MDR/XDR TB – Are we into Pre Antibiotic Era?

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ABSTRACT

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The current TB scenario in India and the world has been reviewed in this paper. The emerging problems of MDR Tuberculosis and XDR Tuberculosis have been detailed and the response to tackling the problem has been mentioned in detail. The role of IMA in this global fight against TB has been highlighted.

Keywords: Tuberculosis, MDR Tuberculosis, XDR Tuberculosis, RNTCP, Drug sensitivity testing, DOTS, IMA.

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The problem of MDR and XDR TB in India and across the world raises the possibility that the current TB epidemic of mostly drug susceptible TB will be replaced with a form of TB with severely restricted treatment options. If this happens it would jeopardize the progress made in recent years to control TB globally as well as in India and would also put at risk the plans to progress towards a world where TB ceases to be a public health problem. The emergence of strains of Mycobacterium tuberculosis that are resistant to antimicrobial agents is a worldwide problem. MDR-TB, defined as resistance to at least isoniazid and rifampicin, two of the most potent anti TB drugs, is a reflection of poor management of TB cases. Drug resistance develops either due to infection with a resistant strain, or as a result of inadequate treatment such as when a patient is exposed to a single drug, or because of selective drug intake, poor compliance, use of inappropriate non standardized treatment regimens, irregular drug supply, poor drug quality, or rarely erratic absorption of medications. Detection of Extensively drug resistant TB popularly known as XDR-TB was reported in 2006 wherein the resistance amplified from Rifampicin and INH to important groups of second line drugs. As per the latest definition, XDR-TB is a subset of MDR-TB with additional resistance to Fluoroquinolones and one of the second line injectables namely Kanamycin, capreomycin or Amikacin. XDR-TB has been reported in all regions of the world.

The Global scene

Like all forms of drugs resistant tuberculosis, XDR TB is man made. MDR-TB can be transformed into XDR-TB through inadequate or interrupted treatment with second line. The most recent estimates suggest that, globally, there were about 489000 cases of MDR-TB in 2006. These cases are very unevenly spread, with 27 countries (of which 15 are in Eastern Europe) accounting for 86% of the total. These 27 countries have been identified as priorities for improved diagnosis and management of MDR-TB at global level. Diagnosis of MDR-TB depends on the extent to which DST (Drug sensitivity Testing) services are available and used. Among the 27 global priority countries, 19503 cases were notified, which is only 4.6% of the estimated number of cases in these countries. The small number of MDR-TB cases diagnosed compared with the number of cases that are estimated to exist shows that an enormous amount of work remains to be done to improve the availability and provision of diagnosis and treatment for MDR-TB. It takes 18-24 months to treat patients with MDR-TB. The principal targets for MDR-TB are (i) that diagnostic DST should be offered to all previously treated and chronic TB cases as well as to 90% of new TB cases with a high risk of having MDR-TB. (ii) That all those in whom MDR-TB is diagnosed should be enrolled in GLC-approved or equivalent treatment programmes.

The Indian Scene

Drug resistance surveillance (DSR) surveys conducted in Gujarat and Maharashtra found that the prevalence of MDR-TB is less than 3% amongst new cases and 12-17 in re-treatment cases. The most effective means of preventing the further development of MDR-TB and subsequently XDR TB is through maintaining and improving the quality of RNTCP-DOTS, and more importantly promotion of the rational use of first

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and second line anti-TB drugs amongst all health care providers especially when treatment is given outside of RNTCP. In2007, the national programme initiated DOTS plus services for the management of MDR-TB in Gujarat and Maharashtra. Irrational use of first and second line anti-TB drugs for the treatment of TB patients needs to be discouraged. RNTCP guidelines need to be followed for the diagnosis and treatment of TB cases and good quality DOTS services ensured for preventing the further development of MDR-TB. Second -line drugs are widely available throughout India. It has been estimated that the size of the second-line drug market in India in 2006 at approximately USD$8.4 million per year. The great majority of this procurement is believed to be done by the private sector. Furthermore, anecdotal reports have suggested the increasing use of fluoroquinolones in combination with standard first line drugs in the treatment of new patients outside the RNTCP.

Table 1. Prevalence of MDR TB among new and previously treated patients : Data from population based studies, 1997-2005 (adapted from Paramasivan et al, IJMR 2004:277-86)

Area surveyed	New Cases		Previously Treated	
	Number Evaluated	MDR among New (% 95% CI)	Number Evaluated	MDR among previously Treated, % (95%Cl)
1997 Tamil Nadu	384	13(3.4%, 2.0- 5.7)		
1999 North Arcot	282	8(2.8%, 1.4-5.5) 278		
1999 Raichur	278	7(2.5%, 1.2-5.1) 197		
2000 Wardha		1(0.5%, 0-2.8)		
2002 Jabalpur	273	3(1.1% ,0.4-3.2)		
2005 Gujarat	1571	37(2.4%, 1.6-3.1%)	1045	180 (17.2% 14.9-19.5%)

Very little data is available in relation to drug resistance to second-line anti-tuberculosis drugs. Second line DST has been performed at the Tuberculosis Research Centre, Chennai, for many years. Based on unpublished data shared by TRC, between May 2000 and March 2005,66 patients from the Chennai area with MDR-TB had isolates tested for second line drug resistance to ofloxacin, kanamycin, and ethionamide. The patient population was composed of three groups, including 20 patients referred by private providers,17 referred from NGOs in Chennai, and 29 patients from the MDP project area in Thiruvallur district identified as MDR-TB cases. XDR TB was found in 1(1.5%) of the MDR-TB isolates. While this represents a minimum estimate, these findings suggest that XDR TB is rare at this time in the Chennai area. The existence of XDR-TB in India has also been reported from a private hospital in Mumbai in 33 (8%) out of409 MDR_TB isolates from a convenience sample, using the previous case definition for XDR-TB.

RNTCP response to dual challenges of MDR and XDR TB:

1) MDR prevention through sustained high quality DOTS implementation

Studies in pilot areas have shown that DOTS has been successful in reducing the prevalence of drug resistant TB on a community level in Mexico, Peru, and India (MDP area).The single most efficient and cost effective strategy for dealing with MDR and XDR-TB is prevention through proper treatment by all providers in the public and private sector, as per the International Standards for TB care. Key challenges include:

a. Reducing initial default and default from treatment
b. Ensuring accurate categorization of previously treated patients as Category II
c. Ensuring reliable DOT throughout treatment
d. Improve re-treatment success through intensified support, supervision, and monitoring of DOT in Category II patients
e. Improving Public-Private Mix (PPM) activities and uptake of DOTS by private sector and medical colleges.
f. Promoting the endorsement and application of the International Standards of TB Care through the IMA and other professional societies, particularly chest physicians to reduce the generation of drug-resistance, especially in the private sector.

2) Improve laboratory capacity: diagnosing MDR-TB

India does not currently have the laboratory capacity to conduct quality-assured culture and DST on the millions of patients annually suspected the capacity to treat MDR-TB, the capacity for culture and DST should be expanded so that those suspected of having MDR_TB can be reliably evaluated.

a. Have one RNTCP-accredited intermediate reference laboratory (IRL) for culture and drug susceptibility testing (DST) in each large state by 2009-10 for the laboratory diagnosis of MDR-TB
b. Ensure a stable supply of trained microbiologists and laboratory technicians for the national reference laboratories (NRLs) and IRLs so that

MDR-TB can be diagnosed accurately and reliably

c. Build capacity of national reference laboratories to accredit IRL's and Medical colleges applying for accreditation.

d. Promote and facilitate the accreditation of medical colleges to conduct quality-assured culture and DST.

e. Build capacity in all the National reference Laboratories in order to enable them to conduct quality-assured DST for second line drugs.

3) RNTCP DOTS plus services

In 2007, RNTCP made a landmark achievement with the launch of the DOTS plus services for the management of MDR-TB patients in the states of Gujarat and Maharashtra. As per the plan 50 patients will be enrolled in each state in the first year, the number being doubled every year subsequently. The first patients were initiated on treatment in August 2007 and a total of 89 patients have been enrolled in these two states till February 2008. DOTS plus services will be available in Kerala from December 2008.

The treatment of MDR is complex and is administered for a period of over two years on a daily basis including 6 to 9 months of injectables. Further the Cat IV drugs are known to cause severe adverse reactions. The management also requires a rigorous follow-up which includes smear, culture, bio-chemical tests and clinical check up at frequent intervals to evaluate the response to treatment. All these factors lead to high rate of default amongst the MDR-TB patients. To ensure patient compliance the programme is emphasising on counseling of patients and their family members on an on-going basis. A pilot project involving NGOs to provide counseling service to the patients admitted at the DOTS plus site and those under domiciliary care has been initiated in Gujarat and will be replicated at other DOTS plus sites.

The Role of IMA and professional medical societies

IMA and professional medical societies can play a leading role in the fight against TB. Concerted action by the medical profession can bring about substantial reduction in resistance to anti TB drugs. A healthy dialogue between clinicians and public health experts and consensual usage of international standards for TB care (ISTC) is needed to achieve this goal. IMA can show the way for other professional medical societies for consolidation of effort by the medical profession in the fight against this dreaded disease.

END NOTE

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REFERENCES

1. TB INDIA 2008 RNTCP- Status Report
2. Global Tuberculosis Control 2008- Surveillance, Planning, Financing-WHO
3. Consensus statement on MDR I XDR TB