

## RNTCP Briefing and Response to Dual Challenges of MDR and XDR TB

### Emergence of extensively drug resistant tuberculosis (XDR-TB)

Multi-drug resistant tuberculosis (MDR-TB) is defined as an isolate of *M. tuberculosis* resistant to at least isoniazid and rifampicin. A sub-class of MDR-TB, labeled extensively drug-resistant tuberculosis (XDR-TB) was first described in March 2006 following a joint survey of laboratories by the WHO, IUATLD, and CDC<sup>1</sup>. The original definition of XDR-TB was revised at the WHO Global Task Force on XDR-TB, October 9-10 2006<sup>2</sup>.

### Definition

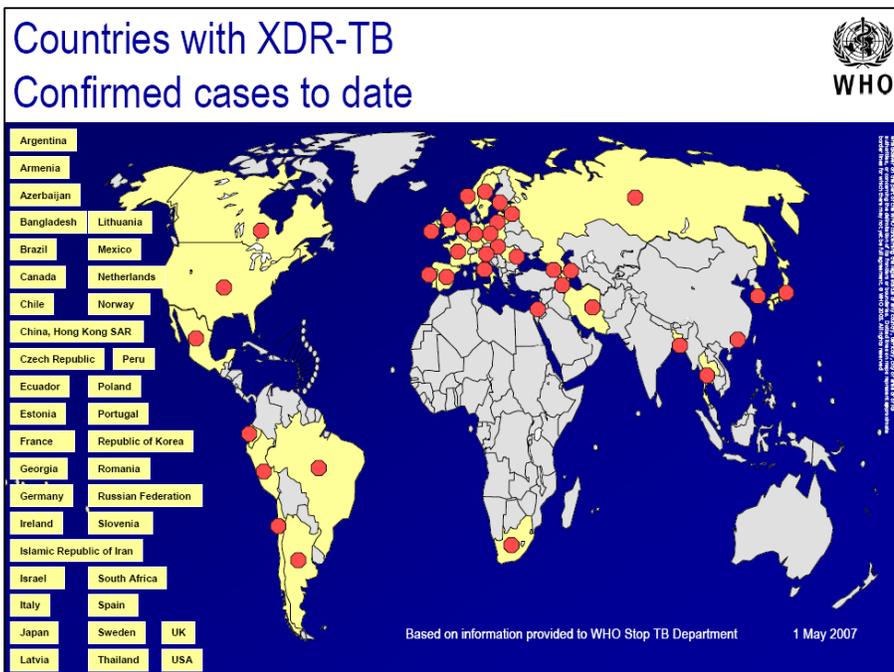
XDR-TB is TB showing resistance to at least rifampicin, isoniazid, and any fluoroquinolone, *and* to at least 1 of the 3 following injectable drugs used in anti-TB treatment: capreomycin, kanamycin and amikacin

### Cause

Like all forms of drug-resistant tuberculosis, XDR TB is man-made. MDR-TB can be transformed into XDR-TB through inadequate or interrupted treatment with second-line anti-TB drugs. This generally occurs when patients are not treated in adherence to national or international guidelines and the treatment is provided unsupervised and outside of structured MDR TB treatment programmes.

### Nature of the public health problem

The extent and magnitude of this problem is yet to be determined. Detection of XDR-TB requires testing for resistance to second-line drugs, which is technically difficult and only done at a very small number of laboratories. In Asia, only three laboratories (TRC Chennai in India and one Reference Laboratory each in South Korea and Thailand) conduct second-line drug susceptibility tests that are quality-assured by the WHO global Supranational Reference Laboratory (SNRL) network. Higher mortality from XDR-TB has been described from HIV-infected patients in the southern African region. Poor treatment outcomes have been reported from Latvia even in HIV-negative XDR-TB patients. Regardless of HIV status, XDR-TB is extremely difficult to treat, and poor treatment outcomes are expected.



### Global reference laboratory survey data

Collaborators from WHO/IUATLD/CDC undertook and published in March 2006 the results of a global survey to ascertain the occurrence of XDR TB (MMWR 2006;55:301-305). The survey was a convenience sample of 17,690 isolates submitted through participating international network of reference laboratories. XDR TB (using a previous case definition of resistance to 3 of 6 classes of second-line drugs) was found to exist in all regions of the world.

<sup>1</sup> MMWR 2006;55:301-305 ; available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5511a2.htm>

<sup>2</sup> Extensively drug resistant tuberculosis (XDR-TB): recommendations for prevention and control. *Weekly Epidemiological Record*. 81(45):430-32. Available at <http://www.who.int/entity/wer/wer8145.pdf>

In 2005, reports of extremely high mortality from TB disease were received from an ARV treatment programme in Tugela Ferry, in rural KZN<sup>3</sup>. In a cross sectional survey of patients attending the hospital, of 1,539 patient isolates sent, 544 were diagnosed with *M. tuberculosis*. Of these, 221 (41%) were identified as MDR-TB, and 53 (24% of the MDR-TB cases) were identified as being resistant to isoniazid, rifampin, ethambutol, streptomycin, as well as against the second-line drugs ciprofloxacin and kanamycin. Fifty-one percent of the 53 patients had no prior history of TB treatment; all 44 patients tested were HIV-infected (mean CD4+ T-lymphocyte count 72/microliter), and 15 (34%) were on ARVs (drug names unknown). Fifty-two (98%) of 53 died. Twenty-six of 30 isolates were found to be genetically similar by spoligotyping (similar strain previously identified by University of KZN researchers in 1995 and labeled as "KZN Strain"). Because these isolates were collected from patients in a single district hospital, the occurrence of nosocomial transmission was felt to be highly likely. However, one-third of the patients affected had never been previously hospitalized, suggesting the occurrence of some degree of community transmission. Since the cross-sectional survey, the Medical University of KZN has documented the existence of this strain in 28 healthcare institutions throughout KZN province.

### Data from India

#### *Availability of second-line anti-tuberculosis drugs*

Second-line drugs are widely available throughout India. An international pharmaceutical consulting firm has estimated the size of the second-line drug market in India in 2006 at approximately USD\$8.4 million per year.<sup>4</sup> The great majority of this procurement is believed to be done by the private sector. It is unknown how many patients have been treated by these drugs. No data exists regarding treatment practices in the private sector or medical colleges for patients with diagnosed or suspected drug-resistant tuberculosis. 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.

#### *Prevalence of MDR TB*

Drug resistance surveys in India have consistently shown a limited prevalence of MDR TB among new cases (Table1). As expected, a higher prevalence of MDR TB has been found in previously treated cases. Regardless of the proportion, in absolute terms the number of patients with MDR TB is substantial. WHO has estimated that in India, about 4.1% of all 2004 incident new and previously treated cases, or 87,413 cases of TB (95% CI 33,180 – 228,655), had MDR TB (Table 2). This is second in absolute terms only to China.

#### *Second-line drug resistance and XDR-TB*

Very little data is available from India 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 of 409 MDR-TB isolates from a convenience sample, using the previous case definition for XDR-TB<sup>5</sup>.

<sup>3</sup> Gandhi et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with Tuberculosis and HIV in a rural area of South Africa. *Lancet*, 2006. Published online October 26, 2006.

<sup>4</sup> IMS Health Inc. *Pathway to Patients: Charting the Dynamics of the Global TB Drug Market*. 2007. Available at <http://www.uptilt.com/c.html?rt=on&s=dj9,s6jv,tup,ceev,4n8e,8qwu,kjpy>

<sup>5</sup> Jain et al. *High prevalence of XDR-TB from a tertiary care hospital in India*. [Abstract#1398] International Conference of the American Thoracic Society, May 2007.

Table 1: Prevalence of MDR TB among new and previously treated patients: Data from population-based studies in India, 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% CI)
1997 Tamil Nadu	384	13 (3.4%, 2.0 – 5.7)	*	
1999 North Arcot	282	8 (2.8%, 1.4 – 5.5)	*	
1999 Raichur	278	7 (2.5%, 1.2 – 5.1)	*	
2000 Wardha	197	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%)

\* Anecdotal data in very small numbers of patients regarding MDR in previously treated; data not included here.

Table 2: Burden of MDR-TB among new and previously treated cases in 2004. Data are shown for the four countries with the highest estimated burden of MDR TB in the world (WHO Global TB Control 2006 ; Zignol et al, JID 2006;194:479-85)

	Total Estimated Number Cases (2004, New and Previously Treated)	Estimated number of MDR Cases (95% CI)	% of Cases That Are MDR (95% CI)
China	1,578,890	139,894 (85,948– 197,440)	8.9 (7.1–10.6)
<b>India</b>	<b>2,114,414</b>	<b>87,413 (33,180– 228,655)</b>	<b>4.1 (1.7–10.2)</b>
Russian Federation	202,735	34,055 (21,083– 48,023)	16.8 (14.1–19.6)
South Africa	401,789	10,348 (6,429– 14,547)	2.6 (2.2–3.0)

## 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. Promote 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 with tuberculosis. But in settings implementing DOTS appropriately and building the capability 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) **XDR-TB Prevention: Effective treatment of MDR-TB burden through DOTS-Plus** – The accurate diagnosis and effective treatment of patients with MDR-TB is crucial to improve treatment outcomes, reduce death, and prevent the generation of XDR-TB. Like all drug-resistant TB, XDR- TB is man-made. Treatment of MDR-TB in DOTS-Plus pilot programmes around the world has shown generally good treatment outcomes, much better than historically reported for treatment of MDR-TB outside of structured treatment programmes. RNTCP has a GLC approved DOTS-Plus pilot site at LRS Hospital, New Delhi. Community-based Category IV treatment for MDR-TB cases is soon to start in Ahmedabad, Gujarat state and Nagpur, Maharashtra state. Based on the experiences of these three initial sites, under RNTCP Phase II it is planned to:
  - a. Establish a nation-wide network of at least 24 RNTCP accredited state-level IRLs and medical college laboratories capable of undertaking DST for first-line anti-tuberculosis drugs (H,R, E and S).
  - b. Create a nation-wide network of at least 25 DOTS-Plus sites, capable of enrolling, and providing care and management for at least 5,000 “new” MDR-TB cases each year.
  - c. Ensure a stable supply of quality assured second-line drugs to all RNTCP DOTS-Plus sites using both Government of India and Green Light Committee procurement mechanisms.

- d. As an interim step to prevent further XDR-TB generation, the Central TB Division (CTD), MoH&FW, GoI will develop a guidance document for states on the rational use of second-line anti-tuberculosis drugs. This guidance document will be placed in the public domain via the RNTCP web-site. States will be requested to disseminate this guidance especially targeting medical colleges, public and private sector hospitals currently engaged in managing patients suspected to have MDR-TB. States will also be requested to monitor the adherence of health care providers in all sectors to this guidance document.
- 4) **Evaluate the extent of the threat of second line drug resistance / XDR-TB** – With the assistance of TRC Chennai, the extent and causes of XDR-TB in India needs to be investigated:
- a. Second-line DST for MDR-TB patients from DOTS-Plus sites is being conducted to inform the design of the DOTS-Plus programme treatment regimen
  - b. Surveillance for second-line drug resistance is being conducted on isolates collected from Gujarat (2005) and Maharashtra (2005-2006) drug resistance surveys. This will give an accurate population-based estimate of the burden of XDR-TB in these 2 states.
  - c. Planning is underway for a rapid case-control study of XDR-TB cases identified from the Gujarat DRS survey, to evaluate causes of XDR-TB.
- 5) **Review the supply and availability of second line anti-TB drugs in India** – As XDR-TB is man made, the supply and use of second-line anti-TB drugs has become a matter of urgent public health importance. The irrational and indiscriminate use of second line drugs by the private sector and medical colleges needs to be, and can be, stopped now, with the result of 'turning off the tap' of XDR-TB creation in India.
- a. A survey of the availability, supply and use of second-line drugs for TB treatment in medical colleges and the private sector will be conducted to understand the extent of use and misuse of such drugs.
  - b. Highlight the challenge of XDR-TB and discuss options for XDR-TB prevention with National and State officials at all potential forums.
  - c. Development and introduction of a system of notification of MDR-TB patients who require treatment with second-line anti-TB drugs.
  - d. Establish the foundation for regulation of the use of second-line drugs outside of RNTCP and to promote rational use of second line anti-TB drugs by an appropriate regulatory mechanism supported by professional associations.