

RNTCP Response to Challenges of Drug resistant TB in India **January 2012 (Update)**

Prevalence of Multi-drug resistant TB (MDR-TB):

MDR-TB is defined as resistance to at least isoniazid and rifampicin (two of the most potent first line anti-TB drugs), with or without resistance to other first-line drugs. MDR TB is important because patients with this type of drug resistance respond extremely poorly to standard anti-TB treatment with first-line drugs. MDR TB requires relatively costly laboratory diagnosis and treatment for at least two-years with drugs that are expensive, toxic, and not particularly potent. A case of MDR TB is about 20-40 times more expensive to manage than a case of drug-sensitive TB, and patient suffering is magnified.

State representative community based drug resistance surveys carried out in the states of Gujarat (56m) and Maharashtra (105m) and Andhra Pradesh (85m) estimate the prevalence of Multidrug resistant TB (MDR-TB) to be ~3% among new TB cases and 12-17% among previously-treated TB cases. These surveys have been used by WHO in the Global TB Report 2011, which estimated among the 1.5 million RNTCP-notified cases of pulmonary TB in India in 2010, approximately 64,000 cases of MDR TB could be diagnosed. Two more surveys are underway in the states of UP (85m) and Tamil Nadu (67m) and there is a plan to undertake a survey in Rajasthan and Madhya Pradesh in near future. There is no information about the prevalence of MDR-TB among TB cases treated in the private sector, as the private sector in India does not notify TB cases to RNTCP.

Emerging threat of Extensively drug resistance TB (XDR-TB):

As with all infectious diseases, the more severe the drug-resistance profile, the more difficult it becomes to successfully treat the patient. XDR-TB is a severe and serious form of MDR-TB, which responds very poorly to MDR TB treatment. XDR TB is defined as resistance to at least Rifampicin, Isoniazid (i.e. MDR TB) plus resistance to any fluoroquinolone, and to any of the 3 second-line injectable drugs (capreomycin, kanamycin and amikacin). Isolated studies have reported XDR TB in India. However, the extent and magnitude of this problem is yet to be determined. The programme is in the process of evaluating the extent of XDR-TB by conducting second-line DST for MDR-TB patients from DOTS Plus sites and also isolates collected from Gujarat and Maharashtra drug resistance surveys. Preliminary results show that there is not yet any XDR amongst new cases and ~0.5% amongst re-treatment cases.

Report from India on Tuberculosis that is “resistant to all drugs”

Recently, a letter to Clinical Infectious Disease Journal in December 2011 described 4 patients from Mumbai, India with “totally drug resistant” tuberculosis (coined “TDR-TB” from earlier reports) i.e. resistant to all first-line and second-line drugs tested. Such cases have been reported sporadically in Europe and 15 cases in Iran in 2009. Subsequent media reports have added reports of further cases in Mumbai and in Bangalore.

A careful audit of their prescriptions revealed that these 3 patients had received erratic, unsupervised second-line drugs, added individually and often in incorrect doses, from multiple private practitioners (on average from 4 physicians during a 18-month period) in an attempt to cure their multi-drug resistant (MDR) tuberculosis. The author urged that patients with MDR tuberculosis only be treated within the confines of government sanctioned MDR TB treatment programs to prevent the emergence and spread of this untreatable form of tuberculosis.

The patients in question represent MDR TB patients, who may also have XDR TB. The term TDR TB “totally drug resistant” is non-standardized, and in any case testing for resistance beyond XDR TB is not reliable, and correlation of DST results with clinical response to treatment has not yet been established, and some treatments might have some efficacy. Current WHO recommendations advise against the use of these DST results beyond those used to identify XDR-TB to guide treatment. Furthermore, new drugs to treat MDR TB are under final stages of development, hence the notion of “total drug resistance” may be fleeting. For these reasons, the term “totally drug resistant” tuberculosis is not yet recognized by the WHO. For now these cases are defined as extensively drug resistant tuberculosis (XDR-TB), according to WHO definitions, and accordingly can be managed by national XDR TB treatment guidelines.

Challenges

Insufficient public sector MDR and XDR TB diagnosis and treatment services

As the country scaled up basic TB services via RNTCP DOTS through 2006, MDR TB services began pilot testing only in 2007. Only in recent years has a public sector option for free diagnosis and treatment of MDR TB become available; in some settings, such as Mumbai, these services have been substantially delayed.

Poor quality of TB and MDR TB laboratory diagnosis in the private sector

TB is often diagnosed with serology, which frequently mis-diagnoses TB. The use of TB serological testing has been recommended against by WHO, RNTCP, and expert groups from India, but such tests are widely available from foreign and domestic manufacturers and widely used by the private sector. Similarly, drug-susceptibility testing from very few private laboratories has been subject to accreditation of quality. Private or NGO laboratories which have been accredited for first-line DST include Hinduja Hospital (Mumbai), SRL (Mumbai and Gurgaon), Quest Diagnostics (Gurgaon), CMC (Vellore), BPRC (Hyderabad) and DFIT (Nellore).

Lack of information about patients diagnosed with TB and MDR TB in the private sector

Patients properly diagnosed with TB and MDR TB in private laboratories are not notified to public health authorities, who would be able to take actions to confirm diagnoses, offer supportive services, and offer free treatment to patients from public sources or at least supervise the quality of care in the private sector.

Anti-TB drugs available without prescription and subsequent widespread irrational and irresponsible use

As with all schedule H drugs, provision without prescription is widespread and commonplace, and pharmacists are not required to maintain records of provision that could be used to identify patients with possible TB or MDR TB. Furthermore, second-line anti-TB drugs are widely available in the private sector and used inappropriately, even in drug sensitive TB where such drugs are not required and should be reserved.

RNTCP Response

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 effective and cost effective strategy for dealing with MDR and XDR is prevention by proper treatment for a patient initially when he/she can be easily cured. The programme is intensifying its ongoing efforts and innovating newer strategies to address the following key challenges:

- a. Universal access to quality diagnosis and treatment for all TB patients including high risk groups like TB-HIV, DR TB, Malnourished, Diabetics etc. through RNTCP by extending TB and DR TB notifications systems through labs, pharmacies and providers outside the government sector and offer quality care as per

International Standards of TB Care (ISTC), to reduce the generation of drug-resistance, especially in the private sector.

- b. Address urban TB control challenges like sub-optimal capacity health systems, overcrowding, migrations etc. in all cities in India
- c. Improving Public-Private Mix (PPM) activities and uptake of DOTS by private sector and medical colleges. In order to make the collaboration sustainable, ensure adequate compensation to other sector facilities for their input to TB control.
- d. Engage with NCDC to scale up implementation of the National Guidelines on Airborne Infection Control (AIC) in health care and other settings in India and its inclusion in the Indian Public Health Standards. Build capacity of key officials, architects and engineers in building design and engineering approaches in AIC.
- e. Reducing initial default, ensuring reliable DOT throughout treatment and reducing default from treatment
- f. Ensuring accurate categorization of previously treated patients and improve success rates through intensified supervision, and monitoring of DOT in previously treated cases
- g. Ensure that HRD needs for basic TB control and needs for scale up of M/XDR-TB control are included in overall health workforce development.
- h. Increasing involvement and empowerment of patients and communities. Ensure communications that increase awareness of how to prevent the spread of tuberculosis, including its drug-resistant forms, through early detection of those who are ill and through quality care.

2. Improve capacity for rapid diagnosis of M/XDR TB:

The programme is in the process of establishing a network of quality assured Culture and Drug Susceptibility testing Laboratories (C-DST) across the country for diagnosis and follow up of M/XDR TB patients. To date, 35 RNTCP accredited labs including 14 LPA and 4 liquid culture labs in public and private sectors are serving patients while another 30 labs are under the process of up-gradation and accreditation under RNTCP most of them include LPA and Liquid Culture for first and second line drugs.

As of January 2012, diagnosis of XDR TB can only be confirmed at 3 laboratories in India, which are quality-assured for second-line anti-TB drug susceptibility testing of fluoroquinolones and injectables. These are the National Reference Laboratories (NRL) of TRC/NIRT Chennai, NTI Bangalore and LRS Institute, New Delhi. Routine fluoroquinolone and injectable DST (i.e. XDR TB diagnosis) on all MDR TB patients at the beginning of treatment has been recommended by the RNTCP National Laboratory Committee in 2011, but the capacity to conduct that testing is not yet present in most culture and DST laboratories used by RNTCP. Capacity building for second line DST is being undertaken through these NRLs.

Under the plan RNTCP will

- a. Establish a nation-wide network of at least 43 RNTCP accredited laboratories in public sector and engage with 22 labs in private sector capable of MDR and XDR TB diagnosis, undertaking DST for first-line and second-line anti-tuberculosis drugs by 2012-13.
- b. Have at least one RNTCP-accredited intermediate reference laboratory (IRL) for culture and drug susceptibility testing (DST) in each large state functional by 2012-13, for the laboratory diagnosis of M/XDR-TB.
- c. Establish a robust system of sample collection and transport from peripheral designated microscopy centres to the C-DST lab.
- d. Ensure recruitment, skill enhancement and retention of trained skilled laboratory HR for the national reference laboratories (NRLs) and accredited labs in the states so that M/XDR-TB can be diagnosed accurately and reliably

- e. Build capacity of national reference laboratories to accredit all laboratories from public and private sector applying for accreditation for first line and second line DST and develop EQA systems for all technologies including WHO-endorsed rapid diagnostics.
- f. Advance MDR TB diagnosis early during the course of TB treatment, to allow patients to be placed onto the correct treatment regimen soon after diagnosis.
- g. Decentralize screening for MDR TB to the district level. Crucial in this step is specimen transportation to laboratories, and automated DST. A multi-centric field demonstration study is underway in 2012-13, to test the feasibility and cost effectiveness of the WHO-approved automated cartridge based nucleic acid amplification test (i.e. GeneXpert) that would offer results in 2 hours against 4 months in conventional C-DST in solid LJ media, scale it up to at least 1- 2 such automated systems offering rapid diagnostics at every district of India by 2016-17. Develop an interim guidance document for judicious use of GeneXpert test for early detection of Rifampicin resistant cases using available evidence with a confirmatory DST from and RNTCP accredited laboratory.
- h. Contracting the Culture and DST services from reliable private sector laboratories, after their accreditation by RNTCP, through the NGO/Private Provider scheme. The programme will upgrade this scheme to address its gaps and concerns of the reputed private labs and include costing for newer diagnostics as well as second line DST.

3. MDR TB treatment and XDR-TB Prevention:

The report on emergence of extensively drug resistant tuberculosis emphasizes the importance of aggressively supporting the Government of India's efforts to control TB and MDR TB, including basic MDR TB prevention through effective TB diagnosis and treatment the first time around, as well as the crucial need for the country to improve the standard of care in the private sector. While it is best to prevent MDR TB, when it occurs, prompt diagnosis and effective MDR TB treatment can still save the patient and prevent the development of further drug resistance and XDR TB.

By the end of 2011, basic programme management of drug-resistant TB (PMDT) services were introduced in all states, in 260 districts covering 508m (43%) population of India. Since August 2007, more than 7000 confirmed MDR TB cases have been diagnosed and initiated on treatment using quality second line anti-TB drugs in a standardized regimen provided free of cost to the patients. All states have developed their PMDT scale up plans for complete geographical coverage of services by 2012-13, while simultaneously advancing the diagnosis early during the course of TB treatment of the patients. Funding for PMDT scale up and second-line drugs is being secured through the 12th five year National Strategic Plan (2012-17) of MoHFW, GoI, to include procurement of GeneXpert machines, while the Global Fund support has been secured till 2015.

- a. Rapid scale up of PMDT services across India and effective treatment of M/XDR-TB – The accurate diagnosis and effective treatment of patients with M/XDR-TB is crucial to improve treatment outcomes, reduce death, and prevent the generation of XDR-TB. RNTCP is rapidly scaling up services for programmatic management of DR TB (PMDT) in India.
- b. Create a nation-wide network of at least 120 DOTS-Plus sites, capable of enrolling, and providing care and management for M/XDR-TB cases. 50 such sites have started reporting PMDT activities to date.
- c. Ensure a stable supply of quality assured second-line drugs for management of MDR and XDR TB to all RNTCP DOTS-Plus sites and districts using both Government of India and Green Light Committee procurement mechanisms.
- d. Till the MDR TB diagnosis and treatment was available from RNTCP nationwide, and to prevent private sector mismanagement of MDR TB, in 2008 RNTCP gathered national TB experts from all sectors and developed a 'consensus statement' for all the health care providers/institutions involved in management of MDR TB patients outside RNTCP. This guidance has been placed in the public domain via the RNTCP

web-site and is being disseminated to all medical colleges and private hospitals currently engaged in managing patients suspected to have MDR-TB.

4. Evaluate the extent of the threat of second line drug resistance / XDR-TB:

- a. To estimate the prevalence of XDR-TB, second line drug susceptibility testing (DST) was conducted on the MDR isolates from the DRS surveys and MDR TB patient registered for treatment in 2006–7 in Gujarat. In that survey, However, among MDR TB isolates fluoroquinolone resistance was exceedingly common, highlighting the potential threat of second-line drug resistance.
- b. Second line DST is also recommended for all the MDR patients registered for treatment who are not responding to standard MDR TB treatment, to assess the need for a new round of ‘salvage’ treatment for XDR TB.
- c. Routine second-line DST for MDR-TB patients from DOTS-Plus sites has been proposed and approved by the RNTCP National Laboratory Committee, and will be implemented from 2012 to inform the design of the RNTCP programme treatment regimen for 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 irresponsible 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. Engage with DCGI for inclusion of all first and second line anti-TB drugs in schedule H & HX, and the completion of schedule HX notification, for monitoring of the use of second-line drugs outside of RNTCP
- b. Strengthen supervision and monitoring through drug control administrators to enforce regulation that prohibits the dispensing of TB drugs without a prescription, and which prohibits physicians to sell TB drugs directly to patients.
- c. Develop and introduce of a system of notification for patients who are treated with second-line anti-TB drugs through pharmacies, so such patients can be offered appropriate free quality-assured second-line drugs under RNTCP, or at least have their private sector treatment quality supervised.
- d. Promote rational use of second line anti-TB drugs by an appropriate regulatory mechanism, supported by professional associations
- e. Disseminate the RNTCP response to M/XDR TB to all medical professionals in public and private sector

Response of WHO at the global level, to address “TDR-TB” specifically:

1. To facilitate discussion and to make surveillance consistent, an initial step is for WHO and partners to develop a consensus on whether a new definition is needed, and if so what the term and definition should be for such patients, taking into account the technological limitations of DST that still exist in 2011. If “totally drug-resistant” TB defines a subset of XDR-TB with different characteristics to other XDR-TB cases, particularly with respect to the outcome of such cases, then an internationally recognized definition may be needed. This should be seen as a call for national TB programmes and research groups to make data available on the outcomes of all highly resistant cases.
2. WHO is organizing an Expert Group Meeting in March, 2012 to assess additional data on DST accuracy obtained since 2008. This meeting will be expanded to include a consultation on possible definitions for “totally drug-resistant” TB. WHO is also convening another Expert Group Meeting in March to assess the latest evidence behind a new molecular line probe assay for detecting XDR-TB.