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The epidemiological consequences of leprosy-tuberculosis co-infection

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ABSTRACT

While in antiquity both leprosy and tuberculosis were prevalent in Europe, leprosy declined thereafter and, simultaneously, tuberculosis prevalence increased. Since both diseases are caused by mycobacterial infections, it has been suggested that there might be a causal relationship between both epidemics.

Chaussinand observed the inverse prevalence of leprosy and tuberculosis and suggested that individuals with a latent tuberculosis infection are protected from acquiring leprosy. His cross-immunity hypothesis has been countered more recently by a co-infection hypothesis. The latter suggestion, proposed by Donoghue, states that people being infected with multi-bacillary leprosy are more susceptible to tuberculosis, which leads to increased mortality from the disease.

This study utilizes mathematical modeling to explore the epidemiological consequences of the co-infection hypothesis for realistically confined parameter values. While the co-infection hypothesis appears plausible at first glance, a second thought reveals that it comprises also substantial consequences for tuberculosis epidemics: if co-infection raises the mortality rate above that of purely tuberculosis infected persons, then tuberculosis might as well be eradicated by leprosy. It is the specific interplay of both increased susceptibility towards tuberculosis and increased death rate when co-infected that determines the epidemiological fate.

As a result of this analysis, it is shown that there is a large parameter region where the eventual disappearance of leprosy could indeed be explained by co-infection. This parameter region is considerably larger than that predicted by the cross-immunity hypothesis. This shows that the co-infection hypothesis should be considered a significant alternative to the cross-immunity hypothesis. The time scales at which the effects of co-infection are observed depend critically on the spatial distribution of the individuals but reach epidemiologically realistic values for rather immobile individuals with local interaction.

1. Introduction

Leprosy was prevalent in Europe until the first millennium and thereafter but nearly disappeared during the great tuberculosis epidemic of the 17th and 18th centuries. Tuberculosis remained at epidemic levels until these days. It has not been agreed why leprosy historically declined. However, it is assumed that the decreasing incidence of leprosy is related to an increasing incidence of tuberculosis. Chaussinand observed an inverse relation between the prevalence of leprosy and that of tuberculosis in the epidemiological evolution of both diseases in different settings [1]. Similarly, Wood reported decreasing incidence of leprosy when the incidence of tuberculosis increased for data from Norway from the mid-19th to the mid-20th century [2]. This evolution is assumed to be independent of socio-economic factors, that are were commonly attributed to both diseases. One explanation of the underlying mechanism that couples the epidemic course of leprosy with that of tuberculosis is the cross-immunity hypothesis. It was proposed by Chaussinand [1] and mathematically assessed by Lietman et al. [3]. The suggestion is that individuals that have been previously exposed to tuberculosis acquire protection against leprosy. If the basic reproductive number of leprosy was low enough, cross-immunity would have significant epidemiological consequences leading to the disappearance of leprosy [3]. Both tuberculosis and leprosy are mycobacterial diseases that are closely related [4], but the nature of their relationship has not been agreed so far. There is evidence that a certain level of cross-immunity exists which protects individuals with a latent tuberculosis infection from acquiring leprosy [5,6]. However, there is also evidence for concomitant occurrence of leprosy and tuberculosis in the same organism. Donoghue and coworkers examined selected archaeological samples, dating from Roman period to the thirteen century [7]. They found that several specimens with palaeopathological signs of leprosy contained DNA from both pathogens, indicating that these diseases coexisted in the past. Therefore, they suggested that the immunological changes found in multi-bacillary leprosy, in association with the socio-economic impact on those suffering from the disease, led to increased susceptibility to and mortality from tuberculosis and thus led to the historical decline in leprosy.

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This is the hypothesis of leprosy-tuberculosis co-infection which provides an alternate mechanism to explain the inverse coupling of leprosy and tuberculosis incidences.

Notice that the term co-infection is used in different meanings in the literature. The usage in this work is according to Donoghue et al. [7]. The concepts of co-infection and super-infection that are applied by Nowak and May [8,9], for instance, are slightly different and not applicable to the situation modeled here.

This study utilizes mathematical modeling to analyze the epidemiological consequences of Donoghue's co-infection hypothesis for realistically constraint parameter values. The epidemic model which is developed here is a system of ordinary differential equations (ODEs). It describes the number of individuals in different states of infection in a well-mixed population. By employing linear stability analysis, it is shown that there is a large parameter region where the eventual disappearance of leprosy could indeed be explained by co-infection. This parameter region is considerably larger than that predicted by the cross-immunity hypothesis. This shows that the co-infection hypothesis should be considered a significant alternative to the cross-immunity hypothesis. These results are supported by exemplary simulations of a related, spatially explicit model where immobile individuals interact with each other locally by following a stochastic rule. The latter model, an interacting particle system (IPS), is linked to the ODE model by a mean-field approximation procedure. Thus, it is demonstrated that the results concerning the long-time behavior are robust with respect to spatial effects. This is important since the motility of individuals might be one factor that has changed over time and since it is known that space matters in the epidemiological context. In fact, the temporal scales at which the effects of co-infection are observed depend critically on the spatial distribution of the individuals. For the IPS model, epidemiologically realistic time scales are reached.

2. Material and methods

The epidemiological model used in this analysis is a system of ordinary differential equations. It describes the number of individuals per unit time that change to or from a state of infection. To assess the impact of spatial effects, the results obtained by analyzing this model are compared to the simulation outcomes of a related spatially extended, individual-based model.

The underlying assumptions follow the main aspects of the co-infection hypothesis of Donoghue, which postulate that

(i) leprosy-infected individuals are more susceptible to tuberculosis infection;
(ii) individuals co-infected with leprosy and tuberculosis have a higher mortality rate than purely leprosy-infected individuals [7].

2.1. ODE model

As a first step, simple transmission models for both tuberculosis in the absence of leprosy and leprosy in the absence of tuberculosis are developed, see Figs. 1 and 2. These models are based on previously developed models where healthy and susceptible people (H) may become latently infected (W) with a certain rate [10,3]. A proportion of the latently infected persons develops the active and infectious disease (T or L). Thereby, the original tuberculosis transmission model, developed in [10] combines a slow and a fast pathway towards infection, see Fig. 1(a). The original leprosy transmission model developed in [3] distinguishes between paucibacillary and multibacillary forms of leprosy. Given the fact that Donoghue's hypothesis bases on the immunological changes found in patients with multibacillary leprosy (see [7]), the paucibacillary form shall be disregarded in the co-infection model developed here (Fig. 2(a)). In the following, when speaking about leprosy the multibacillary form is meant. In addition, the latent state is of minor importance when focusing on the co-infection of the infectious forms of leprosy and tuberculosis. Therefore, the number of infection states is reduced here to healthy and susceptible (H) and infected (L or T). The refined models [10,3] allow to realistically reproduce observed transmission behavior. Here however, the interest lies in developing an analytically accessible model for tuberculosis-leprosy co-infection. Therefore, it is necessary to simplify the basic tuberculosis and leprosy transmission models as much as possible while maintaining their predictive strength. The transition rates from healthy to infected states are adjusted in such a way that the basic reproductive number of either disease is the same as for the according original models, see Figs. 1(b) and 2(b). Notice that the basic reproductive number for a single disease is the product of the transmission risk and the average time a case is infectious. In this context, the transmission risk is the average number of susceptibles that one infectious case infect per unit time. The basic reproductive number thus describes the number of infectious cases produced by a single infectious individual in a totally susceptible population [11]. The basic reproductive number of tuberculosis was determined in [10], that for leprosy in [3]. Choosing

$$\gamma_T = \beta_T\left(p + (1-p)\frac{\upsilon_T}{\upsilon_T + \mu}\right), \quad \gamma_L = \beta_L\frac{\nu_L}{\nu_L + \mu} \tag{1}$$

for the transmission rates in the simplified models (Figs. 1(b) and 2(b)), the basic reproductive numbers of the simple and the more complex models (Figs. 1(a) and 2(a)) agree:

$$\mathcal{R}_T = \frac{\Pi}{\mu}\frac{\gamma_T}{\mu + \mu_T}, \quad \mathcal{R}_L = \frac{\Pi}{\mu}\frac{\gamma_L}{\mu + \mu_L}. \tag{2}$$

That means that, the stability behavior of the simplified transmission models coincides with that of the original models: If the basic reproductive number is smaller than one, the infection fades away. If it is larger than one the infection persists in the long run. In a second step, the transmission models for the single infections are combined into a co-infection model, see Fig. 3. Persons already infected with leprosy can become infected with tuberculosis at a rate γ_T^L. This rate differs from the tuberculosis infection rate γ_T by an factor θ_L, that is $\gamma_T^L = \theta_L\gamma_T$. Individuals with or without tuberculosis become infected with leprosy at rates γ_L^T and γ_L, respectively, where $\gamma_L^T = \theta_T\gamma_L$. The mortality rate of co-infected individuals (C) is μ_C. Following the main aspects of the co-infection hypothesis of Donoghue, it is assumed firstly that $\theta_L > 1$, due to the higher susceptibility of leprosy-infected people. Secondly, it is assumed that $\mu_C \gg \mu_L$, due to the higher mortality rate of co-infected individuals. There is no evidence that pre-infection with tuberculosis increases the susceptibility to leprosy, thus $\theta_T \leqslant 1$. In the case of $0 < \theta_T < 1$, cross-immunity of tuberculosis-infected individuals against acquiring leprosy is modeled, in a slightly simplified way compared to [3]. However, the focus here is put on the effects of co-infection therefore θ_T is set to $\theta_T = 1$. Notice that, the model decouples into two independent transmission models for leprosy and tuberculosis, respectively, if co-infection is excluded by setting $\theta_L = \theta_T = 0$. Regarding the birthrate, the following assumption applies: in the absence of disease-induced death, the birthrate equals the mortality rate. Therefore, the birthrate is set to

$$\Pi = \mu N_0 \quad \text{where } N_0 := N(0) = H(0) + L(0) + T(0) + C(0).$$

Thus, the non-standardized system of differential equations describing the dynamics of the combined model, depicted in Fig. 3, is given by