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TRENDS IN INITIAL DRUG RESISTANCE OVER THREE DECADES IN A RURAL COMMUNITY IN SOUTH INDIA

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Summary:
Background: The magnitude of initial drug resistance has important implications for the tuberculosis control programme.
Aims: To study trend of initial drug resistance over a period of three decades in a rural community in five panchayat unions in Chingleput district in south India.
Methods: A total population survey of tuberculosis in the area was undertaken in 1968-70, comprising radiographic examination of all individuals aged 10 years or more and sputum examination of those with abnormal shadows. Subsequently, the total population survey was repeated on 6 occasions at intervals of 2.5 years along with new entrants found at each survey, and on two more occasions (1991-92, 1994-96) in a subset of two panchayat unions. Prevalence cases and (new) incidence cases of culture-positive tuberculosis were identified in each survey, and their susceptibility to Isoniazid and Streptomycin was determined.
Results: Between 1968 and 1986, initial drug resistance to Isoniazid increased from 12.5% to 20.7% in prevalence cases, at an average annual rate of 3.1%. For Streptomycin, the increase was from 6.4% to 12.1%, at the rate of 4.9% per annum. In incidence cases, the corresponding annual rate of increase was 3.8% for Isoniazid and 7.4% for Streptomycin. In the subset of the population, that was surveyed in 1991-92 and 1994-96, there was some evidence of a decline in the proportion of resistant cases after 1984-86.
Conclusion: There was a steady increase in the magnitude of initial drug resistance in the community between 1968 and 1986, which probably indicates an unsatisfactory tuberculosis programme during the period.
Key words: Initial drug resistance, Trend of drug resistance in community, Tuberculosis epidemiology

INTRODUCTION

The magnitude of drug resistance in tuberculosis patients and changes in it over time are useful indices for understanding the extent of resistant bacterial transmission and for monitoring the effectiveness of drug regimens in the area treatment programme[1]. Information on the former aspect is widely available from out-patients attending tuberculosis clinics,[2-11] but is difficult to obtain at the community level, especially in a large developing country such as India with limited resources. An excellent opportunity arose to do so from a very large randomized trial of BCG vaccines, initiated in 1968, in Chingleput district in south India[12]. The Chingleput population was followed for 15 years by frequent surveys, that included new entrants also, selective follow-up of high risk subjects and passive case finding in subjects with chest symptoms who had attended peripheral health centres. All positive cultures were tested for susceptibility to Isoniazid and Streptomycin by standard methods in a well-established laboratory with in-built quality assurance techniques. This report describes secular trends over time in initial drug resistance (i.e., resistance amongst untreated and treated patients combined), and also assesses the impact of history of previous treatment on the magnitude of resistance in the community.

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MATERIAL AND METHODS

A tuberculosis prevalence survey, consisting of radiographic examination of all individuals aged 10 years or more and sputum examination of those with abnormal shadows, was undertaken in 1968-70 in a population of about 100,000 persons in Chingleput district in south India[12]. The study area comprised Thiruvallur town and five panchayat unions (blocks) of Ellapuram, Kadambathur, Poondi, Thiruvallur and Thiruvalangadu. The population was followed for 15 years by repeat survey every 2.5 years, selective case finding (once every 10 months) amongst those with an abnormal radiographic appearance or chest symptoms, and passive case detection in those who spontaneously attended peripheral health institutions with chronic cough or chest pain. Every repeat survey was undertaken after updating the census through registration of new entrants (e.g., newborns, settlers, and those missed at the previous survey). Thus, prevalence cases were identified in seven total population surveys (1968-70, 1971-73, 1973-75, 1976-78, 1979-81, 1981-83, 1984-86). Excluding those with a positive culture in each prevalence survey, new cases in the rest of the populatioin were identified in the following repeat survey (1971-73, 1973-75, 1976-78, 1979-81, 1981-83, 1984-86), and were labeled as "incidence cases".

In a subset of two blocks (Kadambathur and Thiruvalangadu), two more surveys were undertaken, one in 1991-92 and the other in 1994-96, after an interval of 3.75 years[13]. Prevalence cases in the two surveys were identified, as also incidence cases from the latter survey. Finally, in 1999-2001, a prevalence survey was undertaken in a random sample of the total population in the five blocks[14]. In the two subset blocks (Kadambathur and Thirvalangadu), all subjects (i.e., including those not selected in the random sample) were investigated, to facilitate comparisons with total population surveys undertaken previously in these blocks.

All sputum specimens were examined by fluorescence microscopy and cultured on Lowenstein-Jensen medium. Those yielding growth were subjected to Streptomycin and Isoniazid sensitivity tests and identification tests (niacin test, growth at 25^0C, and para-nitrobenzoic acid test/ catalase test).

Details of procedures and techniques employed for radiography, bacteriology and drug sensitivity have been described earlier[12]. In brief, for all positive cultures and a control strain (H37Rv) in each batch, sensitivty tests were set up on Lowenstein-Jensen medium employing concentrations of 0.1,0.2,1 and 5 mcg/ml for Isoniazid and 8,16,32 and 64 mcg/ml for Streptomycin, and the results were expressed as minimal inhibitory concentration (MIC) for the former, and resistance ratio (RR) for the latter.

Definitions of resistance

A minimal inhibitory concentration (MIC) of 5 or more was regarded as indicative of resistance to Isoniazid, and a resistance ratio (RR) of 8 or more as indicative of resistance to Streptomycin.

Statistical analysis

The findings were analyzed by sex and age (10-24, 25-44, 45+ years), making the tacit assumption that, within each of the 6 sex-age groups, the findings in those not investigated would have been the same as in those investigated.

Statistical methods included $\div^2$ tests for differences and trends in proportions, weighted regression analysis for estimating the annual rate of increase and standardization employing the direct method[15] to adjust for differences in the age-sex composition over time; the population in 1968-70 was taken as the standard population for the prevalence surveys, and the population in 1971-73 for the incidence surveys.

RESULTS

Findings in the total population

Coverage by various investigations

In the various prevalence surveys, the

coverage ranged from 82% to 90% for radiographic examination, and from 88% to 96% for sputum examination of eligible subjects. In the subsequent incidence surveys, the corresponding proportions were 76% to 79%, and 91% to 97%, respectively. Drug sensitivity tests were undertaken for 97% to 99.7% of the positive cultures in the prevalence surveys and for 96% to 99.5% in the incidence surveys.

Drug sensitivity in cases detected in prevalence surveys

The number of patients who had drug sensitivity tests ranged from 507 to 855 in the various periods, the median being 744. Over the years, there was an increasing trend in the proportion of older patients (i.e. 45 years or more) from 50.5% to 65.9% (P<0.001). To allow for these changes, an adjusted estimate of the proportion with resistance was computed (see page 3), and both observed and adjusted estimates are set out in Table I, and the latter illustrated in Figure l.

The observed prevalence of initial drug resistance (in 1968-70) was 12.5% to Isoniazid and 6.4% to Streptomycin, including 4.6% to both drugs. It tended to increase over the next 15 years to 20.7% to Isoniazid in 1984-86(r=0.74, P=0.06) and to 12.1% to Streptomycin (r=0.96, P<0.001), including 9.4% to both drugs (r=0.90, P<0.01). The annual rate of incease was 3.1% for Isoniazid (95% C.I. 0.6-5.6%), 4.9% for Streptomycin (95% C.I.3.6 - 6.2%), and 5.3% for both drugs (95% C.I. 3.0-7.7%).

However, in the more recent survey, in 1999-2001, the observed prevalence of Isoniazid resistance was substantially less than that in the last three surveys (1984-86, 1981-83, 1979-81), namely, 9.5% compared to 20.7%, 21.4% and 19.9%, respectively (P<0.001). Further analyses showed that the decrease in Isoniazid resistance was significant (P<0.01) in males, whether aged less than 45 years or 45 years or more. In females also, there was evidence of a decrease (P<0.05), but only in those aged 45 years or more.

Adjustment by standardization for age and sex did not have much effect, the difference between the observed and standardized estimates being 0.5 or less in all instances for Streptomycin and all but one instance for Isoniazid.

Drug sensitivity in cases detected in incidence surveys

The number of incidence cases with sensitivity results ranged from 520 to 709 in the various periods, the median being 554. The proportion of males was fairly stable over the

Table 1. Drug resistance in cases detected in prevalence surveys (5 blocks)

Period of Survey	Total patients	Percentage of Patients with resistance to the following drug(s)					
		Isoniazid		Streptomycin		Both drugs	
		Obs.	Std.	Obs.	Std.	Obs.	Std.
1968-70	689	12.5	12.5	6.4	6.4	4.6	4.6
1971-73	693	18.5	18.6	7.2	7.2	5.9	5.9
1973-75	755	21.1	21.4	6.8	6.9	5.3	5.4
1976-78	855	15.3	15.6	7.7	8.0	5.0	5.3
1979-81	790	19.9	20.3	10.1	10.5	8.1	9.7
1981-83	832	21.4	21.5	10.9	11.0	7.9	8.0
1984-86	733	20.7	21.4	12.1	12.5	9.4	10.0
1999-01	507 (442)	9.5 (9.7)	9.9 (9.9)	N.A.	N.A.	N.A.	N.A.

Obs.=Observed; Std.=Standardized for sex and age; N.A.=Not available
Figure in brackets is the prevalence based on the random sample survey, while the other is based on all patients tested.

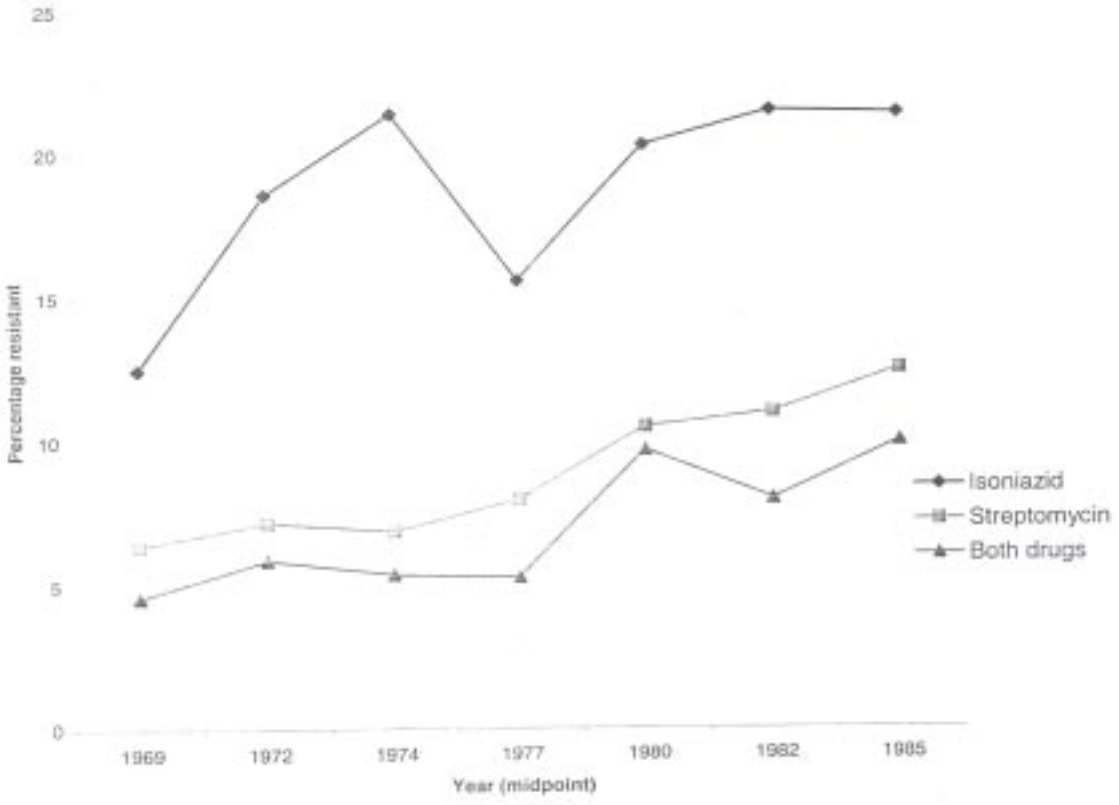

Fig.1 Initial drug resistance in prevalence cases in 5 blocks

years (P>0.1). There was evidence of heterogeneity in the distribution by age (P=0.02), but no distinct trend was seen (P>0.2). Both observed and standardized estimates are set out in Table 2, and the latter are illustrated in Figure 2. Again, the difference between the two was small, namely 0.5 or less in all instances for Streptomycin and all but one instance for Isoniazid.

The proportion of resistant incidence cases in 1971-73 was 6.3% to Isoniazid and 3.1% to Streptomycin, including 1.7% to both drugs. This tended to increase with time, and was 10.0% to Isoniazid in 1984-86 (r=0.63,P=0.2),6.0% to Streptomycin (r=0.85, P=0.03), and 3.8% to both drugs (r=0.87, P=0.03). The annual rate of increase was 3.8% for Isoniazid (95% C.I.-0.7% - 8.6%), 7.4% for Streptomycin (95% C.I. 2.9 - 12.2%), and 8.0% to both drugs (95% C.I. 3.4 - 12.7%).

In every period, the proportion who were resistant was substantially lower in incidence cases (Table 2) than in prevalence cases (Table 1). Thus, the former was 31-47% of the latter for Isoniazid, 43-83% for Streptomycin and 29-61% for both drugs.

Secular trends by age

There were no secular trends in resistance in prevalence or incidence cases aged less than 25 years. In cases aged 25 years or more, however, the proportion with resistance increased significantly (P<0.001) in prevalence cases from 12.4% in 1968-

Table 2. Drug resistance in cases detected in incidence surveys (5 blocks)

Period of survey	Total patients	Percentage of patients with resistance to the following drug(s)					
		Isoniazid		Streptomycin		Both drugs	
		Obs.	Std.	Obs.	Std.	Obs.	Std
1971-73	709	6.3	6.3	3.1	3.1	1.7	1.7
1973-75	621	9.2	9.1	4.2	4.1	2.7	2.7
1976-78	577	5.4	4.9	4.5	4.2	2.8	2.5
1979-81	520	10.0	9.3	6.5	6.2	4.4	4.2
1981-83	531	10.5	10.1	9.6	9.1	5.3	4.9
1984-86	530	10.0	9.9	6.0	6.0	3.8	3.7

Obs.=Observed; Std.=Standardized for sex and age

Table 3. Drug resistance in the blocks surveyed more frequently

Period of survey	Prevalence surveys				Incidence surveys			
	Total patients	Resistant to the following drug(s)*			Total patients	Resistant to the following drug(s)*		
		INH	Strep	Both		INH	Strep	Both
1968-70	189	10.6	5.8	3.2	----	----	----	----
1971-73	254	15.0	8.3	7.1	236	5.9	3.4	1.7
1973-75	232	19.8	7.8	5.6	203	5.9	3.0	2.0
1976-78	294	17.0	5.4	4.4	198	5.1	3.0	2.0
1979-81	263	19.8	9.5	8.0	163	8.0	4.9	3.7
1981-83	269	23.4	11.9	8.6	159	12.6	8.2	5.0
1984-86	262	19.1	11.1	8.0	193	7.3	5.7	3.1
1991-92	292	14.7	11.3	7.5	----	----	----	----
1994-96	238	11.3	6.3	3.4	343**	9.6	6.7	3.2
1999-01	216	10.2	----	----	----	----	----	----

*Observed percentage, as the numbers were not large enough to permit standardization
**The larger number from this survey (343) is due to the observation period being longer (3.75 years) than in the other surveys (2.5 years)
INH=Isoniazid; Strep=Streptomycin

who were resistant increased from 6.2% in 1971-73 to 9.9% in 1984-86 for Isoniazid (P=0.002), 2.8% to 6.0% for Streptomycin (P<0.001), and 1.7% to 3.7% for both drugs (P<0.001).

Secular trends by sex

There were no secular trends in females, either in prevalence or incidence cases. In males, the proportion who were resistant in prevalence cases increased from 12.6% in 1968-70 to 21.0% in 1984-86 for Isoniazid (r=0.44, P=0.28), 6.3% to 12.8% for Streptomycin (r=0.88, P<0.01), and 4.5% to 9.9% for both drugs (r=0.78, P= 0.04). For incidence cases, the proportion resistant increased from 6.7% in 1971-73 to 8.3% in 1984-86 for Isoniazid, from 3.4% to 6.3% for Streptomycin, and from 1.9% to 3.4% for both drugs; however, none of the trends was statistically significant.

Findings in the subset population

In the subset of two blocks (Kadambathur and Thiruvalangadu), prevalence surveys were undertaken (on the total population present) on 10 occasions and incidence surveys on 7 occasions. The findings with respect to drug sensitivity in this more frequently surveyed population are set out in Table 3 and illustrated in Figure 3. In prevalence

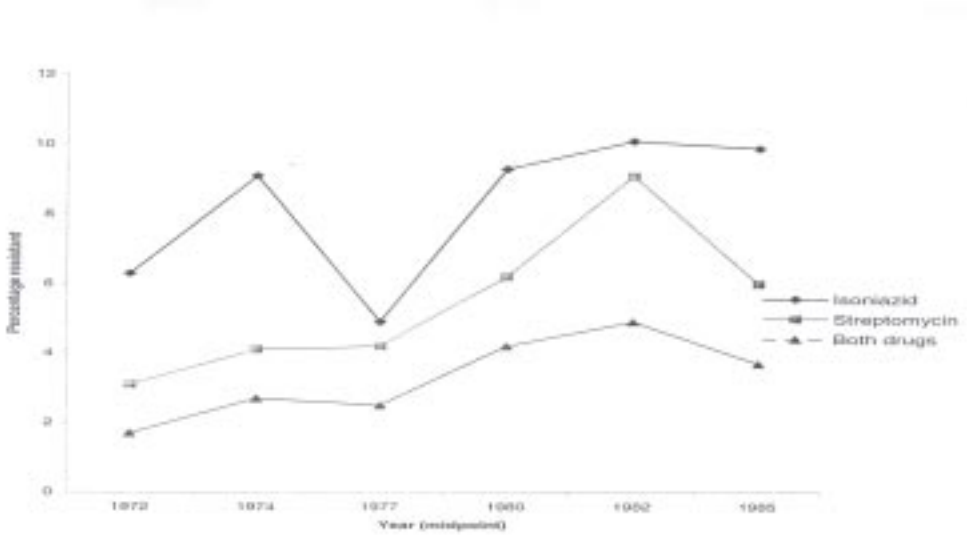

Fig 2. Initial drug resistance in incidence cases in 5 blocks

cases, resistance to Isoniazid increased from 10.6% in 1968-70 to 23.4% in 1981-83 (P=0.02) , to 70 to 20.5% in 1984-86 for Isoniazid, from 6.1% to 12.1% for Streptomycin, and from 4.4% to 9.3% for both drugs. In incidence cases, the proportions Streptomycin from 5.8% to 11.9% (P=0.16), and to both drugs from 3.2% to 8.6% (P=0.1). Thereafter, there was some evidence of a decline, to 10.2% for Isoniazid by 1999-2001 (P=0.01), and to 6.3% for Streptomycin and 3.4% to both drugs by 1994-96 (P=0.2).

The findings in incidence surveys were similar up to 1981-83 (Table 3). The proportion with Isoniazid resistance increased from 5.9% to 12.6% (P = 0.1); the corresponding proportions for Streptomycin resistance were 3.4% and 8.2% (P= 0.08), and for double drug resistance were 1.7% and 5.0%, respectively (P=0.02). Thereafter, there was a suggestion of a decrease up to 1994-96, but it was not statistically significant (P>0.2).

Association between Age, Sex and Drug Resistance

Cases in prevalence surveys

Drug resistance was appreciably less common in cases of tuberculosis aged 45 years or more than in cases aged 10 - 44 years (Table 4, upper half). In males, the proportions were 15.1% and 21.0% for Isoniazid, 7.4% and 10.6% for Streptomycin, and 5.0% and 8.6%, respectively, for double drug resistance, all the differences being statistically significant (P<0.001). In females also, the contrasts were significant (P<0.01), the corresponding proportions being 13.0% and 20.1% for Isoniazid, 6.6% and 11.8% for Streptomycin, and 5.0% and 9.5% for both drugs.

In patients of the same age, there were no differences between males and females (P>0.2).

Cases in incidence surveys

In males, drug resistance tended to decrease significantly with age (Table 4, lower half). Thus, the proportions with resistance in cases aged 10-24, 25-44 and 45+ years were 13.1%, 11.3% and 6.4%, respectively , for Isoniazid (P<0.001), 7.9%, 7.3% and 3.8% for Streptomycin (P<0.001), and 4.9%, 4.0% and 2.4% for both drugs (P<0.02). In female cases, however, there was no association.Among patients of the same age, there were no differences between males and females.

Table 4. Sex and age in relation to drug resistance in cases detected at prevalence and incidence surveys

Source of case	Age (yrs)	Isoniazid sensitivity test				Streptomycin sensitivity test				Sensitivity tests to isoniazid and streptor			
		Male		Female		Male		Female		Male		Female	
		No. tested	Res^ (%)	No. tested	Res (%)	No. tested	Res (%)	No. tested	Res (%)	No. tested	Res to both drugs(%)	No. tested	Res tc drug
Prevalence surveys*	10-24	211	17.1	125	20.0	192	8.9	119	14.3	192	7.8	119	10.9
	25-44	1873	21.5	518	20.1	1762	10.8	481	11.2	1762	8.7	481	9.
	45+	3132	15.1	525	13.0	2839	7.4	484	6.6	2839	5.0	484	5.
Incidence surveys*	10-24	236	13.1	102	9.8	266	7.9	119	6.7	266	4.9	119	3.
	25-44	1063	11.3	323	13.0	1234	7.3	380	5.8	1234	4.0	380	3.
	45+	1265	6.4	312	9.9	1476	3.8	356	5.3	1476	2.4	356	3.

*All the 5-block surveys combined
Res=Resistant

Table 5. Relationship of history of previous treatment with drug resistance

Type of Survey	Period of survey	History elicited (%)	No history of previous treatment				History of previous treatment present			
			Total patients	Resistant(%) to following drug(s)			Total patients	Resistant to following drug(s		
				INH	Strep	Both		INH	Strep.	Bot
Prevalence	1971-73	99.6	406	5.7	3.0	2.0	284	36.6	13.4	11.
	1991-92	99.7	254	12.6	9.4	5.5	37	27.0	21.6	18.
	1994-96	100.0	129	5.1	3.1	0	109	18.3	10.1	7.
	1999-01	98.8	400	8.5	N.A	N.A.	101	12.9	N.A.	N.A
Incidence	1971-73	90.7	575	4.2	2.8	1.6	68	23.5	5.9	2.9

INH=Isoniazid Strep.=Streptomycin

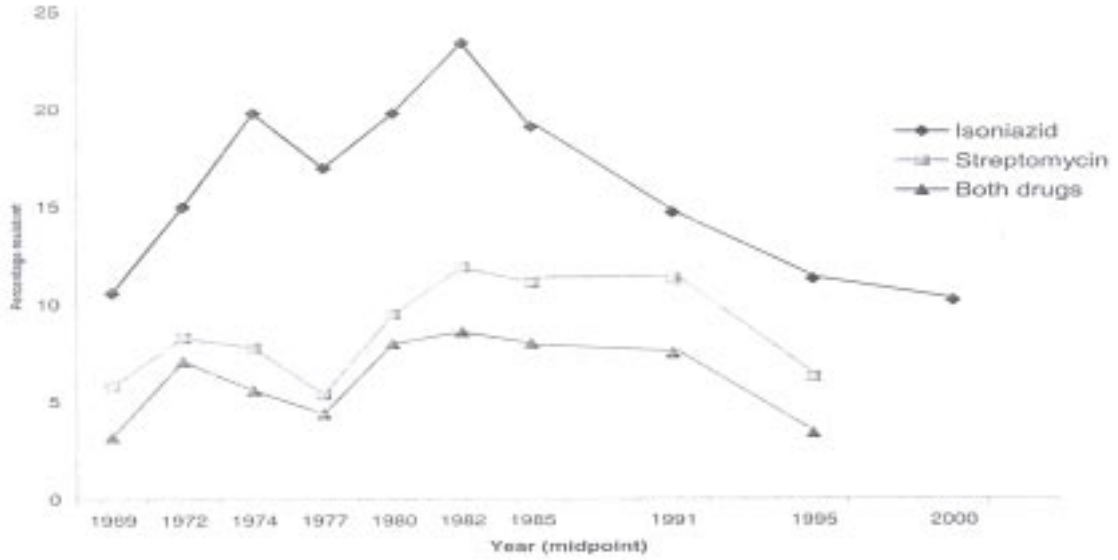

Fig.3. Initial drug resistance in prevalence cases in 2 blocks

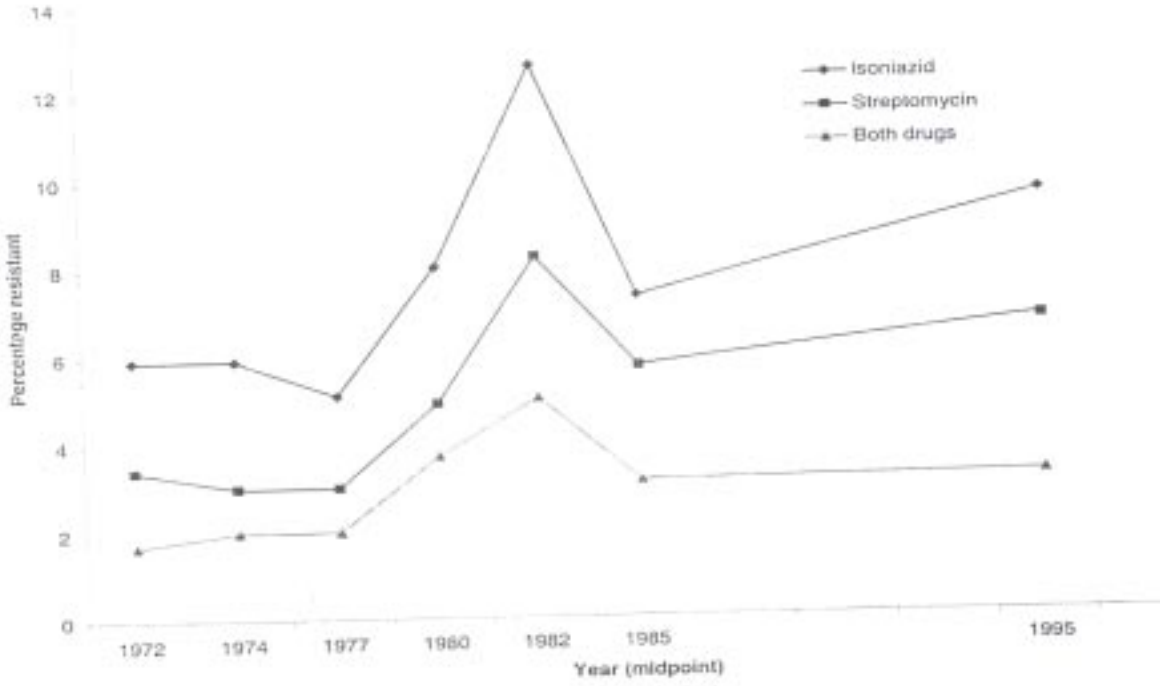

Fig. 4. Initial drug resistance in incidence cases in 2 blocks

History of previous chemotherapy and its effect on drug resistance

Inquiry regarding previous treatment for tuberculosis was undertaken in over 99% of the patients in only four of the ten prevalence surveys; in these, the sensitivity tests results were related to the presence (or absence) of any previous history of chemotherapy (Table 5). Drug resistance was invariably more frequent in patients with a history of previous chemotherapy than in those without, the Relative Risk (RR) for Isoniazid resistance being 6.5 in 1971-73 (P<0.001), 2.1 in 1991-92 (P=0.04), 3.4 in 1994-96 (P<0.01) and 1.5 in 1999-2001 (P>0.2). The corresponding RRs for Streptomycin resistance were 4.5 (P< 0.001), 2.3 (P=0.05) and 3.3 (P=0.05), respectively, in the first three surveys.

Similar findings were obtained in one more survey (1973-75), where only 67% of the cases had been interrogated regarding previous treatment, the RRs for those with previous chemotherapy being 8.1 for Isoniazid (P<0.001), 2.6 for Streptomycin (P=0.05), and 6.0 for both drugs combined (P<0.01). In the remaining five surveys, either the proportion who had a history elicited or the number with a history of previous treatment was too low to permit valid comparisons.

Table 6. Primary drug resistance in outpatients at the Tuberculosis Research Centre, Chennai

Period	No. of patients	% resistant to the following		
		INH	Strep	Both
1957-60	498	5.2	3.1	1.1
1961-64	776	5.4	5.9	1.9
1965-68	692	7.2	7.0	3.1
1969-72	896	9.2	7.9	3.6
1973-76	940	11.4	12.5	5.9
1977-80	748	9.8	7.9	4.1
1981-84	825	10.9	11.6	6.1
1985-88	449	12.2	10.9	6.9
1989-92	356	15.7	13.5	7.0
1993-96	313	15.0	11.8	7.7
1997-00	330	10.3	7.9	3.3

INH=Isoniazid Strep.=Streptomycin

History of previous treatment was obtained for over 90% of cases in only one (1971-73) of the incidence surveys. Resistance was higher in those with a history of previous treatment than in those without (Table 5), the proportions resistant being 23.5% and 4.2% for Isoniazid (RR=5.6, P<0.001), and 5.9% and 2.8% for Streptomycin (RR=2.1, P>0.2) In another survey (1973-75), history was taken in 71% of cases, and the corresponding proportions were 23.7% and 6.8% for Isoniazid (RR=3.5, P<0.001), and 10.2% and 3.6% for Streptomycin (RR = 3.9, P = 0.01). In the remaining four incidence surveys, the proportion that had history elicited was too low (47-55%) to provide valid comparisons.

Primary Isoniazid resistance, that is, the prevalence of Isoniazid resistance in patients with no history of previous treatment, varied appreciably between 5.1% and 12.6% in the four prevalence surveys (P<0.01), but showed no trend (Table 5). The corresponding proportion for primary Streptomycin resistance was 3.0%, 9.4% and 3.1% (P<0.001) in the three surveys with sensitivity tests to Streptomycin. In the 1971-73 incidence survey, the prevalence of primary resistance was 4.2% to Isoniazid and 2.8% to Streptomycin (Table 5).

DISCUSSION

The magnitude of drug resistance prevalent in a community can have significant implications for the outcome of a tuberculosis programme, because patients with drug-resistant bacilli respond much less favourably than those with sensitive bacilli. Also, 'failure' of treatment cases in both the groups would infect the non-infected with drug-resistant bacilli and render treatment ineffective in them. It is, therefore, important for programme managers to monitor the level of drug resistance in the community, and adopt appropriate treatment regimens. Resistance could be primary, i.e., infection from a source with resistant bacilli, or acquired due to inappropriate drug prescription, irregular drug supply to patients or non-compliance on the part of patients. The accuracy of classification, as primary or acquired, depends on the efficiency with which history of previous treatment is elicited. This is

often poor in developing countries because medical prescriptions are seldom available, patients are unaware of details of their treatment or sometimes conceal them, and skills for eliciting an accurate history are not always forthcoming. Therefore, the estimated drug resistance in surveys is usually a mixture of primary and acquired resistance, and is often referred to as "initial drug resistance"[1].

Estimates of primary drug resistance are available over four decades in intensively questioned outpatients attending the Tuberculosis Research Centre, Chennai (Table 6). Primary Isoniazid resistance increased from 5.2% in 1957-60 to 15.0% in 1993-96, at the rate of 3.1% per annum, Streptomycin resistance from 3.1% to 11.8% at the rate of 3.3% per annum, and double drug resistance from 1.1% to 7.7% at the rate of 5.1% per annum. Not all of this increase may be real, as there is a possibility of methodological differences over time. Thus, at this Centre, only patients with no history of previous chemotherapy are offered treatment in randomized clinical trials following intensive inquiry, initially by two physicians and a medical social worker, and a month later (after some confidence building has taken place) by a physician. It is possible that, in their anxiety to avoid being turned away from a reputed institution, patients became increasingly adept, over the years, in concealing details of previous treatment, and this could have resulted in higher proportions with resistance in later years.

A one-time study, in 1964-65, in nine urban centres in the country[2] found the prevalence of primary drug resistance to be 14.7% to Isoniazid (range 11-20%) and 12.5% to Streptomycin (range 8-20%), including 6.5% to both drugs (range 4-11%). Other studies in Chennai[4], Gujarat[5] and North Arcot district[11] yielded a range of 8-19% for Isoniazid and 7-11% for Streptomycin, including 4-7% to both the drugs.

A one-time survey of all patients, previously treated or untreated, in nine urban centres in the country[3] in 1965-67 showed that the prevalence of initial drug resistance varied from 15% to 69% for Isoniazid (median 23%) and 12% to 63% for Streptomycin (median 19%), including a range of 5% to 58% for both the drugs (median 11%). Other studies in Bangalore[6], Kolar[7], New Delhi[8], Jaipur[9], Pondicherry[10], North Arcot district[10] and Raichur district[11] yielded a range of 10-33% for Isoniazid, 5-18% for Streptomycin, including 2-13% for both. A state-wide study in 1997 in Tamil Nadu, involving 145 participating centres, showed that the proportion with initial Isoniazid resistance was 15.4%17. District-wise studies in 1999 showed that initial Isoniazid resistance was 23.4% in North Arcot and 18.7% in Raichur, the corresponding figures for initial Stretomycin resistance being 12.4% and 7.1%, respectively.

In our community study in Tamil Nadu, the initial drug resistance (primary plus acquired) in 1968-70 was 12.5% to Isoniazid and 6.4% to Streptomycin, including 4.6% to both the drugs. The initial drug resistance increased annually by 3.1%, 4.9% and 5.3%, respectively. The increases probably reflect an ineffective tuberculosis control programme during this period. A study from Korea[18] reported that the prevalence of drug resistance increased from 38% in 1965 to 48% in 1980, but dropped to 25% in 1990, the decrease coinciding with treatment efficiency increasing from 60% in 1984 to 77% in 1989. In New York City, an intensive treatment programme resulted in a 29% decrease, over a 3-year period, in the prevalence of drug resistance[19].

Initial drug resistance was observed less frequently in incidence cases than in prevalence cases, which is not surprising as they were new cases that developed in subjects with no disease previously, and were, therefore, less likely to have received previous chemotherapy. However, even among them, there was some evidence of increase over time in initial drug resistance, by 3.8% per annum for Isoniazid and 7.4% per annum for Streptomycin. During the same period (1971-86), the level of primary drug resistance in intensively interviewed out-patients attending the Tuberculosis Research Centre was substantially smaller and the rate of increase over time was also appreciably smaller, namely, 1.8% per annum for

Isoniazid and 1.5% for Streptomycin. **These differences suggest that while the monitoring of the level of initial drug resistance in out-patients attending a tuberculosis centre could be of considerable value to the programme manager, especially for choosing appropriate drug regimens, it may not be a satisfactory tool to understand the epidemiological situation with respect to change in the rate of resistance transmission in the community**.

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