most are able to contain this infection indefinitely, at least 10% will eventually progress to disease and expose others (Sutherland et al., 1982, 1976; Styblo, 1991). Although approximately one-third of the world's population harbors a latent *M. tuberculosis* infection (Dye, 2006), this statistic belies the great heterogeneity in risk among individuals and among different countries. In some areas the lifetime risk of infection nears 100% while in others the probability of exposure is minimal.

Mathematical modeling has proven a valuable tool for understanding TB dynamics (Blower et al., 1995; Vynnycky and Fine, 1997; Feng et al., 2000; Singer and Kirschner, 2004) and has served as the basis for establishing control targets and assessing policy strategies (Blower et al., 1996; Dye et al., 1998; Cohen et al., 2006). However, most such models, with occasional exceptions (Schinazi, 1999), have been differential equation susceptible-exposed-infected-recovered (SEIR) models that assume a homogenously mixed population. In populations where people contact only a small subset of the population (such as their colleagues, friends, families, etc.), respiratory diseases such as TB are more likely to be transmitted among local groups of contacts. Non-random mixing introduces "contact structure", which is defined here as the number of contacts each individual has (degree distribution), the extent to which those contacts are also connected to each other (clustering), and the average distance of those connections in a spatially distributed population (locality; spatial structure). This heterogeneity may substantially affect model predictions about the spatial spread of disease, infection/reinfection dynamics, local inter-strain competition and threshold behavior (May and Lloyd, 2001; Gupta and Hill, 1995; Pastor-Satorras and Vespignani, 2001; Meyers et al., 2003; Schinazi, 1999).

In areas where the burden of TB is low and continues to decline, localized outbreaks nonetheless sporadically occur. Variability in host susceptibility and strain-specific

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differences in virulence and transmissibility (fitness) have been examined as explanatory factors for location-specific disease patterns (Valway et al., 1998; Murphy et al., 2002). Here we explore the null hypothesis that localized outbreaks can occur during declining epidemics as a result of locally constrained contact structure, even when the population is otherwise homogeneous. In order to test this hypothesis, we develop two models of TB epidemics that encapsulate the same natural history: a baseline differential equation model imposing homogeneous mixing, and a network model on a class of spatially structured networks. We modify the extent to which contacts are constrained to be local on the networks and examine declining epidemics under fully homogeneous mixing, networks with long-range contacts and networks with short-range contacts.

2. The models

2.1. Natural history of TB

The dynamics of TB within individual hosts (sometimes called the disease's *natural history*) are complex. Upon infection, individuals enter a latent state during which they are not infectious or symptomatic. From latency, there are three routes to active TB: primary progression, in which the infection progresses to active disease within the first 5 years; endogenous reactivation, in which an old infection activates, and exogenous reinfection, in which a new infection, acquired after an older infection, progresses to active disease.

The rate of progression from latency to active disease varies with the time since infection: for the first approximately 5 years after infection, this progression rate p_1 is considerably higher than it is subsequently (p_2) (Sutherland et al., 1976; Horwitz, 1969; Vynnycky and Fine, 1997). If an individual does not progress from latent infection to active disease during the first few years after the initial infection, he or she may remain latently infected for many years. However, a new exposure to the disease is thought to transiently increase the risk of progression.

The variable progression rate from latency to active disease has been modeled in several ways. Some modelers have split the latent class into "fast" and "slow" progressors, with fixed portions α and $1-\alpha$ of susceptibles entering fast-progressing and slow-progressing latent classes upon infection. This structure specifies that a portion $1-\alpha$ of individuals have some innate protection from TB, while a portion α are predestined to be "fast progressors". While this approach has the advantage of simplicity, it has the disadvantage that such models are very sensitive to α, which is very difficult to measure. Other authors have modeled this variable progression rate by including arbitrarily distributed latent periods (Feng et al., 2001) or using partial differential equations that include age and maturation of infection (Vynnycky and Fine, 1997).

Here, we present two models in which we avoid predestining the portion of fast and slow progressors. Both of the models are based on an SEIR framework where the recovered class, R, is accessible only after antibiotic treatment is introduced (circa 1950). Following Vynnycky and Fine (1997), we assume that the original infection confers some partial immunity which protects against progression to active disease, but not against the acquisition of a new infection.

While infants are at high risk of disease if infected with TB, because smear-positive pulmonary TB (the most infectious manifestation of disease) is rare in childhood, children are not thought to play an important role in the continued transmission of disease within communities (Styblo, 1991). Additionally, in areas where TB has been declining for many years, the average age of infection will be relatively high and there is likely only to be a small number of children who have been infected by TB. For these reasons, we have chosen to represent only adults in our model and have chosen baseline parameter values to represent the natural history of disease among these individuals. Because our intent is to examine the hypothesis that localized outbreaks can emerge in a homogeneous population with contact structure, we do not include sources of individual heterogeneity such as age-specific risks of progression, variable susceptibility or differences in TB strain transmissibility or virulence.

2.2. Modeling approach

Most models of TB epidemics have been differential equation models that assume a homogeneously mixed population. Our goal is to explore the effect of non-random mixing. To this end it is useful to have not only a network model, but also a baseline model that assumes homogeneous mixing and represents the natural history of TB in the same way. We therefore develop a differential equation model, making use of a delay to include the dependence of the risk of disease progression on the time since infection.

In the differential equation model, the population is homogeneously mixed, so it is not possible to examine local inhomogeneities. However, it is possible to directly measure the contribution of reinfection to disease incidence; if disease is locally clustered we expect to observe an increased frequency of reinfection. Therefore, comparing reinfection in the two models allows us to estimate the amount of additional reinfection induced by the introduction of contact structure. If local contact structure leads to substantially increased reinfection, this indicates that there is sufficient local clustering of disease to affect the dynamics of transmission, which has implications for policy control (Gomes et al., 2004).

In the network model, we can also directly estimate the amount of spatial variability in disease burden; this quantity does not have a directly comparable analogue in the differential model.