

# Erasing the World's Slow Stain: Strategies to Beat Multidrug-Resistant Tuberculosis

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Multidrug-resistant tuberculosis (MDR) is perceived as a growing hazard to human health worldwide. Judgments about the true scale of the problem, and strategies for containing it, need to come from a balanced appraisal of the epidemiological evidence. We conclude in this review that MDR is, and will probably remain, a locally severe problem; that epidemics can be prevented by fully exploiting the potential of standard short-course chemotherapy (SCC) based on cheap and safe first-line drugs; and that best-practice SCC may even reduce the incidence of MDR where it has already become endemic. On the basis of the available, imperfect data, we recommend a three-part response to the threat of MDR: widespread implementation of SCC as the cornerstone of good tuberculosis control, improved resistance testing and surveillance, and the careful introduction of second-line drugs after a sound evaluation of cost, effectiveness, and feasibility.

Shelley's poetic casting of tuberculosis (TB) as a slow stain on the world (1), inspired by the death of John Keats, aptly characterizes the TB problem. The *Mycobacterium tuberculosis* complex, including its drug-resistant forms, is a group of pathogens with low reproductive rates and long generation times, causing epidemics that run over centuries (2). TB ranks among the most important burdens on human health, not because the total number of cases is especially large ( $\approx 9$  million/year worldwide, with incidence rates typically measured per 100,000 population), but because about one quarter of sufferers die, most of them young adults. Untreated, or untreatable, disease would kill more, about half of all cases (3). Globally, the number of TB cases is currently rising at 2% per year; the fear is that the number of cases resistant to antibiotics may be increasing much faster.

The perceived threat of drug-resistant TB is enormous. The biggest menace is multidrug-resistant TB (MDR), caused by strains resistant to at least isoniazid and rifampicin, the two principal first-line drugs used in combination chemotherapy. Health warnings have been issued in correspondingly strong language, not just in the popular press, but also in principal scientific and medical journals. Among various readings of the evidence, the spread of MDR has been classified as a global pandemic (4) more deadly than acquired immune deficiency syndrome

(AIDS), with the potential to destabilize society. Drug-resistant mycobacteria are said to be on the rampage, and MDR is thought to have become the norm (5).

The danger appears great for two main reasons. First, the fraction of patients carrying resistant strains has escalated to levels that put TB control in jeopardy in some parts of the world. About 10% of new TB cases tested are carrying MDR strains in Estonia and Latvia; the rate exceeds 25% among cases that have previously been treated. Part of the management problem is that drugs to treat resistant strains are expensive and toxic. The cost of treating a patient carrying MDR is typically hundreds of times greater than that for patients carrying fully sensitive strains. In the United States, the bill will normally run to tens of thousands of dollars per MDR patient (6). The second reason is that people with active TB, including antibiotic-resistant TB, are becoming more mobile internationally. Globalization has consequences for the spread of infectious diseases, and drug-resistant strains could turn up anywhere. Thus, real, or suspected outbreaks of the notorious strain W, multidrug-resistant and possibly imported, have been tracked closely in North America (7).

In the midst of this epidemic of concern, our goal here is to describe the scale of the MDR problem, where it is focused, how it is changing through time, the importance of the link with the human immunodeficiency virus (HIV)/AIDS, and the prospects for control. Although we must not neglect the clinical view of TB patients as individuals, we take a population biological approach to the management of this "social disease."

## MDR TB: How Many Cases and Where?

In year 2000, an estimated 273,000 of 8.7 million new TB cases (3.2%) were MDR (8, 9). In surveys of drug resistance carried out in 64 countries (10), the highest MDR proportions among new cases have been found in Estonia (14%), Henan Province, China (11%), Latvia (9%), and Ivanovo (9%) and Tomsk (7%) oblasts (provinces) in Russia. We are less confident about the number of MDR cases in countries that have not yet been surveyed for resistance. However, measures of independent variables predictive of resistance, such as treatment success, suggest that MDR rates of 10% or more exist in Yemen, Kyrgyzstan, Sudan, Pakistan, and Ukraine. Afghanistan and the Philippines are likely to have lower resistance rates but, because of their large populations, could each have more than 5000 new MDR cases in year 2000 (8). Although resistance rates have become high in parts of Eastern Europe, there is little evidence that these rates were still growing during the 1990s (Fig. 1).

Resistance is very unevenly distributed around the world. An estimated 70% of new MDR cases are in just 10 countries. Thus, MDR, and resistance more generally, are problems of local rather than global importance. By far the majority of TB cases remain treatable (i.e., cure rate  $> 85\%$ ) (11) under standard short-course chemotherapy (SCC) with cheap and safe first-line drugs.

Lower and upper estimates of the number of MDR cases differ by a factor of two. The only way to narrow this uncertainty is to introduce reliable laboratory testing and surveillance more widely. Few countries have the resources to test all TB cases for susceptibility to drugs, so national control programs have to examine a subset of patients, recognizing that sampling plans must balance two conflicting aims. To estimate the proportion and total number of drug-resistant cases, a representative sampling scheme is needed. By contrast, to maximize the number of patients given an optimal drug regimen (and hence maximize the cure rate), the goal will be to select those patients most likely to be carrying drug-resistant strains. In this case, testing will not be at random, but guided by some set of risk factors for resistance, such as the

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history of previous treatment, injection drug use, and homelessness (12, 13). The daily goal of TB control services should be to optimize treatment success; periodic, population-based surveys are needed to assess the changing magnitude of the resistance problem.

### Resistance in the Laboratory and the Clinic

Resistance to a drug as defined by laboratory tests (14) rarely implies total clinical inactivity. In a series of comparisons across six countries, on average of 47% of MDR patients were cured by SCC, with 6- or 8-month treatment regimens with four drugs, including isoniazid and rifampicin (15). The cure rates varied from 6 to 59% but may ultimately have been lower because of relapse. All these outcomes are certainly worse than can be achieved for fully sensitive cases, and inadequate treatment carries a risk of acquiring resistance to more drugs (16). Nevertheless, MDR is not absolutely untreatable by SCC. Rather, there is a graded response, where the cure rate depends on drug concentrations, the immunocompetence of patients, their compliance with treatment, and the number of drugs to which MDR strains are resistant.

We draw three inferences from these observations. First, the clinical evaluation of different first- and second-line drug combinations is an indispensable adjunct to laboratory testing for resistance. Second, it is vital to determine where drug efficacy ends and where patient management begins. The process of finding the best scheme for patient management is complicated by the fact that approaches such as "directly observed treatment" (DOT) do not easily lend themselves to randomized controlled trials: It is hard to generalize from the results of a social intervention. Third, the phenomenon of partial resistance complicates analysis of the question of what is an acceptable cure rate on clinical, epidemiological, and economic grounds. Clearly, the ultimate goal is to provide all MDR patients with the best possible treatment. Costs are an impediment, as are practical difficulties, including the training of health workers to administer toxic second-line drugs, such as the aminoglycosides, thioamides, cycloserine, and para-aminosalicylic acid (PAS) (17).

### The Link with HIV/AIDS

People who are infected with both *M. tuberculosis* and HIV are at progressively higher risk of developing TB as their immunity breaks down (18). Consequently, in those African countries presently suffering the largest epidemics of HIV, TB incidence has been increasing at 10% per year (11). In areas where a high proportion of cases are drug-

resistant, HIV coinfection will obviously increase the number of resistant cases. Much less clear are the circumstances under which HIV coinfection will increase the proportion of cases that are resistant.

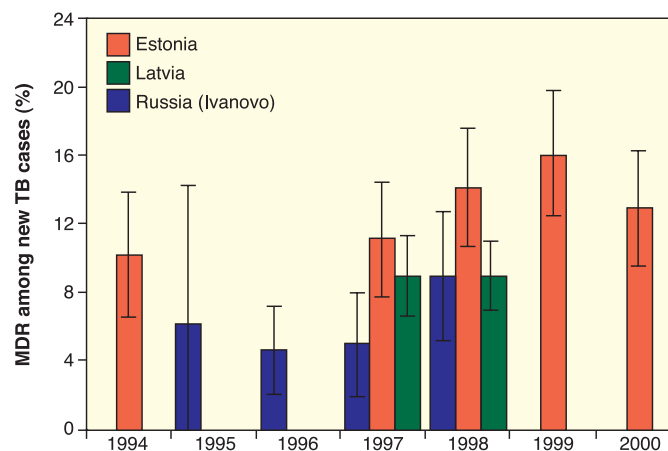
There are at least five reasons, in principle, why antibiotic resistance might be found more often among HIV-infected TB patients. First, *M. tuberculosis* strains with lower genetic fitness, manifested as a lower capacity to cause disease after infection (i.e., they are less virulent), may appear only in immunosuppressed people. Laboratory experiments have shown that resistant strains are less viable than sensitive strains in vitro and often (although not always) less virulent in guinea pigs (19). The second possibility is that TB among HIV-infected persons is due to recent infection, where a higher fraction of recent infections are drug-resistant (20). Third, there may be shared risk factors for infection with HIV and drug-resistant strains of *M. tuberculosis*, such as injection drug use and hospitalization. This is likely to be the main reason for the numerous reported nosocomial outbreaks of MDR among AIDS patients (21). Fourth, the treatment of immunosuppressed TB patients might fail because such patients carry a larger number of bacteria. On top of this, resistance would emerge more readily if the larger population of microorganisms is also genetically more diverse. Finally, HIV-infected TB patients may be subjected more often to functional monotherapy (22). There are various mechanisms by which bacteria may be exposed to one drug only, even while a patient is under treatment with the recommended drug combination. For HIV-uninfected patients carrying drug-sensitive strains, bacterial replication is normally suppressed with four drugs during the first 2 months of intensive phase treatment. Patients then typically switch to a combination of isoniazid and rifampicin during the 4-month continuation phase. If *M. tubercu-*

*losis* in AIDS patients can continue replicating into the continuation phase, then replicating organisms might be exposed to rifampicin alone because isoniazid has a shorter half-life and there are no other supporting drugs. Resistance to rifamycins has been seen repeatedly in HIV-infected TB patients, perhaps for this reason. Another possibility is that the azole antifungal drugs used in AIDS treatment enhance serum concentrations of rifamycins but not isoniazid, increasing exposure to the former (22).

Broadly speaking, HIV has been linked to MDR in small-scale outbreaks, such as those originating in hospitals. But there is no evidence that MDR is associated with HIV in cross-country comparisons (13). In particular, MDR appears to be uncommon in sub-Saharan Africa, the epicenter of the AIDS pandemic (10, 14).

### Reproductive Fitness and the Spread of MDR

Whether drug-resistant strains are likely to spread through a drug-sensitive population, and how fast, is determined by their relative and absolute reproductive fitness. The most important long-term outcomes can be expressed in terms of four conditions on the basic case reproduction number,  $R_0$  (Table 1). First, if the reproduction numbers of both sensitive ( $S$ ) and resistant cases ( $R$ ) are less than 1, TB is condemned to extinction (condition 1). This, clearly, is the ultimate aim of control. Sensitive strains will persist in the long run if  $R_{0S} > 1$  and  $R_{0S} > R_{0R}$ . So long as TB persists, there will be some drug resistance, because resistance arises by mutation at some constant frequency and will be transmitted at least occasionally. However, if  $R_{0R} \ll 1$ , resistant cases will always be relatively few (condition 2). The greater danger arises when  $R_{0R} > 1$ : Then resistant cases not only persist, but they persist in self-sustaining transmission cycles (condition 3). In the worst scenario (condition 4),  $R_{0R} > 1$  and



**Fig. 1.** Trends in the proportion of new TB cases found to be multidrug-resistant in Eastern Europe. Error bars are 95% confidence intervals. MDR rates are among the highest in the world, but there is little evidence that they are still increasing.

$R_{OR} > R_{OS}$ , whereupon resistant cases out-compete sensitive cases (through cross immunity) and completely replace them. These are, however, the eventual outcomes, which will take decades to reach.

Under most circumstances away from equilibrium, the resistance rate among new cases will increase through time. That can happen, in principle, even when a control program is driving both resistant and sensitive cases to extinction. To cut the fraction as well as the number of resistant cases requires an intervention that eliminates drug-resistant cases faster than sensitive cases. This is desirable but formally more stringent than necessary if the goal is simply to keep the absolute numbers of resistant cases low.

Most of the current evidence about the distribution of drug resistance is phenotypic, based on drug failure in vivo or in vitro. The mounting body of data generated by DNA fingerprinting presents the question of how to match resistance phenotypes with genotypes, where the latter are derived mostly from spoligotyping or restriction fragment length polymorphisms (RFLP) (23). Thus, the Beijing complex of strains, and the related strain W, may be spreading in Estonia (24) and Vietnam (25), where they have been linked with drug resistance; there is no such evidence of expansion in Thailand (26) and Indonesia (27) and no discernible

link with resistance. Is the association with resistance strong enough to explain the evolution of Beijing strains in Vietnam and elsewhere?

To show that it is, we must discount the possibility that strains like those in the Beijing complex are no more than arbitrarily defined genotypes drifting at random through the *M. tuberculosis* population. A simple model illustrates how, without any directional selection at all, strains may come and go on a time scale of many *M. tuberculosis* generations, equivalent to decades (Fig. 2). These fluctuations happen irrespective of whether we use a coarse genotyping method that identifies a few abundant strains or a more refined method that identifies many rare ones. They are expected because there is no stable level of abundance to which any strain is attracted. The laboratory challenge here is to define genotypes that functionally specify, or are at least highly correlated with, resistance phenotypes. The analytic challenge is then to measure the absolute ( $R_0$ ) and relative reproductive fitness ( $f$ ) of these resistance genotypes (28). We would reject the null hypothesis of genetic drift if  $f \neq 1$ . However, the tantalizing corollary of long-term drift is that the true average reproductive fitness can only be measured over decades. The evidence for directional selection may therefore need to be

reinforced by laboratory studies showing, for example, that certain genotypes are more likely to develop resistance than others (23).

Current estimates of MDR reproductive fitness suggest that the best control programs based on SCC can both prevent and contain MDR (Table 1, condition 2). Estimates of  $f$  for MDR are more heterogeneous than those for isoniazid resistance, ranging from  $f > 1$  in Estonia (24) and South Africa's Western Cape (29), through  $f \approx 1$  in Brazil (30), to  $f \ll 1$  in South African gold mines (31) and Mexico (32) (Fig. 3A). MDR fitness appears to be linked to the quality of treatment: Overall cure rates for TB patients were 86% on the gold mines (31) and 75% in Mexico (32), but under 65% in Estonia (11). In the Western Cape, only 57% of MDR patients complied with prescribed treatment (33). After more than 20 years of joint isoniazid and rifampicin use, the median global MDR rate remains at only 1% (10). This is the rate predicted for  $f \approx 0.3$ , which may mean that relative fitness is typically at the lower end of the range shown here (Fig. 3B) (34). For  $f \geq 1$ , we expect resistance to spread much more quickly, leading to MDR rates among new cases that could exceed 10% within 20 years as seen, for example, in Estonia.

In sum, there is presently no strong evidence that disparate parts of the world with high resistance rates have been invaded by an MDR superbug with intrinsically high fitness. The more parsimonious explanation for locally high rates of MDR is that primary TB control has failed and that patients carrying bacteria of all kinds, drug-sensitive and drug-resistant, have been subjected to many years of poor treatment.

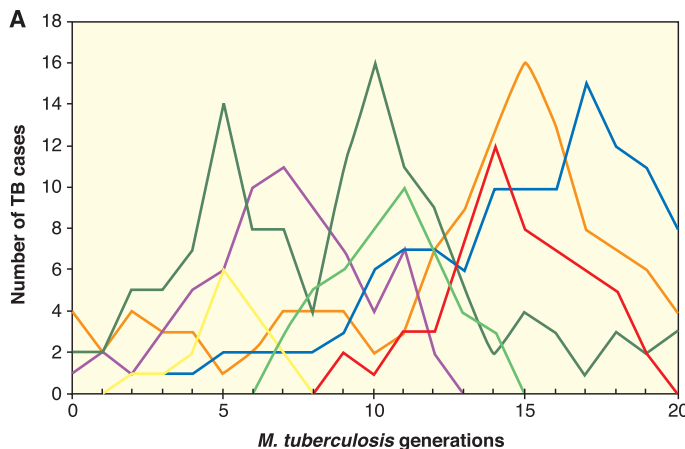
### Successes and Failures in the Management of Resistance

In comparisons across countries, the MDR rate among previously untreated cases is inversely correlated with treatment success under SCC (8). The most straightforward interpretation is

**Table 1.** Four criteria governing the long-term dynamics of drug-sensitive (*S*) and drug-resistant (*R*) tuberculosis.

| Condition                     | Outcomes  |                                 |
|-------------------------------|---|---------------------------------|
|                               | Number of cases   | Fraction of new cases resistant |
| $R_{OS} < 1, R_{OR} < 1$      | Extinction of <i>S</i> and <i>R</i>   | Rising, falling, or steady      |
| $R_{OS} > 1 > R_{OR}$         | Coexistence of <i>S</i> and <i>R</i> ; <i>R</i> persists only with <i>S</i>                     | Rising, then steady             |
| $R_{OS} > R_{OR} > 1$         | Coexistence of <i>S</i> and <i>R</i> ; <i>R</i> persists in self-sustaining transmission cycles | Rising, then steady             |
| $R_{OR} > R_{OS}, R_{OR} > 1$ | Extinction of <i>S</i> ; <i>R</i> persists in self-sustaining transmission cycles               | Rising to fixation              |

**Fig. 2. (A)** Random genetic drift of hypothetical *M. tuberculosis* strains. We assume that each TB case has the potential to generate  $m$  new cases in the next generation, where  $m$  is chosen from a Poisson distribution with mean  $R_0$ . Of these  $m$  cases,  $n$  are randomly selected so as to keep the total number of cases constant. At each round of reproduction, any of the  $m$  cases will mutate to become a new strain with probability  $\sigma$ . The graph shows the dynamics of selected strains, generated with  $R_0 = 2$ ,  $\sigma = 0.1$ , and  $n = 100$ . Without any directional selection ( $f = 1$  on average for all genotypes), strains come and go with a mean life expectancy of 3.8 generations. **(B)** Most strains survive for less than the mean period, but some survive very much longer.



that high cure rates have prevented the emergence of resistance in countries that have made effective use of SCC. It is well known that cure rates over 90% can be achieved under SCC; if few patients fail treatment, fewer still can develop resistance. The efficacy of SCC is little compromised by resistance to isoniazid alone, even under conditions of routine treatment (15, 16). National control programs that have consistently cured a high proportion of patients for many years also report consistently low rates of resistance. Algeria, Chile, China (Beijing), Cuba, and Uruguay, which typically achieve cure rates around or above 80%, have reported average MDR rates of under 1% in surveys carried out since 1976 (10, 35). Conversely,

high rates of resistance tend to be associated with low treatment success. In Ivanovo oblast, Russia, the reported treatment success for patients carrying fully sensitive strains is 63% (14); with a cure rate this low, it is not surprising that 9% of new TB cases are MDR (15).

As well as preventing the emergence of MDR, best-practice SCC may also be able to eliminate MDR epidemics. Observations from the Republic of Korea and Hong Kong point in that direction. In both places, control programs have relied substantially on high-quality SCC. In Korea, treatment failures have been cut by half since 1980 (36, 37). The proportion (and number) of all drug-resistant cases has been falling since 1980, and the MDR rate in new

cases has remained persistently under 2.5%. In Hong Kong, the proportion of cases resistant to any drug has been declining at an average of 3.0% per year for the past 15 years (Fig. 4) (38). Remarkably, the MDR rate has been falling more than twice as fast, at 7.5% per year. This has happened without any reduction in the overall incidence of TB. The implication is that the case reproduction number of drug-resistant TB has been lower than that of drug-sensitive TB and that for MDR is still lower. Hong Kong appears to be eliminating MDR by focusing on the essential elements of TB control. It seems unlikely that the use of second-line drugs, mainly by private practitioners, can explain the principal trends in resistance, but that remains unproven.

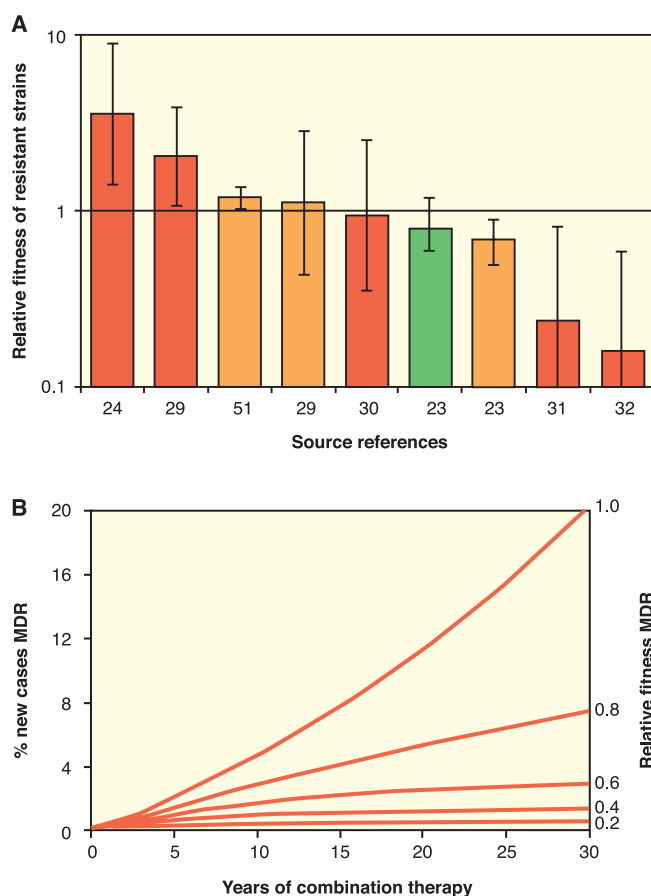
Undoubtedly, the most vigorous program of resistance management was undertaken by New York City in response to a major MDR epidemic beginning in the mid-1980s. The number of new MDR cases peaked at 441 in 1992 and then fell at over 35% annually as a result of measures, including the control of nosocomial infection, SCC backed by second-line drugs, and DOT to encourage patients to complete therapy. The New York MDR epidemic could be contained relatively quickly, not only because of the aggressive control measures introduced in 1992, but also because the majority of cases arose from the recent infection of HIV-positive individuals in a small number of hospitals (39). Endemic tuberculosis, where a high proportion of cases arise from long-standing infection, cannot be so easily eliminated. This is a powerful argument for prompt intervention during MDR epidemics to prevent the buildup of a reservoir of MDR infection.

### Investing in MDR Control

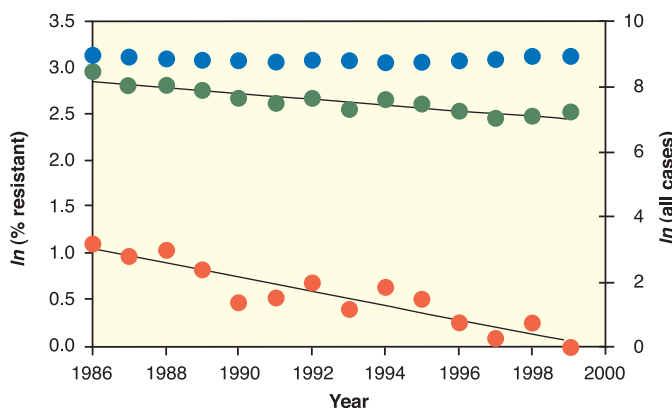
Although SCC appears to be successfully containing resistance in some parts of the world, it is happening with cure rates for MDR patients of no more than 60%. This is unsatisfactory on clinical grounds because higher cure rates are possible, albeit with more complex treatment regimens and at far greater expense (40). It is also unsatisfactory on epidemiological grounds because higher cure rates would reduce MDR incidence more quickly. More investment will buy better results, so program managers must decide how much they are willing and able to spend on treatment.

One approach to resource allocation is to look, among available options, for the strategy that is most cost-effective, subject to costs being below the maximum tolerable and cure rates exceeding the minimum acceptable. The right choice for most settings is not yet obvious because costs are in flux (41), and the efficacy of second-line regimens is poorly understood. One pilot scheme in Peru provides a standardized regimen including second-line drugs for patients that have repeatedly failed treatment with first-line drugs and that are likely to be

**Fig. 3.** Reproductive fitness and its epidemiological consequences. (A) Estimated relative fitness of isoniazid resistant (orange) and MDR strains (red), and strains carrying the AA315 mutation linked to isoniazid resistance (green), as compared with fully sensitive strains. Two estimates were made from studies of contacts (30, 51), and the others were from studies of genotype clustering (23, 24, 29, 31, 32, 52). (B) Consequences of different, hypothetical fitness levels for the spread of MDR. The effect of fitness on the spread of drug resistance is nonlinear; MDR increases much more quickly when  $f$  grows above roughly 0.5, the point at which  $R_{DR}$  exceeds 1 in this model.



**Fig. 4.** Trends in the frequency of all resistant (green) and MDR (red) cases, as compared with the total number of reported TB cases (blue) in Hong Kong (38). The frequency of resistance is in long-term decline, and MDR cases are being eliminated relatively quickly.





MDR. Of the first 466 patients, 89% completed treatment. The cure rate for patients that would otherwise have been incurable is 48%, at a cost of US\$200 to \$500 per year of healthy life saved (42). It will be for the Peruvian authorities to put these results in the broader context of health spending, but the program appears to be affordable and comparatively good value for money.

## Conclusions

It is highly likely that standard short-course chemotherapy (SCC), based on a combination of cheap and safe first-line drugs, can prevent the buildup of resistance in a population of patients in which most carry drug-sensitive TB. One outstanding epidemiological question is whether first-line drugs alone can defeat MDR by reducing the number of cases (or better still the proportion of MDR) through time. The data we have now suggest that they can. Laboratory experiments have often found resistant strains to be less virulent than sensitive strains. Genotype clustering studies suggest that drug-resistant strains have low relative fitness under efficient chemotherapy. Long-term trends in case notifications indicate that MDR can be contained without extensive use of second-line drugs. And, on a broad geographical scale, there is no evidence that the spread of MDR has been exacerbated by HIV.

But the evidence to support these conclusions is not yet incontrovertible. The facts about virulence are predominantly for strains resistant to isoniazid, and we cannot discount the possibility that some MDR strains (e.g., those in the Beijing family) under some circumstances (e.g., crowded prisons and hospital AIDS wards) are intrinsically more virulent or transmissible than others. The downward trends in resistance seen in the Republic of Korea and Hong Kong could turn out to be exceptional and might have been assisted by second-line drugs. And it is not entirely certain that Africa will remain relatively unburdened by MDR. Warnings to the contrary come from Mozambique and Côte d'Ivoire, where more than 3% of new cases are MDR (10, 14).

Our emphasis on the potential effectiveness of first-line drugs is not an argument against the use of more complex or more expensive regimens. Second-line drugs must be part of the long-term solution, and there is a strong case to be made for introducing them sooner rather than later where MDR rates are very high, preferably under the auspices of an international monitoring body such as the Green Light Committee (41).

Nor is it to suggest that we can relax efforts to develop new vaccines, drugs, and diagnostics. Rather, it is to stress that far more can be achieved with SCC. It is vital to remember that 97% of new TB cases are not MDR; most patients can be cured with first-line therapy, and yet most are still not

receiving it (11). Putting in place the basic package for TB control remains the highest priority globally, to be followed by accurate drug susceptibility testing and the careful addition of second-line drugs guided by affordability, cost-effectiveness, and feasibility. The facts at hand portray MDR as a problem that has become locally severe after years of mismanagement. In most parts of the world, there is time for a measured and targeted response.

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28. Epidemiological data provide information about populations of TB cases, rather than populations of bacteria. Absolute fitness can be expressed as the basic case reproduction number,  $R_0$ , of sensitive (S) or resistant cases (R), where  $R_0$  defines the rate of spread through a population previously unexposed to TB (43); relative fitness,  $f$ , is the ratio of  $R_0$ 's for resistant and sensitive types. Variation in strain fitness, and hence  $R_0$ , is expected because there are different genetic mechanisms underpinning resistance (44) among other traits (45), and these could impose different fitness costs, affecting virulence and transmissibility. Further variation is expected because of the way in which drugs are used: Adherence to recommended regimens will shorten the duration of infectiousness, but incomplete treatment can enhance transmission by generating chronically infectious disease. We expect  $R_{OR} < R_{OS}$  in the absence of treatment because resistant strains are commonly (but not always) less virulent in vitro and in experimental animals (79) and did not become common before drugs were available. However, if drugs are misused, this inequality could be reversed. The calculation of  $R_0$  for *M. tuberculosis* has various complications (46, 47). Best estimates for untreated, fully sensitive disease lie in the region of 2 (34);  $R_0$  will usually be lower if patients are treated, and  $R_{OR}$  will be below the threshold for epidemic spread if  $f < 1/2$ . In practice, we estimate  $f$  by comparing the numbers of secondary cases arising by transmission from drug-sensitive or drug-resistant primary or index cases. One method uses the results of genotype clustering studies. A cluster is defined as two or more cases having the same genetic fingerprint, most commonly the same spoligotype or RFLP type (48). One member of the cluster is assumed to be the index case. By counting the number of sensitive (S) and resistant (R) cases that appear singly (N) or in clusters (C), relative fitness can be estimated from the odds ratio  $f = (C_r/N_r)/(C_s/N_s)$  (34). Although clustering is assumed to reflect transmission, it may not reflect recent transmission because patients carrying the same genotype are often widely dispersed and apparently unconnected epidemiologically. A single cluster may include both sensitive and resistant strains, implying that resistance has been acquired without any change to the genetic marker under observation (49). Careful analysis is needed to exclude the possibility that resistance has been acquired since transmission (50) by testing patients for drug susceptibility before treatment. A different approach is to start with putative contacts of resistant and sensitive cases. After counting all the primary cases (S', R') and the secondary (S'', R'') cases arising from them, relative fitness is calculated from  $f = (R''/R')/(S''/S')$ . We can be confident that a second TB case found, after an incubation period, in the same household as a first case did indeed acquire infection from that primary case. However, the origin of cases among casual contacts is usually less clear and should be confirmed by genetic fingerprinting. Neither of these methods can, on its own, determine whether fitness differences are due to variation in virulence, transmissibility, or treatment practices. There is one further dilemma:  $f$  should be measured close to the start of an epidemic when the case reproduction number is close to its maximum value of  $R_0$ , and yet long-term genetic drift may prohibit accurate estimation of  $f$  from observations made over just a few transmission cycles (Fig. 2).
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