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DRUG RESISTANCE IN TUBERCULOSIS AND ISSUES RELATED TO MULTIDRUG RESISTANCE IN PLANNING FOR TB CONTROL INDIA

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There is no clear evidence of an increase in the prevalence of initial drug resistance in India over the years. However, relatively high prevalence of acquired resistance has been reported. The level of initial drug resistance is said to be an epidemiological marker to assess the success of the National TB Programme. This also influences the design of the regimens to be employed as well as policy decisions.

I. INTRODUCTION

Although the phenomenon of drug resistance in M. tuberculosis was observed even in the early days of chemotherapy nearly 50 years ago, the current threat is due to the emergence of strains resistant to the two most potent anti-TB drugs viz., isoniazid (H) and rifampicin (R) (MDR-TB). Despite TB being 100% curable, patients develop drug resistance tuberculosis due to various reasons. The level of initial drug resistance is said to be an epidemiological marker to assess the success of the National TB Programme. This also influences the design of the regimens to be employed as well as policy decisions. The response of patients with MDR-TB to treatment is poor and the mortality rate is usually high. Since these patients need to be treated with expensive and toxic second-line drugs, and may require hospitalization to manage their toxic reactions and other complications, they require a sizeable proportion of health care resources.

Further, an alarming increase in infection due to the human immunodeficiency virus (HIV) has accelerated this situation and it is believed that, as of now, about 3.5 million people in India are infected with HIV(1). The HIV infection is the strongest risk factor for TB infection to develop into active TB and it is also known that the rate of progression from TB infection to active disease is 10-30 times higher among persons with HIV and TB than among those with TB infection alone. Thus, there is a grave concern in India regarding the increase in HIV-associated TB and the emergence of MDR-TB in both magnitude and severity of TB epidemic.

II. DEFINITION OF DRUG RESISTANCE

Professor Mitchison defined drug resistance in mycobacteria as a decrease in sensitivity to a sufficient degree to be reasonably certain that the strain concerned is different from a sample of wild strains of human type that have never in contact with the drugs(2).

A. Types of drug resistance

Drug resistance in TB may be broadly classified as primary or acquired. When drug resistance is demonstrated in a patient who has never received anti-TB treatment previously, it is termed primary resistance. Acquired resistance is that which occurs as a result of specific previous treatment. Some workers prefer a working definition, viz., initial resistance to indicate primary resistance and undisclosed acquired resistance. This is common since sometimes patients are unaware that they, have received anti TB treatment at all or they may sometimes conceal their history of previous treatment. Transient resistance occurs just before sputum conversion in a patient who is responding to therapy. This normally occurs in the form of a few resistant colonies which usually do not multiply and does not warrant a change of treatment. The level of primary resistance in the community is considered to reflect the efficacy of control measures in the past, while the level of acquired resistance is a measure of on-going TB control measures. However the WHO and the IUATLD, in the light of discussions in several international fora, 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(4).

B. Causes of drug resistance

Several explanations are given for the emergence of drug resistance. These include:

* Deficient or deteriorating TB control programmes resulting in inadequate administration of effective treatment
* Poor case holding, administration of sub-standard drugs, inadequste or irregullar drug supply and lack of supervision
* Ignorance of health care workers in epidemiology, treatment and control of TB
* Improper prescription of regimens

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* Interruption of chemotherapy due to side effects
* Non-adherence of patients to the prescribed drug therapy
* Availability of anti-TB drugs across the counter, without prescription
* Massive bacillary load
* Illiteracy and low socio-economic status of the patients
* The epidemic of HIV infection
* Laboratory delays in identification and susceptibility testing of M. tuberculosis isolates
* Lack of the use of uniform laboratory methods, use of reliable drug powders and quality control methods
* Use of anti-TB drugs for indications other than tuberculosis.

The major contributing factors towards development of drug resistance are summarized in Fig.1.

C. Mechanism of drug resistance

Drug resistance in M. tuberculosis occurs by random, single step, spontaneous mutation at a low but predictable frequency, in large bacterial populations. There is also no convincing role for the role of plasmids or transposons as in other pathogens. The probability of incidence of drug resistant mutants is 10-8 for rifampicin, while for isoniazid and some of the other commonly used drugs it is 10-6. Therefore, the probability for resistance to both isoniazid and rifampicin to develop is 10-14, which is much larger than the number of organisms present in a medium sized cavity in a patient with open pulmonary TB. As such, the probability for MDR-TB to develop is an iatrogenic problem.

D. Transmission of drug-resistant TB

For several years, drug resistant strains of M. tuberculosis were considered to be less infectious than the drug susceptible ones. Hence drug resistance in a TB patient was considered as a problem for the concerned patient only and not for the community. However, recent studies have demonstrated that the drug resistant mutants are equally infectious and can cause severe disease in an individual exposed to the same(4).

E. Detection of drug resistance

The conventional methods of culture, identification and drug susceptibility testing of the isolated organism requires a minimum of 10-12 weeks. Although most widely used, the long waiting period in obtaining the results by this method may delay the initiation of proper treatment, resulting in the patient transmitting drug-resistant infection in the community.

The use of direct sensitivity tests, especially to isoniazid and rifampicin, by inoculating the drug-containing slopes along with drug-free culture slopes has resulted in a saving of at least 4 weeks in obtaining the resistance status(5,6). Although found to be useful, the disadvantage of this method is that it is not very useful in smear-negative and paucibacillary specimens. Available evidence from TRC on a limited number of strains using a single LJ slope containing critical concentrations of both isoniazid and rifampicin have shown promising results (unpublished findings).

A simple, inexpensive slide culture drug susceptibility test(7) that can provide results in a week has also shown great promise. This method, however, has been discontinued at present for fear of handling and hepatitis infected blood.

The automated radiometric BACTEC method provides results in less than 3 weeks and has shown a good correlation with conventional methods(8). However, the method is expensive and requires considerable technical competence. In recent years, other non-radiometric faster methods such as the mycobacterial growth indicator test (MGIT) have been developed (Becton Dickinson).
A highly sensitive and specific method using a manual bacteriophage-based test to correctly identify rifampicin susceptibility in clinical strains of Mycobacterium tuberculosis after growth in a semi-automated liquid culture system, FASTPlaqueTB-RIF, has been reported reecently(9).

Polymerase chain reaction (PCR), single stranded conformation polymorphism (SSCP) and line probe assay (LIPA) have made possible the rapid identification of rifampicin-resistant M. Tuberculosis(l0). The results become available within 24 hours. However, an analogous setting for isoniazid resistance is reported to be less favorable, since more than one gene is probably involved in isoniazid resistance.

Restriction fragment length polymorphism (RFLP) using insertion element IS 986/IS 6110 based DNA probe has also been reported to be successful in epidemiological studies in MDR-TB outbreaks. It has also been shown that clustering is more common among patients with MDR isolates than unique isolates(l1).

The newer methods have resulted in cutting down the time interval between collection of the

specimen and the receipt of results to 2-3 weeks. However, these methods require considerable technical expertise and impose financial constraints in a routine laboratory set up in the developing nations.

F. The WHO/IUATLD Global Project on Drug Resistance

Due to difficulties in collecting comparable data from different corntries/regions and in order to assist NTPs in establishing policies for drug resistance surveillance and programme monitoring, the global tuberculosis programme (GTB) of WHO and IUATLD proposed, in 1994, a global tuberculosis surveillance programme. The objectives of this programme included: a) to collect data on the global extent and severity of anti-TB drug resistance in a standardized manner at country/regional level, b) to monitor drug resistance levels in countries identified as a priority for assistance and c) proper bacteriological methodology in national laboratories through an international system of proficiency testing. Guidelines for the performance of anti-TB drug resistance surveillance were developed including standard definitions and procedures for implementation(12).

G. The global drug resistance scenario

During the period 1994-99, a total of 72 surveillance projects on anti-TB drug resistance in 65 countries have been completed. This included 31% of all the countries in the world covering approximately 33% of the world's population and 28% of the reported TB cases(l3). However, the Global Project had the highest coverage in the Americas (89%) and the Western Pacific Region (47%), while the lowest coverage was observed in South-East Asia (17%) and the Eastern Mediterranean Region (12%). The median value for any drug resistance among new cases was found to be 11% (range 1-7%-41%). The lowest median value was 0.6% for any ethambutol resistance and the highest was 7% for any isoniazid resistance. Resistance to all the four drugs tested was found to range from 0% in 24 geographical settings to 8.5% in Estonia. The median prevalence of MDR-TB in new cases of tuberculosis was 1% (range 0%-14.1%). The highest prevalence was reported from Estonia (14.1%) followed by China, Latvia, Ivanovo Oblast, Tomsk Oblast (Russian Federation) and Iran (5%).

Among previously treated cases median prevalence of resistance to any drug was 33.4% (range 0%-93.8%). The lowest median value was 5.5% for any ethambutol resistance and the highest was 21.9% for any isoniazid resistance. The median prevalence of MDR-TB among treated cases was 9.3%, ranging from 0% in four geographical settings to a maximum of 48.2% in Iran. Further, 28 geographical regions provided annual data for 2-4 years for the assessment of trends in drug resistance over the period in new cases of TB. Accordingly, only France and the United States reported a significantly downward trend in MDR-TB while a statistically significant increase was noticed in Estonia(l3).

The main findings of the Global Tuberculosis Programme are summarized in Table 1.

H. Drug Resistance studies in India

Although drug resistance in tuberculosis has been reported frequently during the last four decades, the available information is localized, inaccurafe or incomplete(l4) .Further, drug resistance is diagnosed presumptively based on the lack of improvement in the patient following chemotherapy or a relapse of symptoms. In order to formulate a national treatment policy, reliable and periodic updates on the prevalence of drug resistance for the entire country is needed, which would serve as an indication of the transmission of drug resistant organisms as well as the efficacy of the NTP. In view of the large size of the country and several other administrative as well as financial constraints, surveys of drug resistance at a national level are logistically difficult to undertake. Most of the published reports on drug resistance in India, with the exception of studies reported from the Tuberculosis Research Centre (TRC) in Chennai(l4-21), the National Tuberculosis Institute in Bangalore(22,23) and a few others(l4), are deficient in several aspects, such as lack of standardized methodology, improper elicitation of previous treatment history, sample selection, non-uniformity in bacteriological procedures, sub-standard drug powders used for susceptibility testing and lack of quality assurance studies(14). Some of the more important reports are reviewed below:

I. Initial drug resistance in India

The Indian Council of Medical Research (ICMR) undertook drug resistance studies during 1965-67 in nine urban areas of the country(l7,18). It should be emphasized here that this exercise was not a surveillance study and did not use strict sampling techniques, the centres being selected more for logistic considerations than for epidemiological reasons. Sputum specimens collected from all patients attending chest clinics were tested for drug susceptibility to streptomycin, isoniazid, PAS and thioacetazone. The first study was on patients who had denied any history of previous treatment while in the second study patients with and without previous

chemotherapy were included. The results showed that in the first study resistance to isoniazid ranged from 11-20%, to streptomycin from 8-20% and to both drugs from 4-11%.The second study showed resistance to isoniazid to range from 15-69%, to streptomycin grom 12-63% and to both drugs from 5-58%. Further the level of drug resistance was proportional to the duration of previous treatment.

A decade later, a study was conducted to assess the prevalence of primary drug resistance at the Government Chest Institute and Chest Clinic of Government Stanley Hospital (GCI-SH), Madras(24). The results of the study were similar to those in earlier ICMR surveys, indicating that the prevalence of initial drug resistance had not risen during the span of ten years. However, the above studies were undertaken in the pre-rifampicin era and are not of relevance in the present setting.

During the 1980s, though the levels of initial drug resistance to isoniazid and streptomycin in 11 reports (Table 2) were similar to those in the earlier studies, rifampicin resistance was observed in all the centers studied except Gujarat(19,21-23,25-27). The level of MDR-TB in all the centers (except Wardha) was observed to be less than 5%. 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 initial drug resistance to isoniazid (32.9%) was observed among the rural population in Kolar compared to the urban patients, contradicting a Korean study(28), where a much higher level of initial resistance was seen among urban patients, attributed to easy access to the antituberculosis drugs. There was also an increase in the proportion of initial drug resistance to rifampicin (4.4%) encountered in this rural population in Karnataka.

In the early 1990s, a retrospective study done at New Delhi showed a high level of initial drug resistance to isoniazid (18.5%) and a low level of resistance to rifampicin(29).

Data on the prevalence of drug resistance from the Army Hospital, Pune showed a very low level of initial resistance to isoniazid and the authors have explained that this lower level of drug resistance in this population could be due to the minimal chance of indiscriminate exposure of anti-TB agents prior to reporting to the hospital(30).

Studies undertaken by the Tuberculosis Research Centre, Chennai, during 1997-99 in Tamil Nadu State(l5) as well as the districts of North Arcot and Raichur(16) revealed initial resistance to rifampicin to range from 2.5-4.4% while the prevalence of MDR-TB was around 3%. Interim results of a study just completed in the Wardha district revealed resistance to isoniazid, rifampicin and to both drugs to be 15.2%, 0.5% and 0.5% respectively (TRC, unpublished data).

However, it should be emphasized that several of these reports, except those from the TRC, NTI and the Armed Forces Group, may have inherent limitations due to flaws in methodology and hence need to be interpreted with caution.

J. TRC studies on prevalence of primary drug resistance

Drug resistance data from controlled clinical trials on short course chemotherapy with rifampicin-containing regimens conducted at the Tuberculosis Research Centre (TRC), Chennai involving almost 3500 patients over the last 3 decades is shown in Figure 2. For isoniazid, the resistant rate ranged from 10-16% and for streptomycin from 8-13%. Resistance to rifampicin started appearing in 1990s and still remains at around 1%. Resistance to both isoniazid and rifampicin (MDR) is 1% or less. These figures could be 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.

K. Acquired drug resistance in India

The rates of acquired resistance are invariably higher than those of initial resistance, though data on acquired resistance is limited. The findings of studies on acquired resistance are shown in Table 3. The longitudinal trend of drug resistance noted by Trivedi and Desai(26) during the 1980s 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. During this period MDR-TB was of the order of 30%.

In the course of a study conducted by the TRC in North Arcot district to compare the efficacy of SCC with conventional (non-SCC) chemotherapy, it was found that frequency of acquired drug resistance was 67% to isoniazid, 26% to streptomycin and 12% to rifampicin; in addition, 11% of the strains tested were resistant to both isoniazid and rifampicin(21). A New Delhi study(29) in the 90s also showed a higher leverl of acquired resistance to isoniazid and rifampicin which

is almost similar to that of the Gujarat report(26). A study conducted by the Institute of Thoracic Medicine, Chennai aimed at finding out the prevalence of tuberculosis resistance in four District tuberculosis Centres of Tamil Nadu, showed that acquired resistance was 63%,out ofwhich 23.5%was resistance to single drug and 39.5% to more than one drug. Resistance to isoniazid and rifampicin (MDR-TB)was reported in 20.3%(31).

Studies undertaken by the Tuberculosis Research Centre, Chennai during 1997-2000 in the entire state of Tamil Nadu(l5), North Arcot and Raichur districts(l6) as well as in Wardha (unpublished) revealed the incidence of MDR-TB to vary from 25-100%. However, these data are based on very small numbers of patients. Sincethese studies were not designed to obtain a true picture of acquired resistance in these areas, the results presented should be interpreted with caution.

An ongoing study, with INCLEN funding, in eight different settings in India (two in Maharashtra, three in Tamil Nadu and one each in Uttar Pradesh, Kerala and Delhi) is expected to yield considerable data on the magnitude of drug-resistant tuberculosis in the country.

L. Management of Multi-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. It has been well documented that the currently available short-course regimens of six months duration cures 94-97% of patients with resistance to streptomycin, isoniazid or to both drugs(32). Studies at the TRC have shown that in patients with resistance to streptomycin, isoniazid or both drugs, only 2%, 8% and 17% respectively failed to respond when treated with appropriate regimens(33). On the contrary, the outcome of treatment of patients infected with organisms resistant to rifampicin and isoniazid (MDR) have a high rate of treatment failure. Studies at the TRC had reported that 35 of 38 patients with MDR failed to respond with conventional regimens(33). Patients infected with MDR strains require longer duration of therapy and may die of tuberculosis or continue to have active tuberculosis despite optimal therapy. In a retrospective analysis of 171 patients treated over a ten-year period (1973-83) at the National Jewish Hospital, Denver, the overall favourable outcome was only a little over 50%(34). In the Cape Town Province of South Africa, the 5-year outcome of 240 MDR-TB patients was only 33% cure(35). Experience at the Tuberculosis Research Centre with MDR-TB has been equally discouraging. In about 170 patients with MDR-TB over a 12-year period (1986-97), only one third had a favourable outcome and another one-third had died(36).

However, not all reports are so grim. In a retrospective analysis reported from South Korea on 107 patients with MDR-TB treated with at least four drugs to which they had not been exposed to before, or to which they were known to be susceptible, 52(82.5%) of 63 patients followed up responded to treatment and there were no subsequent relapses or TB-related deaths, when followed up for 17 months(37). Recent studies at the TRC have shown promising results with the use of added ofloxacin in the regimens in treating MDR-TB. While interim reports appear promising, a long term follow up is needed to draw valid conclusions (TRC, unpublished observations).The fluoroquinolones have been shown to have marked anti-mycobacterial activity and are being increasingly used in the treatment of MDR-TB. However, this class of drugs is also widely used for a variety of respiratory and other infections. Caution has to be exercised as indiscriminate use will lead to the development of resistance to this class of drugs also.

The value of some of the older drugs in the treatment of MDR-TB has to be emphasized. Many of the younger patients of today have never received PAS or thioacetazone in the past and these drugs can be used with success. In the recent past, there have been a few reports of the value of B-lactam antibiotics used along with lactamase inhibitors(38), rifabutin(39) and recombinant human interleukin 2(40) in the management of MDR-TB. However, these studies are all based on small numbers of patients and need to be evaluated further in well designed controlled clinical trials.

III. CONCLUSIONS

In view of the results so far observed, there is no clear evidence of an increase in the prevalence of initial drug resistance in India over the years. However, relatively high prevalence of acquired resistance has been reported from Gujarat, New Delhi, Raichur and North Arcot districts. When compared to the global prevalence of drug resistance, initial drug resistance is found to be marginally less while that of acquired resistance is much higher in India in specialized settings. 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 low

level in most of the regions of India. Since paediatric cases and resistance in them are mirror reflection of adult tuberculosis cases, the low level of resistance to isoniazid and streptomycin with 5-10% and 2-11.4% respectively and with a nil resistance to rifampicin reported so far in Indian children really indicates 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.

A strong tuberculosis programme that can reduce the incidence of drug resistance in the community and particularly directly observed therapy (DOTS) which is cost effective, will prove to be effective in treatment completion and in turn proved to be effective against emergence of drug resistance. Newer drugs for tuberculosis are unlikely to come up in the near future and hence the key to success remains in adequate case finding, prompt and correct diagnosis and effective treatment of infective patients for prevention of drug resistance.

All physicians and health care personnel involved in managing tuberculosis patients should strictly adhere to the treatment policies of the government in implementing DOTS and also to ensure completion of treatment which would eventually result in the reduction in the prevalence of MDR-TB in the community as it has been seen elsewhere.

Apart from a strong tuberculosis control programme, there is also need for a continuous or periodic survey of drug resistance, with an emphasis on internal quality control and external quality assessment, 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.

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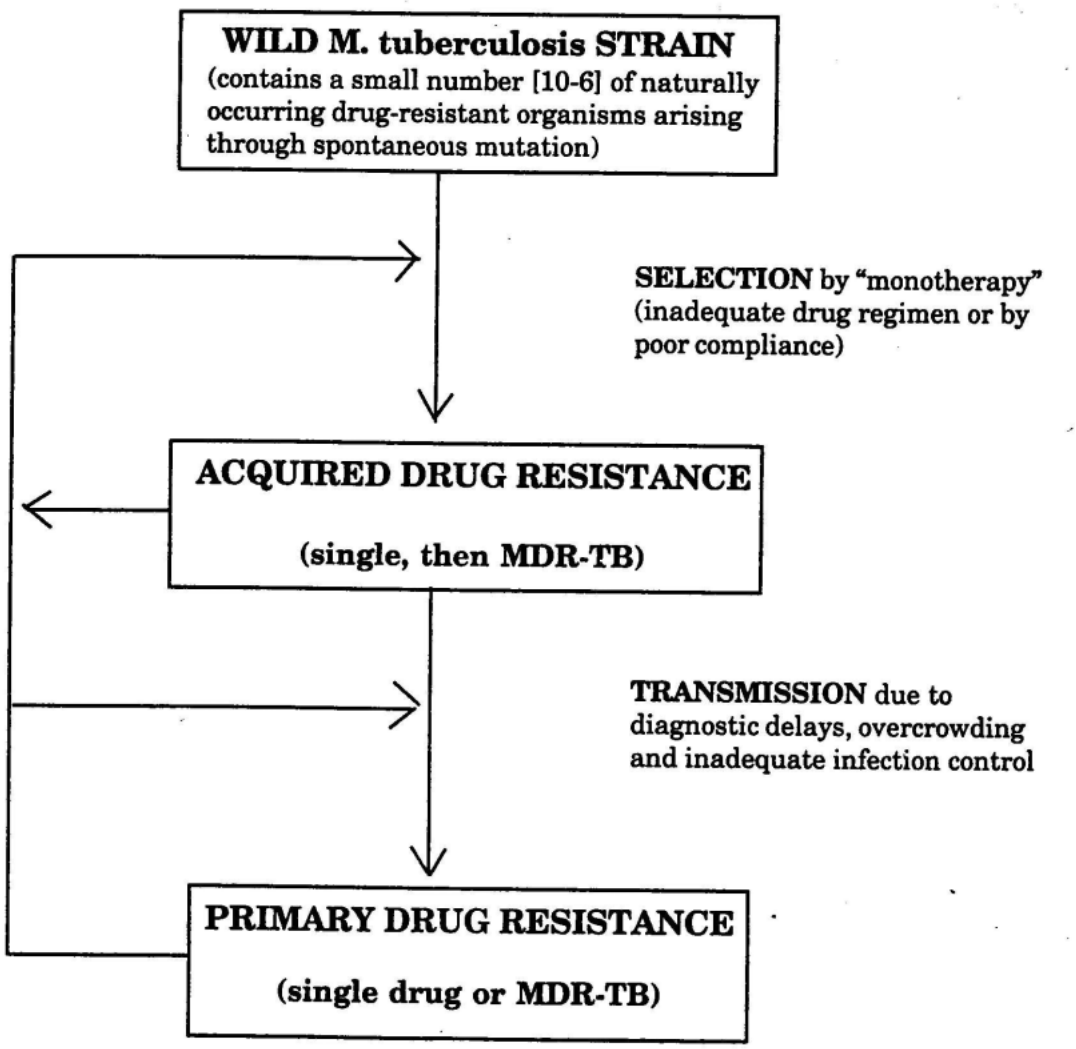
Fig 1. The development and spread of single and multidrug resistant tuberculosis*



Adapted from: WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance Report N0.2. WHO/ CDS / TB/2000.278

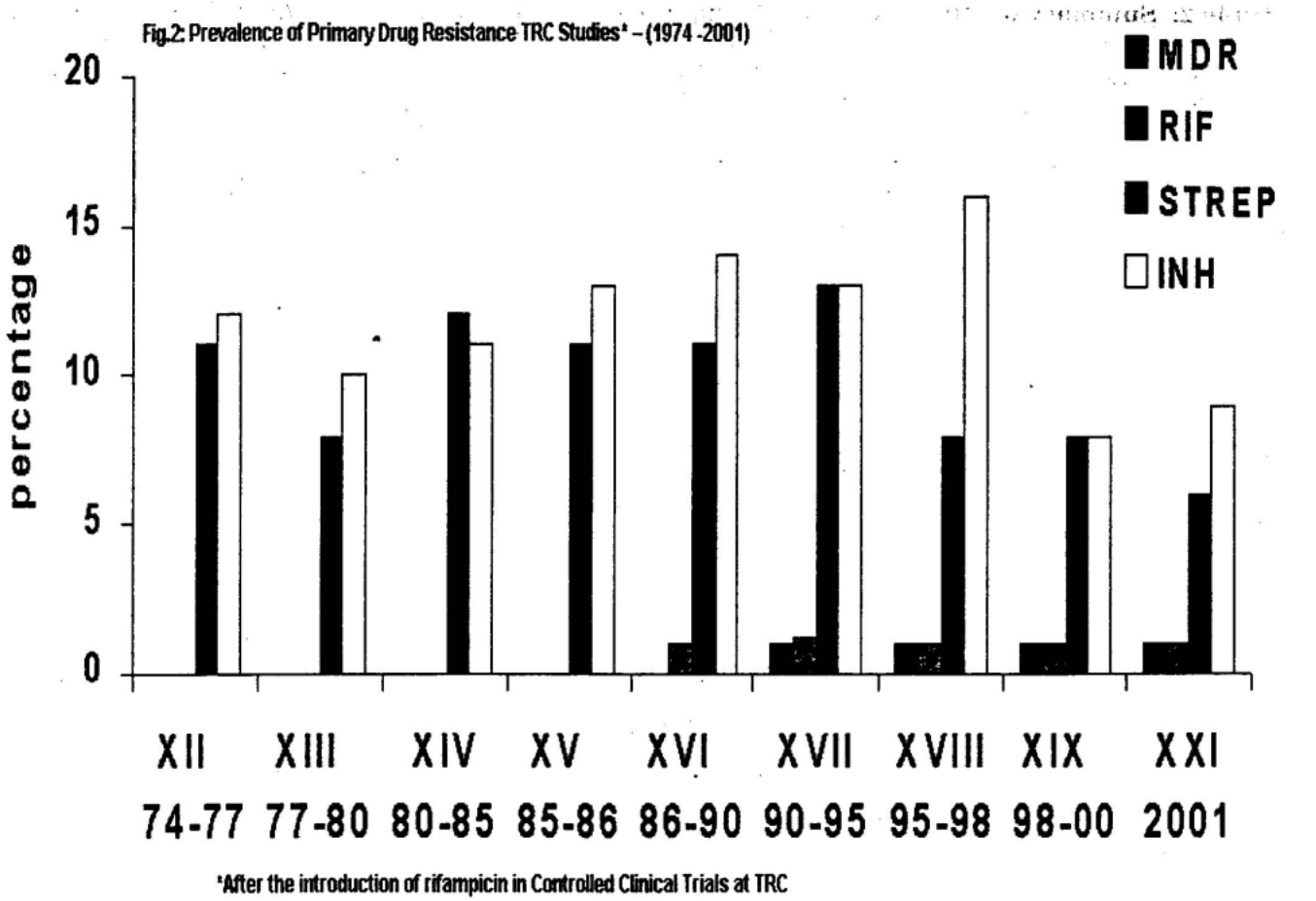


Table 1. Global antituberculosis drug resistance situation

Drug	Range (%) of drug resistance during the period			
	1994-1997		1996-1999	
	Initial	Acquired	Initial	Acquired
Isoniazid	1.5-31.7	5.3-69.7	0.0-28.1	0.0-81.3
Streptomycin	0.3-28.0	0.0-82.6	0.3-32.4	0.0-52.4
Rifampicin	0.0-16.8	0.0-57.9	0.0-15.8	0.0-50.0
Ethambutol	0.0-9.9	0.0-29.6	0.0-11.1	0.0-32.1
MDR (range)	**0.0-14.4**	**0.0-58.0**	**0.0-14.1**	**0.0-48.2**

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

SL No.	Location	Period	No. of isolates	Any resistance (%) to S	H	R	SH	HR
1	9 Centres-ICMR I	1964-65	1838	14.7	12.5	ND	6.5	ND
2	9 Centres-ICMR II	1965-67	851	13.8	15.5		NA	ND
3	GCI-SH, Chennai	1976	254	14.2	15.4	ND	4.7	ND
4	Bangalore	1980's	436	5.7	17.4	3.0	3.9	1.1
5	Wardha	1982-89	323	14.9	21.4	8.0	8.0	5.3
6	Gujarat	1983-86	570	7.4	13.8	0.0	4.2	0.0
7	Bangalore	1985-86	588	4.8	17.3	2.9	3.0	1.4
8	North Arcot	1985-89	2779	11.6	21.3	1.7	8.0	1.6
9	Pondicherry	1985-91	1841	8.1	10.8	1.0	3.7	0.8
10	Kolar	1987-89	292	5.1	32.9	4.4	4.1	3.4
11	Raichur	1988-89	244	11.4	19.3	3.3	6.6	3.3
12	North Arcot *	1989-90	241		12.9	2.5		1.7
13	North Arcot *	1989-98	747		19.0	11.8		4.4
14	Jaipur	1989-91	1009	7.6	10.1	3.0	1.7	0.9
15	New Delhi	1990-91	324	ND	18.5	0.6	ND	0.6
16	Military Hosp.Pune	1992-93	473	8.2	3.2	4.0	2.1	1.0
17	Tamil Nadu State	1997	384	6.8	15.4	4.4	4.4	3.4
18	North Arcot	1999	282	12.4	23.4	2.8	8.5	2.8
19	Raichur	1999	278	7.2	18.7	2.5	4.0	2.5
20	Wardha**	2000	197	7.6	15.0	0.5	3.0	0.5

* Tuberculosis Research Centre, unpublished findings
** Tuberculosis Research Centre, interim findings, unpublished

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

S.No.	Location	Period	No. of isolates	Any resistance (%) to H	R	HR
1	Gujarat	1980-86	1574	47.7	28.3	
2.	Gujarat	1983-86	1259	81.1	33.0	30.2
3.	Wardha	1982-89	302	47.0	12.6	9.6
4.	North Arcot	1988-89	560	67.0	12.0 .	10.9
5.	Raichur	1988-89	111	52.3	17.1	17.1
6.	N.Delhi	1990-91	81	60.5	33.3	33.3
7.	Tamil Nadu (4 dts)	1996	162	-	-	20.3
8.	Tamil Nadu State	1997	16	(50.0)*	(25.0)	(25.0)
9.	North Arcot	1999	16	(81.0)	(69.0)	(69.0)
10.	Raichur	1999	11	(100.0)	(100.0)	(100.0)
11.	Wardha**	2000	9	(78.0)	(78.0)	(78.0)

* Brackets indicate that the percentage is based on a total of less than 25
** TRC, unpublished interim findings