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Modeling epidemics of multidrug-resistant *M. tuberculosis* of heterogeneous fitness*

Mathematical models have recently been used to predict the future burden of multidrug-resistant tuberculosis (MDRTB). These models suggest the threat of multidrug resistance to TB control will depend on the relative «fitness» of MDR strains and imply that if the average fitness of MDR strains is considerably less than that of drug-sensitive strains, the emergence of resistance will not jeopardize the success of tuberculosis control efforts.

Multidrug resistance in *M. tuberculosis* is conferred by the sequential acquisition of a number of different single-locus mutations that have been shown to have heterogeneous phenotypic effects.

Here we model the impact of initial fitness estimates on the emergence of MDRTB assuming that the relative fitness of MDR strains is heterogeneous. We find that even when the average relative fitness of MDR strains is low and a well-functioning control program is in place, a small subpopulation of a relatively fit MDR strain may eventually outcompete both the drug-sensitive strains and the less fit MDR strains.

These results imply that current epidemiological measures and short-term trends in the burden of MDRTB do not provide evidence that MDRTB strains can be contained in the absence of specific efforts to limit transmission from those with MDR disease.

Key words:

Tuberculosis, fitness, MDR, strain.

Tuberculosis (TB) is a global health emergency that demands concerted management efforts. Recent World Health Organization reports reveal that MDRTB is a substantial problem in every region evaluated [4]. However, the impact of the emergence of multidrug-resistant (MDR) strains on global TB control remains unclear. Throughout much of the world, control strategies include case detection through sputum microscopy and standardized treatment regimens administered without drug sensitivity testing. Although this approach is effective in managing TB that is drug-sensitive or resistant to one antibiotic, it neither detects nor cures the majority of cases of MDRTB.

This exclusive focus on drug-sensitive and monoresistant tuberculosis arises from two considerations. The first is the cost and complexity of detecting and treating drug-resistant tuberculosis,

and the second is the perception that drug-resistant pathogens are less likely to cause epidemics than drug-sensitive ones. This perception is based on the observation that mutations that confer resistance often alter gene products important for the pathogen's survival and thus exact a «fitness cost» [5].

Mathematical models have been developed to describe the transmission dynamics and the impact of interventions for many infectious diseases [6, 7], including drug-sensitive [8–11] and drug-resistant tuberculosis [1–3, 12]. Previous work on the population dynamics of drug resistance has shown that the fitness of drug-resistant strains is a key determinant of the future burden of drug-resistant pathogens in general [13, 14] and specifically of drug-resistant TB [1] and MDRTB [2, 3]. When the average fitness of MDR strains is assumed to be substantially less than drug-sensitive strains, these models

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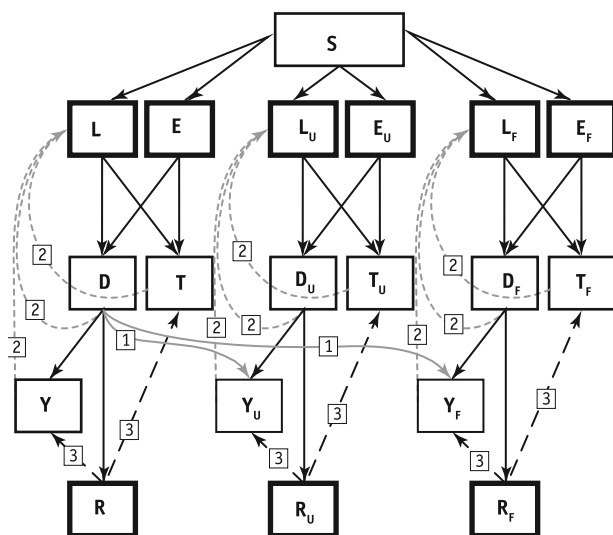


Figure 1. Multistrain tuberculosis model structure

Boxes represent state variables; the flow between states is described by the differential equations in Methods. States of infection with MDR strains are identified by subscript «U» («unfit» MDR strain) and «F» («fit» MDR strain). Heavy boxes indicate states from which individuals can be reinfected. Arrows (1) indicate multidrug resistance acquired through failed therapy, arrows (2) represent self-cure and arrows (3) represent relapse from drug cure. S — susceptible to infection; L — latent infection, slow progression; E — latent infection, fast progression; T — infectious TB, undetected; D — infectious TB, detected; Y — infectious TB, failed therapy; R — cured by drugs.

predict that the emergence of multidrug resistance will not jeopardize the success of control efforts that focus on the treatment of drug-sensitive disease.

The reproductive fitness of an individual strain of *M. tuberculosis* is a complex characteristic determined by the bacterium's ability to infect a susceptible host, persist and proliferate, and be transmitted to a secondary host. Laboratory studies comparing the relative fitness of drug-resistant and drug-sensitive organisms through competition assays have found that although some mutations compromise growth and the ability to survive oxidative stress [15], others have minimal in vitro effects. Furthermore, when fitness costs were detected, they were often short-lived because compensatory mutations rapidly accumulated to restore biological function [16]. The results of empirical studies that have compared the reproductive potential of drug-resistant and drug-sensitive strains in human populations have been similarly heterogeneous; some reports indicate that drug-resistant strains of *M. tuberculosis* spread less readily than drug-sensitive strains [17], whereas others show no difference in disease transmission [18].

Despite the heterogeneity in the fitness of MDR strains suggested by the studies cited, previous models of the transmission dynamics of drug-resistant TB have assumed a single fixed value of average fitness for MDR strains. Given that drug-resis-

tant strains of *M. tuberculosis* show a range of fitness [19], we constructed a model that incorporates the emergence of multidrug resistance during therapy, heterogeneity of fitness of MDR strains, and competition during an epidemic (Fig. 1). Following previous TB models, we assumed that susceptible individuals are infected at a rate that is proportional to the prevalence of people with active disease; once infected, individuals progress to disease through a fast route (primary disease) or a slow route (reactivation), and individuals who are infected but do not have active disease may become reinfected (exogenous reinfection). To incorporate competition between MDR and drug-sensitive organisms, we modeled three distinct strains: one that is drug-sensitive and two MDR strains that differ in relative fitness compared to the drug-sensitive strain. The «unfit» MDR strain (designated by subscript «U») has a low fitness (0.3) relative to the drug-sensitive strain, whereas the «fit» MDR strain (subscript «F») has a relative fitness that ranges from 0.8 and 1.2 (Table 1). As evidence suggests that most mutations conferring a MDR phenotype will incur an initial fitness cost, we assumed that mutation leads to the unfit MDR phenotype (a_U) 100 times as often as the fit MDR phenotype (a_F).

We initially modeled the course of a drug-sensitive tuberculosis epidemic prior to the introduction of combination chemotherapy. This simulation yielded measures of disease consistent with those from selected high-burden regions (Table 2a). We then modeled a 30-year period before the introduction of Directly Observed Treatment, Short-course (DOTS) treatment, during which drugs were available, but detection and cure rates reflected the suboptimal program performance reported before the implementation of the DOTS strategy. We estimated that approximately 3 % of those with initially drug-sensitive disease who fail pre-DOTS treatment acquired multidrug resistance (Table 1). The results of this simulation reflect the current epidemiology observed in high-burden countries (Table 2b). These results also show that the early course of the MDRTB epidemic is insensitive to the relative fitness of the MDR phenotype, with negligible differences in the estimated burden of drug-sensitive or MDRTB over a wide range of fitness costs.

To explore the long-term dynamics of MDRTB, we then modeled the implementation of the DOTS program beginning 30 years after the initiation of unstructured treatment. We assumed case detection and cure rates for drug-sensitive disease consistent with World Health Organization goals [21], improved treatment efficacy for MDR disease and a reduced proportion of those acquiring the multidrug-resistant phenotype through failed treatment

Table 1. Definition and values of model parameters

Parameter	Definition	Unstructured treatment	DOTS-like treatment strategy
μ	Birth/non-TB death rate per year		0.02
β	Transmission rate constant ^a		0.0000085
c_U	Fitness cost for «unfit» MDR strain		0.7
c_F	Fitness cost for «fit» MDR strain	Ranges between 0.2 and -0.2	
p	Proportion of those infected who are fast progressors ^b		0.14
m	Partial immunity afforded by previous infection ^b		0.65
τ_1	Rate of progression from latency to active disease per year ^b		0.000113
τ_2	Rate of progression for fast progressors per year ^b		0.88
φ	TB-specific death rate per year ^b		0.3
σ	Rate of self-cure per year ^b		0.2
κ	Rate at which detected individuals are treated and classified as either cures or failures per year		0.083
f	Proportion of cases identified and treated	0.5	0.7
g	Treatment efficacy for drug-sensitive TB [20, 21]	0.5	0.85
g_R	Treatment efficacy for drug-resistant TB (either fit or unfit) [22]	0.28	0.47
a_U	Proportion of drug-sensitive treatment failures acquiring «unfit» resistant TB	0.03	0.01
a_F	Proportion of drug-sensitive treatment failures acquiring «fit» resistant TB	0.0003	0.0001
δ	Rate of relapse from chemotherapeutic cure per year		0.001

^a β is arbitrarily chosen to yield expected incidence and prevalence in a population size of one million. ^bParameter values are adopted from ref. 2 and 3. References for other parameter values are specified in the text.

Table 2. Model fit and simulation results. a Epidemiology of tuberculosis before drug introduction

Measure ^a	Observed	Model results
Proportion of the population with latent infection [23]	> 90 % over age 11 (Vienna, 1909) > 80 % of 13–14-year-olds (Prague) 44–79 % of 18-year-olds (Europe, 1948–1951)	82 %
Prevalence of smear positive TB [23]	Average 200–300 cases/100,000 Range 150–950/100,000 (Africa and Asia, late 1950s)	1,649/100,000 ^b
TB mortality [23]	600/100,000 per year (London, 1800) 650/100,000 per year (Alaska, 1928–1932) 380/100,000 per year (Czechoslovakia, 1900) 200/100,000 per year (The Netherlands, 1900)	494/100,000
Proportion of all deaths which are due to TB [23]	35 % (Alaska, 1930) 10 % (Germany, 1901) 5 % (Germany, 1938)	20 %

b Current tuberculosis epidemiology from selected high-burden countries [24] and model simulation results

	Model simulations ^c							
	Cambodia	China	India	Russia	S. Africa	RF = 80 %	RF = 100 %	RF = 120 %
Proportion with latent infection (sensitive and MDR)	66 %	31 %	46 %	22 %	39 %	65 %	65 %	65 %
Proportion with latent MDR infection						0.2 %	0.2 %	0.2 %
Detected smear positive TB prevalence/100,000	492	82	215	229	93	234 ^d	235 ^d	235 ^d
Prevalence of infectious TB/100,000						464	464	465
Proportion of detected TB that is MDR [25]	Median for 28 countries and regions = 2.2 % (95 % CI 1.1–3.8)					2.1 %	2.2 %	2.4 %
Proportion of total TB that is MDR						1.3 %	1.4 %	1.6 %
TB deaths/100,000	131	19	40	165	24	104	104	104

^aWe assume that all infections and disease are due to drug-sensitive strains prior to the introduction of antibiotics. ^bThe model result is for both detected and undetected cases. Additionally, the model results include all infectious TB cases (not only those who are sputum smear-positive). ^cRF = relative fitness of the «fit» MDR strain compared with the drug-sensitive strain. ^dIncludes all infectious cases (not only those who are sputum smear-positive).

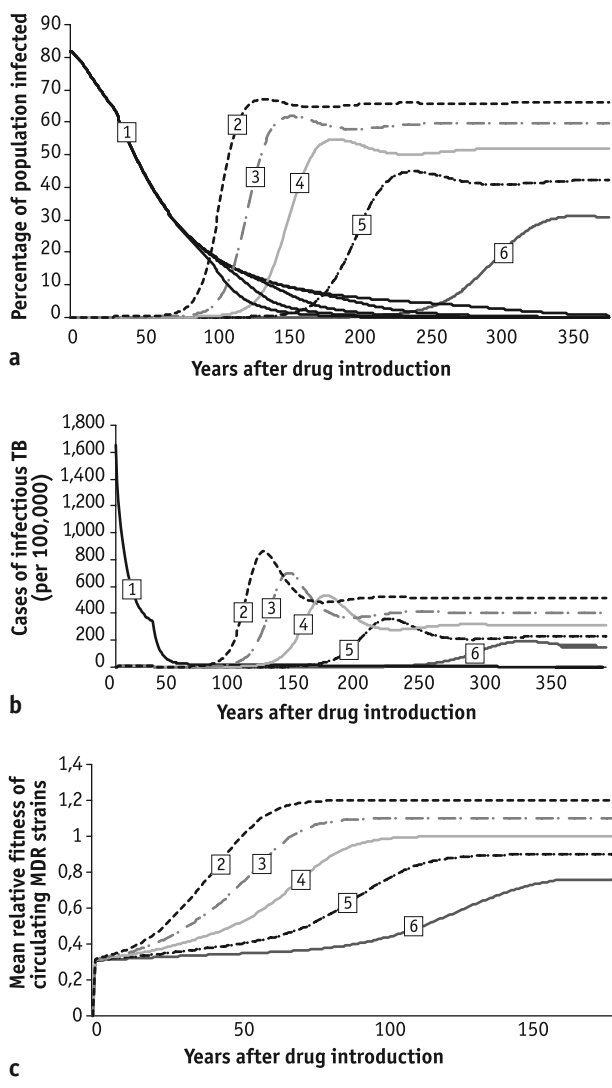


Figure 2. Sensitivity of long-term projections of MDRTB epidemics to the relative fitness of MDR strains

Traces with numbers represent infection and disease with the MDR strains; traces (1) represent infection and disease with the drug-sensitive strain. Numbers represent the projected course of the epidemic given an assumption about the relative fitness of the «fit» MDR strain ((2): $C_f = -0.2$; (3): $C_f = -0.1$; (4): $C_f = 0$; (5): $C_f = 0.1$; (6): $C_f = 0.2$). a — Proportion of population with latent TB infections over time; b — Prevalence of infectious TB over time; c — Evolution of mean fitness of extant MDR strains toward the relative fitness of the «fit» MDR strain.

(Table 1). As was observed in many countries that saw significant reductions in TB incidence after antibiotics became available, drug-sensitive disease is rapidly brought under control through the implementation of DOTS. In contrast to the short-term results discussed above, the simulated long-term course of tuberculosis epidemics depends critically on the relative fitness of MDR strains (Fig. 2).

In this simulation, almost all of the MDR cases generated early in the course of the epidemic harbor the unfit strain; thus, the average fitness is low. When the prevalence of drug-sensitive tuberculosis is reduced through the implementation of DOTS, the impact of acquired drug-resistance on the

emerging MDR epidemic becomes less important and the predominant driving force of incident MDR infections shifts to the transmission of MDR strains. Consequently, the fitness difference between the circulating strains becomes the primary determinant of new infections and interstrain competition leads to the ascent of the most transmissible strains (Fig. 2c).

The model demonstrates that even when the most fit MDR strain is assumed to be less fit than the drug-sensitive strain, the MDR strain will eventually outcompete the drug-susceptible strain (Fig. 2b). However, there exists a fitness threshold for the «fit» MDR strain below which multidrug-resistant disease will not continue to spread as long as DOTS treatment goals are met. In these simulations, this threshold is exceeded when the most fit MDR strains are greater than 70 % as fit as the drug-sensitive strains.

This model makes several simplifying assumptions. First, because the relationship between contact patterns and the spread of airborne infections is not well understood, we modeled the population as a homogeneously mixing unit. Although this is oversimplified, we based this decision on molecular epidemiological data that suggest substantial transmission of TB occurs following casual contact with infectious TB cases [26] and contact tracing fails to identify most secondary cases [27]. Second, we modeled the acquisition of multidrug resistance as a single-step process despite the fact that MDR is acquired through sequential accumulation of point mutations. Because monoresistant strains are thus included in the drug-sensitive (non-MDR) population, we may have underestimated the relative fitness of MDR strains in comparison to the non-MDR strains in the model. Finally, we modeled tuberculosis dynamics in a limited set of scenarios consistent with epidemiological data from developing countries. Recent work demonstrates that tuberculosis dynamics are highly sensitive to the rate of infection and suggests that it may not be possible to generalize our results to the setting of a developed country in which the incidence and prevalence of tuberculosis are declining [28].

Our model suggests that despite a short-term decline in the tuberculosis burden following the implementation of DOTS, the exclusive treatment of drug-sensitive and monoresistant tuberculosis may contribute to the emergence of MDR disease in at least two ways: (i) treatment directly contributes to the pool of MDR cases through acquired resistance, albeit at much lower rates under DOTS than pre-DOTS programs, and (ii) the removal of infectious individuals with predominantly drug-sensitive disease decreases the force of infection and

subsequently replenishes the pool of individuals who are fully susceptible to infection with circulating MDR strains.

Previous studies suggest that the fitness of MDR strains is heterogeneous. We demonstrate that future burden of MDRTB is more dependent on the distribution of fitness among circulating strains than on the initial average reproductive fitness. We show that even if highly transmissible MDR strains are only rarely generated through poor treatment, MDRTB may eventually become a major public health threat. Our simulations indicate that DOTS policies should be coupled with strategies to limit the spread of MDRTB (for example, DOTS-plus [29]) in order to mitigate the long-term threat of MDR disease. Although an optimal approach would include the concurrent administration of high-quality DOTS programs and the introduction of second-line drug therapy for those with MDRTB, limited resources have made this difficult to achieve. How this combined approach can best be implemented in resource-constrained settings is a topic for urgent operational research.

Methods

Model structure

Our deterministic compartmental model is described by the set of ordinary differential equations shown in Supplementary Methods.

Individuals are born susceptible to infection (S) and then may be infected with a circulating strain of *M. tuberculosis*. The strain-specific infection rate is proportional to the prevalence of individuals with active disease due to that strain and a strain-specific transmission parameter β ($1 - c$), where c denotes the fitness «cost» of the particular resistance phenotype of that strain. Thus, for the drug-sensitive strain, $c = 0$. In this formulation, β is proportional to the probability of a transmission event conditional on contact with an infectious individual and inversely proportional to the population size; thus β has units of $\text{persons}^{-1} \text{time}^{-1}$.

A proportion (p) of the infected individuals transitions into a rapidly progressive state (E , E_U and E_F), while the remaining infected individuals ($1 - p$) transition to a latent state (L , L_U , and L_F). Those with latent infections progress to active disease at rate τ_1 , considerably slower than those in the rapidly progressive state who transition to active disease at rate τ_2 .

A proportion of those developing active disease (f) is detected and treated (D , D_U and D_F), while the remaining individuals ($1 - f$) with active disease remain undetected and untreated (T , T_U and T_F). Those detected are processed and treated at rate κ . Of those with drug-sensitive disease who are treated, a proportion g are cured while $1 - g$ fail. Those

who fail may develop drug resistance; a proportion of these (a_U) acquires the «unfit» MDR strain (Y_U), while a much smaller proportion (a_F) acquires the «fit» MDR strain (Y_F). Those detected but not yet treated (D , D_U and D_F) and treatment failures (Y , Y_U and Y_F) continue to be infectious.

Individuals with active disease self-cure at rate σ ; we assume that those who self-cure transition back into the corresponding latently infected state (L , L_U or L_F) and thus remain at risk for reactivation. Treatment cures (R , R_U and R_F) relapse to disease at rate δ . A proportion (f) of these relapses are detected and will be classified as treatment failures (Y , Y_U and Y_F) while the remaining relapses ($1 - f$) remain undetected (T , T_U and T_F).

Except for those with active disease, all individuals with a history of infection may be reinfected by another circulating strain. Prior infection affords partial immunity m to reinfection with any strain. Previous models demonstrate that exogenous reinfection of individuals plays an important role in tuberculosis epidemics in high-incidence areas [10] and epidemiologic studies confirm that reinfection is common in settings where transmission is intense [30].

Individuals die at a fixed mortality rate μ ; those with active disease will also die at an increased tuberculosis-specific rate ϕ . All deaths are replaced by births into the susceptible state.

Modeling the fitness cost of drug resistance

The dynamics of the MDR strains differ from the drug-sensitive strain in two ways: the three strains have different transmission parameters and the proportion of MDR cases cured on therapy (g_R) is smaller than the proportion of drug-sensitive cases cured (g). We modeled different fitness costs for each of the two MDR strains, but assumed that treatment efficacy is equivalent for both MDR strains. Although the MDR phenotype results from the stepwise accumulation of mutations, we collapsed the parameters describing these sequential mutations into a single step in a manner similar to that of other modelers [2, 3]. This reflects the fact that monoresistant strains can be controlled by the therapeutic regimens used in DOTS and consequently will exhibit the same dynamics as do sensitive strains under this strategy. For our base model, the values for all other parameters that describe the natural progression of disease were identical for each of the three strains. Although our base model assumes that the cost of fitness is entirely captured by reducing the transmissibility of MDR tuberculosis, additional analyses demonstrate that MDR strains also outcompete drug-sensitive strains in projected tuberculosis epidemics when fitness costs

are instead exacted from the rates of disease progression (data not shown).

Baseline model prior to the introduction of antituberculosis drugs

We used the historical data on the epidemiological indices of tuberculosis infection and disease to calibrate the transmission parameter, β (Table 2). Because β is parameterized as persons⁻¹ time⁻¹, our fitted β reflects the choice of population under study. To facilitate comparison with other models, we arbitrarily report the β for a population size of 1 million (Table 1) and mod-

eled the introduction of a single case of drug-susceptible tuberculosis into a hypothetical population of 1 million individuals, allowing tuberculosis infection and disease to equilibrate. We used time steps of 0.1 year and an Euler integration method.

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Competing interests statement

The authors declare that they have no competing financial interests.

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Моделювання епідемії мультирезистентного туберкульозу з урахуванням гетерогенного пристосування мікобактерії

Останнім часом математичні моделі використовують для прогнозування майбутньої мультирезистентності туберкульозу. За цими моделями вираховують ступінь загрози мультирезистентності для служб контролю туберкульозу залежно від відносного пристосування мультирезистентних штамів. Якщо середня пристосованість мультирезистентних штамів буде значно меншою від чутливих, тоді утворення резистентних штамів не ставитиме під загрозу успішність боротьби та контролю туберкульозу.

Мультирезистентність туберкульозу формується шляхом послідовно набутої низки різних однолокусних мутацій, які матимуть гетерогенні фенотипічні ефекти.

У запропонованому дослідженні модулюють вплив початкових пристосувань, які оцінюють за появою мультирезистентного туберкульозу за умови, що відносна пристосованість мультирезистентних штамів є гетерогенною.

Ми виявили, що навіть тоді, коли середня відносна пристосованість штамів із мультирезистентністю низька та наявні програми контролю за туберкульозом ефективні, маленькі субпопуляції відповідних мультирезистентних штамів можуть витіснити інші штами, як чутливі, так і стійкі. Це означає, що поточні епідеміологічні та короткострокові заходи з контролю туберкульозу на тлі загального тягаря мультирезистентності не доводять, що кількість мультирезистентних штамів може бути знижена без застосування специфічних зусиль із обмеження передачі інфекції від хворих на мультирезистентний туберкульоз.

Ключові слова: туберкульоз, пристосованість, мультирезистентність, штамп.

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Моделирование эпидемии мультирезистентного туберкулеза с учетом гетерогенной приспособленности микобактерии

В последнее время математические модели часто используют для прогнозирования будущей мультирезистентности туберкулеза. Эти модели примерно высчитывают угрозу мультирезистентности для служб контроля туберкулеза в зависимости от относительной приспособленности мультирезистентных штаммов. Имеется в виду, что если средняя приспособленность мультирезистентных штаммов будет значительно меньше, чем у чувствительных, тогда создание резистентных штаммов не будет ставить под угрозу успех борьбы и контроля туберкулеза.

Мультирезистентность туберкулеза образуется путем последовательно приобретенного ряда различных однолокусных мутаций, которые будут иметь гетерогенные фенотипические эффекты.

В данном исследовании модулируется влияние начальных приспособлений, которые оцениваются появлением мультирезистентного туберкулеза при условии, что относительная приспособленность штаммов с мультирезистентностью является гетерогенной.

Мы обнаружили, что даже тогда, когда средняя относительная приспособленность штаммов с мультирезистентностью низкая и существующие программы контроля над туберкулезом эффективны, маленькие субпопуляции соответствующих мультирезистентных штаммов имеют возможность вытеснить другие штаммы, как чувствительные, так и устойчивые. Это означает, что текущие эпидемиологические и краткосрочные меры по контролю туберкулеза на фоне общего бремени мультирезистентности не обеспечивают доказательства того, что количество мультирезистентных штаммов может быть снижено без применения специфических усилий по ограничению передачи инфекции от больных мультирезистентным туберкулезом.

Ключевые слова: туберкулез, приспособленность, мультирезистентность, штамм.