Status of Drug Resistance in Tuberculosis after the Introduction of Rifampicin in India

The current threat in tuberculosis treatment lies on the fact of emergence of strains resistant to two most antituberculous drugs, isoniazid and rifampicin. Drug resistance to TB may be classified as primary and acquired. Causes of drug resistance are inefficient administration of effective treatment, poor case handling, use of sub-standad drugs, ignorance of healthcare workers, etc. Multi-drug resistant TB (MDR-TB) prevalence (median) in new case is highest (14.1%) in Estonia. Studies undertaken in different regions in India by Tuberculosis Research Centre (TRC) during 1997-2000 revealed acquired MDR-TB resistance levels of 25-100%. The key to successful prevention of the emergence of drug resistance remains adequate case finding, prompt and correct diagnosis and effective treatment of infective patients.

Key words : **Drug resistance, multidrug resistant tuberculosis (MDR-TB), prevalence.**

Despite all the advances in the treatment of tuberculosis (TB), this disease continues to be one of the main public health problems facing mankind in the developing countries, with India accounting for nearly 30% of the global burden.

Although drug-resistant *M tuberculosis* was observed even in the early days of chemotherapy 50 years ago, the current threat is due to the emergence of strains resistant to the two most potent antiTB drugs, namely isoniazid (H) and rifampicin (R) ie, multidrug resistant TB (MDR-TB). The level of initial drug resistance (DR) is an epidemiological indicator to assess the success of a national TB programme. Since current DR data has a bearing on the design of the treatment regimens and policies, reliable DR information is needed at national levels.

Types of Drug Resistance :

DR in TB may be broadly classified as primary and acquired. DR in a patient who has never received anti-TB treatment previously is termed as primary resistance. Acquired resistance is that which occurs as a result of specific previous treatment. The term initial resistance is used to indicate primary resistance and resistance among patients whose history of previous chemotherapy is not known. The WHO and the IUATLD have replaced the term primary resistance by the term "drug resistance among new cases" and acquired resistance by the term "drug resistance among previously treated cases"[1].

Causes of Drug Resistance :

Emergence of DR in TB patients results from a deficient or deteriorating TB control programme. Factors include inadequate or inefficient administration of effective treatment, poor case holding, use of sub-standard drugs, inadequate or irregular drug supply, ignorance of healthcare workers of the treatment and control of TB, and many others,

Detection of Drug Resistance :

The conventional methods of isolation, identification and indirect drug susceptibility testing of *M tuberculosis* usually require 8-10 weeks. In recent years, several new methods have been reported for reducing the time interval between specimen collection and receipt of results to 3 weeks or less. However, these methods require considerable technical expertise and are not financially viable for routine use in the disease endemic low income nations.

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The Global Drug Resistance Scenario :

Based on the WHO/IUATLD Guidelines,[2] a global DR surveillance project was conducted during 1994-99 in 65 countries, which report 28% of global cases.[1] The median value for resistance to any drug among new cases was 11% (range 1.7%-41%7, and highest in H at 7% (range 0.0%-31.7%).The median prevalence of MDR-TB in new cases was 1% (range 0.0%- 14.1 %), with the highest prevalence reponed from Estonia (14.1%). Among previously treated cases, median prevalence of resistance to any drug was 33.4% with MDR-TB of 9.3% [range 0% to 48.2% (Iran)].

Drug Resistance Studies in India :

In order to monitor national treatment policy, reliable and periodic updates on the prevalence of DR for the entire country are needed, which would serve as an indication of the transmission of drug resistant organisms, as well as the erficacy of the TB control programme. However due to obvious reasons (country size, financial constraints, etc). surveys of DR at a national level in India are difficult to undertake. Most of the published reports on DR, with the exception of those from the Tuberculosis Research Centre (TRC) in Chennai and the National Tuberculosis Institute (NTI) in Bangalore, are deficient in varying technical aspects, such as methodology, proper elicitation of previous treatment history, sample selection, uniformity in bacteriological procedures, etc.[3]

Initial Drug Resistance in India :

During the l980s, though the levels of initial DR to H and streptomycin (S) were similar to those in the earlier studies from the 1960s* R resistance was observed in all the centres studied, except Gujarat (Table 1)[3,4]. The reason for this was the introduction of R-containing short course chemotherapy (SCC) regimens during this period. However MDR-TB was <5% in all centres. In the I990s. a New Delhi study showed a high level of initial DR to H (18.5%) but low level of R resistance.[3] Studies undertaken by the TRC in the late 80s. during 1997-99 and 1999-2000, revealed initial resistance to ranging from 1.0-4.4%, with in MDR-TB prevalencence of between 1-3%[4-6],

Table 1 - *Summary of Studies on Initial Drug Resistance among M tuberculosis Isolates in India*

Location	Period	No of isolates	Any resistance (%) to				
			S	H	R	SH	HR
Bangalore	1980's	436	5.7	17.4	3.0	3.9	1.1
Wardha	1982-89	323	14.9	21.4	8.0	8.0	5.3
Gujarat	1983-86	570	7.4	13.8	0.0	4.2	0.0
Bangalore	1985-86	588	4.8	17.3	2.9	3.0	1.4
North Arcot	1985-89	2719	11.6	21.3	1.7	8.0	1.6
Pondicherry	1985-91	1841	8.1	10.8	1.0	3.7	0.8
Kolar	1987-89	292	5.1	32.9	4.4	4.1	3.4
Raichur	1988-89	244	11.4	19.3	3.3	6.6	3.3
Jaipur	1989-91	1009	7.6	10.1	3.0	1.7	0.9
New Delhi	1990.91	324	ND	18.5	0.6	ND	0.6
Military Hospital, Pune	1992-93	413	8.2	3.2	4.0	2.1	1.0
Military Hospital. Pune	1995-99	1120	11.4	10.7	-	-	3.7
Tamil Nadu State	1997	384	6.8	15.4	4.4	4.4	3.4
North Arcot	1999	282	12.4	23.4	2.8	8.5	2.8
Raichur	1999	278	7.2	18.7	2.5	4.0	2.5

TRC Studies on Prevalence of Primary Drug Resistance :

Data on DR from almost 3,500 patients admitted to controlled clinical trials on R-containing SCC regimens conducted at TRC over the last 3 decades showed that H resistance rates ranged from 10-16% and for S from 8-13%. R resistance started appearing in 1990s and remains at around 1%. with MDR-TB levels of 1% or less. These figures are considered to represent an accurate picture of true primary resistance in view of the detailed and repeated questioning methods used for eliciting history of previous treatment from the patients who were enrolled in the trials.

Acquired Drug Resistance in India :

Studies on acquired resistance from Gujarat (1980-86) showed an increase in resistance to H and R. and MDR-TB rates of 30%.[3] A single time-point cross-sectional survey carried out by TRC on a cohort of 3357 smear-positive patients in North Arcot found 67% acquired DR to H. 12% to R and 11% MDR-TB.[7] A New Delhi study in the 1990s also showed high levels of acquired MDR-TB. A study conducted by the Institute of Thoracic Medicine, Chennai in 4 District TB Centres of Tamil Nadu. showed overall acquired resistance levels of 63%, with 20.3% MDR-TB.[3]

Studies undertaken in different regions of India by TRC during 1997-2000, revealed acquired MDR-TB resistance levels of 25-100%.[5,6] However as these studies were not designed to obtain true levels of acquired resistance and data are based on small patient numbers, the results should be interpreted with caution.

An ongoing study in 8 sites, with INCLEN funding, is expected to yield further data on the magnitude of drug resistant TB in India. Another ongoing study being undertaken by TRC in the Model DOTS area in Tiruvellore district is expected to reveal several aspects of disease dynamics and a precise estimate of initial and acquired DR.

Conclusions :

In view of the results presented above, there is no clear evidence of an increase in India of the prevalence of initial DR in the post-refampicin era. The prevalence of MDR-TB is also found to be at low levels in most regions of India. However, relatively high prevalence of acquired resistance has been reported from most regions.

The key to successful prevention of the emergence of drug resistance remains adequate case finding, prompt and correct diagnosis, and effective treatment of infective patients. Directly observed therapy is a critical component of preventing the emergence of DR since it helps to ensure that patients take a full course of treatment. There is also a need for on-going DR surveillance in different regions by several investigators employing a common protocol, with DR levels serving as useful evaluation parameters of current and past TB chemotherapy programmes.

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electronic connectivity with implementing districts, assuring smooth drug logistics, submitting two successful Global Fund Against AIDS, TB and Malaria(GFATM) proposals, receiving Global Drug Facility support and soliciting additional donor support for DOTS expansion activities. Additionally, RNTCP has recently published its operations research agenda and made strides in implementing the national HIV/TB action plan in higher prevalence states.

RNTCP has accomplished a great deal over the past few years. This has been achieved through a collaborative effort that ranges from the individual patient in the most remote community to the international level. However, great challenges lie ahead for the programme and a collective effort will be needed to ensure that RNTCP prevails in its ambitious goal to control TB in India[5].

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