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AN OVERVIEW ON DRUG RESISTANT TUBERCULOSIS IN INDIA

C.N. Paramasivan[†]

Introduction

Tuberculosis remains one of the major public health problems in India. It has been estimated that about 30% of the world's tuberculosis patients are residing in India[1]. Since the control measures for tuberculosis such as BCG vaccination and chemoprophylaxis seem to be unsatisfactory, treatment with anti-tuberculosis drugs becomes inevitable. In recent years, the treatment of tuberculosis has been threatened by the increasing number of patients with drug resistant tuberculosis. Although the phenomenon of drug resistance to *Mycobacterium tuberculosis* was observed even in the early days of streptomycin usage, the current threat is due to the emergence of strains resistant to the potent bactericidal anti-tuberculosis drugs such as isoniazid and rifampicin which are used in the tuberculosis control programmes.

The outcome of treatment of patients harbouring multiple drug resistant *M. tuberculosis* has been poor with a high mortality rate. Their chance of being cured is very low and they require significant expenditure of health care resources. They remain infectious for a prolonged period and may, therefore, be more likely to infect others. The resurgence of tuberculosis in New York city in the 1980s is said to be complicated by an increase in drug resistant strains. Moreover, patients with HIV infection are known to have a high risk of tuberculosis and the case fatality rate is high among patients with AIDS who are infected with strains of drug resistant *M. tuberculosis* [2]. Thus, the major concerns over drug resistance are a fear of the spread of drug resistant organisms and the ineffectiveness of chemotherapy in patients infected with them.'

Although a decline in the percentage of drug resistance in tuberculosis was observed in Korea[3] and New York city[4] in recent years, the prevalence rate in India continues to be similar to that in previous years. In many drug resistance surveys conducted in India, small or non-representative populations have been sampled and there has been no clear distinction between primary and acquired resistance; these surveys, therefore, do not reflect the true situation in the community. In spite of such limitations, an attempt has been made to give an overview of the prevalence of drug resistance over the years in India.

The level of drug resistance is said to provide an epidemiological indicator to assess the amount of resistant bacterial transmission in the community as well as the success or otherwise of the National Tuberculosis Control Programme (NTP). Further, this influences the design of therapeutic regimens and policy decisions also[5]. Before we look at the prevalence data on drug resistance, it is important to define drug resistance and the factors responsible for its emergence.

Definitions

In clinical practice, two types of drug resistance are recognised, namely, primary and acquired. Some investigators categorize drug resistant tuberculosis into primary, acquired, initial, and transitional resistance[6,7]. *Primary resistance is defined as the presence of drug resistance in a tuberculosis patient who has never received prior treatment with anti-tuberculosis drugs.* It is caused by infection with organisms from another patient excreting drug resistant organisms. Primary drug resistance is said to be an indicator of tuberculosis control efforts in the past. *Acquired resistance is defined as resistance that arises during or after a course of treatment,* usually as a result of non-adherence to the recommended drug regimen or a faulty prescription. A high level of this type of resistance is known to be a mark of a poorly functioning tuberculosis control programme. *The term initial resistance is preferred by some investigators to refer to patients presenting with resistant organisms prior to the commencement of therapy, since there is a likelihood of a mixture of true primary drug resistance with acquired drug*

[†] Deputy Director (Senior Grade), Bacteriology Department, Tuberculosis Research Centre, (ICMR), Chennai - 600 031

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resistance because of patient's ignorance about drugs prescibed earlier or deliberate concealing of information regarding prior treatment. *Transitional resistance is found during treatment where occasionally a few colonies of resistant cultures are obtained just before sputum conversion.* These organisms do not multiply, nor does their presence influence treatment response.

Further, a drug resistant isolate can be categorised as single or multiple drug resistant. *Multiple drug resistance (MDR) is defined as resistance to isoniazid (H) and rifampicin (R), with or without resistance to other drugs.*

In contrast to drug resistance in many other bacterial pathogens, plasmids and transposons are not involved in *M. tuberculosis* but unlinked chromosomal mutation is found to be responsible[8]. Inadequate treatment exerts a selective pressure for the emergence of resistant clones which occurs when a single drug is used alone while there is a large viable bacterial population in the lesion.

Factors contributing to the emergence of drug resistance

There are several explanations given for the emergence of drug resistance.

* Deficient or deteriorating tuberculosis control programmes resulting in inadequate administration of effective chemotherapy, poor case holding, poor quality of drugs and inadequate drug supply.
* Inadequate training of health care workers regarding epidemiology, treatment and control of tuberculosis.
* Improper prescription of treatment regimens
* Non-adherence of patient to prescribed drug therapy
* Increase in the number of tuberculosis patients with easy access to anti-tuberculosis medication
* The epidemic of HIV infection
* Laboratory delays in identification and susceptibility testing of *M. tuberculosis* isolates etc.,[6,9]

Drug resistant tuberculosis is mainly an iatrogenic disease arising under the selective pressure of inadequate therapy[9].

Table 1. Global anti-tuberculosis drug resistance situation[10]

Drugs	Drug Resistance		
	Primary (%)	Acquired (%) and	Primary Secondary
Isoniazid	0 – 16.9	0 – 53.7	–
Streptomycin	0.1 – 23.5	0 – 19.4	–
Rifampicin	0 – 3.0	0 – 14.5	–
Ethambutol	0 – 4.2	0 – 13.7	–
MDR	0 – 10.8	0 – 48.0	0.5-14.3

Global prevalence of drug resistant tuberculosis

The prevalence of drug resistant tuberculosis varies considerably throughout the world. The reasons for this variation in different surveys are the degree of selection of patients studied, the degree of misuse of drugs and the quality of enquiry regarding previous treatment[5]. The major limitation for the adequate assessment of drug resistance is the inadequate culture and drug susceptibility facilities in many parts of the world. Therefore, the true magnitude of global drug resistant tuberculosis is not known.

The overall percentages of resistance to different anti-tuberculosis drugs obtained from different surveys done throughout the world arc shown in Table I. The available information shows that the levels of primary resistance to isoniazid as single agent ranged from 0-16%. High rates of primary resistance to isoniazid have been reported from Kenya, India and Haiti, while it is reported to be low in South Eastern England, Melbourne and Argentina. The rates of primary resistance to streptomycin ranges from 0.1-23.5%. High rates of resistance to streptomycin were reported in Zaire, Pakistan and Brazil and low levels of resistance were reported from China, Ethiopia and Bosnia-Herzegovina. Primary resistance to rifampicin as single agent was unusual with a rate ranging from 0-3% and the rate of resistance to ethambutol were similarly low, ranging from 0-4.2%[10].

There are fewer surveys of acquired drug resistance and the rates of acquired resistance are usually higher than those of primary resistance. The rates of acquired resistance to isoniazid ranged from 4 to 53.7%, to streptomycin from 0 to 14.5% and to ethambutol from 0 to 13.7%.

Resistance to multiple drugs also varied by geographical region and was more common in patients with acquired resistance. The rate of MDR-T was very low in most of the surveys ranging from 0-10.8% in the case of primary resistance and from 0-48% for acquired resistance. Multi-drug resistance was reported to range from 0.5-14.3% in surveys where there was no distinction between primary and acquired resistance. Although high rates of acquired MDR were reported from Nepal and New York[11], in most regions of the world, the rates of MDR tuberculosis were very low[10]. In general, resistance to isoniazid and streptomycin was found to be more common than to rifampicin and ethambutol.

Prevalence of drug resistance in India

Drug resistant tuberculosis has frequently been encountered in India and its presence has been known from the time anti-tuberculosis drugs were introduced for the treatment of tuberculosis. The lack of comprehensive reports on this subject is mainly due to limited facilities for culture and susceptibility tests. Much of the drug resistance is presumed clinically, when patients do not improve or the symptoms return after initial relief where sputum remains positive for acid fast bacilli[9].

Primary drug resistance

Though primary resistance is found to be low in developed countries, it is common in India and varies widely from area to area. The data on primary drug resistance estimated by different investigators over the past thirty years are listed in Table 2.

In the 1960s ICMR conducted two nationwide surveys at nine urban chest clinics in India[12,13]. The results of the first survey showed a resistance level of 8.2% to isoniazid alone, 5.8% to streptomycin alone and 6.5% to both the drugs. The primary resistance levels seen respectively in these two surveys were 14.7% and 15.5% to isoniazid and 12.5% and 13.8% to streptomycin.

A decade later, a study was conducted to assess the prevalence of primary drug resistance in Government Chest Institute and, Chest (Tuberculosis) Clinic of Government Stanley Hospital, Madras[14]. The result of the study was almost similar to the earlier ICMR surveys and the authors stated that the prevalence of primary drug resistance had not risen during the span of ten years.

During the 80s, among live reports on primary drug resistance, though the levels of primary drug resistance to isoniazid and streptomycin were similar to the earlier studies, rifampicin resistance started appearing in North Arcot, Pondicherry, Bangalore, and Jaipur but not in Gujarat[15,16,17,18,19] The reason for the emergence of rifampicin resistance during this period may be the introduction of short course chemotherapy- (SCC) regimens containing rifampicin.

Further, a higher level of primary drug resistance to isoniazid was observed in the rural population in Kolar compared to the urban patients, contradicting a Korean study where a much higher level of initial resistance was seen among urban patients giving the reason of easy access to the anti-tuberculosis drugs[3]. There was also an increase in the proportion of primary drug resistance to rifampicin (4.4%) encountered in this rural population.

In the early 1990s, a retrospective study done at New Delhi[20] showed a high level of primary drug resistance to isoniazid (18.5%) and a low level of rifampicin resistance.

Overall, the prevalence rate of primary drug resistance to isoniazid as single agent ranges from 6.0-13.0% except among the rural population in Kolar, Karnataka with a high rate of 26.7%, to streptomycin as single agent from 1.0-5.8% and to rifampicin from 0-1.9%. It is also seen from these studies that ethambutol susceptibility was not performed in many of the surveys.

For a correct evalution of primary drug resistance, standardised methodology should have been used taking care of the following namely, elicting patient history, adequate sample size, uniform laboratory methods, external and internal quality control, reliable drugs for setting up drug susceptibility, media. standard chemicals in the preparation of media etc. The outcome of Indian reports may have limitations on the above points.

TRC studies on prevalence of primary drug resistance

Data from Tuberculosis Research Centre (TRC), Chennai on primary drug resistance are available over the past 4 decades and are shown in Figure 1. Data from 16 different chemotherapy studies from 1956 to 1995 show that there was a gradual increase

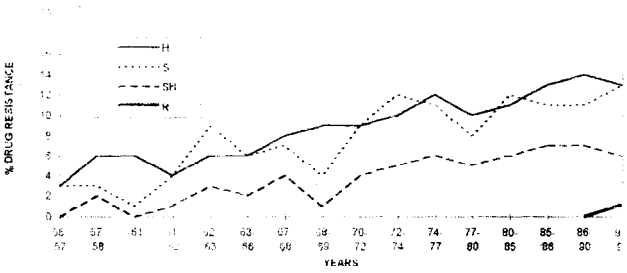

Fig. 1. Prevalence of primary drug resistance : TRC studies - 1956 to 1995

in the prevalence of primary drug resistance to anti-tuberculosis drugs. For isoniazid and streptomycin, the resistance rates were similar and ranged from 3-13% with the highest level of 14% during 1990s for isoniazid. Initial resistance to rifampicin started appearing in 1990s and was 1.2%. Double drug resistance (SH) was also noted to a lesser extent and ranged from 0-7%. Resistance to SHR was observed to be less than 1% in 1990-95.

Acquired resistance

The rates of acquired resistance are invariably higher than the rates of primary resistance, though data on acquired resistance is limited. Studies on acquired resistance are summarised in Table 3. The longitudinal trend of drug resistance noted by Trivedi and Desai between 1980 and 1986 in Gujarat showed that in treatment failure or relapsed patients, resistance to rifampicin increased from 2.8% in 1980 to 37.3% in 1986 and to isoniazid from 34.5% to 55.8%. From this study it was presumed that high level of rifampicin resistance was almost entirely acquired[15].

When a study was conducted by ICMR in North Arcot district to compare the efficacy of SCC with the conventional (non-SCC) chemotherapy, the populations were examined during their follow-up period to confirm the bacterial quiesence and in turn the efficacy of SCC, it was found that there was an increase in the frequency of acquired drug resistance with 67% resistance to isoniazid. 26% to streptomycin and 12% to rifampicin. In addition, 6% of the strains tested were resistant to both isoniazid and rifampicin[21]. A New Delhi study in the 90s also shows a higher level of acquired resistance to isoniazid and rifampicin which is almost similar to that of the Gujarat report[20].

The overall rates of acquired resistance to isoniazid ranged from 34.5-67%. for streptomycin from 26.0-26.9% and for rifampicin from 2.8-37.3%

Initial drug resistance

The results of the studies on initial drug resistant tuberculosis are shown in Table 4. The second ICMR survey conducted in the 1960s showed a higher level of drug resistance among those with a history of previous chemotherapy and it was 7.0% to isoniazid, 9.1% to streptomycin and 15.8% of both the drugs[13]. During the 80s, two surveys were conducted by ICMR at Raichur district, Karnataka[22]. and North Arcot district, Tamil Nadu to estimate the prevalence of tuberculosis and the results of the survey showed a higher level of initial drug resistance in Raichur District compared to that in North Arcot District.

Data on the prevalence of drug resistance from Army Hospital, Pune showed a very low level of initial resistance to isoniazid and the authors have reasoned that this lower level of drug resistance in this population could be due to the minimal chance of indiscriminate exposure of anti-tuberculosis agents prior to reporting to the hospital[23].

Overall, the initial resistance to isoniazid as single agent ranges from 0.6-13.2%, to streptomycin from 2.2-7.0% and to rifampicin from 0-1.7%.

Multi-drug resistance (MDR-TB)

The rate of MDR-TB in India is very low and ranged from 0-6% (Table 2, 3 and 4). Primary MDR-TB is found to be $\leq$ 3.2% and even the level of acquired MDR-TB is $\leq$ 6.0% except in Gujarat where a high level was observed (11.4-18.5%)[15]. When compared to the prevalence of MDR-TB in other parts of the world where upto 18% have been encountered, lower level has been reported in Indian studies.

Diagnosis of drug resistance

Since the spectrum of disease caused by drug resistant and susceptible organisms is similar, only way of diagnosing drug resistance is by isolating the infecting strain and assessing its susceptibility pattern which takes months for the results to be

Table 2. Summary of studies on primary drug resistance among **M. tuberculosis** *isolates in India*

S. No.	Location	Year	No. of isolates tested	Resistace to single drug (%)					Resistance to mutiple drugs (%)			Total resistance (%)	U/R
				H	S	R	E	T	SH	HR	SHR		
1.	9 Urban centres, India[12]	1964-65	1838	8.2 (14.7)	5.8 (12.5)	ND	ND	–	6.5	–	–	20.4	U
2.	9 Urban centres, India[13]	1965-67	851	(15.5)	(13.8)	ND	ND	–	–	–	–	22.0	U
3.	GCI and Stanley Hosp, Madras[14]	1976	254	(10.6)	(9.5)	ND	ND	ND	4.7	–	–	–	U
4.	Gujarat[15]	1983-86	570	7.9 (13.9)	3.2 (7.4)	0	2.5 (4.0)	0.5 (1.5)	3.3 HT-1.0; HE-0.7; SHE-0.9	0	–	20.0	-
5.	North Arcot[16]	1985-89	2779	13.0	4.0	0.07 (2.0)	ND	ND	7.0	0.7	0.9	26.0	R
	Pondicherry	1985-91	2127	6.0	4.0	0.2 (0.9)	ND	ND	3.0	0.4	0.3	13.9	
6.	Bangalore[17]	1980s	436	12.1 (17.4)	1.8 (5.7)	1.8 (3.0)	0 (0.5)	ND	3.6 HE-0.46	0.9	0.2	21.1	U
7.	Bangalore[18]	1985-86	588	12.6 (17.4)	1.7 (4.8)	1.5 (2.3)	0 (0.5)	ND	2.9 HE-0.6	1.2	0.2	20.5	U
	Kolar	1987-89	292	26.7 (32.8)	1.0 (5.1)	1.0 (4.4)	0 (1.7)	ND	2.4 HE-0.34;	3.2 SHE-1.0;	0.7 HRE-0.34	34.9	R
8.	Jaipur[19]	1988-91	1009	7.6 (10.1)	5.2 (7.6)	1.9 (3.0)	2.0 (2.6)	ND	1.6 SR-0.2;	0.7 SE-0.5;	0.1 SHE-0.1	19.9	
9.	New Delhi[20]	1990-91	324	(18.5)		0.6	–	–	–	–	–	–	U

Figure inthe brackets indicate the percentage of total resistance strains.
[(H) = H + SH + HR + SHR; (S) = S + SH + SR + SHR; (R) = R + SR + HR + HSR; (E) = E + HE + SE + SHE + HRE; (T) = T + HT]
H -isoniazid, S-Streptomycin, R-Rifampcin, E-Ethambutol, T-Thiacetazone.
U-Urban, R-Rural, ND-Not Done.

available. New rapid culture and susceptibility tests, namely BACTEC, mycobacterial growth indicator tube (MGIT) and luciferase reporter assay have been developed which offer the possibility of early sensitivity results. In addition, advanced molecular biological techniques such as polymerase chain reaction (PCR), DNA finger printing and ligase reaction are said to be highly specific, sensitive and rapid and make the results available in clinically useful time. These molecular methods not only enable us to identify resistant genes but also help in tracing dissemination[24]. Experience in restriction fragment length polymorphism (RFLP) finger printing of *M. tuberculosis* shows that clustering is more common among patients with multi-drug resistant isolates than unique isolates[26].

Treatment outcome of drug resistant tuberculosis

The emergence of drug resistant strains is known to reduce the efficacy of treatment. Strains resistant to isoniazid and streptomycin (H/S/SH) neither pose a major problem nor affect the result of treatment in a big way provided proper regimens are used[26]. On the contrary, patients infected with organisms resistant to rifampicin and isoniazid (R/HR) have a high rate of treatment failure[16,20,26] and this forms a major threat to tuberculosis control particularly for countries like India with poor resources. Patients infected with MDR strains require longer duration of therapy and may die of tuberculosis or continue to have active tuberculosis despite optional therapy[2].

Comment

In view of the results so for observed, **there is no clear evidence of an increase in the prevalence of primary drug resistance in India over the years. Moreover, relatively high prevalence of acquired resistance has been reported from Gujarat, North Arcot district and New Delhi**[16,22,21]. When compared to the global prevalence of drug resistance, primary drug resistance is found to be marginally lesser and a much higher level of acquired resistance is observed in India. The magnitude of drug resistance problem, to a large extent, is due to acquired resistance. The prevalence of MDR-TB also is found to be at a very low level in most of the regions of India. Since paediatric cases and resistance in them are mirror reflection of adult tuberculosis cases[9], the low level of resistance to isoniazid and streptomycin with 5-10% and 2-11.4% respectively and with a nil resistance to rifampicin observed in Indian children[27,28,29] really indicate that there is apparently no alarming increase in the incidence of initial MDR tuberculosis cases. However, these studies require to be repeated in different regions and in diverse settings to reconfirm this belief.

The lesson learnt from the New York study[4] where a decline in the prevalence of drug resistance was observed, is that a strong tuberculosis programme that can reduce the incidence of drug resistance in a community reduces the level of multiple drug resistance. Particularly, directly observed therapy (DOT) which is cost effective, efficient for treatment completion and in turn effective against emergence of drug resistance[11]. New drugs for tuberculosis arc unlikely to come up in the near future and hence the key success remains in adequate case finding, prompt and correct diagnosis and effective treatment of infectious

Table 3. Summary of studies on acquired drug resistance among* M. tuberculosis *isolates in India

S. No.	Location	Year	No. of isolates	Resistance (%)							U/R
				H	S	R	SH	HR	SR	SHR	
	Gujarat[15]	1980-86	1574	34.5-55.8	26.3-26.9	2.8-37.3					
		1983-86	1267	-.				11.4-18.5	3.5-1.2	14.5-15.3	
2.	North Arcot[21]	1988-89	560	67.0	26.0	12.0	19. 0	6.0			R
3.	New Delhi[20]	1990-91	81	50.7	-	33.7					U

H-Isoniazid, S-Streptomycin, R-Rifampicin, U-Urban, R-Rural

Table 4. Summary of studies on initial (both primary and acquired) drug resistance among **M. tuberculosis** *isolates in India*

S. No.	Location	Year	No. of isolates tested	Resistance to single drug (%)						Resistance to mutiple drugs (%)				Total resistance (%)	U/R
				H	S	R	E	Z	Ethio	SH	HR	SR	SHR		
1.	9 Urban centres, India[13]	1965-67	1181	9.1 (25.0)	7.0 (22.9)	ND	ND	ND	ND	15.8	–	–	–	32.0	U
2.	Raichur[22]	1988-89	355	13.2 (29.5)	4.5 (17.7)	0 (7.6)	ND	ND	ND	8.7	3.1	–	4.5	34.0	–
3.	North Arcot	1988-90	278	9.0 (16.2)	2.2	0.7	ND	ND	ND	7.1	1.4	–	1.8	22.2	R
4.	Pune[23]	1992-93	473	0.6 (3.2)	4.2 (8.2)	1.7 (4.4)	0 (0.2)	1.3 (2.5)	0.2 (0.4)	1.8	0.4	0.6	0.6	12.7	U
										SZ-0.4; RZ-0.2; SRZ-0.6; SRE + Ethio-0.2					

Figures in brackets indicate the percentage of total resistance strains.
[(H) = H + SH + HR + SHR; (S) = S + SH + SR + SHR; (R) = R + SR + HR + SHR; (E) = E + SRE; (Z) = Z + SZ + RZ + SRZ; (Ethio) = Ethio + SRE Ethio)]
H-isoniazid, S-Streptomycin, R-Rifampicin, E-Ethambutol, Z-Pyrazinamide, Ethio-Ethionamide.
U-Urban, R-Rural, ND-NOT Done. *TRC Annual Report, 1990.

patients for prevention of drug resistance.

Although longitudinal studies of TRC and many of the above cited surveys, including studies on childhood tuberculosis, show that there is no real threat due to the increase of MDR-TB in India, it cannot be taken lightly. Every physician and health care personnel should strictly adhere to the treatment policies of the government and ensure completion of treatment which would eventually result in the reduction in the prevalence of MDR-TB in the community as was observed elsewhere.

Apart from a strong tuberculosis control programme, there is also a need for a continuous and/or periodic survey of drug resistance which will provide information on the type of chemotherapy to be used for the treatment of patients and also serve as a useful parameter in the evaluation of current and past chemotherapy programmes [3]. More recently, surveillance systems have been initiated throughout the world including India by the World Health Organisation (WHO) with an emphasis on internal quality control and external quality assessment to monitor the prevalence of drug resistant organisms especially MDR-TB in the community[30] which is expected to provide accurate data on the prevalence of drug resistance in the community.

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