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Editorial

HIV ESTIMATES : METHOD AND SENSITIVITY OF FORECASTING

On the occasion of the World TB Day, why should we be thinking and writing about the HIV epidemic and not TB? For two reasons. One, that HIV infection influences the speed and spread of TB and the latter too fuels the course of HIV. Second, that estimating the prevalence and incidence of TB has been going on in India for long and understanding the impact of HIV on the estimates would be helpful.

The National Intelligence Council(NIC), USA, in a recently published report on HIV situation in five countries, projected, *inter alia*, that by 2010 there would be 25 million HIV infections in India. The report, once again, brought to surface the controversies and concerns associated with such estimates and projections of HIV/AIDS situation in our country. The current official estimate of HIV infections in India is close to 4 million. A projected six times increase in HIV prevalence over next 10 years is likely to heighten the concerns in any country and India can not be an exception. Disagreement would also occur when the database and assumptions used in estimations differ. It is, therefore, useful to examine how these projections are made? Using which parameters?

Estimation of HIV infections in a country with incomplete epidemiological information is fraught with complexities. HIV estimates and projections are influenced by several critical factors viz., the size of vulnerable population, prevalence and incidence of HIV infection among them, presence of determinants that facilitate or hinder HIV transmission, impact of prevention and control programmes in place and mortality rates. The data collected from the nation-wide HIV sentinel surveillance is modelled using various programmes. Since data on every parameter used in modelling may not be available, certain assumptions need to be made. The validity of these assumptions can also be checked by experts using Delphi technique. The question arises; is quality data available for India on these parameters for any one to compute the projections? Which assumptions are being used in modelling data for estimates, currently ?

According to the National AIDS Control Organisation (NACO) of India, as of 31 October 2001, there were about 3.31 million HIV infected Indians. These estimates are based on data collected from 320 sentinel surveillance sites- STD clinics (135), antenatal(ANC) clinics (170), IDU Centres (13) and MSM Centres (2) spread across the country. Since there are no reliable estimates for the number of sex workers, intravenous drug users (IDU), and men having sex with men (MSM), about 20% of the estimates (0.67 million) has been added to the sentinel based estimate to arrive at a working estimate of 3.97 million HIV infections in India. This too is an estimate with which not every one agrees .

Representativeness of surveillance sites and the ensuring constituent sub-populations in the community are important for the accuracy of estimates. The severity of the HIV epidemic varies among sub-populations by time and geographical area. Unless the sentinel sites are representative, such data can at best be used for identifying sub-population and geographic area-specific time trends in HIV epidemic. Otherwise, it accentuates uncertainties surrounding these estimates. Since not many community-based studies have been undertaken so far, crucially at one time point, pregnant women attending the sentinel sites have been assumed to represent low risk sub-population, in general. However, the extrapolation of

the prevalence rates among pregnant women to general population may result in under or over-estimation depending upon the level and maturity of HIV epidemic. Andhra Pradesh, Karnataka, Maharashtra & Tamil Nadu comprise over 75% of all infections in the country, even though they have less than 30% of adult population. The current HIV prevalence based on data of ANC attendees is believed to be less than 1% of the adult population. Estimated prevalence is roughly twice in southern states. The Tamil Nadu community prevalence study found a prevalence of 2% in females in 1998, roughly double the 1% prevalence found in ANCs. A study conducted among pregnant rural women attending primary health centres in Pune district in western India showed prevalence rate of 1.2%. The variations in access to and utilization of health services within and between states may also introduce a significant bias in these estimates. The NFHS-2 data reveal that 49% of pregnant women received at least one ante-natal check up which varies in urban and rural areas (74.8% urban and 41.2% rural woman). Older women were less likely to utilize ante-natal services than younger women. Therefore, adjustments for age-group and urban/rural area may be required in modelling. Besides, the NACO estimates are based on a debatable assumption that STD prevalence rates vary according to the level of HIV epidemic. A recently published community-based STD prevalence study from Tamil Nadu reported that nearly 6% of males and 13% of females had microbiologically confirmed infections, a prevalence higher than that assumed by NACO for high prevalence states. These data suggest that the epidemic is more mature in some states than what has been assumed by the NACO, while computing the estimates.

Forecasting is not only based on current HIV estimates but also on assumptions about future changes in biological and behavioural determinants associated with new HIV infection. And also on the programme activities which are likely to alter the course the epidemic may take. These and similar other factors need to be considered while making future projections. It is not known if this is being done.

A major reason for errors in estimates and projections has been the lack of systematic, reliable information. This is not the first time that predictions about the status of HIV epidemic in India have been made. Projections for India have also been reportedly made by the UNAIDS. Their worst-case scenario number is closer to the NIC estimate of 25 million, while the best-case scenario number is 5 million. Another study predicts 3.93 million and 6.87 million infections by 2005 in commercial sexual networks as best and worst case scenarios, respectively. However, the model does not account for repeated visits of a client to the sex worker.

The NIC report does not mention either the database used or the assumptions made. It does, however, acknowledge a high margin of error in its projections. Such projections succeed more in generating controversies, and even a sense of fear and helplessness. Their utility for evidence-based planning, programme evaluation, development of advocacy tools or raising resources is much less. Responsible agencies estimating the magnitude of HIV infection and forecasting projections could perhaps strengthen the confidence around their efforts by giving a range along with the assumptions made. Only then would they be of help and meaning to any one.

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These are the opinions of individual authors and do not necessarily reflect institutional view point.

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TUBERCULOSIS CONTROL SERVICES IN INDIA - GENESIS, PROGRESS AND FUTURE*

I. Ranga Rao**

At the outset, I would like to convey my deep sense of gratitude to our chairman, Dr. S.P. Agarwal, our Vice-Chairman Dr.M.M. Singh, members of the Technical and Programme Committees for selecting me to deliver the prestigious Lupin-TAI Oration. I frankly confess that I am not a scientist but just a programme worker. During my Government service of 33 years, from 1960 onwards, I have worked at various levels, as Medical Officer of many a TB Clinic, as District TB Officer for about 15 years, as State TB Officer and, finally, Director of State Training and Demonstration Centre for 10 years. After my retirement in 1993, I was involved in training of programme workers of different categories. I also worked as a senior consultant to the Administrative College of India for preparation of the project proposal for expansion of RNTCP in the entire state of Andhra Pradesh. I have had the unique distinction of having worked in the field of tuberculosis from the inception of NTP in 1962. Hence, with all that experience behind me, I have ventured to deliver this oration.

Tuberculosis Control Services - Genesis

If we go back to the pre-independence days and recollect the TB services available to the public, the services were totally unplanned and comprised TB Sanatoria & TB beds, TB Clinics & Dispensaries Rehabilitation Centres and B.C.G. vaccination

Our Tuberculosis Association of India (TAI) was established in 1939, which took up the health education activity for controlling tuberculosis on a regular basis.

After Independence, the erstwhile services were strengthened and properly planned, as recommended by the Bhore Committee. The following changes were made:

1. A separate TB Division was established in the Directorate General of Health Services, with an Adviser
2. Rapid expansion of B.C.G. vaccination was made and a nationwide mass campaign was started in 1951
3. More TB Clinics were opened which offered domiciliary services
4. State Training and Demonstration Centres were established in major states
5. Expansion of TB was achieved by covering areas where there were no beds
6. After-care and rehabilitation centres were established
7. Research was undertaken in a planned manner

Tuberculosis Control Services - After 1955

With the advent of Five Year Plans, the following further developments took place after 1955:

1. National Sample Survey-1955-58
2. Establishment of Tuberculosis Chemotherapy Centre at Chennai in 1956
3. Establishment of National Tuberculosis Institute at Bangalore in 1958
4. Introduction of National Tuberculosis Programme (NTP) in 1962 - a technically sound, economically feasible & operationally acceptable programme integrated with the general health services for the entire population services
5. B.C.G. vaccination made a part of the Expanded Programme of Immunisation (EPI).

*Lupin-TAI Oration delivered at the 57th National Conference on Tuberculosis and Chest Diseases held at Panaji (Goa) from 27th to 29th September, 2002

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It was the National Sample Survey (NSS), carried out between 1955-58 by the ICMR, which gave the following fairly accurate and new information on the extent of tuberculosis problem in the country:

- a) Around 1.3% to 2.8% (Average 1.8%) of the population above the age of 5 years were suffering from radiologically active disease of which 0.2 to 0.8% (Average 0.4%) were sputum positive
- b) There was more disease in males than in females
- c) Prevalence was more in the elderly and aged people
- d) Prevalence of disease was almost equal in urban & rural areas
- e) Higher prevalence was seen in over-crowded slums and in poor socio-economic conditions but there was no difference among those living in *kutch*a houses compared with those in *pucca* houses

These findings of NSS opened the eyes of the Government and more attention was paid to organising TB control services for the entire population.

The Tuberculosis Chemotherapy Centre, now called Tuberculosis Research Centre (TRC) was started at Chennai with the help of WHO, ICMR, &

the Government of Tamilnadu. The TRC showed to the entire world that domiciliary treatment was as effective as institutional treatment and developed effective drug regimens on the basis of controlled clinical trials.

NTP Chemotherapy Policy: 1962-1985

The chemotherapy policy followed by the Government under NTP was as follows:

- * Domiciliary treatment for all newly diagnosed cases; institutional care only for fewer cases admitted selectively
- * Use of standard drug regimens
- * 12-18 months standard duration of treatment (conventional regimens); defaulter actions for those who discontinued treatment earlier than prescribed duration
- * Priority in treatment to sputum positive cases
- * Priority in treatment to newly diagnosed patients
- * Treatment to be provided free of cost
- * Timely follow-up of all patients to ensure the end result of treatment
- * No chemoprophylaxis - an impractical proposition.

The standard (conventional) drug regimens adopted under NTP were as shown in Table 1.

Table 1. Standard (conventional) drug regimens adopted under NTP : 1962-1985

Code	Regimen with dosage of drugs	Duration in months	Efficacy %	Relapse %	Overall efficacy %
R ₁	TH (150 mg + 300 mg) daily	18	82	5	78
R ₂	SH tw (0.75 g + 650 mg) twice weekly	12	94	9	86
R ₃	PH (10g + 300 mg) daily	18	86	5	82
R ₄	EH(1g+300 mg)	12	96	15	83
R ₅	S+TH/PH/EH/daily for 2m, TH/PH/EH daily or SH tw for 10 m	12	96	6	90

Recommended Drug regimens under NTP-1993 Standard Regimens

- R1: 2STH/10TH: For sputum positive or seriously ill patients
R2: 12TH: For sputum negative patients (radiologically active)

Short Course Regimens

- RA: 2EHRZ/6TH for sputum positive or serious forms of extra-pulmonary disease
RB: 2 SHRZ/4 S2H2R2 for failures & relapses

Recommended Drug Regimens under NTP-1997 Standard Regimens

- R1: 2SHE/10EH For sputum positive or seriously ill cases where SCC is not available
R2: 12 EH: For sputum negative patients (radiologically active)

Short Course Regimens

- RA: 2 EHRZ/6EH for sputum positive or serious forms of extra-pulmonary disease
RB: 2 SHRZ/4 S2H2R2 for failures & relapses (every dose supervised)

Introduction of Revised National Tuberculosis Control Programme (RNTCP) in 1997

Before talking about the introduction of RNTCP in 1997, let us consider why we failed to achieve the expected results under NTP. In my opinion, it was a "human failure" because:

1. Implementation and supervision of the NTP was not done on the recommended lines.
2. About 100 districts in the country did not even introduce NTP.
3. All the key personnel at the DTC to run the programme in the districts were never posted continuously.
4. Quality microscopy services, particularly in the PHIs, were not provided.
5. Our case detection remained less than the expected sputum positives per district per

year 2000.

6. Continuous and regular supply of all the anti-tuberculosis drugs, particularly SCC drugs in the PHIS, could not be ensured.
7. The recommended drug regimens of NTP were not prescribed, particularly in the teaching institutions.
8. Administrative and political support to various levels NTP was not provided.
9. Adequate budget required to run the programme, particularly anti-TB drugs, vehicles etc., was not provided.
10. NGOs and private medical practitioners were not involved in the programme.
11. Health education for tuberculosis remained negligible compared to Malaria, Leprosy, immunisation, HIV and AIDs.

The net result of all the mentioned weaknesses was that case finding in NTP was only about 30% of the expectation and treatment completion was about 35% with standard drug regimens and 45% to 50% with SCC.

As there was no significant change in the epidemiological situation inspite of having NTP in place for more than 30 years, and with increasing cases of drug resistance, compounded by the advent of HIV infection, the entire situation was reviewed at the national level by an expert committee of WHO., GOI and SIDA. And RNTCP which is a semi-vertical programme was adopted in 1993. After a pilot phase, the RNTCP was taken up for countrywide implementation in 1997.

Magnitude of Tuberculosis problem at present

The current estimates suggest that there are :

- * 14 million cases (radiologically active)
- * 3.5 million sputum positive cases
- * **2 million radiological cases of whom 0.8 million are annual incidence**
- * 0.8 million are sputum positive cases
- * 0.45 million tuberculosis deaths occur every year

- * There is increasing drug resistance - primary, acquired & MDR-TB
- * HIV infection is spreading - 1% to 2% adults are infected
- * RNTCP aims at least 85% cure rate among the newly detected smear positive cases and 70% case detection which is not always possible.

There is increasing drug resistance especially, MDR-TB. Previously, we used to think that initial drug resistance is not a great problem. Increasingly now, it is a real cause for worry. Table 2 shows various estimates of acquired drug resistance in India.

Future of TB control

Should we think of controlling tuberculosis in the near future? Certainly, this is a million dollar question.

It is believed that if strictly followed, RNTCP DOTS will reduce the burden of TB in the future. Besides, DOTS can reduce drug resistance, will bring down deaths due to TB and improve the quality of life even among the HIV positive patients.

Hence, RNTCP has to be implemented meticulously on the recommended lines at the district and sub-district levels and at all the microscopy

centres and followed strictly. Yet, as per an unpublished report, only about 60% of the patients are actually receiving DOTS in RNTCP and the remaining cases are on unsupervised treatment in RNTCP implemented districts. To succeed better, we have to involve NGOs, ESI, Military and Railways and most important, all teaching institutions in RNTCP. There should be constant supervision and vigilance on the performance of NGOs and private medical practitioners, wherever involved.

The stated NTP objectives are:

- (a) Long term: To reduce the problem of TB in the community sufficiently and quickly to a level where it ceases to be a public health problem.
- (b) Immediate:
 - 1) Detection of maximum number of TB cases among the chest symptomatics attending the outpatients and giving them treatment on domiciliary basis - the so called passive case-finding.
 - 2) Undertake case finding and treatment activities in all the health institutions as integral part of general health services.
 - 3) B.C.G. vaccination at birth or soon after for prevention of childhood forms of TB.

Table 2. Various estimates of acquired drug resistance in India

	Region	Year	% of Acquired Drug Resistances		
			H	S	R
Deshmukh et al	Nagpur	1966	38.6	6.0	-
Gangadharan (ICMR)	India	1967	46.0	-	-
Trivedi et al	Gujarat	1980	34.5	26.3	2.8
Raj et al	Haryana	1980-84	42.5	34.3	3.17
Hardas	Nagpur	1984	46.3	8.9	-
Trivedi SS	Gujarat	1986	55.8	26.9	37.3
Jain et al	Delhi	1992	50.7	-	33.3
Janmeja et al	Haryana	1990-95	72.0	37.0	49.0

Now, RNTCP which is a semi-vertical programme also aims at the above stated objectives more precisely, i.e., by achieving 70% case detection with 3 sputum smear examinations and 85% cure rate with DOTS. So, RNTCP has to be expanded quickly to cover the entire population of the country at least by 2005 yet, RNTCP is implemented in about 219 districts so far including all the metropolitan cities covering a total population of 46%. A lot remains to be done for full coverage, leaving aside performance as shown below :

NTP & RNTCP coverage at the end of first quarter 2002

Total districts in India	548
NTP implemented districts	440
Districts offering SR + SCC	295
Districts offering SR only	145
RNTCP implemented districts (includes metropolitan cities)	219
Population covered	460 million

If we consider the secular epidemiological curve, it is obvious that it may take centuries to bring TB under control, without any interventions. Probably, today, the disease is in the descending limb of the curve and is entering the endemic phase.

WHO had defined, long time back, that TB can be considered to be under control only when the tuberculin reactors at the age of 14 years are less than 1% in the community or a country. This is almost impossible, even to ponder with the present state of population coverage and treatment facilities made available under the programme.

Ladies & Gentlemen, We have travelled a long way our journey of control of tuberculosis during the past 5 decades. But, the destination is very far off still. There is no other alternative but to continue our journey with determination, commitment and sincerity without any failure from our side by meticulously following RNTCP and rededication to our objectives.

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 * **B.C. Roy National Award** *
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 * The Dr. B.C. Roy National Award for the year 2002 has *
 * been conferred on Dr.S.P. Agarwal, Chairman, Tuberculosis *
 * Association of India, for his eminent contributions in the medical *
 * field. *
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 * Another notable awardee is Dr. Pratibha Narang, Dean and *
 * Professor of Microbiology, Mahatma Gandhi Institute of Medical *
 * Sciences, Sewagram and member, Editorial Board of the Indian *
 * Journal of Tuberculosis. *
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LEAVES FROM HISTORY - 15
THE UNION MISSION TUBERCULOSIS SANATORIUM
AROGYAVARAM, MADANAPALLE



Most outstanding among the Indian sanatoria, the Union Mission Tuberculosis (UMT) Sanatorium was jointly started in 1915 by a group of 7 missions. Dr. Vincent Campbell of the London Missionary Society, who had come to India after overcoming pulmonary tuberculosis outside the country, mooted the idea of setting up a sanatorium in south India. Later, many other missions too lent their support to the venture. First, a group of concerned missionaries met in Kodaikanal in 1908, where the idea took a definite shape. Then, on 24 October 1912, at the first Governing Body meeting, the technical leadership of the venture was assigned to a young Danish physician - Dr. C. Frimodt Moller - who advised them to look for 'a place far from a town, free from dust, not exposed to heavy rain - bearing winds, and with cooler nights to ensure good rest and sleep for patients'. Soon, Dr. Louisa Hart of the local Arcot Mission and some others located such a site near Madanapalle (Andhra Pradesh) where the group 'stood at the foot of a low hill in barren land and bowed their heads in prayer, that the site be given to them by the Government for starting the sanatorium'. His Excellency Lord Pentland opened the doors of the sanatorium to patients on July 19, 1915 and named the place as Arogyavaram.

Like a seasoned skipper, Dr.C. Frimodt Moller played the innings well. One after another, such persons joined the staff of the UMT Sanatorium who later rose to become outstanding tuberculosis workers. Dr. J. Gravesen, surgeon, joined in 1922 along with Dr. P.V. Benjamin appointed later as Tuberculosis Adviser to the Government of India; Rev. R.M. Barton, who came to the sanatorium in 1923 as a patient, laid the foundations of a quality bacteriological research laboratory; Dr.C. Frimodt Moller himself became Medical Commissioner in the Government of India in 1939, his son; Dr. J. Frimodt Moller pioneered landmark epidemiological studies near Madanapalle. and Dr.K.T. Jesudian streamlined the training of tuberculosis workers.

Training of tuberculosis workers was made a feature of the sanatorium activities from the very start. The T.D.D. post-graduate course for physicians, the first ever in India, was started in 1940 and became the forerunner of similar courses in several states in India. From 1947 onwards, the research and training programme was expanded and renamed as the Madanapalle Tuberculosis Campaign. Among other things, a BCG Vaccination programme was started with WHO support, which was later extended to the whole of India. Participation in the National Tuberculosis Sample Survey (NSS) of 1955-58, opening of the Rajkumari Amrit Kaur Tuberculosis Hospital in 1950 and a Children's Tuberculosis in Hospital in 1955 are notable milestones. In fact, till the start of the Tuberculosis Chemotherapy Centre in Madras, in 1955 and the National Tuberculosis Institute, Bangalore in 1958, the UMT Sanatorium remained the Mecca for all categories of tuberculosis workers in the country.

With the introduction of National Tuberculosis Programme (NTP) in 1962, the Governing Body decided in 1975 to convert this historic institution into a general hospital - Arogyavaram Medical Centre - in which capacity it continues to function as a medical institution of excellence. Yet, 200 of the 340 beds still serve tuberculosis patients. Like a legendary army general, an institution of this kind never dies, it just fades away.

JUDGING EPIDEMIOLOGICAL TREND OF TUBERCULOSIS - A SITUATIONAL REVIEW IN CHENGULPET AREA OF TAMILNADU

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The Tuberculosis Prevention Trial, Madras, then part of present Tuberculosis Research Centre (TRC), Chennai, had conducted an epidemiological study, starting in 1968 to measure the protective effect of BCG vaccination against pulmonary tuberculosis in the Chengulpet area of Tamil Nadu. Its seven and a half year follow-up report had revealed ineffectiveness of BCG vaccine in preventing adult forms of tuberculosis¹. A subsequent fifteen year follow-up report of the trial too was brought out by the TRC². Recently, the TRC has published a comprehensive epidemiological situational report providing an insight into the trend of tuberculosis in the Chengulpet area during the study period³. The present paper reviews the last named report from various angles keeping in view two similar studies carried out in the country, one in rural areas of Bangalore⁴ district and the other in New Delhi⁵ focussing on some factors that may be kept in view when judging epidemiological trend.

METHODS

In the report under discussion, the prevalence of tuberculosis cases has been estimated on the probability of cases arising out of different radiological risk groups. This approach needs a second look, in relation to the points raised below:

(i) In longitudinal epidemiological surveys where radiographic screening of a population is carried out, different proportions of the X-rayed population are identified as abnormal, from survey to survey, on the basis of X-ray reading. Besides, within these groups, different proportions of abnormal categories are also identified with different risk of breakdown. In the report under review³, it is seen that the proportions of abnormal (X-ray abnormal) had considerably reduced after the 1979-81 period, varying from 827 to 1811 per 100,000. It may not be rational, therefore, to assume, as has been done, that the proportions of abnormal, as also the proportion of

different radiographic categories among absentees (non-response group), would always be similar to those in the examined group. This point needs to be looked into for ensuring comparability between different groups.

(ii) Case prevalence among absentees has been estimated on the proportion of the symptomatics, X-rayed or not, and the probability of cases arising out of these. But the proportion of symptomatics may not have remained the same for all the surveys since the presence of symptoms was recorded only in 1972.

(iii) It is not made clear whether the probability of cases arising from various categories was developed separately for each respective survey, or was extrapolated from the data of the second survey. It appears that the estimate of prevalence by the technique used stands higher than the observed prevalence (by about 20%) in each of the surveys, even though standardized against the distribution of population in the first survey.

For judging epidemiological trend, it is important to ensure that there is adequate consistency in demarcating population groups observed, from survey to survey.

Interpretation of Trend

In the interpretation of epidemiological trend of tuberculosis, it is also important to keep in mind the following points:

(a) There appears to be no change in the culture positive prevalent cases (C+) comprising smear positives (S+) and smear negatives (S-) from I to IV survey in the cited report³. This was so even upto surveys V, by age and sex for males, except for those 10-24 years old, in I-IV survey period, and for females aged 10-24 years between III and IV survey only. Therefore, the overall trend had remained the

same till IV survey, and this interpretation is in line with the observations from the Bangalore rural area⁴. From survey V onwards, a decline is observed in prevalence cases, mostly among the 10-24 years old, and to a lesser extent in persons aged 25-44 years, in both sexes. But the decline is not associated with a shift in prevalence cases to older age groups, as reported from the Bangalore rural area⁶. The authors should have examined this unusual nature of the decline, seen all of a sudden after the IV survey among the younger age group and in females. Of course, they have cited improved socio-economic condition of the people (without proper evidence) and a lower rate of breakdown among the X-ray abnormal, ostensibly owing to the extension of anti-tuberculosis treatment of this group.

The other hypotheses for epidemiologists to ponder over are:

(i) The lower prevalence of disease found in the younger age group could alternatively and more reasonably be attributed to effectiveness of BCG vaccination rather than to socio-economic and other factors. However, this needs to be viewed in the light of the earlier observation that the influence of BCG vaccination on the trend of tuberculosis did not exist during the earlier surveys in the Chengulpet area¹. The above projection on trend for the area probably needs reconsideration, especially in the light of about 20% protection offered by vaccination, as reported now².

(ii) In the Bangalore study⁶, it was found that the prevalence of C+ (S+/S-) cases had remained the same, as per the natural dynamics of tuberculosis (34% of the cases get removed from the pool through death and natural cure, and the same proportion gets added during the course of the year through incidence). An exercise of this nature, by age group, could help in understanding the probable cause for the decline, as observed in the 10-24 year age group.

(iii) Additionally, the composition of prevalence cases on the basis of breakdown into cases from different epidemiological risk groups,

by age and sex, in the manner attempted elsewhere could provide further insight into the trend⁷.

(iv) Report from the New Delhi survey shows no change in the prevalence cases over a period of 30 years in an area where the population and the cases diagnosed at various surveys were offered highly effective domiciliary treatment⁵. It was hypothesized the no change situation that could have been due to gross changes occurring in the study population due to large scale selective migration, mostly immigration of younger people, ostensibly for economic reasons. In the study under review, the decline is observed among the younger age group and among females. This could be attributed to improved awareness and a better action-taking behaviour, especially likely in the younger population group, perhaps due to frequent visits by the BCG study staff to the area. But, why did it take place so selectively? The higher awareness could as well be the result of increased health awareness in younger women caused either by maternity and child welfare services or due to immunization related activities (EPI). Not to be ignored is the fact that the study team had always ensured adequate supply of anti-tuberculosis drugs to the area health services. The higher awareness and action-taking behaviour was probably sustained due to better health service delivery and interaction with research workers. Thus, the longitudinal epidemiological study ended up causing changes which it was seeking to measure.

(b) The report³ shows that there was no change in culture positive, smear positive prevalence cases (C+S+) while the report from Bangalore rural area⁶ shows a gradual decline in the proportion of C+S+ cases to the total C+ cases (C+,S+/S-), over a period of 23 years, even when the service delivery in that area was not adequate⁸. The efficiency of case finding and treatment in the Chengulpet area being certainly better, the lack of reduction in C+S+ cases and consequently of the total C+ cases (C+,S+/S-) is not understood, especially when the only C+ (S-) cases had declined. The lack of decline in prevalence of S+ cases requires a special consideration, as hypothesized below:

It is true that the lack of decline in Annual

Risk of Tuberculosis Infection (ARTI) and C+S+ cases is in agreement with the hypothesis that both are parametrically related. In that context, change not occurring in S+ cases is consistent with the hypothesis. However, in intervention situations, it is generally expected that following the fall in mortality rates, it is the S+ case prevalence which would decline first, taking precedence over decline in the incidence and risk of infection (ARTI), incidence of S+ cases, prevalence and incidence of C+ cases, presumably in that order. It defies logic as to how the C+ cases in Chengulpet had outstripped all other indices in registering a decline. An alternative consideration could be the possible changes that might have occurred over time in the methods of laboratory investigations, especially mycobacterial culture.

(c) In respect of the trend in incidence cases, though selective/passive case finding has been mentioned as a method in the study design, the fact that cases detected were included in incidence is not specifically stated as such. Thus, the method of computing incidence is substantially different from the other studies mentioned.

Besides, while averaging incidence from various groups for estimating the incidence, the observed rates under the placebo groups appear to have been extrapolated on to other two "arms" of the study group, namely those BCG vaccinated with normal strength and those with 1/10 of the normal strength. Probably, this was done due to the unrecognizable level of protection offered by BCG in any of the groups. Increase in the number of intervention variables in calculating average incidence not only makes it less comparable to other Indian studies but overlooks the fact that the objective, as originally planned, was not designed to measure epidemiological trend.

(d) It is not easy to comprehend how the Annual Risk of Tuberculosis Infection (ARTI) had not decreased in the study area even with decrease in prevalence and incidence of C+ cases from survey V onwards. Reason for this could possibly lie in the method of identifying the demarcation level of tuberculin induration between the infected and

uninfected. The demarcation level for 3TU PPDS & 1TU RT 23 with Tween 80 has been put at 12 mm & 9 mm respectively, following the conventional method³. These levels have been further substantiated by the distribution of tuberculin induration in culture positive cases diagnosed in the corresponding survey or the distribution among persons aged 35 years. In the Bangalore area, on the other hand, a gradual shift of demarcation level to higher levels (from 10 mm to 16 mm in IV survey) had been reported⁶. A high level of non-specific sensitivity is seen in both the areas. The shift of antimode to higher levels was attributed to a gradual increase in the proportion of children vaccinated with BCG having unidentifiable scar getting included in the 'no scar' group, from one survey to the next survey. In the Chengulpet area, on the other hand, two-thirds of the study population was vaccinated with different strengths of the vaccine at the start and later the area came under regular immunization (EPI/UIP) programme. Both the situations being similar, the scarless group confounding the demarcation level cannot be overlooked in the Chengulpet area.

Non Specific Infection Factor

The distribution of tuberculin indurations in the general populations in the western countries gives a bi-modal distribution. When high prevalence of non-specific infection is found in an area, as in India, a bi-modal distribution of tuberculin indurations may not be expected. In fact, in recent times, segregation of true reactors in the distribution of indurations by the technique of 'Mixture Analysis' has been attempted. The intermediate range in the distribution of tuberculin indurations, generally attributable to infection caused by mycobacteria other than tuberculosis (MOTT) could be between 7-14 mm, with the overall distribution in the range of 0-30+ mm. Therefore, when a lower demarcation level is taken, as was done in Chengulpet, a proportion of specific reactors is likely to be included in the non-specific group. The proportion of the non-specific group confounding the estimation of specific reactors as well as the strength of the vaccine used for the original study and time interval between vaccination and the time of testing

are likely to alter the level of demarcation with time. This would be in addition to BCG scarless group influencing the estimation of specific reactor group. Could all or some of these considerations explain the finding in the Chengulpet area where no decline in ARTI was observed along with a decline in C+ (S+/S-) cases to avoid an epidemiological inconsistency? In the Bangalore survey⁶, ARTI was found to decline corresponding to the decline of C+S+ cases. The shift of demarcation level to higher levels, from one survey to the next in the Bangalore study was made according to the successive distributions, and explained on the basis of increasing number of scarless BCG vaccinated persons being included among the unvaccinated. This appears to be the crucial difference with the TRC study³.

In the light of the above discussion, it appears that time has come to modify the conventional method for identifying the level of demarcation in the distribution of tuberculin indurations. A review of the Bangalore longitudinal study shows that the proportions of both prevalence and incidence cases were highest among those whose reaction size was 16 mm & above, suggesting that 14 mm+ / 16 mm+ levels could be the demarcations for transverse/longitudinal readings, respectively.

(e) Raj Narain⁹ had reported that tuberculosis cases arose mostly from the group that had shown an increase of 16 mm and over on repeat testing with initial reaction below 10mm to 1 TU RT 23. The distribution of current tuberculin reactions among the diagnosed cases, if available on survey record in the Chengulpet area, could be studied. Tuberculin reactions observed on a preceding occasion, among the cases, could also be analyzed to investigate the source of the cases, according to induration size, especially among children below 14 years of age. If a sufficient number of cases is not available in any survey, cases from different surveys could be cumulated for studying the flow of cases, from groups with different characteristics in the preceding surveys.

CONCLUSION

Study of tuberculosis trend is an area of renewed interest to epidemiologists the world over, especially in view of the resurgence of the disease in recent times. **The focus of the foregoing discussion is that judging of epidemiological trend in an area has to be based on consideration of a fairly large number of factors, often complex and interactive, gleaned from different studies. Unfortunately, longitudinal surveys have already been abandoned and no further knowledge may be added to what is known. The long term trend analysis now reviewed is doubly interesting to the present reviewer, since he was intimately associated with the BCG Trial in Chengulpet during its initial stages.**

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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 programme¹. 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 India¹². 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.

*This report was prepared by Dr.S. Radhakrishna, former Director, Institute for Research in Medical Statistics, Madras Chapter(ICMR) who had primary responsibility for analysis of data and writing it up. Dr. Thomas R Frieden, Medical Officer(TB), WHO-SEARO participated in deciding design of analysis and writing of the report. Mr. R. Subramani, Senior Research Officer, Tuberculosis Research Centre, Chennai was responsible for data management and data output.

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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 India¹². The study area comprised Thiruvallur town and five panchayat unions (blocks) of Ellapuram, Kadambathur, Poondi, Thiruvallur and Thiruvallangadu. 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 population 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 Thiruvallangadu), two more surveys were undertaken, one in 1991-92 and the other in 1994-96, after an interval of 3.75 years¹³. 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 blocks¹⁴. In the two subset blocks (Kadambathur and Thiruvallangadu), 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°C, and para-nitrobenzoic acid test/catalase test).

Details of procedures and techniques employed for radiography, bacteriology and drug sensitivity have been described earlier¹². In brief, for all positive cultures and a control strain (H37Rv) in each batch, sensitivity 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 χ^2 tests for differences and trends in proportions, weighted regression analysis for estimating the annual rate of increase and standardization employing the direct method¹⁵ 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 1.

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 increase 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.

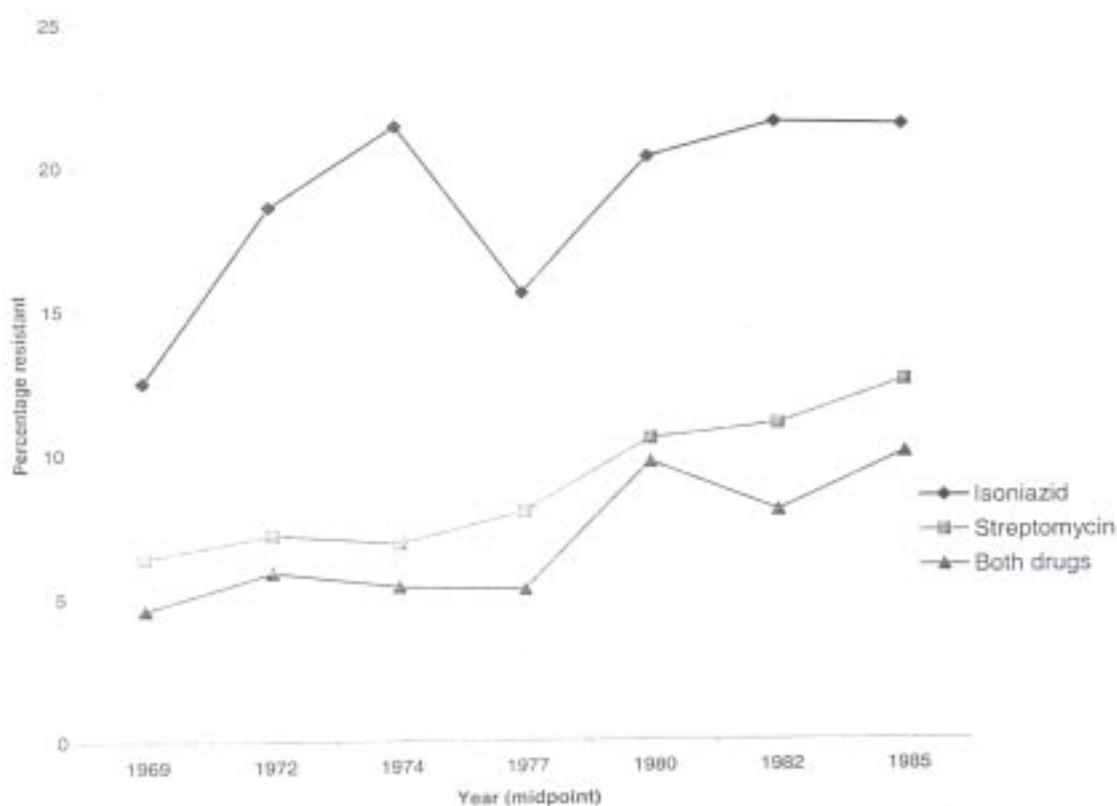


Fig.1 Initial drug resistance in prevalence cases in 5 blocks

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

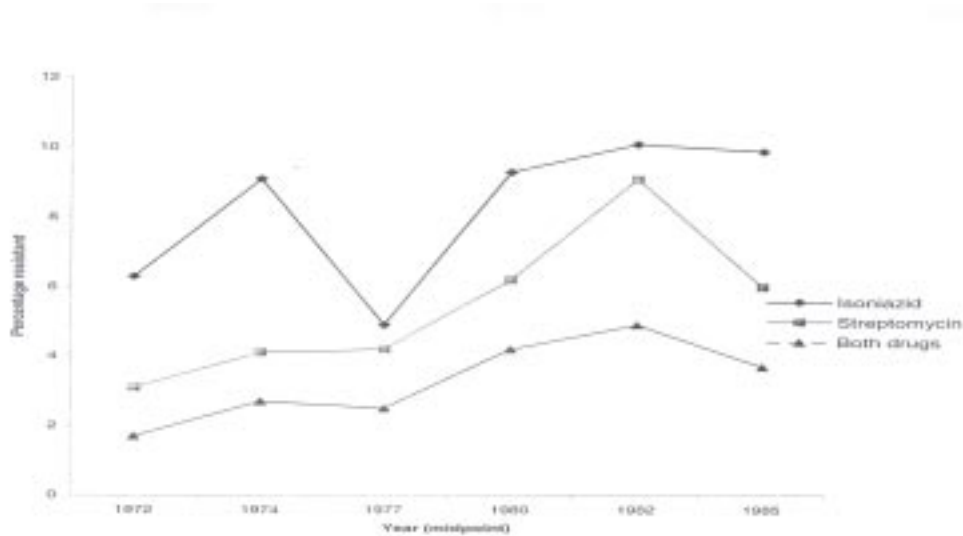


Fig 2. Initial drug resistance in incidence cases in 5 blocks

cases, resistance to Isoniazid increased from 10.6% in 1968-70 to 23.4% in 1981-83 ($P=0.02$), to 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 streptomycin			
		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 to 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	9.9
	45+	3132	15.1	525	13.0	2839	7.4	484	6.6	2839	5.0	484	5.5
Incidence surveys*	10-24	236	13.1	102	9.8	266	7.9	119	6.7	266	4.9	119	3.3
	25-44	1063	11.3	323	13.0	1234	7.3	380	5.8	1234	4.0	380	3.3
	45+	1265	6.4	312	9.9	1476	3.8	356	5.3	1476	2.4	356	3.3

*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				
			Resistant(%) to following drug(s)		Total patients		Resistant to following drug(s)		Total patients		
			INH	Both	Strep	Both	INH	Strep.	Bot	Both	
Prevalence	1971-73	99.6	5.7	2.0	406	3.0	2.0	284	36.6	13.4	11.1
	1991-92	99.7	12.6	5.5	254	9.4	37	37	27.0	21.6	18.1
	1994-96	100.0	5.1	0	129	3.1	0	109	18.3	10.1	7.1
	1999-01	98.8	8.5	N.A.	400	N.A	N.A.	101	12.9	N.A.	N.A.
Incidence	1971-73	90.7	4.2	1.6	575	2.8	68	68	23.5	5.9	2.9

INH=Isoniazid Strep.=Streptomycin

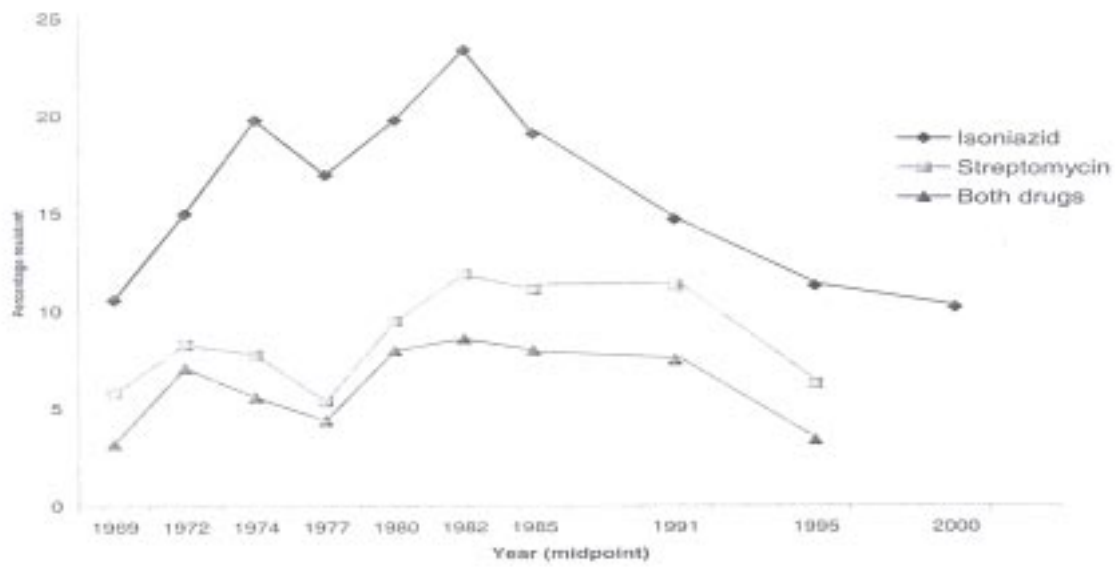


Fig.3. Initial drug resistance in prevalence cases in 2 blocks

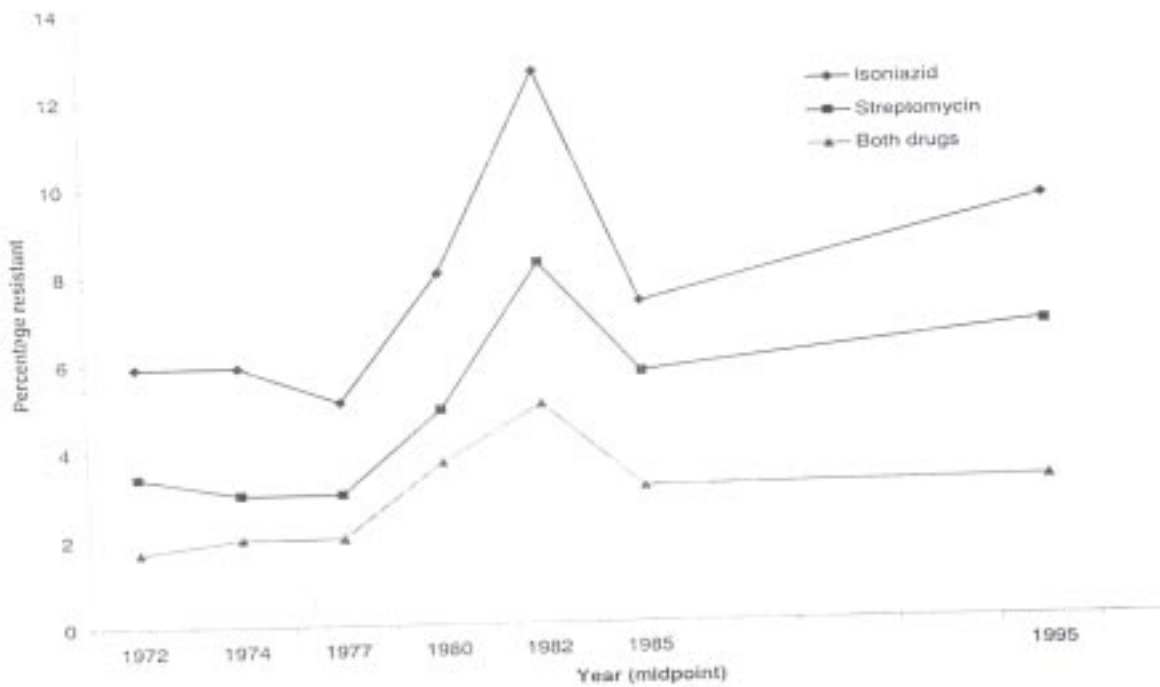


Fig. 4. Initial drug resistance in incidence cases in 2 blocks

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 country² 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 Chennai⁴, Gujarat⁵ and North Arcot district¹¹ 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 country³ 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 Bangalore⁶, Kolar⁷, New Delhi⁸, Jaipur⁹, Pondicherry¹⁰, North Arcot district¹⁰ and Raichur district¹¹ 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 Streptomycin 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 Korea¹⁸ 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 resistance¹⁹.

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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I, Dr. M.M. Singh, Vice-Chairman of the Tuberculosis Association of India, 3, Red Cross Road, New Delhi - 110 001, hereby declare that the particulars given above are true to the best of my knowledge and belief.

M.M. Singh
On behalf of the Tuberculosis Association of India.

TREATMENT SEEKING BEHAVIOUR OF CHEST SYMPTOMATICS

Ashoo Grover¹, Rajesh Kumar² and S.K. Jindal^{2*}*(Original received on 20.8.2002; Revised version received on 20.12.02; Accepted on 18.1.2003)***Summary:****Setting:** Departments of Community Medicine and Pulmonary Medicine, Post-Graduate Institute of Medical Education and Research, Chandigarh**Objective:** To assess the treatment seeking behaviour of chronic chest symptomatics**Methods:** Identification of chronic chest symptomatics by a physician in randomly sampled rural and urban population groups and interviewing them by means of a semi-structural questionnaire. Chronic chest symptomatics were those having one or more of the following symptoms for more than a month: cough, expectoration, breathlessness, blood in sputum, wheezing, pain in chest**Results:** Among 1659 adults (15-65 years), 12.0% were having chronic chest symptoms. Out of 192 chronic chest symptomatics, 19.0% had not taken any treatment. Of those who took action initially, 52.5% had taken home remedies and 47.5% had relied on self-medication. Majority of them (82.0%) later switched over to a health care provider. Delay in seeking treatment varied from 7 to 365 days (mean 56.6, SD 23.5). Thirty four percent changed their health care provider more than two times. At the time of survey, 20.3% were taking treatment from unqualified medical practitioners, 18.2% from allopathic practitioners, 2.0% were in the care of government hospitals, and 8.3% were being treated by practitioners of Indian systems of medicine, and homeopathy. In rural area, major source of care was unqualified medical practitioners and in urban area, majority sought treatment from private allopathic doctors. Eighteen percent were still not satisfied with their current treatment.**Conclusion:** The study shows that most of the chronic chest symptomatics start with home treatment or self-medication, and there is considerable delay in seeking treatment from a proper health care provider.**Key Words:** Health seeking behaviour; Treatment; Action-taking; Health care providers

INTRODUCTION

Chest diseases constitute an important cause of morbidity all over the world.¹ They have become more important lately as some other diseases which used to be major killers in the past are now on the decline due to transition from agricultural to industrial economy². In India, the common chest diseases include bronchitis-empyema syndrome, asthma, and tuberculosis.

Poor compliance with the prescribed treatment is a common problem in persons having chest diseases. Patients' adherence to treatment depends on many psychological and sociological factors including age, education level and patients' own ideas about the disease³. The aim of the physician is to increase patient's perceived level of self control and self-esteem so that, ultimately, patient is able to cope with the daily consequences

of the disease⁴.

Not all persons suffering from chest diseases have symptoms, nor do all symptomatic subjects present themselves at health centres for diagnosis and treatment. The prevalence of symptoms and treatment seeking behaviour of symptomatics provide vital information for planning and organizing national health care delivery system⁵. Moreover, the knowledge and perception of patients about their health care needs have been shown to provide valuable insights into the decision making processes.⁴ The term 'treatment seeking behaviour' refers to actions taken by a person for seeking help from another person or agency in the community. In India, where a variety of medical facilities exist, it would be of interest to study the total spectrum of treatment seeking behaviour, including types of actions taken by the sick people.

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MATERIAL AND METHODS

This study was conducted in randomly chosen two villages of Panchkula district in Haryana, located at a distance of about 5 km from a Community Health Centre, and two urban sectors of Chandigarh City about 3 km from a hospital. Systematic random sampling technique was used to select households in them. All individuals aged 15-65 years in the selected households were interviewed to find out if any of them had one or more of the following chronic chest symptoms for more than a month: cough, expectoration, breathlessness, blood in sputum, wheezing or pain in chest. The first house was selected randomly in each study location, and, using a definite sampling interval, other houses were visited till the required 50 chronic chest symptomatics were identified in each location. A total of 1659 adults were thus interviewed in 433 households to enrol 200 chronic chest symptomatics.

A semi-structured interview schedule was pre-tested and used for data collection (Appendix). The schedule was designed for collecting information on family composition, respiratory symptoms and the treatment seeking behaviour of those who had chronic chest symptoms. The chronic symptomatics were interviewed at home for recording treatment seeking behaviour, mostly in the evening or on a holiday/Sunday. Three repeat visits were made to contact those who were not available on first or second visit. Eight persons, (3 urban and 5 rural) were not interviewed as they did not agree for interview despite explaining the purpose of the study. A community physician, who had been trained in qualitative research methods conducted the interviews. The data were coded and analysed using EPI-Info version 6.02. χ^2 test was used to test statistical significance.

RESULTS

Table 1 shows the distribution of chronic chest symptoms among adults (15-65 years) according to area of residence. Chronic chest symptoms were found among 12.0% of the 1659

persons. As shown in Table 2, the prevalence of symptoms was similar in urban (13.1%) and rural (11.2%) populations ($p=0.2$), significantly higher among 45-65 years-olds (22%) than in the 15-44 years age group (7.6%) ($p<0.001$). Significantly, more males (13.6%) had chronic chest symptoms than females (10.4%) ($p<0.04$). The prevalence of symptoms also varied according to educational level. It was 17.8%, 11.5% and 7.4% among the illiterate, up to high school, and above high school groups respectively ($p<0.001$). Though labourers and agriculturists had higher prevalence than those in business, service, or housework, these differences were not statistically significant ($p<0.06$).

Treatment seeking behaviour is shown in Table 3. Out of the 192 chronic chest symptomatics interviewed, 63.5% were aware of the presence of some chest disease; only 32% of those who had just cough considered themselves to have a disease, whereas 82% of those having blood in sputum perceived themselves to be sick. Cough with breathlessness was perceived as a serious symptom by 70.5% and chest pain by 61%.

Eighty one percent of the respondents had taken some action to relieve their symptoms. Significantly higher proportion of the urban (86.6%) respondents had taken action at the onset of symptoms compared to those in rural area (75.7%) ($p=0.05$). Of those who took action at the onset of symptoms, 52.5% had taken home remedies and 47.5% had relied on self-medication. Home remedies were used more frequently in urban areas whereas self-medication was more frequent in rural area ($p<0.05$). *Ajwain* was the preferred home remedy followed by clarified butter (*ghee*) in rural areas whereas urban people mainly used *trifla* and *khas-khas*. In both rural and urban areas, cough syrups and cough lozenges purchased without any prescription were used frequently.

Many of the chronic chest symptomatics persisted with home remedies/self medication for some period of time before switching over to other sources of health care. The delay in contacting a formal health agency extended from 7 to 365 days: mean delay was 56.6 days (SD 23.5 days) depending

Table 1. Distribution of chronic chest symptoms among adults according to area of residence

Symptoms*	Rural (N-893)		Urban (N-766)		Total (N-1659)	
	No.	%	No.	%	No.	%
Cough	76	8.5	62	8.0	158	9.5
Sputum	48	5.3	37	4.0	85	5.1
Breathlessness	40	4.4	55	7.1	95	5.7
Wheeze	9	1.0	22	2.8	31	1.8
Blood in sputum	6	0.6	6	0.7	12	0.7
Chest pain	7	0.7	12	1.5	19	1.1
Any or a combination of above symptoms	100	11.2	100	13.1	200	12

*Multiple symptoms; hence numbers do not add to 100
No significant differences between urban and rural areas

Table 2. Prevalence of chronic chest symptoms among adults according to socio-demographic characteristics

Socio-demographic characteristics	N	Chest Symptomatics	Prevalence %	P value
Locality				
Rural	893	100	11.2	0.2
Urban	766	100	13.1	
Age				
15-44 years	1201	91	7.6	<0.04
45-65 years	458	101	22.0	
Sex				
Male	852	116	13.6	< 0.04
Female	807	84	10.4	
Education				
Illiterate	366	65	17.8	< 0.001
Upto high school	756	87	11.5	
Above high school	537	40	7.4	
Occupation				
Household work	596	56	9.3	0.06
Students/Unemployed	315	31	9.8	
Service	317	40	12.6	
Business	129	17	13.1	
Labour	109	18	16.5	
Agriculture	193	30	15.5	

upon the severity of symptoms and/or ability to tolerate a particular symptom. The extent of the delay was higher in rural compared to urban areas but it was not statistically significant. At the time of the survey, 128

(82%) respondents had switched over to a health care provider but 18% were still continuing with home remedies and self-medication. Contacts with health care providers were with unqualified medical practitioners (21.9%), private allopathic

Table 3. Treatment seeking behaviour of chronic chest symptomatics

Behaviour	Rural			Urban			Total		
	N	No.	%	N	No.	%	N	no	%
Perception of disease	95	63	66.3	97	59	60.8	192	122	63.5
Primary action taken	95	72	75.7	97	84	86.6*	192	156	81.3
- Home remedy		31	43.0		51	60.7*		82	52.5
- Self medication		41	56.9		33	39.3*		74	47.5
Initial contact made	72	61	84.7	84	67	79.7	156	128	82.0
- with Unqualified person		23	37.7		4	5.9*		27	21.9
- with Private allopathic		8	13.1		36	53.7*		44	34.3
- with Alternate medicine		4	6.5		12	17.9*		16	12.5
- with Government centre		22	36.0		19	28.3*		41	32.0
Contact made out of locality	61	38	60.2	67	39	58.4	128	77	60.1
Changed health care provider	61			67			128		
-Once		19	31.1		28	41.7		47	36.7
-Twice		23	37.7		19	28.3		42	32.8
- More than twice		19	31.1		20	29.8		39	30.4
Complied with treatment	61	56	91.7	67	45	67.1*	128	101	78.9
Treatment still continuing	61	59	90.6	67	54	80.6	128	113	88.2
Satisfied with treatment	59	51	86.4	54	28	50.1*	113	79	70.0
Difficulty in getting relief	95			97			192		
- Very much		8	8.4		4	4.1		12	6.2
- Much		7	7.3		11	11.3		18	9.3
- Not so much		34	35.7		37	38.1		71	36.9
- Not at all		46	48.4		45	46.3		91	47.3

*p<.05 between rural and urban areas

doctors (34.3%), government hospitals (32.0%), and practitioners of alternative medicine like *vaidya*, *hakeem* (12.5%). Significantly higher proportions of rural respondents consulted unqualified medical practitioners whereas a majority of consultations in urban areas were with private allopathic doctors. Thirty three percent had contacted a health care provider on their own and 66% were persuaded by their relatives or neighbours / friends. In rural areas, neighbours played a major role in doing so whereas in the urban areas parents played a significant role for the young, and the spouses often persuaded the elderly. A few started taking such treatment from information gathered through newspapers and/or television.

Sixty percent of the respondents had to go to health care providers out of their localities. Thirty percent had changed the health care provider agencies three to ten times; frequency of change was similar in urban and rural areas. No relief from symptoms or recurrence of symptoms was the major factor in changing the health care agency in 55.6% and 19.9% cases respectively, other reasons were: transfer of doctor, referral by the doctor (13.6%); lack of money (7.4%); long distance from place of residence (2.5%); and attitude of the doctor (5.9%).

Twenty-seven respondents (21.1%) reported that they discontinued treatment on their

own, significantly lower in urban than rural areas, 5 because they felt that their symptoms had subsided, 11 had no relief from symptom, 6 could not afford the cost of treatment, 2 had unpleasant side effects with drugs, and 3 without any particular reason.

Three-fourth of the subjects had purchased their medicines, 11% got the drugs free from government centres and 14% had obtained them from multiple sources. Seventy percent of them were satisfied with their current treatment but 30% wanted a change in their treatment. More rural people were satisfied with their treatment provider compared to urban respondents ($p < 0.01$). While 47.3% subjects did not have any difficulty in getting relief from symptoms, 36.9% had 'some' difficulty; 9.3% had 'much' difficulty and 6.2% had to struggle for getting their symptoms relieved. At the time of the survey, a significantly higher proportion of rural respondents were taking treatment from unqualified medical practitioners (63.7%), whereas a majority in urban areas utilized private allopathic doctors (56.3%); the utilization of government doctors was poor (20%) in both rural and urban areas.

DISCUSSION

Despite the growing awareness of the implications of disease, health and illness behaviour, empirical research related directly to treatment seeking behaviour is little⁶⁻⁸. Among the treatment behavioural aspects, most investigators use variables such as places that persons contacted for help, delay in seeking treatment and the number who continue with treatment or discontinue it. There has hardly been any attempt to study the personal variables such as perception of having a disease and the primary action taken for relief of symptoms, which are likely to influence the treatment seeking behaviour and its pathways. In the present study, an effort has been made to study the perception and the primary actions taken by the chronic chest symptomatics.

Cough, the commonest symptom (9.5%) in our study (Table 1), is a frequently reported problem in general practice as well as in hospitals. Its

prevalence reportedly varies from 5% to 40%⁹. Chronic chest symptoms are more prevalent in the higher age groups and among males²⁻¹⁰.

In the present study, around two-thirds of chest symptomatics were aware of having 'some' chest disease. The extent of treatment seeking depends upon one's perception of the symptoms as a manifestation of some disease. Some of the symptoms are considered as 'normal', such as dry cough only in the morning or cough with sputum among the elderly, and breathlessness among females while doing household chores.

Mostly, primary action takes the form of home remedy or self-medication (Table 3). Different home remedies are taken for different chest symptoms, e.g., for cough, people usually take *ajwain*, honey, ginger, *mishri*, *jushanda*, *zeera tea*, tree leaf, and tea, whereas for breathlessness there are no home remedies. Types of home remedies also vary from area to area. Urban people prefer taking *jushanda*, *elaichi*, *desi ghee*, *badam ghee*, *khas khas*, while the rural subjects prefer *ajwain*, honey, ginger etc.

There was a considerable mean delay (56.6 days) in seeking health care from outside providers because of recourse to home remedies/self medication in both urban and rural areas. Non-specific symptoms such as weight loss, dyspnoea and dry cough, apparently cause little concern in patients and even haemoptysis was tolerated for a mean delay of 50 days⁵.

About 21% of patients did not complete the prescribed treatment. Several authors have studied compliance with prescribed treatment^{9,11-16} and have found adherence to prescribed treatment being influenced by age, gender and socio-economic status. For example, chest symptoms were generally considered as 'normal' by elderly people and even by their family members.

Among rural respondents, source of health care was mostly unqualified private medical practitioners whereas in urban area private allopathic practitioners were the main source. Government

health services were utilized by only 32% even though located within a distance of 5 km. The observed urban/rural differences in treatment seeking behaviour reflect the socio-economic differences in the two groups; lower availability of qualified medical practitioners in rural areas could be another reason. **A significant finding of the study is shopping for health care providers. Chronic chest diseases, such as asthma, chronic bronchitis and tuberculosis are of such a nature and course which make patients switch sources of treatment in the hope of getting a cure. Findings of this study suggest that health services as well as private medical practitioners should initiate steps to increase awareness in the community about the nature of chest symptoms, their probable consequences, if left untreated, and the availability of health centres where chest symptomatics can contact soon after the onset of chest symptoms.**

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INTERVIEW SCHEDULE FOR CHEST SYMPTOMS**Annexure I****1. Cough**

- a) Did you have troublesome cough in last 30 days? Yes/No
- b) Do you have cough on most days for as much as 3 months of the year? Yes/No
- c) For how many years have you had this cough? Number
- d) Do you cough during any particular season of the year, if yes, which season: Yes/No
1. Summer
 2. Winter
 3. Any other (specify)?

2. Sputum

- a) Do you usually bring up sputum from your chest for last 30 days. Yes/No
- b) Since how long have you had sputum from your chest?
1. <1 month
 2. 1-6 months
 3. 6 months- 1 year
 4. >1 year
- c) What is the colour of the sputum raised?
1. Yellow
 2. White
 3. Blood tinged
 4. Any other (specify)

3. Wheezing

- a) Does your breathing ever sound wheezing? Yes/No
- b) Have you had a feeling of tightness in your chest? Yes/No
- c) How frequently does wheezing occur?
1. Daily
 2. Nightly
 3. A few times per week
 4. A few times per month
 5. A few times per year

4. Breathlessness

- a) Do you get short of breath with normal walking ? Yes/No
- b) Do you get short of breath with hard work? Yes/No
- c) Are you awoken up from your sleep because of breathlessness or cough? Yes/No

5. Haemoptysis

- a) Have you ever coughed up blood from your chest? Yes/No
If yes, how many days ago it happened last? _____
- b) Since how long did you blood in your sputum? _____

6. Chest pain

- a) Did you ever had chest pain? Yes/No
If yes, how many days ago it happened last? _____
- b) Since how long did you have chest pain? _____

7. Have you ever had some chest disease in last 3 years, for which you had to leave your daily routine activities? Yes/No

Investigator's remarks:

- Chronic chest symptomatic Yes/No
- If yes, clinical impression about diagnosis _____

Treatment Seeking Behaviour

1. Do you think that you are having any chest disease? Yes/No
 Describe what did you do to have relief from the symptoms.
2. What type of treatment did you take for relief?
 1. Home remedy
 2. Exercises
 3. Medicines
 4. Any other, specify
3. Who had suggested to you to take above treatment?
4. If home remedy was used, what was the type of home remedy used?
5. For how long did you try the above said treatment?
6. Were you getting relief from that treatment?
7. Did you switch over to some other treatment? Yes/No
 If yes, whom
 1. RMP
 2. Qualified doctor (Allopathic or Ayurvedic)
 3. Govt. hospital/dispensary
 4. Vaidya/ Hakim/ Indigenous treatment
 5. Charitable hospital
 6. Religious/Faith healers
 7. No help sought so far
8. Who suggested to you to contact above agencies ?
9. Did you have to go out of your locality for this agency ? Yes/No
 If yes, how far is this place?
10. Did you complete the advised treatment? Yes/No
 If not, why?
11. Did you have to change your doctor for the treatment of same disease? Yes/No
 If yes, why
12. How many times have you changed your doctor?
13. Why have you changed your help givers, so many times?
14. Have you tried faith healers/religious healers? Yes/No
15. If yes, who suggested this?
16. From where are you currently taking the treatment ?
 1. RMP
 2. Qualified doctor (Allopathic or Ayurvedic)
 3. Govt. hospital/dispensary
 4. Vaidya/hakeem/indigenous treatment
 5. Charitable hospital
 6. Religious/Faith healers
17. Who had suggested to you to go to this practitioner?
18. What is the type of treatment provided to you from this agency?
19. Are you satisfied with the treatment provided by this agency?
20. From where did you take the medicines?
 1. Government
 2. Private
21. Did you shift over to private purchase from govt. supply? Yes/No
 If yes, why?
22. How much have you struggled for the treatment of your illness?
 1. Very much
 2. Much
 3. Some
 4. Not at all

TUBERCULOSIS ALTERING ERYTHROCYTE MEMBRANE TOPOLOGY - A LECTIN HAEMAGGLUTINATION STUDY

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Summary:

Background: A factor of great importance in the inflammatory process is the physical interaction between the circulating cells and the blood vessel endothelium. This critical association is mediated by an array of cell-surface adhesion molecules. Glycoconjugates play important roles in cellular functions such as antigen presentation and cell adhesion which may be modulated in patients with lung disease due to alteration in cell membrane glycoproteins.

Methods: Because carbohydrate residues can be recognized by specific lectins, *Pedilanthus tithymaloides* agglutinin-lectin (PTA-lectin) haemagglutination titres obtained from patients were compared with the PTA-lectin binding properties of erythrocytes from healthy volunteers.

Results: Haemagglutination titres from tuberculosis patients were significantly higher than healthy subjects. Compared with untreated patients, the treated patients showed statistically significant shifting of the final titres towards values in healthy persons. Our finding shows that in tuberculosis, pathologically altered erythrocytes membrane determinants differ from the normal cell membrane determinants, in their carbohydrate contents, as reflected by haemagglutination titre against galactose specific PTA-lectin.

Conclusion: Altered expression of surface carbohydrate residues of erythrocytes caused by the inflammatory process in tuberculosis may be due to either the unmasking of galactose residues, non-enzymatic glycosylation, absorption of bacterial polysaccharides on erythrocyte membrane or the effect of toxins from the tubercle bacillus.

Key words: Erythrocyte membrane, Tuberculosis, Lectin, Haemagglutination

INTRODUCTION

The constituents of tubercle bacillus induce numerous pathogenic effects. Studies on cellular components, such as reticuloendothelial cells suggest that in tuberculosis, alterations in surface adhesion molecules of cells may take place¹. Among the cellular components, erythrocytes are continuously subjected to sheer forces and erythrocyte membrane topology may be altered during the inflammatory processes². Agglutination with lectins is of use for studying changes on cell membrane during physiological and pathological processes³. Its study continues to yield important insights into our understanding of erythrocyte membrane.

MATERIAL AND METHODS

The following studies were carried out in the Department of Biochemistry, Dr. V.M. Medical College, Solapur between June 1997 and Dec 1998.

A total of 172 venous blood samples taken from 91 untreated smear positive tuberculosis cases, 20 treated smear negative tuberculosis cases and 61 healthy control subjects (age 25 to 55 years and sex matched) were studied. All the blood samples were collected from the TB OPD and IPD of S.C.S.M. General Hospital, Solapur. Each tuberculosis patient was examined by at least three sputum smears and confirmed by expert physicians and microbiologists.

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The PTA-lectin was isolated and purified in the departmental research laboratory from the latex of *Pedilanthus tithymaloides* plant (family *Euphorbiaceae*). The lectin was screened for its physicochemical properties and confirmed to be specific for galactose and galactose containing disaccharides⁴. The protein concentration of PTA-lectin so prepared was determined by Lowry's method⁵. Haemagglutination assays were carried out in microtitre plates and final titres were calculated according to dilution of lectin³.

Isolation and purification of PTA-lectin

Latex Collection - 5 ml of latex from *Pedilanthus tithymaloides* plant was collected, by making an incision 0.5 to 1 mm deep on the plant stem with a clean knife, into a beaker containing 95 ml of phosphate buffer saline (PBS) of pH 7.4.

Purification - 5% diluted latex was frozen and thawed thrice and centrifuged at 3000 RPM for 30 min. The supernatant was taken, the pH of the supernatant was adjusted to 5.0 with 0.1M acetic acid and centrifuged as above. Supernatant was collected again and its pH was adjusted to 8.0 with 1.0M sodium hydroxide. The resulting product was again centrifuged as above and supernatant was subjected to 80% acetone treatment and centrifuged at 3000 RPM for 30min. Supernatant was discarded and the precipitate was dissolved in minimum volume of PBS (pH 7.4) in a beaker. The beaker was then kept in 70°C water bath for 30 min. After the heat treatment, it was centrifuged at 3000 RPM for 30 min.

The precipitate was discarded and the purified liquid PTA-lectin was collected in a dry stoppered glass bottle and kept at 2°C - 8°C for further use.

Determination of protein concentration of Lectin - the protein concentration of lectin was determined according to the procedure of Lowry et al⁵; bovine serum albumin was used as standard.

Preparation of sample - Venous blood was collected in an EDTA bulb from patients and control subjects and centrifuged for 3000 RPM for 15min. Plasma and buffy coat were discarded and erythrocytes were washed three times with PBS (pH 7.4). The washed erythrocytes were collected and a 2% cell suspension was prepared for haemagglutination assay.

Visual haemagglutination assay - microtitre plates having 96 wells were selected; 0.1 ml of PBS (pH 7.4) was poured in 12 wells of first row, then 0.1 ml of purified PTA-lectin was added to first well and serial dilutions were made up to 12th well. To each well, 0.1ml of 2% cell suspension was added, mixed, and kept at room temperature for 1 hour. At the end of 1 hour, the haemagglutination result was examined visually.

The well in which complete haemagglutination had taken place was noted and protein concentration for that particular well was determined. The same procedure was followed for each sample including the controls. The final titre was expressed as units/mg protein.

Table 1. Distribution of study subjects according to gender and final titres

Group	Gender	Final titre Range Units/mg protein	Final titre Mean± SD Units/mg protein	p value
Controls (n=61)	Males (n=46)	24-86	52.3±13.7	NA
	Females(n=15)	35-76	51.9±12.3	
Untreated (n=91)	Males(n=69)	48-395	134.12±68.96	<0.001
	Females(n=22)	49-296	108.9±49.06	<0.001
Treated (n=20)	Males(n=15)	37-19	68.4±24.2	N.S.
	Females(n=05)	37-148	66.1±46.2	

N.A. = Not Applicable N.S. = Not Significant

Statistical analysis

The results were statistically analysed by using Student's 't' test and a P value less than 0.05 was considered statistically significant.

RESULTS

Table 1 shows the overall distribution of cases and controls according to sex and final haemagglutination titre. In the control group, males had a final titre range between 24 and 86 Units/mg protein (mean 52.3 ± 13.7) and females between 35 and 76 Units / mg protein (mean 51.9 ± 12.3).

In untreated tuberculosis patients, males had a final titre range of 48 to 395 Units / mg protein (mean 134.12 ± 68.95 - $P < 0.001$) while in females the final titre range was 49 to 296 Units / mg protein and (mean 08.9 ± 49.06 - $P < 0.001$). In the treated patients' group, males had the final titre range between 37 and 119 Units / mg protein (mean 68.4 ± 24.2 - $P < 0.05$). while females had a final titre range 37 to 148 Units / mg protein and (mean 66.1 ± 46.2).

We found statistically significant increase in the final titres in untreated patients' group in both the sexes as compared to the control group ($P < 0.001$). The treated patients' group showed a statistically significant shifting of final titre towards the control group in males ($P < 0.05$).

DISCUSSION

Mycobacterial immune responses involve recognition of antigen either by antibodies or by cell surface receptors on lymphocytes followed by generation and amplification of destructive effector mechanisms.

A significant role of complex carbohydrates on cell surface has been predicted, based on the change in chemical and organizational sites of membrane bound carbohydrates. Surface exposed

carbohydrates are, therefore, of great significance and it has become increasingly important to elucidate the exposed chemical structure of cell surfaces. Complex glycoproteins are reliable markers and lectins recognizing these macromolecules have been extensively used as biochemical and histochemical probes in cell biology and pathology⁶.

Under normal conditions, cell membranes and surface of endothelial cells bear repulsive negative charge. During inflammatory injury this negative charge gets decreased and removes the repulsion between circulating inflammatory cells and the vascular walls. It has been reported that the normal negative charge carried by the erythrocyte is reduced in inflammatory conditions. This effect is due to desialation of glycoproteins and exposure of galactose to exterior environment⁷.

Erythrocytes, thus, get adhered to endothelial surface during their passage through the area of inflammation. It is evident that one of the most important factors disturbing the flow in inflamed vessels is a change in the surface character of the blood cells and endothelium². Current concepts of cell surface organization suggest that change in the mobility and distribution of plasma membrane components as well as changes in their chemical composition may significantly alter the function^{8,9}, size, shape and life span of the cell¹⁰⁻¹².

With the functional significance of glycosylation on erythrocyte membrane in mind, we tried to study the carbohydrates linked to erythrocyte membrane. It has been demonstrated that unmasking of subterminal galactose residues of human erythrocyte, by enzymatic removal of sialic acid residues, increases the amount of peanut agglutinin bound to the cells by 20 to 40 fold. Further, it has also been reported that oxidation by galactose oxidase of galactose and N-acetyl galactose residues on the surface of human erythrocytes decreases the amount of soybean agglutinin bound, by up to 90%³.

Increased glycoprotein concentration in serum was observed in tuberculosis and this finding has a positive correlation with the severity of tuberculosis. Decreased levels appear to be a good

prognostic sign¹³. Non-enzymatic glycosylation (NEG) of tissue proteins, including an alteration in connective tissue has also been reported¹⁴.

It is implied that the health or overall state of well-being of an erythrocyte is being communicated through its membrane. Thus, all forms of derangements in erythrocytes would, in theory, be ultimately expressed as some alteration on the erythrocyte surface. With the help of galactose-specific PTA-lectin, we tried to establish baseline haemagglutination titres with PTA-lectin binding properties of erythrocytes in tuberculosis patients.

In conclusion, altered erythrocyte agglutination patterns with PTA-lectin may be due either to unmasking of galactose, or N-acetyl galactose, non enzymatic glycosylation, adsorption of bacterial polysaccharides on erythrocyte membrane or may be due to effects of toxic products from the tubercle bacillus during inflammatory responses. After treatment, shifting of haemagglutination titre towards control may be due to the increasing normal well-being of the erythrocyte membrane. However, the mechanism whereby the erythrocyte membrane glycoproteins alter during the disease condition remains to be explored.

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HEALTH RELATED QUALITY OF LIFE (HRQL) SCORING IN TUBERCULOSIS*

V.K. Dhingra¹ and S. Rajpal²

Summary: Consecutive patients recently diagnosed with tuberculosis completed a HRQL questionnaire thrice over an eight-week period. Its construct validity and responsiveness were tested by comparing baseline and change in scores obtained with sputum conversion at the end of intensive phase (IP) of treatment. A significantly higher HRQL score at 8 weeks was observed in patients who converted at the end of IP as compared to those who failed to convert, both at the end of IP and even after its extension by 4 weeks. HRQL scores showed a statistically significant negative correlation with sputum grading at 0 week, 4 weeks and 8 weeks for each domain (Symptom score, Socio-psychological & exercise adaptation score). The HRQL scoring for tuberculosis (DR-12 Scale) has a strong construct validity and is responsive to change in quality of life and may be a useful additional evaluative tool for follow up of the patients during treatment under RNTCP.

INTRODUCTION

Health is defined as a state of complete physical, mental and social well being and not a mere absence of disease or infirmity¹. Apart from physical symptoms, a patient of tuberculosis faces several physiological, psychological, financial and social problems. These problems have a great impact on the well being of the patient and impair the quality of life of the patient suffering from tuberculosis. It has been recognized that quality of life indices, which focus on patients' own perception of disease, provide additional information that cannot be obtained from conventional clinical and functional measurements². HRQL assessment is a relatively new index for health measurement. It depends on physical, emotional and social impairment during the disease process. Conventional clinical assessment as well as various investigations may not be able to quantify the impairment of quality of life in a patient. Therefore, for a comprehensive assessment of the patient under treatment of tuberculosis, certain questions need to be asked in terms of patient's perception of improvement, besides routine clinical, bacteriological and radiological assessments. These questions have been framed as HRQL scores and the present study proposes a concept of HRQL scoring in tuberculosis and an attempt has been

made to validate the HRQL Questionnaire. These scores assume greater importance under the revised strategy of treatment of tuberculosis i.e. RNTCP, since the follow up for DOTS therapy is based only on bacteriological examination of sputum.

The present study proposes to evaluate the impairment of HRQL in patients with tuberculosis and to validate the questionnaire method for HRQL measurement.

OBJECTIVES

The following were the study objectives:

1. To evaluate the impairment of health related quality of life in patients of tuberculosis by evolving a HRQL questionnaire.
2. To validate the HRQL questionnaire by making serial assessments of health related quality of life of the patient during treatment with anti-tuberculosis drugs at 0 week, 4 weeks and 8 weeks.

MATERIAL AND METHODS

Consecutive patients of tuberculosis, both pulmonary and extra-pulmonary, between 15 and 60 years of age, diagnosed and put on treatment at

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the New Delhi Tuberculosis Centre under Revised National TB Control Programme from April to June 2002, were included in the study. Patients with any associated pulmonary disease i.e. asthma, chronic obstructive lung disease and other associated diseases likely to affect health related quality of life, namely, hypertension, heart disease, diabetes mellitus and epilepsy were excluded.

All these patients were subjected to a specially designed questionnaire developed to ascertain the quality of life of tuberculosis patients. This questionnaire contained questions relating to symptoms (Symptom score - Score I) as well as physiological, psychological and social interaction of patients (Socio-psychological & exercise adaption score - Score II). The questionnaire was pretested and a scoring method was evolved. Various parameters of the HRQL questionnaire and the scores adopted for them are given below:

The patients were asked to evaluate their symptoms, and perception about their weight, on a scale of 1-3 (Score I). The individual parameters were equally weighted. The socio-psychological &

exercise adaption scores (Score II) related to their interest in work, household activities, mental status, exercise and social adaptability. The patients were asked to evaluate these activities also on a scale of 1-3. Estimations of these scores (Scores I & II) were made at 0 week, 4 weeks and 8 weeks of treatment. These scores were combined and the composite score was expressed as Total HRQL score (D-R Score).

It must be admitted that there is a certain arbitrariness about giving equal weightage to the various components of Scores I and II while constructing the composite indices. It may well be, that some components have greater discriminatory value than others. If the components were quantitative, there are statistical methods for constructing an ideal index. However, since practically all the components are non-quantifiable, the task of devising an ideal index is nearly impossible. Assigning weights according to *a priori* considerations, on the other hand, will be equally arbitrary. Hence the equal weights.

The scores data so obtained were analysed

Symptom score (Score I)

S.No.	Parameters	1	2	3
I	Cough and Sputum	Throughout the day	Some time of the day	None
II	Haemoptysis	>One episode	One episode	None
III	Fever	Throughout the day	Only evening rise	None
IV	Breathlessness	At rest	On exercise	None
V	Chest pain	Frequent	Occasional	None
VI	Anorexia	Severe	Moderate/Mild	None
VII	Weight loss (patient's perception)	>5 Kg.	< 5 Kg.	None

Socio-psychological & exercise adaption score (Score II)

S.No.	Parameters	I	2	3
I	Emotional symptoms/ depression	Severe	Moderate/Mild	None
II	Interest in work	Complete loss	Indifferent	Normal
III	Household activities	Extremely troubled	Moderately/Mildly troubled	No trouble
III	Exercise activities (running/ climbing stairs)	Extremely troubled	Moderately/Mildly troubled	No trouble
IV	Social activities	No interest	Tries to avoid	Normal

by SPSS version 10.0, applying the following tests of significance:

- a) Unpaired t test
- b) Paired t test
- c) One way Anova test
- d) Pearson's Correlation Coefficient

The ability of the questionnaire to distinguish between groups of patients (pulmonary/extra-pulmonary; sputum positive/sputum negative) in terms of change in the quality of life was assessed by using unpaired t test, whereas the ability of the questionnaire to detect statistically significant differences in scores in the treated patients during the period of 8 weeks was evaluated by the paired t test.

RESULTS

Patients

Seventy-eight consecutive patients were included in the study but 76 were available for follow up analysis. The demographic and clinical characteristics of the study population are summarized in Table 1.

Discriminatory/reliability properties

The observed values correlating the discriminatory validity of the questionnaire are showed in Tables 2 & 3. The ability of the questionnaire to distinguish between different groups questionnaire is summarized in Tables 4&5. A

Table 1: Clinical characteristics of study population (n=76)

Age (Mean±SD)		Pulmonary TB (n=51)	Extra-pulmonary TB (n=25)
			27±11.8 yrs
Sex	M:F	27:24	7:18
RNTCP Category	I	22	0
	II	14	7
	III	15	18
Sputum Status	Negative	23	25
	Positive	28	0

Table 2: HRQL Scores in TB patients according to site of involvement

		Scores (Mean±SD)				Paired t test
		0 Week	4 Weeks	8 Weeks	Average gain	
Pulmonary (n=51)	Score I	14.94±2.42	18.94±1.55	19.45±1.53	4.51±2.61	NS
	Score II	10.49±2.98	12.92±2.01	13.37±1.78	2.88±2.66	P=0.001
	Total Score	25.43±4.46*	31.86±3.06	32.82±2.73	7.39±4.30**	P=0.009
Extra-pulmonary (n=25)	Score I	17.24±2.35*	19.44±1.61	19.92±1.29	2.68±2.15	P=0.037
	Score II	11.12±2.65	13.56±2.04	13.48±1.90	2.36±2.29	P=0.006
	Total Score	28.36±3.81*	33.00±2.22	33.4±2.36	5.04±3.96	NS

*There was a significant difference between scores of pulmonary and extra-pulmonary TB cases at the start of treatment, both for Score I (P<0.001) and Total HRQL Score (P=0.006)

**A significant increase in Score II was observed at 8 weeks for pulmonary TB cases (P=0.001) and extra-pulmonary cases (P=0.006) besides showing a significant increase in Total HRQL Scores at 8 weeks for pulmonary TB cases (P=0.009)

Table 3. HRQL Scores in pulmonary TB patients according to sputum status

		Scores (Mean \pm SD)				Paired t test
		0 Week	4 Weeks	8 Weeks	Average gain	
Sputum positive (n=28)	Score I	14.32 \pm 2.31*	18.96 \pm 1.37	19.50 \pm 1.60	5.18 \pm 2.40	NS
	Score II	10.71 \pm 2.97	12.93 \pm 1.20	13.25 \pm 1.69	2.54 \pm 2.55**	P=0.005
	Total Score	25.03 \pm 4.01	31.89 \pm 2.90	32.75 \pm 2.76	7.71 \pm 3.92**	P=0.049
Sputum negative (n=23)	Score I	15.70 \pm 2.38*	18.91 \pm 1.78	19.39 \pm 1.47	3.70 \pm 2.67	NS
	Score II	10.22 \pm 3.03	12.91 \pm 2.07	13.52 \pm 1.90	7.00 \pm 2.79	P=0.037
	Total Score	25.91 \pm 5.00	31.83 \pm 3.31	32.91 \pm 2.76	7.00 \pm 4.79	NS

* Sputum negative patients showed a higher Score I as compared to sputum positive patients (P=0.042)

**The Score II as well as Total HRQL Scores showed an increase at 8 weeks for both sputum positive and sputum negative cases, which was found to be statistically significant for sputum positive cases (P=0.005 for Score II; P=0.049 for Total HRQL Score).

HRQL Scores showed a negative correlation with sputum grading at 0 weeks, 4 weeks and 8 weeks, which was found to be significant for Score I, Score II and Total HRQL Scores at 8 weeks ($r=-0.333$, P=0.017 ; $r = -0.331$, P=0.018 ; $r=0.401$, P=0.004 respectively).

Table 4. HRQL Scores in pulmonary TB patients according to their categories

Categories		Score (Mean \pm SD)				Paired t test
		0 Week	4 Weeks	8 Weeks	Average gain	
Cat. I (n=22)	Score I	14.50 \pm 2.04	18.59 \pm 1.56	19.41 \pm 1.44	4.91 \pm 1.87*	P=0.03
	Score II	10.32 \pm 3.17	12.45 \pm 2.13	12.86 \pm 1.91	2.55 \pm 2.69*	P=0.01
	Total score	24.82 \pm 3.85	31.05 \pm 3.29	32.27 \pm 3.07	7.45 \pm 3.32*	P=0.007
Cat. II (n=24)	Score I	14.86 \pm 3.08	19.29 \pm 1.59	19.58 \pm 1.70	4.71 \pm 3.34	NS
	Score II	10.93 \pm 3.07	13.50 \pm 1.83	13.93 \pm 1.49	3.00 \pm 3.21	NS
	Total Score	25.79 \pm 5.26	32.79 \pm 3.07	33.50 \pm 2.38	7.71 \pm 5.46	NS
Cat. III (n=15)	Score 1	15.67 \pm 2.23	19.13 \pm 1.56	19.40 \pm 1.60	3.73 \pm 2.87	NS
	Score 2	10.33 \pm 2.74	13.07 \pm 1.82	13.60 \pm 1.46	3.27 \pm 2.20	P=0.01
	Total Score	26.00 \pm 4.69	32.20 \pm 2.47	33.00 \pm 2.17	7.00 \pm 4.62	NS

*Category I pulmonary TB cases were observed to have a significant gain in scores at 8 weeks for Score I (P=0.03), for Score II (P=0.01) and for Total HRQL Score (P=0.007)

**A positive correlation was observed between weight gain and Total HRQL Scores at 8 weeks ($r =0.328$ and P=0.019)

Table 5. HRQL Scores in pulmonary TB patients according to sex

		Scores (Mean \pm SD)				Paired t test
		0 Week	4 Weeks	8 Weeks	Average gain	
Males (n=27)	Score I	14.70 \pm 2.62	18.78 \pm 1.41	19.11 \pm 1.46	4.41 \pm 2.62	NS
	Score II	11.22 \pm 2.46	12.96 \pm 1.69	13.22 \pm 1.50	2.00 \pm 2.09	P=0.004
	Total Score	25.93 \pm 4.20	31.74 \pm 2.71	32.33 \pm 2.57	6.41 \pm 3.87	NS
Females (n=24)	Score I	15.21 \pm 1.90	19.13 \pm 1.57	19.83 \pm 1.23	4.63 \pm 2.09	NS
	Score II	9.67 \pm 2.90	12.88 \pm 2.10	13.54 \pm 1.94	3.88 \pm 2.68	P=0.017
	Total Score	24.88 \pm 4.27	32.00 \pm 3.32	33.38 \pm 2.77	8.50 \pm 4.12*	P=0.032

*Score gains were observed in both the sexes at 8 weeks with a statistically significant increase in Total HRQL Scores for females at 8 weeks (P=0.032)

Table 6. HRQL Scores in pulmonary TB patients with outcome at the end of IP

		Scores (Mean±SD)				Paired t test
		0 Week	4 Weeks	8 Weeks	Average gain	
Sputum negative at end of IP (n=42)	Score I	15.12±2.36	19.02±1.54	19.52±1.53	4.40±2.74	NS
	Score II	10.71±2.91	12.98±2.01	13.52±1.69	2.81±2.57**	P=0.001
	Total Score	25.83±4.49	32.00±3.02	33.05±2.58*	7.21±4.40**	P=0.039
Sputum positive at end of IP (n=9)	Score I	14.11±3.02	18.56±1.90	19.11±1.70	5.00±2.19	P=0.036
	Score II	9.44±3.39	12.67±2.16	12.67±2.16	3.22±3.48	NS
	Total Score	23.56±4.31	31.22±3.73	31.78±3.50	8.22±4.47	NS
Sputum positive after extension of IP (n=5)	Score I	13.00±3.08	17.80±1.64	18.20±1.30	5.20±2.59	NS
	Score II	9.80±2.59	11.80±2.49	11.80±2.49*	2.00±2.34	NS
	Total Score	22.80±2.77	29.60±3.51	30.00±3.39*	7.20±3.56	NS

*There was a significantly higher score at 8 weeks (Score II and Total HRQL Score) in patients who converted at the end of Intensive Phase (IP) as compared to those who did not convert even after the extension of IP (P=0.046 respectively).

**There was a significant gain in scores for those who converted at the end of IP (P=0.001 for Score II and P=0.039 for Total HRQL Score).

significantly higher HRQL Score at 8 weeks was observed in patients who converted at the end of IP as compared to those who failed to convert both at the end of IP and even after its extension by 4 weeks (Table 6). HRQL scores showed a statistically significant negative correlation with sputum grading at 0 week, 4 weeks and 8 weeks for all the scores (Symptom score, Socio-psychological & exercise adaptation score, Total HRQL Score). Further significant positive correlation was observed with weight gain and scores at 8 weeks in all the groups.

DISCUSSION

HRQL or health related quality of life is a relatively new index. Juniper et al³ evaluated the impairment of life in adult asthmatics and developed an asthma quality of life questionnaire (AQLQ) and concluded that AQLQ has good measurement properties and was valid as an evaluative and a descriptive tool. He also evaluated impairment of life in adolescent patients with allergic rhinitis and observed that scores improved with treatment⁴. Wasserfallen *et al* developed and validated a simple

symptom scale to assess rhinitis and asthma and stated that it provided a comprehensive picture of severity of the disease⁵.

Similar evaluations regarding health related quality of life have been made in patients with chronic obstructive pulmonary disease⁶ and in patients with lung cancer⁷. Studies have been made for creating and evaluating illness specific health related quality of life outcome instruments in relation to common cold in Wisconsin upper respiratory symptom survey⁸ and even in relation to impact of weight on quality of life (IWQOL-lite)⁹. However, no such study has been done in relation to tuberculosis.

Guyatt et al¹⁰ suggested that unless investigators included response and valid disease specific measures of health related quality of life in controlled trials in chronic diseases, they risk reaching misleading conclusions about the effect of treatment on health status. Our study included assessment of Symptom Score and Socio-psychological & exercise adaptation score on 12 parameters (DR-12 Scale) to evaluate a comprehensive picture of the health status in patients at the start of treatment and after

the IP phase of treatment.

The present study revealed that there was a significant difference between the scores of pulmonary and extra-pulmonary tuberculosis patients (higher in extra-pulmonary cases) both in Symptom Scores and Total HRQL Scores at the start of treatment. Moreover, sputum negative patients showed a higher Symptom Score than the sputum positive patients. HRQL Scores showed a negative correlation with sputum grading at 0 week, 4 weeks and 8 weeks for all the three scores.

HRQL scoring was sensitive to changes in the quality of life of patients as demonstrated by statistically significant differences in score changes observed at the end of 8 weeks of treatment. A significantly higher score at 8 weeks (Score II and Total HRQL Score) was observed in patients who converted at the end of IP as compared to those who failed to convert, even after extension of IP.

Therefore, HRQL scoring method in tuberculosis (DR-12 Scale) has a strong construct validity and is sensitive to changes in quality of life and, thus, can be used to evaluate the quality of life of tuberculosis patients. The HRQL questionnaire (D-R Score) may be a useful addition to evaluation of tuberculosis patients under RNTCP, where the follow up is based only on bacteriological examination of sputum.

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ISOLATED ESOPHAGEAL TUBERCULOSIS - A CASE REPORT**A.R. Shah¹, S.K. Agarwal² and K.V. Shah³***(Received on 20.12.02; Accepted on 4.3.03)*

Summary: Isolated primary tuberculosis of esophagus is an extremely rare entity. We report a HIV positive female patient presenting with dysphagia and odynophagia. Endoscopy showed an ulcerative lesion in the esophagus which was confirmed to be tuberculous on biopsy. Extensive search for a primary focus was fruitless. The patient responded well to anti-tuberculosis therapy.

Key Words: Esophageal tuberculosis, HIV/AIDS

INTRODUCTION

Tuberculosis of esophagus is rare and is usually secondary to tuberculosis focus elsewhere¹. The spread to esophagus usually occurs from mediastinal tuberculous glands and is less often due to swallowing of infected sputum, hematogenous dissemination or lymphatic route of infection.² The preferred site of disease is the middle one third of esophagus³. Even though there is increased incidence of extra-pulmonary tuberculosis in HIV positive patients, there is hardly any report on esophageal tuberculosis as an isolated lesion⁴.

generalized weakness. She had no history of vomiting, hematemesis, melaena, regurgitation or aspiration of food. There was no history of cough, sputum production, hemoptysis or breathlessness. Patient had no history of irritative ingestion, cigarette smoking, alcohol use or illicit drug abuse. A blood transfusion was taken 9 years earlier at the time of her first delivery.

Physical examination revealed a poorly nourished female with generalized pallor. Vital signs were normal. There were no lymphadenopathy, oral or skin lesions. Examination of chest and abdomen did not reveal any positive findings.

CLINICAL RECORD

A 37 year old Hindu female patient presented with dysphagia and odynophagia of 3 months duration. She had progressive dysphagia for solid foods at first, which progressed to liquids later on. The odynophagia was limited to the retrosternal region, without any radiation. Other symptoms included low grade fever with evening rise of temperature, more than 20% weight loss and

Investigations: Hemoglobin -11.6 g/dl, total leukocyte count 4,600/cmm with a normal differential count, ESR 140 mm in the first hour (Wintrobe's Method). Peripheral blood smear showed normocytic and normochromic anemia. Liver and renal functions and blood sugar were normal. Tuberculin test was positive (10 mm. induration). Patient was HIV positive with a CD 4 count of 356 cells /cmm. Chest skiagram showed no abnormality.

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Barium swallow showed a filling defect in the mid-esophagus. Barium meal follow through did not show any abnormality. Esophagogastrosocopy showed a polypoidal lesion 25 cm from the incisor teeth. The histopathological report suggested an inflammatory polyp with squamous epithelial lining. Test for *H. pylori* and fungal cultures were negative. Patient was managed symptomatically but there was no significant improvement. A repeat esophagogastrosocopy, one month later revealed a small oval ulcer of about 2.5 cm, diameter with undermined edges and scarring in the peri-ulcer area. (Figure 1) Surrounding area showed a few small ulcers with normal intervening mucosa. There was a polypoidal growth about 3 cm. below the ulcer. Rest of the endoscopy was normal. Endoscopic biopsy from the ulcer showed caseating granulomatous lesion. Acid fast bacilli were detected on Z.N. stain.

The patient was started on anti-tuberculosis treatment comprising Isoniazid (5mg/kg), Rifampicin (10mg/kg), Ethambutol (25mg/kg) and Pyrazinamide (25mg/kg). The patient gradually improved, with decrease in dysphagia and odynophagia and weight gain as well as complete resolution of symptoms. After 6 months of therapy, patient was re-evaluated by esophagogastrosocopy and endoscopic ultrasound. It showed a healing ulcer and some narrowing at the junction of the middle and lower one third of the esophagus, scar formation and hypertrophy of adjacent mucosa. Endoscopic

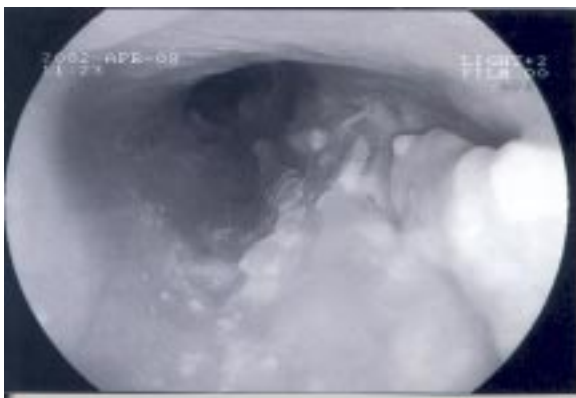


Fig. 1 Esophagogastrosocopy showing an ulcer with undermined edges and scarring in peri-ulcer area

ultrasound revealed a diffuse hypoechoic thickening extending from the 29th to 32nd centimeter across the full thickness of the esophageal wall suggestive of a healing ulcer (Figure 2). Extensive search for primary tuberculous sites by CAT scan of thorax, ultrasound of abdomen and barium meal follow through failed to reveal any lesion. The patient was continued on anti-tuberculosis treatment and advised regular follow-up.

DISCUSSION

Tuberculous involvement of the esophagus is rare even in the presence of extensive pulmonary disease⁵. Primary tuberculosis of the esophagus is extremely rare, perhaps owing to intrinsic protective mechanisms, such as stratified epithelial lining, presence of saliva. Besides, mucous coated tubular structure because of peristalsis discourages stasis and mucosal invasion by organisms^{6, 7}, which needs a physiologically stable environment.⁸ Secondary tuberculosis of the esophagus can occur from mediastinal tuberculosis and less often due to swallowing of infected sputum, hematogenous dissemination or lymphatic infection.²

The diagnosis of esophageal tuberculosis is based on esophagoscopy with biopsy, histopathological examination and identification of causative organism⁹. The clinical and laboratory findings are not always typical and may pose a

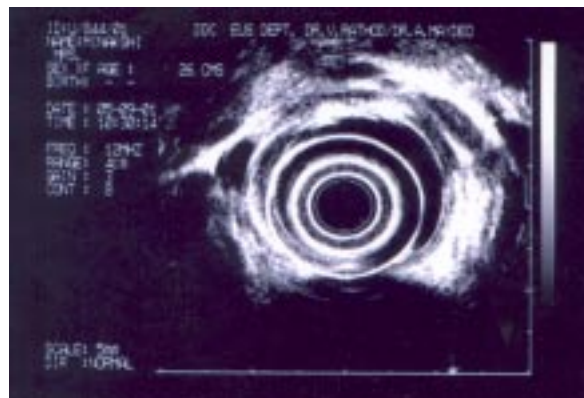


Fig.2 Endoscopic ultrasound picture suggestive of a healing ulcer

diagnostic challenge¹⁰. However, the endoscopic appearance is typical and corresponds with the pathological type. Histology from endoscopic mucosal biopsy has a poor yield with a sensitivity of only 22%.¹² Sometimes, the diagnosis of esophageal tuberculosis is possible only on thoracotomy and demonstration of acid fast bacilli is very rare¹³

HIV prevalence has increased the incidence of tuberculosis with its varying manifestations and complications. The response to anti-tuberculosis treatment in HIV positive patients varies with the status of body immunity

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**Annual General Meeting and
 Central Committee Meeting of
 the Tuberculosis Association of India**

The Annual General Meeting of the Tuberculosis Association of India was held on Tuesday, the 11th March, 2003 and was presided over by Dr.S.P. Agarwal, Chairman of the Association, in the absence of the President.

Drs.R. Prasad, M.S. Agnihotri, I. Ranga Rao, D.R. Patel, N.R. Patel, D.K. Jain and P. Jagota were elected as members of the Central Committee for the year 2003-2003. The Central Committee elected Dr. Bhai Mohan Singh as President of the Association vice Dr. D.R. Nagpaul. The Central Committee also co-opted Drs. V.K. Arora, P.R. Narayanan, R.C. Jain, P. Jagota and M.M. Singh as members.

PROGRESSIVE RIB DESTRUCTION : AN UNUSUAL FEATURE IN A PATIENT WHO HAD IRREGULAR ANTI-TUBERCULOSIS TREATMENT

Prem Parkash Gupta¹, K.B. Gupta², Rajesh Gupta³ and Dipti Agarwal⁴

(Received on 1.11.2002; Revised version received on 3.2.2003; Accepted on 25.2.2003)

Summary: Local rib destruction associated with pulmonary tuberculosis is uncommon. We present a case of pulmonary tuberculosis who had frequent defaults and never completed the entire course of anti-tuberculosis treatment. He later developed pleuro-pulmonary tuberculosis and progressive multiple ribs destruction as a complication.

CASE REPORT

A 29 year old male, farmer, bidi smoker and non-alcoholic, presented with productive cough, low grade fever and chest pain for 2 months. He also had a swelling over left chest. In the past, 3 years back, he had developed pulmonary tuberculosis and was diagnosed on the basis of a chest roentgenogram (Fig.1) and sputum examination. He took anti-tuberculosis treatment (HRE) for roughly 2 months, became asymptomatic and stopped taking

medications. He remained symptom - free for 7 months and again developed chest symptoms which he ignored for about a month and then sought medical opinion again. The patient had a chest skiagram (Fig.2) and was advised anti-tuberculosis therapy (HRZE). This time he stopped treatment after 1½ months. He remained asymptomatic for almost 8 months when he developed chest pain along with fever. The third chest roentgenogram [Fig.3(a)] revealed pleuro-pulmonary involvement with pleural fluid compatible with tuberculous etiology. The



Fig.1 Chest roentgenogram PA view taken 3 years earlier. Bilateral parenchymal lesions but no rib destruction or volume loss are seen. First course of ATT was started



Fig.2 Chest roentgenogram PA view before second course of ATT. Lung parenchymal lesions on left side are more extensive; however, no rib destruction noted

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Fig.3 (a) Chest roentgenogram PA view before third course of ATT showing extensive left lung parenchymal lesions, left pleural involvement and start of left ribs destruction

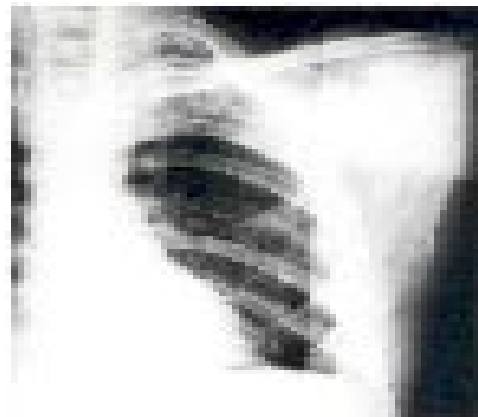


Fig.4 Chest roentgenogram PA view taken on presentation showing multiple left ribs destruction, blunting of left costophrenic angle, left pleural thickening and volume loss over left lung



Fig.3 (b) Chest roentgenogram PA view 2 months after start of third course of ATT showing improvement in parenchymal and pleural lesions

patient took treatment for 3 months (2 HRZE/1HR) with satisfactory radiological response [Fig.3(b)] but defaulted again. After that he had again one more course of ATT which he discontinued after two and a half months following symptomatic improvement.

On presentation, his general physical examination revealed nothing remarkable. There was a painless, fluctuant soft tissue swelling on 5th intercostal space at left anterior axillary line. Clinical features were suggestive of multiple rib involvement and volume loss over left side. The percussion note was dull to stony dull and the breath sound was

significantly decreased over left lower chest. Complete haemogram, urine analysis and other biochemical parameters were within normal limits. Tuberculin test was 18x20 mm after 48 hours. Chest roentgenogram [Fig.4] showed multiple left thoracic rib destruction, blunting of left costophrenic angle, left pleural thickening along with volume loss over left lung. Ultrasound guided pleural biopsy was done and straw coloured pleural fluid was aspirated. Pleural biopsy revealed caseating granulomatous lesion and pleural fluid which contained, predominantly, lymphocytes. Pleural fluid protein and pleural fluid LDH levels were 4.2 g/dl and 296 mg/dl, respectively. FNAC from soft tissue swelling showed chronic inflammatory cells, predominantly lymphocytes along with a few epithelioid cells and Langhans giant cells in a necrotic background. Specimen from the affected rib was positive for *Mycobacterium tuberculosis* by polymerase chain reaction (PCR). Patient's sputum sample showed no acid fast bacilli on direct smear but a positive culture for *Mycobacterium tuberculosis* sensitive to all the first line drugs was grown. Anti-tuberculosis therapy (2SHRZE/1HRZE/5HRE) was started with adequate motivation for treatment adherence. He successfully completed 8 months' treatment with good improvement along with disappearance of the swelling and a stable radiological appearance. He was followed up regularly and has remained symptom free for 2 years after completion of treatment.

Discussion

Rib destruction is usually suggestive of either an aggressive tumor or an infectious disease. The most common tumors leading to chest wall mass with bone destruction are metastases¹ of the small round cell tumors (multiple myeloma, Ewing's tumor and neuroblastoma). Metastatic tumors of the chest wall are more common than primary tumors: the usual primary sites are breast and bronchus. The differential diagnosis in adults is multiple myeloma vs metastases, while in a child the pattern is more suggestive of Ewing's tumor or metastatic neuroblastoma². Clinical course may provide valuable clues; secondary tumors were found to have symptoms averaging 3 months whereas the mean duration of symptoms averaged 4.1 years for primary benign and 1.7 years for primary malignant tumors³. Rib destruction may be subtle, requiring a coned-down view, computed tomograms and even radionuclide bone scans for diagnosis.

Amongst infectious diseases, actinomycosis is one of the more aggressive granulomatous infections and may produce parenchymal infiltrate, pleural effusion, chest wall mass, rib destruction, and even cutaneous fistula^{4,5}. Occasionally, even air-fluid levels are seen in the soft tissues. Other granulomatous infections that produce a similar appearance include aspergillosis⁶, nocardiosis, blastomycosis and, rarely, tuberculosis. Patients with these infections usually have a febrile course, although it may be somewhat indolent.

Skeletal tuberculosis accounts for 1 to 5 percent of all tuberculous lesions and roughly half of them are in vertebral column⁷⁻¹⁰. In bone and joint tuberculosis, rib lesions are uncommon and occur in about zero to 5 percent^{7,11}. In some cases, adjacent pulmonary or pleural lesions have been noted and local spread is the likely route¹². In other cases of osteoarticular tuberculosis, parenchymal lung lesions adjacent to the affected rib were not present or not specifically mentioned^{7,10,11,13}. A series reviewing the skeletal remains of patients dying from pulmonary tuberculosis suggested that periosteitis of the rib subjacent to a pulmonary tuberculous

lesions was often present¹⁴. The missing of clinical diagnosis of rib involvement in pleuro-pulmonary tuberculosis may be partly due to relative insensitivity of the chest roentgenogram in picking up early skeletal disease. Computerized tomography is valuable wherever skeletal involvement is suspected on clinical ground but is not visible in chest roentgenogram¹⁵.

The present case suggests that the tuberculous etiology of rib destruction, though rare, should also be considered particularly in countries with a high prevalence of mycobacterial infection and in a clinical scenario when the patient had a prolonged history of irregular anti-tuberculosis chemotherapy.

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President of the Tuberculosis Association of India
 The Central Committee at its meeting held on 11th March, 2003 unanimously elected Dr. Bhai Mohan Singh, a well-known industrialist, who has dedicated his life for work in the field of tuberculosis and various other social causes in India, as President of the Tuberculosis Association of India *vice* Dr. D.R. Nagpaul. The Association is very fortunate in having at its helm a person of the eminence of Bhai Mohan Singh.

58th National Conference on Tuberculosis and Chest Diseases
 The 58th National Conference on Tuberculosis and Chest Diseases will be held in Mumbai from 8th to 11th January, 2004, under the joint auspices of the Tuberculosis Association of India and the Maharashtra State Anti-TB Association. Those who wish to present papers on any subject related to tuberculosis and chest diseases may kindly forward three copies of the abstracts of the papers to the Vice-Chairman, Tuberculosis Association of India, 3, Red Cross Road, New Delhi 110001, latest by 30.6.2003.
 The subjects chosen for presentation of papers are: MDR-TB, HIV and TB, Lung Cancer, DOT+, NTP and RNTCP, Bronchial Asthma, Immuno-modulators and Ayurveda including Yoga, Non-tuberculous Chest Disease - COPD, Interstitial Lung Diseases, Role of NGOs, Complications of Pulmonary Tuberculosis, Fixed dose combination in treatment of TB, Tobacco and Health, and Occupational Lung Diseases (Pneumoconiosis, etc.).
 It is proposed to have a Continuing Medical Education Programme also preceding the Conference. In addition, as usual, assorted papers/free communications on any subject relating to tuberculosis and chest diseases and Poster Presentations are welcome.

CONTEMPORARY ISSUES

Public Library of Science

The world of published science literature is in for a metamorphosis. A group of prominent scientists has floated the electronic Public Library of Science to promote a free-wheeling access to all published research in the interest of faster progress in science.

Presently, electronic access to all published scientific studies is controlled by a few agencies which follow practices that discriminate, often in order to reap higher profits for their websites, and/or maintaining intact the subscriber lists of their constituent journals. In future, all peer reviewed published literature in biology and medicine could be deposited in the planned public domain library for a no-profit access to anyone. Without seeking permission or paying dues, anyone could read, copy or use the collective product of the world's academic research, as soon as it is published, anywhere.

Most scientists who seek publication of their studies in the journals of their choice assign their copyright to them for no monetary compensation. Their main aim is to distribute their findings as widely as possible. The publishers, on the other hand, have policies which encash the rights transferred to them by the authors and may discriminate or ignore works, many of third world countries, which may not be sufficiently remunerative, on putative grounds either of doubtful quality of studies or shoddy production quality of journals. The Public Library of Science is expected to take birth on the support of a \$ 9 million grant extended by Gordon and Betty Moore Foundation in USA.

Dimensions of the Voluntary Sector in India

The Charities Aid Foundation, U.K. has recently brought out a comprehensive survey of the

voluntary sector in India, as a book with the above title. The 1500 listed organisations are worth Rs. 12 billion and receive Rs. 43 billion as overseas donations, from over 1.5 million estimated big as well as small organisations. The survey, sponsored by the Planning Commission, reveals that the listed organisations spend 15% on salaries, 6% on office maintenance, 2% on travel, 14% on meetings and seminars and the rest on their respective activities.

Human Cloning: Quo Vadis ?

The medical sciences remain agog with excitement as well as expectation in respect of the promised mind-boggling benefits from human cloning, the therapeutic cloning, that is. At the same time, polity, ethics and religious sentiments the world over remain inexorably opposed to reproductive human cloning, for understandable reasons. Both forms of cloning, however, are sides of the same coin. Therapeutic cloning holds a 'revolution in the offing', regarding better understanding of both curable and still incurable diseases, as well as effectively curing them by genetic means. Reproductive human cloning on the other hand has been forbidden by law in most countries because it may demolish the entire societal fabric. Nevertheless, many scientists, who by nature are truant, recalcitrant and even renegade, but loyal to the spirit of science, are swayed neither by the therapeutic benefits nor daunted by the imposed restrictions. And their intention to proceed with reproductive cloning, willy nilly, in search of truth, has not been kept hidden.

A moment of truth appears to have been reached recently in this connection. The Rosalin Institute in Scotland (U.K.) where the world's first successful mammalian clone - "Dolly", the sheep - was born in 1996 had to put the clone to sleep because for unknown reasons, its severe lung infection could not be controlled. It was Dolly's

6th year of life, in a normal life span of 12 years; a life which had been marked by several abnormalities as well as health problems. The distinguished Italian fertility expert, Dr. Severisno Antinori, had announced that the world's first human baby clone would be born in January 2003, the entire operation having been secretly carried out under his care. That moment has passed without an announcement of birth. Earlier, in December 2002, the secret Raelians in USA had announced birth of a human clone under the care of their organisation, Clonaid. When asked to produce the data which could prove that the baby in question was in fact a true clone, they shied away. Speculations on the Antinori and Clonaid claims range from fear of penal legal action or unexpected death of clones, to birth with unacceptable birth abnormalities, to playing a hoax on the people. The Rosalin Institute is investigating, however, the likely connection with the age of the gene donor at the time of cloning. Dolly was cloned in 1996 from the mammary gland of an ewe which was 6 years old then and had died naturally around the time Dolly was sacrificed. In other words, Dolly died when she was genetically as old as her donor mother. There are instances of a sheep cloned in Australia having expired suddenly for no reason and unusually large number of live experimental clones having abnormalities at birth. Expectedly, with the cloning technique itself being far from perfect, the risks accompanying reproductive human cloning are far too great for persisting with it.

Therapeutic cloning process on the other hand branches off at the pre-embryo stage, after the female egg has been injected with the cloning DNA and the first lot of embryo stem cells have been formed. The optimal conditions for culturing embryo stem cells and the agent factors which can trigger them to replicate into the desired tissue are still being experimented. Nevertheless, and as feared by many, serious genetic abnormalities have been reported from the tissues cultured from stem cells

and how this factor will affect further progress remains uncertain. No doubt, some therapeutic agents have been evolved based on genetic engineering, but, currently, human cloning remains at the questionable stage where there are more expectations than results.

HIV/AIDS Vaccine

The recently announced 'failure' of the Vaxgen Inc produced anti-HIV/AIDS Vaccine - AIDS-VAX- has not come as a surprise but, surely, is a source of deep disappointment, coming after protracted research costing billions of dollars. Clinical trials in human volunteers of this promising vaccine were begun in 1998. The results are from the high risk people sampled from USA, Canada, Puerto Rico and Netherlands, while results from Thailand remain to be reported.

Overall, AIDS-VAX reduced HIV infection among more than 5,000 men and women (both vaccinated and controls) by 38 percent. Among the study population were 498 blacks and Asians. Compared with the total 127 persons found HIV infected at the end of the study, 25 were among blacks and Asians giving a protection rate of 67% among them. The observed protection is not reliable enough to be regarded as a success. For ethical reasons, all subjects had been informed about safe sex practices before including them in the trial, but compliance is not known.

After starting in the Americas, and devastating the continent of Africa, the HIV/AIDS epidemic has lately moved into Asia where huge populations are at risk. Therefore, a final judgement on this vaccine should be of interest, especially because HIV/AIDS strains prevalent in North America and Europe are different from those in Asia.

FORUM

MAKING SCC SHORTER OR COSTLIER?

This is with reference to Dr N.R. Patel's suggestion of using an immuno modulator -Immuvac- in the treatment of tuberculosis with the aim of reducing the total duration of treatment (Forum, *Ind J Tub* 2002,49,238). Any suggestion in this direction is welcome as it is a well established fact that compliance with therapy is affected by duration of treatment. Shorter the duration of therapy, better the compliance. Studies show that 6 month courses have better compliance than 12-18 month courses. However, we should not ignore the fact that non-compliance or non-adherence depends upon a large number of factors and not on duration of therapy alone. Mistrust of the health care system, lack of family or social support, migrant status, illiteracy, substance abuse, poor access to transportation and, above all, meagre financial resources are all responsible for non-adherence to therapy.

Even if Dr. Patel's wishful thinking that Immuvac may reduce the total duration of therapy to 3 months (no supportive data are available) proves correct, still therapy with Immuvac will be a very costly alternative. For example, the total cost of medicines for 3 months in the continuation phase will be only Rs. 500/- whereas a full course of Immuvac will cost Rs. 1500/-.

So, for the time being, a costly addition like Immuvac will not be a cost-effective alternative in the Indian scenario.

Rajinder Singh Bedi
Patiala

Dr. N.R. Patel replies:

I appreciate the concern regarding cost of ATT in individual patients, more so in a country like ours. To elaborate on the issue, let me explain that no innovation is possible if cost is considered as a limiting factor.

Before the advent of Rifampicin, the mainstay of standard therapy was INH plus Thioacetozone which were inexpensive. When introduced, Rifampicin was expensive and hardly anybody amongst the poor sufferers in India could afford it. Over a period of time, there has been a substantial decrease in the price of Rifampicin with its increased usage. This would not have been possible if the cost of therapy had been accepted as a limiting factor.

The same consideration applies to trying out a new regimen which includes more expensive drugs like Ofloxacin and increasing the duration of another expensive drug i.e. Pyrazinamide.

The sputum conversion rate does not seem to have improved with the new regimen containing Ofloxacin tried by TRC, Chennai in their report under discussion. Contrary to this, the addition of Immuvac resulted in reduction in time for sputum conversion by 4 weeks, as stated in the article "*Effect of an Immunomodulator containing Mycobacterium W on Sputum Conversion in Pulmonary Tuberculosis*" in March, 2002 issue of *JIMA*. Other workers like Dr.S.K. Luhadia from Udaipur and Dr.K.C. Mohanty from Mumbai presented similar findings at the 57th National Conference on Tuberculosis & Chest Diseases at Goa.

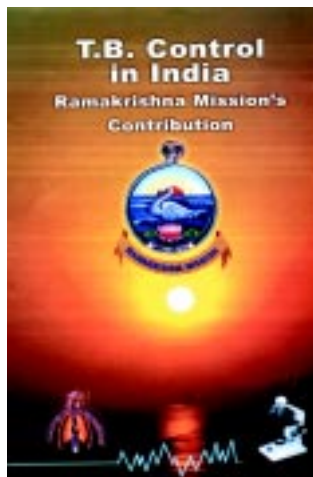
My own suggestion is to combine the two scientific observations, i.e., reduce the intensive phase by adding Immuvac and reduce the continuation phase by adding Ofloxacin and Pyrazinamide to the regimen. The suggestion needs to be tried and proven.

The cost of Immuvac, as reported by Dr. Bedi, is not as high as he believes. At current rates the cost for two months (i.e. 5 doses each of 0.1 ml, 15 days apart) is Rs. 375/-, not Rs. 1500/-.

Another perceived advantage (though not proven) may be that Immuvac effect would be longer lasting and could take care of defaulters more meaningfully than chemotherapy alone, leading to a reduction in relapse rate and the emergence of MDR TB.

BOOK REVIEW

T B Control in India; Ramakrishna Mission's Contribution: Compiled and edited by Swami Deshikatmananda and published by Swami Gokulananda, Secretary Ramakrishan Mission, R.K. Ashrama Marg, New Delhi-110055 First edition, 2002, 253 pages, includes several tables and diagrams, available in soft cover as well as deluxe hard bound volume, Price Rs.250 and Rs.300, respectively; inquiry regarding discounted prices is welcomed by the publishers.



It is rare for a humanitarian organisation to come up with a book with the title “TB Control in India: Ramakrishna Mission's Contribution”. It, thereby, promises both technical content as well as food for thought, in which it succeeds, by and large.

The Ramakrishna Mission is an international monastic and spiritual organisation which was established in 1897 by Swami Vivekananda in the name of his guru, Swami Ramakrishna Paramhansa. It has built up a century old tradition of providing outstanding spiritual as well as humanitarian solace, mainly to the poor and the sick. The book might become a landmark in the kaleidoscope of its numerous services and activities.

Swami Deshikatmananda, presently incharge of the Mission's Free TB Clinic in Delhi deserves to be congratulated for painstakingly delving into old reports, collecting contributions from the Mission's various tuberculosis institutions as well as others involved in controlling tuberculosis in the country and shaping the material into an eminently readable book. The book apparently is meant both for tuberculosis workers as well as such lay persons who have service attitude towards and interest in tuberculosis. Swami Vivekanand's exhortation on the fly page neatly sums up the *raison d'être* of the book: “They alone live who

live for others; the rest are more dead than alive”.

The book contains 35 articles spread out into 6 sections - General Articles, Technical Papers, Research Papers, Mission's Centres for Tuberculosis Control, Success Stories and Appendix. Only 15 of the articles are of a scientific nature while the rest portray tuberculosis activities in general terms. A very wide spectrum has been covered - between India's contribution to tuberculosis control at the one end and Swami Atmasthanand's reminiscences of the time when the Mission's sanatorium was being built in Ranchi in 1951, primarily for the area *adivasis*. This may explain how the opening article was contributed by the present reviewer and why the overall content is uneven and even bumpy at places.

Nestling within the pages of one general interest article is the information that Swamis Ramakrishnanand and Subodhananda, direct disciples of Swami Ramakrishna Paramhansa died of tuberculosis in 1911 and 1932, respectively. No wonder, that the Mission established a mobile medical service unit and a hospital cum nursing school in Calcutta in 1932, opened the first ever TB Clinic in India, in the congested Chunamandi area of Delhi in 1933, and the Tuberculosis Sanatorium in Ranchi in 1951. Today, the Mission runs 14 hospitals and more than 100 dispensaries in different parts of the country rendering service with compassion, mainly for the deprived.

When lay persons join to help out with highly technical services, the views they express in public (about tuberculosis in this case) could at times be economical with scientific facts and coloured with emotions. This need not necessarily lower the value of a book of this kind.

D.R. Nagpaul

Timebomb - The Global Epidemic of Multi-drug Resistant Tuberculosis. (Authors) Lee B. Reichman & Janice Hopkins Tanne, published by McGraw - Hill, 2001, New York, ISBN 0-07-135924-9

The facts of multi-drug resistant tuberculosis are by now known and well projected by the WHO. But, Lee B. Reichman & Janice Hopkins Tanne have, through their book, attracted general attention to the disaster that awaits mankind since multi-drug resistance has now the support of another deadly foe, the HIV. The title of the book is rather chilling but appropriate. The world areas which the authors describe as “hot spots” are mentioned. With globalization and shrinkage of geographic boundaries, no country is likely to remain immune to the effects of drug resistance. The authors have devoted many chapters to the appalling situation in Russia, the prevailing epidemic-like situation there, due to overcrowding in prisons, the lack of proper treatment regimens and availability of drugs, the complacency and indifference of the health administrators and, above all, the dearth of political will to fight the situation. Lee Reichman had been deeply involved in issues related to tuberculosis in Russia and has given first hand knowledge of the situation.

One is bound to ask whether the situation in India is any better? We are aware of “hot spots” in our country and that there are many such areas in South East Asia and Africa. Luckily, we in India have instituted the evidence based DOTS strategy for treatment of tuberculosis. Concerted efforts are needed to bring the disease and the emergence of drug resistance under control on the lines of the New York experience. Chapter 9 of the book deals with the epidemic in New York which gives a vivid account of how the epidemic was contained, the resolve exhibited by the lady Health Commissioner

of New York City and the commitment shown by one and all in the public health sector to eliminate drug-resistant tuberculosis. No doubt, the cost of controlling the outbreak was phenomenal, but nothing in terms of the lives saved, particularly when the city could afford it.

It is surprising how the authors have made such a scientific topic compelling and absorbing reading. The book is meant for the lay public and anyone who has the slightest interest in the disease would find it very gripping. “Timebomb” covers tuberculosis from its history, clinical features, epidemiology, diagnosis and control, yet it reads like a novel and not at all like a textbook. At places, the authors have even given the minutest scientific details without making it heavy on the reader. Some chapters describe contact-tracing of diagnosed cases right down to finger printing of the bacteria to establish the infection link, while the others give a freezing account of lung surgery. The lack of interest shown by the pharmaceuticals in bringing out newer anti-tuberculosis drugs has also been strongly dealt with. References at the end of the book add depth and authenticity to the statements made in the book catering to both the general population and the scientific community.

On the whole, “Timebomb” is a ‘must read’ book for all those who are even remotely connected with tuberculosis and its control. It articulates the need for immediate and proper action very forcefully.

P. Narang

ABSTRACTS

Factors predicting persistent sputum smear positivity among pulmonary tuberculosis patients 2 months after treatment

R. Singla, M.M. Osman, N. Khan, N. Al-Sayegh, M.A. Shaikh, *Int J Tuberc Lung Dis*, 2003, 7, 58

Studies have shown that adverse outcomes are more likely in patients showing persistent sputum positivity at the end of 2 months of anti-tuberculosis treatment. This study was conducted to identify clinical, microbiological or radiological factors associated with persistent sputum positivity resulting under national programme conditions. Sputum smear-positive pulmonary tuberculosis patients, admitted in 2 consecutive years to a referral hospital, who had received standard short course chemotherapy under direct observation, were reviewed retrospectively. A total of 514 patients were available for review. Logistic regression analysis showed that age groups 41-60 years and more than 60 years, presence of numerous bacilli on initial sputum smear examination, and multiple cavitory disease were the significant factors associated with persistent sputum positivity at the end of 2 months of treatment ($P < 0.0001$). Identification of such high risk factors associated with persistent sputum positivity may be helpful in avoiding adverse outcome, thus allowing better resource utilisation.

Voluntary counselling, HIV testing and sexual behaviour among patients with tuberculosis in a rural district of Malawi

R. Zachariah, M.P. Spielmann, A.D. Harries, F.L. Salaniponi, *Int J Tuberc Lung Dis*, 2003, 7, 65

A cross-sectional study was conducted in new tuberculosis patients in a rural district of Malawi to assess acceptability of voluntary counselling, testing for HIV infection, sexual behaviour and condom use in order to identify socio-demographic and behavioural risk factors associated with 'no condom use'. Consecutive patients diagnosed

between January and December 2000 were offered voluntary counselling and HIV testing (VCT) and were subsequently interviewed. Of the 1049 new TB patients enrolled, 1007 (96%) accepted pre-test counselling, 955 (91%) underwent HIV testing, 912 (87%) were post-test counselled and 43 (4%) refused HIV testing. The overall HIV infection rate was 77%. Of all the HIV-positive TB patients, 691 (94%) were put on Cotrimoxazole. There were 479 (49%) patients who reported sexual encounters, of whom only 6% always used condoms. Unprotected sexual practice was associated with duration of symptoms of over 1 month, less than 8 years of school education, single, divorced or widowed status or having sex with the same partner.

Impact of enhanced notification of tuberculosis laboratory results to minimize treatment delay

W. Uthairavit, H. Yanai, J.W. Tappero, K. Limpakarnjanarat, R. Srismith, T.D. Mastro, T. Mori, *Int J Tuberc Lung Dis*, 2003, 7, 46

To improve tuberculosis (TB) services, a study was done to assess the impact of sputum smear-positive result notification associated with the location of sputum collection centre, how quickly sputum was examined and result recorded and delays that occurred between hospital admission and treatment initiation. The 1994-1999 cohort of smear-positive TB patients was identified and reviewed for the time taken from admission to hospital, laboratory diagnosis of TB, registration for treatment, and initiation of therapy were determined and compared with the progress made in improving the laboratory results notification system. The number of unregistered TB patients fell from 44 cases in 1994 to none in 1999. The time elapsed from admission to treatment initiation decreased from a mean of 5.6 days in 1997 ($n=162$) to 3.1 days in 1999 ($n=136$) ($P < 0.001$). This decrease was attributed to a reduction in time between laboratory diagnosis and treatment initiation from 2.7 days in 1997 to 0.6 days in 1999 ($P < 0.001$). Such improved notification systems are inexpensive, improve the TB services

and may even reduce nosocomial transmission of *M. tuberculosis*.

Asthma phenotypes according to the timing of smoking onset in young adults

C. Raherison, I. Baldi, J-M, Tunon-De-Lara, A. Taytard, i. Anesi-Maesano, *Int J Tuberc Lung Dis*, 2003,7,84

Whether and how cigarette smoking influences asthma are still matters of debate. This study aims to identify risk factors associated with asthma according to whether individuals began active smoking before or after asthma onset. A sample of 544 individuals was examined using the protocol of the European Community Respiratory Health Status. Current active smoking (43.6%) was associated with wheezing during the past year (15.2%, OR 3.7; 95% CI 1.7-8.4), but not with asthma (17.6%, OR 0.78; 95% CI 0.48-1.26). However, active smoking modulated risk factors for asthma. Asthma that developed before smoking and asthma without smoking were both significantly related to nasal allergy, parental asthma and atopy (as assessed by skin prick test positivity and increased total and specific IgE levels). Only a lower FEV₁ level was significantly associated with asthma that initiated after starting smoking. The data puts forward different phenotypes of asthma according to the timing of smoking onset and suggests that asthma is either never accompanied by smoking or is followed by smoking onset which might be characterised by an allergic pattern.

Risk of *Mycobacterium tuberculosis* infection and disease among health care workers

H. Yanai, K. Limpakarnjanarat, W. Uthavivoravit, T.D. Mastro, T. Mori, J.W. Tappero, *Int J Tuberc Lung Dis*, 2003,7,36

A cross-sectional study conducted in a provincial referral hospital in northern Thailand, during 1995-96, reported on the occupational risk of *Mycobacterium tuberculosis* transmission. The aim of this study was to describe the effectiveness of prevention strategies for nosocomial tuberculosis

(TB) among health care workers. Following a comprehensive risk assessment, preventive interventions were implemented targeting health care workers (HCW), hospitalised patients, and the hospital environment. The number of pulmonary TB cases diagnosed increased steadily from 102 in 1990 to 356 in 1999. The tuberculosis skin test (TST) conversion rate was 9.3 (95% CI 3.3-15) per 100 person-years (py) in 1995-1997, but declined steadily to 2.2 (95%CI 0.0-5.1) in 1999. HCWs, first screened within 12 months of employment had higher TST conversion rates (adjusted RR = 9.5, 95% CI 1.8-49.5) compared to those employed for longer than 12 months. The annual rate of active TB per 100000 HCWs was 536 in 1995-1999. These HCWs were exposed to active TB patients and were at risk, particularly during their first 12 months of employment. Implementation of nosocomial TB control measures in 1996 was followed by declining TST conversion rates, despite increasing exposure to active TB patients.

Haematological abnormalities in patients of sarcoidosis

D. Gupta, V. Madhava Rao, A.N. Aggarwal, G. Garewal, S.K. Jindal, *Indian J Chest Dis Allied Sci*, 2002; 44:233

Haematological investigations including complete blood cell counts, ESR and peripheral smear examination were carried out in 30 consecutive freshly diagnosed cases of sarcoidosis and compared with equal number of age and sex matched healthy controls. Coagulation parameters such as prothrombin time (PT), prothrombin index (PTI), partial thromboplastin time (PTTK) and fibrinogen levels were studied. There were 15 men (mean age 40.4±10.15 years) in the study group. Haematological abnormalities were present in 11 (36.66%) patients. Four cases (13.33%, all females) were found to have anaemia and in three of them no other cause for this was evident. Lymphopenia (lymphocyte count <1500/ cu mm) was present in 8 (26.66%) patients and 3 (10%) controls (P<0.05). Only 1 patient (3.3%) had leucopenia. Number of subjects with raised ESR and mean ESR were higher in the study group as compared to the controls. No

coagulation abnormalities were encountered.

Isolation and evaluation of diagnostic value of two major secreted proteins of *Mycobacterium tuberculosis*

K.S. Senthil Kumar, K.R. Uma Devi, Raja Alamelu,
Indian J Chest Dis Allied Sci, 2002;44:225

Two secreted antigens of *Mycobacterium tuberculosis*, namely the antigen 85 complex (30/31) and 38kDa antigen, were purified from the whole culture filtrate by using two dimensional preparative electrophoresis and anion exchange chromatography, respectively. Individual

components of the antigen 85 complex, namely antigen 85A, 85B and 85C, were separated using hydrophobic interaction chromatography. The humoral antibody activity to these antigens in sputum positive cases of active pulmonary tuberculosis and normal healthy volunteers was determined by enzyme linked immunosorbent assay (ELISA) and immunoblot. Recombinant 38kDa and antigen 6 were used as reference antigens for the assay. None of the healthy volunteers reacted with the 38kDa antigen, while 52% of the TB sera reacted with it. Of the three components of the antigen 85 complex, 85B gave the highest positivity of 40 percent. The result of combination of 38kDa with antigen 6 offered better results with 76% positivity.

ERRATUM

In the January, 2003 issue of the *Indian Journal of Tuberculosis*, in the paper entitled 'Tuberculosis & Pregnancy', Page 15 Col. 1, para 3, instead of "place²⁰" read "place".