POLICY FORUM: PUBLIC HEALTH

Responding to Market Failures in Tuberculosis Control

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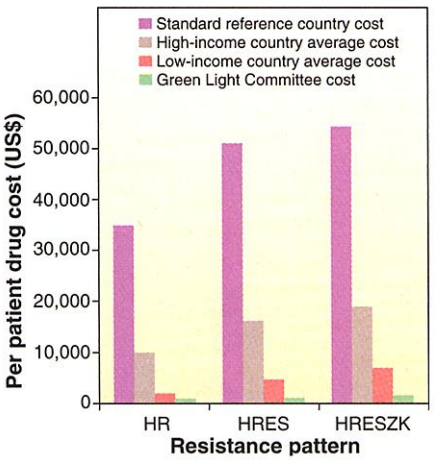
Multidrug-resistant tuberculosis (MDR-TB) is caused by strains of *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampin, the two most powerful first-line antituberculosis (anti-TB) drugs. Although drug resistance in TB is not a new phenomenon (*1*), several factors—including irrational antibiotic use, poor-quality anti-TB drugs, the collapse of public health infrastructures, the HIV epidemic, war, famine, and increasing inequality and poverty—have all contributed to the increasing incidence of TB (*2*, *3*). In recent years, outbreaks of MDR-TB in public institutions (hospitals, prisons, and homeless shelters) in the United States, Europe, and Latin America have caused many deaths and have raised concerns about epidemic transmission of drug-resistant strains of *M. tuberculosis* (*4*).

The World Health Organization's (WHO's) strategy for tuberculosis control, DOTS, consists of five elements: political commitment; case detection using sputum microscopy; standard short-course chemotherapy (SCC) under proper case-management conditions, including directly observed treatment; regular drug supply; and a standardized recording and reporting system. Although DOTS has dramatically increased the effectiveness of TB control programs (*5*) and priority has been placed on preventing MDR-TB via DOTS (*6*, *7*), recent data show that the reemergence of MDR-TB may threaten TB control efforts in some settings, primarily because of the low cure rates achieved with SCC (*8*, *9*).

Some have suggested that MDR-TB may be untreatable in low-income settings in part because of the high costs of treatment regimens (*10*, *11*). In addition, the diagnostic procedures are complex and the laboratory services required may be unavailable. In many cases, there is minimal evidence of successful clinical management or of national-scale management of MDR-TB. There is the further danger of destabilizing DOTS-based TB control programs by focusing on costly MDR-TB management. Ultimately, a vicious cycle between health policy and market economics can result, i.e., a lack of international policy contributes to high drug prices, which, in turn, serve as a primary justification for not implementing projects (to develop policy).



Cost of MDR-TB treatment regimens. Standard prices for first-line drugs were used across all regimens. Treatment regimens were selected according to the WHO guidelines and are available at *Science* Online (*16*). Treatment regimens are selected for resistance to three combinations of the following drugs: isoniazid (H), rifampicin (R), ethambutol (E), pyrazinamide (Z), streptomycin (S), and kanamycin (K).

In response to this scenario, WHO established a Working Group for the DOTS-Plus approach, which is still under development, but which aims to manage MDR-TB using second-line drugs in low- and middle-income countries. The Working Group emphasizes the need for DOTS-Plus projects to be underpinned by functioning national TB programs that promote sound TB control practices for all patients (*12*). One of the main obstacles to implementing DOTS-Plus projects has been the prohibitive cost of second-line drugs (*13*). Nevertheless, the Working Group has achieved major cost reductions, and simultaneously fostered rational use of and access to the drugs. We believe this model could be adopted for other chronic infectious diseases prevalent in resource-poor settings.

Decreasing Cost and Increasing Access

Drug costs have several determinants (*14*, *15*), and our method to decrease prices and increase proper use of second-line drugs focused on a six-step process (*16*).

1) After quality-assurance criteria were used to filter a comprehensive list of manufacturers, market analysis revealed three categories of drugs, i.e., manufacturer holds monopoly status as patent-holder, manufacturer has monopoly status without a patent, and multiple manufacturers are involved. Once the market status for each drug was established, an appropriate negotiation strategy could be chosen.

2) A single negotiator, Médecins Sans Frontières, acted for all parties, thereby consolidating the various sources of demand, and they also provided the technical support and financial capital in advance.

3) Six categories of the most important second-line drugs were submitted for inclusion on the WHO Model List of Essential Drugs (EDL). Two markets were offered to the industry; one constituted countries and organizations that had made firm financial and programmatic commitments to establishing pilot projects (approximately 2000 patients initially constituting over three million doses of the various drugs in total). The second, based on the estimated number of new MDR-TB cases globally (207,000 to 338,000 in 2000) (*17*), included countries assessed by their need for TB drugs and their intention to join DOTS-Plus, together with an estimate of their consumption of second-line drugs. This second potential market is growing because of the decreasing cost of second-line drugs and the increasing number of identified cases.

4) A direct negotiation strategy was used to address the needs for the first market. This was based on quality criteria and price. A "tiered-tender" approach, which gives a large percentage to the quality-assured company with the lowest priced drug and a proportional percentage to a select number of the remaining quality-assured manufacturers (or one other manufacturer), is also being used for the second market.

5) The advantages to the suppliers were highlighted. This included the pooled-procurement process, reflecting a single client for global demand; participation in a high-

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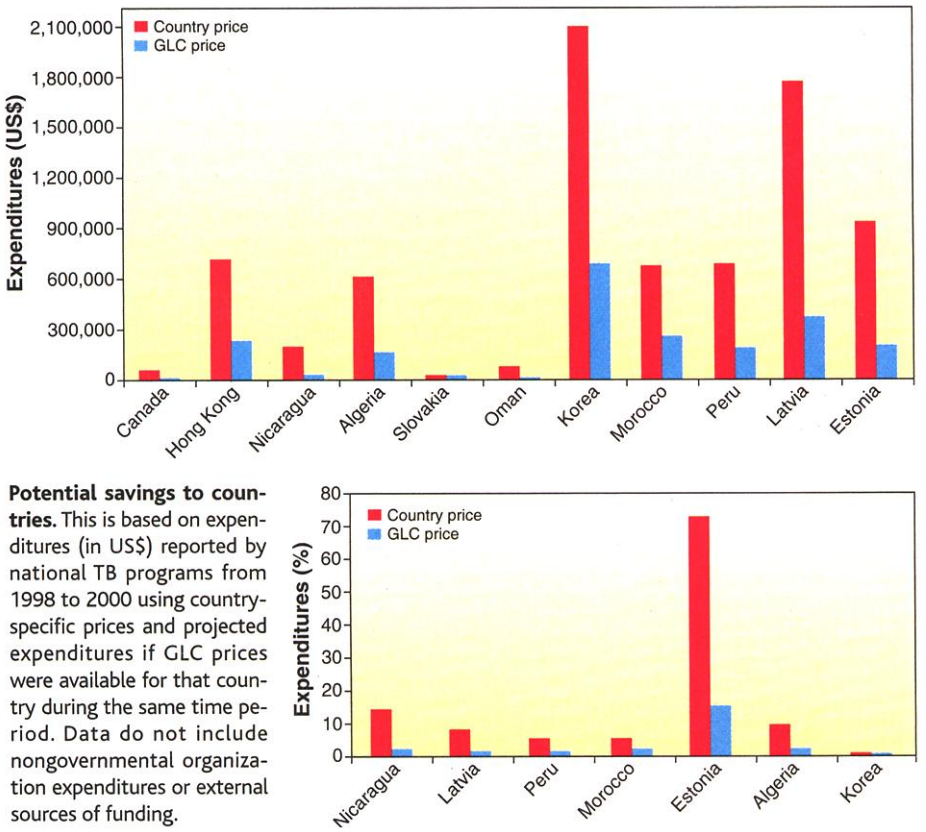
profile partnership; potential penetration to other markets; assurance that drugs would not be lost by further creation of resistance; and potential facilitation of drug registration when needed.

6) Access to the concessionally priced second-line drugs is only given to projects deemed to adhere to the international recommendations for establishing DOTS-Plus pilot projects by a multi-institutional body known as the Green Light Committee (GLC) (*18*, *19*).

Via the GLC mechanism, Nicaragua could spend only 2.7% of its budget for the same drugs. These savings should be reinvested in TB control efforts, including those designed to increase cure rates for MDR-TB patients. The challenge is complex and seems paradoxical: increase access to quality-assured drugs by decreasing costs, while simultaneously increasing rational use of these very drugs. Our response was to consolidate the market and to create a regulatory mechanism promoting access to concessionally priced drugs to projects with adequate technical capacity. The unified approach to both the monopoly and nonmonopoly producers combined with tailored negotiation strategies proved effective in reducing prices and reaching long-term sustainability in price reduction.



Potential savings to countries. This is based on expenditures (in US$) reported by national TB programs from 1998 to 2000 using country-specific prices and projected expenditures if GLC prices were available for that country during the same time period. Data do not include nongovernmental organization expenditures or external sources of funding.

Implementation of the six-step strategy increased supply and decreased the cost of quality-assured second-line drugs (see table, p. 1051) (*20*), and per-patient treatment costs dropped dramatically as a result of unit price decreases (see figure, p. 1049).

If countries continue their spending trend on second-line drugs as they have done for 1998–2000, they could save as much as 93.6% of their expenditure on second-line drugs (see figure, this page). Overall, this could produce a median savings of approximately US$454,000 for the countries surveyed.

Countries with an established TB control program and with budgets that include the purchase of second-line drugs could save up to 57.5% (e.g., Estonia) of their overall budget for TB control. Nicaragua, for example, reports 14.9% of the TB control budget is spent on second-line drugs.

This Is the Beginning, Not the End

However, given the relatively new existence of the GLC and the ever-growing demand for assistance, it remains to be seen whether monitoring of projects and provision of technical assistance can be sustained. It is also unclear whether the industry will view the GLC as a limit to or a stimulus to demand, whether projects will bypass the GLC mechanism in favor of manufacturers that supply outside the mechanism, and whether the modifications needed to ensure that these factors are addressed will be applied to the current model.

Additional issues deserve close examination. Although concessional prices were achieved through direct negotiation with monopoly producers, the price of treatment regimens could be further reduced, as any two of the four highest priced drugs [capreomycin, cycloserine, para-aminosalicylic acid (PAS), and ofloxacin] compose the largest proportion of regimen cost and country expenditures on second-line drugs. The marginal cost of production should be determined to establish a fair price for drugs required for public health emergencies.

Patented drugs remain prohibitively expensive, and still account for a large proportion of the cost of treatment regimens. Nevertheless, some countries are purchasing the same drugs from quality-assured generic manufacturers at much lower costs. Ofloxacin is under patent protection in many countries, where it is currently supplied at a price that is up to eight times the price in countries where ofloxacin is not patented (and where it is comparable to the price for the nonpatented ciprofloxacin). This phenomenon raises the question of whether or not true "at-cost" prices have been achieved by recent efforts targeted at the price reduction of the antiretroviral drugs necessary for the treatment of HIV/AIDS. Although the profit motives of the industry are acknowledged, it is still reasonable to limit profits in the context of public health emergencies.

It is also important to maintain high standards of quality-assurance, as low-quality drugs often penetrate emerging markets, resulting in low cure rates for patients and an increase in resistance to second-line drugs.

Given the increase in expenditure for TB control that may be required in coming years, existing economic analyses (*21*) should be redefined and recalculated. It is no longer acceptable to assume that treatment of patients with infectious diseases is to be denied to resource-poor countries. Treatment of individual patients benefits society as well, by reducing the additional economic burden on the health-care system caused by further transmission of MDR-TB from untreated, infectious patients.

Although TB remains a leading cause of adult mortality, it is appalling that no new classes of drugs have been developed for TB during the past 30 years. Between 1975 and 1997, only 13 of 1223 new chemical entities were approved for use in tropical diseases (*22*). Furthermore, market failures result in millions of people not having access to life-saving treatments

MARKET STATUS OF SECOND-LINE DRUGS

Supply status

Drug	Formulation	Initial status	Current status
Capreomycin	1 g/ml vial	Monopoly-nonpatent	Few
Cycloserine	250-mg tablet	Monopoly-nonpatent	Few
Ethionamide/prothionamide	250-mg tablet/250-mg tablet	Many/many	Many/many
Kanamycin/amikacin	1 g/ml vial	Many/many	Many/many
Para-aminosalicylic acid (PAS)	4-g enteric-coated granules	Monopoly-nonpatent	Few
Ofloxacin/ciprofloxacin	200-mg tablet/250-mg tablet	Monopoly-patent/Monopoly-patent	Monopoly-patent/Monopoly-nonpatent

Price status

	Capreomycin	Cycloserine	PAS	Ethionamide	Prothionamide	Amikacin	Kanamycin	Ciprofloxacin	Ofloxacin
International reference price (Boston, USA)	25.04	8.42	2.50	7.05		16.61	6.38	8.91	8.54
High-income country average price	21.17	3.38	2.50	1.84	0.60	7.46	1.79	2.71	2.60
Low-income country average price	12.00	1.50	5.00	0.26	0.16	5.75	0.89	0.53	0.60
Green light committe (GLC) price	1.02	0.14	1.51	0.10	0.10	0.11	0.36	0.06	0.33
Difference: international reference versus GLC price	95.93%	98.34%	39.60%	98.58%		99.34%	94.36%	99.33%	96.14%
Difference: high-income country average versus GLC price	95.18%	95.86%	39.60%	94.57%	83.33%	98.53%	79.89%	97.79%	87.31%
Difference: low-income country average versus GLC price	91.50%	90.67%	69.80%	61.54%	37.50%	98.09%	59.55%	88.68%	45.00%

Market status of second-line drugs. Few means two to five manufacturers, and many means greater than five.

routinely available in resource-rich countries. Attempts to use international trade agreements to increase access to essential drugs have also been met with political resistance and economic consequences (*23*, *24*). In the case of diseases where demand is evident, we must ask why prices remain prohibitively high for developing countries, and why are such mechanisms for price negotiation needed?

In the context of TB control, HIV/AIDS raises several issues. Despite the recent action by nongovernmental organizations, U.N. agencies, the pharmaceutical industry, and other actors to increase access to anti-HIV drugs, as in the case of MDR-TB drug procurement program, significant long-term problems (including target prices; involvement of the generic industry; rational use; and equitable, efficient distribution) still have to be faced in the purchase of antiviral drugs.

Given the rapid progression of the AIDS pandemic and the potential increase in funding (*25*) for HIV/AIDS control, we have no choice but to move forward, and quickly. And given the epidemic spread of TB in areas with a high prevalence of HIV (*26*), it is imperative that efforts are pursued for both diseases to decrease the costs of medication and to increase access to effective treatment programs.

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19. The Green Light Committee is currently comprised of the following institutions: Royal Netherlands TB Association (KNCV), Harvard Medical School, National TB Program-Peru, U.S. Centers for Disease Control and Prevention (CDC), Médecins Sans Frontières, and WHO.
20. Data for Table and Figs. 1 and 2 were provided by national TB programs (NTPs) responding to a WHO survey sent to countries participating in the WHO/International Union Against TB and Lung Disease (IUATLD) Drug Resistance Surveillance (DRS) project. Data for the USA (Boston) were obtained from the Brigham and Women's Hospital and Harvard Medical School. Unit purchase prices for drugs were supplied in US$ for standard formulations as indicated in Table 1. Second-line drugs purchased in formulations not supplied by the procurement agents were excluded in the analysis, as was pricing information for countries not purchasing drugs from patent holders. PAS in its desired formulation is under Orphan Drug Exclusivity status in the USA until July 2001. Fluoroquinolones (ciprofloxacin and ofloxacin) still remain on patent in some countries, and ofloxacin is under patent in more countries than ciprofloxacin. GLC prices are inclusive of a procurement fee of less than 6%.
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