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Drug resistance in tuberculosis in India

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The current global concern in the treatment of tuberculosis (TB) is the emergence of resistance to the two most potent drugs *viz*., isoniazid and rifampicin. The level of initial drug resistance is an epidemiological indicator to assess the success of the TB control programme. Though drug resistance in TB has frequently been reported from India, most of the available information is localized, sketchy or incomplete. A review of the few authentic reports indicates that there is no clear evidence of an increase in the prevalence of initial resistance over the years. However, a much higher prevalence of acquired resistance has been reported from several regions, though based on smaller numbers of patients. A strong TB control programme and continuous surveillance studies employing standardized methodology and rigorous quality control measures will serve as useful parameters in the evaluation of current treatment policies as well as the management of multidrug resistant (MDR) TB cases.

Key words Current status - drug resistance - India - tuberculosis

Despite all the advances made in the treatment and management, tuberculosis (TB) still remains as one of the main public health problems, particularly in the developing countries. India accounts for nearly 30 per cent of the global TB burden[1].

Although the phenomenon of drug resistance in *Mycobacterium tuberculosis* was observed as early as 50 yr 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) (multidrug resistant-tuberculosis, MDR-TB). 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[2]. 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.

Definition of drug resistance

Drug resistance in mycobacteria is defined 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 come in contact with the drugs[3].

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. 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 World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Diseases (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].

Causes of drug resistance

The emergence of drug resistance in *M.tuberculosis* has been associated with a variety of management, health provider and patient-related factors. These include (*i*) deficient or deteriorating TB control programmes resulting in inadequate administration of effective treatment; (*ii*) poor case holding, administration of sub-standard drugs, inadequate or irregular drug supply and lack of supervision; (*iii*) ignorance of health care workers in epidemiology, treatment and control; (*iv*) improper prescription of regimens; (*v*) interruption of chemotherapy due to side effects; (*vi*) non-adherence of patients to the prescribed drug therapy; (*vii*) availability of anti-TB drugs across the counter, without prescription; (*viii*) massive bacillary load; (*ix*) illiteracy and low socio-economic status of the patients; (*x*) the epidemic of HIV infection; (*xi*) laboratory delays in identification and susceptibility testing of *M. tuberculosis* isolates; (*xii*) use of non-standardized laboratory techniques, poor quality drug powders and lack of quality control measures; and *(xiii)* use of anti-TB drugs for indications other than tuberculosis.

Mechanism and transmission 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. 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.

Although for several years, drug resistant strains of *M. tuberculosis* were considered to be less infectious than the drug susceptible ones, recent studies have demonstrated that the drug resistant mutants are equally infectious and can cause severe disease in an individual exposed to the same[5].

Detection of drug resistance

The conventional methods of culture, identification and drug susceptibility testing of the isolated organism require a minimum of 10-12 wk. Although most widely used, the long waiting period in obtaining the results by these methods 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 has resulted in a saving of at least 4 wk in obtaining the resistance status[6, 7]. However, this method is not very useful in smear-negative and paucibacillary specimens.

Several newer methods including molecular diagnostics have resulted in cutting down the time interval between collection of the specimen and the receipt of results to 2-3 wk or even less. However, these methods require considerable technical expertise and impose financial constraints in a routine laboratory set up in the developing nations.

WHO/IUATLD Global Project on Drug Resistance

Due to difficulties in collecting comparable data from different countries/regions and in order to assist National Tuberculosis Programmes (NTPs) in establishing policies for drug resistance surveillance and programme monitoring, the WHO and IUATLD proposed, in 1994, a global tuberculosis surveillance programme[8]. The objectives of this programme included (*i*) to collect data on the global extent and severity of anti-TB drug resistance in a standardized

Table I. Global antituberculosis drug resistance situation

Drug	Range (%) of drug resistance during the period					
	1994-1997		1996-1999		1999-2002	
	Initial	Acquired	Initial	Acquired	Initial	Acquired
Isoniazid	1.5-31.7	5.3-69.7	0.0-28.1	0.0-81.3	0.0-42.6	0.0-71.0
Streptomycin	0.3-28.0	0.0-82.6	0.3-32.4	0.0-52.4	0.0-51.5	0.0-73.1
Rifampicin	0.0-16.8	0.0-57.9	0.0-15.8	0.0-50.0	0.0-15.6	0.0-61.4
Ethambutol	0.0-9.9	0.0-29.6	0.0-11.1	0.0-32.1	0.0-24.8	0.0-54.2
MDR (range)	0.0-14.4	0.0-58.0	0.0-14.1	0.0-48.2	0.0-14.2	0.0-58.3

MDR, multi drug resistance
Source: Ref. 9

manner at country/regional level; (*ii*) to monitor drug resistance levels in countries identified as a priority for assistance; and (*iii*) 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[8].

The global drug resistance scenario

During the period 1994-2002, a total of 109 surveillance projects on anti-TB drug resistance in 90 countries were completed. This included 43 per cent of all the countries in the world covering approximately 42 per cent of the world's population and 34 per cent of the reported TB cases[9]. However, the Global Project had the highest coverage in the Americas (95%) and the Western Pacific Region (49%), while the lowest coverage was observed in South-East Asia (11%). The median prevalence of MDR-TB in new cases of tuberculosis was 1.1 per cent (range 0-14.2%). Among previously treated cases median prevalence of resistance to any drug was 33.4 per cent (range 0-93.8%). The median prevalence of MDR-TB among treated cases was 7.0 per cent, ranging from 0 per cent in eight geographical settings to a maximum of 58.3 per cent in Oman[9].

Analysis of almost 90,000 strains from countries between 1994 and 2002 confirmed that, globally, more strains were resistant to INH than to any other drug (range 0-42%). In general, INH and SM resistance was more prevalent than RMP or EMB resistance. In previously treated cases, the proportion of strains resistant to three or four drugs was significantly greater than among new cases. This relationship was found globally as well as regionally and suggested amlification of resistance. It also appeared that INH and SM monoresistance are the main gateways to acquisition of additional resistance.

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

Drug resistance studies in India

Although drug resistance in tuberculosis has been reported frequently during the last four decades, the available information from India is localized, inaccurate or incomplete[10]. 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[11-17], the National Tuberculosis Institute (NIT) in Bangalore[18,19] and a few others[10], 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[10].

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[13,14]. However, 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, para amino salicyctic acid (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 per cent, to streptomycin from 8-20 per cent and to both drugs from 4-11 per cent. The second study showed resistance to isoniazid to range from 15-69 per cent, to streptomycin from 12-63 per cent and to both drugs from 5-58 per cent. Further, the level of drug resistance was proportional to the duration of previous treatment.

A decade later, a study at the Government Chest Institute and Chest Clinic of Government Stanley Hospital (GCI-SH), Chennai[20] yielded results 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, both 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 II) were similar to those in the earlier studies, rifampicin resistance was observed in all the centres studied except Gujarat [15, 17-19, 21-23]. The level of MDR-TB in all the centres (except Wardha) was observed to be less than 5 per cent. 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[19] compared to the urban patients, contradicting a Korean study[24], 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[25].

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[26]. 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.

TRC studies on prevalence of primary drug resistance

(i) Controlled clinical studies: Drug resistance data from controlled clinical trials on SCC with rifampicin-containing regimens conducted at the TRC, Chennai involving almost 3500 patients over the last 3 decades is shown in the Figure. For isoniazid, the resistant rate ranged from 10-16 per cent and for streptomycin from 8-13 per cent. Resistance to rifampicin started appearing in 1990s and still remains at around 1 per cent. Resistance to both isoniazid and rifampicin (MDR) is 1 per cent or less. These figures could be considered to represent an accurate picture of true primary resistance in view

Table II. 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
9 Centres-ICMR I[13]	1964-65	1838	14.7	12.5	ND	6.5	ND
9 Centres-ICMR II[14]	1965-67	851	13.8	15.5		NA	ND
GCI-SH, Chennai[20]	1976	254	14.2	15.4	ND	4.7	ND
Bangalore[18]	1980's	436	5.7	17.4	3.0	3.9	1.1
Wardha[21]	1982-89	323	14.9	21.4	8.0	8.0	5.3
Gujarat[22]	1983-86	570	7.4	13.8	0.0	4.2	0.0
Bangalore[19]	1985-86	588	4.8	17.3	2.9	3.0	1.4
North Arcot[15]	1985-89	2779	11.6	21.3	1.7	8.0	1.6
Pondicherry[15]	1985-91	1841	8.1	10.8	1.0	3.7	0.8
Kolar[19]	1987-89	292	5.1	32.9	4.4	4.1	3.4
Raichur[15]	1988-89	244	11.4	19.3	3.3	6.6	3.3
North Arcot*	1989-90	241		12.9	2.5		1.7
North Arcot*	1989-98	747		19.0	11.8		4.4
Jaipur[23]	1989-91	1009	7.6	10.1	3.0	1.7	0.9
New Delhi[25]	1990-91	324	ND	18.5	0.6	ND	0.6
Military Hosp, Pune[26]	1992-93	473	8.2	3.2	4.0	2.1	1.0
Tamil Nadu state[11]	1997	384	6.8	15.4	4.4	4.4	3.4
North Arcot[12]	1999	282	12.4	23.4	2.8	8.5	2.8
Raichur[12]	1999	278	7.2	18.7	2.5	4.0	2.5
Wardha**	2000	197	7.6	15.0	0.5	3.0	0.5
Jabalpur**	2002	273	7.0	16.5	1.8	2.6	1.1

*Tuberculosis Research Centre, unpublished data
**Tuberculosis Research Centre, interim findings, unpublished data
S, streptomycin; H, isoniazid; R, rifamicin; ND, not done

of the detailed and repeated questioning methods used for eliciting history of previous treatment from the patients.

(ii) DRS studies: As part of the WHO/IUATLD Global DRS programme, the Tuberculosis Research Centre, Chennai, undertook studies during 1997-99 in Tamil Nadu State[11] as well as the districts of North Arcot and Raichur[12]. These studies revealed initial resistance to rifampicin to range from 2.5-4.4 per cent while the prevalence of MDR-TB was around 3 per cent. The results of another study in the Wardha district of Maharashtra revealed resistance to isoniazid, rifampicin and to both drugs to be 15.2, 0.5 and 0.5 per cent respectively (TRC, unpublished data). Interim results of a recently concluded study in the Jabalpur district of Madhya Pradesh showed initial resistance to isoniazid, rifampicin and to both drugs to be 16.1, 1.8 and 1.1 per cent, respectively (TRC, unpublished data). Since 1999, TRC has carried out several operational research studies in the model DOTS area in Tiruvallore district of Tamil Nadu, including measurement of drug resistance among patients living in the trial area. Interim data

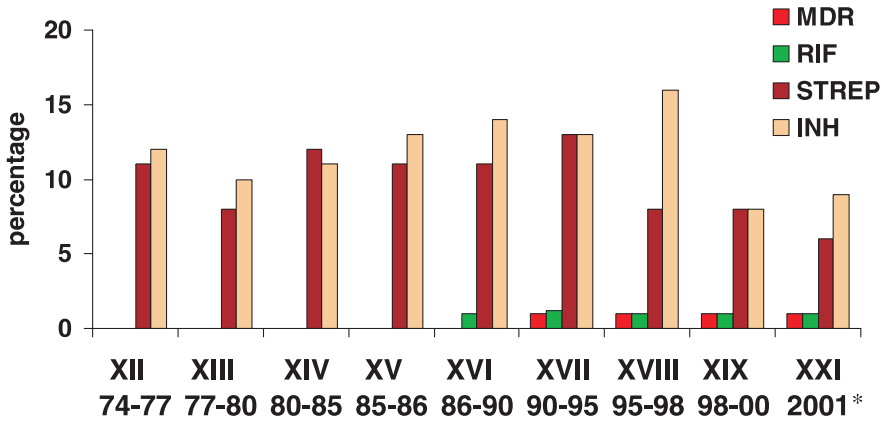

Fig. Prevalence of primary drug resistance TRC studies* - (1974-2001). After the introduction of rifampicin in Controlled Clinical Trials at Tuberculosis Research Centre (TRC). MDR, multidrug resistance (R,H); RIF, rifampicin; STREP, streptomycin; INH, isoniazid.

(1999-2003) revealed resistance to isoniazid and MDR to be 11.8 and 1.6 per cent respectively (TRC unpublished). Likewise, a study on drug resistance carried out on HIV/TB patients (2000-02) revealed resistance to isoniazid and MDR to be 13 and 4.3 per cent respectively (TRC, unpublished).

Studies on DRS have also been undertaken by the National Tuberculosis Institute (NTI) in the districts of Mysore (2001), Hoogly (2003), Mayurghanj (2003) and Naogaon (2003) and also in Bangalore city where MDR TB levels amongst patients with no history of previous treatment were observed to be 1.2, 3.0, 0.7, 7.2 and 2.2 per cent respectively (NTI, unpublished).

Acquired drug resistance in India

The rates of acquired resistance are invariably higher than those of initial resistance, though data on acquired resistance are limited. The findings of studies on acquired resistance are shown in Table III. The longitudinal trend of drug resistance noted by Trivedi and Desai[22] during the 1980s in Gujarat showed that in chronically ill, treatment failure or relapsed patients, resistance to rifampicin increased from 2.8 per cent in 1980 to 37.3 per cent in 1986 and to isoniazid from 34.5 to 55.8 per cent. 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 per cent.

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 per cent to isoniazid, 26 per cent to streptomycin and 12 per cent to rifampicin; in addition, 11 per cent of the strains tested were resistant to both isoniazid and rifampicin[16]. A New Delhi study[25] in the 1990s also showed a higher level of acquired resistance to isoniazid and rifampicin which is almost similar to that of the Gujarat report[22]. A study conducted by the Institute of Thoracic Medicine, Chennai in four District Tuberculosis Centres of Tamil Nadu, showed that acquired resistance was 63 per cent, out of which 23.5 per cent was resistance to single drug and 39.5 per cent to more than one drug. Resistance to isoniazid and rifampicin (MDR-TB) was reported in 20.3 per cent[27].

Studies undertaken by the TRC, Chennai during 1997-2000 in the entire state of Tamil Nadu[11], North Arcot and Raichur districts[12] as well as in Wardha and Jabalpur (unpublished) revealed the incidence of MDR-TB to vary from 25-100 per cent. However, these data are based on very small numbers of patients. Since these studies were not designed to obtain a true picture of acquired resistance in these areas, the results presented should be interpreted with caution. However, DRS data obtained from 440 patients from the model DOTS area in Tiruvallore district of Tamil Nadu (1999-2003) revealed the incidence of MDR TB to be 11.8 per cent

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

Location	Period	No. of isolates	Any resistance (%) to		
			H	R	HR
Gujarat[22]	1980-86	1574	47.7	28.3	—
Gujarat[22]	1983-86	1259	81.1	33.0	30.2
Wardha[21]	1982-89	302	47.0	12.6	9.6
North Arcot[16]	1988-89	560	67.0	12.0	10.9
Raichur[17]	1988-89	111	52.3	17.1	17.1
New Delhi[25]	1990-91	81	60.5	33.3	33.3
Tamil Nadu (4 districts)[27]	1996	162	—	—	20.3
Tamil Nadu State[11]	1997	16	(50.0)	(25.0)	(25.0)
North Arcot[12]	1999	16	(81.0)	(69.0)	(69.0)
Raichur[12]	1999	11	(100.0)	(100.0)	(100.0)
Wardha*	2000	9	(78.0)	(78.0)	(78.0)
Jabalpur*	2002	31	87.1	80.6	80.6

Brackets indicate that the percentage is based on isolates less than 25
*TRC, unpublished interim findings
H, isoniazid; R, rifampicin
Superscript numerals indicate reference nos.

(TRC, unpublished) and in the HIV, TB study, MDR TB was 5.9 per cent, based on 37 patients (2000-02, unpublished).

A recently concluded study, with International Clinical Epidemiology Network (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.

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/or streptomycin neither pose a major problem nor affect the result of treatment in a big way provided proper regimens are used. The currently available short-course regimens of six months duration cure 94-97 per cent of patients with resistance to streptomycin, isoniazid or to both drugs[28]. 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[29]. 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 about 170 patients with MDR-TB over a 12-year period (1986-97) at the TRC, Chennai, only one third had a favourable outcome and another one-third had died[30].

A retrospective analysis reported from South Korea on 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, 82.5 per cent of patients followed up responded to treatment and there were no subsequent relapses or TB-related deaths, when followed up for 17 months[31]. A recent study from the developed countries reported that the cure rates for patients with MDR-TB

increased from 56 per cent in 1973-1983 to 84 per cent in 1983-2000, with the improvement attributed to the use of fluoroquinolones and surgery[32]. Recent studies at the TRC, Chennai 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 re-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 β-lactam antibiotics used along with β-lactamase inhibitors[33], rifabutin[34] and recombinant human interleukin-2[35] 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.

Conclusions

In view of the results presented above, 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. However, these studies need to be repeated in different regions and in diverse settings to reconfirm this belief. TRC, Chennai and NTI, Bangalore have been working closely with central TB division and finalized recently a protocol for carrying out drug resistance surveillance (DRS) at the state level. The central TB division has been providing assistance to investigators in carrying out DRS at their respective places. As a follow-up, DRS protocols have been finalized for two large Indian states, namely, Gujarat and Maharashtha and the results are expected to be known in 2005. Similar efforts are underway for two other states, namely, Andhra Pradesh and Orissa with funds provided by the WHO Global Fund for AIDS, tuberculosis and malaria (GFATM).

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 prove to be effective against generation of resistant strains. 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 including careful introduction of second-line drugs to which the patient is susceptible.

Apart from a strong tuberculosis control programme, there is also need for better and more rapid diagnostic methods, 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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