Round Table Discussion

Case study: South Africa

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For the past decade, a concerted effort to reform TB control in South Africa has resulted in changes in case-finding and treatment policies, standardization of recording and reporting systems, and monitoring of the performance of control programmes using pre-defined indicators; these changes were all made in line with the internationally recommended DOTS strategy. The essential elements of the revised strategy,[1] implemented in 1996 after TB was declared a national emergency, include bacteriological confirmation of disease, standardized first-line treatment regimens that are exclusively based on fixed-dose combination formulations and an electronic recording and reporting system. Expansion of the DOTS strategy followed rapidly: in 2003 there was complete coverage in all nine provinces, covering 183 health districts. Comprehensive programmatic management of patients with MDR-TB became national policy in 2000 and was implemented through a network of dedicated provincial MDR-TB referral centres.

Despite these efforts, however, TB incidence and case–fatality rates have increased threefold in South Africa over the ensuing decade.[2] More than 400 000 cases of TB require treatment annually, but cure rates barely reach 50%,[2] reflecting the classic mistake made in TB control of identifying cases but not treating them adequately. TB mortality is at an all-time high. There are some 10 000 incident cases of MDR-TB per year,[3] representing the largest MDR-TB burden in Africa and further pointing towards a failure of TB control. Although a favourable outcome (cure and treatment completed) is achieved in more than 80% of MDR-TB patients who complete the full course of standardized treatment, deaths (up to 20% of patients who started treatment), defaulting from treatment (up to 25% of patients) and failure of treatment (around 10%) reduce the overall effectiveness of the programme to less than 50% (South African Medical Research Council, unpublished data, 2002–2004). Worryingly, patients with XDR-TB have been identified in each of the nine provinces over the past 18 months.

Determinants of the worsening TB epidemic in South Africa are diverse and multifactorial. Historically, there has been a legacy of neglect, poor management of patients and fragmented health services.[4] Contemporary barriers to effective TB control in South Africa are similar to those elsewhere in Africa, and include an exploding HIV epidemic, deteriorating socioeconomic conditions among already vulnerable populations and constraints on human resources in the health-service sector. Although TB control has been fully integrated into primary health-care services and decentralized to district level, delivery is hampered by competing health priorities, slow district reform and deficient management capacity, especially at the level of implementation. Unemployment rates of up to 40%, as well as the resultant migration and massive growth in informal urban settlements, lead to failures in supervision of treatment and follow-up. Reasons for defaulting from TB and MDR-TB treatment include patients' perceptions of negative attitudes among health-care workers, substance abuse and employment concerns.[5,6]

However, it is the lost opportunity for early, effective HIV intervention in South Africa that has brought the weaknesses in TB control into sharp focus. At least 60% of TB patients are estimated to be coinfected with HIV;[2] this is most strikingly reflected in the excess and rising mortality. Up to half of patients categorized as treatment defaulters in the aforementioned research studies were subsequently found to have died, and the reason for death was often reported as being HIV-related.[5,6] HIV-associated transmission of XDR-TB and the exceptionally high risk of mortality in HIV-positive people coinfected with XDR-TB[7] amplify public health concerns over the threat of a virtually untreatable TB epidemic occurring within the context of HIV coinfection.

The view expressed in the base paper that drug-resistant TB poses a major threat to achieving global targets for TB control also holds true for South Africa. In addition, however, the 2005–2006 XDR-TB outbreak in KwaZulu-Natal[7] serves as a serious warning that gains made in HIV care and treatment might be lost if drug-resistant TB is not effectively and rapidly addressed. Several epidemiological and genetic studies have confirmed both nosocomial and community transmission of drug-resistant TB in South Africa. Increased access to HIV treatment and care will inadvertently bring together highly vulnerable individuals with infectious cases of MDR-TB and XDR-TB, often in settings where large numbers of people congregate. The lack of adequate and appropriate infection-control measures in most public health settings, juxtaposed with an extremely high prevalence of HIV (both in patients and health-care workers), represent a public health emergency requiring much earlier detection of drug resistance, segregation of infectious patients, urgent improvements in infection control measures and a rapid, appropriate response to outbreaks.

Dire predictions of the impact of HIV on TB and MDR-TB in South Africa were made in 1999.[4] Sadly, what had been mere assumptions at the time now seem to have come true. Substandard care, fertile conditions for transmission and the rapidly progressing HIV epidemic all impede the ability of South Africa to reach the required targets for TB control; they also contribute to establishing the endemicity and spread of drug-resistant TB. A dynamic and exceptionally strong collaboration between HIV and TB control programmes will be required to avert large-scale HIV-associated epidemics of drug-resistant TB. Failure to engage in such collaborations is bound to have devastating consequences. ■

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The Philippines case study

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Most TB patients in the Philippines are treated by private practitioners who do not conform to the international standard of TB care.[1] We established a private-public mix DOTS (PPMD) centre to engage private physicians in the DOTS strategy.[2] The cure rate in new cases was 83.9% and failure was 0.01%, with corresponding rates in previously treated cases of 58.6% and 39.7%, respectively. All isolates from the treatment failures were MDR-TB, indicating failure of previous TB treatment outside DOTS.

As a DOTS-Plus pilot project, the Green Light Committee (GLC) of the working group on multidrug-resistant TB provided this PPMD access to second-line anti-TB drugs (SLDs) and technical assistance. Our experience illustrates the challenges in MDR-TB management.

More effective anti-TB drugs needed

SLDs used in the management of MDR-TB are less effective, requiring prolonged regimens, and are also associated with significant side-effects.[3] Although MDR-TB management was found to be highly cost-effective in our setting, drugs alone cost US$ 3500 per patient.[4] Additionally, drug supplies are limited in the face of increased demand with resources provided by the Global Fund to Fight AIDS, TB and Malaria; this is another challenge to drug availability.

With the widespread use of SLDs, XDR-TB (MDR-TB with simultaneous resistance to a fluoroquinolone and one of the injectable SLDs) that is virtually incurable with the available drugs has emerged.[5] Although there is substantial fluoroquinolone resistance among the MDR-TB isolates,[6] XDR-TB was noted in only 4.6% of MDR-TB patients treated. Although there was no known HIV co-infection in these patients, the risk for failure or death from XDR-TB nevertheless was twice as high as that for other MDR-TB patients.[7]

Mobilization of more resources and engagement of the scientific community and the pharmaceutical industry to accelerate the development of affordable, novel anti-TB agents is essential for an effective response to the threat of MDR-TB, particularly XDR-TB.

Rapid methods for diagnosis needed

The diagnosis of MDR-TB relies on conventional culture and drug sensitivity testing (DST). The lag time to MDR-TB diagnosis in 2003 to 2005 declined from 8.5 ± 3.8 months to 5.0 ± 2.3 months and delay of treatment was 10.6 ± 5.6 months to 6.7 ± 3.3 months from consultation (personal communication, unpublished data). In our experience, 12%–20% of confirmed MDR-TB patients died during the long process of diagnosis, 7% while awaiting treatment, 4% to 7% refused treatment, and 22% to 26% were lost before treatment. The public health consequences of continuing transmission, further amplification of resistance, clinical deterioration and death before management underscore the need for rapid methods of MDR-TB diagnosis for more timely treatment.

Enhancing treatment adherence

Cure rates in our cohorts increased from 50% to 74% from 1999 to 2004, with corresponding declines in death and failure rates.[7] However, the default rate during the prolonged treatment regimen, owing largely to adverse drug events, remained substantial. When patients were referred back from the treatment centre to the DOTS facilities, including PPMDs, within the communities where they live during the continuation phase of treatment, the default rate substantially declined compared to patients who continued to report daily to the treatment centre.[8]

Management of adverse drug events, group therapy sessions on psychosocial issues, and engaging patient volunteers as treatment partners were also implemented to improve treatment adherence.

Mainstreaming MDR-TB management into DOTS

To attain the goal of a TB-free world, addressing MDR-TB and other major challenges is one of the key strategies. As DOTS implementation prevents generation of MDR-TB, programmatic MDR-TB management prevents generation of XDR-TB and halts the transmission of MDR-TB. The major challenge of mainstreaming MDR-TB management into the national tuberculosis programme is the development of human resources to provide appropriate services for MDR-TB management. ■

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Treatment and management of MDR-TB in Latvia

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Background

Latvia has consistently ranked among the countries with the highest rates of MDR-TB in the world. In the first Global Tuberculosis Drug Resistance Survey (1996), 14.4%, or 1 out of 7, of all newly diagnosed sputum smear-positive tuberculosis cases in Latvia were diagnosed as MDR-TB.[1]

Data also show that the proportion of cases with additional resistance to second-line anti-tuberculosis drugs is high. In the meantime, HIV seroprevalence is increasing among TB patients.

Latvia, with an estimated population of 2.35 million, joined the European Union on 1 May 2004. The Latvian economy had been severely affected by the collapse of the Soviet Union, with gross domestic product (GDP) per capita falling by nearly 35% in real terms in 1992. The GDP per capita in 1999 was US$ 4200, increasing to US$ 11 500 in 2004. Latvia concurrently experienced dramatic increases in TB morbidity and mortality peaking in 1998, together with the appearance of drug-resistant and MDR-TB.[2,3]

Latvia adopted WHO's recommended DOTS strategy for TB control in 1996 and subsequently introduced MDR-TB management[4] in 1997. This relies on MDR-TB treatment with individualized regimens under the *consilium* or expert consultation process. The treatment is provided at four inpatient treatment centres (including a prison TB ward) followed by outpatient directly observed therapy. All funding for TB and MDR-TB control comes from the government. In 2000 Latvia's National Tuberculosis Program (NTP) sought MDR-TB management support from the Green Light Committee (GLC) and got approval to treat 350 more MDR-TB patients. The GLC enabled Latvia to treat all patients diagnosed with MDR-TB.

Epidemiology

In 1991, the incidence of TB was 29 cases per 100 000 population,[5] increasing to 74/100 000 in 1998 and then declining to 53.5/100 000 in 2005. Case finding shows 49% case detection by smear microscopy.

Drug-resistant TB case detection strategy in Latvia is based on drug sensitivity tests (DST) on solid media. For high-risk MDR-TB cases, the BACTEC/MIGT system is used, as well as the INNO LiPA test to detect rifampicin resistance in 2–4 days.

Extensive resistance to first- and second-line drugs among MDR-TB patients is well known in Latvia. One of the reasons is the country's long and extensive use of second-line drugs before implementing the DOTS strategy. Extensive resistance affects the MDR-TB treatment regimen and outcomes. For cohorts registered from 2000 to 2005, resistance to kanamycin was 49%; capreomycin, 39%; ofloxacine, 9%; protheonamide, 30%; para-aminosalycilic acid, 31%; and thiacethasone, 23%.

In the first worldwide survey, published in May 2006, estimates for years 2000–2004 showed that 19% of MDR-TB patients have resistance to first-line drugs defined as MDR-TB plus resistance to three drugs of six classes of second-line drugs.[6]

Using the new revised extensive drug resistance (XDR-TB) definition of resistance to at least rifampicin and isoniazid, additional resistance to any fluoroquinolone and to any of three second-line injectable drugs (capreomycin, kanamycin or amikacin), such extensively resistant TB was found in 39 cases, or 5.2% of all MDR-TB cases registered during the past six years.

Two-thirds, or 67%, of MDR-TB patients out of 820 treated in the years 2000–2003 were cured; 6% were dead; 14% defaulted; and treatment failed in 13% of cases.[7,8] The treatment success rate for XDR-TB patients is low: out of all 48 patients treated from 2000 to 2005 (including MDR-TB retreatment cases with XDR-TB), only 18 (38%) were cured, while treatment failed for 22 (46%).

Among all MDR-TB cases in the cohorts, 3% were co-infected with HIV; this proportion increased to 12% among XDR-TB cases. Treatment success for TB/HIV co-infected new patients, at 74%, is similar to overall treatment success for new TB patients, but the HIV-associated MDR-TB success rate is 56%.

Overall, Latvia's success with the DOTS program is encouraging: 84% of all registered cases, including outcomes of MDR-TB after 2 years, were cured in cohort 2002, which is close to the level of performance (85%) recommended by WHO (Table 1).[9] Newly registered MDR-TB cases were reduced by 46%, with 332 cases in 1997 falling to 153 registered in 2005.

Conclusion

MDR-TB management is effectively implemented under routine program conditions in Latvia. Using an individual

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Table 1. **All registered MDR-TB cases in Latvia, 1995–2005**

	Primary	Acquired	Total	XDR-TB (MDR-TB + resistance to any second-line injectable + fluoroquinolone)
1995	19	28	47	
1996	82	175	257	
1997	117	215	332	
1998	96	231	327	
1999	101	175	276	
2000	90	153	243	4
2001	100	132	232	1
2002	88	124	212	7
2003	83	80	163	5
2004	111	76	187	15
2005	99	54	153	7

approach to the management of MDR-TB can cure more than two-thirds of patients in settings with high MDR-TB prevalence and extensive resistance to first- and second-line drugs.[10]

Challenges for TB care in Latvia

An area of concern is treatment default, especially among MDR-TB cases (14%), among those with TB/HIV and MDR-TB/HIV[11] co-infection, and among patients with extensive drug resistance.

Rapid drug-resistant case detection, appropriate treatment, extended contact investigation, infection control measures and case management strengthening to decrease treatment interruptions and default are the main challenges Latvia faces in achieving the TB-related Millennium Development Goals. ■

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