Social clustering and the transmission and dynamics of tuberculosis

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Abstract

Tuberculosis (TB) transmission is enhanced by a systematic and long exposure to an infectious individual. This process usually takes place within a cluster of individuals that includes the home, the workplace, and/or the school. Typical TB models ignore this cluster effect. In this work, we present new models for TB transmission that incorporate cluster effects on the transmission dynamics of TB. Our model considers the effect of casual infections, that is, those generated outside a cluster, versus those generated in a cluster. We find expressions for the *Basic Reproductive Number* as a function of cluster size. Our formula helps diferentiate the contributions of cluster vs. casual infections to the generation of secondary infections. The relationship between cluster and typical epidemic models is discussed.

key words: epidemic models, social clusters, tuberculosis, dynamical systems.

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1 Introduction

Tuberculosis (TB) is an air borne transmitted disease that, with some probability, infects individuals who inhale *Mycobacterium tuberculosis* (Daniel, 1991). The re-emergence of TB is a major source of concern in poor, developing, and developed countries. The causes behind the recently observed increases of *active* TB cases are the source of serious studies and intense debate (Castillo Chavez *et al.*, 1997a, 1997b; Castillo-Chavez & Feng, 1996; 1997; Blower *et al.*, 1995, 1996; Bloom, 1994; Reichman & Herschfiled, 1993). TB transmission is enhanced by the systematic and long exposure of susceptible individuals to an infectious individual–a feature that is not taken into account in the models that have been developed until now (Waaler *et al.*, 1962; Brogger, 1967; ReVelle, 1967; ReVelle *et al.*, 1967; Waaler & Piot, 1970; Azuma, 1975; Bermejo *et al.*, 1992; Schulzer *et al.*, 1992, 1994; Blower *et al.*, 1995; 1996; Castillo-Chavez & Feng 1996, 1997; Castillo-Chavez *et al.*, 1997a,b).

Rose *et al.* (1979) established priorities in the evaluation of the risk of transmission per contact within a study that include 1590 contacts. Their study suggests that although the use of a household/nonhousehold status in describing the intensity of TB contacts is a convenient way of categorizing intimacy of exposure (household contacts being more conducive to infection), it is also true, that some nonhousehold contacts have an estimated duration and/or proximity of exposure equal to those experienced within a household. Hence, some nonhousehold contacts may be equally effective. Therefore, Rose *et al.* propose the use of "close" and "casual" rather than household/nonhousehold contacts as more appropriate for the evaluation of the risk of transmission per contact (Rose *et al.*, 1979). In this study, we consider that a cluster of every person is the group of people with whom the individual has daily and prolonged contacts, e.g. people sharing household, workplace, schoolplace.

When an individual in a cluster becomes infectious, then the environment of the cluster changes, that is, the risk of all individuals in the cluster grows significantly. Models that are able to evaluate the relative importance of TB transmission in clusters versus TB transmission via casual community con-

tacts (not cluster generated secondary infections) may be useful in evaluating their importance as an epidemiological control unit on public health policy (a somewhat similar approach was developed by Hethcote and Yorke (1984) via their evaluation of the role of core groups on gonorrhea dynamics).

Here we mainly look at TB dynamics on clusters. Section 2 gives a brief review of the epidemiology of TB. Section 3 introduces the basic cluster model (Equations 11-15) and shows that the *Basic Reproductive Number* is a linear function of the average cluster size and a bounded non-linear function of the transmission rate. Hence, the transmission parameters can be attached a clear and measurable epidemiological meaning. Also in Section 3 via a second model (Equations 18-22) the possibility intra or overlapping cluster effects in the generation of secondary cases is discussed. Section 4 looks at the impact of non-cluster generated secondary infections (casual infections). The new expression for $\mathcal{R}_0$ (Equation 29) shows explicitly the contribution of casual (typical of standard epidemiological models) and cluster generated infections in the number of secondary cases, that is, on $\mathcal{R}_0$. Section 5 uses differences in time scales to reduce our general model to a two-dimensional model for which full analysis is possible. The results of our approximations are supported via numerical simulations while the analysis is described in the appendices. In the Conclusion, we introduce additional bibliographical material on the impact of clusters on disease dynamics. We re-state our results, and suggest possible avenues of future research.

2 Epidemiology of tuberculosis

The number of bacilli excreted by most persons with pulmonary tuberculosis is small (Styblo, 1991). Past studies support this conclusion because mainly individuals who experience intense contact with the TB bacilli, in poorly ventilated areas, are the most likely to become infected. Also long periods of latency (*inactive* TB) imply that new cases of infection are not clinically apparent and therefore they go unobserved for some time. Progression from latent to active TB is not extremely common; it is believed that about 5% to 10% of TB infected individuals develop clinical tuberculosis. The likelihood of progression towards active TB depends on age of infection (Comstock & Caughten, 1993; Williamson County TB Study, 1963; Comstock & Edwards, 1975) as well as on factors that correlate well with socio-economic

status. Individuals who have a latent infection are not clinically ill or capable of transmitting TB (Miller, 1993). The likelihood of adequate treatment is critical. Appropriately treated individuals become non infectious quickly (Daniel, 1991) while latently infected, that is, infected but non-infectious individuals may be stopped from developing active TB by prophylactic therapy (Ferebee, 1970). According to Smith and Moss (1994) most exposed individuals mount an effective immune response to the initial infection. This immune response limits proliferation of the bacilli leading to what appears to be long-lasting partial immunity against re-infection or/a response capable of stopping re-activation of latent bacilli. Exposed individuals may remain in the latent stage for long and variable periods of time, in fact, most die without ever developing active TB. Consequently, age of infection as well as chronological age are important factors in disease progression (Castillo Chavez *et al.*, 1997a).

Tuberculosis morbidity and mortality rates are strongly affected by urban livings conditions. For example, in the USA it was shown that the risk of tuberculosis increases with population size and urban conditions. In Central Harlem, a neighborhood in New York City where income is low, the TB incidence rate is several times greater than the city as a whole. These examples illustrate that tuberculosis is increasingly a disease of the social and economically disadvantaged (Bloch *et al.*, 1989). In the USA, the Centers for Disease Control (CDC) estimates that the follow up of a "typical" case of tuberculosis results in the identification of approximately nine potentially effective contacts for each case of active TB (Etkind, 1993). The infectiousness of the source case, the duration and frequency of exposure, and the characteristics of shared environments contribute to the risk of transmission per contact.

We consider that every infectious individual has the same infectiousness. Also we classify his/her contacts in only two categories: close, daily an prolonged contacts, or *cluster contacts*; and those close but infrequent contacts, or *casual contacts. We call active cluster to the group of persons that experience cluster contacts with an infectious individual during his/her infectious period.* We consider that all of the cluster environments have the same infective risk when an infectious individual is in them. The number of secondary infections produced in each cluster environment depends on the number of susceptible individuals in each of them as well as the time spent by the source case in each of them. As we are not interested is such differences we consider that the *per capita* risk of infection by unit of time is constant in

each cluster environment. The above statement means that the number of secondary infections produced by one source case in a cluster with S susceptible individuals is $S(1 - e^{-\beta\tau})$, where β is the constant risk of infection and τ is the infectious period of the index case. As we said before, the β value associated with an infectious individual depends on its infectiousness and on the features of the cluster environments, and varies from case to case. Length of infectious periods (τ) is difficult to obtain because there is a big uncertainty in determination of time of TB activation. However the non-dimensional quantity $\beta\tau$ which determines the percentage of secondary infections caused by the index case, can be obtained from epidemiological surveys. This percentage ranges between 40% to 80 % of the cluster contacts (Rose *et al.*, 1979; Nardell *et al.*, 1991; Catanzaro, 1982; Riley *et al.*, 1962). Due to the low incidence of TB disease, probability by unit of time that a susceptible individual who does not belong to any active cluster has a close contact with an infectious individual is very low. Therefore the *per capita* risk of infection of these people is significant smaller when compared with the risk of infection of people belonging to an active cluster. However, the number of secondary infections produced by casual contacts may be greater than that produced by cluster contacts because mean cluster size is about 10 but during the infectious period a source case may have hundreds or thousands of close casual contacts. Therefore, the dynamics of tuberculosis at the population level in cities may be increased significantly through the risk of transmission via casual contacts of infectious individual in cities with high contact rates.

3 The basic cluster model.

As we said in the previous section, tuberculosis transmission be enhanced by a cluster of contacts (a small "close" community). Nevertheless, models that incorporate the impact of clusters (small communities) on TB transmission (as well as for any other communicable disease) are non-existent. Most of the deterministic epidemiological models for the transmission dynamics of an infectious disease assume a homogeneous mixing population, that is, they assume that any infectious individual has the same probability to transmit the disease to any susceptible individual in the population. For diseases with a latent period such as TB, the general form of these models is as follows

(Castillo-Chavez & Feng, 1996; Castillo-Chavez *et al.*, 1997a,b; Blower *et al.*, 1995, 1996),

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

$$\frac{dE}{dt} = \beta_h S\frac{I}{N} - (b+k)E, \tag{2}$$

$$\frac{dI}{dt} = kE - (b+d+r)I, \tag{3}$$

$$\frac{dT}{dt} = rI - bT, \tag{4}$$

where Λ is the recruitment rate, b is the natural mortality rate, d is the TB induced mortality rate, β_h is the effective transmission rate, k is the rate of progression to active TB, r is the treatment rate, and where S, E, I and T, represent density or population numbers of susceptible, latent, infectious, and recovered (treated) individuals respectively. $N = S + E + I + T$ is the total population size.

The *Basic Reproductive Number*, $\mathcal{R}_0$, defined as the mean number of secondary cases produced by one infectious individual in a fully susceptible population, for Model (1-4) is given by

$$\mathcal{R}_0 = \frac{\beta_h k}{(b+k)(b+d+r)}. \tag{5}$$

When $\mathcal{R}_0 < 1$ an epidemic is not possible and the disease dies out. The above expression for $\mathcal{R}_0$ depends linearly on the effective transmission rate β_h. In this context β_h is essentially a fitting parameter. Nevertheless, knowledge of the functional dependence on parameters via $\mathcal{R}_0$ is useful in the design of control strategies. Model-based policy decision are usually based on methods that attempt to lower $\mathcal{R}_0$ as much as possible. If modified control measures are such that $\mathcal{R}_0 < 1$ then the disease can be eliminated.

The earlier models for TB disease dynamics do not capture some singular features of TB transmission, particularly the role of cluster transmission. Here, we consider a homogeneous mixing population but not on its usual form. The main assumptions behind our model are that, TB transmission is enhanced by the systematic and prolonged exposure of susceptibles to

an infectious individual and that each infectious individual has a cluster of persons (an *active* cluster) at his/her disposal via close contacts at home and/or work (or school) that can be infected. We assume a mean cluster size constant equal to n. As we said in the preceding section we consider a constant *per capita* risk of infection β for every cluster environment with one infectious individual.

Our modelling of TB transmission discriminates, at each time, between the population belonging to active clusters (of size $N_c(t)$) and the remainder population (of size $N_{nc}(t)$). However we do not follow clusters through time. By definition all of the infectious individuals belong to the N_c-population. Infected individuals of the N_{nc}-population may develop active TB becoming infectious. In such case a cluster of size n, together with the new source case move from N_{nc}-population to the N_c-population. Conversely, by each recovered individual from active disease, a group of people of size n, together with the recovered individual, move from N_c-population to the N_{nc}-population. For notational convenience we call $N_1 \equiv S_1 + E_1$ to the fraction of non infectious population of N_c, and $N_2 = S_2 + E_2$ to the N_{nc}-population. S_i and E_i denote the susceptible and latent populations of the N_i-populations respectively ($i = 1, 2$). We assume negligible probabilities that one active cluster has more than one infectious individual and that an individual belongs to more than one active cluster simultaneously. This is a good approximation for TB because incidence rates are low and, therefore, the N_1 population is significantly smaller than the N_2 population. Therefore, if I is the infectious population, we have $N_1 = nI$, and then $N_c = (n + 1)I$. In this approach, we neglect the contribution of treated classes to the N_i population size, in order to keep the models as simple as possible. Incorporation of the treated classes is straightforward and does not produce significative differences in the resulting dynamics (see Appendix B), although it may be important in the evaluation of control policies.

In addition, we assume that active cluster formation has "no memory." That is, it is assumed that when a latent individual develops active TB, he/she has no information about the cluster from where he/she caught the disease. That is, we assume only that a long period of latency is possible. Of course, this epidemiological assumption is not strictly true. Long periods of latency may be the rule in developed countries (although this is a mater of controversy). The possible impact of short periods of latency will be taken into account later on.

The completion of our basic cluster model follows from these observations:

- When an exposed (belonging to the E_2-population) individual becomes infectious, the N_1 population increases by n (where n is the average cluster size associated with an infectious individual) while the N_2 population decreases by $n+1$. When an infectious individual recovers after treatment or dies the N_1 population decreases by n while the N_2 population increases by n.

- Susceptible and latent proportions are different in each particular case. If k is the progression rate to active TB, there are kE_2 new infectious individuals per unit of time and, the rate of change of the N_1 population is increased by nkE_2. This rate is divided into a susceptible and latent component as follows: the rate of change in the susceptible class is increased by the factor $\frac{S_2}{N_2}$ while the rate of change in the latent class is increased by the factor $\frac{E_2}{N_2}$. Therefore, the gain terms are $\frac{S_2}{N_2}nkE_2$ and $\frac{E_2}{N_2}nkE_2$, for the S_1 and E_1 classes, respectively.

- The loss terms are obtained similarly. If γ is the total removal rate of the infectious population, then there are $n\gamma I$ people going out of the population N_1 per unit of time. It is assumed that $\frac{S_1}{N_1}$ proportion of this rate becomes susceptible and an $\frac{E_1}{N_1}$ proportion becomes latent. The relation $nI = N_1$ implies that the loss terms satisfy $\frac{S_1}{N_1}n\gamma I = \gamma S_1$ and $\frac{E_1}{N_1}n\gamma I = \gamma E_1$.

- We assume that the constant flux of susceptible individuals (Λ) is distributed proportionally to the N_1 and N_2 populations. Furthermore, since $N_1 = nI$, and n is around 10 or 20, we have that $N_c \simeq N_1$.

- We assume that the *per capita* rates of natural mortality (b), disease induced mortality (d), and treatment (r), are also constant. Then, the removal rate of infectious individuals is $\gamma = b + d + r$.

These assumptions and observations lead to following model:

$$\frac{dS_1}{dt} = \Lambda\frac{N_1}{N} - (\beta + \gamma + b)S_1 + \frac{S_2}{N_2}nkE_2, \tag{6}$$

$$\frac{dE_1}{dt} = \beta S_1 - (\gamma + b + k)E_1 + \frac{E_2}{N_2} nkE_2, \tag{7}$$

$$\frac{dI}{dt} = k(E_2 + E_1) - \gamma I, \tag{8}$$

$$\frac{dS_2}{dt} = \Lambda \frac{N_2}{N} - bS_2 + \gamma S_1 - \frac{S_2}{N_2} nkE_2, \tag{9}$$

$$\frac{dE_2}{dt} = \gamma E_1 - (b + k)E_2 - \frac{E_2}{N_2} nkE_2 + \delta rI, \tag{10}$$

where δ is the proportion of treated individuals who may 'return' to the latent class TB again. If the rate of loss of protection conferred by treatment is δ^*, then we have that $\delta = \frac{\delta^*}{b+\delta^*}$ (see Appendix B). The characteristic time of N_1-population dynamics is of the order of $1/\gamma$ which is about three months. Hence, it is possible in this short period of time, to neglect recruitment, natural mortalities, and active TB progression rates in the N_1-population dynamics. This remark leads to the following rough approximation of our the basic cluster model:

$$\frac{dS_1}{dt} = -(\beta + \gamma)S_1 + \frac{S_2}{N_2} nkE_2, \tag{11}$$

$$\frac{dE_1}{dt} = \beta S_1 - \gamma E_1 + \frac{E_2}{N_2} nkE_2, \tag{12}$$

$$\frac{dI}{dt} = kE_2 - \gamma I, \tag{13}$$

$$\frac{dS_2}{dt} = \Lambda - bS_2 + \gamma S_1 - \frac{S_2}{N_2} nkE_2, \tag{14}$$

$$\frac{dE_2}{dt} = \gamma E_1 - (b + k)E_2 - \frac{E_2}{N_2} nkE_2 + \delta rI. \tag{15}$$

The above approximation is not bad as it can be seen from our extensive simulations using realistic parameter values (Fig. 2.): the solutions of Model (6-10) and Model (11-15) are nearly identical. In Section 5, we show how, under suitable assumptions and approximations, Model (6-10) reduces to a

typical epidemiological model like the one given by System (1-4). Also we show that the *Basic Reproductive Number* for Model (11-15) is

$$\mathcal{R}_{01} \equiv \frac{\beta n k}{(\beta+\gamma)B}, \tag{16}$$

where $B = b + k - \delta k r/\gamma$. The threshold condition $\mathcal{R}_{01} > 1$ is equivalent to $\mathcal{R}'_{01} > 1$ with

$$\mathcal{R}'_{01} = \frac{\beta n}{(\beta+\gamma)}\frac{k}{(b+k)} + \frac{r}{(b+d+r)}\frac{\delta^*}{(b+\delta^*)}\frac{k}{(b+k)}. \tag{17}$$

This expression is easier than 16 for biological interpretation. The *Basic Reproductive Number* is defined as the number of secondary cases that one infectious individual produces in a population where every one is susceptible. The number of contagions in such circumstances is $\beta n t$, where t is the average period for which infections can occur. In an active cluster this is the lifetime of the susceptible population, $\frac{1}{\beta+\gamma}$. Finally, only the fraction $\frac{k}{b+k}$ of infected individuals develop active TB. To this amount, the number of treated individuals that lost protection conferred by treatment and develop active TB by endogenous reactivation, must be added. The addition of these two contributions give Expression (17) for $\mathcal{R}_0$.

The main difference between Expression (16) and the standard expressions for $\mathcal{R}_0$ is reflected on the non-linear dependence of $\mathcal{R}_0$ on β. This dependence captures the role of cluster transmission. We can see that the number of infections produced by an infectious individual is bounded by the number of susceptible individual belonging to an active cluster. Since the fraction of infected people that develops active TB is about $\frac{k}{B}$, no matter how big is β and/or how long is the infectious period, the cluster size must still be bigger than $\frac{B}{k}$ for disease persistence ($\mathcal{R}_0 > 1$). For typical parameter values (populations in poverty, and /or for world populations living prior to the existence of treatment) we have that $n \geq 10$, $\beta \sim 2/year$, with a period of infectiousness longer than 1 year. Therefore we see that the proportion of infected individuals who must develop active TB for the disease to remain endemic must be $\geq$0.15. A reasonable value of the percentage of latent individuals who develop active TB is now estimated to be about 0.1 and hence, under current circumstances, cluster transmission may not be enough to support TB. Our model results may explain how TB is (or was) maintained in primitive or rural communities.

3.1 The effect of short latency period.

The "no memory" hypothesis of our model is slightly unrealistic. About 80% of latent individuals that progress to active TB do it within 7 to 12 years after infection (Styblo, 1978; Le & Davidson, 1995). Hence, there may be a significant probability that a fraction of a new active cluster actually belongs to the cluster from where the disease was caught. Therefore, if TB progression is fast (few years), we may expect that a cluster of a given secondary case includes some of the individuals of the index active cluster case. On the other hand, if TB progression happened many years after the primary infection then, it is unlikely, that a cluster of a secondary case actually includes some of the individuals belonging to the cluster of the index case. Therefore, we incorporate a new parameter, ρ, between 0 and 1 that measures, in a rather empirical way, the degree of overlap between successive active cluster formations. We will refer to this index as the 'active cluster overlapping' (or active cluster aggregation) index. The inclusion of this index leads to the following modified model:

$$\frac{dS_1}{dt} = -(\beta+\gamma)S_1 + \left((1-\rho)\frac{S_2}{N_2} + \rho\frac{S_1}{N_1}\right) nkE_2, \tag{18}$$

$$\frac{dE_1}{dt} = \beta S_1 - \gamma E_1 + \left((1-\rho)\frac{E_2}{N_2} + \rho\frac{E_1}{N_1}\right) nkE_2, \tag{19}$$

$$\frac{dI}{dt} = kE_2 - \gamma I, \tag{20}$$

$$\frac{dS_2}{dt} = \Lambda - bS_2 + \gamma S_1 - \left((1-\rho)\frac{S_2}{N_2} + \rho\frac{S_1}{N_1}\right) nkE_2, \tag{21}$$

$$\frac{dE_2}{dt} = \gamma E_1 - (b+k)E_2 + \delta r I - \left((1-\rho)\frac{E_2}{N_2} + \rho\frac{E_1}{N_1}\right) nkE_2, \tag{22}$$

For $\rho = 0$ the memory effect is lost, and Model (11-15) is recovered. In Section 5, we show that the *Basic Reproductive Number* for Model (18-22) is

$$\mathcal{R}_{02}(\rho) \equiv \frac{\beta(1-\rho)nk}{(\beta+(1-\rho)\gamma)B}. \tag{23}$$

That is, in the active cluster formation we use a weighted average of the proportion of susceptible and latent individuals in N_1, and N_2 population. As

periods of latency decrease, a significant overlapping between successive cluster formation is expected, and therefore the ρ value increase. The existence of an endemic equilibrium requires $\mathcal{R}_{02} > 1$. We only obtain this (for certain values of the other parameters) for $\rho < \rho_{max} < 1$. $\mathcal{R}_{02}(\rho)$ is a monotonous increasing function of ρ in its range $(0-\rho_{max})$. For slow progression ($\rho = 0$), we recover Expression (16), its maximum value, while for non zero overlapping ($0 < \rho < \rho_{max}$), we have that $\mathcal{R}_{02} < \mathcal{R}_{01}$. The result is obvious under the assumption that latent individuals can not be re-infected. Successive cluster overlapping reduces the number of susceptible individuals and hence reduces the *Basic Reproductive Number*. In the limit case $\rho = 1$ we have $\mathcal{R}_{02}$=0, and therefore there is no endemic equilibrium. If only household transmission is considered, a significant overlap between successive active clusters is expected, and therefore we expect a ρ-value close to one. This result suggest that TB persistence ($\mathcal{R}_{02} > 1$) may require some type of no-household transmission as occurred at work, school, and eventually, transmission in casual contacts as occurred in public transportation, leisure places, etc. In the next Section we explore the effect of casual infections on the spread of TB.

4 The influence of casual infection

There is extensive evidence that TB can be caught from one or few contacts with an infectious individual (see for reviews, Lincoln, 1965; Rafalli *et al.* 1996). When an infectious individual has contacts with people no belonging to his/her cluster which result in a secondary infection then we are talking of 'casual' infections. We assume that this process is appropiately captured by a classical homogeneous mixing model, as the potential population of close casual contacts of each infectious individuals is large and, therefore, an appreciable saturation phenomena is not expected. The incorporation of casual infections via a classical approach leads to the following modified model:

$$\frac{dS_1}{dt} = -(\beta + \gamma)S_1 + \left((1-\rho)\frac{S_2}{N_2} + \rho\frac{S_1}{N_1}\right) nkE_2, \tag{24}$$

$$\frac{dE_1}{dt} = \beta S_1 - \gamma E_1 + \left((1-\rho)\frac{E_2}{N_2} + \rho\frac{E_1}{N_1}\right) nkE_2, \tag{25}$$

$$\frac{dI}{dt} = kE_2 - \gamma I, \tag{26}$$

$$\frac{dS_2}{dt} = \Lambda - bS_2 + \gamma S_1 - \left((1-\rho)\frac{S_2}{N_2} + \rho\frac{S_1}{N_1}\right) nkE_2 - \beta^* I\frac{S_2}{N_2}, \tag{27}$$

$$\frac{dE_2}{dt} = \gamma E_1 - (b+k)E_2 + \delta r I - \left((1-\rho)\frac{E_2}{N_2} + \rho\frac{E_1}{N_1}\right) nkE_2 + \beta^* I\frac{S_2}{N_2}. \tag{28}$$

This model reduces to Model (18-22) when $\beta^* = 0$ and to Model (11-15) when $\beta^* = 0$, and $\rho = 0$. System (24-28 posses an unique endemic equilibrium. It is straightforward to see that the necessary and sufficient condition for the existence of this endemic equilibrium is given by $\mathcal{R}_0 > 1$, where

$$\mathcal{R}_0 = \frac{\beta n(1-\rho)}{\beta + (1-\rho)\gamma}\frac{k}{B} + \frac{\beta^*}{\gamma}\frac{k}{B}. \tag{29}$$

Numerical exploration of the solutions of the system (24-28) shows that the condition of existence of endemic equilibrium, $\mathcal{R}_0 > 1$, is the same condition of unstability of the free-infection state, that is, $\mathcal{R}_0$ is the *Basic Reproductive Number* for Model (24-28). In the next Section we show that under some approximations the same result can be obtained analytically. When $\beta^* = 0$, $\mathcal{R}_0$ reduces to $\mathcal{R}_{02}$, while for $\beta^* = 0$, and $\rho = 0$ reduces to $\mathcal{R}_{01}$. Expression (29) shows that casual contacts increase $\mathcal{R}_{02}$ additively via the term β^*/γ weighted by the proportion of exposed individuals $\frac{k}{B}$ progressing towards active TB. Since the cluster effect contribution and casual contagion effect are independent processes, the number of secondary cases produced by an infectious individual splits into the above two additive contributions. Expression (29) is equivalent to

$$\mathcal{R}_0 = \frac{\beta(1-\rho)}{(\beta + (1-\rho)\gamma)}\frac{k}{B}(n + \frac{\beta^*}{\beta} + \frac{\beta^*}{(1-\rho)\gamma}) \equiv \frac{\beta(1-\rho)}{(\beta + (1-\rho)\gamma)} n_{eff}\frac{k}{B}, \tag{30}$$

where

$$n_{eff}(\rho) = n + \frac{\beta^*}{\beta} + \frac{\beta^*}{(1-\rho)\gamma}.$$

Hence, we may think that casual infections increase the mean cluster size in an additive way by $\frac{\beta^*}{\beta} + \frac{\beta^*}{(1-\rho)\gamma}$. We may refer to n_{eff} as the effective cluster size.

We said above that the *per capita* risk of infection of people in close contact with an infectious individual depends on the features of the environment as well as the infectiousness of the source case. We assumed an unique risk β for every cluster environment with one infectious individual. Also we mentioned that β as well as the mean infectious period $1/\gamma$ are difficult to obtain but the non-dimensional quantity $Q \equiv \beta/\gamma$ can be obtained from epidemiological surveys. Therefore it is preferable to relate β^* with β. Each infectious individual has a daily network of close casual contacts of mean size n_c. He/she spends a time τ' in this class of contacts while he/she spends a time τ in cluster contacts, with $\tau > \tau'$. The mean number of infections produced by one infectious individual per day is around $(\tau'/\tau)n_c\beta\frac{S}{N}$, where $n_c\frac{S}{N}$ is the susceptible fraction of the total close casual daily contacts of a person. Then, we have that (see Appendix A)

$$\beta^* \sim (\tau'/\tau)n_c\beta \equiv m\beta,$$

with $m \equiv (\tau'/\tau)n_c$.

Therefore, we can rewrite the *Basic Reproductive Number* as follows

$$\mathcal{R}_0 = \left(\frac{Qn(1-\rho)}{Q+(1-\rho)} + mQ\right)\frac{k}{B}. \tag{31}$$

This form of $\mathcal{R}_0$ discriminates between cluster and casual infections. The first term between parentheses is the number of secondary infections caused by the source case in cluster contacts, while the second is the number of the secondary infections produced by casual contacts. It is a function of fundamental parameters which characterizes behavioral, sociological, and epidemiological aspects of infectious individuals.

In Fig. 4 we show the proportion of cluster generated infections respect to the total number of infections produced per unit of time at the endemic equilibrium. For a high rate of close casual contacts ($m = 10$) the contribution of the casual infections is around one half of the total amount. However, the size of the population within clusters is lower than one per cent of the total population. That is, a very small fraction of the total population is responsible for the generation of the one half of the infections produced per unit of time.

Prior to the existence of massive public transportation in big cities (crowded buses, long trips), and the proliferation of places with a high concentration of people (dancing places, pubs, etc.), we must have had that $\beta^* \sim 0$. The emergence of new social behaviors due to urbanization may have increased β^* and, consequently, the observed increase of TB cases may be due in part to 'casual' infections (see Fig. 3). Casual infections such a those occurring in public transportation may be a key component in the re-emergence of TB in the last decades.

5 Reduced system and stability analysis

We consider Model (24-28) which reduces to the Model (18 -22) when β^*=0 and to Model (11-15) when β^*=0 and $\rho = 0$. The time scales of the dynamics in the N_1 and the N_2 populations are very different. S_1, E_1, and I are fast variables when compared to S_2 and E_2 and, therefore, these dynamics can be adiabatically eliminated by replacing the variables by their 'equilibrium' values. Setting the time derivatives of the fast variables equal to zero we have that:

$$S_1(t) \cong \frac{(1-\rho)}{\beta + (1-\rho)\gamma} \frac{S_2(t)}{N_2(t)} nkE_2(t), \tag{32}$$

$$E_1(t) \cong \frac{1}{\gamma} \left(\frac{\beta}{\beta + (1-\rho)\gamma} \frac{S_2(t)}{N_2(t)} + \frac{E_2(t)}{N_2(t)} \right) nkE_2(t), \tag{33}$$

$$I(t) \cong \frac{k}{\gamma} E_2(t). \tag{34}$$

With this approximation System (24-28) reduces to the following two-dimensional system for the slow variables S_2 and E_2,

$$\frac{dS_2}{dt} \cong \Lambda - bS_2 - B\mathcal{R}_0 \frac{S_2 E_2}{N_2}, \tag{35}$$

$$\frac{dE_2}{dt} \cong -BE_2 + B\mathcal{R}_0 \frac{S_2 E_2}{N_2}, \tag{36}$$

where $\mathcal{R}_0$ is given by Expression 29. System (35-36), together with Expressions (32-34) for the fast variables gives the simplest representation of our model for the transmission dynamics of TB. An excellent accord between

the solutions obtained with the five dimensional system of ordinary differential equations (24-28) and those obtained via the reduced system (35-36) is observed for realistic TB-parameter values (Fig. 5). Using 34 the system (35-36) is like an usual epidemiological system (of the type of 1-4) with $\beta_h \equiv B\mathcal{R}_0\gamma/k$.

The equilibrium values of the reduced System (35-36) are given by

$$S_2^{eq} = \frac{\Lambda}{B + b(\mathcal{R}_0 - 1)},$$

$$E_2^{eq} = \frac{\Lambda(\mathcal{R}_0 - 1)}{B + b(\mathcal{R}_0 - 1)}.$$

Defining $s = S_2 - S_2^{eq}$ and $e = E_2 - E_2^{eq}$ and performing the linearization around the endemic equilibrium we obtain:

$$\frac{d}{dt}\begin{pmatrix} s \\ e \end{pmatrix} = \begin{bmatrix} -b - B\frac{(\mathcal{R}_0-1)^2}{\mathcal{R}_0} & -\frac{B}{\mathcal{R}_0} \\ B\frac{(\mathcal{R}_0-1)^2}{\mathcal{R}_0} & -B\frac{(\mathcal{R}_0-1)}{\mathcal{R}_0} \end{bmatrix} \begin{pmatrix} s \\ e \end{pmatrix} \equiv A \begin{pmatrix} s \\ e \end{pmatrix}.$$

The eigenvalues of the A matrix are

$$\begin{aligned} \lambda_\pm &= -\frac{b + B(\mathcal{R}_0 - 1)}{2} \\ &\quad \pm \frac{\sqrt{[b + B(\mathcal{R}_0 - 1)]^2 - 4B\frac{(\mathcal{R}_0-1)}{\mathcal{R}_0}[b + B(\mathcal{R}_0 - 1)]}}{2}. \end{aligned}$$

Therefore, if the endemic equilibrium exists, that is, if $\mathcal{R}_0 > 1$ then both eigenvalues have negative real parts, and the equilibrium is locally stable. On the other hand, linearization around the infection-free state leads to

$$\frac{d}{dt}\begin{pmatrix} s \\ e \end{pmatrix} = \begin{bmatrix} -b & -B\mathcal{R}_0 \\ 0 & -B(1 - \mathcal{R}_0) \end{bmatrix} \begin{pmatrix} s \\ e \end{pmatrix} \equiv A \begin{pmatrix} s \\ e \end{pmatrix}$$

In this latter case, the eigenvalues of matrix A are $\lambda = -b$ and $\lambda = -B(1 - \mathcal{R}_0)$. Therefore, if $\mathcal{R}_0 > 1$ then the equilibrium is unstable.

The *Basic Reproductive Number* is defined as the number of secondary cases produced by one infectious individual in a population where everyone is

susceptible. As we show in the simplified case of Section III, our formula for $\mathcal{R}_0$ can be interpreted in this form which strongly suggest that this expression is the *Basic Reproductive Number* of the model (24-28) (and then, $\mathcal{R}_{01}$ and $\mathcal{R}_{02}$ are the *Basic Reproductive Numbers* for Models (11-15), and (18-22) respectively. For $\mathcal{R}_0 > 1$ the free-infection equilibrium is unstable and an epidemic is possible. We prove that for $\mathcal{R}_0 > 1$ the free-infection state of the reduced system (35-36) is unstable, that is, $\mathcal{R}_0$ is the *Basic Reproductive Number* for this model. At the free-infection state there is no people within active clusters, that is $S_1 = E_1 = I = 0$, and therefore, $dS_1/dt = dE_1/dt = dI/dt = 0$. Then, the relations 32-34 holds exactly, and the reduced system is equivalent to the system 24-28). Therefore $\mathcal{R}_0 > 1$ is the threshold condition for both systems.

6 Discussion and conclusions

Basic homogeneous mixing models have been used to represent tuberculosis dynamics (Blower *et al.*, 1995, 1996; Castillo-Chavez & Feng, 1996; 1997; Castillo-Chavez *et al.*, 1997a,b). These researchers have analyzed the effect of long latent period, exogenous reinfection and coexistence of multidrug-resistance strains. However their models do not take into account an important feature of TB transmission, cluster transmission. Furthermore, most of the epidemiological models that go beyond homogeneous mixing case do not consider cluster effects. The closest contact is, the higher the rate of transmission. But close contacts not only occur in houses. There are closed contacts at work, school, leisure places, or in public transportation (buses, airplanes, ships) (see Lincoln, 1968; Rafalli *et al.*, 1996; Capurro *et al.*, in prep. for revision). An infectious person has associated with him/her a cluster of people to whom he/she is connected via its family, network of friends, work, leisure activities or transportation habits. The concentric-circle approach (Etkin 1993) provides a methodology to determine the number of persons who may have been infected by a primary TB case. Such approach considers the "inner circle" of close contacts as the group of persons more likely to be infected. The inner circle includes contacts at home, work, school, etc. (from which daily and prolonged TB exposures is possible). Etkin's inner circle is what we considered a cluster, our epidemiological unit. Our model captures cluster transmission in a simple way. A result of our approach is

that the transmission rate (β) used is much closer to the real mean infectivity of people with active TB rather than the fitted transmission parameter of standard epidemic models.

Also we have analyzed the effect of fast progression to active TB, in the context of cluster transmission. It is known that 80 % of the latent individuals that progress to active TB develop the disease within 7 to 12 years after infection (Styblo, 1978; Le & Davidson, 1995). These empirical evidence allows to evaluate the probability that an individual of a new cluster were a member of the original cluster index case. The results of our model show that the $\mathcal{R}_0$ of a model with short latency period is smaller than the $\mathcal{R}_0$ of a long latency period model. Computation of $\mathcal{R}_0$ with realistic parameter values give a value for $\mathcal{R}_0$ smaller than one. Therefore the TB can not be maintained without casual infections. As casual contacts have increased only recently then it is likely that, other effect such as exogenous re-infection was a key factor in the maintainance of TB in previous centuries.

Our models discriminate between cluster and casual infections. Casual transmission was not considered important until recently (Rafalli *et al.* . 1996). Our results support Rafalli's observations on the importance of casual transmission. The relative contribution of casual infections, that is, those not within the cluster (leisure places, airplanes, buses, churches, etc.) is included using the typical modeling approach. If we assume that the average number of casual contacts in a day is between 10 to 20 then a casual transmission rate (β^*) of between 0.9β to 10β is estimated (see Section V). Hence, casual infections may be as, or more, important than cluster generated secondary infections. The number of casual contacts may be rising up significantly. Public transportation in urban centers may be the biggest contributor (Capurro *et al.*, 1998). For example, in Buenos Aires Metropolitan Area (Argentina), one of the 20 biggest cities of the world, a 2.5 hours average round trip is required each day to get to work (Kralich, 1993). A bus can carry between 30-40 passengers, increasing the average number of casual contacts per day per person. There is evidence that casual contacts have been responsible of community-based outbreaks of TB, in bars and breweries, rock and roll concerts, choir groups, churches, clubs and friends parties (For a review see Rafalli *et al.*, 1996). Furthermore Grzybowski *et al.* (1975) have found for the British Columbia and Saskatchewan population between 1966-1971 that age-adjusted percentages of positive tuberculin reactors among casual contacts of active tuberculosis patients (37.4%) are about

80% of the age-adjusted percentage of positive tuberculin reactors among those infected via intimate contacts (44.7%). This empirical evidence and our numerical simulations suggest that casual transmission is relevant to the dynamic of tuberculosis.

An additional advantage in discriminating the mode of transmission is in the study of the influence of exogenous reinfection on TB dynamics. Exogenous reinfection may be fundamentally a cluster phenomenon. Therefore, it may have a significant differential influence on each mode of transmission, but this will be studied in the future. In addition, cluster transmission would also have strong influence on the outcome of competition among several TB strains. This effect might be important in the epidemiology of TB in recent years because outbreaks of multidrug-resistant strains are now more frequent and the death rate is around 80% (Smith and Moss 1994, Snider *et al.*, 1994; Gangadharam, 1993).

Modeling TB as a cluster disease may be relevant in evaluating public health policies. This evaluation should take into account the different types of transmission because different strategies must be implemented in each case. If cluster transmission is more important, contact tracing must be the better option. But if causal transmission is more relevant, the effort must be focused on reducing the number of active cases. This implies aiming at a strategy of case finding or of effective vaccination of susceptible individuals.

We have developed a flexible framework for the dynamic of TB in the simplest case of a homogeneous population. We have avoided the use of fitting parameters. Our Model (35-36) depends on parameters that describe the epidemiological state of the infectious individuals, as well as the characteristic of social behavior relevant to the epidemiology, such as: infectivity, size of the cluster, size of the network of daily close casual contacts, and time spent in this type of contacts. Therefore, we can make rough estimations of the impact that each different type of transmission has on the development of the epidemic for different community settings. These features may help in the design of control strategies according to the social characteristics of the community under study. In this study, we have privileged an intuitive and simple approach, and we look mainly for qualitative aspects of the dynamics. Further refinements about epidemiology and behavior, as well as the inclusion of several types of population heterogeneities, should be added in order to obtain more realistic descriptions, but this is a matter of future research. Also, it is important to highlight that this work was inspired on TB epidemi-

ology, but there are many other diseases for which cluster transmission may be relevant.

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A Parameter estimation

We have set the year as unit of time. The constant natural mortality (b) is the inverse of life expectancy which ranges from 60 to 75 years depending on the country. The recruitment rate (Λ) controls the total population size because $N \sim \Lambda/b$. In our simulations we set $\Lambda/b = 10^6$, but our results do not depend on this choice. The mean cluster size (n) is currently about ten (Etkind, 1993); however, it may vary with historical time and among social groups. We take the recovery rate (r) as the inverse of the time between the TB activation and recovery by treatment, which is between 4 and 6 months (Styblo, 1991).

The *per capita* risk of infection of people belonging to an active cluster (β) was chosen by taking into account that the number of contagions produced in the $1/\gamma$ units of time is approximately equal to $S_0(1-e^{-\beta/\gamma})$. Because β and γ are difficult to obtain, we used the non-dimensional parameter $Q \equiv \beta/\gamma$ which can be estimated from epidemiological surveys. Thus, for example, $Q = 1/3$ produce 28% contagions among the susceptible population belonging to active clusters, while $Q = 1$ produce 63% of contagions.

The casual transmission rate β^* is a fitting parameter but it can be related with more fundamental parameters like β. We consider that the mean daily network of close casual contacts of an infectious individual has a size n_c. He/she spends a time τ' in this class of contacts while he/she spends a time τ in cluster contacts. Assuming that the characteristics of the environments where the close casual contacts take place are essentially the same of the cluster ones, we have that the number of infections produced by one infectious individual per day is around $(\tau'/\tau)n_c\beta\frac{S}{N}$. Here, $n_c\frac{S}{N}$ is the susceptible fraction of the total close casual daily contacts of a person. Therefore, we have roughly that

$$\beta^* \sim (\tau'/\tau)n_c\beta \equiv m\beta.$$

The ratio τ'/τ ranges from 2/22 to 8/16 approximately. In communities with low close contact rates n_c may be lower than 10 per day, however in big cities this number increase significantly. In public transportation, usually overcrowded, an infectious individual may have around one hundred of close contacts per day in a poorly ventilated place, and for periods of time of around one or two hours. Therefore, the average value of n_c could be of the order of fifty. Roughly, the m values may range from 1 to 20 depending on

the characteristics of the community under study.

Rate of progression to active TB (k) is estimated from the fact that $\frac{k}{b+k}$ is the proportion of the infected population that develops active TB. For a life expectancy of 65 years and a 10 % of the latent population developing active TB, we obtain a value of k =0.002. TB induced mortality varies from country to country: it is between 0.07 (industrialized countries) and 0.395 (Africa) (Snider *et al.*, 1994). We choose an intermediate value of 0.1 that applies to most of developed and developing countries. Finally the parameter δ is used to control the number of treated individuals that "return" to the latent stage. As it is assumed that treatment delays the development of active TB by 20 years approximately (Moulding, 1995) we take $\delta = \frac{\delta^*}{b+\delta^*}$ with $\delta^* \sim 1/20$ (see Appendix B).

B Model with treated dynamics

We have incorporated the treated class explicitly. The N_1-population is divided in S_1, E_1, T_1 classes while the N_2-population is divided in S_2, E_2, T_2. We assume that the protection conferred by treatment is lost at a rate δ^*. Therefore, the model is (24-28) plus the equations,

$$\frac{dT_1}{dt} = -\gamma T_1 + \left((1-\rho)\frac{T_2}{N_2} + \rho\frac{T_1}{N_1}\right) nkE_2, \tag{37}$$

$$\frac{dT_2}{dt} = rI + \gamma T_1 - (b+\delta^*)T_2 - \left((1-\rho)\frac{T_2}{N_2} + \rho\frac{T_1}{N_1}\right) nkE_2, \tag{38}$$

for the treated class, and considering now that $N_i = S_i + E_i + T_i$, $i = 1, 2$. The necessary and sufficient condition for the existence of an endemic equilibrium is

$$\mathcal{R}_0 \equiv \left(\frac{\beta n(1-\rho)}{\beta + (1-\rho)\gamma} + \frac{\beta^*}{\gamma}\right)\frac{k}{B} > 1 \tag{39}$$

where $B \equiv b + k - \frac{\delta^* rk}{\gamma(b+\delta^*)}$. Defining $\delta \equiv \frac{\delta^*}{b+\delta^*}$ we recover the expression (29). Furthermore, we have that for realistic TB parameter values,

$$T_2^{eq} = \frac{rk}{\gamma(b+\delta^*)} E_2^{eq} \ll E_2^{eq}.$$

Taking into account that E_2 is about $0.1S_2$, we consider the approximation $N_2 = S_2 + E_2$ used in our models reasonable.

Adiabatic elimination of the fast variables lead to the following reduced system,

$$\frac{dS_2}{dt} \cong \Lambda - bS_2 - B\mathcal{R}_0 \frac{S_2 E_2}{N_2}, \tag{40}$$

$$\frac{dE_2}{dt} \cong -(b+k)E_2 + B\mathcal{R}_0 \frac{S_2 E_2}{N_2} + \delta^* T_2. \tag{41}$$

$$\frac{dT_2}{dt} \cong \frac{rk}{\gamma} E_2 - (b+\delta^*)T_2. \tag{42}$$

Reduction of a two dimensional system by taking T_2 at the 'equilibrium' value $\frac{rk}{\gamma(b+\delta^*)}E_2(t)$ produces no significant differences among solutions.

Linearization matrix around free infection equilibrium is

$$\begin{bmatrix} -b & -B\mathcal{R}_0 & 0 \\ 0 & B\mathcal{R}_0 - (b+k) & \delta^* \\ 0 & rk/\gamma & -(b+\delta^*) \end{bmatrix}$$

and the instability condition is as usual given by $\mathcal{R}_0 > 1$.

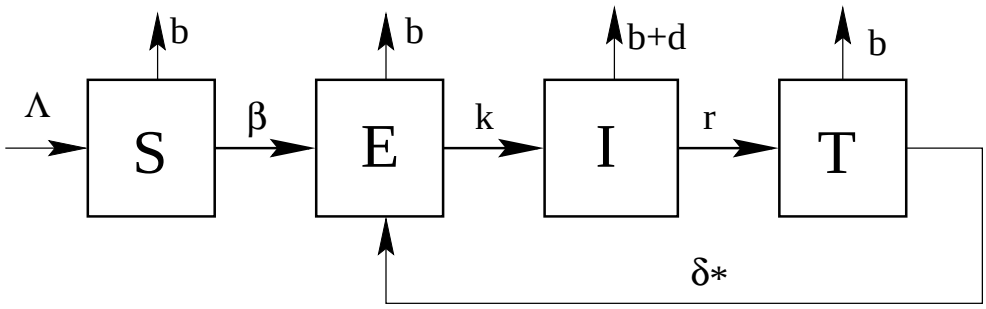

Figure 1: Diagram for TB transmission. S, E, I and T represent the number of susceptible, latent, infectious, and treated individuals respectively. Λ is the recruiment rate, b, and d are the *per capita* death and disease-induced death rates, k is the progression to active TB, r is the treatment rate, and δ^* is the rate of loss of protection conferred by teatment.

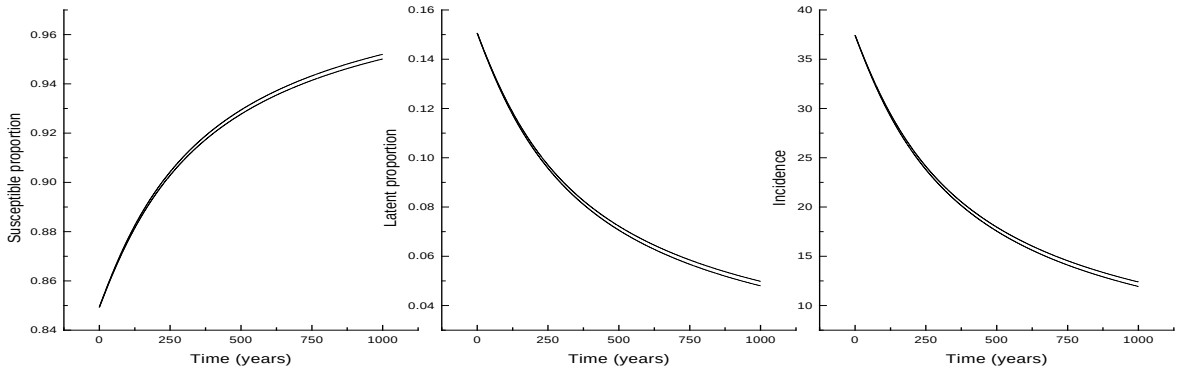

Figure 2: Numerical solutions for Models (6-10) and (11-15) for typical parameter values. The period of time considered (1000 years) is for illustrative reasons only. Obviously, parameter values can not remain constant for such long period of time. a) Susceptible population proportion. b) Latent population proportion (prevalence). c) Number of new cases of active TB by year per 100000 inhabitants (incidence of disease). $\Lambda = 15380$, $b = 0.01538$, $d = 0.1$, $k = 0.003$, $r = 2$, $n = 15$, $\beta = 2$.

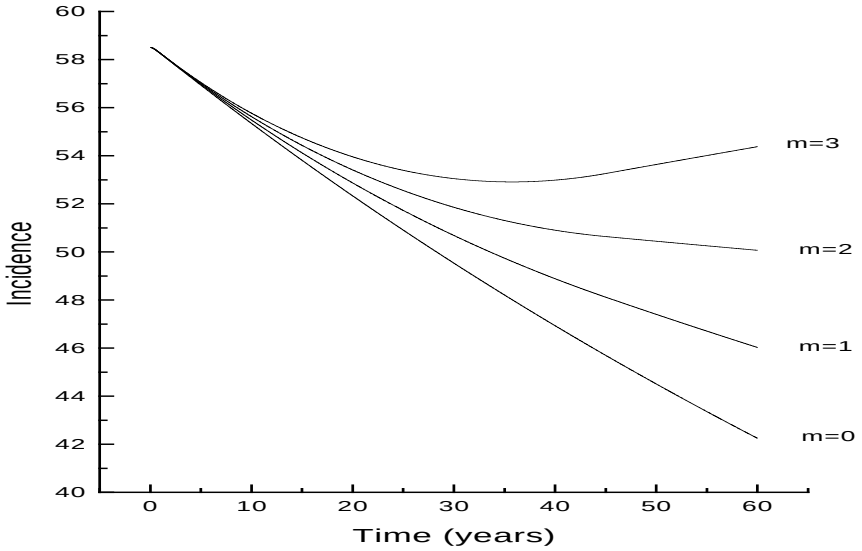

Figure 3: Incidence obtained with Model (18-22) for typical parameter values. We start at an equilibrium of Model (24-25) without treatment (natural recovery rate $r = 0.5$). After $time = 0$ we assume treatment ($r = 2.5$). Each solution was obtained by varying β^* linearly with time between 0 and $m\beta$ (m =0, 1, 2 and 3) during the first 45 years. The β^* value was set constant and equal to $m\beta$ over the last 15 years. The case $m = 2$ represents the case in which the average infectious individual spends only four hours daily with ten casual contacts (a modest value!). $\Lambda = 15380$ $b = 0.01538$, $d = 0.1$, $k = 0.0025$, $r = 2.5$, $n = 10$, $\beta = 2$, $\rho = 0$. Time unit =1 year.

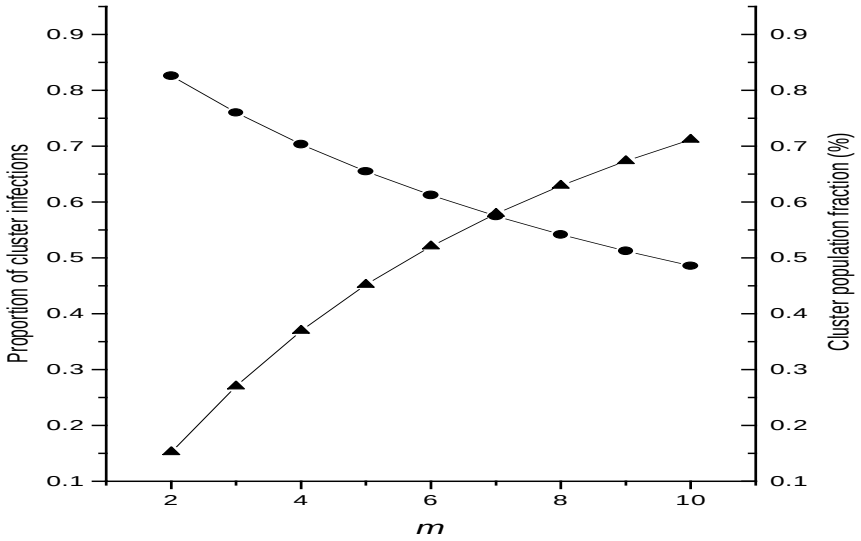

Figure 4: Fraction of the infections produced within clusters (circles), and relative size of the population within clusters in percentage (triangles), at the endemic equilibrium. Parameter values: $\Lambda = 15380$ $b = 0.01538$, $d = 0.1$, $k = b/9$, $r = 2$, $n = 20$, $\beta = 2$, $\rho = 0.25$. Time unit = 1 year.

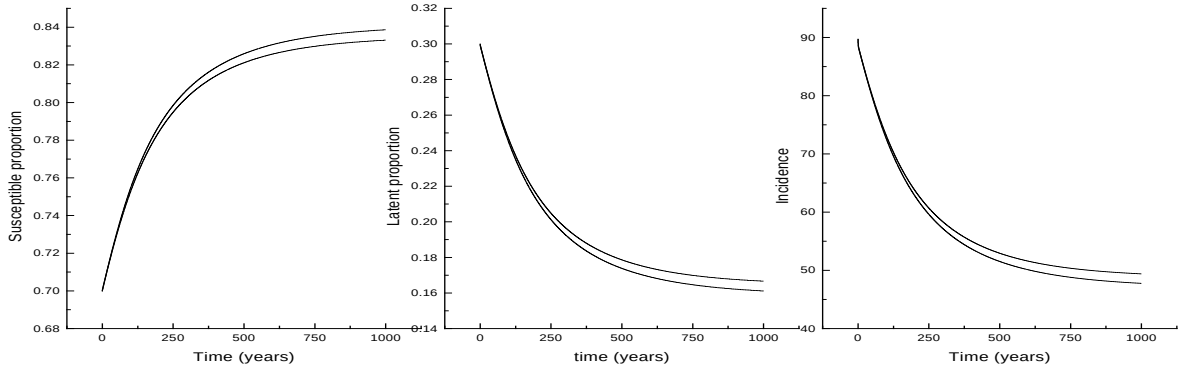

Figure 5: Numerical solutions for Models (18-22) and (35 -36) for typical parameter values. a) Susceptible population proportion. b) Latent population proportion (prevalence). c) Number of new cases of active TB by year per 100000 inhabitants (incidence). $\Lambda = 15380$ $b = 0.01538$, $d = 0.1$, $k = 0.0025$, $r = 2.5$, $n = 10$, $\beta = 2$, $\beta^* = 10$, $\rho = 0.375$.