Report on National Workshop on Drug Susceptibility Testing (DST) Guided Treatment for Drug Resistant Tuberculosis Patients in India

Venue: Hotel Trident, Nariman Point, Mumbai

Dates: 26th to 28th August 2014

Background:

India is implementing Revised National Tuberculosis Control Program (RNTCP) since 1997. Approximately 1.5 million TB cases are being treated with standardised regimen with first line anti-TB drugs every year under RNTCP. More than 85% of the new TB cases and ~70% of the previously treated TB cases are treated successfully with standard first-line regimes. Approximately 2% among new cases and 5% among previously treated cases fail the standard first-line regimens. Presence of various forms of resistance to first-line anti-TB drugs is one of the most important cause of unfavourable outcomes and further amplification of resistance.

To address the issue of drug resistance among TB cases, India introduced the component of Programmatic Management of Drug Resistant TB (PMDT) since 2007 in line with the WHO Stop TB Strategy 2006. Between 2009 and 2014, RNTCP succeeded in establishing 58 quality-assured culture and drug susceptibility testing (C-DST) laboratories which include 37 labs for solid C-DST (Lowenstein Jensen (LJ) media), 48 for Line Probe Assay (LPA) and 14 for Liquid C-DST (Mycobacteria Growth Inhibitor Tube (MGIT)). Cartridge Based Nucleic Acid Amplification Test (CBNAAT) to diagnose Rifampicin resistant TB cases (surrogate for multi-drug resistant (MDR-TB)) is also available at 89 sites. Second-line DST (SL-DST) to diagnose extensively drug resistant TB (XDR-TB) is available in 8 laboratories. 122 drug resistant TB (DR-TB) centres are functional across the country to evaluate drug resistant TB cases and initiate them on treatment. Since inception in 2007, the country has tested 450,000 presumptive MDR-TB cases, placed about 54,000 lab confirmed MDR-TB cases and 1000 lab confirmed XDR-TB cases on standard treatment regimen. Treatment success with the current standard MDR-TB regimen in India is below 50% (similar to global outcomes) while outcomes are yet to be reported for XDR-TB patient cohorts. Around 20% of the MDR-TB patients die, 20% are lost to follow up and treatment fails among 7%. Resistance to second-line drugs and adverse reactions are accounted among the causes for the unfavourable outcomes.

Apart from the MDR-TB and XDR-TB cases, other forms of drug resistance like mono and poly resistance to first line and second line drugs are not being addressed under the PMDT. These cases are currently being treated with standard first line regimes under RNTCP. Often one to three drugs in these standard first line regimes are not effective due to resistance. A recent attempt to analyse the programmatic data has shown that their treatment success is only around 50%. Approximately 25% failed treatment. Among failures, 45% developed resistance to Rifampicin (amplified to MDR-TB) during treatment.

International experiences are not different, a study conducted in South Africa reported (370 - CID 2011:53 (15 August) - BRIEF REPORT) poor treatment outcomes among patients with Isoniazid mono-resistant tuberculosis treated with standard four/five drug regimen (Isoniazid, Rifampicin, Ethambutol and Pyrazinamide with or without Streptomycin)

depending on the history of previous treatment. 16% percent of patients had poor outcomes, 61% of whom progressed to MDR-TB. These observations indicate that specific treatment regimens are required to treat the rifampicin sensitive mono and poly resistant forms of TB. The WHO guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008 recommends various regimens in situations of mono and poly resistance.

As the C-DST laboratory network is being expanded rapidly in India, laboratory capacity to detect mono and poly resistant cases would increase. The first national anti-tuberculosis drug resistance surveillance is under way. It will provide a clear picture about the prevalence of various mono and poly resistance patterns among the TB patients in India by the end of 2015. The current estimates based on the conventional C-DST experience among the presumptive MDR-TB cases show that the number of such cases would be approximately equal to 58% of the MDR-TB cases. This translates to around 38000 cases among the notified pulmonary TB cases. These cases are at a demonstrable risk of failing the standard first line regimen offered currently and at a greater risk to amplify to rifampicin resistance during the course of treatment.

Considering these challenges, a national consultative workshop was organised in Mumbai from 26th to 28th of August 2014 to deliberate on emerging evidences and available global guidelines and draft the evidence based guidelines for drug susceptibility test (DST) guided treatment regimen for all forms of drug resistant TB in India. The participants of the workshop were expert clinicians, microbiologists, pharmacologists, civil society representative, donors, technical partners, administrators and public health experts apart from the national/state program managers.

Day 1: Tuesday, 26th August 2014

Inaugural Session:

The workshop was inaugurated in the gracious presence of Smt. Sujata Saunik - Principal Secretary Health and Family Welfare, Government of Maharashtra; Shri Sitaram Kunte – Municipal Commissioner, Municipal Corporation of Greater Mumbai (MCGM) and Shri Sanjay Deshmukh, Additional Municipal Commissioner, MCGM.

Dr R. S. Gupta, Deputy Director General (TB), GoI welcomed the participants. He emphasized that the key national strategy is to prevent emergence of Drug Resistant TB by effective implementation of DOTS at the time when patients are pan-sensitive to first line drugs. Cure depends on effective regimens, support for adherence to treatment and

management of other co-morbidities. Though the workshop focuses only on a single technical component, i.e. effective regimen, RNTCP is committed to take up the responsibility to promote adherence to treatment and manage co-morbidities in co-ordination with other disease control programs and harnessing the strengths of the existing public health care delivery systems.

Mumbai has taught great lessons to the country by rising to meet the challenges of DR-TB since 2012. Infrastructure and human resources provided by Municipal Corporation of Greater Mumbai (MCGM) and State Government of Maharashtra (GoM), adequately complemented by laboratory consumables, second-line drugs and funds by national program set the best management model for drug resistant TB of epidemic scale so far. As laboratory capacity to diagnose DR-TB is enhanced across the country, the model needs to be customized to suit local DR-TB epidemiological requirements everywhere. Outcomes of this workshop will give more confidence to the clinicians managing drug resistant tuberculosis. He requested all participants to contribute to the best of their abilities to address this critical challenge currently faced by the programme.

Dr A. Sreenivas, National Professional Officer (TB), WHO Country Office for India, addressed the gathering. He reiterated that one of the six components of WHO technical support to RNTCP to formulate normative guidelines. He highlighted that RNTCP possesses good capacity to manage data. Analysis of routine programme data and operational researches contribute to national TB policy revisions. RNTCP's efforts under PMDT to address MDR-TB and XDR-TB cases are comparable to global standards and acknowledged globally. However, other forms of drug resistant TB (mono and poly resistant TB) also require equal attention. From the patients' perspective, treatment regimens should be able to ensure relapse free cure. Logistic feasibility comes only next, which can be effectively addressed by management interventions and commitment of GoI. Mumbai deserves global appreciation for effective leadership in DR-TB care.

Sh. Sanjay Deshmukh, Additional Municipal Commissioner, MCGM welcomed experts to Mumbai. He expressed that the response to the reporting of Totally Drug Resistant TB in Mumbai in early 2012 followed a crisis management strategy with long-term sustenance

plan. While diagnosis and treatment of DR-TB was prioritized by investing into rapid scale up of diagnostic services, establishment of 6 GeneXpert (CBNAAT) sites and ~350 beds at the upgraded Bahadurji Block affiliated to the DR TB centres at Group of TB Hospitals, Sewri, prevention of further emergence of resistance was given equal priority through decentralization of RNTCP program management units by investing into establishments of fully staffed and equipped 24 district TB centres under the Mumbai City TB Office and expanded team of trained supervisory staff. MCGM is committed to further strengthening of care to DR-TB patients with technical support from WHO and overall guidance of Central TB Division, GoI.

Smt. Sujata Saunik, Principal Secretary Health and Family Welfare, Government of Maharashtra felicitated the workshop. She alluded that as the event takes place in the backdrop of Ebola epidemic, we all are reminded how important is efforts to control infectious diseases. With reference to an article in The Week, critical about GoI's approach to TB control, she stressed that more research and advancements are required in the field. Research is not a function of Public Sector alone. Private sector also need to join hands in research in the same way it joins hands with Public and NGO sector in TB care and control. The health department alone cannot meet the goals of universal health coverage and inter sectoral collaboration is need of the hour. The healthcare workers in TB care require proper surveillance along with mechanisms of compensation and insurance. All major cities should have a task force to address the issue of DR-TB like Mumbai, as the cities and towns have crowding, slums, suboptimal access to health care and migration.

Sh. Sitaram Kunte, Commissioner, MCGM made his key note address. He appreciated that remarkable progress has been made by the country in the field of TB control by halving TB deaths and prevalence. Drug Resistance remains a challenge to control TB. Primary transmission of drug resistant TB is a major concern in crowded metros

like Mumbai. Better regimens, support for adherence to treatment should be reinforced along with control of airborne infection in health facilities and community.

Dr K. S. Sachdeva, Additional Deputy Director General (TB), GoI proposed vote of thanks. Tremendous support by MCGM during the TDR incident was acknowledged and appreciated. He proposed that a TB task force may be formed for the state of Maharashtra instead of the metro alone.

Session 1: Introduction and Problem Statement - need of DST guided treatment for TB patients in India

Chair:
1. Dr S. K. Sharma, Professor and Head, Dept. of Medicine, AIIMS New Delhi
2. Dr D. Behera, HOD, Dept. of Pulmonary Medicine, PGIMER Chandigarh
3. Dr Rajendra Prasad, Director, VP Chest Institute, New Delhi

Speakers:
1. Dr Ashwani Khanna, State TB Officer, Delhi
2. Dr Ranjani Ramachandran, National Professional Officer, Labs, WHO India
3. Dr Rupak Singla, Head, Respiratory Medicine, NITRD, New Delhi
4. Dr Rajesh N Solanki, Professor, Respiratory Medicine, BJ Medical College, Ahmedabad

Dr Behera opened the session with a few remarks on RNTCP. While we revise the guidelines and innovate, we also need to introspect about the processes of national TB control. As the review on NTP undertaken in 1992, an in depth review of RNTCP is due. Are we making the progress in the desired way? Are the laboratories prepared adequately to undertake the challenge of conducting DST for all diagnosed TB cases? Is the quality of such laboratories assured? Are there plans to ensure quality of DST laboratories in the private sector? How far shall we ensure standards of TB care? Dr Uplekar's study shows the treatment practices in the private sector has not improved after two decades. Drugs make only one component of TB control. Adherence to standard treatment is also an important component.

Dr Prasad reinforced these statements by adding that implementation of national program needs more attention along with the technical aspects including availability of drugs. Ensuring quality of TB care in the private sector is of utmost importance. Inter sectoral collaboration is pivotal for effective TB control. Education of private providers on standards of TB care, regulation of availability of anti-tuberculosis drugs in open market etc., should complement technical revisions of drug regimens.

Dr S. K. Sharma quoted instances of non-availability of drugs in the program in the recent past and cautioned about the need of a highly vigilant drug procurement and supply chain management system. It is more relevant in the context of introducing the much needed DST guided treatment.

A. Introduction to the workshop (Need, rationale and challenges)

Dr Ashwani Khanna presented the status of PMDT services, current challenges and the need and rationale for DST guided treatment regimen in India. Currently employed DST technologies under RNTCP PMDT across all districts in India are Cartridge Based Nucleic Acid Amplification Test (CBNAAT) that tests only Rifampicin and Line Probe Assay (LPA) that tests Isoniazid and Rifampicin. Other first line drugs are not tested routinely. In the pre-molecular DST era of national program, Streptomycin and Ethambutol were tested with phenotypic DST (solid or liquid C-DST). Second-line phenotypic DST is currently done only for Kanamycin and Ofloxacin in 8 labs. In the absence of routine poly-DST, resistance to other first and second line drugs cannot be identified.

The RNTCP PMDT services prioritize treatment of MDR-TB and XDR-TB. There are standard second-line regimens for these cases with scope for standard modification for additional

mono-resistance to Ofloxacin (O) or Kanamycin (K) in MDR-TB isolates at baseline. However, systematic analysis of the programme data from the pre-molecular DST era under RNTCP reveal other forms of DR-TB like mono and poly resistant TB (other than R resistance) to be 25%. These cases are currently being treated with standard first line regimen that includes these drugs to which the mycobacteria are already resistant in such cases. In a few instances, like resistance to Isoniazid (H), Ethambutol (E) and Streptomycin (S), this practice may lead to treatment with only one drug with known sensitivity i.e., Rifampicin (R) and one drug with unknown sensitivity i.e. Pyrazinamide (Z), in intensive Phase (IP) and a monotherapy with Rifampicin during continuation Phase (CP), when a standard HREZS/HRE regimen is used. This could expose Rifampicin and eventually lead to amplification to MDR-TB.

Drug resistance is a major challenge in Indian TB control. WHO estimates 64,000 MDR-TB among the notified pulmonary TB cases emerging annually in India as per WHO Global TB Report – 2013. However, this is based on the subnational Drug Resistance Surveys (DRS) that observed MDR-TB rates as 12-17% in previously treated TB cases and 2-3% in new TB cases could be MDR. The first nationwide anti-tuberculosis DRS started in July 2014 will provide precise national estimates and prevailing epidemiology of various forms of DR-TB.

Approximately 42% among the culture non-converters of the MDR-TB patients beyond 6 months of standard second line treatment offered SL-DST at NTI Bangalore, were diagnosed to have XDR-TB and 77% had any floroquinolone resistance under RNTCP.

Routine surveillance data disaggregated for outcomes of standard first line treatment by resistance patterns show very poor outcomes of mono and poly resistant cases to first line drugs other than rifampicin. . Approximately 25% of MDR-TB suspects were found to have first-line mono and poly resistance under RNTCP. These cases may have to end up with poor outcomes if treated with current regimen. Current treatment success of MDR-TB is below 50%. XDR-TB outcomes are yet to be reported; however, these are expected to be much lower. . Hence it is highly rational to devise appropriate DST guided treatment regimen with combination of drugs to which the organism is known to be susceptible to provide maximal DST advantage to the patients while simultaneously identifying solutions to the anticipated operational challenges under the programme.

Dr N. Ramraje opened the discussion on the problem statement by asking clarifications

about the estimates. Currently estimated MDR-TB cases are based on the notification statistics. There could be similar cases, probably more in number, among the cases treated in the non-program sector. It is applicable to mono and poly resistant TB cases also. However, is the laboratory capacity adequate to diagnose such cases? Diagnostic capacity

should back up regimen revision. These patients should not be let succumb to the disease when the country has proved its capacity to effectively address MDR-TB problem in Mumbai and elsewhere. Equally important is the prevention of primary transmission of drug resistance. Effective airborne infection control strategies need to be implemented in health facilities and households. Similarly, screening of contacts of drug sensitive and drug resistant TB cases needs to be effectively implemented.

Dr Sachdeva made a few clarifications. Government has a plan to review the program. Laboratory capacity is being exponentially scaled up based on the national laboratory scale up plan 2009-14. However, for policy revisions, we may not need to wait for country wide laboratory scale up since implementation plans are always phased. Quality assurance of laboratories has a built in mechanism with proficiency testing preceded by effective training and supervision. Program certifies DST laboratories based on this mechanism including private labs. Recalibration of equipments, annual proficiency testing and recertification is done periodically. Issues beyond drugs, like adherence to treatment, management of co-morbidities, counselling support, management of adverse reaction to drugs etc. are also taken care of under the program. States have taken local initiative for nutritional and social support and rehabilitation of patients. Research is a well addressed area. In collaboration with technical agencies and national institutes, operational research workshops are routinely being carried out. A few papers published by the program's stakeholders had been supportive in revising program policies in the recent past. Program has taken up initiatives for pharmaco-vigilance in collaboration with Pharmaco-vigilance programme of India (PvPI) and WHO India for early identification and notification of adverse reaction to drugs.

Dr Salhotra, Additional Deputy Director General (TB), GoI also made a few clarifications. Although there were a few instances of delayed supply of drugs and isolated local stock outs last year, the situation of drugs is fully under control. Due to long procurement cycles the mechanism for building up buffers will take some time. During the past 6 months enough steps have been taken to ensure uninterrupted supply of drugs. Approximately 33,000 MDR-TB courses have been received recently by the states.

Dr S. K Sharma requested for clarification on the missing MDR-TB cases and HIV MDR-TB co-infection. If WHO estimates 64,000 MDRTB cases and only approximately 20,000 cases are notified to the program, what is the fate of remaining cases?

Dr Sachdeva clarified that the estimated cases include new TB cases and the current program policy is to do DST for previously treated cases only except PLHIV and contacts. However, program is addressing this issue by establishing more rapid diagnostics across the

country to move towards universal DST to capture the estimated MDR-TB cases yet missing from the programme.

B. Emerging evidences of DST patterns for first and second line anti-TB drugs in India

Dr Ranjani Ramachandran has presented data on various drug resistance patterns from various subnational DRS and MDR-TB suspect examination under RNTCP PMDT services. DST currently is offered only to patients non-converting or failing with the first line regimen or diagnosed TB patients to be initiated on regimen for previously treated patients. Overall the treatment outcomes in patients resistant to INH at the treatment initiation have poor outcomes and patients who received modified regimens based on DST did well. The pooled results of various state level DRS show 40% of the tested had resistance to one or other anti TB drug and among the resistant cases, as high as 80% had any H resistance. This implies that any H resistance is invariably associated with additional resistance to other first line drugs, hence, can be considered as a surrogate of any poly-resistance to first line drugs. Among the poly resistant cases, the highest at 23% was the group with SH. The programme data from laboratories performing FL-DST under RNTCP (2007-2013) on presumptive MDR TB cases shows 63% of those with available DST results had resistance to one or other anti-TB drugs and among the resistant cases, as high as 86% had any H resistance, reiterating its surrogate potential for poly-resistance. The Line Probe assay data (2009-2014) show 27% H resistance among MDR TB suspects tested under the programme.
The initial reports from the 3 states that have recently started baseline SL-DST among MDR-TB isolates show that although XDR-TB patients are ~6%, any fluoroquinolones (FQ) resistance accounts for as high as 31% among patients with available baseline SL-DST results. These prevalent DST patterns to a great extent explain the poor outcomes among patients with mono and poly resistance (other than R) initiated on standard treatment for previously treated cases and poor outcomes among MDR-TB patients with FQ resistance initiated on standard regimen for MDR-TB cases.

Dr Behera requested for clarification on the sources of the data as the data appears to be skewed for treatment experienced patients. Dr Ranjani clarified that the data presented are not population representative and does not contain information on the new cases except in case of the subset of new TB cases in the sub national DRS. H mono resistance was observed to be 10-12% among new cases and 30-40% among previously treated cases.

Dr Sreenivas deliberated on importance of this program DST data as this was from the patients who are being currently treated without taking their other drug DST patterns into consideration leading to poor outcomes.

Dr S K Sharma, raised the issue of reliability and relevance of in vitro DST patterns to in vivo pharmaco-kinetics especially in the group of Extra Pulmonary TB.

Dr Rohit Sarin commented that although the H resistance of ~10% in new cases and ~30% in previously treated cases but the old school teaching was that 4 drug therapies shall address this H mono resistance and this shall not defer the outcomes which now seems to require a revision based on the emerging evidences from RNTCP.

Dr Rajendra Prasad commented that the 4 drug therapies in case of H mono resistance would have been more successful if given daily and not intermittently.

Dr Anurag Bhargava pointed out that apart from the role of H mono-resistance in treatment failures, relapse and augmentation to R resistance, the agent factors, the host factors also need to be considered contributing to emergence of resistance. Nutritional status of the patient, achieved drug levels, extent of the disease etc. are among these factors.

Dr Jawahar also emphasized on the factors other than resistance and treatment regimen that need to be addressed.

Dr Soumya Swaminathan, Director, NIRT Chennai suggested that a break up of inhA and kat-G subsets from the H resistant group from the LPA labs would be useful in devising appropriate regimen. She also drew attention towards slow and fast acetylators and drug dosages. Dr Urvashi Singh further clarified that proportion method would be ideal for testing inh-A and kat-G subsets.

Dr Camilla Rodrigues shared studies revealing that the outcomes of MDR-TB with FQ resistance treated with standard MDR-TB regimen are very poor. Dr Rajendra Prasad invited the attention of the house to a long prevailing issue of misuse of FQs for TB and Non-TB cases.

C. Implications of mono and poly resistant cases treated with standard first line regimen under RNTCP

Dr Rupak Singla presented the disaggregated routine surveillance data from the program on the treatment outcomes of mono and poly resistant TB cases (other than R) treated with standard first-line regimen under RNTCP. Sputum specimen from presumptive MDR-TB cases as per the PMDT definitions are subjected to DST. During early implementation phase, phenotypic DST for 4 first line drugs (SHRE) was offered to diagnose DR-TB. However, by 2012, most of the presumptive MDR-TB cases were subjected to LPA. Hence, INH mono resistant cases by LPA and mono and poly resistant cases (other than R) by phenotypic DST were reviewed separately. A systematic retrospective record review based cohort analysis of mono and poly resistant TB cases (other than R) identified from the respective C-DST laboratory registers and their treatment outcomes collected from the corresponding TB registers was undertaken by the programme. Definitions of treatment outcomes in the program were used. However, for the purpose of analysis, the outcome "switched to Category IV" was considered as failure. After 3 rounds of data cleaning and validation, 8848 patients' data could be included in the analysis. A total of 6426 H resistant cases by LPA were available for analysis. Another 2422 cases by phenotypic DST disaggregated by their DST patterns (other than R) were also available. Failure of treatment is considered as the primary outcome and amplification to R resistance among the failed cases subjected to repeated DST was considered as the secondary outcome of the analysis. It was observed that overall failure ranged from 24 to 67%. A subset analysis of new and previously treated cases revealed that the outcomes did not vary much among these subsets. Among the failed cases subjected to repeat DST, amplification to R resistance ranged from 35 to 64%. Subset analysis of new and previously treated groups did not show much variation. Overall outcomes of treatment are summarised in the table 1.

Table 1 Treatment outcomes of mono and poly resistant TB cases (other than R) treated with standard first line anti-TB regimen under RNTCP.

DST Pattern		Success	Failure	Amplification to Rif Resistance
H Mono (LPA)	**n= 6426**	53%	24%	41%
SHE	**n= 323**	16%	67%	53%
HE	**n=100**	31%	54%	64%
SH	**n=611**	25%	54%	52%
SE	**n=68**	24%	49%	46%
H Mono (Phenotypic DST)	**n= 819**	31%	49%	40%
S Mono	**n= 442**	26%	49%	35%

Very importantly, adherence to first line treatment among mono and poly resistant cases did not vary from their drug sensitive counterparts. It may be inferred that with similar adherence, mono and poly resistant cases have poor chance to have successful treatment with current regimen.

Current definition of MDR-TB suspect under PMDT is confined to patients on first-line TB treatments, who fail or do not respond to treatment, patients who receive first line regimen for previously treated cases after relapse or being lost to follow up, and new TB patients who are HIV positive or contacts of MDR-TB cases. In any case, there is no option to offer phenotypic DST as the rapid molecular DST is available across the country as the first choice of DST. However, the implication of treating mono and poly resistant cases with standard first line regimen and high treatment failures in such cases and resulting amplification to R resistance clearly indicates the need to offer DST to first line drugs and DST guided treatment in all presumptive cases of MDR TB.

Dr Soumya Swaminathan opened discussion on the topic. She stated that HIV infected TB patients are at higher risk of developing R resistance. NIRT is conducting a study on the topic. Interim analysis show that these patients are at increased risk of failure and developing additional resistance to R. New patients with H resistance are observed to be at 9 times higher risk of developing resistance to R.

Dr Rohit Sarin commented that it is true that the analysis did not consider variables like smoking, substance abuse, adherence to treatment, nutritional status, co-morbidities etc. However, this does not undermine the significance of the observations. More importantly, it is a true picture of treatment outcomes under real programme conditions. It is hard to explain that association of the confounding variables may differ between drug sensitive and drug resistant TB cases treated with same regimen. Of greater concern is the amplification to R resistance among the mono and poly resistant TB cases treated with standard first line regimen.

Dr Alladi Mohan suggested that data on relapse among new patients treated with Category I regimen ($2H_3R_3E_3Z_3/4H_3R_3$) may throw more light on the efficacy of regimen.

Dr S.K. Sharma commented that the data presented qualifies only for Grade III evidence. There are other pitfalls too. Approval of protocol, ethical clearance, and multivariate analysis are to be considered for such studies. We should generate level I evidence through prospective studies.

To this Dr Sarin responded that the quality of evidence in the area of management of Drug Resistant TB is very low globally also. While guidelines for MDR-TB treatment were drafted,

5 out of 7 evidences were of very low quality and the corresponding recommendations were conditional. Moreover, prospective studies although important, may not solve the current challenges clearly identified from retrospective analysis of programmatic data in real implementation conditions, as it would take many more years in providing results for decision making.

Dr R.S. Gupta also responded by stating that national programme policies and strategies to address technical and operational challenges must not be dependent on long term prospective research studies alone, however, the systematic retrospective analysis of the rich data generated under RNTCP through service delivery in real implementation field conditions must also be given due weightage in guiding the programme for policy decisions. No programme in the world would continue implementing the same strategies with clear evidences of unfavourable outcomes caused to some section of patients (even if it's of low quality) and wait for high quality evidence for years.

Dr Varinder Singh commented on causality and association, interpretation of data and other factors of programme implementation to be taken into consideration before embarking on newer guidelines.

Dr Ameeta Athawale raised issues of all drugs resistance (XXDR-TB), medico legal issues around treating with a regimen containing drugs to which the bacteria are known to be resistant.

D. Treatment outcomes of MDR-TB cases with/without second line drug resistance treated with standardised second-line regimen under RNTCP

Dr R.N. Solanki presented data on treatment outcomes of first 3 years cohort (Aug 2007– Mar 2011) of MDR-TB cases with and without additional resistance to second line drugs treated with standard second line regimen under RNTCP in India. The cumulative treatment success rate of MDR TB patients was 49% similar to global rates. A retrospective cohort analysis was conducted to 1) To evaluate treatment outcomes among all MDR-TB patients treated in

India under RNTCP PMDT (first 3 years cohort) 2) To evaluate risk factors for a) Initial culture conversion, b) culture *re*-version after initial culture conversion & c) unfavorable treatment outcomes.
The first three year cohort of 3712 MDR TB cases treated between August-07 to March 11 was analyzed. Additional Ethambutol resistance was observed in 56% and a very high Streptomycin resistance in 74% of the cases. 65% of MDR TB cases had additional resistance to other first line anti –TB drugs. Additional any Ofloxacin resistance was found in 60% of MDR-TB isolates tested for second line drugs sensitivity.

Unacceptably low interim 12-month outcomes (26% never culture converted and 19% culture reverted) and final treatment outcomes (66% with unfavourable outcomes – died, failed or lost to follow up) observed with standard MDR-TB regimen in initial 3 years cohort under RNTCP. Current regimen is not sufficiently rendering patients non-infectious with 1 out of 4 never converted and 1 out of 5 who converted, reverted to culture-positive. Even in adherent & less prior treatment experienced cases, outcomes still very poor. Very high prevalence of FQ resistance in initial MDR treatment cohorts (number small, highly treatment experienced, all had failed re-treatment regimen). Undetected baseline resistance to FLD-SLD making situation worse. It was observed that baseline resistance to O and K worsens the probability of initial culture conversion and favourable treatment outcomes. In conclusion, India's MDR-TB epidemic is in large-part inclusive of FQ resistance. Standardized MDR regimen is yielding unfavourable treatment outcomes in nearly 2/3rd of patients. Poor outcomes are not amenable to quick fixes alone (adherence and lesser treatment episodes). This spells out a felt need for routine baseline DST for FLD-SLD build in the diagnostic algorithm of TB at appropriate time to guide treatment along with accelerated shift to universal DST and stronger treatment regimen adjusted for resistance (DST guided treatment for DR TB cases).

Dr Behera commented on the problem statement that the presented data shows 30% of the cases were lost to follow up and 20% died. Poor outcomes of treatment observed are obviously due to these rather than inferiority of the regimen.

Dr Rajendra Prasad expressed concern over high rates of O resistance in previously treated patients with <11 month duration of treatment.

Dr Sharma added that irrational use of FQs may be an important factor leading to high prevalence of FQ resistance and poor treatment outcomes. Regulation of FQ use must be seriously considered by the government. He also expressed apprehensions in extrapolating the cohort results of 77 odd MDR TB patients with FQ resistance at baseline to the entire country. He also requested DDG TB to proceed for drug regulations to stop misuse of FQs and newer drug molecules.

Dr Alpa Dalal commented that it was more important to address the issue of FQ resistance with proper regimen rather than only analysing the reasons of high FQ resistance without regulations to control them.

Dr Rupak Singla commented that poor outcomes in the initial cohorts are also attributed to late diagnosis and late initiation of treatment. He also raised the issue of initial phases of PMDT expansion where migrants were unable to get treatment if their native district was not providing PMDT services. He also commented on urgency of FQ resistance issue and utilization of international studies in FQ resistance in policy formation for the country without waiting for 2-3 years to generate country specific data.

Dr Rohit Sarin summarized that a FQ resistance will respond poorly to standardised treatment regimen, however, if the high default rates are addressed the outcome may still improve with the standardized regimen.

Dr Vikas Oswal emphasized on importance of counselling and counsellors in improving the success rates of MDR-TB treatment along with availability of 2nd line DST, early identification of additional drug resistance and modification of regimen appropriately.

Dr Camilla Rodriguez deliberated that the proportion of FQ resistance is much higher in Mumbai and this is the time to act to stop further deterioration of the scenario.

Dr Radha Munjhe drew attention of house towards addressing comorbidities i.e., HIV and Diabetes and sub set analysis to identify the attributable factors to poor outcomes.

Smt. Sujata Saunik, Principal Secretary, Health and Family Welfare, Govt. of Maharashtra made detailed comments on the problem statements presented and deliberated upon since morning. Drug Resistance among TB patients is pretty high. Whatever the cause is, we cannot neglect its existence. While preventive measures are important to contain further emergence of resistance, management of such cases and cutting the chain of primary transmission are equally important. Figures presented by Dr Ranjani are shocking. It is obvious that failure rates of mono and poly resistant cases under the program are too high. We claim that TB is completely curable, but prove otherwise. How are we going to improve the cure rates?

RNTCP is being implemented since the last 17 years. The program must have matured enough to address these challenges. At any cost we should prevent these fatalities. It is true that research is needed for disease control. However, research should not be to establish facts that have already been established. Here we require convergence and consensus. Advise us on infection control; airborne infection control among health facilities and community. The country should have complete data base of all TB/DRTB cases diagnosed and treated across all sectors. All care providers should have a log-in ID to Nikshay; the web based TB notification system. We need also to ensure improved adherence to treatment with counselling, management of adverse reactions, nutritional support and close supervision. We should also start an on-line forum for a lot of public hearing on TB care and control. The state would examine possibilities of legislation for rational use of anti-TB drugs.

Session 2: Panel discussions on proposed solutions to address the need of DST guided treatment in India

Session 2 was a series of panel discussions followed by a lead presentation to brainstorm on solutions to the stated problems. These discussions were intended for opinions, experience sharing, rationale, and addressing operational challenges.

A. Proposed DST guided treatment regimens with diagnostic algorithm to address the prioritized First Line DST patterns under RNTCP in India

- Moderators:

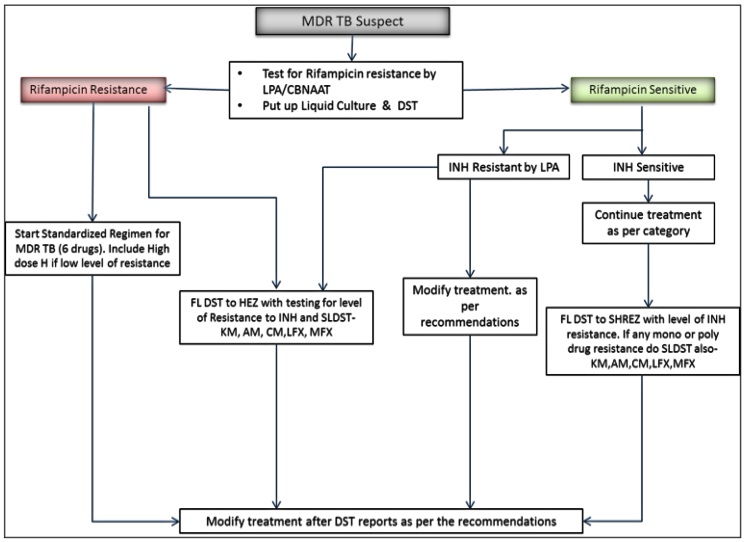
1. Dr Rohit Sarin, Director NITRD, New Delhi
2. Dr Soumya Swaminathan, Director, NIRT, Chennai
3. Dr Prahlad Kumar, Director, NTI, Bangalore

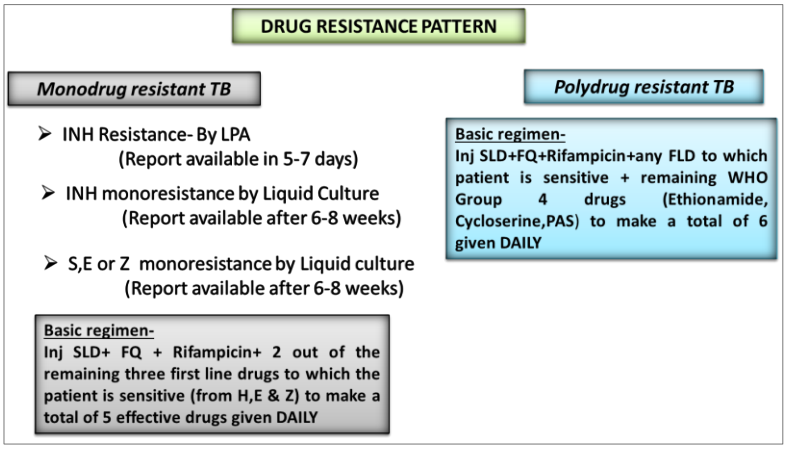
- Panellists:

1. Dr. Ameeta Joshi
2. Dr Ameeta Athawale
3. Dr S. Jawahar
4. Dr Puneet Dewan
5. Dr Rupak Singla
6. Dr Ranjani Ramachandran

- Lead Presenter: Dr Anuj Bhatnagar, Head, Respiratory Medicine, RBIPMT, New Delhi

With a brief recap of the rationale for DST guided treatment, Dr Bhatnagar stated that treating with appropriate regimens based on baseline DST patterns may prevent the emergence of resistance to Rifampicin, improve chance of favourable outcomes & prevent spread of drug-resistant mutants in the community. The challenges in framing the regimen for Mono/Poly DR TB are to keep it simple without technical compromise to cover all possible cases and keep programmatic implementation including lab and treatment capacity with flexibility to DR TB centres for case based decision making in focus. He stressed that the management of any case of DR TB will be decided by the DR TB Centre and district TB officers will manage the ambulatory care based on this.

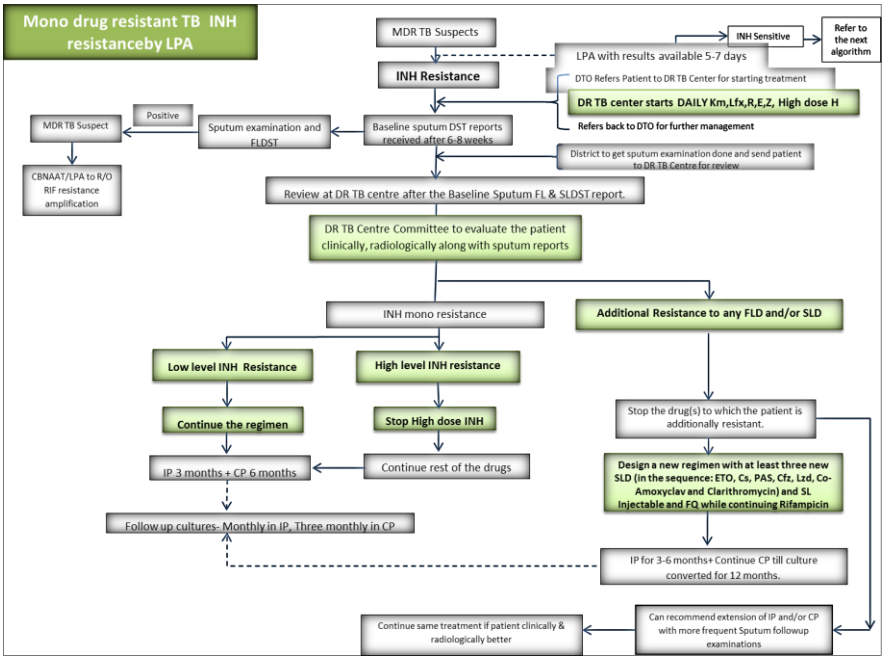




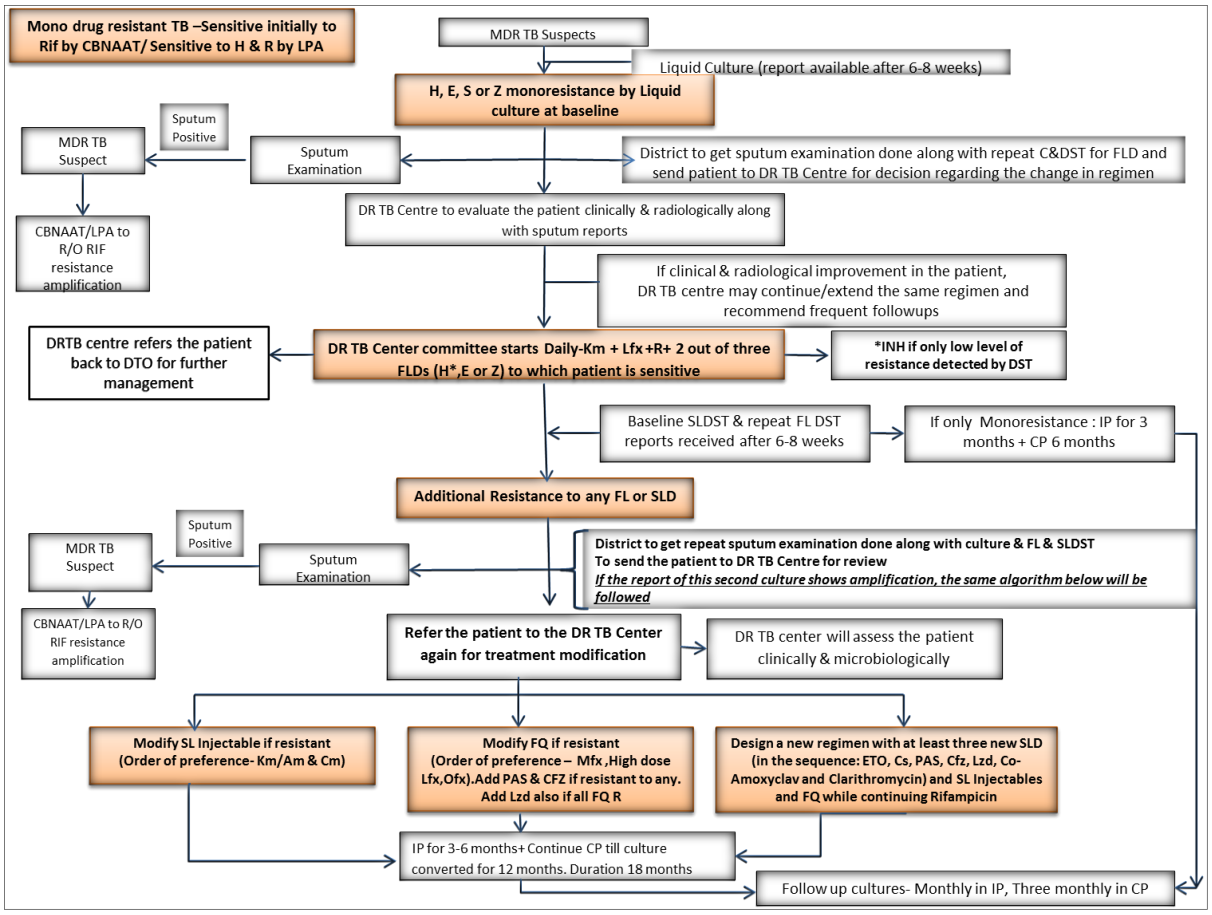
He proposed a diagnostic algorithm for early diagnosis of mono and poly resistant TB cases to be implemented in conjunction with current PMDT guidelines, with MDR-TB suspect as the starting point. It was proposed that H can be used in normal dose in H sensitive cases, in high dose in low level of H resistance detected through LPA (inhA) or liquid culture and it would not be used if high level of H resistance detected through LPA (kat-G) or liquid culture.

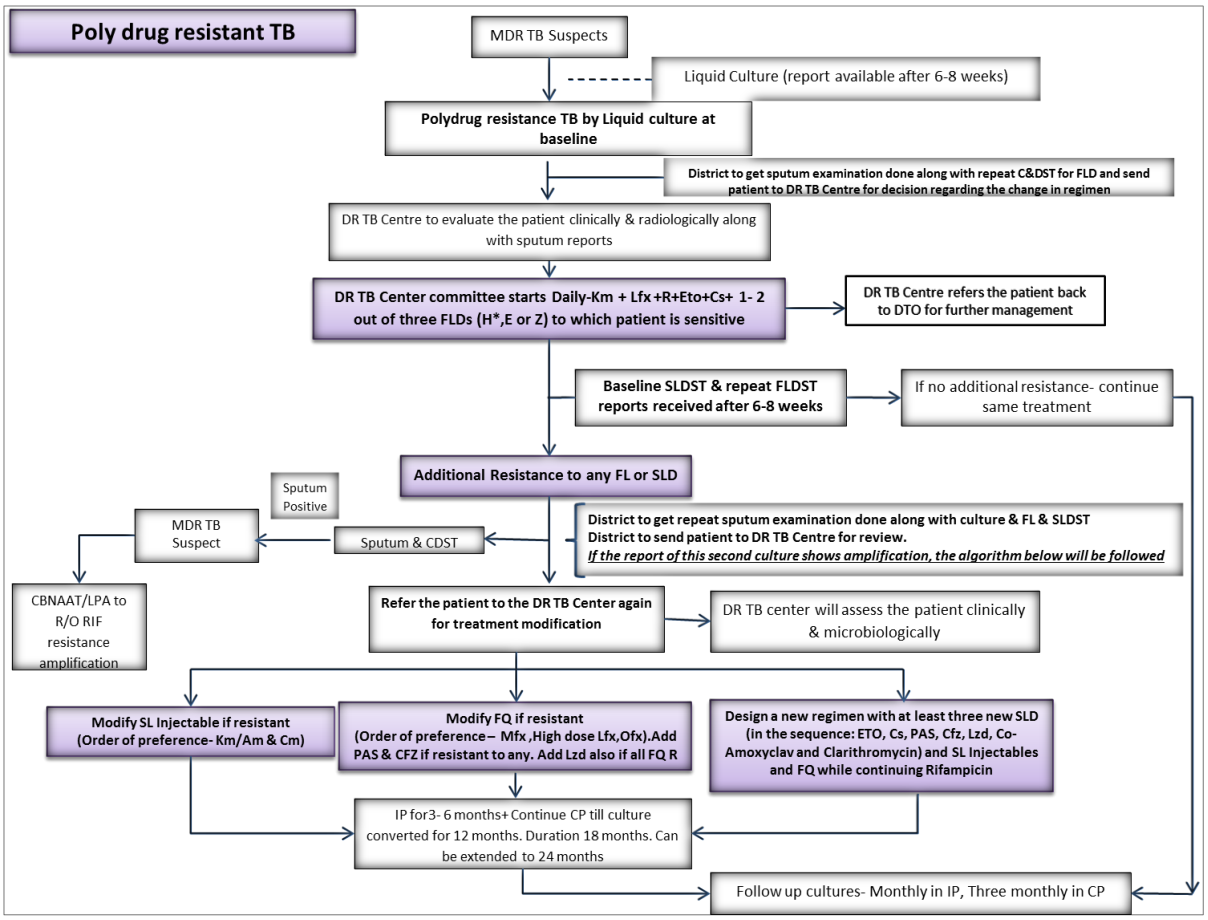
DST guided regimens were proposed with a standardized cafeteria approach to minimize logistic challenges. Taking into consideration the turnaround time for various technologies varying from a day to 3 month, it was proposed to strengthen the basic 1st line regimen for mono resistant TB cases (non-rifampicin) with addition of Inj SLD and FQ along with Rifampicin and 2 known sensitive drugs on daily basis. For Poly-resistant TB cases (non-rifampicin) it was proposed to strengthen the regimen with WHO Group 4 drugs along with Inj SLD, FQ, and R to make it 6 drugs on daily basis.

He presented the detailed flow chart enclosed for 1) managing H mono-resistant TB cases detected by LPA, 2) mono-drug resistant TB detected by liquid culture later (sensitive initially to HR by rapid molecular test) and 3) poly resistant TB cases



The strength of the proposed regimen for mono/poly DR TB cases is addition of two new core drugs and three companion drugs for improving treatment success and prevents resistance amplification keeping in mind feasibility of programmatic implementation and role of DR TB centres in decision making and monitoring.





Dr Sarin made his comments on the proposals. He reminded that finalization of these proposals will be subject to the final recommendations on the previous session. It is obvious that the starting point is not a new TB case, but a presumptive MDR-TB case as per the PMDT definitions according to various Criteria. It means that any regimen proposed would be a modification of current treatment with first line drug rather than initiating such regimen afresh. Even among new cases, waiting period for a conventional DST result should be appropriately managed. Availability of molecular DST for drugs other than H and R may reduce the diagnostic and management challenges in future.

Dr Ranjani shared the limitation of molecular DST to diagnose mono and /or poly resistant TB and rationale of offering systematic upfront 2nd line drug DST.

Dr Mayank, in response to Dr Behera's concern on program capacity to perform DSTs in such huge numbers appraised the house regarding success of National Laboratory Scale up plan 2009-14 and Lab scale up plan 2014-19 which will take care of country requirement of DSTs including for baseline SL-DST and for DST guided treatment.

Dr Sreenivas reminded that full capacity may not be required initially since implementation could be phased-in. It may even be unwise to wait till full lab scale up happens. Designing of regimen and plan for logistics management should happen in parallel to the lab scale up.

Dr Soumya Swaminathan called for a fifty year vision, aim high, and aspire for the aim, advocate for funds and further expand the lab capacity. Dr Sachdeva assured the house of countries capacity to mobilize funds and scale up the capacity.

Dr P. Kumar emphasized on liquid culture facilities scale up along with molecular DST facilities. The science and operational feasibilities should go hand in hand for optimum output from the programme.

Dr Urwashi Singh commented that MGIT may miss some RPOβ mutations. LJ is recommended as the gold standard for RPO β mutations, not MGIT. However, Dr Ranjani reminded about the logistic challenges in preparing LJ media. Hence, globally it is not recommended. Additionally, it delays diagnosis. Program also has accepted MGIT for national lab scale up.

Dr Harkesh raised the issue of non-standardization of DSTs in private sector. Dr Sachdeva responded that the requests by private sector for certification shall be accepted by NRLs through the State TB Officers and labs can be certified under this mechanism.

Dr Salhotra raised a query regarding repeating R DST in mono and /or poly resistant TB cases identified by molecular technique to which Dr Sarin responded as repeating R DST is not required.

B. Proposed DST guided treatment regimens with diagnostic algorithm to address the prioritized Second Line DST patterns under RNTCP in India

- Moderators:

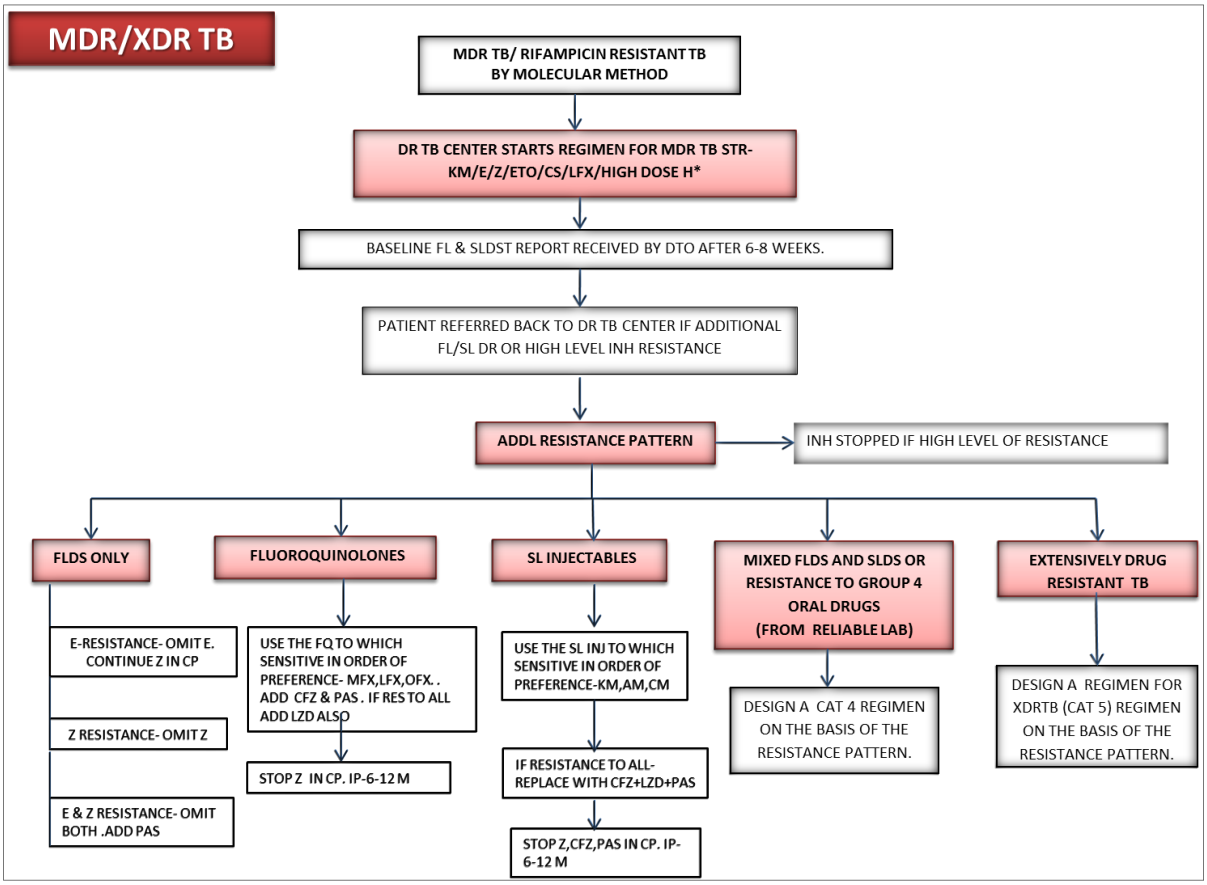
1. Dr Rohit Sarin, Director NITRD, New Delhi
2. Dr Soumya Swaminathan, Director, NIRT, Chennai
3. Dr Prahlad Kumar, Director, NTI, Bangalore

- Panellists:

1. Dr Camilla Rodrigues
2. Dr Alpa Dalal
3. Dr Anurag Bhargava
4. Dr Yatin Dholakia
5. Dr Varinder Singh
6. Dr Urvashi Singh
7. Dr Harjeet Dumra

- Lead Presenter: Dr Anuj Bhatnagar, Head, Respiratory Medicine, RBIPMT, New Delhi

Dr Bhatnagar presented the detailed flow chart enclosed for management of MDR/XDR TB cases.



The DST guided modification in the standard MDR-TB regimen proposed are summarized in the table below:

ADDITIONAL DRUG RESISTANCE	TREATMENT RECOMMENDATION	ADDITIONAL RECOMMENDATION
None	Standard Regimen for MDR-TB	
E	Omit E	Stop K after IP and continue Z in CP to ensure 4 drugs in CP
Z	Omit Z	
ZE	Omit both ZE and add PAS	
Any FQ (L/O/M)	Use FQ to which the patient is sensitive (Select in the following order of preference – M, L, O. Add PAS + CFZ	
All FQ	Replace FQ with LZD + PAS + CFZ Continue E+ETO+CS+CFZ+PAS+LZD in CP	Give IP for 6-12 months
Any SL Injectable	Use one SL injectable to which patient is	

	sensitive in the following order of preference – K, Am, Cm	
All SL Injectables	Replace SL Injectable with LZD + PAS + CFZ Stop Z in CP	Give IP for 6-12 months

The DST guided modification proposed for managing XDR-TB and MDR with mixed pattern of resistance to FL and SL drugs are summarized in the table below:

Type of Resistance	**TREATMENT RECOMMENDATION**	**ADDITIONAL RECOMMENDATION**	**JUSTIFICATION**
XDR-TB	Design a XDR-TB regimen on the basis of the resistance pattern. Use any Injectable and FQ to which patient is sensitive. The oral drugs can be considered in the following sequence: - Z (if sensitive), E (if sensitive), ETO, CS, PAS, CFZ, LZD, Co-Amoxiclav, High dose H and Clarithromycin.	Consider past history of intake of reserve drugs while designing the regimen.	Minimum 7 drugs in IP and 6 drugs in CP are to be given if injectables are included. If not included then 8 to 9 oral drugs are to be given in the complete treatment regimen.
MDR_TB with mixed resistance to FL and SL drugs	Design a MDR-TB regimen on the basis of resistance pattern. Use any Injectable and FQ to which patient is sensitive as per the order of preference of each. The oral drugs can be considered in the following sequence: - Z (if sensitive), E (if sensitive), ETO, CS, PAS, CFZ, LZD, Co-Amoxiclav, High dose H and Clarithromycin.	Can consider resistance pattern to Group 4 drugs (if done from a reliable lab)	Minimum 7 drugs in IP and 6 drugs in CP are to be given if injectables are included. If not included then 8 to 9 oral drugs are to be given in the complete treatment regimen.

Dr Puneet opened the discussion with the comment that we should not depend on low and high resistance to INH. INH should be omitted in the regimen if inhA or kat-G mutation is observed. Proposal of including FQ seems to be logical.

Dr Sharma raised questions on LC DST for Z & E, Dr Ranjani assured about the reliability of Z in LC DST as phenotypic methods. Regarding E, if the LC DST shows resistance then it's reliable. The same is not true about E sensitive results.

With broadened criteria for MDR-TB suspects' post 2011, the MDR-TB suspects currently are not heavily treatment experienced and exposed less to Inj Streptomycin. Dr Radha Munjhe deliberated that this may lead to non-requirement of second line injectables in basic MDR-TB regimen and Inj Streptomycin shall be sufficient.

Responding the query raised by Dr Sarin regarding reliability and reproducibility of Streptomycin DST, Dr Ranjani responded that its sensitivity was 80%, lower compared to 90% of Kanamycin.

Dr Ranjani responded to the concern of some experts regarding using FQ without knowing the sensitivity pattern that the fastest way to get the DST result for FQ DST was 2nd line LPA which has now been approved by WHO as rule in test and can be used after a validation in the country.

Dr Soumya Swaminathan expressed concerns regarding repeated referrals of the patients creating unnecessary burden on patient and DR TB Centre, creating barrier to initiation of treatment and infection control issues.

Dr Sreenivas emphasized on the need of decentralization of DR-TB centres to the linked DR-TB centres and DR-TB OPDs with infection control measures and involvement of local specialists at district level. Dr Ameeta Athawale suggested use of technology for decentralization and training of peripheral staff.

Dr Homa Mansoor deliberated on the access issues in LWE affected areas of Chhattisgarh and suggested a non INH based RZE regimen for H mono resistant TB cases. Dr Anuj responded that due to no evidences regarding success and resistance amplification prevention this regimen was not considered.

Dr Sharma again raised the concern regarding lab capacity for liquid culture and operation feasibility of implementing these algorithms.

The issue of 13 drug DST reliability was discussed and Dr P. Kumar suggested that the RNTCP certification shall be required for consideration of any DST. For implementing these algorithms to diagnose and treat mono/poly resistant TB the lab capacity shall be built for performing DST for all known anti TB drugs.

Dr Rajendra Prasad raised concern regard MDR + FQ resistant patient having huge pill burden and risk of adverse drug reactions.

Dr Soumya Swaminathan deliberated on need of newer drugs in patients with extensive drug resistance and their use should also be allowed on compassionate ground as well as the need to expedite policy for introduction of these drugs. Fast tracking of process for approval of newer drugs shall be required.

Dr Puneet Dewan suggested upgrading Linezolid in case of FQ resistance in place of Clofazimine and / or PAS. Dr Rupak Singla responded that Clofazimine scores more on the front of adverse drug effects and patient tolerance.

Dr Aristomo raised concern regarding using Co-amoxiclav and Clarithromycin instead of TMC-207.

Dr Sreenivas emphasized the importance of lab surveillance, knowing drug resistance patterns and utilizing NIKSHAY platform to get some calculations regarding numbers to guide the programme.

Dr Malik Parmar presented the terms of reference for group work on DST guided treatment for DR-TB cases. The first two groups were asked to review the proposals, deliberate, endorse or propose modifications; highlight modification with justification and present the updated version for DST guided treatment regimens with diagnostic algorithms for first and second line drugs respectively. The other two groups were asked to review the proposal, enlist operational challenges for laboratory, treatment and procurement supply chain management of drugs respectively, identify realistic implementable solutions and present them.

Day 2 Wednesday, 27th August 2014

The second day of the workshop was dedicated for group works on pre-identified topics. Four groups were identified for the following thematic areas. Each group brainstormed on the respective thematic area during pre-lunch and presented their recommendations to the house post-lunch.

Session 3: Group work output presentations:

Chairs: Dr SK Sharma, Dr Rajendra Prasad, Dr P Kumar, Dr D Behara

Group 1: DST guided treatment regimens with diagnostic algorithm for first line drugs

The changes suggested in the diagnostic algorithm were

- Upfront LC DST not required.
- For Rifampicin resistant cases, testing for level of H resistance and use of High Dose H in cases with low H resistance was removed.
- For Rifampicin sensitive cases, extended DST for FL and SL drugs to be offered only to H resistant cases, while H sensitive cases to be managed as per current programme policy.

The changes suggested in treatment regimen are as follows:

a) H Mono resistant TB cases diagnosed by LPA:

The regimen proposed was 3 (Km+Lfx+R+E+Z) / 6 (Lfx+R+E). No role of High dose H in any H resistance. If no additional resistance detected after base line culture report (LC), continue same regimen. Follow up smear at end of IP and every quarter thereafter during CP. Sputum smear positive anytime during the treatment, consider patient as MDR suspect and repeat DST. After completion of treatment, patient to be followed up at 3 month, 6 months, 12 months-clinically and microbiologically. If additional resistance is detected the algorithm for poly-drug resistance to be followed.

b) Mono resistance (other than H monoresistance) TB cases to FLD diagnosed by Liquid Culture:

3 (Km+Lfx+R+two out of H ,E or Z) / 6 (Lfx+R+ H/E). No role of High dose H. If no additional resistance, continue same regimen. Follow up smear at end of IP and every quarter during CP. Sputum smear positive anytime during treatment, consider patient as MDR suspect. After completion of treatment, patient to be followed up 3 month, 6 months, 12 months-clinically and microbiologically. If additional resistance is detected the algorithm for poly-drug resistance to be followed.

c) Poly drug resistance to FLD by Liquid Culture:

3 (Km+Lfx+R+2FLDs if sensitive (E+Z)) / 6 (Lfx+R+ H/E). If Z or E resistance or both, add any of the group 4 drugs (Eto, PAS, Cs) to make it to 5 drugs. Follow up smear at end of IP and every quarter thereafter during CP. Sputum smear positive anytime during the treatment, consider patient as MDR suspect and repeat DST. After completion of treatment, patient to be followed up 3 month, 6 months, 12 months-clinically and microbiologically. If additional resistance is detected to any SLDs, DR-TB committee to build a new regimen.

Group 2: DST guided treatment regimens with diagnostic algorithm for second line drugs

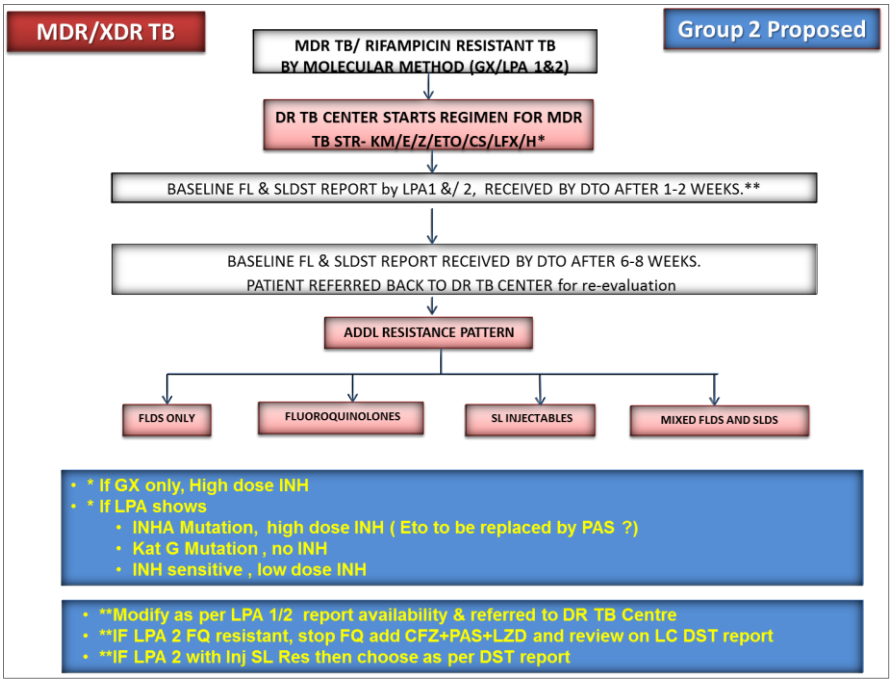
Group 2 started with a word of caution on country's capacity for labs, drugs and logistics management, strengthening basic services through human resource development and strengthening DR-TB centres in terms of HR, clinical skills, linkage with surgical facilities and counselling.

The group requested more deliberations on use of InhA resistance as surrogate marker for Ethionamide resistance. With questionable reliability of DST for E & Z, the group suggested omission of E and / or Z from the regimen in case of resistance. It was suggested to add PAS in case of both E and Z or Eto are not being used.

In case of additional resistance to FQ or SL Injectable, the FQ or SL injectable whichever is sensitive should be administered. The group also suggested to avoid replace Amikacin with

Kanamycin or vice versa based on indication of cross resistance in the recent WHO guidelines.

If there is resistance to all FQs and 2nd line injectable, then PAS and CFZ to be added. The group kept the option of adding LZD also for consideration by the larger group. The group suggested a regimen of (E+ ETO+ CS+ CFZ + PAS + LZD) in CP while IP remains the same. Z must be stopped after IP.



In case of mixed resistance pattern any FLD/Inj SLD/FQ (incl XDR), the group recommended to design a MDR-TB regimen on the basis of the resistance pattern. Use any injectable and FQ to which patient is sensitive as per the order of preference of each.

The oral drugs can be considered in the following sequence: - Z (if sensitive), E (if sensitive), ETO, CS, PAS, CFZ, LZD, Co-Amoxiclav, High dose H and Clarithromycin.

The group also suggested evaluating all DR TB patients for surgery with special considerations for use of Bedaquilline in salvage regimen for XXDR-TB with extensive disease and management for terminally ill patients without any appropriate regimen available. Social and nutritional support, adherence, counseling, extension of services to EPTB and Pediatric group, infection control, prevention & management of contacts of MDR/XDR TB.

Group 3: Operational plan for Laboratory capacity and logistics

The task assigned to group was to a) review the proposed DST Guided treatment and diagnostic algorithms for FL-SLDST patterns presented. b) Enlist operational challenges for laboratory services. c) Identify realistic implementable solutions to each challenge. D) Present the proposed strategy to address identified operational challenges

For the two subgroups of rifampicin sensitive and rifampicin resistant cases the group suggested following methods

a) **Rifampicin Sensitive:**

- Rif Sensitive by molecular (LPA/CBNAAT) - Perform LC and FL-DST (Streptomycin -1, Isoniazid- 0.1, Ethambutol-5, Levofloxacilin-1.5 Pyrazinamide-100)
- If mono or poly resistance perform SLDST - MACK (Kanamycin–2.5, Amikacin-1, Capreomycin -2.5 , Moxifloxacin-2)
- If resistance to SLD perform extended SLDST – CLEP (Ethionamide-5, PAS -4 and Linezolid-1, Clofazimine -1)

b) **Rifampicin Resistance:**

- If Rif resistance: SLD (KEEL & Z- Kanamycin, Levofloxacin, Ethionamide, Ethambutol and Pyrazinamide)
- If additional resistance of SLD perform extended SLD - CCLAMP (PAS -4 and Linezolid-1 Clofazimine -1 , Amikacin -1 , Capreomycin-2.5, Moxi-2)

The group emphasized that the current diagnostic algorithm is based upon the approved and endorsed technologies by RNTCP and WHO. The newer technologies will be incorporated in the algorithm as and when the technologies will be approved and endorsed like Second Line LPA.

Following challenges were listed and solutions suggested by the group

Operational challenges	Implementable solutions
Planning	Development of implementation plan for rolling out services in phase manner with adequate provision of fund for all activities (training, consumables, etc.) and drugs
Sample collection and transportations	Training and retraining of Health staff, specification of consumables by CTD
Development of training module (Lab and DR-TB centre)	Technical Working Group /NRLs
Laboratory capacity (Instruments, Staff, AMC, Infrastructure, Generator, POL, etc.)	Planning based upon the available technologies, workload, performance , LIMS e.g. MGIT for DST, LPA for smear positive and CBNAAT for Smear negative
Logistic supply	Adequate , timely and direct release of funds to laboratory
Coordination with DR-TB centre	PMDT NIKSHAY module , monthly meeting between DR-TB centre and laboratory
Recording and reporting	Revision of registers and formats
Supervision monitoring tools	Quarterly Laboratory review, Supervisory visit
Quality assurance of laboratory	Guidance document to be developed by NRLs

As a way forward, the group recommended that priority need to be given to perform SLD for Rif resistant cases and the laboratory capacity to be used optimally for all technologies. The group also highlighted the need for newer molecular technology for rapid validation e.g. LPA second line / Development- Indigenous technology.

Group 4: Operational plan for SLD procurement and Infrastructure logistics

The task assigned to group was to a) review the proposed DST Guided treatment and diagnostic algorithms for FL-SLDST patterns presented. b) Enlist operational challenges for treatment services (Treatment strategies and Drug procurement, supply management).

C) Identify realistic implementable solutions to each challenge. d) Present the proposed strategy to address identified operational challenges

Following challenges were listed and solutions suggested by the group

Challenges	Solutions
Forecasting 2nd line drugs: would be based on assumption and not on consumption. How would we know, how many patients would require the regimen?	The individual plan can be made with the respective states in coordination with CTD
Expansion of services depends upon lab capacity?	The lab capacity for performing the liquid culture and DST for FLD and SLD would be assessed
Are we able to achieve the desired MDR figures? 160,000 patients (for NSP 2012-17)	Regular monitoring & review of the states on implementation of MDR suspect criteria and put on Rx
Procurement of Drugs for mono-poly cases (considering presentation of Day:1)	58% of the diagnosed MDR cases would be mono-poly cases the lab capacity at the fullest. As per the GDF rates the cost for mono-resistant cases would be 8500 INR and for poly resistant cases would be 34000 INR (separate calculation in MS XL sheet attached)
Making PWBs	Separate HR for making PWBs will be in place
Procurement issues	Government supply (DBS) GDF is the second assured channel Local purchase at state/national level. (RC) Empanel chemist to provide SLD on concessional rate
DR-TB center	Treatment to be initiated at DR-TB center

Day 3 Thursday, 28th August 2014

Session 4: Dissemination of DST Guided Treatment Regimen for DR TB in India

Session topic: DST guided treatment regimens with diagnostic algorithm to address the prioritized DST patterns under RNTCP in India

- Chair:
  1. Dr S.K. Sharma
  2. Dr Rajendra Prasad
  3. Dr Rohit Sarin

- Lead Presenter: Dr Rupak Singla

The session was intended to consolidate recommendations made by each group on Day 2. However, debates on individual group recommendations continued and the consolidated recommendations were further modified according to final consensus. Dr Singla consolidated and summarised the points on the few most relevant questions.

What is the rationale of DST guided treatment in India?

It is true that India has the highest TB Burden including DR-TB in absolute numbers. Prevention of emergence of resistance by well implemented DOTS is the most basic strategy. Prevention of airborne infection by appropriate AIC strategy in clinical settings and households is equally important. The country has developed standards of TB care to be practiced across all sectors. PMDT has evolved reasonable guidelines for management of MDR-TB with or without additional resistance to FQs or second line injectables at baseline and XDR-TB. However, other forms of DR-TB are currently managed with first line regimen. Treatment success of mono and poly resistant cases with standard first line regimen under programmatic setting is unacceptably low in spite of attrition rates similar to drug sensitive cases. During first line treatment, half of mono and poly resistant cases fail treatment and a half among them progress to MDR-TB. Studies from other countries show a similar picture. Designing appropriate regimes may prevent MDR-TB among mono and poly resistant TB cases and improve their treatment outcomes. As the country is enhancing the laboratory capacity to diagnose such cases, it is high time to consider DST guided treatment.

What are the pre-requisites for DST guided treatment?

Before embarking on diagnosis and treatment of mono and poly resistant TB cases, as a prerequisite to the proposed algorithm and regimens, the following recommendations were made:

- Strengthen basic DOTS
- Review of existing standard program regimen
- Strengthen network of accredited labs with capacity for first and second line DST
- Use both LPA & CB-NAAT to detect R & H resistance early
- Ensure timely availability of DST reports to District TB Officers
- Strengthen DR-TB centers (manpower and logistics)
- Capacity building of DTOs and STOs
- Strong advocacy to health authorities to ensure timely availability of funds and logistics- development of a representative task force
- Strict follow up of patients who have completed treatment
- Regulation of over the counter ATT drug availability by legislation
- Consider nutritional supplementation
- Involvement of Medical Council of India (MCI) to implement guidelines in Medical Colleges

Which patients are eligible for DST guided treatment?

Universal access to first and second line DST is the best strategy. However, this could be achieved only in a phased manner. Policy on DST should be in line with PMDT guidelines. Diagnosis of Rifampicin Resistant TB/MDR-TB and XDR-TB is of highest priority. All previously treated cases and non-responders should be considered as presumptive MDR-TB cases. New TB cases with HIV and history of contact with MDR-TB also should be considered as presumptive MDR-TB cases. Subsequently, other new cases like seriously ill, paediatric TB, extensive TB and vulnerable groups (socially and clinically) may be prioritized as presumptive MDR-TB cases. All MDR-TB cases should be offered second line DST at baseline.

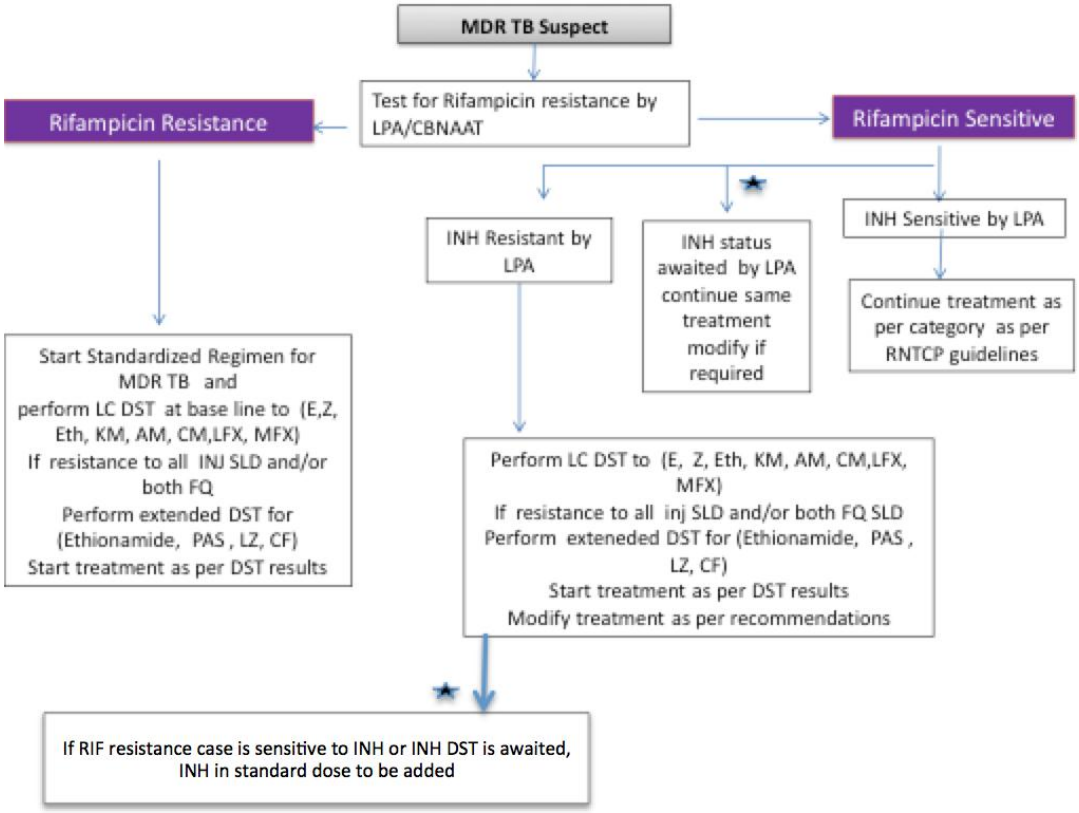
What is the ideal diagnostic technology?

Since priority is attributed to Rifampicin resistant TB/MDRTB, rapid molecular DST that tests Rifampicin with or without INH (CBNAAT and LPA) is to be the first choice. However, poly resistant cases will not be diagnosed with this technology. Hence, Rifampicin sensitive cases are to undergo liquid DST for INH, Streptomycin, Ethambutol and Pyrazinamide. . When rapid molecular tests are available for first line drugs other than INH and Rifampicin and second line drugs, policy may be revisited.

What is the ideal diagnostic algorithm for early and faster diagnosis of mono and poly resistant cases?

Diagnostic algorithm should start with a presumptive MDR-TB case. Rapid molecular DST should be performed on the biological specimen with CB-NAAT or LPA. Rifampicin sensitive cases by CB-NAAT should undergo LPA to identify susceptibility status to INH. Cases sensitive to INH should receive standard first line regimen as per RNTCP guidelines. Cases resistant to INH should further undergo liquid DST for Ethambutol, Pyrazinamide, Kanamycin, Amikacin, Levofloxacin and Moxifloxacin. Rifampicin Resistant cases should be started on standard Cat IV, if Rifampicin resistance case is sensitive to INH or INH DST is awaited, INH in standard dose to be added to standard cat IV regimen and subjected to liquid DST for Ethambutol. Pyrazinamide, Kanamycin, Amikacin, Levofloxacin and Moxifloxacin. If resistant to all injectable second line drugs and/or both FQs, perform extended DST for Ethionamide, PAS, Linezolid and Clofazimine.

Fig.1. Diagnostic algorithm to diagnose first and second line mono and poly resistant TB cases



What is the ideal treatment regimen for cases sensitive to Rifampicin, resistant to Isoniazid and DST status of Streptomycin, Ethambutol and Pyrazinamide is unknown?

Start intensive phase (IP) with Inj. Kanamycin, Levofloxacin, Rifampicin, Ethambutol and Pyrazinamide. Once DST report for Ethambutol, Pyrazinamide, Kanamycin, Amikacin, Capreomycin, Levofloxacin and Moxifloxacin is available, treatment may be modified by DR-TB center committee if required. (by adding 1 or more second line drugs to ensure at least 5 drugs in IP and 4 drugs in CP)

Intensive Phase (IP) is for 3 months with scope for extension to a maximum of 6 months. Continuation phase (CP) is for a fixed duration of 6 months with all drugs except Kanamycin.

Follow up smear and culture to be done at the end of IP and every quarter during CP. After completion of treatment clinically and microbiologically, patients are to be followed up at 3 months, 6 months and 12 months

What is the ideal treatment regimen for MDR-TB with or without additional resistance?

MDR-TB cases without additional resistance are to be treated with standard treatment regimen for MDR-TB that contains 6 to 9 months of IP with Kanamycin, Levofloxacin, Ethambutol, Pyrazinamide, Ethionamide and Cyclocerine and 18 months of CP with Levofloxacin, Ethambutol, Ethionamide and Cyclocerine. All MDR-TB isolates would be subjected to LC DST at baseline for Ethambutol, Pyrazinamide, Kanamycin, Amikacin, Capreomycin, Levofloxacin and Moxifloxacin, the results of which would be received after 6-8 weeks. In case of additional drug resistance, the treatment can be modified as follows:

- In case of resistance to Ethambutol, it is to be omitted.
- In case of resistance to Pyrazinamide, it is to be omitted.
- In case of resistance to both ethambutol and Pyrazinamide, omit both drugs and add PAS.
- In case of resistance to Levofloxacin and Moxifloxacin, the sensitive one is to be used along with PAS.
- In case of resistance to any second line injectable (Amikacin, Kanamycin and Capreomycin), use one of the sensitive injectables in the following order:
    1. Kanamycin
    2. Amikacin
    3. Caperomycin
- In case of resistance to all second line injectables, replace them with Clofazimine and PAS in IP and CP.
- The decision to replace Kanamycin with Amikacin and vice versa to be taken by CTD after due consideration of the recent WHO guidelines.

What is the ideal regimen for MDR-TB with mixed patterns of resistance?

Resistance Pattern	Treatment Recommendation	Additional recommendation & Justification

Mixed resistance pattern any FLD/Inj SLD/FQ / Ethionamide, PAS, LZ, CF
 	
(including XDR-TB)
	Basic regimen : Cat IV or Cat V regimen & modify based on resistance pattern:
	
	USE ANY INJECTABLE and FQ as per recommendation discussed earlier
	
	CONSIDER OTHER ORAL DRUGS as per DST pattern and in following Sequence of preference :- PYRAZINAMIDE (if sensitive), ETHAMBUTOL, ETHIONAMIDE, CYCLOSERINE, PAS, CLOFAZIMINE,LINEZOLID, COAMOXYCLAV, HIGH DOSE INH & CLARITHROMYCIN
		if Injectable SLD & FQ are included:
		
		Minimum 6 Drugs in IP and 4 Drugs in CP
		
		if Injectable SLD and /or FQ are not included:
		
		Minimum 8-9 drugs are to be given in IP and 7-8 drugs in CP

What is the ideal frequency of doses?

All DST guided treatment regimen are to be given on daily basis under supervision similar to standard treatment regimen for MDR-TB.

What are the operational challenges and solutions for the programme to implement DST guided treatment in India?

The operational challenges identified and solutions recommended for the programme to implement DST guided treatment in India are as follows:

Challenges	Solutions
Forecasting 2nd line drugs: would be based on assumption and not on consumption based. How would we know, how many patients would require the regimen?	The individual plan can be made with the respective states in coordination with CTD
Expansion of services depends upon lab capacity?	The lab capacity for performing the liquid culture and DST for FLD and SLD would be assessed

Are we able to achieve the desired MDR figures of 160,000 patients in 2012-2017	Regular monitoring & review of the states on implementation of MDR suspect criteria and put on Rx
Procurement of Drugs for mono-poly cases	58% of the diagnosed MDR cases would be mono-poly cases As per the GDF rates the cost for mono-resistant cases would be 8500 INR and for poly resistant cases would be 34000 INR
Making PWBs	Separate HR for making PWBs will be in place
Procurement issues	Government supply (DBS) GDF is the second assured channel Local purchase at state/national level. (RC) Empanel chemist to provide SLD on concessional rate
DR-TB centre	Additional man power • State Level: Additional Pharmacist • DR-TB Centre: Additional ○ One Medical Officer ○ One Pharmacist ○ Two TBHV/ MPW/equivalent ○ One Helper

Special considerations for the programme include:

- Consideration for Health Care Worker (insurance/compensation)
- Extension of services to Pediatric group and EPTB
- All MDR & XDR TB Patients: evaluate for surgery
- Management of terminally ill patients without any appropriate regimen available
- Salvage regimen for XXDR-TB, newer drugs
- Infection control measures
- Management of contacts of MDR/XDR TB including their mandatory examination

Dr KC Mohanty addressed the gathering with congratulations and appreciations to the initiative taken by Central TB Division, GoI to address this long awaited and important issue on developing normative guidelines for DST guided treatment for prevention and effective management of all forms of drug resistant TB.

This was followed by the valedictory session with address from Shri Sanjay Deshmukh, Additional Municipal Commissioner, MCGM, Mumbai who reiterated the commitment of MCGM in rolling out the DST guided treatment guidelines in Mumbai while moving forward in the implementation of the Mumbai Mission for TB Control.

Dr Asheena Khalakdina, Team Leader, Communicable Diseases, WHO Country Office for India also congratulated the programme and GoI for addressing this important gap and reiterated the consistent technical support of WHO to document, jointly publish, build capacity, effectively address the operational challenges, monitor and evaluate the implementation of DST guided treatment guidelines as part of the larger technical assistance for RNTCP in India.

Dr Salhotra concluded the session by delivering the vote of thanks.

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Workshop Participants

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National Workshop on Drug Susceptibility Testing (DST) Guided Treatment for Drug Resistant Tuberculosis patients in India

Venue: Hotel Trident, Nariman Point, Mumbai

Dates: 26th to 28th August 2014

Agenda:

Objective: To have a national consultation for the development of national guidelines for DST guided treatment regimen for the Drug Resistant TB patients.

Day 1 – Tuesday, 26th August 2014

Time	Topic and method	Speaker/Facilitator
09:30 – 10:00	Registration and refreshments	
10:00 – 10:45	**Inaugural Session:** • Welcome and overview by DDG (TB) • Address by NPO-TB, WHO India • Address by Additional Municipal Commissioner, Municipal Corporation of Greater Mumbai • Address by Municipal Commissioner, Municipal Corporation of Greater Mumbai • Address by Principal Secretary, Health, Govt of Maharashtra • Vote of Thanks	Dr RS Gupta Dr A Sreenivas Sh. Sanjay Deshmukh Sh. Sitaram Kunte Smt. Sujata Saunik Dr K.S. Sachdeva
10:45 – 11:00	Tea Break	
Session 1: Introduction and Problem Statement for need of DST guided treatment in India – Chairs: Dr SK Sharma, Dr D Behera, Dr Rajendra Prasad Rapporteur: Dr Amar S, Dr Mayank G		
11:00 – 13:00	Introduction • Workshop Objectives • PMDT status and challenges • Need and Rationale for DST guided treatment regimen	Dr Ashwani Khanna
	Problem Statement 1 • Emerging evidences of DST patterns for first and second line anti-TB drugs in India	Dr Ranjani Ramachandran
	Problem Statement 2 • Implications of mono and poly resistant cases treated with standard first line regimen under RNTCP	Dr Rupak Singla
	Problem Statement 3 • Treatment outcomes of MDR TB cases, with/without second line drug resistance, treated with standardised second-line regimen under RNTCP	Dr Rajesh Solanki
	Open Discussion	

13:00 to 14:00	Lunch break	
Session 2: Proposed Solutions to address the need of DST guided treatment in India **Moderator: Dr Rohit Sarin, Dr Soumya Swaminathan, Dr P Kumar** **Rapporteur: Dr Shibu B, Dr Imran S**		
14:00 to 15:00	**Panel Discussion -** • Proposed DST guided treatment regimens with diagnostic algorithm to address the prioritized First Line DST patterns under RNTCP in India Lead Presentation by – **Dr Anuj Bhatnagar** (20 minutes)	Panelist: Dr Ameeta Joshi Dr Ameeta Athawale Dr Jawahar Dr Puneet Dewan Dr Rupak Singla Dr Ranjani Ramachandran
15:00 to 16:00	• Proposed DST guided treatment regimens with diagnostic algorithm to address the prioritized Second Line DST patterns under RNTCP in India Lead Presentation by – **Dr Anuj Bhatnagar** (20 minutes)	Dr Camilla Rodrigues Dr Alpa Dalal Dr Anurag Bhargav Dr Yatin Dholakia Dr Harjit Dumra Dr Rupak Singla Dr Ranjani Ramachandran
16:00 – 16:15	Group Formation and TORs – Group 1: DST guided treatment regimens with diagnostic algorithm for first line drugs Group 2: DST guided treatment regimens with diagnostic algorithm for second line drugs Group 3: Operational plan for Laboratory capacity and logistics Group 4: Operational plan for Treatment Capacity, SLD procurement and logistics	Dr Malik Parmar
16:15 – 16:30	Tea Break	
16:30 – 18:00	Group work	

Day 2 – Wednesday, 27th August 2014

Time	Topic and method	Speaker/Facilitator
09:00 to 12:00	Group works continues	
11:00 to 11:15	Tea break	
Session 3: Group Work Output Presentations **– Chairs: Dr SK Sharma, Dr D Behra, Dr RS Gupta, KS Sachdeva** **– Rapporteurs: Dr Shibu B, Dr Imran S**		
12:00 to 01:00	Presentation & Discussion – DST guided treatment regimens with diagnostic algorithm for first	Group 1 - Leader

	line drugs	
01:00 to 02:00	Lunch break	
02:00 to 03:15	Presentation & Discussion – DST guided treatment regimens with diagnostic algorithm for second line drugs	Group 2 - Leader
03:15 to 04:00	Presentation & Discussion – Operational plan for Laboratory capacity and logistics	Group 3 - Leader
04:00 to 05:30	Presentation & Discussion – Operational plan for Treatment capacity, SLD procurement and logistics	Group 4 - Leader

Day 3 – Thursday, 28th August 2014 - Dissemination Session

Time	Topic and method	Speaker/Facilitator
10:00 – 11.00	Inaugural Session: • Welcome • Objectives and methodology of the workshop • Address by Principal Secretary, Health, Govt of Maharashtra • Address by JS (PH) • Address by WR India • Vote of Thanks	Dr RS Gupta Dr KS Sachdeva Smt. Sujata Saunik Sh. Anshu Prakash Dr. Nata Menabde Dr VS Salhotra
Session 4: Dissemination of DST Guided Treatment Regimen for DR TB in India – Chairs: WR India, JS (PH), DDG TB, Dr SK Sharma – Rapporteurs: Dr Shibu B, Dr Imran S		
11:00 to 01:00	"DST guided treatment regimens with diagnostic algorithm to address the prioritized DST patterns under RNTCP in India" Presentation by – **Dr Rupak Singla (1 hour)** Open Discussion	
01.00 to 02.00	Lunch break	
02.00 – 03.00	Valedictory Session	