Drug resistance in tuberculosis in South-East Asia

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Abstract

The South-East Asia Region (SEAR) of WHO bears around one third of the global burden of multidrug-resistant (MDR-TB). Extensively drug-resistant TB (XDR-TB) has also been reported from five countries in the Region. Evidence suggests that drug resistance is essentially a man-made phenomenon because of inadequate or poorly administered treatment. Current treatment regimens recommended under DOTS cure TB patients and prevent emergence of resistance. Even though countries in the Region have 100% geographical coverage, access to DOTS services for marginalized and vulnerable populations remains an issue. International Standards of TB Care is not yet adopted by all providers. For existing resistant cases there is limited capacity and experience in diagnosing and managing MDR-TB cases. Limited laboratory capacity for diagnosis of drug resistant cases and for surveillance, difficulties in procuring quality second-line drugs and long lead times for procurement are some of the constraints. Substantial additional resources are required to scale up programmatic management of drug resistant TB.

Several steps are required to simultaneously scale up diagnosis, treatment and surveillance of MDR and XDR-TB. These include technical and financial support to countries by WHO, technical partners and funding agencies; programme efforts to ensure implementation of all elements of the Stop-TB strategy including mobilization of sufficient resources; regulatory measures to ensure rational use of drugs; an infection control policy to prevent spread and community mobilization to create support structures for TB, MDR-TB and TB-HIV co-infected individuals

Global and Regional situation of MDR-TB

Multidrug-resistant TB (MDR-TB) is caused by bacteria that are resistant to at least isoniazid and rifampicin, the most effective anti-TB drugs. MDR-TB results from either primary infection with resistant bacteria or may develop in the course of a patient's treatment.

WHO estimates that globally, 440 000 MDR-TB cases emerged and 150 000 deaths were caused by MDR-TB[1] in 2008. Well-functioning national TB control programmes in the South-East Asia (SEA) Region achieving high cure rates has resulted in maintaining the slow but steady decline in TB incidence rates during the past decade. This has also led to low levels (Range: 1.7%- 4.2%) of multidrug-resistance among newly detected cases. Among previously treated cases in the Region, MDR-TB rates range from 10.0% - 34.7%. However, given the large numbers of TB cases, this translates to 130 000 cases, (110 000–170 000) accounting for more than one third of the world's MDR-TB cases in the SEA Region, with India estimated to have the second highest number globally (Figure 1). The country-wise estimated burden of MDR-TB is presented in Table 1.

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Figure 1: ***Distribution of MDR cases as per WHO regions***

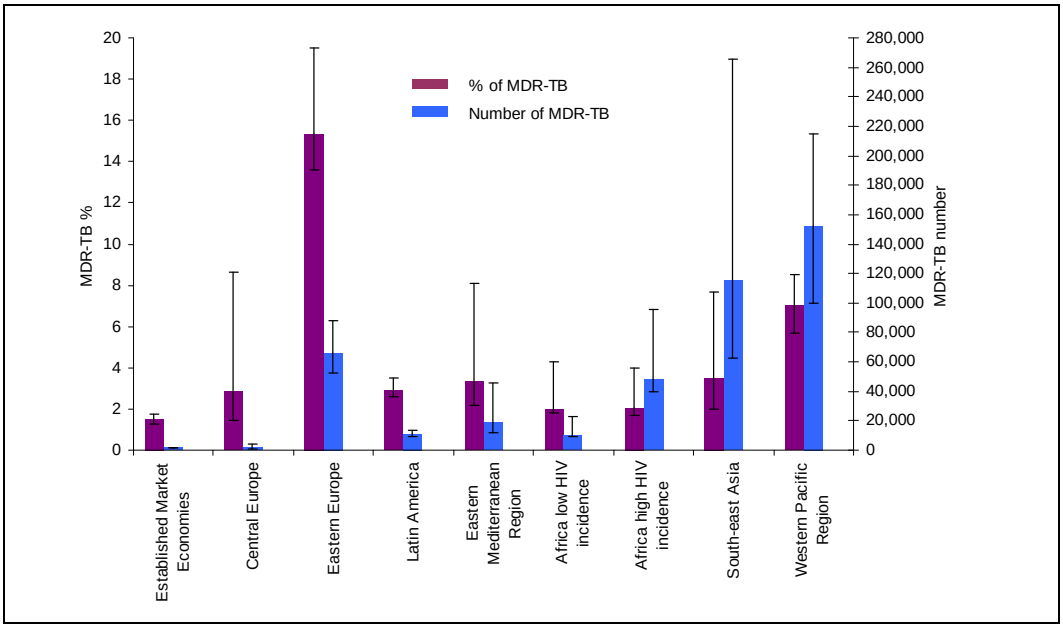


Table 1: *Estimated MDR-TB cases and rates in SEAR Member States, 2010*

Country	Source of estimates	% MDR among new TB cases (95% CI)	% MDR among previously treated TB cases (95% CI)	Number of MDR-TB among incident total TB cases (95% CI)
Bangladesh	model	2.2 (0.0–5.6)	14.7 (0.0–39.6)	9 800 (1 000–19 000)
Bhutan	model	2.2 (0.0–5.6)	14.7 (0.0–39.6)	33 (4–61)
DPR Korea	model	2.2 (0.0–5.6)	14.7 (0.0–39.6)	3 900 (658–7 200)
India	DRS,[a] 2005	2.3 (1.8–2.8)	17.2 (14.9–19.5)	99 000 (79 000–120 000)
Indonesia	DRS,[b] 2004	2.0 (0.5–6.9)	14.7 (0.0–39.6)	9 300 (0–21 000)
Maldives	model	2.2 (0.0–5.6)	14.7 (0.0–39.6)	3 (0–6)
Myanmar	DRS, 2007	4.2 (3.2–5.6)	10.0 (7.1–14.0)	9 300 (6 400–12 000)
Nepal	DRS, 2007	2.9 (1.9–4.3)	11.7 (7.6–17.6)	1 700 (990–2 300)
Sri Lanka	DRS, 2006	0.2 (0.0–1.0)	0.0 (0.0–10.2)	63 (0–130)
Thailand	DRS, 2006	1.7 (1.1–2.6)	34.5 (28.2–41.5)	2 900 (2 100–3 800)
Timor-Leste	model	2.2 (0.0–5.6)	14.7 (0.0–39.6)	130 (6–260)

a Estimates based on subnational drug resistance data.

b DRS Survey in Indonesia was completed for Mimika District (2004) and Central Java province (2006).

Mimika district: MDR-TB in newly diagnosed TB cases: 2.0 %.

Central Java province: preliminary result; MDR-TB in newly diagnosed TB cases was: 1.8 % and among previously treated TB cases was: 16.7 %.

DRS = drug resistance surveillance or survey data; CI = confidence interval; MDR-TB = multidrug-resistant TB

Extensively drug-resistant TB (XDR-TB) has also been reported from five countries in the Region. MDR-TB could potentially replace drug-susceptible TB, and constitutes a threat to global public health security. In areas of high HIV prevalence, the potential for increased transmission of MDR-TB is high.

Considerable efforts are required to expand capacity for quality assured drug susceptibility testing in the Region in order to more accurately estimate the extent of MDR- and XDR-TB. Given the widespread availability and use of second-line drugs, and as laboratory capacity to conduct second-line drugs susceptibility testing increases, additional numbers of patients with XDR-TB are likely to be identified.

Factors influencing emergence of resistance to TB drugs

Evidence suggests that drug resistance is essentially a man-made phenomenon though multiple factors may be involved. Generally it is an inadequate or poorly administered treatment that causes resistance although MDR-TB can then spread from person to person. Some of the many potential causes of resistance are.

- Sub-standard regimen administration particularly when there are a large number of health care providers outside the national programme.
- Failure to directly observe treatment and specifically situations leading to non-adherence and default of TB patients.
- Poorly organized or funded TB control programmes.
- Poor quality of drugs and/or interrupted drug supply.
- Socio-economic or cultural barriers to access diagnosis/ treatment.
- Inadequate infection control measures at health facilities /hospitals.

Though it has not been possible to establish a direct association between MDR-TB and the HIV epidemic because of missing data from several countries, in areas of high HIV prevalence and MDR-TB, the likelihood for increased transmission of MDR-TB is high.

Most of these factors are playing an important role in the Region. This is evident from the fact that:

- With a case detection rate of 65% of all cases[2], more than one third of estimated new cases are not registered by NTPs in the Region.
- While the geographical coverage for DOTS in all Member States has reached 100%, there are challenges to access for several pockets of populations due to various reasons.
- The private sector is the first contact for 65% of TB patients in India[3] and 73% in Myanmar[4] as per studies in the Region. A study in Indonesia also reveals that the majority of people in rural areas preferred private practitioners for treatment of TB[5]. Despite significant progress (Figure 2) the involvement of the private and other health sectors in TB control in the Region is far from being optimal.
- Evidence also suggests that treatment success rates in the private sector (unless a part of public-private PPM initiatives) are usually below 50%.
- Less than 5% of the estimated MDR-TB cases are registered for treatment by NTPs. This means that a huge proportion of cases are either not getting treatment or being treated under unknown conditions with high chances of a non-standardized regimen.

Figure 2: ***Anti Microbial resistance in SEA Region***

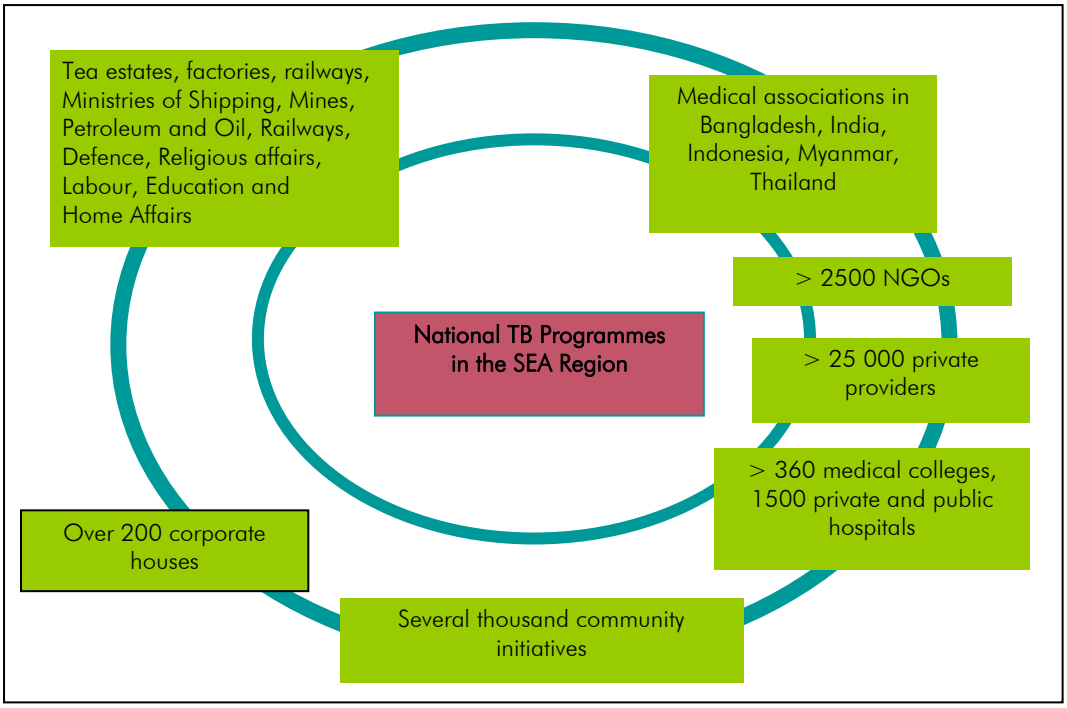
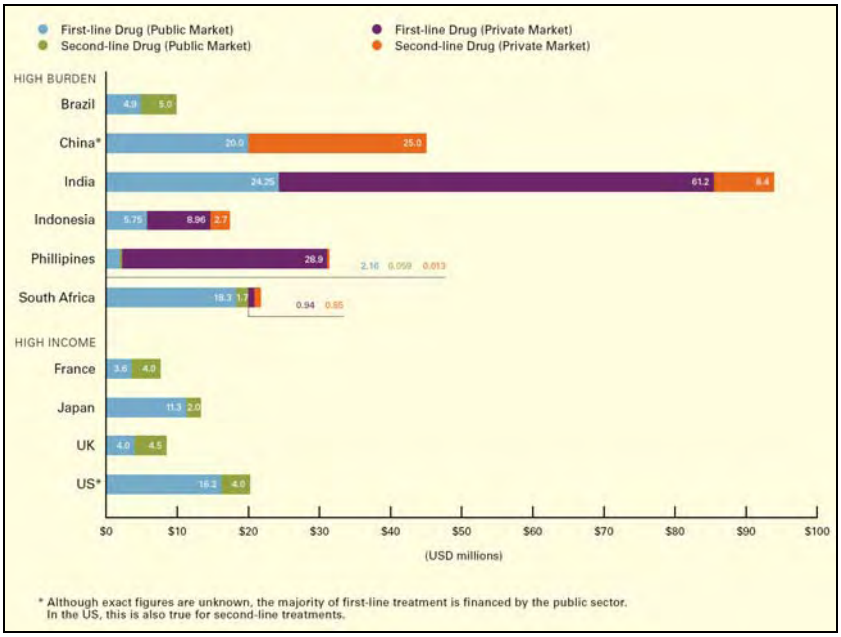


Figure 3: ***Market of anti-TB drugs in some countries***



Ref: Global alliance for TB drug development, May 2007. Pathway to patients: Charting the dynamics of the global TB Drug Market

- Poor drug regulation-TB drugs (both first-and second-line) are available over the counter in several countries in the Region. (ref study report Figure 3)
- The health infrastructure is overburdened, especially over-crowded hospitals with no infection control policy.
- Several countries in the Region face poor housing conditions and specifically overcrowding in urban areas that facilitate spread of infections[6].

Preventing emergence of resistance

Steps to prevent the emergence of resistance include:

(1) Strengthening DOTS – All countries in the Region have 100% coverage under DOTS and are thus providing uniform use of standard regimens, free diagnosis and treatment, DOT, strict monitoring of treatment, defaults, outcomes and use of fixed drugs combinations (FDCs). Providing standardized treatment under the DOTS strategy is one of the foremost measures that needs to be adopted to prevent emergence of resistance. The programmes should now strive to provide universal access.

(2) Involvement of all care providers and provision of services as per International Standards of TB Care (ISTC). Treatment success rates amongst TB patients in private–public mix have been found to be comparable to public health settings[7]. Thus, multi-sector involvement is essential in prevention of drug resistance.

(3) Promoting rational use of drugs and pharmacovigilance. This would be another key area in preventing emergence of resistance. Countries would need to undertake situational analysis that involves - evaluation of prescription policies in health-care settings in public and private sectors and utilization of antimicrobial agents at various levels; assessing therapeutic and non-therapeutic use in animals and appraise impact of pharmaceuticals promotion[8]. Pharmacovigilance is defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems" and involves strengthening of technical and regulatory requirements along with bringing about a change in the behaviour of prescribers and users. Countries need to promote optimal prescription; develop standard national/ local treatment guidelines (STG) advocating evidence-based therapy; train professionals in the use of these STGs and assure use of STGs through hospital committees. Preventing over-the-counter availability of TB drugs is specifically important for promoting rational drug use.

Preventing the spread of drug resistance

(1) Infection control measures: Infection control policies and plans are being pursued in six countries in the Region. All countries need to adapt the international guidelines in the local context.

(2) Early diagnosis of drug resistant cases: This would mean strengthening the lab infrastructure and corresponding human resource

capacity to undertake drug resistance surveys and susceptibility testing.

All Member States (with the exception of Maldives and Timor-Leste) have capacity for myco-bacterial culture. However, capacity is quite limited even in these countries. The national reference laboratories in Bangladesh, Indonesia, and Myanmar have recently been accredited for quality assurance for culture and drug susceptibility testing, while Sri Lanka is in the process of upgrading the national reference laboratory for TB.

The national reference laboratories at the Tuberculosis Research Centre, Chennai, India, and at the Bureau of TB at Bangkok, Thailand, are the two designated supra-national TB reference laboratories in this Region. These labs are also undertaking DST for second-line anti-TB drugs to determine the extent of XDR-TB. Reference laboratories in Bangladesh, Indonesia, Myanmar and Nepal are also engaged in rapid surveys for XDR-TB among mycobacterial isolates from patients who have failed re-treatment regimens, through linking with the SNRLs in the global network.

(3) Adequate management of MDR-TB cases: During the past two years, steady progress has been made in the Region in initiating MDR-TB cases on treatment. The Green Light Committee had approved the case management of patients with MDR-TB under national programmes in nine countries. Bangladesh, India, Indonesia and Myanmar are in the process of expanding these services, while Nepal has already established ambulatory case management services for MDR-TB throughout the country. Maldives continues to treat the few cases that occur on a case-by-case basis. Bhutan, Sri Lanka and Thailand will begin enrolling cases later in 2010, while DPR Korea will apply to the Greenlight Committee (GLC) to establish MDR-TB case management under their respective national programmes in 2010. Countries would need to choose an appropriate model for ongoing MDR-TB care where a selection and balance between need for hospitalization and community-based treatment has to be met.

(4) TB-HIV programme collaboration – TB and HIV programmes need to further strengthen cross-referrals and adequate management of co-infected cases. This will now assume more importance with the emerging challenge of drug resistance.

Challenges

There are unique challenges to tackling the spread of TB drug resistance in the Region as highlighted below:

(1) **Gaps in basic TB control:** DOTS has been recognized and recommended as standard for TB treatment globally and key for preventing emergence of resistance. Though countries in the Region have 100% geographical coverage through programmatic structures, access to services for the entire population remains an issue, particularly for marginalized and vulnerable populations. There is also sub-optimal access to quality first-line drugs through several

sectors and providers outside the programmes. International Standards of TB Care (ISTC) is not yet widely used by all providers.

(2) **Diagnosing and managing MDR-TB:** In the absence of substantive evidence from national drug resistance surveys (DRS) in many countries, the understanding of the burden of MDR/XDR-TB is based on "best estimates". Most countries in the Region have limited laboratory capacity for diagnosis of drug-resistant cases and for DRS. Even countries with culture and drug susceptibility testing facilities do have not enough quality assured laboratories. There is limited capacity and experience in managing MDR-TB cases. Further, many countries face difficulties in procuring quality second-line drugs and long lead times for procurement. Involvement of private and other labs is not easy. Costs for paying for private services are exorbitant (e.g. India) estimated a cost of US$ 20 million for 5% of cultures required for 30 000 MDR-TB cases!) Overall, substantial additional resources need to be mobilized to manage a relatively small number of patients (including training, drugs and service delivery, etc.) which, in turn, inflates the programme budget and countries have to look for additional external funding.

Regional priorities

The first priority in dealing with MDR-TB remains prevention of acquired drug resistance through continuing to ensure higher case detection and cure rates using high quality of DOTS services. Secondly, attention needs to be paid to developing comprehensive national plans for the urgent scale-up of diagnostic and case management capacity for MDR-TB, conforming to internationally recommended protocols, including good infection control measures.

In the context of both of the above, the priorities in the Region are:

- Securing adequate external as well as domestic funds, (including from local governments under decentralized systems) for all aspects of TB control;
- Urgent attention to building health systems capacity: skilled personnel and quality infrastructure, focusing on laboratory capacity for diagnosis, and surveillance;
- Supporting countries to develop updated guidelines for MDR-TB diagnosis and case management and treatment regimen in line with international standards for TB care (ISTC) in place in all sectors;
- Encouraging countries to strengthen legislative measures to ensure rational use of drugs;
- Securing adequate quantities of quality assured first- and second-line anti-TB drugs for uninterrupted treatment of the planned number of MDR-TB cases; and
- Increasing the number of manufacturers in the Region meeting WHO pre-qualification or national drug regulatory standards, equivalent to international standards.

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