bicycls[2.2.2] octane (DABCO)–glycerol and visualized on a Leica DMIRBE microscope equipped for epifluorescence. The DAPI banding was imaged with a cooled CCD camera (Photometrics, Tucson, AZ) or by spectral imaging through a DAPI-specific optical filter.

5. Spectral images were acquired and analyzed with the SD200 spectral bio-imaging system (Applied Spectral Imaging, Ltd., Migdal Haemek, Israel). The optical arrangement is schematically presented in Fig. 1. The SD200 imaging system attached to an inverted microscope (Leica DMIRBE) by means of a C-mount consists of an optical head with a special Fourier transform spectrometer (Sagnac common path interferometer) to measure the spectrum, and a cooled CCD camera (Princeton Instruments, Trenton, NJ) for imaging. The samples were illuminated with a Xenon lamp (OptiQuip 770/1600) and imaged with a 63× oil immersion objective through a custom-designed filter set (Chroma Technology, Brattleboro, VT) with broad emission bands (excitation filter: 486/28 nm, 565/16 nm, 642/22 nm; emission filter: 524/44 nm, 600/38 nm, 720/113 nm; beamsplitter: reflection 421 to 480 nm, 561 to 572 nm, 631 to 651 nm; transmission 495 to 564 nm, 580 to 620 nm, 660 to 740 nm). Excitation through this filter set allows all dyes to be excited and measured simultaneously without an image shift. The generation of a spectral image is achieved by acquiring ~100 frames of the same image. Each two frames differ only in the optical path differences (OPDs) created by a scanner controller in the interferometer. In this way the interferogram as the modulated function of intensity (that is, the intensity as a function of OPD) is measured simultaneously for each pixel in the image. However, each pixel functions like a stand-alone Fourier transform spectrometer. Measurement times vary depending on the brightness and the size of the image, the desired spectral resolution, and the signal-to-noise ratio. A typical measurement for chromosome painting probes takes about 50 s with a 15-nm (at 600 nm) spectral resolution. The spatial resolution of the measurement is ~0.24 μm and is limited by the CCD pixel size (15 μm) and the objective magnification (63×). After the measurement, ~2 min are required to build the spectral image with a software-based fast Fourier transform (FFT) algorithm [E. O. Brigham, *The Fast Fourier Transform and its Application* (Prentice-Hall, Englewood Cliffs, NJ, 1988)]. The conversion of emission spectra to visualize the spectral image in display colors is achieved as follows: The measured spectrum at each pixel is divided into three spectral ranges (475 to 550 nm, 550 to 650 nm, and 650 to 750 nm). Each of the spectral ranges is visualized in a different color (blue, green, and red, respectively). The intensity for each color is proportional to the integrated intensity in the corresponding spectral range (Figs. 1 and 2).
6. One of the most important analysis algorithms is the spectral-based classification algorithm that enables multiple different spectra in the image to be identified and highlighted in classification colors. This allows assignment of a specific classification color to all human chromosomes on the basis of their spectra. This algorithm assumes that the (reference) spectrum of each chromosome has been measured and stored in a reference library in the computer. A classification color is assigned to each pixel in the image according to the classification color assigned to the reference spectrum that is most similar to the spectrum at the given pixel. A minimal square error algorithm $S_{x,y,n} = \Sigma\,[I_{x,y}(\lambda) - I_n(\lambda)]^2$ is computed for every pixel, in which $I_{x,y}(\lambda)$ is the normalized spectrum at pixel coordinates x,y, and $I_n(\lambda)$ represents the normalized reference spectrum for each of the chromosome $n = 1, 2, \ldots 23$ (X), 24 (Y). After calculating the value of $S_{x,y,n}$ for all reference spectra, the smallest value is chosen and a classification color is assigned to that pixel in accordance with the classification color assigned to the most similar reference spectrum.
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Control Strategies for Tuberculosis Epidemics: New Models for Old Problems

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Tuberculosis, although preventable and curable, causes more adult deaths than any other infectious disease. A theoretical framework for designing effective control strategies is developed and used to determine treatment levels for eradication, to assess the effects of noneradicating control, and to examine the global goals of the World Health Organization. The theory is extended to assess how suboptimal control programs contribute to the evolution of drug resistance. A new evaluation criterion is defined and used to suggest how control strategies can be improved. In order to control tuberculosis, treatment failure rates must be lower in developing countries than in developed countries.

For many years tuberculosis has been both a preventable and a curable disease. Isoniazid is used to prevent individuals latently infected with *Mycobacterium tuberculosis* from developing disease, and regimens consisting of multiple drugs are highly successful in curing active cases (*1*). However, tuberculosis still causes more adult deaths worldwide than any other infectious disease (*2*). This finding suggests that many of the current control strategies that have been empirically designed are in need of improvement; recent increases in cases caused by drug-resistant organisms, many of which have arisen as a result of treatment failure, have exacerbated the control problems (*3*). We suggest that new control strategies can be designed based on a quantitative understanding of the transmission dynamics of tuberculosis.

In previous studies, we formulated and analyzed mathematical models that enable understanding of the intrinsic transmission dynamics of untreated tuberculosis epidemics and interpretation of the historical epidemiology of this disease (*4*–*6*). These transmission models reflect current biomedical understanding of the pathogenesis of tuberculosis. We have extended these models to include the population level effects of chemoprophylaxis and treatment (*7*); using this chemoprophylaxis and treatment model (Fig. 1), we have developed a theoretical framework for designing effective tuberculosis control strategies (*8*).

We assessed the epidemic control effects of treatment and chemoprophylaxis by deriving the effective reproductive rate (R) of tuberculosis from our model

$$R = \left(\frac{\beta\Pi}{\mu}\right)\left(\frac{1}{\phi + \mu + \mu_T}\right)\left(p + \frac{(1-p)\nu}{\sigma + \nu + \mu}\right) \quad (1)$$

where β is the transmission coefficient for tuberculosis; the other parameters are defined in (*7*).

R is the average number of secondary infectious cases that are produced when one infectious case is introduced into a disease-free population in which a program of chemoprophylaxis or treatment (or both) is in place (*9*). Consequently, R is an epidemiological measure of the severity of an epidemic; if $R > 1$, an epidemic may occur, but if $R < 1$, an epidemic will die out.

The value of R is determined by the product of three components (Eq. 1): the effective contact rate {defined as the average number of susceptibles that one infectious case infects per unit time $[(\beta\Pi)/\mu]$}, the average duration of infectiousness of a case $[1/(\phi + \mu + \mu_T)]$, and the probability that an infected individual will become an infectious case {defined as p for primary progressive and $[(1-p)\nu]/(\sigma + \nu + \mu)$ for reactivation tuberculosis}. Equation 1 can be used to qualitatively and quantitatively assess the effects of chemoprophylaxis and treatment for epidemic control. Qualitatively, an increase in the chemopro-

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phylaxis rate (σ) will reduce the severity of an epidemic (that is, R) by decreasing the probability that a latently infected individual will progress to disease, and an increase in the treatment rate (ϕ) will reduce the severity of an epidemic by decreasing the average duration of infectiousness of a case. Quantitatively, we can use Eq. 1 to calculate the effect of treatment on decreasing the average duration of infectiousness. For example, if treatment rates are 95%, as in San Francisco (*10*), a case will remain infectious (on average) for ~4 months. In contrast, if treatment rates are only 50%, as in many developing countries (*11*), then a case will remain infectious (on average) for over 3 years (*12*).

Wade Hampton Frost noted in 1937 that there must exist a transmission threshold that would ensure the eradication of tuberculosis (*13*). We have quantified Frost's criterion by using the derived analytical expression for R to calculate the critical chemoprophylaxis and treatment rates that would reduce transmission to the level such that eradication (sensu Frost) will occur (*14*). If both treatment and chemoprophylaxis are used for epidemic control, the critical rates of chemoprophylaxis and treatment that are necessary for eradication can be calculated by setting the value of R to unity and then solving for all possible combinations of σ and ϕ (Fig. 2A). For any specific epidemic there are many different control strategies that would be effective in eradicating tuberculosis; any control strategy (that is, by treatment alone or by a combination of chemoprophylaxis and treatment) that occurs in the subset of control strategies that lie along or above the plotted functions would be effective. For each epidemic, any of the minimum control strategies that lie along the plotted solution to $R = 1$ are functionally equivalent. Higher than the minimum levels of control will decrease $R < 1$. Figure 2A indicates that it is possible to eradicate tuberculosis either by treatment alone or by a combination of treatment and chemoprophylaxis, but that eradication will not be possible by chemoprophylaxis alone. If only treatment of cases is used, then high levels of treatment are necessary to achieve eradication. In operational terms, this analysis assists in allocating resources to increased treatment through directly observed therapy versus chemoprophylaxis.

In developed countries, treatment rates presently range from 70 to 95% (*15*), close to the critical eradication rates. However, in most developing countries, treatment rates range from 50 to 75% (*11*); these treatment rates may be far below the critical eradication rates. The target for the World Health Organization's (WHO) Tuberculosis Control Strategy by the year 2000 is to detect 70% of all sputum-positive cases worldwide (with targets of 60 and 85% for low- and middle-income developing countries, respectively) and to cure 85% of all sputum smear-positive cases detected worldwide (with a target of 95% for developed countries) (*16*). By combining these two objectives, we can estimate that the WHO's target is to effectively treat a cumulative fraction of 60% of all sputum-positive cases worldwide, with targets of 51% in low-income developing countries, 72% in middle-income developing countries, and 67% in developed countries. It is evident from Fig. 2A that it is unlikely that the WHO's target figures would lead to the global eradication of tuberculosis (*17*).

It is essential to specify control strategies in terms of clearly defined treatment variables. Although the WHO's target figures are presented in terms of the cumulative fraction of cases treated (F_T), these target figures should also be considered in terms of the proportion of cases that require treatment per

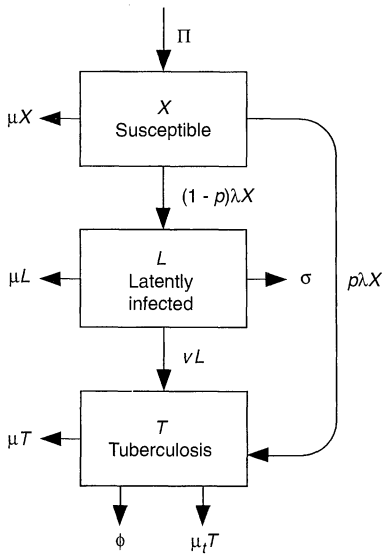

Fig. 1. The model consists of five ordinary differential equations: $dX/dt = \Pi - \lambda X - \mu X$, $dL/dt = (1 - p)\lambda X - (\nu + \mu + \sigma)L$, $dC/dt = \sigma L - \mu C$, $dT/dt = \nu L + p\lambda X - (\mu + \mu_T + \phi)T$, and $dE/dt = \phi T - \mu E$. The model captures the temporal dynamics of five groups of individuals: susceptible individuals (X), noninfectious, nondiseased latently infected individuals (L), effectively chemoprophylaxed individuals (C), active infectious cases of disease (T), and effectively treated cases (E). For a description of the model and definition of parameters, see (*4, 7*).

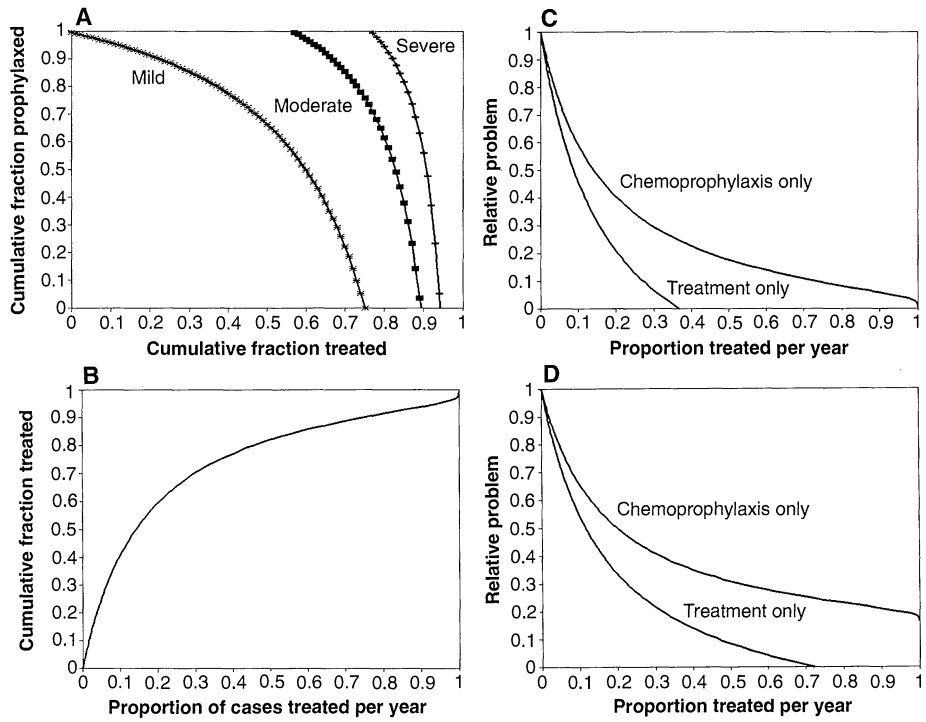

Fig. 2. (**A**) The minimum cumulative fraction of latent infections that require chemoprophylaxis [$\sigma_C/(\sigma_C + \nu + \mu)$] and the minimum cumulative fraction of tuberculosis cases that require treatment [$\phi_C/(\phi_C + \mu + \mu_T)$] in order to eradicate a mild, moderate, or severe tuberculosis epidemic. The severity of the epidemic is specified by the value of the basic reproductive number, R_0 [R_0 is the average number of secondary infectious cases of tuberculosis that are produced when one infectious individual is introduced into a disease-free population (*4*)]. Mild, moderate, and severe epidemics correspond to R_0 values of 4, 9, and 17, respectively (*4*). (**B**) The relation between the cumulative fraction of cases treated and the proportion of cases treated per year (*14*). (**C**) The effects of chemoprophylaxis or treatment on the relative tuberculosis problem (defined as the number of cases that would occur with the control program in place divided by the number of cases that would occur in the absence of any control program). Results for a mild epidemic ($R_0 = 4$) are shown. (**D**) Results for a moderately severe epidemic ($R_0 = 9$).

year (P_C). The relation, derived from our model, between these two treatment variables (*14*) is shown in Fig. 2B. At high levels of treatment, the cumulative fraction of cases treated and the proportion of cases treated per year are the same, but at low or moderate levels they are significantly different. The cumulative fraction of cases treated can be fairly high even with a low proportion of cases treated per year, because tuberculosis cases can survive for several years without treatment (*18, 19*). Figure 2B suggests that the WHO's target treatment levels are attainable even if only a small proportion (~15 to 30%) of cases are treated per year.

Although the WHO's target treatment levels may not lead to eradication, these noneradicating treatment levels could significantly reduce morbidity and mortality (*17*). How many cases of tuberculosis could be prevented if chemoprophylaxis or treatment were applied at noneradicating levels? Figure 2, C and D, presents results for mild and moderately severe epidemics. The epidemiological effect is specified in terms of the relative tuberculosis problem, which is defined in terms of the number of cases that would occur with the control program in place divided by the number of cases that would occur in the absence of any control program. Relative tuberculosis problem results are plotted for two cases: treatment alone and chemoprophylaxis alone. If the WHO's maximum treatment levels are achieved (that is, ~30% of cases are treated per year), then the number of cases could be reduced by as much as 80 to 90%.

Control strategies cannot simply be specified in terms of treatment and chemoprophylaxis rates because treatment failure often occurs and often leads to the evolution of acquired drug resistance (*20*). Cases of acquired drug resistance can then produce cases of primary drug resistance by transmitting their infection to susceptible individuals. Drug-resistant cases present a significant challenge to control programs, because they are more difficult and more expensive to treat (*21*). To evaluate the problem of drug resistance in the design and the evaluation of control strategies, we used our theoretical framework to define a new evaluation criterion, the maximum acceptable probability of treatment failure (r_{MAX}); we defined r_{MAX} as the probability of treatment failure at which X cases of drug resistance are generated for each treated drug-sensitive case (*22*).

We derived the evaluation criterion r_{MAX} by extending our chemoprophylaxis and treatment model to include two strains of tuberculosis, one drug-sensitive and the other drug-resistant (Fig. 3). Both the drug-sensitive and the drug-resistant epidemics are driven by their own intrinsic dynamics, but the two epidemics are also linked because a drug-sensitive case can acquire drug resistance through treatment failure. Failure occurs (with probability r) either because of patient noncompliance or inappropriate and ineffective treatment regimens (or both). In our linked model (as in the real world), treatment failure causes acquired resistance to arise directly and primary resistance to arise indirectly; each treated drug-sensitive case produces (on average) r cases of acquired drug resistance and r^*R_{DR} cases of primary drug resistance (*23*). We specified the effectiveness of treatment of a drug-resistant case relative to the treatment of a drug-sensitive case by δ; consequently, drug-resistant cases are untreatable or untreated (or both) when $\delta = 0$, drug-resistant and drug-susceptible cases are treated with equal effectiveness when $\delta = 1$, and drug-resistant cases are partially effectively treated when $1 > \delta > 0$ (*24*). Our theoretical framework can be used to evaluate the average duration of infectiousness of a drug-resistant case; at low relative treatment efficacy levels, drug-resistant cases can remain infectious for long periods of time, even if treatment rates are high (Fig. 4A). Consequently, low relative treatment efficacy of drug-resistant cases contributes indirectly to generation of primary drug resistance.

Our evaluation criterion, r_{MAX}, can be used to identify counterproductive control programs (defined as having a probability of treatment failure $> r_{MAX}$, hence the number of drug-resistant cases produced per treated drug-sensitive case is greater than the specified value of X). If $X = 1$, then a counterproductive control program causes a perverse outcome by producing more than one drug-resistant case for each drug-sensitive case treated. In Fig. 4B, r_{MAX} is plotted for three levels of relative treatment efficacy ($\delta = 0.7$, 0.5, and 0.0) and with $X = 1$ (so that one drug-resistant case is generated for each treated drug-sensitive case); hence, each plotted curve [which is a solution to the analytical expression for r_{MAX} (*22*)] illustrates the dependence of r_{MAX} on the treatment rate. Figure 4B can be used to identify which control programs are

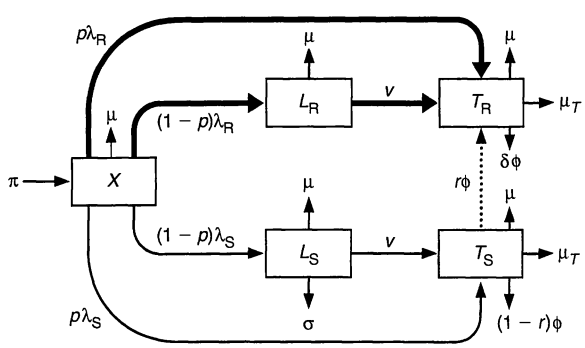

Fig. 3. Drug-sensitive and drug-resistant two-strain model. The model shows the transmission dynamics of the drug-sensitive strain (thin lines) and the drug-resistant strain (bold lines indicate development of primary resistance; dotted line indicates the development of acquired resistance). The model is specified by the following eight equations: (i) $dX/dt = \Pi - X(\beta_S T_S + \beta_R T_R) - \mu X$, (ii) $dL_S/dt = (1-p)\beta_S T_S X - (v + \mu + \sigma)L_S$, (iii) $dC_S/dt = \sigma L_S - \mu C_S$, (iv) $dL_R/dt = (1-p)\beta_R T_R X - (v + \mu)L_R$, (v) $dT_S/dt = p\beta_S T_S X + vL_S - (\mu + \mu_T + \phi)T_S$, (vi) $dE_S/dt = \phi(1-r)T_S - \mu E_S$, (vii) $dT_R/dt = p\beta_R T_R X + vL_R + \phi r T_S - (\mu + \mu_T + \delta\phi)T_R$, and (viii) $dE_R/dt = \delta\phi T_R - \mu E_R$. Parameters: L_S, the number of individuals latently infected with drug-susceptible tuberculosis; L_R, the number of individuals latently infected with drug-resistant tuberculosis; C_S, the number of individuals (with drug-sensitive organisms) effectively chemoprophylaxed; T_S, the number of cases of drug-sensitive tuberculosis; T_R, the number of cases of drug-resistant tuberculosis; E_S, the number of cases of effectively treated drug-sensitive cases; and E_R, the number of cases of effectively treated drug-resistant cases; the remaining parameters are defined in (*7*).

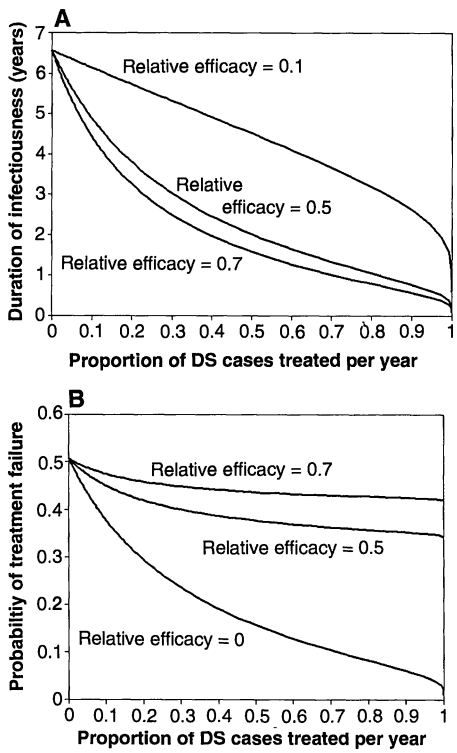

Fig. 4. (**A**) The effect of treatment rate (as defined by the proportion of drug-sensitive cases treated per year) on the average duration of infectiousness of a drug-resistant case. Three levels of relative efficacy (δ = 0.70, 0.50, and 0.10) of treatment of drug-resistant cases are shown. (**B**) The maximum acceptable probability of treatment failure (r_{MAX}) is calculated (*22*) and plotted as a function of the treatment rate (as defined by the proportion of drug-sensitive cases treated per year) assuming that the relative efficacy of treatment (δ) of a drug-resistant case is 0.7, 0.5, untreatable, or untreated (δ = 0.0).

perverse; any control program with a probability of treatment failure that lies in the region above the curve is perverse. This figure demonstrates that any program with a treatment failure rate ⩾50% should not be operating because it will result in a perverse outcome.

The maximum acceptable level of treatment failure increases as treatment rates decrease or the relative efficacy of treatment of drug-resistant cases increases (or both). In developed countries, treatment rates are high (70 to 95%) (*15*), as is the relative efficacy of treatment of drug resistance (50 to 70%) (*25*, *26*). In developing countries, treatment rates are low (50 to 75%) (*11*), as presumably is the relative efficacy of treatment of drug resistance (*27*). At present, treatment failure rates in developing countries are probably much higher than those in areas with good control programs in developed countries (~5%) (*27*), although even in inner city populations of developed countries, treatment failure rates can be nearly 90% (*3*). To prevent perverse outcomes, the treatment failure rate should be <35 to 40% in developed countries (Fig. 4B) and <10% in developing countries (Fig. 4B) (*28*). Thus, higher standards (lower treatment failure rates) should be required of control programs in developing countries than of control programs in developed countries. However, if the relative efficacy of treatment of drug-resistant tuberculosis could be increased in developing countries, then higher treatment failure rates could be tolerated.

Our evaluation criterion, r_{MAX}, can be used to decide how to improve a control program—either by increasing case-finding rates (which increases the proportion of cases treated per year) or by increasing case-holding rates (which increases compliance rates and hence decreases the probability of treatment failure). If the program change results in the probability of treatment failure becoming $>r_{MAX}$, then the change is detrimental; if the probability of treatment failure becomes $<r_{MAX}$, then the change is beneficial. Increasing case-holding rates will always be beneficial (Fig. 4B); however, if the probability of treatment failure is high, then increasing case-finding rates without simultaneously increasing case-holding could be detrimental.

It may be more efficient to adopt a hierarchial two-stage approach when assessing the economics of tuberculosis control. The first stage would consist of the methodology that we propose to identify the subset of effective control strategies (*29*). In the second stage, an economic analysis would be applied to this subset of control strategies to assess the smaller subset of strategies that are cost-effective. Epidemics are nonlinear systems, and hence it is not always intuitive how to design and to improve control programs in order to minimize the evolution of drug resistance. We have derived an analytical expression for a new evaluation criterion—the maximum acceptable probability of treatment failure—which we have used to identify and to suggest how to improve counterproductive control programs. The theoretical framework that we have developed can now be used for building more complex tuberculosis transmission models that can be used for developing control strategies tailored to specific environments.

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7. The structure and the assumptions of the model, without chemoprophylaxis and treatment, have been described elsewhere (*4*). The model structure allows that (i) the majority of latently infected individuals will never develop disease, and (ii) those infected individuals who develop disease will do so by either of two pathogenic mechanisms: primary progression (soon after infection with *M. tuberculosis*) or reactivation of a contained infection (several years to decades after infection). Consequently, two types of disease are modeled: primary progressive tuberculosis and reactivation tuberculosis. The two pathogenic mechanisms are modeled by allowing a proportion p of the newly infected individuals to develop disease directly and a proportion $1 - p$ of the newly infected individuals to enter the latent group. Over time (t), the number of susceptibles (X) increases due to the recruitment rate (Π) (that is, due to birth and to immigration) and decreases due to the incidence rate of infection (λX, where λ is the per capita force of infection) and to the per capita nontuberculosis mortality rate (μ). The number of individuals with latent infections (L) increases due to the number of individuals who enter a latent phase [which is a constant proportion $(1 - p)$ of the incidence rate of infection] and decreases due to individuals with latent infections who either progress to disease (at a per capita rate v), die of other causes (at a per capita rate μ), or receive effective chemoprophylaxis (at a per capita rate σ). The number of cases (T) increases due to individuals with latent infections who slowly develop tuberculosis (at a per capita rate v) and to recently infected individuals who develop disease by direct progression ($p\lambda X$). The number of cases decreases as a result of effective treatment (at a per capita rate ϕ) or mortality [due either to tuberculosis (at a per capita rate μ_T) or due to other causes (at a per capita rate μ)].
8. Elsewhere we examine the epidemiological effect of vaccines on tuberculosis control (T. M. Lietman and S. M. Blower, in preparation). The critical vaccination coverage (p_c) required to eradicate a tuberculosis epidemic can be calculated by the expression $p_c = 1/\Psi[1 - (1/R_0)]$, where Ψ is the vaccine efficacy and R_0 is the basic reproductive number of tuberculosis (*4*).
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$$\sigma_c = \left[\frac{(1-p)v}{\left((\mu+\mu_T)\left(\frac{\mu}{\beta\Pi}\right)\right) - p}\right] - (v+\mu)$$

If an epidemic is controlled only by treatment, then the per capita critical treatment rate for eradication (ϕ_c) is given by the equation

$$\phi_c = \left[\frac{(p\mu+v)}{(v+\mu)}\frac{(\beta\Pi)}{\mu}\right] - (\mu+\mu_T)$$

Our estimates of ϕ_c may be underestimates; if treatment is <100% effective, then the necessary treatment rates are equal to ϕ_c/e (where e represents the efficacy of treatment). The per capita treatment rate ϕ can then be used to estimate the cumulative fraction treated [F_T; by the relation $F_T = \phi/(\phi + \mu + \mu_T)$] and the proportion of cases treated per year (P_c; by the relation $P_c = 1 - e^{-\Phi}$, provided that $\phi >> \mu + \mu_T$).
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22. $r_{MAX} = X/(1 + R_{DR})$, where

$$R_{DR} = \left\{\frac{\beta_R(\phi+\mu+\mu_T)(\sigma+v+\mu)(\mu p+v)}{\beta_S[(\sigma+\mu)p+v](\mu+\mu_T+\phi\delta)(\mu+v)}\right\}$$

R_{DR} is the number of secondary cases of primary drug resistance that are produced by one drug-resistant case, β_R is the transmission coefficient for drug-resistant tuberculosis, β_S is the transmission coefficient for drug-sensitive tuberculosis, and δ is the effectiveness of treatment of a drug-resistant case relative to the treatment of a drug-sensitive case. The analytical expression for r_{MAX} can be used to calculate the value of r_{MAX} for any specified value of X; for example, if $X = 0.5$, then r_{MAX} is the maximum probability of treatment failure at which one case of drug resistance is generated for every two drug-sensitive cases treated.
23. Acquired drug resistance initiates an epidemic of drug-resistant tuberculosis; as the epidemic progresses, the significance of primary drug resistance to the transmission dynamics increases. Tuberculosis epidemics have slow dynamics (*4*); it can take many decades for drug-resistant tuberculosis to reach substantial levels (S. M. Blower, T. C. Porco, P. C. Hopewell, P. M. Small, in preparation).
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28. The suggested levels for treatment failure rates are intended to prevent perverse outcomes; hence, significantly lower treatment failure rates are desirable.
29. Transmission models have been used previously to suggest rational control strategies for many other infectious diseases [for example, A. R. McLean and R. M. Anderson, *Epidemiol. Infect.* **100**, 419 (1988); A. R. McLean and S. M. Blower, *Proc. R. Soc. London Ser. B* **253**, 9 (1993); and S.M. Blower and A. R. McLean, *Science* **265**, 1451 (1994)].

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