Critical Reflection

Directly observed treatment, short-course strategy and multidrug-resistant tuberculosis: are any modifications required?*

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Multidrug-resistant tuberculosis (MDRTB) should be defined as tuberculosis with resistance to at least isoniazid and rifampicin because these drugs are the cornerstone of short-course chemotherapy, and combined isoniazid and rifampicin resistance requires prolonged treatment with second-line agents. Short-course chemotherapy is a key ingredient in the tuberculosis control strategy known as directly observed treatment, short-course (DOTS). For populations in which multidrug-resistant tuberculosis is endemic, the outcome of the standard short-course chemotherapy regimen remains uncertain. Unacceptable failure rates have been reported and resistance to additional agents may be induced. As a consequence there have been calls for well-functioning DOTS programmes to provide additional services in areas with high rates of multidrug-resistant tuberculosis. These ''DOTS-plus for MDRTB programmes'' may need to modify all five elements of the DOTS strategy: the treatment may need to be individualized rather than standardized; laboratory services may need to provide facilities for on-site culture and antibiotic susceptibility testing; reliable supplies of a wide range of expensive second-line agents would have to be supplied; operational studies would be required to determine the indications for and format of the expanded programmes; financial and technical support from international organizations and Western governments would be needed in addition to that obtained from local governments.

Keywords: antitubercular agents, administration and dosage, and supply and distribution; drug therapy, combination; treatment failure; tuberculosis, multidrug-resistant, drug therapy and epidemiology.

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Introduction

The introduction of rifampicin for therapeutic use in 1968 completed three decades of scientific innovation that provided several effective chemotherapeutic agents for the treatment of tuberculosis (TB) (*1*, *2*). Clinical trials by the British Medical Research Council and others elucidated the optimal regimen while operational studies by Karel Styblo and the International Union against Tuberculosis and Lung Disease (IUATLD) demonstrated that short-course chemotherapy (SCC) given under direct observation could succeed in the field (*3*). Unfortunately, these tools for controlling TB have not been used properly. Between 1998 and 2030, 225 million new cases of TB and 79 million deaths attributable to the disease are expected (*4*). A recent global study detected resistance to antituberculosis drugs in all 35 countries and regions surveyed (*5*, *6*).

Responding to this situation, WHO recommended a multifaceted strategy known as directly observed treatment, short-course (DOTS), which includes standardized supervised SCC (*7*). DOTS has proved effective in diverse settings but globally only 16% of all TB cases are treated in DOTS programmes (*8*, *9*). DOTS should be made more widely accessible so that effective treatment is available to patients with drug-susceptible disease and acquired drug resistance is prevented. However, while DOTS is an integral part of the global TB control effort, additional interventions may be necessary in particular circumstances. For example, additional strategies (e.g. active case-finding, TB preventive therapy for persons infected with human immunodeficiency virus (HIV)) may be required in countries with high rates of combined TB/HIV infection (*10*). The term DOTS-plus for TB/HIV could be given to such modified programmes. It has also been suggested that DOTS programmes should provide additional services in areas where multidrug-

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resistant tuberculosis (MDRTB) is prevalent (i.e. DOTS-plus for MDRTB) (*11*–*13*).

While continuing to emphasize that implementation of the DOTS strategy is the top priority, WHO recognized that, in some places where the prevalence of MDRTB is high, it represents a special threat to effective TB control. WHO, in partnership with other agencies and institutions, therefore established the Working Group on DOTS-plus for MDRTB (*14*, *15*). This group has developed protocols for pilot projects intended to assess the feasibility of MDRTB management in TB control programmes.

Below we discuss the rationale for and possible format of a DOTS-plus approach to MDRTB. After outlining the global distribution of MDRTB we indicate the importance of a strict definition for MDRTB, i.e. resistance to at least isoniazid and rifampicin. The potential risks of SCC in areas where MDRTB is prevalent are discussed and possible modifications of the DOTS strategy are proposed. The need for continuing research to determine the indications for and format of such DOTS-plus services is highlighted.

Distribution of MDRTB

Definitions

Acquired drug resistance, involving the emergence of drug-resistant bacilli in previously treated patients, arises through faulty prescription or failure to ensure compliance, and therefore provides a short-term measure of the effectiveness of local treatment regimens and TB control programmes (*6*, *16*). As the pool of patients excreting drug-resistant bacilli expands, there is an increasing risk of transmission of the bacilli to healthy individuals who can develop drug-resistant disease from the outset, i.e. primary resistance (*6*, *16*). The prevalence of primary resistance in a community is therefore an excellent long-term indicator of the quality of TB treatment and control.

Unfortunately, however, it is often difficult in field conditions to make an accurate distinction between previously treated patients and those who have never been treated (*6*, *16*). Consequently, surveillance studies have often only provided the crude (or combined) rate of drug resistance, which is of little epidemiological use (*16*, *17*).

USA, Western Europe and other industrialized countries

Several major outbreaks of MDRTB occurred in hospitals and other institutions in the USA among HIV-positive patients during the early 1990s (*18*, *19*). Similar nosocomial outbreaks of MDRTB were subsequently reported in Europe (*20*–*22*). These outbreaks were associated with high mortality rates (e.g. 70–90%) and the transmission of disease to HIV-positive and HIV-negative contacts, including staff (*23*). Until then, cases of MDRTB in industrialized countries had generally been sporadic and acquired, following prolonged inappropriate therapy (*24*, *25*). The potential public health impact of MDRTB had been heralded by only a few cases of primary resistance (*26*).

In response to the MDRTB outbreaks, a nationwide survey of drug-resistant TB was performed in the USA in 1991 (*27*). Resistance to at least one antituberculosis drug was found in 14.2% of cases. Of 3256 cases tested for susceptibility to isoniazid and rifampicin, 114 (3.5%) were MDRTB. During the study period, New York City accounted for 61.4% of MDRTB cases, with the rate of the condition among culture-positive cases being 13.9%. States with MDRTB resistance rates greater than 3% included Alabama, Florida, Hawaii, and New Jersey. Adequate resources were provided to reinvigorate TB control programmes, particularly in New York City (*28*). Subsequently there has been a significant reduction in MDRTB in the USA from 488 cases (2.8%) in 1993 to 237 (1.6%) in 1996 (*29*). This decrease was largely attributable to successful interventions in New York City, where the rate of MDRTB fell from 9% in 1993 to 5% in 1996 (*28*, 29).

The rate of MDRTB in the United Kingdom between 1994 and 1996 was 1.5% (*30*). Studies during the 1990s in Belgium, France and Germany found MDRTB rates between 0.9% and 1.5% (*6*, *31*, *32*), but higher rates were reported from southern Europe (*6*, *33*). For example, a review of 433 isolates collected in the province of Florence between 1992 and 1995 revealed that 2.5% were of MDRTB, which was found only in patients with a history of TB treatment, among whom the rate was 7.1% (*33*). In Japan the overall rate of MDRTB was 2.4% but the prevalence was 0.1% among "new cases" and 10.1% among "recurrent cases" (*34*). Only seven MDRTB isolates (0.5%) were detected among 1413 culture-positive cases in Australia between 1994 and 1995 (*35*), and a 12-month countrywide survey in New Zealand during 1995 and 1996 revealed an overall MDRTB rate of 0.7% (*5*).

In these industrialized countries, several risk factors for drug-resistant TB have been recognized: a history of previous treatment for TB, birth in an area of high MDRTB incidence (e.g. the South-East Asia Region), known contact with MDRTB, cavitary lung disease, residence in certain urban centres (e.g. London in the United Kingdom, New York City in the USA), HIV infection, and comparatively young age (e.g. 15–44 years) (*29*, *30*, *36*, *37*). Nonetheless, 32–60% of drug-resistant cases have no apparent risk factors (*27*, *36*). It is worth noting that the association of HIV infection with MDRTB does not mean that HIV-positive patients are more prone to MDRTB than to drug-susceptible strains of *Mycobacterium tuberculosis*. The epidemiological association reflects nosocomial transmission of TB (some being MDRTB), and the rapid progression to active disease characteristic of HIV-positive patients.

Developing countries

Cohn et al. reviewed all reports of antibiotic susceptibility surveys for *Mycobacterium tuberculosis* published between 1985 and 1994 (*17*): high rates of acquired MDRTB were reported from Argentina (10.4%), Bolivia (15.3%), Chile (12.2%), Gujarat State in India (33.8%), the Republic of Korea (14.5%), and Nepal (48.0%). However, few developing countries had the facilities needed to perform such studies, and the surveys often used non-standardized laboratory techniques and/or sampled small non-representative groups of patients. Furthermore, many studies failed to distinguish primary and acquired drug resistance.

WHO and IUATLD have attempted to address these deficiencies in the Global Project on Anti-Tuberculosis Drug Resistance Surveillance (*5*, *6*). Between 1994 and 1997 this project used representative sampling techniques and standardized laboratory protocols to conduct antibiotic susceptibility surveys for *M. tuberculosis* in 35 countries from all WHO regions except the Eastern Mediterranean. The project effectively surveyed an aggregate population of 1 142 174 100 (approximately 20% of the world population in 1995) and included countries with varying levels of TB control. Overall, the median prevalences of primary and acquired MDRTB, respectively, were 1.4% (range, 0–14.4%) and 13.0% (range, 0–54.4%). Fig. 1 summarizes the findings for each region.

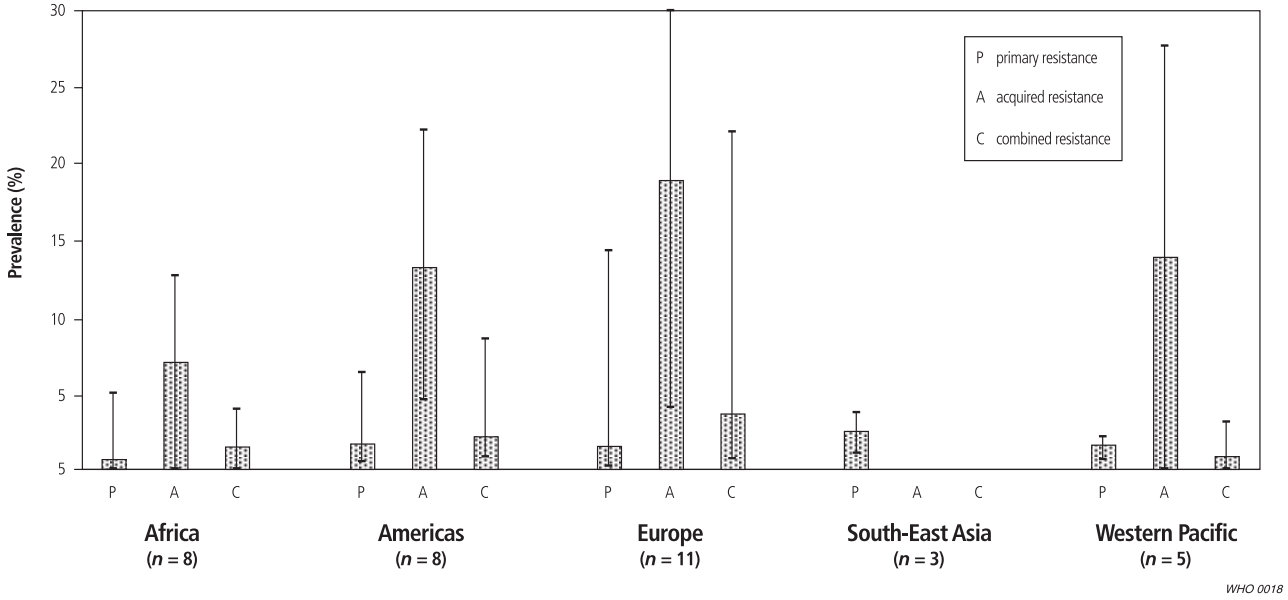
In the eight African countries surveyed, the level of drug resistance was generally low despite the increased TB rate associated with the HIV epidemic. In other African studies, similar low levels of drug resistance have been found and no direct relationship has been shown between HIV infection and drug-resistant TB (*38*). The low level of MDRTB has been attributed to the late and limited introduction of rifampicin (*5*, *6*). However, a primary MDRTB rate of 5.3% in Côte d'Ivoire is cause for concern.

In the Americas the situation in the Dominican Republic was recognized as serious, the primary and acquired rates of MDRTB being 6.6% and 19.7%, respectively. Argentina, Peru, and Puerto Rico had primary MDRTB rates of 4.6%, 2.5% and 1.9%, respectively. In the South-East Asia Region and the Western Pacific Region the rates of primary MDRTB ranged from 0.7% in New Zealand to 2.3% in Viet Nam and 3.8% in Thailand. A combined MDRTB prevalence of 13.3% was reported from Delhi. The data from South-East Asia Region and the Western Pacific Region, which account for more than 60% of the world's TB burden (*39*), highlight some remaining gaps in our understanding of the distribution of MDRTB. In 1990, 1.3 million and 0.4 million TB cases occurred in China and Indonesia, respectively. Neither these countries nor the Philippines were effectively surveyed. MDRTB has been recognized in these countries but has not been accurately quantified (*40–42*).

MDRTB in the former Soviet Union and associated territories and states

In the European Region, extraordinarily high rates of MDRTB were detected in the former Soviet Union and other areas of Eastern Europe (*5*, *6*). Rates of primary MDRTB ranged from 1.0% in the Czech Republic to 10.2% in Estonia and 14.4% in Latvia, and rates of acquired MDRTB reached 54.4% in

Fig. 1. **Prevalence of multidrug-resistant tuberculosis (MDRTB) by WHO region.** Data are adapted from ref. *6*. Columns represent the median percentage prevalence of MDRTB and the bars show the maximum and minimum prevalences reported; the numbers of countries surveyed in each WHO region are shown in parentheses. Maximum reported prevalence of acquired MDRTB in the European Region was 54.4%. Acquired drug resistance was not reported separately from the South-East Asia Region.



Latvia. Independent studies have confirmed these high rates of MDRTB (Table 1).

Even higher prevalences have been detected among prisoners in these countries (*45*, *46*). For example, a TB control programme in the Central Penitentiary Hospital in Baku, Azerbaijan, coordinated by the International Committee of the Red Cross, analysed samples from consecutive newly enrolled cases and from patients with no clinical and/or bacteriological response to at least eight weeks of treatment with a fully supervised WHO treatment regimen (*45*). A total of 9 (23.7%) of the newly enrolled cases and 25 (89.3%) of the non-responding patients had MDRTB. The outcome of SCC in these MDRTB endemic populations, where the condition is strictly defined as TB resistant to at least isoniazid and rifampicin, remains largely unresolved.

Table 1. **Multidrug-resistant TB in the general population of the former Soviet Union and parts of Eastern Europe**

Country or region (Study period)	Primary MDR[a] (%)	Acquired MDR[a] (%)	References
Estonia (1994)	10.2 (266)[b]	19.2 (26)[b]	*5, 6*
Latvia (1996)	14.4 (347)	54.4 (228)	*5, 6*
Ivanovo Oblast (1995–96)	4.0 (248)	27.3 (33)	*5, 6*
Czech Republic (1995)	1.0 (199)	6.3 (16)	*5, 6*
Romania (1995)	3.3 (1636)	14.4 (1521)	*5, 6*
Tomsk Oblast (1997)	5.5 (92)		*43, 44*
Kazakstan (1997–98)	10.9 (55)	33.3 (75)	– [c]

[a] MDR, multidrug resistance (defined as resistance to at least isoniazid and rifampicin).

[b] Figures in parentheses are number of patients in study cohort.

[c] Unpublished data from our laboratory collected in collaboration with Médecins sans Frontières — Luxembourg/Switzerland.

Importance of a strict definition for MDRTB

Rationale for the definition

MDRTB is strictly defined as TB with resistance to at least isoniazid and rifampicin because these two drugs are central to SCC (*5*, *6*, *24*). Isoniazid is bactericidal, inexpensive and easily administered and has a low incidence of side-effects (*47*). It is therefore used for the duration of any treatment regimen unless contraindicated or resistance is documented. Rifampicin is bactericidal, has great sterilizing activity and prevents the emergence of resistance to other drugs (*47*, *48*). It is also quickly absorbed from the gastrointestinal tract and is relatively non-toxic.

Treatment with isoniazid and rifampicin for nine months is effective against drug-susceptible TB (*47*, *49*). The duration of treatment can be shortened to six months by the addition of pyrazinamide for the first two months (*50–52*). In the presence of isoniazid resistance(with or without streptomycin resistance), regimens containing four or five drugs (e.g. HRZE) are still effective (*47*, *53*, *54*). For example, Mitchison & Nunn (*53*) reviewed 12 trials of the British Medical Research Council and found only four failures among 154 patients (2.6%) infected with such strains and treated with four-drug or five-drug regimens. Nonetheless, if isoniazid resistance is confirmed, short-course treatment should be modified so that pyrazinamide is continued for the entire six months; alternatively, rifampicin and ethambutol can be given for 12 months (*47*). In the presence of rifampicin monoresistance, treatment with isoniazid, streptomycin and pyrazinamide for nine months achieves sputum conversion at six months in 95–100% of patients and has a relapse rate of only 5–6% at 30 months (*55*).

While isolated resistance to isoniazid or rifampicin can be managed with first-line drugs, combined isoniazid and rifampicin resistance demands treatment with at least four agents, including a quinolone and an injectable agent, i.e. an aminoglycoside or capreomycin (*24*, *56*). This treatment, which has to be maintained for 18–24 months, is expensive and produces multiple side-effects. Cure rates ranging from 82.5% to 96% have been achieved with these regimens in HIV-negative patients with primary MDRTB or with uncomplicated acquired disease (*36*, *57*). However, a cure rate of only 56% was achieved despite intensive prolonged treatment in a series of 171 HIV-negative MDRTB patients who had chronic disease and had previously received multiple inappropriate retreatment regimens (*58*). Resistance to isoniazid and rifampicin thus has a huge impact on the duration, ease and success of antituberculosis chemotherapy, and justifies the strict definition of MDRTB as TB with resistance to at least these two drugs (*5*, *6*, *24*).

Differentiating MDRTB from other drug resistance

Several questions about MDRTB remain unanswered. Are MDRTB strains as transmissible and as clinically virulent as drug-susceptible *M. tuberculosis*? What is the effectiveness of standard SCC in communities with high pre-existing levels of MDRTB? When addressing these questions it is essential to differentiate MDRTB from other drug-resistant TB (ODRTB, monoresistance or polyresistance not including both isoniazid and rifampicin).

The importance of a universal definition for MDRTB is clear in the debate over the effectiveness of SCC in areas where MDRTB is endemic. DOTS programmes employing rifampicin-based SCC and sound control policies have been shown to decrease the prevalence of drug resistance in China, the Republic of Korea, and Algeria (*40*, *59*, *60*). However, Farmer & Kim (*11*) recently pointed out that these strategies reduced the prevalence of ODRTB but not that of MDRTB. The Beijing Tuberculosis Programme introduced fully supervised chemotherapy in 1978 and rifampicin has been used extensively since 1988 (*40*). Random surveys of over 100 new TB cases were conducted biannually in 1978–79 and 1991–92, during which period the number of cases of initial resistance to isoniazid, streptomycin and *para-*

aminosalicylic acid (PAS) fell from 17 (13.9% of the total), 15 (12.3%) and 5 (4.1%) to 8 (6.8%), 5 (4.2%) and 0 (0%), respectively. However, the introduction of rifampicin resulted in a prevalence of rifampicin resistance of 1.7% (i.e. 2 cases in a cohort of 118) by 1991–92.

The National Tuberculosis Programme in the Republic of Korea instituted SCC in the 1980s and this led to marked improvements in treatment completion rates and cure rates (*59*). Nationwide TB surveys of between 131 and 247 cases were conducted every five years between 1980 and 1995. Importantly, the 1980 survey of 177 patients included 69 old cases (39.0%) but the number and percentage of such cases in the representative survey of 1995 fell to 28 (21.4%). During this period the prevalences and absolute numbers of cases of initial isoniazid and streptomycin resistance fell from 25.0% (27 cases) and 4.6% (5 cases) to 4.9% (5 cases) and 1.9% (2 cases), respectively. However, by 1995 initial MDRTB resistance had emerged at a rate of 1.9%, i.e. 2 cases in a cohort of 103. During the same period the prevalences and absolute numbers of old cases with isoniazid and streptomycin resistance fell from 72.5% (50 cases) and 29.0% (20 cases), to 25.0% (7 cases) and 7.1% (2 cases), respectively. Unfortunately, the rate of MDRTB among old cases remained between 14.5% and 19.8% between 1985 and 1995.

In Algeria, standardized treatments were introduced in 1967 and SCC was introduced in 1980, resulting in falls in both the absolute numbers and percentages of resistant isolates (*60*). For example, between 1965 and 1970, 217 isolates (15.0%) from new cases were resistant to at least one drug but this was true of only 51 (6.3%) by 1980–85. Similarly, acquired isoniazid resistance fell from 510 cases (34.2%) in 1975–80 to 42 cases (10.3%) in 1981–85, but the rate of acquired MDRTB increased from 1.7% (25 MDRTB strains among 1490 isolates tested) to 11.0% (16 MDRTB strains among 406 isolates tested).

The experience gained in these countries without pre-existing problems with MDRTB showed that SCC and DOTS reduced the absolute numbers and prevalences of patients with ODRTB. However, while ODRTB cases were being removed from the pool of chronic cases by successful treatment with WHO-recommended category I (e.g. 2EHRZ/4HR, two months' treatment with ethambutol (E), isoniazid (H), rifampicin (R) and pyrazinamide (Z) followed by four months' treatment with isoniazid and rifampicin) or category II (i.e. 2SHRZE/1HRZE/5HRE, where S represents streptomycin) regimens (*61*), a small number of MDRTB cases remained. These persisting MDRTB cases, although perhaps not increasing in number, therefore came to represent a larger proportion of the declining drug resistance problem confronting a successful DOTS programme.

Short-course chemotherapy and MDRTB

There are few published data on the outcome of DOTS programmes using standardized SCC in areas with high pre-existing levels of MDRTB. New York City provides the only example of a DOTS programme that has effectively reduced the prevalence of MDRTB (strictly defined as TB with resistance to isoniazid and rifampicin) (*28*, *29*). However, the New York City programme involved multiple interventions other than DOTS including expedited laboratory diagnoses, intensive individualized treatment of MDRTB patients, extensive use of chemoprophylaxis, and improved infection control procedures (*28*). The relative contribution of each of these interventions to the reduction of MDRTB has not been defined.

The only other experience with DOTS programmes in populations with endemic MDRTB was among prisoners in the former Soviet Union, and the results were disappointing. For example, Coninx et al. (*62*) reported a DOTS programme in which 467 prisoners were treated in Baku, Azerbaijan. Drug-resistance data on admission were available for 131 patients; only 28 (21%) had fully susceptible strains of *M. tuberculosis* and 30 (23%) had MDRTB. WHO-recommended treatment and retreatment regimens (*61*) were successful for only 54% of the total study population; 71% of those completing treatment were cured. The overall treatment success rate was 26.6% for the 30 patients with confirmed MDRTB. Two of the MDRTB patients died within the first two weeks of therapy and seven did not complete treatment because they were released, transferred or defaulted for other reasons. Only 8 (38%) of the 21 MDRTB patients who completed WHO-recommended treatment were cured. The poor response of MDRTB to SCC was predictable in the light of the British Medical Research Council trials in which eight patients had MDRTB, five did not respond to treatment, two relapsed, and only one was apparently cured (*53*).

Unacceptable failure rates are not the only risk involved in employing standard SCC where MDRTB is prevalent. MDRTB patients may develop resistance to additional agents, e.g. streptomycin, ethambutol and pyrazinamide, while receiving WHO treatment and retreatment regimens. This phenomenon has been termed the amplifier effect (*11*, *12*). Our laboratory has documented the acquisition of resistance to additional agents among Rwandan patients with MDRTB who received standard SCC (*63*), and we have also observed preliminary evidence of the amplifier effect among patients in Colony 33, a prison hospital in Mariinsk, Siberia (*46*). However, the frequency of the effect remains undetermined.

Further work is required to define the incidence of the amplifier effect. Post-treatment isolates with additional resistances could be produced by superinfection with a more resistant strain, selection of a resistant clone from a mixed infection, incorrect labelling of specimens or other laboratory errors. Chaves et al. (*64*) have recently reported

reinfections and a case of mixed infection among HIV-positive inmates in Spanish jails. Cohorts of MDRTB patients treated with standard regimens should be followed up to confirm the high failure rate reported by Coninx et al. (*62*) in Baku and to ascertain the true incidence of the putative amplifier effect. These studies should include antibody susceptibility testing (AST) and restriction fragment length polymorphism analyses of pretreatment and post-treatment isolates. The results of such studies would help to determine the need for alternative DOTS strategies in countries where MDRTB is prevalent.

Possible DOTS modifications for the treatment of MDRTB

The DOTS strategy recommended by WHO comprises five key elements: (i) fully supervised treatment with a standardized short-course regimen; (ii) case detection, with special attention to the use of sputum microscopy; (iii) reliable drug provision; (iv) effective monitoring of TB control programmes; and (v) government commitment to TB control (*7*). Each element may require modification in areas where MDRTB is prevalent (Table 2).

Standardized or individualized treatment regimens

The DOTS strategy currently employs standardized treatment regimens based on the patient's smear status, severity of illness and past history of treatment (*61*). Some programmes have successfully used standard regimens of second-line agents to treat MDRTB (*65*, *66*). The drugs are selected on the basis of the common susceptibility profiles of MDRTB strains in the community. The advantage of using standardized regimens is that only occasional drug-resistance surveys performed by distant national or supranational laboratories are required. Mühlberger et al. successfully treated 21 of 23 Rwandan patients with drug-resistant TB, including 16 MDRTB cases, using a standard regimen containing streptomycin, ofloxacin, cycloserine, prothionamide and isoniazid (*65*, *66*). A similar programme, involving the use of kanamycin, ofloxacin, prothionamide, clofazimine, ethambutol, pyrazinamide and isoniazid for 3 months followed by 12 months of ofloxacin, prothionamide, ethambutol, pyrazinamide and isoniazid and then 6 months of prothionamide and ethambutol, is in progress in Bangladesh (*66*).

In contrast, other successful MDRTB treatment programmes in Peru, the Republic of Korea, and the USA have used individually tailored regimens based on AST results for the most recent isolate from each patient (*11*, *12*, *24*, *36*, *57*). While the AST is performed on the patient's isolate (which may take weeks or months depending on the proximity and turnaround time of the laboratory concerned), a standardized regimen (e.g. an injectable agent, a quinolone, ethionamide, pyrazinamide) based on the susceptibility profiles of local MDRTB strains may be prescribed. The patient's regimen is then adjusted when the AST results become available. These individualized treatment strategies therefore require ready access to a sophisticated laboratory performing reliable ASTs, and medical personnel capable of interpreting the results and prescribing tailored regimens. Neither of these services may be available in the MDRTB hot spots described above (e.g., the Dominican Republic, India, the former Soviet Union, Thailand, and Viet Nam). The outcomes of large MDRTB treatment programmes using standardized and individualized regimens should therefore be compared in order to determine the optimal model.

Irrespective of whether a standardized or individualized regimen is used, directly observed therapy (DOT) should be a mandatory component of any DOTS-plus programme. The importance of adherence to these last-chance regimens must be emphasized to patients and their families, and should be guaranteed by instituting DOT for all patients with drug-resistant disease (*56*, *67*). If adherence does not occur there is a risk not only of failure but also of the

Table 2. **Unresolved issues surrounding DOTS-plus programmes**

Current DOTS strategy	Possible modifications required for DOTS-plus
Standardized treatment throughout therapy	Individualized treatment regimens when AST results available
Diagnosis by microscopy	Local facilities for culture and ASTs[a] Availability of ASTs[a] for second-line drugs
Reliable supply of a limited number of first-line drugs	Provision of an extensive range of highly expensive second-line drugs Supply of laboratory consumables Prevention of uncontrolled use of second-line drugs
Continuous evaluation of patient notifications, smear results and outcomes	Three-monthly culture and AST[a] results, and more extensive programmatic reviews may be necessary
Local government commitment	Additional support from external governments and agencies

[a] Antibiotic susceptibility tests.

acquisition of additional resistance to the second-line drugs.

Case detection and susceptibility testing

The current DOTS strategy emphasizes passive case detection and diagnosis by smear microscopy (*7*). In the absence of facilities for culture and ASTs the detection of MDRTB becomes a diagnosis of exclusion. New smear-positive cases of pulmonary TB receive category I treatment (e.g. 2EHRZ/4HR) (*61*). Patients who relapse, default or fail (i.e. have positive sputum smears despite five months of treatment) are given category II treatment (i.e. 2SHRZE/1HRZE/5HRE). Patients failing a fully supervised category II treatment regimen are classified as chronic cases and are assumed to have MDRTB.

The drug susceptibility patterns of patients at each stage of this algorithm vary between programmes and between countries. In the WHO/IUATLD survey, the median rate of MDRTB among new cases was 1.4% (range 0–14.4%) (*5*, *6*). Among patients who did not respond, relapsed or defaulted after more than one month of therapy, only 36.0% (range 5.3–100%) had drug-resistant strains and the median rate of MDRTB was 13.0% (range 0–54.4%). The category II retreatment regimen should therefore cure the majority of patients with a past history of failure, relapse or default. Unfortunately, patients at the final step of the algorithm, i.e. who have failed a fully supervised category II regimen, have a high rate of drug resistance. Crofton et al. (*67*) suggested that up to 80% of such patients excreted resistant bacilli and that as many as 50% of this group had MDRTB. Preliminary results from studies in Bangladesh coordinated by the Damien Foundation and supported by our laboratory indicated that 25 of 43 patients (58%) who relapsed after receiving category II treatment had MDRTB and that 75 of 86 patients (87%) who did not respond to category II treatment had MDRTB. This algorithmic approach to diagnosing MDRTB in any patient not cured by category II treatment is therefore inaccurate and depends on several variables, including the level of treatment supervision. Hence, DOTS-plus programmes may require ready access to laboratory facilities just to make the diagnosis of MDRTB.

It has been argued that this algorithmic approach to MDRTB diagnosis is not only inaccurate but also dangerous and costly. Individual patients may be in danger of receiving inappropriate treatment, and the cost of treating MDRTB patients, together with any secondary cases infected by MDRTB patients as they pass through this ineffective treatment algorithm, far exceeds the cost of routinely performing ASTs on initial isolates (*68*).

Justification for not performing routine ASTs on initial isolates was provided by a study conducted by the British Medical Research Council in Hong Kong, in which streptomycin, isoniazid and PAS were used in the pre-rifampicin era (*69*). Among patients with drug-resistant TB on admission, 31% of those whose treatment was not adjusted in response to initial AST results had an unfavourable result (i.e. failure, relapse or death) during a three-year follow-up, whereas this was true of only 13% of patients whose treatment was adjusted. However, after all patients with unfavourable outcomes were retreated, e.g. with ethionamide, pyrazinamide and cycloserine, the ultimate outcomes were similar, the final success rates being 93% and 91%, respectively, for patients with drug-resistant disease whose initial treatments were and were not adjusted on the basis of initial AST results. Reviews of the British Medical Research Council trials continued to discourage routine ASTs on initial isolates because four-drug or five-drug regimens produced excellent results (e.g. 2% failure rate) despite the presence of ODRTB (*53*, *70*). These reviews assessed thousands of patients but included no more than 12 cases of rifampicin resistance. The need to perform routine ASTs on initial isolates should therefore be reconsidered in the era of rifampicin resistance and MDRTB.

New DOTS-plus programmes may need to extend the initial susceptibility tests to include second-line drugs. Our laboratory has been performing ASTs on *M. tuberculosis* isolates from prisoners in Baku, Azerbaijan, and Mariinsk, Siberia, in collaboration with the International Committee of the Red Cross and Médecins sans Frontières (*45*, *46*). In addition to detecting high rates of MDRTB, preliminary investigations using approved versions of the proportion method have found no evidence of quinolone resistance but have detected resistance to kanamycin, defined as a critical proportion of bacteria exceeding 1% of the population when cultured on Middlebrook 7H10 agar containing 5.0 μg kanamycin/ml (*71*). Of 367 isolates tested, 148 (40.3%) were found to be MDRTB and 35 (9.5%) were resistant to kanamycin; 23 (15.5%) of the MDRTB strains were also resistant to kanamycin. Kanamycin resistance is likely in the former Soviet Union, where the drug has been used widely and irregularly in non-standardized regimens (*72*). Such resistance can be expected to be particularly prevalent among prisoners with TB, who often receive only intermittent drug treatment (*45*).

Unfortunately, if laboratories supporting DOTS-plus programmes are required to perform ASTs for second-line drugs they are likely to find that the optimal conditions (e.g. of medium composition) and critical concentrations for performing these tests remain ill-defined. Pfyffer et al. (*73*) have begun the process of determining the critical concentrations for the second-line drugs when ASTs are performed using Middlebrook 7H10 agar or the radiometric BACTEC method (Becton-Dickinson Diagnostic Instrument Systems, Sparks, MD). Working groups associated with WHO, IUATLD, and the Centers for Disease Control and Prevention are attempting to standardize these second-line ASTs, as was achieved by Laszlo et al. for the susceptibility testing of streptomycin, isoniazid, rifampicin and ethambutol

during the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance (*5*, *6*, *74*).

In summary, DOTS-plus programmes may require on-site culture and AST facilities for the accurate diagnosis of MDRTB and the guidance of treatment. The laboratories may even need to perform ASTs for second-line drugs in areas where previous TB control efforts have been chaotic and these drugs have been used inappropriately. Continuing operational studies are required to determine the level of laboratory support required by DOTS-plus programmes.

Provision and control of drug supplies

The current DOTS recommendations emphasize the need for reliable supplies of high-quality preparations of the four or five drugs used in standardized short-course regimens (*7*, *61*). Pharmacies supporting DOTS programmes should estimate their drug requirements, prepare a procurement plan, obtain finance, purchase their stock, ensure quality, properly store and distribute their drugs and monitor usage. Each step in this process is more complicated in DOTS-plus programmes. At the inception of such a programme an uncertain number of MDRTB patients may require treatment with individualized regimens containing a diverse range of expensive drugs that are difficult to procure. The ordering of adequate supplies is bound to be problematic and there may be no opportunity to reduce the price of expensive second-line drugs by placing large orders. In DOTS-plus programmes, drug distribution might prove difficult for MDRTB patients scattered over a wide geographical area. Supply services also have to provide the laboratory equipment and reagents required by the diagnostic facilities supporting DOTS-plus programmes.

The cost of second-line drugs is the most important problem facing the procurement services of DOTS-plus programmes. An injectable agent and a quinolone form the basis for successful MDRTB treatment regimens (*24*, *56*, *67*), and both are expensive. Although toxic and seldom used, the other second-line agents (i.e. ethionamide, cycloserine and *para*-aminosalicylic acid) are excessively expensive because only limited supplies are available or because production monopolies exist.

Table 3 outlines various recommended regimens for treating MDRTB in the presence or absence of resistance to additional agents (*24*, *56*, *67*). The cost of each regimen has been estimated on the basis of the average vendor price listed in the International Drug Price Indicator Guide (*75*) and of information obtained from pharmaceutical suppliers and other sources (*67*). Naturally, drug costs vary between DOTS-plus programmes, depending on their geographical locations and on individual procurement arrangements with suppliers. Table 3 shows the high cost of MDRTB treatment regimens. For example, the estimated drug cost of treating MDRTB with associated ethambutol and pyrazinamide resistance is US$ 9188.95 (Table 3), which is 264.9 times the cost of the standard category I regimen recommended by WHO (i.e. 2HRZE/4HR) (*61*). These costings assume an initial three-month phase of intensive treatment, which may need to be extended if the patient's smears do not convert. In fact, some experts recommend that the intensive phase be routinely extended to 4–6 months so as to improve the cure rate (*24*). Furthermore, the free-on-board prices given in Table 3 do not include freight, insurance and

Table 3. **Costing of various treatment regimens for multidrug-resistant TB**[a]

Regimen[b] (US$/month)	Ethambutol (US$ 2.60)	Pyrazinamide (US$ 2.63)	Kanamycin[c] (US$ 13.50)	Ciprofloxacin[d] (US$ 7.34)	Ethionamide (US$ 76.05)	Cycloserine (US$ 318.05)	*para*-aminosalicylic acid (US$ 239.40)	Total cost (US$)
3KEtZQE/18EtQE	54.68	7.90	40.50	154.22	1597.05			1854.36 (53.5)[e]
3KEtZQC/18EtQC		7.90	40.50	154.22	1597.05	6678.97		8478.65 (244.4)
3KEtEQC/18EQEt	54.68		40.50	154.22	1597.05	954.14		2800.60 (80.7)
3KEtQCP/18EtQC			40.50	154.22	1597.05	6678.97	718.20	9188.95 (264.9)

[a] Free-on-board drug prices obtained from the International Drug Price Indicator Guide (*75*) for isoniazid, rifampicin, ethambutol, pyrazinamide, kanamycin and ciprofloxacin (calculations based on the average vendor price), from ECHO International Health Services Limited for cycloserine, and from pharmaceutical companies and reference *67* for ethionamide and *para*-aminosalicylic acid.

[b] Various regimens recommended for treating MDRTB with/without associated ethambutol and pyrazinamide resistance (*24*, *56*, *67*); K, kanamycin; Et, ethionamide; Z, pyrazinamide; E, ethambutol; Q, quinolone; C, cycloserine; P, *para*-aminosalicylic acid.

[c] Kanamycin selected as cheapest injectable agent (assuming streptomycin resistance); amikacin and capreomycin costed at US$ 641 and US$ 828 per month respectively; additional price of needles and syringes must be added to the costings for the injectable agents.

[d] Ciprofloxacin selected as cheapest available quinolone; ofloxacin costed at US$ 196.95 per month.

[e] Figures in parentheses are the costings for the MDRTB treatment regimens compared with the price of the WHO-recommended category I first-line treatment regimen (i.e. 2 HRZE/4 HR) (*58*), which was estimated to be US$ 34.69 (*75*).

other expenses nor do the costings include the price of needles and syringes for administering the injectable agents. Hence, the costings may grossly underestimate the true price of MDRTB treatment.

Drug procurement services should ensure that only patients enrolled in and fully supervised by the DOTS-plus programmes have access to second-line antituberculosis drugs. Uncontrolled use of these agents produces additional resistance, making some MDRTB strains even more expensive to treat or, ultimately, uncontrollable. For example, the detection of kanamycin resistance in the former Soviet Union complicates the treatment of MDRTB. Kanamycin resistance produces cross-resistance to streptomycin and amikacin (*24*, *67*). Patients with MDRTB and associated kanamycin resistance therefore require treatment with the polypeptide antibiotic, capreomycin (*24*, *56*, *67*), which is very expensive, costing US$ 828 per month, whereas kanamycin costs only US$ 13.50 (Table 3).

Although quinolone resistance has not yet been detected in our laboratory among *M. tuberculosis* isolates from prisoners in Baku and Mariinsk, experience in New York City suggests that quinolone resistance is readily acquired. Sullivan et al. (*76*) reported acquired quinolone resistance in 16 patients receiving inappropriate or inadequate unsupervised treatment; the known number of days of quinolone therapy in these 16 patients ranged from 23 to 271 (median 64). There is no recognized cross-resistance with other antituberculous medications but there is complete cross-resistance within the fluoroquinolone group (*67*). Ciprofloxacin is widely and increasingly used for treating gastrointestinal infections and the newer quinolones (e.g. levofloxacin, sparfloxacin and trovafloxacin), which are active against *Streptococcus pneumoniae* as well as Gram-negative respiratory pathogens, are recommended for treating respiratory tract infections in industrialized countries (*77*). While cost is initially bound to limit the widespread use of these new quinolones in many areas where MDRTB is endemic, the risk of TB patients receiving prolonged inappropriate quinolone monotherapy for chronic undiagnosed respiratory symptoms cannot be underestimated. Pharmacy services associated with DOTS-plus programmes therefore have to ensure that only enrolled patients receive these second-line agents while also attempting to maintain reliable supplies of these expensive drugs.

Programme review

The fourth element of the current DOTS strategy is the continuous monitoring of TB control programmes (*7*). Patient notifications, smear results and treatment outcomes are recorded, cross-tabulated, and reviewed in a continuing process of quality assurance. What parameters should be reviewed in DOTS-plus programmes? Are culture and AST results required throughout treatment? If so, how often are they required? How should patients be registered and followed up for up to two years of treatment? Should they be followed up as part of national TB programmes or would a DOTS-plus programme be a discrete entity with its own recording and reviewing processes? The answers to these questions depend on the results of pilot studies.

Protocols for pilot programmes, developed by WHO's Working Group on DOTS-plus for MDRTB (*14*), recommend the collection of an extensive range of clinical and laboratory data. For example, the sputum smear and culture status of patients should be determined at three-monthly intervals in order to elucidate treatment response, relapse and failure rates. Susceptibility tests should also be performed on sequential isolates from treated patients to detect the acquisition of resistance to treatment drugs. Furthermore, these isolates should be subjected to restriction fragment length polymorphism analyses so as to distinguish failures or relapses from cases of reinfection. Detailed programmatic data should also be collected on ease of implementation, rates of adverse effects, rates of abandonment, and cost-effectiveness.

When the data from these pilot studies have been collated and analysed, TB authorities should be able to make firm recommendations on the indications for and nature of DOTS-plus programmes. The optimal indicators of programme efficiency will also be determined so that subsequent DOTS-plus programmes can be efficiently reviewed. Interestingly, initial impressions gained in the Damien Foundation project in Bangladesh suggest that DOTS-plus treatment programmes and routine national TB programmes should be administered as separate entities in the interest of effective management and review, given the extent to which the former programmes are the more complex and intensive.

Government commitment

The current DOTS strategy demands the commitment of local governments to effective TB control. The impact of real government commitment is exemplified by the successful reduction of TB, including MDRTB, in New York City (*28*, *29*). The multiple interventions instituted in New York City, which cost over US$ 1000 million, included an effective DOTS programme and intensive individualized treatment of MDRTB patients (*28*).

Local governments in the MDRTB hot spots detected during the WHO/IUATLD survey do not have such financial resources. The few established DOTS-plus trials have been conducted through collaboration between local TB programmes and international nongovernmental organizations (*11*, *12*, *65*, *66*). DOTS-plus programmes in the MDRTB hot spots clearly require more than local government commitment. They need real commitment and significant financial support from international organizations, nongovernmental organizations, and the governments of the industrialized world, who have a vested interest in and moral responsibility for assisting in global TB control.

Conclusion

The DOTS strategy decreases ODRTB, limits the emergence of MDRTB, and is cost-effective (*8, 40*, *59*, *60*, *78*). Before establishing DOTS-plus facilities, TB control programmes should prevent the development of new drug-resistant cases by effectively implementing the DOTS strategy, i.e. they should have "turned off the tap" (*13*, *67*, *79*). However, limited experience from prison populations in the former Soviet Union suggests that the SCC component of the DOTS strategy is not enough in populations with high pre-existing levels of MDRTB.

Farmer et al. argued persuasively that all TB patients, including those with MDRTB, have the right to effective treatment (*11*, *12*). TB control authorities have to decide at the population level whether DOTS-plus facilities are required, yet the level of MDRTB prevalence justifying such facilities remains undefined. The exact format of DOTS-plus facilities is equally uncertain. Operational studies are required to determine the level of laboratory support required by DOTS-plus programmes and whether standardized or individualized treatment regimens should be used. Regardless of the eventual format of DOTS-plus programmes, they are bound to present enormous problems for drug supply departments in developing countries and to require significant financial support from industrialized countries and international agencies. Recognizing the problems in establishing such programmes, a working group involving WHO and other organizations has been established to oversee pilot studies and assess the feasibility of MDRTB management within TB control programmes (*14*, *15*).

It should be emphasized that without DOTS there can be no DOTS-plus. If industrialized countries and international agencies are willing to establish DOTS-plus programmes it follows that all the TB patients in any country are deserving of treatment. This inclusive argument should be maintained so that the recent interest in MDRTB and DOTS-plus programmes proves beneficial for all TB patients rather than just the 2.2% or so with MDRTB (*5*, *6*). ■

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Résumé

Le traitement de brève durée sous surveillance directe et la tuberculose à bacilles multirésistants : des changements s'imposent-ils ?

Au sens strict, la tuberculose à bacilles multirésistants est une forme de tuberculose résistante à tout le moins à l'isoniazide et à la rifampicine, deux médicaments dont l'efficacité détermine le succès de la chimiothérapie de brève durée. Cette double résistance à l'isoniazide et à la rifampicine exige un traitement prolongé toxique avec des médicaments de seconde intention moins efficaces.

Une enquête mondiale faite récemment par l'OMS et l'Union internationale contre la Tuberculose et les Maladies respiratoires a montré que la prévalence médiane de la tuberculose à bacilles multirésistants parmi les nouveaux cas, c'est-à-dire la tuberculose à bacilles multirésistants primaire, était de 1,4 % (fourchette 0-14,4 %) et, parmi les patients traités auparavant, c'est-à-dire la tuberculose à bacilles multirésistants acquise, de 13,0 % (fourchette 0-54,4 %). La prévalence de la tuberculose à bacilles multirésistants aux Etats-Unis d'Amérique et en Europe de l'Ouest était relativement faible, à savoir 0,9-2,5 %, mais des pics de prévalence ont été notés en ex-Union soviétique et dans des pays en développement d'Asie et d'Amérique du Sud. Les taux de prévalence de la tuberculose à bacilles multirésistants primaire dans ces régions variaient entre 4,6 % et 14,4 %, et le taux de prévalence de la tuberculose à bacilles multirésistants acquise atteignait 54,4 % en Lettonie.

L'OMS a recommandé une stratégie en plusieurs volets connue sous le nom de stratégie DOTS (« directly observed treatment short-course » ou traitement de brève durée sous surveillance directe) pour faire face au fléau mondial que représente la tuberculose et pour freiner la propagation de la pharmacorésistance. La stratégie DOTS, qui comprend une chimiothérapie de brève durée normalisée, donne de bons résultats dans divers contextes, présente un bon rapport coût/efficacité et permet de réduire le phénomène de pharmacorésistance dans les pays où les taux antérieurs de prévalence de la tuberculose à bacilles multirésistants étaient faibles. L'expérience limitée faite parmi des groupes de prisonniers en ex-Union soviétique donne à penser que la chimiothérapie de brève durée, composante essentielle de la stratégie DOTS, comporte des taux d'échec beaucoup trop élevés là où la tuberculose à bacilles multirésistants est endémique. On a également noté un risque non quantifié d'apparition d'une résistance à d'autres agents chimiothérapeutiques (par exemple, streptomycine, éthambutol ou pyrazinamide), c'est-à-dire un effet d'amplification, chez des patients atteints de tuberculose à bacilles multirésistants qui suivaient un traitement normalisé de brève durée. Il a été suggéré que, là où la tuberculose à bacilles multirésistants est endémique, les programmes de lutte antituberculeuse

assurent des services supplémentaires, à savoir DOTS-plus pour la tuberculose à bacilles multirésistants.

La stratégie DOTS actuelle comprend cinq éléments clés dont chacun devra sans doute être modifié là où la tuberculose à bacilles multirésistants est prévalente. En premier lieu, la stratégie DOTS actuelle s'appuie sur des schémas chimiothérapeutiques types. Deux essais avec la stratégie DOTS-plus ont donné de bons résultats avec un schéma type utilisant des médicaments de seconde intention pour soigner des patients atteints de tuberculose à bacilles multirésistants au Bangladesh et au Rwanda. En revanche, les programmes de traitement de la tuberculose à bacilles multirésistants en République de Corée, au Pérou et aux Etats-Unis d'Amérique s'appuyaient sur des schémas thérapeutiques personnalisés. Il faudrait comparer les résultats du traitement normalisé et du traitement personnalisé pour arriver au modèle optimal.

En deuxième lieu, alors que la stratégie DOTS actuelle insiste sur le dépistage passif et le diagnostic moyennant l'examen des étalements au microscope, les programmes DOTS-plus exigeront sans doute des installations permettant de procéder sur place à une culture bactériologique et à des essais de sensibilité aux antibiotiques afin de pouvoir diagnostiquer avec précision la tuberculose à bacilles multirésistants et à orienter le traitement. Les laboratoires devront peut-être même procéder à des essais de sensibilité aux antibiotiques pour les médicaments de seconde intention là où il se manifeste une résistance.

La fiabilité de l'approvisionnement en médicaments de bonne qualité est le troisième élément de la stratégie DOTS actuelle, mais il est vraisemblable que les programmes DOTS-plus imposeront des tâches supplémentaires aux services d'approvisionnement pharmaceutique. Un certain nombre de patients atteints de tuberculose à bacilles multirésistants auront besoin d'un traitement personnalisé reposant sur divers médicaments qu'il est difficile de se procurer. En outre, les médicaments de seconde intention coûtent cher. Ainsi, le coût des médicaments nécessaires au traitement de la tuberculose à bacilles multirésistants lorsqu'il y a aussi résistance à l'éthambutol et à la pyrazinamide est évalué à US $9188,95 au moins, soit 264,9 fois le coût du schéma type OMS de catégorie I (c'est-à-dire 2HRZE/4HR, où E, H, R et Z représentent l'éthambutol, l'isoniazide, la rifampicine et la pyrazinamide, respectivement). Afin d'éviter l'apparition d'une résistance supplémentaire, les services chargés de fournir les médicaments nécessaires aux programmes DOTS-plus doivent veiller à ce que seuls les patients inscrits sur les listes et placés sous supervision aient accès aux médicaments de seconde intention.

Enfin, DOTS-plus est aussi plus exigeant en ce qui concerne les deux derniers éléments de la stratégie DOTS (à savoir le suivi continu des programmes et l'appui des autorités locales). DOTS-plus est un concept en pleine évolution et il faut faire des études opérationnelles pour en déterminer les indications et préciser la forme que prendront les programmes. La surveillance de ces projets pilotes est assurée par le groupe spécial sur la stratégie DOTS-plus pour la tuberculose à bacilles multirésistants, à l'action duquel participent l'OMS et plusieurs autres institutions. Enfin, les programmes DOTS-plus doivent recevoir un appui financier et technique d'organisations internationales et des gouvernements des pays industrialisés, qui ont tout intérêt à ce que la tuberculose soit endiguée dans le monde entier et pour qui cette entreprise est aussi une responsabilité morale.

Resumen

El tratamiento breve bajo observación directa y la tuberculosis polifarmacorresistente: ¿se requieren cambios?

La tuberculosis polifarmacorresistente (TBPFR) se define estrictamente como la tuberculosis resistente a por lo menos la isoniazida y la rifampicina, porque el éxito de la quimioterapia de corta duración depende de la eficacia de esos medicamentos. La resistencia combinada a la isoniazida y la rifampicina exige un tratamiento prolongado con medicamentos de segunda línea menos eficaces.

En una encuesta realizada recientemente a nivel mundial por la OMS y la Unión Internacional contra la Tuberculosis y las Enfermedades Respiratorias, la prevalencia mediana de la TBPFR entre los nuevos casos, es decir, la TBPFR primaria, fue del 1,4% (intervalo: 0%-14,4%) y la tasa entre los pacientes tratados anteriormente, es decir, la TBPFR adquirida, del 13 % (intervalo: 0%-54,4%). La prevalencia de la TBPFR en los Estados Unidos de América y en Europa occidental fue relativamente baja, entre el 0,9% y el 2,5%, pero se registraron focos críticos en la antigua Unión Soviética y en países en desarrollo de Asia y de América del Sur. Las tasas de TBPFR primaria en esas regiones oscilaron entre el 4,6% y el 14,4%, y la tasa de TBPFR adquirida alcanzó el 54,4% en Letonia.

Para hacer frente a los estragos causados por la tuberculosis a nivel mundial y limitar la propagación de la farmacorresistencia, la OMS recomendó una estrategia multiforme conocida como DOTS (estrategia de tratamiento breve bajo observación directa). Esta estrategia, que incluye la quimioterapia breve estándar (QBE), funciona bien en diversos entornos, es eficaz en relación con el costo y reduce la tasa general de farmacorresistencia en los países con niveles preexistentes bajos de TBPFR. La limitada experiencia en la población carcelaria de la antigua Unión Soviética mostró que la QBE, elemento clave de la estrategia DOTS, producía unas tasas de fracaso inaceptablemente altas en los lugares donde la TBPFR era endémica. También existía un riesgo no cuantificado de generar resistencia a otros agentes (por ejemplo, a la estreptomicina, el etambutol y la pirazinamida), es decir, un efecto amplificador, en los pacientes con TBPFR sometidos al tratamiento breve estándar. Se ha sugerido que los programas de lucha

antituberculosa en las zonas donde la TBPFR es endémica deberían prestar servicios adicionales, concretamente la DOTS-plus.

La estrategia DOTS actual abarca cinco elementos clave, cada uno de los cuales puede tener que modificarse en las zonas donde la TBPFR es prevalente. En primer lugar, la estrategia actual recomienda el uso de la quimioterapia estándar. En dos ensayos de DOTS-plus se ha utilizado con éxito un tratamiento estándar con medicamentos de segunda línea en enfermos de TBPFR en Bangladesh y en Rwanda. En cambio, en los programas de tratamiento de la TBPFR en la República de Corea, el Perú y los Estados Unidos de América se ha utilizado un tratamiento personalizado. Para llegar al modelo óptimo habrá que comparar los resultados de los tratamientos normalizados y personalizados.

En segundo lugar, la estrategia DOTS actual hace hincapié en la detección pasiva de casos y en el diagnóstico mediante el examen microscópico del esputo, mientras que los programas de DOTS-plus pueden exigir la presencia en el lugar de instalaciones para el cultivo y las pruebas de sensibilidad a los antibióticos, a fin de diagnosticar con exactitud la TBPFR y orientar el tratamiento. Los laboratorios pueden tener que realizar incluso pruebas de sensibilidad a los medicamentos de segunda línea en las regiones en que existe resistencia.

El suministro fiable de medicamentos de alta calidad es el tercer elemento de la actual estrategia DOTS, pero cabe prever que los programas de DOTS-plus plantearán exigencias aún mayores a sus servicios de suministro de medicamentos. Un número indeterminado de enfermos de TBPFR podría requerir un tratamiento personalizado con una variada gama de medicamentos difíciles de adquirir. Además, los medicamentos de segunda línea son caros. Por ejemplo, el costo farmacológico estimado del tratamiento de la TBPFR con resistencia asociada al etambutol y la pirazinamida es como mínimo de US$ 9188,95, lo que equivale a 264,9 veces el costo del tratamiento estándar de categoría I de la OMS (es decir, 2HRZE/4HR, donde E, H, R y Z representan el etambutol, la isoniazida, la rifampicina y la pirazinamida, respectivamente). Para prevenir el desarrollo de una nueva resistencia, los servicios de suministro de medicamentos para la DOTS-plus deberán velar por que sólo tengan acceso a los medicamentos de segunda línea los enfermos registrados y supervisados.

La DOTS-plus plantea asimismo un nivel de exigencia mayor a los dos últimos elementos de la estrategia DOTS (a saber, la vigilancia constante del programa y el apoyo de la administración local). La DOTS-plus es un concepto en evolución, y hay que realizar estudios operativos a fin de determinar las indicaciones para los programas y sus características. Esos proyectos experimentales están siendo supervisados por el Grupo de Trabajo sobre la DOTS-plus para la TBPFR, en el que participan la OMS y otras varias instituciones. Por último, los programas de DOTS-plus necesitan apoyo financiero y técnico de las organizaciones internacionales y de los gobiernos del mundo industrializado, que tienen un claro interés y una responsabilidad moral en la lucha contra la tuberculosis a escala mundial.

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