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Preventive treatment of tuberculosis through contact tracing

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Abstract. Actual tuberculosis control strategies focus on the treatment of active, infectious cases. In this work we explore the effect of a complementary strategy consisting in the administration of preventive therapy to recently infected (but not infectious) contacts of identified active cases. We show that even when a small fraction of the infected contacts are effectively treated, significant reductions in the incidence of active tuberculosis are achieved. More important such a combined strategy may be less costly than the currently-employed strategy.

1. Introduction

Even after a sustained decline in rates of tuberculosis during the last century one-third of the world's population is still infected with *Mycobacterium tuberculosis*, and tuberculosis is responsible for three million deaths each year. Effective antibiotic treatment with *streptomycin* was introduced in 1946, but preventive therapy was not feasible until the introduction of *isoniazid* in 1952.

Actual control strategies are focused on treatment of active-TB cases. In fact, the global control strategy of the World Health Organization is *Direct Observed Treatment, short-course* (DOTS), whose main component consists in the supervised treatment of active cases to ensure compliance. Although a program like DOTS is essential to reducing TB relapse and emergence of drug resistant strains, its impact on the control of tuberculosis transmission is not clear [**1**].

A complementary tool is preventive therapy, which consists of administration of antibiotics (usually isoniazid) to latently infected individuals, particularly to those at higher risk of developing active-TB.

In the United States the Advisory Committee on the Elimination of Tuberculosis has presented the Strategic Plan for Elimination of Tuberculosis [**2**] with the goal of achieving an incidence lower than one case per million population by the year 2010. The target for the year 2000 was set at 3.5 per one hundred thousand population.

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In this work we develop a model of the transmission dynamics of tuberculosis including preventive treatment. The model is used to evaluate the potential impact of a strategy of preventive treatment of recently infected contacts of reported new cases. We find that a complementary preventive treatment strategy may result in significant reductions in TB transmission at a lower cost than the strategy actually used.

1.1. Basic tuberculosis epidemiology. Most individuals infected with *M. tuberculosis* never develop clinical tuberculosis, remaining asymptomatic for life. The usually-small fraction of infected people who develop active-TB may do so years after infection. Clinical (active) tuberculosis may be pulmonary or extrapulmonary, but only pulmonary cases are infectious. Pulmonary cases represent most of the cases of clinical tuberculosis. The usual symptoms include tiredness, high fever, and cough, but confirmation of active-TB requires a positive sputum culture. Extrapulmonary tuberculosis accounts for between 5% and 30% of the total cases and may affect almost any organ in the body [**3**]. Infectiousness of pulmonary cases is also highly variable; sputum-positive cases are about twice as infectious than sputum-negative cases (see for example [**4**]). Recently-infected individuals present a higher risk of developing active-TB and more than 90% of the new cases are infected within the five years prior to disease onset [**5**]. Individuals who progress to active-TB within 5 years of infection are classified as primary TB cases, while those progressing after 5 years are considered endogenous reactivation cases. Previously infected cases may have some protection, but contact with infectious active-TB cases may result in reinfection. Reinfection increases the risk of developing active-TB.

Tuberculosis is not a highly infectious disease, and therefore it is typically transmitted to a small group of frequent and close contacts of the active case. Identification of recently infected cases is therefore feasible by contact tracing [**6**] which consists in the elucidation of potential contacts of the source case using epidemiological interviews. Recently infected individuals are candidates to receive preventive therapy because they are at a high risk of developing active-TB.

1.2. Some previous models. Previous work has explored the consequences of different treatment regimes in the course of TB epidemics. Castillo-Chavez and Feng [**7**] developed a model with treatment in latent and infectious classes. They explored the consequences of treatment on the coexistence of susceptible and resistant strains of *M. tuberculosis*. Their principal finding was that antibiotic resistance promotes coexistence of the competing strains of *M. tuberculosis*. Murray and Salomon [**8**] used a compartmental model with nineteen classes to evaluate the impact of the DOTS strategy worldwide. They also considered massive preventive therapy. In the work closest to ours Ziv *et al.* [**9**] explored the effect of preventive therapy in reducing the prevalence of active tuberculosis when used in conjunction with treatment of active cases. They found that when 80% of the active-TB cases receive treatment, at least 25% of the recently infected population must be treated in order to achieve tuberculosis elimination. Finally Murphy *et al.* [**10**] developed a model for genetically heterogeneous populations with treatment of both active and latent cases. They found that low levels of treatment in the latent population have almost no appreciable affect on reducing prevalence. A feature common to all these studies

is that they consider constant populations,[1]and treatment of latent populations is modeled by increased transfer rates between latent and treated classes.

Our work departs from previous studies in using demographic and epidemiological data with a model that incorporates time-dependence to capture the dynamics of tuberculosis epidemics in growing populations. In addition we have modeled preventive treatment differently. Rather than increasing the rates at which individuals leave latently infected classes, we have chosen to consider movement of a fraction of the effective contacts of each source case from the susceptible class to the treated class. The level of treatment is therefore the fraction of effective contacts treated.

2. Modeling preventive treatment

2.1. A model without treatment. In this work we use a slightly modified version of the model introduced in [**11**]. The model captures the transmission dynamics of TB in growing urban populations, and was parameterized using historical demographic and epidemiological data from United States.

2.1.1. *Modeling growing populations.* Total per capita mortality and TB mortality have been recorded since about 1850 [**12, 13**]. The data display some large fluctuations during the period 1850-1900 which likely represent errors in measurement. Therefore we replaced these raw data by a smooth function that captures the trend (see Fig. 1). A variety of sigmoid-shaped functions would serve this purpose. We chose the best fit (in the least squares sense) of a Boltzman function to the total mortality data

$$\mu_{TOT}(t) = \mu_f - \frac{\mu_f - \mu_i}{1 + exp[(t - t_\mu)/\Delta_\mu]}, \tag{1}$$

with t the calendar year, $\mu_i = 0.021 yr^{-1}$, and $\mu_f = 0.00887 yr^{-1}$, $t_\mu = 1910 yr$, and $\Delta_\mu = 16 yr$. This functional form has four free parameters which determine the asymptotic values (μ_i and μ_f), the inflection point t_μ and the width Δ_μ.

Per capita non-TB mortality (μ) was obtained by subtracting TB mortality from total mortality. Estimates for TB-induced mortality prior to 1850 were obtained with our model assuming fatality in an average of 50% of cases.

From these mortality data we computed the recruitment rate B in urban populations. Estimates of the proportion of U. S. populations that were urban [**12**] were used to estimate the sizes of urban populations $N_{obs}(t)$ since 1700 (see [**11**] for details). Finally, the recruitment rate was estimated as $B(t) = dN_{obs}/dt + \mu N_{obs}$, where we approximated dN_{obs}/dt by $[N_{obs}(t + dt) - N_{obs}(t)]/dt$, with estimated values of $N_{obs}(t)$ obtained by linear interpolation.

2.1.2. *Modeling epidemics in growing populations.* Recruitment occurs in the uninfected population, which is denoted by $U(t)$. After infection individuals enter a stage of high risk of developing active-TB, $E(t)$. Those who do not progress to the disease are moved to a low risk latent class, of size $L(t)$, at the rate $\alpha = 2/3 yr^{-1}$[**11, 14**]. Long-term studies [**5**] have shown that the risk of progression to active-TB declines exponentially, with more than 95% of progressions taking place within five years of infection. Therefore in this work we disregarded progression to

[1]Strictly speaking all the models consider constant recruitment and mortality rates, and therefore the total population always reaches an equilibrium value. Results obtained with these models were obtained in this equilibrium regime, and therefore, for constant populations.

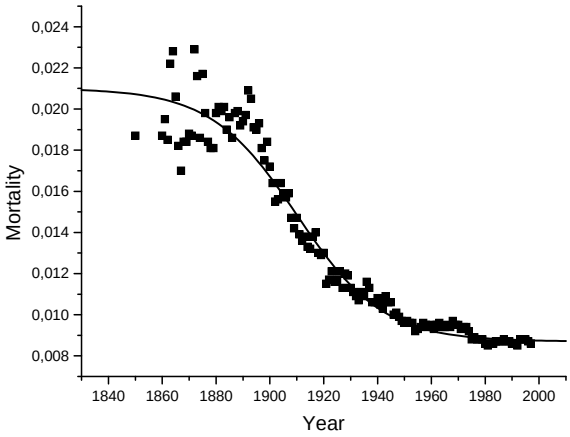

FIGURE 1. Mortality (from all causes) rates in the United States (solid squares) and the best fit by the Boltzman function of equation (1).

active-TB from the low-risk latent class. However low-risk latent individuals may be reinfected and thereby re-enter the high-risk class.

Infectious individuals induce some infections among their contacts, but only a fraction $f(t)$ of infected individuals will develop active-TB [a population denoted $A(t)$], with the fraction $q = 0.7$[**15**] of these being infectious pulmonary cases. The contact number (Q_0) is defined as the number of secondary *infections* produced by an average infectious case placed in a fully susceptible population. Therefore the basic reproduction number (which is defined as the number of secondary (infectious) *cases* produced by an average infectious case placed in a fully susceptible population) is $R_0 = qQ_0f$.

Tuberculosis transmission is modeled as follows. An average pulmonary case placed in a fully susceptible population will produce Q_0 secondary infections (by definition of the contact number) during his/her entire infectious period $1/\gamma$. Therefore the number of new infections produced per infectious case per unit of time at the beginning of the epidemic is given by $\gamma Q_0 I$. As the epidemic progresses not all contacts will be uninfected, and an average pulmonary case will produce $\gamma Q_0 \frac{U}{N}$ new infections and $\sigma\gamma Q_0 \frac{L}{N}$ reinfections per unit of time where $\sigma < 1$ accounts for the protection conferred by previous infections.

We considered a fixed effective mean infectious period of 6 months; therefore $\gamma = (r+d+\mu) = 2/yr$, where r is the recovery rate and d is the tuberculosis-induced mortality. We assumed a 50% fatality rate for active-TB before treatment, thus $d = r = 0.5(\gamma - \mu)$. After the onset of the era of effective treatment (1950 in our simulations) we set $d = 0.1(\gamma - \mu)$ and $r = 0.9(\gamma - \mu)$.

Superimposing the epidemiological model upon the demographic model yields our basic transmission-dynamics model for tuberculosis:

$$\frac{dU}{dt} = B - \mu U - \gamma Q_0 q A \frac{U}{N}, \tag{2}$$

$$\frac{dE}{dt} = \gamma Q_0 q A (U + \sigma L)/N - (k + \mu + \alpha)E, \tag{3}$$

$$\frac{dA}{dt} = kE - \gamma A, \tag{4}$$

$$\frac{dL}{dt} = rA + \alpha E - \mu L - \sigma\gamma Q_0 q A \frac{L}{N}, \tag{5}$$

It is not clear whether tuberculosis transmission per case (Q_0) has been decreasing or increasing during the last century. In this work we considered different constant values of Q_0 spanning a wide range. For each value of Q_0 we used the data on incidence of active-TB to compute the values of rates of progression $k(t)$ needed to match the model solutions to those data (see the Appendix for details).

2.2. A model including preventive treatment. Massive preventive treatment is impractical because it requires screening of large populations. Here we considered a strategy focused on tracing of the contacts of the (reported) new cases of active-TB. For each new case of pulmonary active-TB, potentially infected contacts are identified by standard contact tracing. Some of those already infected receive preventive therapy. This process of contact tracing may be emulated with an agent-based model. Here we followed a different approach; we modeled the average effect of this contact-tracing based strategy. We assumed that only a fraction θ of the total of newly infected contacts of each new case of (pulmonary) active-TB, are elucidated and that those individuals received fully effective preventive chemoprophylaxis. We modeled this by assuming that this fraction moves directly from the susceptible classes (U and L) to a treated class T. The protection conferred by treatment is lost at the rate r_T. Fig. 2 displays a representation of the model, which is

$$\frac{dU}{dt} = B - \mu U - \gamma Q_0 q A \frac{U}{N}, \tag{6}$$

$$\frac{dE}{dt} = (1 - \theta)\gamma Q_0 q A (U + \sigma L)/N - (k + \mu + \alpha)E, \tag{7}$$

$$\frac{dA}{dt} = kE - \gamma A, \tag{8}$$

$$\frac{dL}{dt} = rA + r_T T + \alpha E - \mu L - \sigma\gamma Q_0 q A \frac{L}{N}, \tag{9}$$

$$\frac{dT}{dt} = \theta\gamma Q_0 q A (U + \sigma L)/N - r_T T \tag{10}$$

The values of $k(t)$ used in this model are the same as those obtained with the model of equations (2-5) for each value of Q_0. Therefore the construction of the model guarantees that its solutions match observed data on the incidence of active-TB for $\theta = 0$ (see Figs. 3 and 6). These solutions represent a baseline against which the effect of different levels of treatment can be compared.

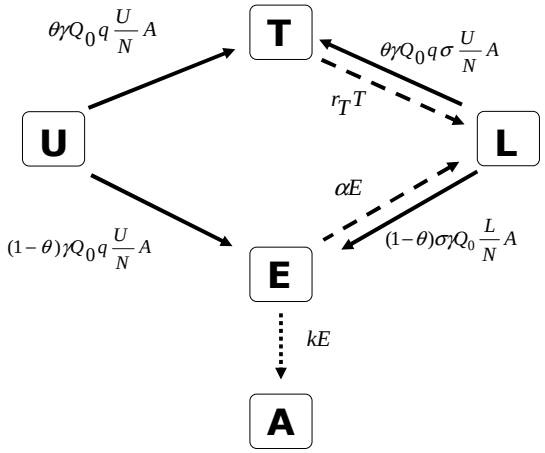

FIGURE 2. Flow diagram of the model. Individuals are recruited from the uninfected class U. After their first infection they move into the high-risk latent class E. Individuals in this class may progress to active TB (class A). Most individuals move to the low-risk latent class L, whence they may become reinfected and again enter the high-risk class E. A fraction θ of newly infected individuals receive preventive therapy, move to the treated class T and return to the low-risk latent class L at the rate r_T. Transmission is represented by solid arrows. Transfer rates per unit of time are also indicated.

The simulated incidence of active-TB is found to be $kE10^5/N_{tot}$, where N_{tot} is the total U. S. population for year t (in the model N is the size of the urban population), and the annual number of treated cases is $\theta\gamma Q_0 qA(U+\sigma L)/N$. The number of prevented cases of active-TB is obtained by subtracting the annual number of new cases (kE) from equations (2-5) from the values obtained with the model of equations (6-10) for different values of θ. The rates are expressed in units of inverse years.

2.2.1. *Basic reproduction number.* In the absence of preventive treatment an average infectious individual placed in a fully susceptible population would produce Q_0 secondary infections (by definition of contact number). However, only a fraction f of such effective contacts will ever progress to active-TB, and only a fraction q will result in pulmonary, i. e. infectious, cases. Therefore the basic reproduction number, which is defined as the number of secondary (infectious) *cases* produced by an average source case in a fully susceptible population, is $R_0 = Q_0 fq$, where $f = k/(\alpha + k + \mu)$.

Where there is preventive treatment, the basic reproduction number is reduced by the factor $1-\theta$ because the fraction θ of effective contacts is protected against progression to active-TB. Now the basic reproduction number becomes

$$R_0(\theta) = Q_0 q f (1-\theta). \tag{11}$$

This resembles the equation for the reproduction number when a fraction θ of the population is effectively vaccinated against the disease. In that case expression (11) is not called the *basic* reproduction number but simply the reproduction number. We retain the term *basic* because, in our case, individuals become protected against disease progression *after* infection. Therefore, strictly speaking, expression (11) is still the number of secondary cases produced in a fully susceptible population.

3. Results

In our model there are only three parameters with significant uncertainty, the contact number Q_0, the rate of loss of protection conferred by treatment r_T, and the degree of protection against reinfection conferred by previous infections σ. All other parameters are determined by demographic or epidemiological data. We considered different scenarios corresponding to different values of Q_0 (7.5; 10; 12.5; 15; 17.5; and 20), and used conservative values for the other uncertain parameters. We assumed that treatment does not confer long-term protection against reinfection, and we therefore set $r_T = 1/yr$. We assumed either that previous infection does not confer any protection against reinfection ($\sigma = 1$), or that it provides only 30% protection ($\sigma = 0.7$).

For each scenario we estimated the impact of different levels of treatment on TB epidemics comparing the observed course of the epidemic with hypothetical courses obtained under different levels of preventive therapy beginning in 1980 (that is we considered $\theta = 0$ for $t < 1980$). It should be noted that our model does not consider the interrelation of TB with HIV. Thus the simulated incidence in the baseline case ($\theta = 0$) reproduces the trend of observed incidence of active-TB but does not capture the AIDS peak. The projected value (disregarding HIV) of the incidence for the year 2000 was 4.4 new cases of active-TB per year per 10^5 population, whereas the actual incidence was 5.8. Results for different levels of preventive treatment were compared with this baseline simulated incidence (see Fig. 3).

For each scenario (consisting of a value of Q_0 and σ) we determined $k(t)$ assuming no treatment ($\theta = 0$ for all t) and also the simulated incidence, number of high-risk latent cases treated, and number of active-TB cases prevented, for several values of $\theta > 0$ after $t = 1980$. We also calculated the level of treatment needed to produce one new case of active-TB per year per one hundred thousand population by year 2000, which is ten times the goal set by the Centers for Disease Control for 2010.

When 5% of the infected contacts of each new case of active-TB receive effective preventive therapy ($\theta = 0.05$), the projected incidence of TB for the year 2000 falls close to 2.5 per hundred thousand for any of the scenarios considered. Similarity among the results is explained by the fact that a given θ represents the same fraction of contacts treated for each value of Q_0 (see fig. 3). However, the public health effort required in each case is not the same; greater effort is needed to administer preventive therapy to θ% of effective contacts when Q_0 is 20 than when Q_0 is 10.

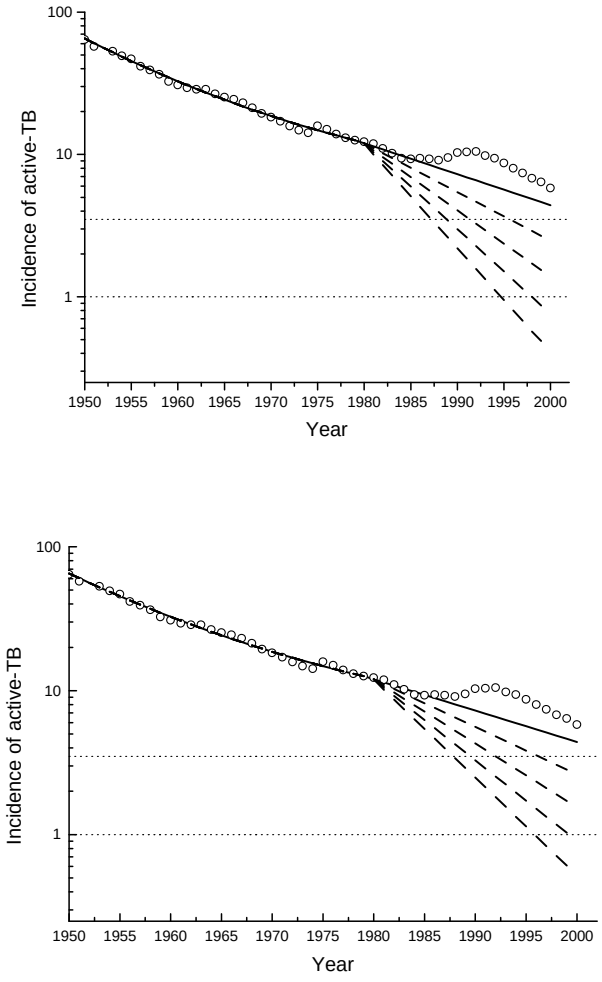

FIGURE 3. Observed incidence of active-TB (open circles), simulated incidence assuming no treatment (continuous line), and simulated incidence for different levels of treatment (θ=0.05; 0.1; 0.15; 0.20; dashed lines). The plot at the top is for contact number $Q_0 = 7.5$, $\sigma = 0.7$ and the bottom plot shows results for $Q_0 = 20$, $\sigma = 1$. Figures obtained for other parameter combinations were similar. All rates of incidence are per 10^5 population. Small differences among the solutions obtained for a given level of treatment for each value of Q_0 are due to the different values of σ. The CDC goal value of 3.5 for year 2000, and the value of one new case per 10^5 population are also shown (dotted lines).

The level of treatment needed to reach an active-TB incidence of one new case per year per 10^5 population in 2000 ranged from $\theta = 0.125$ to 0.14.

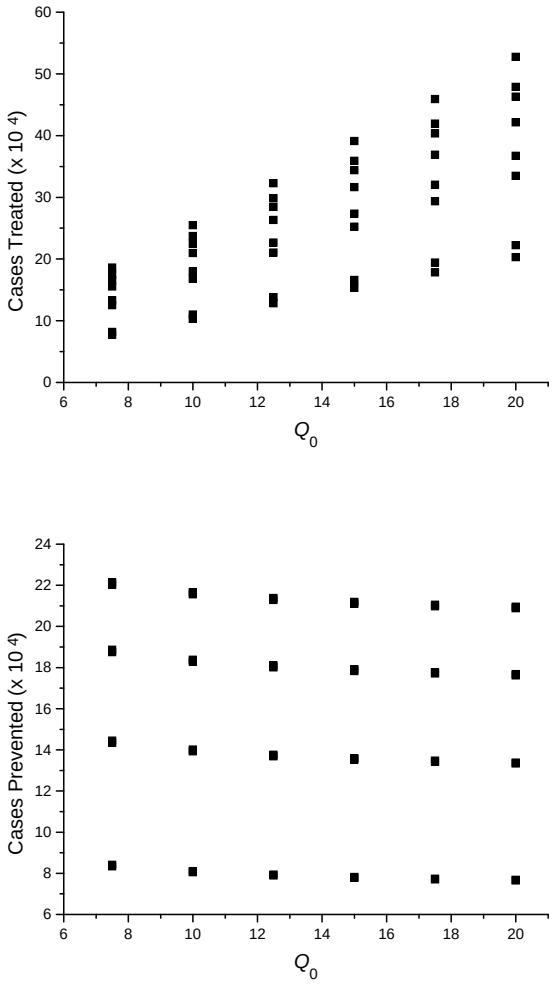

FIGURE 4. Treated (top) and prevented (bottom) cases versus contact number Q_0. For each value of Q_0 the numbers of cases were calculated for σ= 0.7 and 1, and for θ varying from 0.05 to 0.20.

The total number of cases treated during the two decades of the preventive treatment model ranges from 78 to 528 thousand, and total number of cases of active-TB prevented ranges from 77 to 220 thousand (Fig. 4). More significant is the fact that the ratio prevented:treated cases ranges from 0.33 to 1.25 (see Fig. 5).

4. Discussion and Conclusions

In this work we have presented a new model for the transmission dynamics of tuberculosis that incorporates the effect of preventive treatment. Our model differs from previous models [**7, 8, 9, 10**] in several respects.

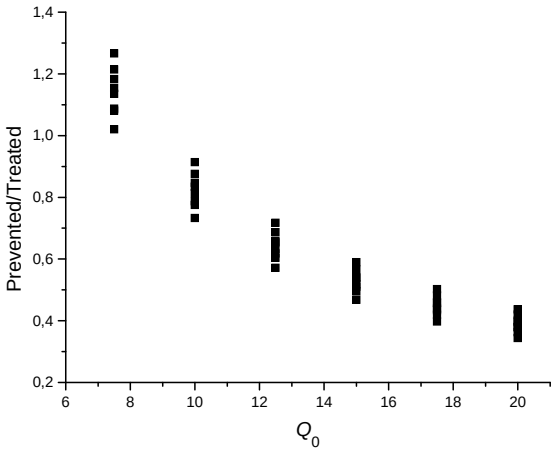

FIGURE 5. Prevented to treated case quotient versus Q_0. For each value of Q_0 the ratio was computed for σ= 0.7 and 1, and for θ varying from 0.05 to 0.20.

First, previous models have assumed constant populations and constant parameter values. However, population growth plays an important role in TB dynamics, and time-dependent parameters are necessary to reproduce the observed trends.

In addition we model treatment somewhat differently. The effect of treatment has previously been simulated by increasing the rates at which individuals leave infected classes. This approach leaves unclear the meaning of a given level of treatment, because these rates are not non-dimensional parameters. We model the effect of treatment as a reduction of the effective contact number. Therefore a θ-level of treatment indicates that a fraction θ of the effective contacts will receive treatment.

While in previous models the basic reproductive number has depended nonlinearly on treatment rates (or levels of treatment), in our model the dependence is linear (see equation 11). Our modeling of preventive treatment has the same effect as does ring vaccination.

It should be noted that the declining trend in incidence of active cases suggests that the basic reproduction number for tuberculosis is near or less than one [**11**], and therefore a low level of treatment may suffice either to drive tuberculosis to extinction or at least to accelerate its decline. Here we see a departure from the results of previous work. Parameter values in other models [**7, 8, 9, 10**] predict basic reproduction numbers well above one. For example Ziv et al. [**9**] found that at least 25% of the recently infected population must be treated in order to achieve tuberculosis elimination (when 80% of the active-TB cases receive treatment), while Murphy *et al.* [**10**] found that low levels of treatment in the latent population have almost no appreciable effect on prevalence. In our case the value of the basic reproduction number varies with time and is determined by the data.

We did not consider the interaction of tuberculosis with HIV although the AIDS epidemic has had an impact on TB incidence that is readily observable (see Fig. 3

for example). In this work we have focused strictly on the potential effect of a preventive treatment strategy. The simulated incidence in the base case (no treatment, $\theta = 0$) does not therefore reproduce the actual trend, rather the hypothetical trend in the absence of TB-HIV interaction. The number of cases prevented for different levels of treatment has been computed using this hypothetical baseline trend.

For a treatment level of $\theta = 0.05$ at $t \geq 1980$, the incidence of active-TB (per 10^5 population) at year 2000 comes out to be about 2.5 in all scenarios considered. This value should be compared with the incidence of 4.4 in the absence of treatment and is below the CDC target value [**2**]. On the other hand the level of treatment required to lower the incidence to near one case per 100,000 population (ten times the goal of the CDC for the year 2010) is approximately $\theta = 0.14$, a level which might well be impossible to achieve in practice.

Twenty-four weeks of preventive therapy has been cited as the most cost-effective duration [**16**]. However, preventive treatment may be more costly than forgoing prevention and treating the additional active cases [**17**]. Treatment of an active-TB case is more expensive than preventive therapy, because treatment is longer than 24 weeks, more clinical visits, which are costly, are needed and in general more tests are administered to active-TB cases. When active cases require hospitalization, differences between costs are dramatic. Therefore the cost-effectiveness of a preventive therapy strategy will depend on how many cases are prevented per infected individual who received preventive therapy.

For $Q_0 \sim 10$ the ratio of prevented cases to preventive-treated cases is between 0.6 and 0.9, perhaps our more important result. In other words for each (preventive) treated case, between 0.6 and 1 case of active-TB is prevented. Therefore, because of differences in cost, complementing the current strategy with a preventive treatment strategy may well lower overall cost, with the additional benefit of an increased reduction in TB-transmission. Differences between our results and other analyses [**16, 17**] is at least partially explained by the fact that earlier studies have not considered the cumulative benefit of reduced transmission.

In summary the cost effectiveness of a complementary preventive treatment strategy greatly depends on the treated-cases:prevented-cases ratio and also on the period of time during which the strategy is implemented. For low values of the ratio and short periods of implementation, preventive therapy proves more costly than simple treatment of the otherwise prevented cases. Opinions are divided [**17**]and certainly further work is needed.

Appendix A

Direct data on the incidence of active-TB is available beginning in 1953. Data for earlier years has been estimated as 2.875 times the mortality due to pulmonary tuberculosis. The value of 2.875 was obtained by using a 50% fatality rate for pulmonary TB and assuming that pulmonary cases represent 70% of the total cases of active-TB. In this work these data on incidence of active-TB have been replaced by the function $Inc(t)$, which captures the trends (Aparicio and Castillo-Chavez, *On the causes of the long term decline of tuberculosis*, submitted):

$$Inc(t) = \begin{cases} exp(-1599.38143 + 1.70781\ t - 0.000454057\ t^2) & 1840 < t < 1944 \\ exp(2667.46 - 2.65571\ t + 0.0006615\ t^2) & 1944 < t < 1979 \\ exp(101.683531 - 0.0501\ t) & 1979 < t < 2000 \end{cases}$$

The function $Inc(t)$ was obtained as the best least-squares polynomial of order two over the first two time intervals, order one for the latest interval.

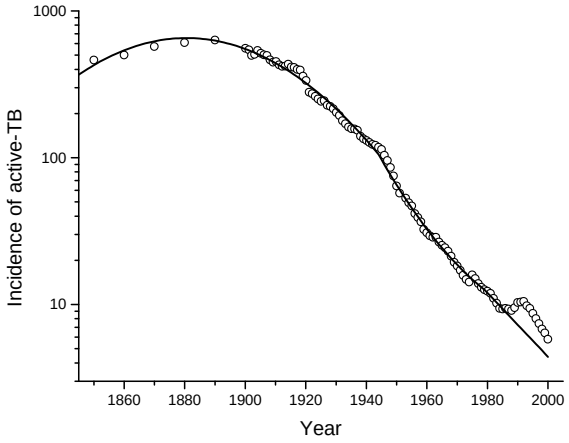

FIGURE 6. Data on incidence of active-TB and model solutions obtained when the fraction f is actualized as $f(t+dt) = (1-\varepsilon)f(t)$ before each step in numerical integration. To avoid large and meaningless fluctuations in the function f the data have been represented by the piecewise smooth function $Inc(t)$ which captures the trend.

The fraction of infected of people who develop active-TB is modeled as $f = k/(k+\alpha+\mu)$. Equations (6-10) were numerically solved using a fourth order Runge-Kutta method. Before each time step dt we computed the error

$$\varepsilon = \frac{Simulated\ incidence(t) - Inc(t)}{Inc(t)}$$

where *Simulated incidence* is given by $kE10^5/N_{tot}$. New values for f were calculated from $f(t+dt) = (1-\varepsilon)f(t)$, and these values yielded the value of $k = f(\alpha+\mu)/(1-f)$ used in the model. This simple method of computing $f(t)$ produced excellent results (see Fig. 6).

Simulations started at $t = 1700$ to minimize the effect of initial conditions, although these are already negligible after less than 50 simulated years.

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