Mathematical models of the epidemiology and control of drug-resistant TB

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Tuberculosis is an infectious disease of global public health importance, causing more than 9 million new cases and 1.7 million deaths in 2006. Although the global incidence per capita of TB has declined over the past 5 years [1] , this figure masks heterogeneity in local trends; TB incidence and mortality rose dramatically in Eastern Europe and Africa, areas afflicted by TB drug resistance and HIV, respectively, over the past decade before stabilizing in the last few years [2] . In 2006, the report of an outbreak of extensively drug-resistant (XDR) TB among HIV-coinfected individuals in KwaZulu-Natal, South Africa [3] triggered speculation that new, virtually untreatable forms of TB were emerging (see Box 1 for major clinical classifications and causes of drug-resistant [DR] TB [4,5]). Reanalysis of surveillance data showed that

highly resistant TB is already present in at least 50 countries [6] . However, since testing for extensive drug resistance is not performed in many settings, the true burden of XDR-TB remains unknown. Recent estimates indicate that, in 2006, almost 500,000 incident multidrug-resistant (MDR) TB cases occurred and that approximately 3% of first-time TB cases and 19% of previously-treated TB cases may have MDR-TB [2] .

Mathematical models of the dynamics of *Mycobacterium tuberculosis* both within and between hosts have improved our current understanding of the natural history of infection [7] , permitted the projection of the future disease burden and provided a framework for the rational adoption of disease-control strategies [8-11] . Models that capture the natural history of infection within hosts and represent the essential processes underlying transmission have helped consolidate current knowledge and have highlighted areas where additional research is necessary (Box 2). These models provide a framework for projecting the possible trajectories of DR-TB epidemics under different assumptions and in the presence of various disease-control strategies. A major strength of dynamic models of infectious diseases is that they make explicit assumptions that may otherwise remain unstated. Competing models that address similar questions but result in different answers often reveal important areas where data are lacking and additional research is required.

Here, we first review mathematical models that focus on the emergence of resistance within individual hosts and then turn to models that explore the processes by which DR-TB spreads within communities. We then discuss models that have been used to evaluate the potential effectiveness and feasibility of strategies to control the emergence of DR-TB and identify important areas of remaining uncertainty. We use the generic term 'DR-TB' to describe disease that has a reduced probability of sputum or culture conversion when standard first-line regimens are used. While evidence indicates that even resistance to a single drug can reduce the likelihood of successful treatment [12] , here we are concerned primarily with MDR and XDR-TB, which are the most refractory to treatment [13] .

How is MDR *M. tuberculosis* selected within individuals?

Mathematical models have been used to explore the processes by which initially rare DR bacteria are selected for during drug treatment of individual patients. Mutations that cause resistance to antibiotics occur at widely variable rates; for example, the probability of a mutation that results in isoniazid resistance is estimated to be on the order of 10^{-8} per cell division; while, for rifampin resistance it is on the order of 10^{-10} [6] . If resistance mutations occur independently, there is a very much smaller probability that untreated individuals infected with a drug-sensitive strain of *M. tuberculosis* will accumulate bacilli with simultaneous resistance to more than one drug. Accordingly, multidrug therapy is used to treat TB in order that those *M. tuberculosis* mutants with resistance to a single drug will be killed.

Despite multidrug therapy, drug resistance often occurs among individuals on treatment. This may occur for one of two reasons: patients receive inadequate treatment regimens or there is differential drug exposure of bacteria within a host, so that even in the presence of adequate therapy, subpopulations of bacteria are exposed to functional monotherapy. To evaluate which of these mechanisms is the primary cause for acquired drug resistance, Lipsitch and Levin developed simple within-host models of bacterial growth in which drug-resistance mutations occur stochastically [14] . The authors modeled a range of different processes including bacterial replication, bacterial death under drug pressure and host adherence to

drug regimens and, subsequently, drew inferences regarding whether 'noncompliance' (mechanism 1 above) or 'heterogeneity' (mechanism 2 above) better reflects observed patterns of acquired resistance. Although they found that both mechanisms can lead to multidrug resistance, the sequence in which resistance to specific antibiotics occurs differs between the two scenarios. Under the assumption that patients are less likely to adhere to treatment as bacterial load declines, the model predicts that noncompliance will result in the emergence of isoniazid monoresistant mutants first, while heterogeneity will lead first to the appearance of rifampin-resistant strains. Since acquired isoniazid monoresistance is much more common than rifampin monoresistance, the authors concluded that noncompliance is the more probable mechanism for acquired resistance.

Statistical models have been used to estimate the frequency at which acquired resistance occurs among individuals who fail TB treatment. Dye and Espinal propose a mathematical relationship that utilizes data from TB drug-resistance surveys to estimate the proportion of patients who acquire resistance after failing TB treatment [15] . Regressing the ratio of previously treated incident DR-TB cases to previously treated incident drug-sensitive TB cases against the ratio of all incident DR-TB cases to all incident drug-sensitive TB cases, Dye and Espinal calculate the probability of acquired resistance to drugs among treatment failures from 47 locations across the globe. Their point estimate of the fraction of treatment failures that acquire isoniazid monoresistance is approximately 13% (standard error: 4.8%), while 7% (standard error: 1.8%) acquire the MDR phenotype. Importantly, these estimates rely on the assumption of an equal ratio of DR disease to drug-sensitive disease among incident and prevalent cases, which will be violated if individuals with drug resistance have a longer average duration of disease.

Areas requiring additional study

That MDR *M. tuberculosis* evolves from mono-DR mutants that are first selected in the presence of inadequate therapy and then subjected to repeated cycles of functional monotherapy is supported by both laboratory and observational data [5] . Nonetheless, this sequential process of 'ratcheting up' of drug resistance is not necessarily the only explanation for how multiple drug resistance appears. Some strains may gain resistance to multiple drugs through other mechanisms, for example through drug efflux pumps [16] or through increased global mutation rates [17] . It is also possible that particular strains of *M. tuberculosis* , such as the Beijing/W family, may accumulate or tolerate resistance-conferring mutations more readily than other strains [18-21] . The study of sequential isolates from patients who acquire resistance while on treatment may help elucidate the mechanisms responsible for the appearance of resistance within individuals. The development of novel within-host models that track bacterial division and mutation can be used to estimate mutation rates, predict the order in which resistance appears and determine which mechanisms are most consistent with data.

Within-host models that capture interactions between HIV, *M. tuberculosis* and the host immune system may be expanded to help clarify reported associations between HIV and DR *M. tuberculosis* [22,23] . Observational studies have, thus far, given conflicting results. While some have reported a positive association between HIV/TB coinfection and DR-TB [24] , others have not confirmed this association [25] . Several possible explanations for an increased risk of DR-TB among HIV-coinfected individuals have been proposed [26] :

* HIV-associated immunosuppression may impair the ability to fend off relatively low-fitness

DR-TB strains;

* HIV-associated TB is more likely to be the result of a recent *M. tuberculosis* infection and in areas where resistance is emerging, a larger fraction of recent infections will be DR;

* Patients with HIV and DR-TB infection may share common risk factors, such as injection-drug use, hospitalization or homelessness;

* HIV-infected individuals may have a higher bacterial burden and, hence, a higher risk of failed therapy and acquired resistance;

* HIV may be associated with functional monotherapy through malabsorption or drug interactions [27-29] .

What is the threat of continued spread of MDR-TB in populations?

A key concept in epidemiology is the 'basic reproductive number' (R_0). This term refers to the expected number of infectious secondary cases when a single untreated infectious individual enters an entirely susceptible population. R_0 is the product of four parameters: (1) the number of respiratory contacts that occur over a given time period (c), (2) the probability that transmission will occur during such contact (b), (3) the duration during which the TB case is infectious (d), and (4) the fraction of new TB infections resulting in clinical disease and, thus, that can produce a secondary infectious individual (x) (because only a fraction of new TB infections result in clinical disease, the expected number of secondary infectious cases resulting from the entry of an infectious individual into a susceptible population is smaller than the number of secondary infections).

The number of expected secondary TB cases is also less than the basic reproductive number if the infectious case enters a population that is not entirely susceptible. If those who are already infected with *M. tuberculosis* (i.e., those who have a latent infection) have acquired some immunity to subsequent infection, fewer people will be infected by a single infectious case. Similarly, if a person with infectious TB receives prompt and effective treatment, his period of infectiousness may be reduced and, consequently, the number of secondary cases he produces is less than if he had not been treated. In these cases, the effective reproductive number (designated R_e), that is, the expected number of secondary cases resulting from a single infectious individual in a partially immune population with access to treatment, is lower than R_0 by a factor that reflects the prevalence of latent infection and the degree of protection conferred by previous infection ($b' < b$; $x' < x$), and the reduction in the duration of infectiousness associated with treatment (d' [proportional to]70-80%), treatment programs that suppress drug-sensitive strains but do not effectively treat those with resistant strains of TB can fuel a rise in the prevalence of resistant strains [30,31] . If, however, the relative transmissibility of resistant strains is low, they are not likely to spread [16,36] .

Most estimates of the relative fitness of DR *M. tuberculosis* come from experiments that demonstrated that resistance mutations have deleterious effects on the bacteria. However, recent studies suggest that while some resistance-conferring mutations impair fitness, others do not [37-41] . Furthermore, mutations that initially reduce fitness may be accompanied by secondary mutations that compensate for these initial costs [42] . Models that use a fixed average reproductive fitness of resistant *M. tuberculosis* fail to capture the variability among different DR strains and are, therefore, unable to simulate the evolutionary dynamics of these

[35]

strains over time. When variations in fitness have been explicitly modeled , the results show that even when the initial average fitness of DR strains is low, highly DR strains may eventually outcompete their drug-sensitive counterparts in the absence of interventions for the diagnosis and treatment of those with DR disease.

Distinguishing the relative contribution of the intrinsic and context-dependent effects of resistance mutations on the R_e for DR strains is challenging. Dye *et al.* have suggested that the observed reproductive capacity of MDR-TB strains is linked with the quality of TB-control programs [26] ; several areas with good DOTS (WHO-endorsed strategy centered on directly observed short-course therapy) uptake have observed recent downward trends in the burden of DR-TB, indicating a low value of R_e for DR strains (e.g., that seen in Hong Kong). However, in other areas with high-quality TB programs, the burden of highly DR-TB has continued to rise, suggesting a substantially greater value of R_e for DR strains (e.g., that seen in Peru) [2] . For strains of *M. tuberculosis* in which the intrinsic replicative capacity of DR pathogens is low, a well-functioning TB-control program, even one that does not include specific measures to diagnose and treat existing drug resistance, may prevent the continued appearance and spread of resistance [43,44] . On the other hand, if DR strains that do not have large intrinsic fitness deficits have already arisen, prevention of further spread can only be ensured by reducing the effective duration of resistant cases through targeted application of second-line treatment. These observations highlight the importance of understanding both the intrinsic biological effects of resistance-conferring mutations and the epidemiological context when predicting trends of resistant disease.

Areas requiring additional study

In order to construct a model to predict the future behavior of DR-TB within a community, it is necessary to distinguish the relative contributions of acquired resistance and transmission to the occurrence of new cases of resistance. While progress has been made in determining the reproductive numbers of pathogens from observational data during ongoing epidemics [45,46] , the long and variable serial interval for TB and the potential for reinfection frustrate these approaches [47] . Estimates of the relative value of R_e for DR strains compared with drug-sensitive strains of *M. tuberculosis* can be based on studies that used molecular fingerprinting to determine the relative number of secondary cases arising from drug-sensitive and DR index cases [26] . However, obtaining valid inference from this type of molecular epidemiologic study is limited by the need to both capture a large fraction of incident cases [48-50] and ensure that cases of transmitted resistance and acquired resistance are appropriately classified [26,51] . Models also suggest that current survey methods for estimating the local burden of resistance may underestimate the extent of the problem [52] . New methods for timely estimation of the effective reproductive number of DR-TB and novel approaches for drug-resistance surveillance, perhaps utilizing new molecular epidemiologic methods and tools for rapid resistance detection, would help to better define the current burden and to identify the risk of continued emergence of resistance in epidemic settings.

The effect of HIV on the dynamics of DR-TB at the community level is also an area where additional research is necessary [53] . The presence of an HIV coepidemic has competing effects on the risk of TB transmission within communities; while HIV-coinfection greatly increases an individual's risk of progression to TB disease, coinfected individuals are more likely to have noninfectious extrapulmonary disease, to have a lower burden of *M. tuberculosis* in sputum and to have shorter durations of infectiousness with TB. Accordingly,

HIV coepidemics profoundly increase the incidence of disease but have a less dramatic effect on the prevalence of infectious TB [54] . It is also worth noting that while, with the exception of South Africa, many countries in Africa are believed to have low rates of drug resistance despite a high prevalence of HIV, there are not yet a sufficient number of surveys of sufficient size to provide precise estimates of the burden of resistance in most African countries [55] . Several models have been developed that explore the effect of HIV on TB dynamics and control [56-61] and these may be further expanded to help project the effects of HIV on the future burden of DR-TB.

A defining feature of the XDR outbreak in KwaZulu-Natal was the role of hospital transmission among individuals with HIV coinfection [3] . Nosocomial transmission, especially affecting those with HIV, has been implicated in outbreaks of highly DR-TB throughout the world [62-67] . Within congregate settings, especially those characterized by a high population density and limited ventilation, DR strains with high intrinsic fitness costs, which would not otherwise be expected to transmit easily in the community, may gain a foothold. Models have been developed to assess the potential role of infection control in limiting the impact of nosocomial outbreaks [68] ; however, more work is required to understand whether outbreaks within congregate settings could trigger a larger epidemic in the community. Additionally, models in which the standard assumptions of homogenous population mixing can be relaxed will provide additional insight into the relationship between the structure of respiratory contact networks and the spread and control of DR-TB. Studies that simultaneously capture the distribution of *M. tuberculosis* and the social networks will be especially valuable in the development of such models [69] .

Over the past 5 years, genetic sequencing tools have uncovered a more complicated global population structure of *M. tuberculosis* than had been previously appreciated [70-74] . Evidence for strain differences in virulence and transmissibility [75-78] , host specificity [71,79,80] , potential for immune system activation [81-85] and association with drug resistance [18-21] suggest that the population dynamics of *M. tuberculosis* may be complex. In particular, the association between drug resistance and Beijing family strains of *M. tuberculosis* , which has been reported in some locations but not observed in others, complicates the task of predicting the future burden of drug resistance in areas where Beijing family strains are circulating. While several modelers have begun to explore the relationship between interstrain TB dynamics and the burden of DR-TB [86-88] , additional research is needed on the mechanisms and outcomes of *M. tuberculosis* strain competition, both within and between hosts. Furthermore, in areas where repeated infection is common and strain diversity is present, the roles of reinfection and mixed strain infection in the spread of drug resistance remain largely unknown.

What interventions are necessary to limit the spread of DR-TB?

Since drug resistance initially appears among those who receive inadequate care for drug-sensitive TB, controlling resistance must begin with an effective approach for the timely detection and treatment of individuals infected with drug-susceptible *M. tuberculosis* . The WHO's 'Stop TB' strategy emphasizes the direct observation of therapy with standardized first-line drug combinations and is designed to minimize the duration of infectivity and the probability of acquired resistance while on therapy. This strategy expands the earlier DOTS program to better address HIV/TB coinfection and DR-TB [89] . While DOTS programs report very high rates of cure among patients with drug-sensitive TB [1] , those with resistant disease [12,13]

fare considerably worse . DOTS-only approaches mean that those with DR disease will receive inadequate care, have higher rates of treatment failure and may experience amplified resistance [90] .

Faced with a growing burden of DR-TB and, often, severe resource constraints, many national TB programs have struggled with the question of whether to augment standard TB control strategies with interventions targeted specifically toward those with DR-TB. Some argue that the increased technical difficulty and expense required to diagnose and treat DR-TB will undermine TB programs oriented toward drug-sensitive TB [91] . These commentators also point to the fact that the use of second- and third-line antibiotics can fuel the emergence of strains with resistance to these agents [92] . However, the current global consensus to actively address DR-TB is reflected in the WHO's Stop TB plan, which highlights both the importance of establishing and maintaining a highly effective program for the detection and cure of drug-sensitive TB and establishing strict guidelines for the use of these second- and third-line agents [93] .

Several options for the implementation of second-line treatments are possible and models have been used to assess the cost-effectiveness of these different approaches. Treatment strategies can be divided into those that use standardized and individualized treatment regimens for DR cases. Standard regimens are selected on the basis of a locally representative sample of resistant cases while individualized regimens are determined by the drug-resistance profiles of each TB case. In one study in Peru, Suarez *et al.* showed that standardized treatment with second-line drugs for individuals failing first-line drug regiments was cost effective, even when the benefits associated with reducing primary resistance through transmission were not included [94] . In a second cost-effectiveness study of treatment strategies for DR-TB in Peru, Resch *et al.* explicitly included the indirect benefits of curtailing the transmission of resistant disease. This study found that individualized treatment of TB patients with a prior history of TB treatment was also cost effective [95] . When the model assumed that DR strains were easily transmitted, the treatment of DR disease was highly favored; however, even when the relative fitness of DR *M. tuberculosis* was assumed to be low, treatment of DR disease remained cost effective. While debate continues regarding the cost-effectiveness of diagnosis and treatment of MDR-TB, the findings of these two studies support the principle that treatment of DR-TB is a cost-effective intervention in the majority of settings, but should be preceded by the implementation of a comprehensive DOTS program for the control of drug-sensitive TB [96,97] .

Where transmission within hospitals and prisons contributes significantly to the local burden of resistance, targeted efforts to improve infection control in congregate settings are likely to produce substantial benefit. A model of the recent XDR-TB outbreak in KwaZulu-Natal estimated that a strategy that includes improved infection control within hospitals, reduces hospitalization time and shifts TB treatment from inpatient to outpatient settings could reduce the projected number of XDR cases by almost 50% over 6 years [68] . This model also suggested that efforts to limit the exposure of the community to patients with XDR-TB through quarantine and isolation may actually result in perverse effects if patients with XDR-TB are housed together within settings where continued exposure to superinfection with highly resistant *M. tuberculosis* is probable [98] .

Areas requiring additional study

Can optimal DOTS administration alone prevent the continued emergence of DR-TB in areas

where resistance already exists? The decline of DR-TB among new TB patients in Mexico after the implementation of a strict DOTS program indicates that, in this setting, the intrinsic costs of resistance prevents the further transmission of highly resistant *M. tuberculosis* [43,99] . However, in other settings with apparently well-performing DOTS programs, (e.g., that present in Peru), the number of incident DR-TB cases per capita continues to rise [2] . A better understanding of strain- and mutation-specific fitness costs of resistance may help to predict in which settings drug resistance is likely to be transmitted.

While the DOTS TB-control strategy recommends passive case detection (i.e., that individuals with symptomatic TB cases seek care rather than health providers looking for TB cases), active case detection and the tracing of respiratory contacts of individuals may help control DR-TB in some communities [100-102] . Several models have addressed the roles of household and community contacts in the dynamics of TB transmission and these approaches may be extended to consider the role of different setting-specific interventions for targeting DR-TB [103,104] . Since there are no evidence-based regimens for treatment of latent infection among contacts of MDR or XDR-TB cases, there is a need for both clinical trials that will determine which drug combinations can be effectively used and new models that can assess the potential effects of enhanced case detection in the community.

Given the increase in risk of TB among those with HIV, there is much interest in integrating care for both diseases within a single clinical setting. However, the integration of services also presents logistical challenges, since the cohorting of immunocompromised HIV patients with infectious TB patients may lead to nosocomial transmission [3] . Further operational work is needed to understand how care for these diseases can be safely integrated in resource-limited settings and mathematical models can play an important role in strategic planning for combined treatment programs.

The use of isoniazid preventive therapy (IPT) to prevent breakdown of latent *M. tuberculosis* infection among those with HIV has been recommended by the WHO for HIV patients without active TB disease. While IPT has the potential to greatly reduce the burden of TB among HIV-coinfected individuals, it may also affect the emergence of DR *M. tuberculosis* . Although there is little evidence that monotherapy is associated with acquired resistance among those with latent *M. tuberculosis* infection [105] , in many settings it may prove difficult to rule out active disease among those with HIV infection and, thus, determine which patients are eligible for IPT [106,107] . Models have also suggested that the use of a single-drug-preventive therapy can increase the selective pressure for DR-TB, even if it does not cause acquired resistance [108] . Results of ongoing trials of community-wide IPT in areas of high HIV prevalence, such as Botswana, may clarify the potential impact of IPT on the emergence of DR-TB. Models have also been used to project the effect of interventions in Eastern Europe and Central Asia, where both HIV and DR-TB are emerging. Results indicate that improving treatment of MDR-TB in areas where HIV is emerging in the Russian Federation can produce substantial population-level benefits [109] , while linked HIV prevention and MDR treatment programs can reduce the expected numbers of TB deaths in Estonia [110] . Future observational studies that improve our understanding of whether there is a causal relationship between HIV and risk of DR-TB for individuals will be essential in the development of the next generation of models that will assess the effects of HIV on the emergence of DR-TB within communities.

Traditional culture-based detection of DR-TB requires specialized laboratory facilities and technical expertise; it also may take several weeks to months between the time that specimens are collected and drug-sensitivity test (DST) results are available. However,

among TB patients with HIV coinfection, standard sputum smear diagnostic methods perform suboptimally. A recent mathematical model suggests that increasing access to sputum culture for both TB diagnosis and DST in South Africa, where there is a high prevalence of both HIV and MDR-TB, can substantially reduce the number of deaths due to TB and MDR-TB [111] . Newer methods for the rapid detection of resistance have also demonstrated great promise and are likely to play a major role in the control of DR-TB in the near future [112-114] . Since these rapid tests are currently designed to detect resistance to isoniazid and rifampin, they provide a rapid screen for disease that is likely to respond poorly to standard first-line regimens. However, since rapid resistance tests for many first- and second-line antibiotics are not available, it will not be possible to use them to construct individualized treatment regimens. Mathematical models that reflect test performance and the drug-resistance profiles of circulating *M. tuberculosis* isolates in the community may be helpful in determining how best to incorporate rapid resistance testing into clinical practice.

Recommended treatment protocols for drug-susceptible TB specify at least 6 months of combination drug therapy. The treatment of highly DR-TB often requires 2 years or more of combination therapy with second- and third-line agents, which are substantially more toxic and expensive than first-line agents. Clinical trials to determine the most effective combinations of existing second-line agents are needed [115,116] . While no novel first-line TB antibiotic has been introduced in over a quarter of a century, several new promising agents are in the drug pipeline and are undergoing tests in clinical trials [117] . Recent models have assessed the potential benefits of new drugs that can shorten the duration of treatment [118] ; these new drugs will probably play an important role in the treatment of TB that is resistant to currently available drugs.

Expert commentary

Mathematical models for the emergence and control of DR forms of TB, both at the host and population level, are tools to improve our understanding of the natural history of disease, facilitate the rational choice between available interventions and prioritize remaining research questions. Since randomized trials of public-health interventions for the control of DR-TB are generally not possible for ethical and practical reasons, models can provide a theoretical testing platform to compare the anticipated benefits and costs of alternative strategic approaches. Our understanding of the natural history and transmission dynamics of TB is limited and will always be incomplete. While sensitivity and uncertainty analyses can help guard against false confidence in the predictive value of these models, we anticipate that improved models will result from the efforts of epidemiologists and laboratory scientists to reduce the number and size of existing gaps in our knowledge.

Throughout this review, we have highlighted areas where new research will inform the development of more robust models for the identification of strategies to prevent the emergence of DR-TB. In particular, we believe that research aimed at understanding both the relative roles of the intrinsic biological fitness costs of drug resistance-conferring mutations and the extrinsic, contextual factors that may facilitate or interrupt the transmission of drug resistance within a community will greatly reduce the amount of uncertainty regarding the trajectory of the DR-TB epidemic over the next few decades. We have cited observational studies that suggest that highly DR strains are substantially weakened relative to drug-sensitive strains [43,119] ; however, there are also settings in which the deleterious effects of resistance are much less clear [120-122] . Studies that find particular resistance-conferring mutations or combinations of resistance-conferring and compensatory mutations not

associated with fitness deficits warrant concern [37-40] . Further work is needed to clarify the pathways by which strains become resistant to multiple drugs and the effect of these phenotypes on the competitive ability of these strains in the absence of antibiotic pressure.

Economic analyses reveal that offering second-line treatment to individuals with MDR-TB is a highly cost-effective public-health strategy in almost all settings. It is comforting that uncertainty regarding the intrinsic fitness effects of resistance does not impair our ability to interpret models with respect to this question; even if we ignore the transmission of drug resistance, the treatment of MDR-TB is favored [94-97] . These analyses consistently find that interventions in the treatment of DR-TB must be implemented as an extension of the DOTS approach to TB control, which prioritizes the rapid detection and effective treatment of infectious TB. Accordingly, we should think of second-line treatment for DR-TB as one generally appropriate element of a comprehensive strategy for TB control within communities. While, at one time, there was much debate regarding whether treating DR-TB would deplete resources from programs that focused on the control of drug-sensitive disease, there has been substantial progress toward both the integration of these efforts and, led by the WHO, a reframing of TB-control priorities to include the treatment of all TB, regardless of drug resistance [93] .

Five-year view

New tools for microbial genome sequencing and bioinformatic analysis promise to advance our understanding of the relationship between mycobacterial genotype and phenotype. Within-host models that leverage such information may reveal novel mechanisms by which multiple drug resistance appears and evolves and may offer clues for interventions that minimize the risk of acquired or amplified resistance. Better knowledge of strain-specific differences in the propensity to develop or the ability to tolerate resistance-conferring mutations can also inform the development of more realistic models. Questions remain regarding how HIV and TB interact within coinfected hosts and in settings where the diseases are cocirculating. New models that focus on the synergy between these pathogens may improve projections of disease trajectory and identify interventions that are likely to assist control.

The development of molecular epidemiologic tools, geographical information systems, and methods for social network analysis also offer modelers new questions and new analytical approaches [69,123] . The integration of these technologies provides exciting opportunities to explore the dynamics of TB transmission within realistically structured populations and uncover new strategies for disease control. Epidemiologic studies that identify links responsible for extending risk from nosocomial outbreaks to surrounding populations and methods for determining the role of population movements and migration in the seeding of new epidemics of resistant TB will also inform the development of models for evaluating novel strategies for the control of highly DR-TB.

Box 1. Most commonly used anti-TB antibiotics and causes of drug-resistant TB.

First-line antibiotics:

* Isoniazid, rifampin, pyrazinamide, ethambutol and streptomycin

Second- and third-line antibiotics:

* Amikacin, kanamycin, capreomycin, cycloserine, para-aminosalicylic acid, fluoroquinolones,

ethionamide and protionamide

Clinical classes of drug-resistant TB:

* Monodrug resistant: resistance to a single drug

* Polydrug resistant: resistance to more than one drug, but not both isoniazid and rifampin

* Multidrug resistant (MDR): resistance to at least isoniazid and rifampin

* Extensively drug resistant: a subclass of MDR; defined as MDR plus additional resistance to at least one injectable agent other than streptomycin (amikacin, kanamycin or capreomycin) and one fluoroquinolone

Causes of drug-resistant TB:

* TB is caused by the bacterium *Mycobacterium tuberculosis* and is transmitted through the respiratory route. By contrast with many other bacterial pathogens for which exchange of genetic material plays a central role in the acquisition of drug-resistance, *M. tuberculosis* is thought to become resistant to antibiotics primarily as the result of spontaneous chromosomal mutation and deletion events [4] . Drug-resistant *M. tuberculosis* mutations arise infrequently, in the range of 1 per 10^8 to 1 per 10^{10} cell divisions [5] , and the resulting drug-resistant strains are generally considered to be unlikely to outcompete wild-type *M. tuberculosis* in the absence of the selective pressure of antibiotics

* Drug-resistant TB arises through two mechanisms: 1) an individual with an initially drug-sensitive infection may acquire resistance if sporadically occurring drug-resistant organisms are selected for by irregularly administered or otherwise ineffective antibiotics ('acquired drug resistance') or 2) an individual may be infected with a strain of *M. tuberculosis* that has already acquired drug resistance ('transmitted' or 'primary drug resistance'). Individuals with resistance to one or more anti-TB drugs may gain additional resistance under the selective pressure of antibiotics if treatment regimens do not adequately target subpopulations of polydrug-resistant strains ('amplified resistance')

Box 2. Models for drug-resistant TB.

Many mathematical models for infectious diseases use ordinary differential equations to describe how the number (or fraction) of individuals within mutually exclusive health states change during the course of an epidemic. These models can be visualized as simple box and arrow diagrams, where the boxes show the health states of individuals and the arrows represent the transitions between these health states. For example, a very simple model of TB (Model **A**) shows four types of individuals as boxes: S (susceptible to infection), L (latent *Mycobacterium tuberculosis* infection), I (active TB disease) and R (recovered from disease). The arrow from S and L represents infection, the one from L to I represents progression from latent infection to disease, and the one from I to R represents recovery. The force of infection (identified as λ and defined as the rate at which susceptible individuals become infected) changes over an epidemic and is determined by the time-specific prevalence of infectious cases, the strain-specific probability of infection given contact between an infectious and susceptible individual, and the expected number of respiratory contacts per time unit.

Processes represented as single arrows in this simple representation often reflect more complicated processes; for example, the rate of progression from infection to disease

depends on several factors including the time since the infection occurred, the age at which the individual was infected and the presence of comorbidities such as HIV or diabetes. Models will include some, but never all, details related to the infection process and natural history of the disease. For example, in the very simple models depicted below, we do not show the process of repeated infection, which has been demonstrated to be important, in certain scenarios, for TB dynamics. The appropriate level of complexity to include in a model depends on the research question for which the model has been developed and the availability of data to inform the values of parameters. Since more complex models require the specification of additional parameters and can also be more difficult to interpret, simple models that include the minimum amount of detail for understanding the dynamic behavior of the system are usually preferred.

Models **B** and **C** represent simple schematic models, which incorporate both drug-sensitive and drug-resistant *M. tuberculosis* . Model **B** is a minimal model structure for exploring the dynamics of competing drug-sensitive and drug-resistant *M. tuberculosis* (indexed by subscript R) and the process of acquired (arrow from I to I_R) and transmitted resistance (S to L_R). In comparison with Model **A** , Model **B** requires the specification of additional parameters for those processes that are expected to differ between phenotypes. Model **C** includes three phenotypes: drug sensitive, monodrug resistant and polydrug resistant. While this more complex model structure permits the additional exploration of amplified resistance (arrow from I_{MR} to I_{PR}), it also requires the specification of additional phenotype-specific parameters, where there may not be sufficient data to inform their value.

Key issues

* TB is an infectious disease responsible for 1.7 million deaths per year. In 2006, there were almost 500,000 new cases of multidrug-resistant TB.

* Drug-resistant strains of *Mycobacterium tuberculosis* are selected for by inadequate antibiotic treatment for disease; drug-resistant TB can subsequently be transmitted among respiratory contacts.

* Mathematical models have been developed to understand the processes by which resistance develops within individual hosts and to project how resistant forms of TB are transmitted within communities.

* Model-projected trends of drug-resistant TB are affected by intrinsic biological consequences of mutations that confer drug resistance, TB-management practices, HIV seroprevalence and nosocomial transmission. Further research is needed to understand the impact and importance of these factors.

* Model-based economic analyses reveal that the treatment of drug-resistant TB is cost effective among other health interventions and should be integrated into control strategies that adequately detect and effectively treat drug-sensitive disease.

* Currently, we do not know whether, with the currently available arsenal of diagnostics and antibiotics, multidrug-resistant and extensively drug-resistant TB can be successfully contained in every part of the world. Models can address this question and can help identify the best strategies for using existing tools and opportunities for novel interventions.

CAPTION(S):

Classification of drug-sensitive TB.

* An individual with DS-TB. Bacterial burden is predominantly *Mycobacterium tuberculosis* sensitive to all antibiotics, but there exists small numbers of bacilli resistant to single drugs (indicated by small light circle) that arise through spontaneous muation. Will most likely transmit drug-sensitive *M. tuberculosis* .

[double dagger] An individual with DR-TB. Bacterial burden is predominantly *M. tuberculosis* resistant to a single antibiotic, but there exist small numbers of bacilli resistant to additional drugs (indicated by small dark circle) which arise through spontaneous mutation. Will most likely transmit single drug-resistant *M. tuberculosis* .

§ An individual with DR-TB. Bacterial burden is predominantly *M. tuberculosis* resistant to multiple antibiotics. Will most likely transmit polydrug-resistant *M. tuberculosis* .

DR-TB: Drug-resistant TB; DS-TB: Drug-sensitive TB.

Schematic model structures.

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