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Challenges to effective control of tuberculosis and drug resistance in African countries

Drug-resistant tuberculosis (TB) appeared soon after the introduction of chemotherapy and is considered a man-made phenomenon. Despite the efficacy of short course chemotherapy, which includes a cocktail of drugs and has been generally recommended since the 1960s, increasing numbers of multi-drug-resistant (MDR) cases were reported worldwide in the early 1990s. In the WHO's 2004 report on surveillance of drug-resistant TB, MDRTB is reported from over 100 countries. Although little data is available on drug-resistant TB in Africa, this paper presents an overview of the current situation on the African continent, which is severely affected by the TB epidemic.

Uitdagingen bij de bestrijding van tuberculose en resistentie aan anti-TB middelen in Afrikaanse landen

Kort na het invoeren van chemotherapie voor de behandeling van tuberculose (TB) trad resistentie op tegen de gebruikte anti-TB middelen. Ondanks de doeltreffendheid van de korte behandeling die bestaat uit een cocktail van middelen en werd aangeraden vanaf de jaren 1960, kwamen er een toenemend aantal gevallen van multiresistente TB (MDRTB) in het begin van de jaren '90. In het WHO 2004 jaarrapport over de surveillance van resistente TB, werd MDRTB geregistreerd in meer dan 100 landen. Hoewel weinig gegevens bekend zijn over resistente TB in Africa, geeft dit artikel een overzicht van de huidige situatie rond de resistentie in het Afrikaanse continent dat erg getroffen is door de TB epidemie.

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As early as 1985, Iseman attempted to encourage research and operational efforts to combat the threat of drug-resistant tuberculosis (TB), which he called the result of "inadvertent genetic engineering" (Iseman 1985: 735). Indeed, the development of drug resistance is a man-made phenomenon following ineffective treatment, which can be due, among other things, to ineffective TB control programmes, mismanagement by physicians or a patient's non-adherence to treatment.

Drug-resistant *Mycobacterium tuberculosis* isolates first appeared in the 1940s-1960s, soon after the introduction of various new chemotherapeutics such as streptomycin (S), para-aminosalicylic acid (PAS) and isoniazid (H), used in mono- or dual therapy (cf McDermott *et al* 1947; Rossman & MacGreggor 1995). The discovery of rifampicin (R) and the implementation of the short-course chemotherapy (SCC) using a combination of drugs were milestones in the campaign against TB. SCC appeared successful in treating drug-susceptible strains as well as H- and/or S- resistant strains (cf Mitchison & Nunn 1986), but also allowed the medical community to continue to ignore the underlying factors that promote drug resistance. Murray *et al* in 1990 called the magnitude of the tuberculosis problem "simply staggering" and pointed out that "tuberculosis has been ignored by much of the international health community" (Murray *et al* 1990: 17-8). In the early 1990s several reports were published on the increasing risk of multidrug-resistant tuberculosis (MDRTB),[1] defined as *M tuberculosis* isolates resistant to at least H and R, the two most potent anti-TB drugs and the key components of SCC.[2]

In 1994, the World Health Organisation (WHO) joined forces with the International Union Against Tuberculosis and Lung Disease (IUATLD, now named the Union) and launched the Global Project on Anti-Tuberuclosis Drug-Resistance Surveillance (cf WHO 1994).

This paper presents an overview of the current situation of drug-resistant TB in Africa, one of the continents most affected by the TB epidemic.

1 Cf Ellner *et al* 1995; Frieden *et al* 1993; Prignot 1993; Rastogi 1993; Sbarbaro 1993.

2 Cf Kochi *et al* 1994; Iseman 1993; Pablos-Mendez *et al* 1998.

1. Available data

1.1 TB control policies

Despite the implementation and success of SCC in treating tuberculosis in the 1960s, TB remains one of the major infectious diseases and is responsible for about eight million cases with the active disease and two million deaths annually (cf Dye *et al* 1999). The mean TB case notification rate for the African region increased from 59 cases per 100 000 inhabitants in 1980 to 148/100 000 in 2002 (cf WHO 2004a). Nine of the forty African countries reporting in 1980 showed a relatively low incidence of less than 20/100 000 and only three countries had high rates of more than 200/100 000 (Botswana, Lesotho and Mauritania). During the last two decades, however, the number of African countries reporting less than 20/100 000 decreased (to four out of 38 in 1994 and only two out of 41 in 2002), whereas the number with notification rates of 200/100 000 or more increased from six out of 38 countries in 1994 to eleven out of 41 countries in 2002 (cf WHO 2004a). The latter group comprised Angola (228), Botswana (577), the Congo (250), Kenya (254), Lesotho (562), Malawi (207), Namibia (647), South Africa (481), Swaziland (631), Zambia (507) and Zimbabwe (461). Although this increase in incidence may be partially biased by better registration systems thanks to more efficient control programmes, TB control is hampered mainly by the HIV pandemic and poor living conditions in middle and low-income countries. Consequently, the highest notification rates in Africa are reported in sub-Saharan countries severely ravaged by the HIV pandemic (cf Asamoah-Odei *et al* 2004). Nevertheless, the growth in notification rates has been decelerating in these regions since the mid-1990s (cf WHO 2004a). The global incidence rate of TB was estimated to have increased at 1.1% per year in 2002, and the total number of cases at 2.4% per year (cf WHO 2004a).

In response to this situation, the WHO recommended a multifaceted strategy known as directly observed treatment short course (DOTS) to fight TB world-wide (cf WHO 1991). It constitutes a management strategy for public health systems that involves political commitment, the detection of infectious patients by microscopy, SCC under DOT for all detected cases, a guaranteed drug supply and outcome monitoring using a standardised recording and reporting system

permitting assessment of treatment results. DOTS should help to reach the targets for global TB control ratified by the 1991 World Health Assembly, and re-set later in 2000: success treatment of 85% of detected smear-positive TB cases and detection of 70% of all smear-positive cases by 2005 (cf WHO 2004a). Direct observation can be achieved in various ways: by supervision in a hospital, daily visits to the clinic, or home visits from healthcare staff or community volunteers. In a rural area in South Africa such unpaid community volunteers proved effective providers of DOT (cf Barker *et al* 2002)

The DOTS population coverage reached 69% of the global population and up to 81% in the high-burden countries of Africa (cf WHO 2004a). DOTS population coverage has been defined as "the percentage of people living in areas where health services have adopted the DOTS strategy" (WHO 2004a: 13). It should be noted, however, that the population units (countries, provinces or districts) nominally covered by DOTS do not necessarily provide full access to DOTS services. For example in South Africa, a DOTS population coverage of 98% was reported in 2002, which reflected the number of smear-positive cases notified within DOTS (97.656, 98.8%) compared to 1143 smear-positive cases (1.2%) reported outside the DOTS system. In Nigeria, 55% of the population lived in districts that had adopted DOTS, yet 89.4% of smear-positive cases were reported within DOTS.

1.2 Treatment outcomes

The global treatment success rate for smear-positive cases registered and treated under DOTS was calculated at 82%, which is close to the targeted 85%. An estimated 26% of all smear-positive cases arising in 2001 were treated successfully by DOTS programmes (cf WHO 2004a). However, significant regional differences were observed, with treatment success rates ranging from 71% in Africa to 93% in the Western Pacific Region. In Africa, where a higher proportion of cases are HIV-positive, the following unfavourable factors were most common: fatal outcomes (7%), treatment interruption (10%) and transfer without follow-up (7%). Among the high-burden African countries, Uganda and South Africa scored the lowest, with a treatment success rate of only 56% and 65% respectively for smear-positive cases in the 2001 DOTS cohort, and 17% and 24% of patients who defaulted or were trans-

ferred without follow-up, respectively. Treatment success in the South African cohort was low because of the high rates of default (12%), death (7%) and transfer without follow-up (12%). In Uganda the poor results are mostly explained by failure to evaluate outcomes (15%), as well as by the rates of default (17%) and death (6%). The Democratic Republic of the Congo (DRC), another high-burden country, reported a high treatment success rate (77%) in combination with a high detection rate (>50%). The remaining high-burden African countries (Ethiopia, Kenya, Nigeria, Tanzania, Zimbabwe and Mozambique) also had high treatment success rates, ranging from 71 to 81%, but with only intermediate case detection (10-49%).

1.3 Drug resistance surveillance

Since the commencement of the Project on Anti-TB Drug-Resistance Surveillance, the number of countries or geographical areas studied has increased, with 35 regions in the first, 58 in the second and 79 in the third global report (Figure 1).[3]

Compared to the American and European regions, the coverage of the project in the African region is low. Since its initiation in 1994, only 49.5% of new smear-positive TB patients in Africa and only 37% of the African countries have been surveyed (cf WHO 2004b). In general, drug resistance in the region is of low magnitude. The median resistance level to any drug among new TB cases in the period between 1999 and 2002 was 7.1% for the five African countries reported (Algeria, Botswana, Gambia, South Africa and Zambia), ranging between 6.2 % for Algeria and 13.6% for Botswana. MDRTB levels among new cases ranged from 0.5 % in Gambia to 2.6 % in the South African Mpumalanga Province (Table 1) (cf WHO 2004b). As expected, the prevalence of drug resistance among previously treated TB cases from the same surveys was higher, with 9.2% to 30.3 % showing any resistance and 1.7 to 13.7 % being found to be MDRTB (Table 1). The latter two values were seen in the South African provinces of the Free State and Mpumalanga, and indicate the importance of variations in local populations and programme management. The importance of conducting region-specific surveys in large high-burden countries is also emphasised.

3 Cf Pablos-Mendez *et al* 1998; WHO 2000; WHO 2004b.

Figure 1: WHO / IUATLD Global Project coverage 1994-2000

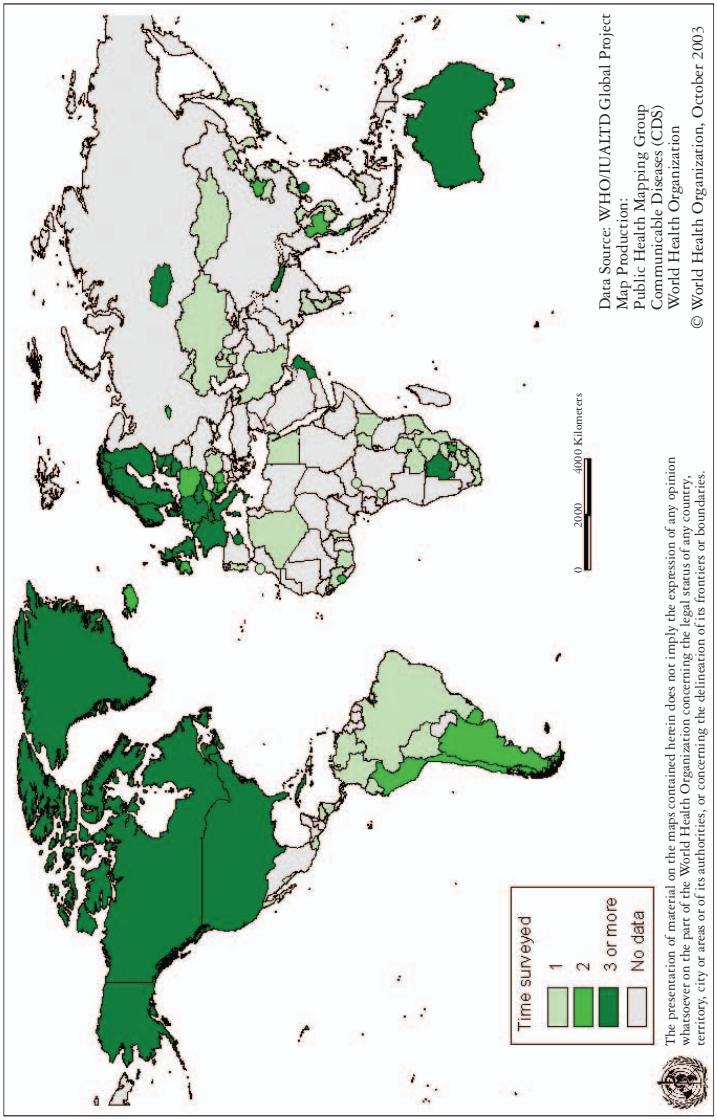

Table 1: Prevalence (%) of drug resistance among new and previously treated TB cases in the African WHO region.

Country/Setting	New TB cases				Previously treated TB cases			
	Year	Number of patients tested	Any resistance	MDR	Year	Number of patients tested	Any resistance	MDR
Algeria	2001	518	6.2	1.2				
Benin	1997	333	8.4	0.3				
Botswana	1996	407	3.7	0.2	1996	114	14.9	4.8
Botswana	1999	638	6.3	0.5	1999	145	22.8	9.0
Botswana	2002	469	13.6	1.3	2002	66	30.3	13.6
Central African Republic	1998	464	16.4	1.1	1998	33	36.4	18.2
Guinea	1998	539	14.7	0.6	1998	32	50.0	28.1
Ivory Coast	1996	320	13.4	5.3				
Kenya	1995	445	6.3	0.0	1995	46	37.0	0.0
Lesotho	1995	330	8.8	0.9	1995	53	34.0	5.7
Mozambique	1998	1028	20.8	3.5	1999	122	45.1	3.3
The Gambia	1999	210	4.3	0.5	1999	15		
Sierra Leone	1996	463	28.1	1.1	1996	172	52.9	12.8
Sierra Leone	1997	117	24.8	0.9	1997	13	61.5	23.1
S Africa / Eastern Cape	2001	506	11.3	1.0	2001	283	17.7	7.4

Table 1: Prevalence (%) of drug resistance among new and previously treated TB cases in the African WHO region (continued).

Country/Setting	New TB cases				Previously treated TB cases			
	Year	Number of patients tested	Any resistance	MDR	Year	Number of patients tested	Any resistance	MDR
S Africa / Free State	2001	453	8.6	1.8	2001	174	9.2	1.7
S Africa / Gauteng province	2001	585	6.7	1.4	2001	163	12.9	5.5
S Africa / Kwazulu Natal	2001	595	6.6	1.7	2001	207	18.4	7.7
S Africa / Limpopo	2001	449	7.1	2.4	2001	86	17.4	7.0
S Africa / North-West province	2001	595	8.1	2.4	2001	175	18.3	6.3
S Africa / Mpumalanga	1997	661	8.0	1.5	1997	100	22.0	8.0
S Africa / Mpumalanga	2001	702	9.1	2.6	2001	175	23.4	13.7
S Africa / Western Cape	2001	360	5.3	1.1	2001	201	8.0	4.0
Uganda	1997	374	19.8	0.5	1997	45	51.1	4.4
Zambia	2000	445	11.5	1.8	2000	44	15.9	2.3
Zimbabwe	1995	676	3.3	1.9	1995	36	13.9	8.3

Adapted from WHO 1997, WHO 2000 & WHO 2004b. Countries/settings in bold have been surveyed more than once. Data in green comes from the most recent report (WHO 2004b).

Data from previous survey periods (1994 to 1998), showed overall resistance levels of more than 15% for new TB cases in the Central African Republic, Uganda, Mozambique and Sierra Leone, and more than 30% in previously treated patients (Table 1). MDRTB levels were accordingly high. None of these countries has available data from the last five years. Nevertheless, the best parameter for monitoring the effectiveness of TB control programmes is the drug-resistance trend, documented by either continuous surveillance or intermittent surveys. Continuous monitoring (surveillance) does not exist in the African region, so subsequent surveys must provide this essential information. However, given the few settings surveyed in Africa, data on drug-resistance trends is scarce. Only Sierra Leone, Botswana and the Mpumalanga Province in South Africa had repeated surveys (Table 1), all of which showed increases in drug-resistance levels, although only slight in Sierra Leone. In Botswana the most pronounced increase was in "any resistance" among new TB cases, with a shift from 3.7 % in 1996 to 6.3 % in 1998 and to 13.6% in 2002 (Table 1) (cf WHO 2000; WHO 2004b). Similarly, "any resistance" among previously treated patients increased from 14.9% to 22.8% and 30.3% (Table 1). Nevertheless, a treatment success rate of 77% was attained in 2001. However, the high prevailing level of drug resistance might jeopardise treatment in the future, creating additional resistance (the amplifier effect) even when SCC is applied correctly (cf Rigouts 2000; Farmer *et al* 1998). Vigilance and follow-up sampling are therefore recommended in this setting. In South Africa's Mpumalanga province MDRTB rates increased significantly over the four-year period from 1997 to 2001: from 1.5% to 2.6% in new cases and from 8.0% to 13.7% in re-treatment cases. In this setting the high drug-resistance levels are reflected in a low cure rate and accompanied by reports of drug stock-outs, high default rates, shortcomings in core components of DOTS and failure in the public health system.

2. Discussion

2.1 The need for drug-resistance surveillance

The scarce information that is currently available highlights the need to expand drug-resistance surveys in the African region. First, the num-

ber of nations surveyed should increase in order to fill the gaps in some crucial areas. Nation-wide surveys are planned in the near future for Ethiopia, Malawi, Zimbabwe, Kenya, Rwanda and Senegal (cf WHO 2004b). Furthermore, within each nation, sampling should be representative of the whole population. A survey performed in 1996 in the city of Kinshasa, DRC, reported high levels of MDRTB and up to 39% prevalence of "any resistance". It is important to expand this survey to rural areas, given the fact that drug-resistance levels in urban centres are generally higher than the national average (cf WHO 2004b). Such a survey is planned in 2005 in Kinshasa and in the province of lower Congo (which comprises rural areas). On the other hand, the surveys conducted in the various provinces of South Africa demonstrated the importance of region-specific surveys in large and/or high-burden countries.

Organising drug-resistance surveys can be done at relatively low cost, but does require a reasonable level of capacity of the TB control services, especially the laboratory services, and in general the support of a Supranational Reference Laboratory. It is thus important to include as many nations/units as is feasible, given the possibility that TB control in some non-surveyed low-capacity areas may be worse than in those surveyed. Finally, repeat surveys provide important information on trends in drug resistance. To this end, a follow-up survey is anticipated in Mozambique, where an MDRTB prevalence of 3.5% was reported among all cases (new and previously treated patients combined) in the 1998-1999 survey. In the Ivory Coast and Uganda repeat surveys are also needed. Alternatively, similar information can be obtained by analysis of re-treatment cases (cf Van Deun *et al* 2001; Van Deun *et al* 2004a). This may be a cheaper and easier alternative for low- and middle-income countries.

2.2 Outstanding questions

Is MDRTB a major threat to TB control? In 1997, the WHO declared that, for MDRTB, "the top priority is not management but prevention". Efficient TB control through DOTS should minimise the two most important risk factors for developing drug resistance, *i e* drug mismanagement and patient non-adherence, thus preventing MDRTB. Whether the transmission of existing, non-treated MDRTB leading

to primary MDRTB in new cases can be prevented in a DOTS system is not known. Although mortality is higher among MDRTB patients,[4] they can become chronic cases and long-term excreters of bacilli, if they are not treated with adequate regimens. It has been suggested that MDRTB bacilli are less virulent than non-MDRTB organisms (cf Gillespie & McHugh 1997), and they are therefore thought to be less easily transmitted. However, there is at present no direct information to support this hypothesis. Gillespie and colleagues demonstrated that differences in the fitness of MDRTB strains are due to each strain's adaptation to the environment of its human host (cf Gillespie *et al* 2002). Furthermore, it should be borne in mind that virulence can vary among genotypes of a particular species (cf Lopez *et al* 2003), and that for some *M tuberculosis* genotypes mutations causing drug resistance do not seem to lessen fitness or viability. One example is the Beijing genotype, which has been associated with various outbreaks of (MDR)TB.[5] In Africa MDR outbreaks of the Beijing and Central African types have been reported in South Africa and Kenya (cf Van Rie *et al* 1999; Githui *et al* 2004). Mathematical modelling suggests that a small subpopulation of relatively fit MDR strains may eventually out-compete both drug-sensitive and less fit MDR strains (cf Cohen & Murray 2004).

These factors indicate that although MDRTB prevention through efficient TB control programmes remains a cornerstone of global TB control, management also becomes a priority when primary MDRTB reaches a certain level. But several questions still remain unanswered. First, at what prevalence of MDRTB do TB-control programmes need to adjust their strategies and treatment regimens to address the problem? Secondly, what are the means and tools currently available to fight MDRTB?

MDRTB treatment experiments started soon after the first cases appeared, mainly using what are called second-line drugs. Those currently available include some old drugs like PAS, ethionamide and cycloserine, as well as drugs that have not previously been used for TB treatment, such as quinolones. It should be borne in mind that second-line drugs are reserve drugs, less effective than first-line drugs; hence

4 Cf Fischl *et al* 1992; Goble *et al* 1993; Drobniewski *et al* 2002.

5 Cf Bifani *et al* 1999; Frieden *et al* 1996; Toungoussova *et al* 2003.

more of them have to be administered for a longer period. Besides, these drugs cause more severe and unpleasant side-effects and are more expensive. Both the choice of drugs and the available supplies are limited in low-income countries, increasing the risk of non-adherence and drug stock-outs, factors which encourage the development of additional drug resistance. The WHO clearly states that "these drugs should be stored and dispensed at specialized health centres with appropriate facilities and well-trained staff" (StopTB 2002b: 3).

The first extensive available data on MDRTB treatment is from the National Jewish Hospital in Denver, USA (cf Goble *et al* 1993). Various treatment regimens, including pyrazinamide, ethionamide, cycloserine, para-aminosalicylic acid and an injectable aminoglycoside, were unsuccessful, partially due to the advanced stage of the disease at entry. Nevertheless, this incomplete data formed the basis for experiments conducted in industrialised countries in the early 1990s that showed prolonged survival both in HIV-negative (cf Park *et al* 1996; Telzak *et al* 1995) and HIV-positive (cf Turett *et al* 1995; Salomon *et al* 1995; Park *et al* 1996) patients. The inclusion of quinolones in the treatment regimens and treatment of patients in whom the disease was less advanced resulted in improved outcomes in trials. Furthermore, appropriate therapy (at least two drugs with *in-vitro* activity against the isolate) for at least two weeks was the only variable determining initial and overall response in the HIV-positive cohort (cf Turett *et al* 1995).

At present, there is little experience of mass treatment of MDRTB in developing countries, and the appropriate policy remains a topic of debate. Two major approaches are under consideration: the individual approach and the standardised approach. The first strategy is based on the patient's probable pattern of resistance as estimated by careful consideration of his/her treatment history and any factors indicative of probable acquired or primary resistance. The regimen is then designed to comprise drugs to which the patient's bacilli are estimated to be sensitive, and in due time resistance profiles are confirmed by laboratory testing. Farmer *et al* (1998) successfully implemented this policy in Lima, Peru (cf Mitchison *et al* 1986; Goble *et al* 1993). In this trial, which had considerable financial support for drugs and DST by a high-quality laboratory in the USA, patients were treated in their homes with

highly organised DOT supervision by paid members of the local community. Such a meticulous, demanding programme might not be feasible in a range of low- and middle income countries.

Alternatively, a simpler standardised approach could be installed, comparable to DOTS. In such a policy, suspected primary MDRTB cases and patients relapsing after standardised re-treatment from a well-run programme could be screened by a reference laboratory for rifampicin resistance, which is a good marker for MDRTB (cf Traore *et al* 2000). Laboratory-confirmed MDRTB cases would thereafter receive a well-chosen standard regimen. This approach has been implemented successfully in Bangladesh (cf Van Deun *et al* 2004b). Limited needs for DST analyses, the limited choice of drugs available and required, and the logistic feasibility of training staff in the use of a single MDRTB regimen are arguments in favour of standardised MDRTB treatment in low-income countries. Various programmes for the treatment of MDRTB have been summarised by Mukherjee and colleagues (cf Mukherjee *et al* 2004).

The choice of drugs used in standardised MDRTB treatment is largely determined by the local prevalence of primary drug resistance to second-line drugs. Even more than for first-line drugs there is a lack of data for these reserve drugs. No global surveillance programme exists for second-line drugs, and data is only sporadically available from scarce studies. Besides, the methodology for resistance testing to second-line drugs has not been fully standardised and evaluated on the international level. Only in 2004 did the WHO launch quality control testing among the supranational laboratories performing DST with second-line drugs. Meanwhile, sporadic data from convenience samples between 1997 and 2002 in some hot spot areas for drug-resistant TB showed relatively high levels of resistance to kanamycin (from 0% in the DRC to 26.9% in Kazachstan and even 38.5% in a prison population in Georgia) and capreomycin (from 0 % in the DRC to 33.0% in the same prison population) among MDRTB cases (cf Portaels, unpublished data). Fortunately, resistance to ofloxacin was absent in most of the settings tested above and limited to 3.8% among MDRTB cases in the Georgian prison population (cf Portaels, unpublished data). It was almost absent among non-MDRTB cases. In South Korea even 69.7% of MDRTB patients in a study cohort were resistant to at least one second-line drug, and 26.1% of them showed resistance to ofloxacin, resulting

in a cure rate of only 44.1 % (cf Park *et al* 2004). Ofloxacin-resistance was the only risk factor related to poor outcome (cf Park *et al* 2004). Resistance to second-line drugs could severely jeopardise the success of MDRTB treatment, and constitute a risk of producing resistance to additional drugs, especially if used without prior knowledge on resistance to these drugs. Therefore, it is recommended that the prevalence of resistance to second-line drugs be estimated prior to implementation of MDRTB treatment, especially if these drugs have been or are available on the private market or have been used in a non-controlled way.

It is clear that whatever the regimen, MDRTB treatment should be well organised and supervised. Besides, as Crofton & Van Deun (2000: 193) have stated:

> It is morally and operationally indefensible to try to cope with MDRTB resulting from a poor or non-existing DOTS program without stemming the MDRTB inflow by addressing this basic priority.

In 1998 the WHO proposed DOTS-plus, a case-management strategy under development, which was designed to manage MDRTB using second-line drugs within the DOTS strategy. It thus works as a supplement to the standard DOTS-based TB programmes already in place.

Furthermore, it is clear that DOTS-plus pilot projects should be carefully introduced and monitored in order to minimise the risk of creating resistance to second-line drugs. In view of this, the WHO set up the Stop TB Working Group on DOTS-plus for MDRTB in 1999, a multi-institutional partnership comprising representatives of governments, academic institutions, civil society organisations, bilateral donors, governments of resource-limited countries, and a specialised United Nations agency. The Green Light Committee (GLC) of this Working Group meets regularly to consider proposals to establish pilot projects to address certain basic criteria. In return, TB programmes applying for GLC approval can obtain cheaper drugs which they can then pass on gratis. Indeed, the Working Group, in collaboration with Médecins sans Frontières, the Harvard Medical School and other partners, have made arrangements with the pharmaceutical industry to reduce prices up to 99 percent for high quality MDRTB medicines (cf StopTB 2002b). For example, on June 5 2003 an agreement was signed with Eli Lilly, an Indiana-based drug company, guaranteeing increasing drug supplies and discounting prices for capreomycine and

D-cycloserine, mainly through sharing drug manufacturing technology with firms in China, India and South Africa. On the other hand, the GLC provides a built-in safeguard to prevent inappropriate or irresponsible drug use by ensuring rational approaches to MDRTB control, including training in prevention and surveillance (cf StopTB 2002b).

The WHO 2004 report on drug-resistant TB shows no African country in which a GLC-approved DOTS-plus project had started as of January 2004. The same report listed Kenya among the countries that have an application under review, and Tanzania as preparing to apply (cf WHO 2004b). However, in South Africa the NTP has had a national policy on MDRTB since 2001: a standardised regimen is given to all culture-proven MDRTB cases. Preliminary results showed successful treatment in 90% of the cases who have finished treatment so far, but a high default rate (30%) brought the final treatment success down to 50% (cf StopTB 2003b).

Currently ongoing DOTS-plus projects outside Africa have obtained relatively good results with culture-negative patients at the end of treatment in 65% to 71% of patients treated. However, non-sustainable drug procurement due to delays in the flow of funds to purchase second-line drugs (Latvia, The Phillipines), the need for technical assistance in conducting cost-effectiveness analyses, and sociological problems like alcoholism (Estonia) were the main logistic difficulties encountered in these projects (cf StopTB 2002a, 2002b).

Treatment of MDRTB in areas with a high prevalence of HIV poses additional problems. In Africa, the percentage of adult TB patients who are HIV-infected was estimated to be over 20% in most reporting countries except Tanzania (9.9%), and even reached 60% and 75% in South Africa and Zimbabwe, respectively (cf WHO 2004a). Most of these countries do not have, or have only partially implemented a systematic surveillance system for assessing HIV infection among TB patients (cf WHO 2004a). Voluntary counselling and testing, as well as anti-retroviral treatment (ART) have started only recently or have been planned for the near future in some areas. Diagnosis of TB in HIV/AIDS co-infected patients is often hampered by non-specific clinical presentation (abnormal chest X-Ray and negative tuberculin skin test) and negative sputum smear examination for acid-fast bacilli (cf Liberato *et al* 2004), leading to a delay in diagnosis and advanced

disease. The currently available data suggests that treatment failure is higher in HIV-infected patients (cf El Sony *et al* 2002; Liberato *et al* 2004), due mainly to a higher need for comprehensive care and intensive medical intervention. Although reduced drug exposure may be related to malabsorption in people with HIV/AIDS (cf Sahai *et al* 1997), HIV-positive TB patients do not seem to be more likely to develop drug resistance than others.[6] However, vigilance is recommended because even if HIV infection is not directly considered to be an independent risk factor for the development of drug resistance and the transmission of drug-resistant TB, the high prevalence of TB among HIV-infected patients may lead to higher transmission rates of both drug-resistant and susceptible TB in areas with a high prevalence of HIV. In Peru, MDRTB in HIV-infected patients was not associated with previous treatment or prophylaxis, but the HIV-infected population represents a risk group for nosocomial MDRTB (cf Campos *et al* 2003). Knowing that by the end of 2001 an estimated 28.5 million people were living with HIV/AIDS in sub-Saharan Africa (cf UNAIDS 2002), the spread of MDRTB constitutes a real risk on this continent.

Little data is available on the treatment of MDRTB in HIV/AIDS patients, but as Iseman and Huitt (2000: 179) claim:

> Drug toxicity, drug malabsorption, and drug-drug interactions all pose significant treatment difficulties for both the patient and the clinician.

It is clear that patients co-infected with MDRTB/HIV will require intense medical intervention and close collaboration between TB and HIV programmes to decrease their high level of mortality.

Another unsolved question is the need for rapid detection of MDRTB. The urgency depends largely on the alternative strategies that can be offered when cases test positive. Can MDRTB patients be given proper treatment, and is isolation recommended and feasible in a particular setting? The latter option could well be considered in specific settings such as prisons, even if appropriate treatment is not available. Rapid detection of drug resistance requires diagnostic methods that are more exepensive and technically more demanding and sophisticated than

6 Cf Dupon *et al* 1995; Espinal *et al* 2001; Campos *et al* 2003; Liberato *et al* 2004; WHO 2004b.

microscopy as routinely used in DOTS. Basically, two categories of tests could be performed, the classical culture-based methods and the molecular methods that do not necessarily depend on culture. To the first category belong commercialised liquid media with radiometric detection (BACTEC from Becton Dickinson), fluorescent detection (MGIT from Becton Dickinson), and colorimetric detection (Bact/Alert from Biomerieux). These tests produce reliable results that are in accordance with the standardised proportion method, within seven to ten days after primary culture, and can be used directly on sputa (cf Goloubeva *et al* 2001). The high costs of the media are the mean drawback. Alternatively, the following non-commercialised assays produce equally good results: the colorimetric Resazurin method,[7] the enzymatic nitratase method (cf Lemus *et al* 2004), and the microcolony detection method (cf Schaberg *et al* 1995). All these methods require additional testing to evaluate their applicability when used directly on sputum specimens, and for second-line drug testing.

The molecular methods aim at the detection of the genomic mutations responsible for drug resistance. Because various drugs are included in anti-TB regimens, and for most drugs multiple genes are involved in resistance with each gene potentially having a variety of mutations, and since for some drugs resistance mechanisms have not been completely elucidated, a single molecular test can not provide the necessary information on resistance to first-line anti-TB drugs. The INNO-LiPA-Rif.TB test is so far the only commercialised molecular test to detect mutations in the rpoB gene responsible for rifampicin resistance. The test detects 95% of R-resistant TB from culture or smear-positive sputum specimens (cf Traore *et al* 2000), but is out of reach in most resource-poor settings. In-house PCR-based systems followed by electrophoresis, sequence analysis or micro-array analysis produce reliable results for various drugs but are too sophisticated for decentralised use.

The ideal method needs to be cheap, easy to perform, applicable to sputum specimens and able to produce rapid (within one week) and reproducible results. Increased need for laboratory support is one of the determining factors in the higher cost of MDRTB treatment and management.

7 Cf Palomino *et al* 2002; Martin *et al* 2003; Lemus *et al* 2004.

But what are the real costs of DOTS and DOTS-plus programmes and how cost-effective and feasible they are, especially in resource-poor countries? The cost of standard treatment in DOTS for sensitive disease has been estimated to be as low as US$12 per patient in resource-poor countries and approximately US$4700 (= £2640) (cf White & Moore-Gillon 2000) in industrialised countries. MDRTB is considerably more expensive, with individualised treatment mounting to US$106 750 (= £60.000) in London, England (cf White & Moore-Gillon 2000) and to US$2 400 per case in a trial in Lima, Peru (cf Suarez *et al* 2002). An economic evaluation based on costs previously estimated in the United States of America and South Africa (selected as examples of the industrialised and the developing worlds) demonstrated the cost-effectiveness of DOT *vis-à-vis* conventional therapy in reducing the spread of MDRTB in both settings (cf Wilton *et al* 2001). Cost savings were more pronounced, especially in South Africa, as the likelihood of MDRTB increases and more expensive second-line drugs have to be administered (cf Wilton *et al* 2004). In the Lima trial the cost per disability-adjusted life-year gained (DALY), including transmission benefits, was calculated at US$211, and estimated to drop to US$165 if reduced drug prices as projected for 2002 onwards were used or if alternative second-line drugs were employed (cf Suarez *et al* 2002). Gupta and colleagues calculated that countries could save as much as 93.6% of their expenditure on second-line drugs if they procured these via the GLC mechanism (cf Gupta *et al* 2001). Specific data on costs for the treatment of drug-resistant TB in Africa are almost non-existent. Even with such reduced costs, however, low-resource countries often depend on funding to combat (MDR)TB, as is the case in Bangladesh, for example, where 40% of the programme is paid by two NGOs (cf WHO 2004a).

3. Conclusion

As the treatment success rate was found to be substantially lower in the African region than in the rest of the world, special efforts must be made to improve the cure rates of drug-sensitive and drug-resistant TB in Africa. Global data from the WHO reports on anti-tuberculosis drug resistance and the sporadic information available from various studies show high levels of (M)DRTB in some countries and areas. Data

for the African region is scarce and incomplete, but nevertheless shows a relatively low rate of resistance among new TB cases. However, local rates may differ from national rates, as was seen in South Africa, and trends in MDRTB rates have shown an increase in two of the three countries in which repeat surveys have been done. It is therefore unacceptable to ignore the problem of drug-resistant TB in Africa, and vigilance is recommended. There is an urgent need for (repeat) surveys, a task which will probably require international support. Furthermore, given the recently reduced prices for MDRTB treatment via the GLC, as well as the increasing success of DOTS in Africa, it no longer seems acceptable to assume that MDRTB patients can be denied treatment.

However, numerous key questions relating to MDRTB and DOTS-plus remain unanswered, and much more research is needed. The Stop TB Working Group has selected three primary research topics and ranked them from highest to lowest priority (cf Stop TB 2003a). Topic one aims to "identify optimal standardised treatment protocols to treat MDRTB", concentrating on effectiveness in adults and children, and on the efficacy of various standard and individual MDRTB regimens. Topic two seeks to "identify optimal protocols for diagnostic testing", hoping to establish the ideal times for identifying MDRTB by means of the existing (optimised) or new instruments. Topic three "identify the minimum requirements for constructing and implementing DOTS-plus" and will include research on setting-specific DOTS-plus approaches.

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