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Modeling the emergence of the 'hot zones': tuberculosis and the amplification dynamics of drug resistance

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'Hot zones' are areas that have >5% prevalence (or incidence) of multidrug-resistant tuberculosis (MDRTB). We present a new mathematical model (the amplifier model) that tracks the emergence and evolution of multiple (pre-MDR, MDR and post-MDR) strains of drug-resistant *Mycobacterium tuberculosis*. We reconstruct possible evolutionary trajectories that generated hot zones over the past three decades, and identify the key causal factors. Results are consistent with recently reported World Health Organization (WHO) data. Our analyses yield three important insights. First, paradoxically we found that areas with programs that successfully reduced wild-type pansensitive strains often evolved into hot zones. Second, some hot zones emerged even when MDR strains were substantially less fit (and thus less transmissible) than wild-type pansensitive strains. Third, levels of MDR are driven by case-finding rates, cure rates and amplification probabilities. To effectively control MDRTB in the hot zones, it is essential that the WHO specify a goal for minimizing the amplification probability.

Mycobacterium tuberculosis has plagued mankind since antiquity[1–3]. Multidrug-resistant tuberculosis (MDRTB) is defined as tuberculosis that is resistant to the two most important antituberculosis drugs, isoniazid and rifampicin. Recent surveys indicate that 3.2% of the 8.7 million new cases of tuberculosis in the year 2000 were MDRTB[4–6], and that over 100 countries have reported MDRTB[7]. However, there is a great deal of heterogeneity worldwide in MDRTB distribution[8]. Localized high incidence rates of MDRTB have been found only in particular regions: for example, Estonia (14%), Latvia (9%), the Russian oblasts of Ivanova (9%) and Tomsk (7%), and Zhejiang (5%) and Henan (11%) provinces in China[8]. Regions with MDR epidemics have been defined as hot zones based on two different criteria. The World Health Organization (WHO) and International Union Against Tuberculosis and Lung Disease have defined a hot zone as an area where the prevalence of MDRTB cases is >5% (that is, where >5% of current cases are MDRTB)[6]. Farmer and colleagues have defined a hot zone as an area where the incidence of MDRTB cases is >5% (that is, where >5% of new cases are MDRTB)[7]. Here, we present a new multistrain mathematical model that we have developed for understanding the evolution of the hot zones. We model the impact of poor treatment control programs and the sequential amplification of drug resistance[7,9–12] over the past three decades, and we reconstruct possible evolutionary trajectories. We calculate the value of the case reproduction numbers (R_0) for multiple pansensitive, pre-MDR, MDR and post-MDR strains that are currently cocirculating, and identify the key causal factors that generated the hot zones. We discuss the implications of our results for designing new and effective global control strategies for MDRTB.

Epidemics of drug-resistant strains of TB are generated by three independent but interacting processes: (i) transmission of drug-resistant strains to uninfected individuals (transmitted resistance) (ii) conversion of wild-type pansensitive cases to drug-resistant cases during treatment (acquired resistance), and (iii) the progressive acquisition, by drug-resistant strains, of resistance to more drugs during repeated treatment episodes (amplified resistance)[7,9–12]. Previously, we[13–16] and subsequently others[17,18] have formulated simple mathematical models that include only two of these processes (transmitted and acquired resistance), but not the third (amplified resistance). These simple models are all two-strain models: hence, individuals can only be infected with either a wild-type pansensitive strain or a drug-resistant strain. The dynamics of mathematical models of TB epidemics can be understood in terms of the case reproduction number (R_0), where R_0 is the average number of secondary cases caused by one infectious case in a population where treatment and chemoprophylaxis are available[13–16]. The qualitative dynamics of the simple models are therefore completely specified by only two case reproduction numbers, the case reproduction number of the pansensitive (R_0^S) and the drug-resistant (R_0^R)[13–18] strain.

Strains of TB can develop resistance to a large number of first- and second-line drugs, and therefore a multitude of different strains cocirculate in the hot zones. Hence, the simple two-strain models of drug resistance do not adequately capture the complexity of the epidemiology of the hot zones, and cannot be used to understand their evolution. Farmer and colleagues have shown that inadequate treatment of a drug-resistant TB case can result in the sequential amplification of drug-resistant strains during repeated episodes of treatment, and have suggested that amplification of resistance may be an extremely important process in generating MDR epidemics[7,9,10]. To address this, we developed a new, complex, multistrain mathematical model (the amplifier model). The amplifier model enables us to

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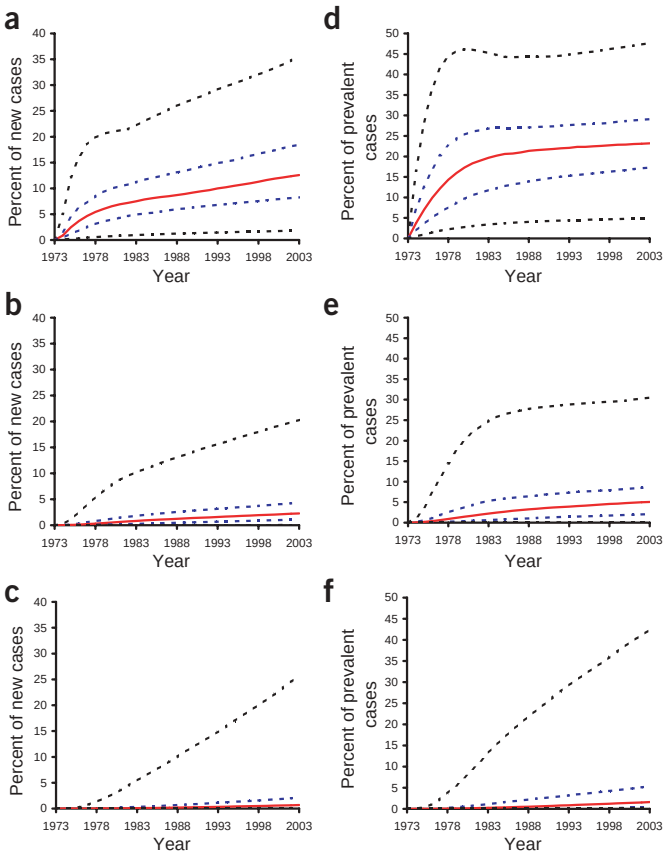

Figure 1 Reconstructed evolutionary trajectories. (**a**–**f**) Evolutionary reconstructions (using the amplifier model and Monte Carlo sampling estimates of parameters) of the effect of poor treatment control programs on the incidence (**a**–**c**) and prevalence (**d**–**f**) of pre-MDR TB (**a**,**d**), MDR TB (**b**,**e**) and post-MDR TB (**c**,**f**). Median values are in red, the dotted blue lines specify the interquartile ranges (IQR), and the dotted black lines specify maximum and minimum values.

track the emergence and the evolution (at different rates) of multiple strains resistant to a wide variety of first- and second-line drugs, the transmission of multiple strains, and the sequential amplification of drug resistance during repeated treatment episodes. Effective treatment for TB has been available for over 30 years in many countries. In certain areas, however, control programs have been inadequate because of low levels of treatment, inadequate drug supply, poor compliance or combinations of these factors[1–3,19,20]. We use our model and Monte Carlo sampling methods[21] to understand the historical effects that poor treatment-control programs have had (over the past three decades) on generating the hot zones, and to identify the key causal factors.

The amplifier model and estimating multistrain R_0

The structure of the amplifier model is general enough that we can model an infinite number of strains of TB that are resistant to any number of drugs, but the model structure also allows us to model strain-specific values for relative fitness, treatment failure rates and treatment cure rates. The dynamics of this complex model can be understood by evaluating the values of multiple strain-specific R_0 values. We used our model to reconstruct the temporal dynamics of interlocking multiple-strain epidemics interconnected through transmission, acquired resistance and sequential amplification of resistance. Our model includes 'fast' TB (cases that occur soon after transmission)[22–24], 'slow' TB (cases that result from endogenous reactivation of latent infections)[22–24] and reinfection TB (cases that result from exogenous reactivation by reinfection of latent infections). See Methods and **Supplementary Note** and **Supplementary Fig. 1** online for mathematical details. We used Monte Carlo methods to estimate the values of the R_0 for four categories of strains: wild-type pansensitive (strains sensitive to all drugs) ($R_0(1)$), pre-MDR (strains resistant to either isoniazid, rifampin, ethambutol or streptomycin, or to any combination of these drugs except isoniazid and rifampin) ($R_0(2)$), MDR (strains resistant to at least isoniazid and rifampin) ($R_0(3)$), and post-MDR (panresistant strains) ($R_0(4)$).

Reconstructing potential evolutionary trajectories

We reconstructed likely evolutionary trajectories of hot zones under the following conditions: low to moderate case detection and treatment rates, low to moderate cure rates and moderate to high amplification probabilities (where the amplification probability specifies the probability that a case will develop further resistance during treatment). We generated 4,000 different strains, each with a specific value for fitness (as specified by the transmissibility), cure rate and amplification probability. These 4,000 strains were then classified into four distinct categories: wild-type pansensitive, pre-MDR, MDR and post-MDR. Currently, it is unclear whether drug-resistant strains of TB are less fit (that is, less transmissible) or more fit than pansensitive strains; hence, we included a wide range of uncertainty in our estimates of relative fitness.

RESULTS

Reconstructing potential evolutionary trajectories

We were able to reconstruct potential evolutionary trajectories that generated hot zones. Our trajectories reveal wide variability in the incidence and prevalence of cases of wild-type pansensitive, pre-MDR (**Fig. 1a**,**d**), MDR (**Fig. 1b**,**e**) and post-MDR TB (**Fig. 1c**,**f**). When treatment was first initiated, strains of pre-MDR TB quickly emerged as a result of incomplete adherence, inadequate drug supply or ineffective treatment regimens, or a combination of these factors; hence, the incidence (**Fig. 1a**) and prevalence (**Fig. 1d**) of pre-MDR strains quickly rose to fairly high levels. Subsequently, amplification of resistance occurred and MDR epidemics were initiated (**Fig. 1b**,**e**). Our evolutionary reconstructions reveal that poor control programs did not always lead to high levels of MDR. In fact, even after 30 years of poor control, the median incidence of MDR is expected to be only 2.3% (IQR 1.1–4.3%) and the median prevalence of MDR only 5% (IQR 2.1–8.5%). Our trajectories also show that it is possible for certain programs to have generated an incidence of MDR as high as 20% (**Fig. 1b**) and a prevalence of 31% (**Fig. 1e**). Our results are consistent with recently reported rates from the hot zones, where MDR incidence rates range from 5% to 14%[8].

We compared the data generated by the amplifier model for 2003 with data recently reported by the WHO[8] (**Fig. 2a**). The WHO data are from 67 countries, some of which have excellent TB control programs. Our data generated by the amplifier model show that the expected incidence of MDR is an increasing function (with a fairly high degree of variability) of the incidence of resistance to at least one drug (**Fig. 2a**). Data generated by the amplifier model are consistent with the WHO data both in terms of the range of values expected and in the form of the statistical relationship (**Fig. 2a**). The prevalence of MDR (generated by the amplifier model) is also an increasing function of the prevalence of resistance to at least one drug (**Fig. 2b**). We

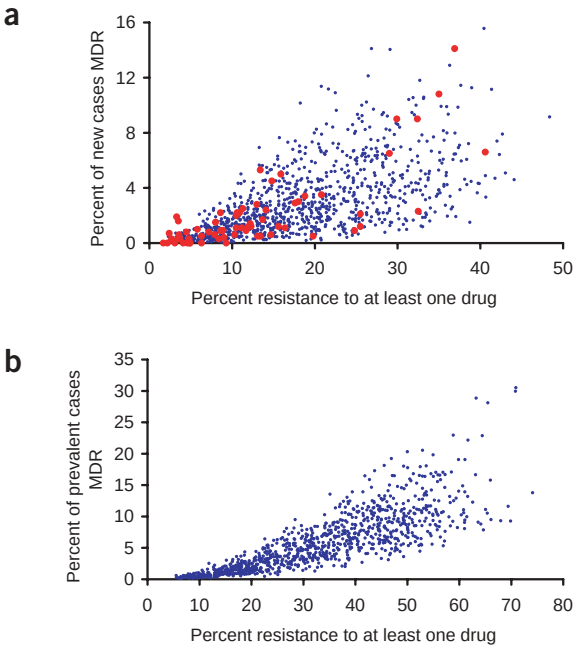

Figure 2 Comparison of theoretical and empirical (WHO) data. (**a**) Predicted relationship (for 2003) between the incidence of MDR and the incidence of resistance to at least one drug. Blue, data from the evolutionary reconstructions; red, data collected by WHO for 67 countries[8]. (**b**) Predicted relationship between the prevalence of MDR and the prevalence of resistance to at least one drug; blue, data from the evolutionary reconstructions generated by the amplifier model.

then determined the quantitative relationship between MDR incidence and prevalence. MDR prevalence can be three times greater than incidence (**Fig. 3a**). We used these results to evaluate the equivalence of defining hot zones by either incidence[7] or prevalence[6]. If the defining criterion is incidence, then only 20% of trajectories are classified as a hot zones by 2003; in contrast, if the criterion is prevalence, then 51% of trajectories are classified as hot zones (**Fig. 3a**).

R_0: pansensitive, pre-MDR, MDR, post-MDR

Even after 30 years of poor TB control, only 51% of programs had generated a hot zone (**Fig. 3a**). We used these data to identify the key causal factors that led to the evolution of a hot zone. Data were stratified, on the basis of MDR prevalence in 2003, into either hot zones or non-hot zones. We then used Monte Carlo methods to estimate R_0 for four categories of strains: pansensitive, pre-MDR, MDR and post-MDR. Hot zones, as compared to non-hot zones, had lower R_0 for pansensitive ($R_0(1)$), pre-MDR ($R_0(2)$) and MDR ($R_0(3)$) strains, but not for post-MDR ($R_0(4)$) strains (**Fig. 3b** and **Table 1**). Notably, areas that evolved into hot zones had substantially lower R_0 for pansensitive strains than areas that remained as non-hot zones. In fact, the majority of control programs that had generated a hot zone had reduced the R_0 for pansensitive strains to below one (median $R_0(1) = 0.82$, IQR 0.68–0.98) (**Fig. 3b** and **Table 1**), revealing that these programs will eventually (but very slowly) lead to the eradication of wild-type pansensitive strains. In contrast, the R_0 for wild-type pansensitive strains in the non-hot zones remained above one (median $R_0(1) = 1.34$, IQR 1.19–1.48) (**Fig. 3b** and **Table 1**). The median case detection and treatment rate in the hot zones had been 54% (IQR 45–62%); in contrast, only a median of 25% of cases (IQR 17–33%) had been detected and treated in the non-hot zones. These results imply that many of the control programs that had been the most successful in reducing wild-type pansensitive TB strains (because of their high case detection and treatment rate) had paradoxically been the most likely to evolve into hot zones.

We also used our evolutionary reconstructions to predict the expected evolution of new hot zones. If poor control programs are not improved, new hot zones will continue to emerge (**Fig. 3c**). In the hot zones, the R_0 of the post-MDR and MDR strains were substantially greater than those of the pansensitive and pre-MDR strains ($R_0(4) > R_0(3) > R_0(2) > R_0(1)$; **Fig. 4b** and **Table 1**); hence, post-MDR and MDR cases generated more secondary cases than pansensitive or pre-MDR cases. We used our estimates of $R_0(i)$ to predict the final epidemiological outcomes. Three outcomes are possible: TB eradication (eradication of wild-type pansensitive, pre-MDR, MDR and post-MDR strains), survival of only post-MDR strains or coexistence of multiple drug-resistant strains. Under the conditions modeled, the probability of eradication is almost zero ($P = 0.01$), the probability of post-MDR strains outcompeting all other strains is possible but improbable ($P = 0.13$), and the most probable outcome is coexistence of all four categories of strains ($P = 0.86$).

Identification of key causal factors

To further identify the key causal factors that generated the hot zones (increased the prevalence of MDR), we conducted time-dependent multivariate sensitivity analyses and calculated partial rank correlation coefficients (PRCCs) (**Fig. 4a**)[21,25]. Four independent key causal

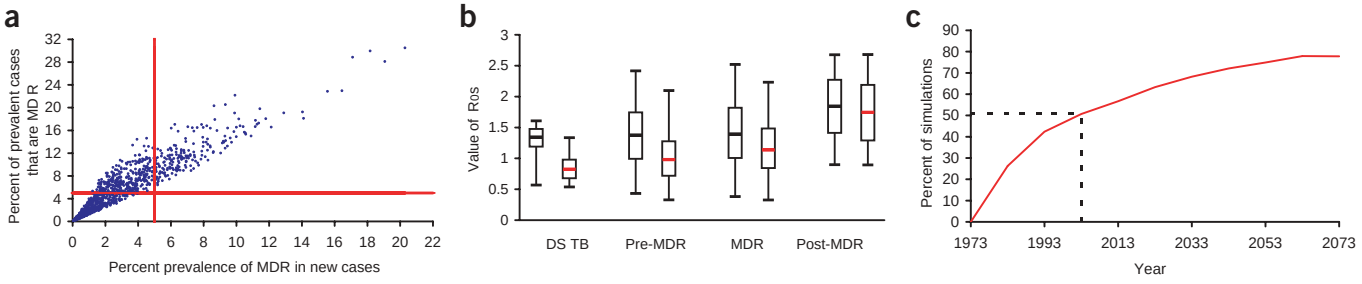

Figure 3 Evolutionary relationships and predictions. (**a**) Predicted relationship (for 2003) between the prevalence of MDR and the incidence of MDR; blue, data from the evolutionary reconstructions generated by the amplifier model. (**b**) R_0 estimated for 4,000 strains, classified into wild-type pansensitive TB (DS TB), pre-MDR TB (pre-MDR), MDR TB (MDR) and post-MDR (post-MDR). Data are stratified into hot zones (red) and non-hot zones (black); a hot zone is an epidemic where the prevalence of MDR in 2003 is >5%. (**c**) One hundred years of poor TB control: percentage of simulations that evolve into a hot zone over time.

Table 1 Monte Carlo estimates (for 4,000 strains) of the case reproduction numbers (R_0) for four categories of TB

	Pan-sensitive TB R_0		Pre-MDR TB R_0		MDR TB R_0		Post-MDR TB R_0	
	Non-hot zones	Hot zones	Non-hot zones	Hot zones	Non-hot zones	Hot zones	Non-hot zones	Hot zones
Minimum	0.57	0.54	0.43	0.33	0.38	0.33	0.90	0.89
Maximum	1.61	1.34	2.42	2.10	2.52	2.23	2.68	2.68
Median	1.34	0.82	1.38	0.98	1.39	1.13	1.84	1.75
IQR	1.19–1.48	0.68–0.98	0.99–1.75	0.72–1.28	1.00–1.82	0.84–1.48	1.41–2.27	1.29–2.19

The R_0 specifies the average number of secondary cases that one case generates in the presence of a treatment control program. A hot zone is defined as having a prevalence of MDR >5% by 2003.

factors were identified: the case detection and treatment rate, the amplification probability of pre-MDR to MDR, the relative transmissibility or fitness of MDR strains and the cure rate of pansensitive TB (**Fig. 4a**). Two key factors were time-dependent: the importance of transmitted MDR on increasing the prevalence of MDR increased with time, whereas the importance of curing pansensitive cases on decreasing the prevalence of MDR decreased with time (**Fig. 4a**). The most important key causal factor in generating a hot zone was the case detection and treatment rate (**Fig. 4a**).

Landscape policy analysis was used to assess the interdependency between the four key causal factors[26] (**Fig. 4b,d**). If case detection and treatment rates had been low (10–30%), then even a high amplification probability did not generate a hot zone; in contrast, if treatment rates had been high (50–70%), then even a relatively low amplification probability had generated a hot zone (**Fig. 4b**). The higher the treatment rate, the higher the prevalence of MDR cases; however, over a period of several decades, even a relatively moderate treatment rate generated a hot zone (**Fig. 4c**). The value of the relative fitness or transmissibility of the MDR strains that evolved was also a key causal factor (**Fig. 4d**). If treatment rates were low (10–30%), then even MDR strains that were more fit or transmissible than the wild-type pansensitive strains were not able to generate a hot zone (**Fig. 4d**). In contrast, if treatment rates were high (40–70%), then even MDR strains considerably less transmissible or fit than the wild-type pansensitive strains generated a hot zone (**Fig. 4d**).

DISCUSSION

We found that wide variability in MDR incidence and prevalence are to be expected; often only low levels of MDR will emerge (even after three decades of poor TB control). Our amplifier model was able to generate results that are consistent with recently reported incidence rates from the hot zones[8]. We determined that MDR prevalence can be three times greater than MDR incidence; hence our results indicate that MDR prevalence in certain areas may be as high as 40%. We found that many control programs that have been the most successful in reducing wild-type pansensitive TB (as a result of high case detection and treatment rates) have paradoxically been the most likely to evolve into hot zones. Moreover, we determined that post-MDR and MDR cases generated more secondary cases than pansensitive or pre-MDR cases; this effect occurred because MDR and post-MDR cases remained infectious for longer than pre-MDR or MDR cases (owing to lower cure rates). Taken together, our results clearly show that case detection and treatment rates of pansensitive TB should not be increased in any region with a high MDR incidence unless high cure rates of MDR are first achieved.

Our trajectories show how poor control programs led to an evolving series of interconnected time-lagged epidemics of partially and completely drug-resistant strains over the past three decades. We have identified many different combinations of four key causal factors that resulted in a hot zone. The most important key causal factor was a high case detection and treatment rate; if treatment rates were high, even a relatively low amplification probability generated a hot zone. We also found that (under certain conditions) even relatively low to moderate treatment rates could generate a hot zone. Taken together, our results imply that standard risk factor analysis applied to geographical MDR incidence and prevalence data may lead to conflicting and confusing results, simply because the underlying processes generating MDR epidemics are complex and multifactorial.

Currently, epidemiological data are being collected and analyzed to estimate the fitness

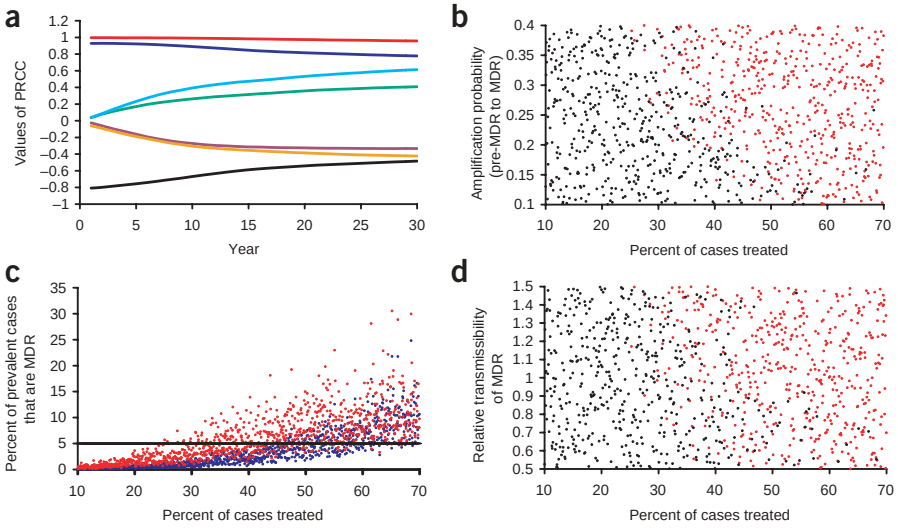

Figure 4 Results of multivariate sensitivity analysis. Hot zones are epidemics with a prevalence of MDR >5% by 2003. (**a**) PRCCs showing the effect of each parameter on increasing MDR prevalence: treatment rate (red), amplification probability of pre-MDR into MDR (dark blue), cure rate of pansensitive TB (black), relative transmissibility or fitness of MDR (light blue), relative transmissibility or fitness of pre-MDRTB (green), cure rate of MDRTB (purple) and amplification probability of MDR to post-MDR (orange). The absolute value of the PRCC of the relative fitness of post-MDR TB, and the cure rate of pre-MDR TB, are always <0.2, and are not plotted. (**b**) Effect of the amplification probability and treatment rate in generating hot zones (red). Black dots signify areas that are not hot zones. (**c**) Effect of treatment rate on increasing the prevalence of MDR in 1983 (blue) and 2003 (red). (**d**) Effect of the relative transmissibility and fitness of MDR and treatment rate in generating hot zones (red). Black dots signify areas that are not hot zones.

of MDR strains in order to determine the potential severity of an MDR epidemic. However, our theoretical analyses suggest that fitness estimates of MDR strains derived from epidemiological data may not be very useful indicators of the potential for MDR to spread. We have found that (under certain conditions) many MDR strains that are substantially more fit than the wild-type pansensitive strains will only lead to a very low MDR incidence. Paradoxically, we have also found that even MDR strains that are considerably less fit than the wild-type pansensitive strains can lead to a high MDR incidence. Thus, our analyses provide new insights as to how epidemiological estimates of fitness of MDR strains should be interpreted. Our results imply that the potential for spread of any specific MDR strain cannot be evaluated simply by measuring its relative fitness value, but should be evaluated within the context of several other factors, including the treatment and case-finding rate, the cure rates and the amplification probability. Hence, the potential for spread of any specific MDR strain can be expected to show substantial geographic variation. We suggest that a more useful approach to assessing the potential for an MDR epidemic should be developed by calculating an aggregate risk index using all four of the key causal factors that we have identified.

Currently, WHO global TB control strategies are based upon achieving a high (70%) case detection rate and a high (85%) cure rate. These goals are aimed at controlling wild-type pansensitive strains, which account for the vast majority of TB cases worldwide. We have identified the key causal factors in generating a hot zone. Three of these factors can be controlled: the case detection and treatment rate, the cure rate and the amplification probability. It is essential to achieve high case detection, treatment and cure rates, but it is also essential to minimize the amplification of resistance. We suggest that to effectively control MDRTB in the hot zones, region-specific threshold values for acceptable amplification probabilities should be specified; threshold values will depend on the stage of the MDR epidemic. MDRTB epidemics are complicated multistrain epidemics driven by transmitted resistance, acquired resistance and amplification of resistance. Our results strongly suggest that, in the hot zones, second-line drugs should be quickly introduced to disrupt the amplification of resistance. There is an urgent need to develop more complex and region-specific control strategies for regions where MDRTB has reached high levels[27,28]. Our amplifier model is a useful and novel health policy tool for designing new and effective control strategies to prevent MDRTB from becoming a global threat.

METHODS

The amplifier model. Our new multistrain model builds upon our earlier models of TB epidemics[13–16,22–24,29–31], but includes many additional complexities. Our model tracks the numbers of susceptible individuals $S(t)$, latently infected individuals $L(t)$, diseased individuals $T(t)$ and recovered individuals $R(t)$ over time for each strain i. The equations that govern the dynamics are:

$$\frac{dS}{dT} = -\left[\sum_{i=1}^{n} (\beta_i^L + \beta_i^T)T_i + \mu_0\right]S + \sum_{i=1}^{n} \theta_i c_i T_i + J^S \quad (1)$$

$$\frac{dL_i}{dt} = -(\nu_i + \mu_i^L)L_i + \beta_i^L S T_i - \sum_{j=1}^{n} \gamma_{ij} L_i T_j + J_i^L \quad (2)$$

$$\frac{dT_i}{dt} = \nu_i L_i + \beta_i^T S T_i - (\mu_i^T + c_i)T_i - \sum_{j=1}^{n} K_{ij} T_j + \sum_{j=1}^{n} \gamma_{ij} L_j T_i + J_i^T \quad (3)$$

$$\frac{dR_i}{dt} = c_i(1-\theta_i)T_i - \mu_0 R_i \quad (4)$$

The parameters β_i^L and β_i^T represent strain-specific transmission rates when a susceptible individual S comes into contact with an individual with strain i; the superscripts L and T represent the conversion of susceptible into latently infected and (infectious) diseased individuals, respectively. Note that β_i^L and βi^T can be represented in terms of our previous terminology[13–16,22–24,29–31]; thus $\beta_i^L = (1-p)\,\beta$ and $\beta_i^T = p\beta$, where p represents the proportion of newly infected individuals who develop 'fast' TB, and β represents the transmissibility coefficient. Strain-specific death rates for susceptible, latently infected and diseased individuals are denoted μ_0, μ_i^L and μ_i^T, respectively; ν_i denotes the progression rate from latently infected to disease for each strain i. Strain-specific cure rates are denoted c_i, while the fraction of cured individuals that revert to susceptible individuals is θ_i. Upon administration of antibiotics, some individuals will acquire drug resistance. The matrix that specifies the degree of amplification of drug resistance is:

$$K_{ij} = k_{i,i+1}\delta_{ij} - k_{j,i}\delta_{i,j+1},\ K_{n,j} = -k_{j,n}\,\delta_{n-1,j} \quad (5)$$

where δ_{ij} is the Kroenecker delta function and n is the total number of strains.

We have also rescaled the model to specify alternative incidence functions and the potential impact of reinfection (**Supplementary Note** online).

The amplifier model also allows for immigration and emigration ($J_i^{S,L,T}$) of individuals of all types, as well as reinfection (γ_{ij}) of latently infected individuals (**Supplementary Note** online). Equations (1–4) were numerically solved using an adaptive fourth-order difference scheme coded in the C programming language. We considered the dynamics only in the absence of immigration and emigration of infected individuals, but allowed for immigration of susceptible individuals to maintain a steady-state population of susceptible individuals. The disease-free equilibrium in the absence of immigration or emigration ($J_i^L = J_i^T = 0$) is at $(S^*, L_i^*, T_i^*) = (J^S/\mu_0, \{0\}, \{0\})$. The stability of this fixed point was found by linear perturbation analysis of equations (1–4) about $(J^S/\mu_0, \{0\}, \{0\})$ by solving the characteristic polynomial for the eigenvalues λ_j (in the most general case of N possible strains):

$$(\lambda + \mu_0)\prod_{i=1}^{N}[\lambda^2 + B_i\lambda + C_i] = 0)\,, \quad (6)$$

where

$$B_i = (\mu_i^L + \mu_i^T - \beta_i^T S^* + \nu_i + c_i + k_{i,i+1})$$
$$C_i = (c_i + \mu_i^T - \beta_i^T S^* + k_{i,i+1})(\mu_i^L + \nu_i) - \beta_i^L \nu_i S^* \quad (7)$$

The eigenvalues

$$\lambda = -\mu_0, \frac{1}{2}\left[-B_i \pm \sqrt{-B_i^2 - 4C_i}\right] \quad (8)$$

that are found from solving equation (6) contain a positive real part, signalling an exponential growth in a linear combination of the variables S, L and T, whenever any B_i or $C_i < 0$. However, from expressions (7), C_i always becomes negative before B_i as the parameters c, μ, β, k, ν are varied. Instability occurs if

$$c_i + k_{i,i+1} + \mu_i^T < S^*\beta_i^T + \frac{S^*\beta_i^L \nu_i}{\nu_i + \mu_i^L}\,, \quad (9)$$

for any i. Thus, in our multistrain model, the reproduction numbers for each strain i are:

$$R_0(i) = S^*\,\frac{(\beta_i^T + \beta_i^L)\nu_i + \beta_i^T \mu_i^L}{(\nu_i + \mu_i^L)(c_i + k_{i,i+1} + \mu_i^T)}\,. \quad (10)$$

Each reproduction number is the product of the average number of secondary infections caused per unit time, the average time a case remains infectious and the probability that an infected individual develops disease (by either 'fast' or 'slow' routes)[22–24].

Reconstructing potential evolutionary trajectories. To reconstruct possible evolutionary trajectories we used the amplifier model and Monte Carlo methods[21], and sampled from the following uniform probability distribution functions (p.d.f.): (i) 10–70% case detection and treatment rates (the lower bound was set at 10%, as currently <20% of cases worldwide receive treatment[11], and the upper bound was set at the WHO target goal for case detection and treatment); (ii) 45–75% cure rates for pansensitive TB (the lower bound corresponds to the natural cure rate for TB[22]; the upper bound was set at 75%, as although cure rates of pansensitive TB with perfect adherence can be as high as 95%, we modeled cure rates assuming poor adherence, ineffective regimens and interrupted drug supply); (iii) 30–60% cure rates of pre-MDRTB (cure rates of pre-MDRTB are similar to those for pansensitive TB as pre-MDR strains respond fairly well to treatment[20]); (iv) 5–45% cure rates of MDR TB[20,32–35]; (v) 0.1–0.4 amplification probabilities of pre-MDR to MDR[7,9,10]; and (vi) 0.1–0.5 amplification probabilities of MDR to post-MDR[7,9,10]. Currently, it is unclear whether drug-resistant TB strains are less fit (less transmissible) or more fit (more transmissible) than pansensitive strains[36]; hence, we included a wide range of uncertainty in our estimates of relative fitness. We varied the transmissibility relative to pansensitive strains (relative fitness) of (i) pre-MDR,(ii) MDR and (iii) post-MDR strains. For each category we varied (independently) relative fitness values from 0.5–1.5, using a uniform p.d.f. Our Monte Carlo sampling procedure enabled us to theoretically construct 4,000 different pansensitive, pre-MDR, MDR and post-MDR strains. We used these 4,000 strains to simulate 1,000 potential evolutionary trajectories for the past thirty years. Baseline values for parameters were based upon previous studies[22], so initial TB incidence was high.

Note: Supplementary information is available on the Nature Medicine website.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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