

DRUG RESISTANT TB - RNTCP RESPONSE****L. S. Chauhan***

I consider it a great privilege and honour for me to deliver the P K Sen Oration on a topic that requires immediate collective action from all health care providers in the country.

On behalf of the Revised National TB Control Programme, I would like to share the concern and response to the threat of drug resistant TB to tuberculosis control in India.

RNTCP achievements and challenges

RNTCP is an application in India of the WHO recommended Directly Observed Treatment Short Course (DOTS) strategy to control TB with the objective of curing at least 85% of new smear positive TB patients and detecting at-least 70% of such patients. Following a stringent preparatory appraisal mechanism, all districts started implementing RNTCP in phased manner and the total population of India was covered under RNTCP on World TB day, March 24th, 2006. Since inception, more than 7.9 million patients have been initiated on treatment and with the treatment success rate of more than 85% among new TB cases and 70% among re-treatment cases, the programme can be termed as highly successful in achieving its objectives. This programme has been internationally recognized as the fastest expansion in the history of DOTS implementation and adopting innovative methods of programme management, especially with respect to monitoring, supervision, evaluation, involvement of other sectors such as NGOs, PPs and medical colleges. As the programme strives to achieve the millennium development goals related to TB it is faced with the several challenges such as consolidating and sustaining the achievements, addressing regional, state and district variation in programme performance, expanding the services for TB-HIV collaborative activities as outlined in the Joint National

Framework to the whole country, and last but not the least is the threat of drug resistance to the ultimate goal of TB control.

Global situation of multi-drug resistant TB

A global project on anti-TB drug resistance surveillance was conducted from 1990-2004 in 109 settings in over 90 countries. WHO estimates that tuberculosis caused by strains of MTB which are resistant in vitro to at-least INH and Rifampicin (MDR-TB) causes over 400,000 cases of multi-drug-resistant tuberculosis every year across the world with estimated deaths of over 100,000 every year. China, India and the Russian federation contribute towards a majority of this global MDR-TB burden with India itself contributing to about 80,000 cases every year. This is mainly due to under investment in basic TB control, poor management of anti-TB drugs and transmission of drug-resistant strains. MDR-TB is much more difficult and costly to treat than drug susceptible TB, but recent work has shown that it is feasible and cost-effective even in settings of limited resources but very resource intensive.

Multi-Drug Resistant TB in India

Drug resistant tuberculosis has frequently been encountered in India and its presence has been known virtually from the time anti-tuberculosis drugs were introduced for the treatment of TB. There have been a number of reports on drug resistance in India, but most studies used non-standardised methodologies and biased or small samples, usually from tertiary level care facilities. To obtain a more precise estimate of the MDR-TB burden in the country, RNTCP has a generic protocol for carrying out representative drug resistance surveillance (DRS) surveys at the state level in selected states. Following training of

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the State TB Training and Demonstration centre (STDC) staff in DRS techniques, and of field staff in patient intake and sample collection mechanisms, state representative DRS surveys have been undertaken in Gujarat and Maharashtra (2005-2006). The results of these surveys indicate prevalence of MDR-TB to be ~3% amongst new cases and 12-18% in re-treatment cases. However, translated into absolute numbers the problem is huge. DRS surveys are planned for Andhra Pradesh, Orissa and Western UP in the near future. Besides estimating the drug resistance levels the DRS surveys also assess the success of the TB control programme which is reflected by the fact that there has been no increase in the levels of drug resistance over the past years which is shown by studies from Tuberculosis Research Center, Chennai.

Although the prevalence of MDR-TB in the country in term of percentage is quite small these rates translate into large absolute numbers (as stated earlier ~80,000). Moreover, MDR-TB patients often live a number of years before succumbing to the disease thus maintaining the chain of transmission of the drug resistant strains. This threatens the success of TB control strategies which is aimed at breaking the chain of transmission. It is estimated that MDR-TB prevalence may be three times greater than its incidence.

Causes of drug resistant TB

Though *Mycobacterium Tuberculosis* can acquire drug resistance by spontaneous mutation, most of the drug resistance is 'man-made'. When I say 'man-made', I mean it is due to inadequate regimen prescribed by the health-care-provider, inadequate supply or poor quality of drugs and poor adherence of the patient to treatment due to multitude of reasons like lack of information, social stigma and adverse drug reactions. Most of these occur if TB Control is attempted outside a structured programme setting.

Contrary to the popular belief I would like to say that "many failures are due to failure to take treatment and not failure of treatment *per se*". The evidence to the statement is the fact that about 60% cases which have failed Cat I and are presumed to

be suffering from MDR-TB are being successfully treated with Cat II under the programme.

Extensively Drug Resistant TB

In the year 2006, MMWR (Mortality and Morbidity Weekly Report), for the first time reported on the detection of extensively drug resistant tuberculosis popularly known as XDR TB wherein the resistance has amplified from Rifampicin and INH to second line drugs. As per the latest definition, XDR TB is a subset of MDR TB with resistance to Fluoroquinolones and one of the three injectables namely Kanamycin, Capreomycin and Amikacin. In 2005, the United States Centers for Disease Control and Prevention (CDC), WHO and 14 SRLs initiated a study to determine the extent to which resistance to second-line anti-TB drugs had emerged among MDR-TB isolates. The data were published by WHO and CDC in March 2006 in an article in which XDR-TB was first defined. The study, which analysed 17,690 isolates from 49 countries, showed that 20% of all isolates collected were MDR-TB and that 2% were XDR-TB.

Extensively drug-resistant TB (XDR-TB) has been reported in all regions of the world and classified rapidly by WHO as a serious emerging threat to public health, especially, but not only, in countries with a high prevalence of the human immunodeficiency virus (HIV).

The potential destruction which can be caused by this virtually untreatable form of TB has been demonstrated in the KwaZulu Natal province of South Africa. In 2006 a deadly outbreak of XDR-TB occurred in the small town of Tugela Ferry in KwaZulu-Natal. Of 536 TB patients at the Church of Scotland Hospital, which serves a rural area with high HIV rates, some 221 patients were found to have MDR-TB and of these, 53 were diagnosed with XDR-TB. Fifty-two of these patients died almost instantaneously.

XDR TB in India

In India too, XDR TB has been reported by isolated studies with non-representative and highly selected clinical samples. The magnitude of the

problem remains to be determined due to the absence of laboratories capable of conducting quality assured second line DST.

However, what is frightening is the potential threat of XDR-TB in India with unregulated availability and injudicious use of the second line drugs along with non-existence of systems to ensure standardized regimens and treatment adherence for MDR-TB outside RNTCP.

Consequences of XDR-TB

The emergence of XDR TB in India and across the world raises the possibility that the current TB epidemic of mostly drug susceptible TB will be replaced with a form of TB with severely restricted treatment options. If this happens it would jeopardize the progress made in recent years to control TB globally as well as in India and would also put at risk the plans to progress towards a world where TB ceases to be a public health problem. Patients with XDR-TB would have to be managed like TB patients before the antibiotic era. The economic, social and health security of countries and communities with a high prevalence of TB would be threatened by virtually untreatable TB among the bread-winners, parents and economically productive age groups.

RNTCP response plan to the threat of MDR and XDR TB

Realizing this threat posed by the emergence of the drug resistant TB to the goal of TB control, RNTCP has developed a multi-faceted strategy to address the issue. The problem of MDR was recognized and an action plan was built into RNTCP Phase 2 Project Implementation Plan (2006-2011) with a vision of developing a network of RNTCP accredited quality assured intermediate reference labs (IRL) for culture and DST and one IRL and DOTS plus site for each in large state capable of enrolling, and providing care and management of at-least 5,000 MDR-TB cases a year. In the year 2007, RNTCP has been advocating a response which was developed by involving all the stake-holders through a series of consultative meetings to counter effectively the threat of MDR and XDR TB. The following are the

components of the response:

1. MDR-TB prevention through sustained high quality DOTS implementation by all providers in the public and private sector
2. Improve laboratory capacity for diagnosing MDR-TB
3. Prevention of XDR-TB by effective treatment of MDR-TB through DOTS-Plus
4. Evaluate extent of threat of SLD resistance and XDR-TB
5. Review the supply and availability of SLDs and address their irrational and indiscriminate use

As you all can see, foremost is the prevention of drug resistant TB through sustained high quality DOTS implementation by all health care providers. The programme has been achieving a treatment success rate of more than 85% among new cases and about 70% among re-treatment cases under programmatic conditions. However instead of basking in the glory of its laurels, RNTCP is consolidating its achievements and striving to deliver quality DOTS services to the community. The programme is also taking adequate steps to reduce the default rate and forging linkages with the private sector and promoting International Standards of TB Care (ISTC) to improve the reach of DOTS services.

The response plan also directs us to work for the establishment of laboratory facilities for diagnosing MDR-TB across the country. Non-viable cultures, culture contamination, and unreliable DST results have major consequences for both individual patients and the TB control programme as a whole. Therefore, the programme is establishing a nation wide network of quality assured accredited Intermediate Reference Laboratories (IRLs) capable of performing culture and DST for the first line drugs. Realising the need for supplementing the diagnostic services which the IRLs will provide, the programme is also facilitating accreditation of existing culture and DST labs in Medical colleges. The programme is also exploring the possibility of engaging with private laboratories in supplementing the diagnostic services.

The response also includes the treatment of MDR-TB patients which RNTCP views as a “standard of care” issue. Recognizing that the treatment of MDR-TB cases is very complex, treatment will follow the internationally recommended DOTS-Plus guidelines and will be done in designated RNTCP DOTS-Plus sites. These sites will be in a limited number of highly specialized centres, at least one in each state, which will have ready access to an RNTCP accredited culture and DST laboratory, with qualified staff available to manage patients, using standardized second-line drug regimens given under daily DOT and standardized follow-up protocols, have systems in place to deliver ambulatory DOT after an initial short period of in-patient care to stabilise the patient on the second-line drug regimen, and with a logistics system and standardized information system in place. The DOTS-Plus sites will be initiated in a phased manner similar to that for the establishment of the culture and DST laboratory network, and sites will be linked geographically to the establishment of the RNTCP accredited Intermediate Reference Laboratories (IRLs). The programme has initiated the DOTS Plus services in the states of Gujarat and Maharashtra in early 2007 with the first MDR patients registered in August we are working towards establishing DOTS-Plus sites in other sites as per the plan of at-least one DOTS-Plus site per large state by 2010 as mentioned earlier.

In the interim, while RNTCP DOTS-Plus services are being expanded across the country a consensus statement guiding all health care providers in the public and private sector managing MDR TB cases has been developed. The statement was the outcome of a meeting at TRC, Chennai of national TB experts on drug resistant TB. The guidance document has been endorsed by the national task force workshop of medical colleges held at AIIMS in November 2007. The document is available on the programme website and is being disseminated through the state governments, state task force and professional bodies.

The programme is also determining the magnitude of the prevalence of XDR-TB by conducting second line DST for all the confirmed

MDR patients initiated on Cat IV treatment in the states of Gujarat and Maharashtra. This is being supplemented by surveillance for second line drug resistance on isolates collected as a part of the recently conducted Drug Resistance Surveys in Gujarat and Maharashtra. However the programme also needs to understand the causes leading to the development of XDR and develop appropriate interventions to address the same. Keeping this in view the programme is planning to conduct a case control study of XDR cases identified from the Gujarat DRS survey.

As per a recent study by ORG the market for second line drugs in the country has seen a quantum jump in the past years. \$8.4m worth of these drugs, primarily fluoroquinolones, have been consumed for the treatment of tuberculosis primarily outside the programme in 2006. The programme is live to the issue of the wide availability and injudicious use of the second line drugs which will amplify the magnitude of XDR TB in the country. The programme is sensitizing the National and state officials on the emerging threat of XDR TB and its prevention at all potential forums. There is a proposal for introduction of a system of notification of MDR TB patients requiring treatment with second line drugs which is being discussed at the highest level. This would be supplemented with a regulation promoting rational use of second line drugs with the support of professional associations.

At this point in time, in the history of tuberculosis control in our country, we are at crossroads. There is apparently only one path that appears to be the most appropriate. The path of preventing the emergence of drug resistance by according highest priority to the implementation of quality DOTS services. I request the esteemed audience present here to pledge for the prevention of emergence of drug resistant tuberculosis.

I would like to end the oration quoting this statement from the Stop TB Strategy 2006:

“Ensuring adherence to a full course of treatment is the key to curing TB patients and preventing the emergence of drug resistance”