Inviting Editorial

DRUG RESISTANCE IN TUBERCULOSIS CONTROL.
A GLOBAL AND INDIAN SITUATION

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INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. Its distribution, morbidity and mortality are linked to socio-economic indices and lifestyle factors. The problem of tuberculosis is universal, with nearly a third of the world's population infected and nearly 3 million people dying annually from the disease of tuberculosis (1). Global tuberculosis control is facing major challenges today. Much effort is still required to make quality care accessible without barriers of gender, age, type of disease, social setting, and ability to pay. Coinfection with *M. tuberculosis* and HIV (TB/HIV) especially in Africa, multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis in all regions, make control activities more complex and demanding.

India has been declared by the WHO as a high TB burden country. Tuberculosis is one of the most important public health problems in India. It is present since many centuries and most commonly affects people from lower socio economic status. The average prevalence of all forms of tuberculosis in India is estimated to be 5.05 per thousand, prevalence of smear-positive cases 2.27 per thousand and average annual incidence of smear-positive cases at 84 per 1,00,000 annually (2). TB is also one of the leading causes of mortality in India. It kills more than 300,000 people in India every year. Different health care providers' following different health systems tries to provide treatment and control the problem. Major challenges facing TB control are to achieve equity, improve access, availability and affordability, increase quality of services etc.

Revised National TB Control Programme (RNTCP) in India

India had a National Tuberculosis Programme (NTP) in place from the sixties. It did not make much progress except in terms of achieving substantially high cure rates. WHO recommended Directly Observed Treatment Short Course (DOTS) strategy to control TB.

The Benefits of DOTS are many like more diagnostic accuracy, 95% treatment success rate, prioritizing sputum positive patients thus reducing

the incidence and prevalence of TB, preventing treatment failure and the emergence of MDR-TB by ensuring patient adherence to treatment and uninterrupted supply of anti -TB drugs.

RNTCP is an application of the DOTS strategy to control TB in India. It was launched to overcome the problems of the NTP since 1992. The emphasis was on cure of sputum positive patients in order to interrupt the chain of transmission of the disease. The objectives of the RNTCP are to achieve at least 85 percent of treatment success amongst new smear positive cases and thereafter detect at least 70 percent of all such cases and consolidation of the TB control measures introduced earlier.

While most of the targets have been achieved under RNTCP (Revised National Tuberculosis Control Programme) at all India level, there are still inequities across states, gender, rural/urban areas etc (3). Also it is not able to detect all estimated cases. One of the key reasons for its inability to reach out to more patients is because almost half the patients prefer to take TB treatment in the private sector. The RNTCP formulated the NGO Guidelines schemes in 2000 which extend support to the NGOs in form of grant-in –aid and logistics to encourage their involvement in RNTCP.

Drug resistant TB

The subject of drug resistant and multi drug resistant tuberculosis has been an area of growing concern among clinicians, epidemiologists and public health workers world wide (4).

Multidrug-resistant TB (MDR-TB) is a form of TB that does not respond to the standard six month treatment using first line-drugs (i.e. resistant to Isoniazid and Rifampicin). MDR TB can only be diagnosed in a specialized laboratory. It requires at least 18-24 months of treatment with medicines which are 100 times more expensive and often highly toxic. If the drugs to treat MDR-TB are mismanaged, further resistance can occur. This becomes a major problem since there are very few drugs available to treat TB. Extensively drug-resistant TB (XDR-TB) is a form of TB caused by bacteria resistant to all the most effective drugs (i.e. MDR-TB plus resistance to any fluoroquinolone and any of the second-line anti-TB injectable drugs: amikacin, kanamycin or capreomycin) (5).

Magnitude of the problem

Prevalence of MDR-TB mirrors the functional state and efficacy of tuberculosis control programmes and realistic attitude of the community towards implementation of such programmes (6).

Global and Indian situation of MDR TB: The first global project on anti-tuberculosis drugs resistance surveillance initiated by WHO and IUAT-LD during 1994-97 gave the exact magnitude of the problem of resistance to anti-tuberculosis drug worldwide. The median prevalence of primary and acquired multi drug resistance was found to be 1.4% and 13% respectively. A second WHO-IUATLD global project on drug surveillance carried out in 1996-1999 in 58 countries found that the median

prevalence of primary and acquired multi-drug resistance was 1% and 9% respectively (7).

A study shows that an estimated 273,000 new cases of MDR TB occurred worldwide in 2000, 3.2% of all new TB cases (8). The total number of MDR-TB cases estimated to have occurred worldwide in 2004 is 424,203 or 4.3% of all new and previously treated TB cases. In the same year, 181,408 MDR-TB cases were estimated to have occurred among previously treated TB cases alone. Three countries—China, India, and the Russian Federation— accounted for 261,362 MDR-TB cases or 62% of the estimated global burden with India itself contributing to about 80,000 cases every year (9, 10).

WHO survey findings in 2002-2006 shows that MDR-TB, on average, is seen in 5.3% of all TB cases which are highest rates ever recorded of MDR-TB. 490,000 MDR-TB cases emerge every year, with more than 110,000 deaths. Highest rates are seen in countries of the former Soviet Union and China. Severely limited laboratory capacity has meant limited data availability in Africa. Insufficient efforts are made in many areas of the world to treat and control MDR-TB. Equipment to rapidly diagnose MDR-TB in 1 week instead of 3 months exists but most patients cannot access such services (5).

TB is one of the leading causes of mortality in India- killing -2 persons every three minute, nearly 1,000 every day. A review of 63 surveys conducted between 1985 and 1994 suggested that primary and acquired MDR-TB was between 0-10.8% and 0-48% respectively. However, the qualities of these studies were variable due to the lack of proper representativeness, size of population sampled and lack of standardized laboratory methods in some of them. Current estimates report, the prevalence of primary and acquired multidrug resistance in India as 3.4% and 25% respectively (7). Drug Resistance Surveillance (DRS) surveys in Gujarat and Maharashtra (2005-2006) shows prevalence of MDR-TB to be almost 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 other states in the near future. There has been no increase in the levels of drug resistance over the past years. It is estimated that MDR-TB prevalence may be three times greater than its incidence (9).

XDR TB: Global and Indian situation: - In a 2005 study by the United States Centre for Disease Control and Prevention (CDC), WHO and 14 SRLs 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) (9).

WHO estimates that around 40,000 XDR-TB cases emerge every year (5). 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 (9).

Reasons / causes

M. tuberculosis can acquire drug resistance either by spontaneous mutation (primary) or due to man-made reasons (acquired). Acquired drug resistance arises due to the inappropriate use of chemotherapy, which is a result of administration of improper treatment regimens by health care providers, inadequate/poor quality of drugs and failure to ensure patients complete the whole course of treatment. Essentially, drug-resistance arises in areas with poor TB control programmes.

In India, 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. Thus many failures are due to impossibility to take treatment and not failure of treatment per se (9). Lack of information, social stigma and adverse drug reactions also plays major role. Many patients who start TB treatment in the private sector (TB Control attempted outside a structured programme setting) are not able to afford to continue and complete their treatment. Private practitioners also lack the resources to follow up these patients, thus several patients may land up with MDR and XDR TB. Poor knowledge among the providers and community, poor availability/access to public/free treatment, HIV/TB combination, inadequate motivation and provision of health education to patients are other important reasons.

Consequences

Currently, the large majority of patients with MDRTB in low-resource countries do not have access to proper diagnostic services and to the quality-assured second-line drugs needed to treat drug-resistant TB (10). Drug-resistant TB, like drug-sensitive TB, is also transmitted through the air from an infected person to a non-infected person. Over the last few years the incidence of drug resistance is increasing. Often these patients live a number of years 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. The organism becomes so resistant that treatment options will be severely restricted and it becomes difficult to treat these cases. With this, the progress made in recent years to control TB globally as well as in India will be neutralised. The dream of TB free world will not be achieved.

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. 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 (9).

Solutions / way ahead

Prevention of MDR TB: - It is important to prevent the development of MDR TB in the first place. Effective use of first line drugs in every category I and category II patients as suggested by DOTS strategy and ensuring adherence to a full course of treatment is the key to curing TB patients and preventing the emergence of drug resistance. Control and prevention of multidrug-resistant tuberculosis (MDR-TB) is possible through increased access to quality-assured SLDs and prevention of development of resistance to anti-TB drugs. The WHO's Stop TB Strategy has also been revised to address the issue of drug-resistant TB (11).

Management of MDR TB: Along with strategies to prevent the emergence of MDR TB, plans to expand appropriate diagnostic and treatment services for patients with MDR-TB are urgently needed especially in countries with highest burden of MDR-TB (e.g., China, India, Russia) and in areas with the highest MDR-TB rates (e.g., Eastern Europe). Integrating management of DR-TB within TB control programs in resource-poor settings will be useful given the size of the problem and the availability of tools and resources to address it (10). Several pilot projects are underway in these countries that will provide necessary evidence to design policy guidelines for management of MDRTB (7). Till such time, it must be managed with careful use of SLDs at specialized centres. When strong TB control programme is in place, use of second line drugs is feasible and cost effective (4). The goal during management and control of MDR TB is to reduce morbidity / mortality, prevent further transmission of MDR TB and prevent emergence of XDR TB.

Role of Research: - New researches in the areas involving molecular biology and application of these in the field of epidemiology could help in better understanding of the mechanisms of drug resistance, development of newer diagnostic tools and effective drugs to control MDR TB (4).

Global Strategy for MDR-TB and XDR-TB: - Strengthening TB control through the Stop TB Strategy prevents MDR-TB and XDR-TB. The Global Plan to Stop TB 2006-2015 outlines the actions needed to prevent drug-resistant TB and treat all diagnosed MDR-TB patients by 2015. Principal actions proposed by the WHO Global Task Force on XDR-TB are Strengthen TB control through the Stop TB Strategy; Scale-up MDR-TB and XDR-TB programmes; Expand and improve laboratory services; Expand MDR-TB and XDR-TB surveillance; Prevent transmission through infection control; Increase awareness and information; Pursue funding and resources; Promote research and development (5).

More opportunities to treat MDR-TB are now available through the Global

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Fund to Fight AIDS, TB, and Malaria and through the Green Light Committee (GLC) for Access to Second-Line Anti-tuberculosis Drugs (12, 13). Evidence-based guidelines for the management of drug-resistant TB are also now available (14). The GLC Initiative, together with the Working Group on MDR-TB, promotes implementation of Stop TB strategy in accordance with the Global Plan to Stop TB and the Global MDR/XDR-TB Response plan (2007–2008). It is the mechanism that enables effective control of MDR-TB and access to affordable, high-quality, SLDs for the treatment of MDR-TB (15).

Indian Strategy: RNTCP has developed a multi-faceted strategy, the components of which are MDR-TB prevention through sustained high quality DOTS implementation by all providers; improving laboratory capacity for diagnosing MDR-TB; prevention of XDR-TB by effective treatment of MDR-TB through DOTS-Plus; evaluating extent of threat of SLD resistance and XDR-TB; and reviewing the supply and availability of SLDs and address their irrational and indiscriminate use. The problem of MDR was recognized and an action plan was built into RNTCP Phase 2 Project Implementation Plan (2006-2011) (9).

In India in addition to above, there is a need to improve interactions between the RNTCP programme and NGOs/ private practitioners. Availability and accessibility of DOTS centre should be improved. Possibilities for coordination with private sector in management of MDR, XDR-TB and TB-HIV patients needed to be explored. Promoting capacity building of all stakeholders and quality assurance of the treatment is essential. There is also need to give more priority to TB research in the areas like problems of migrants, stigma, equity in access to care, regulatory mechanisms, etc so that DR TB is prevented.

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