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Tuberculosis models with fast and slow dynamics: the role of close and casual contacts

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This paper is dedicated to the memory of John A. Jacquez, our friend and teacher.

Abstract

Models that incorporate local and individual interactions are introduced in the context of the transmission dynamics of tuberculosis (TB). The multi-level contact structure implicitly assumes that individuals are at risk of infection from close contacts in generalized household (clusters) as well as from casual (random) contacts in the general population. Epidemiological time scales are used to reduce the dimensionality of the model and singular perturbation methods are used to corroborate the results of time-scale approximations. The concept and impact of optimal average cluster or generalized household size on TB dynamics is discussed. We also discuss the potential impact of our results on the spread of TB.

Keywords: Generalized households; Epidemic models; Social networks; Time scales; Singular perturbation theory; Tuberculosis

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1. Introduction

Disease and population dynamics have characteristic time scales. Influenza dynamics in humans exhibit 'super fast' dynamics at the individual and community levels when compared to the host's (humans) demography [1,2]. This is so, because the average life span of a human host is about 4000–8000 times greater than the average duration of a 'flu' infection and, consequently, most 'flu' outbreaks go through local communities before any significant demographic change can be observed (a couple of months). Hence, in the study of 'flu' epidemics often two characteristic time scales are useful in the study of its dynamics: the time scale of the disease and the host's life span.

Tuberculosis (TB) is 'typically' described as a slow disease because of its long and variable latency period distribution and because of its short and relatively narrow infectious period distribution. Most latently infected individuals do not become actively infectious (active TB). Some become infectious within a five-year window while others do it after a long period of time (possibly decades). On the other hand, infectious individuals remain so for relatively short periods of time in part due to the generalized use of antibiotics (an average of six months but see [3]). Since secondary infections are generated from infectious individuals then actively infectious individuals have a relatively small window of opportunity to infect others. Hence, TB infections of susceptible individuals occur on the same time scale as that of the recovery of individuals from active TB. TB progression, movement from the latent to the active stage, takes place on a time scale which is of the same order of magnitude as that of the average life span of the human host population.

TB may be acquired at random (individual level), that is, via casual contacts, or through membership in an epidemiologically active (e.a.) generalized household (cluster) that includes at least one actively infected individual. The selection of these (non-independent) levels of transmission is not arbitrary but tied in to the observed sociology of TB spread as well as two of the characteristic time scales associated with TB's life history [4].

This view of the transmission process (adopted in this paper) induces the division of the host population under consideration into two sub-populations. The first is composed of groups of individuals (clusters), which, as a first approximation, are assumed to have the same average size while the second is composed of those individuals who are not members of e.a. clusters. Clusters come into epidemiological existence, that is, become e.a. when one of its members develops active TB.

The first sub-population is therefore composed of individuals in e.a. clusters. Arguments that support our assumption of non-overlap between e.a. clusters are provided later on. The assumption of non-overlapping cluster implies that the average life span of an e.a. cluster is roughly the same as that of the average period of TB infectiousness. It is also assumed that individuals who are not members of an e.a. cluster have a significantly lower risk of infection than those in e.a. clusters. This two-level approach, while increasing the dimensionality, allows for the use of some individual-level measurable epidemiological parameters, namely, those associated with the risk of transmission at the cluster level. We use singular perturbation theory and TB characteristic time scales to simplify the study of this higher dimensional model.

In summary, population and individual-level transmission processes that operate at different time scales are used to construct TB epidemic models with two levels of mixing. This approach is based on the belief that an individual's risk of infection is significantly higher within an e.a. cluster than from the 'general' population. This paper is organized as follows: a brief introduction to the epidemiology of TB is provided in Section 2; Section 3 reviews recent TB cluster models; Section 4

carries out the mathematical analysis of the cluster model; the existence of a globally transcritical bifurcation is established for the full two-level model and singular perturbation theory is used to establish the global nature of this bifurcation; Section 5 expands the framework to account for additional factors, for example, the concept of optimal cluster size is defined towards the end of Section 5; theoretical results are corroborated with the help of numerical simulations in Section 6; final remarks and conclusions are collected in Section 7.

2. Epidemiology of TB

TB was assumed to be on its way 'out' in developed countries until the number of TB cases began to increase in the late 1980s. The causes behind recent observed increases of active TB cases are the source of many studies (see e.g., [5–12]). TB is an airborne transmitted disease. *Mycobacterium tuberculosis* droplets are released in the air by coughing or sneezing infectious individuals [13]. Tubercle bacillus carried by such droplets lives in the air for a short period time (about two hours) and, therefore, it is believed that occasional contacts with TB-active persons (infectious individuals) rarely lead to transmission (but see [14]) and that most secondary cases are the result of prolonged and sustained close contacts with a primary case. The case of a teacher–librarian with active TB who infected the children in her classroom but not the children who visited the library [15] supports the incorporation of differences between casual and close contacts. Latently infected individuals (inactive TB) become infectious (active TB) after a variable (typically long) latency period. Latent periods range from months to decades. Most infected individuals never progress towards the active TB state. On the other hand, average infectious periods are relatively short (few months but see [3]) and becoming shorter in developing nations due to the availability of treatment. There is a strong evidence [15] that TB transmission occurs mostly in groups of close associates of infectious individuals and that such a risk is limited to the life of the e.a. cluster (a couple of months) to which they belong. These beliefs, views and facts are incorporated into *as simple framework as possible* in the next section. In other words, a pedagogical model is used to explore the role of *casual* and *close* contacts on TB dynamics.

3. TB cluster-transmission models

Classical epidemic models (see e.g., [16]) incorporate heterogeneity at the population level via proportional or weighted random mixing. This approach pioneered by Nold in 1980 [17] and others has been quite successful in the study of the dynamics of communicable diseases, particularly childhood diseases. Efforts to expand the role of social dynamics (heterogeneity) on disease transmission and evolution have led researchers to the development of more comprehensive mixing frameworks [18,19]. Most specific efforts, with some notable exceptions [20–28], have focused on developing modeling frameworks that allow for non-random mixing at the population level. That is, most extensions operate at a single mixing level and, consequently, their use on the study of TB dynamics neglects important features, namely, the relative impact of close and casual contacts. The model and framework developed in [29], in which the concept of core group was introduced, provided the simplest caricature of a two-level approach. Their approach has found applications not only in gonorrhea control but also in the study of HIV [30–32].

TB models assume that the total population is divided into four epidemiological classes: susceptible (S), latent/exposed (E), infectious (I) and recovery/treated class (R). For diseases with a latent period such as TB, the general form of these models is as follows [8,9]:

$$\frac{dS}{dt} = \Lambda - \mu S - \beta_1 S\frac{I}{N}, \tag{1}$$

$$\frac{dE}{dt} = \beta_1 S\frac{I}{N} - (\mu + k + r_1)E - \beta_2 E\frac{I}{N} + \beta_3 R\frac{I}{N}, \tag{2}$$

$$\frac{dI}{dt} = kE + \beta_2 E\frac{I}{N} - (\mu + d + r_2)I, \tag{3}$$

$$\frac{dR}{dt} = r_2 I + r_1 E - \mu R - \beta_3 R\frac{I}{N}. \tag{4}$$

Here Λ is the recruitment rate; μ the natural mortality rate; d the TB induced mortality rate; β_1, β_2 and β_3 are the effective transmission rates; k is the rate of progression to active TB; r_1 and r_2 denote the treatment rates for latent class and infectious class, respectively; and, S, E, I and R represent the densities or population numbers of susceptible, latent, infectious, and recovered (treated) individuals, respectively. $N = S + E + I + R$ gives the total population size. The mixing in this model is homogeneous, that is, there is no assumed differences between individuals while disease transmission depends on the frequency of infecteds.

The *Basic Reproductive Number*, defined as the mean number of secondary cases produced by a 'typical' infectious individual in a population of (mostly) susceptibles, is given by

$$\mathscr{R}_0^{\mathrm{HM}} = \frac{\beta_1}{(\mu + d + r_2)}\frac{k}{(k + \mu + r_1)} = Q_0\frac{k}{(k + \mu + r_1)}, \tag{5}$$

where

$$Q_0 = \frac{\beta_1}{\gamma} \quad \text{and} \quad \gamma = \mu + d + r_2. \tag{6}$$

Q_0 represents the number of secondary (latently) infections produced by a typical infectious individual during the mean infectious period $1/\gamma$ while $f = k/(k + \mu + r_1)$ gives the probability of survival from the latent into the infectious stage.

It has been shown [9] that $\mathscr{R}_0^{\mathrm{HM}}$ is a sharp threshold. That is, whenever $\mathscr{R}_0^{\mathrm{HM}} \leqslant 1$ the disease-free equilibrium is globally asymptotically stable (an epidemic is not possible) while $\mathscr{R}_0^{\mathrm{HM}} > 1$ implies the existence of a unique globally asymptotically stable endemic equilibrium [33,34]. In other words, the disease either dies out or persists regardless of initial conditions. The assumption of homogenous mixing implies $\mathscr{R}_0^{\mathrm{HM}}$ is linear in the transmission parameter β_1. This is not only a limitation but obviously not correct in general.

A different approach introduced in [25] is briefly described below. It is assumed that only individuals who have frequent and long interactions with infectious individuals experience a high risk of TB infection. New infectious individuals activate clusters (group of individuals who come into regular and close contacts with an active case) increasing the risk of TB infection for the susceptible members of the e.a. cluster. A time scale argument and data (8×10^6 world new cases of active TB per year) support the assumption that most e.a. clusters include just one TB-infec-

tious individual. This simplification is useful because most latently infected individuals remain so for long periods of time (possibly decades) while most actively infectious individuals remain so for just a few months.

The average generalized household or average cluster size is assumed to be given by the constant n. The risk of acquiring TB in an e.a. cluster is assumed to be exponentially distributed with parameter β. Prevalence of active TB (I/N) is typically extremely low in developed as well as in most developing countries [35]. Hence, the probability that an infectious individual belongs to more than one e.a. cluster is so low that it is initially neglected. Consequently, the population of individuals in an e.a. cluster at time t has size $N_c(t) \approx (n+1)I(t)$, while the population size of non-infectious individuals in e.a. clusters is $N_1(t) = nI(t)$. By design, $N_1(t)$ includes two sub-populations: susceptibles (S_1) and latently infected (E_1), that is, $N_1(t) = nI(t) = S_1(t) + E_1(t)$. The population of individuals not belonging to e.a. clusters at time t will be denoted by $N_2(t)$. This last population consists only of susceptible and latently infected individuals, denoted by $S_2(t)$ and $E_2(t)$, respectively. The sub-population of recovered individuals is not included in this model in order to simplify the discussion (but its incorporation is straightforward [25]). A diagram of the model is given in Fig. 1 and definitions of parameters can be found in Table 1. The nature of the flows between compartments is described below:

Latently infected individuals, not belonging to e.a. clusters, are assumed to develop active TB at the rate kE_2. Each new infectious individual 'activates' a new cluster and in the process 'moves' nkE_2 individuals from the N_2 population into the N_1 population. It is assumed that $nkE_2(S_2/N_2)$ individuals go to the S_1 class per unit time while $nkE_2(E_2/N_2)$ individuals go to E_1 class per unit time. Furthermore, since infectious individuals recover or die (at rate γI) then the rate at which e.a. clusters become inactive (or die) is γI. Bookkeeping requires that recovery (or cluster dissolution) must be accompanied by the return of cluster members to the N_2 population. It is assumed that $n\gamma IS_1/N_1$ individuals are returned to S_2 and $n\gamma IE_1/N_1$ are returned to E_2, per unit time, respectively. The fact that $N_1 = nI$ reduces the last expression for the flow from S_1 to S_2 to simply γS_1 and that from E_1 to E_2 to γE_2. The (assumed) low prevalence of active TB implies that $N_1 \ll N_2$. We use this observation to neglect births into the N_1 population.

TB progression in the E_1 class is extremely unlikely because of the short average life of e.a. clusters. Hence, it is ignored. Finally, the assumption that $\gamma \gg \mu$, implies that deaths in the N_1

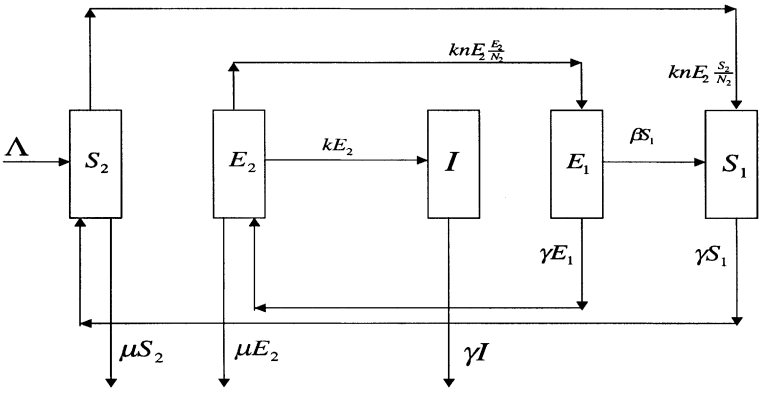

Fig. 1. Diagram of basic cluster model.

Table 1
Table of parameters

Symbol	Definition
Λ	Recruitment rate
μ	Natural mortality rate
n	Average size of generalized households
β_i	Transmission rates
$1/\gamma$	Mean infectious period
k	Per capita progression rate

population can also be neglected. The above considerations and *rough* approximations lead to the following basic cluster model [25]:

$$\frac{dS_1}{dt} = -(\beta+\gamma)S_1 + \frac{S_2}{N_2}nkE_2, \tag{7}$$

$$\frac{dE_1}{dt} = \beta S_1 - \gamma E_1 + \frac{E_2}{N_2}nkE_2, \tag{8}$$

$$\frac{dI}{dt} = kE_2 - \gamma I, \tag{9}$$

$$\frac{dS_2}{dt} = \Lambda - \mu S_2 + \gamma S_1 - \frac{S_2}{N_2}nkE_2, \tag{10}$$

$$\frac{dE_2}{dt} = \gamma E_1 - (\mu+k)E_2 - \frac{E_2}{N_2}nkE_2. \tag{11}$$

The basic reproductive number for the above model is

$$\mathscr{R}_0^c = \frac{\beta n}{(\beta+\gamma)}\frac{k}{(\mu+k)} = Q_0 f, \tag{12}$$

where the superscript c is used to identify it as the basic reproductive number associated with the cluster model. $\mathscr{R}_0^c$ is a non-linear function of β, the individual risk of infection in a cluster of size n and the mean infectious period $1/\gamma$. It is also a linear function of cluster size n. Hence, the expected number of infections produced by one infectious individual within his/her cluster is $Q_0 = \beta n/(\beta+\gamma)$ [25,28]. Among infected individuals only the fraction $f = k/(k+\mu)$ survives the latency period.

4. The dynamics analysis of cluster models

Previous work [25] directly regarded S_1, E_1 and I as fast variables and used quasi-steady-state assumptions (for definition, see [36,37]) justified by simulations. The goal of this section is to carry out a rigorous mathematical justification of the quasi-steady-state approximation used in [25].

The identification of radically distinct time scales provides an opportunity to look at disease dynamics under two different time windows. Systems with processor with characteristic multiple

time scales have been extensively studied [38,39]. Singular perturbation theory provides the foundation for the use of a multiple time-scale approach to the analysis of the dynamics of such systems. In fact, it has been systematically and rigorously applied to the study of dynamics on invariant manifolds. It often allows for the exploration of the dynamics of *some* perturbed system from unperturbed systems [40–42]. Two important results are: (1) when the slow manifold is not normally hyperbolic (see the definition in a review paper [43]) then periodic solutions are possible (for instance, relaxation oscillations in the van der Pol Equation) and (2) when the slow manifold is normally hyperbolic then a global attractor is possible. Hoppensteadt's earlier work [44] includes already sufficient conditions for the asymptotic stability of equilibria when the slow manifold is normally hyperbolic.

The variables in System (7)–(11) evolve at markedly different time scales. The time evolution of the variables S_1, E_1 and I is much faster than the time evolution of the variables S_2 and E_2.

Here, using singular perturbation theory, it is shown that the endemic equilibrium of System (7)–(11) is globally asymptotically stable when $\mathscr{R}_0^c > 1$. It is also shown, with the help of a Liapunov function, that when $\mathscr{R}_0^c \leqslant 1$ the disease-free equilibrium of System (7)–(11) is globally stable. That is, the global asymptotic dynamics are governed by a global transcritical bifurcation.

4.1. Re-scaling the model equations

The average period of infectiousness (about 3–4 months but see [3]) determines disease dynamics in the population of clusters while the disease evolves slowly in the N_2 population because progression to active TB is slow and uncommon. It has been estimated that only between 5% and 10% of infected individuals actually develop active TB during their entire life [45].

Time is re-scaled using the characteristic time of the N_2 population dynamics. That is, time is measured using the latency period $1/k$ as the unit of time, that is, time is re-scaled by letting $\tau = kt$. The independent variables S_2 and E_2 are rescaled by Ω, the total asymptotic population size ($\Omega = \Lambda/\mu$). N_1 could be re-scaled by Ω but it turns out more useful to rescale it by the balance factor $(k/(\beta+\gamma)\Omega)$. The re-scaled non-dimensional variables are: $x_1 = S_2/\Omega$, $x_2 = E_2/\Omega$, $y_1 = ((\beta+\gamma)/k)(S_1/\Omega)$, $y_2 = ((\beta+\gamma)/k)(E_1/\Omega)$, $y_3 = ((\beta+\gamma)/k)(I/\Omega)$. The re-scaled model equations can be written as

$$\frac{dx_1}{d\tau} = B(1-x_1) + (1-m)y_1 - n\frac{x_1x_2}{x_1+x_2}, \tag{13}$$

$$\frac{dx_2}{d\tau} = (1-m)y_2 - (1+B)x_2 - n\frac{x_2^2}{x_1+x_2}, \tag{14}$$

$$\epsilon\frac{dy_1}{d\tau} = -y_1 + n\frac{x_1x_2}{x_1+x_2}, \tag{15}$$

$$\epsilon\frac{dy_2}{d\tau} = my_1 - (1-m)y_2 + n\frac{x_2^2}{x_1+x_2}, \tag{16}$$

$$\epsilon\frac{dy_3}{d\tau} = x_2 - (1-m)y_3, \tag{17}$$

where $\epsilon = k/(\beta+\gamma)$, $m = \beta/(\beta+\gamma) < 1$ and $B = \mu/k$. The terms in the right-hand side of System (13)–(14) all have the same order of magnitude whenever $\epsilon \ll 1$ (see Section 6). Therefore, y_1, y_2 and y_3 are fast variables and x_1 and x_2 are slow variables.

4.2. TB dynamics on the slow manifold

Solving for the quasi-steady states y_1, y_2 and y_3 in terms x_1 and x_2 gives

$$y_1(t) = n\frac{x_1(t)x_2(t)}{x_1(t)+x_2(t)}, \tag{18}$$

$$y_2(t) = \frac{x_2(t)}{x_1(t)+x_2(t)}\,\frac{Q_0x_1(t)+nx_2(t)}{1-m}, \tag{19}$$

$$y_3(t) = \frac{x_2(t)}{(1-m)}. \tag{20}$$

Substituting these expressions into the equations for x_1 and x_2 in (13)–(14) leads to the equations of motion on the slow manifold, that is, to the system

$$\frac{\mathrm{d}x_1}{\mathrm{d}\tau} = B(1-x_1) - Q_0\frac{x_1x_2}{x_1+x_2}, \tag{21}$$

$$\frac{\mathrm{d}x_2}{\mathrm{d}\tau} = -(1+B)x_2 + Q_0\frac{x_1x_2}{x_1+x_2}, \tag{22}$$

where $Q_0 = nm = \beta n/(\beta+\gamma)$ is the number of secondary infections produced by one infectious individual in a population where everyone is susceptible. System (21)–(22) is a homogeneous mixing model whose transmission parameter, $Q_0 = \beta n/(\beta+\gamma)$, is a function of the microscopic individual-level parameters β, n, and γ. By definition, the basic reproductive number is $\mathscr{R}_0^{\mathrm{c}} = Q_0k/(k+\mu)$. It is straightforward to see that $\mathscr{R}_0^{\mathrm{c}}$ is a threshold parameter for the dynamics of Model (21)–(22). Theorem 1 characterizes the disease dynamics on the slow manifold:

Theorem 1. *If* $\mathscr{R}_0^c \leqslant 1$ *the disease-free equilibrium* (1,0) *is globally asymptotically stable. While if* $\mathscr{R}_0^c > 1$, (1,0) *is unstable and the endemic equilibrium*

$$x^* = (x_1^*, x_2^*) = \frac{B}{Q_0-1}(1, \mathscr{R}_0^{\mathrm{c}} - 1) \tag{23}$$

is globally asymptotically stable.

4.3. Global stability of endemic equilibrium

Whenever the basic reproductive number $\mathscr{R}_0^{\mathrm{c}}$ is greater than one, there exists a unique endemic equilibrium (see Theorem 4 in Appendix A). Furthermore, when ϵ is very small, it can be shown that the endemic equilibrium is globally asymptotically stable. In order to show this, we consider the following general singular perturbation system

$$\frac{dx}{dt} = f(x, y, \epsilon),$$

$$\epsilon \frac{dy}{dt} = g(x, y, \epsilon),$$

where ϵ is a small positive parameter, $x \in R^m$ and $y \in R^n$. The corresponding reduced system is given by the set of equations obtained when $\epsilon = 0$, namely,

$$\frac{dx}{dt} = f(x, y, 0),$$

$$0 = g(x, y, 0).$$

Let (x^*, y^*) be an equilibrium of the reduced system, that is, $g(x^*, y^*, 0) = 0$ and $f(x^*, y^*, 0) = 0$, then Theorem 2 (below), a special case Hoppensteadt's Theorem 2 [44], helps characterize the dynamics of this system near the slow manifold.

Theorem 2. Ref. [44].

Assume

(i) *The slow manifold,* $g(x, y, 0) = 0$, *is a graph, that is, there exists a function* $y = \phi(x)$ *such that* $g(x, \phi(x), 0) \equiv 0$.
(ii) *Both* $f(x, y, \epsilon)$ *and* $g(x, y, \epsilon)$ *have continuous and bounded derivatives with respect to* ϵ *and the state variables* x *and* y.
(iii) *The system* $dx/dt = f(x, \phi(x), 0)$ *has a globally stable fixed point* x^* *and* $y^* = \phi(x^*)$. *The matrix* $(f_x - f_y g_y^{-1} g_x)(x^*, y^*, 0)$ *has all eigenvalues with negative real parts.*
(iv) *The zero solution of the system* $dY/d\tau = g(\xi, \phi(\xi) + Y, 0)$ *is globally stable for any* ξ.
(v) *The eigenvalues of matrix* $g_y(x^*, y^*, 0)$ *have negative real parts.*

If there is a locally stable equilibrium of the full system then it is globally stable when ϵ *is small.*

Letting $(\tilde{x}(t, \epsilon), \tilde{y}(t, \epsilon))$ denote the equilibrium solution (x_0, y_0) of the full system, D be R^m and $E_\xi = R^n$ in Hoppensteadt's Theorem 2 [44], we obtain the following theorem (proof is in the Appendix):

Theorem 3. *If* $\mathscr{R}_0^c > 1$ *and* ϵ *is small then the endemic equilibrium of System* (7)–(11) *is globally asymptotically stable.*

5. Extended cluster models

The risk of infection per susceptible depends, among other factors, on the infectiousness of the source case and environmental characteristics (like ventilation and air volume per occupant). In an environment that is 'not too large', the risk of infection is likely to be (roughly) independent of the number of inhabitants (cluster size) and β can be assumed to be independent of the generalized household or average cluster size n. This assumption is likely to be a reasonable approximation

when n is not too large. However, in populations where the average size of the network of close contacts of an individual is large then an alternative view of risk needs to be considered.

Members of large clusters are likely to share their environment with only a (relatively) small fraction of the members of the generalized household at each time thus decreasing the average risk of infection per cluster susceptible. Hence, within some range of average cluster sizes, it may be reasonable to assume that the (per susceptible) risk of infection per unit time is actually a decreasing function of cluster size n. This restriction can be incorporated by assuming that $\beta \equiv \beta(n)$. It could be assumed that $\beta(n)$ is a piecewise-defined continuous or decreasing function of n.

Casual contacts (that is, random contacts in the general population) can indeed lead to TB infections [14]. There is ample evidence that supports the view that TB can indeed be acquired from just one or few contacts with an infectious individual (for review, see [15,46]). The rate of generation of secondary infections then must include at least two contributions: infections generated within generalized households and casual or random infections (that is, infections acquired through random associations with the population at large). The weights assigned to these two sources of secondary infections are assumed to be proportional to the average time spent by infectious individuals within their e.a. clusters and outside their e.a. clusters. If p denotes the average fraction of time spent by the source case within his/her generalized household and $1-p$ the average fraction of time spent by this source case outside then the rate of infection within clusters becomes $p\beta(n)S_1$ while the rate of infection in the general population is given by $(1-p)\beta^*(I/(N-n))(S_1+S_2)$, where N is the total population size and $N-n$ represents the total number of individuals outside the cluster. Hence, $(1-p)\beta^*(I/(N-n))S_1$ gives the number of new infections per unit time in the N_1 population, that is, the incidence from S_1 to E_1 while $(1-p)\beta^*(I/(N-n))S_2$ gives the incidence from S_2 to E_2. Within an e.a. cluster, the infection rate is modeled by $p\beta(n)S_1$, while outside the cluster the risk of infection is modeled via proportional mixing. These definitions and assumptions lead to the following generalized cluster model for TB transmission:

$$\frac{\mathrm{d}S_1}{\mathrm{d}t} = -(p\beta(n)+\gamma)S_1 + \frac{S_2}{N_2}nkE_2 - (1-p)\beta^*\frac{I}{N-n}S_1, \tag{24}$$

$$\frac{\mathrm{d}E_1}{\mathrm{d}t} = p\beta(n)S_1 - \gamma E_1 + \frac{E_2}{N_2}nkE_2 + (1-p)\beta^*\frac{I}{N-n}S_1, \tag{25}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = kE_2 - \gamma I, \tag{26}$$

$$\frac{\mathrm{d}S_2}{\mathrm{d}t} = \Lambda - \mu S_2 + \gamma S_1 - \frac{S_2}{N_2}nkE_2 - (1-p)\beta^*\frac{I}{N-n}S_2, \tag{27}$$

$$\frac{\mathrm{d}E_2}{\mathrm{d}t} = \gamma E_1 - (\mu+k)E_2 - \frac{E_2}{N_2}nkE_2 + (1-p)\beta^*\frac{I}{N-n}S_2. \tag{28}$$

The basic reproductive number associated with the generalized cluster model is

$$\mathscr{R}_0 = \left(\frac{p\beta(n)n}{p\beta(n)+\gamma} + (1-p)\frac{\beta^*}{\gamma}\frac{K}{K-n}\right)\frac{k}{(\mu+k)}, \tag{29}$$

where $K = \Lambda/\mu$ is the asymptotic carrying capacity of the total population. In order to gain some insights into the potential use of (29), two specific forms of $\beta(n)$ are discussed:

Case 1. If $\beta(n)$ is a piecewise-defined continuous function, that is,

$$\beta(n) = \begin{cases} \beta_0 & \text{for } n \leqslant n_L, \\ \dfrac{\beta_1}{n} & \text{for } n_L < n < n_M, \end{cases}$$

where n_L is the cluster size after which $\beta(n)$ begins to decrease and n_M its upper bound then

$$\mathscr{R}_0(n) = \begin{cases} \left(\frac{p\beta_0 n}{p\beta_0+\gamma} + (1-p)\frac{\beta^*}{\gamma}\frac{K}{K-n} \right) \frac{k}{(\mu+k)} & \text{for } n \leqslant n_L, \\ \left(\frac{p\beta_1}{\frac{\beta_1}{n}+\gamma} + (1-p)\frac{\beta^*}{\gamma}\frac{K}{K-n} \right) \frac{k}{(\mu+k)} & \text{for } n \geqslant n_L. \end{cases}$$

Since the maximum cluster size n_M is significantly smaller than the carrying capacity K then $K/(K-n) \approx 1$. Therefore, whenever $n < n_L$, $\mathscr{R}_0$ increases linearly with cluster size and $Q_0 \approx (p\beta_0/(p\beta_0+\gamma))n + (1-p)\beta^*/\gamma$. While $n > n_L$ implies that $Q_0 \approx (p\beta_1 n/(p\beta_1+n\gamma)) + (1-p)(\beta^*/\gamma) \times (K/K-n)$ which levels off at the value $p(\beta_1/\gamma) + (1-p)\beta^*/\gamma$. Hence, an increase in n always translates in an increase on TB transmission but the increase is non-linear. The end result is that $\mathscr{R}_0(n)$ is bounded by a constant value and this bound limits the size of TB prevalence.

Case 2. $\beta(n)$ is inversely related to n, for example, $\beta(n) = \beta_1/n$. $\mathscr{R}_0(n)$ is the sum of contributions from both the within and out of cluster contributions to the generation of secondary cases. We use $\beta(n) = \beta_1/n$ to compare the relative impact of each of these contributions to $\mathscr{R}_0(n)$. Hence, the ratio $E(n)$ of within cluster to between cluster contributions,

$$E(n) = \frac{\gamma\beta_1 p}{K\beta^*(1-p)} \frac{n(K-n)}{(p\beta_1+\gamma n)},$$

is considered. $E(n)$ increases and reaches its maximum value at $n^* = K/(1+\sqrt{1+(\gamma K/p\beta_1)})$. Naturally n^* is referred to as the *optimal cluster size* when $\beta(n) = \beta_1/n$; a value that results from maximizing the within cluster and between cluster contributions to the initial growth rate of TB infections.

The analysis of model (24)–(28) may also be carried out using the previously outlined approach with β replaced by $\beta(n)$. Since for most populations $N \gg n$ or, equivalently, $N - n \approx N$, the analysis is not too different. Hence it is omitted.

6. Parameter estimation and numerical results

The number of frequent contacts of a person in his/her generalized household is variable and it depends on many factors including the population's age structure and density. However, the mean generalized household size is of the order of 10 [47]. Mortality is estimated as the inverse of life expectancy at birth which is around 70 years in developed countries. TB induced per capita mortality rate is very low in developed countries (around 0.07 yr^{-1}) but reaches values of the order of 0.395 yr^{-1} in some African countries [48]. An intermediate value of 0.1 yr^{-1} applies to most of developed and developing nations.

The fraction of infected people who develop active TB, f, has been estimated to be between 5% and 10% in developed countries [45]. Our approach implicitly assumes long latency periods, that is, slow progression rates. The relationship between f and the rate of progression towards active TB, k is roughly given by $f = k/(k+\mu)$ from which we get that $k = (0.1/(0.9 \times 70)) \simeq 0.0016\ \mathrm{yr}^{-1}$, that is, k has an extremely low value.

The mean effective infectious period $(1/\gamma)$ is less than one year since antibiotic treatment and quarantine have greatly reduced the likelihood of TB transmission. Therefore, although individuals may remain as *potentially* infectious for a few years, most of them do not and, hence, most secondary infections are generated a few months after the onset of active TB [45]. In fact, the effective mean infectious period, even for people without treatment, is of the order of months [3]. Hence, γ has order of one. The value of β, individual's risk, is also of order one [25]. Therefore $k \ll \gamma$ and $\epsilon = k/(\beta+\gamma) \ll 1$ while $B = \mu/k$ is of order one or higher.

Individuals spend around eight hours daily at work, school or home. Hence, we take $p \sim 8/24$ and the average fraction of infections produced by one infectious individual in his/her generalized household is $m = p\beta/(p\beta+\gamma)$. Epidemiological surveys have estimated this fraction to be between 0.4 and 0.8 [49–52]. Therefore, $p\beta$ is of the same order of magnitude as γ and m which are of order one.

Our numerical simulations (see Fig. 2) have assumed an average effective infectious period of one year (but see [3]), that is, we have taken a value that may overestimate the real situation. Reductions on ε values improve the approximation between solutions generated from the full

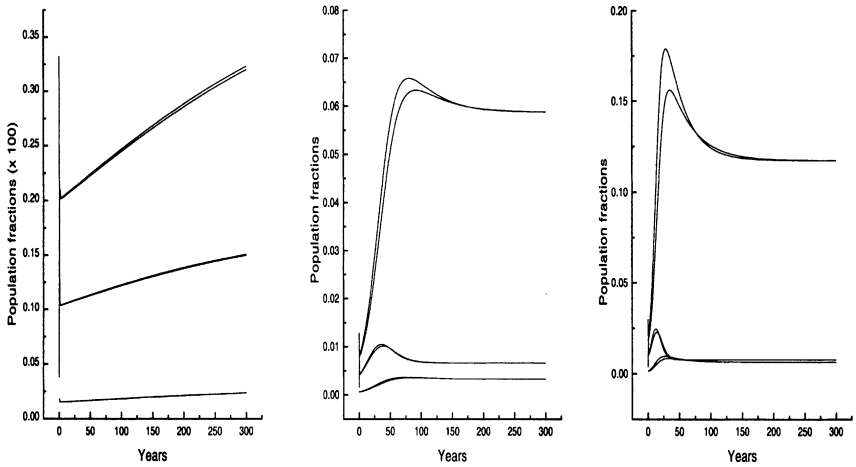

Fig. 2. Population fractions S_1/Ω, E_1/Ω and I/Ω obtained from the full model (7)–(11) are compared with those obtained from expressions (18)–(20) when slow variables evolve according to the reduced system (21)–(22). We considered different values for the fraction $f = k/(k+\mu)$, which determines the value of the progression rate k. In the left figure $f = 0.1$ ($\epsilon = 0.00053$) a relatively low value (this fraction is estimated between 0.05 and 0.1 for the USA population). In this case $\mathscr{R}_0^c$ is about 1.3 and the epidemic evolves very slowly and both solutions almost superimpose. In the center figure we show solutions when $f = 0.3$ ($\epsilon = 0.00204$), a high value. The figure in the right uses $f = 0.5$ ($\epsilon = 0.00476$) an extremely high value. In all these cases the solutions from the full and approximate models are qualitatively and quantitatively similar. The parameter values used were: $\mu = (1/60)\ \mathrm{yr}^{-1}$, $\beta = 2$, $\Lambda = \mu \times 10^5\ \mathrm{yr}^{-1}$, $n = 20$, $\gamma = 1\ \mathrm{yr}^{-1}$. Unit of time = 1 yr.

model (7)–(11) and those obtained under our quasi-steady-state approximation. We also have taken reasonable values for the fraction f, the proportion of infected people who progress towards active TB over their lifetimes. Increasing the values of f gives rise to higher values for ϵ. Exact and approximate solutions almost superimpose when $f = 0.10$, a value which is of the order of magnitude of those estimated for developed countries. If one assumes that $f = 0.30$, a high value which could only be reasonable in some developing countries, or if one assumes that $f = 0.50$, an extremely high and unrealistic value then one sees that even in these extreme cases the approximations given under the quasi-steady approximation are reasonable. The situations $f = 0.10$, 0.30 and 0.50 correspond to $\epsilon = 0.00053$, 0.00204 and 0.00476, respectively.

7. Discussion and conclusions

Knowledge of microscopic laws of motion allows for the adiabatic elimination of fast variables. Their elimination is typically used in the reduction of the dimensionality of a system. Population dynamics are described by phenomenological equations that use macroscopic parameters. However, since populations are collections of individuals, one would expect to be able to obtain macroscopic parameters as functions of more fundamental microscopic individual-level parameters, that is, from parameters that characterize individual behavior. The link between population-level and individual-level parameters is of central importance not only for our understanding of population processes but also for the reasonable use of epidemiological models beyond theoretical considerations.

Research on the connections between individual characteristics and population characteristics has increased [53,54]. Understanding of how population dynamics emerge from individual behavior is often studied through the simulation of individually based models. Here, we use a different but reasonable approach in the context of TB. The population of interest is divided in two sub-populations. Membership in the first population depends on an individual's association (or not) with an infectious individual. Our approach does not discriminate between individuals. Instead, our approach differentiates between membership in the (small) population that has close epidemiological contacts with infectious individuals and membership in the large population where transmission is unlikely. The model obtained is slightly more complex than classical epidemiological models but because transmission occurs in a (relative) short period of time on the average, then the adiabatic elimination of variables is possible. The resulting system is a standard homogeneous mixing model but the macroscopic parameters of this model are functions of the individual-level parameters introduced in the original model.

Our model for TB is still, in some aspects, unrealistic. For example, we considered only one latent class and justify its use on the fact that the risk of developing active TB decreases fast from the time of the initial infection. In fact, the values used here for the progression rate k are too low. 'Fast' TB can be added (in its most simple version) through the incorporation of an additional latent class [4,55,56]. Furthermore our model did not consider re-infection, a process which may play a significant role on the transmission dynamics and evolution of TB. We also neglected the contribution of the recovered class. Our simplified model led to a simple and useful homogeneous mixing approximation (21)–(22). An approximation helped identify analytical expressions for the macroscopic parameters as functions of the microscopic ones.

Finally, population structure was ignored (but see [57,58]). The incorporation of age structure is critical but a model that incorporates the two levels of mixing and population structure may not be tractable. Some of our earlier studies address these issues in the context of fast diseases [1,2]. The insights gained from the simple case treated in this article have proved to be useful in the study of the impact of the evolution of TB virulence on TB dynamics [59].

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Appendix A. The global stability of disease-free equilibrium

The proof of the global stability of the disease-free equilibrium when the basic reproductive number is less than unity follows.

Theorem 4. *If $\mathscr{R}_0^c < 1$, then the disease-free equilibrium is globally asymptotically stable. $\mathscr{R}_0^c > 1$, there exists a unique endemic equilibrium.*

Proof. The Liapunov function

$$V = \frac{\beta}{\beta+\gamma} S_1 + E_1 + E_2$$

does the trick since derivative of V along the trajectories is

$$\frac{\mathrm{d}V}{\mathrm{d}t} = (\mu+k)E_2\left(\frac{\beta n}{\beta+\gamma}\frac{k}{k+\mu} - 1\right) = (\mu+k)E_2(\mathscr{R}_0^c - 1) \leqslant 0.$$

The global stability of the disease-free state follows from LaSalle's Invariance Principle [60]. The proof of the uniqueness of endemic equilibrium when $\mathscr{R}_0^c > 1$ is straightforward. Explicitly, the endemic equilibrium is given by $\{S_1^*, E_1^*, I^*, S_2^*, E_2^*\}$, where

$$S_1^* = \frac{\Lambda}{\beta}\left(\frac{\mathscr{R}_0^c - 1}{\mathscr{R}_0^c - f}\right),$$

$$E_1^* = \frac{\Lambda}{\gamma}\left(\frac{\mathscr{R}_0^c - 1}{\mathscr{R}_0^c - f}\right)\left(\frac{\gamma+\beta}{\gamma}\mathscr{R}_0^c - 1\right),$$

$$I^* = \frac{k}{\gamma}\frac{\Lambda}{\mu+k}\left(\frac{\mathscr{R}_0^c - 1}{\mathscr{R}_0^c - f}\right),$$

$$S_2^* = \frac{\Lambda}{\mu}\left(\frac{1-f}{\mathscr{R}_0^c - f}\right),$$

$$E_2^* = \frac{\Lambda}{\mu+k}\left(\frac{\mathscr{R}_0^c - 1}{\mathscr{R}_0^c - f}\right). \qquad \square$$

Appendix B. Boundness of solutions

Because we ignored natural mortality in some classes in our model, the boundness of the solutions is not obvious.

Lemma 1. *The solutions of the System* (7)–(11) *are bounded.*

Proof. $S_1 + S_2$ is bounded from above since

$$\frac{d(S_1 + S_2)}{dt} = \Lambda - \beta S_1 - \mu S_2 \leqslant \Lambda - M(S_1 + S_2) \quad \text{where } M = min\{\beta, \mu\}.$$

It follows from the comparison principle that $S_1 + S_2$ is bounded from above. The boundness of $S_1(t)$ and $S_2(t)$ (from (8) and (11)) implies that $E_1(t)$ is bounded from above if and only if $E_2(t)$ is bounded from above. Hence, $E_1(t) + E_2(t)$ is bounded from above if and only if both $E_1(t)$ and $E_2(t)$ are bounded from above. From $d(E_1 + E_2)/dt = \beta S_1 - (\mu + k)E_2$ one sees that if $E_2(t)$ is large enough then $E_1(t) + E_2(t)$ will decrease, that is, $E_2(t)$ has to be bounded from above and, consequently, so does $E_1(t)$. Clearly, all solutions are bounded from below. Hence, the proof of Lemma 1 is complete. □

Some terms of the right-hand side functions of (7)–(11) contain $N_2 = S_2 + E_2$ as denominator. Hence, it is not clear whether or not we can use Theorem 2. Therefore, we must examine the continuity or differentiability of these functions. Lemma 2 gives the desired result, that is, that the solutions of System (7)–(11) move eventually away from the super plane $S_2 + E_2 = 0$.

Lemma 2. *If t is large enough, $S_2 + E_2$ has a uniform positive lower bound regardless of initial conditions.*

Proof.

$$\frac{d(S_2 + E_2)}{dt} = \Lambda - \mu S_2 + \gamma(S_1 + E_1) - (\mu + k)E_2 - nkE_2 r \geqslant \Lambda - (\mu + k(n+1))(S_2 + E_2).$$

Then

$$\begin{aligned} S_2 + E_2 &\geqslant \left(S_2(0) + E_2(0) - \frac{\Lambda}{\mu + k(n+1)}\right) e^{-(\mu + k(n+1))t} + \frac{\Lambda}{\mu + k(n+1)} \\ &\geqslant -\frac{\Lambda}{\mu + k(n+1)} e^{-(\mu + k(n+1))t} + \frac{\Lambda}{\mu + k(n+1)} \\ &\geqslant \frac{1}{2}\frac{\Lambda}{\mu + k(n+1)} > 0 \quad \text{if } t \geqslant T_0 = \frac{\ln 2}{\mu + k(n+1)}. \end{aligned}$$ □

Remark 1. Lemmas 1 and 2 ensure that one can study the dynamics of System (7)–(11) in a closed (compact) sub-set of R^5_+ that excludes the super plane $S_2 + E_2 = 0$.

Appendix C. Proof of theorem 1

Proof. Take the Dulac function $D(x_1, x_2) = 1/x_1x_2$ defined inside the first quadrant. The divergence is

$$\frac{\partial}{\partial x_1}\left(D\left(B(1-x_1) - Q_0\frac{x_1x_2}{x_1+x_2}\right)\right) + \frac{\partial}{\partial x_2}\left(D\left(-(1+B)x_2 + Q_0\frac{x_1x_2}{x_1+x_2}\right)\right)$$
$$= -\frac{B}{x_1^2x_2} + Q_0\frac{1}{(x_1+x_2)^2} - Q_0\frac{1}{(x_1+x_2)^2} = -\frac{B}{x_1^2x_2} \leqslant 0.$$

Therefore, there is no closed orbit. When $\mathscr{R}_0^c < 1$, (1,0) is a unique equilibrium that is locally asymptotically stable. Furthermore, $\mathscr{R}_0^c > 1$ yields that (1,0) is unstable while $\left(\frac{B}{Q_0-1}, \frac{B}{Q_0-1}(\mathscr{R}_0^c - 1)\right)$ is locally asymptotically stable. Dulac–Bendixson theory implies that Theorem 1 is true. □

Appendix D. Proof of theorem 3

Proof. To prove Theorem 3, we need to check that the five conditions of Theorem 2 are satisfied. In our model f and g are

$$f = \begin{bmatrix} f_1 \\ f_2 \end{bmatrix} = \begin{bmatrix} B(1-x_1) + (1-m)y_1 - n\frac{x_1x_2}{x_1+x_2} \\ (1-m)y_2 - (1+B)x_2 - n\frac{x_2^2}{x_1+x_2} \end{bmatrix},$$

$$g = \begin{bmatrix} g_1 \\ g_2 \\ g_3 \end{bmatrix} = \begin{bmatrix} -y_1 + n\frac{x_1x_2}{x_1+x_2} \\ my_1 - (1-m)y_2 + n\frac{x_2^2}{x_1+x_2} \\ x_2 - (1-m)y_3 \end{bmatrix}.$$

Note: In our case, both f and g are independent of the small parameter ϵ.

1. The slow manifold is the graph given by $M_0 : y = \phi(x), y \in R^3$ and $x \in R^2$,
$$y_1 = \phi_1(x_1, x_2) = n\frac{x_1x_2}{x_1+x_2},$$
$$y_2 = \phi_2(x_1, x_2) = \left(\frac{n}{1-m}\right)\left(\frac{x_2}{x_1+x_2}\right)(mx_1 + x_2),$$
and
$$y_3 = \phi_3(x_1, x_2) = \frac{x_2}{1-m}.$$
$(x_1, x_2) \in \Omega_0$ and Ω_0 (an interesting domain) does not contain the super plane $x_1 + x_2 = 0$.
2. The continuity and boundness of the derivative of f and g follow from Remark 1 in Appendix B.
3. To compute the eigenvalues of the matrix $(f_x - f_y g_y^{-1} g_x)(x^*, y^*)$, where x^* is given in (23) and $y^* = \phi(x^*)$, we need the matrices f_x, f_y, g_x and g_y:
$$f_x = \begin{bmatrix} -B - n\frac{x_2^{*2}}{(x_1^*+x_2^*)^2} & -n\frac{x_1^{*2}}{(x_1^*+x_2^*)^2} \\ n\frac{x_2^{*2}}{(x_1^*+x_2^*)^2} & -(1+B) - n\frac{2x_1^*x_2^* + x_2^{*2}}{(x_1^*+x_2^*)^2} \end{bmatrix},$$

$$f_y = \begin{bmatrix} (1-m) & 0 & 0 \\ 0 & (1-m) & 0 \end{bmatrix}, \quad g_x = \begin{bmatrix} n\frac{x_2^{*2}}{(x_1^*+x_2^*)^2} & n\frac{x_1^{*2}}{(x_1^*+x_2^*)^2} \\ -n\frac{x_2^{*2}}{(x_1^*+x_2^*)^2} & n\frac{2x_1^*x_2^*+x_2^{*2}}{(x_1^*+x_2^*)^2} \\ 0 & 1 \end{bmatrix}, \text{ and}$$

$$g_y = \begin{bmatrix} -1 & 0 & 0 \\ m & -(1-m) & 0 \\ 0 & 0 & -(1-m) \end{bmatrix}. \tag{D.1}$$

Thus

$$J = (f_x - f_y g_y^{-1} g_x)(x^*, y^*) = \begin{bmatrix} -B - Q_0\frac{x_2^{*2}}{(x_1^*+x_2^*)^2} & Q_0\frac{x_1^{*2}}{(x_1^*+x_2^*)^2} \\ Q_0\frac{x_2^{*2}}{(x_1^*+x_2^*)^2} & -(1+B) + Q_0\frac{x_1^{*2}}{(x_1^*+x_2^*)^2} \end{bmatrix}.$$

J is a 2×2 matrix. Since $\text{Trace}(J) = -B\mathscr{R}_0^c + (1 - \mathscr{R}_0^c) < 0$ and $\det(J) = B(1+B)(\mathscr{R}_0^c - 1) + Q_0(x_2^{*2}/(x_1^* + x_2^*)^2) > 0$ then the matrix $(f_x - f_y g_y^{-1} g_x)(x^*, y^*)$ has only eigenvalues with negative real parts when $\mathscr{R}_0^c > 1$. Theorem 1 ensures that x^* is a globally stable equilibrium to the system $dx/d\tau = f(x, \phi(x))$.

4. $$\frac{dY}{d\tau} = g(\xi, \phi(\xi) + Y) = \begin{bmatrix} -1 & 0 & 0 \\ m & m-1 & 0 \\ 0 & 0 & m-1 \end{bmatrix} \begin{bmatrix} y_1 \\ y_2 \\ y_3 \end{bmatrix}$$

is a linear system that is independent of the parameter ξ. The zero solution of the above system is globally asymptotically stable for any ξ, because all its eigenvalues are negative (Note: $m < 1$).

5. From (D.1), it is true that the eigenvalues of the matrix $g_y(x^*, y^*)$ all have negative real parts.

All five conditions in Theorem 2 are satisfied. This completes the proof of Theorem 3. □

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