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On the fall and rise of tuberculosis

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Abstract

A sudden and dramatic decrease on the risk of developing active-TB was observed from the time of the *Industrial Revolution* to that prior to the introduction of antibiotics. In this note we show that the coupling of this reduction with continuous population growth are enough to explain, to a great degree, the natural history of tuberculosis on humans over the last two centuries.

Key words: natural history of tuberculosis, epidemic model, demographic model, mathematical modeling,

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Introduction

Re-emergence of tuberculosis (TB) around the world has sparked a renewed interest in the study of its transmission and evolutionary dynamics[1, 2, 3, 4, 5, 6, 7, 8]. HIV co-infections, increased contact-rates (from systemic urbanization) chronic poverty and the use of antibiotics have all contributed to *recent* changes on TB-dynamics.

In the fight against disease, the introduction of antibiotics, is often causally linked to observed (often significant) reductions on morbidity and/or disease-induced mortality. TB death-rates data show a steep and sustained decline that began *at least a century prior to the introduction of antibiotics.* The causes behind this decline are still a matter of controversy [9]. Some support the view that it is due largely to increases in the total population average standard of living [9, 10, 11]. Others attribute it to a successful implementation of public health measures that included the isolation of active cases[9, 11]. Long-term co-evolutionary interactions between TB and its human host must have also played a role [12].

Nonlinear contact processes and variability in disease progression drive infectious disease dynamics. Blower *et al.*[2] have shown that downward TB trends can result just from nonlinear population dynamics. The decline observed in their model is mostly due to individuals with fast progression rates. This decline captures some of the qualitative features encountered in data but the time scale in which they take place is too short. Hence, Blower *et al.* conclude that " ... other causal factors must have also influenced the decline."

Here, we show that natural population growth (urban expansion) and a sudden reduction on the risk of progression towards active-TB are enough to explain the dramatic historical decrease of active-TB rates. Furthermore, these two factors can also account for the *apparent* minor increase and/or stabilization of active-TB cases over the last few decades. Demographic and epidemiological data are used to build and validate our model. Our results provide the first quantitative explanation of the last two hundred years TB's natural history.

Modeling tuberculosis epidemics

TB is an airborn disease with a latency (non-infectious) period ranging from months to decades. The number of secondary infections produced by a source case (actively-infected individual) is variable but has been estimated [13] to be as high as 200. The situation is complex as the mean and the variance on the number of secondary infections depend, among other factors, on the number of close contacts as well as on the infectiousness of the source cases. The conclusions of most studies are not applicable in general as they are based on data from highly infectious source cases.

Average TB progression has always been slow but now it appears to be substantially slower. Currently, between five and ten per cent of latently infected individuals develop clinical or active-TB during their lifetimes. *However, TB progression rates are not uniform as there is a strong correlation between TB prevalence and the average standard of living of each community*[14].

To support our claims, a simple model that uses only few time-dependent parameters (estimated from data) is introduced. $S(t)$, $E(t)$, $I(t)$ and $R(t)$ denote the susceptible, latently-infected, infectious (active-TB), and recovered (or treated) populations at time t, while $N(t) = S(t)+E(t)+I(t)+R(t)$ denotes the total population size at time t. The time evolution of $N(t)$ is determined by time-dependent *per capita* birth and mortality rates. Life-expectancy at birth is used as surrogate estimator of mortality. Birth-rates are estimated from the total net population growth rate. TB transmission dynamics are modeled using a nonlinear infection-rate, $G(S, I, N)$, and a per-individual risk of developing active-TB, $k(t)$. Hence, $G(S, I, N)$ models the flow of individuals from the susceptible to the latent class (new cases of latent infection per unit of time) while $k(t)E$ governs their flow from the latent to the infectious class. The number of secondary infections caused by an infectious individual is $Q_0\frac{S}{N}$ where Q_0 is the total number of secondary infections produced (by one infectious individual) in a fully-susceptible population. The per-capita removal rate from the actively-infectious class, $\gamma(t)$, is the sum of time-dependent recovery and mortality rates and, therefore, $1/\gamma$ is an estimator of the mean infectious period. The per-infective force of infection $Q_0\frac{S}{N}$ applies during $\frac{1}{\gamma}$ units of time (be-

cause the definition of Q_0), hence, the rate of new infections (incidence of latent infections) is given by $G(S,I,N) = \gamma Q_0 \frac{S}{N} I$. This form for the infection rate is typical of models with variable population size[15].

The fraction $f = \frac{k}{k+\mu}$ of latently infected people who develops active-TB during their life-span is taken as a measure of the TB-activation risk [16]. A rough idea of the past values of f is needed. Tuberculosis mortality rates were substantially higher in the past. In fact, they may have been higher than a thousand per 100,000 inhabitants during the eighteenth century[17, 18]. If we assume 100% prevalence of infection, 0% probability of survivorship from active-TB, and life-expectancy at birth of 40 years, we get a lower bound for f of 0.285. A change in the probability of survivorship from active-TB from 0% to 50% gives the more reasonable estimate for f of about 0.5. The present values of f have been estimated at between 0.05 and 0.1. Hence, the values of f have experienced a decrease of roughly *one order of magnitude* over a short period of time. These conservative estimates on the values of $f(t)$ are at the heart of our analysis and conclusions.

The risk of developing active-TB correlates negatively with (a rather difficult concept to quantify) standard of living[14]. *The observed increases in total population average life-expectancy at birth are used as surrogate measures for the increases (over time) on the total population average standard of living.* Figure 1b highlights the abrupt change in the average life-expectancy at birth that took place during an approximately one-hundred year time window between the time of the Industrial Revolution and today. From an epidemiological point of view, the main effect of such *transition period*, was to substantially change the values of population and epidemiological parameters. The evolution of the average life-expectancy at birth is modeled using the following sigmoid shape function,

$$\tau = \tau_f + \frac{(\tau_0 - \tau_f)}{1 + exp[(t - t_{1/2})/\Delta]}. \tag{1}$$

The parameters τ_0 and τ_f denote the asymptotic values (before 1800 and after 2050 approximately) of life-expectancy at birth; $t_{1/2}$ denotes the time at which life-expectancy at birth reaches its half value ($\tau = (\tau_f + \tau_0)/2$); and, Δ is a shape parameter–the width of the sigmoid shape function. Given the data on average life-expectancy at birth, the parameter values are

obtained from best fit. The choice of the functional form (1) is not essential.

Given the negative correlation between the standard of living and the risk of developing active-TB , it is reasonable to assume that the fraction $f(t)$ can also be modeled using the same functional form (1), that is,

$$f(t) = f_f + \frac{(f_i - f_f)}{1 + exp[(t - t_{1/2})/\Delta]}, \tag{2}$$

where f_i and f_f denote the model-dependent asymptotic f-values (before 1800 and after 2050 approximately). The values of the shape parameters $t_{1/2}$ and Δ used in (2) are given by those obtained from the best fit of total average life-expectancy at birth data to model (1). Surprisingly, the use of this two-parameter model (2) into our epidemiological model produces solutions that fit the historical trend of active-TB incidence very well. A better fit is obtained using slightly different shape parameters values (Δ' and $t'_{1/2}$). These new values are very near to those obtained from best fit to the life-expectancy at birth data.

Our epidemiological model uses the demographic parameters, $B(t)$, and $\mu(t)$ (both estimated from census data) and three epidemiological parameters, $r \simeq \gamma$, Q_0, and $f(t)$. The recovery rate r, as it will be shown later, does not play a significant role on the time scale of interest (see Methods).

Results

Our hypothesis is tested using data from the United States. A census of the US-population has been conducted every ten years beginning in 1790. Population size values prior to 1790 come from US-government estimates computed via back-extrapolation [19]. Unfortunately, not all the required data have been collected. Data on life-expectancy at birth are available but only from 1850 [20]. TB mortality-rates are available beginning in 1860 [20] while data on incidence of active-tuberculosis are only available since 1953. We use the available data to generate potential best and worst case scenarios (see Methods).

The ratio of active-TB incidence to TB-mortality at time t is denoted by $\rho(t)$. It is likely that this ratio was increasing in time as a consequence of historical improvements in living conditions. Because population density has been increasing with urban growth and Q_0 is a

function of contact rates, it is natural to assume that Q_0 has also been growing with time. There are not reliable estimates of ρ and Q_0 over time. Here, we assume that both are constant and by varying their values we manage to cover a wide range of possible scenarios. The results obtained from six different scenarios are presented. The values of ρ used range from 2 to 3, and from 10 to 30, for Q_0. The results are not too different than those obtained from simulations where ρ and Q_0 were allowed to vary in time within the same range (see Methods). Simulations were started in 1700 to minimize the effect of initial conditions during the period of interest. The parameter values obtained from the best fit of the Model (1) to US data on the average total-population life-expectancy at birth are listed in Figure 1.

The fitting of historical TB-trend

The use of expression (2) for the fraction $f(t)$ implies that our epidemiological model has only two free parameters; the limit values f_i and f_f. The values of f_i and f_f producing the best fit to active-TB incidence trends are listed in Table 1. Recent data are more reliable. Hence, we have privileged parameter values that give the best match to the last fifty years of data. Simulations fit very well the secular trend (see Figure 2a) except for the case $\rho = 2$ and $Q_0 = 10$ where model solutions do not fit well the last 50 years of recorded data (see figure 2b). Small changes in the shape parameters (see Table 2) correct this failure while improving the fit in all other cases (see Figures 2c and 2d).

The values of f_i and f_f were obtained from the best fit to the scenarios considered. The resulting values for f_i are between 0.3 and 0.5 which are within the range of those estimated using TB mortality data. The values for f_f are in the (approximate) range of 0.02 to 0.04, while todays' values obtained with (2) are in the 0.023 to 0.046 range, that is, they are quite close to the asymptotic values. Values in the range 0.028 to 0.08 for today's f-values are obtained using today's incidence of active-TB US cases ($\sim$ 6 per 100000 population) and reasonable values for the prevalence of latent infections (E/N), in the range of 5 to 15 %.

The asymptotic basic reproductive numbers

The basic reproductive number ($\mathcal{R}_0$) determines the long-term survival of a disease. If $\mathcal{R}_0 \leq 1$ then the disease goes to extinction otherwise it survives. If our parameters were time-independent then the basic reproductive number of our model would be $\mathcal{R}_0 = Q_0 f$. It is clear from data that parameter values are nearly constant prior to and after the dramatic 100 year transition period. Consequently, $\mathcal{R}_{0i} \equiv Q_0 f_i$ and $\mathcal{R}_{0f} \equiv Q_0 f_f$ give a reasonable measure of the potential reproductive value for tuberculosis before and after this dramatic transition period. These values correspond, approximately, to the values experienced at the beginning of the TB-epidemic and at the end (current values), respectively. Using the values of f_i and f_f obtained from the best fit (for each of the scenarios considered) to the data, we obtain values for $\mathcal{R}_{0i}$ in the range 4 to 12, and in the range 0.3 to 0.6 for $\mathcal{R}_{0f}$ (see tables 1 and 2). These results do not imply, even in the United States, that tuberculosis is going to extinction. The model considers homogeneously-mixing populations. Hence, model predictions break down whenever heterogeneity plays a critical role on TB transmission.

Discussion

For many centuries the risk of developing active-TB per latently-infected individual was high. However, a sudden and dramatic reduction on this risk took place over a short-period of about 100 years. In the United States, this reduction occurred mainly during the twentieth century. The impact of this change has been to reduce the prevalence of active-TB.

The causes of this reduction in risk are directly or indirectly tied in to the process of urbanization (urban city growth). In many parts of the world, particularly, in what is now known as the industrialized world, the total population average standard of living has increased. Improved nutrition and diets, better housing and sanitary conditions, have fostered a direct reduction on the risk of developing active-TB. On the other hand, growth in population density and increases in activities that have fostered mobility (the use of public transportation, travel, etc.) have resulted on higher per-capita contact rates. These factors are perhaps the most significant contributors to the spread and persistence of tuberculosis. However, one cannot

ignore the role of evolution in patchy landscapes. Fragmented landscapes naturally give selective advantages to particular types of individuals and pathogens. The persistence of less virulent TB-strains and enhanced cross-immunity [21] are but two examples of the impact of selective pressures.

There is no effective way of estimating the impact of all of the above, often confounding factors, on the risk of developing active-TB. However, data support a net evolutionary response (reduction of TB virulence) in the direction of risk reduction (over time). There are indirect (albeit strong) measures of this reduction. The dramatic increases experienced by the total population average life-expectancy at birth over the last one hundred years is but one of them.

Our results conclude that distinct temporal patterns followed by these reductions (regardless of what caused them) on the average total population risk of developing active-TB coupled with increases on the average total population growth explain, in a rather simple way, past and present trends of TB dynamics.

US TB-epidemiological and demographic data (over the last 200 years) and a simple model are used to support this simple explanation for the time evolution of the tuberculosis epidemic. Factors like re-infection, age-dependence of the risk of progression to active-TB, existence of non-exponentially distributed latency period, HIV co-infections, immigration and related factors have indeed contributors to TB dynamics. Their inclusion may improve the fit of our model to data. However, increased level of detail is not necessary to explain (in a crude way) the overall trends of TB dynamics over the last two-hundred years.

Antibiotic treatment and the causes of the secular decline of TB

TB was one of the main causes of death prior to 1900. Antibiotic treatment was introduced around 1950 and it produced a significant decrease in TB mortality. Its impact on the reduction of new cases of active-TB is unclear. Treatment reduced the length of the average infectious-period but other forces were still pulling in the opposite direction. The birth and growth of urban centers and the use of public transportation[22] increased contact rates. It is theoretically possible (TB-data is not available) to observe a high prevalence in the latently-infected class and yet, a significant reduction on the number of new cases of active-TBunder the above

conditions. In fact, dramatic decreases on rates of progression from latent-to-active TB will accomplish just that. In the United States, it is estimated that about 10% of the population are latently-infected and yet, there are only 6/100000 new cases of active-TB per year. In Buenos Aires, Argentina, is estimated that more than 20% of the population are latently-infected and yet, there are only 30/100000 cases of active-TB per year. During the last decades of the eighteenth century, prevalence of latently-infected individuals may have been as high[23] as 80% while TB-mortality rates were in the order of 500/100000. These values correspond to about 1000/100000 new cases of active-TB per year, a value more than 150 times higher than the present value in the United States.

TB is a slowly progressing disease, endemic, and with a large reservoir of infected people. Hence, it is reasonable to assume, that short-term (50 years) dynamics of active-TB are mostly governed by the risk of developing TB-disease (k). Treatment reduces the mean infectious period and, hence, it reduces Q_0. Furthermore, since most of the infections produced by an active case usually occur before TB is diagnosed [11] then the impact of antibiotic treatment on Q_0 is even less. Simulations show that dramatic variations on Q_0 do not produce significant changes in the generation of new cases of *active-TB* over a period of 50 years. Hence, the impact of antibiotic treatment on active-TB incidence cannot be detected on this time scale. Fig. 4 shows the results of simulations when the force of infection has been reduced to zero (by setting $Q_0 = 0$) and the model ran from 1950 to the present. Even in this last extreme case, the model was not capable of generating dramatic changes on the time-evolution of active-TB cases over a 50 year time scale. *Hence, public health measures implemented over the past centuries cannot explain either the long-term decline of TB.*

Reductions on the force of infection play a crucial role on the *long-term evolution* of TB-dynamics. Therefore, the impact of treatment cannot be ignored in dealing with questions related to the long-term evolution of TB including questions related to the evolution of resistance to antibiotics [5].

The interaction between HIV and TB epidemics

The long-term declining trend on notifications of active-TB stopped in 1985 in the United States, that is, just precisely at the beginning of the AIDS epidemic. In 1992, about 6000 active TB-cases were directly associated with the progression to active TB from people with HIV co-infections [1]. This value of 6000 matches almost exactly with the observed difference between data and model solutions. TB notifications began to decline after 1992. TB seems to continue to follow the trend observed before 1985 while AIDS incidence seems to be reaching a stable value. AIDS cases have shown a marked and sustained decline in numbers after 1996. Therefore, it is likely that a significative part of the difference between TB notifications and model solutions may due to HIV-*Mycobacterium tuberculosis* co-infections.

Possible future trends in the TB-epidemic

After the sharp transition period occurred after the *Industrial Revolution*, variation in the fraction $f(t)$ has been slow again. In the scenarios presented in this work, the resulting "asymptotic" basic reproductive numbers turn out to be less than one (see Tables 1and 2). The low values obtained for f_f are the result of the model's homogeneity assumption (individuals belong to a homogeneously randomly mixing population). Hence, our results suggest at best, that heterogeneity on TB transmission (immigration, re-infection, core groups, HIV, etc.) are critical to TB survival. Clearly, neither our model nor the data used here can address the question of extinction.

With this in mind, we can draw two different scenarios for the next decades assuming that no further dramatic changes in the epidemiological conditions take place (parameters remain fix). If the *actual* average basic reproductive number is less than one, a slow decline to extinction would take place. However, if $\mathcal{R}_0 > 1$ then a slow growth in the number of active-TB cases would be expected. Hence, TB re-emergence does not necessary imply a deterioration of epidemiological conditions but rather the natural course of a disease in a continuously increasing population.

Methods

The epidemiological model

We considered a simple model for TB disease dynamic in which a homogeneous population of varying size $N(t)$ is classified using the epidemiological classes: susceptible (S), latent (E), infectious (I), and recovered, naturally or by treatment, (R). Using the parameters and rates previously defined we arrive at the following epidemiological model

$$\frac{dS}{dt} = BN - \mu S - \gamma Q_0 \frac{S}{N} I, \tag{3}$$

$$\frac{dE}{dt} = \gamma Q_0 \frac{S}{N} I - \frac{\mu}{1-f} E, \tag{4}$$

$$\frac{dI}{dt} = \frac{\mu f}{1-f} E - \gamma I, \tag{5}$$

$$\frac{dR}{dt} = rI - \mu R. \tag{6}$$

TB-relapse contributions are ignored as our goal is to validate our hypothesis with as simple model as possible. Mortality (μ) is set as the inverse of life-expectancy at birth (which includes death by TB). Therefore, disease-induced mortality is distributed among all the classes. Life-expectancy at birth is fitted, from historical data (see Fig. 1b), using a model based on a flexible functional form (Expression 1). The birthrate $B(t)$ is taken to be such that it reproduces observed population values. Linear interpolation, between successive census data, is used to estimate population values at all times.

The role of the mean infectious period

The removal rate γ for the infectious class is approximated by the inverse of the average time between TB activation and either recovery (naturally or by treatment) or death (a process that lasts a couple of years). In both cases $1/\gamma \ll 1/\mu$.

The natural time-scale for the dynamics of the infectious population $I(t)$ is $1/\gamma$ while the natural time-scale for the population dynamics is about $1/\mu$. In dynamical-systems terminology, $I(t)$ is a fast variable when compared to the others and, can be (adiabatically) eliminated by substituting it, in Equations 3, 4, and 6, using the quasi-equilibrium assumption $I(t) \simeq \frac{k}{\gamma} E(t)$.

This last approximation combined with the fact that $\gamma \simeq r$ reduces our model to a system of three equations with two relevant epidemiological parameters, f and Q_0. The validity of this approximation was tested numerically. Solutions to the full model (3-6) are computed using values of the infectious period that range from one month to one year. The dynamics in all cases are nearly identical, that is, the full model is not sensitive to variations on the length of the infectious period (at least for the above range). Therefore, varying the mean infectious period mostly impacts the number of secondary latent-infections produced by each active case (because $Q_0 = Q_0(\gamma)$ is a function of the mean infectious period).

The tune of the shape parameters for $f(t)$

Tuberculosis was a major contributor to total population mortality rates in the recent past. TB was responsible for roughly ten-to-twenty percent of the total deaths in the United States during the nineteenth century. [11, 24] The leading cause of death as of 1960 is heart-disease. TB-death rates did not even make the list of the top ten leading-causes of death even at in 1960. Hence, an increase in life-expectancy at birth does not necessarily translates into a direct reduction in the fraction f. Therefore, we allow for differences between the width of the functions (1) and (2) by replacing Δ by $\Delta' \equiv \sigma\Delta$ with $\sigma < 1$. On the other hand, life-expectancy at birth is partially determined by future conditions while progression to active-TB is mostly determined by present conditions. To capture the effect of this delay, a shift in time is introduced so what the half-value of f is reached at a later time than the half-value of life expectancy at birth. Hence, we replace $t_{1/2}$ by $t'_{1/2} \equiv t_{1/2} + \alpha\tau$, with $\alpha > 0$.

Generation of possible scenarios

United States data have been use to test our hypothesis. The number of new cases of active-TB per year has been recorded since 1953. Earlier data includes active and inactive cases during 1912-1953. Data on mortality rates since 1900 to the present time are available while data on mortality rates for Massachusetts can be found for the period of 1860-1900. We use Massachusetts' data as typical for TB because although the majority of the US population during this period was living in rural areas the overwhelming number and percentage of TB-

cases occurred in cities. The validation of our hypothesis is carried out with our simple model, using the above data as well as 'data' obtained from reasonable extrapolation of available data (such as the Massachusetts' data).

We use TB annual-mortality data to generate possible values for the incidence of active-TB for the 1860-1950 period. Potential values for TB incidence (new active-TB cases per year) were taken to be proportional to TB-mortality rates. The constant of proportionality is ρ. It was assumed that in the absence of treatment 50% of the active-TB cases died because of TB (ρ would be approximately equal to 2). In the simulations presented in this work we use the values 2 and 3 for ρ. For each of the two generated series of incidence of active-TB, the results obtained with each of the three constant values for Q_0, namely, 10, 20 and 30, are presented. We have explored additional possibilities including those that correspond lower values for ρ (as low as 1.5). Similar results were obtained when both ρ and Q_0 were allowed to vary in time.

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Q_0	ρ	f_i	f_f	$\mathcal{R}_{0i}$	$\mathcal{R}_{0f}$
10	2	0.4125	0.041	4.125	0.41
10	3	0.52	0.032	5.2	0.32
20	2	0.35	0.025	7	0.5
20	3	0.425	0.018	8.5	0.36
30	2	0.318	0.0185	9.54	0.555
30	3	0.405	0.019	12.075	0.57

Table 1: Parameter values used for the simulations shown in Fig. 2a. For each combination of Q_0 and ρ, the only two free parameters used in our epidemiological model (3-6) are the asymptotic values f_i and f_f. The values for the shape parameters ($t_{1/2}$ and Δ) are those obtained from the best fit to the observed time evolution of the average life expectancy at birth. The values for the corresponding "asymptotic" basic reproductive numbers $\mathcal{R}_{0i} \equiv Q_0 f_i$ and $\mathcal{R}_{0f} \equiv Q_0 f_f$ are included.

Q_0	ρ	α	σ	f_i	f_f	$\mathcal{R}_{0i}$	$\mathcal{R}_{0f}$
10	2	0.075	1	0.4	0.035	4	0.35
10	3	0.1	0.9	0.48	0.033	4.8	0.33
20	2	0.05	1	0.33	0.022	6.6	0.44
20	3	0.05	0.85	0.42	0.022	8.4	0.44
30	2	0.015	1	0.3075	0.018	9.225	0.54
30	3	0.02	0.84	0.4025	0.0195	12.075	0.585

Table 2: Parameter values used in the simulations shown in Figures 2c and 2d. The shape parameters of the functional form for $f(t)$ (expression 2) are $t'_{1/2} \equiv t_{1/2} + \alpha\tau$ and $\Delta' \equiv \sigma\Delta$. The values of the two parameters added (α and σ) to improve the fit are $\alpha \sim 0$ and $\sigma \sim 1$. In three of the six cases considered only a small shift in the $t_{1/2}$ value is required to get a good fit. $\mathcal{R}_{0i}$ and $\mathcal{R}_{0f}$ values are listed in the last two columns.

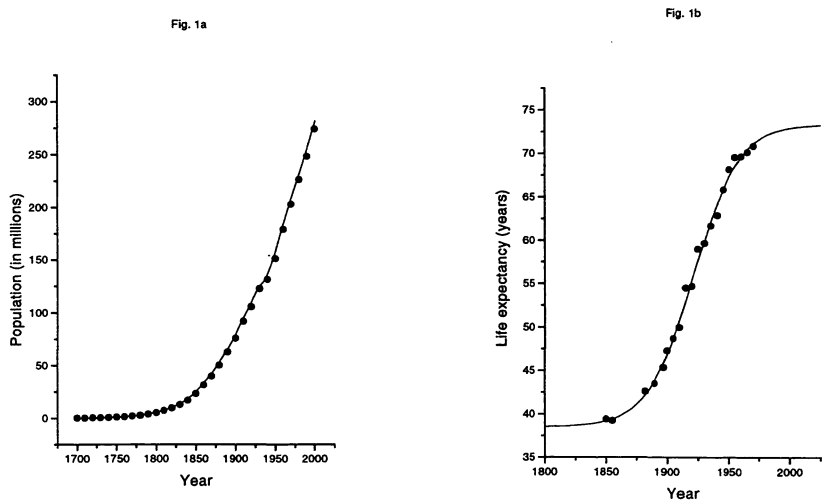

Figure 1: a) Observed population growth (•) contrasted with population growth obtained with the model driven by mortality rates (inverse of the life expectancy at birth function (1)) as well as birthrates obtained via linear interpolation from census data. b) Observed average life expectancy at birth (•) and its best fit (continuous line) using Expression (1). Fitted parameter values are $t_{1/2} = 1921.3$, $\Delta = 18.445$, $\tau_i = 38.5$ and $\tau_f = 73.5$.

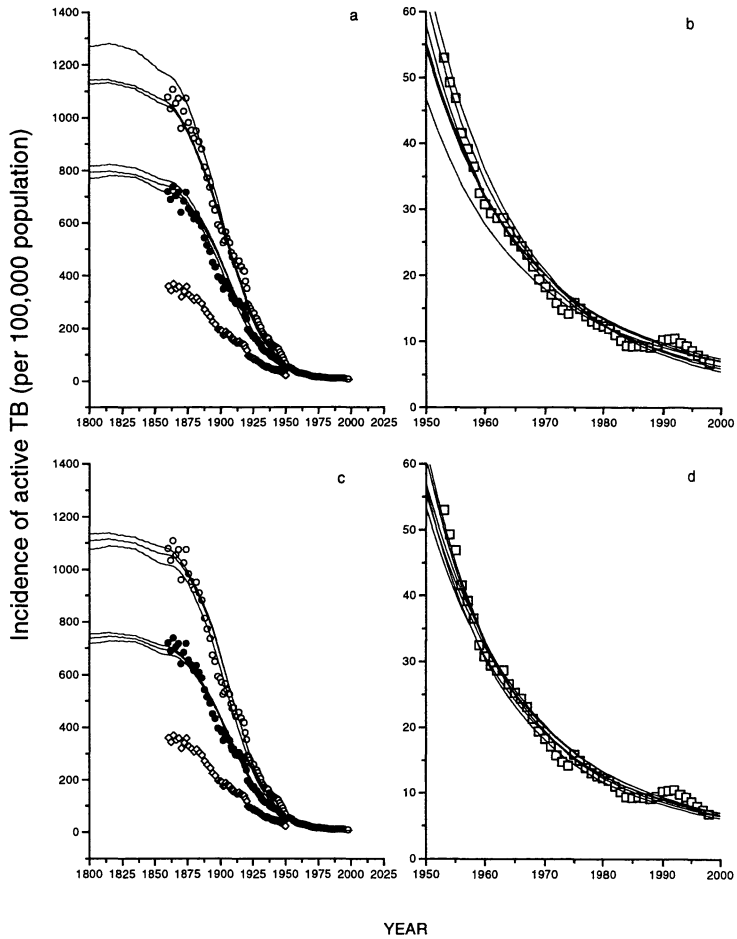

Figure 2: Observed (□), estimated (○ and •), and model solution for the incidence of active-TB rate. In each case, the fitting gives preponderance to data from 1953-2000. In order to show the historical trend and the magnitude of TB rates, possible values for active-TB incidence rate are presented (1860-1940). These possible values of past incidence of active-TB rates were obtained using observed mortality rates for those times (◇) multiplied by the factor ρ. This figure illustrates the cases $\rho = 2$ (•) and $\rho = 3$ (○). For each of these two series, we show the best fitting-to-data solutions obtained when the values of 10, 20 and 30 were used for Q_0. Figures a) and b) shows solutions obtained using two free parameters (see Table 1). Figure c) and d) shows solutions using four free parameters (see Table 2).

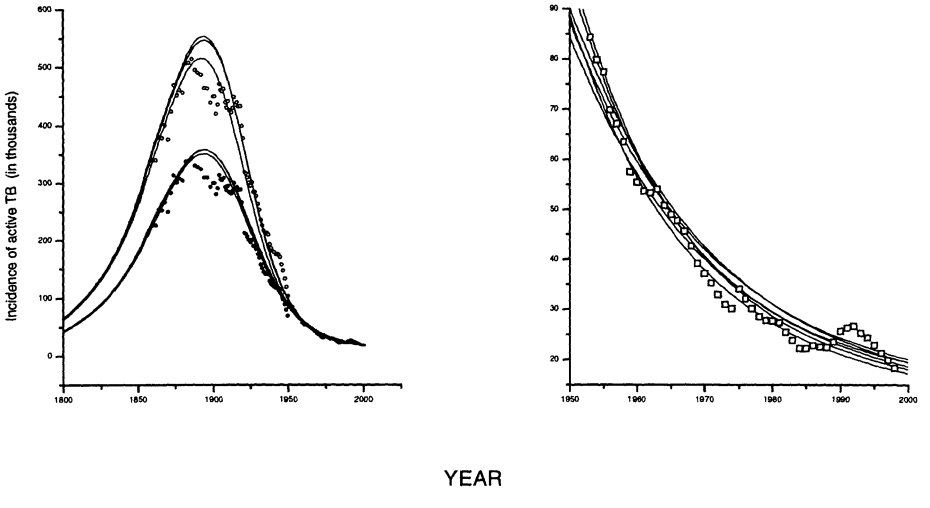

Figure 3: a) Observed (□), estimated (○ and •), and model solutions (continuous line) for the incidence of active-TB (total number of new cases per year). Until the beginning of the twentieth century $f(t)$ was varying slowly and the number of TB-cases grew together with population size. Afterwards, the decline in risk, $k = \mu f/(1-f)$ became faster than the rate of increase of the infected population, $E(t)$. The net effect was a decrease on the number of cases per unit of time, kE. b) These figures zoom on the last 50 years. In 1992, it was estimated that about 6000 TB-cases were due to the progression to active TB from people with AIDS. This value almost matches the difference between data and model solutions. After 1996, AIDS cases have shown a marked and sustained decline in numbers. Hence, we expect less discrepancies between model solutions and data after 1996.

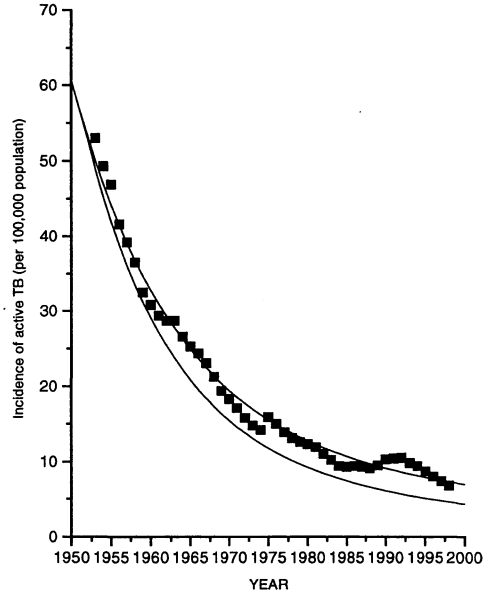

Figure 4: A model solution (upper line) and the corresponding solution obtained with the same parameter values after setting Q_0=0 over the last fifty years (lower line). The last case represent, a limit case, in which treatment has the effect of reducing the infectious period to zero over the last fifty years. Clearly, treatment does not play a significant role on the short-term dynamics of the TB epidemic.