Round Table

Controlling multidrug-resistant tuberculosis and access to expensive drugs: a rational framework

Ariel Pablos-Méndez,[1, 2] Deepthiman K. Gowda,[1] & Thomas R. Frieden[3]

Abstract The emergence and spread of multidrug-resistant tuberculosis (MDR-TB), i.e. involving resistance to at least isoniazid and rifampicin, could threaten the control of TB globally. Controversy has emerged about the best way of confronting MDR-TB in settings with very limited resources. In 1999, the World Health Organization (WHO) created a working group on DOTS-Plus, an initiative exploring the programmatic feasibility and cost-effectiveness of treating MDR-TB in low-income and middle-income countries, in order to consider the management of MDR-TB under programme conditions. The challenges of implementation have proved more daunting than those of access to second-line drugs, the prices of which are dropping.

Using data from the WHO/International Union Against Tuberculosis and Lung Disease surveillance project, we have grouped countries according to the proportion of TB patients completing treatment successfully and the level of MDR-TB among previously untreated patients. The resulting matrix provides a reasonable framework for deciding whether to use second-line drugs in a national programme. Countries in which the treatment success rate, i.e. the proportion of new patients who complete the scheduled treatment, irrespective of whether bacteriological cure is documented, is below 70% should give the highest priority to introducing or improving DOTS, the five-point TB control strategy recommended by WHO and the International Union Against Tuberculosis and Lung Disease. A poorly functioning programme can create MDR-TB much faster than it can be treated, even if unlimited resources are available.

There is no single prescription for controlling MDR-TB but the various tools available should be applied wisely. Firstly, good DOTS and infection control; then appropriate use of second-line drug treatment. The interval between the two depends on the local context and resources. As funds are allocated to treat MDR-TB, human and financial resources should be increased to expand DOTS worldwide.

Keywords Tuberculosis, Multidrug-resistant/drug therapy/epidemiology/history; Antitubercular agents/therapeutic use/economics; Treatment outcome; Developing countries (*source: MeSH, NLM*).

Mots clés Tuberculose résistante à la polychimiothérapie/chimiothérapie/épidémiologie/histoire; Antituberculeux/usage thérapeutique/économie; Evaluation résultats traitement; Pays en développement (*source: MeSH, INSERM*).

Palabras clave Tuberculosis resistente a multidrogas/quimioterapia/epidemiología/historia; Agentes antituberculosos/uso terapéutico/economía; Resultado del tratamiento; Países en desarrollo (*fuente: DeCS, BIREME*).

Bulletin of the World Health Organization 2002;80:489-500.

Voir page 493 le résumé en français. En la página 493 figura un resumen en español.

Introduction

The emergence and spread of multidrug-resistant tuberculosis (MDR-TB) could threaten global TB control. The treatment of patients with MDR-TB is prolonged, expensive and often unsuccessful (*1*, *2*). Many experts assert that standard TB control prevents the emergence of MDR-TB in a cost-effective way (*3*). Others argue that it is unethical to abandon patients with MDR-TB and maintain that, if untreated, MDR-TB strains will become dominant and undermine TB control in future generations (*4*). These arguments are of particular consequence in settings where resources are scarce. While additional evidence would help to define the right point between efficiency and equity, we propose a preliminary rational framework for addressing the problem of MDR-TB in various circumstances.

Genesis and magnitude of multidrug-resistant TB

Treatment with only one effective drug, because of inappropriate prescription or poor adherence, suppresses the growth of organisms susceptible to it but permits the multiplication of isolated strains with spontaneous drug-resistance mutations. This phenomenon is called acquired drug resistance. Subsequent transmission leads to TB disease in new patients which is drug-resistant at the outset, a phenomenon known as primary resistance (*5*). Independent, cumulative events result in MDR-TB, defined as resistance to at least isoniazid and rifampicin. Both the creation and the transmission of drug resistance contribute to its incidence.

[1] College of Physicians and Surgeons, Columbia University, New York, USA.

[2] The Rockefeller Foundation, New York, USA. Correspondence should be addressed to Dr Pablos-Méndez, The Rockefeller Foundation, 420 Fifth Avenue, 21st Floor, New York, NY 10018, USA (email: ap39@columbia.edu).

[3] Department of Health, New York City, USA.

Ref. No. **02-0027**

Resistance to TB drugs emerged soon after their introduction 50 years ago (*6*). A survey conducted by the International Union Against Tuberculosis and Lung Disease in 17 countries during the late 1950s found primary resistance of 3.7% for streptomycin, 3% for isoniazid, and 1% for both drugs together (*7*). Clinical outcomes were poorer with dual resistance (analogous to MDR-TB today), but the problem was deemed unimportant because it accounted for only a small proportion of treatment failures (*8*). Furthermore, clinical trials demonstrated that standard treatment without routine baseline testing for drug susceptibility produced outcomes similar to those obtained where such testing was applied and individualized treatment was given (*9*). The introduction of rifampicin in the early 1970s brought about ambulatory short-course chemotherapy, a regimen of three or four drugs including rifampicin for at least the first two months, given over six to nine months (*10*). This reinforced hopes for the elimination of TB.

By the early 1990s the incidence of TB had increased in the USA (*11*), following reductions in control programmes associated with the HIV epidemic, growing poverty, and homelessness (*12*). Poor adherence to recommended treatment regimens by doctors and patients fostered high levels of MDR-TB (*13*). MDR-TB came to widespread attention with the occurrence of nosocomial and prison outbreaks (*14*). High case-fatality rates (*15*) and cases of MDR-TB among health care workers and others (*16*) led to an increase in public concern (*17*). WHO declared TB a global emergency in 1993, focusing on developing countries where 95% of cases occurred (*18*).

Although MDR-TB was one of many concerns in global TB control, there were no data on the magnitude of the problem. For this reason, WHO and the International Union Against Tuberculosis and Lung Disease began the Global Project on Anti-tuberculosis Drug Resistance Surveillance in 1994. A network of supranational reference laboratories provided quality control for drug susceptibility-testing (*19*). It emerged that the prevalence of multidrug resistance among new patients was generally low, the median value being 1%, especially in Africa. However, several hot spots, i.e. countries or regions where the prevalence of multidrug resistance among new TB patients exceeded 3%, were identified, particularly in the former Soviet Union (*20*). Drug resistance was found in all 72 countries surveyed by 2000 (*21*).

International response to growing problem of multidrug-resistant TB

Because of the low prevalence of multidrug resistance in most countries, WHO stressed basic TB control as the priority for the prevention of MDR-TB in low-income countries (*20*). The world body did not advocate treatment against MDR-TB on a large scale but recommended that individual patients with MDR-TB be referred to clinical experts (*22*). The reasons for these recommendations included: i) uncertainties about the risk posed by MDR-TB and the rapidity of its spread; ii) the high costs and poor results of treatment in patients with chronic MDR-TB before the 1990s (*23*); and iii) the potential diversion of resources to MDR-TB instead of expanding the DOTS strategy (the TB control strategy recommended by WHO and the International Union Against Tuberculosis and Lung Disease) (*24*).

The scenario changed in the second half of the 1990s. In New York City, individualized chemotherapy based on drug susceptibility-testing became nearly as effective in new patients with MDR-TB as in those with drug-susceptible TB (*25*) and the number of MDR-TB cases decreased by more than 90% during the decade (*26*). The relatively large number of cases in rich countries made second-line drugs (amikacin, kanamycin, capreomycin, cycloserine, para-aminosalicylic acid (PAS), ethionamide, and the fluoroquinolones) more available and affordable. Yet questions remained about which interventions had led to New York City's success, and about the need, feasibility and cost-effectiveness of this approach in countries with fewer resources.

A pilot project involving community-based treatment of MDR-TB in northern Lima, Peru, challenged the status quo (*27*): it was shown that it was possible to cure MDR-TB on an outpatient basis in a country where TB was endemic. Advocates of individualized treatment for the control of MDR-TB argued that empirical short-course chemotherapy regimes could amplify the problem of MDR-TB in patients already infected with strains resistant to one or more drugs (*27*). The human rights of patients dying with MDR-TB in Russian prisons were highlighted (*28*). The spectre of an explosive, transnational epidemic of MDR-TB was raised, and the price of inaction became a subject of intense debate.

In 1999, WHO created a working group on "DOTS-Plus for multidrug-resistant tuberculosis" to address the management of MDR-TB under programme conditions (*29*). This initiative seeks to assess the feasibility and cost-effectiveness of treating MDR-TB in low-income and middle-income countries (*30*). Several pilot projects, using different management and therapeutic strategies, are under way (*31*). DOTS-Plus has already successfully negotiated a 90% price reduction for selected projects with the pharmaceutical industry (*32*).

Significance of multidrug-resistant TB

MDR-TB is still infrequent in most countries. Its global prevalence in new patients remains below 2% (*20*, *21*), decades after the introduction of tuberculosis drugs. Increases, although rapid in outbreak settings with immunocompromised people, e.g. those affected by AIDS or malnutrition, have generally been gradual (*21*). On the other hand, in hot spots in Eastern Europe and elsewhere the levels of MDR-TB are alarming (*20*, *21*).

While some strains of MDR-TB have caused large outbreaks, recent analyses based on molecular epidemiology suggest that they are, on average, less infectious than drug-susceptible organisms (*33*, *34*). Genetic mutations that confer a survival advantage in the presence of an environmental factor may become a functional burden in the absence of such selective pressure (*35*). The selection factor for MDR-TB is inadequate drug treatment (*12*), which is prevented by directly observed therapy (*36*). Thus, even in the absence of widespread treatment of MDR-TB, the prevalence of the latter does not necessarily increase (*37*).

After TB control was strengthened in New York City the number of MDR-TB cases fell much faster than the total number of TB cases (*26*). Similarly, during the 1960s in Kolin, then in Czechoslovakia, the number of chronic cases fell ten times faster than new TB cases (*38*). While second-line drugs were used in those instances, strains that were virtually pan-resistant also disappeared and declines in MDR-TB were achieved with standard short-course chemotherapy (*39*). With

DOTS in place, curing MDR-TB appears to accelerate such trends, with a time-limited increase in costs.

Globally, an estimated 20% of patients with TB default or fail to respond to therapy (*40*) but less than 2% have MDR-TB. The vast majority of patients who are not successfully treated do not have MDR-TB (Fig. 1), even in hot spots, indicating failure to ensure that drugs are taken properly. This represents inadequacy in the implementation of basic DOTS programmes more than failure in the drugs themselves.

Furthermore, a poorly functioning programme can create MDR-TB much faster than it can be treated, even if unlimited resources are available. MDR-TB results from poor TB management, i.e. inadequate drug treatment followed by lapses in infection control (*41*), and its prevalence is up to ten times higher in previously treated patients than in new patients (*20*). The highest priority in stopping MDR-TB must therefore be its prevention. The establishment of DOTS programmes has been shown to reduce the development of MDR-TB in addition to cutting TB mortality by 70% (*42*).

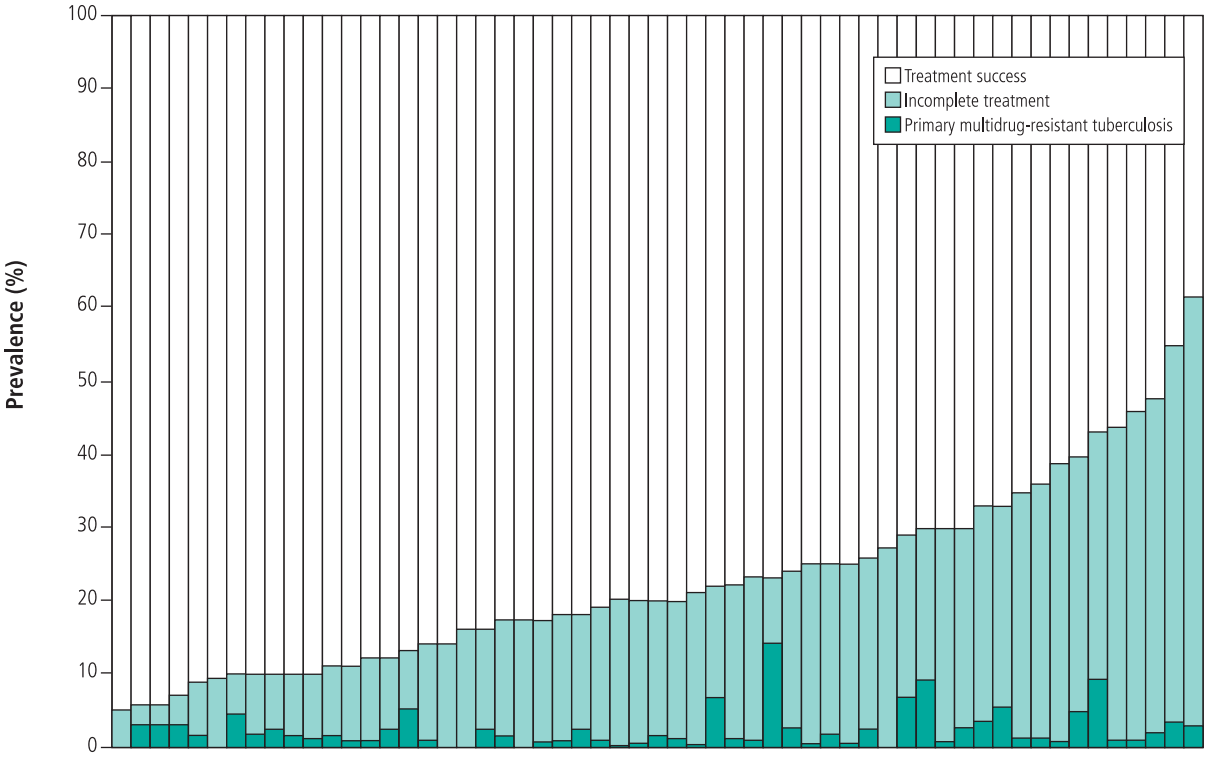
The programme benefits of treatment against MDR-TB are being evaluated. The costs are substantial. Such treatment requires the administration of drugs that are more toxic and less effective and are given for at least three times as long and at 100 times the cost of basic short-course chemotherapy regimens (*22*). TB control programmes could spend over 30% of their budgets on less than 3% of their cases. Cost-effectiveness analyses are needed before treatment against MDR-TB is implemented in national programmes.

Susceptibility-testing for second-line anti-TB drugs has not been standardized and has yet to be systematically evaluated for individual clinical management in developing countries. In a community with a true prevalence of MDR-TB of 3%, a laboratory with an average drug susceptibility-testing specificity for rifampicin of 98% and a sensitivity of 96% would report a prevalence of 4.8%, but one-third of patients reported as having MDR-TB would not have it. Widespread testing and treatment of MDR-TB might subject some patients without it to unnecessary expense and toxicity.

The DOTS strategy, developed and field-tested during the 1970s and 1980s, was not designed to cure patients with MDR-TB, especially those with chronic disease (*2*). However, DOTS can prevent MDR-TB from becoming a serious problem in a population. This has been demonstrated in Benin, Cuba, the Czech Republic, and Kenya, where MDR-TB is virtually non-existent (*20*). It is also possible that DOTS can reduce MDR-TB once it has occurred; in Burkina Faso (*39*), Hong Kong (China) (*37*), Chile, Sierra Leone, and Uruguay, MDR-TB is rare and decreasing (*21*).

Worldwide, less than one-third of patients with TB are treated in DOTS programmes (*40*). At most, half the estimated number of patients with TB are officially detected and barely 60% of these complete treatment (*40*). From a global public

Fig. 1. **Disconnect between the prevalence of multidrug-resistant tuberculosis and treatment outcomes among new patients in various tuberculosis programmes**



Each bar corresponds to a country or area surveyed. The prevalence of primary multidrug-resistant tuberculosis in 57 areas or countries (1994–99) averages 1% and the majority of new tuberculosis cases failing to complete treatment do not have multidrug-resistant tuberculosis. Excluded are countries without data on prevalence of primary multidrug resistance (Australia, Belgium, Canada, Israel) or treatment completion rates (Colombia, England, Finland, France, Germany, Scotland, Swaziland), as well as countries with laboratory specificity for rifampicin resistance of less than 95% (China (Henan Province), Slovak Republic, South Africa).

Source: data for graph obtained from the WHO / International Union Against Tuberculosis and Lung Disease Global Project on Anti-tuberculosis Drug Resistance (*20, 21*).

WHO 02.74

health perspective, therefore, the top priority should be the expansion of DOTS. In individual countries or parts of countries, however, additional strategies may be appropriate. In settings where there are large outbreaks of MDR-TB an intensive approach, including infection control, is essential.

Rational strategy for controlling multidrug-resistant TB

On the basis of data from the WHO/International Union Against Tuberculosis and Lung Disease surveillance project (*21*), Fig. 2 groups countries according to the proportion of TB patients completing treatment successfully and the level of MDR-TB among previously untreated patients. Specific cut-points for what constitutes good clinical outcomes and high levels of MDR-TB have not been empirically validated (*43*). The resulting matrix provides a reasonable framework for deciding whether to implement treatment against MDR-TB. Since approximately 70% of new cases of MDR-TB occur in only 10 countries a global strategy could emerge while individual countries take appropriate action.

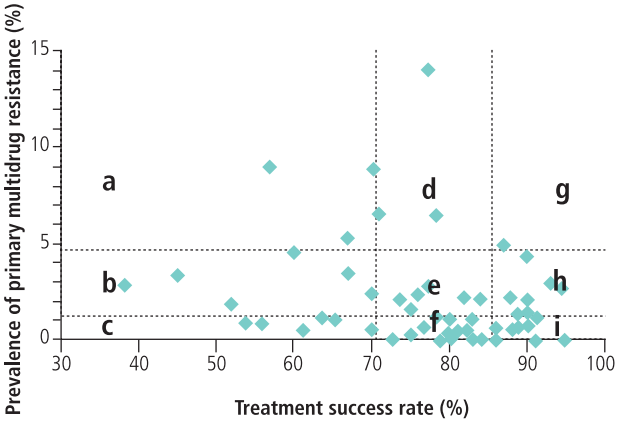
Countries in which the treatment success rate, i.e. the proportion of new patients who complete the scheduled treatment whether bacteriological cure is documented or not, is less than 70% (Fig. 2, quadrants a, b, and c) should give top priority to the introduction or improvement of the DOTS programme. Second-line drugs should not be widely available in such settings. Similarly, in countries with multidrug resistance levels below 1.5% (c, f, i) the treatment of MDR-TB is not a priority, although it could be undertaken on individual clinical grounds with appropriate laboratory support. This category would include most African countries, where it is more important to expand DOTS and to consider interventions to limit the impact of HIV on TB.

Notably, quadrant g is empty: almost no country with treatment success above 85% has a rate of primary MDR-TB above 5%. Countries in quadrant h with intermediate levels of multidrug resistance and achieving more than 85% treatment success, generally countries where DOTS has been well implemented in recent years, are prime locations for DOTS-Plus programmes. A good laboratory and directly observed therapy are essential for the avoidance of patient misclassification and the selection of resistance to second-line drugs. In these few countries, resource mobilization and international assistance for the treatment of MDR-TB is justified.

Countries or regions in the middle of the grid (quadrant e) would benefit from additional evidence. Resource-rich countries in this category would generally offer treatment for patients with MDR-TB. In resource-poor countries, where national programmes can barely afford DOTS, nongovernmental organizations could provide assistance in the implementation and evaluation of DOTS-Plus pilot projects.

The hot spots with multidrug resistance levels above 5% (a, d) represent international public health emergencies. The countries concerned cannot administer individualized treatment against MDR-TB without creating even more drug resistance. If a programme cannot deliver two to four non-toxic drugs for six to nine months after sputum smear microscopy has been performed, the delivery of five to eight drugs that are often toxic for 18–30 months with culture and first-line and second-line drug susceptibility-testing is nearly impossible. Such settings require a complete overhaul of control activities and outbreak control operations, and coordinated, intensive and sustained international assistance.

Fig. 2. **Rational framework for targeting multidrug-resistant tuberculosis in different settings**



The scattered situation of tuberculosis control in various settings calls for different approaches to multidrug-resistant tuberculosis (see text for explanations on areas a to i).

Source: data for graph obtained from the WHO / International Union Against Tuberculosis and Lung Disease Global Project on Anti-tuberculosis Drug Resistance (*20, 21*).

WHO 02.75

The importance of infection control practices should be emphasized (*44*). Outbreaks in crowded settings such as hospitals, shelters or prisons, particularly among immunocompromised individuals (with AIDS or malnutrition), are a common denominator in MDR-TB hot spots. Ending such outbreaks was vital in turning the tide of MDR-TB in New York City (*45*) and Milan (*46*). No single intervention can control MDR-TB but the various tools available should be applied wisely: firstly, good DOTS and infection control; then second-line drug treatment. The interval between the two depends on the local context and resources.

Conclusions

At present, most national TB programmes do not need to introduce second-line anti-TB therapy in order to control the disease. Access, in this case, is a secondary question. First-line DOTS remains one of the most cost-effective of all public health strategies (*47*). Relatively simple, standardized short-course chemotherapy regimens can cure more than 90% of new TB patients and prevent transmission of the disease (*24*).

The emergence and spread of MDR-TB is a symptom of poor programme performance. In the absence of an effective TB control programme, a narrow focus on MDR-TB therapy could, paradoxically, make a bad situation worse. In countries where TB is endemic, resources spent curing a single case of MDR-TB could be used to treat 100 new TB patients. Many lives could thus be saved and the development of new MDR-TB cases could be reduced. This would be fundamentally in keeping with human rights and public health principles. Drug resistance is ubiquitous, but primary MDR-TB is still infrequent after decades of drug treatment. However, the several hot spots that have emerged require urgent attention.

The framework that we propose for dealing with MDR-TB highlights important differences in various programmes. Countries differ not only in their resources but also in matters of epidemiology and health care. The

differences may determine which strategy is most appropriate for preventing and controlling TB and MDR-TB. Formal modelling and cost-effectiveness analyses are needed in order to refine the framework, as is research on the transmissibility and overall impact of MDR-TB under programme conditions (*43*). As a recent paper put it, "the future may not be so dark" (*48*).

The DOTS-Plus initiative has led to dramatic reductions in the prices of second-line drugs. Pilot projects around the world have qualified for implementation (*49*) and can be expected to provide important guidance on the evidence-based expansion of treatment against MDR-TB. As funds are allocated for the treatment of MDR-TB in hot spots it is essential to increase human and financial resources for the expansion of DOTS worldwide. The top priority should continue to be the improvement of basic treatment programmes in order to prevent the emergence of MDR-TB. For treatment to be undertaken on a large scale it is important to reduce further the cost of second-line drugs, implement outbreak control, maintain surveillance, improve diagnostic testing, and develop new anti-TB drugs. Only a comprehensive approach, tailored to local conditions, can be expected to prevent a global epidemic of MDR-TB (*50*). ■

Acknowledgements

The authors thank Mario Raviglione, Marcos Espinal and Chris Dye for valuable comments and suggestions on an earlier version of the manuscript. The Rockefeller Foundation has provided funding for WHO's DOTS-Plus initiative. Dr Pablos-Méndez is a member of the Board of Directors of the non-profit Global Alliance for Tuberculosis Drug Development.

Conflicts of interest: none declared.

Résumé

Lutte contre la tuberculose multirésistante et accès aux médicaments coûteux : un cadre rationnel

L'émergence et la propagation de la tuberculose multirésistante, c'est-à-dire présentant une résistance à au moins l'isoniazide et la rifampicine, pourrait menacer la lutte antituberculeuse dans le monde entier. La conduite à tenir face à la tuberculose multirésistante dans des contextes de ressources limitées est controversée. En 1999, l'OMS a créé un groupe de travail sur le DOTS-Plus, une initiative explorant la faisabilité programmatique et le rapport coût-efficacité du traitement de la tuberculose multirésistante dans les pays de revenu faible à moyen, afin d'examiner la prise en charge de cette affection dans les conditions de mise en œuvre du programme. En fait, les problèmes de cette mise en œuvre se sont avérés plus ardus que ceux posés par l'accès à des médicaments de deuxième intention, dont les prix ont commencé à baisser.

A partir de données du projet de surveillance OMS/Union internationale contre la Tuberculose et les Maladies respiratoires, nous avons groupé les pays selon la proportion de malades tuberculeux ayant achevé leur traitement avec succès et la proportion de cas de tuberculose multirésistante parmi les patients n'ayant encore jamais été traités. La matrice ainsi obtenue fournit un cadre permettant de décider d'utiliser ou non des médicaments de deuxième intention dans un programme national. Les pays dans lesquels le taux de réussite du traitement – c'est-à-dire la proportion de nouveaux malades qui vont jusqu'au bout du traitement prévu, que la guérison bactériologique soit documentée ou non – est inférieur à 70 % devraient donner la priorité à l'introduction ou à l'amélioration du DOTS, la stratégie de lutte antituberculeuse en cinq points recommandée par l'OMS et l'Union internationale contre la Tuberculose et les Maladies respiratoires. Un programme défectueux peut générer une multirésistance plus vite qu'il n'est capable de la traiter, même en disposant de ressources illimitées.

Il n'existe pas de recette unique pour lutter contre la Tuberculose Multirésistante sinon une utilisation judicieuse des divers outils disponibles : tout d'abord un DOTS correctement appliqué et des pratiques de lutte contre l'infection, et ensuite le recours approprié à des médicaments de deuxième intention. L'intervalle entre ces deux phases dépendra du contexte et des ressources locaux. Lorsque des fonds sont alloués pour le traitement de la tuberculose multirésistante, il est nécessaire d'augmenter les ressources humaines et financières pour étendre l'utilisation du DOTS dans le monde.

Resumen

Control de la tuberculosis polifarmacorresistente y acceso a medicamentos costosos: un marco racional

La aparición y propagación de la tuberculosis polifarmacorresistente — es decir, la caracterizada por la resistencia a por lo menos la isoniazida y la rifampicina — podría poner en peligro el control de la tuberculosis a nivel mundial. Hay opiniones discrepantes respecto a la mejor manera de hacer frente a la tuberculosis polifarmacorresistente en los entornos con recursos muy limitados. En 1999 la OMS creó un grupo de trabajo sobre la DOTS-Plus, una iniciativa que analiza la viabilidad programática y la costoeficacia del tratamiento de la tuberculosis polifarmacorresistente en los países de ingresos bajos y de ingresos medios, a fin de considerar el tratamiento de la tuberculosis polifarmacorresistente en el marco de las condiciones de los programas. Los problemas de ejecución han resultado ser más desalentadores que los asociados al acceso a los medicamentos de segunda línea, cuyos precios están disminuyendo.

Usando datos del proyecto de vigilancia de la OMS/Unión Internacional Contra la Tuberculosis y las Enfermedades Pulmonares, hemos agrupado a los países según la proporción de enfermos tuberculosos que terminan el tratamiento con éxito y según el nivel de tuberculosis polifarmacorresistente entre los pacientes no tratados con anterioridad. La matriz resultante brinda un marco razonable para decidir si conviene usar medicamentos de segunda línea en un programa nacional. Los países en los que la tasa de éxito terapéutico — esto es, la proporción de nuevos pacientes que terminan el tratamiento previsto, esté o no documentada la curación bacteriológica — es inferior al 70% deberían asignar la máxima prioridad a la introducción o la mejora de la DOTS, la estrategia de cinco puntos para el control de la tuberculosis recomendada por la OMS y la Unión Internacional contra la Tuberculosis y las Enfermedades Pulmonares. Un programa mal ejecutado puede

generar tuberculosis polifarmacorresistente a un ritmo muy superior al de su tratamiento, aun con recursos ilimitados.

No hay una receta única para combatir la tuberculosis polifarmacorresistente, pero es preciso aplicar juiciosamente las diversas herramientas disponibles. En primer lugar, hay que aplicar bien el DOTS para controlar la infección; y a continuación debe aplicarse debidamente el tratamiento farmacológico de segunda línea. El intervalo entre los dos dependerá del contexto y de los recursos locales. Al tiempo que se asignen fondos para tratar la tuberculosis polifarmacorresistente, deberán aumentarse los recursos humanos y financieros para ampliar la estrategia DOTS a nivel mundial.

References

1. Iseman MD. Treatment of multidrug-resistant tuberculosis. *New England Journal of Medicine* 1993;329:784-91.
2. Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcome in six countries. *JAMA* 2000; 283:2537-45.
3. Chaulet P, Raviglione M, Bustreo F. Epidemiology, control and treatment of multidrug-resistant tuberculosis. *Drugs* 1996;52 Suppl 2:103-8.
4. Farmer P, Becerra M, Kim J, editors. *The global impact of drug-resistant tuberculosis.* Boston, (MA): Harvard Medical School and Open Society Institute; 1999.
5. World Health Organization / International Union Against Tuberculosis and Lung Disease. Guidelines for surveillance of drug resistance in tuberculosis. *International Journal of Tuberculosis and Lung Disease* 1998;2:72-89.
6. Crofton J, Mitchison DA. Streptomycin resistance in pulmonary tuberculosis. *British Medical Journal* 1948;2:1009-15.
7. Crofton J. Tuberculosis undefeated. *British Medical Journal* 1960;ii:679-87.
8. WHO Expert Committee on Tuberculosis. Working paper, Ninth Session of the WHO Secretariat. Geneva: World Health Organization; 1973. Unpublished document TB/WP/73.7.
9. Hong Kong Tuberculosis Treatment Services — British Medical Research. A study in Hong Kong to evaluate the role of pretreatment susceptibility tests in the selection of regimens of chemotherapy for pulmonary tuberculosis. *American Review of Respiratory Disease* 1972;106:1-22
10. Fox W, Mitchison DA. Short-course chemotherapy for pulmonary tuberculosis. *American Review of Respiratory Disease* 1975;ii:325-53.
11. Jereb JA, Kelly GD, Dooley SW, Cauthen GM, Snider DE. Tuberculosis morbidity in the United States: final data, 1990. *Morbidity and Mortality Weekly Report* 1992;4023-7.
12. Brudney K, Dobkin J. Resurgent tuberculosis in New York City: human immunodeficiency virus, homelessness, and the decline of tuberculosis control programs. *American Review of Respiratory Disease* 1991;144;745-9.
13. Frieden TR, Sterling T, Pablos-Méndez A, Kilburn JO, Cauthen GM, Doodley SW. The emergence of drug-resistant tuberculosis in New York City. *New England Journal of Medicine* 1993;328:521-6.
14. Centers for Disease Control and Prevention. Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected persons — Florida and New York, 1988-1991. *Morbidity and Mortality Weekly Report* 1991;40: 585-91.
15. Pablos-Méndez A, Sterling TR, Frieden TR. The relationship between delayed or incomplete treatment and all-cause mortality in patients with tuberculosis. *JAMA* 1996;276:1223-8.
16. Pearson ML, Jereb JA, Frieden TR, Crawford JT, Davis BJ, Dooley SW, et al. Nosocomial transmission of multi-drug resistant *Mycobacterium tuberculosis*: a risk to patients and health care workers. *Annals of Internal Medicine* 1992;117:191-6.
17. Centers for Disease Control and Prevention. National action plan to combat multidrug-resistant tuberculosis. *Morbidity and Mortality Weekly Report* 1992; 41:5-48.
18. Raviglione MC, Snider DE, Kochi A. Global epidemiology of tuberculosis: morbidity and mortality of a worldwide epidemic. *JAMA* 1995;273:220-6.
19. Laszlo A, Rahman M, Raviglione M, Bustreo F, WHO/International Union Against Tuberculosis and Lung Disease Network of Supranational Reference Laboratories. Quality assurance program for drug susceptibility testing of *Mycobacterium tuberculosis* in the WHO / International Union Against Tuberculosis and Lung Disease Supranational Laboratory Network: first round of proficiency testing. *International Journal of Tuberculosis and Lung Disease* 1997;1:231-8.
20. Pablos-Méndez A, Bustreo F, Laszlo A, Binkin N, Cohn D, Lambregts C, et al., for the WHO / International Union Against Tuberculosis and Lung Disease Global Working Group on Anti-tuberculosis Drug Resistance Surveillance. *Anti-tuberculosis drug resistance in the world.* Geneva: World Health Organization; 1997. Unpublished document WHO/TB/97.229. Available from: URL: http://www.who.int/gtb/publications/dritw/summary.html
21. Espinal MA, Simonsen L, Laszlo A, Boulahbal F, Kim SJ, Reneiro A, et al., for the WHO/International Union Against Tuberculosis and Lung Disease Global Working Group on Anti-tuberculosis Drug Resistance Surveillance. *Anti-tuberculosis drug resistance in the world. Report No. 2.* Geneva: World Health Organization; 2000. Unpublished document WHO/TB/2000.278. Available from: URL: http://www.who.int/gtb/publications/drugresistance/PDF/fullversion.pdf.
22. Crofton J, Chaulet P, Maher D. *Guidelines for the management of drug-resistant tuberculosis.* Geneva: World Health Organization; 1997. Unpublished document WHO/TB/96.210 (Rev.1).
23. Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh CR. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampicin. *New England Journal of Medicine* 1993;328:527-32.
24. *Framework for effective tuberculosis control.* Geneva: World Health Organization; 1994. Unpublished document WHO/TB/94.179.
25. Telzak EE, Sepkowitz K, Alpert P, Mannheimer S, Medard F, el-Sadr W, et al. Multidrug-resistant tuberculosis in patients without HIV infection. *New England Journal of Medicine* 1995;333:907-11.
26. Fujiwara PI, Cook SV, Rutherford CM, Crawford JT, Glickman SE, Kreiswirth BN, et al. A continuing survey of drug-resistant tuberculosis, New York City, April 1994. *Archives of Internal Medicine* 1997;157:531-6.
27. Farmer P, Bayona J, Becerra M, Furin J, Henry C, Hiatt H, et al. The dilemma of multidrug-resistant tuberculosis in the global era. *International Journal of Tuberculosis and Lung Disease* 1998;2:869-76.
28. Partners in Health / Harvard Medical School. Symposium on Community-based Approaches to the Treatment and Control of Multidrug-resistant Tuberculosis. Cambridge, MA: American Academy of Arts and Sciences; 4-5 April 1998.
29. Farmer P, Kim JY. Community based approaches to the control of multidrug resistant tuberculosis: introducing ''DOTS-plus''. *BM J* 1999;317:671-4.
30. WHO Working Group on DOTS-Plus for multidrug-resistant tuberculosis. Meeting on second-line anti-tuberculosis drug procurement. Cambridge, MA: 5-6 July 1999.
31. Gupta R, Arnadottir T, editors. *Guidelines for establishing DOTS-Plus pilot projects for the management of multidrug-resistant tuberculosis.* Geneva: World Health Organization; 2001.
32. Gupta R, Kim JY, Espinal MA, Caudron JM, Pecoul B, Farmer PE, et al. Responding to market failures in tuberculosis control. *Science* 2001;293: 1049-51.
33. García-García ML, Ponce-de-Leon A, Jiménez-Corona ME, Jiménez-Corona A, Palacios-Martínez M, Balandrano-Campos S, et al. Clinical consequences and transmissibility of drug-resistant tuberculosis in Southern Mexico. *Archives of Internal Medicine* 2000;160:630-6.
34. van Soolingen D, Borgdorff MW, de Haas PE, Sebek MM, Veen J, Dessens M, et al. Molecular epidemiology of tuberculosis in the Netherlands: a nationwide study from 1993 through 1997. *Journal of Infectious Diseases* 1999;180: 726-36.
35. Cohn ML, Kovitz C, Oda U, Middlebrook G. Studies on isoniazid and tubercle bacilli: the growth requirements, catalase activities, and pathogenic properties of isoniazid-resistant mutants. *American Review of Tuberculosis* 1954;70: 641-64.

36. Weis SE, Slocum PC, Blais FX, King B, Nunn M, Matney B, et al.The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. *New England Journal of Medicine* 1994;330:1179-84.
37. Kam KM,Yip CW. Surveillance of *Mycobacterium tuberculosis* drug resistance in Hong Kong, 1986–1999, after the implementation of directly observed treatment. *International Journal of Tuberculosis and Lung Disease* 2001; 5:815-23.
38. Styblo K, Dankova D, Drapela J, Galliova J, Jezek Z, Krivanek J, et al. Epidemiological and clinical study of tuberculosis in the district of Kolin, Czechoslovakia: report for the first 4 years of the study, 1961–64. *Bulletin of the World Health Organization* 1967;37:819-74.
39. Ledru S, Cauchoix B, Yameogo M, Zoubga A, Lamande-Chiron J, Portaels F, et al. Impact of short-course therapy on tuberculosis drug resistance in South-West Burkina Faso. *Tuberculosis and Lung Disease* 1996;77:429-36.
40. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC, for the WHO Global Surveillance and Monitoring Project. Global burden of tuberculosis. Estimated incidence, prevalence, and mortality by country. *JAMA* 1999;282(7):677-86.
41. Brudney K, Dobkin J. A tale of two cities: tuberculosis control in Nicaragua and New York City. *Seminars in Respiratory Infections* 1991;6:261-72.
42. Suárez PG, Watt CJ, Alarcón E, Portocarrero J, Zavala D, Canales R, et al. The dynamics of tuberculosis in response to 10 years of intensive control effort in Peru. *Journal of Infectious Diseases* 2001;184:473-8.
43. Dye D, Williams BG. Population biology criteria for the control of drug-resistant tuberculosis. *Proceedings of the National Academy of Sciences* 2000; 97:8180-5.
44. Kaye K, Frieden TR. Tuberculosis control: the relevance of classic principles in an era of acquired immunodeficiency syndrome and multidrug resistance. *Epidemiological Reviews* 1996;18:52-63.
45. Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City — turning the tide. *New England Journal of Medicine* 1995;333:229-33.
46. Moro ML, Errante I, Infuso A, Sodano L, Gori A, Orcese CA, et al. Effectiveness of infection control measures in controlling a nosocomial outbreak of MDR tuberculosis among HIV patients in Italy. *International Journal of Tuberculosis and Lung Disease* 2000;4:61-8.
47. Iseman MD, Cohn DL, Sbarbaro JA. Directly observed treatment of tuberculosis. We can't afford not to do it. *New England Journal of Medicine* 1993;328:576-8.
48. Espinal MA, Gupta R, Raviglione MC. The future may not be so dark. *International Journal of Tuberculosis and Lung Disease* 2001;5:787-8.
49. Gupta R, Espinal MA. *Progress in DOTS-Plus and the management of drug-resistant tuberculosis. Proceedings of the Meeting of the Stop Tuberculosis Working Group on DOTS-Plus for Multidrug-resistant Tuberculosis.* Geneva: World Health Organization; 25-27 January 2001. Unpublished document WHO/CDS/TB/2001.292.
50. Dye C, Williams BG, Espinal MA, Raviglione MC. Erasing the world's slow stain: strategies to beat multidrug-resistant tuberculosis. *Science* 2002;295:2042-6.

Round Table Discussion

TB control and access to second-line drugs: better model needed

Marcos A. Espinal[1] & Richard Zaleski[2]

Pablos-Méndez et al. rightly point out that multidrug-resistant tuberculosis (MDR-TB) is not a major pandemic (see pp. 489–494). However, as drug-susceptible TB is a worldwide problem, the first priority for national TB programmes should be the implementation or expansion of the DOTS strategy. MDR-TB is in most cases a sign of poor programme performance, although there may be highly virulent strains spreading rapidly. A weak national programme can do more harm than good if its main focus is the widespread introduction of second-line drugs to manage this problem.

To tackle MDR-TB Pablos-Méndez et al. propose a matrix based on two variables: treatment success for new TB cases, and prevalence of primary MDR-TB. They propose that the use of second-line drugs should be limited to countries which belong in specified quadrants according to these two variables. We find it questionable that the management of a MDR-TB, or any other disease, should be based on only two variables. We live in a world in which the control of illness calls for modern multidisciplinary approaches (*1*). We will come back to this point.

The proposal of Pablos-Méndez et al. is difficult to accept for at least two reasons. Firstly, more than two variables are needed to decide if a country should treat MDR-TB. For instance, a country may score well on treatment success, have a low number of primary MDR-TB cases but still have a high number of treatment failure cases (a variable not taken into account in the proposed model), which are likely to have MDR (*2*). Such a country may need to implement management of MDR-TB as well as DOTS, regardless of its level of primary MDR and treatment success. Furthermore, treatment success could be a very misleading variable since it is the result of cure plus treatment completion. There are some examples of poor national TB programmes having high rates of success upon completion of treatment but low cure rates.

Secondly, do we really need cut-off points to manage a disease? On what basis can we choose 5% and not, say, 3% for MDR prevalence, or 70% and not, say, 60% for treatment success? No biological, statistical or epidemiological reason is given for choosing such cut-off points. A straightforward indication of the point at which to start management of MDR-TB could be helpful, but the issue is not that simple, and other matters need to be carefully looked at when taking such a decision. The assertion that DOTS can reduce MDR-TB has not been fully proved, although it is clear that short-course chemotherapy can prevent MDR-TB. Countries that have reduced MDR-TB have also used second-line drugs and it is not clear to what extent the use of both first-line and second-line drugs have contributed to reducing MDR-TB. It is also well known that short-course chemotherapy, one of the pillars of DOTS, only cures an unacceptably low fraction of MDR-TB (*3*).

The approach suggested by Pablos-Méndez et al. needs rethinking. First of all, any model for managing MDR-TB must recognize that such a decision has to be made by the countries concerned. It will depend on several national factors, including the resources available, the epidemiological profile, the status of TB control, and ethical and humanitarian issues. Certainly an economic threshold is likely to exist. A country choosing whether to manage MDR-TB may benefit from a comprehensive multidisciplinary assessment of its situation, in order to decide if such drugs are needed or not. If the decision to go ahead is made, the path to follow should be a strategy that includes — but is not limited to — DOTS to reduce transmission of MDR *M. tuberculosis* strains.

The international community needs to pursue a feasible and cost-effective strategy to manage MDR-TB, which enables countries to offer a cure to patients (*4*). Although current evidence is limited, there are indications that treatment of

[1] World Health Organization, STOP TB Department, 1211 Geneva 27, Switzerland (email: espinalm@who.int).
[2] World Health Organization, Copenhagen, Denmark.

MDR in resource-limited setting with strong TB control programmes may be feasible and cost-effective (*5*). This information can benefit patients even in settings where MDR-TB rates are below or above the threshold proposed by Pablos-Méndez et al. ■

1. Porter J, Ogden J, Pronyk P. Infectious disease policy: towards the production of health. *Health Policy and Planning* 1999;14:322-8.
2. Sabogal I, Velarde N, Palhua M, Rodriguez F, Paredes M. Resistencia a farmacos antituberculosos en fracasos a un esquema de tratamiento primario. [Resistance to anti-TB drugs in primary treatment] In: *Tuberculosis en el Peru.* Informe 1997. Lima: Ministry of Health. p. 141-4.
3. Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, et al. Standard short-course chemotherapy for drug resistant tuberculosis. *JAMA* 2000; 283:2537-45.
4. Espinal MA, Dye C, Raviglione M, Kochi A. Rational 'DOTS-Plus' for the control of MDR-TB. *International Journal of Tuberculosis and Lung Disease* 1999;3:561-3.
5. Suaréz PG, Floyd K, Portocarrero J, Alarcón E, Rapiti E, Ramos G, et al. Feasibility and cost-effectiveness of second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. *Lancet.* In press 2002.

First requirement for control of multidrug-resistant TB: realism

Pedro Guillermo Suárez[1]

The primary cause of an uncontrolled and increasing TB epidemic worldwide is the neglect of TB control programmes. This neglect is evidenced by lack of political support, scarce financial resources, and little or no leadership. Successful programmes in both industrialized and developing countries indicate that a DOTS strategy prevents multidrug-resistant tuberculosis (MDR-TB). The timely and appropriate diagnosis and treatment of new and previously-treated TB patients is the focus in DOTS. As Pablos-Méndez et al. suggest (see pp. 489–494), a DOTS-Plus strategy is needed to control MDR-TB only after the DOTS programme has been established and is being adequately implemented.

However, besides the epidemiological and operative factors involved in implementing a DOTS-Plus strategy, there is an international debate about the ethics and humanism involved. To deny treatment to patients with MDR-TB is to violate their human rights. Experience in Peru indicates the need for sustained and long-term efforts in preventing the emergence of MDR-TB with a DOTS strategy. Only then does it become possible to treat MDR-TB by applying a DOTS-Plus strategy in the context of an efficient, sustainable and comprehensive TB control programme.

The major area of controversy in applying a DOTS-Plus strategy is about the use of standardized or individualized regimens to treat MDR-TB in countries with limited resources. In high-income countries with a low incidence of TB and sufficient financial, technical and human resources, MDR-TB treatment with individualized regimens is based on drug susceptibility tests. The feasibility of using this approach in low- or medium-income countries has not been assessed. The options for using standardized or individualized regimens for MDR-TB in these countries should be examined in pilot projects. These should obtain comparable data and have the following aims: to develop an evidence-based approach; to design and implement the most appropriate strategy according to the epidemiology and operational conditions in each country; and to be subject to rigorous evaluation by international standards. A DOTS-Plus strategy should also be based on national and international technical assistance to tackle MDR-TB.

The major components for the implementation of a DOTS-Plus strategy would then be: (i) an efficient, effective and integrated TB control programme; (ii) first-line and second-line anti-TB drugs provided free of charge to each patient with MDR-TB; (iii) drug susceptibility tests for first-line and second-line anti-TB drugs, not charged to the patients; (iv) appropriately designed regimens for MDR-TB, standardized or individualized; (v) a reporting system for data management, monitoring and evaluation of individual and aggregated data on MDR-TB cases; (vi) community-based strategies, with the participation of local governments in order to enhance adherence to the regimens; and (vii) the adequate training and organization of health professionals responsible for the care of MDR-TB patients.

Countrywide public health and political commitment to sustaining the DOTS strategy remains the most important element for implementing DOTS-Plus strategies. In reality it may be the only means of achieving MDR-TB control. ■

Multidrug-resistant TB — unexamined costs and complexities

Tim Cullinan[2]

Pablo-Méndez et al. (see pp. 489-494) touch on many problems that have to be considered carefully before even the first steps towards comprehensive control of multidrug-resistant tuberculosis (MDR-TB) can be contemplated. I will mention only three of these, and only very briefly.

The first is the administration of second-line drugs, once they have been obtained. Such slight experience as currently exists in cohort treatment of MDR-TB comes mainly from relatively controlled situations. In these places it has been possible to marshal the resources needed to ensure compliance over the long period of treatment and the management of its manifold side-effects. Even in an urban situation such as Lima, Peru, the cost of establishing the basis for ambulatory care was enormous, and those arrangements cannot yet be contemplated for the rural areas.

As the authors point out, case-holding and compliance are the major difficulties in first-line DOTS programmes and a potent cause of MDR-TB. Yet few of the situations which might qualify as MDR sites on the authors' matrix have anything like the support mechanisms in place to ensure an effective control programme. Also, control must, presumably, imply legislative regulation of the drug supply.

[1] Former Medical Director of the National Tuberculosis Control Programme, Av. Alameda los Horizontes Mz. D8-Lt.10, Urb. Los Cedros de Villa, Chorrillos, Lima, Peru (email: pgsuarez@terra.com.pe).

[2] Health Adviser, Merlin, 5–13 Trinity St. London SE1 1DB, England (email: Tim.Cullinan@merlin.org.uk).

A second issue is how countries, until now supposedly not exposed to heavy burdens of MDR-TB, discover they have problems. Many countries, especially in sub-Saharan Africa, have managed to institute effective DOTS programmes on the basis of microscopy alone. Few have culture facilities for the majority of patients, let alone the quality control mechanisms to maintain their performance. In these countries, the outcome "treatment failure" tends to play a much smaller role than elsewhere, and it is rarely subjected to further investigation. To set up culture facilities in order to investigate and treat MDR-TB would entail costs that few of these countries could contemplate.

A third difficulty, common to all too many WHO papers, is to base statements about a whole country on findings from a small, often atypical, model area. Yet the difference between a special, usually heavily funded, trial area and the rest of a country is often greater than differences between countries. With suitable caveats, such matters are not of great importance in a summary paper except that they may inhibit discussion of the potential for disease control in isolated circumstances such as prisons, displaced persons' camps etc. Such sites may meet criteria for MDR-TB control which exist nowhere else in the country and they should be considered eligible, even in isolation.

These thoughts are proffered only as an addendum to what seems to me a very useful and well-written paper. ■

DOTS-Plus in the Philippines, a high-burden country: funds needed

Thelma Tupasi[1]

Multidrug-resistant tuberculosis (MDR-TB) is a global problem requiring a global solution. The article of Pablos-Mendez et al. (see pp. 489–494) provides a rational framework for finding such a solution.

The Philippines is ranked No.7 on the list of 22 high-burden countries for TB (*1*). DOTS was introduced at the public health centres only in 1992, and treatment success was 87%. (J. Lagahid on the DOTS strategy at the Department of Health, personal communication). MDR-TB is estimated to be present in 1.5% of new cases (*2*), although a precise assessment still has to be made. These rates would put the Philippines in the "f" category on the matrix of Pablos-Méndez et al. (see p. 492) for rationalizing the control of MDR-TB. Here MDR-TB treatment is not seen as a priority of the national TB control service, but to be allowed in specialized centres with appropriate laboratory support and help from nongovernmental organizations.

Only a third of the patients who seek medical care for TB in the Philippines are treated at a public health centre. The majority are treated by private practitioners (*3*). The Makati Medical Center, a tertiary referral private hospital, established a DOTS Clinic in 1999 in the spirit of private–public collaboration in TB control (*4*). Re-treatment cases in this clinic steadily increased, and now account for 44% of the patients enrolled. Treatment success in two cohorts analysed showed a decline from 85.3% in the first year to 68.2% in the second, with a corresponding increase in failure rates from 5.6% to 10.3%. All the failures were MDR-TB among the re-treatment cases. Treatment for these MDR-TB cases, in spite of logistical constraints, was called for for clinical, public health, and socioeconomic reasons.

The transmissibility of MDR-TB, contrary to previously held beliefs, is equal to that of pan-susceptible strains (*5*). Most of our patients live in poverty, under the most adverse conditions, characterized by heavy population density and malnutrition. To leave them untreated would prolong the period of their contagiousness and increase the number of MDR-TB cases among the highly susceptible malnourished members of their community.

Despite severely limited resources, outpatient treatment was made possible for 117 patients with MDR-TB through the DOTS-Plus pilot project. Support was provided by the national TB programme of the Department of Health, the Philippines Charity Sweepstakes, and the local government unit. Results so far have been encouraging, with a 75% preliminary estimate of cure and likely cure, and 9.1% failure or likely failure, and a default rate of 7.7%. Patients who are household heads and have responded to therapy have gone back to work and are now gainfully employed.

DOTS expansion in the country, which includes harnessing the private sector to the programme, remains the priority, as this should put a stop to the generation of more MDR-TB (*6*). However, with a large segment of the population very susceptible owing to malnutrition and crowding, treatment for MDR-TB should also be pursued, in a well-supervised fashion as practised at the Makati Medical Center's DOTS-Plus pilot project. An epidemiological study of the extent of MDR-TB in the country is urgently needed, to determine whether the Philippines should be regarded as a hot spot fuelling a global pandemic. If it is, funds for DOTS-Plus are urgently needed. ■

1. Dye C, Sckheele S, Dolin P, Pathania V, Raviglione MC. The WHO Global Surveillance and Monitoring Project. Global burden of tuberculosis: estimated incidence, prevalence and mortality by country. *JAMA* 1999;282:677-86.
2. Tupasi TE, Sistla R, Co VM, Villa MLA, Quelapio MID, Mangubat NV, et al. Bacillary disease and health-seeking behavior among Filipinos with symptoms of tuberculosis: implications for control. *International Journal of Tuberculosis and Lung Diseases* 2000;4:1126-32.
3. Rivera AB, Tupasi TE, Balagtas ED, Cardano RC, Baello BQ, Quelapio MID, et al. Drug resistant tuberculosis in the Philippines. *The International Journal of Tuberculosis and Lung Disease* 1999;3:639.
4. Quelapio MID, Mira NRC, Abeleda MR, Rivera AB, Tupasi TE. Directly observed therapy – short-course (DOTS) at the Makati Medical Center. *Philippine Journal of Microbiology and Infectious Diseases* 2000;29:80-6.
5. Schaaf H, Vermeulen H, Gie R, Beyers N, Donal P. Evaluation of young children in household contact with adult multidrug-resistant pulmonary tuberculosis cases. *Pediatric Infectious Disease Journal* 1999;18:494-500
6. Dye C, Williams BG, Espinal MA, Raviglione MC. Erasing the world's slow stain: strategies to beat multidrug-resistant tuberculosis. *Science* 2002;295: 2042-6.

[1] Senior Scientist, Tropical Disease Foundation, Makati Medical Center, Manila, the Philippines (email: drcramos@info.com.ph).

Examining assumptions about multidrug-resistant TB control

Jim Yong Kim[1], Carole D. Mitnick[1], Jaime Bayona[1, 2], Ross Blank[1], Edward A. Nardell[1], Joia S. Mukherjee[1], Michael Rich[1], Paul Farmer[1, 3], Mercedes C. Becerra,[1] & Megan Murray[4]

Pablos-Méndez, Gowda, and Frieden aim to establish a "rational" base for the control of multidrug-resistant tuberculosis (MDR-TB) in resource-poor settings (see pp. 489–494). To assess the rationality of their framework, we must examine its core assumptions.

The first assumption — that strains of MDR-TB "are, on average, less infectious" — is not supported by the literature. The cluster studies referenced found that drug-susceptible TB was more likely to occur in clusters than drug-resistant TB. Nonetheless, other such studies have identified MDR-TB as a risk factor for clustering (*1*). Similarly, multiple observational reports describe the widespread dissemination of MDR clones from the W-strain family (*2, 3*). Other groups have also raised questions about the interpretability of cluster studies for inference (*4–6*). Finally, longitudinal epidemiological studies of TB transmission among household contacts have failed to support this finding (*7, 8*).

A second assumption — that DOTS "can reduce MDR-TB once it has occurred" — is supported only by examples of falling MDR-TB rates: no evidence has causally linked the use of DOTS alone to observed declines. In fact, the claim that DOTS can reduce rates of MDR-TB is not supported by the growing body of evidence that patients with MDR-TB have poor outcomes with short-course chemotherapy (*9–14*). New York City is cited as an example of successful control, yet this success was achieved through comprehensive interventions that included massive investments in infrastructure, infection control, improved case detection, and treatment of active cases of MDR-TB (*2*).

The third assumption — that "the need to introduce second-line therapy should be determined by countrywide statistics on treatment success rates and the proportion of all cases caused by MDR strains" — may result in dangerous policy decisions. The authors suggest an arbitrary threshold for their "rational" framework; however, they note that "specific cut-points for ... good clinical outcomes and high levels of MDR-TB have not been empirically validated." Because MDR-TB outbreaks are focal, countrywide averages may underestimate the seriousness of the problem (*15*). Additionally, focal outbreaks present an opportunity to develop a control strategy before the MDR-TB rates compromise the efficacy of DOTS programmes.

Lastly, it is assumed that to prioritize DOTS expansion "most national TB programmes do not need to introduce second-line anti-TB therapy". Poor outcomes of DOTS re-treatment regimens documented in patients who fail their initial round of short-course chemotherapy, however, raise an important ethical challenge to this assertion (*14*). As a result, WHO must now make a decision about whether or not to recommend second-line drugs as part of standard re-treatment regimens for all DOTS programmes.

DOTS expansion is the first priority in global TB control, but it is short-sighted to conclude that the latter can be achieved without effective strategies to treat and control MDR-TB. Rather than pit DOTS expansion against MDR-TB therapy, the task at hand is to obtain dramatically increased funds for comprehensive global TB control. With the new Global Fund to Fight AIDS, TB and Malaria (*16*), these resources may soon be forthcoming. We would argue that, now, to deny access to effective treatment for those already sick on the grounds that resources are scarce would be irrational or worse. ■

1. Alland D, Kalkut GE, Moss AR, McAdam RA, Hahn JA, Bosworth W, et al. Transmission of tuberculosis in New York City. An analysis by DNA fingerprinting and conventional epidemiologic methods. *New England Journal of Medicine* 1994;330:1710-6.
2. Frieden TR, Sherman LF, Maw KL, Fujiwara PI, Crawford JT, Nivin B, et al. A multi-institutional outbreak of highly drug-resistant tuberculosis: epidemiology and clinical outcomes. *JAMA* 1996;276:1229-35.
3. Bifani PJ, Mathema B, Kurepina NE and Kreiswirth BN. Global dissemination of the *Mycobacterium tuberculosis* W-Beijing family strains. *Trends in Microbiology* 2002;10:45-51.
4. Glynn JR, Vynnycky E, Fine PEM. Influence of sampling on estimates of clustering and recent transmission of *Mycobacterium tuberculosis* derived from DNA fingerprinting techniques. *American Journal of Epidemiology* 1999;149:366-71.
5. Murray M, Alland D. Methodological problems in the molecular epidemiology of tuberculosis. *American Journal of Epidemiology* 2002;155:565-71.
6. Murray M. Determinants of cluster distribution in the molecular epidemiology of tuberculosis. *Proceedings of the National Academy of Sciences USA* 2002;99:1538-43.
7. Snider DE Jr, Kelly GD, Cauthen GM, Thompson NJ, Kilburn JO. Infection and disease among contacts of tuberculosis cases with drug-resistant and drug-susceptible bacilli. *American Review of Respiratory Disease* 1985;132:125-32.
8. Teixeira L, Perkins MD, Johnson JL, Keller R, Palaci M, do Valle Dettoni V, et al. Infection and disease among household contacts of patients with multidrug-resistant tuberculosis. *International Journal of Tuberculosis and Lung Disease* 2001;5:321-8.
9. Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. *American Review of Respiratory Disease* 1986;133:423-30.
10. Manalo F, Tan F, Sbarbaro JA, Iseman MD. Community-based short-course treatment of pulmonary tuberculosis in a developing nation. Initial report of an eight-month, largely intermittent regimen in a population with a high prevalence of drug resistance. *American Review of Respiratory Disease* 1990;142:1301-5.
11. Kimerling ME, Kluge H, Vezhnina N, Iacovazzi T, Demeulenaere T, Portaels F, et al. Inadequacy of the current WHO re-treatment regimen in a central Siberian prison: treatment failure and MDR-TB. *International Journal of Tuberculosis and Lung Disease* 1999;3:451-3.
12. Centers for Disease Control and Prevention. Primary multidrug-resistant tuberculosis — Ivanovo Oblast, Russia, 1999. *Morbidity and Mortality Weekly Report* 1999;48:661-3.
13. Coninx R, Mathieu C, Debacker M, Mirzoev F, Ismaelov A, de Haller R, et al. First-line tuberculosis therapy and drug-resistant *Mycobacterium tuberculosis* in prisons. *Lancet* 1999;353:969-73.

[1] Partners In Health and Program in Infectious Disease and Social Change, Department of Social Medicine, Harvard Medical School, 641 Huntington Avenue, Boston, MA 02115, USA. Correspondence should be addressed to Jim Yong Kim (email: jimkimpih@pih.org).
[2] Socios En Salud—Sucursal Perú, Lima, Peru.
[3] Zanmi Lasante, Cange, Haiti.
[4] Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA.

14. Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, et al. Standard short-course chemotherapy for drug resistant tuberculosis: treatment outcomes in six countries. *JAMA* 2000;283:2537-45.
15. Becerra MC, Bayona J, Freeman J, Farmer PE, Kim JY. Redefining MDR-TB transmission ''hot spots''. *International Journal of Tuberculosis and Lung Disease* 2000;4:387-94.
16. *The Global Fund to Fight AIDS, Tuberculosis and Malaria*. Available from: URL: http://www.globalfundatm.org

Sustainable TB control: the questions that have to be answered

Hans L. Rieder[1] & Catharina S.B. Lambregts-van Weezenbeek[2]

Multidrug-resistant tuberculosis (MDR-TB) is virtually never amenable to successful treatment with the six essential anti-TB medications. Patients who have it remain potential transmitters until spontaneous recovery or the more frequent fatal outcome. Several questions need thus to be addressed that are raised in the paper by Pablos-Méndez and collaborators in this issue of the *Bulletin* (see pp. 489–494)

The magnitude of the problem. A patient continuing to excrete sufficiently large numbers of bacilli at five months or later in treatment in an order of magnitude that they can be seen on a microscopic examination is defined as treatment failure. If the patient has been on a rifampicin-throughout regimen, it is thus tempting to assume that the strain is multidrug resistant. However, while there is a strong correlation between culture and microscopy results in patients on a regimen not containing rifampicin (*1*), the correlation is poor in patients who are on such a regimen (*2*). Furthermore, if the bacilli are indeed viable, failure is most often attributable to non-adherence rather than to drug resistance.

Technically demanding tests are required to demonstrate drug resistance (*3*). Pablos-Méndez and colleagues show that the failure to account for the operating characteristics of susceptibility testing often grossly overestimates the level of resistance. The published reports have not adjusted for this, and have identified "hot spots" which may not be ones (*4, 5*).

Conversely, the global map of resistance is very incomplete, and the information has usually been obtained from countries which have made efforts for national TB control, allowing representative sampling required for inclusion in the surveys. There is a critical need to expand coverage of the global surveillance system significantly and quickly.

Natural history. Untreated and untreatable sputum smear-positive TB has a very high case fatality (*6–8*). However, patients may survive and disseminate *M. tuberculosis* for years before succumbing. Drug-resistant organisms are therefore expected to have a comparative advantage. If the risk of secondary disease in the case of infection is the same, resistant organisms will ultimately gain the upper hand. Curiously, this has not always been the case. Pablos-Méndez and colleagues cite the example of New York City. When appropriate TB control measures were introduced for all patients, the number of multidrug-resistant cases dropped much faster than the number of fully drug-susceptible cases. Multidrug-resistant strains may thus actually have a disadvantage. This hypothesis fits with data from countries with a solid TB control programme such as Benin, where primary multidrug resistance remained barely measurable even after over a decade of rifampicin-containing chemotherapy (*9*). It is also congruent with experimental data that demonstrate inferior virulence of the subset of isoniazid-resistant strains whose resistance is attributable to *katG* gene deletion (*10*).

HIV infection may change the pattern of circulation of strains importantly. If virulence of *Mycobacterium tuberculosis* matters for non-compromised hosts, any selective advantage of less virulent strains becomes almost certainly irrelevant in the compromised host. On the other hand, the high death rate in HIV-infected TB patients may importantly curtail their ability to transmit. How this affects the epidemiology from drug resistance is far from clear.

Required public health action. Pablos-Méndez and colleagues propose a framework for how national programmes could prioritize their actions concerning DOTS and DOTS-Plus. Chemotherapy as recommended for DOTS programmes is highly cost-effective (*11*). An unbiased analysis of the ranking of a so-called DOTS-Plus strategy (*12*), providing more costly treatment to patients with MDR-TB has never been carried out.

The proposed framework considers essentially the prevalence of primary multidrug resistance, but not the total burden in a country. In some high-prevalence countries, such as South Africa, the proportion of re-treatment cases is considerable and related to a high burden of multidrug resistance, despite primary drug resistance rates that are still low. For this reason, we think that any framework should take into account the prevalence of combined resistance and an "acquired multidrug resistance index" in order to make a realistic estimate of the overall problem in the community (*4*).

In reality many countries already have second-line drugs at their disposal. It is fairly straightforward to develop a policy when these drugs are not available, but when they are avaiable they are used, and not always wisely. Therefore, we are in favour of a framework that works for both settings — with and without second-line drugs. Misuse of second-line drugs is a public health emergency in itself!

DOTS-Plus programmes must be sustainable if disaster is to be prevented. The WHO-coordinated Green Light Committee that reviews applications for preferentially priced second-line drugs plays a major role in ensuring access to high-quality drugs and at the same time ensures that these drugs are adequately used within the context of an integrated DOTS/DOTS-Plus strategy. In addition, it has a critical role in developing an evidence base to make more rational decisions on when and how to implement a comprehensive TB control policy that includes treatment of all patients, both those with susceptible and those with resistant strains. ■

[1] International Union Against Tuberculosis and Lung Disease, Jetzikofenstrasse 12, 3038 Kirchlindach, Switzerland (email: TBRieder@cs.com). Correspondence should be addressed to this author.
[2] Royal Netherlands Tuberculosis Association, The Hague, The Netherlands.

1. Mount FW, Ferebee SH. United States Public Health Service Cooperative Investigation of antimicrobial therapy of tuberculosis. V. Report of thirty-two-week observations on combinations of isoniazid, streptomycin, and para-aminosalicylic acid. *American Review of Tuberculosis* 1954;70:521-6.
2. Newman R, Doster B, Murray FJ, Woolpert SF. Rifampin in initial treatment of pulmonary tuberculosis. A U.S. Public Health Service tuberculosis therapy trial. *American Review of Respiratory Diseases* 1974;109:216-32.
3. Laszlo A, Rahman M, Raviglione M, Bustreo F. Quality assurance programme for drug susceptibility testing of *Mycobcterium tuberculosis* in the WHO/IUATLD supranational laboratory network: first round of proficiency testing. *International Journal of Tuberculosis and Lung Disease* 1997;1:231-8.
4. *Anti-tuberculosis drug resistance in the world. The WHO / IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance*. Geneva: World Health Organization 1997. Unpublished document WHO/TB/97.229.
5. *Anti-tuberculosis drug resistance in the world. Report No. 2.* Geneva: World Health Organization; 2000. Unpublished document WHO/CDS/TB/2000.278.
6. Berg G. *The prognosis of open pulmonary tuberculosis. A clinical-statistical analysis.* Lund, Sweden: Håkan Ohlson; 1939.
7. Thompson BC. Survival rates in pulmonary tuberculosis. *British Medical Journal* 1943;2:721.
8. Buhl K, Nyboe J. Epidemiological basis of tuberculosis eradication. 9. Changes in mortality of Danish tuberculosis patients since 1925. *Bulletin of the World Health Organization* 1967;37:907-25.
9. Trébucq A, Anagonou S, Gninafon M, Lambregts K, Boulahbal F. Prevalence of primary and acquired resistance of *Mycobacterium tuberculosis* to antituberculosis drugs in Benin after 12 years of short-course chemotherapy. *International Journal of Tuberculosis and Lung Disease* 1999;3:466-70.
10. Li Z, Kelley C, Collins F, Rouse D, Morris S. Expression of *katG* in *Mycobacterium tuberculosis* is associated with its growth and persistence in mice and guinea pigs. *Journal of Infectious Diseases* 1998;177:1030-5.
11. Murray CJL, De Jonghe E, Chum HJ, Nyangulu DS, Salomao A, Styblo K. Cost effectiveness of chemotherapy for pulmonary tuberculosis in three sub-Saharan African countries. *Lancet* 1991;338:1305-8.
12. Guidelines for establishing DOTS-Plus projects for the managment of multidrug-resistant tuberculosis (MDR-TB). Geneva: World Health Organization; 2000. Unpublished document WHO document WHO/CDS/TB/2000.279:1-87.